REA's

Problem Solvers

ORGANIC CHEMISTRY

A Complete Solution Guide to Any Textbook

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- For use with introductory and advanced texts and courses
- Includes every type of problem that may be assigned by your instructor or given on a test
- Each problem worked out in step-by-step detail, enabling you to understand the subject fully
- Will save you hours of time in finding solutions to problems

Research & Education Association

THE ORGANIC CHEMISTRY PROBLEM SOLVER®

REGISTERED TRADEMARK

A Complete Solution Guide to Any Textbook

Staff of Research and Education Association
Dr. M. Fogiel, Director

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THE ORGANIC CHEMISTRY
PROBLEM SOLVER ®

Printed in the United States of America

Library of Congress Catalog Card Number 94-67819

International Standard Book Number 0-87891-512-5

WHAT THIS BOOK IS FOR

For as long as organic chemistry has been taught in schools, students have found this subject difficult to understand and learn. Despite the publication of hundreds of textbooks in this field, each one intended to provide an improvement over previous textbooks, students continue to remain perplexed, and the subject is often taken in class only to meet school/departmental requirements for a selected course of study.

In a study of the problem, REA found the following basic reasons underlying students' difficulties with organic chemistry taught in schools:

(a) No systematic rules of analysis have been developed which students may follow in a step-by-step manner to solve the usual problems encountered. This results from the fact that the numerous different conditions and principles which may be involved in a problem, lead to many possible different methods of solution. To prescribe a set of rules to be followed for each of the possible variations, would involve an enormous number of rules and steps to be searched through by students, and this task would perhaps be more burdensome than solving the problem directly with some accompanying trial and error to find the correct solution route.

(b) Textbooks currently available will usually explain a given principle in a few pages written by a professional who has an insight in the subject matter that is not shared by students. The explanations are often written in an abstract manner which leaves the students confused as to the application of the principle. The explanations given are not sufficiently detailed and extensive to make the student aware of the wide range of applications and different aspects of the principle being studied. The numerous possible variations of principles and their applications are usually not discussed, and it is left for the students to discover these for themselves while doing the exercises. Accordingly, the average student is expected to rediscover that which has been long known and practiced, but not published or explained extensively.

(c) The examples usually following the explanation of a topic are too few in number and too simple to enable the student to obtain a thorough grasp of the principles involved. The explanations do not provide sufficient basis to enable a student to solve problems that may be subsequently assigned for homework or given on examinations.

The examples are presented in abbreviated form which leaves out much material between steps, and requires that students derive the omitted material themselves. As a result, students find the examples difficult to understand contrary to the purpose of the examples.

Examples are, furthermore, often worded in a confusing manner. They do not state the problem and then present the solution. Instead, they pass through a general discussion, never revealing what is to be solved for.

Examples, also, do not always include diagrams/graphs, wherever appropriate, and students do not obtain the training to draw diagrams or graphs to simplify and organize their thinking.

(d) Students can learn the subject only by doing the exercises themselves and reviewing them in class, to obtain experience in applying the principles with their different ramifications.

In doing the exercises by themselves, students find that they are required to devote considerably more time to organic chemistry than to other subjects of comparable credits, because they are uncertain with regard to the selection and application of the theorems and principles involved. It is also often necessary for students to discover those "tricks" not revealed in their texts (or review books), that make it possible to solve problems easily. Students must usually resort to methods of trial-and-error to discover these "tricks", and as a result they find that they may sometimes spend several hours to solve a single problem.

(e) When reviewing the exercises in classrooms, instructors usually request students to take turns in writing solutions on the board and explaining them to the class. Students often find it difficult to explain in a manner that holds the interest of the class, and does not enable the remaining students to follow the material written on the boards. The remaining students seated in the class are, furthermore, too occupied with copying the material from the boards, to listen to the oral explanations and concentrate on the methods of solution.

This book is intended to aid students in organic chemistry to overcome the difficulties described, by supplying detailed illustrations of the solution methods which are usually not apparent to students. The solution methods are illustrated by problems selected from those that are most often assigned for class work and given on examinations. The problems are arranged in order of complexity to enable students to learn and understand a particular topic by reviewing the problems in sequence. The problems are illustrated with detailed step by step explanations, to save the students the large amount of time that is often needed to fill in the gaps that are usually found between steps of illustrations in textbooks or review/outline books.

The staff of REA considers organic chemistry a subject that is best learned by allowing students to view the methods of analysis and solution techniques themselves. This approach to learning the subject matter is similar to that practiced in various scientific laboratories, particularly in the medical fields.

In using this book, students may review and study the illustrated problems at their own pace; they are not limited to the time allowed for explaining problems on the board in class.

When students want to look up a particular type of problem and solution, they can readily locate it in the book by referring to the index which has been extensively prepared. It is also possible to locate a particular type of problem by glancing at just the material within the boxed portions. To facilitate rapid scanning of the problems, each problem has a heavy border around it. Furthermore, each problem is identified with a number immediately above the problem at the right-hand margin.

To obtain maximum benefit from the book, students should familiarize themselves with the section, "How To Use This Book," located in the front pages.

To meet the objectives of this book, staff members of REA have selected problems usually encountered in assignments and examinations, and have solved each problem meticulously to illustrate the steps which are difficult for students to comprehend. Special gratitude is expressed to them for their efforts in this area, as well as to the numerous contributors who devoted brief periods of time to this work.

Gratitude is also expressed to the many persons involved in the difficult task of typing the manuscript with its endless changes, and to the REA art staff who prepared the numerous detailed illustrations together with the layout and physical features of the book.

The difficult task of coordinating the efforts of all persons was carried out by Carl Fuchs. His conscientious work deserves much appreciation. He also trained and supervised art and production personnel in the preparation of the book for printing.

Finally, special thanks are due to Helen Kaufmann for her unique talents in rendering those difficult border-line decisions and in making constructive suggestions related to the design and organization of the book.

Max Fogiel, Ph.D.
Program Director

HOW TO USE THIS BOOK

This book can be an invaluable aid to students in organic chemistry as a supplement to their textbooks. The book is subdivided into 35 chapters, each dealing with a separate topic. The subject matter is developed beginning with structure and properties and extending through spectroscopy, stereochemistry, molecular orbital theory, and all of the principal classes of organic compounds. Sections on natural products, photochemistry, and color have also been included. Wherever applicable, topics include nomenclature, preparation, synthesis and reactions, characterization tests, and spectroscopy.

TO LEARN AND UNDERSTAND A TOPIC THOROUGHLY

1. Refer to your class text and read the section pertaining to the topic. You should become acquainted with the principles discussed there. These principles, however, may not be clear to you at that time.

2. Then locate the topic you are looking for by referring to the "Table of Contents" in the front of this book, "The Organic Chemistry Problem Solver."

3. Turn to the page where the topic begins and review the problems under each topic, in the order given. For each topic, the problems are arranged in order of complexity, from the simplest to the more difficult. Some problems may appear similar to others, but each problem has been selected to illustrate a different point or solution method.

To learn and understand a topic thoroughly and retain its contents, it will be generally necessary for students to review the problems several times. Repeated review is essential in order to gain experience in recognizing the principles that should be applied, and in selecting the best solution technique.

TO FIND A PARTICULAR PROBLEM

To locate one or more problems related to a particular subject matter, refer to the index. In using the index, be certain to note that the numbers given there refer to problem numbers, not page numbers. This arrangement of the index is intended to facilitate finding a problem more rapidly, since two or more problems may appear on a page.

If a particular type of problem cannot be found readily, it is recommended that the student refer to the "Table of Contents" in the front pages, and then turn to the chapter which is applicable to the problem being sought. By scanning or glancing at the material that is boxed, it will generally be possible to find problems related to the one being sought, without consuming considerable time. After the problems have been located, the solutions can be reviewed and studied in detail. For this purpose of locating problems rapidly, students should acquaint themselves with the organization of the book as found in the "Table of Contents."

In preparing for an exam, it is useful to find the topics to be covered on the exam in the "Table of Contents," and then review the problems under those topics several times. This should equip the student with what might be needed for the exam.

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UNITS CONVERSION FACTORS

This section includes a particularly useful and comprehensive table to aid students and teachers in converting between systems of units.

The problems and their solutions in this book use SI (International System) as well as English units. Both of these units are in extensive use throughout the world, and therefore students should develop a good facility to work with both sets of units until a single standard of units has been found acceptable internationally.

In working out or solving a problem in one system of units or the other, essentially only the numbers change. Also, the conversion from one unit system to another is easily achieved through the use of conversion factors that are given in the subsequent table. Accordingly, the units are one of the least important aspects of a problem. For these reasons, a student should not be concerned mainly with which units are used in any particular problem. Instead, a student should obtain from that problem and its solution an understanding of the underlying principles and solution techniques that are illustrated there.

To convert	To	Multiply by	For the reverse, multiply by
acres	square feet	4.356×10^{4}	2.296×10^{-5}
acres	square meters	4047	2.471×10^{-4}
ampere-hours	coulombs	3600	2.778×10^{-4}
ampere-turns	gilberts	1.257	0.7958
ampere-turns per cm	ampere-turns per inch	2.54	0.3937
angstrom units	inches	3.937×10^{-9}	2.54×10^{8}
angstrom units	meters	10^{-10}	10^{10}
atmospheres	feet of water	33.90	0.02950
atmospheres	inch of mercury at 0°C	29.92	3.342×10^{-2}
atmospheres	kilogram per square meter	1.033×10^{4}	9.678×10^{-5}
atmospheres	millimeter of mercury at 0°C	760	1.316×10^{-3}
atmospheres	pascals	1.0133×10^{5}	0.9869×10^{-5}
atmospheres	pounds per square inch	14.70	0.06804
bars	atmospheres	9.870×10^{-1}	1.0133
bars	dynes per square cm	10^{6}	10^{-6}
bars	pascals	10^{5}	10^{-5}
bars	pounds per square inch	14.504	6.8947×10^{-2}
Btu	ergs	1.0548×10^{10}	9.486×10^{-11}
Btu	foot-pounds	778.3	1.285×10^{-3}
Btu	joules	1054.8	9.480×10^{-4}
Btu	kilogram calories	0.252	3.969
calories, gram	Btu	3.968×10^{-3}	252
calories, gram	foot-pounds	3.087	0.324
calories, gram	joules	4.185	0.2389
Celsius	Fahrenheit	$(°C \times 9/5) + 32 = °F$	$(°F - 32) \times 5/9 = °C$

To convert	To	Multiply	For the reverse, multiply by
Celsius	kelvin	°C + 273.15 = K	K − 273.15 = °C
centimeters	angstrom units	1×10^{8}	1×10^{-8}
centimeters	feet	0.03281	30.48
centistokes	square meters per second	1×10^{-6}	1×10^{6}
circular mils	square centimeters	5.067×10^{-6}	1.973×10^{5}
circular mils	square mils	0.7854	1.273
cubic feet	gallons (liquid U.S.)	7.481	0.1337
cubic feet	liters	28.32	3.531×10^{-2}
cubic inches	cubic centimeters	16.39	6.102×10^{-2}
cubic inches	cubic feet	5.787×10^{-4}	1728
cubic inches	cubic meters	1.639×10^{-5}	6.102×10^{4}
cubic inches	gallons (liquid U.S.)	4.329×10^{-3}	231
cubic meters	cubic feet	35.31	2.832×10^{-2}
cubic meters	cubic yards	1.308	0.7646
curies	coulombs per minute	1.1×10^{12}	0.91×10^{-12}
cycles per second	hertz	1	1
degrees (angle)	mils	17.45	5.73×10^{-2}
degrees (angle)	radians	1.745×10^{-2}	57.3
dynes	pounds	2.248×10^{-6}	4.448×10^{5}
electron volts	joules	1.602×10^{-19}	0.624×10^{19}
ergs	foot pounds	7.376×10^{-8}	1.356×10^{7}
ergs	joules	10^{-7}	10^{7}
ergs per second	watts	10^{-7}	10^{7}
ergs per square cm	watts per square cm	10^{-7}	10^{7}
Fahrenheit	kelvin	(°F + 459.67)/1.8	1.8K − 459.67
Fahrenheit	Rankine	°F + 459.67 = °R	°R − 459.67 = °F
faradays	ampere-hours	26.8	3.731×10^{-2}
feet	centimeters	30.48	3.281×10^{-2}
feet	meters	0.3048	3.281
feet	mils	1.2×10^{4}	8.333×10^{-5}
fermis	meters	10^{-15}	10^{15}
foot candles	lux	10.764	0.0929
foot lamberts	candelas per square meter	3.4263	0.2919
foot-pounds	gram-centimeters	1.383×10^{4}	7.233×10^{-5}
foot-pounds	horsepower-hours	5.05×10^{-7}	1.98×10^{6}
foot-pounds	kilogram-meters	0.1383	7.233
foot-pounds	kilowatt-hours	3.766×10^{-7}	2.655×10^{6}
foot-pounds	ounce-inches	192	5.208×10^{-3}
gallons (liquid U.S.)	cubic meters	3.785×10^{-3}	264.2
gallons (liquid U.S.)	gallons (liquid British Imperial)	0.8327	1.201
gammas	teslas	10^{-9}	10^{9}
gausses	lines per square cm	1.0	1.0
gausses	lines per square inch	6.452	0.155
gausses	teslas	10^{-4}	10^{4}
gausses	webers per square inch	6.452×10^{-8}	1.55×10^{7}
gilberts	amperes	0.7958	1.257
grades	radians	1.571×10^{-2}	63.66
grains	grams	0.06480	15.43
grains	pounds	$1/7000$	7000
grams	dynes	980.7	1.02×10^{-3}
grams	grains	15.43	6.481×10^{-2}

To convert	To	Multiply	For the reverse, multiply by
grams	ounces (avdp)	3.527×10^{-2}	28.35
grams	poundals	7.093×10^{-2}	14.1
hectares	acres	2.471	0.4047
horsepower	Btu per minute	42.418	2.357×10^{-2}
horsepower	foot-pounds per minute	3.3×10^{4}	3.03×10^{-5}
horsepower	foot-pounds per second	550	1.818×10^{-3}
horsepower	horsepower (metric)	1.014	0.9863
horsepower	kilowatts	0.746	1.341
inches	centimeters	2.54	0.3937
inches	feet	8.333×10^{-2}	12
inches	meters	2.54×10^{-2}	39.37
inches	miles	1.578×10^{-5}	6.336×10^{4}
inches	mils	10^{3}	10^{-3}
inches	yards	2.778×10^{-2}	36
joules	foot-pounds	0.7376	1.356
joules	watt-hours	2.778×10^{-4}	3600
kilograms	tons (long)	9.842×10^{-4}	1016
kilograms	tons (short)	1.102×10^{-3}	907.2
kilograms	pounds (avdp)	2.205	0.4536
kilometers	feet	3281	3.048×10^{-4}
kilometers	inches	3.937×10^{4}	2.54×10^{-5}
kilometers per hour	feet per minute	54.68	1.829×10^{-2}
kilowatt-hours	Btu	3413	2.93×10^{-4}
kilowatt-hours	foot-pounds	2.655×10^{6}	3.766×10^{-7}
kilowatt-hours	horsepower-hours	1.341	0.7457
kilowatt-hours	joules	3.6×10^{6}	2.778×10^{-7}
knots	feet per second	1.688	0.5925
knots	miles per hour	1.1508	0.869
lamberts	candles per square cm	0.3183	3.142
lamberts	candles per square inch	2.054	0.4869
liters	cubic centimeters	10^{3}	10^{-3}
liters	cubic inches	61.02	1.639×10^{-2}
liters	gallons (liquid U.S.)	0.2642	3.785
liters	pints (liquid U.S.)	2.113	0.4732
lumens per square foot	foot-candles	1	1
lumens per square meter	foot-candles	0.0929	10.764
lux	foot-candles	0.0929	10.764
maxwells	kilolines	10^{-3}	10^{3}
maxwells	webers	10^{-8}	10^{8}
meters	feet	3.28	30.48×10^{-2}
meters	inches	39.37	2.54×10^{-2}
meters	miles	6.214×10^{-4}	1609.35
meters	yards	1.094	0.9144
miles (nautical)	feet	6076.1	1.646×10^{-4}
miles (nautical)	meters	1852	5.4×10^{-4}
miles (statute)	feet	5280	1.894×10^{-4}
miles (statute)	kilometers	1.609	0.6214
miles (statute)	miles (nautical)	0.869	1.1508
miles per hour	feet per second	1.467	0.6818
miles per hour	knots	0.8684	1.152
millimeters	microns	10^{3}	10^{-3}

To convert	To	Multiply	For the reverse, multiply by
mils	meters	2.54×10^{-5}	3.94×10^{4}
mils	minutes	3.438	0.2909
minutes (angle)	degrees	1.666×10^{-2}	60
minutes (angle)	radians	2.909×10^{-4}	3438
newtons	dynes	10^{5}	10^{-5}
newtons	kilograms	0.1020	9.807
newtons per sq. meter	pascals	1	1
newtons	pounds (avdp)	0.2248	4.448
oersteds	amperes per meter	7.9577×10	1.257×10^{-2}
ounces (fluid)	quarts	3.125×10^{-2}	32
ounces (avdp)	pounds	6.25×10^{-2}	16
pints	quarts (liquid U.S.)	0.50	2
poundals	dynes	1.383×10^{4}	7.233×10^{-5}
poundals	pounds (avdp)	3.108×10^{-2}	32.17
pounds	grams	453.6	2.205×10^{-3}
pounds (force)	newtons	4.4482	0.2248
pounds per square inch	dynes per square cm	6.8946×10^{4}	1.450×10^{-5}
pounds per square inch	pascals	6.895×10^{3}	1.45×10^{-4}
quarts (U.S. liquid)	cubic centimeters	946.4	1.057×10^{-3}
radians	mils	10^{3}	10^{-3}
radians	minutes of arc	3.438×10^{3}	2.909×10^{-4}
radians	seconds of arc	2.06265×10^{5}	4.848×10^{-6}
revolutions per minute	radians per second	0.1047	9.549
roentgens	coulombs per kilogram	2.58×10^{-4}	3.876×10^{3}
slugs	kilograms	14.59	0.0685
slugs	pounds (avdp)	32.174	3.108×10^{-2}
square feet	square centimeters	929.0304	1.076×10^{-3}
square feet	square inches	144	6.944×10^{-3}
square feet	square miles	3.587×10^{-8}	27.88×10^{6}
square inches	square centimeters	6.452	0.155
square kilometers	square miles	0.3861	2.59
stokes	square meter per second	10^{-4}	10^{4}
tons (metric)	kilograms	10^{3}	10^{-3}
tons (short)	pounds	2000	5×10^{-4}
torrs	newtons per square meter	133.32	7.5×10^{-3}
watts	Btu per hour	3.413	0.293
watts	foot-pounds per minute	44.26	2.26×10^{-2}
watts	horsepower	1.341×10^{-3}	746
watt-seconds	joules	1	1
webers	maxwells	10^{8}	10^{-8}
webers per square meter	gausses	10^{4}	10^{-4}

PERIODIC TABLE OF THE ELEMENTS

ATOMIC NUMBER → 46 — ← OXIDATION STATES
SYMBOL → Pd
ATOMIC WEIGHT → 106.4
18-18-0 ← ELECTRON CONFIGURATION

1a	2a	3b	4b	5b	6b	7b	8	8	8	1b	2b	3a	4a	5a	6a	7a	0	Orbit
1 H 1.0079																	2 He 4.00260	K
3 Li 6.941	4 Be 9.01218											5 B 10.81	6 C 12.011	7 N 14.0067	8 O 15.9994	9 F 18.998403	10 Ne 20.179	K-L
11 Na 22.98977	12 Mg 24.305											13 Al 26.98154	14 Si 28.0855	15 P 30.97376	16 S 32.06	17 Cl 35.453	18 Ar 39.948	K-L-M
19 K 39.0983	20 Ca 40.08	21 Sc 44.9559	22 Ti 47.88	23 V 50.9415	24 Cr 51.996	25 Mn 54.9380	26 Fe 55.847	27 Co 58.9332	28 Ni 58.69	29 Cu 63.546	30 Zn 65.38	31 Ga 69.72	32 Ge 72.59	33 As 74.9216	34 Se 78.96	35 Br 79.904	36 Kr 83.80	-L-M-N
37 Rb 85.4678	38 Sr 87.62	39 Y 88.9059	40 Zr 91.22	41 Nb 92.9064	42 Mo 95.94	43 Tc (98)	44 Ru 101.07	45 Rh 102.9055	46 Pd 106.42	47 Ag 107.868	48 Cd 112.41	49 In 114.82	50 Sn 118.69	51 Sb 121.75	52 Te 127.60	53 I 126.9045	54 Xe 131.29	-M-N-O
55 Cs 132.9054	56 Ba 137.33	57* La 138.9055	72 Hf 178.49	73 Ta 180.9479	74 W 183.85	75 Re 186.207	76 Os 190.2	77 Ir 192.22	78 Pt 195.08	79 Au 196.9665	80 Hg 200.59	81 Tl 204.383	82 Pb 207.2	83 Bi 208.9804	84 Po (209)	85 At (210)	86 Rn (222)	-N-O-P
87 Fr (223)	88 Ra 226.0254	89** Ac 227.0278	104 Rf (261)	105 Ha (262)	106 (263)												NOBLE GASES	-O-P-Q

Numbers in parentheses are mass numbers of most stable isotope of that element.

*LANTHANIDES	58 Ce 140.12	59 Pr 140.9077	60 Nd 144.24	61 Pm (145)	62 Sm 150.36	63 Eu 151.96	64 Gd 157.25	65 Tb 158.9254	66 Dy 162.50	67 Ho 164.9304	68 Er 167.26	69 Tm 168.9342	70 Yb 173.04	71 Lu 174.967	-N-O-P
**ACTINIDES	90 Th 232.0381	91 Pa 231.0359	92 U 238.0289	93 Np 237.0482	94 Pu (244)	95 Am (243)	96 Cm (247)	97 Bk (247)	98 Cf (251)	99 Es (252)	100 Fm (257)	101 Md (258)	102 No (259)	103 Lr (260)	-O-P-Q

TRANSITION ELEMENTS

GROUP 8

CHAPTER 1

STRUCTURE AND PROPERTIES

LEWIS STRUCTURES

• PROBLEM 1-1

Provide a likely single electronic structure for each of the following, assuming them to be completely covalent. Assume that every atom has a complete octet (except hydrogen, of course), and that two atoms may share more than one pair of electrons.

(a) H_2SO_4 (b) N_2H_4 (c) $COCl_2$ (d) HONC (e) HSO_4^-

(f) C_2H_2 (g) CH_2O_2

Solution: The consideration of the structure of molecules requires an understanding of chemical bonds, the forces that hold atoms together in a molecule.

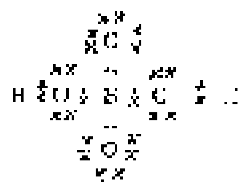
One type of chemical bond is the covalent bond, which results from sharing of electrons. The bonding force is electrostatic attraction: this time between each electron and both nuclei. The formation of ammonia serves as an example of this and an electronic structure below depicts how the electrons are shared.

$$3H\cdot \;+\; \cdot\ddot{N}: \longrightarrow H\overset{\displaystyle H}{\overset{\times\times}{\ddot{N}}}\!:\!H \qquad \text{(ammonia)}$$

Each dot or "x" denotes an electron. (The different symbols for the electron are meant for clarity, and not to suggest a difference.) In writing the electronic structures for the formation of ammonia, one had to realize the number of electrons in the incomplete shell. Each hydrogen atom has one and the nitrogen atom has five. These numbers are obtained from inspection of their electronic configurations. By hydrogen and nitrogen bonding, nitrogen obtains a complete octet (8 electrons surrounding it) for stability and completion of outer shell and each hydrogen atom is now surrounded by 2 electrons for completion of its shell.

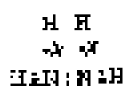
One can now proceed to write the electronic structures the problem calls for.

(a) H_2SO_4. Consider first the number of electrons in the incomplete shell for each atom. Hydrogen has one, oxygen has six, and sulfur has six. Both sulfur and oxygen must have a complete octet. Hydrogen must have two electrons for a complete shell. To distinguish the electrons for clarity and see how they are arranged in the electronic structure, the following symbols will be used: Hydrogen's electrons will be represented by +, sulfur's by •, and oxygen's by x. The electronic structure can be written as:



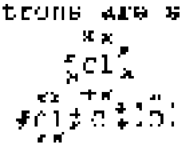
Notice how only this configuration satisfies the requirement that sulfur donates six electrons, oxygen six electrons, and hydrogen one electron.

(b) N_2H_4



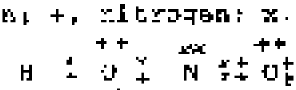
Here, each nitrogen contributes 5 electrons (•) and each hydrogen contributes 1 electron (x).

(c) $COCl_2$ The carbon atom can contribute only 4 electrons (this is the number in its incomplete shell - represented by +) and the chlorine atom can contribute 7 (represented by x). Oxygen's electrons are shown as dots (•).

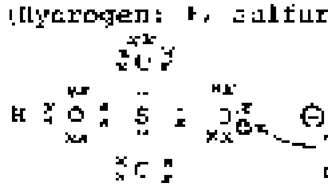


Notice at arrow that two pairs of electrons must be shared for complete octets to be attained. This denotes the presence of a double bond. (A triple bond would have three pairs of electrons shared between two atoms.)

(d) $HONO$ (Oxygen: +, nitrogen: x, and hydrogen: •)

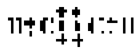


(e) HSO_4^- (Hydrogen: +, sulfur: •, and oxygen by x)

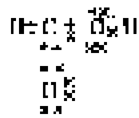


This electron accounts for negative charge

(f) C_2H_2 (Carbon: — and hydrogen: ·)



(g) CH_2O (Carbon: | , hydrogen: · , and oxygen: x)



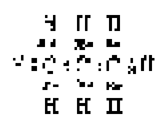
• PROBLEM 1 2

Draw Lewis structures for the following substances. Use distinct, correctly placed dots for the electrons. Mark all atoms which are not neutral with charges of the proper sign.

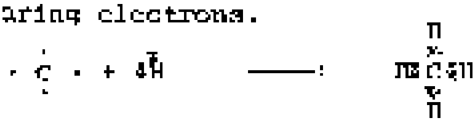
a. propane
b. cyclopropane
c. benzene
d. methyl bromide
e. methanol
f. ethylene oxide
g. sodium acetate ($CH_3CO_2^{\ominus}Na^{\oplus}$)
h. methylamine
i. acetamide
j. nitromethane

Solution: In drawing the Lewis structure of the following compounds, it should be noted that each element should have a complete octet (eight electrons in its outer shell). The exception to this rule is hydrogen which has a duet shell.

(a) Propane: C_3H_8

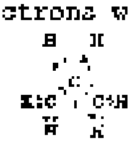


Elements that are in the middle of the periodic table tend to acquire the electrons to complete their octets by sharing electrons.

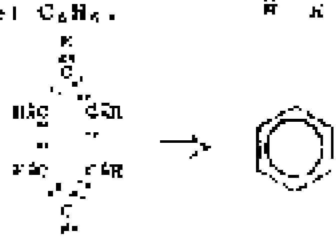


× and · both represent electrons, though from different sources.

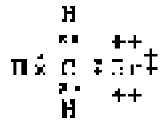
(b) Cyclopropane: C_3H_6. In this compound, the 3 carbon atoms mutually share electrons with one another thus forming a ring.



(c) benzene: C_6H_6.

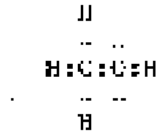


(d) methyl bromide: CH_3Br

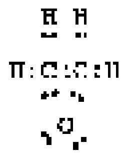


Electrons from bromine are represented by +

(e) methanol CH_3OH

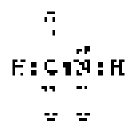


(f) ethylene oxide



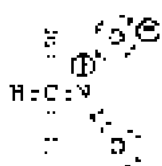
(g) sodium acetate $CH_3COO^-Na^+$

(h) methyl amine CH_3NH_2



(i) acetamide CH_3CONH_2

(j) nitromethane CH_3NO_2



STRUCTURAL FORMULAS

• PROBLEM 1-3

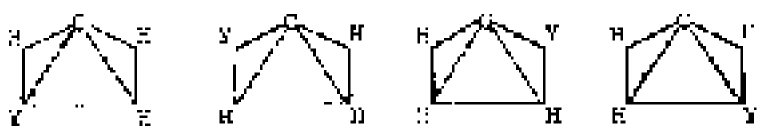
> How many isomers of formula CH_3Y would be possible if methane were a pyramid with a rectangular base? What are they?

Solution: Any compound, no matter how complicated, that contains carbon bonded to four other atoms can be considered as a derivative of methane. For any atom Y, only one substance of the formula CH_3Y has ever been found. Chlorination of methane yields only one compound of formula CH_3Cl; bromination yields only CH_3Br. The same holds true even if

Y were not only an atom, but a group of atoms (i.e., if the group itself is not too complicated to bring about isomerism). This means that every hydrogen atom in methane is equivalent, so that replacement of one hydrogen as opposed to another always yields the same product.

To answer this problem one makes two identical pyramidal models of CH_4 (with C at the apex), and then replace, for instance, the upper right-hand H with a different atom Y; in the other model replace the lower right-hand H. Next determine whether or not, by any manipulation except bending or breaking bonds, the models can be made to coincide in all their parts. If the two models are superimposable, then they represent two molecules of the same structure. If the models are not superimposable, then they represent molecules of different structures which, since they have the same molecular formula, are by definition isomers.

All the possible pyramidal structures of CH_3Y are drawn and shown in figures A through D.



(A) (B) (C) (D)

In each of these structures the Y atom has been shifted to each of the four corners of the rectangular base. With close inspection and imagination one can distinguish only two non-superimposable molecules. Figures A and C are the same, as are figures B and D. Thus, only 2 isomers of CH_3Y can be formed if the structure were a pyramid with a rectangular base.

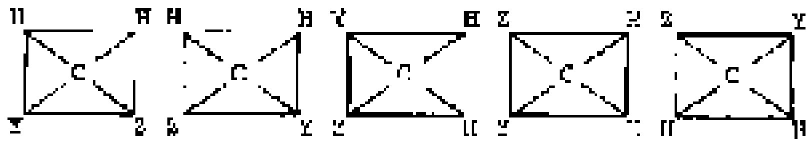
• PROBLEM 1-4

How many isomers of formula CH_2YZ would be expected from each of the following structures for methane? (a) Carbon at the center of a rectangle; (b) Carbon at the center of a square; (c) carbon at the apex of a square base pyramid; (d) carbon in the center of a tetrahedron.

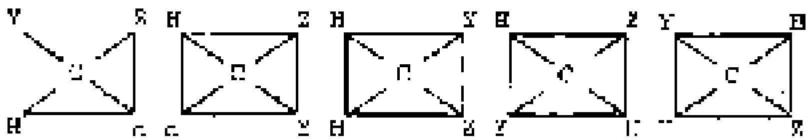
Solution: For any atom Y and for any atom Z, only one substance of the formula CH_2YZ has ever been found. Halogenation of methane yields only one compound of formula CH_2Cl_2, only one compound of formula CH_2Br_2, and only one compound of formula CH_2ClBr.

To answer this problem one must make molecular models of CH_4 in the particular shape in question. One then proceeds to replace two hydrogen atoms by a Y and Z atom. Next determine whether or not, by any manipulation except bending or breaking bonds, the models can be made to coincide in all their parts. If the models are superimposable, then they represent molecules of the same structure; if the models are not superimposable, then they represent molecules of different structures which are by definition isomers.

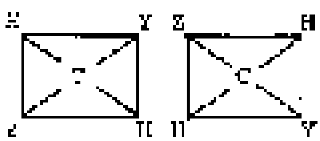
(a) Carbon at the center of a rectangle: Draw all the possible structures of CH_2YZ in this arrangement. These are shown in figures A through L.



(A) (B) (C) (D) (E)



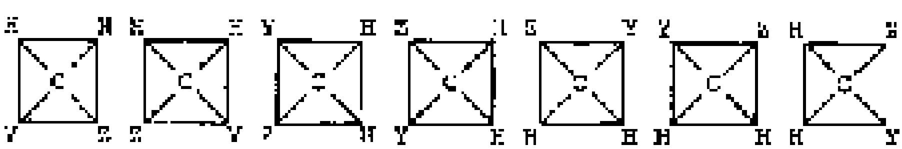
(F) (G) (H) (I) (J)



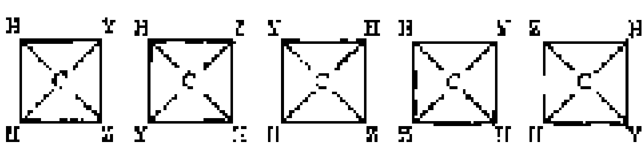
(K) (L)

With some intuition one can distinguish only three different structures. Figures A, B, E, and F are the same; figures C, D, G, and H are the same; and figures I, J, K, and L are the same.

(b) Carbon at the center of a square:



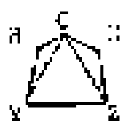
A' B' C' D' E' F' G'



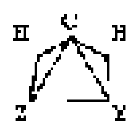
H I' J' K' L'

Draw all the possible structures of CH_2YZ in this arrangement. These are shown in figures A' through L'. With some intuition one can distinguish only two different structures or isomers. Figures A', B', C', D', E', F', G', and H' are the same; and figures I', J', K', and L' are the same.

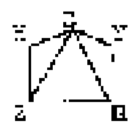
(c) Carbon at the apex of a square-base pyramid. Draw all the possible structures of CH_2YZ in this arrangement. With a little imagination figures A' through L' can be seen as the top view of a pyramid with a square base. However, care must be taken when rotating these structures; their bases must not be removed from the plane of the paper. With some intuition one can distinguish three different structures or isomers. Figures A', C', E', and G' are the same; figures B', D', F', and H' are the same; and figures I', J', K', and L' are the same. These three figures are redrawn as figures 1, 2, and 3, respectively.



(1)

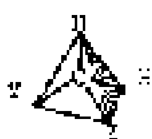


(2)



(3)

(d) Carbon in the center of a tetrahedron. As stated at the beginning of this problem only one structure of the methane derivative, CH_2YZ, has ever been found. This structure is a tetrahedron and is shown in figure M.



(M)

• PROBLEM 1-6

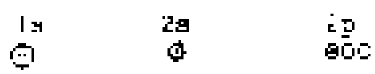
In the complex ion $Co(NH_3)_6^{+3}$, the bonds to the central atom can be pictured as utilizing six equivalent sp^3d^2 (or d^2sp^3) hybrid orbitals. On the basis of maximum separation of orbitals, what geometry would one expect this complex to have?

Solution: An understanding of hybridization will be necessary for the solution. Consider the case of beryllium chloride, $BeCl_2$. Beryllium may be pictured as:

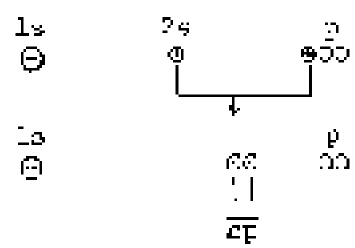
1s	2s	2p
⊙	⊙	OOO

S and P represent atomic orbitals. The former is a sphere with its center at the nucleus of the atom, while the latter is dumbbell shaped. It consists of two lobes with the atomic nucleus lying between them. Since the axis of each P orbital is perpendicular to the axes of the other two, they are differentiated by the names P_x, P_y and P_z. An orbital may be defined as the region in space where an electron is likely to be found. An orbital may hold no more than 2 electrons (the Pauli Exclusion Principle). (Electrons are shown as dots.) The coefficients represent energy levels, with 1s as the lowest energy level and 2s and 2p being positioned at the next highest energy levels.

Inspection of the picture of beryllium shows it has no unpaired electrons. Hence, to account for beryllium combining with two chlorine atoms, one could promote one of 2s electrons to an empty p orbital:

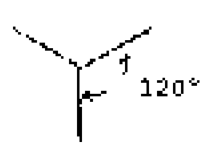


This procedure creates two unpaired electrons which could theoretically bond to chlorine in two different bonds, one using a p orbital, the other a s orbital. However, it is an established fact the two bonds in beryllium are equivalent. Consequently, the orbitals must be combined. The scheme below shows the combination of one s and one p orbitals to produce two mixed (hybrid) orbitals:



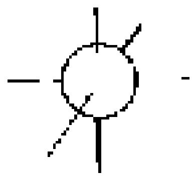
In sp hybridization, two orbitals are produced that represent a mixture of s and p orbitals. These orbitals are equivalent and much more strongly directed than either the s or p orbital. The sp hybrid orbitals point in exactly opposite directions; this arrangement permits them to get as far away from each other as possible. For note that electrons of like spin tend to get as far away from each other as possible, and it is this that mostly determines the geometry or shapes and properties of molecules.

In sp^2 hybridization, one has three orbitals, so that a trigonal (three-cornered) arrangement permits the least contact of the orbitals. It can be visualized as shown:



Sp^3 hybridization requires a tetrahedral (angle = 109.5°) arrangement for the least possible overlap of orbitals.

These considerations, then, should provide an important insight into the geometry of $Co(NH_3)_6^{+3}$. In this instance, one has the hybridization sp^3d^2, which indicates that six equivalent orbitals are involved. (The mixture is 3 from p, 2 from d, and 1 from s.) The point is to think of a geometry that will keep these six hybrid orbitals as far apart as possible. The best configuration or geometry would have to be the octahedral as shown:



BONDING

■ PROBLEM 1-6

Assign all the electrons in acetaldehyde ($CH_3-CH=O$) to their atomic or molecular orbitals.

Solution: The formation of covalent bonds by the sharing of electrons results from the overlapping and interaction of partially filled atomic orbitals. The molecular orbitals (bonds) so formed are represented adequately by the summation of the geometrical properties of the individual atomic orbitals.

Since bond formation is produced by the interaction of orbitals, which can be highly directional, the most effective bonds will be formed when the relative spatial positions of the atoms are such as to produce the best possible overlap of orbitals.

To be able to assign all the electrons in $CH_3-CH=O$ to their orbitals, first set up the electron dot formula:

$$\begin{array}{c} \;\;H\;\;H \\ H:\underset{\cdot\cdot}{\overset{\cdot\cdot}{C}}:\overset{\cdot\cdot}{C}::\ddot{O}: \\ H \end{array}$$

When an atom forms a compound in which it is attached to four neighboring atoms by single bonds, sp^3 hybrid orbitals are used to form these bonds. Thus carbon 1 is sp^3 hybridized. All hydrogen atoms have s orbitals, therefore, the three carbon-hydrogen bonds on the first carbon atom are sp^3-s bonds.

The carbon-carbon bond between the first and the second carbon are sp^3-sp^2 bonds. Sp^2 orbitals are utilized only in the formation of molecules containing double bonds. This gives a trigonal arrangement (planar) in space as opposed to the tetrahedral arrangement of the sp^3 hybrid orbital. Thus the carbon-hydrogen bond on the second carbon atom is an sp^2-s bond, while the double bond on the oxygen atom is composed of two different bonds. One bond is the sp^2-p bond and the other (weaker) bond is a p-p bond.

• PROBLEM 1-7

Write an expanded structural formula with a line for each bond for each of the substances represented below by a condensed formula:

(a) $CH_3CH(CH_3)_2$ (e) $CH_3CONHCH_3$

(b) CH_3CCCH_3

(c) CH_2ClOCH_2CHO (f) $CH_2CH_2OCH_2CH_2O$

(d) $(CH_2)_4$

Solution: (a) In 2-methylpropane, $CH_3CH(CH_3)_2$, 3 hydrogens are joined with the first and third carbons and a fourth bond with the second carbon (thus acquiring the four bonds or eight valence electrons in its outer shell). The second carbon atom is joined together with 3 methyl groups and a hydrogen atom. The methyl group consists of a carbon atom bonded with three hydrogen atoms.

```
    H   H   H
    |       |
H - C - C - C - H
    |       |
    H       H
      H C H

        H
```

(b) CH_3CCCH_3: The first carbon has three hydrogen atoms and is bonded to the second carbon. The second carbon is only joined to the first carbon and the third carbon atom.

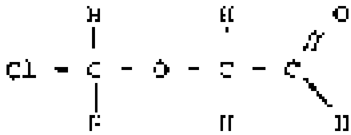
In order to complete an octet around the second carbon it is absolutely necessary for the linkage with the third carbon atom to be triple bonded. The third carbon is attached to a methyl group.

```
    H           H
                |
H - C - C   C - C - H          2-butyne
                |
    H           H
```

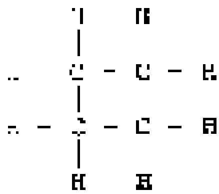
(c) CH_2ClOCH_2CHO

The first methyl group has a hydrogen replaced by a chlorine atom and is attached to an oxygen atom. The last carbon is attached to a methylene group and an oxygen atom. Since the oxygen is not linked to any other atom and

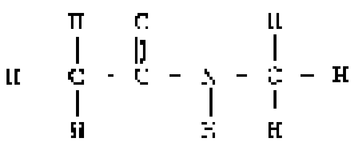
In order to be neutral it must be doubly bonded to the last carbon.



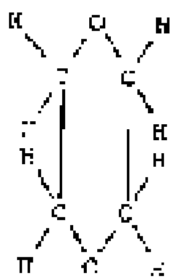
(d) $(CH_2)_4$ Each carbon atom is attached to two other carbon atoms (in a ring) and two hydrogen atoms:



(e) $CH_3CONHCH_3$. A methyl group is attached to the middle carbon. The latter has an oxygen atom but since it needs to bond twice more it should be bonded doubly to either nitrogen or oxygen. But since nitrogen (needing 3 bonds) is linked to hydrogen and a methyl group it can only form a single bond with the middle carbon.

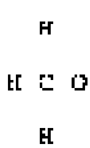


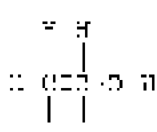
(f) $CH_2-CH_2OCH_2CH_2O$ In this compound the two oxygens are bonded with two $-CH_2-$ groups each and the carbon atoms are linked to an oxygen, another $-CH_2-$ and two hydrogen atoms.

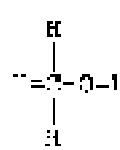


PROBLEM 1-8

What is wrong with the following structures:

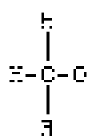
(a) 

(b) 

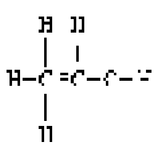
(c) 

Solution: Carbon, hydrogen and oxygen each forms a specific number of bonds when they combine with other elements. This number is called their valence and is determined by their position in the periodic table. Carbon is in group IV and thus forms four bonds when it combines with other elements. Hydrogen is in group I and forms one bond. Oxygen is in group VI. It does not form six bonds, though. The actual number of bonds formed by any element is dependent upon the number of electrons in the outer shell of the atom. In nature, there is a rule that is followed which states that every element in combining with another element seeks to attain eight electrons in its outer shell. This is called the octet rule. Thus, hydrogen in group I will seek to combine with an element in group VII. This is because hydrogen has one electron to contribute and an element in group VII will have seven. Getting back to oxygen; it is in group VI and will, therefore have six electrons to share. This means that it needs two more electrons to make up its octet. Oxygen needs to form two bonds to complete its octet.

In each one of the structures above the error is in the number of bonds drawn to the various elements.

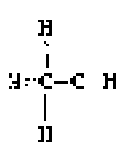
(a)  Taking the elements one by one, it is

seen that each hydrogen atom forms one bond and is thus correct; the carbon atom forms four bonds which is also correct but the oxygen has only formed one bond. This indicates that there are only seven electrons in its outer shell and is not correct.

(b)  Each of the hydrogen atoms has formed

one bond and is thus correct. The carbon atom on the left has formed three single bonds with the hydrogen atoms and a triple bond with the other carbon for a total of six bonds which is incorrect. The carbon on the right also participates in the triple bond and in single bonds with the oxygen and hydrogen atoms. This is a total of five bonds and is also incorrect.

The oxygen atom has formed two bonds which is correct.

(c)  Here, two hydrogen atoms are drawn with one bond and two are drawn with two bonds. The latter two are incorrect. There is a total of five bonds drawn to the carbon, which is incorrect. Carbon can form only four bonds. There are three bonds drawn to the oxygen atom. This is also incorrect because oxygen can form only two bonds.

• PROBLEM 1-9

Would you expect $He_2^{\oplus}$ to be more stable than He_2? than He?

Solution: This problem requires a consideration of bonding and antibonding orbitals. An atomic orbital may be thought of as a particular volume element at a given distance and direction from the nucleus where there is a probability of finding an electron. According to the Pauli exclusion principle, no more than two electrons can occupy an orbital. Two overlapping orbitals can be considered to combine to give one low-energy bonding orbital and one high-energy antibonding orbital.

Consider the electron configuration of a helium atom (He): $1s^2$. We can readily see that the outermost shell of helium, the s orbital, is filled with 2 electrons, which is the maximal and stable capacity. Thus the helium atom is very stable. In fact, it is inert to most chemical reactions and is for this reason known as one of the inert gases.

To form He_2, each helium atom contributes 2 1s electrons for a total of 4 electrons. Since the molecular bonding orbital can accommodate only 2 electrons, the remaining 2 must go into the antibonding orbital. Hence, any stabilization gained by filling the bonding orbital is offset by the required filling of the antibonding orbital. Hence, there exists no net decrease in energy when He_2 is produced, so that He_2 is less stable than He.

The only difference between He_2 and $He_2^{\oplus}$ is that the latter has only 1 electron (not 2) in the antibonding orbital. It possesses two electrons in the bonding orbital as does He_2, but because of the one less electron in destabilizing antibonding orbital in $He_2^{\oplus}$, it should be more stable than He_2. (It is, of course, less stable than He which has no electrons in the antibonding orbital.)

• PROBLEM 1-10

When hydrogen chloride dissolves in water, the product is "hydrochloric acid." Such a solution contains water, $H_3O^{\oplus}$, and $Cl^{\ominus}$. Which of these species are Lewis acids? Lewis bases? If you have more than one compound per category, arrange them in order of decreasing strength.

Solution: According to the Lewis definition, an acid is any species capable of accepting a pair of electrons into an unfilled orbital, thereby forming a mutual bond. A Lewis base may be defined as any species which possesses a nonbonding or weakly bonding pair of electrons and which is capable of donating these electrons to a Lewis acid.

The reaction of hydrogen chloride in water may be written as:

$$H-\ddot{O}-H + H-\ddot{Cl}: \longrightarrow H-\underset{\oplus}{\overset{H}{\ddot{O}}}-H + :\ddot{Cl}:^{\ominus}$$

The initial reaction of HCl with water involves a strong hydrogen-bonding interaction of the hydrogen of HCl with an unshared electron pair on the water molecule. Thus one can consider this to be a Lewis acid-base interaction between the HCl, which acts as an electron acceptor, and the water molecule which acts as the electron pair donor.

However, water ($H-\ddot{O}-H$) is the stronger base (that is, it has the greater tendency to donate a pair of non-bonded electrons). As such, it donates a pair of electrons to HCl, which is a Lewis acid. This reaction produces $:\ddot{Cl}:^{\ominus}$ which is a Lewis base (it can accept no more pairs of nonbonded electrons since its outer shell now has the 8 electrons needed to fill it). The hydronium ion

$$\left[H-\underset{\oplus}{\overset{H}{\overset{|}{\dot{O}}}}-H \right]$$

formed may be considered, then, a Lewis acid.

ACIDS AND BASES

• PROBLEM 1-11

What is the Lowry-Brønsted acid in (a) HCl dissolved in water; (b) HCl (unionized) dissolved in benzene? (c) Which solution is the more strongly acidic?

Solution: A Lowry-Brønsted acid may be defined as a substance that gives up a proton (hydrogen nucleus). A base, according to the Lowry-Brønsted idea, would then be a substance that accepts the proton.

(a) When HCl is dissolved in water, the water acts as a base due to the electron pairs available for sharing around the oxygen. Hence, the HCl can donate a proton ($H^{\oplus}$) and protonate the oxygen atom in H_2O as shown:

$$HCl + H_2O \rightleftarrows H_3O^{\oplus} + Cl^{\ominus}$$

The hydronium ion ($H_3O^{\oplus}$) generated on the right is then the Lowry-Brønsted acid in solution, for it can donate the proton in the reverse reaction and hence acts as an acid.

(b) When unionized HCl is added to benzene, a hydrocarbon (that is, a compound containing only hydrogen and carbon atoms), the Lowry-Brønsted acid can only be HCl. No reaction occurs between the benzene and HCl to generate any other acid.

(c) The Lowry-Brønsted acid $H_3O^{\oplus}$ is weaker than HCl. The strength of an acid depends upon its tendency to give up a proton. HCl gives up its proton very readily, whereas $H_3O^{\oplus}$ has a greater tendency to hold onto its proton. The strengths of some common acids are indicated below.

$$\text{Acid strength} \quad \begin{matrix} H_2SO_4 \\ HCl \end{matrix} > H_3O^{\oplus} > NH_4^{\oplus} > H_2O$$

Since HCl is the stronger acid, the HCl in benzene is the more acidic solution.

• PROBLEM 1-17

Account for the fact that nearly every organic compound containing oxygen dissolves in cold concentrated sulfuric acid to yield a solution from which the compound can be recovered by dilution with water.

Solution: The solution to this problem can be obtained by a consideration of the Lowry-Brønsted definition of acids and bases.

In the Lowry-Brønsted sense, an acid is a substance that gives up a proton, and a base is a substance that accepts a proton. When the cold concentrated sulfuric acid is added to the organic compound containing oxygen, it gives up a proton (hydrogen nucleus) and protonates the oxygen atom, which possesses electron pairs available for sharing. The reaction may be illustrated as shown:

$$-\ddot{\underset{..}{O}}: + H_2SO_4 \rightleftarrows -\overset{|}{\underset{..}{O}}:H^{\oplus} + HSO_4^{\ominus}$$

The oxygen atom of the organic compound is acting as the base because it accepts the proton from the sulfuric acid. It is this protonation, which is reversible, that accounts for the organic compound dissolving in the cold concentrated sulfuric acid.

The protonation generates (as shown previously) the following: $-\overset{|}{\underset{..}{O}}:H^{\oplus}$ and $HSO_4^{\ominus}$

A B

"A" is the new acid formed because it can donate the proton: "A" is a weak acid (it will tend not to give up the proton readily). "B" is the new base generated, and it is also weak (it will tend not to accept a proton donated). If water is added to this solution, the organic compound will be regenerated, because water is a stronger base than $HSO_4^{\ominus}$ so that it will accept the proton from "A". The reaction can be written as:

$$-\overset{|}{C}H^{\oplus} + H_2O \rightleftarrows -C= + H_3O^{\oplus}$$ hydronium ion obtained

organic compound recovered

IDENTIFICATION AND STRUCTURE DETERMINATION

• PROBLEM 1-13

A qualitative analysis of Atebrin, an antimalarial drug used extensively by Allied troops during the Second World War, showed carbon, hydrogen, nitrogen, chlorine and oxygen. A quantitative analysis showed 69.1% carbon, 7.5% hydrogen, 10.5% nitrogen, 8.9% chlorine and 4.0% oxygen. What is the empirical formula for Atebrin?

Solution: When the percent composition of a compound is given the percents refer to weight percent unless it is stated otherwise. To calculate the empirical formula for a compound from its composition first assume that 100 g of the compound is present and then determine the mass of each component. From these masses the number of moles of each element can be found and from this the empirical formula.

In 100 g of Atebrin there will be 69.1 g C, 7.5 g H, 10.5 g N, 8.9 g Cl and 4.0 g O.

The molecular weights (MW) of these elements are 12, 1, 14, 35.5 and 16 respectively. Solving for the number of moles of each in 100 g of Atebrin:

$$\text{no. of moles} = \frac{\text{no. of grams}}{MW}$$

$$\text{no. of moles of C} = \frac{69.1\text{ g}}{12\text{ g/mole}} = 5.76\text{ moles}$$

$$\text{no. of moles of H} = \frac{7.5\text{ g}}{1\text{ g/mole}} = 7.5\text{ moles}$$

$$\text{no. of moles of N} = \frac{10.5\text{ g}}{14\text{ g/mole}} = 0.75\text{ moles}$$

$$\text{no. of moles of Cl} = \frac{8.9\text{ g}}{35.5\text{ g/mole}} = 0.25\text{ moles}$$

$$\text{no. of moles of O} = \frac{4.0\text{ g}}{16.0\text{ g/mole}} = 0.25\text{ moles}$$

The number of moles of each element in the empirical formula must be integers. The formula that has been derived above is $C_{5.76}H_{7.5}N_{0.75}Cl_{0.25}O_{0.25}$. There are 0.25 moles of each Cl and O, thus multiplying the number of moles of each element by 4 will yield [illegible], which is the empirical formula.

• PROBLEM 1-14

A gas of molecular weight 58 was found to contain 82.8% C and 17.2% H. What is the molecular formula of this compound?

Solution: The molecular formula for this compound can be written C_xH_y, where x is the number of moles of carbon present in one mole of the compound and y is the number of moles of hydrogen present in each mole of the hydrocarbon.

The number of moles of each compound can be determined by multiplying the molecular weight (MW) of the compound by the fraction of the element present divided by its own MW.

$$\text{(i)} \qquad \text{no. of moles} = \frac{\text{fraction of C or H}}{\text{MW of C or H}} \times 58 \text{ g}$$

MW of C = 12; MW of H = 1

Substituting into equation (i):

$$\text{no. of moles of C} = \frac{.828}{12 \text{ g/mole}} \times 58 \text{ g} = 4.0 \text{ moles}$$

$$\text{no. of moles of H} = \frac{.172}{1 \text{ g/mole}} \times 58 \text{ g} = 10.0 \text{ moles}$$

The formula for this compound is C_4H_{10}.

• PROBLEM 1-15

A sample of aspirin (acetylsalicylic acid) was determined to be 60.0% carbon, 4.4% hydrogen and 35.6% oxygen. The molecular weight is 180. What is the molecular formula for aspirin?

Solution: The molecular formula for a given compound can be calculated from its molecular weight and the percent composition.

One mole of aspirin weighs 180 g; 60.0% of this weight is contributed by carbon. After determining the mass of the carbon present, the number of moles of carbon in one mole of aspirin can be found. (MW of C = 12)

$$\text{mass of carbon in one mole of aspirin} = .60 \times 180 \text{ g} = 108 \text{ g}$$

$$\text{no. of moles} = \frac{\text{mass}}{\text{MW}} = \frac{108 \text{ g}}{12 \text{ g/mole}} = 9 \text{ moles}$$

Similar calculations can be made for hydrogen and oxygen to determine the molecular formula. (MW of H = 1)

mass of H in 1 mole of aspirin = 0.044 × 180 g = 8 g

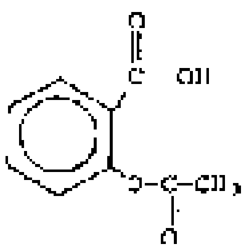
$$\text{no. of moles} = \frac{8\text{ g}}{1\text{ g/mole}} = 8\text{ moles}$$

(MW of O = 16)

mass of O in 1 mole of aspirin = .356 × 180 g = 64 g

$$\text{no. of moles} = \frac{64\text{ g}}{16\text{ g/mole}} = 4\text{ moles}$$

The molecular formula for aspirin is $C_9H_8O_4$. Its structure is shown below.



Acetylsalicylic Acid
(Aspirin)

■ PROBLEM 1-16

What do the differences in properties between lithium acetylacetone (m.p. very high, insoluble in chloroform) and beryllium acetylacetone (m.p. 108°, b.p. 270°, soluble in chloroform) suggest about their structures?

<u>Solution:</u> From their melting and solubility properties, the structures of lithium acetylacetonate and beryllium acetylacetonate are, respectively, ionic or salt-like and non-ionic or covalent.

Melting may be considered to be a change from a highly ordered arrangement of particles to a more random arrangement. When a temperature is reached at which the thermal energy of the particles is great enough to overcome the forces holding the particles together, melting occurs. An ionic compound or salt forms crystals in which the structural units are ions. These ions are held together by the electrostatic forces that derive from an ion of any positive charge being surrounded by ions of opposite charge (negative charge) in the structure. These powerful forces, which are interionic, can be overcome only at a very high temperature. In a non-ionic compound, the atoms are held together by covalent bonds and form crystals in which the structural units are molecules. For melting to occur, the forces holding these molecules together must be overcome. These intermolecular forces are weak compared to the electrostatic forces, so that a much lower temperature is required for melting. Since the melting point of lithium acetylacetonate is very high, and beryllium acetylacetonate relatively low, one expects the former to be ionic with the latter being non-ionic.

These same expectations could have been obtained by examination of the solubilities. For something to dissolve, the structural units—ions or molecules - must become separated from each other, and the spaces in between become occupied by solvent molecules. To dissolve an ionic compound, the solvent must be able to form ion-dipole bonds and have a high dielectric constant, that is, possess high insulating properties to lower the attraction between oppositely charged ions once they are solvated (surrounded by a cluster of solvent molecules). Only water or other highly polar solvents possess these properties, and hence can dissolve ionic compounds to a large extent. (A polar molecule has a positive end and a negative end, so that there is an electrostatic interaction between a positive ion and a negative end of a solvent molecule, and between a negative ion and a positive end of a solvent molecule - ion-dipole bonds.) Solubility of non-ionic compounds is determined by their polarity. Non-polar or weakly polar compounds dissolve readily in non-polar or weakly polar solvents, whereas highly polar compounds dissolve in highly polar solvents. These facts are often remembered by the "like dissolves like" rule. Chloroform is a non-polar solvent, so that it should dissolve only non-polar compounds. Since beryllium acetylacetonate dissolves in it, one expects its structure to be non-ionic. Likewise, since lithium acetylacetonate is not soluble in it, it is probably ionic or salt-like.

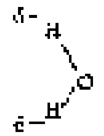
POLARITY

• PROBLEM 1-17

What are the characteristics which ionic, ion-dipole, and dipole-dipole bonds have in common? How do they differ?

Solution: A bond between two species is defined in terms of the amount of energy liberated because of adduct formation. The strength of the bond increases as the amount of heat generated is increased at the expense of the total energy of the system.

An ionic bond is produced when an electropositive and an electronegative element react by transferring electrons. For example, when Na· and :C̈l· react the electropositive sodium transfers one electron to chlorine; Na^+ and $:\ddot{C}l:^-$ are produced. This ionic bond is non directional.

An ion-dipole bond is generated when one of the ions in an ionic bond is replaced by a highly polar molecule such as water:  δ^- ≡ (+ −)

When an ion such as Na^+ reacts with H_2O, the positive ion aligns with respect to the polar molecule as shown:

$$Na^+ + (+\ -) \longrightarrow Na^+\ (-\ +)$$

Similarly, if another polar molecule replaces the ion in the ion-dipole bond, the formation of a dipole-dipole bond occurs. If we consider two polar molecules (e.g., two H_2O molecules) the alignment of the molecules is such:

The other hydrogen atoms also attract oxygen atoms in other water molecules.

Ionic bonds form stronger bonds than ion-dipole bonds, and the latter are stronger than dipole-dipole bonds.

• PROBLEM 1-13

Why does hydrogen fluoride undergo intermolecular self-association while the other hydrogen halides do not?

Solution: The fluorine atom is the most electronegative, that is, strongest attractor of electrons, of all the halogen atoms. Since fluorine will tend to attract electrons, the fluorine atom should possess a negative charge and the hydrogen atom a positive charge in HF. That is, HF is a polar molecule with one end (F) electron rich and one end (H) electron deficient. In a solution of HF, the opposite charges can attract each other, that is, one has intermolecular self-association. When opposite and equal charges are separated by some distance in a molecule (such as HF), a dipole is formed. Hence, the intermolecular self-association can be considered dipole-dipole interaction. This particular kind of interaction is also referred to as hydrogen bonding. It may be pictured as shown:

H–F · · · H F

hydrogen bonding.

The tremendous electronegativity of fluorine is what allows the formation of hydrogen bonds in an HF solution. Since the other halogens possess less of a tendency to attract electrons, they will be less able to form hydrogen bonds required for intermolecular self-association.

(a) Although HCl (1.27 Å) is a longer molecule than HF (0.92 Å), it has a smaller dipole moment (1.03 D compared to 1.75 D). How do you account for this fact? (b) The dipole moment of CH_3F is 1.847 D, and of CD_3F, 1.858 D. (D is ^2H, deuterium.) Compared with the C-H bond, what is the direction of the C-D dipole?

Solution: (a) Both HCl and HF are polar compounds. This means one end of the bond between the two atoms in the molecule is relatively negative and the other end is relatively positive. In other words, there exists a negative pole and a positive pole. A covalent bond will be polar if it joins atoms that differ in their tendency to attract electrons, that is, atoms that differ in electronegativity. The greater the difference in electronegativity, the more polar the bond. The following relates the electronegativity of some common elements: F>O>Cl,N>Br>C>H.

The molecules HF and HCl constitute dipoles because of this difference in electronegativity. A dipole may be defined as a molecule with two equal and opposite charges separated in space. A dipole possesses a dipole moment, μ, which equals the magnitude of the charge, e, multiplied by the distance, d, between the centers of charge: $\mu = e \times d$.

Since HCl is longer than HF, the "d" will be larger for HCl in the computation of its dipole moment. Thus, to explain why HCl's dipole moment is smaller than HF, one must examine the other parameter, "e". The magnitude of the charge will reflect the extent of the difference in electronegativities of the elements. As previously indicated, the electronegativity of F is greater than Cl by a significant amount. Thus, when both F and Cl are compared with H's electronegativity, the difference is greatest for F. Hence, the magnitude of "e" must be much larger for HF than HCl. Consequently, the dipole moment is larger in HF. In essence, then, the greater electronegativity of F is responsible for the larger dipole moment.

(b) The fact that the dipole of CH_3F is less than CD_3F means that D must be attracting the electrons less than H does. If one assumes there exists no difference in "d", or the distance between the charges, when D is substituted for H, then the difference in dipole moment can only stem from magnitude of charge, "e". If the electronegativity of D is less than H, that is, it tends to attract less electrons, then F is more negative so that the magnitude of "e" is increased, which would account for higher dipole moment of CD_3F. What this means is that the dipole is less directed toward D than toward H.

• PROBLEM 1-20

Predict the direction of polarization of the following bonds, considering only the relative electronegativity of the atoms involved.

C–H; B–H; N–Br; I–Cl

Solution: The electronegativity of an element is a measure of the ability of an atom of the element to attract electrons to itself in a chemical bond. It is generally found that electronegativity increases from left to right across the periodic table and decreases on on going down any group. The most electronegative elements are therefore found in the top right-hand corner (O, F, Cl) and the least electronegative (most electropositive) in the bottom left-hand corner (Cs, Fr, Rb). A qualitative list of relative electronegativity is given below, but it should be realized that the molecular environment of an atom may affect its electronegativity to a limited extent.

The relative electronegativities of some common elements occur in the following order:

F>O>Cl,N>Br>I,S,C>P,H>B>Mg>Li>Na

The distribution of electrons in a single covalent bond between two atoms is not equally shared. In a symmetrical molecule A–A (e.g. H_2, Cl_2) the two nuclei, in whose neighborhood the bonding electrons are found, are indistinguishable, and in the absence of any external effects the electron distribution will be symmetrical. If, however, a molecule such as A–X is considered where A and X are different (e.g. HF, ICl), then the nuclei are distinct and the atoms A and X may differ greatly in electronegativity. In these circumstances the distribution of electrons may be asymmetric and the electron density will be greater near the more electronegative element. This electron displacement carried to an extreme leads to the production of ions, but in many covalent bonds only causes slight polarization of the bond, represented as $\overrightarrow{AX}$ or $A^{\delta+}$——$X^{\delta-}$ where X is the more electronegative atom, and $\delta+$, $\delta-$ represent small electrical charges produced by polarization.

Thus, referring to the relative electronegativities of the individual atoms, and the above definition of polarization:

$$\overset{\delta-}{C} - \overset{\delta+}{H} \qquad \overset{\delta+}{B} - \overset{\delta-}{H} \qquad \overset{\delta-}{N} - \overset{\delta+}{Br} \qquad \overset{\delta+}{I} - \overset{\delta-}{Cl}$$

$$\longleftarrow \qquad \longrightarrow \qquad \longleftarrow\!\!\!\longrightarrow \qquad \longrightarrow$$

CHAPTER 2

SPECTROSCOPY

LINE SPECTRA

• PROBLEM 2-1

Calculate the energy in Kcal which corresponds to the absorption of 1 einstein of light of 5893 Å (sodium D line) by sodium vapor. Explain how this absorption of light by sodium vapor might have chemical utility.

Solution: One einstein of light refers to the change in energy (ΔE) that occurs from the absorption of electromagnetic radiation by one gram-atom (or mole) of a monatomic gas such as sodium vapor. The absorption of radiation results in the excitation of the molecule. The energy difference between the excited state and the ground state of the molecule is the change in energy. This change in energy is related to the frequency (ν) or wavelength (λ) by the equations:

$$\Delta E = h\nu = \frac{hc}{\lambda}$$

where h = Planck's constant

c = velocity of light.

Since Planck's constant and the velocity of light are numerical constants, this equation can be written as:

$$\Delta E = \frac{286,000}{\lambda(\text{Å})} \text{ Kcal}$$

where λ(Å) indicates that the wavelength is measured in angstrom units (Å). Hence we can calculate the energy, in Kcal (kilocalories) which corresponds to the absorption of one einstein of light at 5893 Å by sodium vapor as follows:

$$\Delta E = \frac{286,000}{5893} \text{ Kcal}$$

$$\Delta E = 48.5 \text{ kcal.}$$

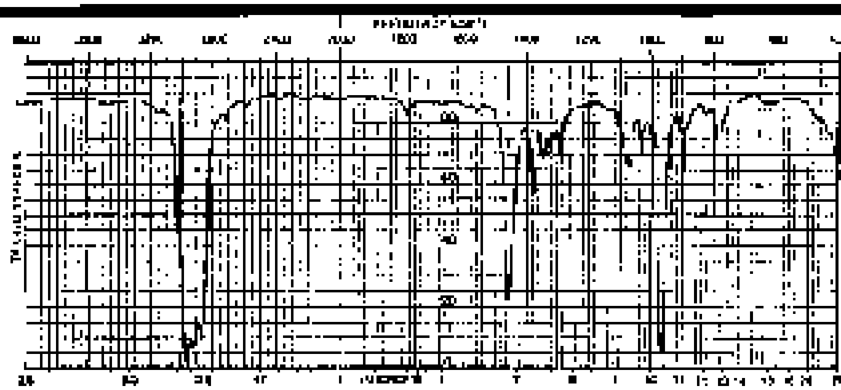
The energy requirements of many chemical reactions are within the range of 48.5 kcal/mole. Hence when the excited electron in sodium drops to its ground state, the energy transferred (48.5 kcal/mole) can cause a chemical reaction to occur.

INFRARED SPECTROSCOPY

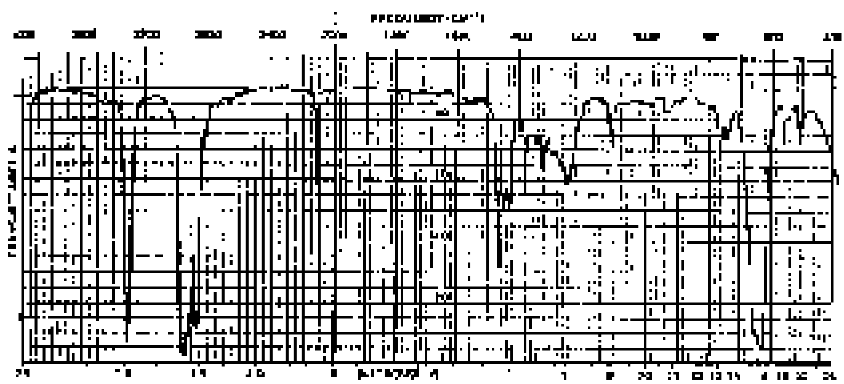
• PROBLEM 2-2

Identify the functional groups in each compound from the following infrared spectra.

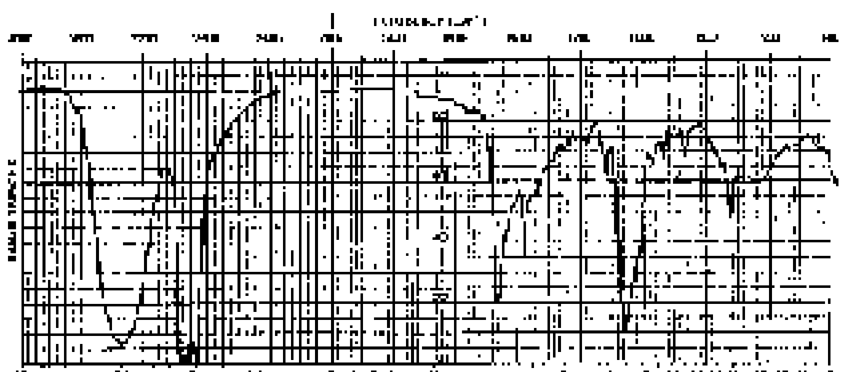
(a)



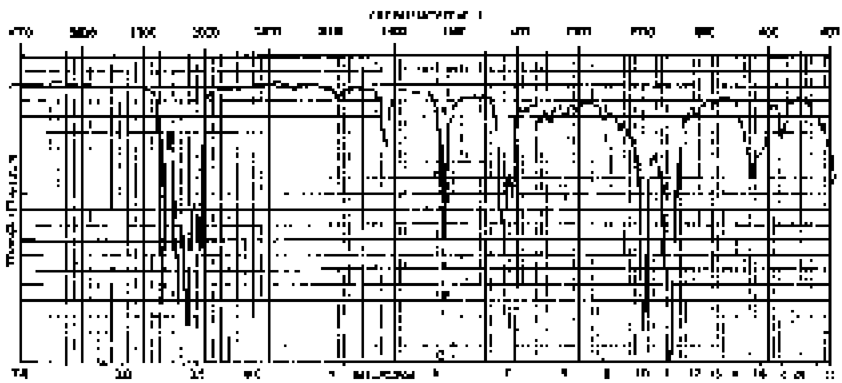
(b)



(c)

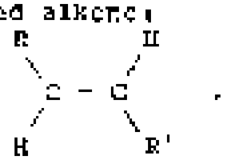


(d)



Solution: Infrared (i.r.) spectroscopy is a common technique that is used to identify the major functional groups in a compound. The identification of these groups depends upon the amount of infrared radiation absorbed and the particular frequency (measured in cm^{-1}, wave-numbers) at which these groups absorb. An infrared spectrum measures the degree of the molecular vibration and rotation of the bonds in the molecule. Each type of functionality will absorb at certain characteristic frequencies and with characteristic strengths. With this knowledge at hand, we can identify the major functional groups from the i.r. spectra (a) through (d).

(a) This spectrum has a moderate band at 3050 cm^{-1} which is characteristic of the –C–H stretch of a dialkylated alkene: RHC = CHR'. There is also a strong sharp band at approximately 965 cm^{-1}, which is the characteristic absorption of the C–H out-of-plane bending of a trans-1,2-dialkylated alkene:

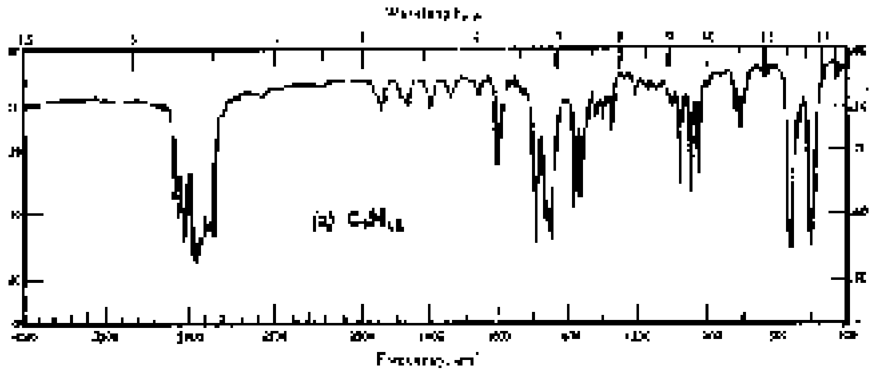


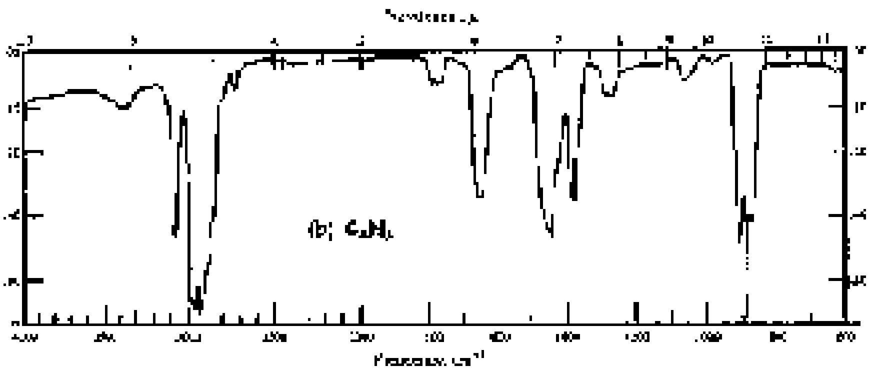
(b) The strong sharp band at 3300 cm^{-1} is characteristic of a ≡ C – H stretch and is suggestive of a terminal alkyne: R–C ≡ C—H. The medium sharp band at 2170 cm^{-1} is the characteristic absorption band of the C ≡ C stretch of terminal alkynes. The strong broad band at 630 cm^{-1} is the absorption of the ≡ C – H bend of R – C ≡ C – H. We can see from this i.r. spectrum that the compound is conclusively a terminal alkyne.

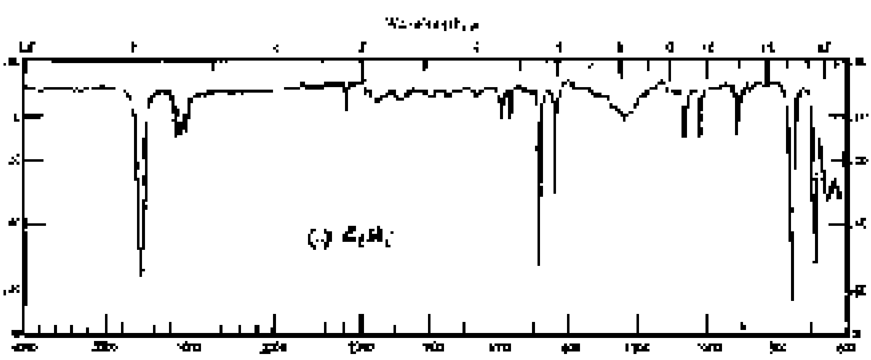
(c) The broad band centered at 3350 cm^{-1} is indicative of a bonded O—H stretch. The complex absorption pattern at 1050 cm^{-1} is the C—O vibrations of a primary alcohol, RCH_2OH.

(d) The strong sharp bands at 995 cm^{-1} and 905 cm^{-1} are characteristic of the C – H out-of-plane bend of mono alkylated alkenes: RHC = CH_2. This is strongly supported by the other spectral evidence. The moderate sharp band at 3080 cm^{-1} is the absorption of the = C – H stretch and the medium sharp band at 1640 cm^{-1} is the C = C stretch absorption.

Give a structure or structures consistent with each of the following infrared spectra.





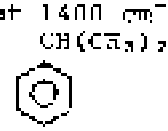


Solution: Infrared (i.r.) spectra can reveal the molecular structure of an organic compound. It is based on the fact that a molecule is constantly vibrating. Chemical bonds stretch (and contract) and bend with respect to each other. The absorption of infrared light (that is, light lying beyond the red end of the visible spectrum – lower frequency, longer wavelength, less energy) causes changes in vibrations of a molecule.

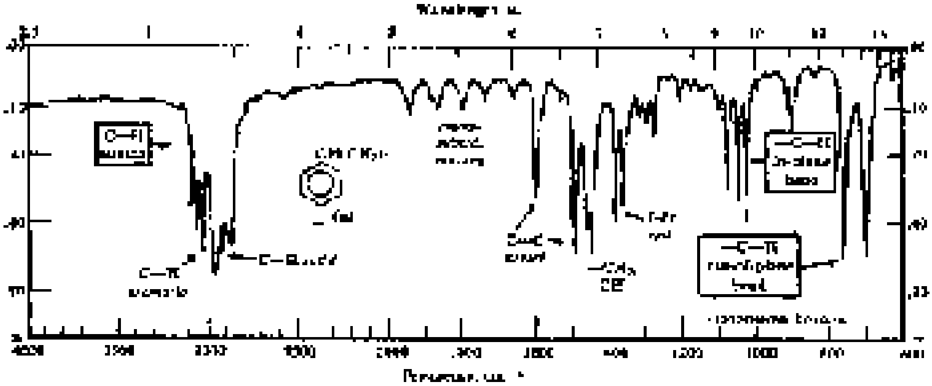
An infrared spectrum may be referred to by its wavelength or, preferably, by its frequency which is expressed in wavenumbers, cm^{-1}, as can be seen in the spectra given in the problem. (Wavenumbers may be defined as the number of waves per centimeter.)

Two substances that possess identical infrared spectra are identical in thousands of different physical properties; they must almost certainly be the same compound. The infrared spectrum reveals the molecular structure by indicating what groups are present (or absent) in the molecule. This is based on the fact that a group of atoms gives rise to characteristic absorption bands. In other words, a particular group absorbs light of certain frequencies that are essentially the same from compound to compound. For example, the carbonyl group (C=O) of ketones absorbs at 1710 cm^{-1}. Now, the absorption band of a particular group of atoms can be shifted by various structural features such as angle strain, van der Waals strain, conjugation, electron withdrawal, and hydrogen bonding. Hence, the interpretation of an infrared spectrum may not be easy. The table provided lists some characteristic infrared absorption frequencies. In solving for the molecular structure, try to correlate the frequencies in the table with those for bands indicated in the problem.

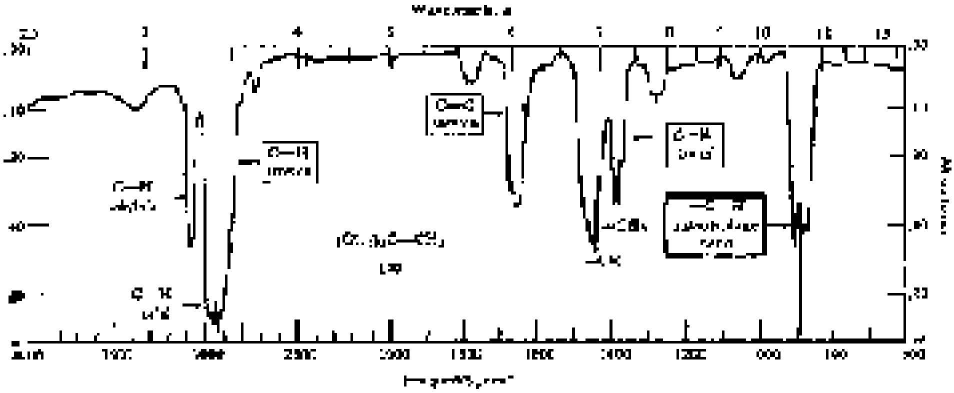
(a) A band is present in the 3000-3100 cm^{-1} region; this indicates an aromatic ring. This can be confirmed by the presence of a band in the 1500, 1600 region which would indicate the stretch of the C=C bond in the ring. Such a band is present. Therefore, one knows that six of the nine carbons in C_9H_{12} belong to an aromatic portion: a benzene ring. The weak finger like bands from 2000 cm^{-1} to 1700 cm^{-1} are characteristic of the absorption of mono-substituted aromatic rings. Hence the remaining three carbons must be part of a single substituent. The aromatic bands account also for five hydrogen atoms, so that the substituent possesses seven hydrogen atoms. There exist two possibilities for an organic structure with three carbons and seven hydrogens: isopropyl ($-CH(CH_3)_2$) and propyl ($-CH_2CH_2CH_3$). That it is isopropyl can be determined from the isopropyl split at about 1400 cm^{-1}. So,

the structure in (a) can be written as 

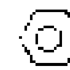
The diagram below assigns groups of atoms to each band for further clarity.

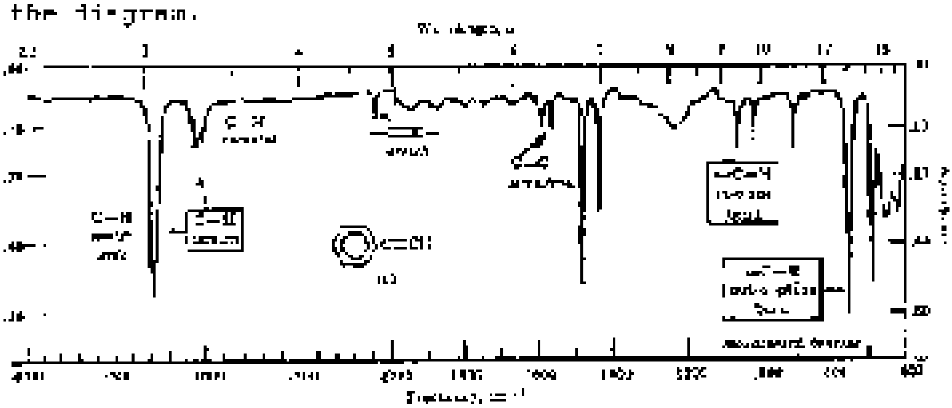


(b) That this is an alkene can be seen from the strong band present in the 1640-1680 cm^{-1} region, due to the C=C stretch. Also, the molecular formula given, C_4H_8, fits the general formula for an alkene, C_nH_{2n}. There exists a band in the region of 3020-3080 cm^{-1} which indicates the C-H absorption for alkenes. The diagram below assigns structures to the bands which lead to the conclusion that the structure is $(CH_3)_2C{=}CH_2$, isobutylene.



(c) That the structure is phenylacetylene may be determined by examining two prominent bands. There exist the C-H stretch of aromatics (confirmed by the C=C stretch at 1500, 1600 cm^{-1}) at 3000-3100 cm^{-1} and the -C≡C- stretch characteristic of alkynes at 2100-2260 cm^{-1}.

One concludes therefore, that C_8H_6 represents  -C≡CH, phenylacetylene. Other bands are assigned structures in the diagram.

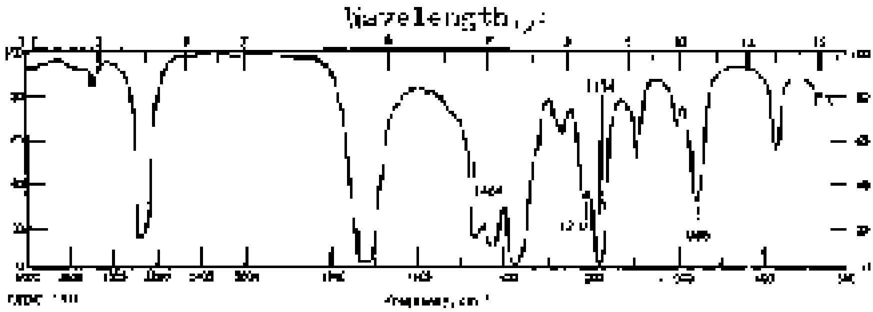


PROBLEM 2-4

Which (if any) of the following compounds could give rise to each of the infrared spectra shown?

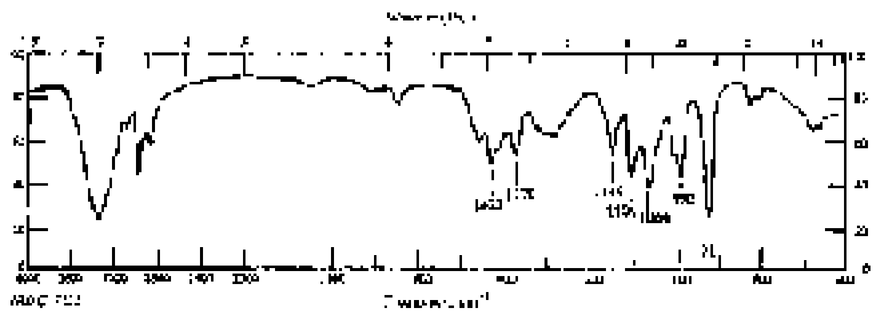
isobutyraldehyde	ethyl vinyl ether
2-butanone	cyclopropylcarbinol
tetrahydrofuran	3-buten-2-ol

a)



b)

c)

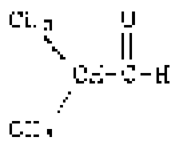


Solution: (a) This infrared spectrum shows a strong absorption near 1720 cm^{-1}. This is the characteristic absorption of a C=O stretch for saturated aldehydes and saturated acyclic ketones. The weak absorption at 3400 cm^{-1} is the C=O overtone and it further supports our conclusion that we are dealing with a carbonyl compound. The C=O overtone is noticeable in the spectrum because the C=O stretch is such an intense absorption. The only given carbonyl compounds are isobutyraldehyde (an aldehyde, RCHO) and 2-butanone (a ketone, $R\overset{O}{\overset{\|}{C}}R'$). The C-H stretch of the aldehyde proton characteristically shows absorptions at 2820 cm^{-1} and 2720 cm^{-1}. The i.r. spectrum shows only a strong band at 2900 cm^{-1} in this vicinity. Hence the compound is not the aldehyde and must be the ketone, 2-butanone. The band at 2900 cm^{-1} is the characteristic absorption band of the C-H stretch of methyl and methylene groups. 2-Butanone has the structure:

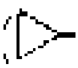
$$CH_3-\overset{O}{\overset{\|}{C}}-CH_2-CH_3$$

(b) This i.r. spectrum shows a strong absorption at

1737 cm^{-1}. This is suggestive of the C=O stretch of a saturated aldehyde because the frequency at which aldehydes absorb infrared radiation is greater than that of ketones. The sharp bands at 2820 cm^{-1} and 2740 cm^{-1} are the absorptions of the C-H stretch of an aldehyde. Hence the compound is an aldehyde and must be isobutyraldehyde.

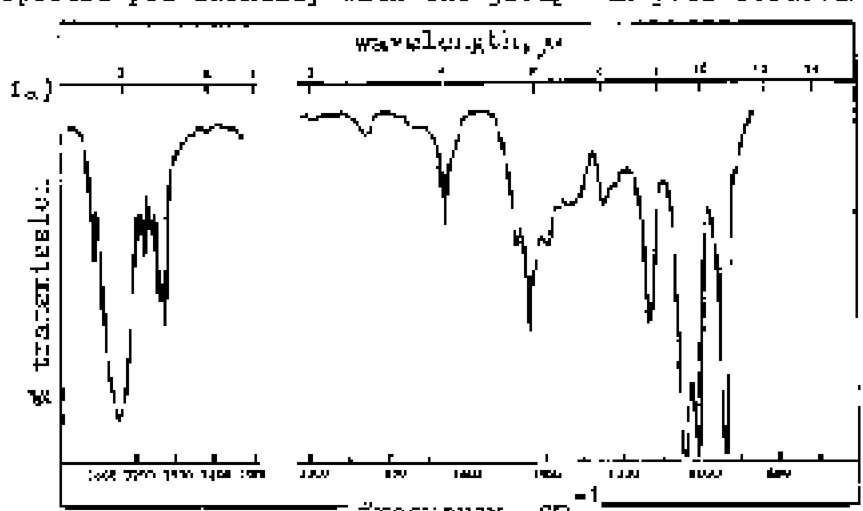


(b) This spectrum shows a strong broad band at 3400 cm^{-1}, which is indicative of a bonded O-H stretch of an alcohol. The choice is therefore narrowed down to cyclopropylcarbinol

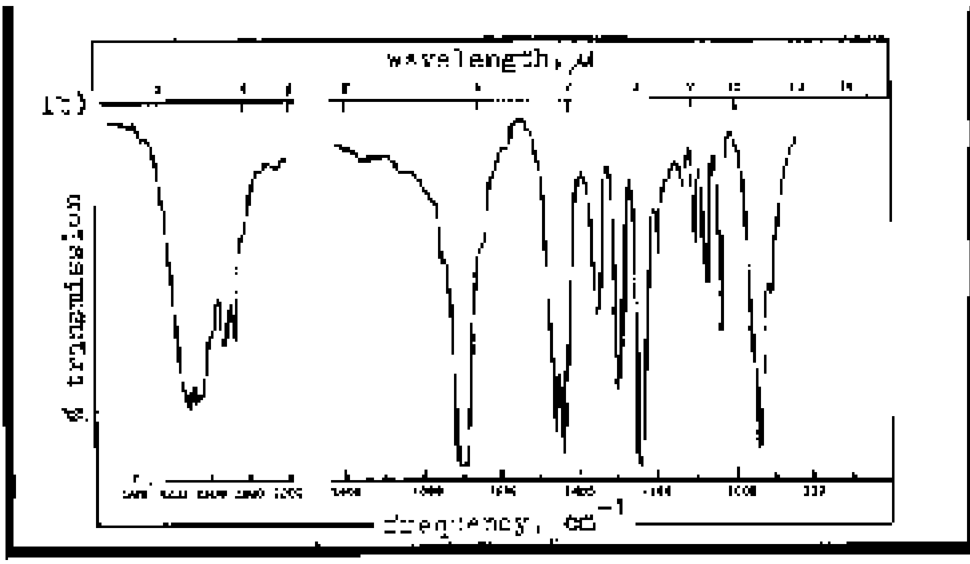
(-CH$_2$OH, a primary alcohol) and 3-buten-2-ol (CH_2=CH-CHOHCH$_3$, a secondary alcohol). The C-O stretch of primary alcohols characteristically absorbs at 1050 cm^{-1} and that of secondary alcohols absorbs at 1100 cm^{-1}. Since the spectrum shows a complex absorption pattern in this range, we must look for other clues. There is a weak absorption at 1642 cm^{-1}. This is the characteristic absorption of the C=C stretch of terminal alkenes (RHC=CH_2 or $R_2C=CH_2$). Hence the compound must be 3-buten-2-ol because it possesses a double bond whereas cyclopropylcarbinol has none.

• PROBLEM 2-6

The infrared spectra shown in Figures 1 a and b are for compounds of formula C_4H_8O and $C_4H_8O_2$, respectively. Deduce a structure for each of these substances from its infrared spectrum. Indicate clearly which lines in the spectra you identify with the groups in your structures.



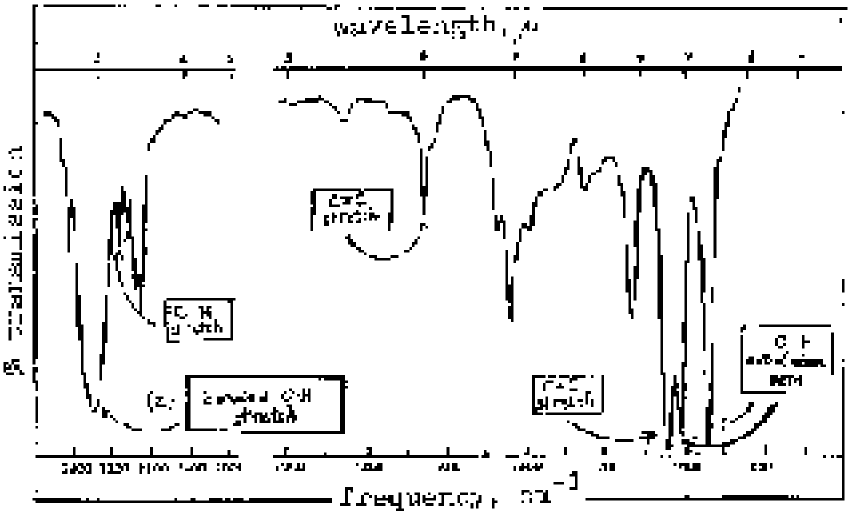
(b)



Solution: (a) The most noticeable feature in this infrared spectrum is the strong broad band at 3400 cm^{-1}. This absorption is characteristic of the bonded O-H stretch of alcohols. We can furthermore deduce that the compound is a primary alcohol by noticing the strong sharp C-O stretch absorption at 1030 cm^{-1}. The C-O stretch of secondary and tertiary alcohols absorbs at frequencies greater than 1050 cm^{-1}. Another significant band in this spectrum is the weak sharp absorption at 1650 cm^{-1}. This is the characteristic absorption band of the C=C stretch of monoalkylated alkenes ($RHC{=}CH_2$) and dialkylated terminal alkenes ($R_2C{=}CH_2$). These types of alkenes are distinguished by their methylene C-H out-of-plane bending. The spectrum shows two strong sharp bands at 1010 cm^{-1} and 930 cm^{-1}, the characteristic absorption bands of the C-H out-of-plane bend of monoalkylated alkenes. As if this were not enough proof, the molecular formula of the compound (C_3H_6O) restricts it to three carbons; the smallest dialkylated terminal alkene requires four carbons:

$$\begin{array}{l} CH_3 \\ \quad \diagdown \\ \qquad C{=}CH_2 \\ \quad \diagup \\ CH_3 \end{array}$$

. A monoalkylated alkene of three carbons is $CH_3CH{=}CH_2$. Hence the compound is a monoalkylated alkene and is also a primary alcohol. Since there is only one carbon attached to the $-CH{=}CH_2$ portion, it must contain the OH functionality (the sp^2-hybridized carbons cannot bear the -OH, for it would not account for the spectrum shown). Hence, the compound is an allyl alcohol and has the structure $CH_2{=}CHCH_2OH$. The principle absorptions of the infrared spectrum are labeled below:



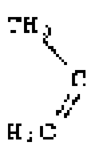
Infrared Spectrum of Allyl Alcohol

(b) The major feature of this spectrum is the strong sharp absorption at 1700 cm^{-1}. This is the typical absorption of the C=O stretch of a carboxylic acid (R–COOH). The strong band at 1240 cm^{-1} is the C–O stretch. Further spectral evidence of a carboxylic acid is the strong O–H band near 1455 cm^{-1} and 950 cm^{-1}, and the very broad O–H stretch centered at 2800 cm^{-1}. If we subtract the molecular formula (M.F.) of the known portion (–COOH) from the M.F. of the compound ($C_4H_6O_2$), we will have the M.F. of the unidentified portion of the compound. We find that a C_3H_5 portion remains to be identified. By manipulating the atoms in various arrangements we see that there are only four possibilities for the structure of a C_3H_5 group. They are:

(1) $H_2C=CH-CH_2-$

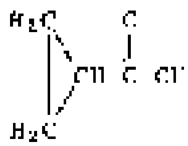
(2) $CH_3-CH=CH-$

(3)

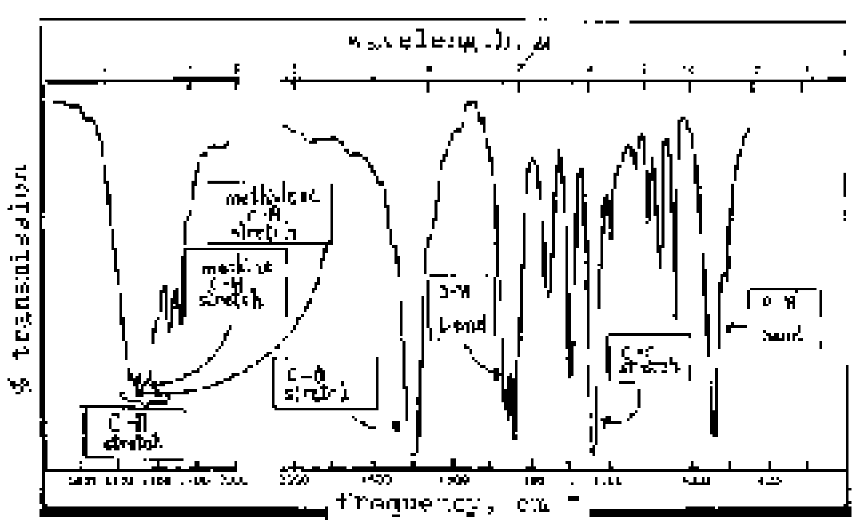


(4)

Structures (1), (2) and (3) each has one π bond; structure (4) does not due to its cyclic nature. The spectral data show that structure (4) is the C_3H_5 portion of the compound. The methylene C-H stretch of the cyclopropyl group absorbs at 3075 cm^{-1}. The methine C-H stretch absorbs at 3000 cm^{-1}. These absorptions are difficult to notice because they overlap with the broad band of the O-H stretch. Structures (1), (2) and (3) can be ruled out as the C_3H_5 group because the i.r. spectrum shows none of the characteristic bands for alkenes. For example, there are no strong sharp bands at 700 cm^{-1}, 890 cm^{-1}, 910 cm^{-1} or 990 cm^{-1}, which is characteristic of the C-H out-of-plane bending of alkenes. There is, however, a strong broad band at 950 cm^{-1} which is the O-H bend. Hence the compound is cyclopropylcarboxylic acid and has the structure



. The principle absorption bands of the infrared spectrum are labeled below:



Infrared Spectrum of Cyclopropyl carboxylic Acid

RAMAN SPECTROSCOPY

• PROBLEM 2-6

Classify the following molecules according to the general characteristics expected for their infrared and Raman spectra: (a) Cl_2; (b) HCl; (c) CO; (d) $CH_2=CH_2$ (double bond stretch only).

Solution: Raman spectroscopy is often used in conjunction with infrared spectroscopy in the identification of organic functionalities. Raman spectra arise from the absorption of monochromatic light by a sample before it is emitted as scattered light. As in infrared spectra, Raman spectra are recorded in wavenumbers. Frequently, a Raman spectrum will reveal something that was missed in the infrared spectrum. This is because a bond which has no dipole moment (i.e., is electrically symmetrical) will appear in the Raman spectrum but will not appear in the infrared spectrum. With this information we can predict the general characteristics expected for the infrared and Raman spectra of compounds (a) through (d).

(a) The Cl-Cl bond of the chlorine molecule has no dipole moment because, like all other diatomic molecules (H_2, O_2, Br_2), the two identical atoms exert equal and opposite electronegative effects upon each other. Hence the infrared spectrum of Cl_2 will show no absorptions and the Raman spectrum will show a strong Cl-Cl absorption.

(b) The H-Cl bond of hydrogen chloride is fairly polar due to the considerable difference in electronegativity of hydrogen and chlorine, whose electronegativities are 2.1 and 3.0, respectively. As a result, both the infrared and Raman spectrum of HCl will show a strong H-Cl stretch. The dipole moment of HCl is directed toward the chlorine (because of its greater electronegativity) as shown:

$$H \;{+}\!\!\longrightarrow\; Cl$$

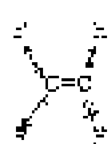
(c) Carbon monoxide is a polar molecule and its structure can be shown by two main resonance structures:

$$\bar{:}C\equiv O{:}^{+} \quad \longleftrightarrow \quad :C=\ddot{O}$$

Note: Resonance structures do not exist independently; they only approximate what the molecule really looks like. That is, the molecule is actually a hybrid of the resonance structures.

The principal characteristic of the infrared and Raman spectra will be the strong C-O stretch.

(d) The C=C double bond of 1,1-difluoroethylene is polar because of the powerful electron withdrawing effects of the two fluorine atoms:



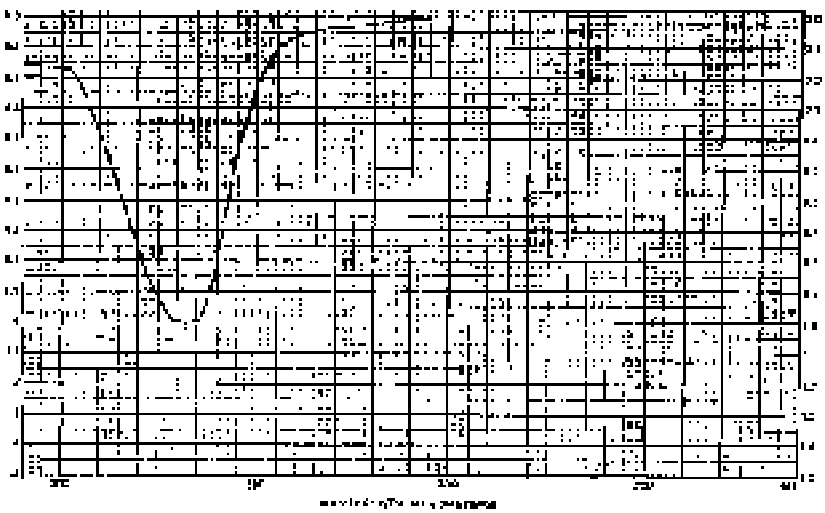
The net result is:

$$F_2C \longleftarrow\!\!{+}\; CH_2$$

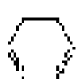
The C=C bond will appear as a strong band in both the infrared and Raman spectra.

• PROBLEM 2-7

The ultraviolet spectrum of 3,6,6-trimethylcyclohex-2-en-1-one, is shown below. The concentration is 1.406 × 10^{-3} g dl^{-1} in ethanol and the path length is 1.0 cm. Calculate ε and compare λ_{max} with the value predicted by Woodward's rules.



Empirical Parameters for π → π Transitions of Conjugated Systems in Ethanol (Woodward's Rules)*

Parent System	λ_{max}, nm	Substituent Corrections	
Polyenes			
		double bond[a]	+30
	214	alkyl group	+5
		exocyclic C=C double bond	+5
	253	OR group	0
		Cl, Br	+5
α,β-Unsaturated ketones			
	215	double bond[a]	+30
		alkyl group	+10
		exocyclic C=C double bond	+5

[a] The double bond must be attached at one end of the π-system to produce a linear conjugated system.

Solution: Ultraviolet spectroscopy involves the excitation of an electron in its ground state level to a higher energy level. This is accomplished by irradiating a sample with ultraviolet light (electromagnetic radiation with wavelengths in the range of 200 nanometers (nm) to 400 nm). The wavelength of maximum absorption (λ_{max}) can be calculated by using Woodward's Rules.

λ_{max} has a specific degree of absorbance associated with it. The absorbance at a particular wavelength is dependent upon the intensity or molar absorptivity, ε, of the incident light. The molar absorptivity is related to the absorbance by the equation

$$\varepsilon = \frac{\log (I_0/I)}{c\,l}$$

where I_0 = initial light intensity

I = final light intensity

c = concentration of sample in moles per liter

l = path length of sample tube in centimeters

Beer's Law relates the absorbance A to I_0 and I by the equation:

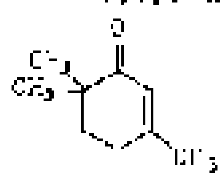
$$A = \log (I_0/I)$$

Hence the equation for molar absorptivity can be written as:

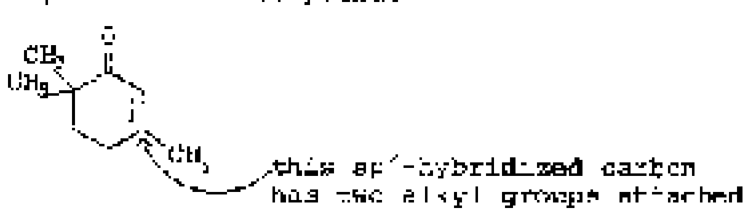
$$\varepsilon = \frac{A}{cl}$$

where A = absorbance at λ_{max}.

To calculate λ_{max} by Woodward's Rules, we must look at the parent system of 3,6,6-trimethylcyclohex-2-en-1-one:

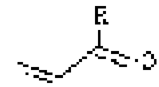


The parent compound is an α,β-unsaturated ketone, therefore λ_{max} is at least 215 nm. There are two alkyl substituents on the parent system of our compound:



For each alkyl group substituted on the α,β unsaturated ketone, a correction of + 10 nm must be made according to Woodward's Rules. Therefore, the calculated λ_{max}

$\left[\lambda_{max}^{calc}\right]$ for 3,6,6-trimethylcyclohex-2-en-1-one is

215 nm for the parent system $\left\{\right.$  $\left.\right\}$ plus 2

(10 nm) or 20 nm for the two alkyl groups substituted on the β-carbon of the α,β unsaturated ketone.

$$\lambda_{max}^{calc} = 215 \text{ nm} + 20 \text{ nm}$$

$$\lambda_{max}^{calc} = 235 \text{ nm}$$

By looking at the ultraviolet spectrum of our compound, we see that λ_{max}^{calc} is very close to the experimental λ_{max}

$\left(\lambda_{max}^{expl}\right)$. The λ_{max}^{expl} is 233 nm whereas the λ_{max}^{calc} is 235 nm; this discrepancy of 2 nm falls within the experimental margin of error and confirms the validity (and accuracy) of Woodward's Rules.

The molar absorptivity (ε) may be calculated by using the aforementioned equation

$$\varepsilon = \frac{A}{cl}$$

where A = absorbance at λ_{max}^{expl}

c = concentration of sample in moles per liter

l = path length of sample tube in centimeters.

By looking at the ultraviolet spectrum, we see that the absorbance at λ_{max}^{expl} (233 nm) is 1.0. There are no units for absorbance and the molar absorptivity is expressed in liters per mole per centimeter (liters $mole^{-1}$ cm^{-1}). The path length of the sample tube is given as 1.0 centimeter. The concentration of the sample in ethanol is given in grams (g) per milliliter (ml). This must be converted to moles per liter. Since 1 liter = 1000 ml, multiplying the given concentration by 1000 will give us the concentration in grams per liter:

$$1.486 \times 10^{-3} \text{ (g/ml)} \times 10^{3} \text{ (ml/liter)} =$$

$$1.486 \times 10^{-[illegible]} \text{ (g/liter)}$$

We must now convert grams to moles to give us the proper units. Since moles = $\frac{g}{MW}$ (MW is the molecular weight of the sample), and the MW of 3,6,6-trimethylcyclohex-2-en-1-one is 138, we can calculate the concentration in moles per liter as shown:

$$1.486 \times 10^{-2}\ (\text{g/liter}) \times \frac{1}{137\ (\text{g/mole})}$$

$$= 1.08 \times 10^{-4}\ (\text{moles/liter})$$

The molar absorptivity may now be calculated as follows.

$$\epsilon = \frac{1.0}{1.08 \times 10^{-4}\ (\text{moles/liter}) \times 1.0\ (\text{cm})}$$

$$\epsilon = 9260\ \text{liters mole}^{-1}\ \text{cm}^{-1}$$

• PROBLEM 2-5

Calculate the percentage of the incident light which would be absorbed by an 0.010-M solution of acetone in cyclohexane contained in a quartz cell 0.1 cm long at 2800 Å and 1900 Å.

Some Electronic Transitions of Simple Organic Molecules

Compound	Type	λ_{max}, Å	ϵ_{max}[a]	Solvent[b]
$(CH_3)_2C{=}O$	$n \to \pi^*$	2800	15	cyclohexane
	$\pi \to \pi^*$[c]	1900	1,100	
	$n \to \sigma^*$	1560	strong	
$CH_2{=}CH_2$	$\pi \to \pi^*$	1620	10,000	vapor
$CH_2{=}CH{-}CH{=}CH_2$	$\pi \to \pi^*$	2170	20,900	hexane
$CH_3{-}CH{=}CH{-}CH{=}CH{-}CH_3$	$\pi \to \pi^*$	2270	22,500	hexane
$CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2$	$\pi \to \pi^*$	1850	20,000	alcohol
$CH_3{-}C{\equiv}CH$	$\pi \to \pi^*$	1870	450	cyclohexane
$CH_2{=}CH{-}C(CH_3){=}O$	$n \to \pi^*$	3240	24	alcohol
	$\pi \to \pi^*$	2190	3,600	
CH_4	$\sigma \to \sigma^*$[d]	1220	strong	vapor
$CH_3{-}CH_3$	$\sigma \to \sigma^*$	1350	strong	vapor
$CH_3{-}Cl$	$n \to \sigma^*$[e]	1725	weak	vapor
$CH_3{-}Br$	$n \to \sigma^*$	2040	200	vapor
$CH_3{-}I$	$n \to \sigma^*$	2575	365	pentane
$CH_3{-}O{-}H$	$n \to \sigma^*$	1835	150	vapor
$CH_3{-}O{-}CH_3$	$n \to \sigma^*$	1838	2,520	vapor
$(CH_3)_3N$	$n \to \sigma^*$	2273	900	vapor

[a] The molar extinction coefficient ϵ is a measure of the absorption intensity at the wavelength λ_{max}. Since the amount of absorption will be proportional to the concentration (c, moles/liter) and thickness of the sample (l, cm), ϵ is obtained from the equation

$$\epsilon = \frac{1}{cl} \log_{10} \frac{I_0}{I}$$

where I_0/I is the ratio of intensity of incident light I_0 to transmitted light I. The percent transmission of a solution is $(I/I_0) \times 100$. An equation like this in which ϵ is independent of c is said to obey Beer's law (or the Beer-Lambert law).

[b] It is necessary to specify the solvent since λ_{max} and ϵ vary somewhat with solvent.

[c] These assignments are not certain.

[d] Transitions $\sigma \to \sigma^*$ correspond to excitation of an electron of a single bond (designated σ) to a higher antibonding state (designated σ^*).

[e] Transitions $n \to \sigma^*$ correspond to excitation of an electron of an unshared (n, nonbonding) pair to an antibonding state (σ^*) of a bond in the molecule.

Solution: The percentage of light absorbed is related to the percentage of light transmitted by the equation

$\% A = 100 - \% T$

where $\% A$ = % absorbance

$\% T$ = % transmittance

The absorbance (A) is related to the initial intensity (I_0) and the final intensity (I) by Beer's Law:

$$A = \log\left[\frac{I_0}{I}\right]$$

We can therefore relate the transmittance (T) to I_0 and I as:

$$T = \frac{I}{I_0}$$

The absorbance of the incident light of a sample solution may be calculated by using the equation for molar absorptivity (ε):

$$\varepsilon = \frac{1}{c\ell} \log\left(\frac{I_0}{I}\right)$$

where ε = molar absorptivity in liters mole^{-1} cm^{-1}

c = concentration of sample in moles per liter

ℓ = path length of sample tube in centimeters

At a wavelength of 2800 Å (Angstrom: 10 Å = 1 nm), a solution of acetone in cyclohexane solvent has a molar absorptivity of 15 liters mole^{-1} cm^{-1}. The path length is 0.1 cm and the molar concentration is 0.01. The absorbance can be calculated as follows:

$$\varepsilon = \frac{1}{c\ell} \log\left[\frac{I_0}{I}\right]$$

$$15 = \frac{1}{(0.01)(0.1)} \log\left[\frac{I_0}{I}\right]$$

$$0.015 = \log\left[\frac{I_0}{I}\right]$$

$$\frac{I_0}{I} = 1.04$$

Since $T = \frac{I}{I_0}$, then:

$$T = \frac{1}{\frac{I_0}{I}} = \frac{1}{1.04} = 0.9615$$

$$\% T = 100 \times T$$

$$\% T = 100 \times 0.9615$$

$$\% T = 96.15$$

$$\% A = 100 - \% T$$

$$\% A = 100 - 96.15$$

$$\% A = 3.85$$

Hence at 2800 Å there is 3.85% absorption of the incident light. At a wavelength of 1900 Å the molar absorptivity is 1100 liters mole^{-1} cm^{-1}. The percentage absorbance may be calculated as:

$$\varepsilon = \frac{1}{cl} \log \left(\frac{I_0}{I}\right)$$

$$1100 = \frac{1}{(0.01)(0.1)} \log \left(\frac{I_0}{I}\right)$$

$$1.10 = \log \left(\frac{I_0}{I}\right)$$

$$\frac{I_0}{I} = 12.6$$

$$T = \frac{1}{\frac{I_0}{I}} = \frac{1}{12.6} = 0.0794$$

$$\% T = 100 \times T = 100 \times 0.0794$$

$$\% T = 7.94$$

$$\% A = 100 - \% T = 100 - 7.94$$

$$\% A = 92.06$$

Hence at 1900 Å there is 92.06% absorption of the incident light by a 0.01 M solution of acetone in cyclohexane.

• PROBLEM 2-9

Compounds A, B and C have the formula C_5H_8, and on hydrogenation all yield n-pentane. Their ultraviolet spectra show the following values of λ_{max}: A, 176 nm; B, 211 nm; C, 215 nm. (1-Pentene has λ_{max} 178 nm.) (a) What is a likely structure for A? For B and C? (b) What kind of information might enable you to assign specific structures to B and C?

Solution: (a) The molecular formula of compounds A, B and C is of the general form C_nH_{2n-2}. This formula indicates that the compounds are hydrocarbons with either one carbon-carbon triple bond (an alkyne), two carbon-carbon double bonds (a diene), two rings, or one ring and one carbon-carbon double bond; that is, the compounds have two units of unsaturation. Since hydrogenation of the compounds yield n-pentane, and hydrogenation of alkynes and dienes does not change the carbon skeleton, all the compounds must be straight-chained. Hence the compounds are normal five-carbon alkynes or dienes.

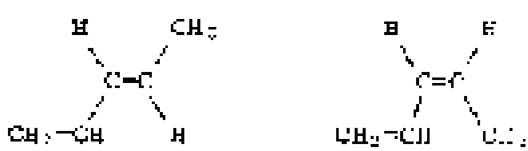
Compound A has maximum absorption at a wavelength of 176 nm (λ_{max}). Since this is very close to the λ_{max} of 1-pentene, compound A must have a chromophore similar to that of 1-pentene. A chromophore is a functional group that gives rise to an absorption with characteristic λ_{max} and ε (molar absorptivity) values. Hence compound A's chromophore, like 1-pentene, is an isolated double bond. The only structure of a normal five-carbon compound with two units of unsaturation and isolated double bonds is 1,4-pentadiene:

$H_2C{=}CH{-}CH_2{-}HC{=}CH_2$

1,4-pentadiene

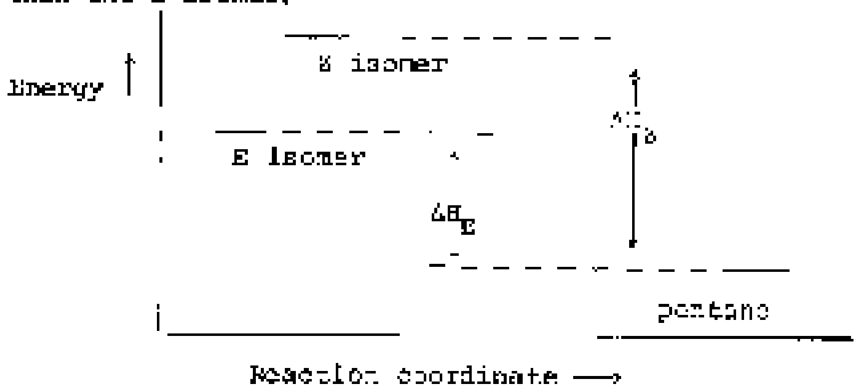
(Compound A)

Compounds B and C have λ_{max} of 211 nm and 215 nm, respectively. These values are greater than that of compound A and are of lower energies (longer wavelength (λ), lower frequency, lower energy). One thing that could account for this is if B and C were conjugated dienes. Conjugated dienes are compounds that have two double bonds separated by one single bond (R-CH=CH-CH=CH-R'). The extra stability of conjugated dienes as compared to the analogous non-conjugated dienes is due to electron delocalization in the former. This extra stability lessens the energy difference between the ground state and excited state. Hence the frequency necessary for the maximum absorption of the compound is less than expected and the wavelength (λ_{max}) will be greater. Therefore compounds B and C must be geometric isomers of the conjugated compound, 1,3-pentadiene. These are the "E" and "Z" isomers:



E isomer Z isomer

(b) The E and Z isomers of the diene can be distinguished by their heats of hydrogenation. The Z isomer is less stable than the E isomer because of steric considerations, due to the proximity of the vinyl and methyl groups. This means that the Z isomer will have a higher heat of hydrogenation than the E isomer.



$|\Delta H_Z| > |\Delta H_E|$

where

ΔH_Z = heat of hydrogenation

for the Z isomer

ΔH_E = heat of hydrogenation

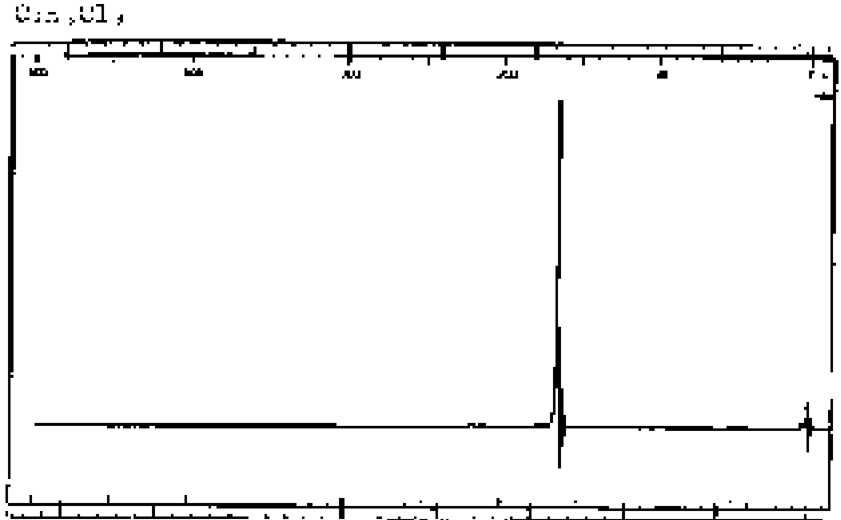
for the E isomer.

NMR SPECTROSCOPY

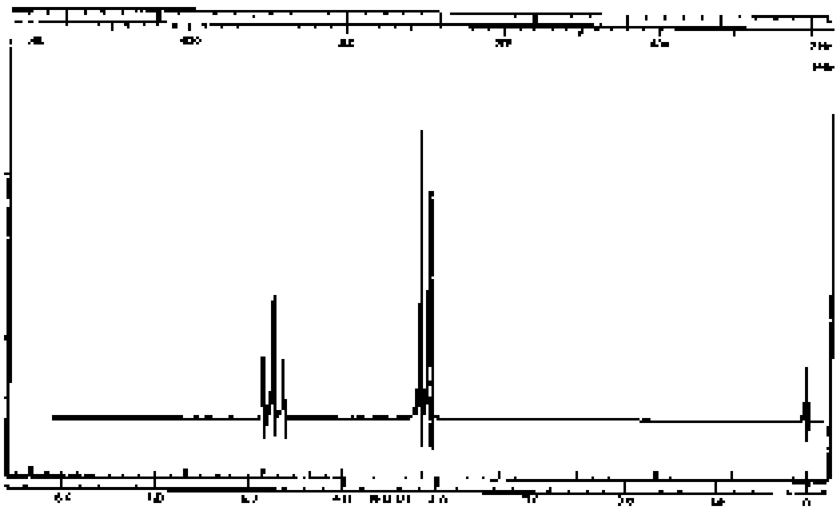
• PROBLEM 2-10

Deduce the structure corresponding to each of the following nmr spectra:

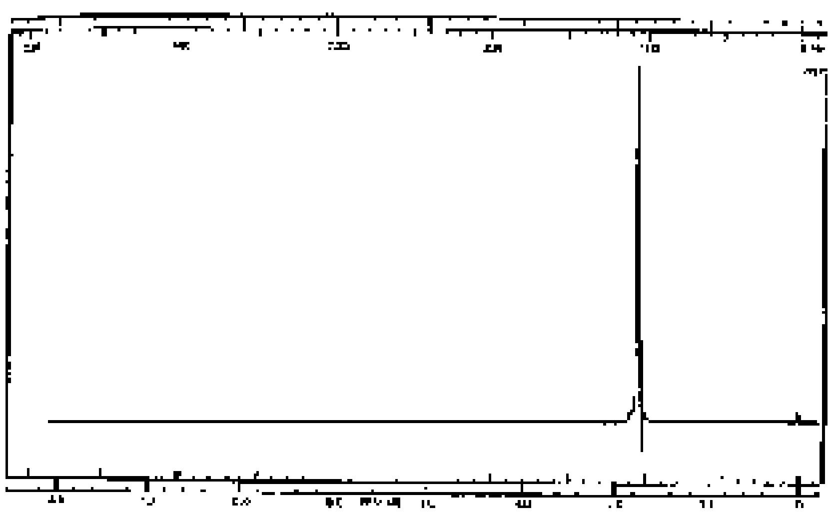
(a) $C_2H_4Cl_2$



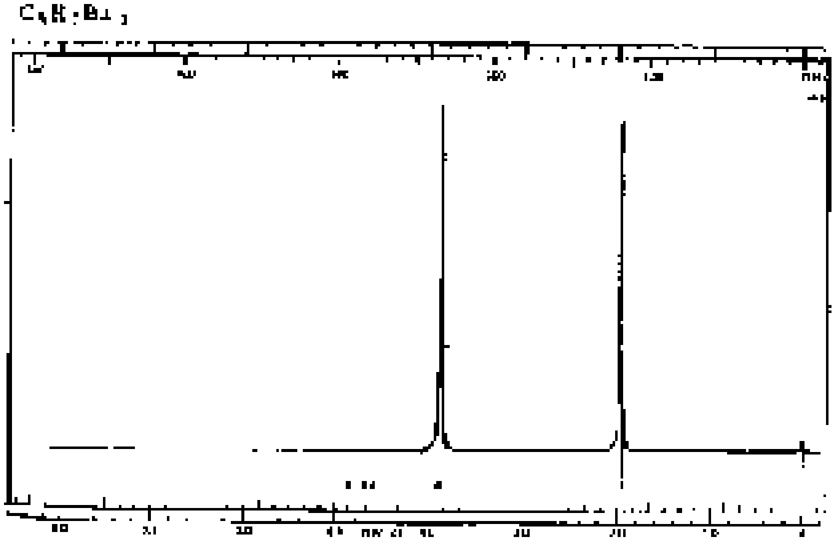
(b) $C_2H_3Br_3$



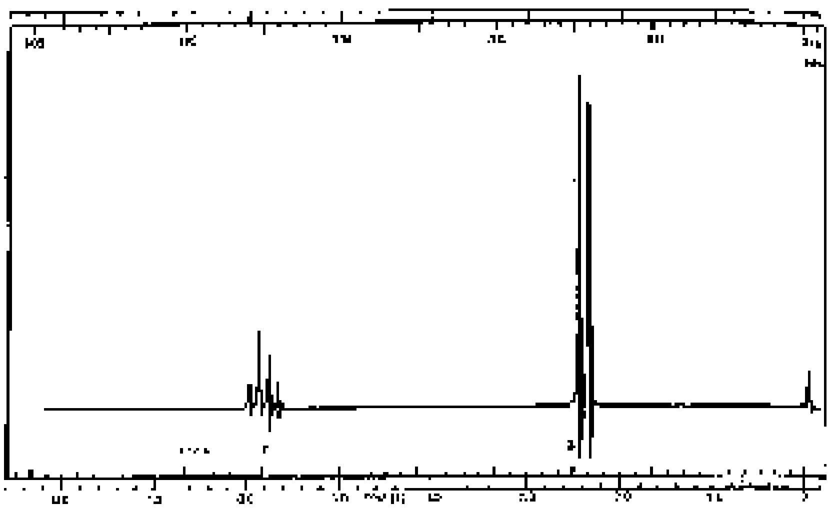
(c) C_4H_9Br



(d) $C_4H_7Br_3$



(e) $C_2H_4Br_2$



Solution: Certain atoms have a nuclear spin similar to the spin of an electron. The spinning of charged particles (the proton(s) in the nucleus bears a positive charge) generates a magnetic field. When an atom is placed in an external magnetic field, the magnetic field generated by the nucleus will be aligned with or against the external magnetic field. At some frequency of electromagnetic radiation, the nucleus will absorb energy and "flip" over so that it reverses its alignment with respect to the external magnetic field. This is known as the nuclear magnetic resonance (nmr) phenomenon. It is generally concerned with the nuclear magnetic resonance of hydrogen atoms and is therefore sometimes called proton magnetic resonance (pmr). It is also standard practice for the frequency of radiation to be kept constant while the strength of the external magnetic field is varied. At some value of the magnetic field strength, the energy required to flip the proton matches the energy of the radiation. Absorption will occur and a signal will be observed. The spectrum that results from all these absorptions is called an nmr spectrum. Absorptions that occur at relatively low field strengths are downfield relative to those that occur at higher field strengths. The field strength at which a proton will absorb energy is called the chemical shift (measured in parts per million, ppm or δ, relative to the absorbance of $Si(CH_3)_4$, tetramethylsilane). The chemical shift of a proton depends upon the proton's electronic environment. Electron withdrawing atoms (or groups) that are nearby a proton will decrease the electron density about that proton; this is known as a deshielding effect. The proton's absorption will occur downfield from what is expected. Specifically, the proton will absorb at a smaller field strength than a proton experiencing no deshielding effects. Electron releasing atoms (or groups) that are nearby a proton will increase the proton's electron density; the proton is experiencing a shielding effect. The proton's absorbance will occur upfield (higher magnetic field strength) from what is expected.

The signal that arises from a proton's absorption may occur as a singlet, a doublet, a triplet, etc. The number of peaks in the signal depends upon the neighboring protons. Protons that are in identical electronic environments are equivalent protons; those that are in non-identical electronic environments are non-equivalent protons. A proton that has n non-equivalent adjacent protons will have a signal with n + 1 peaks, called a n + 1 multiplet. This is the result of spin-spin splitting of the protons. For example, all the protons of ethane (CH_3-CH_3) are in identical electronic environments and are therefore equivalent. Hence there will be no spin-spin splitting of the protons; the nmr spectrum will contain only singlets (signals with one peak). Furthermore, since all the protons in ethane are equivalent they will have identical chemical shifts, and will occur as one signal. Hence the nmr spectrum of ethane will have one singlet. An example where spin-spin splitting occurs is propane. The methylene protons are non-equivalent to the methyl protons. As a result, the six non-equivalent adjacent methyl protons will split the methylene proton's signal into a heptet (seven peak multiplet).

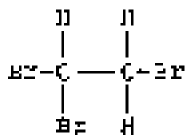
The relative areas under the signals in an nmr spectrum indicate the relative number of protons that give rise to each signal.

With our basic understanding of nuclear magnetic resonance, we can now deduce the structures of (a) through (e).

(a) The compound's molecular formula ($C_2H_3Cl_3$) is of the type C_2*_6, where * represents an atom that forms a single bond with carbon. The formula C_2*_6 is of the form C_n*_{2n+2} and indicates that the carbon compound is saturated; there are only σ bonds in this compound. The nmr spectrum shows a singlet at about 2.7 δ. Since the signal is a singlet there is no spin spin splitting. This means that the three protons in the compound are equivalent. Since the two carbons are adjacent all three protons must be on one carbon for no spin-spin splitting to occur. Hence the compound is 1,1,1-trichloroethane and has the structure:

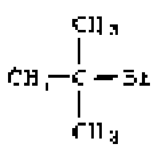
```
   H Cl
   | |
 H-C-C-Cl
   | |
   H Cl
```

(b) As in part (a), the molecular formula ($C_2H_3Br_3$) is of the form C_n*_{2n+2}, and is hence a saturated carbon compound. The nmr spectrum has a doublet near 4.2 δ and a triplet near 5.7 δ. These multiplets occurred as a result of spin-spin splitting. Since there is a doublet and a triplet in the spectrum, and there are three hydrogen atoms in the compound, we can conclude that there is one hydrogen adjacent to two non-equivalent hydrogens. This means that the carbon with one hydrogen has two bromines and the carbon bearing two hydrogens has one bromine. The compound is 1,1,2 tribromoethane:



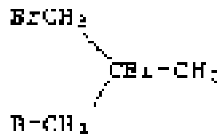
The lone $-CHBr_2$ hydrogen split the $-CH_2Br$ signal into a doublet; the two $-CH_2Br$ hydrogens split the $-CHBr_2$ signal into a triplet. The $-CHBr_2$ signal occurred downfield from the $-CH_2Br$ signal because the deshielding effect of two bromine atoms is greater than that of one bromine atom.

(c) The molecular formula (C_4H_9Br) is of the form $C_nH_{2n+1}X$ and is therefore a saturated carbon compound. The nmr spectrum has a singlet at 1.7 δ; this indicates that there is no spin-spin splitting. Hence, all the hydrogens are equivalent; they are in identical electronic environments. The only manner in which all the hydrogens are equivalent is if there are three methyl ($-CH_3$) groups. This leaves us with a -CBr position. The only possible structure is:



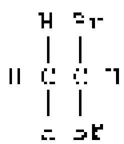
2-bromo-2-methylpropane

(d) As in parts (a) through (c) the molecular formula ($C_4H_7Br_3$) of the compound indicates that the compound is saturated. The nmr spectrum shows a singlet at 3.9 δ and another singlet at 2.0 δ, having relative intensities (relative areas) of four and three, respectively. The absence of multiplets means that no spin-spin splitting occurred. If all the protons were equivalent, the spectrum would show only one signal because equivalent protons have identical chemical shifts. The fact that there are two signals indicates that there are two sets of non-equivalent protons. Since there are seven hydrogens in the compound, and the sum of the relative intensities is seven, the relative intensities show the actual number of protons absorbing per molecule. The signal at 2.0 δ with a relative intensity of three must have arisen from the absorption of a methyl group's protons. This is because in a saturated four-carbon compound, a methyl group is the only group that has three equivalent hydrogens. Since no spin-spin splitting occurred the methyl group must be separated from the other hydrogens by a carbon bearing no hydrogens. In order for the four remaining hydrogens to be equivalent (they gave rise to the same signal), they must be part of equivalent groups. The signal that occurs at 3.9 δ is characteristic of an $R-CH_2-Br$ chemical shift. With this in mind we can conclude that the four remaining hydrogens are part of two $-CH_2Br$ groups. The structure of the compound is:



2-bromomethyl-1,3-dibromopropane

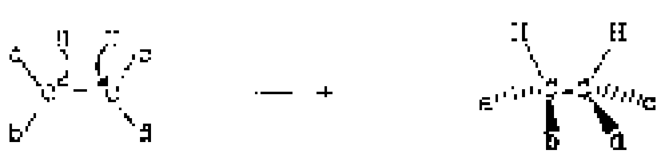
(e) Once again we are dealing with a saturated carbon compound, this one having a molecular formula of $C_2H_4Br_2$. The nmr spectrum shows a doublet at 2.4 δ and a quartet at 5.8 δ, with relative intensities of three and one, respectively. The presence of these multiplets means that spin-spin splitting occurred. The protons that gave rise to the doublet were split by one non equivalent proton. The proton that gave rise to the quartet was split by three non-equivalent protons. Since we are restricted to two carbons, the only possible compound is 1,1-dibromoethane:



• PROBLEM 2-11

(a) On catalytic hydrogenation, compound A, C_5H_8, gave cis-1,2-dimethylcyclopropane. On this basis, three isomeric structures were considered possible for A. What were they? (b) Absence of infrared absorption at 890 cm^{-1} made one of the structures unlikely. Which one was it? (c) The nmr spectrum of A showed signals at δ 2.22 and δ 1.04 with intensity ratio 3:1. Which of the three structures in (a) is consistent with this? (d) The base peak in the mass spectrum was found at m/e 67. What ion was this peak probably due to, and how do you account for its abundance? (e) Compound A was synthesized in one step from open-chain compounds. How do you think this was done?

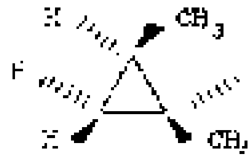
<u>Solution:</u> (a) Catalytic hydrogenation of alkenes (compounds with a carbon-carbon double bond) yields the corresponding alkanes (saturated hydrocarbons). The reaction proceeds with the cis addition of two hydrogen atoms to the double bond; the hydrogens add onto the same side of the double bond.



Note:  = bond coming towards reader

 = bond going away from reader

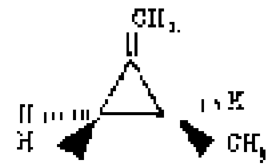
Compound A underwent catalytic hydrogenation to yield cis-1,2-dimethylcyclopropane:

C_5H_8 $\xrightarrow[\text{}]{\text{catalytic hydrogenation}}$ 

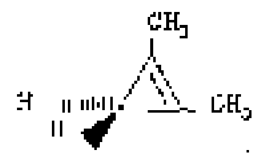
Compound A

cis-1,2-dimethylcyclopropane

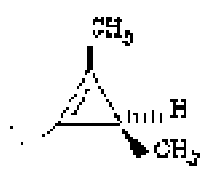
Since compound A's molecular formula (C_5H_8) contains two less hydrogens than the hydrogenation product's molecular formula (C_5H_{10}), there must have only been one double bond in compound A because only one mole of hydrogen gas was consumed in the reaction. There are three possible positions for a double bond to be created in cis-1,2-dimethylcyclopropane. There can be a double bond coming off the ring to a methylene group:



There can be a tetrasubstituted alkene;

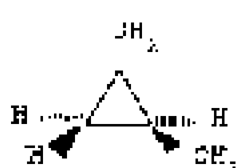


The third possibility is a trisubstituted alkene:



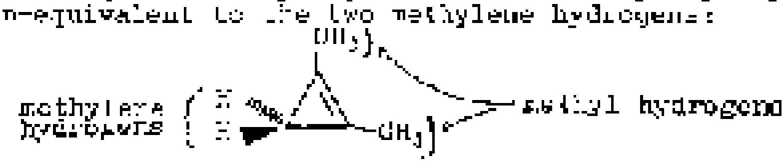
Catalytic hydrogenation of these three compounds will yield cis-1,2-dimethylcyclopropane. Note that the tetrasubstituted alkene yields only the cis product upon catalytic hydrogenation. The other two yield cis and trans products, depending upon which side of the double bond was hydrogenated.

(b) Disubstituted terminal alkenes ($R_2C{=}CH_2$) characteristically have a strong band at 890 cm^{-1} in the infrared spectrum. This is the absorption of the C-H out-of-plane bending vibrations. Since the infrared spectrum of compound A has no such band, we can eliminate the terminal alkene

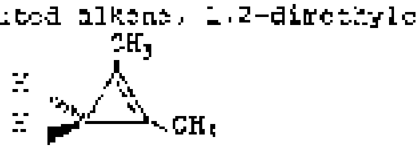


as a possible structure for A.

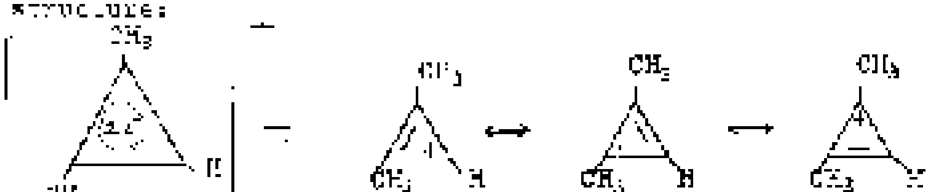
(c) Since there are eight hydrogens in compound A, and the sum of the relative intensities is four, the relative intensities represent one half the number of protons absorbed per molecule. Hence for every molecule there are six protons absorbing at δ 2.32 and two protons absorbing at δ 1.04. The presence of two signals in the nmr spectrum indicates that there are two sets of non-equivalent protons (that have different chemical shifts, hence different signals). Of the three possible structures for compound A in part (a), only the tetrasubstituted alkene has two sets of non-equivalent hydrogens. The six methyl hydrogens are non-equivalent to the two methylene hydrogens:



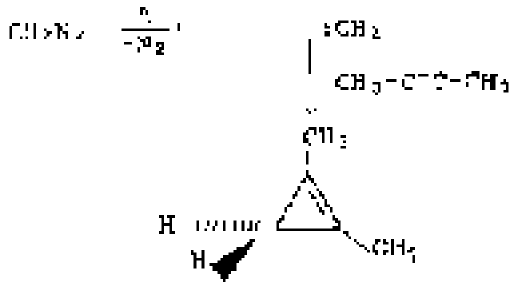
The terminal alkene that was previously suggested as a possible structure for A has five sets of non-equivalent hydrogens. The trisubstituted alkene that was suggested has four sets of non equivalent hydrogens. Hence the only structure from part (a) that is consistent with the nmr spectrum is the tetrasubstituted alkene, 1,2-dimethylcyclopropene:



(d) The base peak in a mass spectrum is the peak which corresponds to the positively charged species of highest stability upon a compound's fragmentation. The cation with molecular weight 67 must be formed by loss of a hydride anion from compound A which has a molecular weight of 68. This cation will be consistent with the proposal that compound A is 1,2-dimethylcyclopropene in that the subsequently formed cation will contain two π electrons and be aromatic. Its aromaticity is determined by Hückel's rule which states that a cyclic, conjugated π system of 4n+ 2π electrons (where n is an integer) is aromatic. Aromaticity and its associated electron delocalization confer stability upon the cation, agreeing with the spectral data. The cyclopropenyl ion has the following structure:

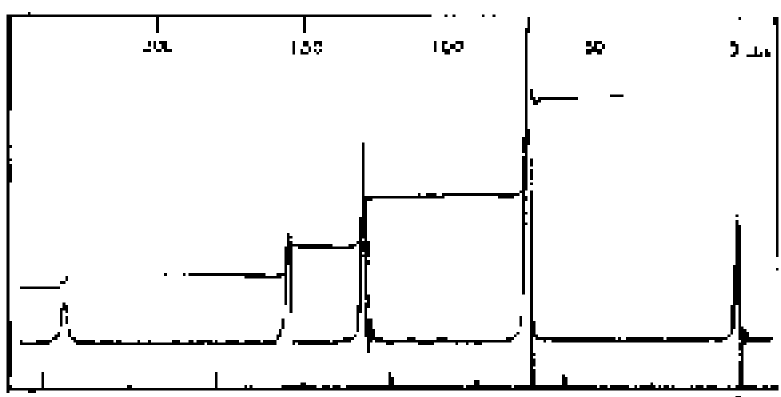


(e) The only way to synthesize this cyclopropene ring from open chain reagents would be through the use of the carbene, methylene (CH_2:) and the acetylene derivative, 2-butyne. The carbene is generated via diazomethane's loss of nitrogen upon heating, and its free pair of electrons allow it to be reactive enough to add to sites of unsaturation such as a triple bond. On occasion, it may even add to alkenes. Thus the synthesis would be as follows:



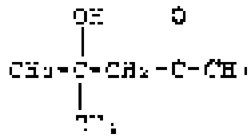
▾ PROBLEM 2-13

The Figure below shows the proton n.m.r. spectrum of $(CH_3)_2C(OH)CH_2COCH_3$ with tetramethylsilane as standard. The stepped line is an electronic integration of the areas under the signal peaks. (a) List the chemical shift of each proton signal in ppm, and deduce, from the trace of the integrated areas, the identity of the protons that give rise to each line. (b) List the line positions in cps relative to tetramethylsilane expected at 100 Mcps. (c) Sketch out the spectrum and integral expected for $CH_3COC(CH_3)_2OH$ at 60 Mcps.



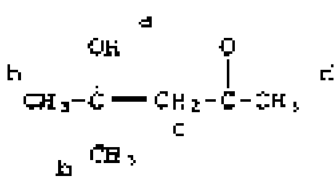
N.m.r. spectrum of diacetone alcohol, $(CH_3)_2C(OH)CH_2COCH_3$ at 60 Mcps relative to TMS 0.00 ppm. The stepped line is the integrated spectrum.

Solution: (a) To assign the identity of the protons to the spectral lines, we must look at the different types of protons within the molecule. Once we have identified all the non-equivalent protons in the molecule, we must determine their relative chemical shifts. When we have deduced the relative order of chemical shifts, we can read off the chemical shift of each signal and assign these values to particular protons. Diacetone alcohol has the following structure:



There are no two adjacent carbons in this molecule that bear non-equivalent hydrogens. This is supported by the fact that all the signals in the nmr spectrum are singlets; no spin-spin splitting took place. The methylene ($-CH_2-$) and hydroxyl ($-OH$) protons are unique in this molecule and hence constitute their own type of proton.

The protons of the ketone methyl group ($-\overset{O}{\overset{\|}{C}}CH_3$) are non equivalent to the protons of the other methyl groups by inspection. The protons of the two methyl groups bonded to the carbinol carbon ($(CH_3)_2COH$) are in identical electronic environments (made possible by the ability of the carbinol carbon to rotate about its single bonds) and are therefore equivalent. Hence there are four sets of non-equivalent protons in diacetone alcohol; they are labeled below as a through d:



The nmr signal of proton a will be downfield from all the other signals; it will absorb energy at a lower field strength (higher chemical shift) than any other proton in the molecule. This is due to the powerful deshielding effect of oxygen; this proton's electron density is the least of all the protons in the molecule. The next most deshielded protons are those of the methylene (c) group. The electron withdrawing effects of the adjacent carbonyl group ($-\overset{O}{\overset{\|}{C}}-$) and the nearby hydroxyl group ($-OH$) have a powerful combined deshielding effect. The ketone methyl group experiences deshielding from only the carbonyl group, and the b protons experience deshielding from only the nearby hydroxyl group. Since the carbonyl group has greater electron-withdrawing capabilities than the carbinol group ($-\overset{OH}{\overset{|}{C}}-$), the ketone methyl group is more deshielded than the b protons. Hence the relative order of deshielding and chemical shift values of the proton types a through d are:

a > c > d > b

By looking at the nmr spectrum of diacetone alcohol, we can see that the chemical shifts of the four signals are 3.85, 2.6, 2.15 and 1.2. By using the relative amounts of deshielding of each type of proton, we can assign the protons to a particular chemical shift as follows:

-OH proton, 3.85 ppm; $-CH_2-$ proton, 2.6 ppm; $-COCH_3$ proton, 2.15 ppm; $(CH_3)_2\overset{|}{C}-OH$ proton, 1.2 ppm.

(b) The signals in an nmr spectrum are measured relative to an internal standard such as tetramethylsilane ($Si(CH_3)_4$) for matters of convenience. Traditionally the chemical shift is measured in ppm (parts per million), but it can also be measured in cps (cycles per second) or H_z (Hertz). The line positions in cps relative to TMS (tetramethylsilane) expected at a frequency of 100 Mcps (1 mega cps = 1 million cps) can be calculated by using the line positions of the spectrum at 60 Mcps. This is accomplished by using a direct proportion:

$$\frac{60 \text{ Mcps}}{100 \text{ Mcps}} = \frac{\text{relative cps at } \nu = 60 \text{ Mcps}}{\text{expected cps at } \nu = 100 \text{ Mcps}}$$

The line positions in cps of the nmr spectrum shown at 60 Mcps are: -OH proton, 232 cps; $-CH_2-$ proton, 157 cps; $-COCH_3$ proton, 128 cps; $(CH_3)_2\overset{|}{C}-$ proton, 72 cps. We can calculate the expected line positions in cps relative to TMS at 100 Mcps as shown.

For the -OH proton:

$$\frac{60 \text{ Mcps}}{100 \text{ Mcps}} = \frac{232 \text{ cps (at } \nu = 60 \text{ Mcps)}}{\text{expected cps (at } \nu = 100 \text{ Mcps)}}$$

expected cps = 387

For the CH_2 proton:

$$\frac{60 \text{ Mcps}}{100 \text{ Mcps}} = \frac{157 \text{ cps}}{\text{expected cps}}$$

expected cps = 262

For the $-COCH_3$ proton:

$$\frac{60 \text{ Mcps}}{100 \text{ Mcps}} = \frac{128 \text{ cps}}{\text{expected cps}}$$

expected cps = 213

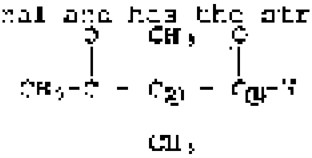
For the $(CH_3)_2\overset{|}{C}$ proton:

$$\frac{60 \text{ Mcps}}{100 \text{ Mcps}} = \frac{72 \text{ cps}}{\text{expected cps}}$$

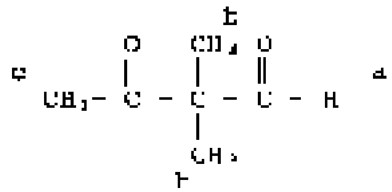
expected cps = 120

The expected line positions in cps relative to TMS at 100 Mcps are: - OH proton, 387 cps; $-CH_2-$ proton, 262 cps; $COCH_3$ proton, 213 cps; $(CH_3)_2-\overset{|}{C}$ proton, 120 cps.

(c) The compound $CH_3COC(CH_3)_2CHO$ is 2,2-dimethyl-3-oxobutanal and has the structure:

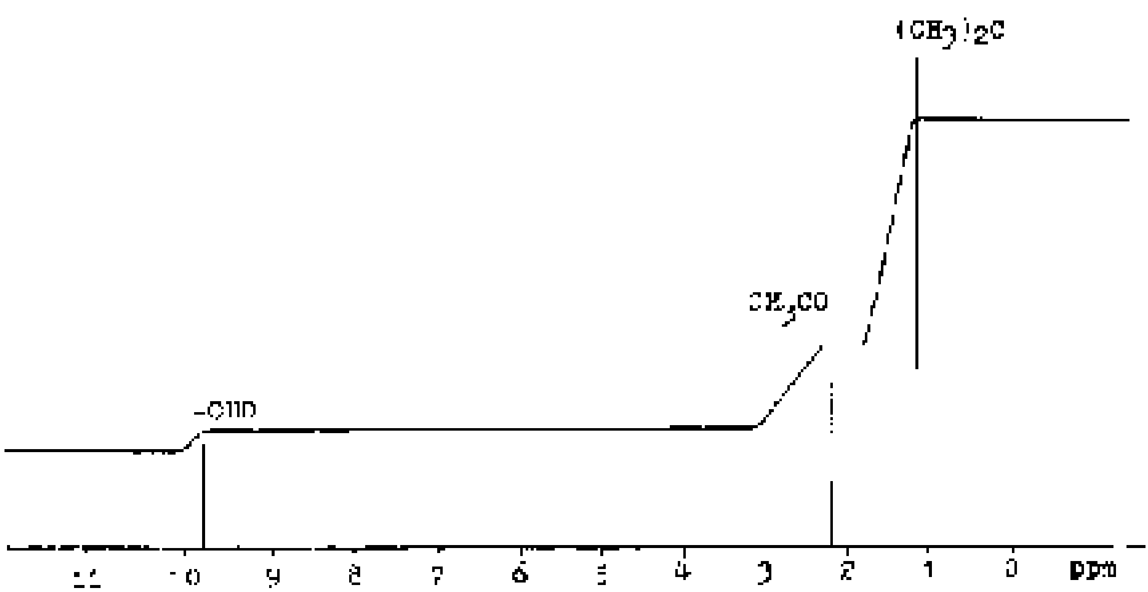


The ketone methyl group is non-equivalent to the other methyl groups by inspection. These other methyl groups, bonded to carbon number 2, are in identical electronic environments (because of carbon 2's ability to rotate about its single bonds) and are hence equivalent to each other. Therefore there are three sets of non-equivalent protons in the compound. They are labeled as:

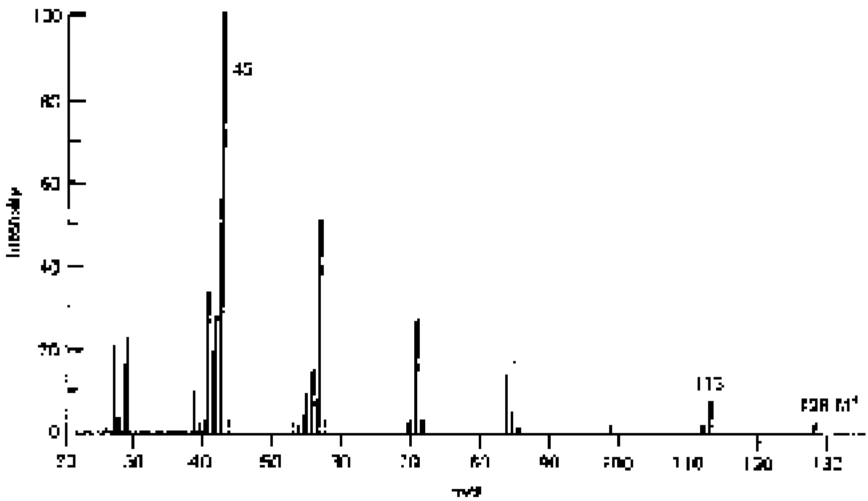


At a frequency of 60 Mcps, an aldehydic proton (a) will characteristically absorb between 9.4 and 10.4 ppm. Hence proton a will absorb in this range. The protons of a ketone methyl group (c) characteristically absorb between 2.1 and 2.4 ppm. The protons of the two equivalent methyl groups (b) are slightly deshielded by the carbonyl groups and will absorb between 1.0 and 1.4 ppm. Note that the signal of proton c will occur downfield from that of proton b due to greater deshielding effects: proton c is adjacent to the carbonyl group whereas proton b is separated from the carbonyl groups by one carbon.

The integration curve of an nmr spectrum indicates the relative intensities or relative areas of the peaks. The signal for proton a will have a relative intensity of one. Likewise, the signals for protons b and c will have relative intensities of six and three, respectively. These relative intensities will be represented on the integration curve as the relative changes in height at each peak. The nmr spectrum of 2,2-dimethyl-3-oxo-butanal is sketched below:



An unknown compound contains only carbon and hydrogen. Its mass spectrum is shown. Propose a structure for the compound.



Solution: Mass spectroscopy is a technique used to determine the molecular weight, formula and structure of a compound. It differs from infrared, raman, ultraviolet and nuclear magnetic resonance spectroscopy in that it is a destructive spectroscopy; the sample is fragmented by the technique and cannot be recovered in its original form. Mass spectroscopy involves the bombardment of a sample with an electron beam of a particular energy. If the sample is subjected to a low energy electron beam (about 10 eV-electron volts) the molecule will lose an electron to produce the molecular ion, $M^{\oplus}$.

$$\underset{\text{sample}}{M:} \xrightarrow{10\ eV} \underset{\text{electron}}{e^{\ominus}} \qquad \underset{\text{molecular ion}}{M^{\oplus}}$$

If the sample is subjected to a high energy electron beam (about 70 eV) the molecule will undergo fragmentation to yield various ionic species.

$$\underset{\text{sample}}{A\text{-}B\text{-}C:} \xrightarrow{70\ eV} \underset{\text{molecular ion}}{A\text{-}B\text{-}C^{\oplus}} + e^{\ominus}$$

$$A\text{-}B\text{-}C^{\oplus} \xrightarrow[70\ eV]{\text{fragmentation}} A^{\oplus} + B\text{-}C^{\cdot}$$

The mass spectrum of a compound plots the relative intensity of the ionic species versus the mass to charge ratio of each species. Note that only cationic species (those species that bear positive charge(s)) are recorded in the mass spectrum. The mass spectrum of a compound is taken by sequentially bombarding the sample with a low energy electron beam and a high energy electron beam. Bombardment by a low energy electron beam principally produces the molecular ion. The molecular ion has a charge of + 1 and has the same molecular weight as the sample compound and therefore its mass to charge ratio (m/e) will be the molecular weight of the compound. As a result the molecular ion peak indicates the molecular weight of the compound and is called the parent peak (generally indicated by M^+ in the mass spectrum). One may reason that the peak with the greatest m/e is the parent peak, but this is not necessarily true. The existence of isotopes will produce small peaks with m/e values of M + 1, M + 2, etc. The relative abundance or intensity of these peaks reflect the relative abundance of the isotopes. For example C^{13} and C^{12} are isotopes of carbon with relative abundances of 1% and 99%, respectively. In the mass spectrum of methane, CH_4, the parent peak will be at m/e = 16. There will however be a peak at m/e = 17, which was derived from the methane molecules containing C^{13}. The peak at 17 will be 1/99 the intensity of the peak at 16.

The parent peak is usually of moderate intensity and may sometimes be the peak of greatest intensity. There is another type of peak in the mass spectrum that is essential in determining the structure of the compound. This peak is the one that arises from the most abundant species that resulted from the fragmentation of the compound, which occurred upon bombardment by the high energy electron beam. This species is often the most stable one that resulted from the fragmentation of the compound. Its peak is the one of greatest intensity and is called the base peak. Sometimes the base peak and the parent peak may be the same, as in the case of methane, although this usually does not happen. For example, the mass spectrum of isobutane

$\left[CH_3-\underset{H}{\overset{CH_3}{C}}-CH_3\right]$ has its parent peak at m/e = 58 and its base peak at m/e = 57. The species that gives rise to the base

peak is $CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3$, which was formed by the loss of a hydrogen atom from the molecular ion, $\left[CH_3-\underset{H}{\overset{CH_3}{C}}-CH_3\right]^{\oplus}$.

Note that $CH_3-\underset{\oplus}{\overset{CH_3}{C}}-CH_3$ is the most abundant fragment because of the relatively high stability of a tertiary carbocation, a trialkylated carbon bearing a positive charge. (The relative order of carbocation stability is:

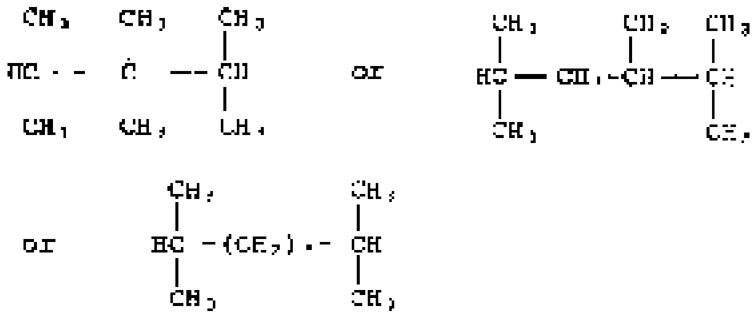
tertiary > secondary > primary > $CH_3^{\oplus}$.)

With these basic principles of mass spectroscopy, we may now attempt to identify the compound whose mass spectrum is shown. The spectrum indicates that the parent peak (M^+) is the one with m/e = 128; hence the molecular weight of the compound is 128. Since the compound is a hydrocarbon (contains only carbon and hydrogen) the molecular weight restricts the number of carbons to nine or ten. The possible molecular formulas are C_9H_{20} and $C_{10}H_8$. Note that the compound cannot contain eight carbons because the molecular formula would then be C_8H_{32}; the greatest number of hydrogens an eight-carbon compound can accommodate is 18. Hence the compound must contain more than eight carbons. A compound with a molecular formula of C_9H_{20} is a saturated hydrocarbon and is in the class of alkanes. A compound with a molecular formula of $C_{10}H_8$ has seven units of unsaturation. This is determined by the fact that a fully saturated ten-carbon compound has twenty-two hydrogens and for each unit of unsaturation gained, there is a loss of two hydrogens. Since the parent peak has a small relative intensity, the compound is more likely to be the saturated hydrocarbon (C_9H_{20}) than the unsaturated one ($C_{10}H_8$). This is because fragments with multiple bonds have higher stability and less tendency to rearrange than saturated fragments. The unsaturated compound will therefore have a great relative intensity for its parent peak whereas the saturated compound will not. We can conclude that the compound is a saturated hydrocarbon with the molecular formula C_9H_{20}.

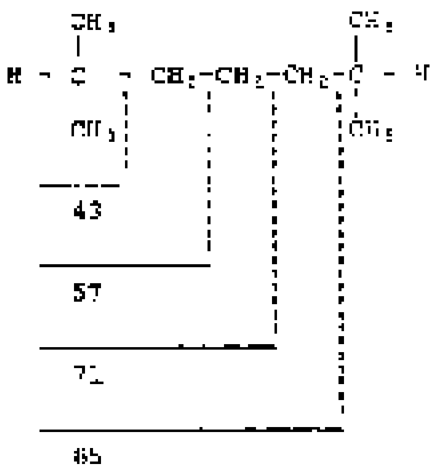
Examining the mass spectrum further, we note that the peak with the greatest relative intensity (possessing a value of 100) has a m/e value of 43. This peak, the base peak, most probably represents the isopropyl cation

$$\left[\begin{array}{c} H \\ | \\ CH_3CCH_3 \\ \oplus \end{array}\right]$$ and therefore the compound contains one or

more isopropyl fragments. A n-propyl fragment would have the same molecular weight but would not have such a high relative intensity value. The absence of any significant peak for m/e = 29 tells us that the compound does not produce the ethyl cation ($C_2H_5^{\oplus}$) and therefore is not of the type $R\text{-}C_2H_5$ because compounds of this type would produce the pertinent cation. Thus, the compound seems to have branched terminal groups, probably isopropyl portions. Assuming this, we have accounted for 85 grams of the molecular weight of 128 grams. Hence, we hypothesize the unknown compound to have one of the following three structures:



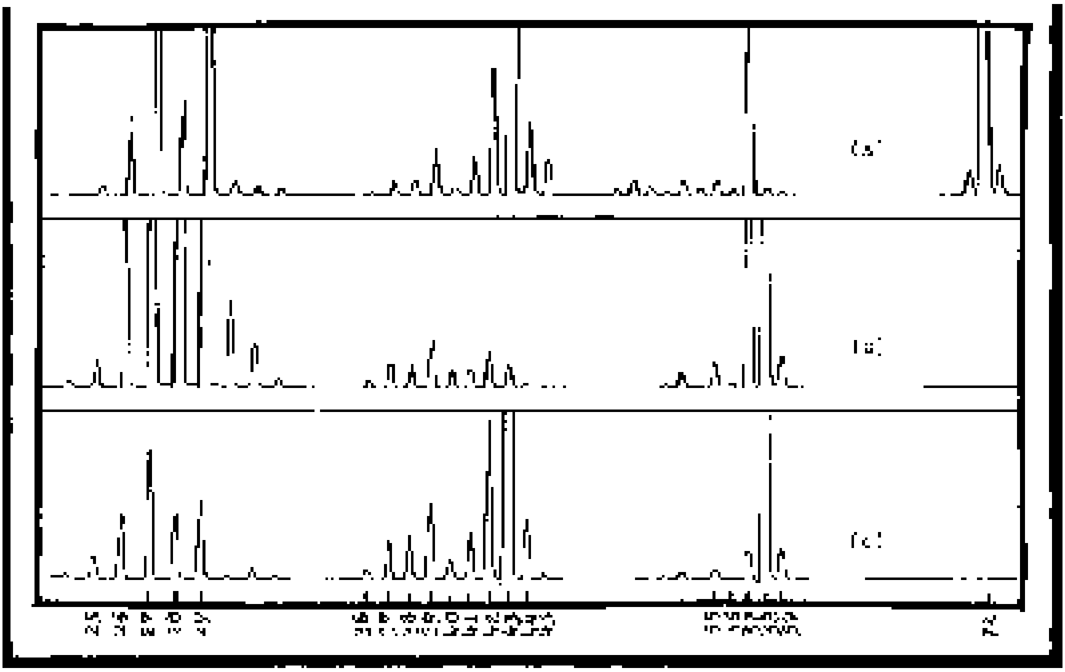
We can deduce that the compound has the third structure in that there is only a moderate peak at m/e = 113 which corresponds to the compound's loss of a methyl fragment. (The other structures have five or six methyl groups.) More importantly, we can relate the different moieties to their m/e values in the mass spectrum upon fragmentation of the molecule along the chain.



We note that peak at m/e value of 57 is particularly intense and this can be related to the formation of the stable t-butyl cation, exemplifying the problem of carbocation rearrangements that plague alkyl cations and make analysis of mass spectra more difficult.

• PROBLEM 2-14

Show how the molecular weights of acetone, propionaldehyde, and methyl ethyl ketone can be estimated from the mass spectra in the figure below. Suggest a possible origin for the strong peaks of mass 57 in the spectra of methyl ethyl ketone and propionaldehyde, which is in accord with the fact that this peak is essentially absent in acetone, although acetone shows a strong peak at 43.



Solution: The parent peak in a mass spectrum is derived from the molecular ion, M^+. The m/e value of the parent peak indicates the molecular weight of the compound. In the mass spectra shown above, the m/e of the parent peak and hence the molecular weight of the compounds is: (a) 72 (b) 58, (c) 58. Hence spectrum (a) is that of methyl ethyl ketone $\left(CH_3\overset{\overset{O}{\|}}{C}CH_2CH_3\right)$ and spectra (b) and (c) are those of acetone $\left(CH_3\overset{\overset{O}{\|}}{C}CH_3\right)$ and propionaldehyde $\left(CH_3CH_2\overset{\overset{O}{\|}}{C}H\right)$ which have identical molecular weights. Since we know from the problem that propionaldehyde has a strong peak at m/e = 57 and acetone does not, we can conclude that spectrum (b) is that of propionaldehyde and spectrum (c) is that of acetone. The species responsible for the strong peaks at m/e = 57 for methyl ethyl ketone and propionaldehyde and that of m/e = 43 for acetone is an acylium ion $[R-\overset{\oplus}{C}=O]$. The acylium ion is very abundant due to its relative stability. The acylium ion is stabilized by resonance. The two principal resonance structures are:

$$R-\overset{\oplus}{C}=O \longleftrightarrow R-C\equiv\overset{\oplus}{O}$$

Note that resonance structures do not exist as independent molecules; they only serve to approximate what the real molecule looks like, that is, the molecule is actually a hybrid of its resonance structures.

The acylium ion is formed from ketones $\left(R-\overset{O}{\overset{\|}{C}}-R\right)$ by fragmentation occurring at the C-R bond and from aldehydes $\left(R-\overset{O}{\overset{\|}{C}}-H\right)$ at the C-H bond.

The peak at m/e = 57 in spectrum (a) is derived from the species $CH_3CH_2C{\equiv}\overset{\oplus}{O}$. This species was formed by the loss of a methide ion ($CH_3^{\ominus}$) from methyl ethyl ketone. A methide ion is lost in preference to an ethide ion ($\overset{\ominus}{C}H_2CH_3$) because the order of carbanion stabilities is: $CH_3^{\ominus} > 1° > 2° > 3°$.

The peak at m/e = 57 in spectrum (b) is derived from the species $CH_3CH_2C{\equiv}\overset{\oplus}{O}$. This species was formed by the loss of a hydride ion ($H^{\ominus}$) from propionaldehyde.

The peak at m/e = 43 in spectrum (c) is derived from the species $CH_3C{\equiv}\overset{\oplus}{O}$ which is formed by the loss of a methide ion from acetone.

● PROBLEM 2-15

Explain how a mass spectrometer, capable of distinguishing between ions with m/e values differing by 1 part in 50,000, could be used to tell whether an ion of mass 29 is $C_2H_5^{\oplus}$ or $CHO^{\oplus}$.

Solution: The exact mass of the ethyl and formyl cations is not 29. By using the international atomic weights based on the C^{12} isotope, we can calculate the exact mass of both ions as shown:

C^{12} = 12.0000

H = 1.0080

O = 15.9994

MW of $CHO^{\oplus}$ = 12.0000 + 1.0080 + 15.9994 = 29.0074

MW of $C_2H_5^{\oplus}$ = 2(12.0000) + 5(1.0080) = 29.0400

The difference in weights is 0.0326. A mass spectrometer that can distinguish between ions with m/e values differing by one part in 50,000 means one that is able to resolve ions that differ in weight by 1/50,000 or 0.00002. Since $CHO^{\oplus}$ and $C_2H_5^{\oplus}$ differ in weight by more than 0.00002, they can readily be resolved in the mass spectrum.

ELECTRON SPIN RESONANCE

• PROBLEM 2-16

Although all electrons spin, only molecules containing unpaired electrons – only free radicals – give esr spectra. Why is this? (Hint: Consider the possibility (a) that one electron of a pair has its spin reversed, or (b) that both electrons of a pair have their spins reversed.)

Solution: Electron spin resonance (esr) is a phenomenon involving electrons that occurs in a similar fashion as nuclear magnetic resonance. The odd electron of a free radical generates a magnetic moment by spinning; the free radical therefore has a net magnetic moment. Each electron of an electron pair also generates a magnetic moment but of equal and opposite magnitude (because the two electrons have equal and opposite spins); the electron pair therefore has no net magnetic moment. When a free radical is placed in a magnetic field, the magnetic moment generated by the odd electron may be aligned with or against the external magnetic field. When this system is exposed to electromagnetic radiation of the proper frequency, the odd electron absorbs the radiation and reverses its spin; like the proton in nmr, the electron "flips" over in esr. An absorption spectrum is obtained which is called an electron spin resonance (esr) spectrum or an electron paramagnetic resonance (epr) spectrum.

The signals of an esr spectrum may show splitting for the same reason that nmr signals maybe split. The esr signal will be split by n neighboring protons into n + 1 peaks. The protons that are responsible for splitting the signal indicates the distribution of the odd electron in the free radical.

(a) Every electron that resides in an atomic or molecular orbital can be described by a set of four quantum numbers. Quantum numbers are used to depict the relative energies and distribution of electrons. The first quantum number is called the principal quantum number (n); it gives the order of increasing distance of the average electron density from the nucleus. The second quantum number is the orbital quantum number (ℓ); it gives the subshell in which the electron resides and the spatial geometry of the electron distribution. The third quantum number is the magnetic quantum number (m); it describes the circulation of the electric charge which generates a magnetic moment. The fourth quantum number is the spin quantum number (s); it describes the orientation of electron spin and can be either +1/2 or – 1/2.

The Pauli exclusion principle states that no two electrons in the same atom are identical, that is, no two electrons in the same atom have an identical set of quantum numbers. Each electron of an electron pair differs only by their spin orientation; they have identical principal, orbital and magnetic quantum numbers. One electron has a spin quantum number of + 1/2 and the other one of the pair has a spin quantum number of − 1/2. If one electron of a pair has its spin reversed, it would have a set of quantum numbers identical to the other electron. This is a violation of the Pauli exclusion principle and will hence not occur. As a result, no esr spectrum is expected to arise in this manner.

(b) If both electrons of a pair have their spins reversed, there is no net change in the energy because the resulting electron pair is identical to the initial electron pair in all respects. Hence there will be no absorption signals and no esr spectrum.

• PROBLEM 2-17

In each of the following cases, tell what free radical is responsible for the esr spectrum, and show how the observed splitting arises. (a) X-irradiation of methyl iodide at low temperatures: a four-line signal, (b) γ-irradiation at 77°K of propane and of n-butane: symmetrical signals of, respectively, 8 lines and 7 lines. (c) Triphenylmethyl chloride + zinc: a very complex signal.

Solution: (a) A four line signal in the esr spectrum indicates that there are three nearby (adjacent) hydrogens that split the signal. This is deduced from the fact that the esr signal will be split by n adjacent protons into n + 1 peaks. Hence the free radical that gave rise to the esr spectrum has three hydrogens near the odd electron and must be $CH_3\cdot$.

$$CH_3I \xrightarrow[\text{low temp.}]{\text{X-rays}} CH_3\cdot + I\cdot$$

methyl iodide

(b) The eight line esr signal of propane indicates that there are seven neighboring hydrogens about the odd electron. The only way in which a free radical of propane can have this arrangement is if the odd electron is on the middle carbon, an isopropyl radical, $CH_3\dot{C}HCH_3$. The seven neighboring hydrogens split the esr signal into eight peaks.

$$CH_3CH_2CH_3 \xrightarrow[77°K]{\gamma\text{-rays}} CH_3\dot{C}HCH_3 + H\cdot$$

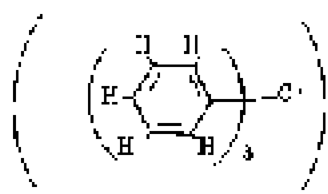
propane

The seven line esr signal of n-butane indicates that there are six neighboring hydrogens about the odd electron. There are two possible free radicals that n-butane can form: $CH_3CH_2CH_2CH_2\cdot$ and $CH_3CH_2\dot{C}HCH_3$. The former has four neighboring hydrogens about the odd electron and will give an esr signal having five lines. The latter has six neighboring hydrogens and will give a seven line esr signal. Hence the free radical is $CH_3CH_2\dot{C}HCH_3$ and is formed as shown:

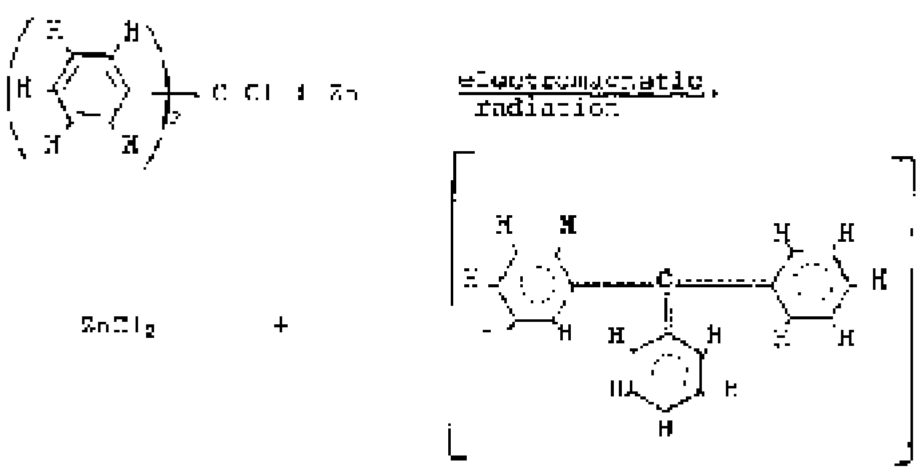
$$\underset{\text{n-butane}}{CH_3CH_2CH_2CH_3} \xrightarrow[77°K]{\gamma\text{-rays}} CH_3CH_2\dot{C}HCH_3 + H\cdot$$

(c) The fact that the esr signal of a mixture of triphenylmethyl chloride and zinc is very complex indicates that there are many neighboring hydrogens about the odd electron. This means that the odd electron is delocalized.

Triphenylmethyl chloride reacts with zinc to produce zinc chloride and a free radical that is stabilized by resonance. This triphenylmethyl radical

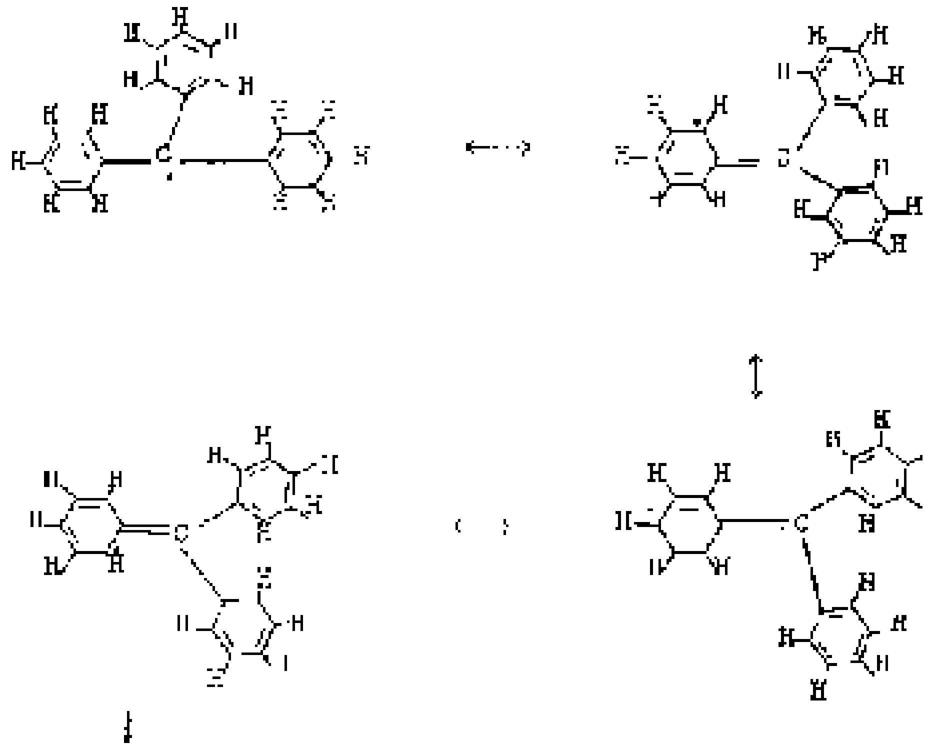


distributes the odd electron about the three phenyl rings. As a result the odd electron is surrounded by many neighboring hydrogens which split the esr signal into a very complex one. The formation of the triphenylmethyl radical and the distribution of the odd electron in the radical is shown below:



triphenylmethyl radical

Triphenylmethyl radical's odd electron distribution is also indicated by:



etc.

Note: the structures above are resonance structures and are indicated by resonance arrows (↔). Resonance structures do not exist independently; they only approximate what the actual species looks like.

CHAPTER 3

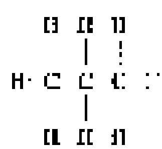
ALKANES

NOMENCLATURE AND STRUCTURE

■ **PROBLEM 3-1**

What is an alkane?

Solution: An alkane is a saturated hydrocarbon with the formula C_nH_{2n+2} where n is the number of carbon atoms. As can be seen from the formula, an alkane consists of only carbon and hydrogen atoms. In a saturated hydrocarbon each carbon atom is bound to four other atoms by sigma bonds. An example of an alkane is propane, a three carbon alkane.



propane

The general formula for an alkane is often written RH. Here R is called an alkyl group; in propane the alkyl group is called a propyl group and is written $CH_3CH_2CH_2\cdot$. Notice that if a hydrogen atom is added to the last carbon, the propyl group becomes propane.

(i)	$CH_3CH_2CH_2\cdot$	+	H	→	$CH_3CH_2CH_3$
	propyl group				propane
(ii)	$R\cdot$	+	H	=	RH
	alkyl group				alkane

● **PROBLEM 3-2**

Name the following alkanes. (a) CH_4

(b) CH_3CH_3 (c) $CH_3\overset{\overset{CH_3}{|}}{CH_2}$ (d) $CH_3CH_2CH_2CH_3$

Solution: Four steps can be followed in naming alkanes.

Step I: In naming open-chain alkanes, first find the longest chain of carbon atoms.

Step II: Write down the parent name.

Step III: Identify any side chains.

Step IV: Number these side chains and add their names and locations as a prefix to the name of the parent compound.

These steps are illustrated in the naming of the four compounds above.

```
        H
        |
(a)   H-C-H
        |
        H
```

This compound contains only one carbon atom and is the simplest of all the alkanes. It is called methane.

```
        H H

(b)   H-C-C-H

        H H
```

This is a two carbon alkane. A chain of two carbon atoms is given the root 'eth'. The parent names of alkanes are formed by adding the suffix 'ane' to the root name of the longest carbon chain. This compound is called ethane.

```
                H

        H     H-C-H
        |
(c)   H-C ----- C-H

        H       H
```

The longest chain in this compound is three carbons long. It is not significant that the chain is bent. The root used in naming three carbon chains is 'prop'. The name of this compound is propane.

```
        H H H H

(d)   H C C C C H

        H H H H
```

The longest chain here is four carbons long. The root used in naming four carbon chains is 'but'. The name of this compound is butane.

• PROBLEM 3-3

Distinguish between primary, secondary and tertiary carbons.

Solution: Carbon atoms are often characterized as being either primary, secondary or tertiary. A primary (1°) carbon is attached to only one other carbon atom. A secondary (2°) carbon is attached to two other carbon atoms and a tertiary (3°) carbon is attached to three other carbons. In the diagram below the carbons are labelled as 1°, 2°, or 3°.

```
                    1°
                    CH3
      1°      2°    3°  2°    1°
    H3C  — H2C  — C  — CH2 — CH3

                    H

      3-methylpentane
```

• PROBLEM 3-4

Name the following compounds:

```
         CH3
(a)  CH3-CH -CH2-CH2-CH -CH3        (b)  CH3-CH2-CH-CH2CH2CH3
                     |                            |
                    CH2CH3                       CH3

           CH2CH2CH3                           CH3    CH3
                                                |      |
(c)  CH3CH2CH-CH2CH2CHCH3           (d)  CH3CH-CH-CH-CH2CH2CH3
                   |
                  CH3                             CH3

           CH3
(e)  CH3CH2C -CH2CH3

           CH3
```

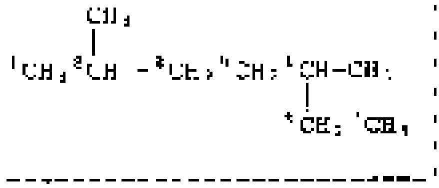
Solution: In brief, the rules for naming organic compounds are as follows:

(a) determine and identify the longest continuous carbon chain

(b) locate and name any side chains

(c) add the names and positions of the side chains as a prefix to the name of the parent compound.

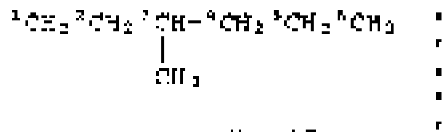
After looking at the structures above, it is seen that all of the compounds are saturated hydrocarbons or alkanes. They all have the formula C_nH_{2n+2} where n is the number of carbon atoms. Another characteristic of alkanes is that the compounds contain only single or sigma bonds.

(a) 

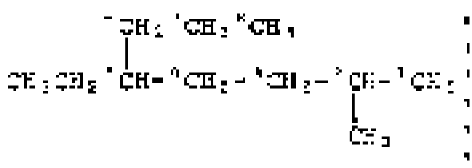
The longest continuous chain contains seven carbons. These carbons have been numbered in the accompanying diagram.

The root of the name of a seven carbon chain is 'hept-'.

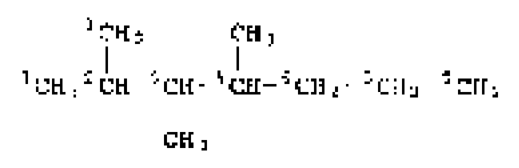
The carbons are numbered from lowest to highest beginning with the end of the chain which contains the side chain of greatest molecular weight closest to the end of the chain. The substituents on this chain are two CH_3- groups placed one at C2 and one at C5. The CH_3- side chain has one carbon and is called methyl. The name of this compound is 2,5-dimethylheptane.

(b) 

As shown in the accompanying figure, the longest carbon chain contains six carbons. The root of the names of compounds containing a six carbon chain is 'hex-'. In this compound there is also a methyl group at C3. The compound is called 3-methylhexane.

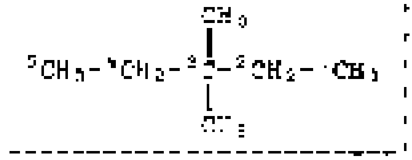
(c) 

As shown, the longest carbon chain contains eight carbons. The root used in naming eight carbon chains is 'oct-'. As the accompanying figure shows, the numbering of the carbons proceeds from the right end of the molecule towards the left. The methyl group here is given precedence over the ethyl group because it is closer to an end of the chain. The two methyl groups attached to C2 are equivalent. The name of this compound is 2-methyl-5-ethyloctane.

(d) 

The longest chain in this compound contains seven carbons. There are methyl groups present at C2, C3, and C4. The compound is named 2,3,4-trimethylheptane.

(e)



The longest chain is five carbons long. There are two methyl groups attached to C3. The root used in naming five carbon chains is "pent-"; thus the name of this compound is 3,3 dimethyl pentane.

• PROBLEM 3-5

Give the structural formula of:

(a) 2,3-dimethylbutane
(b) 2,2 dimethylpropane (neopentane)
(c) 3,4-dimethylheptane
(d) 2,4-dimethyl 4 ethylheptane.

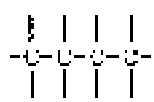
Solution: To derive the structural formula from the name of a compound follow the following steps:

(1) determine the parent compound

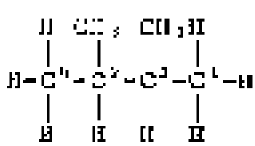
(2) identify and position the side chains.

These steps will be illustrated in the examples below.

(a) 2,3 dimethylbutane. The parent compound here is butane which can be drawn:

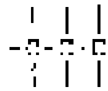


The lines around the carbon atoms indicate bonds to other atoms. This compound contains two methyl groups as indicated by the prefix dimethyl. They are placed at the second and third carbon of the chain. Both ends of the chain are equivalent, therefore the carbons can be numbered from either end. Here they will be numbered from right to left.

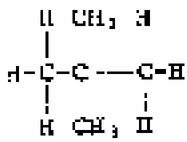


2,3-dimethylbutane

(b) 2,2 dimethylpropane. Here, the same procedure can be followed as was used for part a. The parent compound is propane, which is drawn:

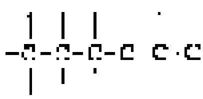


The two methyl groups are placed at the two position.

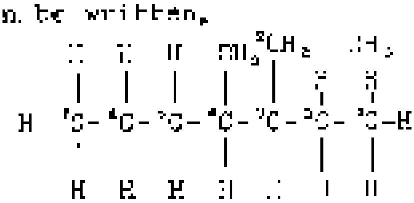


2,2-dimethylpropane

(c) 2-ethyl-3-methylhexane: The parent compound, hexane, is drawn:

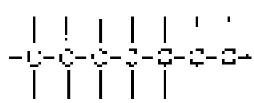


By numbering the carbons from right to left, the required structure can be written.



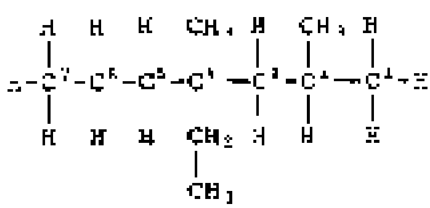
3,4-dimethylheptane

(d) 2,4-dimethyl-4-ethylheptane: The parent structure is heptane.



heptane

After drawing in the side chains, the following structure is obtained.

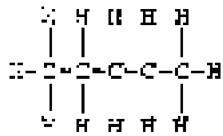


2,4 dimethyl 4 ethylheptane

• PROBLEM 3-6

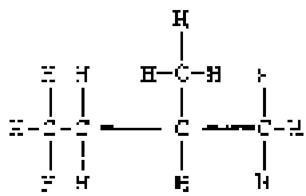
Draw all the isomers of C_7H_{16}.

Solution: A systematic approach for drawing all the structures of a compound is necessary. First, start with the straight chain isomer. Next, draw the possible structures using a straight chain of carbon length one less than the first isomer. Repeating this second step will lead to the formation of all of the isomers. This method will be illustrated using pentane (C_5H_{12}). The straight chain isomer is



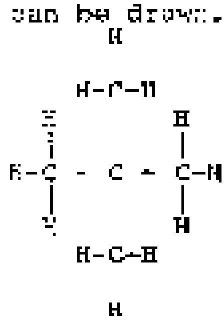
Straight chained isomers are designated by adding the prefix n- to the name of the compound. This isomer is called n-pentane.

The next shortest chain contains four carbons. The fifth carbon appears as a methyl group on C2. There is only this one isomer with a chain length of four.



This structure is called 2 methylbutane.

When the chain is reduced to three carbons, one further isomer can be drawn.



The name of this structure is 2,2-dimethyl propane or neopentane.

When the carbon chain is reduced to two carbons, the isomer 2-methylbutane is produced again. It is exactly the same isomer as the one with 4 carbon atoms in the straight chain.

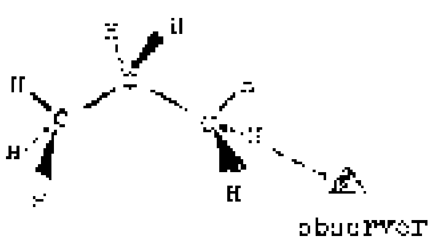
■ **PROBLEM 3-7**

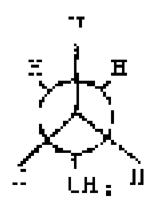
Draw perspective formulas and Newman projections for the eclipsed and staggered forms of propane.

Solution: Propane (C_3H_8) is a member of the paraffins (saturated hydrocarbons). The eclipsed and staggered forms of a molecule are different conformations of that molecule. Conformations of a molecule are structures of that molecule that differ only in the torsional angle of carbon carbon single bonds. Since perspective formulas are three dimensional we can represent them on paper by having a dashed bond represent a projection away from the reader, the heavy wedge bond projecting towards the reader, while a normal bond would represent the plane of the paper.

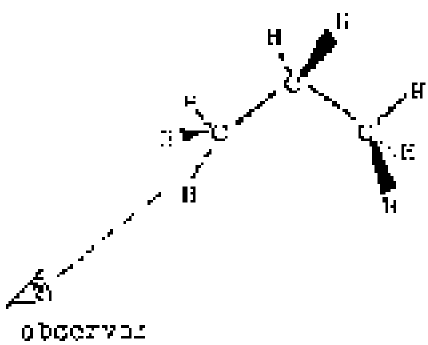
In the eclipsed form of propane there is more steric hindrance than in the staggered form. There is also a greater torsional strain in the eclipsed form. As a result, the eclipsed form is expected to be higher in energy than the staggered form. Therefore the staggered conformation is more stable. The perspective formulas and Newman projections are sketched below:

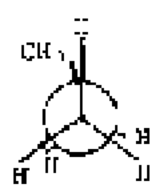
Perspective Formula — Newman Projection





Staggered





Eclipsed

PHYSICAL PROPERTIES

• PROBLEM 3-8

Without referring to a table, place the following hydro carbons in order of increasing boiling points

(a) methane
(b) n hexane
(c) n-undecane
(d) neopentane
(e) 2,3-dimethylbutane

Solution: For a compound to change states, i.e. go from solid to liquid (melt) or liquid to gas (boil), energy must be added to the system. This energy is used to weaken the intermolecular forces holding the molecules together. These intermolecular forces are greater the larger the molecule is. As a general rule, except for very small alkanes, the boiling point rises 20 to 30 degrees for each carbon that is added to the chain. A branched chain isomer has a lower boiling point than a straight chain.

In the group of alkanes given above, the straight chain isomers are methane, n-hexane and n-undecane. There is one carbon in methane, six in n-hexane and eleven in undecane. Since shorter chains have lower boiling points the order of increasing boiling points for these compounds is methane, n-hexane and n-undecane.

The other two compounds that must be considered are neopentane and 2,3-dimethylbutane. The latter compound has six carbons and neopentane or 2,2-dimethylpropane has five, but since 2,3-dimethylbutane is much more branched than neopentane it will have a lower boiling point. These two compounds will fit in between methane and n-hexane in the above order because straight chain compounds generally boil higher than branched compounds and hydrocarbons with greater number of carbons also boil at higher temperatures. The order of increasing boiling points is:

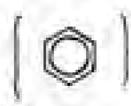
methane < 2,3-dimethylbutane < neopentane < n-hexane < n-undecane.

The actual boiling points of these compounds are shown in the following table.

Compound	Boiling Point (°C)
methane	− 162
2,3-dimethylbutane	− 129
neopentane	− 17
n-hexane	69
n-undecane	196

• PROBLEM 3-9

Isobutane is thermodynamically more stable than butane. Which has the lower boiling point? Is there any relationship between thermodynamic stability and boiling point? Would you expect such a relationship between thermodynamic stability and melting point?

Solution: Thermodynamic stability refers to the intramolecular forces (Van der Waals forces) acting within the molecular structure of a compound. Thus benzene  which has a low ground state energy, is considered to be thermodynamically stable. An enormous amount of energy is required for the degradation of this compound. However, the boiling point is related to the intermolecular forces in a given compound. When the temperature is raised, thus increasing the kinetic energy, the molecular collisions are greatly enhanced and the distance between molecules is widened. The transition from the liquid to the vapor phase occurs and the relatively cohesive liquid is transformed to wandering molecules in the gaseous phase.

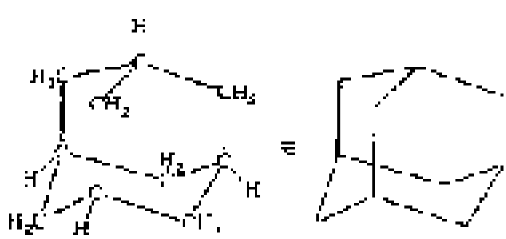
Isobutane $\left[\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ H \end{array}\right]$ is expected to have a

lower boiling point (b.p. = -12°C) than the straight chain isomer (b.p. = 0°C). The boiling points of alkanes rise as the molecules get larger. Branching decreases the boiling point because the shape of the molecule approaches that of a sphere, thus decreasing the surface area. This results in the weakening of the intermolecular forces which are overcome at a lower temperature.

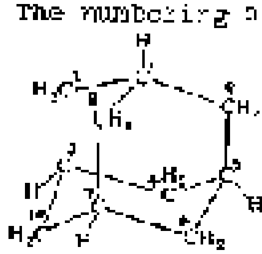
Considering the above descriptions of stability and boiling points, there is absolutely no correlation between the two.

• PROBLEM 3-10

Examine a molecular model of adamantane. Give a rough estimate of its b.p. Would you expect the m.p. to be far below the b.p.? Give another example to illustrate its properties.



Solution: The numbering of adamantane, a tricyclic hydrocarbon is:

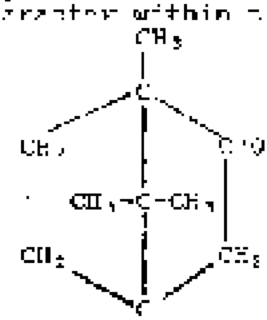


. Its name is

tricyclo[3.3.1.1^{3,7}] decane. The melting point is the temperature at which the substance undergoes a transition from a solid state to a liquid one. The movement of molecules is greatly increased and instead of vibrating about a fixed axis, they can wander without any restriction except for leaving the container in which they are held. The boiling point is defined as the temperature at which the vapor pressure of the compound is equal to external pressure (at S.T.P., 760 mmHg).

Adamantane has a very symmetrical appearance. Crystal lattices are easily formed and therefore a high melting point and low boiling point would be expected. Sublimation is possible when adamantane is heated; it will directly change from the solid state to the gaseous state upon heating. The melting point could be about 250°C while its boiling point could be about 258°C.

Another example of a compound that readily sublimates would be camphor, which also has a high degree of symmetry and spherical character within the structure.



Camphor

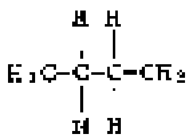
PREPARATION AND REACTIONS

• PROBLEM 3-11

Write equations for the preparation of n-butane from:

(a) n-butyl bromide
(b) sec-butyl bromide
(c) ethyl chloride
(d) 1-butene, $CH_3CH_2CH=CH_2$
(e) 2-butene, $CH_3CH=CHCH_3$

Solution: The structure of n-butane (C_4H_{10}) may be written as:



(a) To prepare n-butane from n-butyl bromide ($CH_3CH_2CH_2CH_2Br$), first take note that both compounds have the same carbon content. This means the reactions to remove the bromide must not alter the carbon skeleton. To replace the bromine atom with a hydrogen atom without altering the carbon skeleton, employ a reaction that results in the reduction of the alkyl halide. Two such reactions are the hydrolysis of a Grignard reagent and the reduction by metal and acid.

When a solution of alkyl halide is placed in dry ethyl ether with metallic magnesium, a vigorous reaction takes place - a Grignard reagent is formed. The Grignard reagent has the general formula RMgX, where R is an alkyl or aryl group and X is a halogen atom. The Grignard reagent is extremely reactive. It reacts with numerous inorganic and organic compounds. If water is added, hydrolysis occurs to produce R-H, a hydrocarbon of the same carbon skeleton. The hydrolysis may be viewed as the reaction of a salt (the Grignard reagent) with an acid (H_2O) to produce a weaker acid (R-H). This reaction which can produce the n-butane desired, is illustrated in the following reaction sequence:

$$\underset{\text{(n-butyl bromide)}}{CH_3CH_2CH_2CH_2Br} \xrightarrow[\text{Ether (Dry)}]{Mg} \underset{\text{(n-butylmagnesium bromide)}}{CH_3CH_2CH_2CH_2MgBr} \xrightarrow{H_2O}$$

$$\underset{\text{(n-butane)}}{CH_3CH_2CH_2CH_3} + Mg(OH)Br$$

Reduction of n-butyl bromide with metal and acid will accomplish the same thing as shown:

$$CH_3CH_2CH_2CH_2Br + Zn + H^+ \rightarrow CH_3CH_2CH_2CH_3 + Zn^{++} + Br^-$$

(b) Sec-butyl bromide may be written as:

$CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3$. Here, again, hydrolysis of Grignard reagent or reduction by metal and acid gives the desired product, n-butane.

$$CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3 \xrightarrow[\text{(Dry)}]{\substack{Mg \\ \text{Ether}}} CH_3CH_2\underset{\underset{MgBr}{|}}{C}HCH_3 \xrightarrow{H_2O} CH_3CH_2CH_2CH_3$$

$$CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3 + Zn + H \rightarrow CH_3CH_2CH_2CH_3 + Zn^{++} + Br$$

(c) Ethyl chloride possesses only a 2 carbon backbone: CH_3CH_2Cl. To produce n-butane, which has four carbons, one must use a reaction that will add two carbons. To manufacture an alkane of higher carbon number than the starting material will require the formation of carbon carbon bonds. This is most directly accomplished by the coupling together of two alkyl groups. An excellent method of doing this was developed by Corey and House. It is the coupling of alkyl halides with organometallic compounds. Coupling takes place between a lithium dialkylcopper, R_2CuLi, and an alkyl halide, R'X (R' may be different or the same as R). The general reaction may be illustrated as shown:

$$R_2CuLi + R'X \rightarrow \underset{\text{(Alkane)}}{R-R'} + RCu + LiX$$

The lithium dialkylcopper is prepared by adding lithium to the alkyl halide which may be primary, secondary or tertiary. After this, one adds cuprous halide, CuX. Overall,

$$RX \xrightarrow{Li} \underset{\text{(Alkyl lithium)}}{RLi} \xrightarrow{CuX} \underset{\text{(Lithium dialkylcopper)}}{R_2CuLi}$$

The alkyl halide (R'X) which will be added to R_2CuLi (to produce R-R') should be primary to obtain good yields. The reaction sequence that generates n-butane from ethyl chloride can now be written:

$$CH_3CH_2Cl \xrightarrow{Li} CH_3CH_2Li \xrightarrow{CuX} (CH_3CH_2)_2CuLi$$

$$(CH_3CH_2)_2CuLi + CH_3CH_2Cl \rightarrow CH_3CH_2CH_2CH_3 + CH_3CH_2Cu + LiCl$$

(d) and (e) Alkenes (compounds with double bonds) such as 1-butene and 2-butene can be readily converted to the corresponding alkane with a hydrogenation reaction. In this reaction, hydrogen gas is passed over the alkene in the presence of Pt, Pd, or Ni, which act as catalysts. The hydrogen adds across the double bond to produce an alkane of the same carbon number. Hydrogenation of 1-butene and 2-butene directly produces the desired product as shown:

$$\underset{\text{(1-butene)}}{CH_3CH_2CH{=}CH_2} + H_2 \xrightarrow{Pt,\ Pd\ or\ Ni} CH_3CH_2CH_2CH_3$$

$$CH_3CH{=}CHCH_3 + H_2 \xrightarrow{Pt,\ Pd\ or\ Ni} CH_3CH_2CH_2CH_3$$

• PROBLEM 3-12

On the basis of certain evidence, including its infrared spectrum, an unknown compound of formula $C_{10}H_{22}$ is suspected of being 2,7-dimethyloctane. How could you confirm or disprove this tentatively assigned structure?

Solution: It is possible to obtain a pure sample of 2,7-dimethyloctane by synthesizing it using the Corey-House method. If the compound's infrared spectrum coincides with the IR of the suspected 2,7-dimethyloctane, and if the other properties are similar to the compound in doubt we could ascertain the nature of $C_{10}H_{22}$.

An interesting feature about the structure of 2,7-dimethyloctane

$$\left[CH_3\underset{}{\overset{CH_3}{\overset{|}{C}}}HCH_2CH_2-CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3 \right]$$

is that it is symmetrical; it is composed of two identical alkyl groups

$$\left\{ -CH_2CH_2\overset{CH_3}{\overset{|}{C}}HCH_3 \right\}$$

This characteristic, along with the knowledge that alkyl halides could be coupled with organometallic compounds to form hydrocarbons, makes it possible to synthesize 2-7, dimethyloctane by starting with isopentylbromide

$$\left[Br-CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_3 \right].$$

The mechanism for coupling with these organometallic compounds could be illustrated as follows. First an organolithium (RLi) compound is prepared from the alkyl halide. In this case the alkyl halide is isopentylbromide.

$$CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2CH_2Br + Li \rightarrow CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2CH_2Li$$

isopentyl lithium

If cuprous halide (e.g. CuX) is added to isopentyl lithium, cuprous lithium diisopentane is formed. On addition of isopentyl bromide (since isopentyl bromide is a primary halide the yield of the reaction would be high. The alkyl group in the organometallic group could be either primary, secondary or tertiary without affecting the yield), the alkyl group (isopentyl) is transferred from copper. The alkyl group leaves with two electrons and attaches itself to the other alkyl halide by displacing the halide ion (bromide) by nucleophilic aliphatic substitution.

$$\left(CH_3\underset{}{\overset{CH_3}{\overset{|}{C}}}HCH_2CH_2CH_2 \right)_2 CuLi + CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2CH_2Br \rightarrow$$

$$CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2 \quad CH_2CH_2\underset{CH_3}{\underset{|}{C}}HCH_3$$

■ **PROBLEM** 3-13

A chemist was asked to determine the identity of a clear liquid. He sniffed it and found that it smelled like lighter fluid. He performed a quantitative analysis and calculated that the liquid was 83.3% carbon and 16.7% hydrogen. He decided that the compound was n-pentane. Was it? Assume that this chemist was working during the summer and that his lab was 29°C.

Solution: The molecular formula for n-pentane is $CH_3CH_2CH_2CH_2CH_3$, or C_5H_{12}. Since there is no common denominator except the number one for 5 and 12, the empirical formula for n-pentane is also C_5H_{12}. The empirical formula can be derived from the weight percentages of carbon and hydrogen.

Assume that 100 g of the liquid is available. By using the weight percentages it is seen that there is 83.3 g. carbon and 16.7 g. hydrogen. In each mole of n-pentane there exists 5 moles of carbon and 12 moles of hydrogen. If this liquid is n-pentane the ratio of the number of moles of carbon to the number of moles of hydrogen must be 5 : 12 or .417:1. To determine this ratio from the data given, calculate the number of moles of carbon in 83.3 g. and the number of moles of hydrogen in 16.7 g. (MW of C = 12, MW of H = 1).

$$\text{no. of moles} = \frac{\text{mass}}{\text{MW}}$$

$$\text{no. of moles of C} = \frac{83.3\text{ g}}{12\text{ g/mole}} = 6.94\text{ moles}$$

$$\text{no. of moles of H} = \frac{16.7\text{ g}}{1\text{ g/mole}} = 16.7\text{ moles}$$

The ratio of C:H is

$$\frac{\text{moles of C}}{\text{moles of H}} = \frac{6.94}{16.7} = .416 : 1,$$

which proves that the formula for the compound is C_5H_{12}. There are compounds which have the formula C_5H_{12} other than n-pentane but these branched isomers have boiling points lower than 25°C and will be gases at this temperature.

COMBUSTION AND BOND DISSOCIATION ENERGY

• PROBLEM 3-11

Kilogram for kilogram, would the combustion of gaseous methane or of liquid n-decane (to liquid water) give more heat? Refer to the table below.

Bond Energies (kcal/mole at 25°C)

Diatomic Molecules

H-H	104.2	F-F	36.6	H-F	134.6
O=O	119.1	Cl-Cl	58.0	H-Cl	103.2
N≡N	225.8	Br-Br	46.1	H-Br	87.5
C≡O[b]	255.8	I-I	36.1	H-I	71.4

Polyatomic Molecules

C-H	98.7	C-C	82.6	C-F	116
N-H	93.4	C=C	145.8	C-Cl	81
O-H	110.6	C≡C	199.6	C-Br	68
S-H	83	C-N	72.8	C-I	51
P-H	76	C=N	147	C-S	65
N-N	39	C≡N	212.6	C=S[c]	128
N=N	100	C-O	85.5	N-F	65
O-O	[illegible]	C=O[d]	192.0	N-Cl	46
S-S	54	C=O[e]	166	O-F	45
N-O	53	C=O[f]	176	O-Cl	52
N=O	14[illegible]	C=O[g]	179	O-Br	48

[b]Carbon monoxide.
[c]For carbon disulfide.
[d]For carbon dioxide.
[e]For formaldehyde.
[f]Other aldehydes.
[g]Ketones.

Solution: This problem calls for the determination of the heat of combustion of gaseous methane and liquid n decane, given the various bond energies. First we must sketch the balanced equation of the combustion of the two hydrocarbons in the presence of oxygen.

$$CH_4(g) + 2\,O_2(g) \rightarrow CO_2(g) + 2\,H_2O\,(l)$$

Note that carbon dioxide and water are the only products of combustion.

ΔH for methane could be calculated by 4(98.7), the energy for the C-H bonds.

bonds broken - endothermic and ΔH>0

$$H{:}\overset{H}{\underset{H}{C}}{:}H \rightarrow \cdot\dot{\underset{\cdot}{C}}\cdot + 4H\cdot \quad \Delta H = 4 \times 98.7 = 394.8 \text{ kcal.}$$

Energy of double bond in O_2 = 119.1 kcal

$$2{:}\ddot{O}{::}\ddot{O}{:} \rightarrow 4{:}\ddot{O}{:} \qquad \Delta H = 2 \times 119.1 \text{ kcal} = 238.2 \text{ kcal}$$

bonds formed exothermic and ΔH<0

2[C=O] bonds in carbon dioxide = (192 × 2) kcal = − 384.0 kcal

Each of the O-H bonds in water = − 110.6 kcal

Since 4 O-H bonds are present in 2 molecules of water ΔH=4 × 110.6 kcal = − 442.4

$$\Sigma\Delta H = 394.8 + 238.2 - 384.0 - 442.4 = -193.4 \text{ kcal}$$

The heat of vaporization for water is represented by

H_2O (g) → H_2O (l)

$\Delta H = - 10.4.$

Since 2 molecules of water are present $\Delta H_v = 2 \times - 10.4 = - 20.8$ kcal.

1000 g constitute 1 kilogram. M.W. of methane = 16;

no. of moles = $\frac{1000 \text{ g}}{16 \text{ g/mole}}$ = 62.5 moles

Total $\Delta H = - 193.4 - 20.8 = - 214.2$ kcal/mole.

Heat evolved by 1000 g methane

= 62.5 moles × 214.2 = 13,400kcal

In order to determine the heat evolved from n-decane we will follow a similar procedure as above. The balanced equation for the combustion of n-decane is:

$$C_{10}H_{22} + \frac{31}{2} O_2 \rightarrow 10\ CO_2 + 11\ H_2O$$

$C_{10}H_{22}$ has 9 C-C bonds and 22 C-H bonds broken.

$\Delta H = 9 \times 82.6 + 22 \times 98.7 = 2914.8.$

$$\Delta H_{O_2} = \frac{31}{2}\ (119.1) = 1846.05$$

$$\Delta H_{CO_2} = 10\ (2 \times - 192.0) = - 3840.0$$

$$\Delta H_{H_2O} = 11 \times 2\ (- 110.6) = - 2433.2$$

$$\Delta H_{vap.} = 11\ (- 10.4) = - 114.4$$

$$\Sigma\Delta H = 2914.8 + 1846.05 - 3840.0 - 2433.2 - 114.4$$

$$= - 1630.0 \text{ kcal/mole.}$$

no. of moles of n-decane = $\frac{1 \text{ kg} \times 1000 \text{ g/kg}}{\text{M.W.} = 142}$

Amount of heat evolved = $\frac{1000}{42}$ moles × − 1630 kcal/mole

= − 11500 kcal.

Thus methane yields about 14% more heat than n-decane per mole.

5.82 g of a compound was burned in the presence of oxygen. The products were 17.1 g of carbon dioxide and 10.5 g of water. Calculate the empirical formulas for this compound. What is its name? Find the percent yield of this reaction.

Solution: A compound whose sole products of combustion are carbon dioxide and water must be a hydrocarbon. Hydrocarbons consist of only carbon and hydrogen atoms; alkanes, alkenes and alkynes fall into this category.

The general equation for the combustion of a hydrocarbon could be represented by

$$C_nH_x + \left(n + \frac{x}{4}\right) O_2 \xrightarrow{\Delta} nCO_2 + \frac{x}{2} H_2O.$$

Notice that this reaction is balanced. Identical amounts of atoms of the various constituents are present in both the products and reactants.

The empirical formula of the hydrocarbon C_nH_x can be calculated as follows:

$$C_n H_x + \left[n + \frac{x}{4}\right] O_2 \xrightarrow{\Delta} nCO_2 + \frac{x}{2} H_2O.$$

17.1 g of CO_2 is produced:

no. of moles of $CO_2 = \frac{17.1}{44} = .388$ moles

10.5 g of H_2O is produced:

no. of moles of water produced $= \frac{10.5}{18} = .5833.$

Next, we determine the ratio of water to carbon dioxide:

$$\frac{\text{moles } H_2O}{\text{moles } CO_2} = \frac{\frac{x}{2}}{n} = \frac{.5833}{.388} = \frac{3}{2}$$

Hence, $\frac{x}{2} = 3$, or $x = 6$ and $n = 2$.

So the empirical formula of the hydrocarbon = C_2H_6.

The general form of C_2H_6 could be written as C_nH_{2n+2}. Therefore, it comes under the class of alkanes (saturated hydrocarbons). Since there are two carbon atoms, its name is

ethane $\left[\text{structure is } \begin{array}{c} H\ H \\ H-C-C-H \\ H\ H \end{array}\right].$

To determine the % yield we must first calculate how much ethane is required to produce the amounts of CO_2 and H_2O.

$$C_2H_6 + \frac{7}{2} O_2 \xrightarrow{\Delta} 2\ CO_2 + 3\ H_2O.$$

This is the balanced equation for the combustion of ethane.

$$\text{No. of moles of } CO_2 \text{ produced} = \frac{17.1}{44} = .388 \text{ moles.}$$

Since 2 moles of CO_2 are evolved from 1 mole of ethane, the amount of ethane needed for .388 moles of CO_2 = .388/2 = .194 moles.

$$\text{Wt. of ethane reacting} = .194 \times (MW_{ethane})$$

$$= .194 \times 30 = 5.82$$

$$\text{Hence, the \% yield} = \frac{\text{Reacted ethane} \times 100\ \%}{\text{Initial amount of ethane}}$$

$$= \frac{5.82}{5.82} \times 100\ \% = 100\%$$

• PROBLEM 3-10

(a) If a rocket were fueled with kerosine and liquid oxygen, what weight of oxygen would be required for every liter of kerosine? (Assume kerosine to have the average composition of $n\text{-}C_{14}H_{30}$ and a density of 0.764 g/ml). (b) How much energy would be required to fragment the molecules in one liter of kerosine? (Assume 157 kcal mole for each $-CH_2-$ group and 186 kcal mole for each $-CH_3-$ group.)

Solution: To answer this problem we must first determine the balanced equation for the combustion of kerosine in the presence of oxygen. Since any hydrocarbon on combustion produces carbon dioxide and water, the skeleton equation could be written as $n\text{-}C_{14}H_{30} + O_2 \rightarrow CO_2 + H_2O$. To balance this equation we could balance each type of atom separately. 14 atoms of carbon are present in kerosine, therefore there must be 14 molecules of CO_2 evolved for each molecule of kerosine; 30 molecules of hydrogen present in kerosine contribute to 15 molecules of water. Therefore the balanced equation could be represented by:

$$n\text{-}C_{14}H_{30} + \frac{43}{2} O_2 \rightarrow 14\ CO_2 + 15\ H_2O.$$

Since the density of kerosine (0.764 g/ml) is given, the weight of 1 liter of kerosine is:

$$\text{vol.} \times \text{density} = 1\ \ell \times \frac{1000\ \text{ml}}{1\ \ell} \times \frac{0.764\ \text{g}}{\text{ml}} = 764\ \text{g}.$$

$$\text{no. of moles of kerosine: } \frac{\text{weight}}{\text{M.W.}} = \frac{764\ \text{g}}{198\ \text{g/mole}}$$

From the balanced equation we can accurately predict that one mole of kerosine requires 43/2 moles of oxygen for total combustion.

Hence $\frac{764}{198}$ moles need $\frac{764}{198} \times \frac{43}{2}$ moles = 83.0 moles of oxygen required.

Weight of oxygen: 83.0 moles × 32 g/mole = 2,660 g.

(b) When each $-CH_2-$ and CH_3- group disintegrates to form the products of combustion, the former requires 157 kcal/mole, whereas CH_3- requires 186 kcal/mole. The structural formula for kerosine ($C_{14}H_{30}$) is $CH_3-(CH_2)_{12}-CH_3$.

The total amount of heat required per mole is

$$(157\ \text{kcal/mole} \times 12) + (186\ \text{kcal/mole} \times 2) = 2{,}256\ \text{kcal/mole}$$

$$\text{One liter of kerosine} = \frac{764}{198}\ \text{moles}$$

$$\text{Total energy per liter kerosine} = \frac{764}{198} \times 2{,}256 = 8710\ \text{kcal.}$$

• PROBLEM 3-47

Suppose we assume the following bond energies (kcal):

≡C–H	110.7	C≡C	173.6
=C–H	102.7	C=C	173.8
$-\overset{\vert}{\underset{\vert}{C}}-H$	98.7	C–C	82.6

What corresponding values would we have to assign to C–Br bonds if the ΔH values calculated for the reactions HC≡CH + Br_2 → BrHC=CHBr and BrHC=CHBr + Br_2 → $CHBr_2CHBr_2$ are to be exactly the same as those calculated using just the bond energies from the table given?

Bond Energies (kcal/mole at 25°C)

Diatomic Molecules

H–H	104.2	F–F	36.6	H–F	134.6
O=O	119.1	Cl–Cl	58.0	H–Cl	103.2
N≡N	225.8	Br–Br	46.1	H–Br	87.5
C≡O	255.8	I–I	36.1	H–I	71.4

Polyatomic Molecules

C-H	98.7	C-C	82.6	C-F	116
N-H	93.4	C=C	145.8	C-Cl	81
O-H	110.6	C≡C	199.6	C-Br	68
S-H	83	C-N	72.8	C-I	51
P-H	76	C=N	147	C-S	65
N-N	39	C≡N	212.6	C=S[c]	128
N=N	100	C-O	85.5	N-F	65
O-O	35	C=O[d]	192.0	N-Cl	46
S-S	54	C=O[e]	166	O-F	45
N-O	53	C=O[f]	176	O-Cl	52
N=O	145	C=O[g]	179	O-Br	48

[b]Carbon monoxide.
[c]For carbon disulfide.
[d]For carbon dioxide.
[e]For formaldehyde.
[f]Other aldehydes.
[g]Ketones.

Solution: In order to evaluate the values for the bond energies of $-C-Br$ and $=C-Br$ we must first determine the ΔH values using the table of the Bond Energies:

First equation: $HC \equiv CH + Br_2 \rightarrow BrHC=CHBr$.

$$\Delta H = -[199.6 + 2(98.7) + 46.1] - [145.8 + 2(98.7) + 2(68)]$$

$$= -281.8 + 245.7 = -36.1 \text{ kcal/mole.}$$

Due to further bromination:

$BrHC=CHBr + Br_2 \rightarrow Br_2HC-CHBr_2$.

$$\Sigma H = 145.8 + 2(98.7) + 2(68) + 46.1 - [82.6 + 2(98.7) + 4(68)]$$

$$= -26.7 \text{ kcal/mole.}$$

If we now use the assumed bond energies and allow $=C-Br$ to be x and $-C-Br$ to be y:

$H-C \equiv C-H + Br_2 \rightarrow BrHC=HBr$.

$$\Sigma\Delta H = 175.6 + 2(111.7) + 46.1 - [128.8 + 2(102.7) - 2x]$$

$$= 443.1 - 334.2 - 2x = -36.1$$

$$-2x = -143 \therefore x = 71.5 \approx 72 \text{ kcal/mole.}$$

$BrHC=HBr + Br_2 \rightarrow Br_2HC-CHBr_2$.

$$\Sigma\Delta H = 129.8 + 2(102.7) + (71.5)2 + 46.1 - [82.6 + 2(98.7) + 4y] = -72.8$$

$$524.3 - 280 - 4y = -26.7$$

$$y = \frac{-26.7 - 244.3}{-4} \approx 68 \text{ kcal.}$$

• PROBLEM 3-16

Calculate ΔH (bond dissociation energy) for the following reactions:

(a) $t\text{-}C_4H_{10} + Br_2 \rightarrow t\text{-}C_4H_9Br + HBr$

(b) $CH_4 + I_2 \rightarrow CH_3I + HI$

(c) $C_6H_6 + Cl_2 \rightarrow C_6H_5Cl + HCl$

(d) $H\text{-}C_2H_6 + CH_4 \rightarrow 2\ C_2H_6$

Table 1 Bond Dissociation Energies, Kcal/Mole

$A{:}B \longrightarrow A\cdot + \cdot B$ ΔH = Bond Dissociation Energy or $D(A\text{-}B)$

H—H	104			CH_3—H	104		
H—F	136	F—F	38	CH_3—F	108		
H—Cl	103	Cl—Cl	58	CH_3—Cl	84		
H—Br	88	Br—Br	46	CH_3—Br	70		
H—I	71	I—I	36	CH_3—I	56		
CH_3—H	104	CH_3—CH_3	88	CH_3—Cl	84	CH_3—Br	70
C_2H_5—H	98	C_2H_5—CH_3	85	C_2H_5—Cl	81	C_2H_5—Br	69
n-C_3H_7—H	98	n-C_3H_7—CH_3	85	n-C_3H_7—Cl	82	n-C_3H_7—Br	69
i-C_3H_7—H	95	i-C_3H_7—CH_3	84	i-C_3H_7—Cl	81	i-C_3H_7—Br	68
t-C_4H_9—H	91	t-C_4H_9—CH_3	80	t-C_4H_9—Cl	79	t-C_4H_9—Br	63
H_2C=CH—H	104	H_2C=CH—CH_3	92	H_2C=CH—Cl	84		
H_2C=$CHCH_2$—H	88	H_2C=$CHCH_2$—CH_3	72	H_2C=$CHCH_2$—Cl	60	H_2C=$CHCH_2$—Br	47
C_6H_5—H	112	C_6H_5—CH_3	93	C_6H_5—Cl	86	C_6H_5—Br	72
$C_6H_5CH_2$—H	85	$C_6H_5CH_2$—CH_3	70	$C_6H_5CH_2$—Cl	68	$C_6H_5CH_2$—Br	51

Solution: The amount of energy consumed or liberated when a bond is broken or formed is called the bond dissociation energy, D. The ΔH for a reaction can be determined by subtracting the bond dissociation energies of the products from those of the reactants. The ΔH values for various compounds are given in the accompanying table.

(a) $t\text{-}C_4H_{10} + Br_2 \rightarrow t\text{-}C_4H_9Br + HBr$

This reaction can be rewritten to show the bonds that are being broken and those being formed.

$$t\text{-}C_4H_9\text{-}H + Br\text{-}Br \rightarrow t\text{-}C_4H_9\text{-}Br + H\text{-}Br$$

The hyphens indicate the bonds involved in the reactions. ΔH for this reaction is found by using the following equation:

$$\Delta H = \left[\Delta H_{t\text{-}C_4H_9\text{-}H} + \Delta H_{Br\text{-}Br}\right] - \left[\Delta H_{t\text{-}C_4H_9\text{-}Br} + \Delta H_{H\text{-}Br}\right]$$

Using the values from the table:

$$\Delta H = (91 \text{ kcal/mole} + 46 \text{ kcal/mole}) - (55 \text{ kcal/mole} + 96 \text{ kcal/mole})$$

$$= 137 \text{ kcal/mole} - 151 \text{ kcal/mole} = -14 \text{ kcal/mole}$$

(b) $CH_4 + I_2 \rightarrow CH_3I + HI$

Rewriting the reaction to show the bonds involved:

$$CH_3-H + I-I \rightarrow CH_3-I + H-I$$

Solving for ΔH:

$$\Delta H = \left(\Delta H_{CH_3-H} + \Delta H_{I-I}\right) - \left(\Delta H_{CH_3-I} + \Delta H_{H-I}\right)$$

$$= (104 \text{ kcal/mole} + 36 \text{ kcal/mole}) - (56 \text{ kcal/mole} + 71 \text{ kcal/mole})$$

$$= 140 \text{ kcal/mole} - 127 \text{ kcal/mole} = 13 \text{ kcal/mole}$$

(c) $C_6H_6 + Cl_2 \rightarrow C_6H_5Cl + HCl$

Rewriting the equation to show the bonds:

$$C_6H_5-H + Cl-Cl \rightarrow C_6H_5-Cl + H-Cl$$

Solving for ΔH:

$$\Delta H = \left(\Delta H_{C_6H_5-H} + \Delta H_{Cl-Cl}\right) - \left(\Delta H_{C_6H_5-Cl} + \Delta H_{H-Cl}\right)$$

$$= (112 \text{ kcal/mole} + 58 \text{ kcal/mole}) - (86 \text{ kcal/mole} + 103 \text{ kcal/mole})$$

$$= 170 \text{ kcal/mole} - 189 \text{ kcal/mole} = -19 \text{ kcal/mole}$$

(d) $n\text{-}C_3H_8 + CH_4 \rightarrow 2\, C_2H_6$

Rewriting this equation to show the bonds:

$$n\text{-}C_2H_5-CH_3 + CH_3-H \rightarrow C_2H_5-H + CH_3-CH_3$$

Solving for ΔH:

$$\Delta H = \left(\Delta H_{n\text{-}C_2H_5-CH_3} + \Delta H_{CH_3-H}\right) - \left(\Delta H_{C_2H_5-H} + \Delta H_{CH_3-CH_3}\right)$$

$$= (85 \text{ kcal/mole} + 104 \text{ kcal/mole}) - (98 \text{ kcal/mole} + 88 \text{ kcal/mole})$$

$$= 189 \text{ kcal/mole} - 186 \text{ kcal/mole} = 3 \text{ kcal/mole}$$

HALOGENATION

• PROBLEM 3-15

Why would the bromination of ethane to ethyl bromide be a more efficient synthesis than the bromination of hexane to 1-bromohexane?

Solution: There is only one possible monobrominated product formed from ethane, that is, ethyl bromide. This is true because the two carbons making up the ethane molecule are equivalent and the bromine radical will attack either one with equal frequency. This makes the synthesis of ethyl bromide from ethane an extremely efficient process.

This is not true of the production of 1-bromohexane from hexane. The six carbon atoms comprising hexane are not equivalent and will not be attacked by the bromine radical with equal frequency. In hexane there are two sets of equivalent carbons. One set is composed of the two carbons on the ends of the chain. These carbons are referred to as primary carbons because they are bound to only one other carbon atom. The four carbons in the center of the chain comprise the other set. These carbons are referred to as secondary carbons because they are each bound to two other carbon atoms. Secondary carbons are more reactive than primary carbons and will bind the bromine radical more readily. This will cause the production of more 2 and 3 bromohexane than 1-bromohexane. As a synthesis for 1-bromohexane, monobromination of hexane is a rather inefficient procedure.

• PROBLEM 3-20

A possible mechanism for the reaction of chlorine with methane would be to have collisions where a chlorine molecule removes a hydrogen according to the following scheme:

$$CH_3{:}H + {:}\ddot{\underset{..}{Cl}}{:}\ddot{\underset{..}{Cl}}{:} \xrightarrow{\text{slow}} CH_3\cdot + H{:}\ddot{\underset{..}{Cl}}{:} + {:}\ddot{\underset{..}{Cl}}\cdot$$

$$CH_3\cdot + {:}\ddot{\underset{..}{Cl}}\cdot \xrightarrow{\text{fast}} CH_3{:}\ddot{\underset{..}{Cl}}{:}$$

Use appropriate bond energies to assess the likelihood of this reaction mechanism. What about the possibility of a similar mechanism with elemental fluorine and methane?

Solution: Refer to the table on bond energies of various molecules in a previous problem. Given the bond energies we can determine whether the reaction requires energy or whether it liberates energy to the surroundings. This quantity of energy is known as the change in enthalpy (ΔH) of the reaction. When $\Delta H > 0$, external energy is required for the reaction to proceed, whereas if $\Delta H < 0$, then the reaction occurs spontaneously. Since in this problem external energy is not provided, the reaction will not proceed unless $\Delta H < 0$.

$$CH_3{:}H + {:}\ddot{\underset{..}{Cl}}{:}\ddot{\underset{..}{Cl}}{:} \xrightarrow{\text{slow}} CH_3\cdot + H{:}\ddot{\underset{..}{Cl}}{:} + {:}\ddot{\underset{..}{Cl}}\cdot$$

From the table of bond energies, C-H = 98.7 kcal/mole, Cl-Cl = 58.0, and H-Cl = 103.2.

$\Sigma\Delta H = + 98.7 - 58.0 - 103.2 = 53.5$ kcal.

Since $\Delta H = + 53.5$ is very high, it is improbable that this reaction will proceed in the direction indicated in the equation.

The equation for fluorine and methane would be given by:

$$CH_3{:}H + {:}\ddot{\underset{..}{F}}{:}\ddot{\underset{..}{F}}{:} \rightarrow CH_3\cdot + H{:}\ddot{\underset{..}{F}}{:} + {:}\ddot{\underset{..}{F}}\cdot$$

F-F = 36.6, C-F = 116, H-F=134.6.

Hence, $\Sigma\Delta H = 98.7 - 36.6 - 134.6 = - 0.7$ kcal.

It is possible for this reaction to take place because $\Delta H < 0$; but in order to determine whether fluoro-methane is the end product or not we have to calculate ΔH for the second step.

$$CH_3\cdot + \cdot\ddot{\underset{..}{F}}{:} \rightarrow CH_3{:}\ddot{\underset{..}{F}}{:}$$

$\Sigma\Delta H = (98.7)3 + 0 - [3(98.7) - 116] = - 116$ kcal.

$\Delta H = - 116 < 0$ implies that the second step occurs with ease. Therefore the reaction that produces fluoro-methane is more probable than that which produces chloro-methane.

• PROBLEM 3-21

Suggest a reason for the fact that ultraviolet light causes Cl_2 (gas) to cleave homolytically, to produce two chlorine radicals, rather than heterolytically, to produce Cl^- and Cl^+.

Solution: The fragmentation of molecules is associated with the consumption of energy; however, when the converse occurs, i.e. when atoms combine, energy is liberated. The quantity of energy involved during the breakage or formation of bonds is known as the bond dissociation energy.

Let us consider a molecule A:B. The fragmentation of the A-B bond could be presented by:

$$A : B \rightarrow A\cdot + B\cdot$$

or

$$A : B \rightarrow A + {:}B$$

In the first case the two atoms break and leave with an equal share of electrons (one each). This is known as homolytic cleavage whereas in the latter reaction, both the electrons are deposited with one atom making that atom more electronegative than the other. The second type of fragmentation could also be viewed in terms of the production of ions, i.e. A^+ and B^-.

Recall that like charges repel and unlike charges attract. Since the two ions are opposite in charge they will tend to attract each other and the energy required to overcome this powerful electrostatic attractive force is in the order of about 100 kcal/mole. The fragments of homolysis on the other hand, are neutral in charge and therefore a molecule will need less dissociation energy in this type of reaction.

Since chlorine is in the gaseous state, cleavage occurs more easily by homolysis.

• PROBLEM 3-22

Predict the proportions of isomeric products from chlorination at room temperature of: (a) propane; (b) isobutane; (c) 2,3-dimethylbutane; (d) n-pentane (Note: There are three isomeric products); (e) isopentane.

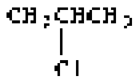
Solution: The answer to this problem involves a consideration of orientation, the factors that determine where in a molecule reaction is most likely to occur. Orientation is determined by the relative rates of competing reactions.

Suppose one compared the rate of abstraction of primary hydrogens with the rate of abstraction of secondary hydrogens. What are the factors that determine the rates of these two reactions?

(1) Collision frequency. Since both reactions involve collision of the same particles, a specific alkane and a halogen, this must be the same for the two reactions. (2) Probability factor. If a primary hydrogen is to be abstracted, the alkane must be so oriented at the time of collision that the halogen atom strikes a primary hydrogen. Likewise, if a secondary hydrogen is to be abstracted, the alkane must be so oriented that the halogen atom strikes a secondary hydrogen. Now, if the alkane has, say, six primary hydrogens and only two secondary hydrogens, it could be estimated that the probability factor favors abstraction of primary hydrogens by the ratio of 6:2, or 3:1. (3) Energy of activation (E_{act}) is more for abstraction of a primary hydrogen than for abstraction of a secondary hydrogen. In fact, the E_{act} is greater for abstraction of a secondary hydrogen than for abstraction of a tertiary hydrogen. Hence, abstraction of hydrogens is found to follow the sequence 3°>2°>1° in reactivity. In chlorination at room temperature, the relative rates per hydrogen atom are 5.0:3.8:1.0.

With this information, the proportions of isomeric products from chlorination can be predicted.

(a) Propane's isomeric products (from chlorination):



$CH_3CH_2CH_2Cl$

(iso-propyl chloride) (n-propyl chloride)

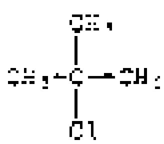
To figure out the relative amounts of these products, remember that the probability and reactivity (E_{act}) of the hydrogens must be examined. In n-propyl chloride, the chlorine halogen abstracted a primary hydrogen (1°H) of relative rate 1, whereas in iso propyl chloride the halogen abstracted a secondary hydrogen (2°H) of relative rate 3.8. The calculation of isomeric proportion is as follows:

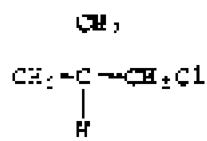
$$\frac{n\text{-PrCl}}{i\text{-PrCl}} = \frac{\text{no. of } 1°\text{ H}}{\text{no. of } 2°\text{ H}} \times \frac{\text{reactivity of } 1°\text{ H}}{\text{reactivity of } 2°\text{ H}}$$

$$= \frac{6}{2} \times \frac{1.0}{3.8} = \frac{6.0}{7.6},$$ hence, the percentage of 1° isomeric product (that is, n-propyl chloride) is equal

to $\frac{6.0}{6.0 + 7.6} \times 100 = 44\ \%$. Consequently, percentage of 2° isomeric product (that is, iso-propyl chloride) is 56 %, which is $\frac{7.6}{6.0 + 7.6} \times 100$.

(b) Isobutane's isomeric products:





(tert butyl chloride) (iso butyl chloride)

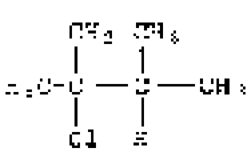
The method of calculation of their proportion is the same as in (a).

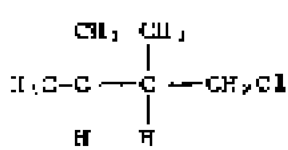
$$\frac{\text{tert butyl chloride}}{\text{iso-butyl chloride}} = \frac{\text{no. of } 3°\text{ H}}{\text{no. of } 1°\text{ H}} \times \frac{\text{reactivity of } 3°\text{ H}}{\text{reactivity of } 1°\text{ H}}$$

$$= \frac{1}{9} \times \frac{5}{1} = \frac{5}{9}.$$ Therefore, the

percentage of t-butyl chloride = $\frac{5}{5 + 9} \times 100 = 36\ \%$. The percentage of iso-butyl chloride must be $\frac{9}{9 + 5} \times 100 = 64\ \%$.

(c) 2,3-dimethylbutane's isomeric products:



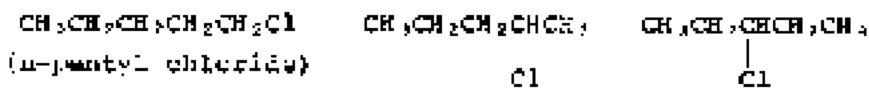


(2 chloro 2,3 dimethyl butane) (1-chloro 2,3 dimethyl butane)

$$\frac{\text{2-chloro}}{\text{1-chloro}} = \frac{\text{no. of } 3^\circ \text{ H}}{\text{no. of } 1^\circ \text{ H}} \times \frac{\text{reactivity of } 3^\circ \text{ H}}{\text{reactivity of } 1^\circ \text{ H}}$$

$$= \frac{2}{12} \times \frac{5}{1} = \frac{10}{12} = \frac{5}{6}.$$ Consequently, $\frac{5}{5+6} \times 100 =$ 45% is the percentage of 2-chloro-2,3-dimethylbutane, while $\frac{6}{6+5} \times 100 =$ 55% is the amount of 1-chloro-2,3-dimethylbutane.

(d) n-pentane's isomeric products:



(n-pentyl chloride) (2-chloropentane) (3-chloropentane)

n-pentyl chloride: 6 primary hydrogens with reactivity of 1.0, so that 6 × 1.0 = 6.

2-chloropentane: 4 secondary hydrogens with reactivity of 3.8, so that 4 × 3.8 = 15.2.

3-chloropentane: 2 secondary hydrogens with reactivity of 3.8, so that 2 × 3.8 = 7.6.

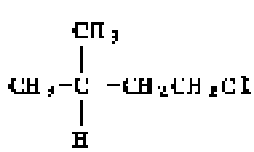
The total number × reactivity = 6.0 + 15.2 + 7.6 = 28.8. Hence, the percentage of n-pentyl chloride is

$\frac{6}{28.8} \times 100 = 21\%$.

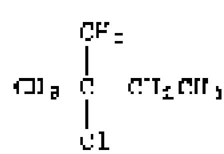
2-chloropentane: $\frac{15.2}{28.8} \times 100 = 53\%$

3-chloropentane: $\frac{7.6}{28.8} \times 100 = 26\%$.

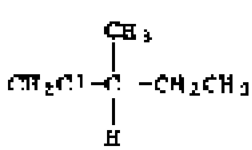
(e) Isopentane's isomeric products:



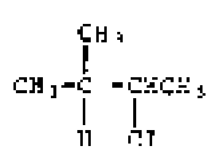
(1-chloro-3-methylbutane)



(2-chloro-2-methylbutane)



(1-chloro-2-methylbutane)



(3-chloro-2-methylbutane)

1-chloro-3-methylbutane: 3 primary hydrogens with reactivity of 1.0. 3 × 1 = 3.

2-chloro-2-methylbutane: 1 tertiary hydrogen with reactivity of 5.0. 5 × 1 = 5.

1-chloro-2-methylbutane: 6 primary hydrogens with reactivity of 1.0. 6 × 1 = 6.

3-chloro-2-methylbutane: 2 secondary hydrogens with reactivity of 3.8. 2 × 3.8 = 7.6.

The total number × reactivity = 3 + 5 + 6 + 7.6 = 21.6.

The percentages for the four isomeric compounds are as follows:

1-chloro-3-methylbutane: $\frac{3}{21.6} \times 100 = 14\ \%$

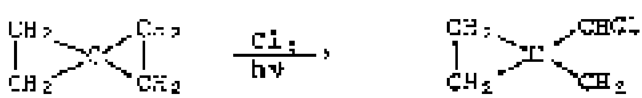
2-chloro-2-methylbutane: $\frac{5}{21.6} \times 100 = 23\ \%$

1-chloro-3-methylbutane: $\frac{6}{21.6} \times 100 = 28\ \%$

3-chloro-2-methylbutane: $\frac{7.6}{21.6} \times 100 = 35\ \%$

• PROBLEM 8-23

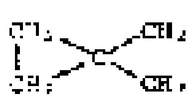
The reaction of the unusual hydrocarbon spiropentane with chlorine and light is one of the best ways of preparing chlorospiropentane.



spiropentane chlorospiropentane

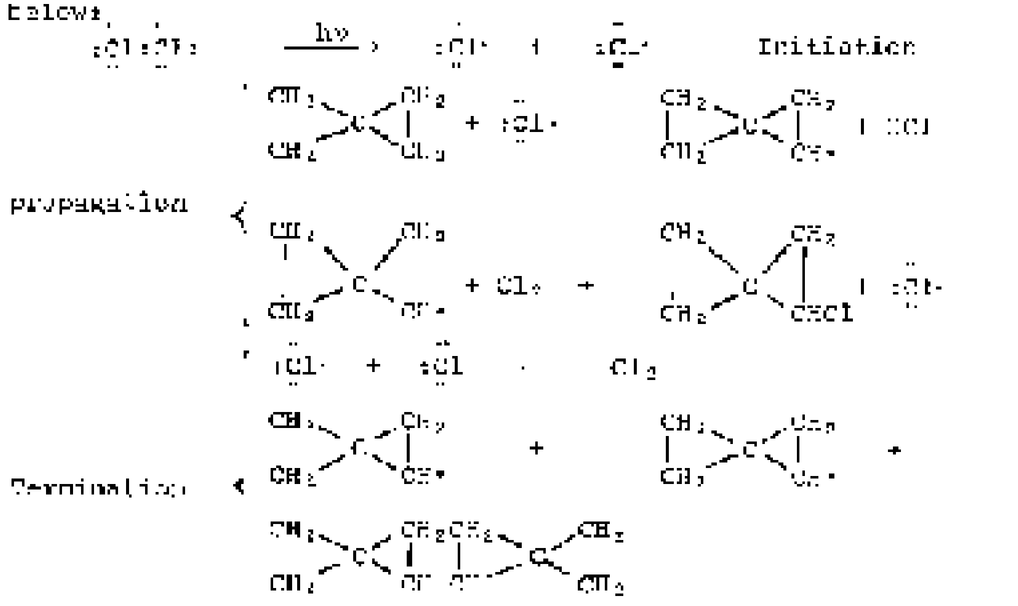
(a) Explain why chlorination is such a useful preparative method in this case. (b) Write the reaction mechanism.

Solution: (a) Since all the hydrogen atoms in spiro-

pentane  are equivalent, there is only

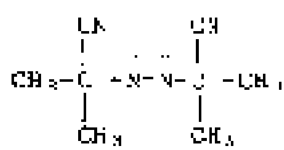
one possible monochlorinated product. If any dichlorospiropentane is formed it can be separated from the monochloro spiropentane by fractional distillation. This is possible because the boiling point of the dichlorinated compound is higher than the monochlorinated compound.

(b) In any reaction mechanism there are three general steps: initiation, propagation and termination. In the initiation step, light catalyzes the homolytic cleavage of a chlorine molecule to produce two chlorine radicals. Further reactions which are believed to occur are sketched below:



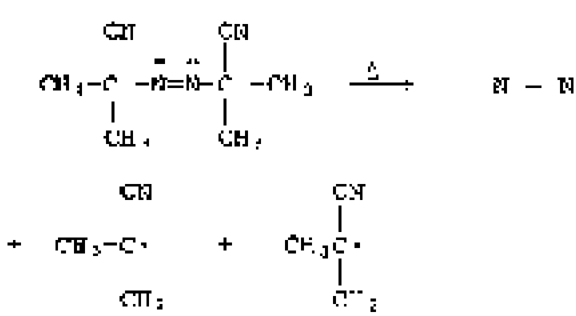
• PROBLEM 3-24

A commonly used free-radical initiator is AIBN (azobisisobutyronitrile). What are the products of its decomposition in an inert solvent?



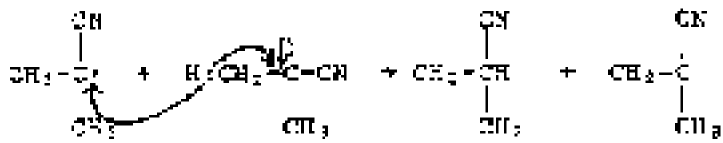
AIBN

Solution: Aliphatic azo compounds in general decompose on heating, with the formation of nitrogen and two radicals.



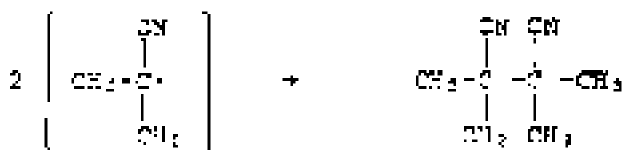
Because of the high propensity of the formation of radicals, AIBN is used extensively for the synthesis of polymers where a radical is the initiator of a reaction.

These two radicals can undergo disproportionation, where, through the process of hydrogen transfer, two equivalent amounts of saturated and unsaturated compounds are produced:



Since each of the six hydrogens are equivalent it does not matter which of the two places the double bond is placed.

A different reaction (dimerization) could also occur whereby two radicals join together:



SPECTROSCOPY

• PROBLEM 3-25

Give a structure or structures consistent with each of the following sets of nmr data.

(a) $C_3H_3Cl_5$
a triplet, δ 4.52, 1H
b doublet, δ 6.07, 2H

(b) $C_3H_5Cl_3$
a singlet, δ 2.20, 3H
b singlet, δ 4.02, 2H

(c) $C_{10}H_{14}$
a singlet, δ 1.30, 9H
b singlet, δ 7.28, 5H

(d) $C_{10}H_{14}$
a doublet, δ 0.88, 6H
b multiplet, δ 1.86, 1H
c doublet, δ 2.45, 2H
d singlet, δ 7.12, 5H

(e) $C_{10}H_{13}Cl$
a singlet, δ 1.57, 6H
b singlet, δ 3.07, 2H
c singlet, δ 7.27, 5H

Solution: (a) The molecular formula ($C_3H_3Cl_5$) suggests that the compound is a penta-chloro substituted propane. This is because there are 8 substituents (3 hydrogens, 5 chlorines) for 3 carbons. A propane (3 carbon alkane) has the general formula $C_3{*}_8$, where * represents all the substituents in the molecule. The nuclear magnetic resonance (nmr) spectrum of the compound shows a doublet downfield from a triplet. The splittings indicate that the protons that gave rise to the doublet are deshielded relative to the protons that gave rise to the triplet; that is, the electron density about the "doublet protons" is less than that about the "triplet protons". This means that there are more chlorine atoms on the carbons with the "doublet protons" than there are on the carbons with the "triplet protons". Since there are only two signals in the nmr spectrum, two of the three protons must be in identical environments. The only situation that can satisfy this requirement as well as the molecular formula is:

```
   Cl  H   Cl
   |   |   |
H -C  -C  -C  -H    1,1,2,3,3-pentachloropropane
   |   |   |
   Cl  Cl  Cl
```

The two terminal protons gave rise to the doublet and the middle proton gave rise to the triplet.

(b) The molecular formula ($C_3H_5Cl_3$) suggests that the compound is a tri chloro substituted propane. The nmr spectrum shows that there is no spin-spin splitting. This means that all the protons are on the terminal carbons; there are none on the middle carbon (if there were, splitting would occur). The only possible structure could be:

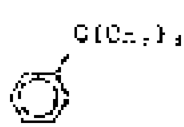
```
    H  Cl  H
    |  |   |
Cl -C -C  -C -H,   1,2,2 trichloropropane.
    |  |   |
    H  Cl  H
```

The singlet at 2.20 δ is the methyl protons' signal and the singlet at 4.02 δ is the methylene protons' signal.

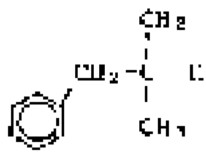
The methylene protons occur quite downfield because of the deshielding effects of the chloro groups.

(c) The nmr spectrum of the compound $C_{10}H_{14}$ shows a singlet at 7.28 δ. This is indicative of a benzene ring. If we subtract the phenyl group (C_6H_5-) from the molecular formula ($C_{10}H_{14}$) we are left with a $-C_4H_9$ portion. The fact that these nine remaining protons occur as a singlet indicates that they are in identical environments (they are equivalent). The only $-C_4H_9$ group that has all its protons in identical environments is a t butyl group:

```
 CH3
 |
-C -CH3  . This is attached to the benzene ring; the compound
 |
 CH3
```

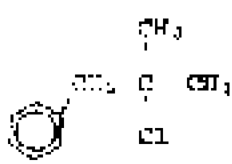
is t-butylbenzene; 

(d) The singlet at 7.12 δ indicates the presence of a benzene ring. Subtracting the phenyl group (C_6H_5-) from the molecular formula ($C_{10}H_{14}$) gives us a $-C_4H_9$ portion. This group's protons must account for the remaining signals. The protons responsible for the doublets were split by a single proton and hence must be adjacent to a carbon bearing one hydrogen. The fact that one of the doublets has a relative intensity of 6H indicates that there must be at least two methyl groups attached to the carbon bearing one hydrogen. Since we are limited to four carbons to account for these signals, there must be only two methyl groups bonded to the carbon with one hydrogen. The other doublet has a relative intensity of 2H and a methylene group must have given rise to this signal. The $-C_4H_9$ portion must be an isobutyl group: $-CH_2CH(CH_3)_2$. The isobutyl group is bonded to the benzene ring. The compound is isobutylbenzene:



This compound is a structural isomer of the one in part (c).

(e) There is a singlet at 7.27 δ, hence a benzene ring is in the compound. Subtraction of the phenyl group (C_6H_5-) from the molecular formula ($C_{10}H_{13}Cl$) leaves us with a C_4H_8Cl portion. The protons in this portion must account for the remaining signals. The fact that there is a singlet with relative intensity 6H indicates that there are two methyl groups in identical environments. Since there is no splitting in the nmr spectrum, the two methyl groups must be bonded to a carbon with no hydrogens; this implies that the chlorine group is bonded to this carbon: $-\overset{CH_3}{\underset{Cl}{C}}-CH_3$. The singlet with relative intensity of 2H must be a methylene protons signal. This is because it is the only group that will bond to the $-\underset{Cl}{C}(CH_3)_2$ portion to satisfy the required molecular formula ($C_{10}H_{13}Cl$). This group is bonded to the benzene ring. The compound is 2-chloro-2-methyl-1-phenyl propane:



CHAPTER 4

CYCLOALKANES

NOMENCLATURE

• PROBLEM 4-1

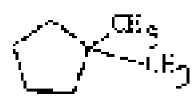
Give the IUPAC name for each of the following hydrocarbons.

(a) $(CH_3)_2CHCH_2CH_2CH(CH_3)_2$

(b)
$$\begin{array}{l} \quad\quad\quad\;\; CH_3 \quad CH_3 \;\; CH_2CH_3 \\ \quad\quad\quad\quad | \quad\quad\;\; | \\ CH_3CH_2CHCH_2CCH_2CHCH_2CH_3 \\ \quad\quad\quad\quad\quad\quad\;\; | \\ \quad\quad\quad\quad\quad\quad CH_3 \end{array}$$

(c)
$$\begin{array}{l} \quad\quad\quad\; CH_2CHCH_2CH_3 \\ \quad\quad\quad\quad\;\; | \\ CH_3CH_2CH_2CHCH_2CH_3 \end{array}$$

(d)
$$\begin{array}{l} \quad\quad\quad CH_2CHCH_3 \quad CH_2CH_3 \\ \quad\quad\quad\quad | \quad\quad\quad\quad | \\ CH_3CH_2CHCH_2CH_2CCH_2CH_3 \\ \quad\quad\quad\quad\quad\quad\quad\;\; | \\ \quad\quad\quad\quad\quad\quad\quad CH_3 \end{array}$$

(e) 

(f)
$$\begin{array}{l} \quad\;\; CH_3 \\ \quad\;\; | \\ CH_2CHCH_2CH_2CH_3 \end{array}$$

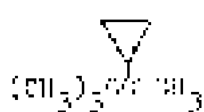
(g)
$$\begin{array}{l} \quad\quad\; CH_3 \\ \quad\quad\; | \\ (CH_3CH_2CCH_2CH_2CH_2)_3CH \\ \quad\quad\; | \\ \quad\quad\; CH_3 \end{array}$$

(h) $(CH_3CH_2)_3C$

CH_3

(i) $(CH_3CH_2)_2CHCHCH_2CH_3$

(j)
$$\begin{array}{l} \quad\quad\quad\quad\quad\quad CH_3 \\ \quad\quad\quad\quad\quad\quad | \\ (CH_3CH_2)_2CHCCH_2CH_3 \\ \quad\quad\quad\quad\quad\quad | \\ \quad\quad\quad\quad\quad\quad CH_3 \end{array}$$

(k) 

Solution: The naming of organic compounds by the IUPAC system follows certain procedures:

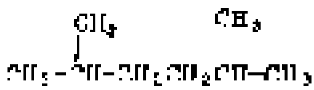
(1) Determine and identify by inspection the longest continuous carbon chain in the molecule or compound.

(2) Locate and name all the side chains attached to the longest continuous carbon chain.

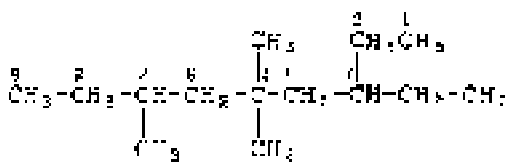
(3) Indicate the names and positions and numbers of each type of side chain by means of prefixes to the name of the parent chain. The side chains are named in alphabetical order.

(4) Since cycloalkanes are basically saturated hydrocarbons, they are given the same name as their corresponding chain alkane, with the addition of the prefix cyclo- to signify the presence of a ring structure.

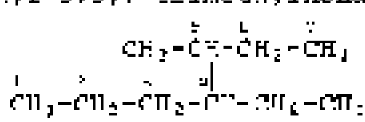
(a) We can rewrite the compound in its expanded form in order to make the structure more evident.



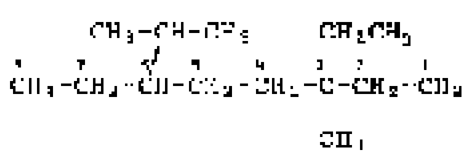
The longest continuous carbon chain consists of 6 carbon atoms, and one methyl group is attached to each of the two terminal carbons. The IUPAC name is thus 2,5 dimethylhexane.

(b) 

The longest chain contains 9 carbon atoms. A methyl group is attached to the 7th carbon; 2 methyl groups are attached to the 5th carbon; and an ethyl group is bonded to the third carbon. The name of this compound is thus 3-ethyl-5,5,7-trimethylnonane.

(c) 

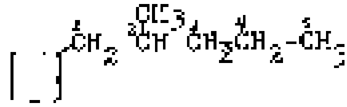
The longest chain has 7 carbon atoms. The 3rd carbon has a methyl group attached to it and the 4th carbon an ethyl group. The name given to this compound is 4-ethyl-3 methyl heptane (alphabetical order has precedence over numerical order in side chains).

(d) 

Using the same principles illustrated above, this compound is named 3-ethyl-6-isopropyl-3-methyloctane.

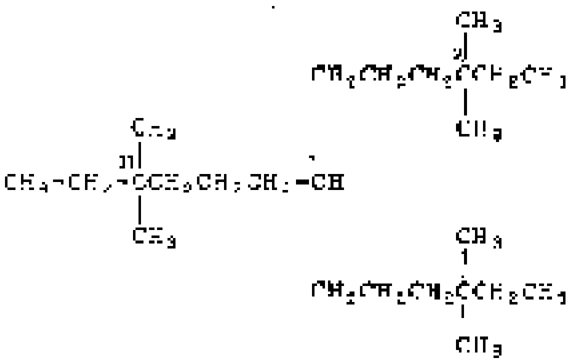
(e) 

This structure is a 5 carbon ring (cyclopentane) having 2 methyl groups attached to the same carbon (conventionally designated as C_1). The name of the structure is 1,1-dimethylcyclopentane.

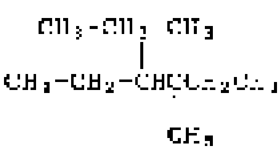
(i) 

The longest chain has 5 carbon atoms. The ring is composed of four carbon atoms and is therefore cyclobutane. Thus, the name of the compound is 1-cyclobutyl-2-methylpentane.

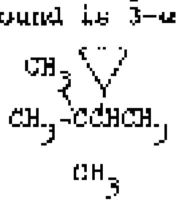
(g) Written in expanded form:



The longest chain has 13 carbon atoms (tridecane). The seventh carbon has one 4,4-dimethylhexyl group attached to it; in addition 2 methyl groups are bonded to both the 3rd and the eleventh carbon. The IUPAC name of the compound is written as 7-(4,4 dimethylhexyl)-3,3,11,11-tetramethyltridecane.

(j) 

The longest chain has 5 carbons. The name of the compound is 3-ethyl-4,4-dimethylhexane.

(k) 

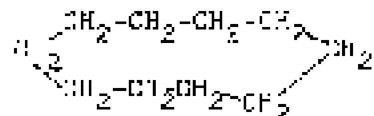
The longest chain has 4 carbon atoms. The name of this compound is 2-cyclopropyl-3,3-dimethylbutane.

Write expanded structures showing the C–C bonds for each of the following condensed formulas. Name each substance by an accepted system.

a. $(CH_2)_{10}$ (saturated compound only)
b. $(CH_2)_5CHCH_3$
c. $(CH_3)_2C(CH_2)_6CHC_2H_5$
d. The isomers of trimethylcyclobutane
e. $(CH_3)_2CHCH_2C(CH_3)_2CH_2Cl$
f. $[(CH_3)_2CH]_2C(CH_3)C_2H_5$

Solution:

(a) $(CH_2)_{10}$



This is the only structural formula that satisfies a saturated compound with 10 CH_2 groups. Note that the structure must be a ring since there are no suitable end groups.

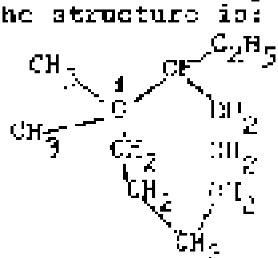
The name of this ring is cyclodecane.

(b) $(CH_2)_5CHCH_3$

The formula given indicates that there is only one group that could possibly serve as an end group, namely CH_3. Since a chain type structure would require two end groups, this compound must be in ring form, with the CH_3 as a substituent. The structure indicated is a 6-membered ring, with a methyl substituent. It can be named methylcyclohexane.

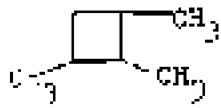
(c) $(CH_3)_2C(CH_2)_6CHC_2H_5$

The bar between the two carbon atoms indicates that they are linked into a ring-type structure. In expanded form, then, the structure is:

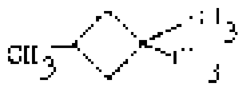


This compound can be named 1,1-dimethyl-2-ethylcyclooctane.

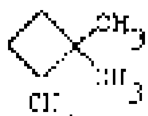
(d) The isomers of trimethylcyclobutane. Isomers are defined as compounds that have exactly the same kind and number of atoms, but have different structural forms with different bonding relationships between the atoms. Trimethylcyclobutane can be represented structurally as



and named 1,2,3 trimethylcyclobutane. The methyl groups could just as well be attached to any other carbon atom(s) in the ring, and thus the compound can be modified structurally into two other isomeric forms;



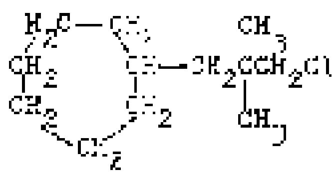
(1,1,3-trimethylcyclobutane)

and 

(1,1,2-trimethylcyclobutane).

Therefore a total of three isomeric forms are possible for trimethylcyclobutane.

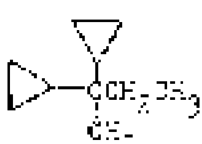
(e) $(CH_2)_6CHCH_2C(CH_3)_2CH_2Cl$ can be written as



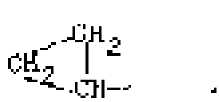
since there are 7 carbon atoms in the ring attached to a dimethyl propyl chloride group, this structure is named 2,2-dimethyl-3-cycloheptylpropyl chloride.

(f) $[(CH_2)_2CH]_2C(CH_3)C_2H_5$

Two rings, each consisting of 3 carbon atoms, are attached to the second carbon of butane. This can be written as



where the triangle (Δ) represents the cyclopropyl group, i.e.,



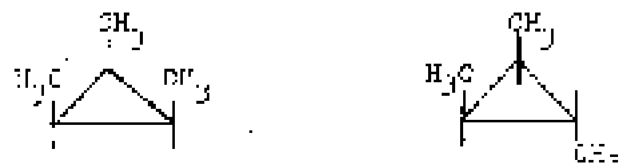
The name given to this structure is 2,2-dicyclopropylbutane.

Write structural formulas for all of the possible cis-trans isomers of the following compounds.

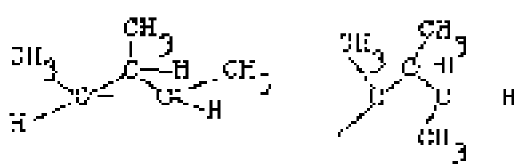
a. 1,2,3-trimethylcyclopropane
b. 1,3-dichlorocyclopentane
c. 1,1,3-trimethylcyclohexane
d. (3-methylcyclobutyl)-3-methylcyclobutane

Solution: The first step undertaken in writing the structural formula for a compound is to draw the structure for the longest continuous carbon chain, which is indicated in the name. The next step is to attach the subgroups, denoted in the prefixes, to the parent chain at the positions indicated.

(a) 1,2,3-trimethylcyclopropane. Cyclopropane is planar and is a 3-carbon ring (Δ) structure. Here, one methyl group is bonded to each carbon in the ring. Each methyl group can either be attached above the plane of the cyclopropane ring or below the plane. Only 2 different combinations of methyl group attachment are possible for this compound, resulting in two isomers.

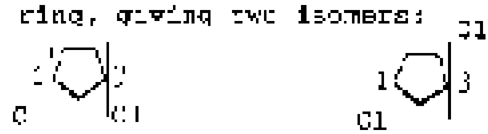


The structural formulas can also be represented by



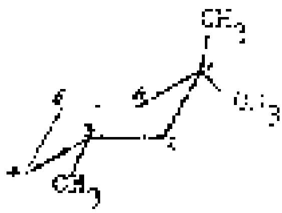
respectively, but we will use the first type of representation in our solutions due to its clarity.

(b) 1,3-dichlorocyclopentane. The last part of the name tells us that the compound is a 5 carbon ring structure. Again, the substituents of the ring can be attached either above or below the ring, giving two isomers:

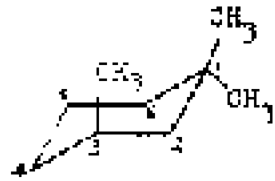


When both substituents are above or below the ring, they are cis with respect to the ring. If one is above and one is below the ring, they are trans.

(c) 1,1,3-trimethylcyclohexane. With some careful inspection one will notice that there is only one isomer present if the compound has a planar structure. However, because cyclohexane in reality is not planar, there are two conformational isomers of 1,1,3 trimethylcyclohexane:



Equatorial $-CH_3$

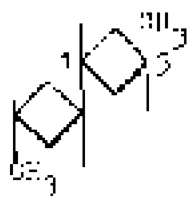


Axial $-CH_3$

Since in room temperature these two forms undergo rapid interconversion, it is very difficult to distinguish them from each other.

(d) (3-methylcyclobutyl)-3-methylcyclobutane. A 3-methylcyclobutyl group is attached to the first carbon atom of 3-methylcyclobutane. Three possible arrangements of the two methyl groups exist:

cis



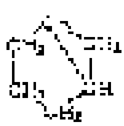
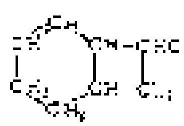
trans

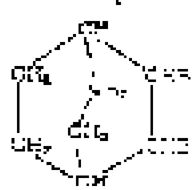
trans

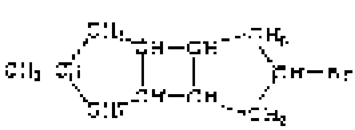
Note that the two trans forms cannot be made to superimpose upon each other and are therefore not identical compounds.

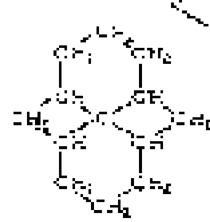
• **PROBLEM** 4-4

Name each of the following compounds by an accepted system.

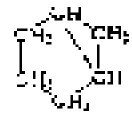
a.  = 

c. 

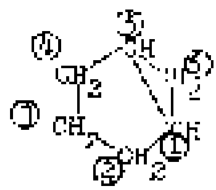
d. 

• 

Solution: (a)



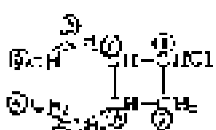
This is an example of a polycycloalkane, an alkane with more than one ring. Compounds of this type are named systematically by attaching the prefix "bicyclo", "tricyclo", etc., as the case may be, to the name of an open chain hydrocarbon with the same number of carbon atoms as the polycycloalkane. The number of carbon atoms in each linkage is noted in a square bracket immediately following the prefix.



Here, the presence of two rings calls for the prefix 'bicyclo'. There are a total of 6 carbon atoms in the two rings, and so the compound is a bicyclohexane. The different carbon atoms have been numbered for convenience. Going in the order of increasing carbon number, there are 3 carbon atoms following C_1 up to its bonded partner, C_5 ($C_2 \rightarrow C_4$), and 1 carbon atom following C_5 (C_6). The linkage responsible for forming a second ring is between C_1 and C_5 and there are no internal carbon atoms (0) within this linkage.

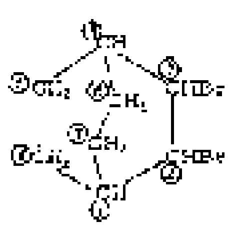
These numbers are placed in decreasing order within brackets and are separated by periods. We can thus write the name for the above compound as bicyclo[3.1.0]hexane.

(b)



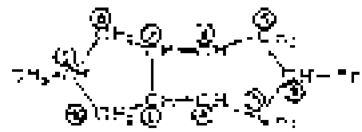
This is a bicyclic compound (because the carbon atoms form two rings) consisting of 8 carbon atoms in all, which are numbered as shown. Look at the linkages between C_1 and C_6. Four carbon atoms follow C_1 ($C_2 \rightarrow C_5$), while 2 atoms follow C_6 ($C_7 \rightarrow C_8$). There are no atoms internal in the $C_1 - C_6$ bond itself. Since a chlorine atom is bonded to C_8, we can name this compound as 8-chloro bicyclo[4.2.0]-2-octene. 2-octene signifies the presence of a double bond between C_2 and C_3 in a 8-carbon compound.

(c)



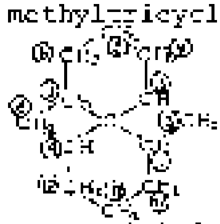
There are two rings and 8 carbon atoms in this compound. The central linkage between C_1 and C_4 contains 2 internal carbon atoms (C_7 and C_8). There are 2 carbon atoms following both C_1 (C_2 + C_3) and C_4 (C_5 + C_6). Bromine atoms are bonded to both C_7 and C_8. Therefore, the correct name for the compound is 2,3-dibromobicyclo[2.2.2]octane.

(d)



This compound consists of 10 carbon atoms arranged into 3 rings (hence tricyclodecane) to which is attached a methyl group at C_9 and a bromine atom at C_4. Looking at the bonding between C_1 and C_7, we see there are 5 carbon atoms following C_1 (C_2 – C_6) and 3 atoms following C_7 (C_8 + C_{10}). There are no carbon atoms within the linkage between C_1 and C_7. We designate any further bonds, after the first has been established, by the number of carbon atoms internal to the bonds (here C_2 and C_6 with 0 atoms in between). A superscript names the carbons between which that bond occurs. Therefore, the name of the compound is 4-bromo-9-methyltricyclo[5.3.0.$0^{2,6}$]decane.

(e)



There are a total of four rings and 13 carbon atoms in this structure, hence it is a tetracyclotridecane.

Looking first at the linkages between C_1 and C_9, we find there are 7 carbon atoms following C_1 (C_2 – C_8) and 3 carbon atoms following C_9 (C_{10} – C_{12}). There is one carbon atom within the bond (C_{13}).

There is a bond between C_3 and C_{13} with no atoms in between, and a bond between C_7 and C_{13}, again with no atoms in between.

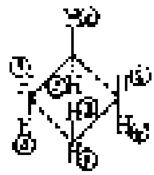
The name of the compound is thus tetracyclo [7.3.1.$0^{3,13}$.$0^{7,13}$]tridecane.

CONFORMATIONS

• PROBLEM 4-5

(a) How many pairs of eclipsed hydrogens are present in planar cyclobutane? (b) In puckered cyclobutane?

Solution: First let us look at the structure of planar cyclobutane.

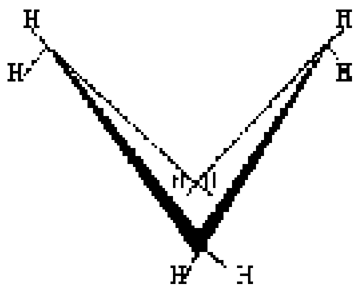


(a) planar cyclobutane

As we can see, eight pairs of hydrogens in planar cyclobutane are eclipsed:

1 and 2	5 and 6
2 and 3	6 and 7
3 and 4	7 and 8
4 and 1	8 and 5

In puckered cyclobutane, we can tell from examining its structure that no eclipsed hydrogens are present.



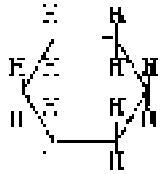
(b) puckered cyclobutane

The student should use a model if the above is not clear.

• PROBLEM 4-6

> The energy barrier for rotation about the C-C bond in ethane is about 3 kcal, which suggests that the energy required to bring one pair of hydrogens into an eclipsed arrangement is 1 kcal. Calculate how many kilocalories the planar form and extreme boat form of cyclohexane are likely to be unstable relative to the chair form on account of H-H eclipsing and flagpole interactions.

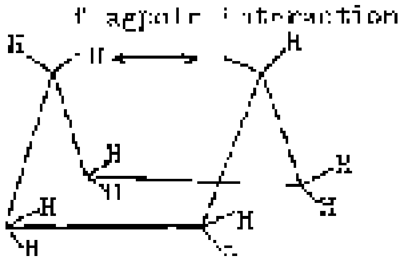
Solution: First let us study the structure of planar cyclohexane:



planar cyclohexane

In this structure, we expect a considerable degree of instability due to the 12 pairs of eclipsed hydrogens. Since 1 pair of eclipsed hydrogens requires 1 kcal of energy, 12 pairs of eclipsed hydrogens in planar cyclohexane will present an eclipsing strain of 12 kcal.

In the extreme boat form of cyclohexane, 4 pairs of eclipsed hydrogens are present:



extreme boat form of cyclohexane

Here, 4 kcal of eclipsing strain is involved. In addition, a pair of hydrogens are forced to come together in a flagpole type of interaction. It is experimentally measured that each flagpole interaction (where the hydrogens are about 1.83 Å apart) carries 3 kcal of energy. Therefore the extreme boat form of cyclohexane has a total of 7 kcal of energy more than the most stable chair form, in which there are no eclipsed hydrogen pairs.

• PROBLEM 4-7

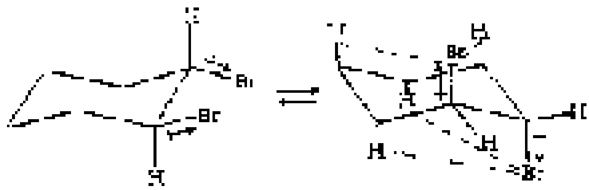
(a) trans-1,2-Dimethylcyclohexane exists about 99% in the diequatorial conformation; trans-1,2-dibromocyclohexane on the other hand, exists about equally in diequatorial and diaxial conformations. Furthermore, the fraction of the diaxial conformation decreases with increasing polarity of the solvent. How do you account for the contrast between the dimethyl and dibromo compounds?

(b) If trans-3-cis-4-dibromo-tert-butylcyclohexane is subjected to prolonged heating, it is converted into an equilibrium mixture (about 50:50) of itself and a diastereomer. What is the diastereomer likely to be? How do you account for the approximately equal stability of these two diastereomers? (Here, and in (c), consider the more stable conformation of each diastereomer to be the one with an equatorial tert-butyl group).

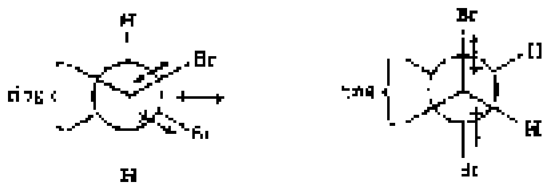
(c) There are two more diastereomeric 3,4-dibromo-tert-butylcyclohexanes. What are they? How do you account for the fact that neither is present to an appreciable extent in the equilibrium mixture?

Solution: (a) Two types of strain are about equally important in trans-1,2-dibromocyclohexane. First, steric strain dictates that the compound exist in the diequatorial conformation. By having the two bromo groups pointing away from the ring in equatorial positions (see Figure) non-bonded interactions between hydrogen and bromine atoms, which will occur in diaxial conformation, will be prevented.

However, since the bromine atom is electron-rich, two bromine atoms in the diequatorial conformation will repel each other. This dipole-dipole repulsion will be relieved as the bromine atoms become axially oriented in the diaxial conformation. Thus at equilibrium, trans 1,2-dibromocyclohexane will exist in both the diequatorial and the diaxial conformations in approximately equal parts, since the two forms are of about equal energy.



Diequatorial   Diaxial



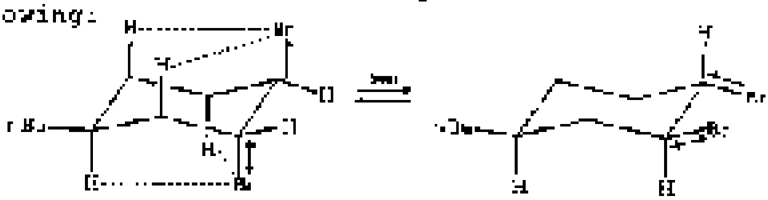
steric strain low   dipole-dipole repulsion low
dipole-dipole repulsion high   steric strain high

(Dotted line indicates steric interaction; arrow indicates direction of dipole moment.)

As polarity of the solvent is increased, any dipole-dipole repulsion is relieved through interaction with the solvent. Therefore, the favored form is the polar one, that is, the diequatorial conformation, since both its steric strain and its dipole-dipole repulsion will be low.

Trans 1,2-dimethylcyclohexane exists mainly in the diequatorial conformation. This is because the repulsion between $-CH_3$ groups is much weaker, and steric strain is the controlling factor.

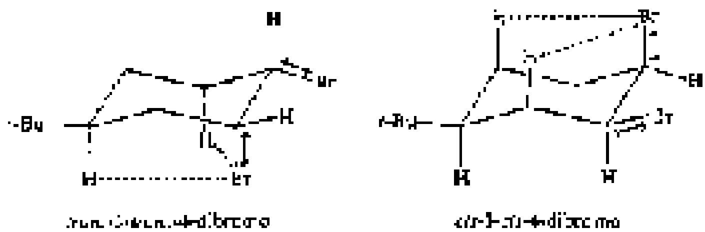
(b) As trans-3-cis-4-dibromo-tert-butylcyclohexane is heated, a diastereomer, cis-3-trans-4-dibromo-tert-butylcyclohexane is formed. An equilibrium mixture shows the following:



(i) trans-3-cis-4-dibromo (both Br's axial)   (ii) cis-3-trans-4-dibromo (both Br's equatorial)

In (i) there are four 1,3-diaxial interactions between Br's and H's, but there is relief of dipole-dipole repulsion. In (ii) there are no 1,3-diaxial interactions between Br's and H's, but there is increased dipole dipole repulsion. Dipole-dipole repulsion and 1,3-diaxial interactions just about balance each other; thus (i) and (ii) are of about equal stability.

(c) Two other possible diastereomers are:



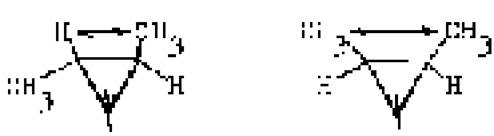
In each, there are both considerable 1,3-diaxial interactions and unrelieved dipole-dipole repulsion. Hence they are relatively unstable and do not occur in appreciable amounts in the equilibrium mixture.

● PROBLEM 4-8

Would you expect cis- or trans-1,2-dimethylcyclopropane to be the more stable? Explain.

Solution: The trans form is expected to be more stable than the cis form. As we can see, the former has its methyl groups farther apart from each other than the latter. The non-bonded interaction between the hydrogen and the methyl group in the trans conformation is smaller than that between the two methyl groups in the cis conformation. Thus the cis form has a greater strain, and is less stable.

non-bonded interaction



trans　　　　cis

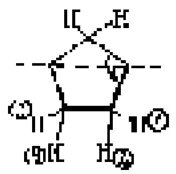
ANGLE STRAIN

● PROBLEM 4-9

(a) Estimate the amount of eclipsing strain in planar cyclopentane. (b) Is the amount of eclipsing strain decreased in going from the planar to the puckered form?

Solution: Eclipsing strain has a value of approximately 1 Kcal/mole for two adjacent, eclipsed bonds. In planar cyclopentane 10 pairs of eclipsed hydrogens are found, thus 10 Kcal of eclipsing strain is present.

As planar cyclopentane folds, the number of eclipsed hydrogens decreases, and thus eclipsing strain decreases.

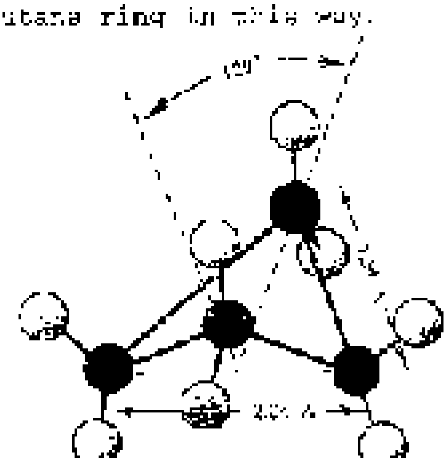


In puckered cyclopentane, only two pairs of eclipsed hydrogens are found: 1 and 3, 2 and 4. Hence only 2 Kcal of eclipsing strain is present.

Therefore, as planar cyclopentane becomes puckered, a loss of 8 Kcal of eclipsing strain enables the puckered form to become more stable.

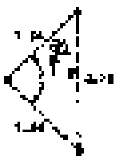
• PROBLEM 4-10

Calculate and compare the total angle strain in kcal for planar cyclobutane and for a folded cyclobutane with all C-C bond lengths of 1.54 Å and the carbons on opposite corners 2.04 Å apart (which corresponds to a dihedral angle of about 120°, see Figure). Assume that the energy of changing a C-C-C bond angle is 17.5 kcal per degree^2 per mole. Estimate relief in hydrogen-hydrogen eclipsing interactions which would be associated with bending a cyclobutane ring in this way.



Folded cyclobutane ring.

Solution: From the given information we can calculate the value of the C-C-C bond angles in the 60°-folded cyclobutane:



$$\sin \frac{\theta}{2} = \frac{2.04/2}{1.54} = \frac{1.02}{1.54} = 0.662$$

$$\frac{\theta}{2} = 41.5°$$

$$\theta = 2 \times 41.5° = 83°$$

Since the stable angle of a C-C-C bond in hydrocarbons is 109.5° (tetrahedral angle), keeping the angles in puckered cyclobutane at 83° requires additional energy. This energy is called the angle strain. The total angle strain for a mole of puckered cyclobutane is calculated from the following:

$$\text{angle strain} = 17.5 \times 4 \times (109.5 - 83)^2 \text{ kcal}$$

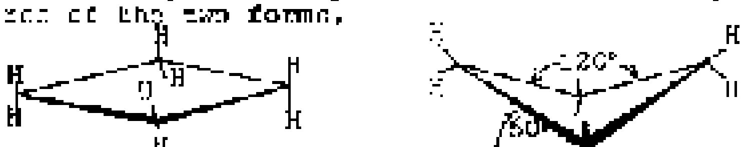
$$= 49.2 \text{ kcal}$$

where 4 is the number of C-C-C bond angles in cyclobutane. The 49.2 kcal is the total energy required to keep the four C-C-C bond angles each at 83° rather than the more stable value of 109.5°.

In planar cyclobutane, each C-C-C bond angle measures 90°. Thus the angle strain is

$$17.5 \times 4 \times (109.5 - 90)^2 \text{ kcal or } 26.6 \text{ kcal.}$$

The greater angle strain present in the folded form of cyclobutane (49.2 kcal) as compared to that in the planar form (26.6 kcal) indicates that the former is more unstable than the latter. But this is true judging on the basis of angle strain alone. We have to take into account the energy involved in hydrogen-hydrogen eclipsing interactions which we find are stronger in planar cyclobutane than puckered cyclobutane. Considering the structures of the two forms,



planar puckered

we can see that the planar form requires that all 8 hydrogens be kept in eclipsing positions. Their repulsion of each other presents an eclipsing strain which decreases as the planar form becomes puckered, and the hydrogens are moved somewhat apart. This hydrogen-hydrogen eclipsing strain alone dictates that the puckered form be more stable than the planar.

It is experimentally observed that as a pair of hydrogens loses their eclipsing relationship, about 1 kcal of energy is released. So as planar cyclobutane is folded, so that all hydrogen-hydrogen eclipsing interactions are lost, 8 kcal (8 × 1 kcal) of energy is liberated.

Most cyclobutanes in nature show a 30°-folding corresponding to C-C-C bond angles of 88° and a calculated angle strain of 32.4 kcal, which is a compromise between the planar and the 60° folded form.

30°-folded cyclobutane

• PROBLEM 4-11

Investigate the thermodynamic feasibility of the following propagation steps for opening the rings of cycloalkanes with n = 2-6 by a free-radical mechanism.

(1) $(CH_2)_n + Br\cdot \rightarrow BrCH_2(CH_2)_{n-2}CH_2\cdot$

(2) $BrCH_2(CH_2)_{n-2}CH_2\cdot + Br_2 \rightarrow (CH_2)_{n-2}(CH_2Br)_2 + Br\cdot$

Use 83 kcal for the bond-dissociation energy of a normal C-C bond and 68 kcal for the bond-dissociation energy of a C-Br bond. (An easy way to solve a problem of this type is to first calculate ΔH of each step for cyclohexane where there is no strain, and then make suitable corrections for the strain which is present for small values of n.) Refer to the following table for your answer.

Table 1. Total Strain of Cycloalkanes

Cycloalkane $(CH_2)_n$	n	Total strain (kcal/mole)
ethylene	2	22.4
cyclopropane	3	27.6
cyclobutane	4	26.4
cyclopentane	5	6.5
cyclohexane	6	0.0

Solution: ΔH of a reaction is the energy change as a reactant gives rise to a product. Since chemical substances contain energy in chemical bonds, a change in energy (ΔH) can be considered as a change in total bond energy as a reactant (or reactants) yields a product (or products). In other words,

$$\Delta H = E_{product} - E_{reactant}.$$

where E = bond energy. If ΔH carries a positive sign, the energy of the products is greater than that of the reactants, and the reaction is defined as endothermic, meaning that energy must be absorbed in order for the reaction to occur. If ΔH is negative, the energy of the products is less than that of the reactants; the reaction is said to be exothermic, meaning energy is released as a result of the reaction. Exothermic reactions are feasible whereas endothermic reactions are not, since the latter requires a net input of energy.

In solving the problem, we must find the sign of the ΔH of the reaction in order to tell whether the reaction is feasible.

When n = 6, the cycloalkane is a cyclohexane. In the first step of the given reaction,

$$(CH_2)_6 + Br\cdot \rightarrow BrCH_2-(CH_2)_4-CH_2\cdot$$

one bond - the C-C bond in cyclohexane - is broken, and one bond - the C-Br bond in the product - is formed. We know that a C-C bond carries with it 83 kcal of energy, and a C-Br bond 68 kcal. Thus in this reaction, 83 kcal is absorbed in order to break a C-C bond while only 68 kcal is released as a C-Br bond forms. There is a net absorption of 15 kcal (83 - 68) of energy. ΔH therefore is + 15 kcal and the reaction is endothermic. Endothermic reactions are not readily feasible.

In calculating the ΔH's for the same reaction involving smaller ring sizes (n = 2, 3, 4, 5) we need to know the additional energy stored in the cycloalkanes due to angle strain. As n decreases, angle strain becomes stronger. In addition, there is also the hydrogen-hydrogen colliding strain that has to be taken into consideration. The total strain, then, equals to the sum of angle strain and colliding strain. When the ring is opened in reaction (1), the additional energy required to maintain the strain in the cyclic form is released. We can find the ΔH's for smaller cycloalkanes by subtracting the total strain (given in Table 1) from the + 15 kcal found previously for the ΔH of cyclohexane's ring-opening reaction. Therefore, when

		Total strain	
n = 5	ΔH = + 15 kcal	- 6.5 kcal	= + 8.5 kcal
n = 4	ΔH = + 15 kcal	- 26.4 kcal	= - 11.4 kcal
n = 3	ΔH = + 15 kcal	- 27.6 kcal	= - 12.6 kcal
n = 2	ΔH = + 15 kcal	- 22.4 kcal	= - 7.4 kcal

As we can see, only ring-opening reactions of n = 2, 3, and 4 will be exothermic (with negative ΔH's). Thus only those reactions will be feasible.

In the second step of the reaction,

$$BrCH_2-(CH_2)_{n-2}CH_2\cdot + Br_2 \rightarrow (CH_2)_{n-2}(CH_2Br)_2 + Br\cdot \; .$$

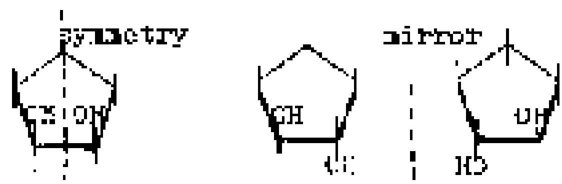
there is simply a Br-addition onto the CH radical. Strains related to ring structures do not apply, since no breakage of the ring structure occurs. The ΔH of this reaction will then be the same for all n's. In this step one Br–Br bond is broken while another C–Br bond is formed. The energy absorbed in breaking a Br–Br bond is experimentally found to be 46 kcal. The ΔH can then be calculated from 46 kcal – 68 kcal, which gives –22 kcal.

STEREOISOMERISM

• PROBLEM 4-12

You have two bottles labeled "1,2-Cyclopentanediol," one containing a compound of m.p. 30°, the other a compound of m.p. 55°; both compounds are optically inactive. How could you decide, beyond any doubt, which bottle should be labeled "cis" and which "trans"?

Solution:



meso compound — enantiomers

cis — trans

The mirror image of cis-1,2-cyclopentanediol is identical to and superimposable upon the cis compound itself. By examining the structure a bit more closely, we find that the compound is actually a meso compound. By definition, its mirror images are identical and so unresolvable, and the compound is optically inactive.

Trans-1,2 cyclopentanediol has non-superimposable mirror images, and so can exist as two enantiomers. When equal parts of enantiomers are mixed, trans 1,2 cyclopentanediol is a racemic modification and appears to be optically inactive. This is because the equal parts of enantiomers rotate light to the same degree but in opposite directions, and the net effect is no observable optical activity. However, the trans compound can be resolved into its enantiomers by special methods, such as reacting them with reagents that are themselves optically active.

Thus, if the solution is resolvable into two optically active compounds, it must contain the trans isomers.

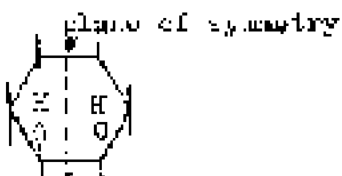
• PROBLEM 4-13

Which of the following compounds are resolvable, and which are non resolvable? Which are truly meso compounds? Use models as well as drawings.

(a) cis-1,2-cyclohexanediol (d) trans-1,3-cyclohexanediol
(b) trans-1,2-cyclohexanediol (e) cis-1,4-cyclohexanediol
(c) cis 1,3 cyclohexanediol (f) trans-1,4-cyclohexanediol

Solution: Every compound has a mirror image. But not all mirror images are superimposable on each other. Mirror images that are nonsuperimposable are called enantiomers. Enantiomers can be resolved and are characterized by optical activity. A compound with a chiral center (atom bonded to 4 different groups) has enantiomers, whereas one with no chiral center has no enantiomers. However, there are compounds with chiral carbons whose mirror images are superimposable. These compounds are called meso compounds. Meso compounds cannot be resolved.

(a) cis-1,2-cyclohexanediol

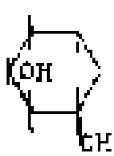


(a)

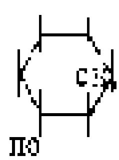
mirror image of (a)

These mirror images are actually identical and superimposable on each other. On closer inspection one half of the compound is superimposable on its other half. This is equivalent to saying that there is a plane of symmetry in the compound. Cis 1,2 cyclohexanediol is a meso compound and is not resolvable, although it contains two chiral carbons.

(b) trans-1,2-cyclohexanediol



(b)

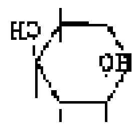


mirror image of (b)

These mirror images are not superimposable. Note also that there is no internal plane of symmetry in (b). Trans 1,2 cyclohexanediol therefore exists as enantiomers which are resolvable.

(c) cis 1,3 cyclohexanediol

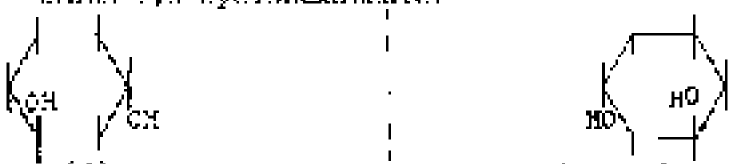
(c)



mirror image of (c)

These two forms are superimposable. They are actually identical. In addition, an internal symmetry exists making cis-1,3-cyclohexanediol a meso compound. Meso compounds are not resolvable.

(d) trans-1,3-cyclohexanediol



(d) mirror image of (d)

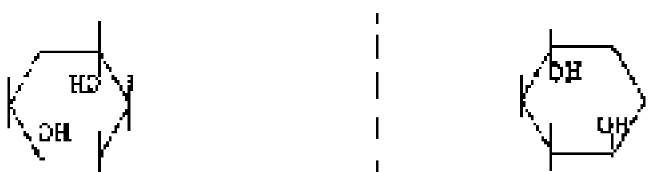
These two mirror images are enantiomers and are therefore resolvable.

(e) cis-1,4-cyclohexanediol

(e) mirror image of (e)

These two compounds are perfectly superimposable and thus non resolvable. They are actually identical compounds.

(f) trans-1,4-cyclohexanediol



(f) mirror image of (f)

Like compound (e), these are identical compounds and not enantiomers. They cannot be resolved.

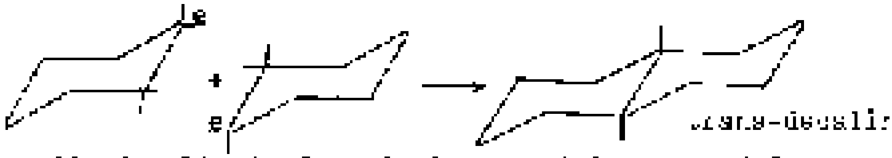
Note that (e) and (f) are not meso compounds since they contain no chiral carbons.

POLYCYCLOALKANES

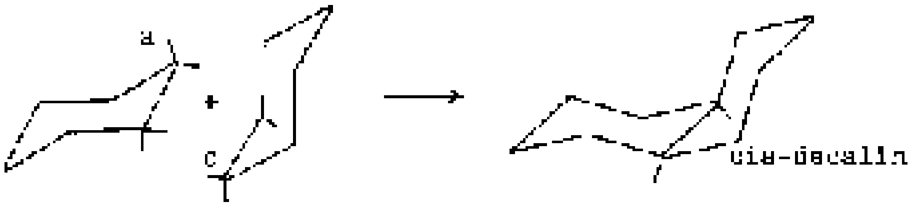
• PROBLEM 4-14

Use ball-and-stick models to assess the degree of stability to be expected for a decalin with chair-form rings and an axial axial ring fusion.

Solution: Trans decalin is formed by fusion of two chair-form cyclohexane molecules via two equatorial-type bonds;



Cis-decalin is formed via an axial-equatorial union:

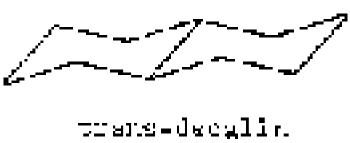


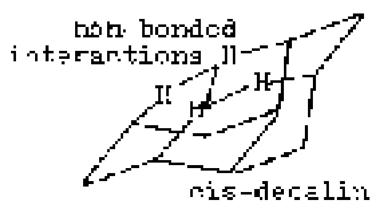
An axial axial type of fusion is not possible for steric reasons.

• PROBLEM 4-15

> There are two isomers of decalin. One is of higher energy and the other is more stable. Which is the stabler form? Why?

Solution: To answer this question we have to look into the structures of the two forms. Trans-decalin is formed by two equatorial-type bonds while cis-decalin is formed via an axial equatorial fusion of two cyclohexane molecules:





As we can see, within the concave area of cis-decalin, there is a considerable amount of non bonded interactions between hydrogen atoms. The repulsion of the closely spaced hydrogen atoms causes instability of the cis compound. In the trans form, non bonded hydrogen interactions are less and the compound is more stable than the cis isomer.

CHAPTER 5

STEREOCHEMISTRY

OPTICAL ACTIVITY

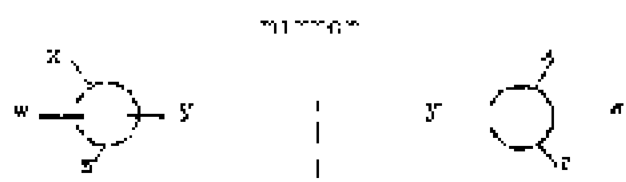
• PROBLEM 5-1

Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and meso compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active.

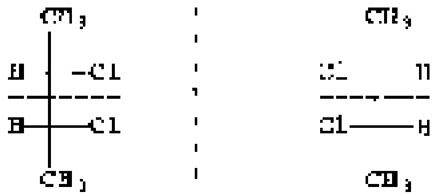
(a) 1,2-dibromopropane (b) 1,2,3,4-tetrabromobutane

Solution: A knowledge of enantiomers, diastereomers, meso compounds, chirality, and optical activity will be necessary to solve this problem.

Stereoisomers may be defined as isomers that are different from each other only in the way the atoms are oriented in space. Non-superimposable mirror-image stereoisomers are referred to as enantiomers.



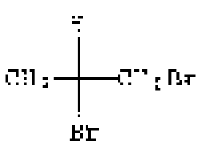
These two models are not superimposable. Although two substituent groups may coincide as they are twisted and turned, the other two do not. When molecules are not superimposable on their own mirror images, they are chiral. A compound whose molecules are chiral can exist as enantiomers; a compound whose molecules are without chirality (achiral) cannot exist as enantiomers. Enantiomers have identical physical and chemical properties, except for the direction of rotation of the plane of polarized light and the reaction with optically active reagents. Because enantiomers can rotate the plane of polarized light, they are called optically active substances. Stereoisomers that are not mirror images of each other are called diastereomers. A meso compound is defined as one whose molecules are superimposable on their mirror images, even though they contain chiral centers. Therefore, meso compounds contain chiral centers but nevertheless are not chiral. For example, 2,3-dichlorobutane would be a meso compound with an internal plane of symmetry (indicated by a dotted line):



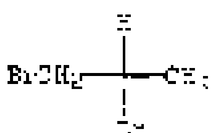
superimposable

In solving this problem, we need to draw the compounds and look for possible configurations that would give rise to enantiomers, diastereomers, or meso compounds. One method of drawing the compound is to use a cross in which the intersection marks the location of the chiral carbon and the four groups attached to the carbon are at the ends of the cross.

(a) 1,2-dibromopropane ($CH_3CHBrCH_2Br$). This structure may be drawn as follows:



. Note what happens if we rewrite this as

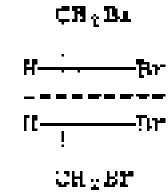


. This is indeed the mirror image of the first structure. Try to superimpose these two forms. The fact is that they cannot be made to superimpose.

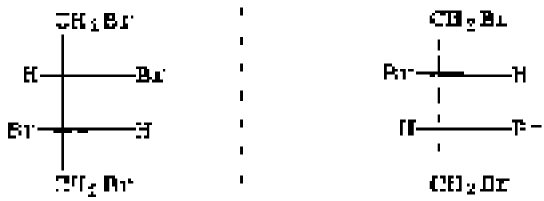
mirror

Hence, for 1,2-dibromopropane there exist two enantiomers, which when separated will rotate the plane of polarized light to the same degree but in opposite directions.

(b) 1,2,3,4-tetrabromobutane ($BrCH_2CHBrCHBrCH_2Br$). Three stereochemical formulas may be drawn in this case. Two of the three represent enantiomers that would be optically active if separated, whereas the third is an optically inactive meso compound.



<= This configuration represents the meso compound. A plane of symmetry is evident as indicated by the dotted line.



mirror

These two mirror images cannot be superimposed. They are enantiomers.

• PROBLEM 5-2

The concentration of cholesterol dissolved in chloroform is 6.15 g per 100 ml of solution. (a) A portion of this solution in a 5-cm polarimeter tube causes an observed rotation of $-1.2°$. Calculate the specific rotation of cholesterol. (b) Predict the observed rotation if the same solution were placed in a 10-cm tube. (c) Predict the observed rotation if 10 ml of the solution were diluted to 20 ml and placed in a 5-cm tube.

Solution: An optically active substance may be defined as one that rotates the plane of polarized light. This rotation is measured and detected by an instrument called the polarimeter. The amount of rotation observed will reflect the number of molecules the light encounters in passing through the polarimeter tube. The specific rotation may be defined as the number of degrees of rotation observed if a 1-decimeter tube is used, and the compound being examined is present to the extent of 1g/cc. The following equation is employed:

$$[\alpha] = \frac{\alpha}{l \times d}, \text{ that is,}$$

$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/cc}},$$

where g/cc represents density for a pure liquid or concentration for a solution. To calculate (a), (b), and (c), we can use this equation and the given information.

(a) The observed rotation, α, is $-1.2°$ in a 5-cm, or 0.5-dm polarimeter. Since the concentration of cholesterol dissolved in chloroform is 6.15 g per 100 ml of solution,

$$d = \frac{6.15}{100}\ \frac{g}{ml}\ . \quad \text{Substituting:}$$

$$[\alpha] = \frac{\alpha}{l \times d} = \frac{-1.2°}{0.5 \times \frac{6.15}{100}} = -39.0°$$

(b) Here, the same situation exists except that the tube is 10 cm or 1 dm, that is, it is twice as long. A doubled observed rotation should be anticipated, that is, α should now be $-2.4°$. This is confirmed by the following calculation:

$$-39.0 = \frac{\alpha}{1.0 \times \frac{6.15}{100}}\ ; \qquad \alpha = -2.4°.$$

(c) Here, the concentration has been halved by diluting from 10 ml. to 20 ml. Hence, it can be expected that the observed rotation should be halved from part (a) since the number of molecules is halved. In other words, α should be $-0.6°$. This is indeed found to be the case by calculation:

$$-39.0 = \frac{\alpha}{0.5 \times \frac{6.15}{200}}\ ; \qquad \alpha = -0.6°.$$

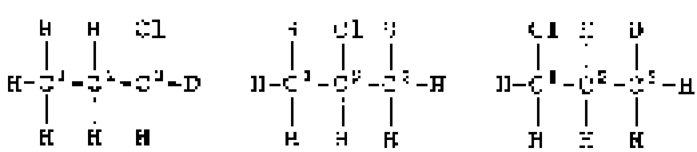
CHIRALITY

• PROBLEM 5-3

(a) Neglecting stereoisomers for the moment, draw all isomers of the formula C_3H_6DCl. (b) Decide which of these are chiral.

Solution: Chiral organic molecules are those that contain at least one chiral carbon, that is, a carbon with four different groups attached to it.

(a) The isomers of C_3H_6DCl are:



(A) (B) (C)

(D) (E)

(b) To tell whether a molecule is chiral one must locate the chiral carbon, if it exists. Thus in structure A, C³ is a chiral carbon and this isomer is chiral. In structure B, C⁴ is a chiral carbon and this isomer is chiral. Isomers C and D contain no chiral carbons and are thus not chiral. Isomer E is a chiral molecule because C³ is a chiral carbon.

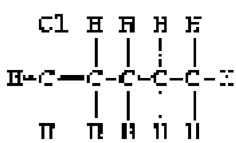
• PROBLEM 5-9

Which of the following formulas are chiral?

(a) 1-chloropentane	(e) 2-chloro-2-methylpentane
(b) 2-chloropentane	(f) 3-chloro-2-methylpentane
(c) 3-chloropentane	(g) 4-chloro-2-methylpentane
(d) 1-chloro-2-methylpentane	(h) 1-chloro-2-bromobutane

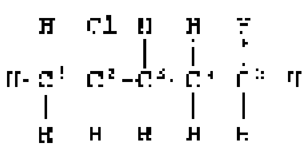
Solution: To answer this question, one must first determine if a particular molecule or compound contains at least one carbon atom with four different groups attached to it. If it does then the molecule is chiral.

(a) 1-chloropentane

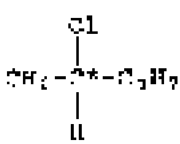


There is no chiral carbon in this molecule since no carbon contains four different substituent groups. The molecule is therefore not chiral.

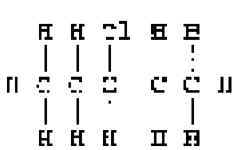
(b) 2-chloropentane



C² is a chiral carbon since it has four different groups attached to it: H_3C-, $Cl-$, $H-$ and $CH_2CH_2CH_3-$. It can better be represented as:

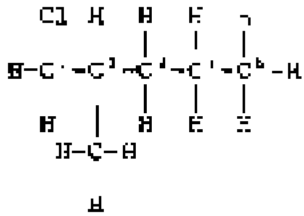


(c) 3-chloropentane

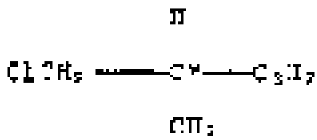


This molecule contains no chiral center since no carbon atom contains four different groups.

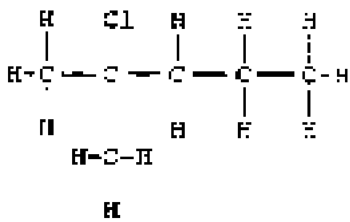
(d) 1-chloro-2-methylpentane



C^2 is a chiral carbon, thus this molecule is chiral. It can be better represented as:

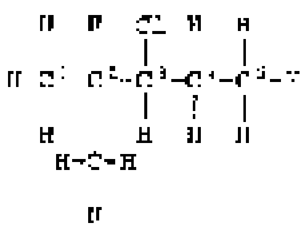


(e) 2-chloro-2-methylpentane

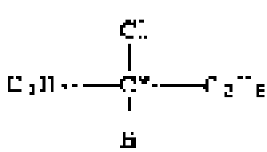


This molecule contains no chiral center and is not chiral.

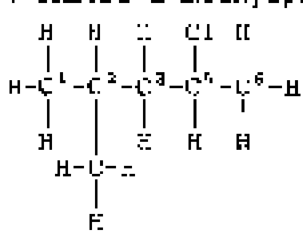
(f) 3-chloro-2-methylpentane



C^3 is a chiral carbon and thus the molecule is chiral. It can be better represented as:



(g) 4-chloro-2-methylpentane



C^1 is a chiral carbon and thus the molecule is chiral. It can be better represented as:

```
        Cl
        |
C2H5 —— C* —— CH3
        |
        H
```

(h) 1 chloro 2 bromobutane

```
  Cl  H   H   H
  |   |   |   |
H-C1 -C2 -C3 -C4 -H
  |   |   |   |
  H   Br  H   H
```

C^2 is the chiral carbon and thus this molecule is chiral. It can be better represented as:

```
          H
          |
ClCH2 ——— C* ——— C2H5
          |
          Br
```

Thus, only molecules b, c, f, g, and h contain chiral carbons and are thus chiral.

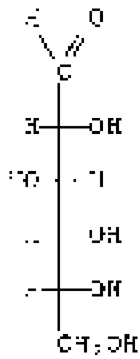
• PROBLEM 5-6

Each of the following compounds is involved in biological chemistry or medicine. Identify all of the chiral centers and indicate how many stereoisomers of each compound are possible. (Note that the biological activity is usually associated with a particular stereoisomer.)

(a) general formula for a hexose sugar

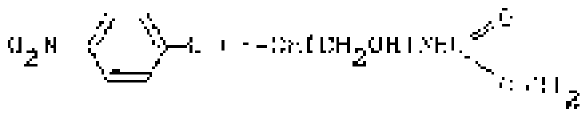
```
H   O
 \ //
  C
  |
 CHOH
  |
 CHOH
  |
 CHOH
  |
 CHOH
  |
 CH2OH
```

(b) glucose (blood sugar)



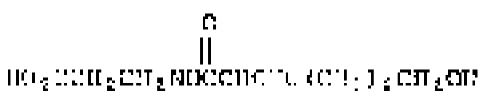
(c) ambucetamide (anti-spasmodic)

(d) chloramphenicol (antimicrobial)

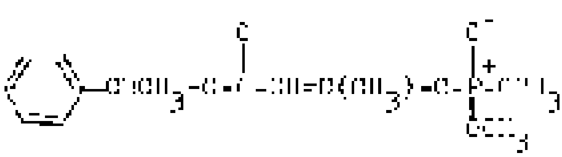


(e) α-chloro-α-phenylacetylurea (anti-epileptic)

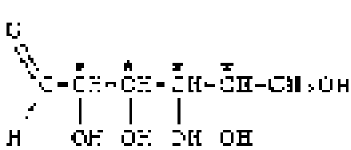
(f) pantothenic acid (human nutrition)



(g) Ciodrin (ectoparasite control in livestock)



Solution: In general, the maximum number of stereoisomers that are possible for a compound with n chiral centers is given by 2^n. For example, a compound with 3 chiral centers can have a maximum of 2^3 or 8 stereoisomers.

(a) 

The chiral centers are marked by *. There are 2^4 or 16 stereoisomers possible.

(b) This molecule is one of the 16 possible stereoisomers of (a). So this molecule can have 15 possible stereoisomers.

(c) There is only one chiral center in this structure:

```
C    NH2
 \\ /
  C
  |
-*C-H
  |
```

Thus there are 2^1 or two possible stereoisomers.

(d) There are two chiral centers in this structure:

```
 *   *
-CH-CH-
 |   |
 OH  CH2OH
```

Four possible stereoisomers are thus present.

```
      *
(e)  -CH-                 one chiral center
      |
      Cl           ∴      two possible stereoisomers

      *
(f)  -CH-                 one chiral center
      |
      OH           ∴      two possible stereoisomers

      *
(g)  -CHCH3-              one chiral center

                   ∴      two possible stereoisomers
```

• PROBLEM 5-5

Many biologically important compounds contain prochiral centers. Identify all of the prochiral centers in the following:

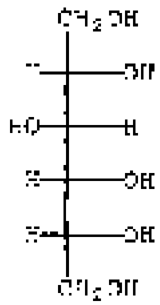
(a) nitroglycerin (coronary vasodilator)

```
*CH2ONO2
 |
*CHONO2
 |
*CH2ONO2
```

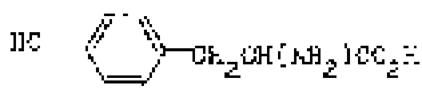
(b) Phorate (systemic insecticide)

```
               OCH2CH3
               |
CH3CH2-O——P-S-CH2-S-CH2CH3
               ‖
               S
```

(c) sorbitol (humectant; candy manufacture)

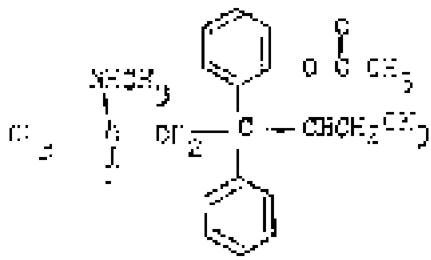


(d) tyrosine (amino acid)

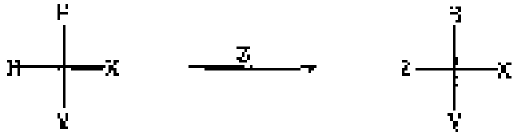


(e) tyramine (sympathomimetic)

(f) noracymethadol (narcotic analgesic)



Solution: A prochiral center contains two identical and two unidentical substituents, and is thus not chiral. However, replacement of one of the identical substituents with a completely different one (which is not identical to any of the other substituents) will convert the prochiral center into a chiral center.



prochiral center chiral center

(a) All three carbons are prochiral centers. The first and third carbon atoms can become chiral by replacement of either hydrogen. The middle carbon can become chiral if replacement of either of the $-ONO_2$ groups on carbons 1 and 3 or of an entire $-CH_2ONO_2$ group occurs.

(b) All $-CH_2$ groups have prochiral carbons, and replacement of their hydrogens would give chirality. The P atom is prochiral, and replacement of either $-OCH_2CH_3$ group would result in a chiral P.

(c) Replacement of the hydrogens of C_1 and C_3 would convert these carbons to chiral centers. All other carbons are already chiral.

(d) Both the CH_2 and the NH_2 group have prochiral centers, and substitution of hydrogen atoms would give chirality. (The unshared pair of electrons in $-NH_2$ can be thought of as a substituent.)

(e) Replacing the H's of the CH_2 groups or the H's of the NH_2 group would give rise to chiral centers.

(f) The carbons of the CH_3 groups are prochiral. The central carbon atom is prochiral, with replacement of either phenyl group leading to chirality.

ENANTIOMERISM

● PROBLEM 5-7

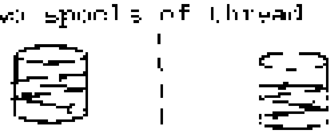
Which of the following idealized objects is capable of existing as pairs of enantiomers?

(a) a spool of thread
(b) a spool of thread with all the thread and labels removed
(c) a conch shell
(d) a coiled cable connecting a telephone receiver to the instrument

Solution: Enantiomers are compounds that are non-superimposable mirror images of each other. They contain identical subunits which are oriented differently. Enantiomers are a class of stereoisomers.

Stereoisomers are compounds with the same molecular formula, but different molecular structures due to different spatial arrangement or orientation of substituent atoms or groups.

(a) A spool of thread can exist as a pair of enantiomers. This is because the thread has a direction which it is wound in. Two spools of thread



can exist which are wound in opposite direction to each other.

(b) A spool of thread with all the thread and labels removed would not exist as an enantiomeric pair. This is because there is nothing on the symmetric spool to show direction. The mirror image of the spool will be superimposable upon it.

(c) A conch shell could exist as an enantiomeric pair. The spirality of the shell can be in two possible directions which are opposite to each other, like two spirals wound in different directions. These two spirals

cannot be superimposed. They are therefore not identical.

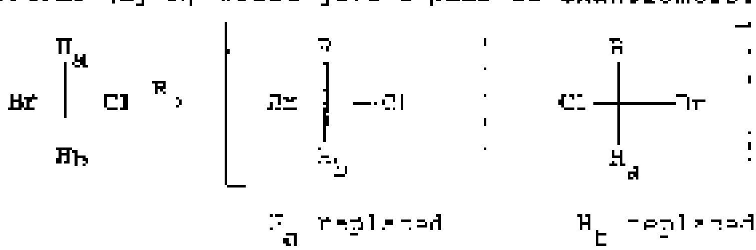
(d) A coiled cable connecting a telephone receiver to the instrument is capable of existing as a pair of enantiomers. The coil of the telephone is similar to the spiral in (c). There are two possible directions to the coil (clockwise and counterclockwise) so that the coil and its mirror image cannot be made to superimpose.

● **PROBLEM 5-8**

Identify one pair of enantiotopic groups in each of the following:

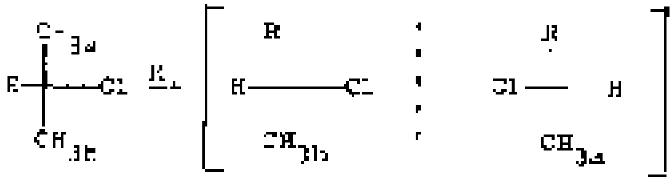
(a) CH_2ClBr (d) $ClCH_2CH_2Br$
(b) $CHCl(CH_3)_2$ (e) $ClCH_2CH_2Cl$
(c) $CHCl(CH_2CH_3)_2$

Solution: (a) Replacement of either of the two methylene protons (by R) would give a pair of enantiomers.

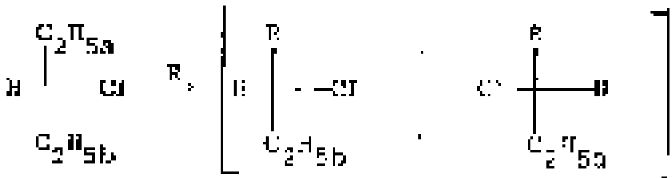


H_a replaced H_b replaced

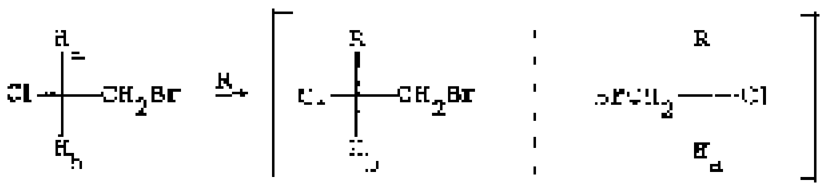
Such pairs of protons (H_a and H_b) are called enantiotopic protons.

(b) 

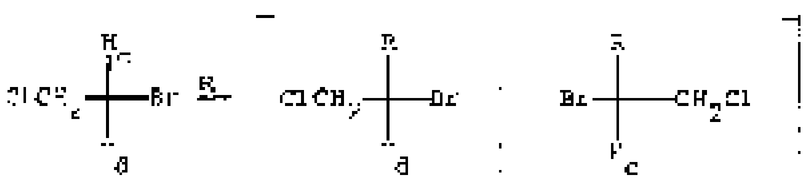
The two methyl groups are enantiotopic groups. So we see that not only protons (H) may be enantiotopic, but entire groups of atoms can be enantiotopic.

(c) 

Replacement of either ethyl group gives a pair of enantiomers. Thus the two ethyl groups are enantiotopic.

(d) 

AND

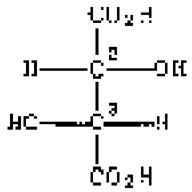


Thus, there are two pairs of enantiotopic protons: H_a and H_b, and H_c and H_d.

(e) $ClCH_2CH_2Cl$. In the same way as in problem (d) we can see that the hydrogens of either methylene group are enantiotopic hydrogens.

• PROBLEM 5-9

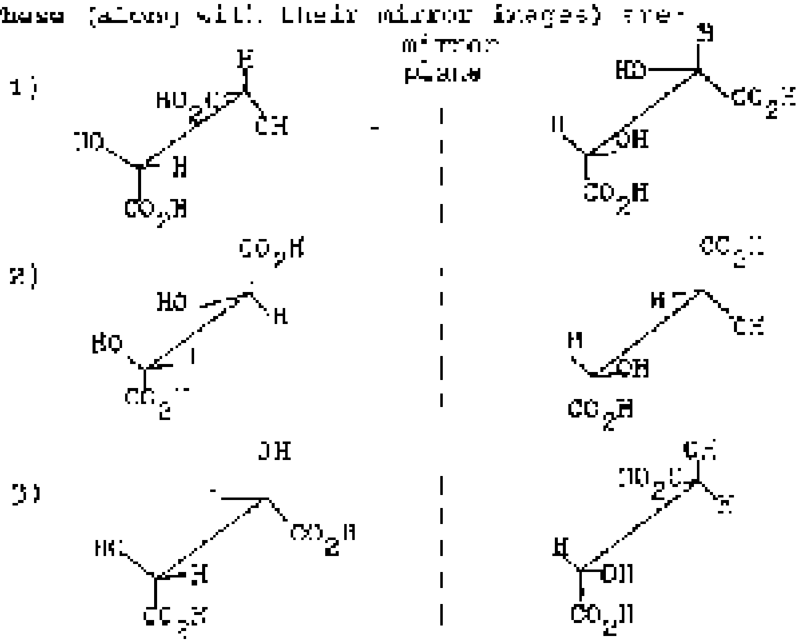
Draw the structures of all the different staggered conformations possible for (+) tartaric acid (shown below). Are any of these identical with their mirror images? How many optically active forms of tartaric acid could there be altogether if rotation were not possible about the C_2-C_3 bond and only the staggered conformations were allowed.



(+)-tartaric acid

Solution: Different conformations of a molecule result from rotation about single bonds. The bonding between atoms does not change, so different conformational isomers have the same configuration about their chiral centers.

Three different staggered conformations of (+)-tartaric acid result from rotation about the C_2–C_3 bond. These (along with their mirror images) are:



(+)-tartaric acid (–) tartaric acid

None of the staggered conformations of (+)-tartaric acid have superimposable mirror images.

If rotation were not possible about the C_2–C_3 bond, then any molecule of tartaric acid would be "locked" in one conformation. Assuming that only staggered conformers are allowed, there would be three enantiomeric pairs of tartaric acid possible (or a total of six isomers that are staggered).

If rotation about the C_2–C_3 bond were allowed to occur, interconversion between the conformers would render the three forms indistinguishable from each other.

• PROBLEM 5-10

Arrange the following sets in order of decreasing priority.

(a) $-H$, $-CH_3$, $-C_2H_5$, $-C(CH_3)_3$, $-CH(CH_3)_2$

(b) $-CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_2CH_3)_2$

(c) $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_2CH_2CH_2CH_3$, $-C(CH_3)_2CH_2CH_3$

__Solution:__ To answer this question we must know the rules used to assign priority. Priority is given to the substituent atom highest in atomic number. Thus I has priority over Br and Br has priority over Cl. Here are some more examples:

$$Cl > O > N > H$$

But when two atoms in comparison are identical and hence have equal priority, precedence is given to the one that has substituent groups of higher atomic number, or one that has a greater number of heavy substituent atoms. For example,

$$-CHCl_2 > -CH_2Cl,$$

because in the first group, the carbon is attached to two chlorine atoms, while in the other structure the carbon is bonded to only one chlorine.

```
       CH3         CH3        H
                    |
(a)    C—CH3 ,      C—H ,     C—CH3 ,   —CH3 ,    H
                    |
       CH3         CH3        H

       (1)         (2)        (3)        (4)       (5)
```

In structure 1 we have three carbons bonded to the central carbon. In structure 2 we have only two carbons bonded to the central carbon. In structure 3 there is only one carbon bonded to the central carbon. Structure 4 has only one carbon, while structure 5 has only a hydrogen atom. So we have in order of decreasing priority:

$$C(CH_3)_3 > CH(CH_3)_2 > C_2H_5 > CH_3 > H$$

```
       C2H5      H CH3       H H
        |        | |         | |
(b)   —C—H  >  —C—C—H  >  —C—C—CH3
        |        | |         | |
       C2H5      H CH3       H H

       CH3                  CH3                  CH3
        |                    |                    |
(c)   —C—CH2—CH2—CH3  >  —C—CH2—CH3  >   —CH—CH2—CH3
        |                    |
       CH3                  CH3
```

Draw and specify as R or S the enantiomers of:

(a) 3-chloro-1-pentene
(b) 3-chloro-4-methyl-1-pentene
(c) $HOOCCH_2CHOHCOOH$, malic acid
(d) $C_6H_5CH(CH_3)NH_2$

Solution: This problem deals with configuration, the arrangement of atoms that characterizes a particular stereoisomer. One method of assigning configuration, called the Cahn-Ingold-Prelog Method, is by use of the prefixes R and S. Two steps are involved in this process: In step 1, a set of sequence rules is followed. A sequence of priority is assigned to the four atoms or groups of atoms attached to the chiral center. (Recall, an atom to which four different groups are attached is a chiral center.) In step 2, the molecule is oriented so that the group of lowest priority is directed away from us. We observe, then, the arrangement of the remaining groups. If our eye travels in a clockwise direction in going from the group of highest priority to the groups of lower priority, the configuration is specified R. If eye movement is counterclockwise, the configuration is specified S.

At this point, the problem is how do we assign priority, that is, what are the sequence rules? For simplicity, we can note three sequence rules:

Sequence Rule 1: If the four atoms attached to the chiral center are all different, then priority depends on atomic number, with the atom of higher atomic number getting higher priority. In the case of two atoms being isotopes of the same element, the atom of higher mass number has the higher priority.

Sequence Rule 2: If sequence rule 1 fails to establish priority, then a similar comparison of the next atoms attached to the groups is made. In other words, if two atoms attached to the chiral center are the same, the atoms attached to each of these first atoms are compared.

Sequence Rule 3: Both atoms are considered to be duplicated or triplicated when there exists between them a double or triple bond. For example:

```
  H            H                          N  C
  |                                          |
-C=O  equals -C-O   and  -C≡N   equals  -C-N
                 |                        |  |
               O C                        N  C
```

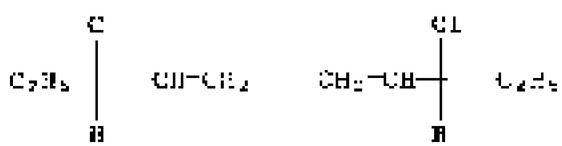
Now that we know how to specify configuration, we need to know a method that allows us to draw these enantiomers. One method is to draw a cross (+) and attach to the four ends the four groups that are bonded to the chiral center; the point where the lines cross denotes the location of the chiral center. For example, 2-chlorobutane ($CH_3CHClCH_2CH_3$) may be represented by

, which are enantiomeric forms.

It is important to recognize the fact that in such representation the horizontal lines denote bonds coming toward us out of the plane of the paper, whereas the vertical lines represent bonds going away from us behind the plane of the paper.

With this information, it is now possible to draw and specify as R or S the following enantiomers (mirror image isomers):

(a) 3-chloro-1-pentene ($CH_2=CHCHClCH_2CH_3$)



R S

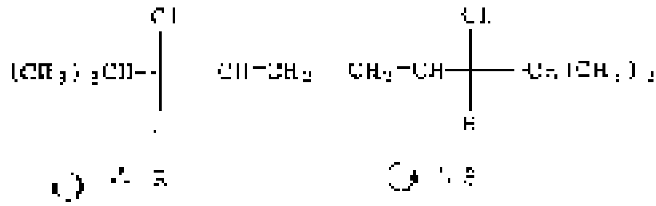
Explanation: These enantiomers are drawn so that the chiral carbon of each structure is located at the intersection of the lines. The four groups attached to the chiral center are positioned at the four ends. To establish configuration, the priority of the groups must be determined. To do this recall that sequence rules must be followed. As mentioned in sequence rule 1, priority depends on atomic number. Chlorine has the highest atomic number, so that it has the highest priority. Hydrogen, with the lowest atomic number, has the lowest priority. The two other atoms bonded to the chiral center are carbon atoms. But note that one carbon atom is involved in a double bond, so (in accordance with rule 3) it is duplicated and has the higher priority. Overall, then, we can rank in increasing priority the following groups of atoms:

H, C_2H_5, $CH=CH_2$, Cl →
increasing priority

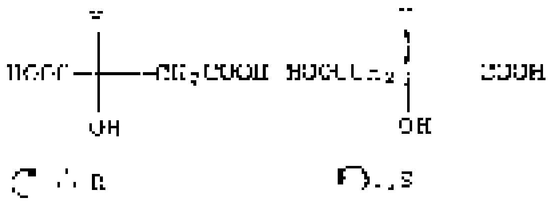
At this point, recall that the group of lowest priority must be directed away from us. Note that the drawings given accomplish this. The hydrogen atom, the group of the lowest priority, is at the end of a vertical line. Consequently, it is directed away from us behind the plane of the paper. Finally, note that in the first configuration (the one to the left), our eyes move in clockwise (↻) direction in going from the group of highest priority (-Cl) to the groups of second ($CH=CH_2$) and third priority ($-C_2H_5$). Hence, this configuration is considered to be R. In the other configuration (the one to the right) our eyes move counterclockwise (↺), so that S should be assigned to this configuration.

In (b) – (d), the same kind of reasoning is used to obtain the following:

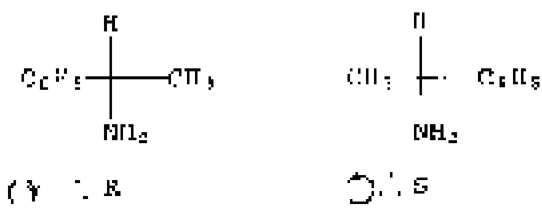
(b)



(c)



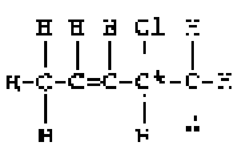
(d)



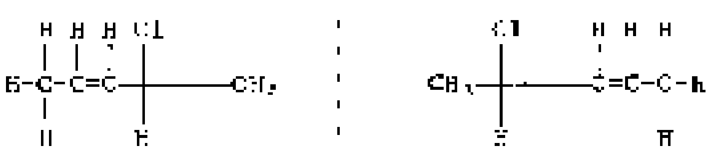
• **PROBLEM 5-12**

> Draw and label the enantiomers of each of the following compounds as either R or S:
>
> (a) 4-chloro-2-pentene (c) isopentylbenzene
> (b) isobutyl alcohol (d) phenylalanine

__Solution:__ (a) 4-chloro-2-pentene



Since there is one chiral center (C*), two (2) enantiomeric forms exist for this compound:



I II

According to the rules of sequence, the order of priority for the four groups is:

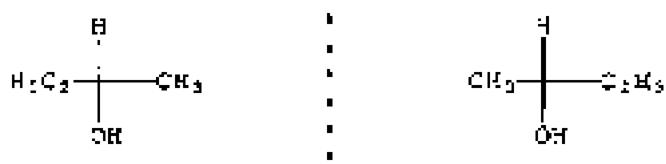
```
          H H H
          
Cl > H-C-C-C > CH3 > H

          H
```

H, the atom of the lowest priority, is visualized as extending away from us behind the plane of the paper. Now follow the three remaining groups in decreasing priority. In doing this, figure I leads our eye into a counterclockwise movement, thus the chiral carbon of this structure is assigned an absolute configuration of S. Figure II leads our eye into a clockwise movement, thus II has an absolute configuration of R. Notice that since these two structures are enantiomers, they are assigned opposite absolute configurations as expected.

(b) Isobutyl alcohol

```
   H H H  H
   | | |  |
H-C-C-C*-C-H
   | |  |
   H H OH H
```

C* is a chiral center. We can immediately see that two enantiomers are possible for this compound:

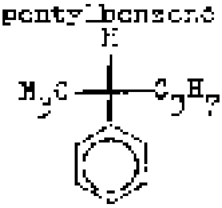


I   II

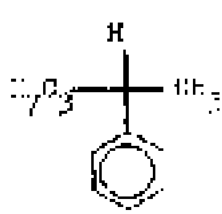
The order of priority is $OH > C_2H_5 > CH_3 > H$. With H visualized as projecting away from us, we can see that the remaining groups are arranged, according to decreasing priority, in a clockwise manner in I and in a counterclockwise manner in II. Thus I has an absolute configuration of R while that of II is S.

Using the same reasoning, we can determine the configuration of the enantiomers of (c) and (d).

(c) Isopentylbenzene



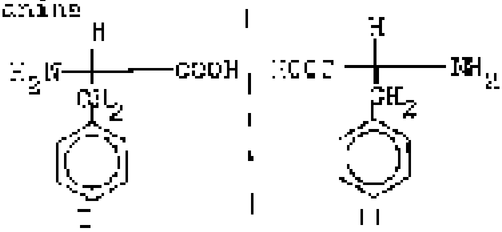
I



II

	I	II
Priority	$C_6H_5 > C_2H_5 > CH_3 > H$	
Arrangement of substituents in decreasing priority	counterclockwise	clockwise
Configuration	S	R

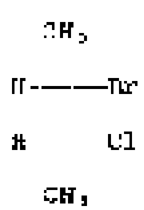
(d) Phenylalanine

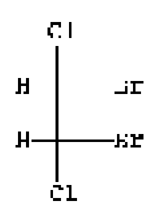


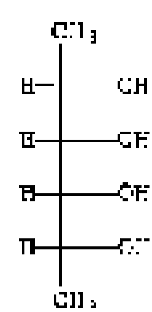
	I	II
Priority	$NH_2 > COOH > CH_2C_6H_5 > H$	
Arrangement	clockwise	counterclockwise
Configuration	R	S

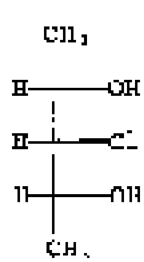
PROBLEM 5 18

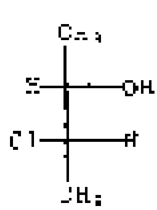
Assign R or S to each asymmetric atom in the following compounds:

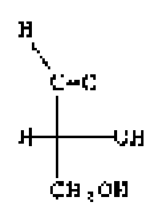
(a) 

(b) 

(c) 

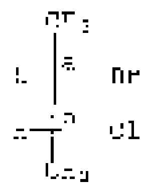
(d) 

(e) 

(f) 

Solution: This problem differs from the previous two only in that it calls for the determination of absolute configuration for more than 1 chiral carbon in the same compound. The solution to this problem makes use of the knowledge we have gained previously concerning priority determination and R-S assignment.

(a)



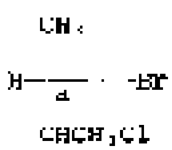
As we can see immediately, there are two chiral carbons in this structure (C_a and C_b). The order of priority of the substituent groups with the chiral center at C_a is

$$Br > \underset{\displaystyle CH_3}{\overset{\displaystyle Cl}{C}}-H > CH_3 > H$$

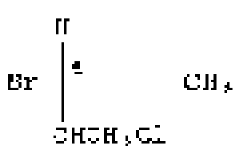
the order of priority with the chiral center at C_b is

$$Cl > \underset{\displaystyle CH_3}{\overset{\displaystyle Br}{C}}-H > CH_3 > H .$$

Focusing our attention first on chiral carbon a, we can draw the following:

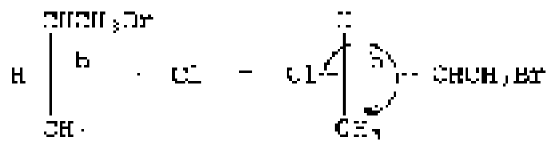


Recall that in this type of representation horizontal lines indicate bonds coming toward us out of the plane of the paper, and vertical lines bonds that point away from us behind the plane of the paper. We can draw an equivalent structure in which H, the lowest priority group, is at the end of a vertical line and pointing away from us (in accordance with step 2 in the method for R-S assignment. See last two solutions.):



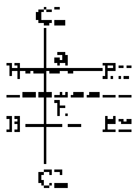
Now, with H visualized as extending away from us, follow the remaining groups in decreasing priority. This will lead our eye into a counterclockwise movement. Thus C_a has a S configuration.

Let us now focus on chiral carbon b. Using the same approach we can find that C_b has a R configuration.



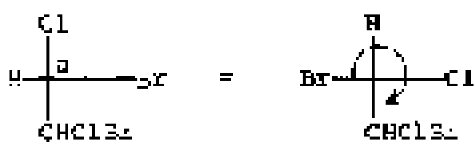
R

(b)

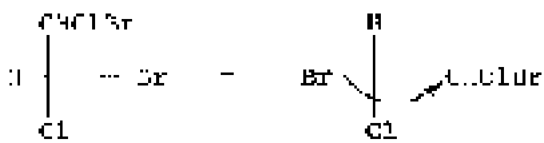


Again, there are two chiral carbons in this structure (C_a and C_b). This is a meso compound.

Focusing on one chiral center at a time, we can find that C_a has a configuration of R while C_b a configuration of S.



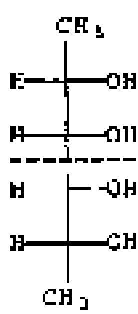
∴ R



∴ S

Using the same approach, we can assign R-S configuration to the chiral centers in compounds (c) to (f).

(c)

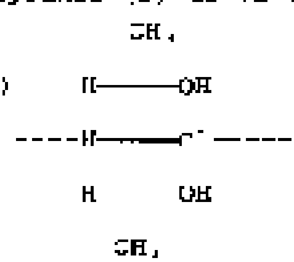


[illegible]
[illegible]
R
R

meso compound

(with 4 chiral centers)

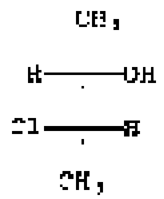
(d)



S
R

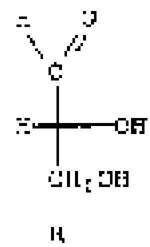
meso compound

(with 2 chiral centers)

(e)  S

S

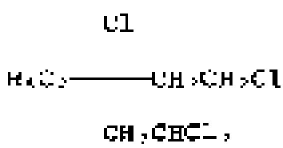
(2 chiral centers)

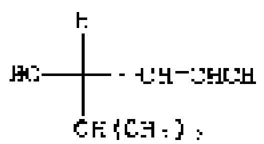
(f) 

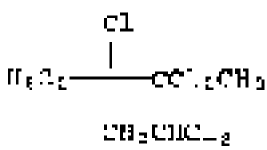
(1 chiral center)

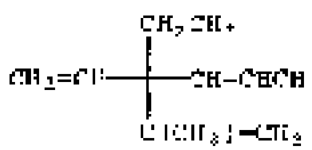
• PROBLEM 5-14

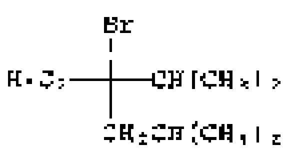
Assign absolute configuration to the chiral centers below.

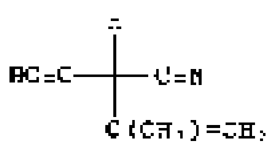
(a) 

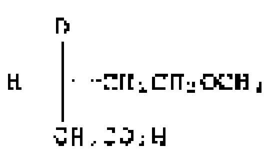
(f) 

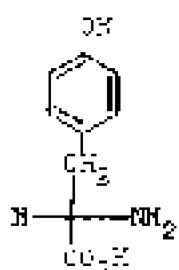
(b) 

(g) 

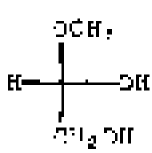
(c) 

(h) 

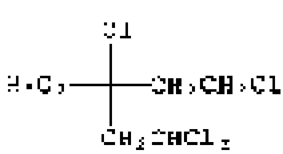
(d) 

(i) 

(tyrosine)

(e) 

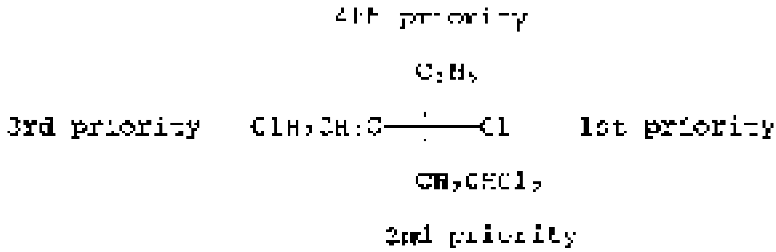
Solution:

(a) 

The order of priority of the substituent groups in this compound is

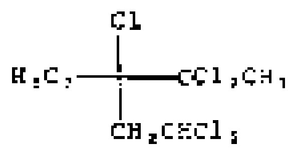
$Cl > CH_2CHCl_2 > CH_2CH_2Cl > C_2H_5$.

Rewriting the structure so that C_2H_5, the group of the lowest priority, is at the end of a vertical line (symbolizing a bond pointing away from us) gives the following:

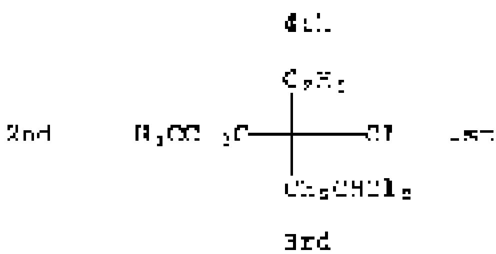


We can now see that the substituent groups are arranged in a clockwise (R) manner according to priority, and the chiral center therefore has a R configuration.

(b)

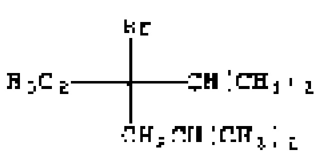


The order of priority is $Cl > CCl_2CH_3 > CH_2CHCl_2 > C_2H_5$. Redrawing the structure gives

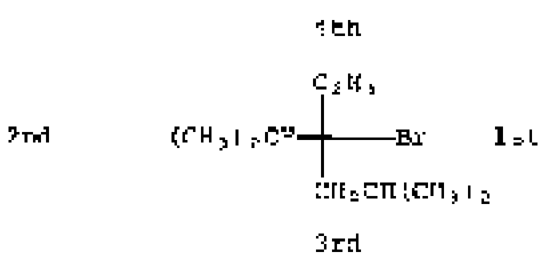


in which C_2H_5, the lowest priority group, is directed away from us. The substituents show a counterclockwise arrangement according to priority, and the absolute configuration about the chiral center is therefore S.

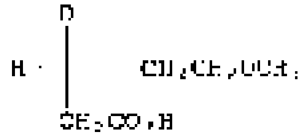
(c)



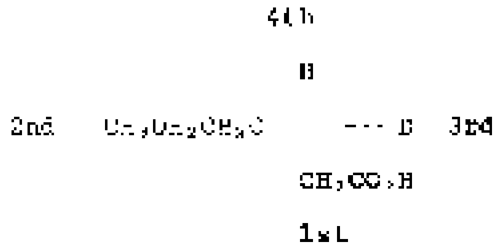
Redrawing gives



The chiral center has a configuration of S.

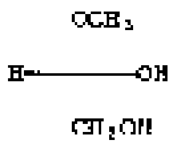
(d) 

Redrawing gives

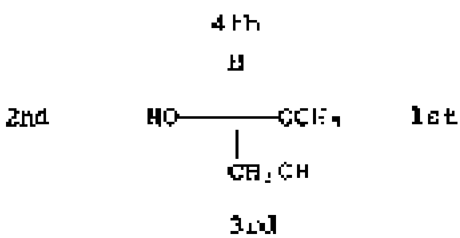


Note:
H and D are isotopes of the same element, D being the heavier of the two.

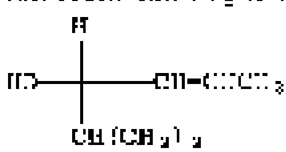
The chiral center of this structure should be assigned a R configuration.

(e) 

Redrawing gives:

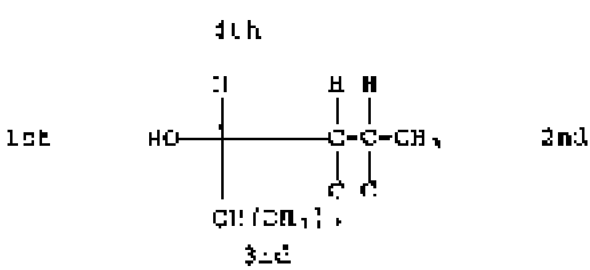


The correct configuration therefore is S.

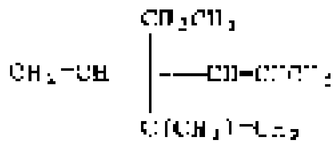
(f) 

Recall that Sequence Rule # 3 states, that atoms involved in a double bond are duplicated, and those in a triple bond are triplicated.

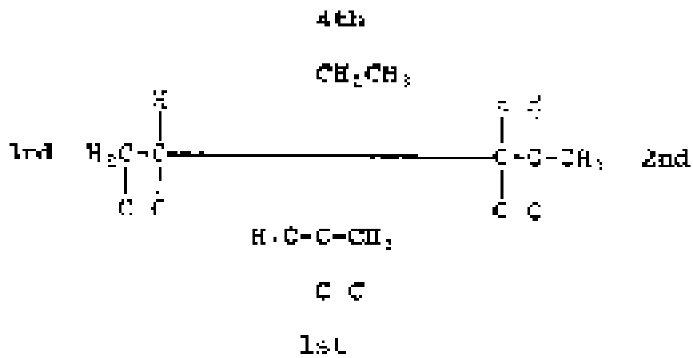
Redrawing the structure gives us the following:



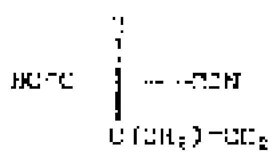
The correct configuration assigned to the chiral center of this structure is therefore R.

(g) 

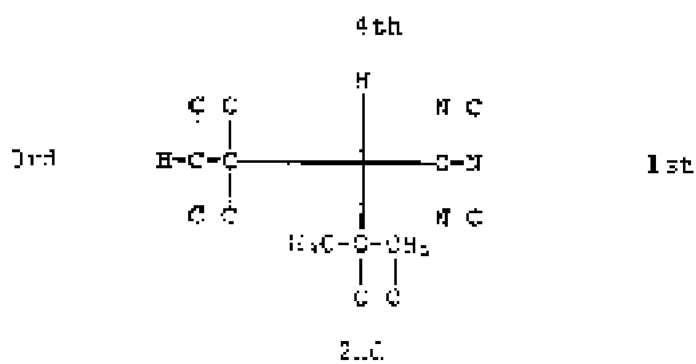
The expanded form of this structure is



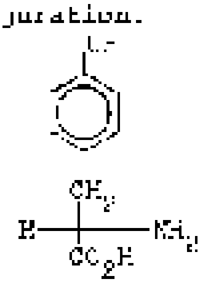
The configuration therefore is S.

(h) 

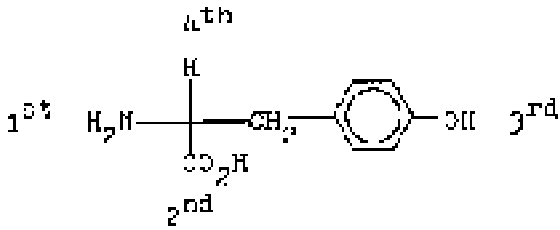
The expanded form is



The chiral center of this structure has a R configuration.

(i) 

Redrawing gives:



S is the correct configuration.

● PROBLEM 5-15

The enantiomer of (+)-(R)-malic acid occurs in many fruits and is called "apple acid." Draw a three dimensional structure of apple acid. What is its sign of rotation? What is its absolute configuration?

Solution: The sign of rotation tells us the direction that the molecule will rotate the plane of polarization: to the right if it is (+) or to the left if it is (-). The signs of rotation of a pair of enantiomers are always opposite.

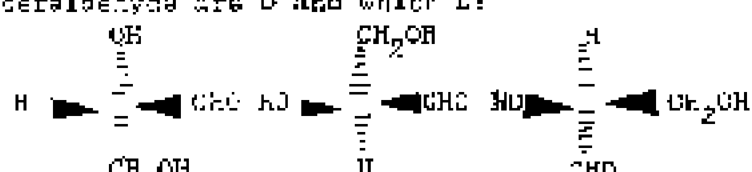
The arrangement of atoms that characterizes a particular stereoisomer is called its configuration. To assign absolute configuration we use the R and S system. A pair of enantiomers will always have opposite absolute configurations.

Hence, the enantiomer of (+)-(R)-malic acid must be (-)-(S)-malic acid, also called "apple acid".

(+)-(R)-malic acid (-)-(S)-malic acid

● PROBLEM 5-16

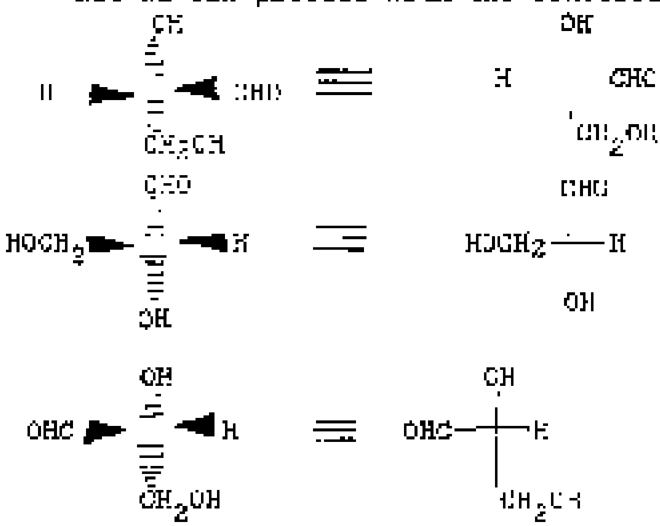
Designate which of the following configurations of glyceraldehyde are D and which L:



Solution: The use of D and L to specify the configuration about a chiral carbon is the Fischer Convention. It is an older method now used primarily for sugars.

In the Fischer Convention, the type of structural formula used is the Fischer projection. Thus we should convert the structural representation of the glyceraldehydes given in the problem into the Fischer projection. First, a cross is drawn. The location of the chiral (assymmetric) carbon is represented by the intersecting point of the two lines of the cross. The horizontal lines extending to the left and right of this point represent bonds extending forward, above the plane of the paper. The vertical lines represent bonds extending back, below the plane of the paper.

Now we can proceed with the conversion.



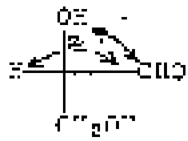
As we can see, all these molecules are enantiomers. In the Fischer system, each member of a pair of enantiomers is specified as either D or L. An isomer is said to be D

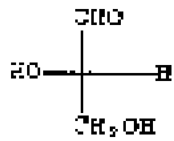
D-glyceraldehyde L-glyceraldehyde

if, when it is written with the aldehyde group at the top and the other carbon-containing group at the bottom in the Fischer projection, the OH group is on the right hand side. Its enantiomer is said to be L. (Note that D or L does not refer to the sign of rotation of the plane of polarized light which is indicated by (+) or (−). D or L isomers may be either positive or negative depending on the particular compound involved.)

In order to put the molecule into the correct con figuration (CHO at the top, CH_2OH at the bottom) one may interchange any two pairs of substituents and still retain the same configuration. (If only one pair of substituents is interchanged, the enantiomer is generated.)

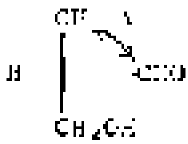
Applying these principles to the configurations of glyceraldehyde given:

(1) 



L-glyceraldehyde

The OH is on the left, so the molecule is L-glyceraldehyde. Note that exchanging only one pair of substituents would give rise to the D isomer, its enantiomer:



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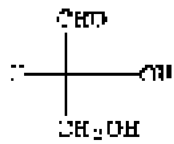
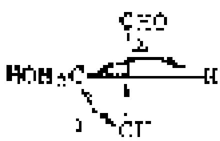


D-glyceraldehyde

(2) 

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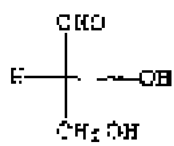
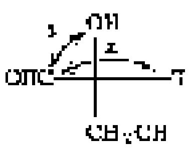


D-glyceraldehyde

(3) 

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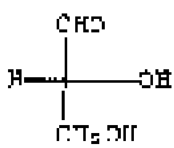


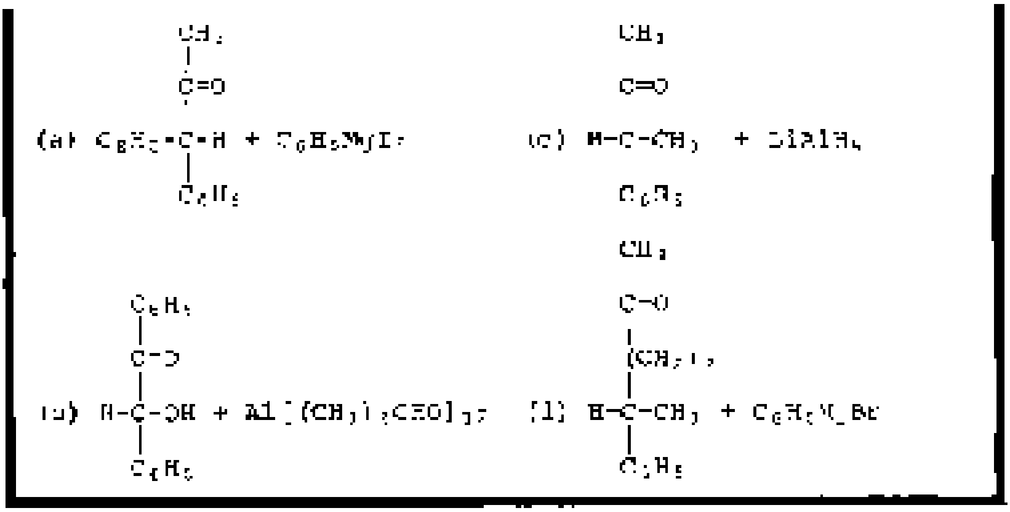
D-glyceraldehyde

In (2) and (3), the OH is on the right. The molecules are D-glyceraldehyde.

DIASTEREOMERISM

• PROBLEM 5-17

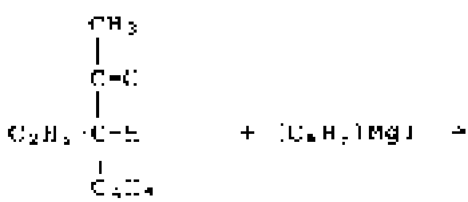
Write structures showing the configuration of each of the possible products to be expected from the following reactions. Which diastereomer would you expect to be formed preferentially, assuming that the substituents decrease in size in the order C_6H_5 > C_2H_5 > CH_3 > OH > H?



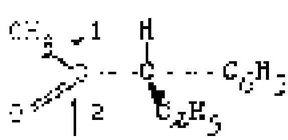
Solution: An understanding of the mechanism of the four reactions is necessary in order to be able to predict the predominating product of each reaction.

All four reductions involve attack of the carbonyl group. Since the atoms of the carbonyl group lie in a plane, attack can occur from either of the two sides of the plane, that is, either from above or below the plane and perpendicular to it. Because of the two possible directions of attack, the resultant tetrahedral carbon (originally of the carbonyl group), if chiral, will have one of two possible configurations (R or S). The predominating product of the reduction will result from the more sterically favored and thus more frequent attack.

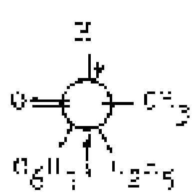
(a)



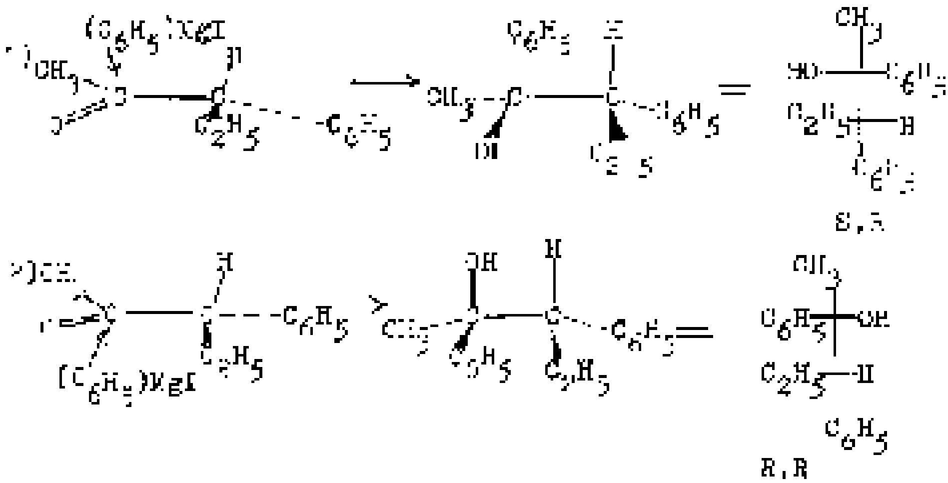
First, it is helpful to picture the compound in a three dimensional manner. (Use models if necessary.)



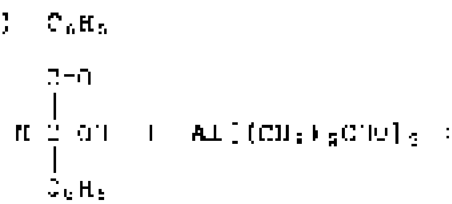
or



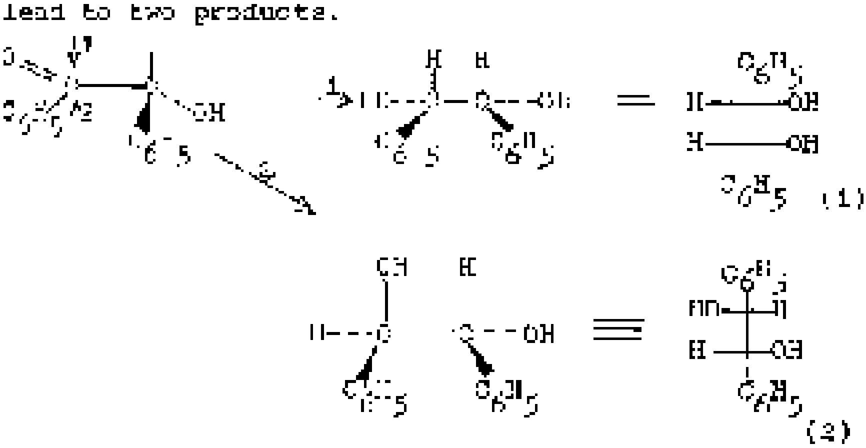
The two possible directions of attack of the carbonyl group are indicated by arrows so we have the following possible reaction mechanisms:



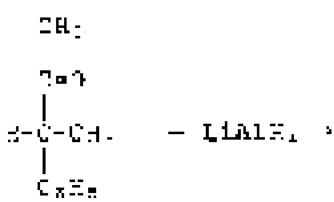
As we can see, attack 2 will have to overcome more steric hindrance (due to $-C_2H_5$ and $-C_6H_5$ groups) than attack 1. Therefore, the S, R product will predominate over the R,R product.

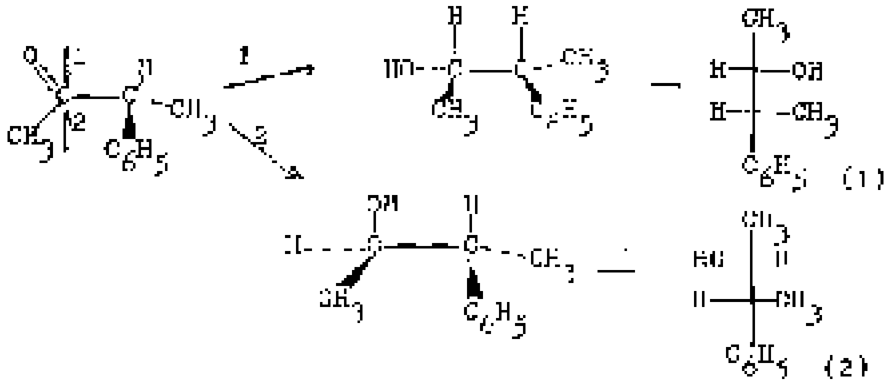
(b) 

Again, the two possible directions of attack will lead to two products.



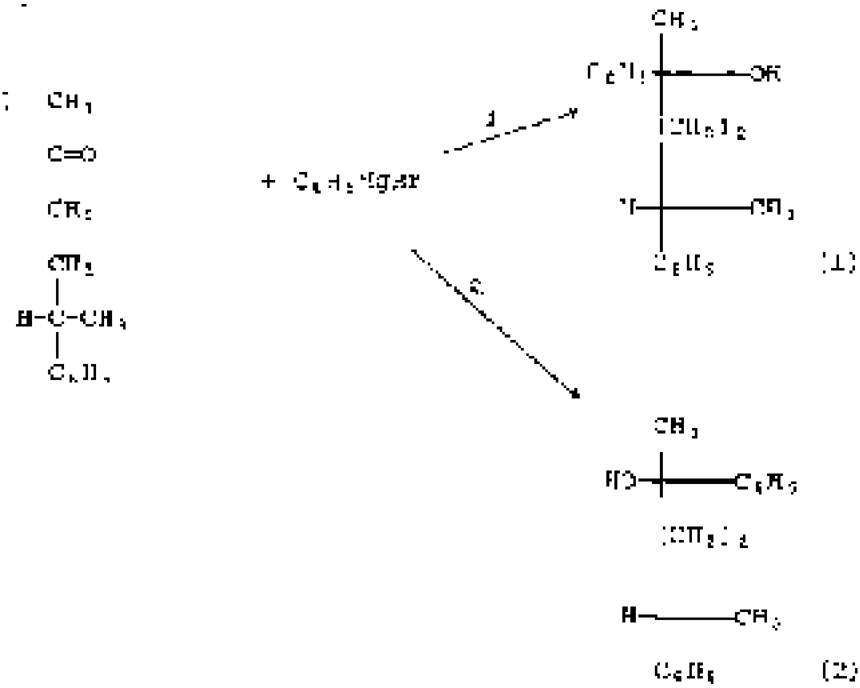
Attack 1 is more sterically favored, therefore, the first product will be formed preferentially.

(c) 



Product 1 will be formed in preference to product 2.

(d)



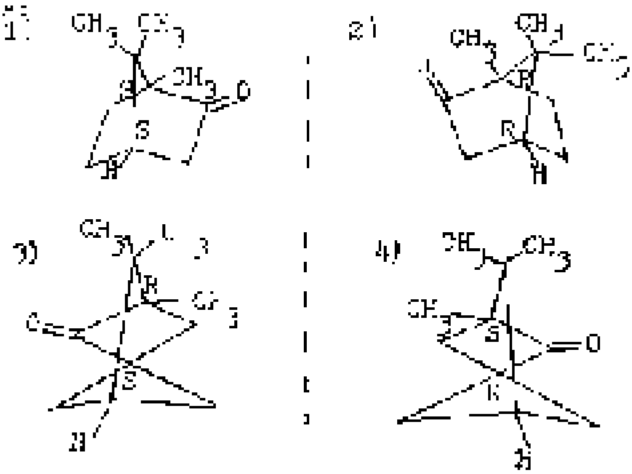
Due to the presence of the two $-CH_2$ groups, which increases the distance between the carbonyl group and the bulky $-CH_3$ and $-C_6H_5$ substituents, there is no significant difference in the steric environment at the carbonyl group in formation of either product. Thus, 1 and 2 will be formed in approximately equal amounts.

• PROBLEM 5-18

Camphor has two asymmetric carbons, but only two optical isomers are known. Explain. (Models will be helpful.)

camphor

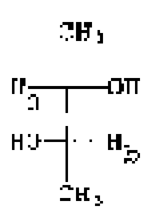
Solution: C_1 and C_4 are asymmetric carbons and therefore chiral centers. Theoretically, the number of possible stereoisomers of a molecule with n chiral centers is 2^n. In this case, $2^n = 2^2$ or 4. Drawing the possible isomers:

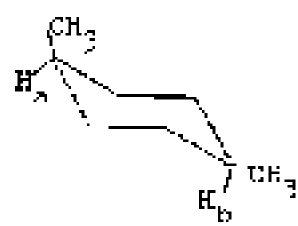


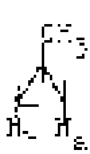
It is obvious that isomers 3 and 4 are impossibly strained. These isomers would not normally be formed. Note that isomers 3 and 4 would have been diastereomers of isomers 1 and 2. Therefore, camphor exists only in two enantiomeric forms (1 and 2).

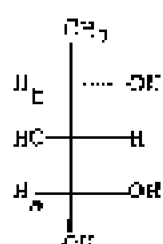
■ PROBLEM 5-19

In the following structures, indicate if H_a and H_b are identical, enantiotopic, or diastereotopic.

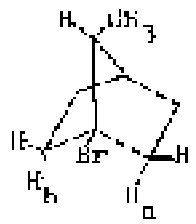
(a) 

(b) 

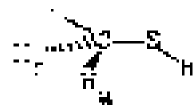
(c) 

(d) 

(e)

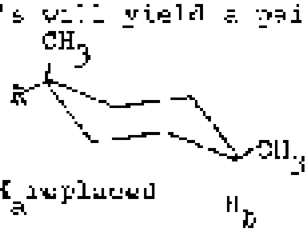


(f)



Solution: (a) If we replace either H_a or H_b we get identical structures, therefore we can call these two hydrogens identical.

(b) Here H_a and H_b are diastereotopic protons. Note that one hydrogen (H_b) is axial while the other (H_a) is equatorial. Since the environments of these two protons are not mirror images and lack a chiral center, replacing either of the two H's will yield a pair of diastereomers:



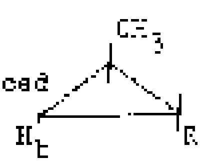
H_a replaced

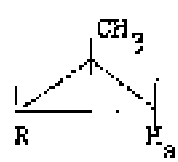
H_b replaced

These two protons can be identical if we allow the ring to undergo inversion.

(c) H_a and H_b are enantiotopic protons in this structure. Replacement of either of the two protons results in a pair of enantiomers:

H_a replaced





H_b replaced

Note that if the H's were positioned on the same side of the ring as $-CH_3$, the protons would be identical.

(d) Notice that both the carbons to which H_a and H_b are attached are chiral. Replacement of either H_a or H_b gives us a pair of enantiomers, hence the hydrogens are enantiotopic.

(e) H_a and H_b are enantiotopic. The reason is the same as that given in (d).

(f) The carbon to which H_a and H_b are attached is achiral. Replacement of either H_a or H_b gives us two identical structures and so the protons are identical.

Give the stereoisomers of:

(a) 2-butene (d) 1-bromo-1-chloropropene
(b) 2-pentene (e) 2-bromo-1-chloropropene
(c) 2,4-hexadiene (f) 1-bromo-1,2-dichloroethene

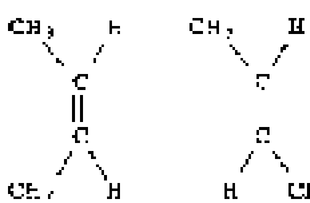
Indicate for each the isomer that is expected to predominate in an equilibrium mixture. Justify your answer.

Solution: Isomers differing from one another only in the way the atoms are oriented in space (but are like one another with respect to which atoms are attached to which other atoms) belong to the general class of stereoisomers. The particular kind of stereoisomers that owe their existence to hindered rotation about double bonds are called geometric isomers. Geometric isomerism can exist only when both atoms of the double bond carries two different substituent groups.

Geometric isomers have different physical properties: different melting points, boiling points, refractive indices, solubilities, densities, and so on. Therefore in principle geometric isomers can be separated from each other.

(a) Stereoisomers of 2-butene

2-Butene exists in two forms due to the presence of a double bond. The two geometric isomers of 2-butene are:

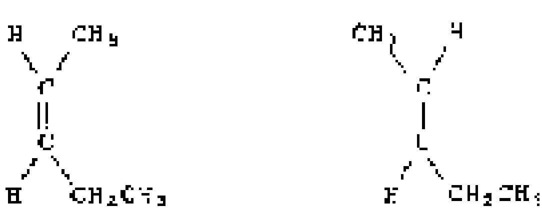


cis-2-Butene trans-2-Butene

In cis-2-butene, the methyl groups are on the same side of the double bond. In trans-2-butene they are on opposite sides. Thus cis isomers have the substituted groups on the same side of the double bond, while trans isomers have the substituted groups on opposite sides.

(b) Stereoisomers of 2-pentene

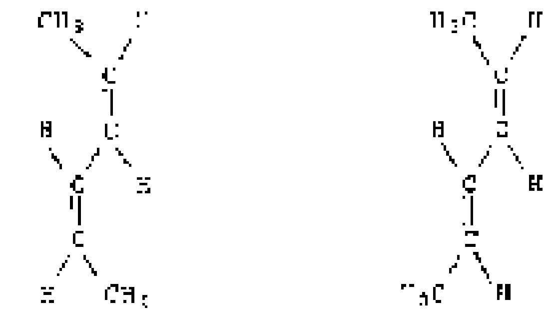
Two geometric isomers of 2-pentene exist:



cis trans

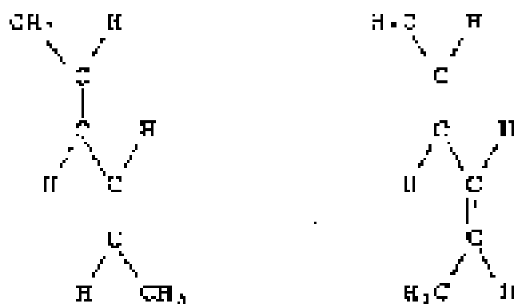
(c) Stereoisomers of 2,4-hexadiene

Owing to the presence of 2 double bonds, 3 geometric isomers are present:



cis, cis   cis, trans

identical

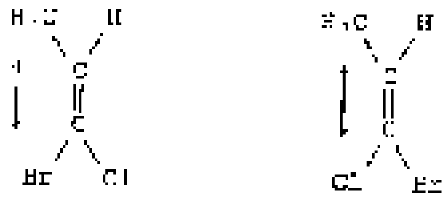


trans, trans   trans, cis

In general, because of greater steric strain present in the cis isomer due to closer spatial relationship of the substituted groups, the cis isomer is less stable than the trans. In an equilibrium mixture the trans isomer is expected to predominate on the basis of thermodynamic stability. Thus, trans-2-butene will predominate over cis-2-butene and trans-2-pentene will predominate over cis-2-pentene. In 2,4 hexadiene, the order of stability of the isomers is: trans, trans > trans, cis (same as cis, trans) > cis, cis. Therefore, the trans, trans isomer will predominate in an equilibrium mixture.

For the geometric isomers of (d), (e), and (f) the cis and trans prefixes are not useful. For them we use a different system of specification. We take the group of higher priority (determined by the Cahn Ingold Prelog Method) on the one carbon of the double bond and the group of higher priority on the other carbon, and see whether they are on the same side of the double bond or on opposite sides. If they are on the same side, the molecule is specified as Z (German: zusammen, together). If they are on opposite sides, the molecule is specified as E (German: entgegen, opposite).

(d) Stereoisomers of 1-bromo-1-chloropropene



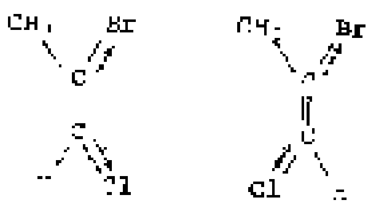
Z E

$CH_3 > H$

$Br > Cl$

The non-bonded interaction between $-CH_3$ and $-Br$ in the Z isomer is greater than that between $-CH_3$ and $-Cl$ in the E isomer. Therefore, the latter is more stable and is expected to predominate in equilibrium.

(e) Stereoisomers of 2-bromo-1-chloropropene



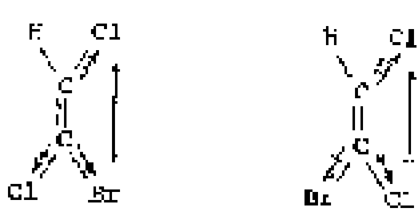
Z E

$Br > CH_3$

$Cl > H$

The strong electrostatic repulsion between the electron-rich bromine and chlorine atoms in the Z isomer renders it less stable than the E isomer.

(f) Stereoisomers of 1-bromo-1,2-dichloroethene



Z E

$Cl > H$

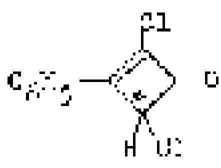
$Br > Cl$

Electrostatic repulsion is strong in both geometric isomers. The steric strain however is stronger in the Z structure (due primarily to non-bonded Br ↔ Cl interaction) than in the E structure (due primarily to Cl ↔ Cl interaction) for Br has a larger atomic size than Cl. Therefore the latter is a more stable form. It will, at least in principle, predominate in the equilibrium mixture.

RACEMIZATION

• PROBLEM 5-21

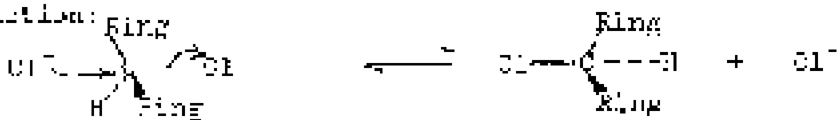
Compound A racemizes readily on heating to 100° but the rate is not affected by chloride ion and is the same in chloroform and acetic acid. Racemization in deuteroacetic acid (CH_3CO_2D) gives only undeuterated racemic A. Devise a mechanism for the reaction in accord with all the experimental facts.



(A)

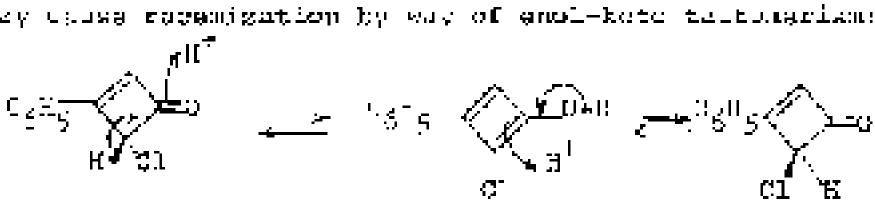
Solution: Racemization is the process which leads to formation of a racemic modification, a mixture of equal parts of enantiomers.

In compound A, there is only one asymmetric carbon (*). Chloride ion could promote racemization by a S_N2-type of reaction:



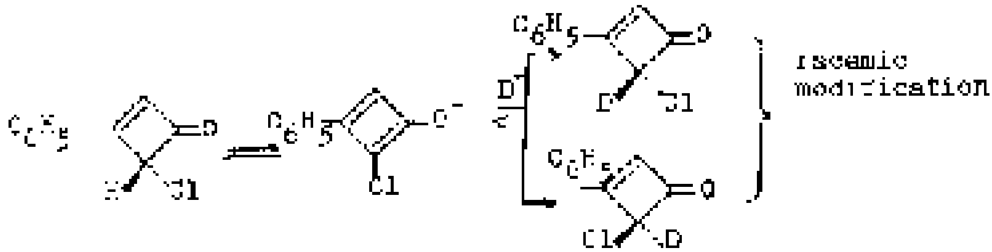
Attack by Cl^- inverts the configuration at the chiral carbon. Since the reaction is reversible, a racemic mixture will form as equilibrium is established. We are told, however, that chloride ion does not affect the rate of racemization. This is due likely to hindrance of chloride ion attack by the ring structure. Therefore, racemization probably does not proceed via the S_N2 mechanism.

Chloroform and acetic acid are both acidic solvents and may cause racemization by way of enol-keto tautomerism:



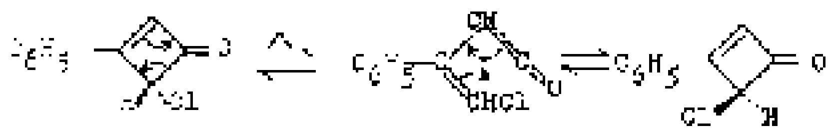
keto enol keto

If the racemization indeed proceeded via enol-keto interconversion, deuteroacetic acid could give deuterated racemic A in the following manner:



However, reaction with CH_3CO_2D does not result in any deuterated A, so we can conclude that racemization does not occur via enolization.

The racemization is therefore most reasonably explained by a single thermal reaction at 100°. Heat could cause reversible ring opening in the following manner:



Since the reaction is reversible, equilibrium will give the racemic mixture. Note that the reaction proceeds via electron exchange, and no substitution or addition of atoms occurs. Therefore, the reaction rate would not be affected by acids or chloride ions.

SPECTROSCOPY

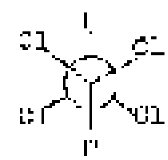
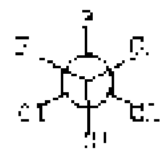
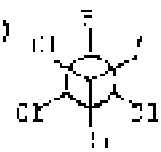
• PROBLEM 5-22

The fluorine nmr spectrum of 1,2-difluoro-tetrachloroethane, $CFCl_2CFCl_2$, shows a single peak at room temperature, but at − 120° shows two peaks of unequal area. Explain.

Solution: This observation is caused by the presence of conformational isomers of $CFCl_2CFCl_2$. Conformational isomers result from the rotation of groups of atoms about a single bond. (Recall that a single bond, in contrast to a double bond, allows free rotation.) Since they differ only in the way the atoms are oriented in space, conformational isomers are also stereoisomers. However, they should not be confused with other kinds of stereoisomers, which differ in their configurations about a chiral atom. For example, different configurational isomers can be either the R or the S forms of a compound. Yet each of the two forms has its own set of conformational isomers. All the conformational isomers of either form have the same configuration, but their subunits' orientation in space is different due to difference in the degree of bond rotation.

Since interconversion between conformational isomers involves only the rotation of a bond, the energy barrier between these isomers is relatively small, and thus interconversion will be rapid once the energy barrier is surpassed. (Interconversion between configurational isomers—R ⇌ S—would involve the breaking of covalent bonds, which requires a greater amount of energy.)

$CFCl_2CFCl_2$ has three possible staggered conformational isomers (the eclipsed conformers are too unstable to exist in significant amounts):

1) 
2) 
3) 

At room temperature, the speed of rotation about the C-C bond is fast, and the interconversion between the three isomers is rapid. A fluorine nmr spectrum of the molecule will then reflect only the average of the three environments (resulting from the three isomers) of the fluorine atoms. Thus only a single average signal is observed.

At − 120°, the speed of bond rotation is considerably slowed down. At this temperature there is not enough thermal energy to overcome the barriers. Interconversion is therefore very slow: so slow that separate signals are observed in the fluorine nmr, one for each environment. In isomers 2 and 3, the positions of the fluorine atoms with respect to each other and to the chlorine atoms are equivalent, so they are reflected by a single peak in the nmr. The environment of the fluorine atoms in isomer 1 is clearly different from that in 2 or 3, and it will give a separate peak (of only half the area of the other signal which results from the contributions of two isomers).

PREPARATION

• PROBLEM 5-23

(a) In a study of chlorination of propane, four products (A, B, C and D) of formula $C_3H_6Cl_2$ were isolated. What are their structures?

(b) Each was chlorinated further, and the number of trichloro products ($C_3H_5Cl_3$) obtained from each was determined by gas chromatography. A gave one trichloro product; B gave two; and C and D each gave three. What is the structure of A? Of B? Of C and D?

(c) By another synthetic method, compound C was obtained in optically active form. Now what is the structure of C? Of D?

(d) When optically active C was chlorinated, one of the trichloropropanes (E) obtained was optically active, and the other two were optically inactive. What is the structure of E? Of the other two?

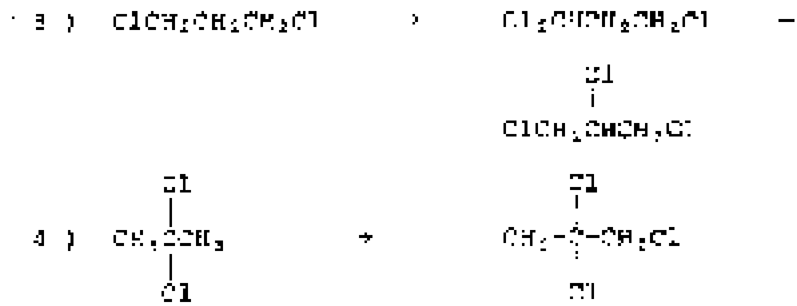
Solution: (a) There are a number of possible ways in which two chlorine atoms can bind to propane. Indeed there are four isomers of the formula $C_3H_6Cl_2$.

$$CH_3CH_2CH_3 \xrightarrow{Cl_2} \begin{array}{ll} 1) & Cl_2CHCH_2CH_3 \; + \\ 2) & ClCH_2CHClCH_3 \; + \\ 3) & ClCH_2CH_2CH_2Cl \; + \\ 4) & CH_3CCl_2CH_3 \end{array}$$

(b) If each isomer were chlorinated further, each would produce its own trichloro-substituted isomers.

$$1) \quad Cl_2CHCH_2CH_3 \rightarrow \begin{array}{l} Cl_3CCH_2CH_3 \; + \\ Cl_2CHCH_2CH_2Cl \; + \\ Cl_2CHCHClCH_3 \end{array}$$

$$2) \quad ClCH_2CHClCH_3 \rightarrow \begin{array}{l} Cl_2CHCHClCH_3 \; + \\ ClCH_2CCl_2CH_3 \; + \\ ClCH_2CHClCH_2Cl \end{array}$$



Therefore A is 4 ($CH_3CCl_2CH_3$)

B is 3 ($ClCH_2CH_2CH_2Cl$)

C is 1 or 2

D is 1 or 2

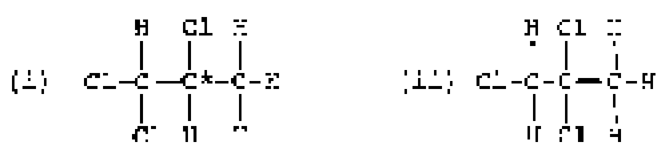
(c) If C is optically active, it must possess a chiral center. Let us look at the structures of 1 and 2.

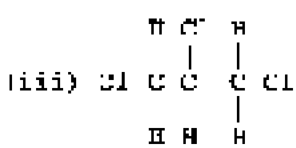
It is evident that isomer 1 has no chiral center. In isomer 2 however, C* is chiral and this isomer is optically active. Therefore

C is 2 ($ClCH_2CHClCH_3$) optically active

D is 1 ($Cl_2CHCH_2CH_3$) - optically inactive

(d) Let us look more closely at the trichloropropane isomers formed when C was chlorinated further.





Isomers ii and iii have no chiral centers. In isomer i, C* is a chiral carbon and the isomer is thus optically active. Therefore E is $Cl_2CHCHClCH_3$ (i).

Isopentane is allowed to undergo free radical chlorination, and the reaction mixture is separated by careful fractional distillation. (a) How many fractions of formula $C_5H_{11}Cl$ would you expect to collect? Draw structural formulas, stereochemical where pertinent, for the compounds making up each fraction. Specify each enantiomer as R or S. (b) Which if any, of the fractions, as collected, would show optical activity? Account in detail for the optical activity or inactivity of each fraction.

Solution: (a) Since the products of the chlorination of isopentane can be separated by fractional distillation, they must be isomeric forms of $C_5H_{11}Cl$. They will differ in respect to which carbon atom the chlorine attacks and then bonds to.

$$\underset{\substack{|\\ {}^{5}CH_3}}{\overset{1\ \ 2\ \ 3\ \ 4}{CH_3CH_2CHCH_3}} \xrightarrow{Cl_2}$$

isopentane

1) $CH_2ClCH_2\underset{\substack{|\\ CH_3}}{C}HCH_3$ — C_1 attacked

2) $CH_3\overset{*}{C}H(Cl)CH(CH_3)CH_3$, i.e. $CH_3\underset{\substack{|\\ Cl}}{\overset{*}{C}}H\underset{\substack{|\\ CH_3}}{C}HCH_3$ — C_2 attacked

3) $CH_3CH_2\underset{\substack{|\\ CH_3}}{\overset{\substack{Cl\\ |}}{C}}-CH_3$ — C_3 attacked

4) $CH_3CH_2\underset{\substack{|\\ CH_3}}{\overset{*}{C}}HCH_2Cl$ — C_4 attacked

$CH_3CH_2\underset{\substack{|\\ CH_2Cl}}{\overset{*}{C}}HCH_3$ — C_5 attacked

Note that these two are identical.

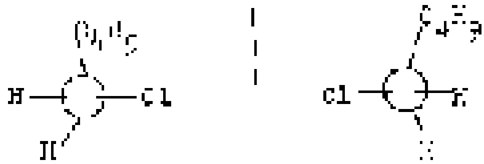
(* indicates a chiral center)

As we can see, four fractions of $C_5H_{11}Cl$ will result from distillation.

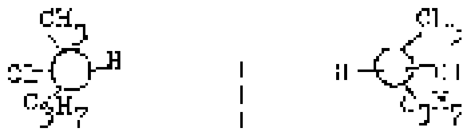
Fraction 1: There is no chiral center in this isomer, so it exists as only one isomer.

$$\begin{array}{c} Cl \\ | \\ H-C-H \\ | \\ H-C-H \\ | \\ CH_3-C-H \\ | \\ CH_3 \end{array}$$

(Look at the mirror images; they are superimposable.)



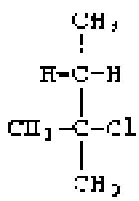
Fraction 2: C_2 is chiral, so molecules of this fraction exist as enantiomers.



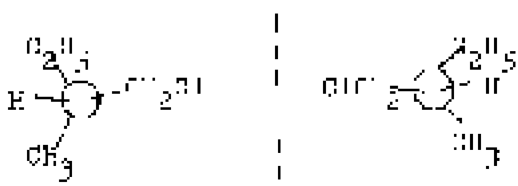
R S

Recall that enantiomers have the same physical properties; therefore they cannot be separated by fractional distillation.

Fraction 3: Again, there is no chiral center in this isomer, so it exists in only one, optically inactive, form.



Fraction 4: C_2 is chiral, so this fraction consists of enantiomers.



R S

(b) Fraction 2: Because the hydrogen atoms on a tetrahedral carbon are equivalent, the chlorine will not replace one hydrogen preferentially over the other. Therefore the two enantiomers exist in equal proportions, and the fraction is a racemic modification. Since the result of a racemic mixture is cancellation of optical activity (as one enantiomer rotates light in one direction to a certain degree, and the other rotates light in the opposite direction and to the same degree), Fraction 2 will show no optical activity.

Fraction 1, 3: Since the isomers have no chiral center, and their mirror images are superimposable, these fractions will show no optical activity.

Fraction 4: Again, replacement by chlorine of any hydrogen on either of the two methyl groups attached to C_3 is equally probable, so that the enantiomers exist in equal proportions. The fraction is racemic, and shows no optical activity.

• PROBLEM 5-25

On treatment with permanganate, cis-2-butene yields a glycol of m.p. 34°, and trans-2-butene yields a glycol of m.p. 19°. Both glycols are optically inactive. The glycol of m.p. 19° is resolvable (through reaction with optically active salts) into two fractions of equal but opposite rotation. The glycol of m.p. 34° is not.

(a) What are the configurations of the two glycols?

(b) Assuming these results are typical (they are), what is the stereochemistry of hydroxylation with permanganate (syn or anti?)

(c) Treatment of the same alkenes with peroxy acids gives the opposite results: the glycol of m.p. 19° from cis-2-butene, and the glycol of m.p. 34° from trans-2-butene. What is the stereochemistry of hydroxylation with peroxy acids?

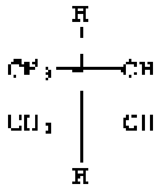
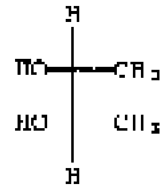
Solution: (a) The general reaction of either cis- or trans-2-butene with permanganate forms a glycol, 2,3-butanediol.

$$CH_3CH{=}CHCH_3 \xrightarrow{KMnO_4} CH_3-\underset{\displaystyle H}{\overset{\displaystyle OH}{C}}-\underset{\displaystyle H}{\overset{\displaystyle OH}{C}}-CH_3$$

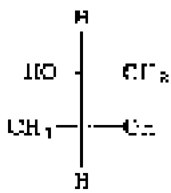
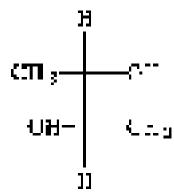
2,3-butanediol

Now we know that the hydroxylation of cis- and trans-2-butene yields two fractions of glycols with the same formula ($CH_3CHOHCHOHCH_3$) but having different melting points. The two fractions formed must therefore be stereoisomers. Since their chemical properties (here m.p.'s) are similar but not identical, they are not enantiomers of each other (which by definition differ only in optical rotation), but diastereomers. Note that the glycol contains two chiral centers, C_2 and C_3, which is compatible with diastereomer formation.

Since the total possible number of stereoisomers is 2^n, where n equals the number of chiral centers, the glycol has 2^2 or 4 possible stereoisomers.

1   2

R,S S,R

3   4

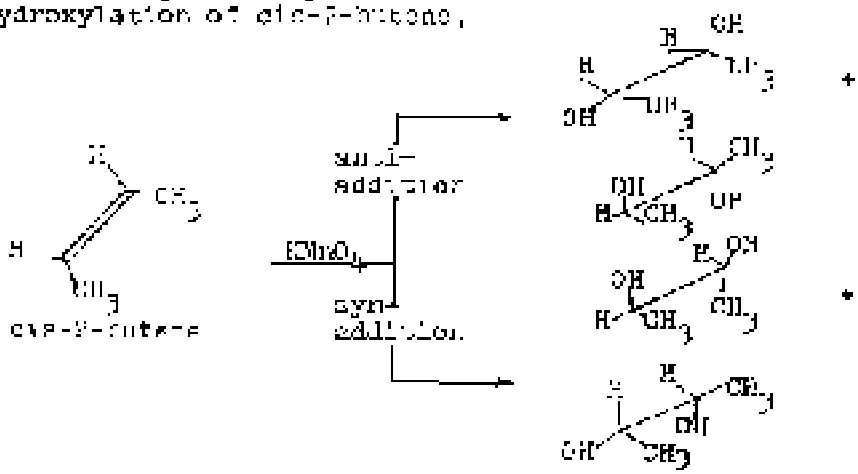
S,S R,R

Isomers 1 and 2 are identical. Isomers 3 and 4 are enantiomers.

Since the fraction of m.p. 19° is optically inactive, but resolvable, it must be a racemic mixture of enantiomers. The other fraction is not resolvable. Therefore, the two isomers composing it must be superimposable mirror images, even though they contain chiral centers, and so must be meso compounds. Looking at the two fractions, it becomes evident that compounds 1 and 2 are superimposable and are meso compounds. Therefore the fraction of m.p. 34° is actually the meso compound of 2,3-butanediol. The fraction of m.p. 19° is a racemic mixture of isomers 3 and 4, which we see are enantiomers.

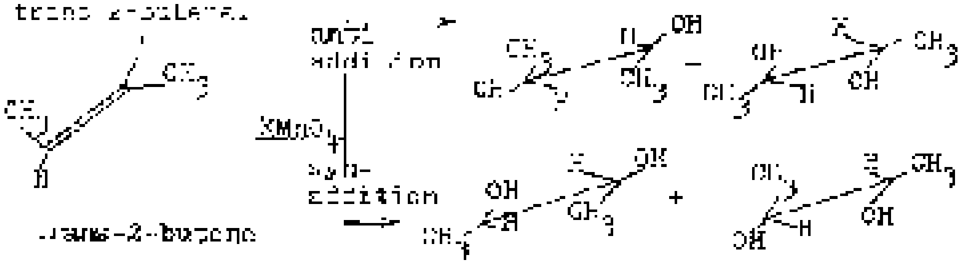
(b) We know then that cis-2-butene yields meso-2,3-butanediol, and trans-2-butene yields racemic-2,3-butanediol.

Looking at the possible addition mechanisms in the hydroxylation of cis-2-butene,



we see that only syn-addition yields the meso compound. Anti-addition gives two enantiomers. Thus permanganate gives syn-hydroxylation.

We can verify this by looking at the reaction with trans-2-butene.



Here, anti hydroxylation would have resulted in the meso compound. Only syn-hydroxylation gives the two enantiomers.

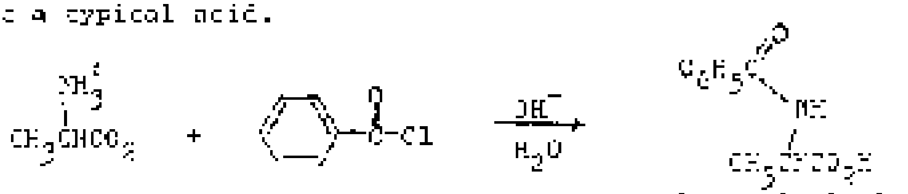
(b) Here, the opposite results are obtained, with cis-2-butene yielding the racemic mixture and trans-2-butene yielding the meso compound. These results are compatible with anti-hydroxylation.

RESOLUTION OF STEREOISOMERS

• PROBLEM 5-26

Describe the technique of resolution of DL-alanine.

Solution: Amino acids that are synthesized by the usual methods are obtained as racemates. One method that may be used for the resolution of amino acids involves converting them into diastereomeric salts. The amino group is usually converted into an amide so that the material is not amphoteric. For example, alanine reacts with benzoyl chloride in aqueous base to give N-benzoyl-alanine, which is a typical acid.



alanine　　benzoyl chloride　　N-benzoyl-alanine

The racemic N-benzoyl-alanine is resolved with brucine or strychnine. If brucine is used, it is the brucine salt of D-alanine that is less soluble. If strychnine is used, the strychnine salt of L-alanine crystallizes. Acidification of the salts yields the D and L-enantiomers of N-benzoylalanine. Basic hydrolysis then gives the pure enantiomeric amino acids. The process is outlined schematically as follows:

DL-alanine

↓

N-benzoyl-DL-alanine

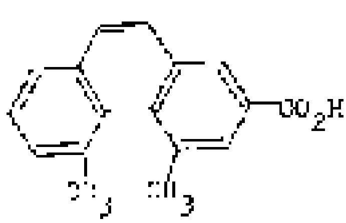
↓ brucine

brucine salt of N-benzoyl-D-alanine "insoluble"	brucine salt of N-benzoyl-L-alanine "soluble"
↓ H_3O^+	↓ H_3O^+
N-benzoyl-D-alanine	N-benzoyl-L-alanine
↓ 1. OH^-, H_2O, Δ 2. H_3O^+	↓ 1. OH^-, H_2O, Δ 2. H_3O^+
D-alanine (optically pure)	L-alanine (optically impure)

In cases such as that outlined, the enantiomer that forms the less soluble salt is usually obtained in an optically pure state. The other enantiomer is usually obtained in an impure state, because some of the less soluble salt invariably remains in solution. In the case diagrammed, the impure N-benzoyl-L-alanine may be treated with strychnine to give the insoluble strychnine salt. In this way, both enantiomers may be obtained in an optically pure state.

• PROBLEM 5-27

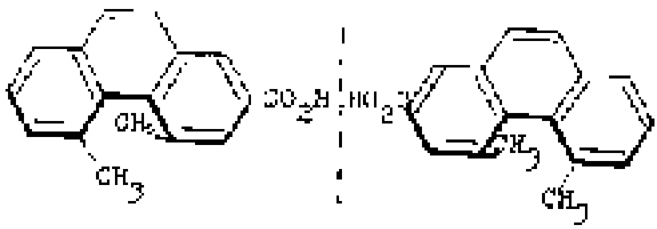
Compounds of the type shown below have been found to be resolvable into two optically active forms. Explain.



Solution: Compounds composed of fused benzene rings are usually planar, due to the presence of conjugated double bonds. The groups attached to the fused rings lie in the same plane as the rings.

However, in the compound given, such a planar arrangement would result in the two ortho methyl groups lying very close together. The steric hindrance resulting from this may be sufficient to force the methyl groups out of the plane of the ring. The groups would necessarily position themselves as far apart from each other as possible, in the more sterically favorable trans conformation. Thus, with one methyl group above and the other below the plane of the rings, the compound now exists in enantiomeric forms which can be resolved by virtue of their optical activity.

Notice that this compound actually has no chiral center. This is an example of compounds with chirality in the absence of chiral centers.



CHAPTER 6

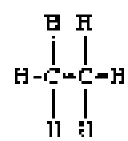
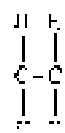
ALKENES

NOMENCLATURE AND STRUCTURE

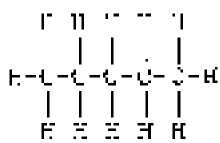
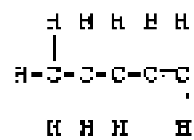
• PROBLEM 6-1

What is an alkene?

Solution: Hydrocarbons with one or more double bonds are known as alkenes, or sometimes called olefins. This class of hydrocarbons is unsaturated, and since alkenes differ from alkanes in this respect, their nomenclature must be modified. Refer to the following examples to attain an idea of unsaturation:

(1)  as opposed to 

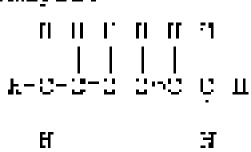
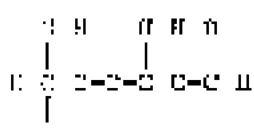
Ethane (Alkane) — Ethene (Alkene)

(2)  as opposed to 

Pentane — 1-Pentene

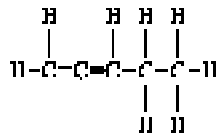
From the examples, note that the parent part of the name (eth- and pent-) remains the same for alkenes, and only the suffix changes to -ene. This is true for all alkenes that possess only one double bond.

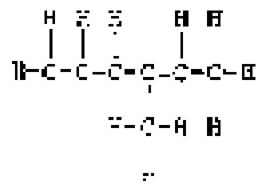
If alkenes have more than one double bond, it is referred to as a polyunsaturated alkene. These compounds require another modification in nomenclature. Specifically, an alkene with two double bonds has the suffix -diene and one with three double bonds has the suffix -triene. For example:

2,4-Hexadiene — 1,3,4-Hexatriene

In the compound 1,3,4 hexatriene, the double bonds are counted from the right side, because a compound must always be named beginning with the double bond (or functional group) closest to one end. The following examples will make this concept clear:





1,2-Pentadiene

(NOT: 3,4-Pentadiene)

3-Methyl 2,4 hexadiene

(NOT: 4-Methyl-2,4-hexadiene)

◆ PROBLEM 6-2

Name the following compounds using the IUPAC system of nomenclature:

(a) $CH_3-CH=CH_2$, (b) $CH_3-CH_2-CH=CH_2$, (c) $CH_3-C(CH_3)_2-CH=CH_2$

(d) $CH_3-CH_2-CH=CH-CH(Cl)-CH_3$, (e) $CH_3-C(Br)_2-CH=C-CH-CH(CH_3)-CH_3$

Solution: (1) Select as the parent structure the longest continuous chain that contains the carbon carbon double bond; then consider the compound to have been derived from this structure.

(2) Indicate by a number the position of the double bond. The position is designated by the number of the first doubly bonded carbon encountered when numbering from the end of the chain nearest the double bond.

(3) Indicate by numbers the positions of the alkyl groups or other functional groups attached to the parent chain.

With this in mind, the names become:

(a) $CH_3-CH=CH_2$ Propene

(b) $CH_3-CH_2-CH=CH_2$ 1-Butene

(c) $CH_3-C(CH_3)_2-CH=CH_2$ 3,3-Dimethyl-1-butene

```
(d)  CH3-CH2-CH=CH-CH-CH3     2-Chloro-3-hexene
                   |
                   Cl

         Br         CH3

(e)  CH3-C-CH=C=CH-CH-CH3     2,2-Dibromo-6-methyl-3,4-
                               heptadiene
         Br
```

To illustrate how these names were obtained, consider structure (c). The longest continuous chain that contains the double bond is made up of 4 carbons. Therefore, the parent chain is butene, the "ene" indicative of the presence of a double bond. The double bond is situated on carbon #1 so that it is 1-butene. The two substituents, both methyl groups (CH_3), are positioned on carbon #3 because the numbering system is from the end of the parent chain nearest the double bond. Hence, for (c) the nomenclature is 3,3-Dimethyl-1-butene.

• PROBLEM 6-8

Write the IUPAC names for each of the following chemical structures:

```
                                                          OH CH3
                                                          |  |
(a) CH3-CH2-CH2-CH-CH-C-CH2   (b) CH3-CH2-CH2-CH=C-C——CH3
                |  |  |                                  |
                I  I  I                                  CH3 CH3

                                                   CH2-CH3 Cl
                                                   |
(c) CH3-CH=C-CH2-CH——C=CH2   (d) CH3-CH2-CH=CH-C——CH=C-CH3
           |        |   |                          |
           CH2      CH2 Br                         CH2
           |        |                              |
           CH3      CH3                            CH3
```

Solution: To write the IUPAC names for these alkenes, use the following rules:

(1) Select the parent structure of each compound by choosing the longest chain that contains the carbon-carbon double bond.

(2) Denote by number the position of the double bond in the parent chain. Designate its position by the number of the first doubly bonded carbon encountered when numbering from the end of the chain nearest the double bond.

(3) Indicate the positions of all functional groups attached to the parent chain by number.

With this in mind, the names of the compounds become:

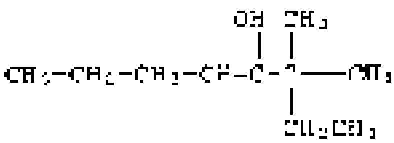
(a) 2,3,4-Triiodo-1-heptene

(b) 3,3-dimethyl-4-hydroxy-4-octene

(c) 3,5-Diethyl-2-bromo-1,5-heptadiene

(d) 4,4-Diethyl-2-chloro-2,5-octadiene.

To understand the reasoning behind this naming, consider (b):



The longest continuous chain that contains the carbon-carbon double is eight carbons in length. Hence, the name must include the word "octene". The number of the first doubly bonded carbon encountered is four. (In this instance, numbering can be from either end because the double bond is located exactly equidistant from the ends.) Consequently, one has 4-octene. At this point, consider the substituents on the parent chain. Two methyl groups (CH_3) and a hydroxyl group (OH) are present. The methyls are said to be on the third carbon, while the hydroxyl is on the fourth carbon. In this fashion, the lowest possible numbers are used. (For example, if numbering started from the other end of the molecule, the hydroxyl would be on the fifth carbon and the methyls on the sixth carbon.) Overall, then, the name becomes 3,3-dimethyl-4-hydroxy-4-octene.

The other names of the compounds follow readily from this process.

• PROBLEM 6-1

Write the chemical structures for each compound listed.

(a) 1-Hexene (b) 3-Methyl-1-butene (c) 2,4-Hexadiene

(d) 1-Iodo-2-methyl-2-pentene (e) 2-Chloro-3-methyl-2-hexene

(f) 6,6-Dibromo-5-methyl-5-ethyl-2,3-heptadiene

Solution: (1) Look at the complete name of the compound and pick out the parent name. It is usually the last word of the complete name and it denotes the longest continuous chain that contains the carbon-carbon double bond. (All of the structures are alkenes.)

(2) Write out the carbon skeleton that makes up the parent chain. Determine the number of double bonds present by examining the suffix of the parent name. For example, "ene" means one double bond, whereas "diene" means two.

(3) Position the double bond (or bonds) in the carbon skeleton as specified by the number directly (usually) in front of the parent name. For example, if the compound is 2-pentene, one would write

```
C-C-C=C-C.
5 4 3 2 1
```

(Recall, the position of the double bond is given by the number of the first doubly bonded carbon encountered when numbering from the end of the chain nearest the double bond.)

(4) Position the functional group substituents on the chain as specified by the number directly in front. For example, 3-methyl-2-pentene would be:

```
      C
      |
C-C-C=C-C
5 4 3 2 1
```

The structures of the compounds in (a)-(f) become:

(a) $CH_3CH_2CH_2CH_2CH=CH_2$

```
(b) CH2=CH-CH-CH3
           |
           CH3
```

(c) $CH_3-CH=CH-CH=CH-CH_3$

```
(d) CH3CH2CH=C——CH2I
              |
              CH3
```

```
(e) CH3CH2CH2C ==C-CH3
              |   |
              CH3 Cl
```

```
                        CH3 Br
                        |   |
(f)  CH3-CH=C=CH-C —— C-CH3
                 |   |
                 CH2 Br
                 |
                 CH3
```

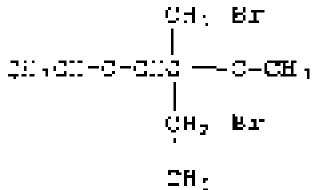
To see how this process works, examine how structure (f) was written. The parent name is heptadiene. The prefix "hepta" indicates that seven carbons are present in the skeleton: C-C-C-C-C-C-C. The 2,3 indicates the positions of the two double bonds - it is a diene. So, one can write

```
C-C=C=C-C-C-C.
1 2 3 4 5 6 7
```

With this numbering system, the substituents are now added as specified by the 6 for the bromines and 5 for the methyl (CH_3) and ethyl groups.

```
          CH3 Br
          |   |
C-C=C=C-C ——C-C
1 2 3 4 |   | 7
        CH2 Br
        |
        CH3
```

And now only the hydrogens need be added to obtain:

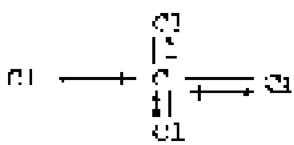


PHYSICAL PROPERTIES

• PROBLEM 6-5

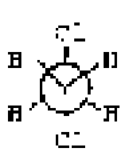
The dipole moment of 1,2-dichloroethane is 1.12 D at room temperature. Show how one could use this dipole moment to calculate the proportions of the possible conformations that are expected to be present.

Solution: When the center of negative charge does not coincide with the center of positive charge in a molecule, it is said to be polar. The molecule constitutes a dipole: two equal and opposite charges separated in space. The molecule possesses a dipole moment which is equal to the magnitude of the charge multiplied by the distance between the centers of charge. In carbon tetrachloride,

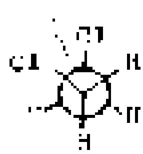


, the dipole moment is zero: the individual bonds are polar but because of the symmetrical arrangement, they exactly cancel each other out. So, the dipole moment of a molecule depends not only upon the polarity of its individual bonds but also upon the way the bonds are directed, that is, upon the shape of the molecule. Consequently, in calculating the proportions of the possible conformations (shapes) of 1,2-dichloroethane, one wants to consider the dipole moment of each conformation and assign a percentage to each so that the sum of all the individual dipole moments yields the value 1.12 D at room temperature.

A useful representation of the conformations of 1,2-dichloroethane is the Newman projection:  . 1,2-Dichloroethane possesses two possible conformations (a and b) as illustrated:



(a)



(b)

In figure "a", the polar C-Cl bonds are directed opposite to each other. A symmetrical relationship is established (as was the case with CCl_4) so that there exists a dipole moment of zero. The polarity of the individual bonds is cancelled out by the arrangement.

In figure "b", the polar bonds do not cancel each other so that a dipole exists. The dipole moment of each C-Cl bond is approximately 2.2 D. But, the dipole moment of "b" is not 2 × 2.2 = 4.4 D but 3.1 D. Remember, the vector sum must be taken — the direction must always be noted. (The direction is indicated by the dotted line in the figure.)

With this in mind, one can now predict the proportions of "a" and "b". If "b" has a dipole moment of 3.1 D and 1,2-dichloroethane has 1.12 D at room temperature, then the "b" conformation cannot be the shape of most of the molecules. In fact, it represents only 36%. For note: .36 of 3.1 D is 1.12 D, the observed value. What about the other 64%? It can only be conformation "a" with dipole moment zero, and .64 of 0.00 D is, of course, 0.00 D.

In summary, then, one has 64% of "a" with dipole moment zero and 36% of "b" with dipole moment 3.1 D.

• PROBLEM 6-6

The trans alkenes are generally more stable than the cis alkenes. Give two examples of unsaturated systems where you would expect the cis form to be more stable and explain the reason for your choice.

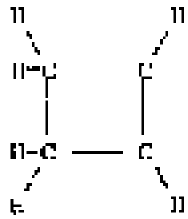
Solution: To solve this problem, look for factors affecting stability of conformations. Two such factors include angle strain and van der Waals strain (steric strain).

Any atom tends to have bond angles that match those of its bonding orbitals: tetrahedral (109.5°) for sp^3 hybridized carbon, for example. If there is a deviation from the "normal" bond angles, then angle strain results.

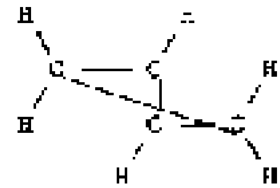
Non-bonded groups or atoms that just touch each other — that is, that are about as far apart as the sum of their van der Waals radii — attract each other. If the groups or atoms are brought any closer together, they repel each other. This crowding produces steric strain.

Consequently, when selecting two examples where a cis form will be more stable than a trans form, consider a situation where the trans conformation produces angle and/or steric strain and the cis does not, or does so to a lesser extent.

One example is cycloalkenes with small to medium sized rings. Cyclooctene fits in this category. The cis and trans forms are illustrated below:



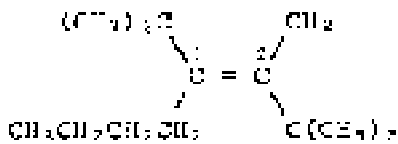
cis



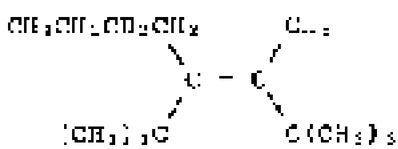
trans

As can be seen in the diagram, the trans form would possess tremendous angle strain. Hence, the cis conformation would be more stable.

The second example of a situation where cis is favored over trans occurs in compounds such as:



Note that the highest priority group of the carbon labeled 1, $CH_3CH_2CH_2CH_2$, and the highest priority group of the carbon labeled 2, $C(CH_3)_3$, are on the same side of the molecule. Hence, this is the cis (NOT trans) conformation. This conformation is favored in stability over the trans form shown:



CH_3

The reason stems from the fact that $C(CH_3)_3$ (H_3C–C–CH_3) is more bulky than $CH_3CH_2CH_2CH_2$ and, as such, creates more steric strain when positioned next to another $C(CH_3)_3$ as is the situation in the trans conformation.

GEOMETRIC ISOMERISM

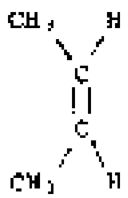
• PROBLEM 6-7

Indicate which of the following compounds show geometric (cis-trans) isomerism, draw the isomeric structures, and specify each as Z or E.

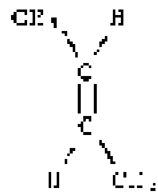
(a) 1-butene
(b) 2-butene
(c) 1,1-dichloroethene
(d) 1,2-dichloroethene
(e) 2-methyl-2-butene
(f) 1-pentene
(g) 2-pentene
(h) 1-chloropropene
(i) 1-chloro-2-methyl-2-butene
(j) 3-methyl-4-ethyl-3-hexene
(k) 2,4-hexadiene
($CH_3CH=CHCH=CHCH_3$)

Solution: If two isomeric substances differ from one another only in the way the atoms are oriented in space (but are like one another with respect to which atoms are attached to which other atoms), they are considered stereoisomers. Stereoisomers that are not mirror images of each other are called diastereomers. The particular kind of diastereomers that result from hindered rotation about double bonds are called geometric isomers.

The arrangement that characterizes a stereoisomer is referred to as its configuration. Configurations are differentiated in their names by the prefixes cis- (on this side) and trans- (across). For example:

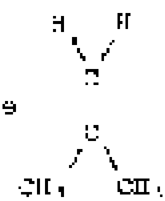


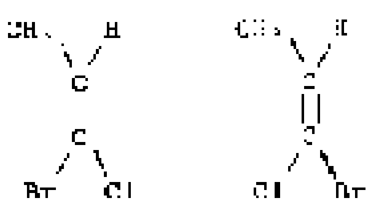
cis



trans

Cis and trans indicate here whether the methyl groups are on the same side or on opposite sides of the molecule.

The structure  does not show geometric isomerism; geometric isomerism cannot exist if either carbon carries two identical groups. While the prefixes cis and trans work well for disubstituted ethylenes and some trisubstituted ethylenes, it would be difficult to assign a configuration to



1-Bromo-1-chloropropene

The problem is which group represents the reference. This problem can be solved by looking at each doubly bonded carbon in turn. Of the two atoms or groups of atoms on the one carbon, take the atom or group of atoms of highest priority (highest atomic number) and compare it with the atom or group of atoms of highest priority on the other atom. Now check whether they are on the same side of the double bond or opposite sides. If they are on the same side, use the letter Z to indicate that configuration; if on opposite sides, use the letter E.

Therefore, to solve this problem, one writes out the structures of the compounds given, and looks for that relationship among the groups attached to the doubly-bonded carbons. Then, configuration is assigned using the letters Z and E.

(a) 

No geometrical isomerism, since one carbon carries identical groups (H).

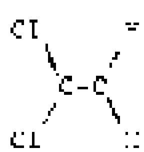
1-Butene

(b) 

(E)-2-Butene

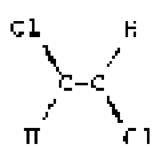
(Z)-2-Butene

In (E)-2-butene, the highest priority groups, CH_3, are on opposite sides of the double bond. Therefore it is so named. In (Z)-2 butene, the methyl groups are on the same side of the double bond. Note that the molecule's geometric isomers can also be named by the cis-trans system in this case. (E)-2-butene can also be named trans-2 butene, and (Z)-2-butene cis-2-butene.

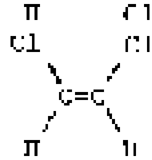
(c) 

No geometric isomerism, since the carbons carry identical groups.

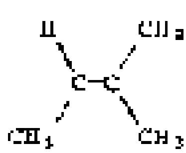
1,1 dichloroethene

(d)  E

Geometric isomerism present.

 Z

1,2-dichloroethene

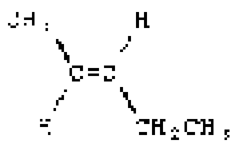
(e) 

No geometric isomerism.

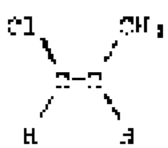
2-methyl-2-butene

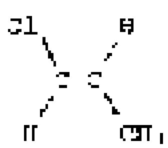
(f)  No geometric isomerism.

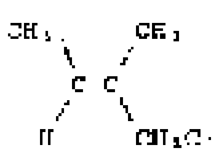
1-pentene

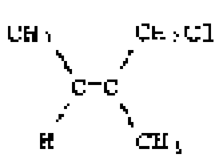
(g)  E Geometric isomerism present in 2-pentene

 Z

(h)  Z Geometric isomerism present in 1-chloropropene.

 E

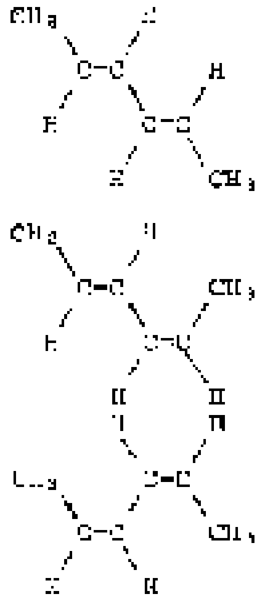
(i)  E Geometric isomerism indicated in 1-chloro-2-methyl-2-butene.

 Z

(j)  No geometrical isomerism present.

3-methyl-4-ethyl-3-hexene

(x)



E,E

E,Z

Z,Z

Geometrical isomerism indicated for 2,4-hexadiene.

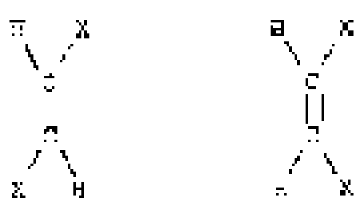
Note: These structures were written by taking the configuration about each carbon-carbon double bond separately.

• PROBLEM 6-8

(a) Indicate the direction of the net dipole moment for each of the dihaloethenes. (b) Would cis-2,3-dichloro-2-butene have a larger or smaller dipole moment than cis-1,2-dichloroethene? (c) Indicate the direction of the net dipole moment of cis-1,2-dibromo-1,2-dichloroethene. Will it be larger or smaller than the dipole moment of cis-1,2-dichloroethene? Why?

Solution: When two atoms are held by a covalent bond, the bond can be expected to be polar (that is, possess a negative pole and a positive pole) if the two atoms differ in their tendency to attract electrons; that is, if the two atoms differ in electronegativity. The greater the difference in electronegativity, the more polar the bond. When the center of negative charge does not coincide with the center of positive charge of such a molecule, a dipole is said to exist. A dipole moment (μ) equals charge multiplied by distance between the centers of charge.

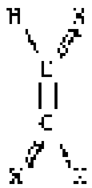
(a) All of the dihaloethenes can exist in cis or trans forms as indicated:

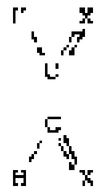


trans cis

X = a halogen atom (Cl, F, Br, I)

The halogens are strongly electron attracting, so that the halogen will acquire a negative charge. This means the dipole between a halogen and a carbon atom will point to the halogen atom as illustrated:



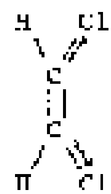


trans — cis

net dipole = 0 — net dipole = ⟶

The trans configuration has the dipoles pointing in two opposite directions so that the net dipole moment is 0, whereas for the cis configuration the net dipole lies in the plane of molecule along the bisector of angle between the Cl atoms.

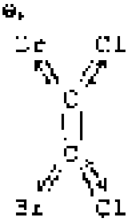
(b)



cis 2,3 dichloro 2 butene — cis 1,2 dichloroethene

Inspection of the structures of the two compounds reveals that the four-carbon compound has the larger dipole moment. This is due to the extra electron release by the two CH_3 groups in the same direction as the C Cl dipole.

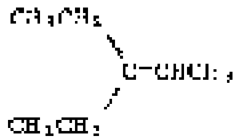
(c)



cis-1,2-dibromo-1,2-dichloroethene

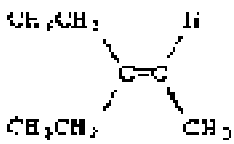
Even though the bromine and chlorine are attracting the electrons in opposite directions, chlorine is the more electronegative element. This fact accounts for the direction of the dipole moment. It also explains why the dipole moment should be less than the moment of cis-1,2-dichloroethene; the C-Br dipoles oppose the C-Cl dipoles in cis 1,2 dibromo 1,2 dichloroethene.

How many stereoisomers are there for each of the following?

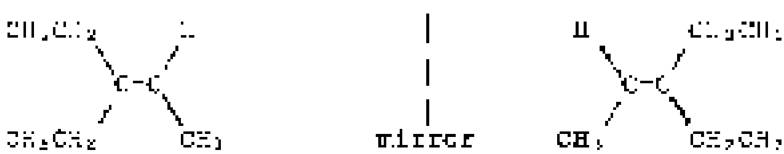
(a)  (b)  (c) 

Solution: Stereoisomers may be defined as compounds with identical molecular formulas whose atoms, while linked together in the same order, are arranged differently in space. Stereoisomers must be either enantiomers or diastereomers. Enantiomers refer to stereoisomers that are mirror images of each other, whereas diastereomers are stereoisomers that are not mirror images of each other. Diastereomers that result from different arrangements of atoms about a double bond are called geometrical isomers.

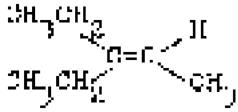
For (a), there is only one stereoisomer. To see this, let,



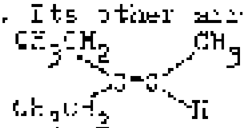
be the arrangement of atoms given in (a). The mirror images can now be written as shown:



But as we can see, the two mirror images are identical compounds. Also, because (a) has no chiral carbons, it can not exist as a pair of enantiomers.



also does not exist as a pair of geometric isomers. Its other arrangement of atoms about the double bond:



is actually identical to itself. Thus (a) exists in only one form.

For (b), there is again only one stereoisomer. It may be reasoned in the same manner as was done in (a).

For (c) there exist two stereoisomers which are geometric isomers of each other:

cis   trans

The cis conformation has the highest priority groups of each doubly bonded carbon on the same side of the double bond, whereas the trans conformation has the highest priority groups on opposite sides.

PREPARATION

■ PROBLEM 8-10

How are alkenes prepared?

Solution: There are four basic methods of preparing alkenes which are as follows:

(1) Dehydrohalogenation of alkyl halides

(2) Dehydration of alcohols

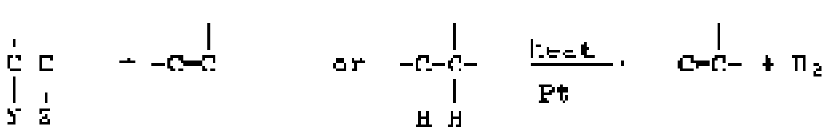
(3) Dehalogenation of vicinal dihalides

(4) Reduction of alkynes

The most important of these methods of preparation - since they are the most generally applicable - are the dehydrohalogenation of alkyl halides and the dehydration of alcohols.

Alkenes containing up to five carbon atoms can be obtained in pure form from the petroleum industry. Pure samples of more complicated alkenes must be prepared by methods like those outlined above.

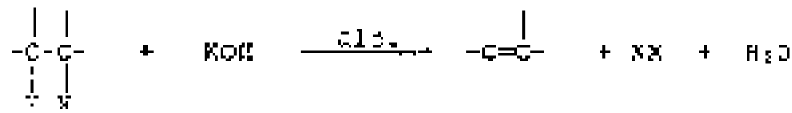
The introduction of a carbon-carbon double bond (C=C) into a molecule containing only single bonds must necessarily involve the elimination of atoms or groups from two adjacent carbons:



The elimination reactions not only can be used to make simple alkenes, but also provide the best general ways to introduce carbon-carbon double bonds into molecules of all kinds.

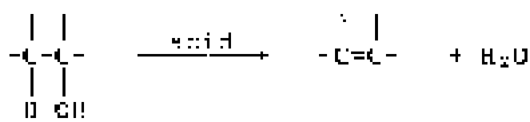
The four basic methods of preparing alkenes are outlined below:

(1) Dehydrohalogenation of alkyl halides



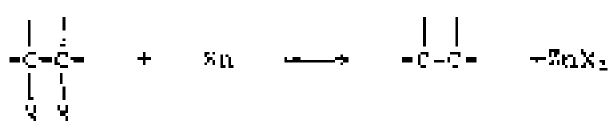
The ease of dehydrohalogenation: 3°>2°>1°

(2) Dehydration of alcohols

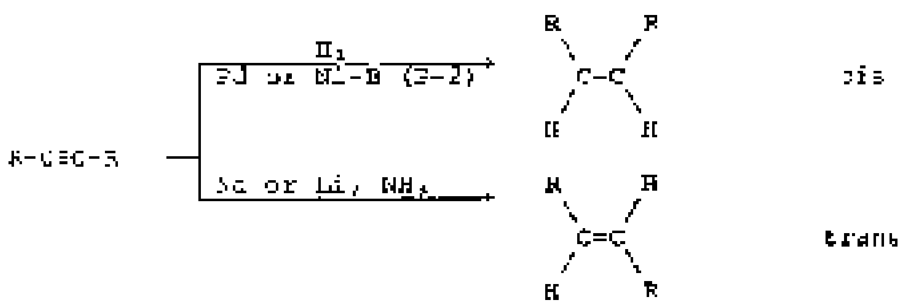


The ease of dehydration: 3°>2°>1°

(3) Dehalogenation of vicinal dihalides



(4) Reduction of alkynes



• PROBLEM 6-11

Describe dehydrohalogenation of alkyl halides to obtain an alkene.

Solution: Alkyl halides are converted into alkenes by the process known as dehydrohalogenation, which is the elimination of the halogen atom together with a hydrogen atom from a carbon adjacent to the one bearing the halogen. The general equation for this process is:

$$-\overset{|}{\underset{H}{\underset{|}{C}}}-\overset{|}{\underset{X}{\underset{|}{C}}}- \quad + \quad \text{KOH (alcoholic)} \longrightarrow \quad -C{=}C- \quad + KX \quad + \quad H_2O$$

It is known from general chemistry that

$$\frac{\text{acid}}{(HCl)} + \frac{\text{base}}{(KOH)} \longrightarrow \frac{\text{salt}}{(KCl)} + \underset{(H_2O)}{\text{water}}.$$

So it is not surprising that the reagent required for the elimination of what amounts to a molecule of acid is a strong base.

The alkene is prepared by heating together the alkyl halide and a solution of potassium hydroxide in alcohol. For example:

(1) $CH_3CH_2CH_2Cl \xrightarrow{\text{KOH (alc)}} CH_3CH{=}CH_2 + KCl + H_2O$

n-Propyl chloride $\qquad\qquad$ Propylene

(2) $CH_3CH_2CH_2CH_2Cl \xrightarrow{\text{KOH (alc)}} CH_3CH_2CH{=}CH_2 + KCl + H_2O$

n-Butyl chloride $\qquad\qquad$ 1-Butene

In dehydrohalogenation, the more stable the alkene, the more easily it is formed as can be seen by the fact that the sequence for ease of formation of alkenes,
$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2$, $RCH{=}CHR > RCH{=}CH_2$,
is the same for stability of alkenes. As one moves through the series of alkyl halides, that is, from 1° to 2° to 3°, the structure becomes more branched at the carbon carrying the halogen. Branching provides a greater number of hydrogens for attack by base, and hence a more favorable probability factor toward elimination, and it leads to a more highly branched, more stable alkene, and hence a more stable transition state and lower E_{act}. The result is that in dehydrohalogenation the order of reactivity of RX is 3°>2°>1°.

The orientation of elimination reflects the stability of the alkene that would result. For example:

$$CH_3CH_2CHBrCH_3 \xrightarrow{\text{KOH (alc)}} \underset{81\%}{CH_3CH{=}CHCH_3} \quad \text{and}$$

$$\underset{19\%}{CH_3CH_2CH{=}CH_2}$$

2-butene (81%) predominates over 1-butene (19%) because the preferred alkene is the one with the greater number of alkyl groups attached to the doubly bonded carbon atoms as shown above in the sequence for ease of formation of alkenes.

■ PROBLEM 6-12

Describe dehydration of alcohols to obtain an alkene.

Solution: An alcohol is converted into an alkene by a process known as dehydration, which is the elimination of a molecule of water. Dehydration requires the presence of an acid and the application of heat. The general reaction for this method of preparation is as follows:

$$\underset{\displaystyle H\;\;OH}{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-} \xrightarrow[\text{heat}]{\text{acid}} -\overset{|}{C}=\overset{|}{C}- \;+\; H_2O$$

This method for obtaining an alkene is generally carried out in either of two ways:

(a) Heating the alcohol with sulfuric acid or phosphoric acid (H_2SO_4, H_3PO_4, respectively) to temperatures as high as 200°C, or

(b) Passing the alcohol vapor over alumina, Al_2O_3, at 350-400°C.

Alcohols are organic compounds of the general formula ROH, where R is any alkyl group and OH, the hydroxyl group, is characteristic of alcohols. An alcohol is named by naming the alkyl group that holds the hydroxyl group and following this by the word alcohol, for example:

CH_3-CH_2OH	$(CH_3)_2CHOH$	$CH_3-\underset{\underset{\displaystyle CH_3}{\vert}}{\overset{\overset{\displaystyle CH_3}{\vert}}{C}}-OH$
Ethyl Alcohol	Isopropyl Alcohol	t-Butyl Alcohol

In dehydration of alcohols, these various classes differ widely in reactivity and conditions. In other words, some alcohols dehydrate easier than others, depending upon whether the alcohol is primary, secondary or tertiary. The ease of dehydration of alcohols is 3°>2°>1°.

The following examples show how these differences in reactivity affect the experimental conditions of the dehydration.

Primary Alcohol Dehydration:

$$\underset{\text{Ethyl Alcohol}}{CH_3CH_2OH} \xrightarrow[170^\circ]{95\%\ H_2SO_4} \underset{\text{Ethylene}}{CH_2=CH_2} + H_2O$$

Secondary Alcohol Dehydration:

$$\underset{\text{sec-Butyl Alcohol}}{CH_3CH_2\underset{\underset{\displaystyle OH}{\vert}}{CH}-CH_3} \xrightarrow[100^\circ]{60\%\ H_2SO_4} \underset{\substack{\text{2-Butene} \\ \text{chief product}}}{CH_3CH=CHCH_3} + H_2O$$

Tertiary Alcohol Dehydration:

$$CH_3-\underset{OH}{\overset{CH_3}{C}}-CH_3 \xrightarrow[85-90^\circ]{20\%\ H_2SO_4} CH_3-\overset{CH_3}{C}=CH_2 + H_2O$$

t-Butyl Alcohol   Isobutylene

• PROBLEM 6-13

> Describe dehalogenation of vicinal dihalides to obtain an alkene.

Solution: Dehalogenation of vicinal dihalides is the process of eliminating two halogens to yield an alkene. The two halogens must be vicinal (Latin: vicinalis, neighboring) in order for a double bond to be formed. The general reaction for this process is:

$$-\underset{X}{\overset{|}{C}}-\underset{X}{\overset{|}{C}}- + Zn \longrightarrow -\overset{|}{C}=\overset{|}{C}- + ZnX_2$$

Note that this reaction must employ the use of a metal such as zinc or magnesium. A good example of the reaction is:

$$CH_3\underset{Br}{CH}-\underset{Br}{CH}-CH_3 \xrightarrow{Zn} CH_3CH=CHCH_3 + ZnBr_2$$

2,3-Dibromobutane   2-Butene

Dehalogenation of vicinal dihalides is severely limited by the fact that these dihalides are themselves generally prepared from the alkenes. However, it is sometimes useful to convert an alkene to a dihalide while some operation on another part of the molecule is being performed, and then regenerate the alkene by treatment with zinc.

• PROBLEM 6-14

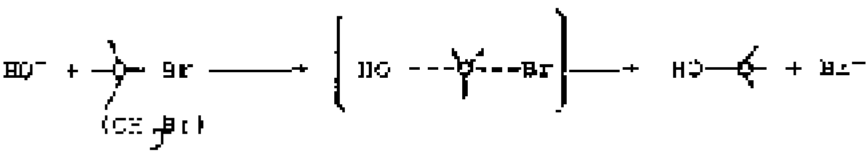
> When isopropyl bromide is treated with sodium ethoxide in ethanol, propylene and ethyl isopropyl ether are formed in a 3:1 ratio. If the hexadeuteroisopropyl bromide, $CD_3CHBrCD_3$ is used, $CD_3CH=CD_2$ and $(CD_3)_2CHOC_2H_5$ are formed in a ratio of 1:2. Explain.

Solution: Isopropyl bromide is an alkyl halide. To solve this problem, it will be necessary to consider the typical reactions of alkyl halides.

The halide ion may be characterized as a weak base. It can readily be displaced by stronger bases that possess an unshared pair of electrons and seek a relatively positive site. Such basic, electron-rich reagents are nucleophilic reagents. Consequently, one typical reaction of alkyl halides is nucleophilic substitution:

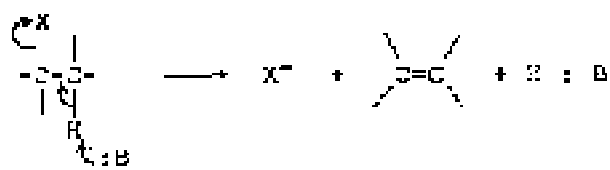
$$\underset{\text{(Alkyl halide)}}{R:X} + \underset{\text{(Nucleophilic Reagent)}}{:Z} \rightarrow R:Z + \underset{\text{(leaving group)}}{:X^-}$$

One type of nucleophilic substitution is called S_N2, which means bimolecular nucleophilic substitution. Bimolecular deals with the kinetics of the reaction; it indicates that the rate determining step involves collision of two particles. For example:



In S_N2 reactions, the order of reactivity of RX is $CH_3X > 1° > 2° > 3°$. As the number and size of substituents attached to the carbon bearing the halogen is increased, the reactivity toward S_N2 decreases.

Another typical reaction of alkyl halides is bimolecular elimination (called E2) to produce alkenes. A base abstracts a hydrogen ion away from carbon, and simultaneously a halide ion separates. It is depicted below:



This reaction has an isotope effect in that deuterium-carbon bonds are broken more slowly than C-H bonds. The order of reactivity of alkyl halides toward E2 elimination is 3° > 2° > 1°. It reflects the relative stabilities of the alkenes being formed.

The structure of isopropyl bromide may be written as

$$CH_3-\overset{H}{\underset{Br}{C}}-CH_3.$$ Hence this alkyl halide is secondary

(2°). This means that in the presence of the strong base sodium ethoxide in ethanol, both the S_N2 and E2 reactions occur; that is, they compete with each other. This explains why two products, propylene and ethyl isopropyl ether, are obtained.

$$CH_3\underset{Br}{\overset{H}{C}}CH_3 \xrightarrow{S_N2} CH_3\underset{OC_2H_5}{CH}CH_3 \text{ (ethyl isopropyl ether)}$$

$$CH_3\underset{Br}{\overset{H}{C}}CH_3 \xrightarrow{E_2} CH_3-CH=CH_2 \text{ (propylene)}$$

The ratio of the alkene to the ether is 3:1.

With hexadeuterioisopropyl bromide, $CD_3CHBrCD_3$, the ratio changes to 1:2. This is to be expected for the loss of deuterium in E_2 is slower than hydrogen (the isotope effect). The S_N2 reaction that produces the ether begins to predominate. It may be pictured in the following manner:

$$CD_3\underset{}{\overset{OC_2H_5}{CH}}CD_3 \xleftarrow[\text{same rate}]{S_N2} CD_3CHBrCD_3 \xrightarrow[\text{slower}]{E_2} CD_3CH=CD_2$$

The deuterium isotope effect may be calculated as shown:

$$\frac{k_D}{k_H}\ (E_2) = \frac{1/2}{3/1} = \frac{1}{6}\ .$$

HYDROGENATION

• PROBLEM 6-15

Describe the catalytic hydrogenation reaction of alkenes.

Solution: Catalytic hydrogenation is the addition of hydrogen atoms across the carbon-carbon double bond of alkenes. The general reaction is:

$$>C=C< \ + \ H_2 \xrightarrow{\text{Pt, Pd, or Ni}} -\underset{H}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}- \ ,$$

where the function of the catalyst (Pt, Pd, or Ni) is to lower the energy of activation so that the reaction can proceed rapidly at room temperature. An example of catalytic hydrogenation is:

$$CH_3CH=CH_2 + H_2 \xrightarrow{Ni} CH_3CH_2CH_3$$

Propene Propane

• PROBLEM 6-16

Predict the product after catalytic hydrogenation of each of the following reactants:

$$\text{(a)}\quad \underset{\displaystyle CH_3}{CH_2{=}CH{-}\overset{}{CH}{-}CH_3} \qquad\qquad \text{(b)}\quad CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}CH_2CH{=}CH_2$$

3-Methyl-1-butene 4,4-Dimethyl-1-pentene

$$\text{(c)}\quad CH_2{=}CH{-}CH_2CH_2CH_2CH_2CH_3 \qquad\qquad \text{(d)}\quad H_2C{=}CH_2$$

1-Heptene Ethylene

Solution: When alkenes are shaken under the presence of hydrogen gas at low pressure, including a small amount of catalyst (Pt, Pd, or Ni), they are converted smoothly and quantitatively into alkanes of the same carbon skeleton by hydrogen adding across the carbon-carbon double bond. This reaction, called catalytic hydrogenation, may be illustrated as:

$$\underset{\text{alkene}}{>C{=}C<} \xrightarrow{H_2 \;-\; \text{Pt, Pd, or Ni}} \underset{\text{alkane}}{-\overset{|}{\underset{\underset{H}{|}}{C}}-\overset{|}{\underset{\underset{H}{|}}{C}}-}$$

All of the reagents in this problem are alkenes, so that catalytic hydrogenation produces the alkane as shown:

$$\text{(a)}\quad \underset{\displaystyle CH_3}{CH_2{=}CH{-}CH{-}CH_3} \xrightarrow[\text{Pt, Pd or Ni}]{H_2} \underset{\displaystyle CH_3}{CH_3CH{-}CH_2{-}CH_3}$$

3-Methyl-1-butene Isopentane

$$\text{(b)}\quad CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}CH_2CH{=}CH_2 \xrightarrow[\text{Pt, Pd or Ni}]{H_2} CH_3{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}CH_2CH_2CH_3$$

4,4-Dimethyl-1-pentene 2,2-Dimethylpentane

$$\text{(c)}\quad CH_2{=}CH{-}CH_2CH_2CH_2CH_2CH_3 \xrightarrow[\text{Pt, Pd or Ni}]{H_2} CH_3CH_2CH_2CH_2CH_2CH_2CH_3$$

1-Heptene Heptane

$$\text{(d)}\quad H_2C{=}CH_2 \xrightarrow[\text{Pt, Pd or Ni}]{H_2} H_3C{-}CH_3$$

Ethylene Ethane

• PROBLEM 6-17

For each pair of compounds, which one do you expect to show the greater (more negative) heat of hydrogenation? Explain.

```
            H
            |
(a) CH3CH2-C=C-CH3     and   (CH3)2CH-C=CH2
           |                          |
           H                          H
            H
            |
(b) CH3CH2-C=C-CH3     and   CH3CH2-C=C CH3
           |                        | |
           H                        H H
```

Solution: Information on the meaning of heat of hydrogenation and how it is related to stability of alkenes will be necessary to solve this problem.

Heat of hydrogenation (ΔH_h) is the enthalpy of the reaction when 1 mole of an unsaturated compound is hydrogenated as shown:

```
 \   /                  |  |
  C=C     + H2  --->   -C--C-   + heat
 /   \                  |  |
                        H  H
```

Since the reaction is exothermic (that is, evolves heat), ΔH_h is a negative number; the difference in strength of a C=C bond and a C-C bond is 62 Kcal/mole.

If one alkene is less stable than an isomeric unsaturated compound, the internal energy of the former will be higher. This means more heat should be released on hydrogenation of the less stable alkene, and the heat of hydrogenation will have a larger negative value. Hence, for (a) and (b), the compound that shows the greater (more negative) heat of hydrogenation will be the less stable.

What will determine the stability of the isomeric alkenes? One factor is cis-trans conformations. In 2-butene, for example, the cis conformation

```
 CH3     CH3
   \     /
    C=C          is less stable than the trans conformation
   /     \
  H       H

  H      CH3
   \     /
    C=C          due to the fact that in the cis conformation,
   /     \
 H3C      H
```

two bulky substituents on the double bond crowd each other, creating steric compression in the molecule, and raising the van der Waals strain energy. The strain is enhanced as the substituents grow larger.

Another factor that influences the stability of isomeric alkenes is the alkyl groups attached to the carbon-carbon double bond. Results indicate that the alkenes which are highly substituted by alkyl groups are more stable. It is believed the inductive effects of alkyl groups and an effect called hyperconjugation are of importance in determining the following order of stability of substituted alkenes:

$$R_2C{=}CR_2 > R_2C{=}CHR > R_2C{=}CH_2 \approx trans\text{-}RCH{=}CHR > cis\text{-}RCH{=}CHR > RCH{=}CH_2 > CH_2{=}CH_2$$

(a) $CH_3CH_2-\underset{H}{C}=\overset{H}{C}-CH_3$ and $(CH_3)_2CH-\underset{H}{C}=CH_2$

2-Pentene 3-Methyl-1-butene

Examination of these isomeric alkenes shows that 3-methyl-1-butene should give the greater (more negative) heat of hydrogenation; it is the less stable of the pair because it is less substituted with alkyl groups as compared to 2-pentene.

(b) $CH_3CH_2-\underset{H}{C}=\overset{H}{C}-CH_3$ and $CH_3CH_2-\underset{H}{C}=\underset{H}{C}-CH_3$

trans-2-Pentene cis-2-Pentene

The cis conformation of 2-pentene should give the greater heat of hydrogenation for the reasons mentioned earlier - there exists steric repulsion between the alkyl groups.

• PROBLEM 5-18

Consider the feasibility of a free-radical chain mechanism for hydrogenation of ethylene in the vapor state at 25° by the following propagation steps:

$$CH_3-CH_2\cdot + H_2 \rightarrow CH_3-CH_3 + H\cdot$$

$$CH_2{=}CH_2 + H\cdot \rightarrow CH_3CH_2\cdot$$

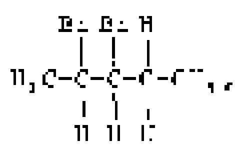
Solution: To determine whether the mechanism is feasible at room temperature (25°C), it will be necessary to calculate ΔH, the heat of the reaction. By convention, the ΔH is given a negative sign when heat is evolved (exothermic reaction) and a positive sign when heat is absorbed (endothermic reaction). If one of the propagation steps of the proposed free-radical mechanism for hydrogenation of ethylene has a positive ΔH, that reaction is unfavorable and will not proceed at room temperature, so that the overall mechanism will not be feasible.

To calculate the heat of reaction, the bond dissociation energies of the reactants must be noted. In $CH_3CH_2\cdot + H_2 \rightarrow CH_3CH_3 + H\cdot$, the hydrogen molecule is broken into a hydrogen radical which, in turn, reacts with the ethyl radical to produce ethane. Now, it takes 104.2 Kcal/mole at 25°C ($\Delta H = +104.2$) to break the H-H bond to form two H· radicals. The addition of one of the H· radicals to the ethyl radical (to give ethane) releases 96 Kcal/mole ($\Delta H = -96.0$). Overall, the heat of reaction is $+104.2 - 96.0 = +8.2$ Kcal/mole. Since the sign is positive, heat is being absorbed (overall); hence, the reaction is unfavorable. The second reaction, $CH_3-CH_3 \rightarrow H\cdot + CH_3CH_2\cdot$, turns out to have an overall $\Delta H = -36$ kcal. Even though this reaction releases a large amount of energy (enough to make the overall ΔH favorable: $-36 + 8.2 = -27.8$), the reaction with $\Delta H = +8.2$ makes the mechanism not feasible.

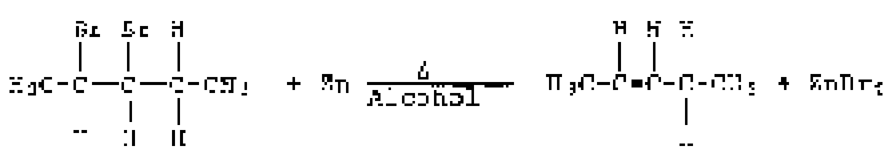
• PROBLEM 6-10

Synthesize pentane from 2,3-dibromopentane using any inorganic reagents.

Solution: The structure of 2,3-dibromopentane,



indicates it is a dihalide. To obtain pentane ($H_3C-CH_2-CH_2-CH_2-CH_3$) from this compound, the intermediate 2 pentene ($H_3C-CH=CH-CH_2-CH_3$) would be useful. For from 2-pentene, a hydrogenation reaction can be performed to obtain pentane. To perform this reaction, 2-pentene is required. This can be obtained directly from 2,3-dibromopentane by the addition of zinc (Zn):



This reaction is called the dehalogenation of vicinal dihalides, i.e. it is the abstraction of two halogens from adjacent carbon atoms to yield the alkene. The metal Zn acts as a donor of electrons.

With 2-pentene formed, hydrogenation is the next reaction. This characteristic reaction of alkenes is the addition of hydrogen across the double bond in the presence of a catalyst such as Pt, Pd, or Ni. The catalyst serves to speed up the reaction by lowering the energy of activation. The reaction can then be written as:

```
     H H H
         |
H3C-C=C-C-CH3  +  H2  --catalyst-->  H3C-CH2-CH2-CH2-CH3
         |
         H
 2-Pentene                            Pentane
```

ADDITION REACTIONS

■ PROBLEM 6-20

> What are addition reactions of alkenes?

Solution: To understand addition reactions of alkenes, there must first be a good understanding of the nature of the double bond. The double bond consists of a strong sigma (σ) bond and a weak pi (π) bond. Therefore it is expected that the reaction would involve breakage of the weaker bond. The typical reactions of the double bond are of the sort where the weaker π bond is broken and stronger σ bonds are formed:

```
 | |                    | |
-C=C-  +  YZ  ------>  -C-C-        Addition
                        | |
                        Y Z
```

A reaction in which two molecules combine to yield a single molecule of product is called an addition reaction. The various types of addition reactions are:

(1) Catalytic Hydrogenation - Addition of Hydrogen

(2) Addition of Halogens

(3) Addition of Hydrogen Halides

(4) Addition of Sulfuric Acid

(5) Addition of Water - Hydration

(6) Halohydrin Formation

(7) Dimerization

(8) Alkylation

(9) Oxymercuration - Demercuration

(10) Hydroboration - Oxidation

(11) Addition of Free Radicals

(12) Polymerization

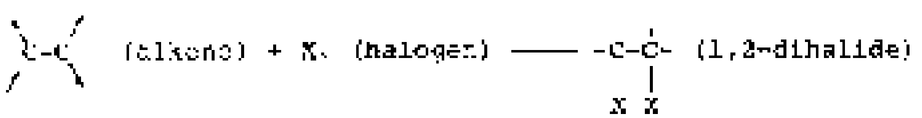
(13) Addition of Carbenes

(14) Hydroxylation, Glycol Formation.

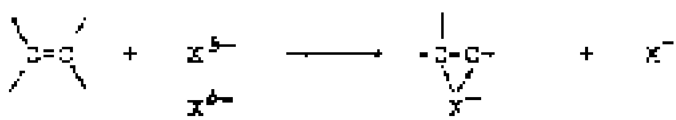
• PROBLEM 6-21

What product is formed when X_2 ($X = Br, Cl$) is added to alkenes in the dark? Explain the mechanism of the reaction.

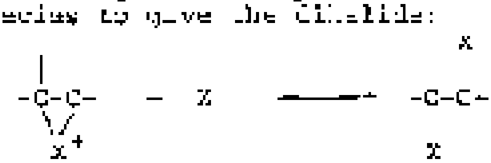
Solution: The addition of halogens such as Br_2 and Cl_2 to alkenes results in the formation of 1,2-dihalides. The reaction can be written as:



The mechanism of this reaction begins by recognizing the fact that X_2 is polarized on contact with the double bond due to the negatively charged π electron cloud of the bond. One end of the halogen molecule becomes positively charged, with the other negatively charged, i.e., $^{\delta-}X-X^{\delta+}$. The positively charged end is attracted to the negative electron cloud. This results in the cleavage of the X–X bond; the negatively charged $X^{\delta-}$ leaves as shown:



Through a nucleophilic attack, the X^- adds to this species to give the dihalide:



• PROBLEM 6-22

Write the products of addition of halogens to each of the following reactants:

(c) $CH_3CH{=}CH{-}CH_2CH_3$ (d) $CH_3CH{=}CH{-}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CH_2{-}CH_3}{C}}{-}CH_2CH_3$

2-Pentene 4,4-Diethyl-2-hexene

Use Cl_2 or Br_2.

Solution: Alkenes can be readily converted by chlorine or bromine into saturated compounds that contain two atoms of halogen attached to adjacent carbons; iodine generally fails to react.

The reaction takes place readily by mixing together the alkene with chlorine or bromine in an inert solvent such as carbon tetrachloride. The general reaction is:

$$-\overset{|}{C}=\overset{|}{C}- \;+\; X_2 \xrightarrow{CCl_4} -\underset{X}{\underset{|}{\overset{|}{C}}}-\underset{X}{\underset{|}{\overset{|}{C}}}- \qquad (X_2 = Cl_2 \text{ or } Br_2)$$

Keeping this in mind, the product of each reaction can be written:

$$\text{(a)}\quad CH_3{-}CH{=}CH_2 + Cl_2 \xrightarrow{CCl_4} CH_3\underset{Cl}{\underset{|}{C}}H{-}\underset{Cl}{\underset{|}{C}}H_2$$

Propene 1,2-Dichloropropane

$$\text{(b)}\quad CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 + Cl_2 \xrightarrow{CCl_4} CH_3{-}\underset{Cl}{\overset{\displaystyle CH_3}{C}}{-}\underset{Cl}{\underset{|}{C}}H_2$$

Isobutylene 1,2-Dichloro-2-methylpropane

$$\text{(c)}\quad CH_3CH{=}CHCH_2CH_3 + Br_2 \xrightarrow{CCl_4} CH_3{-}\overset{\displaystyle Br}{\overset{|}{C}}H{-}\overset{\displaystyle Br}{\overset{|}{C}}H{-}CH_2CH_3$$

2-Pentene 2,3-Dibromopentane

$$\text{(d)}\quad CH_3CH{=}CH{-}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CH_2CH_3}{C}}{-}CH_2CH_3 + Br_2 \xrightarrow{CCl_4} CH_3\overset{\displaystyle Br}{C}H\overset{\displaystyle Br}{C}H{-}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle CH_2CH_3}{C}}CH_2CH_3$$

4,4-Diethyl-2-hexene 4,4-Diethyl-2,3-dibromohexane

• PROBLEM 8-23

From the following alkene precursors, show products of halohydrin formation.

(a) $CH_3CH{=}CHCH_2CH_3$ (b) $CH_3CH{=}CH_2$

2-Pentene Propylene

(c) $CH_2{=}C(CH_3){-}CH_2{-}C(CH_3)_2{-}CH_3$

2,4,4 Trimethyl 1 pentene

Solution: Halohydrin formation is the process of adding chlorine or bromine in the presence of water to an alkene to yield compounds containing halogen and hydroxyl groups on adjacent carbon atoms. This reaction changes an alkene to an alcohol that is halogenated, and the product is referred to as a halohydrin. The general reaction is:

$$-\overset{|}{C}-\overset{|}{C}- \; + \; X_2 \; + \; H_2O \longrightarrow -\underset{X}{C}-\underset{OH}{C}- \; + \; HX \quad (X = Cl \text{ or } Br)$$

The products in these reactions also have a modification in nomenclature which is used more than the IUPAC names in some cases. For example:

$$CH_2{=}CH_2 + Br_2 + H_2O \longrightarrow \underset{OH}{CH_2}-\underset{Br}{CH_2} + HBr$$

Ethylene (Ethene) → Ethylene bromohydrin (2 Bromoethanol)

This example shows that the double bond is broken when reacted with Br_2 in the presence of water, and the product becomes an alcohol with a halogen. Remembering the general formula of the reaction, it can be written that:

(a) $CH_3CH{=}CHCH_2CH_3 \xrightarrow{Br_2+H_2O} CH_3\underset{}{\overset{Br}{C}H}-\overset{OH}{C}HCH_2CH_3 + HBr$

2-Pentene → 2-Bromo-3-pentanol

(b) $CH_3CH{=}CH_2 \xrightarrow{Cl_2,\ H_2O} CH_3\overset{OH}{C}H-\overset{Cl}{C}H_2 + HCl$

Propylene → Propylene chlorohydrin (1-Chloro-2-Propanol)

(c) $CH_2{=}\overset{CH_3}{C}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 \xrightarrow{Br_2+H_2O} \underset{Br}{\overset{H}{C}H}-\underset{OH}{\overset{CH_3}{C}}-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-CH_3 + HBr$

2,4,4-Trimethyl-1-pentene → 2,4,4-Trimethyl-1-bromo-2-pentanol

How can the orientation of the halogen and hydroxyl be explained in these reactions? For example, in propylene chlorohydrin, the chlorine is attached to the terminal carbon, not the middle one. This orientation, and the others, can be accounted for by the mechanism of halohydrin formation. It involves intermediate carbonium ions.

The stability of carbonium ions is $3° > 2° > 1° > CH_3^+$. The greater the number of alkyl groups, the more stable the carbonium ion. Now, in halohydrin formation, the halogen adds to the carbon-carbon double bond of the alkene to generate the most stable carbonium ion. Only after this will the hydroxyl be added.

Let us now consider the case of propylene (b) as an illustration. The initial addition of Cl (from Cl_2) to propylene can generate two types of carbonium ions, shown below:

(1) $CH_3CH{=}CH_2 + Cl_2 \rightarrow CH_3\overset{+}{C}H{-}CH_2Cl$ (2° carbonium ion)

(2) $CH_3CH{=}CH_2 + Cl_2 \rightarrow CH_3\underset{Cl}{CH}{-}CH_2^+$ (1° carbonium ion).

As mentioned above, the 2° carbonium ion is more stable, and will predominate over the 1° carbonium ion. Hence, the hydroxyl adds to $CH_3\overset{+}{C}H{-}CH_2Cl$, not $CH_3\underset{Cl}{CH}{-}CH_2^+$, to obtain

$CH_3\underset{OH}{CH}CH_2Cl$, the observed product.

• PROBLEM 6-31

Predict the products of the following reactants after addition of hydrogen halides:

(a) $CH_3\underset{CH_3}{C}{=}CH{-}CH_3$ (b) $CH_3CH{=}CHCH_3$

2-Methyl-2-butene 2-Butene

(c) $CH_3CH{=}\underset{CH_3}{C}{-}\underset{CH_3}{CH}{-}CH_3$ (d) $CH_3CH{=}CH_2$

3,4-Dimethyl-2-pentene Propylene

Solution: Alkenes can be converted to saturated compounds by addition of hydrogen halides such as hydrogen chloride, hydrogen bromide, or hydrogen iodide. The general reaction for this process is:

$$-\overset{|}{C}=\overset{|}{C}- \;+\; HX \longrightarrow -\underset{H}{\underset{|}{\overset{|}{C}}}-\underset{X}{\underset{|}{\overset{|}{C}}}- \qquad (HX = HCl,\ HBr \text{ or } HI)$$

The product is generally referred to as an alkyl halide, and it is produced by passing dry gaseous hydrogen halide through the alkene.

In ionic addition of an acid (such as hydrogen halide) to the carbon-carbon double bond of an alkene, the hydrogen of the acid attaches itself to the carbon atom that already holds the greater number of hydrogens. This principle is known as Markovnikov's Rule. Remembering this principle, the products are written as:

(a) $$CH_3-\underset{CH_3}{\underset{|}{C}}=CH-CH_3 \;+\; HI \longrightarrow CH_3-\overset{I}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-CH_2-CH_3$$

2-Methyl-2-butene — tert-Pentyl iodide (2-Iodo-2-methylbutane)

(b) $$CH_3CH=CHCH_3 \;+\; HBr \longrightarrow CH_3\underset{Br}{\underset{|}{C}}HCH_2CH_3$$

2-Butene — 2-Bromobutane

(c) $$CH_3CH=\underset{CH_3}{\underset{|}{C}}-\underset{CH_3}{CHCH_3} \;+\; HCl \longrightarrow CH_3-CH_2-\overset{Cl}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-\underset{CH_3}{\underset{|}{CH}}-CH_3$$

3,4-Dimethyl-2 pentene — 3-Chloro-2,3-dimethylpentane

(d) $$CH_3CH=CH_2 \;+\; HI \longrightarrow CH_3-\overset{I}{\overset{|}{CH}}-CH_3$$

Propylene — Isopropyl iodide

• PROBLEM 6-23

In the dark at room temperature, a solution of chlorine in tetrachloroethylene can be kept for long periods with no sign of reaction. When irradiated with ultraviolet light, however, the chlorine is rapidly consumed, with the formation of hexachloroethane; many molecules of product are formed for each photon of light absorbed, and the reaction is slowed down markedly when oxygen is bubbled through the solution.

(a) How do you account for the absence of reaction in the dark? (b) Outline all steps in the most likely mechanism for the photochemical reaction. Show how it accounts for the facts, including the effect of oxygen.

Solution: The information strongly points to a free-radical addition of chlorine to tetrachloroethylene. The fact that the reaction does not take place in the dark, forms many molecules of hexachloroethane with massive consumption of chlorine upon exposure to U.V., and is inhibited by the addition of oxygen can all be explained readily by a free-radical process.

In such a mechanism, a free-radical must be formed. Chlorine exists as Cl_2, but a radical must be an atom or group of atoms possessing an unpaired electron. For a chlorine radical ($Cl\cdot$) to be formed, the Cl_2 molecule must undergo homolysis, which is the cleavage of the chlorine-chlorine bond in a symmetrical way so that each atom retains one electron of the pair that formed the covalent bond. For this to occur, energy must be supplied. The energy is supplied by either heat or light. Hence, the reaction cannot take place in the dark.

Free-radicals often are involved in a chain reaction. Here, a reaction involves a series of steps, each of which generates a reactive substance that brings about the next step. When the chlorine radical produced by addition of U.V. light collides with tetrachloroethylene, it produces another radical, $Cl_3C-\dot{C}Cl_2$, which acts in a chain propagating step. This radical reacts with a chlorine molecule to produce the product, hexachloroethane, and another radical, $Cl\cdot$, which can go back and react with tetrachloroethylene. In other words, once a reactive particle is consumed, another reactive particle is produced, so that everything is propagated. This accounts for the many molecules of hexachloroethane formed per photon of light.

The inhibition of the process with oxygen can be explained by its combining with a free radical such as $Cl\cdot$. This makes it much less reactive, so that it can do little to continue the chain; this prevents the formation of many molecules, and, as such, slows down the reaction tremendously by breaking down the chain.

The overall mechanism of the reaction can be written as follows:

(1) $Cl_2 \xrightarrow{\text{light}} 2Cl\cdot$ Chain initiation

(2) $Cl\cdot + Cl_2C{=}CCl_2 \longrightarrow Cl_3C-\dot{C}Cl_2$
(tetrachloroethylene)

(3) $Cl_3C-\dot{C}Cl_2 + Cl_2 \longrightarrow Cl_3C-CCl_3 + Cl\cdot$
(hexachloroethane)

Chain propagation (steps 2 and 3)

then (2), (3), (2), (3), etc.

What are the products of the following alkenes after hydration?

(a) $CH_3-\underset{}{\overset{CH_3}{\overset{|}{C}}}=CH_2$ (b) $CH_2=CH_2$

Solution: Hydration of alkenes involves the addition of a water molecule in the presence of acid to yield an alcohol. This addition reaction follows Markovnikov's rule,

$$-\overset{|}{C}=\overset{|}{C}- \;+\; H_2O \xrightarrow{H^+} -\underset{H}{\underset{|}{\overset{|}{C}}}-\underset{OH}{\underset{|}{\overset{|}{C}}}-$$

Knowing the definition and the general principles, it can now be written:

$$\text{(a)}\quad \underset{\text{Isobutylene}}{CH_3-\overset{CH_3}{\overset{|}{C}}=CH_2} \;+\; H_2O \xrightarrow{H^+} \underset{\text{t-Butyl alcohol}}{CH_3-\underset{OH}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}-CH_3}$$

$$\text{(b)}\quad \underset{\text{Ethylene}}{CH_2=CH_2 + H_2O} \xrightarrow{H^+} \underset{\text{ethyl alcohol}}{CH_3CH_2OH}$$

• PROBLEM 6-27

Predict the products of the following reactants after addition of sulfuric acid:

(a) $CH_3CH=CH_2$ (propylene), (b) $CH_2=CH_2$ (ethylene), (c) $CH_3CH_2\overset{CH_3}{\overset{|}{C}}=CH_2$ (2-methyl-1-butene)

Solution: Alkenes react with cold, concentrated sulfuric acid (H_2SO_4) to form compounds known as alkyl hydrogen sulfates ($ROSO_3H$). These products are formed by addition of hydrogen ion to one side of the double bond and bisulfate ion to the other. It is important to notice that carbon is bonded to oxygen and not to sulfur. The general reaction is:

$$\underset{\text{Alkene}}{-\overset{|}{C}=\overset{|}{C}-} \;+\; \underset{\text{Sulfuric Acid}}{H-O-\underset{O^-}{\underset{|}{\overset{O^-}{\overset{|}{S^{++}}}}}-O-H} \longrightarrow \underset{\text{Alkyl hydrogen sulfate}}{-\underset{H}{\underset{|}{\overset{|}{C}}}-\underset{|}{\overset{|}{C}}-O-\underset{O^-}{\underset{|}{\overset{O^-}{\overset{|}{S^{++}}}}}-O-H}$$

The concentration of sulfuric acid required for reaction depends upon the particular alkene involved. It must also be understood that Markovnikov's rule is involved in this type of addition reaction.

(a) $CH_3CH{=}CH_2 \xrightarrow{\text{?\% } H_2SO_4} CH_3\underset{\displaystyle OSO_3H}{\underset{|}{C}}HCH_3$

Propylene $\qquad\qquad$ Isopropyl hydrogen sulfate

(b) $CH_2{=}CH_2 \xrightarrow{\text{93\% } H_2SO_4} CH_3-\underset{\displaystyle OSO_3H}{\underset{|}{C}}H_2$

Ethylene $\qquad\qquad$ Ethyl hydrogen sulfate

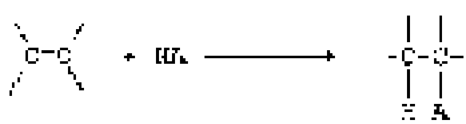
(c) $CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 + H_2SO_4 \longrightarrow CH_3CH_2-\overset{\displaystyle CH_3}{\underset{\displaystyle OSO_3H}{\overset{|}{\underset{|}{C}}}}-CH_3$

2-Methyl-1-butene $\qquad\qquad$ Isopentyl hydrogen sulfate

• PROBLEM 6-24

Compound X has the molecular formula C_5H_{10}. Compound Y is obtained when hydrogen bromide is added to X. Compound Y reacts with AgOH to form a tertiary alcohol. Identify all structures.

Solution: Compound X's molecular formula fits the general formula of an alkene, C_nH_{2n}. The presence of the double bond in compound X means unsymmetrical reagents such as HA (where A = Br, Cl) can be added across the bond to obtain the alkyl halide. This is exactly what occurs when hydrogen bromide (HBr) is added to compound X. The general reaction can be written as follows:



Alkene $\qquad\qquad$ Alkyl halide

The alkyl halide produced in this reaction (compound Y) reacts with silver hydroxide to produce an alcohol. This reaction illustrates a method of generating alcohols as shown:

$$R-X + AgOH \xrightarrow[\text{ether}]{\text{moist}} R-OH + AgX$$

Alkyl halide

The fact that a tertiary alcohol $\left[R-\overset{\displaystyle R}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}-R \right]$ is produced can tell what the actual structures of X and Y are. If no carbon atoms are added in a reaction sequence, then the initial number of carbon atoms should equal the final number (assuming no degradation). The tertiary alcohol should, therefore, contain only four carbon atoms. The only way to arrange a 3° alcohol with 4 carbons is to surround a central carbon with three others. In other words, the

tertiary alcohol must be $\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ OH \end{array}$ (t-butyl alcohol).

Working backwards, one can determine the structure of the other compounds. Only the alkyl halide t-butyl bromide could have reacted with AgOH to produce this tertiary alcohol:

$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ Br \end{array} + AgOH \longrightarrow \begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ OH \end{array}$$

(t-butyl bromide, compound Y)

With similar reasoning, it can be concluded that compound X has the following structure:

$$\begin{array}{c} CH_3 \\ | \\ CH_2=C-CH_3 \end{array} \quad \text{(isobutylene, compound X)}$$

One will notice that when HBr is added (keeping in mind Markovnikov's rule) compound Y is obtained.

• PROBLEM 8-29

Treatment of $C_7H_{15}Br$ with strong base gave an alkene mixture that was shown by careful gas chromatographic analysis and separation to consist of three alkenes, C_7H_{14}, A, B, and C. Catalytic hydrogenation of each alkene gave 2-methylhexane. Reaction of A with B_2H_6 followed by H_2O_2 and OH^- gave mostly an alcohol, D. Similar reaction of B or C gave approximately equal amounts of D and an isomeric alcohol E. What structural assignments can be made for A to E on the basis of these observations? What structural element is left undetermined by these data alone?

Solution: The problem indicates that $C_7H_{15}Br$ produces a mixture of three alkenes in the presence of strong base. The formula $C_7H_{15}Br$ suggests the compound is an alkyl halide. In the presence of strong base, dehydrohalogenation of alkyl halides occurs to produce alkenes as illustrated:

$$\underset{\text{Alkyl halide}}{-\overset{|}{\underset{\vdots}{C}}-\overset{|}{\underset{X}{C}}-} + \underset{\text{Base}}{KOH} \xrightarrow{\text{alcohol}} \underset{\text{Alkene}}{-\overset{|}{C}=\overset{|}{C}-} + KX + H_2O$$

Hence, a dehydrohalogenation reaction produced the mixture of alkenes.

In catalytic hydrogenation, H_2 adds across the double bond of the alkene and converts it into the alkane as shown:

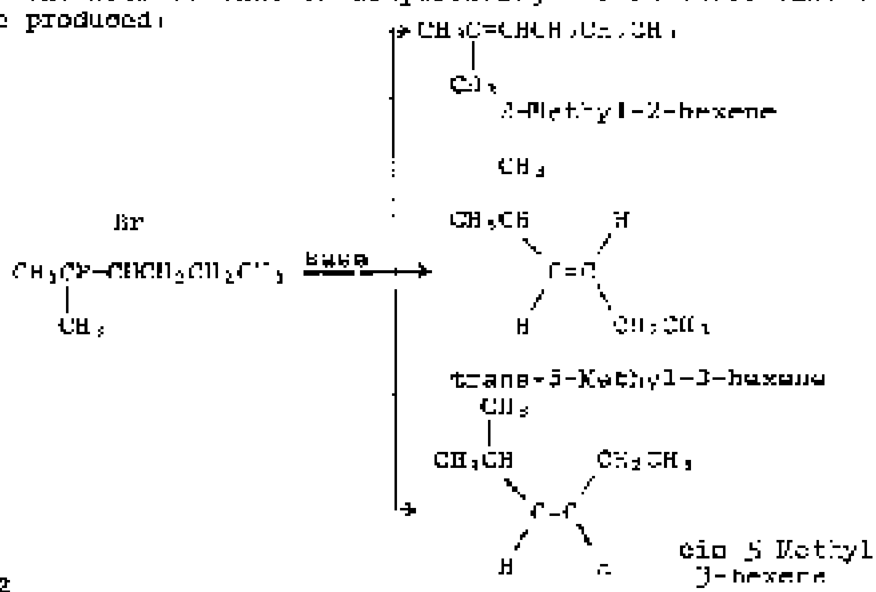
$$\underset{\text{Alkene}}{-\overset{|}{C}=\overset{|}{C}-} + H_2 \xrightarrow{\text{Pt, Pd, or Ni}} \underset{\text{Alkane}}{-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{H}{C}}-}$$

In this problem, all the alkenes give rise to 2-methylhexane $\left[CH_3-\underset{CH_3}{\underset{|}{C}H}CH_2CH_2CH_2CH_3\right]$ after catalytic hydrogenation. This provides information on the structure of the $C_7H_{15}Br$. The compound must have the same carbon skeleton as 2-methylhexane; no carbon atoms were added or degraded. In fact, if one writes the formula for 2-methylhexane, C_7H_{16}, one sees the two compounds differ by a bromine atom which replaces one of the hydrogens. Hence, to write the structure of $C_7H_{15}Br$, one needs only to replace one of the hydrogens in 2-methylhexane with Br. The question is which hydrogen is to be replaced? This can be answered by using the fact that three alkenes are obtained after dehydrohalogenation. One asks: where is it possible to place the Br to give three different alkenes on dehydrohalogenation? Now, through trial and error, one finds the Br must be positioned as shown:

$$CH_3-\underset{CH_3}{\underset{|}{C}H}-\overset{Br}{\overset{|}{C}H}CH_2CH_2CH_3$$

2-Methyl-3-bromohexane

One notices that on dehydrohalogenation three alkenes are produced:



The structures drawn show that two of the three alkenes are cis-trans geometric isomers.

These alkenes fit the formula, C_7H_{14} and represent A, B, and C. (Note: The Br at the 5th position will also give 3 alkenes, but the remaining reactions with B_2H_6, H_2O_2 and OH^- rule this out. The 5th position Br would give 5-methyl-1-hexene and cis and trans 5-methyl-2-hexenes. However, the cis-trans alkenes cannot give the same alcohol, 5-methyl-1-hexanol, which 5-methyl-1-hexene produces on reaction with B_2H_6, H_2O_2 and OH^-. Consequently, since the problem states that A, B, and C, that is, all the alkenes, can generate the same alcohol (D), this possibility is eliminated.)

At this point, one cannot assign particular structures to A, B, and C. The reagents B_2H_6, H_2O_2 and OH^- will aid in pinpointing the structures. These reagents that generate the alcohols D and E add the hydroxyl group in anti-Markovnikov fashion. Hence, 2-methyl-2-hexene gives mostly one alcohol as shown:

$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{C}}=CHCH_2CH_2CH_3 \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2} CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\overset{\displaystyle OH}{CH}CH_2CH_2CH_3$$

(D)

(Very little $CH_3\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{C}}}-CH_2CH_2CH_2CH_3$ would be produced because the reaction would have been in Markovnikov fashion.) This fits the information for compound A giving mostly the alcohol D. Therefore, it can be concluded that compound A is 2-methyl-2-hexene. Consequently, B and C must be the cis-trans geometric isomers. From the data provided, it cannot be determined whether B is cis or trans. The structure of the alcohols, D and E, can be discerned as indicated below:

$$CH_3CH_2CH=CHCH(CH_3)_2 \xrightarrow{B_2H_6} \xrightarrow[OH^-]{H_2O_2}$$

B + C, cis and trans

$$CH_3CH_2CH_2\underset{\displaystyle OH}{CH}CH(CH_3)_2 + CH_3CH_2\overset{\displaystyle OH}{CH}CH_2CH(CH_3)_2$$

D E

OXIDATION

● PROBLEM 6-30

Describe the mechanism of the peroxide effect.

Solution: In the absence of peroxides, hydrogen bromide adds to alkenes in agreement with Markovnikov's rule; that is, the hydrogen of HBr goes to that carbon of the double bond that carries the greater number of hydrogens. In the presence of peroxides, the addition proceeds in a reverse direction, or anti-Markovnikov. This phenomenon is known as the peroxide effect.

The main point of the mechanism is that hydrogen and bromine add to the double bond as atoms rather than as ions; the intermediate is a free radical rather than a carbonium ion. As in halogenation of alkanes, this is a chain reaction, this time involving addition rather than substitution.

Step 1 of the mechanism is the decomposition of the peroxide to yield free radicals. The free radical thus formed abstracts hydrogen from hydrogen bromide (step 2) to form a bromine atom.

$$(1)\quad \text{peroxides} \longrightarrow \text{Rad}\cdot$$

$$(2)\quad \text{Rad}\cdot + \text{H}:\text{Br} \longrightarrow \text{Rad}:\text{H} + \text{Br}\cdot$$

The bromine atom then adds to the double bond converting the alkene into the most stable radical (step 3). This free radical abstracts hydrogen from hydrogen bromide (step 4).

$$(3)\quad \text{Br}\cdot + -\overset{|}{C}=\overset{|}{C}- \longrightarrow -\overset{|}{\underset{Br}{\underset{|}{C}}}-\overset{|}{C}\cdot-$$

$$(4)\quad -\underset{Br}{\underset{|}{C}}-\overset{|}{C}\cdot- + \text{H}:\text{Br} \longrightarrow -\underset{Br}{\underset{|}{C}}-\overset{|}{\underset{H}{\underset{|}{C}}}- + \text{Br}\cdot$$

Addition is now complete, and a new bromine atom has been generated to continue the chain.

● PROBLEM 6-31

Determine the oxidation number of each atom in the following:

(a) propane
(b) 1-butene
(c) cis-2-butene
(d) 1-chloro-2-butene
(e) (E)-2-chloro-2-butene
(f) 1,1-dichloropropane
(g) acetic acid, CH_3CO_2H
(h) methanethiol, CH_3SH

Solution: In general chemistry, the term oxidation means loss of electrons and reduction means gain of electrons. The change in degree of oxidation or reduction can be recognized by a change in oxidation number.

In organic chemistry, this approach cannot be used because the changes accompanying reaction involve covalent bonds and there is no clear ownership of bonding electrons. Consequently, ownership is assigned based upon the electro negativity of the elements. The rules are as follows: (1) Electronegative elements (such as O, N, S, Br) are considered to make a +1 contribution to the oxidation number of the carbon to which it is attached. (2) A hydrogen atom, being less electronegative, makes a −1 contribution to the carbon to which it is attached. (3) A zero contribution occurs when a carbon is bonded to another carbon. (4) Multiple bonds are counted according to the multiplicity of the bond. For example, in C=O, the oxygen contributes +2 because it is a double bond.

(a) Propene: $CH_3\text{-}CH{=}CH_2$
$\quad -3 \quad -1 \quad -2$

Explanation: In the CH_3 portion, there are three H's each of which makes a −1 contribution for a total of −3. In CH_2, there exist two hydrogens for a contribution of −2. CH has only a −1 contribution for only one hydrogen is present. The carbons bonded together make no contribution.

(b) − (h) follow readily with such reasoning.

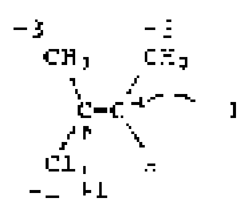
(b) 1-Butene: $CH_3\text{-}CH_2\text{-}CH{=}CH_2$
$\quad -3 \quad -2 \quad -1 \quad -2$

(c) cis-2-Butene: $CH_3\text{-}\underset{|}{\overset{H}{C}}{=}\overset{H}{C}\text{-}CH_3$
$\quad -3 \quad -1 \quad -1 \quad -3$

(d) 1-Chloro-2-butene: $CH_3\text{-}CH{=}CH\text{-}CH_2\text{-}Cl$
$\quad -3 \quad -1 \quad -1 \quad -1 \quad -1$

Note: The CH_2 portion contributes −1 because the two hydrogens yield −2 and Cl, more electronegative than carbon, imparts +1 to the carbon to which it is attached.

(e) (E) 2-Chloro-2-butene:



(f) 1,1-Dichloropropane:
$\quad -3 \quad -2 \quad +1 \quad -1$
$CH_3\text{-}CH_2\text{-}CH\text{-}Cl$
$\qquad\qquad\quad Cl$
$\qquad\qquad\quad -1$

Note: Each chlorine imparts +1 (for a total of +2) to the carbon to which it is attached, but H imparts −1 for a net of +1.

(g) Acetic acid:

$$\begin{array}{c} \quad\; O \\ \quad\; \| \\ CH_3-C-O-H \\ -3 \;\; + \;\; -2 \\ \;+3 \end{array}$$

The +3 charge of the carbon comes about as follows: The doubly bonded oxygen contributes +2 (twice +1 because of the double bond) and the singly bonded oxygen +1. The charge on the oxygen atom itself is −2.

(h) Methanethiol: $\underset{-2\;\;-2}{CH_3S-H}$

The three hydrogens contribute a −3 but the electronegative sulfur imparts +1 to the carbon to which it is attached for a net of −2. (The S, itself, is −2.)

• PROBLEM 6-32

In the presence of a trace of peroxide or under the influence of ultraviolet light, 1-octene reacts:

(a) with $CHCl_3$ to form 1,1,1-trichlorononane;
(b) with $CHBr_3$ to form 1,1,1-tribromononane;
(c) with $CBrCl_3$ to form 1,1,1-trichloro-3-bromononane;
(d) with $H-S-CH_2COOH$ (thioglycolic acid) to yield $n\text{-}C_8H_{17}-S-CH_2COOH$;
(e) with aldehydes, $\underset{H}{\underset{|}{R-C}}=O$, to yield ketones, $n\text{-}C_8H_{17}-\underset{O}{\underset{\|}{C}}-R$.

Show all steps of a likely mechanism for these reactions.

Solution: In the presence of peroxides numerous reagents can add to alkenes through free-radical addition. Likewise, free-radical addition occurs in the presence of light. Peroxides decompose to yield free radicals, while light generates free radicals by causing homolytic cleavage across covalent bonds. Only trace amounts of peroxide or light are needed, for once the reaction has been initiated, the consumption of one radical generates another so that there exist chain propagating steps. The following mechanism has been proposed (illustrated with $CHCl_3$):

(1) $\text{Peroxide} \rightarrow \text{Rad}\cdot$

(2) $\text{Rad}\cdot + CHCl_3 \longrightarrow \text{Rad}:H + \cdot CCl_3$

(3) $\cdot CCl_3 + \underset{\text{(1-octene)}}{CH_2=CH-(CH_2)_5-CH_3} \rightarrow Cl_3C-CH_2-\dot{C}H-(CH_2)_5-CH_3$

(4) $Cl_3C-CH_2-\dot{C}H-(CH_2)_5-CH_3 + CHCl_3 \rightarrow \underset{\text{(1,1,1-trichlorononane)}}{Cl_3C-CH_2CH_2(CH_2)_5CH_3}$

$+ \cdot CCl_3$

then (3), (4), (3), (4), etc.

The peroxide radical abstracts a hydrogen atom from the $CHCl_3$ to produce another radical, $\cdot CCl_3$. This, in turn, adds across the double bond of 1-octene to produce the next radical, $Cl_3C{-}CH_2{-}\dot{C}H{-}(CH_2)_5{-}CH_3$, which reacts with $CHCl_3$ to yield 1,1,1-trichlorononane and $\cdot CCl_3$ which can repeat the process.

The same mechanism occurs in (b)-(e), except with radicals in steps (2) and (4) abstracting: (b) Br, (c) Br, (d) H from S, (e) H.

• PROBLEM 6-33

The following physical properties and analytical data pertain to two isomeric hydrocarbons A and B, isolated from a gasoline:

	b.p.	m.p.	%C	%H
A	68.6°	-141°	85.63	14.34
B	67.9°	-133°	85.63	14.34

Both A and B readily decolorize bromine and permanganate solutions and give the same products on ozonization. Suggest possible structures for A and B. What experiments would you consider necessary to further establish the structure and configuration of A and B?

Solution: One of the best ways an alkene can be characterized is by its ability to decolorize both a solution of bromine in CCl_4 and a cold, dilute, neutral permanganate solution as shown:

$$\underset{\text{Alkene}}{>C{=}C<} \quad \underset{\text{Red}}{Br_2/CCl_4} \longrightarrow \underset{\text{Colorless}}{\underset{Br\ \ Br}{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-}}$$

$$\underset{\text{Alkene}}{>C{=}C<} + \underset{\text{Purple}}{MnO_4^-} \longrightarrow \underset{\text{Brown ppt.}}{MnO_2} + \underset{\text{Colorless}}{\underset{OH\ \ OH}{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-}}$$

The fact that both A and B decolorize these solutions indicates they possess double bonds, that is, they are alkenes.

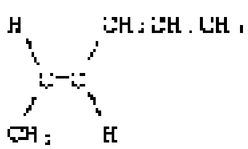
The problem states that the same products are obtained from A and B after ozonization, a process that cleaves the carbon-carbon double bond to produce aldehydes and ketones as illustrated:

Alkene Cleavage Products

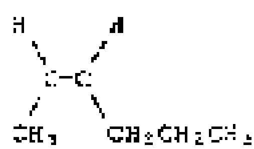
The fact that the same cleavage products are obtained from A and B must mean that the groups originally attached to the doubly bonded carbons were the same in both molecules. If this is the case, it would appear that A and B are the same compound. And yet, how can you account for the different physical properties of the two compounds indicated in the table? One way is to consider the possibility of geometric isomerism, that is, cis-trans conformations.

The information provided indicates the percentages of carbon and hydrogen in both A and B to be 85.63 and 14.34, respectively. A likely formula for such percentages is C_6H_{12}. That this is the formula may be shown in the following manner: the molecular weight of C_6H_{12} is 12(6)+1(12)= 84. The carbons total 12(6)=72. Hence, the percentage of carbon is 72/84 × 100 ≈ 85.63. The percentage of hydrogen, 12/84 × 100 ≈ 14.34, checks also.

With this in mind, the possible structures are the cis-trans isomer of 2-hexene or the cis-trans isomer of 3-hexene as shown:

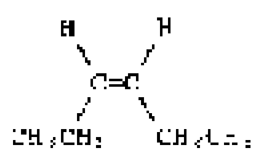


trans-2-Hexene



cis-2-Hexene

trans-3-Hexene



cis-3-Hexene

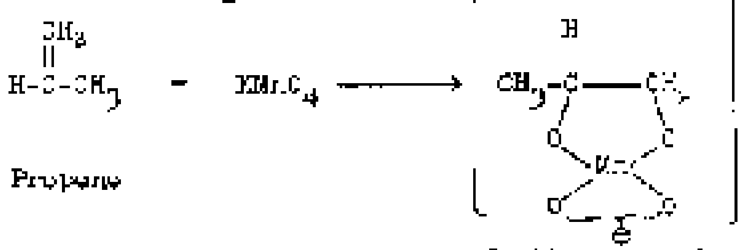
One can narrow down whether A is cis or trans and likewise B. Examination of the melting and boiling points shows that compound A has the lower melting point and higher boiling point which probably suggests the conformation of A is cis. (Except for 3-hexenes, cis isomers have lower melting points and higher boiling points than trans isomers.)

To pinpoint whether the molecule is 2-hexene or 3-hexene, one could use nuclear magnetic resonance. One could also analyze the products of ozonization: they should be identified as acetaldehyde and butyraldehyde in the case of 2-hexene or only as propionaldehyde in the case of 3-hexene.

• PROBLEM 6-31

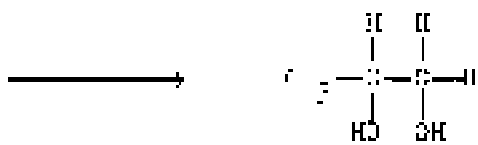
Write the equation for the oxidation of propene by $KMnO_4$ solution at pH = 7.0. Show any intermediates. Assume cold and dilute conditions.

Solution: Alkenes such as propene $\left(CH_2=\overset{H}{\overset{|}{C}}-CH_3\right)$ can be hydroxylated with potassium permanganate solution ($KMnO_4$) under cold, dilute and neutral conditions. The 1,2-diol products that form are almost exclusively syn-adducts. This stereospecificity of the reaction can be explained by the formation of a cyclic ester intermediate. The overall mechanism is given below.



Propene

Cyclic ester intermediate



Syn-adduct:
1,2-dihydroxypropane

• PROBLEM 6-32

On ozonolysis of a hydrocarbon two equivalents of formaldehyde and one equivalent of

$$O=CH-C(CH_3)_2-\underset{\underset{O}{\|}}{C}-C_6H_5$$

were obtained. Give the structure of the hydrocarbon.

Solution: Ozonolysis is a characteristic reaction of alkenes. It degrades alkenes to aldehydes $\left(\begin{array}{l}H\\ \quad\diagdown\\ \quad\; C=O,\\ \quad\diagup\\ R\end{array}\right.$ where R is a hydrocarbon$\left.\right)$ and ketones $\left(\begin{array}{l}R'\\ \quad\diagdown\\ \quad\; C=O,\\ \quad\diagup\\ R\end{array}\right.$

where R may be the same as R$'$) by cleaving the double bond with ozone (O_3) in the presence of zinc dust (Zn) and acid (H^+).

The mechanism of the reaction is as follows: ozone is passed through the alkene which causes the formation of ozonides; the ozonides, which are explosive, are converted into aldehydes and ketones in the presence of zinc dust and acid.

$R_2C{=}CR_2$ (alkene) + O_3 (ozone) $\longrightarrow$

$\longrightarrow R_2C\overset{O-O}{\underset{O}{\diamond}}CR_2$ (ozonide) $\xrightarrow[Zn,\ H^+]{H_2O}$ $R_2C{=}O$ +

$O{=}CR_2$ (Ketones) + H_2O

The products of ozonolysis can be used to identify the structure from which they came.

The position of the double bond in the original alkene will be indicated by the carbonyl (i.e., C=O) formed in the products after ozonolysis.

In this problem, $O{=}CH{-}C(CH_3)_2{-}\underset{\underset{O}{\|}}{C}{-}C_2H_5$ and 2 equivalents of

formaldehyde $\left[\begin{matrix}H \\ & \diagdown \\ & & C{=}O \\ & \diagup \\ H\end{matrix}\right]$ are given as the products of ozonolysis. There are two carbonyls in $O{=}CH{-}C(CH_3)_2{-}\underset{\underset{O}{\|}}{C}{-}C_2H_5$,

which indicate the locations of the two double bonds. Therefore,

$\begin{matrix}H \\ & \diagdown \\ & & C{=}CH{-}C(CH_3)_2{-}\underset{\underset{\underset{H\quad H}{\diagup\ \diagdown}}{C}}{\|}{C}{-}C_2H_5 \\ & \diagup \\ H\end{matrix}$ can be deduced to be

the structure of the hydrocarbon; ozonolysis of it across its double bonds yields two equivalents of formaldehyde

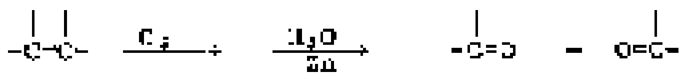
and one of $O{=}CH{-}C(CH_3)_2{-}\underset{\underset{O}{\|}}{C}{-}C_2H_5$, as experimentally

observed.

An unknown compound A rapidly decolorized a solution of bromine in carbon tetrachloride. When A was subjected to ozonolysis, the products were butanone and propanal. What might be the structure of A?

Solution: Bromine in carbon tetrachloride is a standard test for olefins. It uses the fact that bromine can add across a carbon-carbon double bond by an electrophilic addition reaction. As the reaction proceeds, the depletion of Br_2 decolorizes the reddish-brown bromine solution. The reaction is so rapid that this decolorization is almost instantaneous.

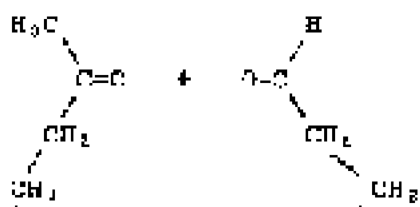
Since A decolorizes a bromine solution, it is an olefin. This is further confirmed by the fact that A undergoes ozonolysis, which is an oxidation reaction of olefins. In this oxidation process, the carbon-carbon double bond is cleaved, producing two separate carbonyl compounds. The general reaction may be written as:



Alkene

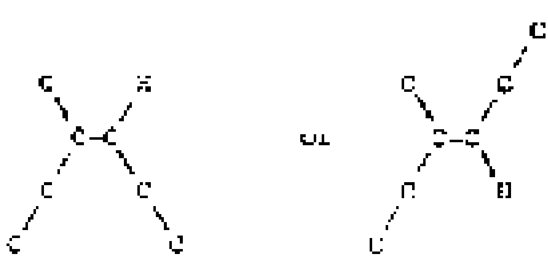
Cleavage products: Aldehydes and Ketones

As can be seen, in the cleavage products a doubly bonded oxygen is found attached to each of the originally doubly bonded carbons. Knowing the structure of the cleavage products allows one to work back to the structure of the alkene or olefin. Since compound A gives rise to the cleavage products below,



Butanone Propanal

unknown A has the following carbon skeletal structure:



cis trans

Therefore, compound A can be either cis or trans-3-methyl-3-hexene.

POLYMERIZATION

• PROBLEM 6-51

Give the structure of the monomer from which each of the following polymers would most likely be made:
(a) Orlon (fibers, fabrics), $\sim CH_2CH(CN)CH_2CH(CN)\sim$
(b) Saran (packaging film, seat covers) $\sim CH_2CCl_2CH_2CCl_2\sim$
(c) Teflon (chemically resistant articles), $\sim CF_2CF_2CF_2CF_2\sim$

Solution: Each of the polymers indicated results from a process called polymerization. It may be defined as the joining together of many small molecules to make large molecules. The compound made up of many smaller units is termed the polymer, whereas the simple compounds from which polymers are made are referred to as monomers.

Polymerization requires the presence of a minute amount of initiator. Peroxides serve as initiators by breaking down to form a free radical. The free radical adds across the double bond of an alkene, which creates another radical. This radical then can add to another alkene to create a still larger radical, and so on. This type of sequence is known as chain-reaction polymerization and can be illustrated as follows:

$$\text{Peroxide} \longrightarrow \text{Rad}\cdot$$

$$\text{Rad}\cdot + CH_2{=}\underset{\displaystyle R}{\underset{|}{CH}} \longrightarrow \text{Rad}CH_2{-}\underset{\displaystyle R}{\underset{|}{CH}}\cdot$$

$$\text{Rad}CH_2\underset{\displaystyle R}{\underset{|}{CH}}\cdot + CH_2{=}\underset{\displaystyle R}{\underset{|}{CH}} \longrightarrow \text{Rad}CH_2\underset{\displaystyle R}{\underset{|}{CH}}CH_2{-}\underset{\displaystyle R}{\underset{|}{CH}}\cdot$$

This continues until termination, such as the union of two radicals, that consume but do not generate radicals.

Hence, to find the monomer that generates a polymer, look for the sequence that constantly repeats; this sequence represents the smallest building block, the alkene monomer, which adds to others with the help of the radical initiators.

(a) Orlon, $\sim CH_2CH(CN)CH_2CH(CN)\sim$. The repeating sequence is (by inspection) $CH_2CH(CN)$. The monomer must be $CH_2{=}CH{-}CN$, acrylonitrile.

(b) Saran, $\sim CH_2CCl_2CH_2CCl_2\sim$. Since the repeating sequence is CH_2CCl_2, the monomer must be $CH_2{=}CCl_2$, 1,1-dichloroethene.

(c) Teflon, $\sim CF_2CF_2CF_2CF_2 \sim$. Since the repeating sequence is CF_2CF_2, the monomer can only be CF_2=CF_2, tetrafluoroethylene.

ALKYLATION

• PROBLEM 6-38

When ethylene is alkylated by isobutane in the presence of acid, there is obtained not neohexane, $(CH_3)_3CCH_2CH_3$, but chiefly 2,3-dimethylbutane. Account in detail for the formation of this product.

Solution: This problem can be solved by a consideration of the mechanism of alkylation and the rearrangement of carbonium ions through an alkyl and/or hydride shift.

Alkylation involves three basic steps. The first two steps are identical to the dimerization reaction, while the 3rd step involves a carbonium ion (that is, a group of atoms that contains a carbon atom bearing only six electrons so that it possesses a positive charge) abstraction of a hydrogen atom with its pair of electrons (a hydride ion) from a molecule of alkane.

Addition of acid in the presence of the alkene ethylene results in the formation of ethyl cation, a carbonium ion, as shown:

$$CH_2{=}CH_2 \xrightarrow{H^+} CH_3CH_2^+$$

Ethylene   Ethyl cation

Carbonium ions undergo reactions that provide electrons to complete the octet of the positively charged carbon atom. Hence, one reaction that CH_3-CH_2^+ can undergo is to abstract a hydride ion from isobutane.

$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ H \end{array}$$

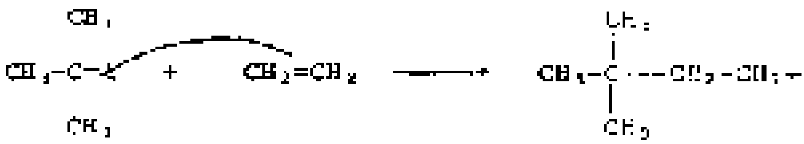
It does this in a manner so that the most stable carbonium is obtained. (Remember, the stability of carbonium ions is $3° > 2° > 1° > CH_3^+$.) The abstraction of the hydride ion can be illustrated as follows:

$$CH_3{-}CH_2^+ \;+\; \begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ H \end{array} \longrightarrow$$

$$\underset{\text{Ethane}}{CH_3{-}CH_3} \;+\; \underset{\text{t-Butyl cation}}{\begin{array}{c} CH_3 \\ | \\ CH_3-\overset{}{\underset{+}{C}}-CH_3 \end{array}}$$. Notice that the t-

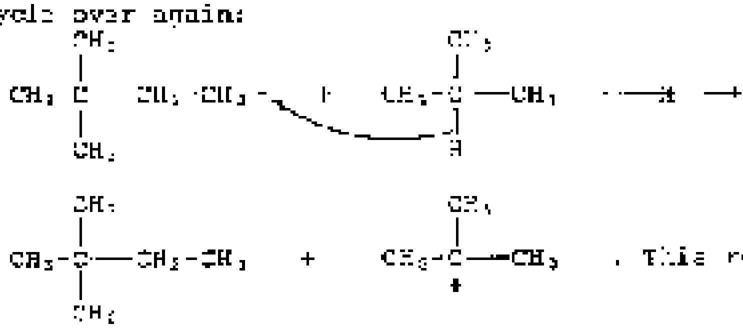
butyl cation is a 3° carbonium ion and, therefore, the most stable.

What will the t-butyl cation do? As mentioned, the carbonium wants to complete its octet. The carbon-carbon double bond of ethylene is an excellent electron source to complete its octet, so that the carbonium ion may go there in quest of electrons as shown:



Neohexane cation

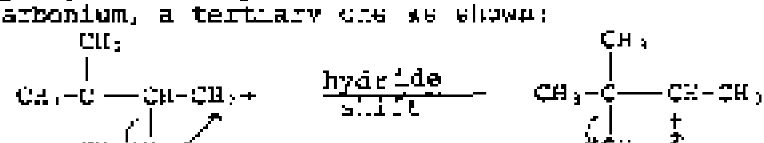
A new carbonium ion is formed. Now, if neohexane had been produced, it would have resulted from the cation abstracting a hydride ion from isobutane, which would, in turn, produce the t-butyl cation to start the entire cycle over again:



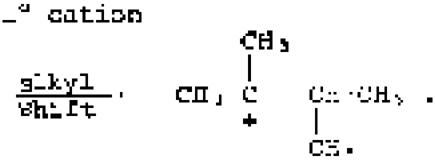
. This reaction

Neohexane

does NOT occur. The reason can be found from inspection of the neohexane cation; it is a primary carbonium ion. This is not a very stable carbonium. By a 1,2 shift of a hydrogen and alkyl group it can yield a more stable carbonium, a tertiary one as shown:



1° cation 3° cation

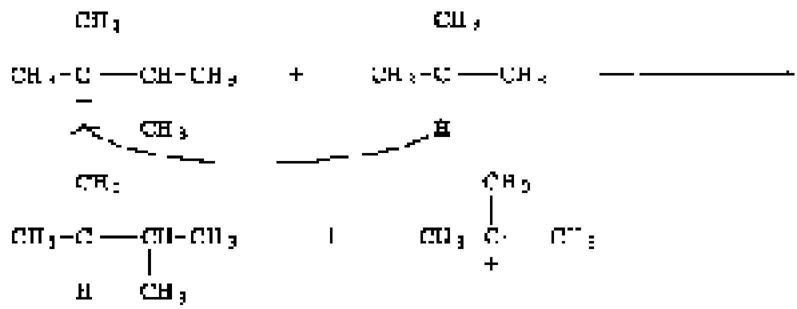


. This process demonstrates

3° cation

carbonium ion rearrangement. The rule to note is that if a 1,2 shift of hydrogen or alkyl can form a more stable carbonium ion, then such a rearrangement will occur.

The 3° cation, $CH_3-\overset{CH_3}{\underset{+}{C}}-\underset{CH_3}{CH}-CH_3$, can now abstract the hydride ion from isobutane to produce the 2,3-dimethylbutane. This reaction also produces the t-butyl cation, which continues the chain.



2,3-Dimethylbutane   t-Butyl cation

• PROBLEM 6-39

Using only isobutene and any inorganic reagents synthesize 2,2,4-trimethylpentane.

<u>Solution:</u> 2,2,4-trimethylpentane $\left(CH_3C(CH_3)_2-CH_2-CH(CH_3)-CH_3\right)$ can be made from isobutene $\left(CH_3-C(CH_3)=CH_2\right)$ by performing a dimerization reaction followed by hydrogenation.

Dimerization is a reaction that allows one to obtain higher molecular weights of alkene than the starting material. Carbonium ion mechanism explains the formation of a dimer.

Step 1: Acid is added to isobutene to form the most stable carbonium ion.

$$CH_3-\underset{}{\overset{CH_3}{\overset{|}{C}}}=CH_2 + H^+ \text{ (acid)} \rightarrow CH_3-\underset{+}{\overset{CH_3}{\overset{|}{C}}}-CH_3$$

The acid adds across the double bond of isobutene to give a 3° carbonium ion (i.e., one with 3 alkyl groups attached to the positive charged carbon) rather than $CH_3-\underset{H}{\overset{CH_3}{\overset{|}{C}}}-CH_2+$, which is a 1° carbonium ion (i.e., one with 1 alkyl group attached to the positive-charged carbon). A

3° carbonium ion is more stable than a 2° or 1° carbonium for the alkyl groups stabilize the charge by feeding in electrons.

Step 2: The 3° carbonium ion can now add to another isobutene in a dimerization by electrophilic addition:

$$(CH_3)_3C^+ + CH_2{=}C(CH_3){-}CH_3 \rightarrow CH_3{-}C(CH_3)_2{-}CH_2{-}\overset{+}{C}(CH_3){-}CH_3$$

A pair of electrons is donated by the pi cloud of isobutene to the t-butyl cation, resulting in a dimer. Again,

$$CH_3{-}C(CH_3)_2{-}CH_2{-}\overset{+}{C}(CH_3){-}CH_3$$ is formed, not $$CH_3{-}C(CH_3)_2{-}C(CH_3)_2{-}CH_2^+$$

due to the fact that a 3° carbonium ion is more stable than a 2° carbonium ion.

Step 3: $CH_3{-}C(CH_3)_2{-}CH_2{-}\overset{+}{C}(CH_3){-}CH_3$ can eliminate a proton (H^+) to form $CH_3{-}C(CH_3)_2{-}CH{=}C(CH_3){-}CH_3$, 2,4,4-trimethyl-2-pentene. (2,4,4-trimethyl-1-pentene is also formed, but only in minor amounts since the other alkene is more stable.)

From 2,4,4-trimethyl-2-pentene, 2,2,4-trimethylpentane is obtained by a hydrogenation reaction:

$$CH_3{-}C(CH_3)_2{-}CH{=}C(CH_3){-}CH_3 + H_2 \xrightarrow{\text{catalyst}} CH_3{-}C(CH_3)_2{-}CH_2{-}CH(CH_3){-}CH_3$$

SYNTHESIS

• PROBLEM 6-40

Indicate how you would synthesize each of the following compounds from any one of the given organic starting materials and inorganic reagents. Specify reagents and the reaction conditions. Starting materials: propylene, isobutylene.

a. $CH_3-C(CH_3)(OH)-CH_3$

b. $CH_3-C(CH_3)(F)-CH_3$

c. $CH_3CH(OH)-CH_2Br$

d. $CH_3-C(CH_3)_2-CH_2-C(CH_3)(I)-CH_3$

e. $CH_3-C(CH_3)_2-CH_2-C(=O)-CH_3$

f. $CH_3-C(CH_3)(H)-CH_2Br$

g. $CH_3-CH_2-CH_2OH$

h. $CH_3-C(CH_3)_2-CH_2-C(CH_3)(OH)-CH_2OH$

Solution: The chemistry in this problem involves the reactions of the carbon-carbon double bond in alkenes. Alkenes usually undergo electrophilic and free-radical addition across the double bond: one-half of the double bond is broken and two new groups are attached to give a saturated compound.

The double bond of alkenes consists of a strong sigma bond and a weak pi bond. The loosely held π (pi) electrons are readily available to a reagent that seeks electrons. Hence, the double bond acts as a source of electrons, that is, it acts as a base. Compounds deficient in electrons (acids), such as electrophilic reagents (which seek a pair of electrons) and free radicals (which seek an electron), react with the bond.

(a) To produce $CH_3-C(CH_3)(OH)-CH_3$, an alcohol, one could hydrate isobutylene, $CH_3-C(CH_3)=CH_2$, with H_2O and a 10% solution of H_2SO_4 at 25°. The reaction can be written as follows:

$$CH_3-C(CH_3)=CH_2 \xrightarrow[25^\circ]{H_2O,\ H_2SO_4\,(10\%)} CH_3-C(CH_3)(OH)-CH_3$$

Water adds to the more reactive alkenes in the presence of acids to yield alcohols.

Note: The addition of H_2O follows Markovnikov's rule, which may be stated as follows: in the addition of HX to an unsymmetrical carbon carbon double bond, the hydrogen of HX goes to that carbon of the double bond that carries the greater number of hydrogens. This rule is by no means universal, but in this problem it applies. In

$$CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=\overset{*}{C}H_2,$$

the starred carbon has two hydrogens, whereas the other carbon involved in the double bond has no attached hydrogens. Hence, the hydrogen of HOH adds to the CH_2, whereas OH adds to the other carbon.

(b) $CH_3-\underset{\displaystyle F}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$, an alkyl halide, may be prepared from isobutylene by the addition of the hydrogen halide HF as shown:

$$CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 \xrightarrow[-80^\circ]{HF} CH_3-\underset{\displaystyle F}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$$

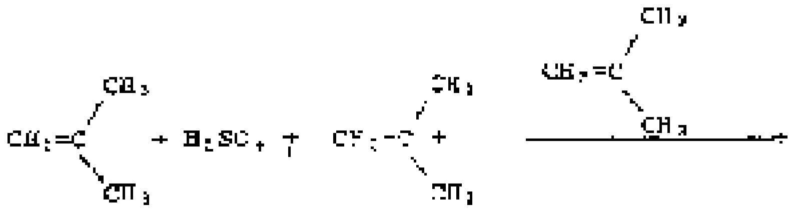
The reaction follows Markovnikov's rule. A low temperature is used to reduce polymerization.

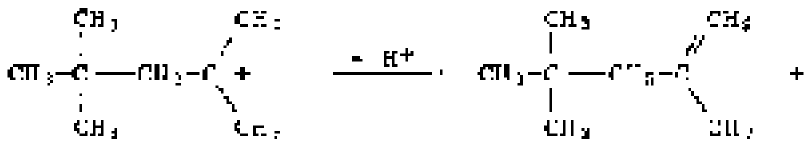
(c) To synthesize $CH_3\underset{\displaystyle OH}{CH}\underset{\displaystyle Br}{CH_2}$, one may start with propylene, $CH_3CH=CH_2$, and allow halohydrin formation to occur with Br_2 and NaOH at 25°. Addition of bromine (or chlorine) with water or sodium hydroxide results in compounds containing halogen and hydroxyl groups on adjacent carbon atoms. The reaction is:

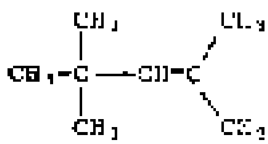
$$CH_3CH=CH_2 \xrightarrow[25^\circ]{Br_2,\ NaOH} CH_3\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle Br}{CH_2}$$

The bromine is attached to the terminal carbon, not the middle one, for if the mechanism of this reaction is studied, the initial addition of bromine in this fashion yields the more stable carbonium ion, a secondary cation. If the bromine had added to the middle carbon, a primary carbonium ion would have been produced. The order of stability of carbonium ions is 3°>2°>1°, so that the terminal addition of bromine is favored.

(d) $CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{C}}-CH_2-\underset{\displaystyle I}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_3$ can be synthesized from the starting material isobutylene in two steps. In the first step, a 60% H_2SO_4 solution is added to isobutylene at 70°. This results in polymerization as indicated:

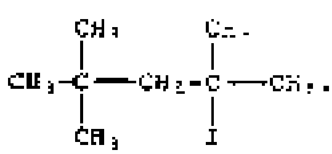


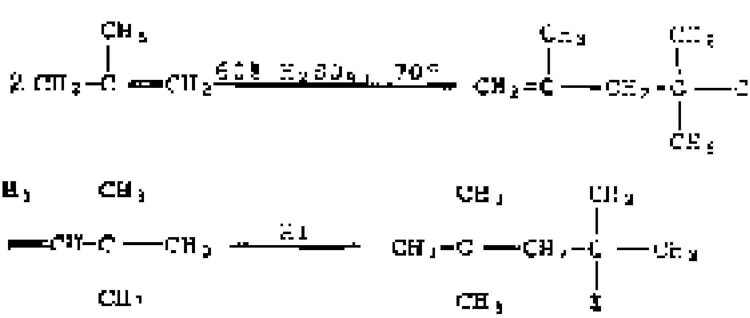




. This dimerization reaction may be described in the following way: a proton from the acid, H_2SO_4, adds to the alkane to yield the most stable carbonium ion. Then another isobutylene molecule donates an electron pair to the cation, forming a larger cation. This carbonium can then lose a hydrogen ion from either side of the positively charged carbon to obtain two products. (See above.)

In the second step, the hydrogen halide, HI, is added to either one of the above products to obtain



Overall: 

(d) $CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$, a ketone, may be produced by starting with isobutylene and allowing it to undergo dimerization in 60% H_2SO_4 at 70° in the same reaction as illustrated in step 1 of part (c). One obtains, as indicated in the previous section, $CH_2{=}\overset{CH_3}{C}-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$. To obtain the ketone, a reaction must be performed on this substance that yields a carbonyl group, C=O. Such a reaction is ozonization. Carbon-carbon double bonds may be cleaved with ozone (O_3) and then Zn and H_2O into aldehydes and ketones as illustrated:

$$-C{=}C- \xrightarrow{O_3} \xrightarrow[Zn]{H_2O} -C{=}O \quad + \quad O{=}C- \text{ . Consequently,}$$

aldehydes & ketones

to produce the desired product, perform ozonolysis as illustrated:

$$CH_2{=}\overset{CH_3}{C}-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3 \xrightarrow{O_3} \xrightarrow{H_2O,\ Zn}$$

$$CH_2{=}O + O{=}\overset{CH_3}{C}-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$$

(e) Using the starting material isobutylene and adding HBr in the presence of peroxides at 25° gives the desired product, $CH_3-\overset{CH_3}{\underset{H}{C}}-CH_2Br$, as indicated:

$$CH_3-\overset{CH_3}{C}{=}CH_2 + HBr \xrightarrow[25°]{\text{peroxides}} CH_3-\overset{CH_3}{\underset{H}{C}}-CH_2Br$$

It appears that the reaction violates Markovnikov's rule, for the hydrogen of HBr does not add to the carbon with the greatest number of hydrogens. The explanation lies in the mechanism of the reaction. It is typical of free-radical addition. The peroxides decompose to free-radicals. The free radical abstracts hydrogen from HBr to form a bromine atom, which, in turn, adds to the double bond of the alkene, and so converts the alkene into a free radical. The stability of free radicals is 3°>2°>1°>$CH_3\cdot$. Now examine the free radicals formed when the bromine atom adds to isobutylene:

$$CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 \xrightarrow{Br\cdot} CH_3-\overset{\displaystyle CH_3}{\overset{|}{\dot{C}}}-CH_2Br$$

, a 2° free radical is obtained. Now, if the Br· had added in the other fashion:

$$CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 \xrightarrow{Br\cdot} CH_3-\underset{\displaystyle Br}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2\cdot$$

, a 1° free radical would have been produced. From the order of free radical stability given previously, we know that the 2° free radical will be favored over the 1°. This explains the anti-Markovnikov type of addition.

(g) $CH_3CH_2CH_2OH$ may be obtained directly from propylene using B_2H_6 and H_2O_2 as shown:

$$CH_3CH=CH_2 \xrightarrow[2.\ H_2O_2,\ OH^-]{1.\ B_2H_6} CH_3CH_2CH_2OH$$

This reaction (termed hydroboration-oxidation) is an excellent method of making alcohols of anti-Markovnikov orientation. The addition of water to the carbon-carbon double bond in anti-Markovnikov fashion probably occurs because the boron group attaches first to the terminal doubly bonded carbon to give the most stable transition state. However, no carbonium ion is formed in this reaction.

(h) If one of the products from the dimerization reaction of part (f) is used

$$\left[CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{C}}}-CH_2-\overset{\displaystyle CH_3}{C}=CH_2 \right], \text{ then } CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{C}}}-CH_2-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-\underset{\displaystyle OH}{\underset{|}{CH_2}}$$

may be obtained readily from it via a hydroxylation with $KMnO_4$ and H_2O. $KMnO_4$ is an oxidizing reagent that reacts with alkenes, under mild conditions, to give, as the overall result, addition of hydrogen peroxide as HO-OH. In other words, a glycol results as shown:

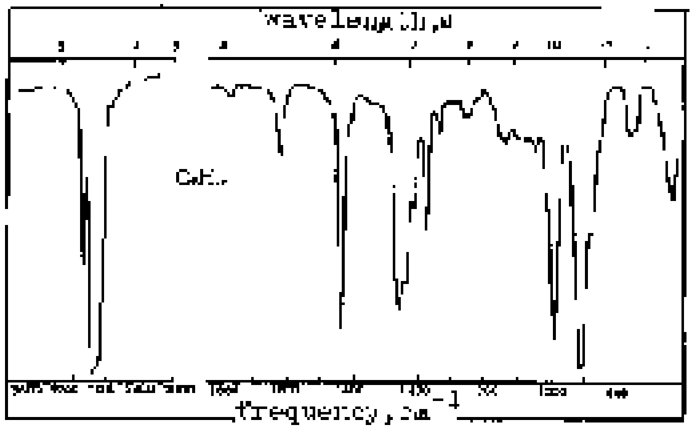
$$\underset{\text{(alkene)}}{\overset{|\ \ |}{C=C}} \xrightarrow{\text{Cold } KMnO_4} \underset{\text{(glycol)}}{\underset{OH\ OH}{\underset{|\ \ \ |}{\overset{|\ \ \ |}{-C-C-}}}}$$

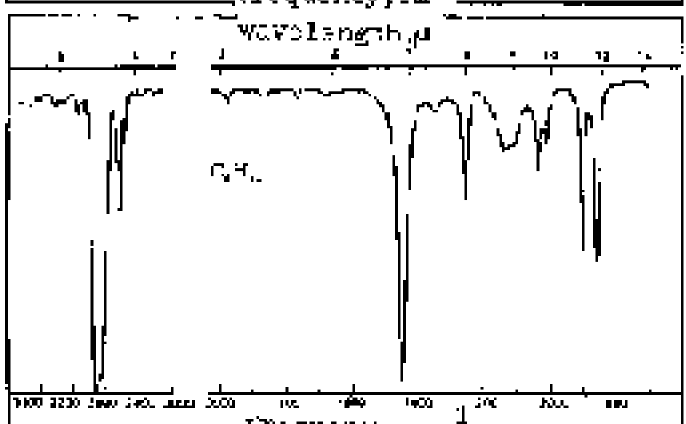
(Note: This reaction may also be performed with peroxyformic acid, HCO_3H.) Hence, the synthesis to be performed is:

$$CH_3-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-CH_2-\overset{\displaystyle CH_3}{\overset{|}{C}}=CH_2 \xrightarrow{KMnO_4,\ H_2O} CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{C}}}-CH_2-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-\underset{\displaystyle OH}{\underset{|}{CH_2}}$$

• PROBLEM 8-41

Deduce the structures of the substances whose infrared spectra are shown. Assign as many of the bands as you can to specific stretching and bending vibrations.





Solution: The formula C_6H_{12} may represent an alkene or a cycloalkane. That it is an alkene may be determined from the two strong bands between 800 and 1000 cm^{-1}. These bands are characteristic of the out-of-plane bending of the alkenes. The band near 1650 cm^{-1} may represent the carbon-carbon stretching for double bonds. (This band may be unreliable for it may disappear entirely for fairly symmetrically substituted alkenes.) Between 3000-3100 cm^{-1} bands are present. The bands present in this location may reflect the carbon-hydrogen stretching which occurs for trigonal carbons, which denote alkenes (and aromatic rings). This information strongly points to the presence of an alkene, not a cycloalkane.

For more detail about the structure of the alkene, concentrate on the 800-1000 cm^{-1} region. As mentioned, this area is indicative of out-of-plane bending for alkenes. The exact location of the bands reflects the nature and number of substituents. The two bands are extremely close to 910-920 cm^{-1} and 990-1000 cm^{-1}. This is typical of the structure $RCH=CH_2$. Therefore, R need only be determined. The $CH=CH_2$ accounts for all atoms except C_3H_7 in C_5H_{10}. C_3H_7, which represents R, can be arranged in two ways:

$$CH_3CH_2CH_2 \quad \text{or} \quad CH_3-\underset{CH_3}{\overset{H}{\underset{|}{\overset{|}{C}}}} \; .$$

So, $RCH=CH_2$ can be either

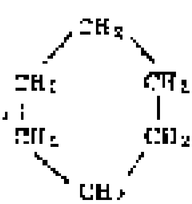
$$CH_3CH_2CH_2CH=CH_2 \qquad \text{or} \qquad CH_3-\underset{CH_3}{\overset{H}{\underset{|}{\overset{|}{C}}}}-CH=CH_2 .$$

If the latter structure were the true one, then a characteristic band at 1170 cm^{-1} would be present to denote the existence of the isopropyl, $CH_3\underset{CH_3}{\underset{|}{C}}-H$.

What is present is a band 1430-1470 cm^{-1} that indicates carbon-hydrogen bending for methyl and methylene groups. Also, the small band at 1375 cm^{-1} confirms the methyl. R can only be $CH_3CH_2CH_2$, so that C_5H_{10} is $CH_3CH_2CH_2CH=CH_2$, or 1 pentene.

The formula C_6H_{12} may also represent an alkene or cycloalkane. However, this time the cycloalkane is the correct choice. The possibility of an alkene may be eliminated because there exists no band at 1650 cm^{-1} to denote carbon-carbon stretching of double bonds. Also, the band for out-of-plane bending is not present.

Between 2850 and 3000 cm^{-1} one finds the C-H stretching of alkanes. There must be methylene groups ($-CH_2-$) present because the band for their characteristic C-H bending is found at 1400 to 1470 cm^{-1}. When there are no alkyl substituents on the ring, the characteristic bending frequencies of methyl groups at 1380 cm^{-1} are absent. Such is the case here. If there are no alkyl substituents on the cycloalkane C_6H_{12}, the only possible structure is

cyclohexane, 

● PROBLEM 6-42

> Deduce the structures of the substances whose n.m.r. spectra are shown. Analyze the spectra in as much detail as you can in terms of chemical shifts and spin-spin splitting.

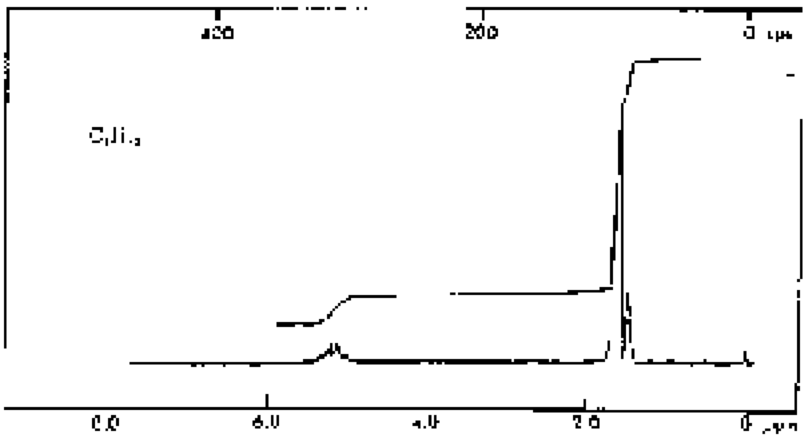


Fig.1

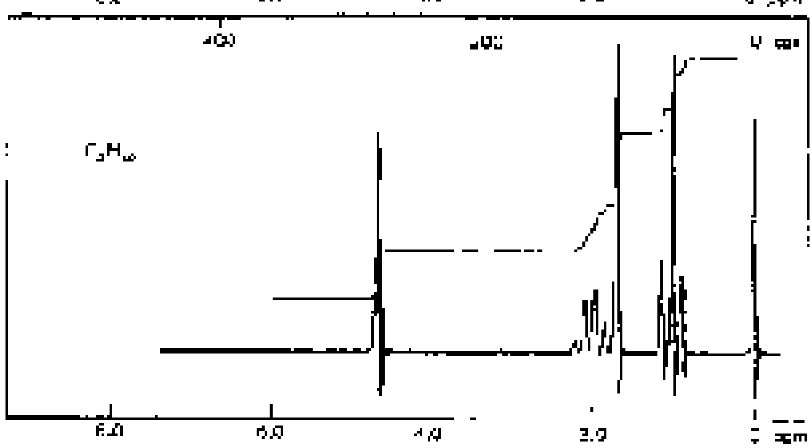


Fig.2

Solution: A review of the various aspects of the n.m.r. spectrum will aid in solving this problem. The number of signals provides information on the number of different kinds of protons in a molecule; the positions of the signals indicate something about the electronic environment of each kind of proton; the intensities of the signals tell how many protons of each kind are present; the splitting of a signal into several peaks gives information about the environment of a proton with respect to other, nearby protons.

In the first n.m.r. spectrum, the formula given, C_5H_{10}, fits the general formula for an alkene or cycloalkane (C_nH_{2n}). To distinguish between the two, try to locate the chemical shift of the vinylic proton (C=C-H) that would be indicative of the double bond of the alkene. From a table of characteristic proton shifts, absorption for a vinylic proton should occur between 4.6 and 5.9 ppm. Indeed, in this area absorption is seen. Hence, C_5H_{10} is probably an alkene. At approximately 1.6 ppm, an intense peak can be seen. This chemical shift often derives from allylic protons ($C=C-CH_3$). The intensity suggests a larger number of such protons is present. (Recall, the area under an n.m.r. signal is directly proportional to the number of protons giving rise to the signal.) At this point, the skeletal structure must be $C=C-CH_3$ or $C-C-CH_3$.

H H

Note that in these structures 3 carbons and 4 hydrogens have been accounted for. This leaves only 2 carbons and 6 hydrogens to determine. The possibilities are as follows: C_2H_6 could represent two methyl groups, each of them attached to a carbon that participates in the double bond. This would give rise to (from either $C{=}\underset{|}{\overset{}{C}}{-}CH_3$ or $C{=}C{-}CH_3$)

H   H

$$CH_3{-}\underset{\underset{H}{|}}{C}{=}\overset{\overset{CH_3}{|}}{C}{-}CH_3\ ;$$ the other possibility is that one of the

hydrogens of C_3H_4 is a vinyl one, with C_2H_5 representing the ethyl group as shown:

$$H{-}C{=}\overset{\overset{H}{|}}{C}{-}CH_3$$

CH_2CH_3

Examination of the first spectrum eliminates

$$H_2C{=}\underset{\underset{CH_2CH_3}{|}}{C}\ CH_3$$ to leave $$CH_3{-}CH{=}\underset{\underset{CH_3}{|}}{C}{-}CH_3$$

as the structure. To understand why, look at the spin-spin splitting. The protons of the ethyl group are adjacent and non-equivalent, so that if $H_2C{=}\underset{\underset{CH_2CH_3}{|}}{C}{-}CH_3$ were correct,

the typical three-four spin-spin splitting for ethyl should be seen. It is not. In fact, the spin-spin splitting indicated could only support $CH_3{-}\overset{\overset{CH_3}{|}}{C}{=}CH{-}CH_3$ as the structure. The vinylic proton is split into a broad quartet by the adjacent methyl. It is somewhat obscured by long range effects. Half of the doublet expected for the terminal methyl falls under the $(CH_3)_2$ resonances; the other half is the low part on the high field side of the 1.6 ppm peak.

It turns out that the second n.m.r. spectrum with
CH_2CH_3

formula C_5H_{10} is $H_2C{=}\overset{|}{C}{-}CH_3$, the structure rejected in the first spectrum. As before, the chemical shifts indicate the existence of allylic and vinylic protons. This time, however, the typical three-four ethyl pattern shows at 1.1 and 2.0 ppm to establish the structure

$$H_2C{=}\underset{\underset{CH_2CH_3}{|}}{C}{-}CH_3$$ as the correct one.

CHAPTER 7

ALKYNES

• PROBLEM 7-1

What is an alkyne?

Solution: An alkyne is an organic compound distinguished by the carbon-carbon triple bond. The simplest member of the alkyne family is acetylene, with the formula C_2H_2 or $H-C \equiv C-H$. The general formula for alkynes is C_NH_{2N-2}.

The alkynes are named according to two systems:

(1) They are considered to be derived from acetylene by replacement of one or both hydrogen atoms by alkyl groups. For example,

(a) $HC \equiv CCH_2CH_3$ (b) $CH_3C \equiv CCH_3$

ethylacetylene dimethylacetylene

(2) For more complicated alkynes the IUPAC names are used. The rules are exactly the same as for the naming of alkenes, except that the ending -yne replaces -ene. The parent structure is the longest continuous chain that contains the triple bond, and the positions both of substituents and of the triple bond are indicated by numbers. The triple bond is given the number of the first triply-bonded carbon encountered, starting from the end of the chain nearest the triple bond. For example,

$$CH_3-C \equiv C-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3$$

4-methyl-2-pentyne

• PROBLEM 7-2

How many sites of unsaturation does a compound with the formula $C_6H_{10}O_2$ contain?

Solution: Carbon compounds which have no multiple bonds are defined as saturated compounds. They can be distinguished from unsaturated compounds which contain double bonds, triple bonds, or rings.

If it is first assumed that the compound is saturated, then we can predict the number of hydrogen atoms that must be present to meet this assumption. This is calculated by using the general formula of a saturated compound, C_nH_{2n+2}. Since the compound in question possesses 8 carbon atoms, we expect 2(8) + 2 or 18 hydrogen atoms to be present if the compound is saturated. But in $C_8H_{12}O_2$ only 12 such atoms are present. The deficiency in hydrogen atoms = 18 − 12 = 6.

The degree of unsaturation is the number of double bonds, triple bonds, or rings present in a particular compound. For example, C_2H_6 (Ethane), written as

$$\begin{array}{c} \quad H\ H \\ \quad |\ \ | \\ H-C-C-H, \\ \quad |\ \ | \\ \quad H\ H \end{array}$$

is saturated, whereas C_2H_4 (Ethene), structural formula

$$\begin{array}{c} H-C=C-H, \\ \ \ |\quad\ | \\ \ \ H\quad H \end{array}$$

has one double bond (one site of unsaturation) and two hydrogen atoms less than its fully saturated counterpart. So, two hydrogen atoms are associated with every site of unsaturation. Since each site of unsaturation is associated with the loss of two hydrogen atoms, the number of sites of unsaturation for $C_8H_{12}O_2$ must be 6 ÷ 2 or 3.

PREPARATION

• PROBLEM 7-3

Write equations for all steps in the manufacture of acetylene starting from limestone and coal.

Solution: Acetylene can be prepared by the action of water on calcium carbide (CaC_2), which itself is prepared by the reaction between calcium oxide and coke at very high temperatures. The calcium oxide and coke are in turn obtained from limestone and coal, respectively. Acetylene is thus obtained by a few steps from water, coal, and limestone as shown below:

$$\left.\begin{array}{l} \text{Coal} \longrightarrow \text{Coke} \\ \\ \text{Limestone} \longrightarrow \text{CaO} \end{array}\right] \xrightarrow{2,000°C} CaC_2 \xrightarrow{H_2O} H-C\equiv C-H$$

• PROBLEM 7-4

> Prepare an alkyne from each alkene precursor by the dehydrohalogenation of alkyl dihalides method.
>
> (a) $CH_3CH=CH_2$ propene
>
> (b) $CH_3CH_2\overset{\displaystyle CH_3 \atop |}{C}HCH=CH_2$ 3-methyl-1-pentene

Solution: A carbon-carbon triple bond is formed in the same way as a double bond: elimination of atoms or groups from two adjacent carbons. The groups eliminated and the reagents used are essentially the same as in the preparation of alkenes.

In the first reaction of the synthesis, either Br_2 or Cl_2 is bubbled through the precursor alkene yielding an

alkyl dihalide, $-\underset{X}{\overset{H}{C}}-\underset{X}{\overset{H}{C}}-$. This product is then treated with

an alcohol-potassium hydroxide solution to form a vinyl

halide, $-C=\underset{X}{\overset{H}{C}}-$. Sodamide ($NaNH_2$) is added to the vinyl

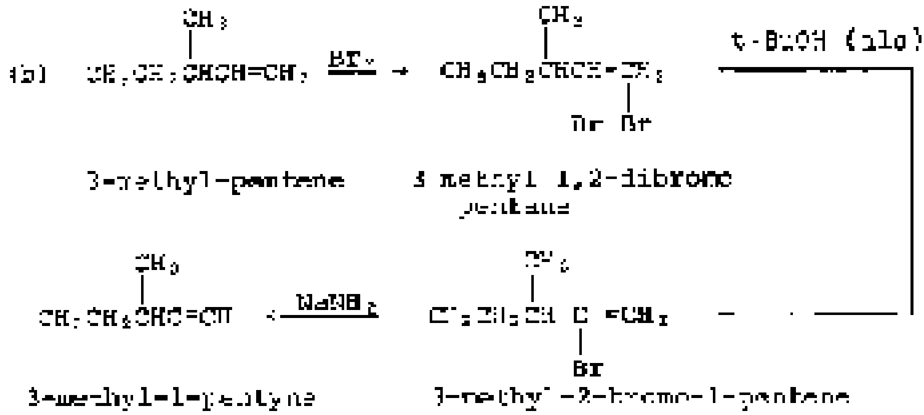
halide to produce a carbon-carbon triple bond, or alkyne. Overall, the synthetic preparation is:

$$\overset{H}{-C}=\overset{H}{C}- \xrightarrow{X_2} -\underset{X}{\overset{H}{C}}-\underset{X}{\overset{H}{C}}- \xrightarrow{KOH\ (alc)} -\underset{X}{C}=\overset{H}{C} \xrightarrow{NaNH_2} C\equiv C-$$

Vinyl halides are very unreactive so that under mild conditions the dehydrohalogenation stops here. Only under more vigorous conditions - use of a strong base ($NaNH_2$) is the alkyne generated.

Employing the general reaction of synthesis, problems (a) and (b) can be solved.

$$\text{(a)}\quad \underset{\text{propene}}{CH_3CH=CH_2} \xrightarrow{Br_2} \underset{\text{1,2-dibromo-propane}}{CH_3\underset{Br}{C}H\underset{Br}{C}H_2} \xrightarrow{KOH\ (alc)} \underset{\text{1-bromo-1-propene}}{CH_3CH=CHBr} \xrightarrow{NaNH_2} \underset{\text{propyne}}{CH_3C\equiv CH}$$

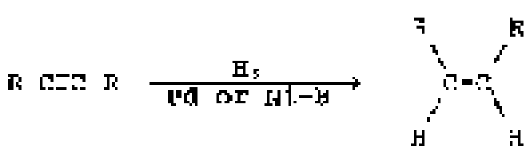


ADDITION REACTIONS

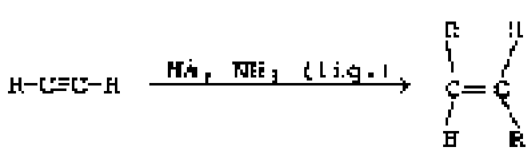
• PROBLEM 7-5

Describe the reduction of alkynes to obtain an alkene.

Solution: Reduction of an alkyne to form an alkene is the conversion of the carbon-carbon triple bond of the alkyne to the carbon-carbon double bond of the alkene. Unless the triple bond is at the end of the alkyne, the reaction will yield either a cis-alkene or a trans-alkene. The predominant isomer depends entirely upon the reducing agent used. Examples will make this concept clearer.



cis-alkene



trans-alkene

By reduction of alkynes with sodium in liquid ammonia, the trans-alkene will predominate. On the other hand, almost entirely cis-alkene (as high as 98%) is obtained by hydrogenation of alkynes with specially prepared palladium called Lindlar's catalyst or a nickel boride called P-2 catalyst.

• PROBLEM 7-6

(a) Write the equation for the two-stage addition of bromine to 2-butyne. (b) How will the first two bromine atoms affect the reactivity of the double bond? (c) How will this influence the competition for halogen between 2-butyne and 2,3 dibromo 2 butene? (d) In what proportions would you mix the reagents to help limit reaction to the first stage? (e) Would you bubble 2-butyne into a solution of Br_2 in CCl_4, or drip the bromine solution into a solution of 2-butyne?

Solution: (a) The addition reactions of alkynes are similar to addition to alkenes, except that two molecules of reagent can be consumed for each triple bond. In the addition reactions, it is possible, by proper selection of conditions, to limit reaction to the first stage of addition, formation of alkenes. The addition of halogens to alkynes may be generalized as:

$$-C\equiv C- \xrightarrow[\text{(first stage)}]{X_2} -\underset{X}{\underset{|}{C}}=\underset{X}{\underset{|}{C}}- \xrightarrow[\text{(second stage)}]{X_2} -\underset{X}{\underset{|}{\overset{X}{\overset{|}{C}}}}-\underset{X}{\underset{|}{\overset{X}{\overset{|}{C}}}}- ,$$

where $X_2 = Cl_2, Br_2$.

This means that the two stage addition of bromine to 2-butyne becomes:

$$H_3C-C\equiv C-CH_3 \xrightarrow{Br_2} H_3C-\underset{Br}{\underset{|}{C}}=\underset{Br}{\underset{|}{C}}-CH_3 \xrightarrow{Br_2} H_3C-\underset{Br}{\underset{|}{\overset{Br}{\overset{|}{C}}}}-\underset{Br}{\underset{|}{\overset{Br}{\overset{|}{C}}}}-CH_3 .$$

(b) The first two bromines decrease the reactivity of the double bond to further addition. To understand this, recall that addition of halogen proceeds via an intermediate carbonium ion. Halogens tend to withdraw electrons so that the bromine atoms would intensify the positive charge and destabilize the carbonium ion.

(c) Since the 2-butyne lacks the electron-withdrawing halogens, it should favorably compete with the 2,3 dibromo 2-butene $\left(H_3C-\underset{Br}{\underset{|}{C}}=\underset{Br}{\underset{|}{C}}-CH_3\right)$ for halogen. The 2 butyne carbonium ion will be more stable relative to the carbonium ion of 2,3 dibromo 2 butene. In other words, the dibromo compound is made a poor competitor.

(d) If the 2-butyne reagent is added in excess, then at any one moment it should predominate over the dibromo compound. In this way, there is little dibromo compound relative to 2 butyne to continue to react past the first stage.

(e) In order to keep 2 butyne in excess throughout the reaction, it would be advisable to drip Br_2 into a solution of 2-butyne.

Reaction of 4-octyne with n-propylamine, $CH_3CH_2CH_2NH_2$, produces two enamines in unequal amounts. Explain.

Solution: Alkynes can participate in nucleophilic addition reactions. When amines are added to alkynes, enamines, nitrogen analogs of enols, are produced. The general reaction is shown below:

$$R-C\equiv C-R \quad + \quad R'NH_2 \longrightarrow RCH=\underset{\displaystyle NHR'}{\underset{|}{C}}-R$$

(an enamine)

When 4-octyne [$CH_3CH_2CH_2-C\equiv C-CH_2CH_2CH_3$] is added to n-propylamine ($CH_3CH_2CH_2NH_2$), two enamines result. This can be accounted for on the basis of Z-E geometric isomerism. The two isomers may be written as follows:

Z-isomer E-isomer

The E-isomer should predominate over the Z-isomer on the basis of steric hinderance. The NHC_3H_7 is bulkier than the C_3H_7, so that there exists less stability when the C_3H_7 and NHC_3H_7 are located on the same side of the double bond(Z) as compared to when the C_3H_7 and C_3H_7 are located on the same side of the double bond (E).

• PROBLEM 7-8

Give structures and names of the organic products expected from the reaction of 1-butyne with the following:

(a) 1 mole H_2, Ni (b) 2 moles Br_2 (c) 2 moles HCl

Solution: Addition of hydrogen to alkynes leads to the formation of alkenes, if reaction can be limited to the first stage of addition. Two molecules of reagent can be consumed for each triple bond. If the reaction proceeds in two stages, alkanes are formed. In (a), only one mole of H_2 is added, so that the alkene results.

(a) $CH_3CH_2C\equiv CH \quad + \quad H_2 \xrightarrow{Ni} CH_3CH_2CH=CH_2$

1-butyne 1-butene

Alkynes react with halogens by addition reactions also. In (b), two moles of the halogen Br_2 react with the triple bond to form a tetrahalide. The reaction scheme appears as:

(b)

$$CH_3CH_2C{\equiv}CH + 2\,Br_2 \rightarrow CH_3CH_2\overset{Br}{\underset{Br}{C}}-\overset{Br}{\underset{Br}{C}}-H$$

1-butyne $\qquad\qquad$ 1,1,2,2-tetrabromobutane

Reaction (c) involves the addition of hydrogen halide. The general equation for the reaction is:

$$RC{\equiv}CH \xrightarrow{HX} R-\underset{X}{C}{=}CH_2 \xrightarrow{HX} R\overset{X}{\underset{X}{C}}-CH_3$$

Hydrogen chloride, bromide, or iodide adds to alkynes in two steps. The reaction may be stopped after the first step to give the vinyl halide, or a second molecule of HX may be allowed to react to give a gem-dihalide. (The prefix "Gem," from the latin geminus, twin, signifies that both halogens are on the same carbon.)

The reaction of 1-butyne with hydrogen chloride follows:

$$CH_3CH_2C{\equiv}CH \xrightarrow{HCl} CH_3CH_2\underset{Cl}{C}{=}CH_2 \xrightarrow{HCl} CH_3CH_2\overset{Cl}{\underset{Cl}{C}}-CH_3$$

1-butyne $\qquad$ 2-chloro-1-butene $\qquad$ 2,2-dichloro-butane

PROBLEM 7-9

Acetylene has an acid ionization constant (K_A) of $\approx 10^{-22}$.

(a) Calculate the concentration of acetylide ion expected to be present in a 1.0 M solution of potassium hydroxide that is 0.01 M in acetylene (assuming ideal solutions).

(b) Outline a practical method (or methods) that you think might be suitable to determine an approximate experimental value of K_A for acetylene, remembering that water has K_A of about 10^{-16}.

(c) Would you expect H-C≡N to be a stronger acid than H-C≡C-H? Why?

Solution: (a) The acid ionization constant (K_A) for acetylene ($HC{\equiv}CH$) is determined by the ratio of the concentrations of the products to the concentrations of the reactants in the following equation:

$$HC \equiv CH \rightleftarrows HC \equiv C^- + H^+ .$$

$$K_A = \frac{[HC \equiv C^-][H^+]}{[HC \equiv CH]} \approx 10^{-22} \qquad \text{(given)}$$

In the presence of potassium hydroxide,

$$HC \equiv CH + {}^-OH \rightleftarrows H_2O + HC \equiv C^-$$

For this reaction, the K_A becomes

$$\frac{[H_2O][HC \equiv C^-]}{[HC \equiv CH][^-OH]} \text{, which can be rewritten as}$$

$$\frac{[H_2O][HC \equiv C^-][H^+]}{[H^+][OH^-][HC \equiv CH]} \text{, where } \frac{[HC \equiv C^-][H^+]}{[HC \equiv CH]} \approx 10^{-22} .$$

The ion product constant for water is 10^{-14}. This means $[H^+][OH^-]$ is equal to 10^{-14}. Substituting this value in

$$\frac{[H_2O]\,10^{-22}}{[H^+][OH^-]} \text{, we obtain } \frac{[H_2O]\,10^{-22}}{10^{-14}} \text{ or } [H_2O]\,10^{-8}$$

for the K_A of acetylene in potassium hydroxide.

Let X be the concentration of acetylide ion at 25°C. If the initial concentration of acetylene is .01 M, then we have left .01 − X of acetylene at equilibrium. Likewise, 14 − X should be the concentration of hydroxide at equilibrium. Hence, the expression for K_A (ionization constant)

can be written as $\frac{X\,(H_2O)}{(.01 - X)(14 - X)}$. From above, we

calculated K_A to be equal to $[H_2O]\,10^{-8}$. Consequently,

$$\frac{X\,(H_2O)}{(.01 - X)(14 - X)} = (H_2O)\,10^{-8} \text{ or } \frac{X}{(.01 - X)(14 - X)} = 10^{-8}$$

Solving for X, X = 1.4×10^{-9} moles/liter, which is the concentration of acetylide ion.

(b) The ionization equilibria of very weak acids, such as acetylene, can only be measured in solvents which are less acidic than water. For example, ammonia, ether, or (possibly) hydrocarbons. The problem is that no solvent can usually be found in which a very weak acid ($K_A < 10^{-22}$) will dissociate significantly. This means the strengths of such acids are determined relative to one another by determining the position of the equilibrium. This measurement of relative acidities permits the assignment of approximate ionization constants to weak acids.

(c) We would expect H−C≡N to be the stronger acid than H−C≡C−H due to the greater electronegativity (tendency to attract electrons) of the nitrogen as compared to the carbon. As such, the cyanide ion ($^-C \equiv N$) possesses more stability than the acetylide ion ($^-C \equiv CH$).

Outline all steps in the synthesis of

(a) 1-butyne and (b) 2-butyne

from acetylene using any needed organic or inorganic reagents.

Solution: Alkynes of chain length longer than two carbons can be formed from acetylene by using sodamide ($NaNH_2$) in ether and alkyl halides.

A triply-bonded carbon acts as a more electronegative element. As a result, hydrogen attached to triply-bonded carbon, as in acetylene, shows appreciable acidity. Hence, addition of $NaNH_2$ to acetylene produces sodium acetylide in an acid-base reaction as shown:

$$HC \equiv CH + NaNH_2 \xrightarrow{\text{ether}} HC \equiv C^- Na^+ + NH_3$$

(Sodium Acetylide)

Sodium acetylide can react with alkyl halides in a substitution reaction to produce higher alkynes. The reaction involves substitution of acetylide ion for halide ion as shown:

Now, the acetylide ion could also have caused elimination to give the alkene. The proportion of the elimination product increases as the structure of the alkyl halide is changed from primary to secondary to tertiary.

To synthesize 1-butyne, we add an ethyl halide, say ethyl bromide, to sodium acetylide as illustrated:

$$HC \equiv C^- Na^+ + CH_3CH_2Br \rightarrow HC \equiv C-CH_2CH_3 + NaBr$$

(1-butyne)

Since the alkyl halide is primary, the elimination reaction will be minimal.

The synthesis of 2-butyne is a little more complicated. The initial steps are, however, the same. We commence by reacting acetylene with $NaNH_2$ in ether (or alternatively sodium in liquid ammonia) to give the sodium acetylide:

$$H-C \equiv C-H + NaNH_2 \xrightarrow{\text{ether}} H-C \equiv C^- Na^+ + NH_3$$

At this point, a methyl halide should be added. For example, methyl bromide. This results in the synthesis of propyne as shown:

$$H-C\equiv C^- Na^+ + CH_3Br \rightarrow H-C\equiv C-CH_3 + NaBr$$

(Propyne)

Propyne can be converted to the alkali metal acetylide by addition of $NaNH_2$ in ether:

$$H-C\equiv C-CH_3 + NaNH_2 \xrightarrow{\text{ether}} Na^+\ ^-C\equiv C-CH_3 + NH_3$$

From this species, the 2-butyne is produced by the addition of methyl bromide.

$$CH_3C\equiv C^- Na^+ + CH_3Br \longrightarrow CH_3-C\equiv C-CH_3 + NaBr$$

(2-butyne)

• PROBLEM 7-11

Give the equations and mechanisms for the reactions of sodium methyl acetylide with:

(a) 1-bromobutane (b) 2-bromobutane.

Solution: Sodium methyl acetylide ($CH_3C\equiv C^-Na^+$) is the precursor in both reactions and involves the addition of a halogenated alkane. The expected product from each reaction is a longer chain alkyne, with the general mechanism appearing as:

$$CH_3C\equiv C^-\ \overset{+}{Na} \quad R-X \rightarrow CH_3C\equiv C-R \quad Na^+ X^-$$

Since sodium methyl acetylide is the salt of the extremely weak acid, methyl acetylene, the acetylide ion is a stronger base, thus this reaction involves substitution of acetylide ion for halide ion. From this it can readily be seen that the metal ion, sodium, bonds to the released halide ion and the acetylide ion bonds to the alkyl group yielding a higher alkyne, plus a metal halide as the by-product.

The reactions and their mechanisms are:

(a) $CH_3C\equiv C^-\overset{+}{Na} + CH_3CH_2CH_2CH_2-Br \rightarrow CH_3C\equiv CCH_2CH_2CH_2CH_3 + \overset{+}{Na}\overset{-}{Br}$

sodium methyl acetylide; 1-bromobutane; 2-heptyne

(b) $CH_3C\equiv C^-\overset{+}{Na} + CH_3CH_2\underset{Br}{C}HCH_3 \rightarrow CH_3CH_2\overset{CH_3}{C}HC\equiv C-CH_3 + \overset{+}{Na}\overset{-}{Br}$

sodium methyl acetylide; 2-bromobutane; 4-methyl-2-hexyne

• PROBLEM 7-12

Outline all steps in the synthesis of propyne from acetylene using any needed organic or inorganic reagents.

Solution: The synthesis should be the one that gives a reasonably pure product in reasonably good yield. The synthetic equation is as follows:

$$HC{\equiv}CH \xrightarrow{NaNH_2} \overset{+}{Na}\bar{C}{\equiv}CH \xrightarrow{CH_3I} CH_3C{\equiv}CH$$

(Acetylene) (Propyne)

Alkynes of chain length longer than two carbons can be formed from acetylene by using sodamide ($NaNH_2$). Sodamide reacts with acetylene in an acid-base type of reaction. The hydrogen attached to the triply-bonded carbon shows appreciable acidity. Hence,

$$HC{\equiv}CH + Na^+ NH_2^- \rightleftharpoons HC{\equiv}C^- Na^+ + NH_3$$

Stronger acid	Stronger base	Weaker base (Sodium acetylide)	Weaker acid

Sodium acetylides react with primary alkyl halides in a substitution reaction to give alkynes of carbon skeleton greater than two. Hence, if methyl iodide is added to sodium acetylide, propyne results:

$$HC{\equiv}C^- Na^+ + CH_3I \rightarrow HC{\equiv}CCH_3 + NaI$$

Propyne

• PROBLEM 7-13

Using propyne as the starting material, carry out the necessary reaction sequences to give the following products:

(a) 2-butyne (b) 2-octene
(c) 2-bromobutane (d) pentane.

Solution: In this set of reactions, propyne ($CH_3C{\equiv}CH$) is used as the precursor to obtain all of the various products desired.

Beginning with problem (a), the general reaction sequence is:

$$R{-}C{\equiv}CH \xrightarrow{NaNH_2} RC{\equiv}\bar{C}\overset{+}{N}a \xrightarrow{CH_3I} RC{\equiv}C{-}CH_3$$

where sodamide ($NaNH_2$) reacts with an alkyne (R-C≡CH) to produce a sodium alkyl acetylide ($RC\equiv\bar{C}\overset{+}{N}a$). This intermediate reacts very well with primary alkyl halides, such as methyl iodide, to produce a longer chain alkyne. With the above concepts, the first synthesis proceeds as follows:

$$\text{(a)}\quad \underset{\text{Propyne}}{CH_3C\equiv CH} \xrightarrow{NaNH_2} \underset{\substack{\text{Sodium methyl}\\ \text{acetylide}}}{CH_3C\equiv\bar{C}\overset{+}{N}a} \xrightarrow{CH_3I} \underset{\text{2-butyne}}{CH_3C\equiv C\,CH_3} + NaI$$

In problem (b), 2-butene is desired, and is obtained by the same method as problem (a). The only modification is the addition of one mole of H_2 to 2-butyne across the triple bond in a catalytic hydrogenation reaction. The solution to (b) is as follows:

$$\text{(b)}\quad \underset{\text{Propyne}}{CH_3C\equiv CH} \xrightarrow{NaNH_2} \underset{\substack{\text{Sodium methyl}\\ \text{acetylide}}}{CH_3C\equiv\bar{C}\overset{+}{N}a} \xrightarrow{CH_3I} \underset{\text{2-butyne}}{CH_3C\equiv CCH_3} + NaI$$

$$\underset{\text{2-butyne}}{CH_3C\equiv CCH_3} \xrightarrow{Ni,\ H_2} \underset{\text{2-butene}}{CH_3CH=CHCH_3}$$

Problem (c) can also be done the same way as syntheses (a) and (b) with the addition of one more reaction. This reaction is the addition of hydrogen bromide, HBr, across the carbon-carbon double bond of 2-butene.

$$\text{(c)}\quad \underset{\text{Propyne}}{CH_3C\equiv CH} \xrightarrow{NaNH_2} \underset{\substack{\text{Sodium methyl}\\ \text{acetylide}}}{CH_3C\equiv\bar{C}\overset{+}{N}a} \xrightarrow{CH_3I} \underset{\text{2-butyne}}{CH_3C\equiv CCH_3} + NaI$$

$$\underset{\text{2-butyne}}{CH_3C\equiv CCH_3} \xrightarrow{Ni,\ H_2} \underset{\text{2-butene}}{CH_3CH=CHCH_3} \xrightarrow{HBr} \underset{\text{2-bromobutane}}{CH_3\underset{|}{\overset{Br}{C}}HCH_2CH_3}$$

Problem (d) involves some of the same reagents as the first three syntheses. Ethyl iodide will be used in the place of methyl iodide. This reagent will add two carbons to the sodium methyl acetylide.

After the addition of the ethyl group, the product, 2-pentyne, can be hydrogenated to the corresponding alkane, pentane. Thus:

(d) $CH_3C\equiv CH \xrightarrow{NaNH_2} CH_3C\equiv C^-Na^+ \xrightarrow{CH_3CH_2I} CH_3C\equiv CCH_2CH_3 + NaI$

Propyne — Na methyl acetylide — 2-pentyne

$$CH_3C\equiv CCH_2CH_3 \xrightarrow[Ni]{2H_2} CH_3CH_2CH_2CH_2CH_3$$

Pentane

■ PROBLEM 7-14

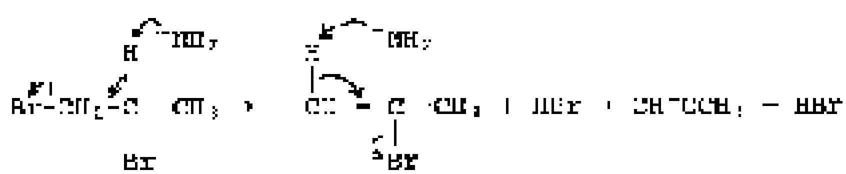
Outline all steps in the synthesis of propyne from each of the following compounds, using any needed organic or inorganic reagents.

(a) 1,2-dibromopropane
(b) propylene
(c) isopropyl bromide
(d) propane
(e) n-propyl alcohol
(f) 1,1-dichloropropane
(g) acetylene
(h) 1,1,2,2-tetrabromopropane.

<u>Solution:</u> (a) 1,2 dibromopropane:

$$\begin{array}{ccccc} Br & & Br & & H \\ | & & | & & | \\ H-C & - & C & - & C-H \\ | & & | & & | \\ H & & H & & H \end{array} \qquad C_3H_6Br_2.$$

Propyne can be prepared by introducing a triple bond by eliminating two molecules of hydrogen bromide. The dehydrohalogenation proceeds in two steps. Sodium amide ($Na^+\,NH_2^-$) in liquid ammonia is used to create the triple bond:



(b) propylene: $CH_3CH=CH_2$.

As there is no direct way to change the double bond to a triple bond it is however possible to produce the 1,2-dibromopropane by brominating in the presence of carbon tetrachloride and then proceeding in the same process outlined in (a).

$$CH_3CH=CH_2 + Br_2 \xrightarrow{CCl_4} CH_3CHBrCH_2Br$$

1,2-dibromopropane

(c) Isopropyl bromide: $(CH_3)_2CHBr$.

Isopropyl bromide cannot be directly transformed to propyne. Reacting with $NaNH_2$ would not give the desired products:

$$(CH_3)_2CHBr \xrightarrow{Na^+NH_2^-} CH_2=CH-CH_3 \quad \text{Propylene}$$

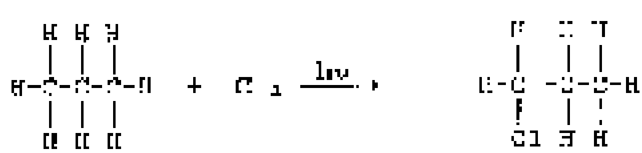
However, propylene can be converted to propyne in the synthesis given in part (b).

$$CH_3CH=CH_2 + Br_2 \rightarrow CH_3CHBrCH_2Br$$

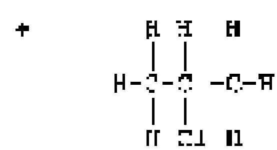
$$CH_3CHBrCH_2Br \xrightarrow[NH_3]{Na^+NH_2^-} CH_3-C\equiv CH$$

(d) propane; C_3H_8. Since this compound is completely saturated it can't be halogenated by Br_2 and CCl_4. But by free radical chain reaction, however, we could chlorinate propane.

1-chloropropane



Two isomers are formed:



2-chloropropane.

If both these isomers are dehydrohalogenated by potassium hydroxide in alcohol propylene will result.

$$CH_2Cl-CH_2-CH_3 \xrightarrow[alcohol]{KOH} CH_2=CH-CH_3$$

Propylene could be converted to propyne by the method outlined in part (b).

(e) n-propyl alcohol: $CH_3CH_2CH_2OH$.

First propylene can be produced by the dehydration of n-propyl alcohol (to eliminate the hydroxy group).

$$CH_3CH_2CH_2OH + H_2SO_4 \xrightarrow[-H_2O]{heat} CH_3CH=CH_2$$

The hot conc. acid protonates the -OH of the alcohol; subsequent loss of H_2O and H^+ forms the alkene. Propylene can then be converted to propyne as illustrated in part (b).

(f) 1,1-dichloropropane: $H-\underset{Cl}{\overset{Cl}{C}}-CH_2CH_3$

By dehydrohalogenation of the dichloropropane we can produce propyne.

$$H-\underset{Cl}{\overset{Cl}{C}}-CH_2CH_3 \xrightarrow{\overset{+}{Na}\,\overset{-}{NH_2}/NH_3} HC\equiv C-CH_3 .$$

(g) Starting from acetylene $HC\equiv CH$ the carbanion $HC\equiv C^-$ must be obtained. By using $\overset{+}{Na}\,\overset{-}{NH_2}$, which is basic relative to acetylene, the end products are $HC\equiv C^-\,\overset{+}{Na} + NH_3$. It is necessary to increase the carbanion by a methyl group to get the desired product, propyne. Since $HC\equiv C^-\,\overset{+}{Na}$ is fairly nucleophilic it will participate in an S_N2 displacement reaction with methyl iodide.

$$HC\equiv C^-\,\overset{+}{Na} + CH_3I \rightarrow HC\equiv CCH_3 + \overset{+}{Na}\,\overset{-}{I} .$$

(h) 1,1,2,2-tetrabromopropane: $H-\underset{Br}{\overset{Br}{C}}-\underset{Br}{\overset{Br}{C}}-CH_3$

Instead of dehydrohalogenation, it would be sufficient to remove all the bromine atoms from the molecule and thus form 2 sites of unsaturation (a triple bond) between the first two carbon atoms. Zinc is a highly reactive element and readily forms zinc bromide.

$$2\,Zn + CHBr_2CBr_2CH_3 \xrightarrow{heat} 2\,ZnBr_2 + HC\equiv CCH_3 .$$

• PROBLEM 7-15

From isopentyl alcohol (3-methyl-1-butanol), acetylene, and any required straight chain primary alcohols, derive a practical synthesis for 2-methylheptadecane, the sex attractant for the Tiger moth.

Solution: First the isopentyl alcohol has to be converted to isopentyl bromide. This reaction is brought about by nucleophilic substitution; the protonated alcohol being the substrate and bromide ion as the nucleophile. The mechanism is as follows:

(1) $(CH_3)_2CHCH_2CH_2OH \xrightarrow{H_2SO_4} (CH_3)_2CHCH_2CH_2\overset{+}{O}H_2$

(2) S_N2 displacement of the protonated hydroxyl group:

$$(CH_3)_2CHCH_2CH_2\overset{+}{O}H_2 + H{-}Br \rightarrow (CH_3)_2CHCH_2CH_2Br + H_2O.$$

If phosphorous tribromide is used instead, then the bromine anion will be formed by ionization of Br^- from PBr_3. The Br^- will then react with isopentyl alcohol to produce isopentyl bromide.

Next undecanol is reacted with HBr/H_2SO_4 or PBr_3, thus obtaining $CH_3(CH_2)_9CH_2Br$. The mechanism is similar to the one outlined above.

Acetylene is next reacted with $NaNH_2$ and liquid ammonia to produce the carbanion $HC{\equiv}C^-$, acetylene being much more acidic than ammonia:

$$HC{\equiv}CH + \overset{+}{Na}\overset{-}{N}H_2 \rightarrow HC{\equiv}\overset{-}{C}\ \overset{+}{Na} + NH_3. \quad \text{Then:}$$

$$HC{\equiv}\overset{-}{C}: + (CH_3)_2CHCH_2CH_2{-}Br \rightarrow (CH_3)_2CHCH_2CH_2C{\equiv}CH + Br^-$$

The carbanion $HC{\equiv}C^-$ (being fairly nucleophilic) participates readily in S_N2 displacement reactions.

In order to lengthen the chain to the desired number of carbon atoms the carbanion is reproduced by the addition of $NaNH_2$ and liquid ammonia:

$$(CH_3)_2CHCH_2CH_2C{\equiv}CH + \overset{+}{Na}\overset{-}{N}H_2 \rightarrow (CH_3)_2CHCH_2CH_2C{\equiv}\overset{-}{C}\ \overset{+}{Na} + NH_3$$

If $CH_3(CH_2)_9CH_2Br$ (which was previously obtained) were reacted with the carbanion, we would get the appropriate alkyne.

$$(CH_3)_2CHCH_2CH_2C{\equiv}\overset{-}{C}: + CH_3(CH_2)_9CH_2{-}Br \longrightarrow$$

$$(CH_3)_2CHCH_2CH_2C{\equiv}C(CH_2)_{10}{-}CH_3 + Br^-.$$

Catalytic hydrogenation yields the desired product.

$$(CH_3)_2CHCH_2CH_2C{\equiv}C(CH_2)_{10}CH_3 + 2H_2 \xrightarrow{Pt}$$

$$(CH_3)_2CHCH_2CH_2-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-(CH_2)_{10}CH_3$$

which may be written compactly as $(CH_3)_2CH(CH_2)_{14}CH_3$.

● PROBLEM 7-16

Muscalure, cis-9-tricosene, is the sex-attractant insect pheromone of the common housefly. Give a practical synthesis of this compound from acetylene and straight chain alcohols.

Solution: The formula for cis-9-tricosene is $CH_3(CH_2)_7CH{=}CH(CH_2)_{12}CH_3$, where the octanyl and tridecanyl groups are cis to each other.

In order to synthesize cis-9-tricosene, we start with a straight chain alcohol $CH_3(CH_2)_6CH_2OH$. Hydrogen bromide is added in the presence of a catalyst (H_2SO_4) and the following reaction takes place:

$$CH_3(CH_2)_6CH_2OH \xrightarrow{H_2SO_4} CH_3(CH_2)_6CH_2OH_2^+ \xrightarrow{HBr} CH_3(CH_2)_6CH_2Br + H_2O.$$

The hydroxyl group is replaced by the bromine ion thus forming the alkyl bromide. This is an S_N2 (bimolecular nucleophilic substitution) reaction with H_2O as a leaving group and bromide ion as the nucleophile.

OR: Bromination can also be brought about by phosphorus tribromide. The alcohol and PBr_3 react to produce the bromide, $CH_3(CH_2)_6CH_2Br$.

Acetylene is then reacted with $\overset{+}{Na}NH_2$ and liquid ammonia to produce the carbanion $HC{\equiv}C^-$. Acetylene is much more acidic (pKa = 25) than ammonia (pKa = 35). Thus the amide ion reacts in the following manner:

$$HC{\equiv}CH + NH_2^- \rightleftharpoons HC{\equiv}C^- + NH_3.$$

The carbanion $HC{\equiv}C^-$ undergoes an S_N2 reaction with the bromide, producing $CH_3(CH_2)_6CH_2C{\equiv}CH$.

$$HC{\equiv}C^- + CH_3(CH_2)_6CH_2{-}Br \rightarrow HC{\equiv}CCH_2(CH_2)_6CH_3 + Br^-.$$

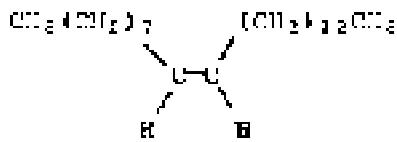
In order to lengthen the chain, $NaNH_2$ is added to the alkyne to form the carbanion $CH_3(CH_2)_6CH_2C{\equiv}C^-$. This is obtained by the mechanism previously outlined. This carbanion is reacted with $CH_3(CH_2)_{11}CH_2Br$, which is formed in the reaction:

$$CH_3(CH_2)_{11}CH_2OH \xrightarrow[HBr]{H_2SO_4} CH_3(CH_2)_{11}CH_2Br$$

The product obtained from the reaction of $CH_3(CH_2)_{11}CH_2Br$ with $CH_3(CH_2)_6CH_2C{\equiv}C^-$ is $CH_3(CH_2)_7C{\equiv}C(CH_2)_{12}CH_3$. This fulfills the total requirements of carbon atoms in 9-tricosene.

The alkyne is then hydrogenated to the cis-alkene. This is accomplished by using palladium, barium sulfate and quinoline; the hydrogen adds on the same side of the triple bond. The reaction is:

$$CH_3(CH_2)_7C{\equiv}C(CH_2)_{12}CH_3 + H_2 \xrightarrow[\text{quinoline}]{Pd/BaSO_4}$$



cis-9-tricosene

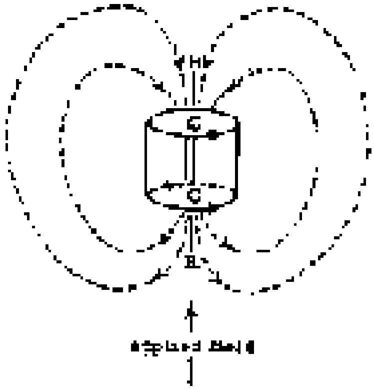
SPECTROSCOPY

• PROBLEM 7-17

> **The chemical shifts (2.4 ppm) of acetylenic hydrogens (RC≡C H) are considerably more toward higher magnetic fields than those of alkene hydrogens (4.5 to 6.5 ppm). Show how this shielding effect might be explained in terms of the atomic orbital representation of acetylenes.**

Solution: If a molecule is placed in a magnetic field the electrons are caused to move around and in circulating they induce secondary magnetic fields. This is the underlying concept behind the determination of an n.m.r. spectrum. Circulation of such electrons about a proton generates a field which aligns itself so as to decrease the applied magnetic field, thus diminishing the field felt by the proton. This is known as shielding. Shielding shifts the absorption upfield and the ppm decreases. The unit of measurement of these chemical shifts is in parts per million, abbreviated by ppm.

In the case of RC≡C H (2.4 ppm), the atomic orbitals' π electrons will circulate in a cylindrical region around the axis of the triple bond. This will generate a magnetic field which will tend to decrease the applied magnetic field when directed parallel to the axis of the triple bond. The magnetic field generated by the π electrons of alkenes is not as great as in alkynes. This is because alkenes have only one π bond whereas alkynes have two π bonds. As a result, the chemical shift of alkenes will be downfield (higher ppm) relative to those of alkynes. The magnetic field generated by the π electrons of the alkyne RC≡CH is illustrated in the following:



• **PROBLEM 7-19**

Indicate the features you would expect for the infrared and n.m.r. spectra of the following substances.

(a) $CH_3C{\equiv}CCH_3$
(b) $CH_3C{\equiv}CH$ (expect a long-range n.m.r. coupling of 3 cps)
(c) $CH_3CH_2C{\equiv}CCH_2CH_3$

Solution: (a) A bond that is electrically symmetrical has no dipole moment and will not absorb infrared radiation. As a result, such bonds will not be seen in infrared spectra. The infrared spectrum of 2-butyne would show, then, only two identifying bands: the stretching of the C-H bond near 2900 cm^{-1} (reciprocal centimeters) and the bending vibrations of the C-H bond at 1400 cm^{-1}. The carbon-carbon triple bond of 2-butyne will not appear in the infrared spectrum because of symmetry. In the nuclear magnetic resonance (n.m.r.) spectrum, the two methyl groups occur as a singlet and absorb near 1.0 δ. The methyl groups resonate at the same frequency because their protons are in identical environments; they are equivalent.

(b) The infrared spectrum of propyne would show the C≡C bond stretching near 2100 cm^{-1}. The C≡C stretch appears because the molecule is not electronically symmetrical; it has a dipole moment. The ≡C-H bond will stretch near 3300 cm^{-1}. Like 2-butyne (part a), propyne will show the methyl group C-H stretching and bending near 2900 cm^{-1} and 1400 cm^{-1}, respectively. The n.m.r. spectrum of propyne will have a quartet near 2.5 δ and a doublet near 1.0 δ. These multiplets occur as a result of spin-spin splitting between the $-CH_3$ protons and the ≡C-H proton. Although spin-spin splitting is expected to occur only between non-equivalent adjacent protons, splitting may occur between protons that are further removed from each other, particularly if π bonds intervene. The presence of two π bonds in propyne facilitates spin-spin splitting to occur between the methyl protons and the ≡C-H proton. The three methyl protons split the ≡C-H signal into a quartet and the lone ≡C-H proton splits the methyl signal into a doublet. The ≡C-H signal occurs downfield from the methyl signal because the lower electron density of the ≡C-H proton causes it to be deshielded relative to the methyl protons. This deshielding causes the chemical shift to move downfield. The $\equiv C-H$ proton has a lower electron density than the methyl proton because the sp-hybridized carbon of the $\equiv C-H$ is more electronegative than the sp^3-hybridized carbon of the $-CH_3$; this makes the $\equiv C-H$ hydrogen more positive than the $-CH_3$ hydrogen.

(c) The molecule 3-hexyne is electronically symmetrical; it has no dipole moment. Hence the $C\equiv C$ bond will not appear in the infrared spectrum. The only bands will be the C-H stretch near 2900 cm^{-1} and the C-H bending near 1400 cm^{-1}. The n.m.r. spectrum of 3-hexyne will show a triplet near 1.0 δ and a quartet near 1.5 δ. These signals occur as a result of spin-spin splitting between the methylene ($-CH_2-$) protons and the methyl protons. The two methylene protons split the methyl signal into a triplet and the three methyl protons split the methylene signal into a quartet. The methylene signal occurs downfield from the methyl signal because its protons are deshielded more than the methyl protons.

CHARACTERIZATION TESTS

• PROBLEM 7-19

You are given a mixture of 1-butyne (bp 8°) and 2-butyne (bp 27°). How could you separate, and then recover, each of these compounds using chemical means?

Solution: The acidity of $CH_3CH_2C\equiv CH$ is prevalent due to the high degree of s character in the sp orbital used to bond the carbon (the one which is triply bonded to the other carbon atom) to hydrogen. The greater s character increases the electronegativity and therefore makes it more suitable to react with bases. 2-butyne $CH_3C\equiv CCH_3$ is not as acidic since it does not have a hydrogen bonded to the sp hybridized carbon atom; for this reason it does not give any reaction with heavy metals. 1-butyne on the other hand undergoes nucleophilic substitution with heavy metals as represented by the following reaction:

$$CH_3CH_2C\equiv CH + Ag(NH_3)_2NO_3 \rightarrow \underset{\text{(precipitate)}}{CH_3CH_2C\equiv C-Ag}$$

2-butyne however does not react with $Ag(NH_3)_2NO_3$, since it lacks acidic hydrogens ($H-C\equiv$) and will not form the carbanion necessary for the reaction to occur.

The 2-butyne can be separated from the mixture by filtration.

We can obtain 1-butyne from $CH_3CH_2C\equiv C-Ag$ by displacing the silver atom with a hydrogen atom.

Since silver (I) forms a very stable complex with cyanide ions, silver acetylides regenerate the acetylene by reacting with cyanide ion in H_2O:

$$CH_3CH_2CH_2C\equiv C\text{-}Ag \xrightarrow[H_2O]{CN^-} CH_3CH_2CH_2C\equiv CH + Ag(CN)_2^- + OH^-$$

The 1-butyne can be separated from the mixture by filtration.

• PROBLEM 7-20

Suppose you were given four unlabeled bottles, each of which is known to contain one of the following compounds: n-pentane, 1-pentene, 2-pentyne, and 1-pentyne. Explain how you could use simple chemical tests (preferably test-tube reactions) to identify the contents of each bottle. (Note that all four compounds are low-boiling liquids.)

Solution: n-Pentane is different than the other three compounds, as it is saturated and therefore will not react with cold dilute potassium permanganate. $KMnO_4$ reacts with double or triple bonds to give vicinal diols (formerly known as glycols) and carboxylic acids, respectively. This causes the intense purple colored potassium permanganate to decolorize. n-Pentane does not cause any color change.

Bromine in carbon tetrachloride can also be used to identify the presence of the saturated n-pentane. The unsaturated compounds will add bromine to their double and triple bonds forming multibrominated compounds. This causes the reddish-brown color of bromine to disappear. n-Pentane does not cause decolorization and it can be labeled.

The three unsaturated compounds remain to be identified. On adding a silver-ammonia solution to a sample from each of the three 1-pentyne will be observed to form a precipitate. 1-Pentyne ($HC\equiv C\text{-}CH_2CH_2CH_3$) has an acidic hydrogen ($H\text{-}C\equiv$) and in NH_3 solution forms the carbanion $CH_3(CH_2)_2C\equiv C^-$. This is fairly nucleophilic and reacts with the silver ion to form a precipitate:

$$CH_3(CH_2)_2C\equiv C^- + Ag^+ \xrightarrow{NH_3\ sol.} CH_3(CH_2)_2C\equiv C\text{-}Ag$$

2-Pentyne ($CH_3C\equiv CCH_2CH_3$) has no available acidic hydrogens and cannot form a carbanion and react with the silver ion. 1-pentene ($H_2C=CH\text{-}(CH_2)_2CH_3$) does not give any reaction because there are no hydrogen atoms that would readily leave the molecule so as to make a carbanion.

The two compounds 1-pentene and 2-pentyne cannot be classified by any qualitative analysis. However by measuring the amount of bromine required for total bromination and recognizing that 2-pentyne consumes more bromine we could differentiate between them.

first: $CH_3C \equiv CCH_2CH_3 + Br_2 \xrightarrow{CCl_4} CH_3\overset{\overset{Br}{|}}{C} = \overset{\overset{Br}{|}}{C}-CH_2CH_3$

2,3-dibromo, 2-pentene

second: $CH_3\overset{\overset{Br}{|}}{C} = \overset{\overset{Br}{|}}{C}-CH_2CH_3 + Br_2 \xrightarrow{CCl_4} CH_3-\underset{\underset{Br}{|}}{\overset{\overset{Br}{|}}{C}} — \underset{\underset{Br}{|}}{\overset{\overset{Br}{|}}{C}}CH_2CH_3$

2,2,3,3 tetra bromo
pentane

2 moles of bromine are required for each mole of 2 pentyne for complete saturation.

$CH_2{=}CHCH_2CH_2CH_3 + Br_2 \xrightarrow{CCl_4} \overset{Br}{C}H_2-\overset{Br}{C}HCH_2CH_2CH_3$

1,2, dibromopentane

Only 1 mole of bromine is required for each mole of 1-pentene.

CHAPTER 8

MOLECULAR ORBITAL THEORY

FUNDAMENTALS

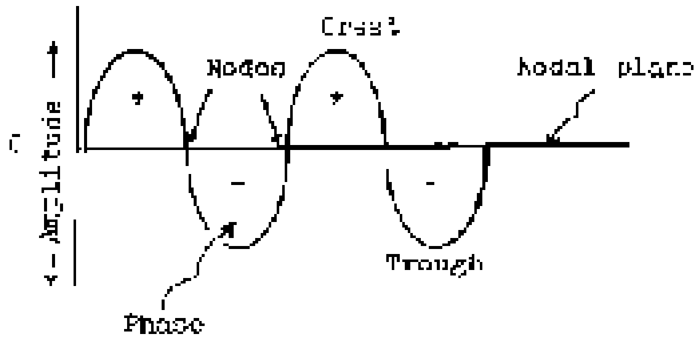
► PROBLEM 8-1

(a) Define the following terms, and draw a diagram showing their relationship to each other.

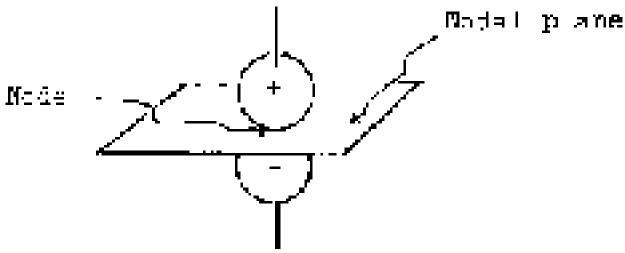
Amplitude
Nodes
Nodal plane
Phase
'Out of phase'
Wave equation

(b) How do they pertain to molecular orbitals?

Solution: (a) The terms given above all pertain to wave theory, and in particular to standing waves. The amplitude of a wave is defined as its vertical displacement; the nodes as the points at which the amplitude is equal to zero; the nodal plane as the plane passing through the nodal points; the phase as the upward or downward displacement (distinguished by positive and negative signs, respectively). If two waves were exactly out of phase, then the crests of one would line up with the troughs of the other and the sum of their amplitudes would therefore be zero. The wave equation is little more than the differential equation which describes the wave.



(5) Electron waves are described by a wave equation similar to that of standing waves. The solution to the wave equation given by $\phi(x)$, where x = distance, is the amplitude. Electron waves can have nodes, and amplitudes of different signs. It should be noted that the two lobes of a p orbital lie between a nodal plane.

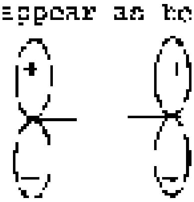


It should further be noted that, while $\phi(x,y,z)$ is the orbital, ϕ^2 has an actual physical meaning: ϕ^2 is the probability of finding an electron within a given volume. The shapes of orbitals are actually crude representations of the region within which ϕ^2 has a particular value, or the space within which electrons are significantly likely to be found (> 95% probability).

• PROBLEM 8-2

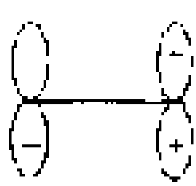
Draw the LCAO model of ethylene in the bonding and anti-bonding orbitals. Distinguish the ground state of ethylene from its excited state. Distinguish π^2 from $\pi\pi^*$.

Solution: In drawing the LCAO form of ethylene, only the π-orbital form will be drawn, as these orbitals are the subject of chief interest here. Hence, the bonding orbital of ethylene should appear as below:



Ethylene: bonding orbital

Conversely, using the definition of antibonding orbitals, the anti-bonding orbital for ethylene may be written as:



Ethylene: antibonding orbital

The ground state of a molecule occurs when the electrons have the lowest energy levels. The excited state is when the electrons of a molecule rise to higher energy levels. This is usually upon application of an external energetic stimulus (e.g., light).

Ground state of ethylene

First excited state of ethylene

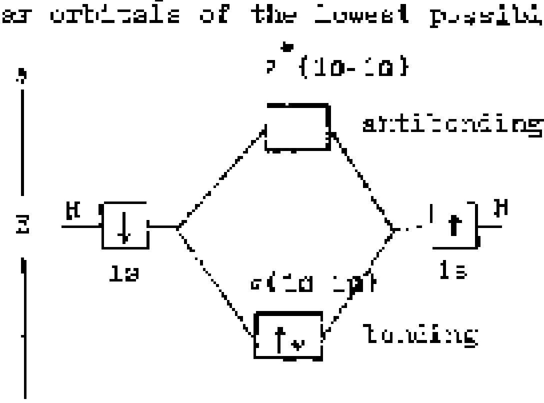
The ground state of ethylene is referred to as being in the π^2 configuration, in that both electrons are in the π bonding orbital. The notation used to describe this excited state of ethylene is $\pi^*\pi$. This shows that one electron is in the π antibonding orbital and one electron is in the π bonding orbital.

• PROBLEM 8-3

Show the molecular orbital structure of H_2. Explain the molecular orbital structure both in terms of electron configuration and LCAO. Show the bonding orbital and antibonding orbital, and calculate the bond order.

Solution: When two atomic orbitals come together, two molecular orbitals are formed - one of higher energy and one of lower energy. The lower energy one is termed the bonding orbital, which is more stable than the component orbitals. The higher-energy one is the antibonding orbital and is less stable than the component orbitals.

The bonding between the atoms of H_2 involves molecular orbitals of the lowest possible energy states:



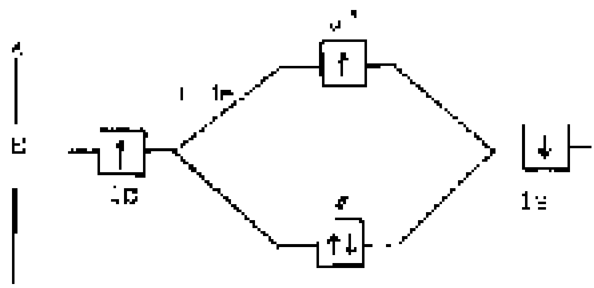
It should be noted that in molecular bonding, bonding orbitals (being orbitals of lower energy levels) will fill first and each will accommodate a pair of electrons, which must have opposite signs. It should further be seen that electrons in a bonding orbital will stabilize the molecule, whereas electrons in an antibonding orbital will destabilike the molecule. Furthermore, the effect of an electron in a bonding orbital will negate the effect of an electron in an antibonding orbital. The bond order is defined as half the number of bonding electrons less half the number of antibonding ones.

Bond order = ½(no. bonding electrons - no. anti-bonding electrons)

Using this expression, the bond order of H_2 is found to be 1.

$$\text{Bond order} = \frac{1}{2}(2 - 0) = 1$$

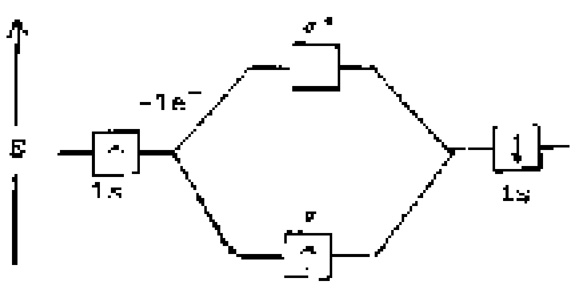
These concepts may be solidified in the confused reader by examining the case of H_2^-. Since it is formed by the union of two 1s orbitals, it may be represented as below.



H_2^- differs from H_2 in that it possesses three electrons, instead of two. Since only two electrons are permitted per orbital, a third electron (in H_2^-) must be forced into the energetically unfavorable antibonding sigma orbital (σ*). Hence, this will have a net effect of cancelling one of the electrons in the σ bonding orbital.

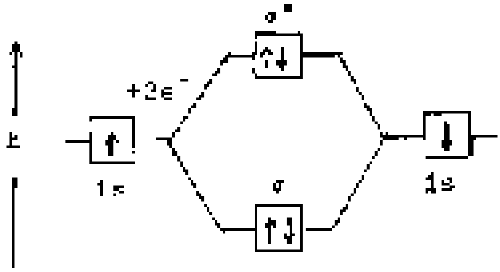
$$\text{Bond order} = \frac{1}{2}(2 - 1) = \frac{1}{2}$$

Similarly, in the case of H_2^+,



$$\text{bond order} = \frac{1}{2}(1 - 0) = \frac{1}{2}$$

And in the case of H_2^{-2},



$$\text{bond order} = \tfrac{1}{2}(2 - 2) = 0$$

This concept may further be expressed using LCAO (linear combination of atomic orbitals). This is, as the name implies, an expression of the molecular orbital in terms of its component atomic orbitals in a linear equation.

$$\psi = \phi_1 + \phi_2$$

where ψ = molecular orbital

ϕ_1 = the first atomic orbital

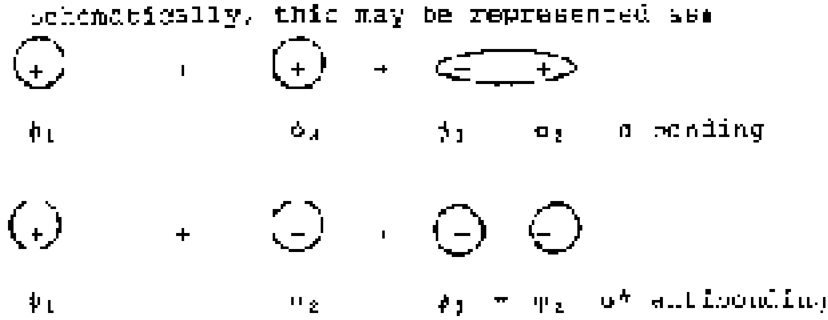
ϕ_2 = the second atomic orbital

Addition of atomic orbitals will result in the stabilizing bonding orbital, and subtraction will result in the destabilizing antibonding orbital.

$$\psi = \phi_1 + \phi_2$$

$$\psi^* = \phi_1 - \phi_2$$

Schematically, this may be represented as:



• PROBLEM 8-4

Explain the molecular orbital structure of O_2. Calculate the bond order.

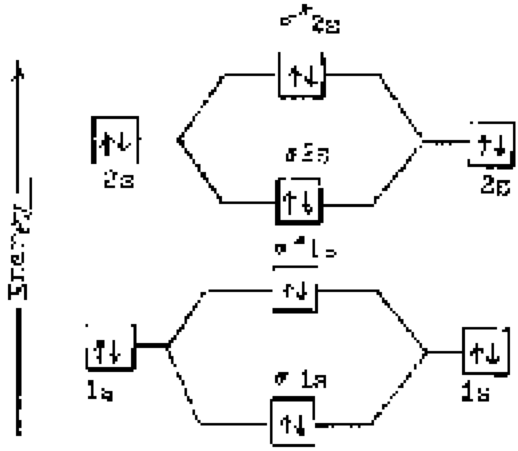
Solution. When reading the last problem, one may have come to the realization that not all molecular orbitals are as simple as the case presented for H_2. Oxygen, for instance, presents the problem of forming molecular orbitals from atomic p orbitals. To examine this, one must first examine the electron configuration of oxygen.

$\underline{\uparrow\downarrow}$ $2p_x$ $\underline{\uparrow}$ $2p_y$ $\underline{\uparrow}$ $2p_z$

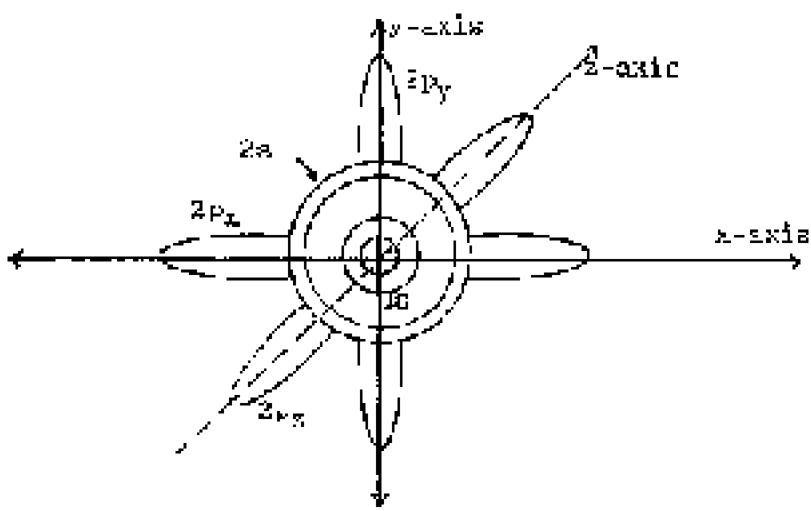
$\underline{\uparrow\downarrow}$ $2s$

$\underline{\uparrow\downarrow}$ $1s$

The two s orbitals will form σ bonds in a manner similar to those in H_2.



Since both the sigma bonding orbitals and the sigma anti-bonding orbitals are filled, the net effect of these will be zero. They may be neglected in discussing the molecular bonding of oxygen.



Above is shown the orbital picture of the oxygen atom. If one remembers the three dimensional configuration of the p orbitals, the difficulties can be seen. Which p sub-orbital (P_x, P_y or P_z) will bond with which? As a rule each P_y or P_z orbital will bond with a corresponding p sub-orbital to give one π-bonding orbital and one π* antibonding orbital. In the case of P_x, one σ bonding and one σ* antibonding orbital are formed.

In its bonded state, therefore, O_2 can be represented as:

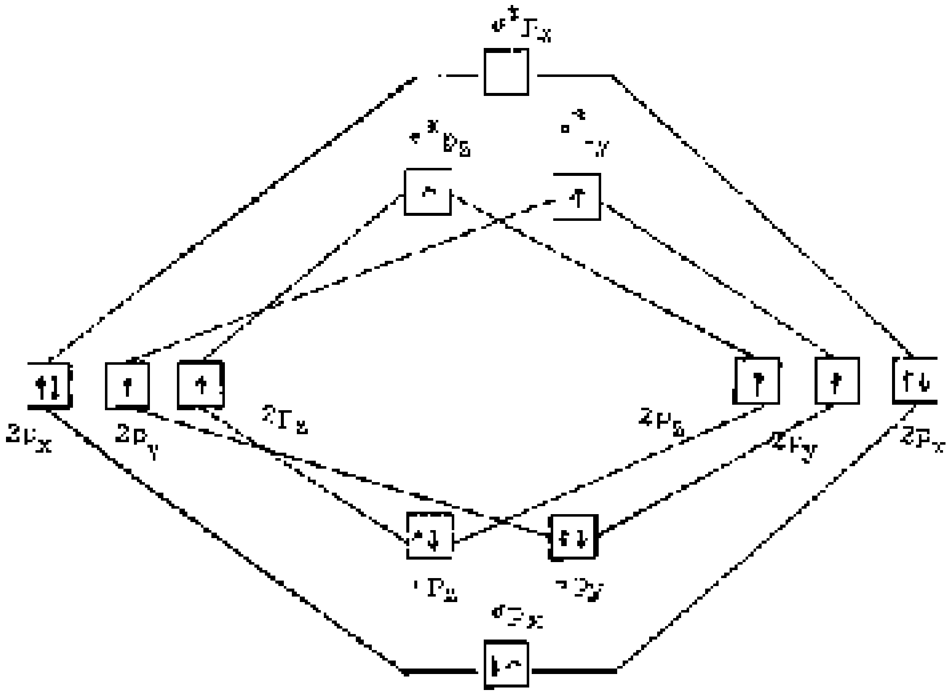
$$\underline{\quad}\ \sigma^* P_x$$

$$\underline{\uparrow}\ \pi_z^* \qquad \underline{\uparrow}\ \pi_y^*$$

$$\underline{\uparrow\downarrow}\ \pi_z \qquad \underline{\uparrow\downarrow}\ \pi_y$$

$$\underline{\uparrow\downarrow}\ \sigma P_x$$

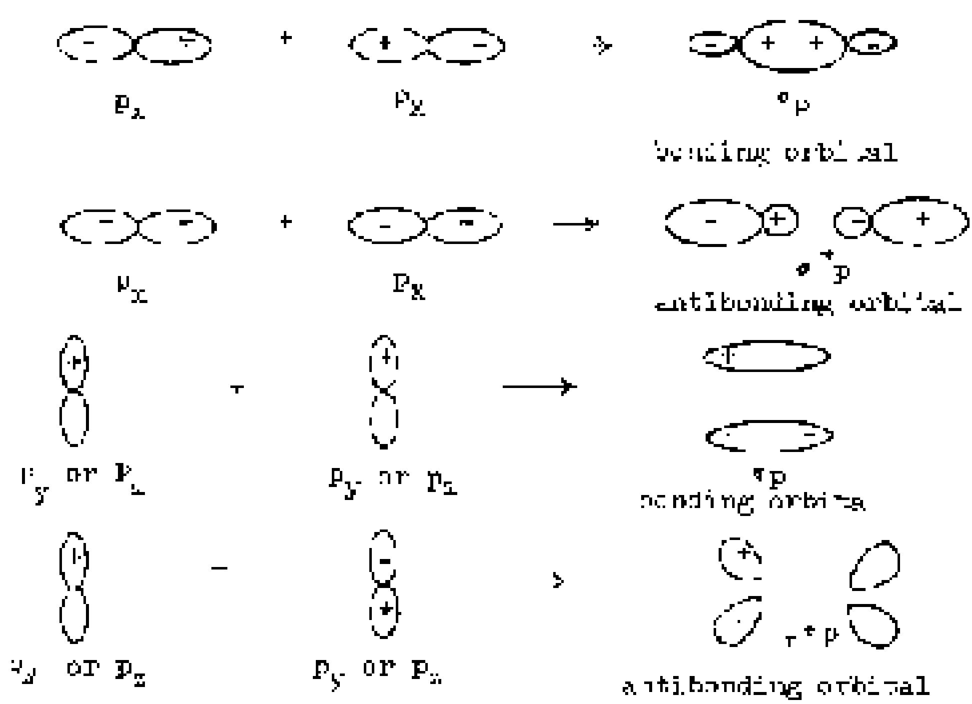
(plus 8 electrons in 2 σ s and 2 σ* s orbitals)



Electronic Configuration of Oxygen (O_2)

Therefore, the bond order can be calculated as $\frac{1}{2}(6 - 2)$, or two. The reader may convince himself of this by drawing a Lewis dot diagram (:O::O:).

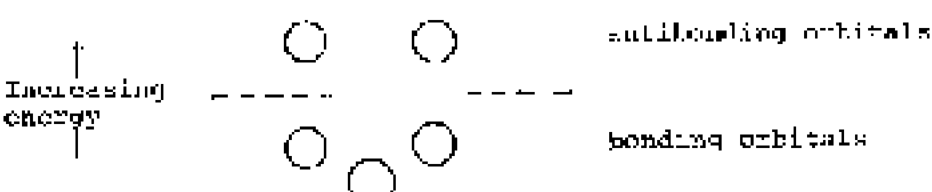
The LCAO models may readily be understood by viewing each orbital as a wave function, whereby like phases will add, and opposite phases will tend to cancel each other. As two methods of approach between two nodes are possible, then two types of orbitals will form.



As can be seen from the above diagrams, the addition of like orbitals will result in the formation of favorable bonding orbitals; the addition of opposite orbitals will result in the formation of unfavorable antibonding orbitals.

• PROBLEM 8-5

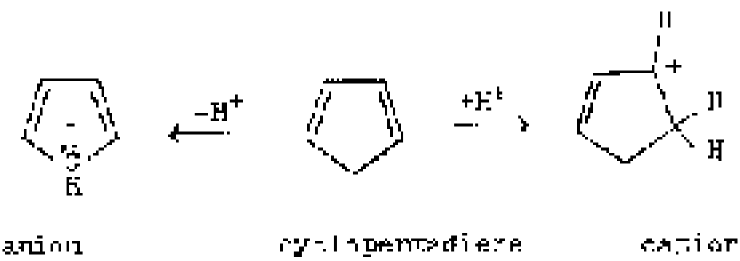
The LCAO molecular orbitals of the cyclopentadienate system (C_5H_5) have schematic energies as follows:



Indicate a possible point of difference between $C_5H_5^+$ and $C_5H_5^-$ that can be deduced from molecular orbital theory.

Solution:

The anion is a closed, cyclic, planar system with 6 π electrons, all of which satisfy Hückel's rule for aromaticity. The cation is clearly nonaromatic and its formation is thus not favored thermodynamically.



Another way to evaluate the stability, or bond energy of the cyclopentadienate system is by examining its molecular orbitals. A conventional way of drawing the closed-shell π-electronic configuration of a cyclic molecule includes the following steps:

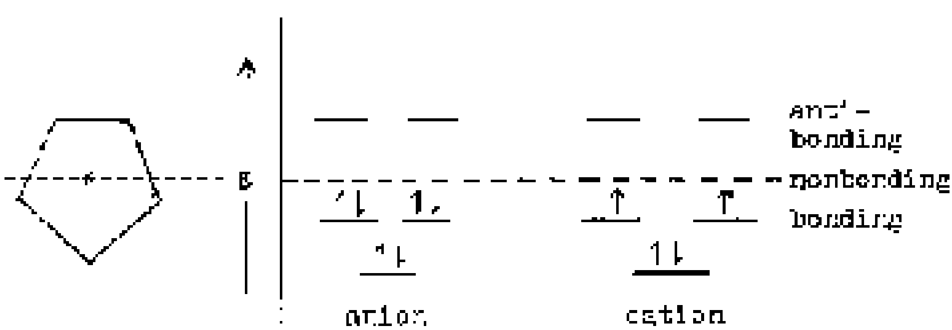
1) Draw the structure of the molecule as resting on one corner.

2) Extend a broken line through the center of the molecule ----- this line represents the non-bonding energy level; below it lies the bonding orbital(s), π, and above it lies the antibonding orbital(s), π*.

3) For each of the corners in the structure mark a line; this represents a molecular orbital available to accommodate one pair of electrons.

4) Following Pauli's principle and Hund's rule, place electrons into the orbitals. There can be only two electrons - and of opposite spin - in each orbital, with orbitals of lower energy being filled up first. For orbitals of equal energy, each gets an electron before any one of them gets a pair of electrons.

Using this convention, we arrive at the following π-electronic configuration of the cyclopentadienate system:



We can see from the above diagram that all the bonding orbitals are filled in $C_5H_5^-$; this is responsible for the aromaticity and stability of the anion. In $C_5H_5^+$, there will be two unpaired electrons, and this diradical character imparts instability to the cation.

● PROBLEM 8-6

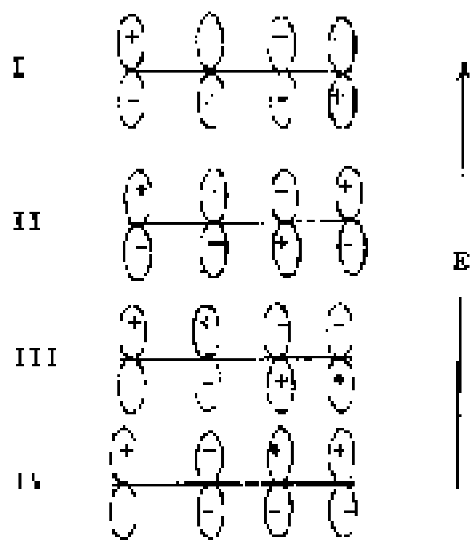
Discuss the various bonding and antibonding orbitals of 1,3-butadiene. Place them in order of increasing energy. What is the electronic configuration of butadiene in both the ground and the excited state.

Solution:

$CH_2{=}CH{-}CH{=}CH_2$

1,3-Butadiene

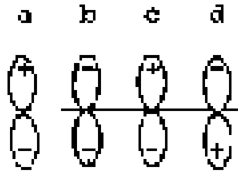
Since there are four p orbitals, four LCAO structures exist for 1,3-butadiene:



Two of these structures with high energy levels represent antibonding orbitals, while the other two of lower energy represent bonding orbitals.

Placing LCAO structures in increasing order of energy is tricky. The best way to go about this is to calculate the number of bonding interactions and the number of antibonding interactions. The structure with the greatest number of bonding interactions will be the most stable and hence the structure of least energy. The structure with the least number of bonding interactions, and hence the greatest number of antibonding interactions, will be the least stable and hence the structure of highest energy.

Examining each LCAO structure, we find

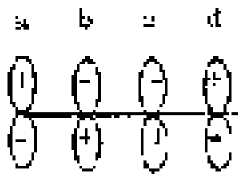


I

no bonding interactions

3 antibonding interactions (a–b) (b–c) (c–d)

3 net antibonding interactions

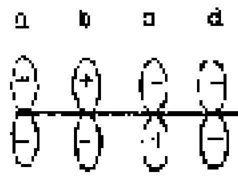


II

2 antibonding interactions (a–b, c–d)

1 bonding interaction (b–c)

1 net antibonding interaction

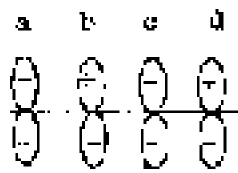


III

1 antibonding interaction (b–c)

2 bonding interactions (a–b, c–d)

1 net bonding interaction



IV

no antibonding interactions

3 bonding interactions (a–b, b–c, c–d)

3 net bonding interactions

As can readily be seen, the order of the four structures in increasing energy is IV, III, II, I.

The four molecular orbital (ψ) levels are thus:

I ___ ψ_4

II ___ ψ_3 antibonding

III ___ ψ_2 bonding

IV ___ ψ_1

Since there are four π electrons, the ground state of 1,3-butadiene would have the following electronic configuration:

___ ψ_4

___ ψ_3 antibonding

$\uparrow\downarrow$ ψ_2 bonding

$\uparrow\downarrow$ ψ_1

This can be expressed as $\psi_1{}^2\psi_2{}^2$ bonding.

Upon ultraviolet stimulation, an electron from ψ_2 will jump to the ψ_3 antibonding orbital. This excited state configuration is shown below and can be expressed as $\psi_1{}^2\psi_2\psi_3$ bonding.

ψ_4 ——

ψ_3 —↑— antibonding

ψ_2 —↑— bonding

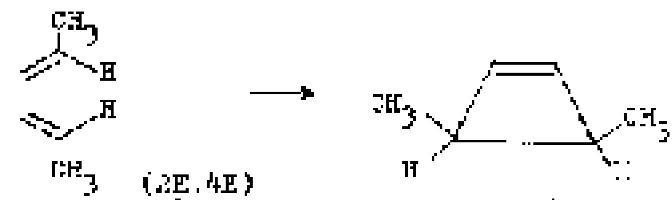
ψ_1 —↑↓—

ELECTROCYCLIC REACTIONS

• PROBLEM 8-7

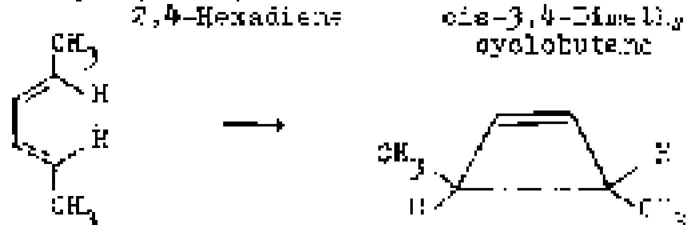
What catalysts may be utilized in order to achieve the following one step transformations?

(a)



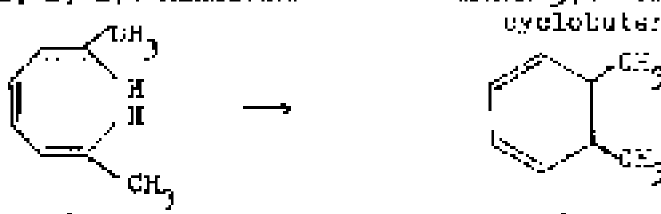
(2E,4E) 2,4-Hexadiene → cis-3,4-Dimethyl-cyclobutene

(b)



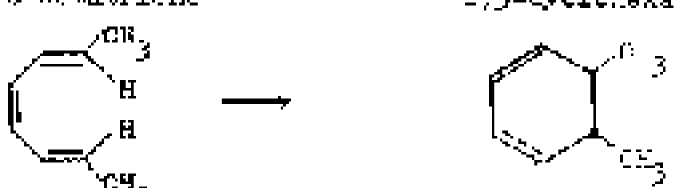
(2E,4E) 2,4-Hexadiene → trans-3,4-dimethyl-cyclobutene

(c)

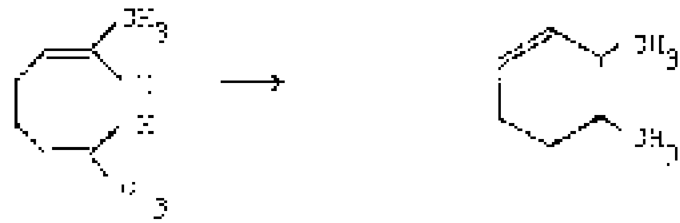


trans,cis,trans 2,4,6-Octatriene → cis-5,6-Dimethyl-1,3-cyclohexadiene

(d)



trans,cis,trans-2,4,6-Octatriene → trans-5,6-Dimethyl-1,3-cyclohexadiene

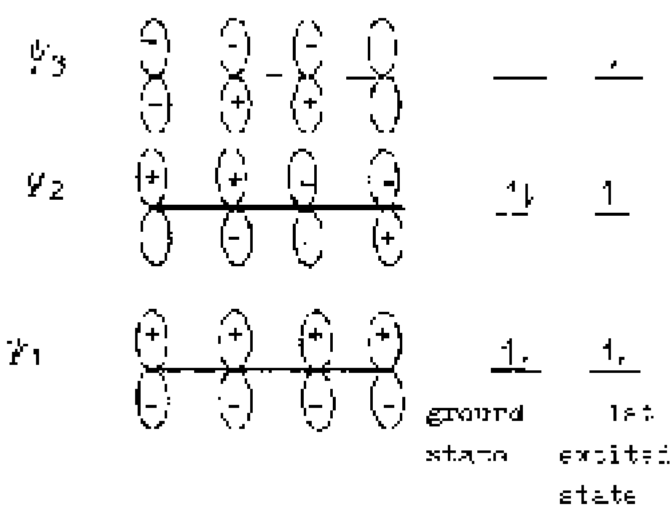
(a) 

trans,trans-2,6-Octadiene   cis-3,4-Dimethyl-cyclohexene

Solution: Electrocyclic reactions are concerted, therefore they are completely stereospecific. The exact stereochemistry of the product depends upon the number of double bonds in the polyene; molecular orbital theory allows us to predict this stereochemistry. Let us look at the π electron configuration of butadiene, a four-π-electron system, in the ground state and in the first excited state (achieved by the absorption of radiation):

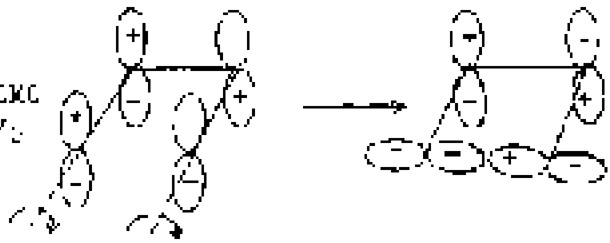
HOMO of the 1st excited state

HOMO of the ground state



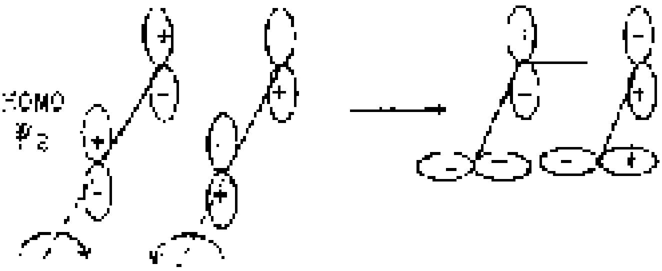
The electron that is least tightly held, and therefore the one that is involved in the reaction, is the electron in the highest occupied molecular orbital (HOMO) of the polyene. As we can see from the above diagram, the highest occupied molecular orbital of the conjugated diene in the ground state is ψ_2; it is the electrons in this orbital that will form the bond that closes the ring. Bond formation requires overlap of the lobes on the terminal carbons (C_1 and C_4 in this case). Only a conrotatory motion, in which the p orbitals of the terminal carbons rotate in the same direction, can bring together lobes of the same phase. A disrotatory motion, in which the orbitals rotate in opposite directions, would on the other hand bring together lobes of opposite phases, resulting in the formation of an antibonding orbital:

HOMO ψ_2



Conrotatory: bonding

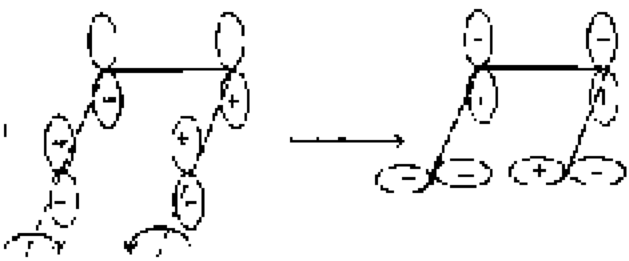
HOMO ψ_2



Disrotatory: antibonding

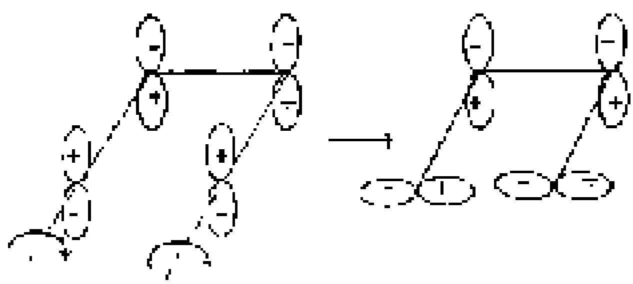
For photocyclic reactions, the HOMO is ψ_3, hence only disrotatory motion would result in effective cyclization of a diene:

HOMO ψ_3



Disrotatory: bonding

HOMO ψ_3



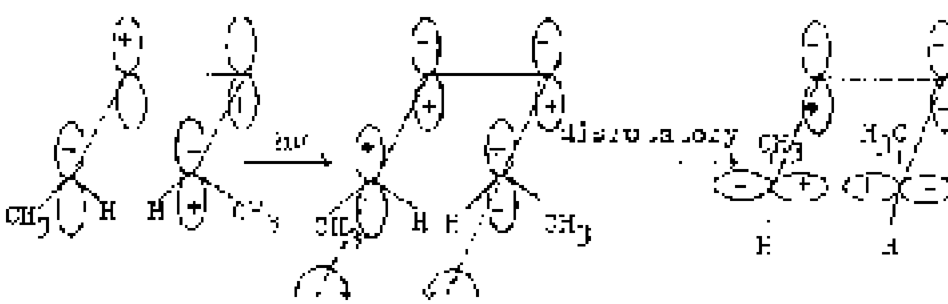
Conrotatory: antibonding

Therefore, thermal electrocyclic reactions of four π electrons can only occur in a conrotatory manner, while photochemical electrocyclic reactions of four π electrons can only occur in a disrotatory manner. This is summarized by the Woodward-Hoffman rules for electrocyclic reactions (given in Table 1 below).

Table 1 Woodward-Hoffman Rules for Electrocyclic Reactions

Number of π Electrons	Reaction	Motion
4n (n=any integers)	Thermal	Conrotatory
4n	Photochemical	Disrotatory
4n + 2	Thermal	Disrotatory
4n + 2	Photochemical	Conrotatory

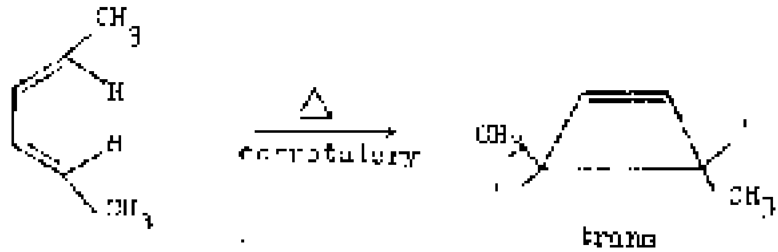
(a) Since the cis product is desired, a disrotatory motion is required. From the Woodward-Hoffman rules, a 4n(n=1)-π-electron system undergoing disrotatory motion must be a photochemical reaction.



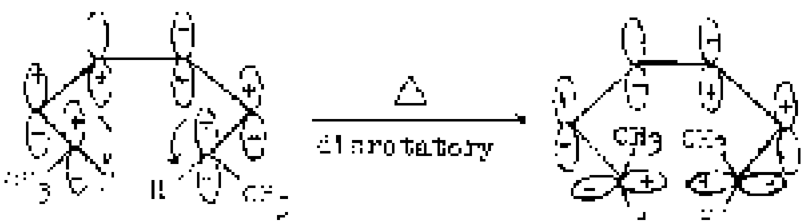
(2E,4E)
2,4-Hexadiene

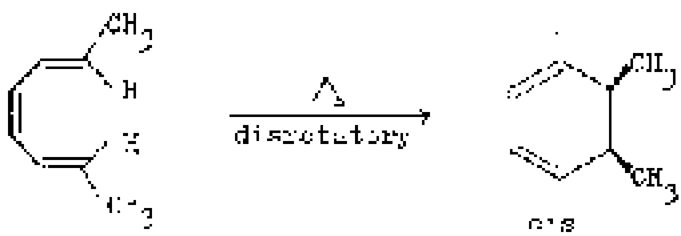
cis-3,4-Dimethyl-
cyclobutene

(b) Since the trans isomer is desired, a conrotatory motion is required. Therefore, a thermal reaction is required.

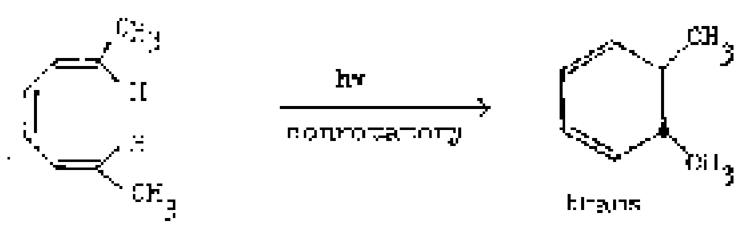


(c) Since the cis product is desired, a disrotatory motion is required. From the Woodward-Hoffman rules, a 4n + 2(n=1) π-electron system undergoing disrotatory motion must be a thermal reaction:





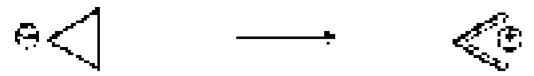
(d) Since the trans isomer is desired, conrotatory motion is required. According to the Woodward-Hoffman rules, a 4n + 2(n-1)-π-electron system undergoing conrotatory motion must be a photochemical reaction. Therefore:



(e) Since this polyene is not in conjugated form, no electrocyclic reaction will occur.

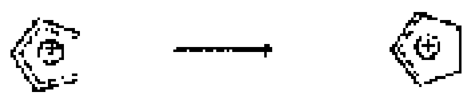
• PROBLEM 8-8

The commonly observed conversion of cyclopropyl cations into allyl cations is considered to be an example of an electrocyclic reaction. (a) What is the HOMO of the



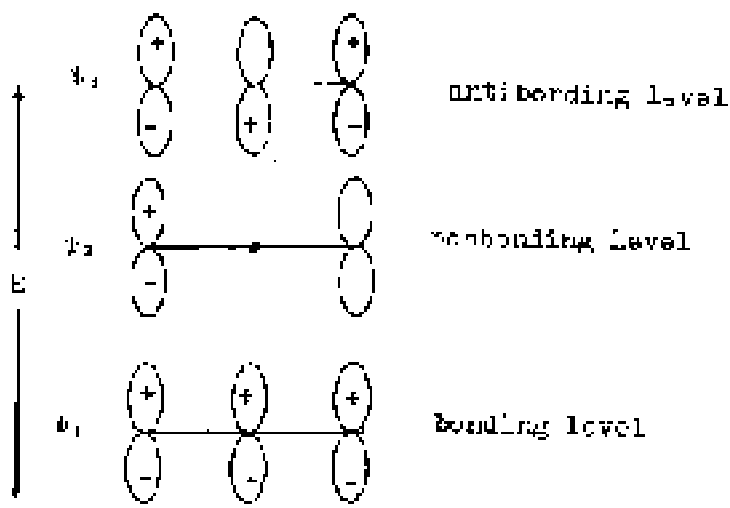
Cyclopropyl cation Allyl cation

allyl cation? How many π electrons has it? (b) Would you expect conrotatory or disrotatory motion? (c) What prediction would you make about interconversion of allyl and cyclopropyl anions? (d) About the interconversion of pentadienyl cations and cyclopentenyl cations?



Pentadienyl cation Cyclopentenyl cation

Solution: (a) The molecular orbitals for the allyl system in the form of their linear combinations of atom orbitals (LCAO's) are



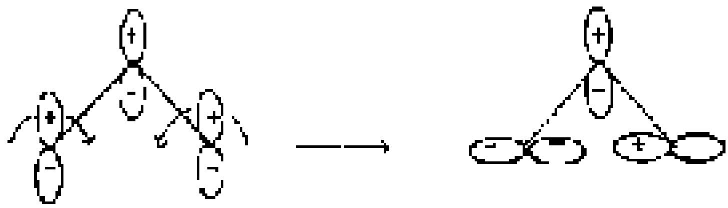
Note that the energy of the molecular orbital increases as the number of non-bonding interactions increases. The allyl cation will have the first molecular orbital (ψ_1) filled. This orbital, at the bonding level, is considered to be the highest occupied molecular orbital (HOMO) and it has two π electrons

___ ψ_3

___ ψ_2

↑↓ ψ_1

(b) The Woodward-Hoffmann rules dictate that the thermally induced electrolytic ring closure of a polyene of 4n π electrons will involve a conrotatory motion of the terminal p orbitals; conversely, a polyene of 4n + 2 π electrons will have its terminal p orbitals undergoing disrotatory motion. The allyl cation with 2 π electrons falls into the latter category and we would expect the ring closure to involve disrotatory motion.



HOMO ψ_1

Disrotatory; bonding

(c) Using the same approach as in (b), we predict that the allyl anion, with 4 π electrons, would involve conrotatory motion of the terminal p orbitals in its thermal cyclization.

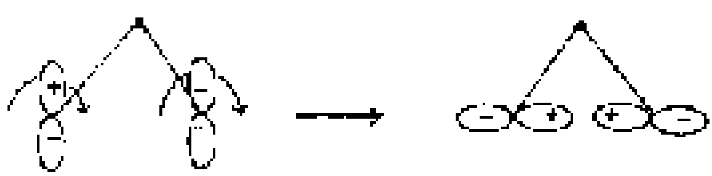
Another way to arrive at this prediction is by examining the HOMO of the allyl anion. With 4 π electrons, 2 electrons are forced into the nonbonding orbital (ψ_2).

ψ_3 ___

ψ_2 ↑↓

ψ_1 ↑↓

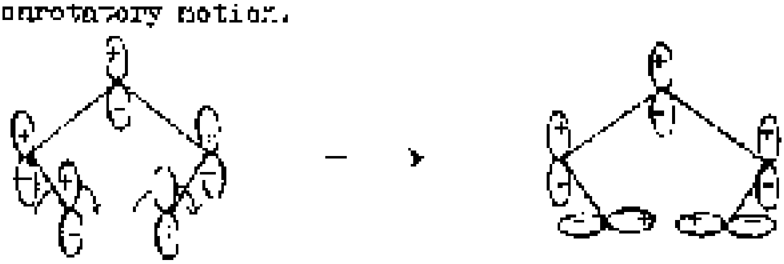
ψ_2 is now the HOMO state, and only conrotatory motion of the terminal p orbitals will allow effective cyclization.



HOMO ψ_2

Conrotatory; bonding

(d) In the pentadienyl cation, there are 4 π electrons. Thus, by the Woodward-Hoffman rules, the thermal ring closure forming the cyclopentenyl cation would involve conrotatory motion.



HOMO ψ_2

Conrotatory; bonding

CYCLOADDITION REACTIONS

• **PROBLEM 8-9**

Discuss the direct, concerted addition of H_2 to an alkene from the standpoint of orbital symmetry. (a) In the absence of catalyst, and (b) in the presence of photochemical stimulation.

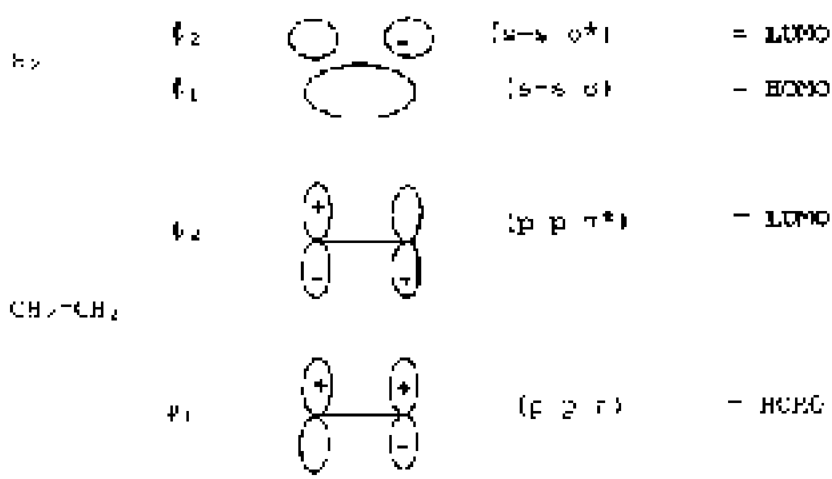
Solution: It is best to begin with a review of the molecular orbital basis of a concerted addition reaction.

(1) In concerted addition, two new σ bonds are formed. The electrons involved in new bond formation come from the highest occupied molecular orbital (HOMO) because they are the least tightly held and thus most reactive.

(2) Since the HOMO of each reactant already contains two electrons, it must overlap an empty orbital of the other reactant. In doing this, it picks the most stable of these (the lowest unoccupied molecular orbital (LUMO). In the transition state of the addition, then, stabilization comes chiefly from overlap between the HOMO of one reactant and the LUMO of the other.

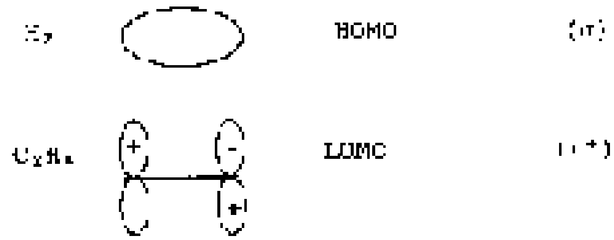
(3) In the absence of a catalytic agent (such as light or chemicals), only the ground state HOMO and LUMO are the reacting orbitals. For the converse, excited state HOMO and LUMO may take part in orbital overlap.

(4) In the concerted reaction between H_2 and ethylene, the molecular orbitals of chief focus are:



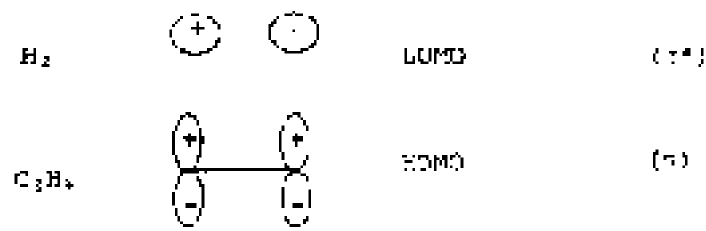
Note that since the hydrogenation is noncatalyzed, the reacting molecules have ground state configurations in accordance with (3) above. Also, according to (2), such reaction involves the overlap of the HOMO of one reactant with the LUMO of the other. Hence we have two possible orbital combinations - (i) $HOMO_{H_2}$ - $LUMO_{C_2H_4}$ and (ii) $LUMO_{H_2}$ + $HOMO_{C_2H_4}$.

(i)



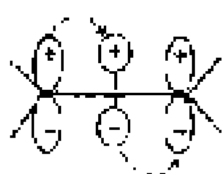
symmetry forbidden

(ii)



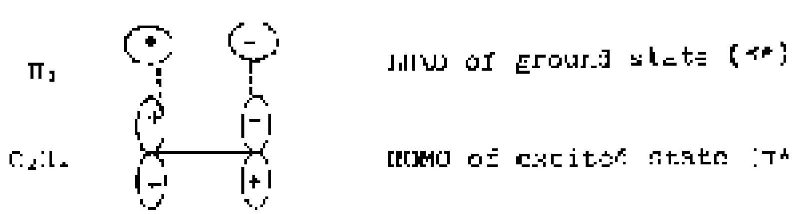
symmetry forbidden

As the above shows, lobes of opposite phase (indicated by opposite signs) would approach each other. Since H_2 is only two atoms long, a suprafacial-antarafacial reaction is sterically very difficult:

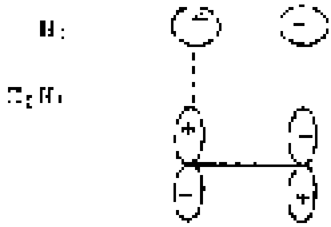


Hence, concerted hydrogenation of ethylene in the absence of a catalyst is not possible.

(b) In the presence of photochemical stimulation, some molecules will exist in excited state. The HOMO of an excited molecules can actually overlap in a suprafacial-suprafacial manner with the LUMO of a ground state molecule, allowing orbital symmetry and effective bond formation. Thus catalyzed concerted addition of H_2 to ethylene will result in hydrogenation.



symmetry allowed



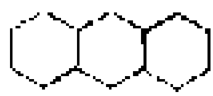
HOMO of excited state (σ*)

LUMO of ground state (π*)

symmetry allowed

• PROBLEM 8-10

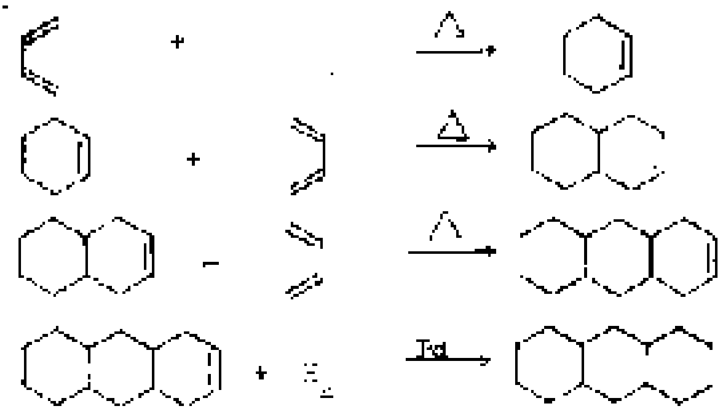
Starting with any organic compounds of less than four carbon atoms and any inorganic or physical reagents that may be required, synthesize

(a) 

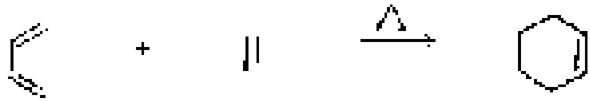
(b) 

(c) 

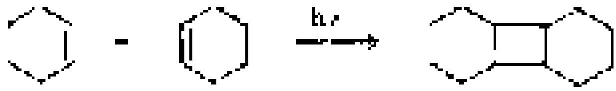
Solution: Diels-Alder reactions, as well as other electrocyclic reactions are very valuable synthetic tools. They enable the chemist to perform ring closings, build up molecules and are used extensively in the syntheses of drugs.

(a) 

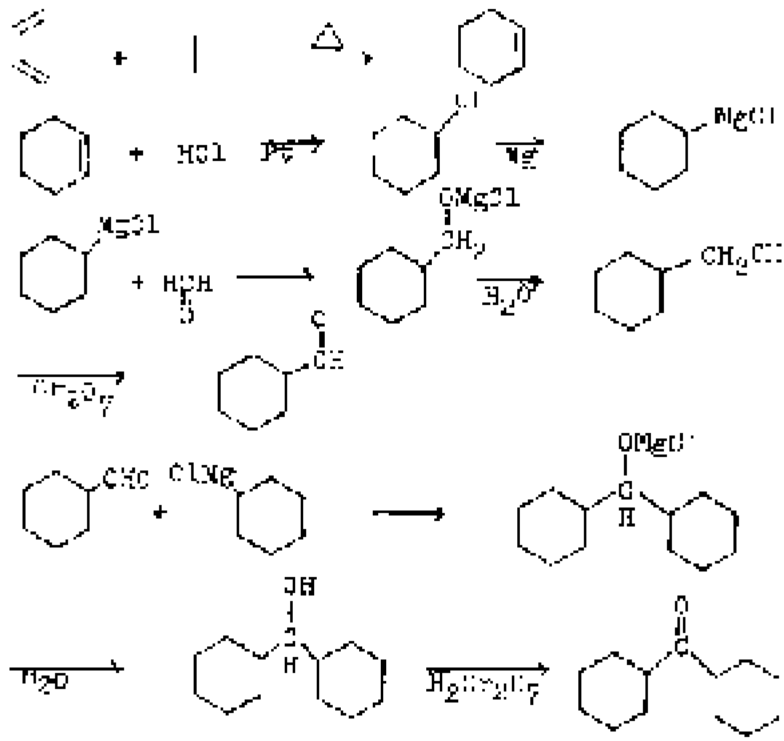
(b) This reaction is a slight variation on the Diels-Alder. The first step consists of the formation of cyclohexene.



Now, if two cyclohexenes are exposed to ultraviolet light the desired moiety will be obtained.



(c) This reaction involves little more than cyclohexane formation followed by two Grignard reactions.



RESONANCE THEORY

PROBLEM 8-11

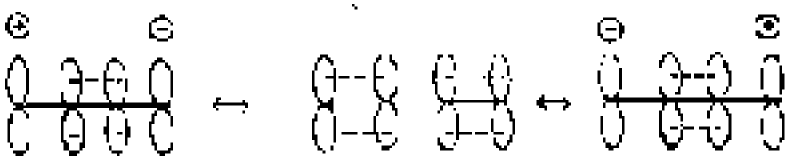
In 1,3-butadiene, the observed length of the C_2-C_3 bond is 1.48 Å, while the "standard" single bond distance is generally accepted to be 1.54 Å. Explain this discrepancy and calculate the π bond order of the C_2-C_3 butadiene bond. (**Hint**, consider the resonance effects and the molecular orbital structure).

<u>Solution</u>:

$$H_2C{=}\overset{H}{C}{-}\overset{H}{C}{=}CH_2$$

1,3-Butadiene

The above structure is the accepted structure for 1,3-butadiene. This structure, however, is not altogether correct in that 1,3-butadiene has several resonance forms which originate from the interactions of the π-cloud electrons.



$\overset{\oplus}{C}H_2-CH=CH-\overset{\ominus}{C}H_2 \leftrightarrow CH_2=CH-CH=CH_2 \leftrightarrow \overset{\ominus}{C}H_2-CH=CH-\overset{\oplus}{C}H_2$

It should be stressed that the correct structure of 1,3-butadiene is a hybrid of these structures, not an equilibrium condition of the three forms.

Hence, the best representation of 1,3-butadiene would be,

CH_2---------CH ========CH ------CH_2

So, as one can see, the C_2-C_3 bond, which was previously represented as a single bond, is really a single bond with some double bond character. The C_1-C_2 and C_3-C_4 bonds, conversely, are double bonds with some single bond character. Empirically the C_2-C_3 bond length has been observed at 1.48 Å, while the "standard" single bond distance (as found in ethane) is 1.54 Å.

In recent years, a second theory has developed which not only account for shorter bond distances, but predicts them as well. If the bonding about the various carbons is examined, it will be seen that the C_2-C_3 single bond is a bond between two sp^2-hybridized carbons, which would have a shorter length than a bond between two sp^3-hybridized carbons.

$CH_2-\overset{H}{C}-\overset{H}{C}-CH_2$

sp^2 sp^2 sp^2 sp^2

The shortness of the C_2-C_3 butadiene bond is attributable to both the sp^2 hybridization and to resonance stabilization.

The π bond order is simply a measure of the double bond character of a given bond. The C_2-C_3 single bond should possess some double bond character. The general formula for the calculation of the π bond order order (πBO) is:

$$\pi BO = \frac{r_s - r}{2r - 3r_d + r_s}$$

where r = observed bond length

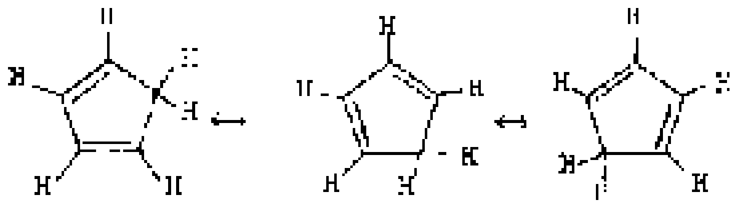
r_s = normal single bond length (1.54 Å)

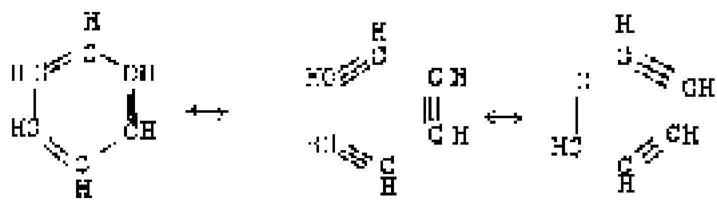
r_d = normal double bond length (1.33 Å)

$$TBO_{C_2-C_3} = \frac{(1.54 - 1.48)}{(2 \times 1.48) - (3 \times 1.33) + 1.54} = .12$$

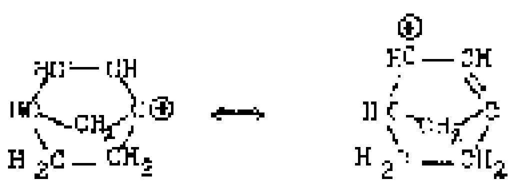
• PROBLEM 8-12

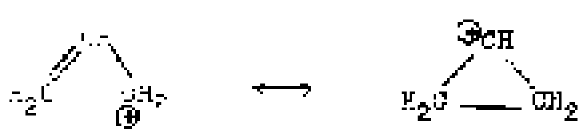
Evaluate the importance of resonance of the following types:

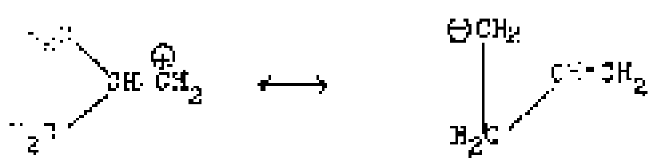
(a) 

(b) 

(c) $CH_2=CH-\overset{\oplus}{O} \longleftrightarrow \overset{\oplus}{C}H_2-CH=O$

(d) 

(e) 

(f) 

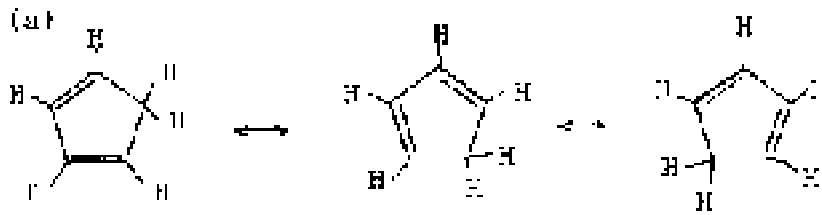
Solution: In solving these problems, one should keep in mind the three criteria for resonance:

(1) There is no change in the positions of nuclei in resonance structures, the only change involved is in electron distribution.

(2) Structures with filled octets are more important than structures with unfilled octets.

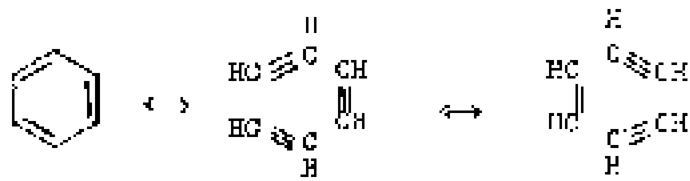
(3) More important structures involve a minimum of charge separation.

(a)

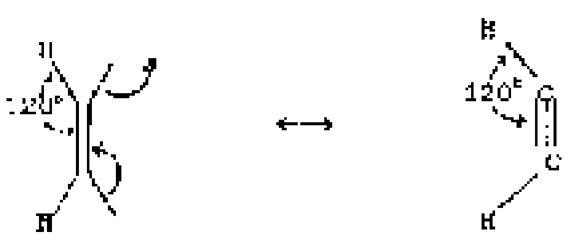


The above resonance is expected to be relatively unimportant. The carbon atoms in these resonance structures would have to vary between sp^3 and sp^2 hybridizations. This involves a change in molecular bonding, and as such represents a change in bond angles and nuclear positions.

(b)



This resonance is considered to be unimportant, as they involve the existence of acetylene molecules in highly strained conformation.



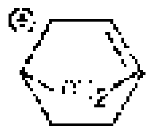
Acetylene prefers a linear molecular arrangement with bond angles of 180° rather than 120° as assumed in the resonance contributing structures.

(c) $CH_2=CH-\overset{\ominus}{O} \longleftrightarrow \overset{\ominus}{C}H_2-CH=O$

In going from one resonance form to the other, there is no change in the nuclear configuration of the molecule, Each has an unfilled octet as well as an identical positive charge. Therefore this type of resonance is expected to be important.

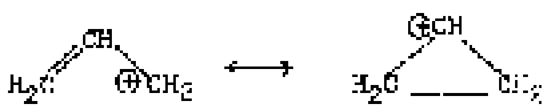
Of the two, $\overset{\oplus}{C}H_2-OCH_3$ will be slightly more favorable, as a positive charge on oxygen is less stable than a positive charge on carbon.

(d) A superficial examination would indicate that these resonance structures satisfy the three criteria for resonance. There is no change in the nuclear configuration. The structures are alike in having one unfilled octet, and also in having the same charge separation.

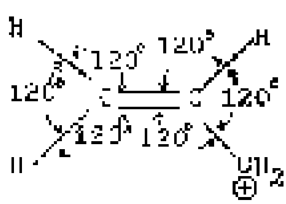


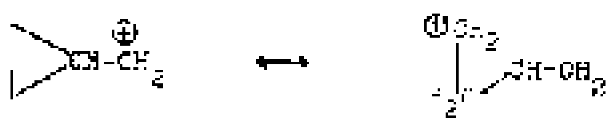
II

Resonance form II, however, violates Bredt's rule which states that for steric reasons a double bond at a bridgehead carbon is forbidden. Therefore, the resonance is not important.

(e) 

This type of resonance is considered unimportant, since the cyclic cation involves an unfavorable conformation with highly strained bond angles. The conformation in which the allyl carbon will most likely be found is:



(f) 

The above resonance will be of importance since it follows the three criteria of resonance. In addition, a primary cation is highly unstable, therefore the tendency for the cation to be in a conformation which would allow for the cyclic resonance form is high.

Which chloride of each of the following pairs would be expected to lose chloride ion most readily and form a carbonium ion? Explain.

(a) $CH_2=CH-CH_2-CH_2Cl$ and $CH_2=CH-CH_2Cl$

(b) $CH_2=CH-\underset{\displaystyle Cl}{CH}-CH=CH_2$ and $CH_2=CH-CH=CH-CH_2Cl$

Solution: (a) To determine which chloride will be likely to become a carbocation most readily, it is best to look at the various resonance forms of the carbocations. The carbocation with the most resonance forms will be the most stable due to resonance energy.

Examining allyl chloride first, we find the following resonance:

$$CH_2=CH-CH_2Cl \xrightarrow{-Cl^{\ominus}} CH_2=CH-\overset{\oplus}{C}H_2 \leftrightarrow \overset{\oplus}{C}H_2-CH=CH_2$$

4-Chloro-1-butene will not undergo any appreciable resonance stabilization upon ionization (loss of Cl^-); therefore the positive charge will not be stabilized by electrons from the double bond.

(b) In this case, these two isomers will form identical resonance structures.

$$CH_2=CH-\underset{\displaystyle Cl}{CH}-CH=CH_2 \xrightarrow{Cl^{\ominus}} CH_2=CH-\overset{\oplus}{C}H-CH=CH_2$$

$$CH_2=CH-CH=CH-\overset{\oplus}{C}H_2 \longleftrightarrow \overset{\oplus}{C}H_2-CH=CH-CH=CH_2$$

$$CH_2=CH-CH=CH-CH_2Cl \xrightarrow{Cl^{\ominus}} CH_2=CH-CH=CH-\overset{\oplus}{C}H_2$$

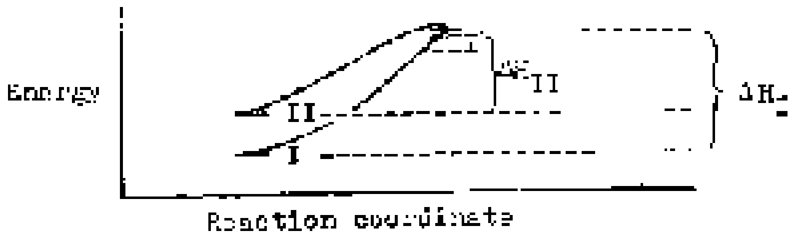
$$\updownarrow$$

$$CH_2=CH-\overset{\oplus}{C}H-CH=CH_2$$

$$\updownarrow$$

$$\overset{\oplus}{C}H_2-CH=CH-CH=CH_2$$

Since the conjugated compound $(CH_2=CH-CH=CH-CH_2Cl)$ is more stable thermodynamically than the nonconjugated compound $(CH_2=CH-CHCl-CH=CH_2)$, the energy of activation (E_{act}) in the ionization process is greater for the former than the latter. Hence the nonconjugated compound will lose Cl^- more easily than the conjugated one.



$\Delta H_I > \Delta H_{II}$

I = $CH_2=CH-CH=CH-CH_2Cl$

II = $CH_2=CH\ CHCl\ CH=CH_2$

III = $\underset{\delta+}{CH_2}$ — CH $=\!=$ $\underset{\delta:}{CH}$ $=\!=$ CH $=\!=$ $\underset{\delta+}{CH_2}$

CHAPTER 9

ALKADIENES

• PROBLEM 9-1

What are dienes? Briefly discuss their properties and system of nomenclature.

Solution: Dienes are alkenes which contain two carbon-carbon double bonds. These double bonds can be either adjacent (called cumulated double bonds), or separated by one carbon-carbon single bond (conjugated), or separated by two or more carbon single bonds (isolated).

The nomenclature of dienes is analogous to that of alkenes, with certain modifications to indicate the extra double bond. The numbering of carbons is the same as that of alkenes. The numbers of the olefinic carbons are placed at the beginning of the name, which is suffixed by -diene instead of -ene. For example, a compound of the structure

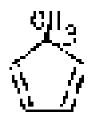
$\overset{5}{C}H_3\overset{4}{C}H=\overset{3}{C}H\overset{2}{C}H=\overset{1}{C}H_2$ is called 1,3 pentadiene, where '1,3' indicates the positions of the double bonds.

The properties of dienes depend upon the arrangement of the double bonds and the other substituents. If the double bonds are widely separated (as in isolated dienes), the compound behaves like a simple alkene. If the compound is conjugated, there is potential delocalization of the π electrons. Conjugated double bonds are, in general, more stable than isolated double bonds because of the resonance effect. Cumulated double bonds (allenes) are more unstable than isolated double bonds because of their geometry and electron density.

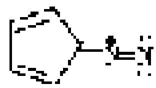
Of all the dienes studied so far, the most important one is 1,3-butadiene, $CH_2=CH-CH=CH_2$. It is used in making synthetic rubber by free-radical polymerization.

• PROBLEM 9-2

Name or draw structures for the following compounds.

(a) 

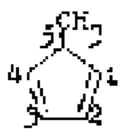
(b) $CH_3CH{-}CH{=}CH{-}CH{=}C\!\!\begin{array}{l}{/\!\!/}O\\ \backslash OH\end{array}$

(c) 

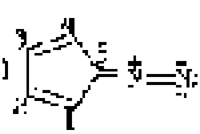
(d) 2,3 dimethyl 1,4-hexadiene

(e) 3,6 dinitro-1,4-cyclohexadiene

Solution: The IUPAC system of naming for dienes is similar to that for simple alkenes, except that it is prefixed by two numbers to indicate the positions of the double bonds, and suffixed by -diene instead of -ene. The numbers are assigned so as to have the lowest combination.

(a)  is a cyclic compound containing five carbons in the ring, a methyl substituent, and two carbon-carbon double bonds. The name of the compound is 5-methyl-1,3-cyclopentadiene.

(b) $\underset{6}{CH_3}{-}\underset{5}{CH}{=}\underset{4}{CH}{-}\underset{3}{CH}{=}\underset{2}{CH}{-}\underset{1}{C}\!\!\begin{array}{l}{/\!\!/}O\\ \backslash OH\end{array}$ contains six carbons in a chain, two carbon-carbon double bonds, and a carboxyl functional group. Since the COOH group takes precedence over diene in naming, the compound is named as a derivative of hexanoic acid. The numbering of carbons in carboxylic acid starts with the carboxyl carbon as number one. Thus, the name of the compound is 2,4-dienehexanoic acid.

(c)  is a cyclic diene with the double bonds at carbons 1 and 3. At carbon number 5 there is a diazo substituent. The IUPAC name for the compound is 5-diazo-1,3-cyclopentadiene.

(d) 2,3-Dimethyl-1,4 hexadiene has a straight chain of six carbons with double bonds at carbons 1 and 4. At carbons 2 and 3, there are methyl substitutions. Therefore, the structure of the compound is:

$$\begin{array}{cccccc} & CH_3 & CH_3 & & & \\ & | & | & & & \\ H_2C= & C - & CH - & CH= & CH- & CH_3 \\ 1 & 2 & 3 & 4 & 5 & 6 \end{array}$$

(e) 3,6-Dinitro-1,4 cyclohexadiene is a six carbon cyclic compound with double bonds at carbon numbers 1 and 4. At carbons 3 and 6, there are two nitro  substitutions. The structure of the compound is:

CONJUGATED DIENES

• PROBLEM 9-3

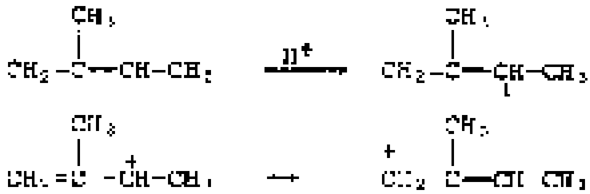
Account for the fact that 2-methyl-1,3-butadiene reacts (a) with HCl to yield only 3-chloro-3-methyl-1-butene and 1-chloro-3-methyl-2-butene; (b) with bromine to yield only 3,4-dibromo-3-methyl-1-butene and 1,4-dibromo-2-methyl-2-butene.

Solution: (a) In acid solution, one of the double bonds in a diene becomes protonated. As in the case of alkenes, protonation will occur to form the most stable cation. 2-methyl-1,3-butadiene is protonated at carbon #1 because it forms the most stable cation; there is electron delocalization involving the remaining double bond which stabilizes the cation:

$$CH_2=\underset{\displaystyle CH_3}{\overset{}{C}}-CH=CH_2 \xrightarrow{H^+} CH_3-\overset{\displaystyle CH_3}{\underset{+}{C}}-CH=CH_2$$

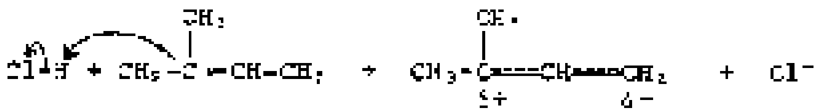
$$CH_3-\overset{\displaystyle CH_3}{C}=CH-\underset{+}{CH_2} \longleftrightarrow CH_3-\overset{\displaystyle CH_3}{\underset{+}{C}}-CH=CH_2$$

Had protonation occurred at carbons # 2 or 3, no electron delocalization would have been possible; the cation would be relatively unstable. Had protonation occurred at carbon # 4, electron delocalization is possible. However, protonation at carbon # 4 distributes the positive charge between a secondary and primary carbon, whereas protonation of carbon # 1 distributes the charge between a tertiary and primary carbon.

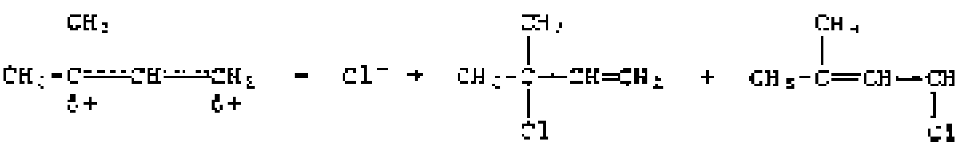


Above: Protonation and stabilization at carbon # 4.

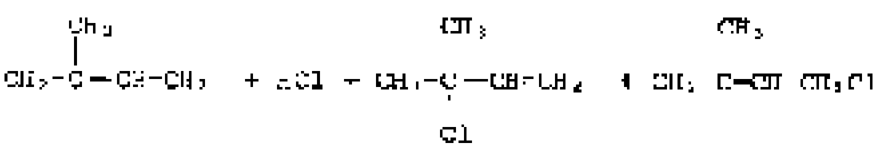
Since tertiary carbon stabilizes a positive charge more than a secondary carbon, the cation formed by protonation of carbon # 1 is more stable than the one formed by protonation of carbon #4. Hence, 2 methyl 1,3 butadiene will be protonated by HCl as follows:



The chloride will react with the diene cation to form two products. This is because the positive charge is distributed between two carbons (# 2 and # 4); hence there are two sites to which the chloride could attach.

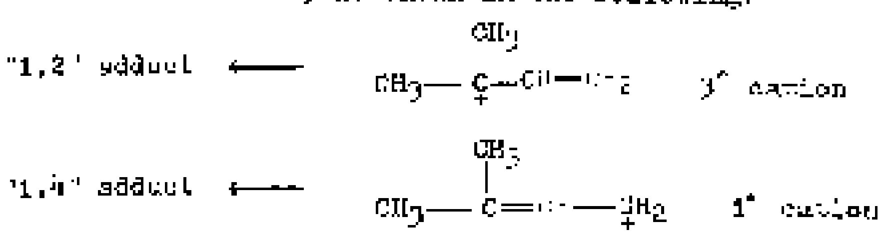


The overall reaction can be written as:



2-methyl-1,3-butadiene	3-chloro-3-methyl-1-butene	1-chloro-3-methyl-2-butene

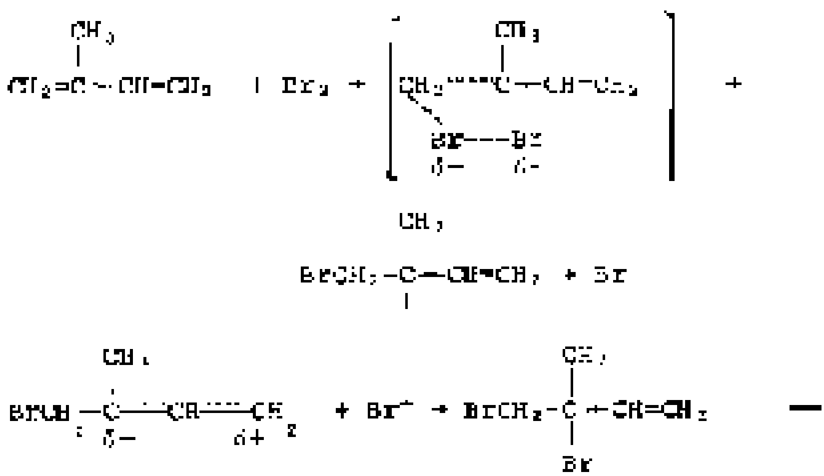
3-Chloro-3-methyl-1-butene is referred to as the "1,2" adduct. This is because addition of hydrogen halide took place at carbons #1 and 2. 1 chloro-3-methyl-2-butene is referred to as the "1,4" adduct because addition occurred at carbons # 1 and 4. The product distribution kinetically will favor the "1,2" adduct over the "1,4" adduct because the former actually resulted from a more stable carbonium ion than the latter, as shown in the following.



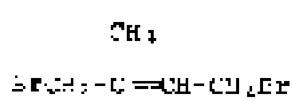
Products:

The product distribution will thermodynamically favor the "1,4" adduct over the "1,2" adduct. This is because an internal double bond ("1,4" adduct) is more stable than a terminal double bond ("1,2" adduct); that is, the more substituted an alkene, the more stable the molecule. Hence, the product distribution depends totally upon the reaction conditions.

(b) Reaction of 2-methyl-1,3-butadiene with bromine is similar to part (a) in that addition occurs at carbons # 1 and 2 and at carbons # 1 and 4. The difference is that in part (a) the diene undergoes a hydrohalogenation whereas in part (b) the diene is halogenated. The electron-rich carbon # 1 - carbon # 2 double bond polarizes the bromine molecule so that a Br^+ is added to carbon # 1. The Br^- can then add to carbon # 2 or carbon # 4. The reaction occurs as:

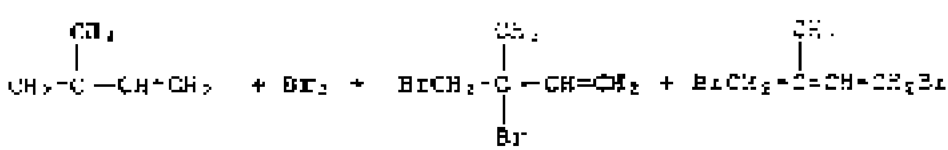


3,4-dibromo-3-methyl-1-butene



1,4-dibromo-2-methyl-2-butene

The overall reaction can be written as:



Draw energy diagrams analogous to Figure 1 for simple addition of H^+ to 1,3-pentadiene and 1,4-pentadiene so as to give the most stable carbonium ions possible. It turns out that the 1,3-isomer is both the more reactive and the more energetically stable diene. Explain how this information can be used to deduce the relative stabilities of the carbonium ions formed from these dienes.

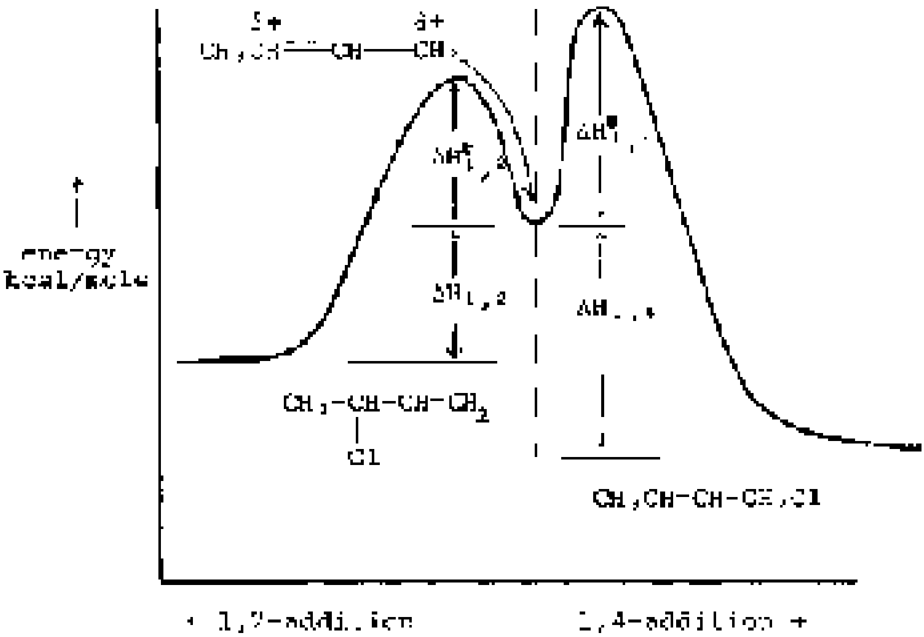


Figure 1. Energy profile for the two possible second steps in the reaction

Solution: Protonation of 1,3-pentadiene occurs so that the resulting positive charge can be delocalized, involving the second double bond's π electrons. This will increase the stability of the carbocation. 1,3-pentadiene will be protonated at carbon # 1 to facilitate electron delocalization which stabilizes the positive charge. This is shown as:

$$CH_2=CH-CH=CH-CH_3 \xrightarrow{H^+} CH_3-\overset{+}{C}H-CH=CH-CH_3 \leftrightarrow CH_3-CH=CH-\overset{+}{C}H-CH_3$$

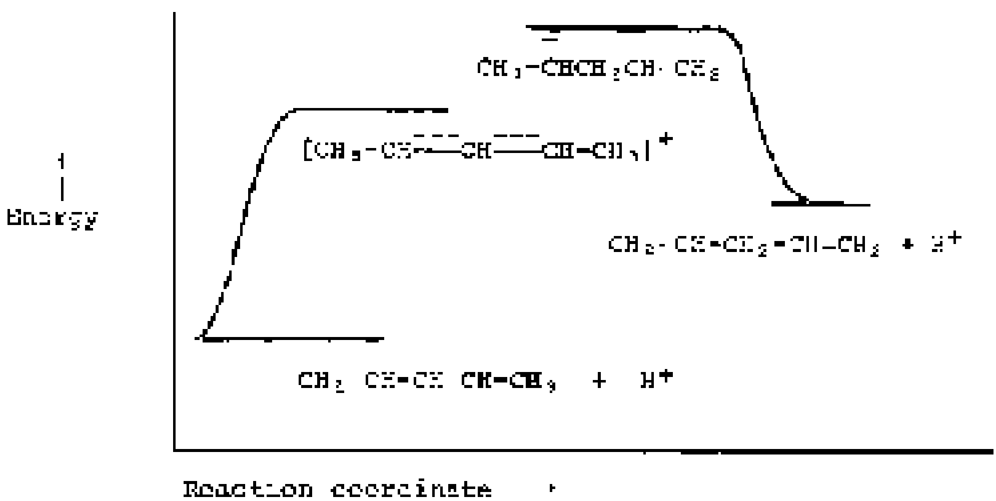
This electron delocalization can alternately be represented as:

$$CH_3-\overset{\delta+}{C}H—CH—\overset{\delta+}{C}H-CH_3$$

Protonation at carbons # 2 and 3 does not occur because the resulting species would be relatively unstable; no electron delocalization could occur. Protonation at carbon # 4 also does not occur despite the fact that the resulting species would undergo electron delocalization. The reason for this is that the positive charge would be distributed between a secondary and a primary carbon, whereas protonation of carbon # 1 results in the positive charge distributed between two secondary carbons. Since secondary carbons can stabilize a positive charge more than primary carbons, protonation will preferentially occur at carbon # 1.

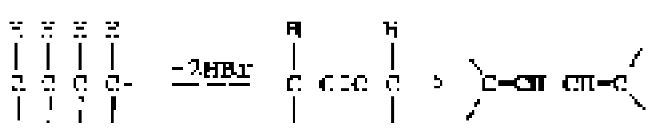
The double bonds of 1,4-pentadiene are equivalent and it will not matter which one becomes protonated. What is important is which carbon of the double bond becomes protonated. Protonation at carbon # 1 gives a secondary carbocation whereas protonation of carbon # 2 gives a primary carbocation. Neither species can undergo electron delocalization. Since secondary carbocations are more stable than primary carbocations, protonation will occur at carbon # 1.

Since 1,3-pentadiene is more reactive to protonation than 1,4 pentadiene, the activation energy for an addition reaction is lower for 1,3-pentadiene than for 1,4-pentadiene. From the problem we know that 1,3 pentadiene is energetically more stable than 1,4-pentadiene. This, coupled with the fact that the activation energy is less for 1,3-pentadiene can lead us to conclude that the cation of the 1,3-diene is more energetically stable than the cation of the 1,4-diene. An energy diagram of the protonation of both dienes is shown below.



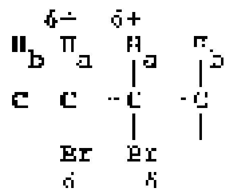
• PROBLEM 9-8

vic-Dibromides usually react with bases to produce more alkyne than conjugated diene. What factor(s) may be controlling this?

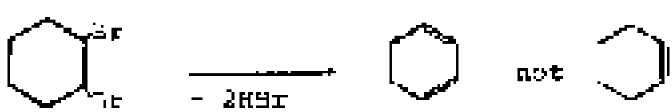


Two exceptions to this behavior are 1,2-dibromocyclohexane and 2,3-dichloro-2,3-dimethylbutane. How do you account for these exceptions?

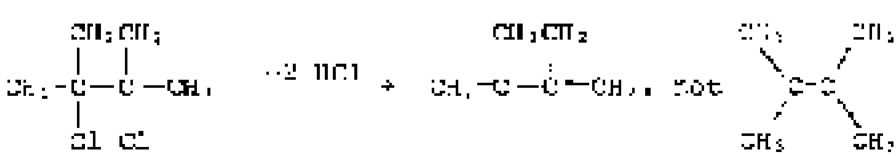
Solution: The hydrogens that are bonded to the carbons bearing the bromine atoms are more acidic than the hydrogens on the adjacent carbon atoms. This is due to the inductive effect of the bromide group [i.e., its powerful electron withdrawing effect makes the hydrogen (H_a in diagram below) partially positively charged].



Hence, the proton H_a is more easily removed from the molecule than the proton H_b. This results in elimination occurring principally between the carbons bearing the bromine atoms. Therefore, triple bond formation is favored over the formation of two separate double bonds. In 1,2-dibromocyclohexane, triple bond formation is impossible due to ring strain. In other words, sp-hybridized carbons cannot exist in a cyclic structure. Thus only the cycloalkadiene is produced from this compound in the presence of base. Therefore:



2,3-Dichloro-2,3-dimethylbutane will form only the conjugated diene (2,3-dimethyl-1,3 butadiene) and not the alkyne because there are no hydrogens on the carbons bearing the chloro groups; elimination will not occur between these two carbons.

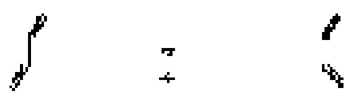


DIELS-ALDER REACTIONS

• PROBLEM 9-6

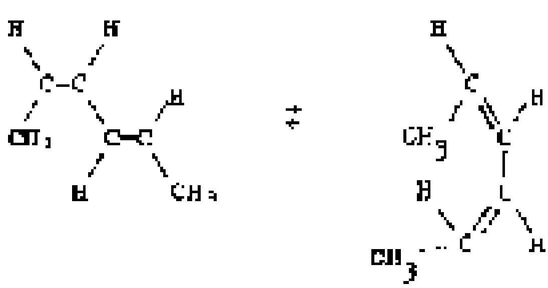
What products would you expect from the Diels-Alder addition of tetracyanoethylene to cis,trans-2,4-hexadiene and cis,cis-2,4-hexadiene? Explain.

Solution: The Diels-Alder reaction is a cycloaddition reaction that occurs between a conjugated diene and an alkene. This reaction is thermally induced and can be called a [4+2] process because it involves the reaction of a system of four π electrons (the diene) with a system of two π electrons (the alkene). The alkene in the Diels-Alder reaction is called the dienophile; the diene reacts with the dienophile to form a cyclohexene derivative. The Diels-Alder reaction has some strict stereochemical requirements. First, the diene must be in the s-cis configuration to react with the dienophile. The s-cis configuration is in equilibrium with the s-trans configuration; they are conformational diastereomers. The equilibrium between the s-cis and s-trans isomers of 1,3-butadiene is shown as:



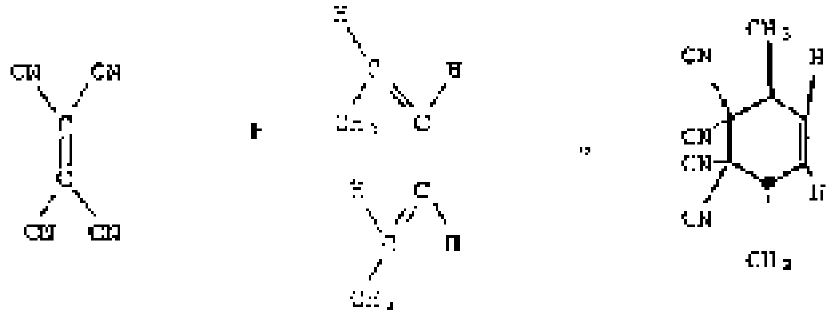
s-trans s-cis

This equilibration takes place by rotation about the carbon-carbon single bond. Another requirement of the Diels-Alder reaction is that the diene must add onto the dienophile in a suprafacial process; that is, both bonds are formed on the same face of the dienophile. The last requirement of the Diels-Alder reaction is that the addition of a diene to a dienophile bearing an unsaturated group will occur in an endo fashion; that is, the unsaturated group will lie near the developing double bond in the diene portion. Cis,trans-2,4-hexadiene exists in s-trans – s-cis equilibrium as shown:



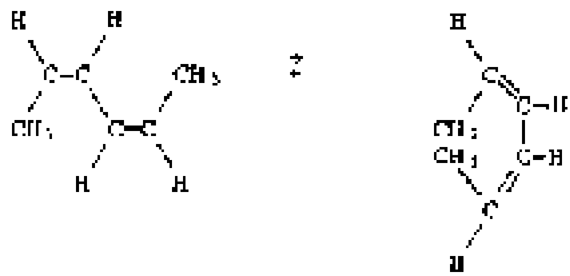
s-trans s-cis

The molecule in the s-cis geometry will react with the dienophile (tetracyanoethylene) in a suprafacial process. Since the dienophile has unsaturated groups (the cyano groups), the reaction should occur in an endo fashion. But note that the dienophile has four equivalent unsaturated groups; hence, it does not matter how the dienophile is oriented for the reaction to occur. Cis,trans-2,4-hexadiene undergoes a Diels-Alder reaction with tetracyanoethylene as shown:



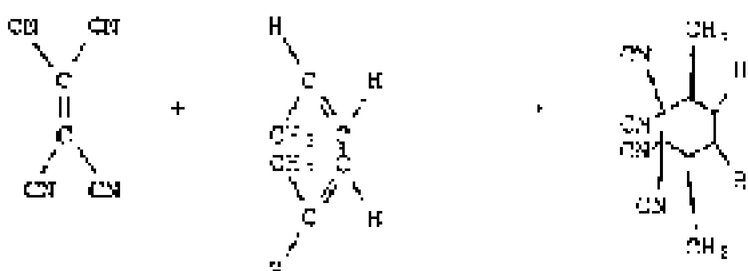
Note: The two methyl groups are trans to each other.

Cis,cis-2,4-hexadiene exists in s-trans - s-cis equilibrium as follows:



s-trans s-cis

The molecule in the s-cis geometry will react with the dienophile (tetracyanoethylene) in a suprafacial process. Cis,cis-2,4-hexadiene undergoes a Diels-Alder reaction with the dienophile as follows:

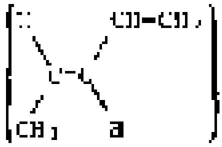


Note: The two methyl groups are cis to each other.

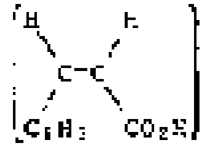
• PROBLEM 9-7

Consider whether formation of ionic rather than di-radical intermediates would affect the argument in favor of a two-step mechanism for the Diels-Alder reaction. What information does the fact that typical Diels-Alder additions occur in the vapor state give about free-radical vs. ionic reaction mechanisms?

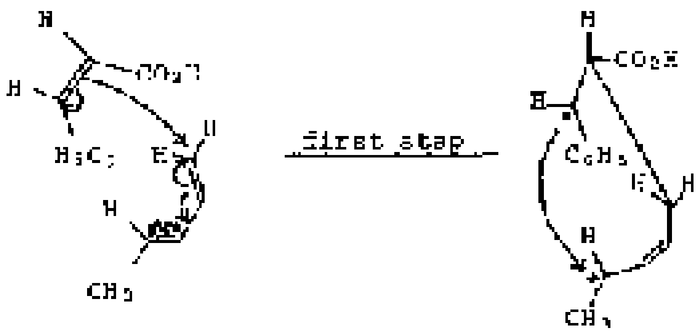
Solution: Let's look at a specific Diels-Alder reaction and proposed mechanisms for ionic and diradical intermediates. The Diels-Alder reaction between trans-piperylene

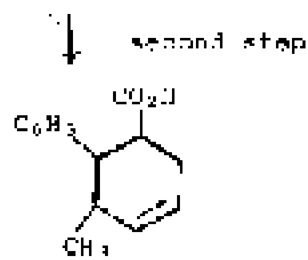


and cis-cinnamic acid



produces only one product due to the stereospecificity of the reaction. A proposed free radical mechanism is:

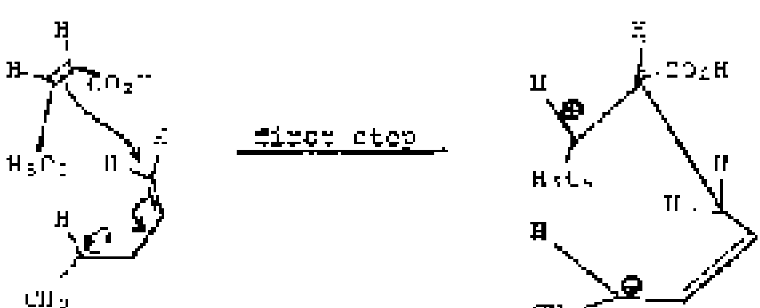


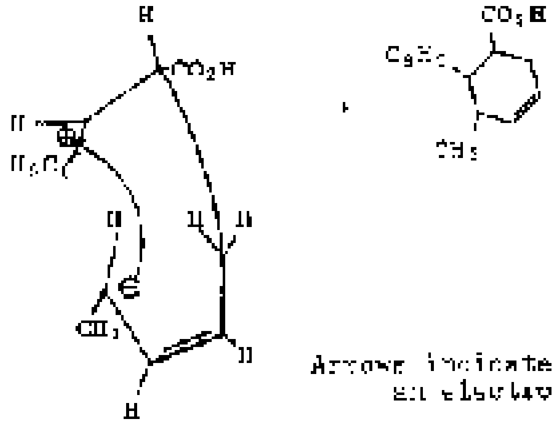


Arrows indicate movement of one electron.

†(Note: All ring substituents are cis to each other.)

The fact that there is only one product formed indicates that the second step occurs faster than does rotation about the carbon-carbon single bonds in the diradical intermediate. The diradical intermediate has a free electron on carbon # 3 (and not carbon # 2) of cis-cinnamic acid because it can undergo resonance stabilization involving the phenyl group. A proposed ionic mechanism for the same Diels-Alder reaction is:





Arrows indicate movement of an electron pair.

As in the free radical mechanism, the ring is formed in the second step faster than rotation about the carbon-carbon single bond. Hence, this explains how only one product is formed. The fact that Diels-Alder reactions can occur in the vapor state suggests that the reaction does not occur through an ionic mechanism. Ions cannot easily exist in the vapor state. The ions must be solvated; that is, the charges must be separated by a solvent. In the vapor phase, there is no solvent. Since free radicals can easily exist in the vapor state, the Diels-Alder reaction seems to occur more through a free radical mechanism than an ionic mechanism.

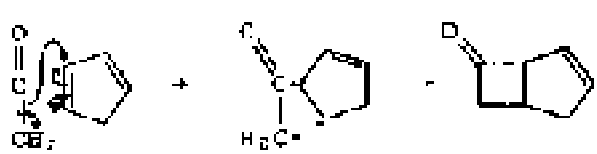
1,2-CYCLOADDITION REACTIONS

PROBLEM 9-6

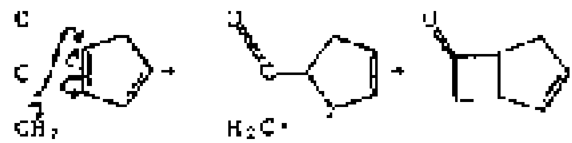
Assuming the mechanism of 1,2-cycloaddition is similar to 1,4-cycloaddition (i.e., the Diels-Alder reaction), is the product obtained from the addition of cyclopentadiene and ketene the expected one? Explain.

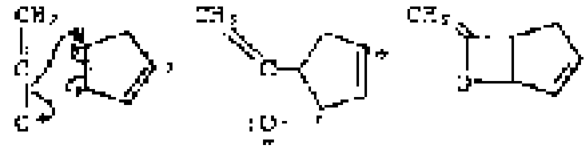
Solution: It is thought that 1,4 cycloaddition reactions proceed through a mechanism involving a diradical intermediate. If we assume that the mechanism of 1,2-cycloaddition is similar to 1,4-cycloaddition, there are four possible products from the reaction of cyclopentadiene and ketene. The reactions and their mechanisms are presented below (arrows show movement of one electron):

I.

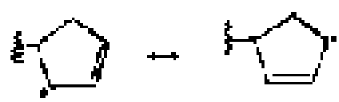


II.

III. 

IV. 

The expected product would be the one that proceeds through the most stable intermediate. The intermediates in reactions III and IV have allylic radicals; they will be stabilized by electron delocalization of the type:

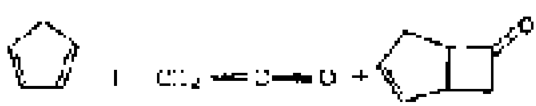


(Note: ξ— represents the rest of the diradical)

The intermediates in reactions I and II are less stable than those in reactions III and IV; this is because I and II intermediates do not undergo resonance stabilization. The product from reaction III will be expected over the product from reaction IV because

$$|\Delta H_{III}| > |\Delta H_{IV}| .$$

This means that reaction III is more exothermic than reaction IV, and the product of reaction III is thermodynamically more stable than the product of reaction IV. Hence, the expected product is the one formed in reaction III. This is in fact the actual product obtained from the 1,2-cycloaddition reaction of ketene with cyclopentadiene.

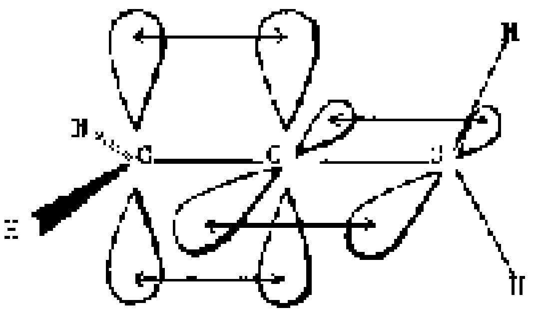


ALLENES

• PROBLEM 9-2

(a) Make a model of allene, $CH_2=C=CH_2$, a cumulated diene. What is the spatial relationship between the pair of hydrogens at one end of the molecule and the pair of hydrogens at the other end? (b) Substituted allenes of the type RCH=C=CHR have been obtained in optically active form. Is this consistent with the shape of the molecule in (a)? Where are the chiral centers in the substituted allene? (c) Work out the electronic configuration of allene. (Hint: How many atoms are attached to the middle carbon? To each of the end carbons?) Does this lead to the same shape of molecule that you worked out in (a) and (b)?

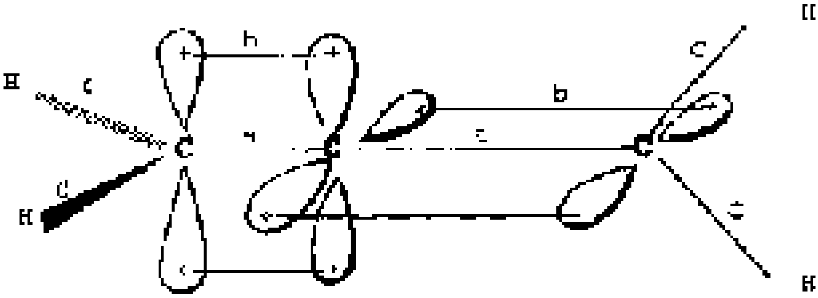
Solution: (a) Allene is the simplest cumulated diene; its molecular formula is C_3H_4. The two pairs of methylene hydrogens lie in planes that are perpendicular to each other. This spatial relationship is the only one that will allow for efficient overlap of 2p-2p orbitals in the π bonds.



Above: Diagram showing 2p 2p orbital overlap in allene.

(b) Compounds of the type RCH=C=CHR have the same molecular shape as allene. This is because the carbons involved in π bonding for allene have the same hybridization as those in RCH=C=CHR. There are no chiral carbons in RCH=C=CHR, but the molecule itself is chiral; that is, there is no plane of symmetry in the molecule. As the molecule is chiral, it will be optically active. Note that a compound of the type $R_2C=C=CH_2$ is achiral because there are two planes of symmetry (R_2C- plane and the $-CH_2$ plane).

(c) Each of the end carbons in allene is bonded to three atoms and possesses one double bond. All chemical double bonds contain a sigma (σ) bond and a pi (π) bond. The π bond involves the overlap of two 2p electron orbitals. The remaining three bonds of the end carbons (the σ bond of the double, and the two single bonds to the hydrogens) must be hybridized. The orbitals involved in bonding for carbon are one 2s orbital and three 2p orbitals. Since for each end carbon in allene one of the 2p orbitals are involved in π bonding, this leaves one 2s orbital and two 2p orbitals to be involved in the hybridization. The end carbons in allene are sp^2 hybridized carbons; there are three $2sp^2$ orbitals involved in σ bonds and one 2p orbital involved in a π bond. The trigonal planar configuration of the end carbons' orbitals (as seen in the diagram in part a) supports our conclusion; the end carbons are sp^2 hybridized. The middle carbon is bonded to two atoms and has two double bonds; that is, it has two σ bonds and two π bonds. Each π bond involves a 2p orbital. The remaining two bonds of the middle carbon must be involved in orbital hybridization. Since two 2p orbitals have been accounted for, it must be the remaining 2s orbital and 2p orbital that are hybridized. The middle carbon is sp hybridized; there are two 2sp orbitals involved in σ bonding and two 2p orbitals involved in π bonding. The linear configuration of the orbitals (as seen in the diagram in part a) supports our conclusion; the middle carbon is sp hybridized. Below is a diagram of allene indicating the orbitals involved in the different types of bonds:



$a = \sigma\ 2sp^2 - 2sp$

$b = \pi\ 2p - 2p$

$c = \sigma\ 1s - 2sp^2$

These hybridizations of the carbons in allene lead to the same shape that we worked out in part (a) and part (b).

• PROBLEM 9-10

(a) Predict the heat of hydrogenation of allene, $CH_2{=}C{=}CH_2$. (b) The actual value is -71 kcal. What can you say about the stability of a cumulated diene?

Solution: (a) The general range of heats of hydrogenation of alkenes is from -27 to -31 kcal/mole. Here we are dealing with the hydrogenation of double bonds between two sp^2-hybridized carbons and an sp hybridized carbon. We will assume a ΔH (heat of hydrogenation) value of -28 to -30 kcal/mole for each double bond in allene.

$$CH_2{=}C{=}CH_2 + 2H_2 \rightarrow CH_3CH_2CH_3$$

allene → propane

$\Delta H = (2 \times -28)$ to (2×-30)

$\Delta H = -56$ to -60 kcal/mole.

(b) The lower ΔH value means that the reaction is more exothermic than predicted; there is more energy actually released than we expected. This indicates that allene is more reactive, and hence more unstable relative to compounds having conjugated or isolated double bonds.

POLYMERIZATION

• PROBLEM 9-11

Formulate chain initiation, propagation, and termination steps for the polymerization of butadiene by a peroxide catalyst. Consider carefully possible structures for the growing-chain radical. Show the expected structure of the polymer.

Solution: Peroxides are very unstable compounds which are often used as a catalyst for free radical polymerization reactions. The peroxide breaks down into two alkoxy radicals as shown:

$$ROOR' \longrightarrow RO\cdot + R'O\cdot$$

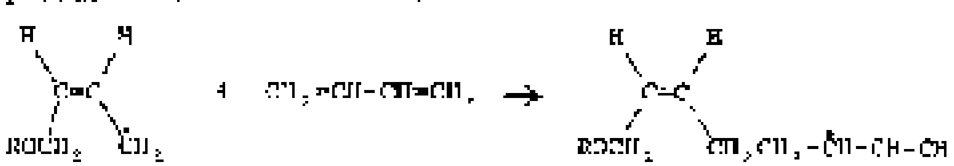
peroxide   alkoxy radicals

This is the initiation step of a free radical polymerization process. Free radical polymerizations, like all addition polymerization reactions, produce head to tail polymerization; that is, the growing end of the polymer is the most stable possible radical. In the case of 1,3-butadiene the alkoxy radical attacks an end carbon and not an internal carbon. This is because attack of an end carbon forms a resonance stabilized free radical whereas attack of an internal carbon forms a radical with no such stabilization. Hence, the end carbon will be attacked by the alkoxy radical to form the more stable species. This is shown as:

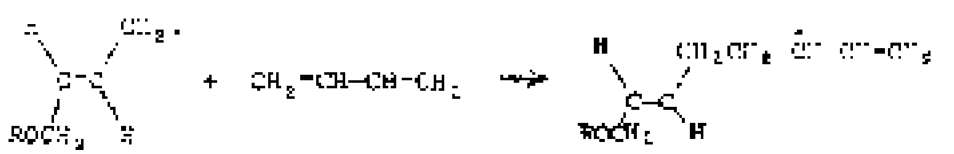
$$RO\cdot + CH_2{=}CHCH{=}CH_2 \rightarrow ROCH_2{-}\dot{C}H{-}CH{=}CH_2 \leftrightarrow ROCH_2{-}CH{=}CH{-}\dot{C}H_2$$

The resulting radical will attack an end carbon of another 1,3 butadiene molecule. There are three possible products which all depend on where the end carbon of the diene is bonded to the radical. Note that the free electron of the radical $ROCH_2\dot{C}HCH{=}CH_2$ distributes its time between carbons # 2 and 4 (where carbon # 1 is the $RO\text{ }CH_2-$ carbon).

Polymerization can occur as a 1,2-addition or a 1,4-addition; that is, the radical can attack a diene molecule with the free electron on either carbon # 2 or carbon # 4. This accounts for two possible polymerization products, but there is a third one. Note that the growing polymer in 1,4-addition can have two different configurations: cis and trans. The radical can add to a diene by 1,4-addition to produce a trans or a cis product:



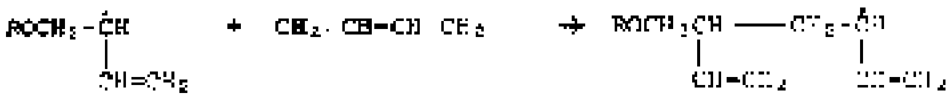
cis



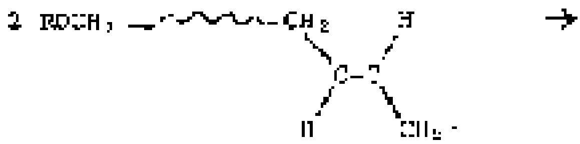
trans

1,4-addition

The radical adds to the diene by 1,2 addition as shown:



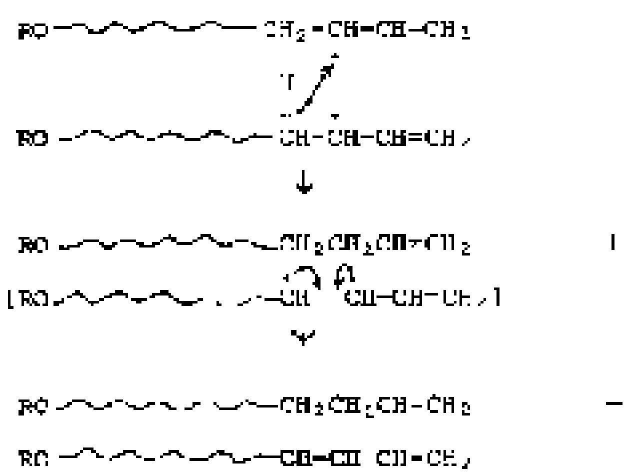
The chain lengthening of the polymeric radical is the propagation step. The polymer can be formed as any combination of 1,2-, 1,4-cis or 1,4-trans additions; the polymer can be a result of one or all of the three addition processes. The termination step of a polymerization reaction puts a stop to the growing polymer. In free radical polymerization, the termination step rids the growing polymer of its free electron. This generally proceeds by any one of three different methods: dimerization, disproportionation and abstraction. Dimerization involves the joining of two growing polymer radicals. It can be shown as:



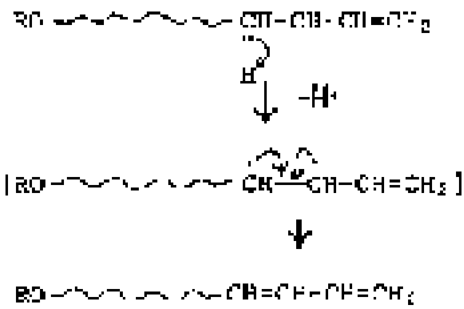
growing polymer radical

polymer (formed by dimerization)

Disproportionation reactions involve the transfer of a hydrogen radical from one growing polymer radical to another. This results in the joining of a hydrogen radical with a growing polymer radical and the formation of a carbon-carbon bond in the other growing polymer radical. This is shown as:



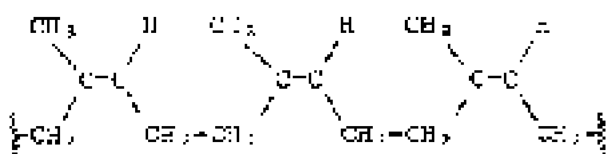
Abstraction involves the loss of a hydrogen atom to form a carbon-carbon bond. This is shown as:



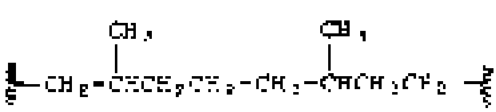
• PROBLEM 9-12

Gutta percha is a non-elastic naturally-occurring polymer used in covering golf balls and underwater cables. It has the same formula $(C_5H_8)_n$, and yields the same hydrogenation product and the same ozonolysis product as natural rubber. Using structural formulas, show the most likely structural difference between Gutta percha and rubber.

Solution: Natural rubber or poly-cis-isoprene has the structure:



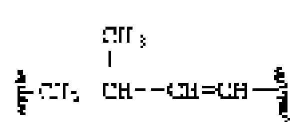
The hydrogenation product of natural rubber is poly-2-methylbutane or poly-isopentane:

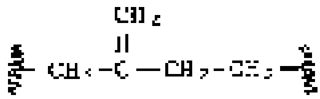


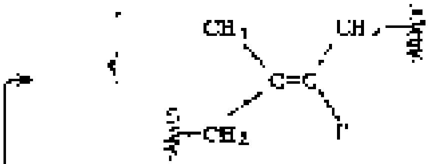
Hydrogenation of Gutta percha yields the same product. Hence, there are six possible structural formulas that correspond to the molecular formula of Gutta percha, $(C_5H_8)_n$. They are:

cis and trans isomers

cis and trans isomers





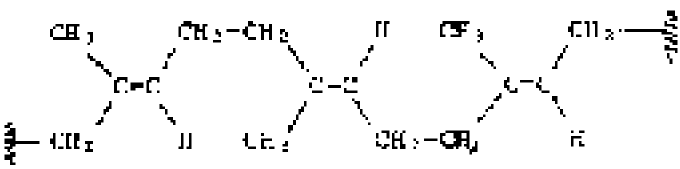


This is the trans isomer of natural rubber (that is, poly-trans-isoprene).

Ozonolysis of natural rubber yields 4-oxo pentanal:

$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}H$$

Since ozonolysis of Gutta percha gives the same product as natural rubber, the only structural formula for Gutta percha (from our list of possibles) would be the trans isomer of natural rubber. Hence, Gutta percha is also known as poly-trans-isoprene.

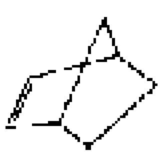


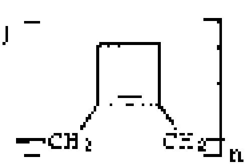
SYNTHESIS

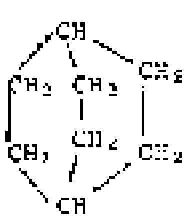
• PROBLEM 9-13

Show the last step in a synthesis of each of the following substances (give approximate reaction conditions):

(a) $CH_2=CHCH=CH_2$

(b) 

(d) 

(c) 

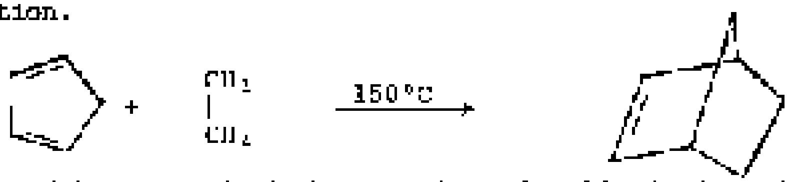
(e) $\left[CH_2-\overset{F}{\overset{|}{C}}=CH-CH_2\right]_n$

Solution: (a) We can synthesize the desired product, 3-bromo-1-butene, by reacting 1,3-butadiene with hydrobromic acid. There will be competition between the 1,2 and 1,4 addition processes. Since our desired product is a result of 1,2-addition, we want to set the reaction conditions so that the 1,2 addition product is the major one. Since the 1,2-addition product is kinetically more stable than the 1,4-addition product, we would want to slow down the reaction so that it is easy for "1,2"-adduct and difficult for "1,4"-adduct to form. We can slow the reaction by maintaining a low temperature.

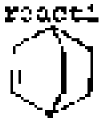
$$CH_2{=}CH\,CH{=}CH_2 \xrightarrow[0°C \text{ or less}]{HBr}$$

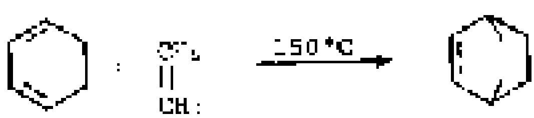
$$CH_2{=}\ CH{-}CHBr{-}CH_3 \qquad \text{(main product)}$$

(b) Many bridged bicyclic alkenes can be prepared by a Diels Alder reaction. The desired product can be prepared by a Diels-Alder reaction involving cyclopentadiene and ethylene. Since Diels-Alder reactions are thermally induced, a high temperature must be maintained throughout the reaction.

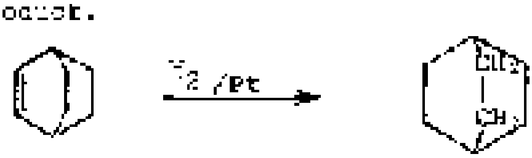


(c) Catalytic hydrogenation of bridged bicyclic alkenes will yield bridged bicyclic alkanes (which is our desired product). A Diels-Alder reaction between 1,3-cyclohexadiene

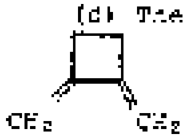
and ethylene will yield  :

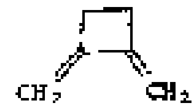


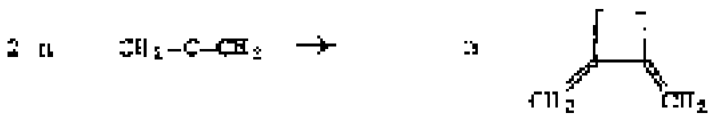
If this compound underwent catalytic hydrogenation, it would form our desired product.

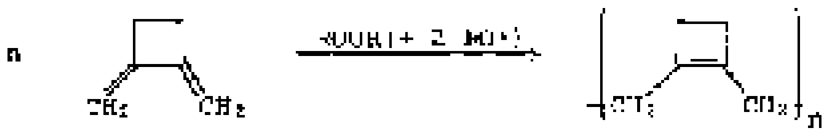


(d) The desired product is formed by polymerization of

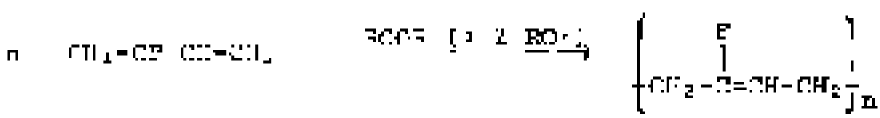


. This compound is made by a [2+2] cycloaddition reaction (a system with two π electrons acting upon another system with two π electrons). Allene will react with itself to produce  Polymerization can be accomplished by using peroxides. A peroxide will break down to an alkoxy free radical; free radical polymerization will then occur.





(c) The desired product can be made by the free radical polymerization of $CH_2=CF\ CH=CH_2$. The desired product is one that results from a 1,4-addition process.



SPECTROSCOPY

• PROBLEM 9-14

Sketch out the n.m.r. spectra, including spin-spin splitting (if any), expected for the following compounds:

(a) $BrCH=C=CH_2$
(b) $CH_3CH_2C\equiv CH$
(c) $(CH_3)_2CCH=C=CHCH_2CH_3$

Solution: Generally, we can expect spin-spin splitting to occur only between non-equivalent adjacent protons. When there is a significant amount of π bond interaction in a molecule, non-equivalent protons that are separated by one carbon (where there is significant π bonding) will undergo spin-spin splitting.

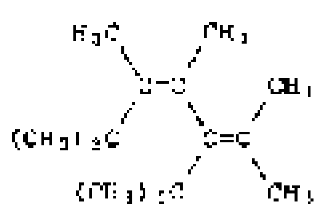
(a) Cumulated dienes have significant π bond interaction about the -C- carbon. As a result, there will be spin spin splitting between the protons adjacent to the central carbon. The methylene ($=CH_2$) protons will be split into a doublet by the bromomethylene ($BrCH=$) proton. The methylene signal will be near 5.5 δ due to deshielding by the nearby π electrons. The bromomethylene proton will be split into a triplet by the two methylene protons. The bromomethylene proton will absorb near 6.5 δ. It is upfield from the methylene signal because of the shielding effect of the bromo group.

(b) Alkynes also have significant π bond interaction about the -C≡C- bond. The n.m.r. spectrum of terminal alkynes will show spin spin splitting between the terminal proton (-C≡C-H) and the $-CH_2-C\equiv C-$ protons. The n.m.r. spectrum of 1-butyne has the -C≡C-H proton split into a triplet by the two methylene protons. The -C≡C-H signal will be near 2.4 δ. This is due to the deshielding effect of the π electrons. The methyl protons will be split into a triplet by the two methylene protons. The methyl group will absorb at the characteristic value of 0.9 δ. The methylene protons will be split by the non-equivalent methyl and terminal protons. The methylene protons are split into a doublet by the terminal proton; these in turn are split into a quartet by the three methyl protons. The signal that results is an octet. It occurs near 1.5 δ, which is slightly down field from the characteristic methylene absorption. This is because of the deshielding effect of the π electrons.

(c) This compound is a cumulated diene and will have the same type of splitting described in part (a). The methyl protons of the t-butyl group will not be split and will occur as a singlet near 0.9 δ. The t-Bu-CH=C= proton will be split into a doublet by the =C=CH- proton and will absorb near 5 δ. The =C=CH- proton will be split into a doublet by the t-Bu-CH=C= proton. This in turn will be split into a triplet by the two methylene protons (=C=CH-CH_2-). As a result, the =C=CH- signal will appear as a sextet. This signal occurs near 5 δ and is slightly upfield (lower δ value) relative to the t-Bu-CH=C= signal. This is because the =C=CH- proton is closer to the oxygen and will be shielded more than the t-Bu-CH=C= proton. The methylene signal will be split into a doublet by the =C=CH- proton; it will occur near 3.1 δ. This is because the methylene is adjacent to the electron withdrawing oxygen. The $-OCH_3$ protons will not be split and will occur at 3.3 δ.

• PROBLEM 9-13

Why is the electronic spectrum of the compound shown below more like that of tetramethylethylene than that of hexamethyl-1,3-butadiene? (Hint: Build a model.)



Solution: As the electron delocalization in a molecule increases, the maximum wavelength absorption in the electronic spectrum will also increase. The electron delocalization of a conjugated diene such as 1,3-butadiene is great enough so that the electronic spectrum will not appear as "two ethylenes." That is, 1,3-butadiene will have its own characteristic electronic spectrum and constitutes a different chromophore from a compound with two isolated double bonds. In the compound shown above (Z-2,4,5,6,6-pentamethyl-3-t-butyl 2,4 heptadiene), the steric repulsion between the t-butyl groups prevents coplanarity of the double bonds. As a result, there is some loss of electron delocalization. The loss in electron delocalization causes a decrease in the maximum wavelength absorption in the electronic spectrum. This decrease in absorption is great enough that the electronic spectrum of the compound is more like an ethylene chromophore spectrum than a conjugated diene chromophore spectrum. Hence, the electronic spectrum of the compound is more like that of tetramethylethylene than that of hexamethyl 1,3-butadiene.

CHARACTERIZATION TESTS

• PROBLEM 9-10

On the basis of physical properties, an unknown compound is believed to be one of the following:

n-pentane (b.p. 36°)	1-pentyne (b.p. 40°)
2-pentene (b.p. 36°)	methylene chloride (b.p. 40°)
1-chloropropene (b.p. 37°)	3,3-dimethyl-1-butene (b.p. 41°)
trimethylethylene (b.p. 39°)	1,3-pentadiene (b.p. 42°)

Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation and cleavage. Tell exactly what you would do and see.

Solution: We can separate the saturated compounds from the unsaturated compounds by testing with $KMnO_4$ (potassium permanganate). Potassium permanganate is a strong oxidizing agent and will oxidize alkenes to vicinal diols and alkynes to carboxylic acids. Manganese dioxide (MnO_2) is the reduced $KMnO_4$ product; $KMnO_4$ is purple and MnO_2 is brown. Hence, all the compounds except n-pentane and methylene chloride will show a color change in $KMnO_4$ solution (purple → brown). To distinguish between methylene chloride and n-pentane, we will test each for the presence of halogen; only methylene chloride should give a positive test. In this case, we can't just add silver ion and expect to see a silver chloride precipitate from methylene chloride. We must first liberate chloride ion from methylene chloride. This can be accomplished by using an S_N2 reaction: the chloride is a good leaving group and will go into solution. n-Pentane has no good leaving groups and will not undergo an S_N2 reaction. If both compounds are treated with silver hydroxide, methylene chloride will show a white silver chloride precipitate and n-pentane will not.

CH_3Cl_2 $\quad Ag^{\oplus}OH^{\ominus} \rightarrow$ $\quad Cl-CH_2OH$ $+$ $Ag^{\oplus}Cl^{\ominus}$

colorless $\qquad\qquad\qquad\qquad$ white

$CH_3CH_2CH_2CH_2CH_3$ $+$ $Ag^{\oplus}OH^{\ominus} \rightarrow$ $\quad$ no reaction

colorless $\qquad\qquad\qquad\qquad$ colorless

Now we can turn to the unsaturated compounds. Of these, 1-pentyne is the only alkyne. Terminal alkynes (R-C≡C-H), when treated with ammoniacal silver nitrate ($Ag^{\oplus}(NH_3)_2NO_3^{\ominus}$), will give a precipitate of silver acetylide (R-C≡C-Ag). 1-Pentyne can be distinguished from the other unsaturated compounds by this method.

$$CH_3CH_2CH_2-C\equiv CH \xrightarrow{Ag^{\oplus}(NH_3)_2NO_3^{\ominus}} CH_3CH_2CH_2-C\equiv C-Ag$$

solution $\qquad\qquad\qquad\qquad$ precipitate

Of the remaining compounds, 1-chloropropene is the only one that has a halogen. In the presence of silver amide in ammonia, an elimination reaction will occur to yield propyne; this will liberate chloride ion into the solution. As a result, the white silver chloride precipitate will form:

$$Cl-CH=CHCH_3 \xrightarrow[NH_3]{Ag^{\oplus}NH_2^{\ominus}} HC\equiv C-CH_3 + Ag^{\oplus}Cl^{\ominus}$$

colorless $\qquad\qquad\qquad\qquad$ white

We are now left with four compounds; three are alkenes and one is a diene. By quantitative catalytic hydrogenation, we can identify the diene (1,3-pentadiene). Quantitative catalytic hydrogenation is accomplished by treating the compound with a known amount of hydrogen gas in the presence of a catalyst (Pd, Ni or Pt). After the reaction is completed, the amount of hydrogen gas remaining is measured. From this it can be determined how many moles of H_2 gas was consumed by the compound. All the compounds will be reduced to an alkane. 1,3-pentadiene will consume two moles of H_2 gas whereas the other compounds will consume one mole of H_2 gas.

$$CH_2=CH-CH=CHCH_3 + 2\ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_2CH_3$$

1,3-pentadiene

$$CH_3CH=CHCH_2CH_3 + 1\ H_2 \xrightarrow{Pt} CH_3CH_2CH_2CH_2CH_3$$

2-pentene

$$(CH_3)_2C=CHCH_3 + 1\ H_2 \xrightarrow{Pt} (CH_3)_2CHCH_2CH_3$$

trimethylethylene

$$CH_2{=}CHC(CH_3)_3 \quad + \quad 1\ H_2 \xrightarrow{Pt} CH_3CH_2C(CH_3)_3$$

3,3-dimethyl-1
butene

Of the three remaining compounds, two will form methyl carbonyl compounds $\left(\overset{O}{\overset{|}{C}}{-}CH_3\right)$ upon ozonolysis with reductive workup. In general, methyl carbonyl compounds can be identified by using an iodoform reaction. The iodoform reaction is one between methyl carbonyl compounds and iodine in alkaline solution. The methyl group is converted to $-CI_3$, which then leaves the molecule when a hydroxide ion attacks the carbonyl carbon. This produces a yellow precipitate, iodoform (CHI_3).

$$\overset{O}{\overset{||}{C}}CH_3 \quad + \quad 3\ I_2 \xrightarrow{OH^{\ominus}} \overset{O}{\overset{||}{-C}}CI_3 \quad + \quad 3\ I^{\ominus}$$

$$\overset{O}{\overset{||}{C}}{-}CI_3 \quad + \quad {}^{\ominus}OH \rightarrow \overset{O}{\overset{||}{-C}}{-}OH \quad + \quad {}^{\ominus}CI_3$$

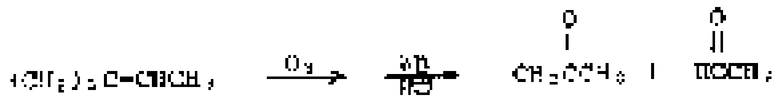
$$\overset{O}{\overset{||}{-C}}OH \quad + \quad {}^{\ominus}CI_3 \rightarrow \overset{O}{\overset{||}{-C}}{-}O^{\ominus} \quad + \quad \underset{\text{yellow}}{HCI_3}$$

3,3-Dimethyl-1-butene will not yield a methyl carbonyl compound upon ozonolysis with reductive workup. Hence, it will subsequently not give a positive iodoform reaction. The other two compounds, after ozonolysis, will give positive iodoform reactions.

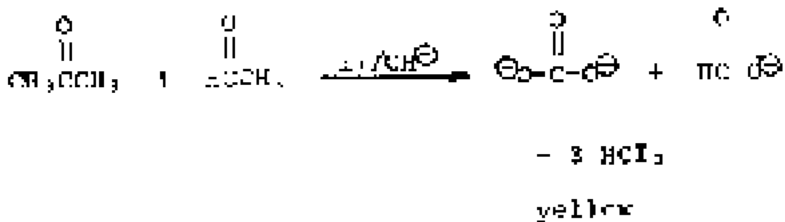
$$\underset{\text{3,3-dimethyl-1-butene}}{CH_2{=}CHC(CH_3)_3} \xrightarrow{O_3} \xrightarrow[H^{\oplus}]{Zn} \overset{O}{\overset{||}{HCH}} \quad + \quad \overset{O}{\overset{||}{HCC}}(CH_3)_3 \xrightarrow{I_2/OH^{\ominus}} \text{no reaction}$$

$$\underset{\text{2 pentene}}{CH_3CH{=}CHCH_2CH_3} \xrightarrow{O_3} \xrightarrow[H^{\oplus}]{Zn} CH_3\overset{O}{\overset{||}{CH}} \quad + \quad \overset{O}{\overset{||}{HCC}}H_2CH_3$$

$$\xrightarrow{I_2/OH^{\ominus}} \underset{\text{yellow}}{HCI_3} \quad + \quad \overset{O}{\overset{||}{HC}}{-}O^{\ominus}$$



trimethylethylene



Of the two remaining compounds, 2-pentene and trimethylethylene, only 2-pentene will show an upfield triplet and downfield quartet (typical of ethyl groups) in its n.m.r. spectrum.

CHAPTER 10

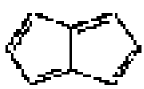
BENZENE

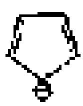
AROMATIC CHARACTER AND PROPERTIES

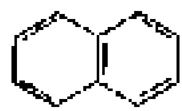
• PROBLEM 10-1

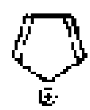
Which of the following structures are aromatic according to Hückel's rule?

(a) 

(b) 

(c) 

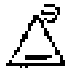
(d) 

(e) 

Solution: Aromatic systems are found to be unusually stable. These systems are composed of cyclic structures with conjugated double bonds. Conjugated double bonds are sets of bonds which alternate between single and double bonds. Conjugated double bonds are seen in benzene.

Benzene

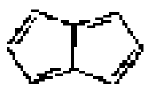
Not all conjugated systems are aromatic, though. Aromaticity can be determined by using Hückel's rule. Using theoretical data, Hückel formulated the $4n + 2$ rule which states that exceptional resonance stability is to be expected with π electron systems containing $4n + 2$ electrons in planar, cyclic structures, where n is an integer. This applies to a continuous series of p orbitals which are capable of effective overlapping. For example, benzene has 6, or $4(1) + 2$ (with $n=1$) π electrons. Therefore, according to Hückel's rule, benzene is aromatic and is stabilized by resonance.

(a)  This structure is called the cyclopropenyl anion. In this system two π electrons are donated by the double bond and two by the lone pair. This gives a total of four π electrons. Solving for n:

$$4n + 2 = 4$$

$$n = 0.5.$$

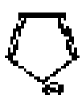
n is not an integer and therefore the system is not aromatic.

(b)  There are four double bonds each contributing two π electrons. The total number of π electrons is eight. Solving for n:

$$4n + 2 = 8$$

$$n = 1.5$$

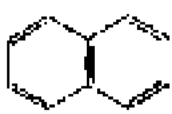
Therefore, the system is not aromatic.

(c)  In this system four π electrons are donated by the double bonds and two by the lone pair. The total number of π electrons is six. Solving for n:

$$4n + 2 = 6$$

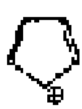
$$n = 1.0$$

Because n is an integer, this system is aromatic.

(d)  This ten carbon structure is known as napthalene. There are two π electrons contributed by each double bond. The total number of π electrons is ten. Solving for n:

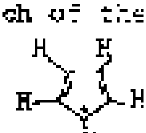
$$4n + 2 = 10 \quad \text{and} \quad n = 2$$

Napthalene is aromatic because n is an integer.

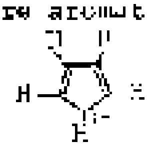
(e)  There are four π electrons in this system, two donated by each double bond. As has already been shown, systems containing four π electrons are not aromatic.

• PROBLEM 15-2

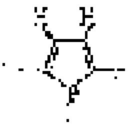
Which of the following are aromatic?

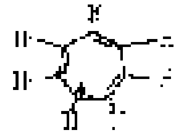
(a) 

Cyclopentadienyl cation

(b) 

Cyclopentadienyl anion

(c) 

(d) 

Cyclopentadienyl radical | Cycloheptatrienyl cation

Solution: In order to answer this question, a knowledge of the properties of aromatic compounds is necessary.

An aromatic compound is a cyclic structure that contains continuous π electron clouds above and below the plane of the molecule. The π clouds must also contain a total of 4n+2 π electrons, where n can be any integer. This requirement is called the 4n+2 rule or Hückel's rule and is derived from quantum mechanics. Thus, to determine whether any given compound is aromatic, first inspect the structure to see if it is cyclic and planar. Then determine the number of π electrons and see if all these satisfy Huckel's rule.

(a) The cyclopentadienyl cation possesses a total of four π electrons. Hence, it does not agree with Huckel's 4n + 2 rule and therefore is not an aromatic compound.

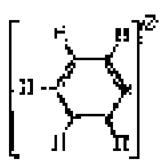
(b) All five carbons of the cyclopentadienyl anion are sp2-hybridized and the compound therefore lies in a plane. Six π electrons are delocalized about the ring, one being responsible for the net negative charge. According to Huckel's rule, then, the compound is aromatic.

(c) The cyclopentadienyl radical possesses five π electrons, one of which is a unpaired electron. Since five electrons do not agree with Huckel's rule, the compound is not aromatic.

(d) The cycloheptatrienyl cation has a total of six π electrons which account for the compound's aromaticity.

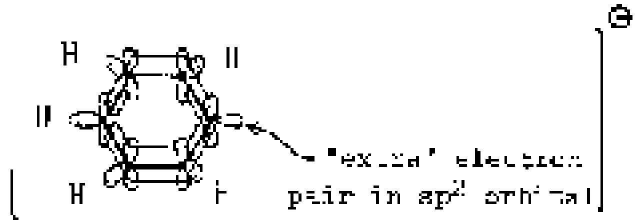
• **PROBLEM** 10-3

The anion of benzene $C_6H_5^-$, is aromatic although it contains a total of eight "free" electrons. How do you account for this?



phenyl anion

Solution: Let us first look at the orbital representation of the phenyl anion:



From this, we can see that the "extra" electron pair is in an orbital perpendicular to the π cloud. Since only electrons in the plane of the π cloud can participate in it, these two "extra" electrons cannot participate in the π cloud. In effect, there are only six electrons in the π cloud, which is an aromatic number, according to Hückel's $4n + 2$ rule for aromaticity (for $n = 1$).

● PROBLEM 10-4

For which of the following might you expect aromaticity (geometry permitting)?

(a) The annulenes containing up to 20 carbons. (Annulenes are monocyclic compounds of the general formula $[-CH=CH-]_n$.)
(b) The monocyclic polyenes C_8H_8, $C_9H_9^+$, $C_9H_9^-$.

Solution: (a) To be aromatic, a cyclic compound must follow Hückel's $4n + 2$ Rule for π electrons.

$n = 1 : 4n + 2 = 6$ π electrons

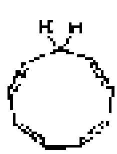
$n = 2 : 4n + 2 = 10$ π electrons

$n = 3 : 4n + 2 = 14$ π electrons

$n = 4 : 4n + 2 = 18$ π electrons

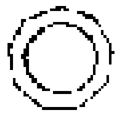
Therefore, the annulenes that are aromatic are: [6] annulene (benzene); [10] annulene; [14] annulene; [18] annulene. (The number in the bracket indicates the number of π electrons.) For [10] and [14] annulenes, the geometry is unfavorable due to the crowding of hydrogens inside the ring. This crowding prevents planarity and would therefore interfere with the formation of the π cloud. The use of models is highly recommended, in order to see the crowding of hydrogens inside the ring.

(b) C_8H_8:

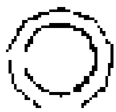


There are only 8 π electrons, therefore this system is not aromatic (see part a - Hückel's Rule).

$C_9H_9^+$



There are only 8 π electrons, which is not an aromatic number.



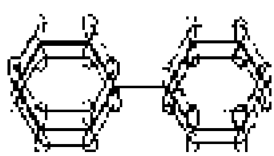
$C_9H_9^-$

The pictorial representation for $C_9H_9^-$ is the same as that for $C_9H_9^+$ (see above), except there is now 10 π electrons in a circle, instead of 8. Ten π electrons fit Hückel's rule for n = 2. Therefore this anion is aromatic.

• PROBLEM 10-8

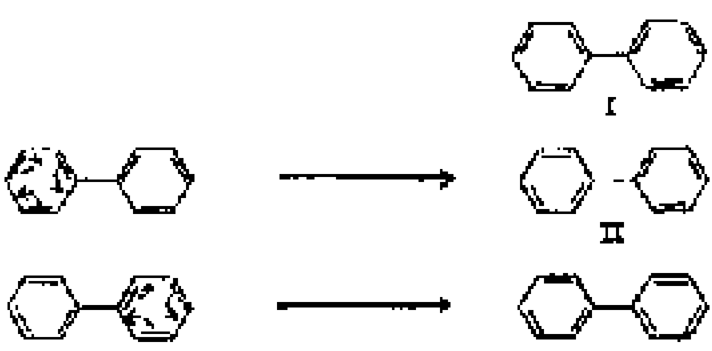
> Biphenyl, $C_6H_5C_6H_5$, has a conjugation energy of 71 kcal/mole. (a) Draw an atomic orbital picture of biphenyl. (b) What are its most important resonance contributing structures? (c) Estimate the heat of hydrogenation of biphenyl.

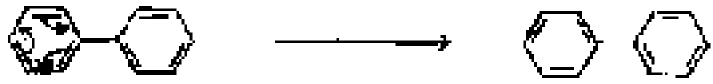
Solution: (a) The atomic orbital picture should show the p orbitals in a π cloud.



Biphenyl

(b) The most important resonance structures are the ones without separation of charge. We will use the arrow convention of moving electrons to get the different resonance structures.





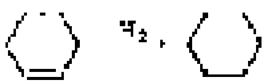
IV.

All other structures will result in a separation of charge.

(c) The heat of hydrogenation is the quantity of heat evolved when one mole of an unsaturated compound is hydrogenated. The heat of hydrogenation is the ΔH (change in heat) of the reaction:

$$-\overset{|}{C}=\overset{|}{C}- \; + \; H-H \; \rightarrow \; -\underset{H}{C}-\underset{H}{C}-$$

The heat of hydrogenation for cyclohexene is 28.8 kcal/mole:



$\Delta H = -28.8$ kcal/mole.

Since there are six C=C bonds in biphenyl; 28.8 × 6 = 172.8 kcal/mole; but biphenyl is aromatic. Therefore, we must subtract the 71 kcal of resonance stabilization energy (conjugation energy) from our calculated heat of hydrogenation;

172.8 kcal/mole − 71 kcal/mole = 101.8 kcal/mole − estimated heat of hydrogenation

• PROBLEM 10-6

For a large number of organic compounds, the heat of combustion actually measured agrees rather closely with that calculated by assuming a certain characteristic contribution from each kind of bond, e.g. 54.0 kcal for each C-H bond, 49.3 kcal for each C-C bond, and 117.4 kcal for each C=C bond (cis-1,2-disubstituted). (a) On this basis, what is the calculated heat of combustion for benzene? (b) How does this compare with the measured value of 789.1 kcal for benzene?

Solution: Benzene has the following structure:

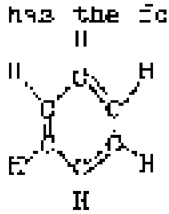


Fig. 1

Since benzene rings are so often used in organic chemistry, the carbons and hydrogens are often left out, and the structure is simply drawn as:

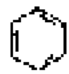


Fig. 2

The hydrogens are implicit, since carbon must have 4 bonds connected to it.

The calculated heat of combustion is determined by adding up all the bond energies of the various bonds. There are 3 different types of bonds in benzene.
By adding these up, we get:

6 C-H bonds : 6 × 54.0 = 324.0 kcal

3 C-C bonds : 3 × 117.4 = 352.2 kcal

3 C=C bonds : 3 × 49.3 = 147.9 kcal

The calculated heat of combustion = 824.1 kcal

(b) To compare the different values, we take the difference:

824.1 − 789.1 = 35.0 kcal

(calc.) (meas.)

The calculated value is 35.0 kcal greater than the measured value. The reason for this huge discrepancy is the resonance effect of benzene. The 35.0 kcal of energy is called resonance energy, and is responsible for the aromatic properties of benzene. The resonance effect is due to the delocalization of electrons in the benzene ring. Besides the structure shown in Fig. 1, the structure of benzene can also be drawn as:

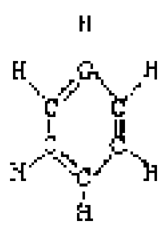


Fig. 3

These two structures of benzene are the Kekulé's structures, named after August Kekulé, who first proposed them in 1865. As resonance structures, they do not exist in equilibrium, nor do they exist independently; rather, they are used to represent the actual structure of benzene. Another representation of benzene is shown below.

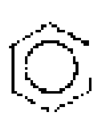


Fig. 4

Fig. 4 represents the resonance hybrid of the two Kekulé's structures shown earlier. The circle stands for the cloud of six delocalized π electrons, while the straight lines represent bonds joining the carbon atoms.

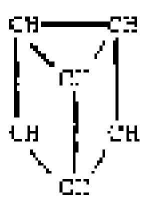
Since equivalent structures can be drawn for benzene (see figures) the π electrons therefore participate in several bonds. The π electrons are delocalized, and the molecule is therefore more stable.

Benzene is aromatic because its π electrons are delocalized in a cyclic cloud above and below the plane of the molecule, and its π cloud contains $4n+2$ π electrons (where $n = 1$ for benzene). This stipulation, known as Hückel's $4n+2$ Rule, is the defining condition for aromaticity. This special stability, due to the property of aromaticity, is based on quantum mechanics and has to do with the filling up of the bonding orbitals of the π electrons.

STRUCTURE OF BENZENE

■ PROBLEM 10-7

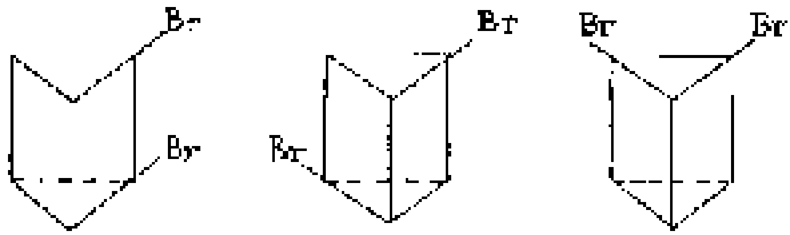
For a time the prism formula VI, proposed in 1869 by Albert Ladenburg of Germany, was considered as a possible structure for benzene, on the grounds that it would yield one monosubstitution product and three isomeric disubstitution products.



VI

(a) Draw Ladenburg structures of three possible isomeric dibromobenzenes.
(b) On the basis of the Körner method of absolute orientation, label each Ladenburg structure in (a) as ortho, meta, or para.
(c) Can the Ladenburg formula actually pass the test of isomer number?
(Derivatives of Ladenburg "benzene," called prismanes, have actually been made.)

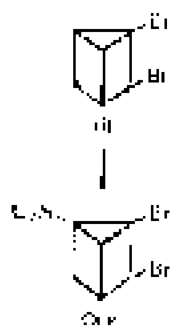
Solution: The three isomeric "dibromobenzenes" are:



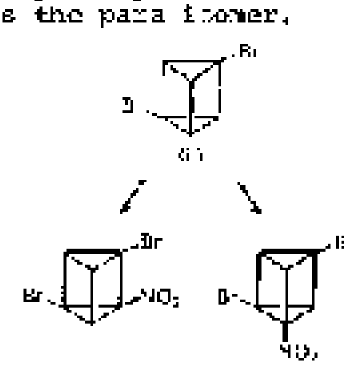
I II III

These three structures are different isomers because isomer I has the two bromines between the edges of two squares; isomer II has one bromine on the corner of one triangle, and the other bromine on the corner of the other triangle; isomer III has the two bromines on the two corners of the same triangle. These are the only three possible isomeric Ladenburg dibromobenzenes.

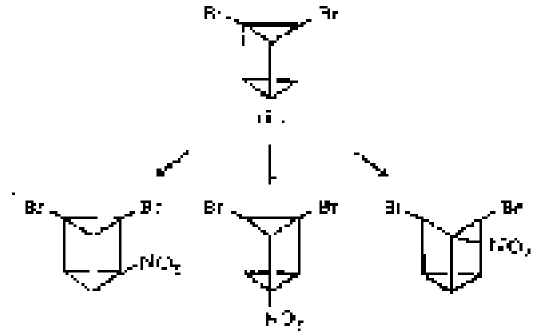
(b) According to the Körner method of absolute orientation, the dibromobenzene isomer that reacts to form one isomer of dibromonitrobenzene is the para-dibromobenzene; the one that forms two isomers is the ortho-dibromobenzene; the one that forms three isomers is the meta-dibromobenzene. By drawing the possible isomeric dibromonitrobenzenes for each isomer of dibromobenzene, we can label each Ladenburg structure in (a) as ortho, meta, or para:



Since there is only one possible isomeric product, this dibromobenzene is the para isomer.



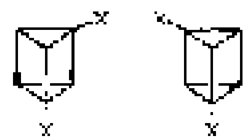
There are two isomeric products, therefore this is ortho-dibromobenzene.



Three

There are three isomeric products, therefore this is meta dibromobenzene.

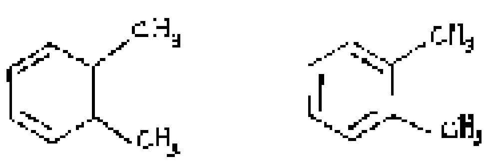
(c) No. All three disubstituted benzenes are not chiral. For the Ladenburg formula, the ortho isomer is chiral; thus enantiomeric structures are possible. (Recall that molecules that are not superimposable on their mirror images are chiral and that enantiomers are mirror-image isomers):



Enantiomers

♦ **PROBLEM 10-8**

In Kekulé's day, one puzzling aspect of his dynamic theory for benzene was provided by 1,2-dimethylbenzene. According to this theory, there should be two distinct such compounds, one with a double bond between the two methyl-substituted carbons and one with a single bond in this position.



Only a single 1,2-dimethylbenzene is known, however.

(a) Does Ladenburg's formula solve this problem?
(b) Explain with modern resonance theory.

Solution: Ladenburg's structure for benzene is a tetracyclic one (notice the absence of double bonds):

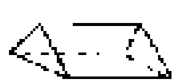


Fig. 1

This structure accounts for the fact that benzene has only one monosubstitution product and three isomeric disubstitution products. However, Ladenburg's formula is not able to solve the problem of there being only one 1,2-dimethyl benzene. According to this formula, there would be two possible isomers for this compound:

I II

Fig. 2

The two methyl groups in isomer I are shared by the edges of two squares, while those of isomer II are shared by the edges of a square and a triangle. Since the methyl groups in these two structures have different spatial orientations, they are isomers of each other, thereby contradicting the experimental observation of one isomer.

(b) Modern resonance theory says that the π electrons are delocalized in a π cloud. A pictorial representation of the π cloud in the benzene ring is:

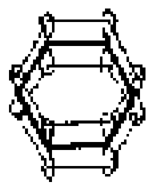
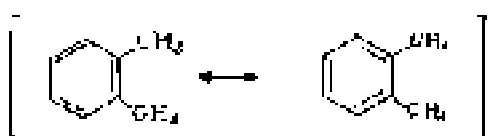


Fig. 3

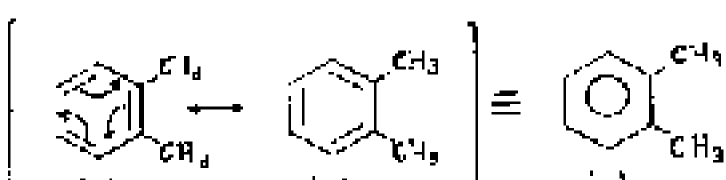
The thin lines depict delocalization of the 6π electrons. One structural representation of this system is the Kekulé's structure (shown in Fig. 4.).



(a) (b)

Fig. 4

The double-headed arrow and the brackets are used to indicate that the two structures are resonance structures. Remembering the concept of resonance (that is, the delocalization of electrons) we can see why these two structures are equivalent. Using the arrow convention of moving electrons, we have:



(a) (b) (c)

Fig. 5

These two resonance structures (Fig. 5a and 5b) can also be represented by Fig. 5c, with the circle representing the cloud of six delocalized π electrons.

NOMENCLATURE AND STRUCTURE OF BENZENE DERIVATIVES

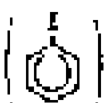
● PROBLEM 10-3

Draw structures of:

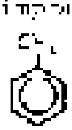
(a) p-dinitrobenzene
(b) m-bromonitrobenzene
(c) o-chlorobenzoic acid
(d) m-nitrotoluene
(e) p-bromoaniline
(f) m-iodophenol
(g) mesitylene (1,3,5-trimethylbenzene)
(h) 3,5-dinitrobenzenesulfonic acid
(i) 4-chloro-2,3-dinitrotoluene
(j) 2-amino-5-bromo-3-nitrobenzoic acid
(k) p-hydroxybenzoic acid
(l) 2,4,6-trinitrophenol (picric acid)

Solution: All of these structures are derivatives of benzene. Hence, a consideration of the nomenclature of benzene derivatives will aid in the drawing of these compounds.

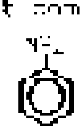
For many derivatives, the name of the substituent is prefixed to the word benzene, as in iodobenzene



Others possess special names which show no resemblance to the name of the attached substituent group. For example, methylbenzene is termed toluene. The most important compounds in this class include:

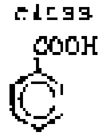


Toluene

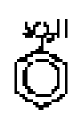


Aniline

Phenol

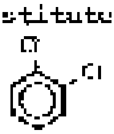


Benzoic acid

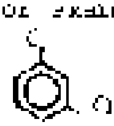


Benzenesulfonic acid

When several groups are attached to the benzene ring, the positions as well as the names of the substituents must be indicated. The words ortho (o), meta (m), and para (p) are used to designate the three possible isomers of a disubstituted benzene. For example,



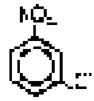
o-dichlorobenzene
ortho



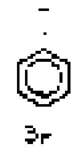
m-dichlorobenzene
meta

p-dichlorobenzene
para

If the two groups are different, and neither group imparts a special name to the compound, then the two groups are named successively and end the word with -benzene. For example:

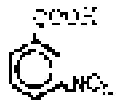


m-chloronitrobenzene

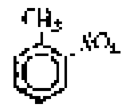


p-bromoiodobenzene

If one of the two groups does impart a special name, then the compound is named as a derivative of that special compound. For example:

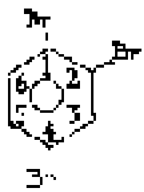


m-nitrobenzoic acid

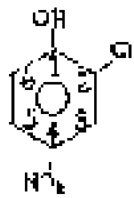


o-nitrotoluene

When more than two groups are attached to the benzene, numbers are used to indicate their relative positions. For example:



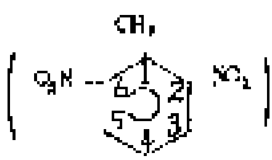
1,2,4-tribromobenzene



2-chloro-4-nitrophenol

3-bromo-5-chloronitrobenzene

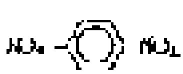
When the groups are all the same, each is given a number, the sequence being the one that gives the lowest combination of numbers. When the groups are different, the last named group is understood to be in position 1 and the other numbers conform to that, as in 3-bromo-5-chloronitrobenzene. When one of the groups that gives a special name exists, then the compound is named as having the special group in position 1; thus, in 2,6-dinitrotoluene



the methyl group is considered to be at the 1-position.

From their names, the chemical structure of the given compounds can now be determined.

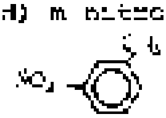
(a) p-dinitrobenzene



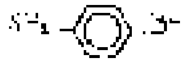
(b) m-bromonitrobenzene

(c) o-chlorobenzoic acid

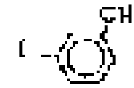
(d) m-nitrotoluene



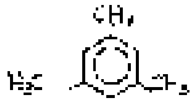
(e) p-Bromoaniline



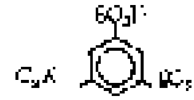
(f) m-Iodophenol



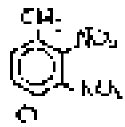
(g) mesitylene



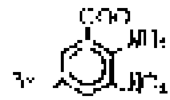
(h) 3,5-dinitrobenzene sulfonic acid



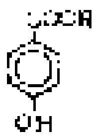
(i) 4-chloro-2,3,-dinitro-toluene



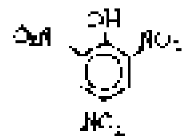
(j) 2-amino-5-bromo-3-nitrobenzoic acid



(k) p hydroxybenzoic acid



(l) 2,4,6 trinitrophenol



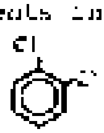
• **PROBLEM 10-10**

Draw structures for each of the following:

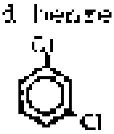
(a) m-Bromonitrobenzene
(b) o-Ethyltoluene
(c) p-Xylene
(d) 3-Nitrobenzene
(e) 2,4-Dibromomesitylene
(f) Phenylcyclohexane
(g) Biphenyl
(h) Benzyl cyanide

Solution: Benzene belongs to the class of cyclic unsaturated compounds called aromatics. In benzene (C_6H_6) all the C-C bonds have equal lengths and all the C-C-C bond angles are equal (120°).

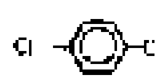
The terms ortho, meta, and para (abbreviated o, m, and p) are used to indicate the relative positions of substituents in disubstituted benzenes:



o-Dichlorobenzene

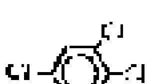


m-Dichlorobenzene



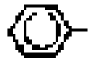
p-Dichlorobenzene

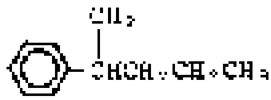
For more complicated derivatives, the positions on the ring are numbered 1 to 6.



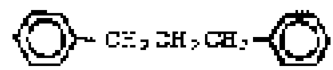
1,2,4-Trichlorobenzene

1-Bromo 2-nitro-4-fluorobenzene

The group , in which one hydrogen is replaced, is known as the phenyl group (abbreviated as C_6H_5- or sometimes Ph).



2-Phenylpentane



1,3-Diphenylpropane

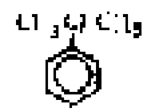
The symbol Ar(aryl) is used to stand for any aromatic substituent group in a way analogous to the use of R to mean any alkyl group. For example, aryl halides (ArX) vs. alkyl halides (RX).

Some of the common mixed aliphatic-aromatic hydrocarbons are:

Toluene (methylbenzene)

o-Xylene (1,2-dimethylbenzene)

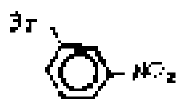
Mesitylene (1,3,5-trimethylbenzene)



Cumene (isopropylbenzene)

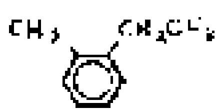
(a) m-Bromonitrobenzene

This compound has a bromo and a nitro group in the meta orientation on the benzene ring. Its structure looks like



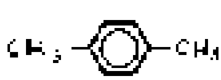
(b) o-Ethyltoluene

This structure contains an ethyl group attached at the ortho position to the toluene molecule. This structure looks like:



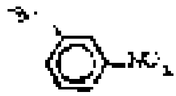
(c) p-Xylene

Xylene is a benzene ring with two methyl groups in place of 2 hydrogen atoms. The p means these 2 groups are para to one another. The structure is:



(d) 3-Nitrobromobenzene

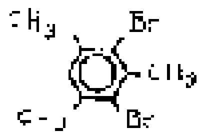
This structure contains a bromo and a nitro group attached to a benzene ring. The nitro group, however, is positioned on the third carbon from the carbon containing the bromo group. The structure is



This compound has the same structure as m-bromonitrobenzene.

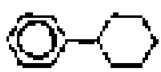
(e) 2,4-Dibromomesitylene

This structure contains 2 bromo groups located on the second and fourth carbons of the mesitylene structure (1,3,5-trimethylbenzene). This structure can be rewritten as 2,4-dibromo-1,3,5-trimethylbenzene.



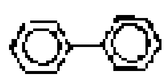
(f) Phenylcyclohexane

Phenylcyclohexane is a benzene ring attached to cyclohexane. The structure is



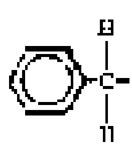
(g) Biphenyl

This compound is two benzene rings attached together. The structure is

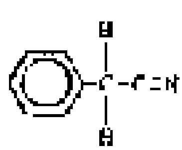


(h) Benzyl cyanide

This compound contains the benzyl group and the cyanide group. The cyanide group consists of a nitrogen atom triply bonded to a carbon atom. The point of attachment to the benzyl group is at the carbon. This group looks like: -C≡N. The benzyl group is a toluene molecule with a hydrogen replaced, as depicted below.



Thus the structure of this compound looks like:



• PROBLEM 10-11

1,3,5,7-Cyclooctatetraene, C_8H_8, has a heat of combustion of 1095 kcal; it rapidly decolorizes cold aqueous $KMnO_4$, and reacts with Br_2/CCl_4 to yield $C_8H_8Br_8$. (a) How should its structure be represented? (b) Upon what theoretical grounds might one have predicted its structure and properties? (c) Treatment of cyclooctatetraene with potassium metal has been found to yield a stable compound $2K^+C_8H_8^{--}$. Of what significance is the formation of this salt? (d) Using models, suggest a possible shape (or shapes) for cyclooctatetraene. What shape would you predict for the $C_8H_8^{--}$ anion?

Solution: From the name of the compound we know that it is an eight-carbon ring (cycloocta-), with 4 double bonds at positions 1, 3, 5, 7 (tetraene). The structure should therefore be represented as:

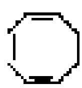


Fig. 1

(b) The number of π electrons is 8, which is not a Hückel number, therefore, it is not aromatic. Non-aromatic alkenes decolorize cold aqueous $KMnO_4$ and react with Br_2/CCl_4 to form addition products. The calculated heat of combustion (total bond energies of the molecule) is:

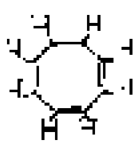


Fig. 2

8 C-H bonds : 8 × 54.0 = 432 kcal

4 C-C bonds : 4 × 49.3 = 197.2 kcal

4 C=C bonds : 4 × 117.4 = 469.6 kcal

calculated heat of combustion = 1098.8 kcal

The difference between the calculated value and the observed value is:

1098.8 − 1095 = 3.8 kcal

This difference of 3.8 kcal is due to resonance stabilization energy. This energy is much lower than the resonance energy for the aromatic compounds, for example, benzene with a resonance stabilization energy of 36 kcal.

(c) The willingness of cyclooctatetraene to accept two electrons is significant; the number of π electrons in the anion is 10, which is a Hückel number (for n = 2). Stabilization due to aromaticity is enough to outweigh the double negative charge and angle strain. Remember that in order for the anion to be aromatic, the ring must be flat for π overlap. This will cause the carbon-carbon angle to be 135°, which is a large deviation from the tetrahedral angle of 109.5°.

(d) For cyclooctatetraene, the shape would minimize angle and torsional strain, therefore the most stable conformation would be:

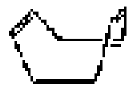


Fig. 3

This conformation is analogous to the boat conformation of cyclohexane. (See the chapter on stereochemistry.)

The shape for $C_8H_8^{--}$ would be a planar (see part c), regular octagon:

Fig. 4 Cyclooctatetraenyl dianion

The octagon must be regular because all the bonds in an aromatic ring are the same. This is due to the equivalence of the resonance structures. This last point is best illustrated by the benzene ring:

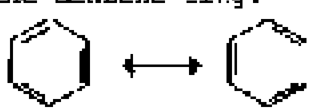


Fig. 5

Both of these resonance structures are equivalent, therefore all the bonds are equivalent.

■ **PROBLEM 10-12**

You have three bottles containing the three isomeric dibromobenzenes; they have the melting points +87°, +6°, and −7°. By a great deal of work, you prepare six dibromonitrobenzenes ($C_6H_3Br_2NO_2$) and find that, of the six, one is related to (derived from or convertible into) the dibromobenzene of m.p. +87°, two to the isomer of m.p. +6°, and three to the isomer of m.p. −7°.

Label each bottle with the correct name of ortho, meta, or para.

(This work was actually carried out by Wilhelm Körner, of the University of Milan, and was the first example of the Körner method of absolute orientation.)

Solution: All the hydrogen positions on para-dibromobenzene are equivalent; one neighboring carbon carries Br, while the other neighboring carbon contains H:

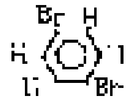
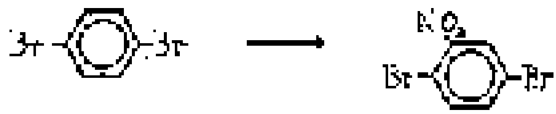


Fig. 1

Therefore, the only possible product in a mono substitution reaction is:



2,5-dibromonitrobenzene

Fig. 2

There are three sets of hydrogen positions in meta-dibromobenzene:

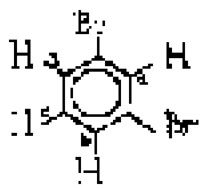


Fig. 3

Therefore, NO_2 can replace hydrogen in 3 different positions; a, b, and c:

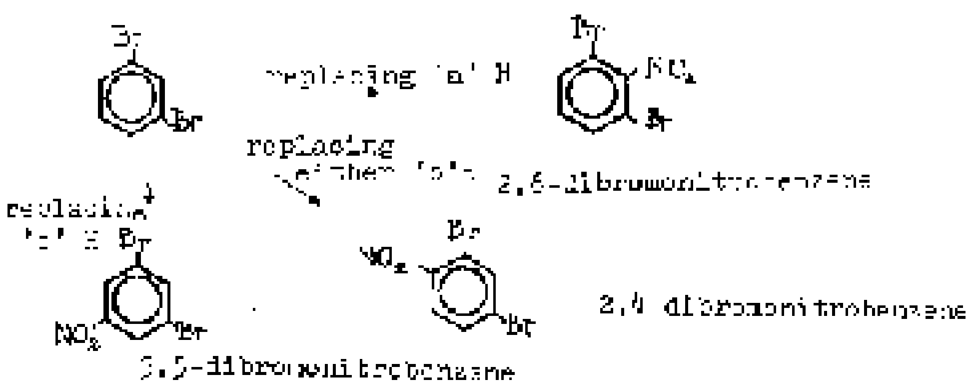


Fig. 4

There are two sets of hydrogen positions in ortho-dibromobenzene:

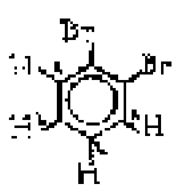
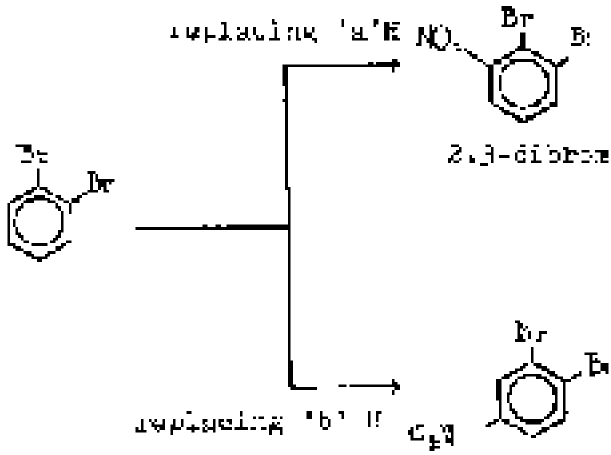


Fig. 5

Therefore, NO_2 can replace hydrogen in 2 different positions, a and b;



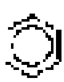
3,4-dibromonitrobenzene

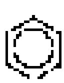
Fig. 6

The bottle of dibromobenzene with the melting point of 87° is the para isomer; the bottle with the melting point of 6° is the ortho-isomer; the bottle with the melting point of -7° is the meta-isomer.

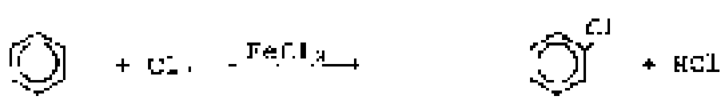
• PROBLEM 10-13

Complete the following equations. Name each organic product.

(a)  + Cl_2 $\xrightarrow{FeCl_3}$

(b)  + SO_3 $\xrightarrow{H_2SO_4}$

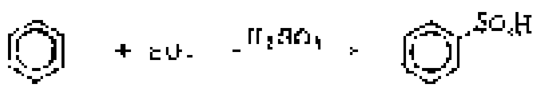
Solution: When a substitution reaction is carried out with benzene, only one monosubstituted product can result. When benzene is treated with chlorine in the presence of ferric chloride catalyst, chlorobenzene and hydrogen chloride result. This reaction is called a chlorination reaction.



Similarly, other reagents can attack the benzene ring and replace a hydrogen atom.

In substitution reactions, the product is aromatic and a group or atom has been substituted for a hydrogen on the ring. Each of these reactions is carried out under acidic conditions: chlorination with the Lewis acid $FeCl_3$; nitration with sulfuric acid; and alkylation with $AlCl_3$, another Lewis acid.

In the case of sulfonation of benzene, one or more hydrogen atoms are replaced by the sulfonic acid group ($-SO_3H$). Sulfonation of benzene with fuming sulfuric acid ($H_2SO_4 + SO_3$) yields benzenesulfonic acid.



• PROBLEM 13-14

Consider the possible free radical chain chlorination of benzene:

$$C_6H_6 + Cl\cdot \rightarrow C_6H_5\cdot + HCl$$

$$C_6H_5\cdot + Cl_2 \rightarrow C_6H_5Cl + Cl\cdot$$

Calculate ΔH for each reaction. Use these results to explain why this method is not a satisfactory way of preparing chlorobenzene.

Solution: ΔH, or enthalpy, is the heat of reaction and is generally associated with bonding. It is calculated by subtracting the sum of the $\Delta H°$s of the reactants from the sum of the $\Delta H°$s of the products, that is, $\Sigma\Delta H°_{(prod.)} - \Sigma\Delta H°_{(react.)}$. ("$\Sigma$" is the mathematical symbol for "the sum of".) $\Delta H°$ is the standard heat of formation of a molecule, and is usually tabulated. Therefore, the ΔH of the first reaction is:

$$C_6H_6 + Cl\cdot \rightarrow C_6H_5\cdot + HCl$$

$$\Delta H° \quad 19.8 \quad 28.9 \quad 80 \quad -22.1$$

$$\Delta H_1 = \Sigma\Delta H°_{(prod.)} - \Sigma\Delta H°_{(react.)}$$

$$= (80 - 22.1) - (19.8 + 28.9)$$

$$= 57.9 - 48.7 = +9.2 \text{ kcal-mole}^{-1}$$

Similarly, the ΔH of the second reaction is:

$$C_6H_5\cdot + Cl_2 \rightarrow C_6H_5Cl + Cl\cdot$$

$\Delta H°$ [illegible] 0 12.2 28.9

$\Delta H_2 = (12.2 - 28.9) - (50) = -38.9$ kcal-mole^{-1}

ΔH of the overall reaction $= -38.9 + 9.2$

$= -29.7$ kcal-mole^{-1}.

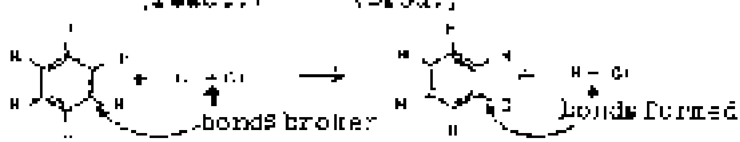
Although the overall reaction is highly exothermic ($\Delta H = (-)$ = exothermic, $\Delta H = (+)$ = endothermic), the first step is endothermic, with $\Delta H_1 = + 9.2$. The activation energy for this step is at least 9.2 kcal-mole^{-1}, since the activation energy is always greater than or equal to the ΔH of an endothermic reaction. The rate of reaction is dependent on the activation energy of an elementary reaction. Since the activation energy for this step is high, the rate will be very low, and the chlorine radicals, instead of reacting with benzene, will eventually react with each other. These conditions will not support a chain reaction. Therefore, this method is not a satisfactory way of preparing chlorobenzene.

• PROBLEM 10-15

Calculate from appropriate bond and stabilization energies the heats of reaction of chlorine with benzene to give (a) chlorobenzene and (b) 1,2-dichloro-3,5-cyclohexadiene. Your answer should indicate that substitution is energetically more favorable than addition. Assume the bond dissociation energy for a C–Cl π bond to be 65 kcal; the resonance stabilization energy of benzene to be 36 kcal, and that of 1,2 dichloro 3,5 cyclohexadiene to be 3 kcal.

Solution: The heat of reaction is the enthalpy, ΔH. In a reaction, if more stable bonds are formed, ΔH is negative and the reaction is exothermic. A reaction with positive ΔH is endothermic. To solve for ΔH, we substract the sum of the bond dissociation energies of the products from the sum of the bond dissociation energies of the reactants. In mathematical symbols, if "D" is the bond dissociation energy of the bond formed or broken, then:

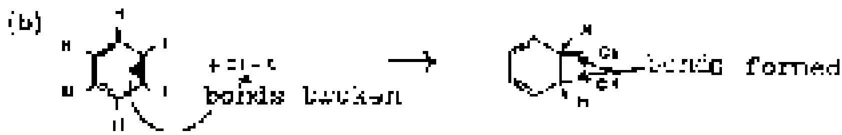
$$\Delta H = \Sigma D_{(react.)} - \Sigma D_{(prod.)}$$

(a) 

112 kcal benzene; 58 kcal chlorine; 86 kcal chlorobenzene; 103 kcal hydrogen chloride

$$\Delta H = (112 + 58) - (86 + 103) = 170 - 189 = -19 \text{ kcal}$$

(b)



65 + 36 kcal benzene   58 kcal chlorine   2(81) + 3 kcal 1,2-dichloro-3,5-cyclohexadiene

$$\Delta H = 65 + 36 + 58 - 2(81) - 3 = -6 \text{ kcal}$$

The 36 kcal of resonance stabilization energy is added to the equation because that amount of energy is expended when we break the aromatic structure of benzene.

The larger negative ΔH (−23 kcal) for the substitution reaction as compared to the one (−6 kcal) for the addition reaction of benzene indicates that the former type of reaction is more exothermic than the latter. In other words, substitution is energetically more favorable than addition for benzene.

• PROBLEM 10-16

When benzene is treated with chlorine under the influence of ultraviolet light, a solid material of m.wt. 291 is formed. Quantitative analysis gives an empirical formula of CHCl. (a) What is the molecular formula of the product? (b) What is a possible structural formula? (c) What kind of reaction has taken place? (d) Is the product aromatic? (e) Actually, the product can be isolated into six isomeric compounds, one of which is used as an insecticide (Gammexane or Lindane). How do these isomers differ from each other? (f) Are more than six isomers possible?

Solution: The empirical formula is the simplest integral formula for a compound. Since the molecular weight of the compound is given, we must first calculate the unit weight of CHCl:

$$\begin{aligned}\text{unit wt. of CHCl} &= \text{atomic weight of C} + \text{atomic weight of H} + \text{atomic weight of Cl}\\ &= 12 + 1 + 35.5 = 48.5.\end{aligned}$$

To determine the molecular formula, we have to determine the number of units of CHCl per molecule. From unit analysis:

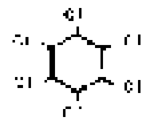
$$\frac{\text{wt./molecule}}{\text{wt./unit}} = \frac{\text{number of units}}{\text{molecule}}$$

Therefore, we must divide the molecular weight by the unit weight:

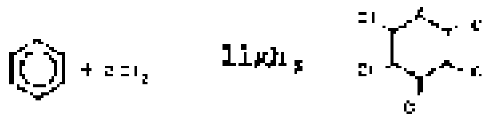
$$\frac{\text{M.W.}}{\text{U.W.}} = \frac{291}{48.5} = 6 \text{ CHCl units per molecule.}$$

Therefore, the molecular formula is $C_6H_6Cl_6$.

(b) Since benzene is treated with chlorine, we must have a cyclic structure; a possible compound is 1,2,3,4,5,6 hexachlorocyclohexane:



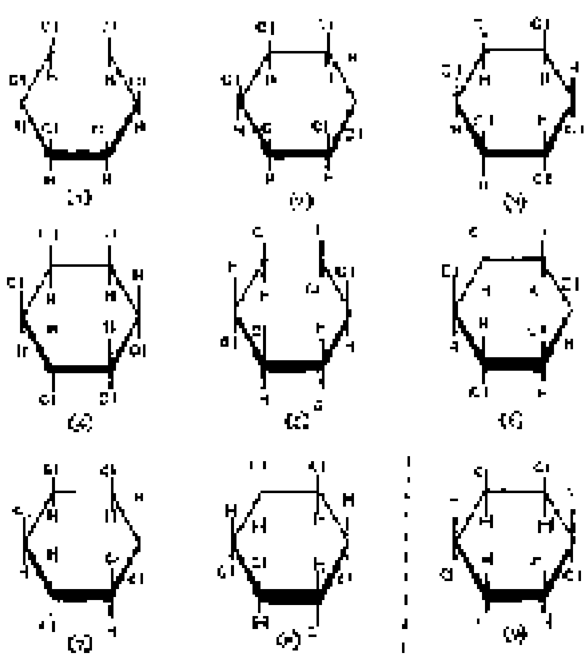
(c) The molecular formula for benzene is: C_6H_6, while the molecular formula of this compound is $C_6H_6Cl_6$. Since nothing is substituted or eliminated, the reaction that has taken place is an addition reaction.



1,2,3,4,5,6-hexachlorocyclohexane

(d) Since this compound has no double bonds, and therefore no π electrons, this compound is not aromatic.

(e-f) There are nine possible stereoisomers, consisting of different combinations of cis and trans Cl's in the cyclohexane ring. Structures 8 and 9 are a pair of enantiomers, that is, mirror-image isomers. The other seven structures are achiral. The method for determining chirality is to draw the mirror image of the given structure, and see if the two structures match exactly. If the two structures do not match, they are chiral. Remember that a chiral molecule is a molecule that is not superimposable on its mirror image. The use of models is the best method for determining chirality, as well as determining the possible stereoisomers. The nine possible stereoisomers are:



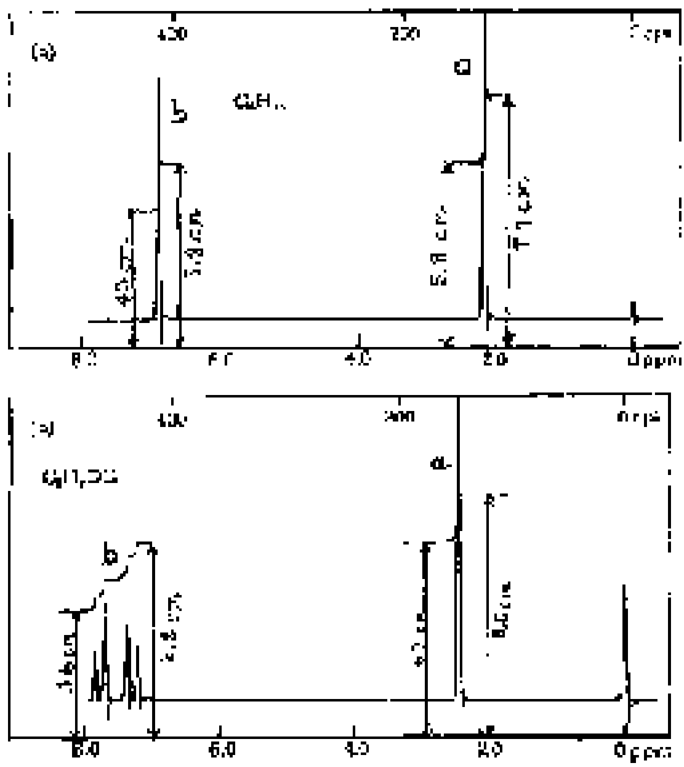
enantiomers

• PROBLEM 10-17

Establish the structures of the following benzene derivatives on the basis of their empirical formulas and n.m.r. spectra. Remember that equivalent protons do not normally split each other's resonances.

(a) C_9H_{12}

(b) C_8H_9Cl



Proton n.m.r. spectra of some benzene derivatives at 60 Mcps with reference to TMS at 0 ppm

Solution: Before we evaluate these nuclear magnetic resonance (n.m.r.) spectra, let us briefly review the basic principles of n.m.r. spectroscopy.

At a given radiofrequency, all protons absorb at the same effective field strength. Note that the effective field strength is not the same as the applied field strength. The effective field strength is the magnetic field that the proton feels, and is therefore dependent on the environment of the proton. Since every set of equivalent protons has a different environment from other sets of protons, they will absorb at different applied field strengths. It is this applied field strength that is measured, and the absorption plotted. Aromatic protons, Ar-H, absorb far downfield (δ = 6 – 8.5) due to the powerful deshielding effect of the circulating π electrons. Benzylic protons are close enough to the ring to feel a little of the deshielding effect of the π electrons, therefore they absorb at a δ value further downfield, that is, greater δ value from ordinary alkyl protons.

The main aspects of the n.m.r. spectra are:

(1) the number of signals. This tells us how many different sets of protons there are in the molecule.

(2) the position of the signals. This tells us the electronic environment of each kind of proton.

(3) the intensity of the signals. This tells us the number of protons of each kind. To measure the area, we need only measure the height of the step curve above or at the signal.

(4) the splitting of a signal into several peaks. This tells us about the environment of a proton with respect to other nearby protons, specifically protons on a neighboring carbon. The number of splits is equal to the number of neighboring protons plus one.

(b) To evaluate this spectrum, let us go down the above list. (1) Since there are two signals, we can conclude that there are two kinds of protons.

(2) The position of the first signal is approximately 2.2 δ. Looking at the Proton Chemical Shifts table, the possible groups are:

(1) Acetylenic −C≡C−H ; δ = 2 – 3

(2) Benzylic Ar−C−H ; δ = 2.2 – 3

(3) Iodides I−C−H ; δ = 2 – 4

(4) Esters RCOO−C−H ; δ = 2 – 2.2

(5) Acids HOOC−C−H ; δ = 2 – 2.6

(6) Carbonyl Compounds O=C−C−H ; δ = 2 – 2.7

(7) Hydroxylic R−O−H ; δ = 1 – 5.5

(8) Amino RNH$_2$; δ = 1 – 5

The given empirical formula is C_9H_{12}; there are only carbons and hydrogens in this molecule, therefore we can eliminate choices 3 – 8, since they contain atoms other than carbon and hydrogen. This elimination leaves us with two possible groups for signal a:

(1) Acetylenic —C≡C–H ; δ = 2 – 3

(2) Benzylic Ar–C–H ; δ = 2.2 – 3

The δ value for signal b is approximately 6.8. The only possible group, after eliminating the groups that contain atoms other than carbon and hydrogen is: Aromatic-Ar–H; δ = 6 – 8.5.

(3) The height of the step curve for:

signal a = 7.9 cm – 5.8 cm = 2.1 cm.

signal b = 5.8 cm – 4.3 cm = 1.5 cm.

The molecular formula for this compound is C_8H_{10}, therefore there are 10 protons in the molecule. The fraction of protons responsible for signal a =

$$\frac{(\text{height of a})}{(\text{height of a} + \text{height of b})} = \frac{2.1}{(2.1 + 1.5)}$$

$$= \frac{2.1}{3.6} = .583$$

$$\left(.583 \frac{\text{a protons}}{\text{total no. of protons}}\right) (10 \text{ total no. of protons})$$

= 5.8 signal a protons

≈ 6 signal a protons

The no. of signal b protons = total no. of protons – no. of signal a protons
= 10 – 6 = 4 signal b protons

With this information, and the fact that signal b is aromatic, we can conclude that set a is not acetylenic. There is only one possible proton per acetylenic group. Since set a has six protons, that would require six acetylenic groups. But there are only two carbons left (subtracting the six carbons for the benzene ring), therefore set a must be benzylic.

(4) Since there are no splitting of signals, the two groups of protons are not neighbors.

Let us now summarize what we know:

(1) There are six benzylic protons.

(2) There are two groups attached to the benzene ring. (Remember that there are 4 protons to set b: 6 possible aromatic protons – 4 existing aromatic protons = 2 aromatic protons that are replaced by substituent groups.)

With the molecular formula of C_8H_{10}, we can now draw three possible structures for this compound:

ortho-xylene meta-xylene para-xylene

Fig. 1

The ortho xylene has two sets of aromatic protons. The d protons (see Fig. 1) are different from the e protons since the d protons are next to a carbon carrying a methyl group, while the e protons are only next to carbons carrying aromatic protons. We know that there is no splitting in signal b (see 4 above), therefore ortho-xylene is not the correct structure. Meta-xylene has 3 different sets of aromatic protons (see Fig. 1); we can eliminate this structure based on the above argument with ortho-xylene. The aromatic protons of para-xylene are all equivalent. Each aromatic proton has one neighboring carbon carrying a methyl group, with the other neighboring carbon carrying an aromatic proton. Therefore, the correct structure based on this n.m.r. spectrum is p-xylene.

(b) Using the same method as in part a, we have:

(1) There are two signals, therefore there are two kinds of protons. Note that signal b is one signal split into four peaks, a quartet. We can recognize this signal as a quartet from the even spacings within it and from its symmetrical intensity pattern.

The δ value for signal a is approximately 2.2. The possible groups are:

(a) acetylenic —C≡C-H ; δ = 2 - 3

(b) benzylic Ar-C-H ; δ = 2.2 - 3

(c) carbonyl compounds O=C-C-H; δ = 2 - 2.7

(d) hydroxylic R-OH ; δ = 1 - 5.5

We can eliminate the hydroxylic group because there is an absence of a signal at δ = 3.4 - 4 (the alcohol HO-C-H group range).

The δ value for signal b is approximately 7.5. The only possible group is: Aromatic - Ar-H: δ = 6 - 8.5.

(3) The height of the step curve for:

signal a = 8.0 cm - 6.2 cm = 1.8 cm.

signal b = 6.2 cm - 4.0 cm = 2.2 cm.

The ratio of a : b = 1.8 : 2.2 = 3 : 4

Since there are seven protons; set a has 3 protons and set b has 4 protons, we can now eliminate the acetylenic group as a possibility based on the argument in part a of this problem.

Let us now summarize:

(1) There is a group of 3 equivalent protons that are either carbonyl or benzylic.

(2) There is a group of 4 non equivalent protons that are aromatic.

With the molecular formula of C_8H_7OCl, we can now draw out six possible structures:

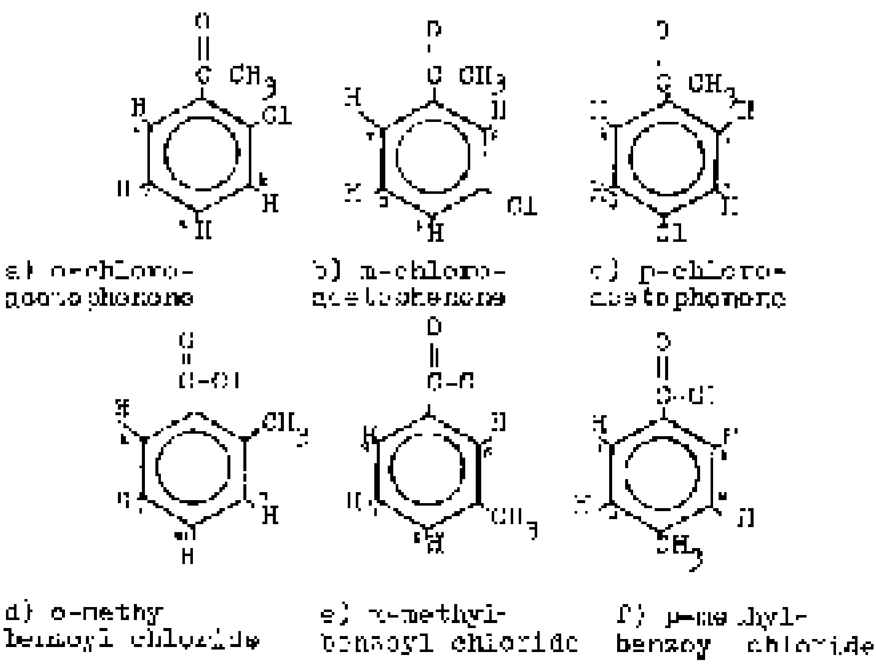


Fig. 2

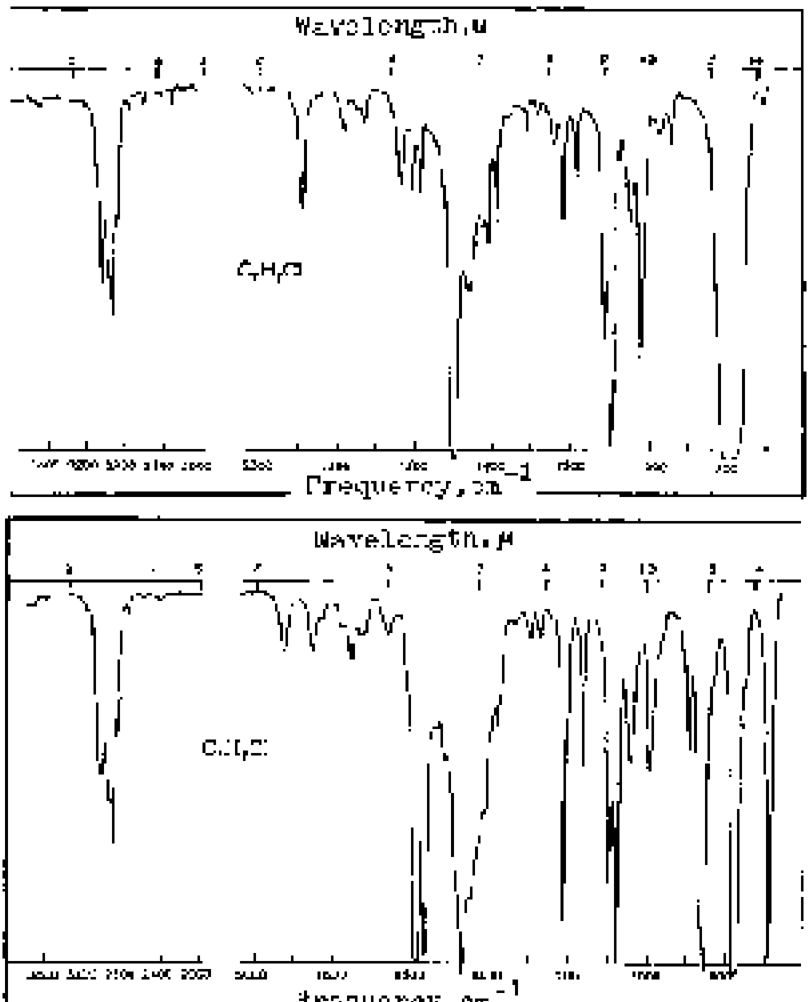
The ortho and meta structures can be eliminated because signal b is split into a symmetrical quartet, signifying the para structure. The ortho and meta structures have four non-equivalent aromatic protons, therefore, the splitting for these two compounds would be far more complex. Hence, there are two possible structures:

(1) para-chloroacetophenone

(2) para-methyl-benzoyl chloride.

Further information would be necessary to distinguish between these two structures.

Identify the two compounds with molecular formula C_7H_7Cl from their infrared spectra shown in the figure below.



Solution: The infrared (IR) spectrum is important for aromatic compounds because the presence of an aromatic group can be easily distinguished in an IR spectrum.

Aliphatic absorption is strongest at higher frequencies and is almost missing below 900 cm^{-1}; aromatic absorption is strong at lower frequencies: between 650 cm^{-1} and 900 cm^{-1}. We can also determine the number and position of substituent groups on the benzene ring from the IR spectrum.

Before we evaluate the above two IR spectra, let us look at four IR spectra (toluene, o-, m-, and p-xylenes) that show bands typical of benzene compounds. Looking at Fig. 1 notice the 2 bands near 1600 cm^{-1} and 1500 cm^{-1}.

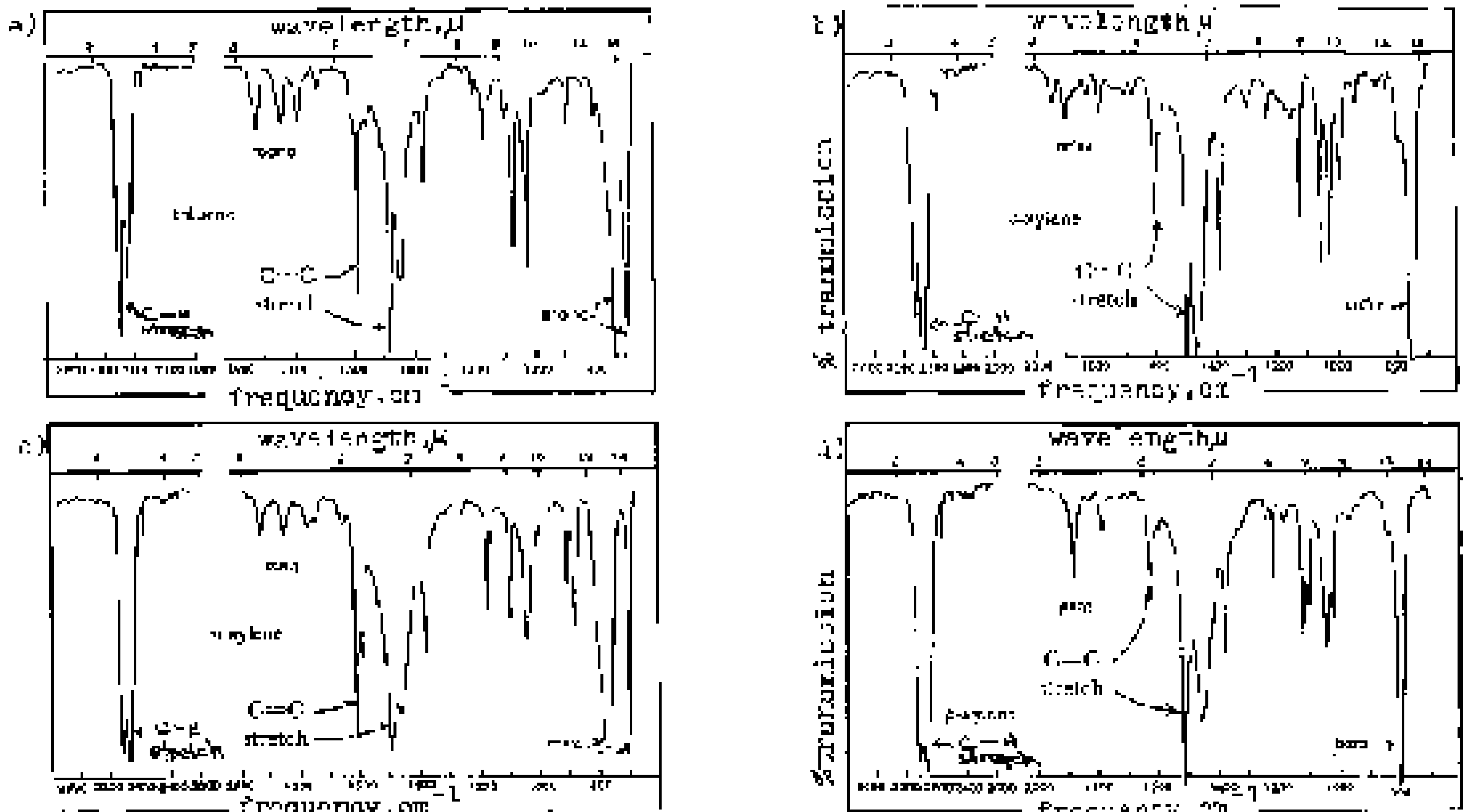


Fig. 1 Characteristic bonds of mono- and disubstituted benzene derivatives

These 2 bands are characteristic of the C$\overset{---}{—}$C bonds in aromatic rings. These 2 bands have variable intensities and a weak band should not be overlooked (see the weak band in Fig. 1d). The sharp bands near 3000 cm^{-1} are characteristic of aromatic C-H bonds. The bands between 1650 cm^{-1} and 2000 cm^{-1}, between 1225 cm^{-1} and 950 cm^{-1}, and below 900 cm^{-1} are correlated with the number and position of the substituent groups on the benzene ring. Notice the difference between the peaks of Fig. 1a - d (at 1650 - 2000 cm^{-1}), corresponding to the mono-substituted benzene ring, and the ortho-, meta-, and para-isomers respectively. Perhaps the most helpful bands in this respect are the ones between 690 cm^{-1} and 840 cm^{-1}. For many aromatic compounds, absorption occurs at:

(a) mono-substituted: (1) 690 - 710 cm^{-1}

2 strong peaks (2) 730 - 770 cm^{-1}

(b) ortho-disubstituted: (1) 735 - 770 cm^{-1}

1 strong peak

(c) meta-disubstituted: (1) 680 - 710 cm^{-1}

2 strong peaks (2) 750 - 810 cm^{-1}

(d) para-disubstituted: (1) 810 - 840 cm^{-1}

1 strong peak

Locate these peaks in Fig. 1a - d to familiarize yourself with these important bands.

(a) This compound is a derivative of benzene (see Fig. 2a), as indicated by the bands at 3000 cm^{-1} (=C-H stretch), and 1600 cm^{-1} and 1500 cm^{-1} (C$\overset{---}{—}$C) stretch. The absorption pattern in the region of 2000 - 1650 cm^{-1} is consistent with

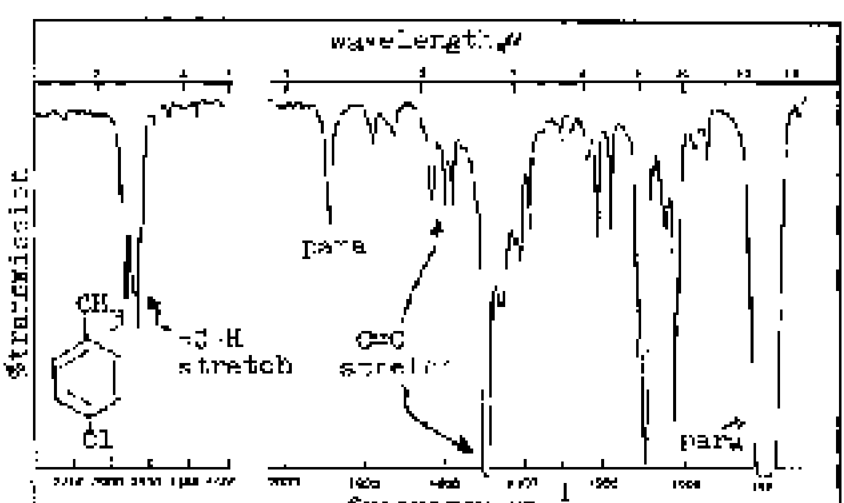


Fig. 2a

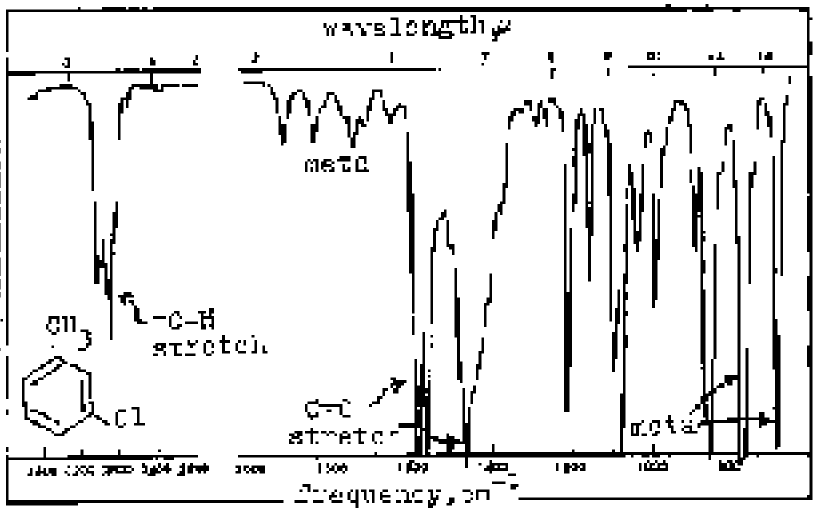


Fig. 2b

this compound being a para-isomer (compare with Fig. 1d). The single strong band at 80[illegible] cm^{-1} clearly shows that this compound is a para-disubstituted benzene derivative. The only structure with the molecular formula C_7H_7Cl that is consistent with this data is para chlorotoluene:

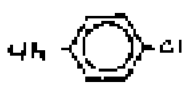


Fig. 3

(b) This compound is also a benzene derivative, as evidenced by the 2 bands (see Fig. 2b) at 1600 cm^{-1} and 1580 cm^{-1} (C=C stretch), and at 3000 cm^{-1} (=C-H stretch). The 2 bands at 690 cm^{-1} and 780 cm^{-1} is characteristic of meta-substituted benzene derivatives; the absorption pattern at 2000 - 1650 cm^{-1} is also consistent with this compound being a meta-isomer (compare with Fig. 1c). The only structure with the molecular formula C_7H_7Cl that is consistent with this data is meta-chlorotoluene:

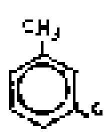


Fig. 4

CHAPTER 11

ELECTROPHILIC AROMATIC SUBSTITUTION

NITRATION

• PROBLEM 11-1

Draw the principal resonance forms of the nitronium ion.

Solution: Resonance structures differ from each other only by the arrangement of electrons about the atoms in the molecule. The actual structure of a molecule is a hybrid of all the possible resonance structures. When the contributing structures to the hybrid are of about the same stability, the resonance is important. The resonance hybrid is more stable than any of the contributing structures. For the nitronium ion ($^{+}NO_2$), there exist two resonance forms as shown:

$$\left[\overset{\ominus}{O} - \overset{(+2)}{N} - O \longleftrightarrow O - \overset{(+2)}{N} - \overset{\ominus}{O}\right]^{\oplus}$$

The formal charge of each atom is calculated by using the equation:

formal charge = A + B - C, where

A = number of valence electrons in the isolated atom

B = number of covalent bonds to atom

C = number of electrons present

For nitrogen, the number of valence electrons is five (A = 5). There exist three covalent bonds to the nitrogen in the nitronium ion, so that B = 3. Each covalent bond is composed of two electrons for a total of six. Hence, A + B - C = 5 + 3 - 6 = 2.

• PROBLEM 11-2

Nitration by nitric acid alone is believed to proceed by essentially the same mechanism as nitration in the presence of sulfuric acid. Write an equation for the generation of $NO_2^{\oplus}$ from nitric acid alone.

Solution: Nitration is an example of electrophilic aromatic substitution. These reactions are typical of the benzene ring in which the ring serves as a source of electrons. In nitration, sulfuric acid (H_2SO_4) and nitric acid (HNO_3) are mixed together in the presence of an arene to generate a nitro compound as shown:

$$ArH + HONO_2 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$$

The electrophile (that is, the acidic, electron seeking reagent) for nitration reactions is the nitronium ion, $NO_2^{\oplus}$.

Needing electrons the nitronium ion finds them in the π cloud of the benzene ring. Hence, it attaches itself to one of the carbon atoms by a covalent bond to form a

benzenonium ion, $\overset{\oplus}{C_6H_5}\genfrac{}{}{0pt}{}{\diagup H}{\diagdown NO_2}$

This ion can then lose a proton by abstraction with HSO_4^- (which came about by $HONO_2 + 2H_2SO_4 \rightleftharpoons H_3O^+ + 2HSO_4^- + {}^{\oplus}NO_2$) to create the nitrobenzene. The production of nitronium ion from nitric acid alone may be accounted by a consideration of the Lowry-Brønsted acid-base equilibrium.

Any acid or base is constantly in a Lowry-Brønsted acid-base equilibrium. Nitric acid, therefore, is constantly in acid-base equilibrium where one molecule of nitric acid serves as acid, and another serves as base (step (1), see below). Once a protonated nitric acid molecule is formed, it loses water to give the nitronium ion. (Step (2)).

$$(1) \quad HONO_2 + HONO_2 \rightleftharpoons H\overset{H}{\underset{\oplus}{O}}NO_2 + {}^{\ominus}ONO_2$$

$$(2) \quad H\underset{\oplus}{\overset{H}{O}}NO_2 \rightleftharpoons H_2O + \overset{\oplus}{N}O_2$$

$$(3) \quad H_2O + HONO_2 \rightleftharpoons H_3\overset{\oplus}{O} + {}^{\ominus}ONO_2$$

$$\text{Overall:} \quad 3\,HONO_2 \rightleftharpoons \overset{\oplus}{N}O_2 + 2\,{}^{\ominus}ONO_2 + H_3O^{\oplus}$$

• PROBLEM 11-8

Account for the fact that fairly reactive arenes (e.g., benzene, toluene, and ethylbenzene) are nitrated with excess nitric acid in nitromethane solution at a rate that is independent of the concentration of the arene (i.e., zeroth order) Does this mean that nitration of an equimolal mixture of benzene and toluene would necessarily give an equimolal mixture of nitrobenzene and nitrotoluenes? Why or why not?

Solution: The fact that the rate of reaction is independent of the concentration of arene indicates that the rate determining step is not the attack of nitronium ion ($^+NO_2$) upon the arene to form the benzenonium ion

. The rate determining step must be formation of the nitronium ion.

$$HNO_3\,(\text{excess}) \xrightarrow[CH_3NO_2]{\text{slow}} \overset{+}{N}O_2 \xrightarrow[C_6H_6]{\text{fast}} C_6H_5NO_2 .$$

Nitration of an equimolal mixture of benzene and toluene will not yield an equimolal mixture of nitrobenzene and nitrotoluene. This is because benzene and toluene react with nitronium ion at different rates. Toluene reacts faster than benzene because toluene has an activating group (CH_3) on the aromatic ring, whereas benzene has none. The methyl group is an activating group because it can stabilize the positive charge of the carbonium ion by releasing electrons in electrophilic aromatic substitution reactions. This lowers the activation energy and increases the rate of reaction. The reaction rates of benzene and toluene with nitronium ion are greater than the rate determining step. If this were not true, then the overall rate of nitration would be dependent upon the concentration of arene.

HALOGENATION

• PROBLEM 11-4

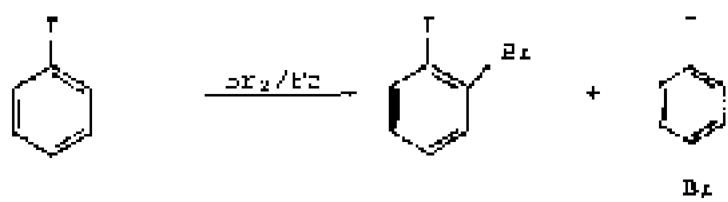
Give structures and names of the principal products expected from the ring monobromination of each of the following compounds. In each case, tell whether bromination will occur faster than with benzene itself.

(a) iodobenzene
(b) sec-butylbenzene
(c) acetophenone ($C_6H_5COCH_3$)
(d) phenetole ($C_6H_5OC_2H_5$)
(e) diphenylmethane ($C_6H_5CH_2C_6H_5$)
(f) benzotrifluoride ($C_6H_5CF_3$)

Solution: Aromatic compounds with activating groups are ortho, para directors; they are electron releasing groups and will direct the electrophile to add ortho and para to the substituent. Deactivating groups are meta directors; they are electron withdrawing groups and they will direct the electrophile to add meta to the substituent. The halogens are an exception; they are deactivating groups, but they are ortho, para directors. Halogens, through their inductive effect, tend to withdraw electrons and thus to deactivate the intermediate carbonium ions. This effect is felt particularly at the ortho and para positions. Through their resonance effect, halogens release electrons. This stabilizes the carbonium ion, and it is felt most strongly at the ortho and para. The reactivity of the species is controlled by the inductive effect, whereas the resonance effect seems to govern orientation.

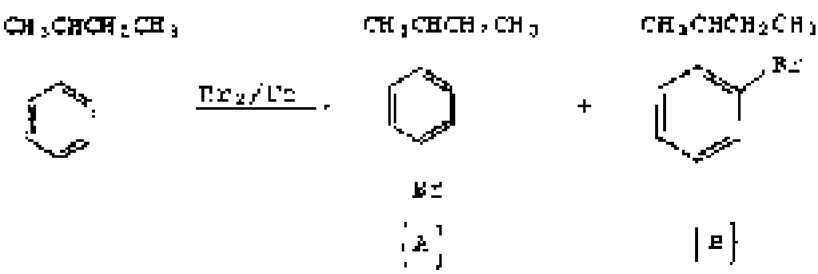
Those aromatic compounds with activating groups have a faster rate of ring monobromination than benzene. This is because the activating group helps stabilize the activated complex. This lowers the energy of activation and increases the rate of reaction. The opposite holds true for aromatic compounds with deactivating groups; they react slower than benzene in a ring monobromination reaction.

(a) Reacts slower than benzene. The substituent, a halide (I), deactivates the ring.



Iodobenzene ⟶ o and p-bromoiodobenzene

(b) Reacts faster than benzene. The alkyl group (sec propyl) activates the ring.

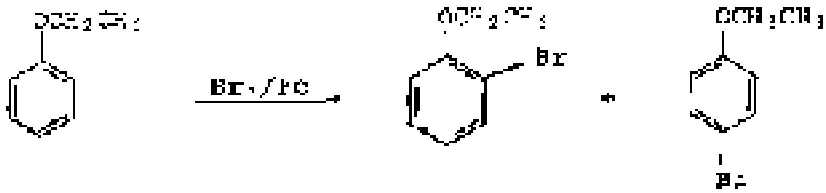


sec butylbenzene ⟶ (A) p-Bromo-sec-butylbenzene
(B) o-Bromo-sec-butylbenzene

(c) Reacts slower than benzene. All COR groups are deactivating.

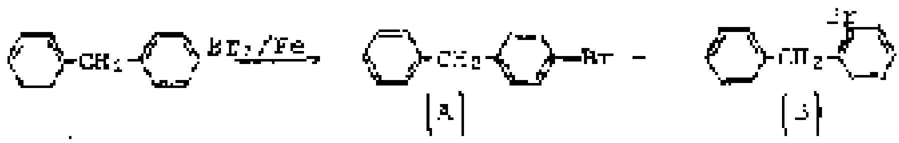
Acetophenone ⟶ m-bromoacetophenone

(d) Reacts faster than benzene. -OR groups tend to be moderately activating.



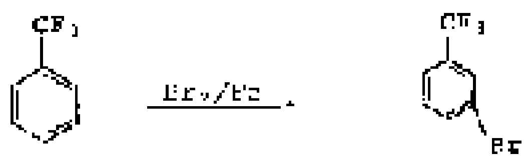
phenetole ⟶ o- and p-bromophenetole

(e) Reacts faster than benzene.



diphenylmethane → [A] p-bromobenzylbenzene
[B] o-bromobenzylbenzene

(f) Reacts slower than benzene.



benzotrifluoride ⟶ m-bromobenzotrifluoride

● **PROBLEM 11-5**

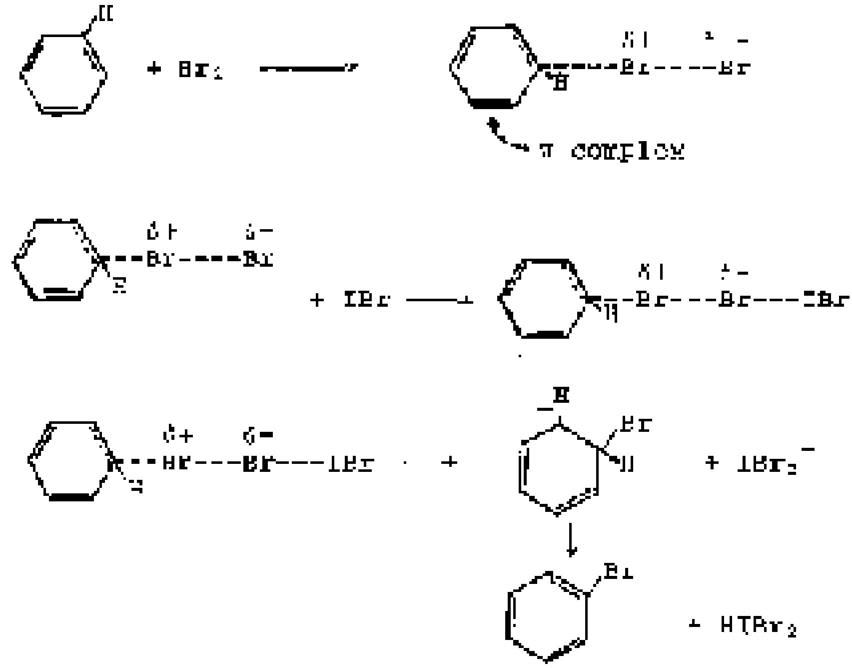
(a) The bromination of benzene is catalyzed by small amounts of iodine. Consider a possible explanation for this catalytic effect.
(b) The kinetic expression for the bromination of naphthalene in glacial acetic acid involves a term that is first order in naphthalene and second order in bromine. Consider how two molecules of bromine and one of naphthalene could be involved in the rate-determining step of bromination. Suggest a reason why the kinetic expression simplifies to first order in naphthalenes and first order in bromine in 50 per cent aqueous acetic acid.

Solution:

(a) Iodine first reacts with bromine to form iodobromide (IBr).

$$Br_2 + I_2 \longrightarrow 2\ IBr$$

Benzene will polarize the I-Br bond and will form a π complex. The iodobromide serves to further polarize the Br-Br bond until it breaks the bond.



The aromatic ring loses a proton to form bromobenzene.

(b) Naphthalene will form a π complex with the first bromine molecule. A second bromine molecule helps to break the Br-Br bond in the π complex. This would make the reaction first order in naphthalene and second order in bromine. The kinetic expression is:

$$R = K[A][B]^2,$$

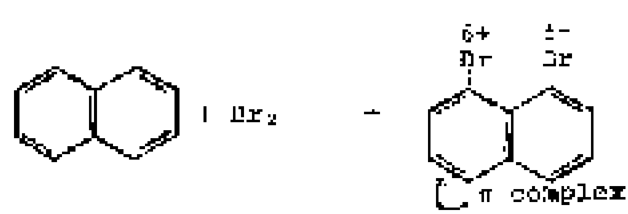
where R = rate of reaction

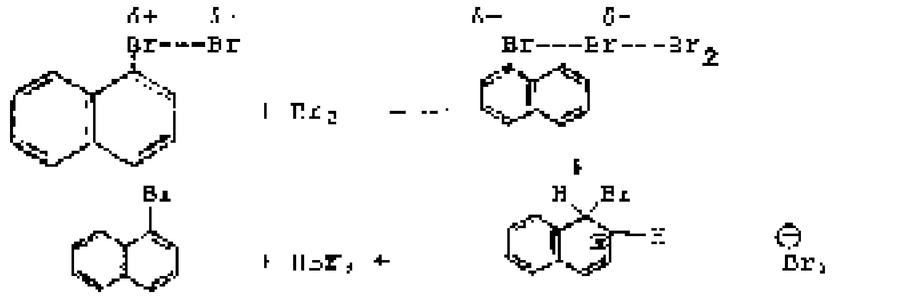
K = rate constant for the reaction,

$[A]$ = concentration of naphthalene and

$[B]$ = concentration of bromine.

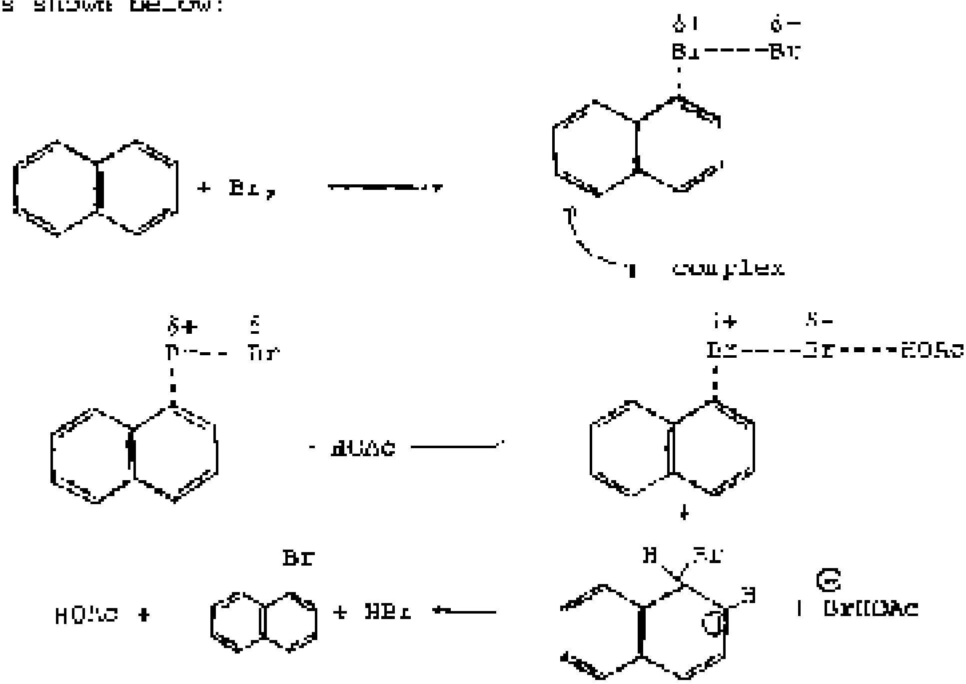
Kinetically, the reaction is third order overall. The reactions for the bromination of naphthalene in glacial acetic acid are given as:





The naphthalene is halogenated at the α position because that is the place where there is greatest stabilization.

In 50% aqueous acetic acid, the kinetic order in bromine is first order because the acid replaces bromine in breaking the Br-Br bond in the π complex. The sequence is shown below:



• PROBLEM 11-6

Certain activated benzene rings can be chlorinated by hypochlorous acid, HOCl, and this reaction is catalyzed by H^+. Can you suggest a possible function of H^+?

Solution: The mechanism of chlorination of activated benzene rings using hypochlorous acid involves the formation of Cl^+. The chlorine cation is extremely reactive because it has only six electrons in its valence shell. Once the chlorine cation has been formed, it undergoes an electrophilic aromatic substitution reaction with benzene.

Hypochlorous acid by itself will not readily form Cl^+ because ^-OH is a poor leaving group, and also because Cl^+ is very reactive and is more stable in the unionized form. In acidic solution, however, the oxygen in hypochlorous acid is protonated. This makes it easier for the Cl^+ to be formed because the leaving group would now be H_2O. Another reason why ionization is easier in acidic solution is that the protonated oxygen tends to give up its positive charge. Once ionization occurs, the Cl^+ is generated and can react with benzene.

In neutral solution:

$$\text{Difficult} \quad H - O - Cl \rightleftarrows H - O^- + Cl^+$$

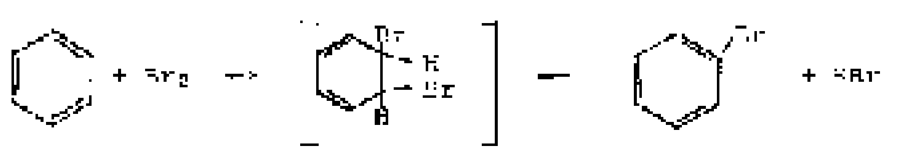
In acidic solution:

$$H - O - Cl + H^+ \rightleftarrows H - \overset{H}{\overset{|}{O^+}} - Cl$$

$$\text{Easy} \quad H - \overset{H}{\overset{|}{O^+}} - Cl \rightleftarrows H_2O + Cl^+$$

PROBLEM 11-7

On what basis (other than a thermodynamic one) could we decide whether or not the following addition-elimination mechanism for bromination of benzene actually takes place?

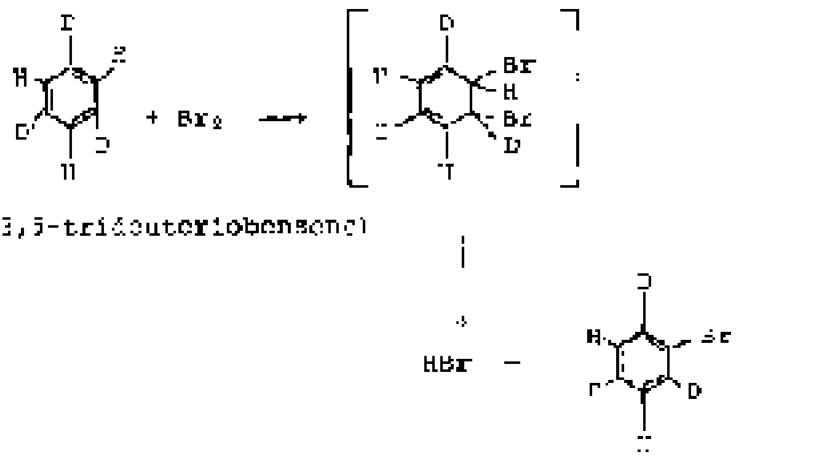


Solution: There are three ways in which we can decide whether bromination of benzene occurs in this fashion.

(1) If the addition product has any appreciable lifetime, it should be possible to trap it by addition to its double bonds. We could do this by using an excess of bromine or an oxidizing agent.

(2) If we brominated something like 1,3,5-trideuteriobenzene, we would expect to get 2,4,6 trideuteriobromobenzene as our major product. This is accounted for by the primary isotope effect, which explains why the carbon-hydrogen bond preferentially breaks to the carbon deuterium bond. Deuterium is more electronegative than hydrogen. Since carbon is more electronegative than both deuterium and hydrogen, the electronegativity difference between carbon and deuterium is less than that between carbon and hydrogen.

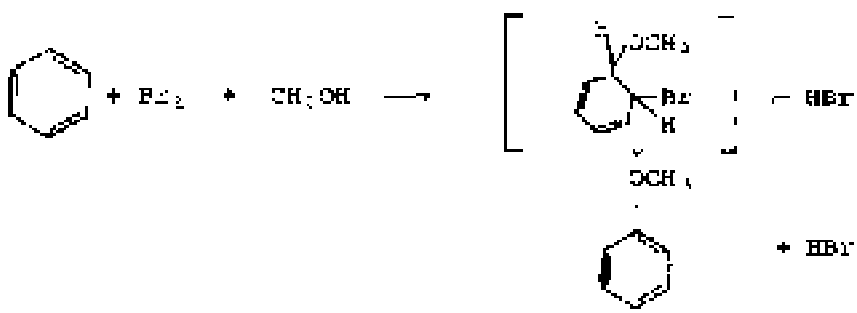
This means that the carbon-hydrogen bond is more polar than the carbon-deuterium bond, and is therefore easier to break. The reaction that would support the addition-elimination mechanism is:



(1,3,5-trideuteriobenzene)

(2,4,6,-trideuteriobromobenzene)

(b) If we brominated benzene in the presence of methanol, we should expect the formation of anisole ($C_6H_5OCH_3$) instead of bromobenzene.



The reason why it is the bromo group and not the methoxy group that leaves in the elimination step is that the bromo group is a better leaving group than the methoxy group. A good leaving group is one with weak basicity, that is, one with little tendency to donate a pair of electrons. This leads to the formation of anisole and not bromobenzene.

FRIEDEL-CRAFTS REACTIONS

• PROBLEM 11-8

Is BH_3 a nucleophile or an electrophile? Explain.

Solution: Electrophilic reagents are species with a deficiency of electrons, e.g. a vacant atomic orbital, sometimes bearing a positive charge. These reagents attack positions of high electron density or negative charge. H^+, $AlCl_3$, and SO_3 are examples of electrophiles.

Nucleophilic reagents are species with a lone pair of electrons, sometimes bearing a negative charge, which attack positions of low electron density or positive charge. OH^-, I^-, NH_3 are examples of nucleophiles.

Thus, to answer this question draw the electron dot formula of BH_3; if BH_3 has a lone pair of electrons or is deficient in electrons, it will be a nucleophile or an electrophile, respectively.

The electron dot formula of BH_3 is

$$\begin{matrix} & H & \\ & \cdot\cdot & \\ H & :B: & H \end{matrix}$$

The B-H bonds are sp^2-hybridized orbitals, therefore there is an empty p orbital. Since BH_3 is electron-deficient, it is an electrophile. In fact, it is a Lewis acid.

• PROBLEM 11-9

Suggest a reason why liquid hydrogen fluoride is preferable to concentrated, aqueous hydrobromic acid in inducing propene to react with benzene to produce isopropylbenzene.

Solution:

Hydrogen fluoride and hydrobromic acid are acidic compounds; both will protonate propene to form the isopropyl cation ($CH_3\overset{+}{C}HCH_3$) and not the n-propyl cation ($CH_3CH_2\overset{+}{C}H_2$). This is because secondary carbocations are more stable than primary carbocations. The isopropyl cation can undergo an electrophilic aromatic substitution reaction with benzene or it can react with halide ion (X^-) to form the isopropyl halide. The reason why hydrogen fluoride (HF) is preferred over hydrobromic acid (HBr) in inducing formation of isopropylbenzene is that HF will give less addition of halide ion to the isopropyl cation than will HBr. This is because of relative nucleophilicities. Nucleophilicity is a measure of the polarizability of basic, electron rich reagents called nucleophiles; if the electrons are easily polarizable (if the outer electron cloud is easily deformed) they will respond better to a positive charge. In general, polarizability increases as one moves down a group of elements in the periodic table; this is because the larger the atom, the more polarizable it is. Bromide is larger and therefore more polarizable than fluoride. Hence, bromide is more nucleophilic. The better the nucleophile, the faster it will react with a source of positive charge. Since bromide is a better nucleophile than fluoride, there will be more unreacted isopropyl cation in a solution of HF than in HBr.

This greater amount of isopropyl cation in HF can react with benzene to form isopropyl benzene. Hence, hydrogen fluoride is preferred to hydrobromic acid in inducing formation of isopropylbenzene because hydrogen fluoride will give a greater yield of product.

• PROBLEM 11-10

How do you account for the fact that benzene in the presence of $AlCl_3$ reacts: (a) with n-propyl bromide to give isopropylbenzene; (b) with isobutyl bromide to yield tert-butylbenzene; (c) with neopentyl bromide to yield tert-pentylbenzene? (d) By which of the alternative mechanisms for the Friedel-Crafts reaction are these products probably formed?

Solution: Aromatic compounds can be alkylated by using an alkylating agent in the presence of aluminum chloride, the "Friedel-Crafts catalyst." The alkylating agent is an alkyl halide which will form a complex with aluminum chloride. The complex breaks down to form a carbocation. The carbocation will undergo rearrangements if it will lead to a more stable species. Carbocation stability follows the order: tertiary > secondary > primary > $\overset{\oplus}{C}H_3$. The electron rich aromatic ring attacks the carbocation. Subsequent proton loss gives an alkylated aromatic compound.

$$\text{(a) } \underset{\text{(n-propyl bromide)}}{CH_3CH_2CH_2-Br} + AlCl_3 \rightarrow CH_3CH_2-\underset{H}{\overset{H}{\overset{|\delta+}{C}}}---Br-----\overset{\delta-}{AlCl_3}$$

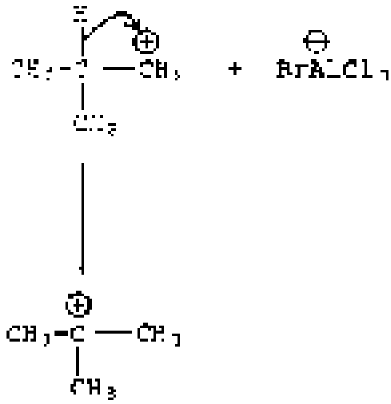
$$+$$

$$CH_3CH_2\overset{\oplus}{C}H_2 + Br\overset{\ominus}{A}lCl_3$$

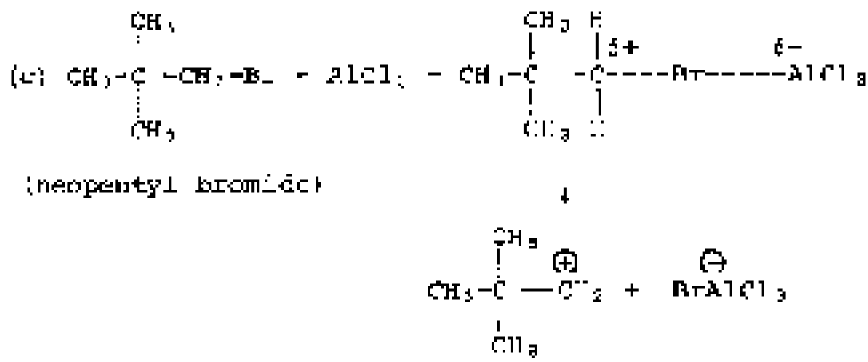
$$CH_3-\underset{H}{\overset{H}{C}}-\overset{\oplus}{C}H_2 \xrightarrow[\text{hydride shift to a more stable carbocation}]{} CH_3-\underset{H}{\overset{\oplus}{C}}-CH_3$$

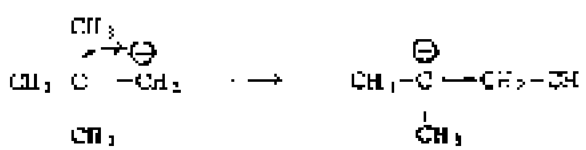
The primary carbocation underwent a 1,2-hydride shift to form the more stable secondary carbocation. The benzene ring now reacts with the isopropyl cation to form isopropylbenzene.

$$\text{(b) } \underset{\text{(isobutyl bromide)}}{CH_3-\underset{CH_3}{CH}-CH_2-Br} + AlCl_3 \rightarrow CH_3-\underset{CH_3}{CH}-\underset{H}{\overset{H}{\overset{\delta+}{C}}}---Br-----\overset{\delta-}{AlCl_3} +$$



The primary carbocation underwent a 1,2-hydride shift to form the more stable tertiary carbocation. The benzene ring now reacts with the t-butyl carbocation to form t-butylbenzene.

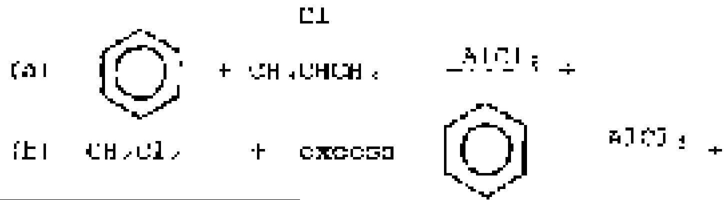




The primary carbocation underwent a 1,2 methyl group shift to form the more stable tertiary carbocation. The benzene ring now reacts with the tertiary carbocation to form t-pentylbenzene.

(d) There are two possible mechanisms for a Friedel-Crafts alkylation: a concerted process and a two step process. In the concerted process, the benzene ring reacts with the alkyl halide-aluminum chloride complex to form the alkylated benzene. In this mechanism, there is no carbocation rearrangement because there is no free carbocation stage. In the two step process, however, there is a free carbocation stage. The alkyl halide complexes with the aluminum chloride. This complex breaks down to form the free carbocation, which can then undergo rearrangement to form a more stable species. The benzene ring can then react with the carbocation to form the alkylated benzene. Therefore, reactions (a), (b) and (c) must have followed the two step mechanism; that is, the carbocation mechanism.

Complete the following reactions. Name each organic product.



Solution: In alkylation reactions, the alkyl group from any alkyl halide may be substituted on the benzene ring in the presence of a Lewis acid such as aluminum chloride ($AlCl_3$).

In the first reaction the chlorine atom is pulled off the isopropylchloride molecule and replaced by the benzene ring. This reaction is presented in figure A. The product is isopropylbenzene.

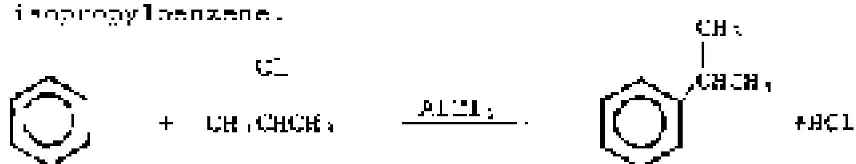


Figure A

In the second reaction, the dihalide (methylene chloride) may react with 2 benzene rings to yield a diphenyl compound. Since benzene is in excess this reaction will take place. The second reaction is presented in figure B and the product is diphenylmethane.

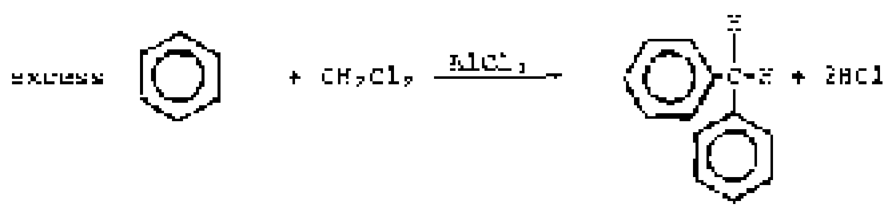
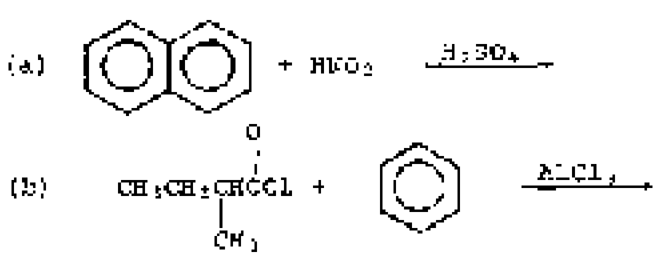
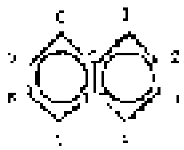


Figure B

Complete the following reactions. Name each organic product.



Solution: Naphthalene and other aromatic hydrocarbons also undergo aromatic substitution reactions. Naphthalene (shown in figure A) substitutes at the 1- or α-position - that is, on a carbon atom adjacent to the other ring. The numbering of the positions of naphthalene is shown. It can be seen that naphthalene has four α positions at 1,4,5, and 8 - and four β positions - at 2, 3, 6, and 7.



naphthalene

figure A

The nitration of naphthalene is shown in figure B and the product is α-nitronaphthalene (1-nitronaphthalene).

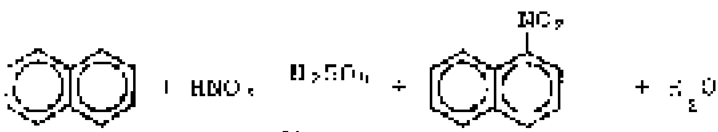


figure B

The second reaction is an acylation. In the presence of a Lewis acid, an acid halide also reacts with benzene. The product of this reaction is a phenyl ketone. The general acylation reaction is shown in Figure C. The chlorine atom is replaced by the benzene ring to produce a phenyl ketone.

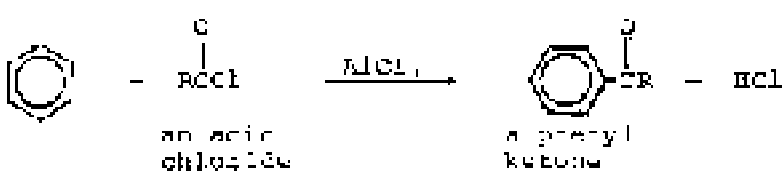


figure C

The complete reaction for the second equation is shown in figure D. The product is sec butyl phenyl ketone.

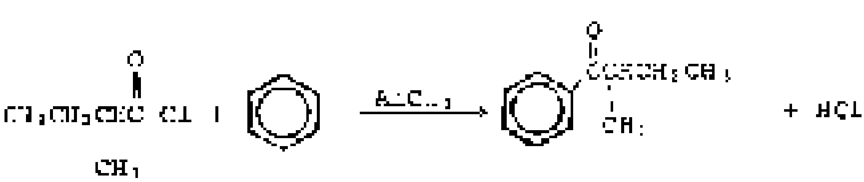


figure D

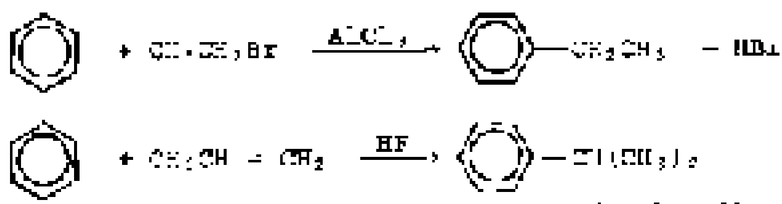
Provide the missing reactant or reaction condition for the following:

(a) Benzene + __?__ $\xrightarrow{AlCl_3}$ t-butylbenzene

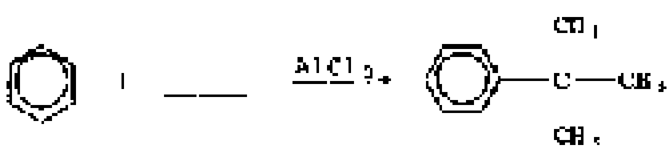
(b) Dimethyl sulfate + __?__ → ethylbenzene.

Solution: The reactions of benzene are very important in the study of aromatic compounds. This necessitates the learning of some of the more important reactions that the benzene ring can undergo. One such important reaction is that of alkylation (Friedel-Crafts reaction).

Alkylation (reaction (a)) occurs when alkyl halides react with benzene in the presence of a Lewis acid (ex: $AlCl_3$) or when alcohols or olefins react with benzene in the presence of a mineral acid. For example,



If the structures of benzene and t-butylbenzene are drawn for reaction (a), it will make the reaction clearer.

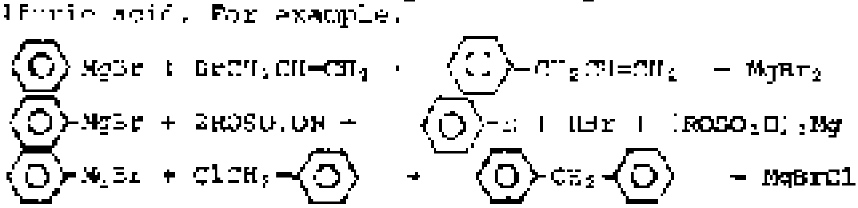


From previous examples of an alkylation reaction, the missing reactant must have the structure of

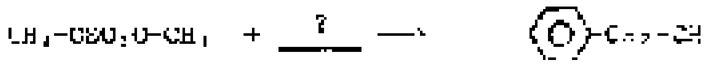
$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ X \end{array} \qquad \text{where } X$$

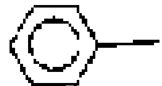
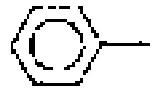
can be a halogen (Cl, Br, I) or a hydroxyl group (OH). This missing reactant can also be any isobutyl halide or hydroxyl that will rearrange.

Another important reaction which applies not only to aromatic but to all organic compounds is illustrated by reaction (b). This alkylation reaction occurs by way of the Grignard reagent. Grignard reagents are alkylated by very active halides (such as allyl and benzyl) and esters of sulfuric acid. For example,



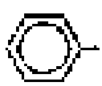
To find the missing reactant in reaction (b), first draw the structures of dimethyl sulfate and ethylbenzene.



From the previous examples, the missing reactant must have the structure of CH_2MgBr. The bromine can be replaced by any halogen, so that the general structure for the missing reactant is CH_2MgX where X is any halogen.

• PROBLEM 11-14

Prepare a ketone from each of the following precursors by the Friedel-Crafts acylation method.

(a) $-COCl$ (b) $CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3$

Benzoyl Chloride   Acetic Anhydride

Solution: One of the most important syntheses of ketone preparation is the Friedel-Crafts acylation. This reaction is modified to involve the use of acid chlorides and anhydrides rather than alkyl halides. In this reaction an acyl group, RCO—, is always reacted with the ring of an aromatic compound, thus forming a ketone. The catalyst used in these reactions is aluminum chloride, $AlCl_3$, and having the general equation:

$$R-\underset{\underset{O}{\|}}{C}Cl + ArH \xrightarrow{AlCl_3} R-\underset{\underset{O}{\|}}{C}-Ar + HCl$$

Acid Chloride   Aromatic Hydrocarbon   Ketone

Acid chlorides are the most common source of compounds for Friedel-Crafts acylations but they are not the sole source. Carboxylic acid anhydrides are also used in this capacity, the other product being a carboxylic acid. The general equation for this type of reaction is:

$$R\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R + ArH \xrightarrow{AlCl_3} R\underset{\underset{O}{\|}}{C}-Ar + R\underset{\underset{O}{\|}}{C}OH$$

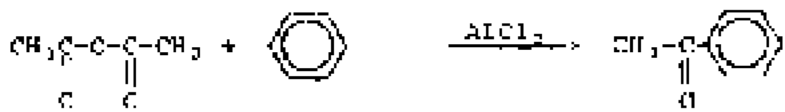
Anhydride   Aromatic Hydrocarbon   Ketone   Carboxylic Acid

These reactions, either using acid chlorides or anhydrides yield a ketone as the main product and either an inorganic or an organic acid as the byproduct.

With the above discussion about the Friedel-Crafts acylation, and the general equations for the ketone synthesis, problems (a) and (b) can be derived.

(a)  +HCl

Benzoyl chloride Benzene Benzophenone (Phenyl Ketone)

(b) 

Acetic Anhydride Benzene Acetophenone

$+ CH_3COOH$

Acetic Acid

SULFONATION

• PROBLEM 11-15

Give structures and names of the principal organic products expected from the monosulfonation of:

(a) cyclohexylbenzene
(b) benzenesulfonic acid
(c) salicylaldehyde (o-HOC_6H_4CHO)
(d) m-nitrophenol
(e) p-methylanisole
(f) o-nitroacetanilide (o-$O_2NC_6H_4NHCOCH_3$)
(g) o-xylene

Solution: When there are two substituents on an aromatic ring, one activating and one deactivating, the activating substituent will generally direct the addition of any incoming electrophiles. If there are two activating substituents on the aromatic ring, the electrophilic substitution will be directed by the more strongly activating substituent. The more strongly activating substituent is the one that can best stabilize the positive charge of the intermediate carbonium ion.

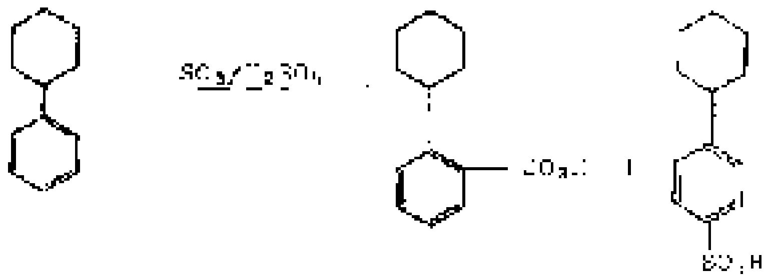
Sulfonation involves the addition of a sulfonyl group (SO_3H) to the aromatic ring. The general reaction for sulfonation may be written as:

$$ArH + HOSO_3H \xrightarrow{SO_3} ArSO_3H + H_2O$$

(A sulfonic acid)

All products of sulfonation may be named as sulfonic acids, with $-SO_3H$ on carbon number one.

(a)



cyclohexylbenzene ——→ o and p-cyclohexylbenzene sulfonic acid

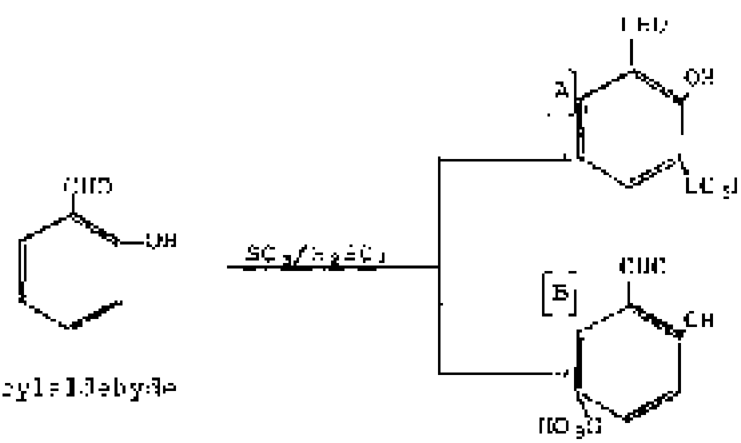
The cyclohexyl substituent is an activating one, so that it directs ortho and para.

(b)

benzenesulfonic acid ——→ m-benzenedisulfonic acid

The sulfonyl group is deactivating and directs meta.

(c)

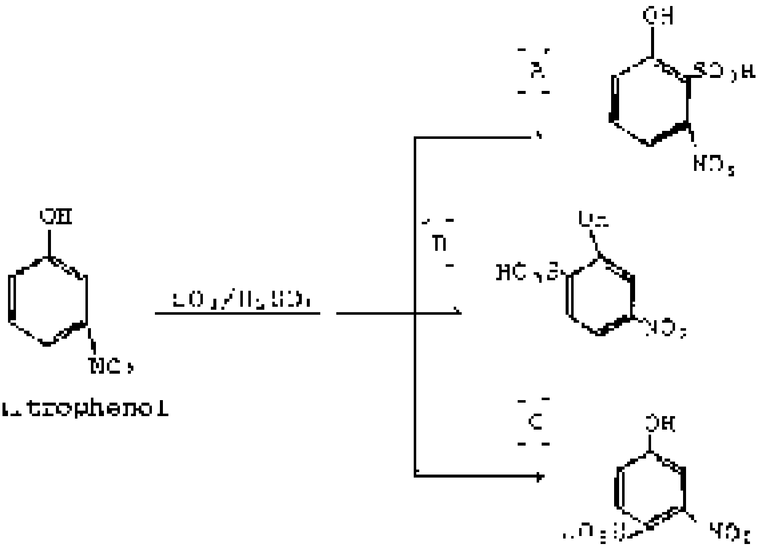


A   3-formyl-2-hydroxybenzenesulfonic acid

B   3-formyl-4-hydroxybenzenesulfonic acid

Even though the -CHO is meta directing, the -OH is strongly activating so that it prevails and directs o and p.

(d)

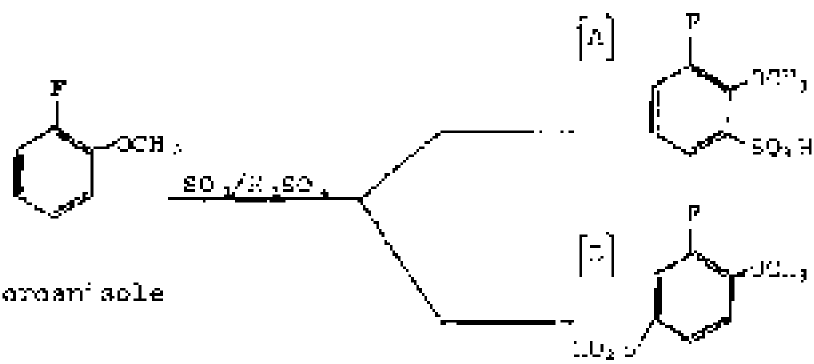


o-nitrophenol

A 2-hydroxy-6-nitrobenzenesulfonic acid
B 2-hydroxy-4-nitrobenzenesulfonic acid
C 4-hydroxy-2-nitrobenzenesulfonic acid

Again, the activating $-OH$ prevails over the deactivating $-NO_2$ so that the orientation is o and p.

(e)

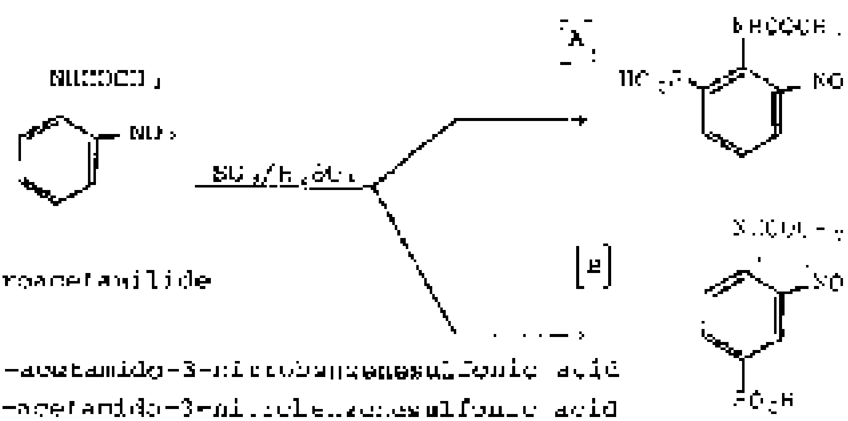


o-fluoroanisole

[A] 3-fluoro-2-methoxybenzenesulfonic acid
[B] 3-fluoro-2-methoxybenzenesulfonic acid

The moderately activating $-OCH_3$ predominates over the halide, F.

(f)

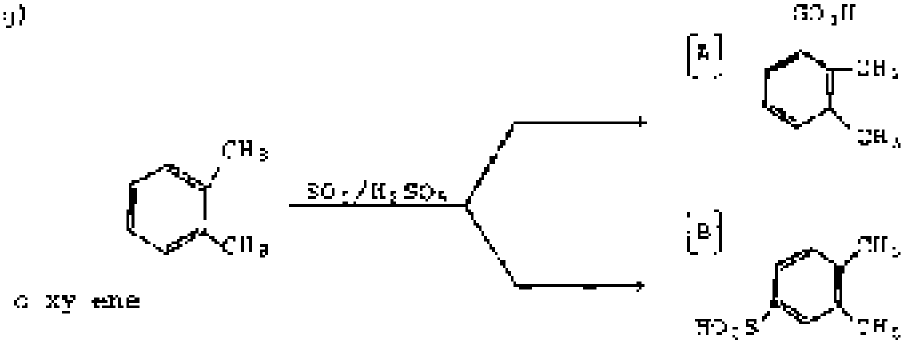


o-nitroacetanilide

[A] 2-acetamido-3-nitrobenzenesulfonic acid
[B] 4-acetamido-3-nitrobenzenesulfonic acid

Both $-NHCOCH_3$ and $-NO_2$ activate the same positions on the ring.

(g)



A 2,3-dimethylbenzenesulfonic acid

B 3,4-dimethylbenzenesulfonic acid

The methyl group is activating and directs the sulfonyl group to ortho and para.

EFFECT OF SUBSTITUENTS ON REACTIVITY

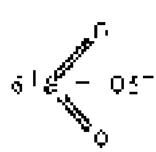
• PROBLEM 11-16

Explain the following observations: (1) The ortho-para ratio of the products obtained by sulfonation of toluene is lower than that of nitration; (2) The ortho-para ratio of the products obtained by nitration of isopropylbenzene is lower than that of nitration of toluene.

Solution: (1) The sulfonation of aromatic compounds such as toluene occurs by treatment with concentrated sulfuric acid. One has the formation of the electrophilic reagent, SO_3:

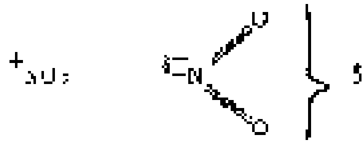
$$2H_2SO_4 \rightleftarrows H_3O^+ + HSO_4^- + SO_3$$

SO_3 is a strong electrophile because of the partial positive charge on the sulfur atom:



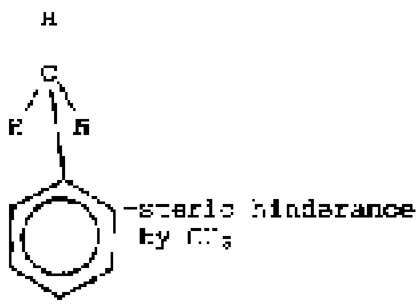
In nitration of aromatic compounds, one starts treatment by mixing concentrated nitric and sulfuric acids to form the electrophilic reagent $^+NO_2$, the nitronium ion which attacks the ring

$$2H_2SO_4 + HONO_2 \rightleftarrows {}^+NO_2 + 2HSO_4^- + H_3O^+$$



It can be seen from the representation of SO_3 and $^{+}NO_2$ that the former is more bulky. Thus, the more bulky SO_3 will be more hindered in its attack at the ortho position by CH_3 that is, the lower ratio in the case of sulfonation can be accounted for by steric hinderance by the methyl group of toluene at the ortho position. The larger or more bulky the group that attempts to bind at this position, the more difficult it becomes.

Toluene

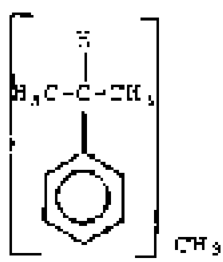


If it

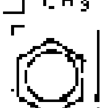
is easier to bind somewhere else, the electrophilic reagent will. Methyl directs or activates ortho and para, so that the SO_3 group will prefer to bind to para, which causes the reduced ratio as compared to nitration.

(2) Here, one again deals with steric hinderance. However, this time the variable is not the electrophilic reagent binding, but the substituents on the benzene ring.

Isopropylbenzene



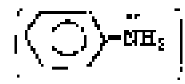
has a more bulky substituent than toluene

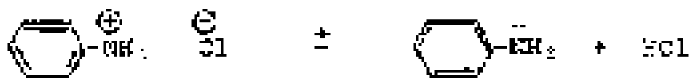


. Hence for the same reasons as noted in (1), the isopropylbenzene will hinder binding of the nitronium species at the ortho ring more effectively than toluene due to the bulkiness of the isopropyl.

• PROBLEM 11-17

Even in dilute acidic solution, aniline, which exists mainly as the anilinium ion ($C_6H_5NH_3^{+}$), undergoes o,p-substitution. Account for this.

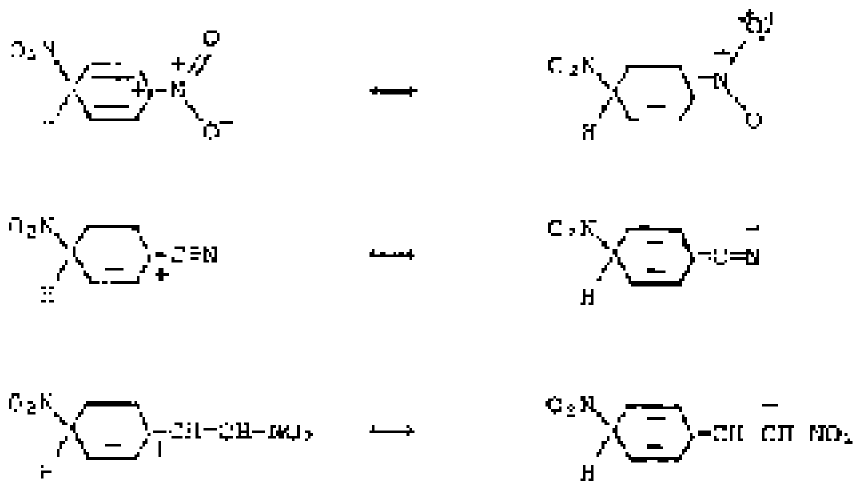
Solution: In acidic solution, aniline  exists in equilibrium with the anilinium ion $(C_6H_5NH_3^+)$. Assume that hydrochloric acid was used to acidify an aqueous solution of aniline. The solution will constantly be undergoing an acid-base equilibrium as follows:



In acidic solution, aniline undergoes o,p-substitution because it is the  in low concentration that reacts with the electrophile. The amino group (NH_2) is an ortho, para director because it can stabilize a positive charge. As more and more aniline is reacted, the acid-base equilibrium is shifted to the right. This produces more aniline which will react to give o,p-substitution.

• PROBLEM 11-18

Explain how comparison of the following resonance structures for para substitution with the corresponding ones for meta substitution might (or might not) lead to the expectation that ortho-para orientation would be favored for the nitro, cyano, and $-CH{=}CHNO_2$ groups.



Solution: The ortho, para orientation for NO_2, CN, and $CH{=}CHNO_2$ groups leads to an activated complex with an unfavorable distribution of charge. Ortho, para substitution in aromatic nitro compounds will place two positive charges in close proximity to one another. This situation is less stable than the activated complex for meta substitution where this proximity is relieved.

Ortho, para substitution in aromatic cyano compounds places a partial positive charge on the aromatic carbon bearing the cyano group. The cyano group is an electron withdrawing group because it contains an sp hybridized carbon and a nitrogen, both of which are more electronegative than the sp^2 hybridized carbon to which they are bonded. The electron withdrawing ability of the cyano group causes destabilization by intensifying this positive charge. The meta orientation places no charge on the carbon bonded to the cyano group. This situation is more stable than in ortho, para orientation.

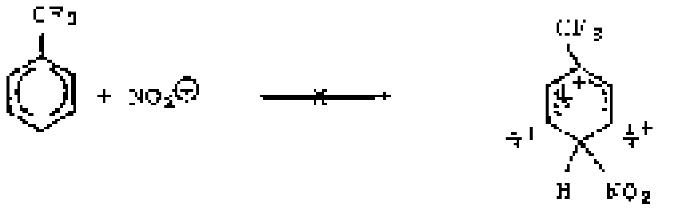
Ortho, para orientation in aromatic compounds bearing the $-CH=CH-NO_2$ group places a positive charge on the carbon adjacent to the electron withdrawing nitro group. This destabilizes the molecule and makes the $-CH=CH-NO_2$ group a ring deactivator. This would normally make the $-CH=CH-NO_2$ group a meta directing group. In actuality, however, the $-CH=CH-NO_2$ group is an ortho, para director with deactivation. The reason for this is that the $-CH=CH-NO_2$ group has a destabilizing effect as well as a stabilizing effect. The destabilizing effect is a result of the electron withdrawing nitrogroup residing next to a positively charged carbon in the activated complex for ortho, para substitution. The nitro group makes the cationic carbon more positive, an inductive effect. $-CH=CH-NO_2$ also has a stabilizing effect. In ortho, para orientation the carbon carbon double bond is involved in the resonance for the molecule. This resonance effect tends to release electrons and stabilize the molecule. This is more important than the inductive effect for orientation of substituents. Hence, the $-CH=CH-NO_2$ group is an ortho, para directing group with deactivation. This situation is similar to the case of the halogens.

• PROBLEM 11-19

Explain why the $-CF_3$, $-NO_2$, and $-CHO$ groups should be meta-orienting with deactivation.

Solution: All three groups have a full or partial positive charge on the atom directly bonded to the aromatic ring. The three fluorine atoms, being highly electronegative, tend to severely decrease the electron density about the carbon atom. This gives the carbon a partial positive charge. The nitro group is represented by two principal resonance structures, both of which place a full positive charge on the nitrogen. The highly electronegative oxygen atom of the formyl group decreases the electron density about the carbon, which gives the carbon a partial positive charge. So, $-CF_3$, $-NO_2$, and $-CHO$ will possess a partial or full positive charge on the atom bonded to the aromatic carbon of the ring.

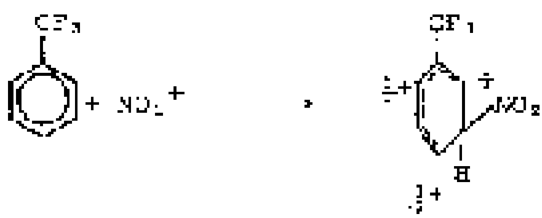
In such a situation, aromatic electrophilic substitution will follow a meta pathway. This is explained by the fact that when an electrophile (an electron-deficient species) attacks the aromatic ring, a carbonium ion results, that is, positive charge is introduced. If the electrophile added ortho or para to the substituent, some of this positive charge would be centered at the aromatic carbon bonded to the atom of the substituent that already possesses positive charge. This would be an unfavorable situation because of the proximity of two like charges. The situation is illustrated using the substituent CF_3 and the nitronium ion ($^+NO_2$) as the electrophile below:



unfavorable

The nitronium ion added para to $-CF_3$ so that a partial positive charge now exists under the CF_3, which already has positive charge character.

Now, if the electrophile adds meta, this close proximity of like charges is avoided. The positive charge of the electrophile is not centered directly under the substituent as shown below:



Since the close proximity of like charges is relieved, this intermediate is more stable. This, then accounts for the meta-directing orientation of $-CF_3$, $-NO_2$, and $-CHO$.

These three groups all withdraw electrons, so that they intensify the positive charge in the intermediate carbonium ion. This results in deactivation of the aromatic ring.

• PROBLEM 11-20

Starting with the definition of partial rate factor, derive an expression relating p_f^G to the rate of substitution para to G in C_6H_5G.

Solution: The partial rate factor compares the rate of substitution at a single position on C_6H_5G to the rate of a single substitution on benzene. The partial rate factor for the para position $\left(p_f^G\right)$ is defined to be

$$p_f^G = \frac{K_p G}{K_H} \qquad \text{where}$$

$K_p G$ = rate of reaction for para attack upon C_6H_5G and

K_H = rate of substitution at one position on benzene.

The rate of substitution para to G in C_6H_5G can be expressed as a function of the overall rate of substitution in C_6H_5G and the fraction of para isomer formed.

$$\text{fraction of para product} = \frac{\%\ \text{para product}}{100}$$

$$\frac{\%\ \text{para product}}{100} = \frac{K_p G}{K_{C_6H_5G}}$$

where $K_{C_6H_5G}$ = overall rate of reaction of C_6H_5G.

From this equation, we find that:

$$K_p G = \frac{\%\ \text{para product}}{100} \times K_{C_6H_5G}$$

Substituting this equality for $K_p G$ into the partial rate factor equation will give us:

$$p_f^G = \frac{\%\ \text{para product}}{100} \times \frac{K_{C_6H_5G}}{K_H}$$

Since the overall rate of substitution on benzene must be six times the rate of substitution at any one position on benzene, we can form the following equality:

$$K_H = \frac{1}{6} K_{C_6H_6}, \qquad \text{where}$$

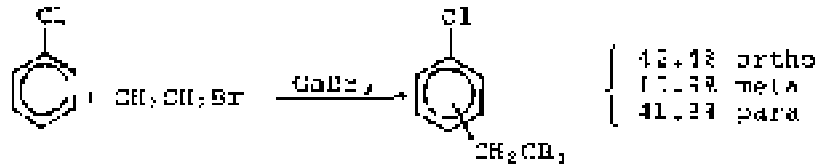
K_H = rate of substitution at one position on benzene

and $K_{C_6H_6}$ = overall rate of substitution on benzene.

Substituting the equality for K_H into the partial rate factor equation will give us an expression relating p_f^G to the rate of substitution para to G in C_6H_5G.

$$p_f^G = \frac{\%\ \text{para product}}{100} \times \frac{6\ K_{C_6H_5G}}{K_{C_6H_6}}$$

Ethylation of chlorobenzene is slower than is ethylation of benzene ($k_{C_6H_5Cl}/k_{C_6H_6}$ = 0.20). Using this, and the product distribution shown below, calculate o_f^{Cl}, m_f^{Cl}, and p_f^{Cl} for this alkylation.



Solution: The partial rate factors for the ortho, meta and para positions are o_f^G, m_f^G, and p_f^G, respectively. They are defined to be:

$$o_f^G = \frac{K_o G}{K_H}\ ;\ m_f^G = \frac{K_m G}{K_H}\ ;\ \text{and}\ p_f^G = \frac{K_p G}{K_H}\ ,\quad \text{where}$$

$K_o G$ = rate of ortho attack on C_6H_5G

$K_m G$ = rate of meta attack on C_6H_5G

$K_p G$ = rate of para attack on C_6H_5G

K_H = rate of substitution at one position on benzene.

Using these equations, one can derive an expression relating the partial rate factors to the rate of ortho, para, and meta substitution in C_6H_5G.

$$\frac{\%\ \text{ortho product}}{100} = \frac{2\ K_o G}{K_{C_6H_5G}}$$

$$\frac{\%\ \text{meta product}}{100} = \frac{2\ K_m G}{K_{C_6H_5G}}$$

$$\frac{\%\ \text{para product}}{100} = \frac{K_p G}{K_{C_6H_5G}}$$

where $K_{C_6H_5G}$ = overall rate of substitution of C_6H_5G and the coefficients 2,2 and 1 represent the possible number of sites of attack.

$$K_H = \frac{1}{6}\left(K_{C_6H_6}\right)$$

where $K_{C_6H_6}$ = overall rate of substitution of benzene.

The above equations together with the partial rate factor equations can be used to get the following expressions:

$$o_f^G = \frac{\%\ \text{ortho isomer}}{100} \times \frac{3\ K_{C_6H_5G}}{K_{C_6H_6}}$$

$$p_f^G = \frac{\%\ \text{para product}}{100} \times \frac{6\ K_{C_6H_5G}}{K_{C_6H_6}}$$

$$m_f^G = \frac{\%\ \text{meta product}}{100} \times \frac{3\ K_{C_6H_5G}}{K_{C_6H_6}}$$

Since we are given the ratio

$$\frac{K_{C_6H_5Cl}}{K_{C_6H_6}} = 0.20 \qquad \text{and the product distribution,}$$

we can calculate o_f^G, m_f^G, and p_f^G, where G is chlorine.

$$o_f^{Cl} = \frac{42.4}{100} \times 3(0.20) = 0.25$$

$$m_f^{Cl} = \frac{15.9}{100} \times 3(0.20) = 0.09$$

$$p_f^{Cl} = \frac{41.3}{100} \times 6(0.20) = 0.50.$$

• PROBLEM 11-22

Even though 1,3,5-trinitrobenzene (TNB) has more shattering power (more brisance) and is no more dangerous to handle, 2,4,6-trinitrotoluene (TNT) has always been the high explosive in more general use. Can you suggest a reason (connected with manufacture) for the popularity of TNT? (Benzene and toluene are both readily available materials; for many years benzene was cheaper.)

Solution: The difference between toluene and benzene is that toluene has a methyl group substituent on the aromatic ring. The methyl group is an activating group; it releases electrons so that it stabilizes the intermediate carbonium ion in electrophilic aromatic substitution.

The activated complex for nitration of toluene is slightly stabilized by the activating methyl group. Since benzene has no such groups on the aromatic ring, its activated complex for nitration is not as stable as toluene's. Since benzene will have a less stable activated complex than toluene, the rate of reaction is slower for benzene than for toluene. Toluene is more easily nitrated, and therefore more easily polynitrated than benzene.

Arrange the following in order of reactivity toward ring nitration, listing by structure the most reactive at the top, the least reactive at the bottom.

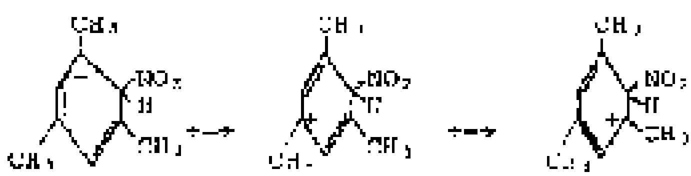
(a) benzene, mesitylene ($1,3,5-C_6H_3(CH_3)_3$), toluene, m-xylene, p-xylene

(b) acetanilide ($C_6H_5NHCOCH_3$), acetophenone ($C_6H_5COCH_3$), aniline, benzene

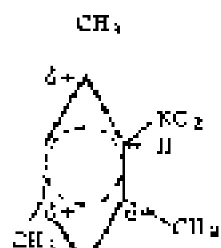
(c) 2,4-dinitrochlorobenzene, 2,4-dinitrophenol.

Solution: Reactivity towards ring nitration depends upon the energy level of the activated complex. The higher the energy level of the activated complex, the less stable is the activated complex and the slower is the rate of reaction. Conversely, the more stable is the activated complex, the greater are the rate of reaction and reactivity.

(a) When nitronium ion ($^+NO_2$) is added to benzene, the positive charge is distributed amongst three secondary carbons. In the case of ortho, para substitution in mesitylene, the positive charge in the activated complex is distributed amongst three tertiary carbons as shown.



-or-



Since tertiary carbocations are more stable than secondary carbocations, the activated complex for mesitylene is more stable than for benzene. Therefore, mesitylene is more reactive toward ring nitration than is benzene. Looking at the other compounds' activated complexes for ortho, para substitution, we find: toluene has two secondary carbocations and one tertiary carbocation; m-xylene has one secondary carbocation and two tertiary carbocations; p-xylene has two secondary carbocations and one tertiary carbocation. We see that toluene and p-xylene have the same number of secondary and tertiary carbocations in the activated complex. The activated complex for p-xylene is, however, more stable than for toluene because of the presence of an extra methyl group. The methyl group has an activating effect on the entire molecule. From the relative stabilities of the activated complexes, we can show the relative reactivities toward ring nitration to be:

mesitylene > m-xylene > p-xylene > toluene > benzene.

(b) In its activated complex, acetanilide has its positive charge distributed amongst three carbons, one of which is bonded to an acetamido group. The acetamido group activates the ring by stabilizing the positive charge. Acetophenone is an aromatic ring with an acetyl group. The acetyl group destabilizes the ring and will likewise destabilize the activated complex. Aniline is an aromatic ring with an activating amino group. The amino group will stabilize the positive charge in aniline's activated complex more than the acetamido group will stabilize the positive charge in acetanilide's activated complex. This is because the acetyl portion of the acetamido group is electron withdrawing and weakens the full stabilizing effect of the activating substituent. Benzene is an aromatic ring with no substituents. Acetophenone is the least reactive; it is the only compound with a deactivating group. Both aniline and acetanilide are more reactive towards nitration than benzene, because they both have an activating group, whereas benzene has none. The relative reactivity towards ring nitration is:

aniline > acetanilide > benzene > acetophenone.

(c) The activated complex for the nitration of 2,4-dinitrochlorobenzene has some positive charge nearby the deactivating chloro group. The electron withdrawing chloro group destabilizes the positive charge. In the case of 2,4-dinitrophenol, there is some positive charge nearby the activating hydroxyl group. The hydroxyl group stabilizes positive charge in the activated complex. Since both compounds have two nitro groups in the same relative positions, the reactivity towards ring nitration is:

2,4-dinitrophenol > 2,4-dinitrochlorobenzene.

SYNTHESIS

• PROBLEM 11-24

Outline all steps in the laboratory synthesis of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents. Assume that a pure para isomer can be separated from an ortho, para mixture.

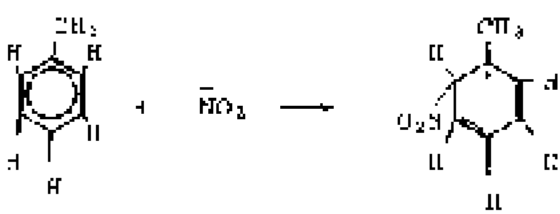
(a) p-nitrotoluene
(b) p-bromonitrobenzene
(c) m-bromobenzenesulfonic acid
(d) p-bromobenzoic acid
(e) o-iodobenzoic acid
(f) 1,3,5-trinitrobenzene
(g) 3,5-dinitrobenzoic acid

Solution: (a) Nitration of an aromatic compound is the addition of a nitro group (NO_2) to that compound. A nitro group can be added onto an aromatic ring by reacting it with a mixture of concentrated nitric acid (HNO_3) and concentrated sulfuric acid (H_2SO_4). The electrophile in this case is the nitronium ion, $\overset{+}{N}O_2$. The electrophile is supplied by the nitric acid. The purpose of the sulfuric acid is to increase the concentration of nitronium ion by protonating the nitric acid.

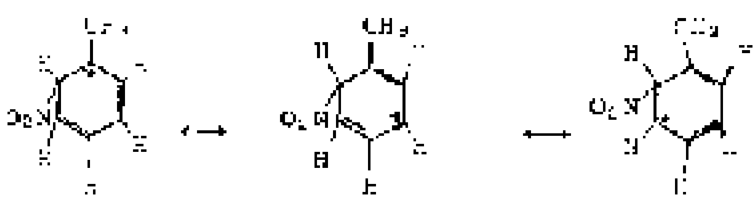
$$HONO_2 + 2\,H_2SO_4 \rightleftharpoons H\overset{+}{O}{-}NO_2\;(H) + HSO_4^- + H_2SO_4 \rightleftharpoons O{=}\overset{+}{N}{=}O + H_3O^+ + 2\,HSO_4^-$$

nitronium ion

Nitration of toluene results in the addition of nitronium ion mainly at the ortho and para positions of toluene. This occurs because the methyl group in toluene is an activating group; it will tend to stabilize a nearby positive charge. When the nitronium ion adds to toluene, it introduces a resonance stabilized positive charge onto the aromatic ring. When the nitronium ion adds to the ortho or para positions of toluene, the resonance stabilizing structures place some positive charge on the aromatic carbon bonded to the methyl group. The positive charge is stabilized by the electron release of the methyl group. When the nitronium ion adds to the meta position of toluene, the positive charge is not positioned directly under the methyl group so that the stabilization by electron release is not as extensive. Since chemical reactions tend to occur through the activated complex with the lowest energy (or the greatest amount of stabilization), nitration of toluene will occur mainly at the ortho and para positions.

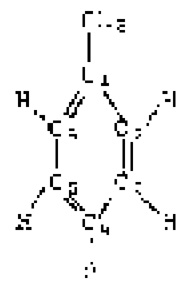


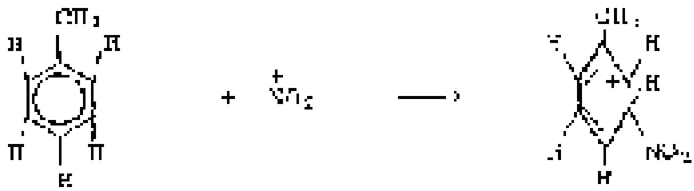
Addition of nitronium ion to ortho position.



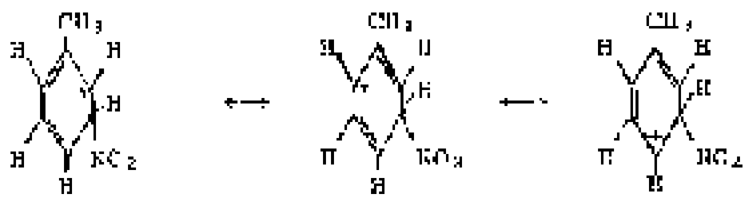
Resonance stabilization of resulting cation. Note that one of the resonance structures has the positive charge on carbon number one, which is especially stable due to the electron release.

IUPAC numbering system for toluene

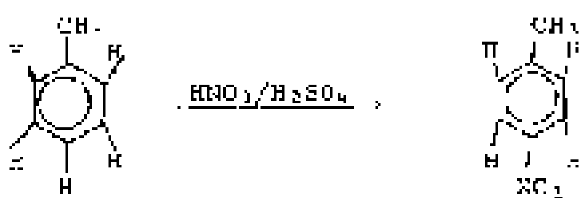




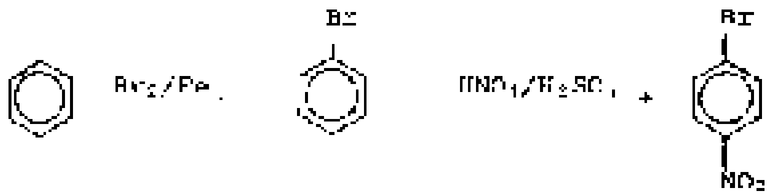
Addition of nitronium ion to meta position.



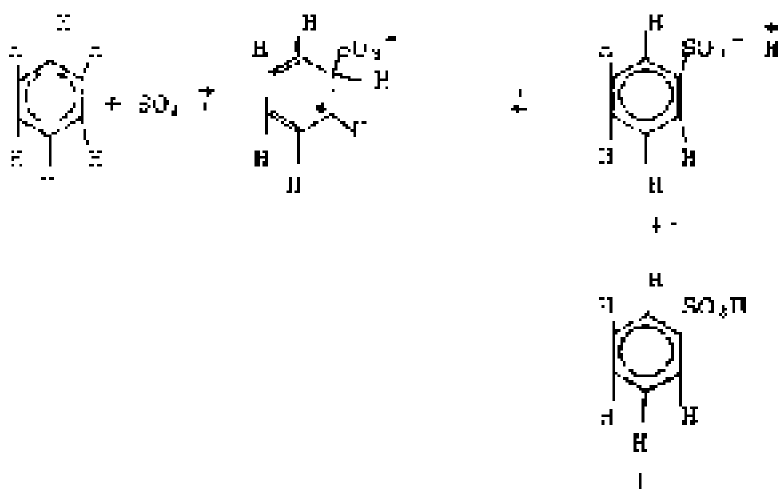
Resonance stabilization of meta substituted toluene. Note that positive charge does not reside directly under the methyl group. This is, therefore, not as low in energy as the ortho and para substituted toluenes. As a result, the main products of nitration of toluene are o-nitrotoluene and p-nitrotoluene. These can be separated to give p-nitrotoluene. The synthesis of p-nitrotoluene from toluene can be summarized as:



(b) The problem faced here is which substituent should be added first: the bromo group or the nitro group? Since we want p-bromonitrobenzene, the first substituent to be added should be one which directs the addition of the second substituent in a para position. The nitro group is a meta director. That is, a nitro group on an aromatic ring destabilizes positive charge and as a result will direct the addition of a second substituent mainly in a meta position. The bromo group, however, is an ortho, para director. The bromo group (a halogen) is a deactivating group; it destabilizes positive charge by its inductive effect, that is, by its ability to withdraw electrons. Through its resonance effect, the bromine releases electrons to stabilize the intermediate carbonium ion. This electron release is effective only for attack at the ortho and para positions. The resonance effect of the bromo group is possible because of the free electron pairs on bromine. Knowing that the bromo group is an ortho, para director, we would want to first brominate the aromatic ring. Subsequent nitration will result in mainly ortho and para bromonitrobenzene. These can be separated to give p-bromonitrobenzene. Bromination of aromatic compounds is accomplished by reacting with bromine gas and a metal catalyst, such as iron. Synthesis of p-bromonitrobenzene from benzene is:

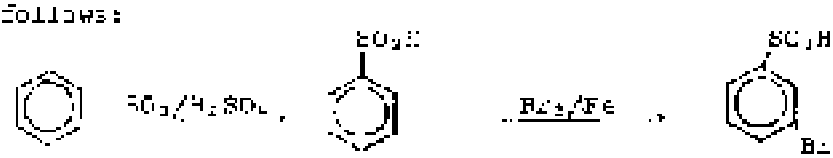


(c) The sulfonyl (SO_3H) group is a meta director whereas the bromo group is an ortho, para director. Since we want to synthesize m-bromobenzenesulfonic acid, we should first add the sulfonyl group to the aromatic ring so that subsequent bromination will give the desired product. Sulfonation of aromatic compounds is the addition of a sulfonyl group to the compound. This is accomplished by using fuming sulfuric acid; that is, sulfur trioxide dissolved in concentrated sulfuric acid. The actual electrophile is sulfur trioxide, and the reaction is as follows:

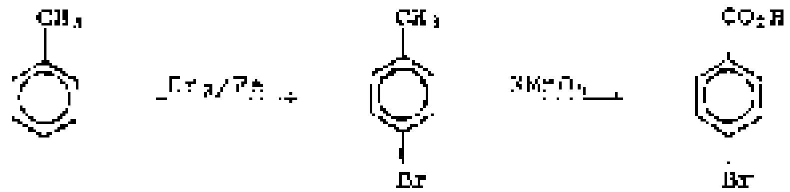


benzenesulfonic acid

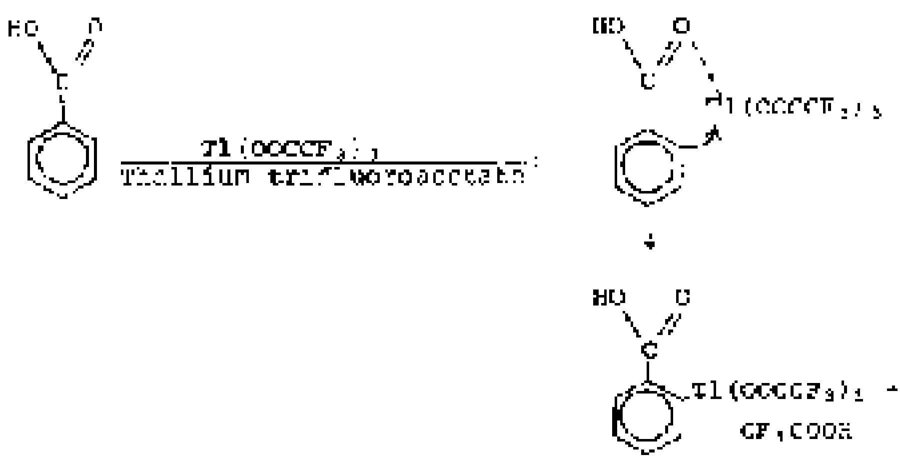
Bromination of benzenesulfonic acid will result mainly in the formation of m-bromobenzenesulfonic acid, because of the meta directing $-SO_3H$ group. The synthesis of m-bromobenzenesulfonic acid from benzene can be summarized as follows:



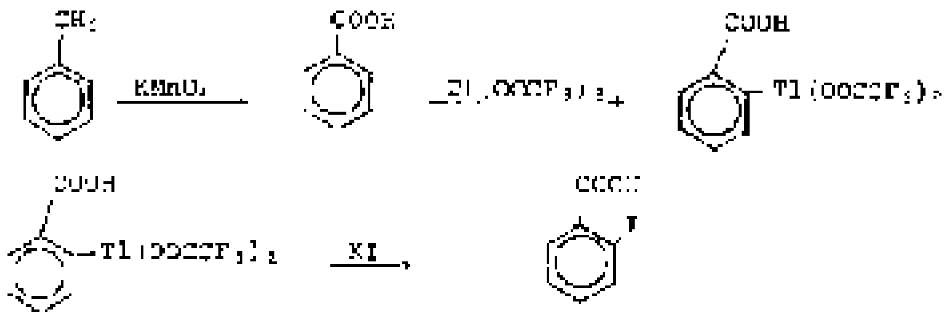
(d) A carboxylic acid group (-COOH) is a meta director because it is an electron withdrawing group and will destabilize positive charge. A methyl group, on the other hand, is an ortho, para director. Since we want to synthesize p-bromobenzoic acid, we should first add a bromo group to toluene. This will give both o- and p-bromotoluene as the major products. This can be separated to give p-bromotoluene. Now we can convert the methyl group on the aromatic ring to a carboxylic acid group. This is accomplished by using potassium permanganate, a powerful oxidizing agent. The synthesis of p-bromobenzoic acid from toluene is:



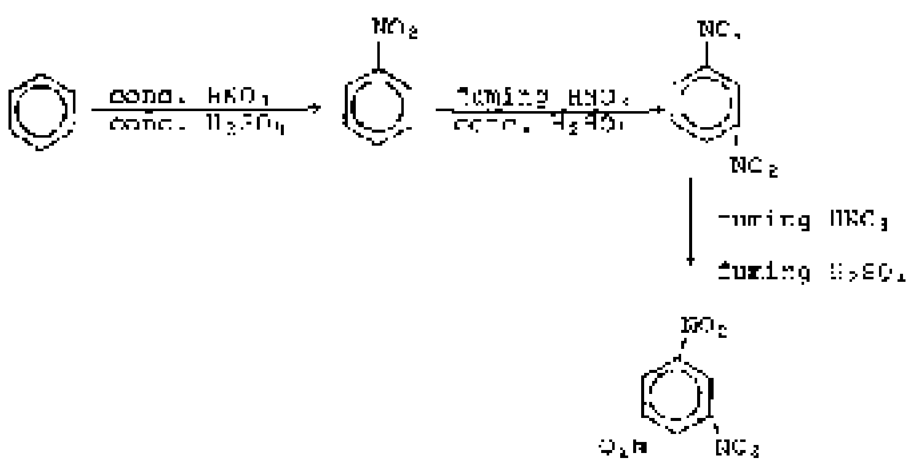
(e) Vigorous oxidation of any alkylated aromatic compound will oxidize the alkyl group to a carboxylic acid group. It can be accomplished by using potassium permanganate. Using this method we can convert toluene to benzoic acid. Since the carboxylic acid group is a meta director, direct iodination will not give the desired product. One way to get the iodo group substituted at the ortho position is by thallation. Thallation is the treatment of aromatic compounds with thallium trifluoroacetate. The products of this reaction are trifluoroacetic acid and an arylthallium ditrifluoroacetate. The reaction involves electrophilic attack by the (Lewis) acidic thallium upon the aromatic ring. When thallium trifluoroacetate reacts with benzoic acid, it adds in an ortho fashion despite the fact that the carboxylic acid group is a meta director. This is because the electrophile first complexes with the carboxylic acid group. It is easier for thallium to move from the substituent to the ortho position than to the meta position.



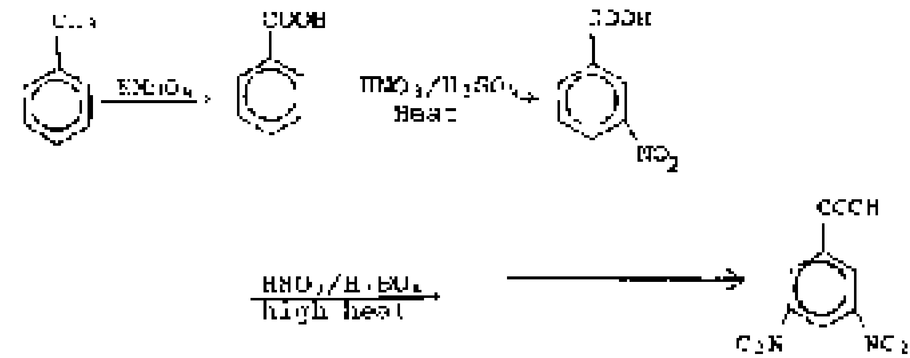
Thallation is almost exclusively para to other substituents because of the bulk of the electrophilic. The process of thallation followed by reaction with iodide ion forms aryl iodide compounds in high yield. The synthesis of o-iodobenzoic acid from toluene is:



(f) Nitration of benzene is accomplished by using a mixture of concentrated nitric acid and concentrated sulfuric acid. The nitronium ion adds to the benzene ring to give nitrobenzene. The nitro group of nitrobenzene has a destabilizing effect upon the entire aromatic ring. This makes the molecule less reactive to further nitration. Nitration of nitrobenzene can be accomplished by increasing the concentration of the electrophile. The electrophile is the nitronium ion and its concentration can be increased by using fuming nitric acid with concentrated sulfuric acid. Fuming nitric acid is nitrous oxide dissolved in nitric acid. The nitronium ion adds to nitrobenzene in a meta fashion because that is the position where the least destabilization occurs. Further nitration is extremely difficult because of the combined destabilization effect of the two nitro groups. Nitration of m-dinitrobenzene is accomplished by reacting with fuming nitric acid and fuming sulfuric acid. Fuming sulfuric acid increases the acidity of the mixture and increases the concentration of nitronium ion. Nitration occurs in a meta fashion because that is where the least destabilization occurs. The synthesis of 1,3,5-trinitrobenzene from benzene is:

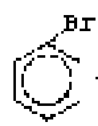


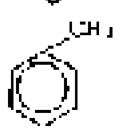
(g) Oxidation of toluene using potassium permanganate will yield benzoic acid. Nitration of benzoic acid occurs slowly at room temperature because of the destabilizing effect of the carboxylic acid group upon the aromatic ring. The rate of reaction will increase if heat is applied. Nitration of benzoic acid will produce mainly the meta substituted compound due to the electron withdrawing carboxylic acid group. Further nitration will occur very slowly because of the destabilization effect of both the carboxylic acid group and the nitro group. The reaction will progress at an acceptable rate if heated very strongly. Nitration will occur in a meta fashion because that is where there is least destabilization. Synthesis of 3,5-dinitrobenzoic acid from toluene is:



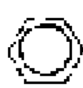
• PROBLEM 11-27

Suggest the major product(s) from the following reactions.

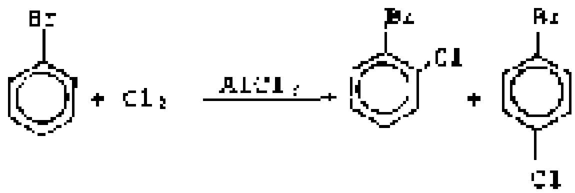
(a)  + Cl_2 $\xrightarrow{AlCl_3}$

(b)  + $CH_3CH_2C(O)Cl$ $\xrightarrow{AlCl_3}$

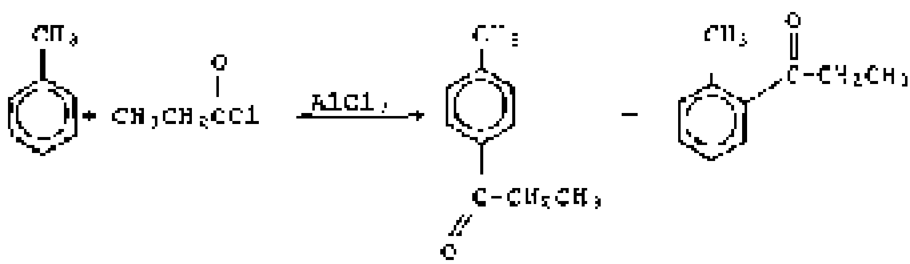
(c)  + I_2 $\xrightarrow{HNO_3}$

(d) —SO_3H + $NO_2{}^+BF_4{}^-$ →

Solution: (a) The bromo group is an ortho, para director. Although it is a deactivating group by its inductive effect (due to its great electronegativity), it can stabilize a positive charge by its resonance effect (due to its free electron pairs). While reactivity is controlled by the inductive effect, the orientation (ortho, para directing) is controlled by the resonance effect. When an aromatic compound reacts with chlorine gas and aluminum chloride, chlorination of the aromatic ring will occur.

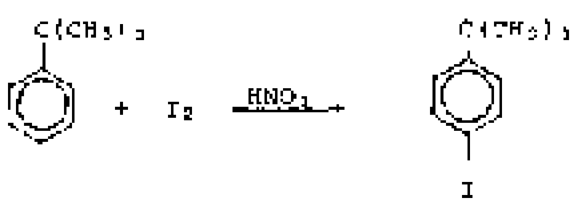


(b) A methyl group on an aromatic ring releases electrons to stabilize the intermediate carbonium ion. This group directs ortho and para. When an aromatic compound reacts with an acyl chloride in the presence of aluminum chloride, Friedel-Crafts acylation occurs. An acyl chloride has the general formula RCOCl. Acylation of aromatic compounds involves the addition of an acyl group (RCO-) to the aromatic ring. The acyl chloride first complexes with aluminum chloride. This complex breaks down to form the acylium ion, $R-\overset{+}{C}=O$. Once formed, the acylium ion undergoes an electrophilic aromatic substitution reaction with the aromatic compound. The product of this acylation reaction is an aromatic ketone. Toluene is acylated by propanoyl chloride to give both ortho and para substituted products.

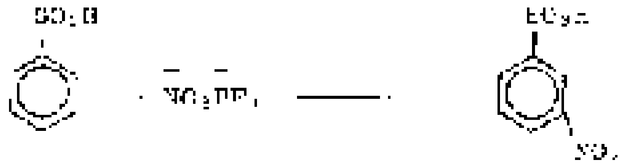


(c) Bromination and chlorination of aromatic compounds can be accomplished by using the halogen gas with aluminum chloride. Iodination will not occur using these conditions because iodine is too unreactive. Iodination can be accomplished by using iodine in the presence of an oxidant such as nitric acid.

t-Butylbenzene can be iodinated only at its para position, even though the t-butyl group is an ortho, para director. This is because of steric hindrance; both the t-butyl group and the iodo group are relatively large. It is too difficult for the iodo group to substitute for the aromatic hydrogen at the ortho position because of "interference" by the large t-butyl group. It is much easier for the iodo group to add para to the t-butyl group. As a result, none or very little ortho substituted product is formed.



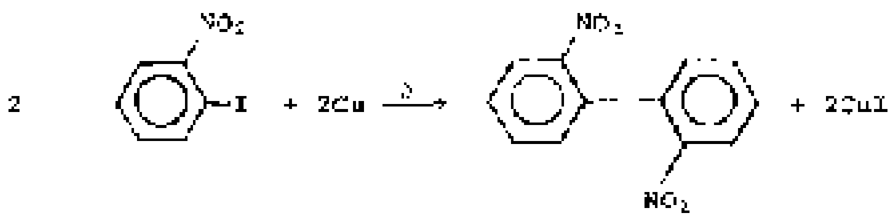
(d) Nitration of aromatic compounds can be performed using nitronium tetrafluoroborate, a direct source of nitronium ion. Benzenesulfonic acid has a meta directing $-SO_3H$ group. The $-SO_3H$ group is electron withdrawing and will destabilize the aromatic ring. As a result, benzenesulfonic acid will be nitrated at the meta position.



■ PROBLEM 11-20

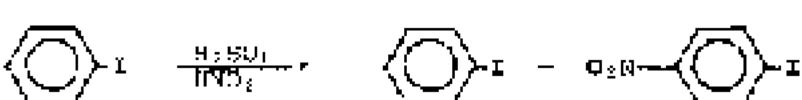
2,2'-Dinitrobiphenyl is to be synthesized. Outline the method of preparation from iodobenzene. No other organic reagent may be used. Any inorganic reagent may be employed.

Solution: 2,2'-Dinitrobiphenyl can be produced directly from 2 moles of o-iodonitrobenzene by use of the Ullmann reaction, which is used for the synthesis of biphenyl derivatives. The reaction is outlined below:



O-iodonitrobenzene 2,2'-Dinitrobiphenyl

Hence, this synthesis can be performed when iodonitrobenzene is obtained from iodobenzene. This can be accomplished by a nitration reaction, where concentrated nitric and sulfuric acids are mixed to produce the nitronium ion ($^+NO_2$) which is the electrophilic reagent that attacks the ring. One must consider the direction of the attack. If benzene possesses an iodine substituent, the iodine will direct para and ortho, so that one obtains the following upon nitration:



iodobenzene

o-iodonitrobenzene p-iodonitrobenzene

These two can be separated. The Ullmann reaction is performed with the ortho compound and 2,2'-dinitrobiphenyl is obtained.

● PROBLEM 11-27

Hydrocarbon B, C_6H_8, gave an nmr spectrum with two signals: δ 5.85 and δ 2.84, peak area ratio 2:1. When warmed in pyridine for three hours, B was quantitatively converted into benzene.

Mild hydrogenation of B yielded C, whose spectra showed the following: mass spectrum, mol. wt. 82; infrared spectrum, no double bonds; nmr spectrum, one broad peak at δ 2.34.

(a) How many rings are there in C? (b) How many rings are there (probably) in B? How many double bonds in B? (c) Can you suggest a structure for B? for C?

(d) In the nmr spectrum of B the downfield signal was a triplet. How must you account for these splittings?

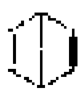
Solution: (a) Mild hydrogenation of B yielded C, whose mass spectrum reveals that its molecular weight is 82. The molecular weight of B (C_6H_8) is 78. From this data, we can conclude that B received four hydrogen atoms upon mild hydrogenation. This would give C the molecular formula C_6H_{10}. This formula is of the general form C_nH_{2n-2}, which denotes unsaturation. Since the infrared spectrum of structure C showed that there were no double bonds, the molecular formula suggests that C may be cyclic.

Ring formation in hydrocarbons can account for unsaturation. As the carbon-carbon single bond is formed, two hydrogens are lost. In other words, when an alkane gives rise to a cycloalkane, two hydrogens are lost from the original molecular formula (C_nH_{2n+2}). To determine how many rings compound C possesses, we shall look at the molecular formula of C (C_6H_{10}). We find that C has four less hydrogens than the corresponding non-cyclic alkane (C_6H_{14}). This means that to go from C_6H_{14} to C_6H_{10}, two rings must have been established. Only with the formation of two rings can four hydrogens be lost to give the molecular formula of C_6H_{10}. Structure C has, therefore, two rings.

(b) To figure out the number of rings in structure B, we can use the same method as in part (a). Structure B accepted four hydrogens under mild hydrogenation in conversion to C. This means that B had either one carbon-carbon triple bond or two carbon-carbon double bonds, since both will accept four hydrogens upon hydrogenation.

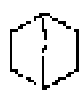
The spectral data seems to support the suggestion that B has two carbon-carbon double bonds. The carbon-carbon triple bond would resonate at about 2.5 to 3.0 parts per million. The lowest absorbance in the nuclear magnetic resonance (nmr) spectrum of structure B is 2.84 parts per million. The carbon-carbon double bond would resonate at about 5.5 to 6.5 parts per million. There is an absorbance at 5.85 in the nmr spectrum of B. This corresponds to the two carbon-carbon double bonds' absorbances. Hence, structure B has two carbon-carbon double bonds. The reason why a carbon-carbon double bond resonates downfield from a carbon-carbon triple bond has to do with shielding effects. The triple bond has a higher electron density about the hydrogens than does a double bond; this means the hydrogens of the carbon-carbon triple bond will be shielded more than the hydrogens of the carbon-carbon double bond. As a result, the carbon-carbon double bond resonates downfield from the carbon-carbon triple bond. We now know that structure B has the molecular formula C_6H_6 and contains two double bonds. The general molecular formula for a non-cyclic diene is C_nH_{2n-2}. The molecular formula for B can be written as C_nH_{2n-6}. As in part (a), for every cyclization two hydrogens are lost. Since we see that B has four less hydrogens than a non-cyclic diene, we can conclude that B has two rings. Structure B contains two rings and two double bonds.

(c) The structures for B and C that are consistent with the data are as follows:

Structure B: 

bicyclo [2.2.0] hexa-2,5-diene

This can also be called "Dewar benzene".

Structure C: 

bicyclo [2.2.0] hexane

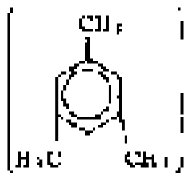
(d) The tertiary carbons in B are bonded to two equivalent vinylic carbons and to each other.

Since the two tertiary hydrogens are equivalent, they will not split each other. Each tertiary hydrogen will be split into a triplet by the two equivalent vinylic hydrogens. This happens because n equivalent protons lying adjacent to the reference proton will split the reference proton into an n+1 multiplet. The two tertiary hydrogens are equivalent and therefore absorb at the same frequency. They appear as one triplet in the nmr spectrum.

• PROBLEM 11-28

Mesitylene reacts (- 80°) with ethyl fluoride and boron trifluoride to form a salt. Upon warming to - 15°, this salt is converted to a hydrocarbon whose nmr spectrum exhibits three different types of methyl resonances of relative intensities 2:1:1. Account for this, suggesting a structure for the salt. What would its nmr spectrum be like?

Solution: The reaction of ethyl fluoride (CH_3CH_2F) and boron trifluoride (BF_3) with mesitylene



indicates a Friedel-Crafts alkylation is taking place. One possible mechanism for the reaction is:

(1) RF (Alkyl halide) $+ BF_3$ (Lewis Acid) $\rightarrow R^+$ (Carbonium ion) $+ BF_4^-$

(2) $R^+ + C_6H_6 \longrightarrow \overset{+}{C_6H_6}\genfrac{}{}{0pt}{}{\diagup R}{\diagdown H}$

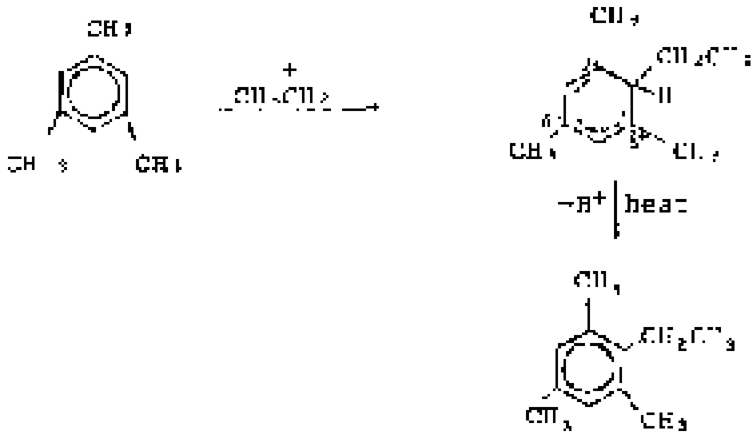
(3) $\overset{+}{C_6H_5}\genfrac{}{}{0pt}{}{\diagup R}{\diagdown H} + BF_4^- \longrightarrow C_6H_5R + BF_3 + HF$

The electrophile that attacks the aromatic compound is a carbonium ion. The Lewis acid functions by abstracting the halide ion from the alkyl halide to create the carbonium ion.

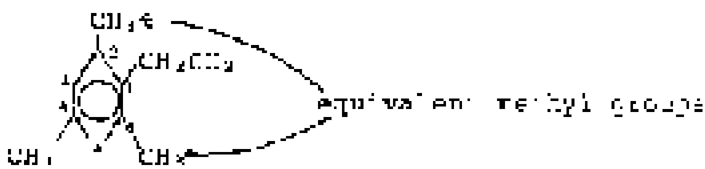
In this problem, boron trifluoride abstracts fluoride ion from ethyl fluoride to produce ethyl cation:

$$CH_3CH_2F \overset{BF_3}{\rightleftarrows} BF_4^- + CH_3CH_2^+$$

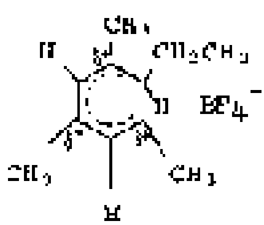
The ethyl cation attacks the aromatic ring of mesitylene seeking the rich source of electrons in the π cloud. This results in the formation of an intermediate carbonium ion (the $\overset{+}{C_6H_6}\genfrac{}{}{0pt}{}{\diagup R}{\diagdown H}$ in the mechanism outlined above). The salt isolated at 80° in this problem is this intermediate carbonium ion in conjunction with BF_4^-. That is, we have tetrafluoroborate salt of ethyl mesitylene. Subsequent proton loss occurs by heating to give the hydrocarbon. Now, it is important to note that the mesitylene will only be monoalkylated. When an ethyl cation attacks the ring, positive charge is introduced. An additional attack by another ethyl cation would create an unstable situation with the addition of another positive (like) charge. The formation of the hydrocarbon from mesitylene may be illustrated as follows:



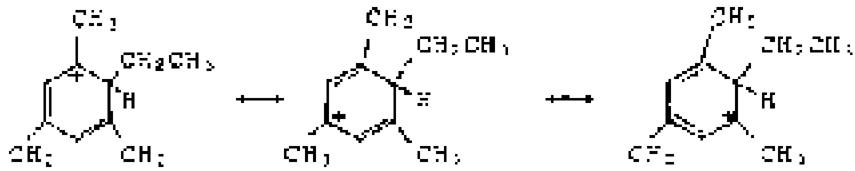
There are three different types of environment, in which the methyl groups reside. This means that there are three methyl groups that are non-equivalent. As a result, there will be three different types of methyl chemical shifts in nmr. Since the hydrocarbon contains four methyl groups, two of the four groups must be equivalent to each other. The two equivalent methyl groups are the ones that are bonded to carbon numbers 2 and 6 of the aromatic ring. The numbering system for the aromatic ring of this hydrocarbon is:



As in the hydrocarbon, the nmr spectrum of the salt would contain three different types of methyl chemical shifts (of relative intensities 2:1:1). The structure of the salt is:

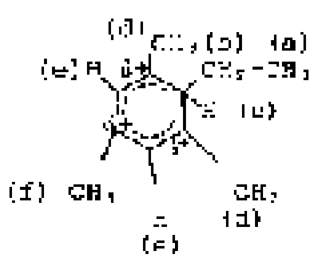


The frequency at which a substituent's proton will absorb depends upon the electronic environment about that substituent. The greater the electron density, the greater shielding there is and the farther upfield will be the absorption. The principal resonance structures for the salt are:



We see from the resonance structures that the positive charge is distributed among carbon #2, 4 and 6. The carbons furthest from the positive charge have the greatest electron density, and will absorb at the lowest frequency; that is, their signal will be the most upfield. The nmr spectrum of the salt is as follows:

The methyl portion of the ethyl group at carbon #1 is the carbon that is furthest from the positive charge; it has the greatest electron density and will be the most upfield signal in the spectrum. This methyl group absorbs near 1.2 δ. This methyl absorption also occurs as a triplet; this is the result of the spin-spin splitting by the two protons on the adjacent methylene ($-CH_2-$) group. The methylene protons will absorb near 1.9 δ and will occur as a quartet. It absorbs downfield from the adjacent methyl group because it is deshielded relative to the methyl group; the methylene is lower in electron density because it is closer to the positive charge. The methylene group occurs as a quartet because of spin-spin splitting by the three protons of the adjacent methyl group. The proton at carbon #1 occurs as a triplet. This happens because there is an adjacent methylene group for spin-spin splitting to occur. The proton absorbs near 1.. δ, which is characteristic of an R_3CH proton. The methyl groups at carbons #2 and 6 absorb as singlets near 7.0 δ. Absorption occurs at a high δ value because of the low electron density of carbons #2 and 6, due to their partial positive charge. The methyl group at carbon #4 occurs as a singlet near 7.0 δ; it is slightly downfield from the methyl groups at carbons #2 and 6. The methyl groups at carbons #2 and 6 have slightly greater electron density because of the adjacent ethyl group. The two protons at carbons #3 and 5 are equivalent and will absorb at the same frequency. They occur as a singlet and absorb near 7.2 δ. Their signal is the most downfield one in the nmr spectrum of the salt. This is because the electron density is lowest at carbons #3 and 5, and therefore the greatest amount of deshielding occurs at these carbons. As a result, the protons absorb downfield from all the other signals in the nmr spectrum. The nmr spectrum of the salt can be summarized as follows:



(a) 3H, triplet near 1.0 δ

(b) 2H, quartet near 1.5 δ

(c) 1H, triplet near 1.3 δ

(d) 5H, singlet near 7.0 δ

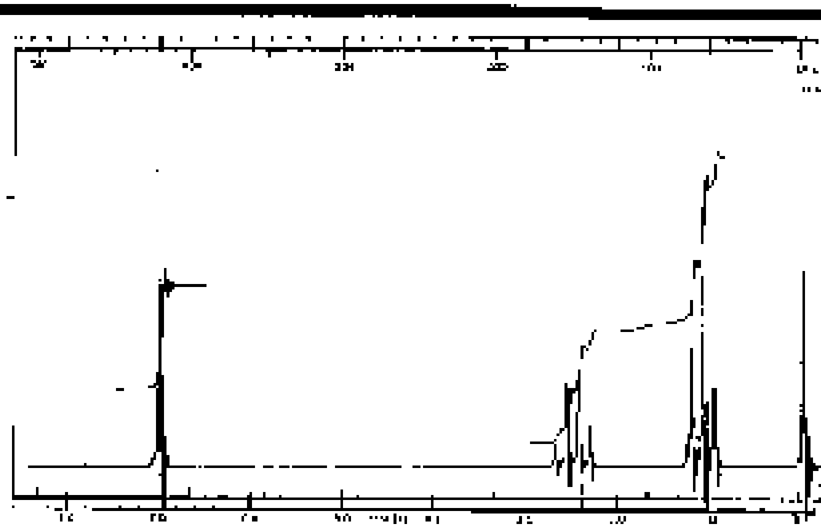
(e) 2H, singlet near 7.2 δ

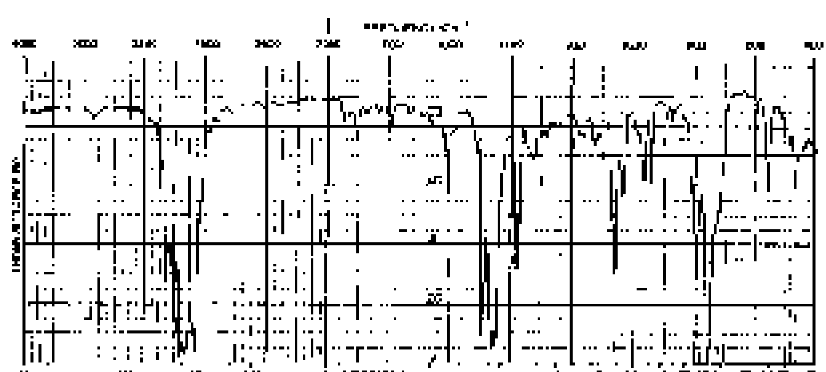
(f) 3H, singlet near 7.0 δ (downfield from d)

Note that nH (n is an integer) indicates the relative number of protons in each constituent absorbed.

• PROBLEM 11-29

A compound, [illegible], has the following nmr and ir spectra. Determine the structure of the compound.





Solution: The nmr spectrum shows a quartet signal downfield from a triplet signal, and a singlet as the most downfield signal. The value of 7.0 δ for the singlet strong ly suggests the presence of a benzene ring. The multiplet signals must have occurred as a result of spin-spin splitting. The quartet and triplet indicate that there is a carbon with two protons adjacent to a carbon with three protons. Such is the case with an ethyl group. We are now aware of the presence of an ethyl group and a benzene ring. Since the molecular formula is $C_{10}H_{14}$, and eight carbons (six from benzene and two from ethyl) have been accounted for, we have two carbons still to be solved for. These two carbons make up another ethyl group, because of the fact only the absorption peaks for an ethyl group are seen in the aliphatic region of the nmr. Hence, the nmr suggests the existence of a diethylbenzene.

The infrared spectrum shows a band at 3000 cm^{-1}. This is the characteristic absorption of an aryl C-H bond stretching. The methyl C-H bonds and the methylene C-H bonds absorb in the range of 1400 cm^{-1} to 1470 cm^{-1} for carbon-hydrogen bending. This band is seen in the infrared spectrum, and supports our conclusion that the compound is a diethylbenzene. The only thing left to be determined is the orientation of the ethyl groups on the benzene ring. The infrared spectrum shows a band between 750 - 810 cm^{-1}. This is indicative of a meta orientation on a benzene ring. Hence, the compound with the molecular formula $C_{10}H_{14}$, which is consistent with the spectral data given is m-diethylbenzene.

CHAPTER 12

ARENES

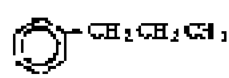
NOMENCLATURE AND STRUCTURE

• PROBLEM 12-1

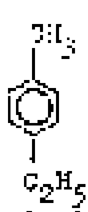
Draw the structure of:

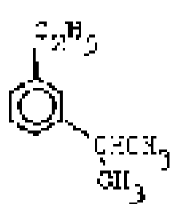
(a) m-xylene
(b) mesitylene
(c) o-ethyltoluene
(d) p-di-tert-butylbenzene
(e) cyclohexylbenzene
(f) 3-phenylpentane
(g) isopropylbenzene (cumene)
(h) trans-stilbene
(i) 1,4-diphenyl-1,3-butadiene
(j) p-dibenzylbenzene
(k) m-bromostyrene
(l) diphenylacetylene

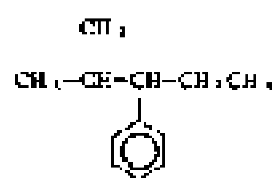
Solution: To draw these structures, it will be necessary to consider the nomenclature of arenes (compounds that contain both aromatic and aliphatic units).

The simplest of the alkylbenzenes (compounds made up of aromatic and alkane units), methylbenzene, is given the name of toluene. Compounds with longer side chains are named by prefixing the name of the alkyl group to the word -benzene. For example, n-propylbenzene: .

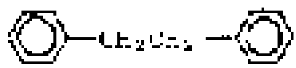
The name xylene is the special name given to the simplest of the dialkylbenzenes, the dimethylbenzenes. There is o-xylene, m-xylene, and p-xylene. Dialkylbenzenes containing one methyl group are named as derivatives of toluene, while others are named by prefixing the names of both alkyl groups to the word -benzene. A compound containing a very complicated side chain might be named as a phenylalkane (C_6H_5=phenyl). Examples:


p-Ethyltoluene

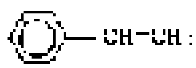

m-Ethylisopropylbenzene


2-Methyl-3-phenylpentane

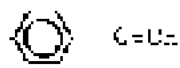
Compounds containing more than one benzene ring are nearly always named as derivatives of alkanes as can be seen in the following example:



Styrene is the special name given to the simplest alkenylbenzene. Others are generally named as substituted alkenes (sometimes as substituted benzenes). Alkynylbenzenes are named as substituted alkynes. Examples:



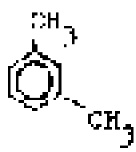
Styrene



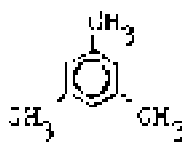
Phenylacetylene

The following structures can now be written:

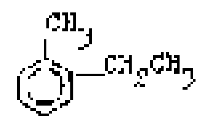
(a) m-xylene



(b) mesitylene

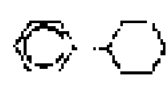


(c) o-Ethyltoluene



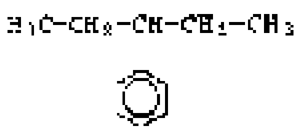
(d) p-di-tert-butylbenzene

(e) cyclohexylbenzene

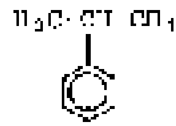


(equatorial bond)

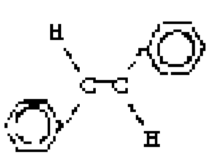
(f) 3-phenylpentane



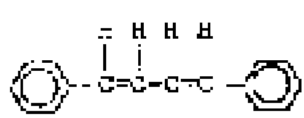
(g) isopropylbenzene



(h) trans-stilbene

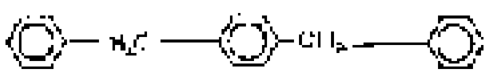


(i) 1,4-diphenyl-1,3-butadiene

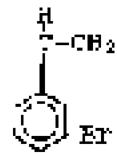


[all isomers possible - Z,Z- or E,E- or E,Z-]

(j) p-dibenzylbenzene



(k) m-bromostyrene

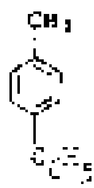


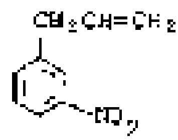
(l) diphenylacetylene

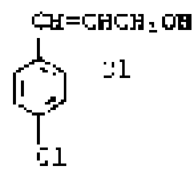
• PROBLEM 12-2

Name each of the following compounds by an accepted system.

(a) $(C_6H_5)_2CHCl$ (b) $C_6H_5CHCl_2$

(c) 

(d) 

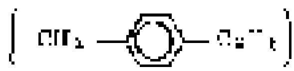
(e) 

Solution: This problem requires a knowledge of arene nomenclature. Benzene (C_6H_6) is the simplest aromatic hydrocarbon. Benzene compounds can be named as a derivative of benzene or as a phenyl-substituted compound.

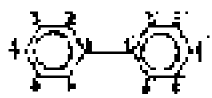
(a) In IUPAC (International Union of Pure and Applied Chemistry) nomenclature, a compound having two benzene rings separated by a carbon is named as a methane derivative. Since the compound $(C_6H_5)_2CHCl$ has a chloro group on the middle carbon, it is named as a chloro-substituted compound. There are two phenyl groups (the benzene rings) attached to the methane carbon. Two phenyl substituents can be written as a diphenyl substituted compound. In IUPAC nomenclature, the names of substituents appear in alphabetical order. Hence, the IUPAC name for the compound $(C_6H_5)_2CHCl$ is chlorodiphenylmethane. There is no numbering system used for naming methane derivatives because the parent chain is only one carbon long. The compound can alternatively be named as a benzhydrol derivative. Benzhydrol has the formula $(C_6H_5)_2CHOH$. The $(C_6H_5)_2CH-$ portion is called the benzhydryl group. A chloro group in place of the hydroxyl group (-OH) in benzhydrol can be named as a chloride compound. The compound $(C_6H_5)_2CHCl$ can be called benzhydryl chloride.

(b) Benzaldehyde has the formula C_6H_5CHO. The C_6H_5-CH- group is called the benzal group. The compound $C_6H_5CHCl_2$ is named as a chloride. The presence of the benzal group gives it the name benzalchloride. In IUPAC nomenclature, the compound $C_6H_5CHCl_2$ would be named as a benzene derivative and not as a methane derivative. The $-CHCl_2$ group is a chloro substituted methyl group. The presence of two chloro groups gives it the name 'dichloromethyl'. Hence the IUPAC name for the compound $C_6H_5CHCl_2$ is dichloromethylbenzene.

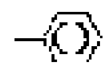
(c) The compound $C_6H_5-C_6H_5$ is called biphenyl. The compound

whose name we desire  can be named as a

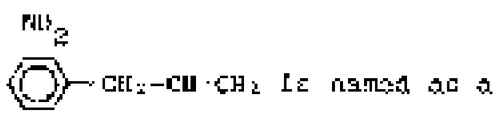
derivative of biphenyl. The compound is a methyl substituted biphenyl compound. The numbering system of biphenyl is:



The n,n' nomenclature of biphenyl compounds is used only when there is a substituent on each ring. If only one ring bears substituents, the n nomenclature is used and not the n'. In this problem, the methyl group is the only

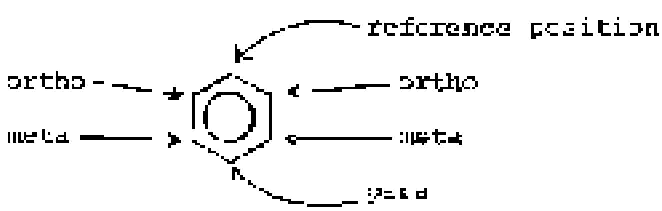
substituent on the biphenyl compound  C_6H_5.

Hence the methyl is considered to be in the 4 position and not the 4' position. Therefore, the compound is named as 4-methylbiphenyl.

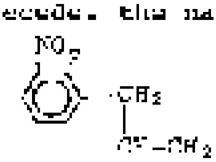
(d) The compound 

is named as a

benzene derivative. There are two substituents on the ring: allyl ($-CH_2-CH=CH_2$) and nitro (NO_2). These groups are located meta with respect to each other.

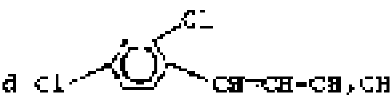
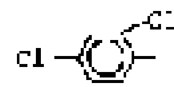
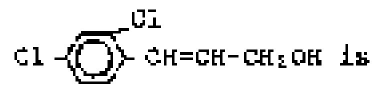


Above: Orientations on a disubstituted benzene ring.

The names of the two groups on the compound appear in alphabetical order. Their relative orientation on the ring is meta (abbreviated as m-) and precedes the name of the compound. Hence the compound 

is

named m-allylnitrobenzene.

(c) The compound  can be named as a derivative of allyl alcohol (CH_2=CH CH_2OH). The numbering system of allyl alcohol is: $\overset{3}{C}H_2$=$\overset{2}{C}H$-$\overset{1}{C}H_2OH$. In the compound we want to name, there is a substituted phenyl substituent at carbon # 3 of allyl alcohol. The benzene carbon bonded to carbon # 3 of allyl alcohol will be carbon # 1 of the aromatic ring. Hence the substituent  is called 2,4-dichlorophenyl. The compound  is therefore named as 3-(2,4-dichlorophenyl)-allyl alcohol.

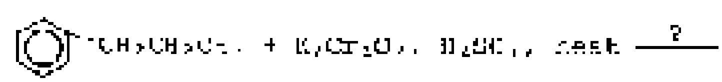
REACTIONS

• PROBLEM 12-3

Give structures and names of the principal organic products expected from the reaction of n-propylbenzene with each of the following:

(1) $K_2Cr_2O_7$, H_2SO_4, heat (3) Cl_2, Fe
(2) HNO_3, H_2SO_4 (4) Br_2, heat, light
(5) cyclohexene, HF

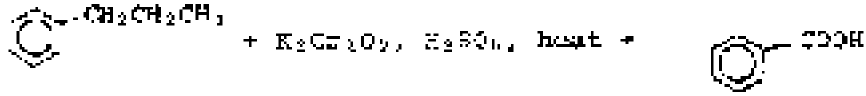
Solution: N-propylbenzene is a compound made up of aromatic and alkane units. Hence, it belongs in the category of alkylbenzenes, which, in turn, are part of the group of compounds known as arenes (compounds that contain both aliphatic and aromatic units). Such compounds show two sets of chemical properties. The ring undergoes the electrophilic substitution characteristic of benzene, whereas the side chain undergoes the free-radical substitution characteristic of alkanes. Each should modify the other. Except for oxidation and hydrogenation these are the reactions to be expected for arenes.

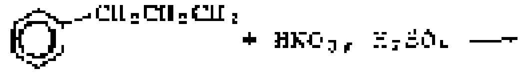
(1) 

n-propylbenzene

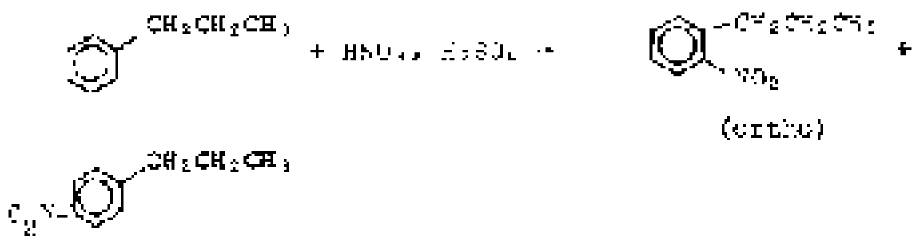
While benzene and alkanes are very unreactive to oxidizing agents ($KMnO_4$, $K_2Cr_2O_7$, etc.) the benzene ring makes an aliphatic side chain susceptible to oxidation. Only a carboxyl group (-COOH) remains to indicate the position of the original side chain after oxidation. Potassium permanganate ($KMnO_4$), potassium dichromate ($K_2Cr_2O_7$) or dilute nitric acid (HNO_3) can be used to oxidize the alkylbenzenes. Consequently, when $K_2Cr_2O_7$,

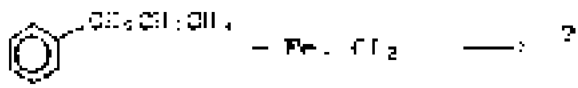
H_2SO_4 (heat) is added to n-propylbenzene the n-propyl side chain should be oxidized to the carboxyl group as shown:



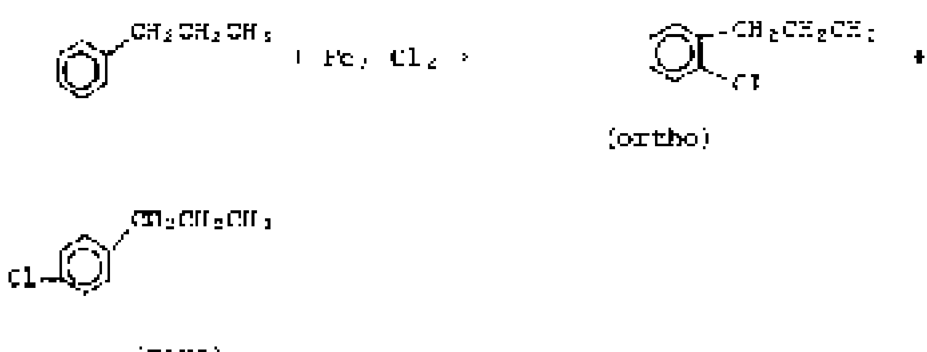
(2) 

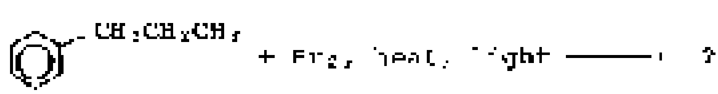
The alkyl groups of alkylbenzenes release electrons in electrophilic aromatic substitution so that they activate the ring and direct ortho and para. Hence, when nitric acid and sulfuric acid are mixed to generate a nitronium ion ($^+NO_2$) for a nitration reaction, the ortho and para products are to be expected as shown:



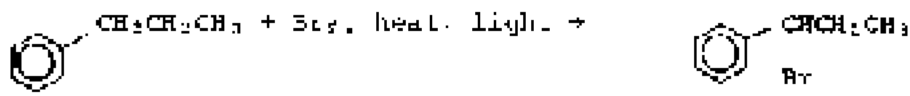
(3) 

When ferric halogen and a halogen are added together, aromatic halogenation occurs. In this instance, it would be chlorination. The attacking species, $Cl_3\bar{F}e-\overset{+}{Cl}-Cl$, does not react with the side chain of the compound; only the aromatic ring is involved. As mentioned above, the alkyl side chain directs ortho and para, so that the following results:

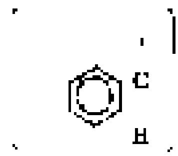


(4) 

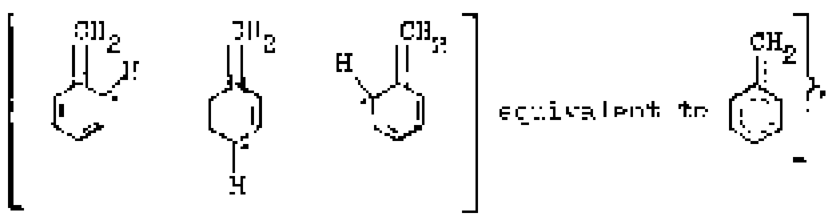
It is known that halogenation of alkanes requires conditions that favor the creation of halogen radicals. High temperature or light is necessary. The halogenation of benzene involves transfer of a positive halogen (X^+) which is promoted by acid catalysts. This means that the position of attack (whether on the benzene or on the side chain) will depend on the nature of the attacking species (an ion or a radical). Since the conditions in this problem are those that favor the production of bromine radicals, halogenation occurs exclusively to the n-propyl side chain. Hence,



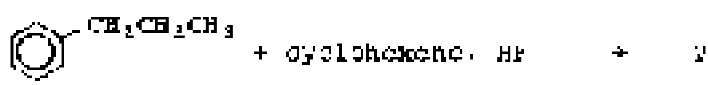
Note: The bromine replaces a benzylic hydrogen



i.e., the hydrogen atom attached to the carbon joined directly to the aromatic ring. These hydrogens are easy to abstract due to resonance stabilization:



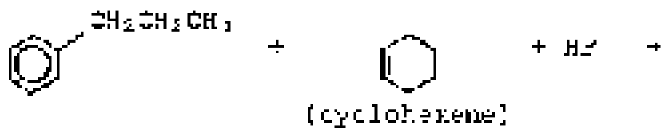
The odd electron is not located on the side chain in the benzyl radical but is delocalized, being distributed about the ring.

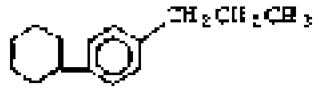
(5) 

This reaction is an example of Friedel Crafts alkylation, which permits direct attachment of an alkyl group to the aromatic ring. The general reaction may be written as:

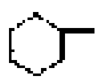
Lewis acid: $AlCl_3$, BF_3, HF, etc. RX may be an alkyl halide, substituted alkyl halide, alkene or alcohol. The Lewis acid functions to generate the electrophile that attacks the ring. Since the n-propyl group is activating, the reaction should occur with orientation ortho and para.

Hence,





. Note: Only the para product results. The reason the ortho product fails to be produced derives from the bulkiness of the substituents. There exists a steric problem when

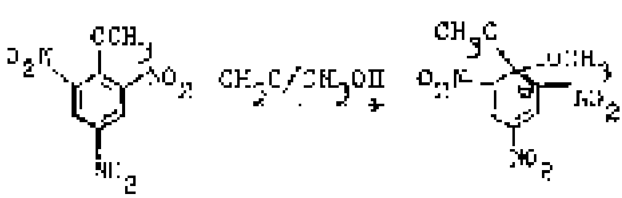


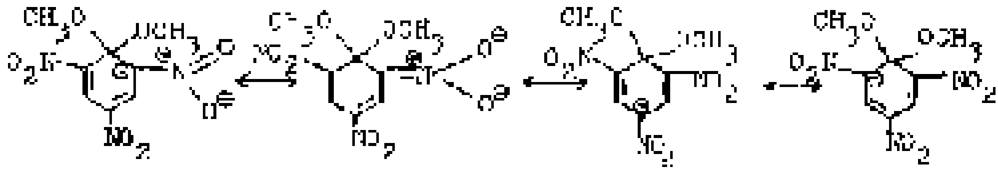
and $-CH_2CH_2CH_3$ are ortho to each other.

• PROBLEM 12-4

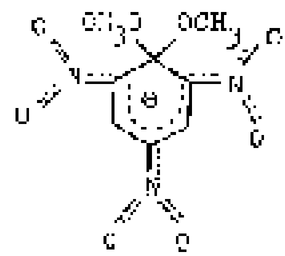
When 2,4,6-trinitroanisole is treated with methoxide in methanol, a red anion having the composition $[C_8H_8O_8N_3]^-$ is produced. Such anions are called Meisenheimer complexes after the chemist who first suggested the correct structure. What structure do you think he suggested? One of Meisenheimer's experiments compared the product of reaction of 2,4,6-trinitroanisole with ethoxide ion with the product of 2,4,6-trinitrophenyl ethyl ether with methoxide ion. What do you think he found?

Solution: Benzene compounds that possess a potential leaving group and also contain substituents that can stabilize a negative charge by resonance will undergo a nucleophilic aromatic substitution reaction upon treatment with a nucleophilic reagent. The reaction proceeds through an isolable intermediate benzenanion called a Meisenheimer complex. The nucleophile attacks the carbon in the aromatic ring that bears the leaving group and destroys the aromaticity of the compound. The negative charge is resonance stabilized by the groups on the ring. The greatest stabilization occurs when the stabilizing groups are ortho and para to the leaving group. When 2,4,6-trinitroanisole is treated with methoxide in methanol, the nucleophilic methoxide which attacks the carbon bearing the methoxy group. The resulting negative charge will be resonance stabilized by the three nitro groups:



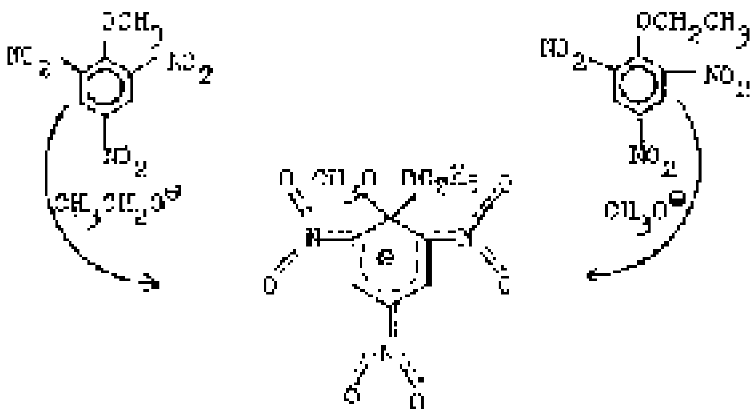


Above: Resonance stabilization of intermediate benzene anion; shown only for the nitro group. The overall structure for the resonance stabilized species is:



Above: Meisenheimer complex.

When 2,4,6-trinitroanisole is treated with ethoxide ion, it will produce the same Meisenheimer complex that 2,4,6-trinitrophenyl ethyl ether produces when reacted with methoxide ion. This Meisenheimer complex can be represented as follows:



• PROBLEM 12-5

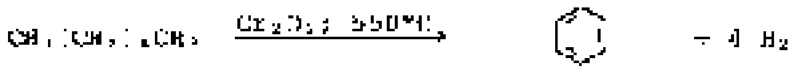
Provide the missing reactant or reaction condition for the following:

(a) n-heptane + ___?___ → toluene

(b) Iodobenzene + ___?___ → biphenyl

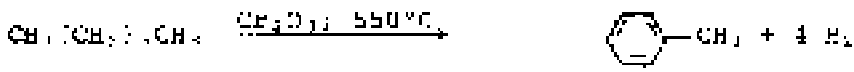
(c) $C_6H_5COCH_3$ + ___?___ → ethyl benzene

Solution: Reaction (a) belongs to the general class of reactions known as dehydrocyclization reactions. An example of such a reaction is



The reagent involved in the reaction is Cr_2O_3 and the reactants are heated to a temperature of 550°C.

In the given reaction n-heptane changes into cyclic toluene through the same process. Thus,



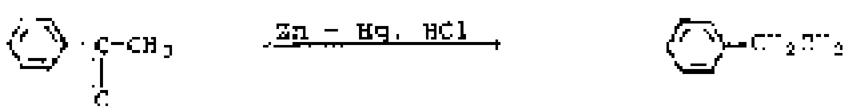
Reaction (b) is known as an Ullmann reaction. The general reaction is

For reaction (b) the R group is a hydrogen atom and the missing reactant is Cu.

Reaction (c) is known as a Clemmensen Reduction. The general reaction is

$$\underset{\substack{| \\ O}}{ArCR} \xrightarrow{Zn\ -\ Hg,\ HCl} ArCH_2R$$

For the given reaction,



Thus, the reagent used is Zn - Hg in HCl; this produces ethyl benzene from $C_6H_5COCH_3$.

♦ **PROBLEM 12-6**

Show how to make the following conversions using any necessary reagents:

(a) Benzene to ethylbenzene
(b) Toluene to benzyl alcohol
(c) Iodobenzene to benzene

Solution: Synthesis of complicated organic molecules should be done in such a manner so that each individual step of the synthesis is one that has high yields of reasonably pure product. It is not necessary to complete and balance each equation, however, it is important that each step be given the proper reagents and experimental conditions needed for the reaction to take place.

(a) For the synthesis of ethylbenzene from benzene, first draw these structures and using the knowledge of the reactions of benzene with various reagents set up a series of reactions until the final product has been produced. Thus

$$C_6H_6 \xrightarrow[FeBr_3]{Br_2} C_6H_5Br$$

$$C_6H_5Br \xrightarrow[ether]{Mg} C_6H_5MgBr$$

$$C_6H_5MgBr \xrightarrow{Et_2SO_4} C_6H_5Et$$

These steps can be combined to give:

$$C_6H_6 \xrightarrow[FeBr_3]{Br_2} C_6H_5Br \xrightarrow[ether]{Mg} C_6H_5MgBr \xrightarrow{Et_2SO_4} C_6H_5Et$$

(b) The synthesis of benzyl alcohol from toluene can be set up in a similar manner. Using the knowledge previously gained of the reactions of the benzene ring and other organic molecules, the synthesis can be shown as follows:

$$C_6H_5CH_3 \xrightarrow{Cl_2,\ uv\ light} C_6H_5CH_2Cl$$

$$C_6H_5CH_2Cl \xrightarrow{OH^-} C_6H_5CH_2OH$$

Combining these steps:

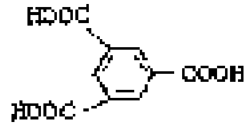
$$C_6H_5CH_3 \xrightarrow{Cl_2,\ uv\ light} C_6H_5CH_2Cl \xrightarrow{OH^-} C_6H_5CH_2OH$$

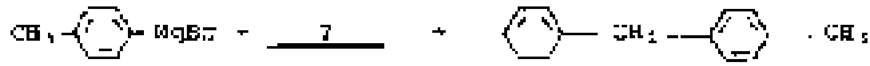
(c) For the reaction of iodobenzene to benzene, we can make the Grignard reagent and treat it with an acid (any proton source).

$$C_6H_5I \xrightarrow[ether]{Mg} C_6H_5MgI \xrightarrow[H^+]{H_2O} C_6H_6$$

Provide the missing reactant or reaction condition for the following:

(a) Mesitylene + ? →



(b) 

Solution: From a previous problem, the structure of mesitylene (1,3,5 trimethylbenzene) is shown in Figure A.

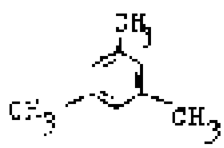
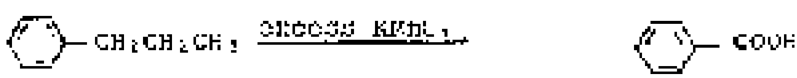


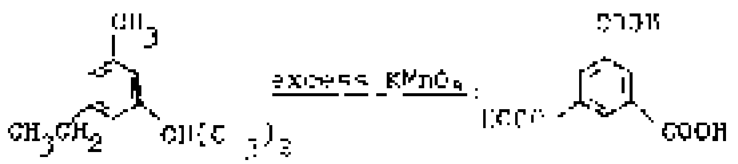
Fig. A.

In reaction (a) the positions of the side chains remain the same. This reaction is a typical example of an oxidation reaction.

Some examples of oxidation reactions are

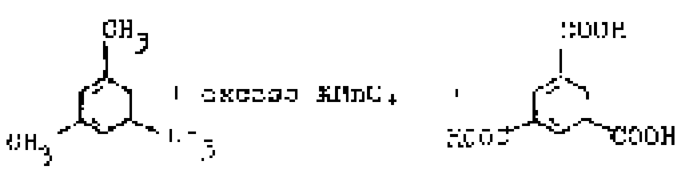


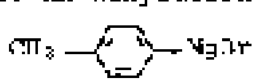
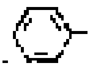
Benzoic Acid

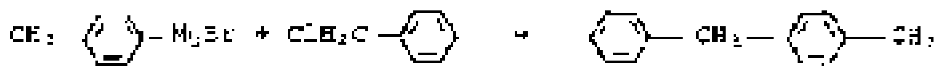


1,3,5-benzenetricarboxylic acid

Note that primary and secondary side chains are oxidized to carboxyl groups but tertiary groups are unaffected. The complete reaction of part (a) is



Reaction (b) is an alkylation reaction by means of the Grignard reagents.  is the Grignard reagent where -MgBr is replaced by an alkyl group. The only possible alkyl group that would produce the desired result is a benzyl group:  CH_2—. In this reaction any benzyl halide would work.

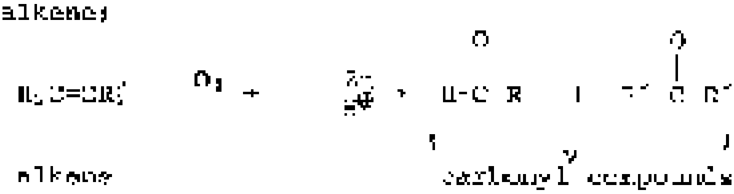


• PROBLEM 12-8

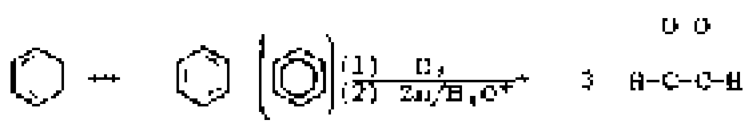
What products would you expect to be formed in the ozonization (with reductive workup) of the following substances (consider carefully which bonds are likely to be most reactive)?

(a) o-xylene
(b) naphthalene

Solution: Ozonization of compounds with carbon-carbon double bonds, followed by reductive workup, will break the double bond and form two carbonyl compounds: In an alkene;

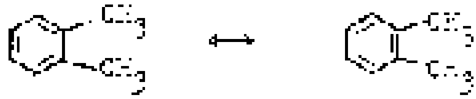


The ozonization of aromatic compounds is more interesting and complex in that each bond in the aromatic system has a certain degree of double bond character and this is reflected in the amounts of ozonization products since this reaction is specific for double bonds. Benzene, for example, has six bonds of equal double bond character. This can be represented by its two Kekulé resonance structures which we must realize do not denote independent, existing forms but they do approximate the relative amount of double bond character for each bond.

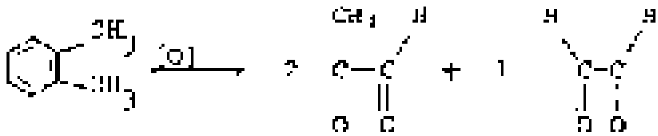


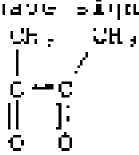
Benzene's
resonance structures

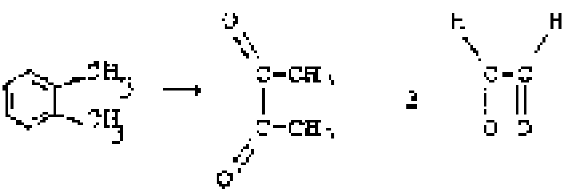
(a) In o-xylene , we can also represent the structure as two resonance forms but the second of the two seems to be more important in that it contains a double bond substituted by two methyl groups. A methyl group like any alkyl substituent stabilizes a double bond by its electron-releasing inductive effect. Therefore a methyl substituted double bond will be more stable than an unmethylated one and a dimethyl substituted double bond would be even more stable



Since the bond between the two methyl groups has the most double-bond character, it will be most reactive to the double bond specific ozonization. The ozonization products for the structure containing this bond:

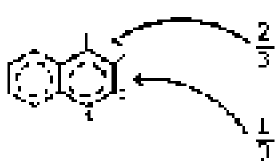


The stabilization of the methyl groups is not that great and the double bonds not shown in the previous structure do have significant occurrence and therefore the compound  is an additional ozonization product.

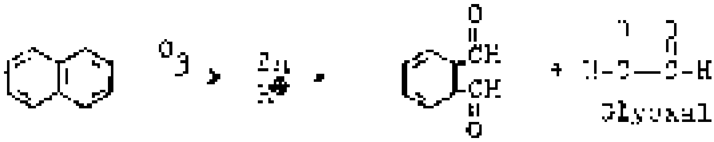


(b) Naphthalene, a bicyclic, aromatic compound can be presented as several resonance forms and we can determine the fraction of double bond character by examining these structures.

From this we can conclude:



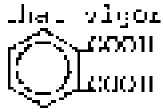
We should therefore expect that the bond with $\frac{2}{3}$ double bond character should react more than the bond with $\frac{1}{3}$ double bond character. This, coupled with the fact that the subsequent product is conjugated and retains aromaticity ensures the major reaction to involve cleavage of the C_1–C_2 and C_3–C_4 bonds. Thus, the ozonization of naphthalene is as follows:



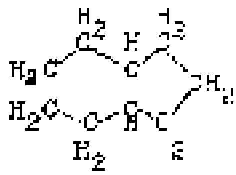
■ **PROBLEM 12-9**

The compound indene, C_9H_8, found in coal tar, rapidly decolorizes Br_2/CCl_4 and dilute $KMnO_4$. Only one mole of hydrogen is absorbed readily to form indane, C_9H_{10}. More vigorous hydrogenation yields a compound of formula C_9H_{16}. Vigorous oxidation of indene yields phthalic acid. What is the structure of indene? Of indane?

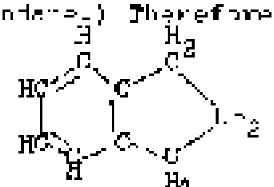
Solution: An alkene (a compound with a double bond) is best characterized by its property of decolorizing both a solution of bromine in carbon tetrachloride (Br_2/CCl_4) and a cold, dilute, neutral permanganate solution ($KMnO_4$). The fact that indene undergoes these reactions indicates the presence of a reactive double bond. The fact that only one mole of hydrogen is absorbed readily suggests that only one of these reactive double bonds is present, since hydrogen adds across a double bond in a one to one mole ratio. Three more double bonds are present, however; vigorous hydrogenation results in the addition of three more hydrogen molecules (H_2) as can be seen by the fact that the molecular formula changes from C_9H_{10} to C_9H_{16}, a difference of 6 hydrogens. The fact that this hydrogenation is vigorous means the double bonds are especially stable; such a situation may be explained by the resonance stabilization that occurs in aromatic compounds such as benzene.

The evidence so far points to an aromatic group (benzene) and a reactive double bond, which must be part of some substituent attached to the benzene ring. In other words, the presence of an arene is suggested. An arene is a hydrocarbon that contains both aliphatic and aromatic units. The presence of the benzene ring is confirmed by the fact that vigorous oxidation of indene yields phthalic acid,  . This reaction is typical of arenes. Hot oxidizing agents such as $KMnO_4$ and $K_2Cr_2O_7$ oxidize the side chain (the aliphatic portion) to the carboxyl group (COOH) and leave the benzene ring untouched. The presence of the COOH on the ring indicates where the original side chain was located. Hence, indene must contain the benzene ring, which would account for six carbons of the nine carbons in C_9H_8.

Consider now the compound obtained after all the hydrogenation is completed, C_9H_{16}. It no longer possesses any unsaturated bonds (double bonds), since the hydrogen would have added across them. And yet, it "looks" unsaturated, since the saturated hydrocarbon would possess the formula C_9H_{20}, in accordance with the C_nH_{2n+2} rule for saturated alkanes. The absence of the 4 hydrogens (20-16=4) can only be accounted for by ring formation. For each ring formed, two hydrogens are 'lost' from the saturated alkane. Here, then, there must be two rings present since 4 hydrogens disappear. The only structure for C_9H_{16} that can possess two rings (with one containing six carbons recall, one ring must be from the vigorously hydrogenated benzene) is

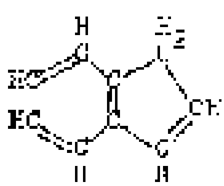


To find the structures of indane and indene just retrace your steps. This compound resulted from vigorous hydrogenation of indane. (Three hydrogen molecules were added across the resonance stabilized double bonds of indane.) Therefore, the structure indane must be:



C_9H_{10}

Recall that indane resulted from indene by the addition of one molecule of hydrogen across a reactive double bond. Hence, indene must be:



C_9H_8

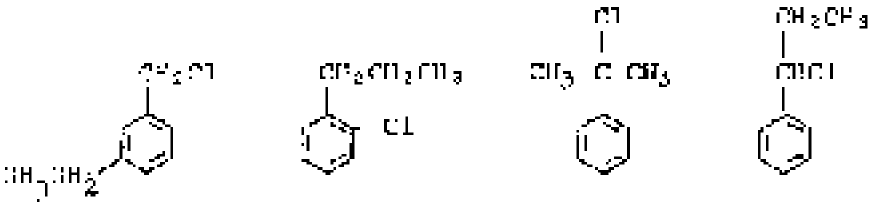
Notice how the oxidation of this produces phthalic acid with the carboxyls in the correct positions on the benzene ring.

SPECTROSCOPY

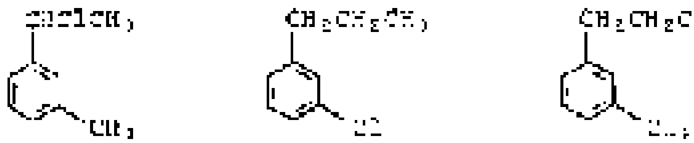
● PROBLEM 13-10

There are many isomers of $C_9H_{11}Cl$, even when we specify the presence of a benzene ring. One such compound is 2-chloro-1,3,5-trimethylbenzene.

(a) Sketch its expected nmr spectrum.
Other isomers are:



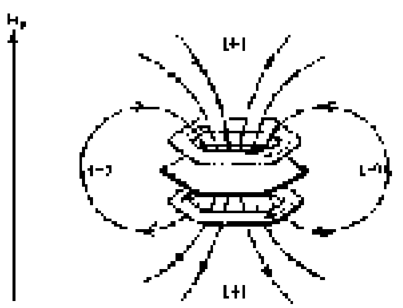
[A] [B] [C] [D]



[E] [F] [G]

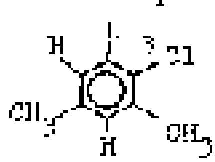
Associate these isomers with the properties listed. For those questions that have more than one correct answer, list all of the correct structures.

(b) Most reactive in carbonium ion reactions (one answer).
(c) Does not react with alcoholic silver nitrate.
(d) Nmr spectrum contains two triplets.
(e) Can give direct substitution reaction (S_N2), but not elimination (E2).
(f) Can give both S_N2 and E2 reactions.



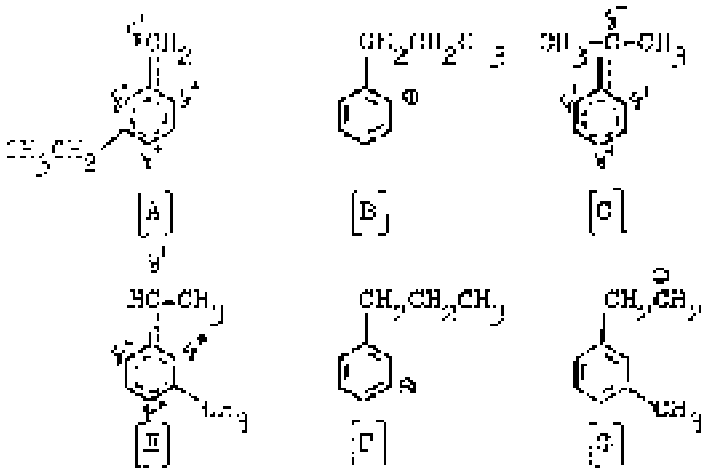
The two magnetic fields generated by an aromatic ring.

Solution: (a) 2-Chloro-1,3,5-trimethylbenzene has the following structure:

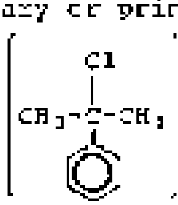


Its nmr spectrum will show three singlets. The two aromatic protons are in identical electronic environments and will therefore absorb at the same frequency. Their singlet appears near 7.5 δ, the characteristic absorption of an aromatic proton. The two methyl groups ortho to the chloro group are in identical environments, and will absorb at the same chemical shift. The methyl group para to the chloro group is in a different environment than the other methyl groups. The para methyl group will absorb near 2.0 δ whereas the ortho methyl groups will absorb near 3.0 δ. The ortho methyl groups absorb downfield relative to the para methyl group because the ortho methyls are de shielded relative to the para methyl. This is due to the fact that the ortho methyls have a lower electron density because of the inductive effect of the nearby chloro group. All signals in the nmr spectrum will occur as singlets because there are no two non equivalent protons that lie on adjacent carbons for spin-spin splitting to occur.

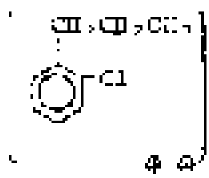
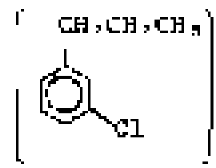
(b) To determine which isomer is the most reactive in carbonium ion reactions, we will have to look at the carbocations formed upon the leaving of Cl. The most stable carbocation will be the one that reacts fastest, hence the most reactive. This is because carbocation formation is the rate determining step in carbonium ion reactions. The more thermodynamically stable the carbocation, the lower the activation energy and the faster is the reaction. The carbocations of these isomers are as follows:



Since cations B, F and G do not undergo electron delocalization, they are less stable than the other cations. Cations A, C, D and E have the positive charge distributed amongst four carbons, three of which are the same (ring carbons). Since carbocation stability follows the order 3° > 2° > 1°, cation C is the most stable one. Cation C is a tertiary benzylic cation. Cations A, D, and E are either secondary or primary benzylic cations. Hence,

compound C  must be the most reactive in carbonium ion reactions.

(c) Alkyl halides undergo a nucleophilic substitution reaction (either S_N1 or S_N2) when reacted with silver nitrate ($AgNO_3$). The silver cation helps to pull off the halide ion and the resulting silver halide precipitates from the solution. Since aryl halides do not undergo S_N1 or S_N2 reactions, the halide ion will not leave and no precipitate will form. Hence, by inspection we can predict

that only compounds B  and F 

will not react with alcoholic $AgNO_3$.

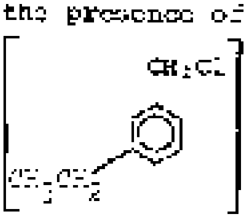
(d) Triplets in an nmr spectrum occur as a result of spin-spin splitting by two protons. The only compounds that will have two distinct triplets in its nmr spectrum are those that have: (1) a methylene group bonded to two carbons bearing hydrogens; these two carbons must be non-equivalent so that they absorb at different chemical shifts. For example: $Cl-CH_2-CH_2-CH_2-R$ -OR-

(2) two non equivalent adjacent methylene groups, both of which are bonded to atoms that lack hydrogens. For example;

$$Cl-CH_2-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-R$$.

According to these conditions, compounds C, D, F and G all have two triplets in their nmr spectrum.

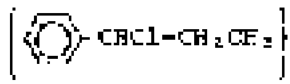
(e) For an arene to be able to undergo an S_N2 reaction but not an E2 reaction (elimination), there must not be any hydrogens adjacent to the carbon undergoing the substitution reaction. Of the compounds A through G, all except B, C and F can undergo S_N2 reactions. Compounds B and F cannot do so because the leaving group (chlorine) is attached to an sp^2 hybridized carbon; S_N2 reactions occur only on sp^3 hybridized carbons. Compound C undergoes S_N1 reactions and not S_N2 reactions because of the stability of a tertiary carbocation (formed only in S_N1). Of the remaining compounds only A will not undergo an E2 reaction (elimination). This is because compound A is the only one that lacks β-hydrogens (hydrogens adjacent to the carbon bearing the leaving group). Elimination reactions require the presence of β hydrogens. Hence, compound A



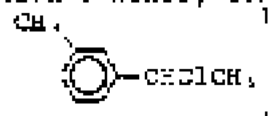
is the only one that will undergo S_N2

but not E2 reactions.

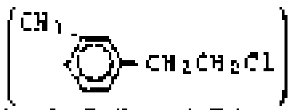
(f) In part (c) we reasoned that only compounds A, D, E, and G were able to undergo S_N2 reactions. We also reasoned that of these compounds only A was not able to undergo an E2 reaction. Since compounds D, E and G have β hydrogens they can undergo E2 reactions. Hence, compounds D



, E



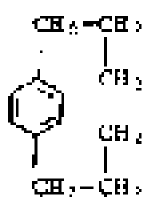
and G

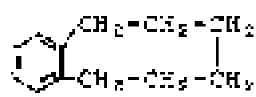


are the only ones that can undergo both S_N2 and E2 reactions.

• PROBLEM 12-11

What would you predict for the general character of the chemical shifts of the protons of (a) the separate CH_2 groups of 1,4-hexamethylenebenzene as compared with 1,2-hexamethylenebenzene;

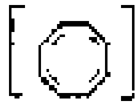




1,4-hexamethylenebenzene　　1,2-hexamethylenebenzene

(b) cyclooctatetraene

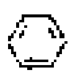
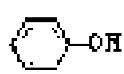
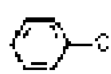
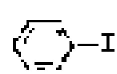
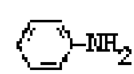
Solution: (a) When an aromatic compound's π system is treated by a magnetic field, a flow of π electrons is induced around the ring (ring current) which generates a secondary magnetic field which opposes the applied magnetic field at the center of the ring but augments it around the vicinity of the benzene protons. The alpha (the benzylic carbon may be considered the α-carbon) methylene protons of 1,2-hexamethylenebenzene as well as its beta protons may be considered to have similar chemical shifts compared to their corresponding sets of protons in 1,4-hexamethylenebenzene because they have the same proximal relationship to the aromatic ring. The auxiliary magnetic field of the ring causes these protons to be shifted downfield (to a higher chemical shift) since they are approximately in the same plane of the aromatic ring. On the other hand, the ring's magnetic field causes the gamma protons of 1,4-hexamethylenebenzene to be shifted upfield, probably because the geometry of the molecule is such that these gamma protons are approximately perpendicular to the aromatic ring. The gamma protons of 1,2-hexamethylenebenzene do not achieve this degree of perpendicularity and thus they are not shifted as much upfield as the gamma protons of 1,4-hexamethylenebenzene. Therefore, the difference in molecular geometry can lead to spectroscopic separation of these two compounds.

(b) Cyclooctatetraene,  has four double bonds and a total of 8 π electrons. We note that Hückel's Rule for aromaticity states that any species containing 4n+2 π electrons in a cyclic π system will be aromatic. This is not true of cyclooctatetraene and therefore the compound is antiaromatic. The compound's protons should have chemical shifts typical of a vinyl proton of an alkene.

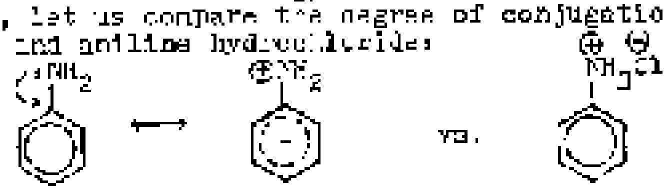
• PROBLEM 12-12

Predict the effect on the ultraviolet spectrum of a solution of aniline in water when hydrochloric acid is added. Explain why a solution of sodium phenoxide absorbs at longer wave lengths than a solution of phenol (see Table below).

Table: Effect of Auxochromic Substituents on the Ultraviolet Spectrum of the Benzene Chromophore

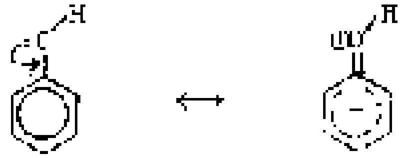
	 Benzene	 Phenol	 Phenoxide Ion	 Iodobenzene	 Aniline
λ_{max}, Å	1,980	2,100	2,350	2,260	2,300
ϵ_{max}	8,000	6,200	9,400	13,000	8,600

Solution: In general, the λ max of a UV spectrum will shift to a longer wavelength for a more conjugated system and a shorter wavelength for a less conjugated system. This rule of thumb is derived from the fact that the energy difference between the first π* state of a compound decreases as the system becomes more conjugated. Since E=hC/λ, the wavelength will increase as the energy difference decreases. With this in mind, let us compare the degree of conjugation between aniline and aniline hydrochloride:

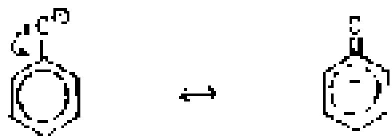


Since the lone-pair electrons of aniline hydrochloride are not able to conjugate with the ring, it is less conjugated than aniline. Therefore it should absorb at a shorter wavelength as compared to aniline.

when the lone-pair electrons of oxygen in phenol conjugate with the ring, there is charge separation :



but when the lone-pair electrons in the phenoxide ion conjugate with the ring, there is no charge separation:



Since the resonance in the phenoxide ion is more important than that in phenol, the former is much more extensively conjugated than the latter, resulting in phenoxide's absorption at longer wavelengths in the UV spectrum.

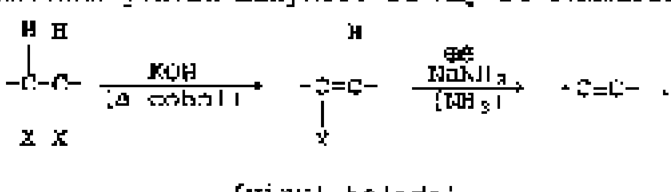
SYNTHESIS

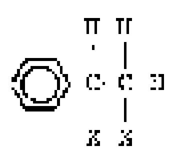
• PROBLEM 12-13

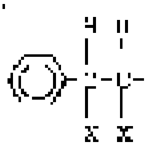
Outline all steps in the conversion of: (a) ethylbenzene into phenylacetylene; (b) trans-1-phenylpropene into cis-1-phenylpropene.

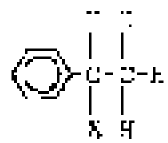
Solution: (a) The preparation of phenylacetylene, an alkynylbenzene, follows from the chemistry of benzene and the alkynes.

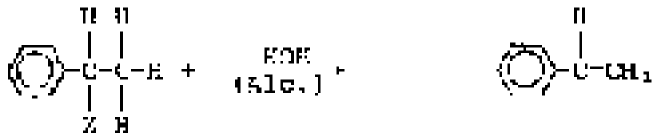
Recall that the dehydrohalogenation of vicinal dihalides yields alkynes. It may be summarized as:



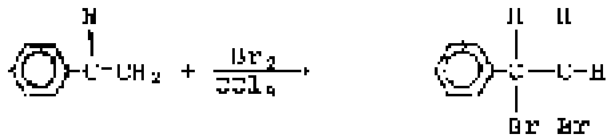
Consequently, if one can obtain  one can readily produce phenylacetylene, the desired product.

 may be synthesized from the starting material (ethylbenzene) in the following manner:

Ethylbenzene may be halogenated in the presence of light to obtain  . Next, employ KOH to de-hydrohalogenate to styrene as shown:



Bromine in carbon tetrachloride may be added to styrene to obtain the vicinal dihalide:

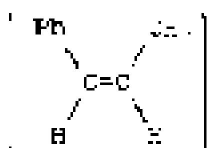
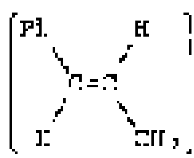


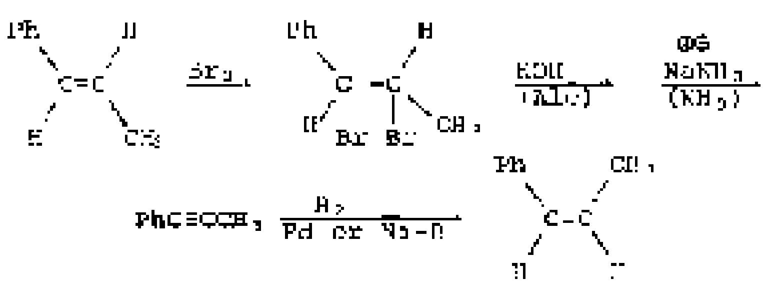
, From this one proceeds to the desired product as previously mentioned. The overall sequence may be written as:

$$PhCH_2CH_3 \xrightarrow[\text{light}]{X_2} PhCHXCH_3 \xrightarrow[(Alc.)]{KOH} PhCH{=}CH_2 \xrightarrow[CCl_4]{Br_2}$$

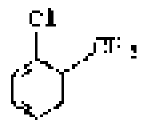
$$PhCHBrCH_2Br \xrightarrow[(Alc.)]{KOH} \xrightarrow[(NH_3)]{\ominus\oplus\ NaNH_2} PhC{\equiv}CH$$

(phenyl acetylene)

(b) Cis-1-phenylpropene  can be synthesized from trans-1-phenylpropene  through the alkyne intermediate. Recall that the addition of hydrogen to produce the corresponding alkene can occur in the cis fashion with Pd or Ni-B (P-2) or trans fashion with Na or Li in ammonia. To prepare the alkyne, one wants to produce the vicinal dihalide and dehydrohalogenate as mentioned in (a). Therefore, the following sequence can be employed to make the conversion.



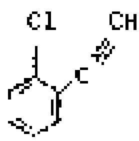
What arene derivatives are expected from the oxidation of the following with hot, alkaline potassium permanganate followed by acidification?

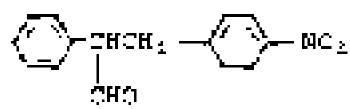
(a) 

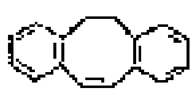
(e) 

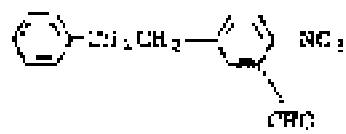
(b) 

(f) 

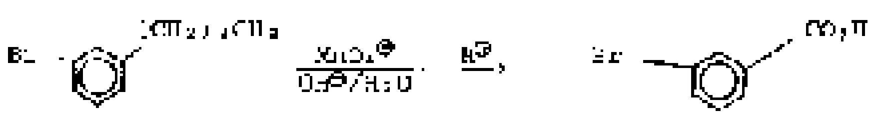
(c) 

(g) 

(d) 

(h) 

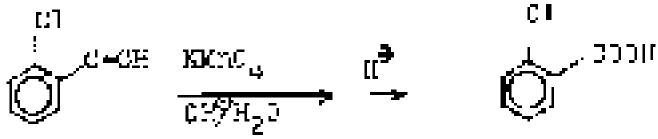
Solution: It is known that alkanes and benzene are quite inert to oxidation with potassium permanganate in aqueous alkali. However, alkyl and aryl groups attached to benzene rings can be oxidized to carboxyl (-COOH) groups with hot, alkaline permanganate. For example,

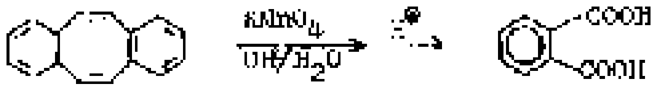


With this in mind, we can predict the products of the following reactions:

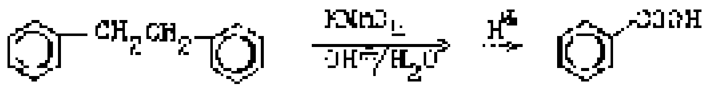
(a) 

(b) 

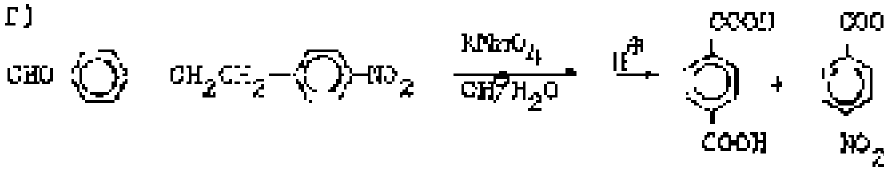
(c) 

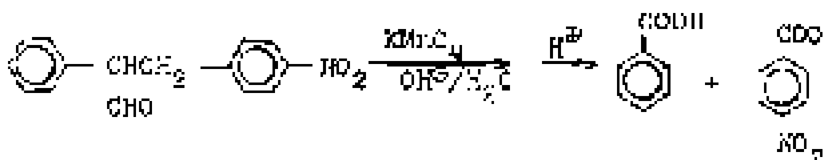
(d) 

(e)

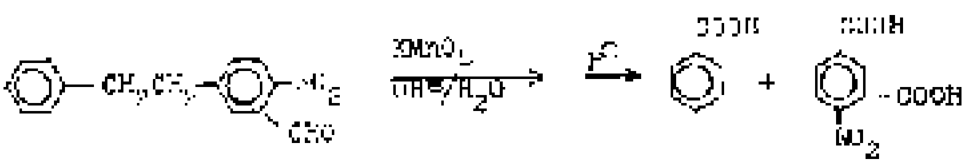


(f)



(g) 

(h)

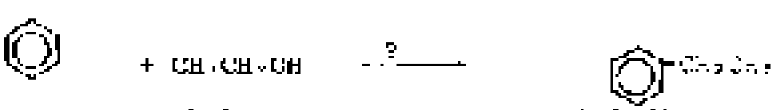


ELECTROPHILIC AROMATIC SUBSTITUTION

• PROBLEM 12-15

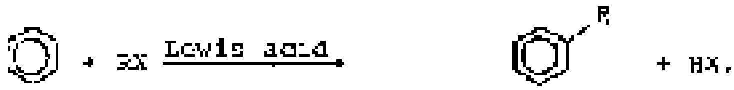
How might you prepare ethylbenzene from: (a) benzene and ethyl alcohol; (b) acetophenone, $C_6H_5COCH_3$; (c) styrene, $C_6H_5CH{=}CH_2$; (d) α-phenylethyl alcohol, $C_6H_5CHOHCH_3$; and (e) β-phenylethyl chloride, $C_6H_5CH_2CH_2Cl$?

Solution:

(a) 

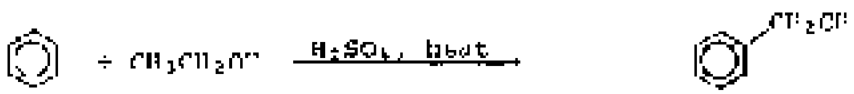
Benzene Ethyl alcohol Ethylbenzene

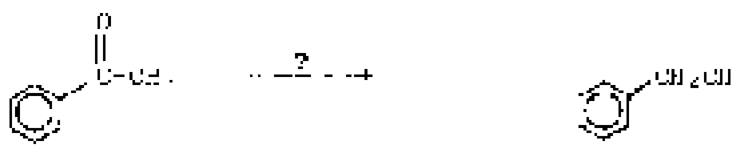
In this problem we want to add an alkyl group to an aromatic ring to obtain an alkylbenzene. Attachment of an alkyl group may be accomplished by Friedel-Crafts alkylation. The general reaction may be written as:



The Lewis acid may be $AlCl_3$, BF_3, HF, etc. RX represents an alkyl halide, alcohol, or alkene, but not an aryl halide. The Lewis acid functions by generating a carbonium ion (R^+) from RX, which subsequently attacks the electron rich aromatic (benzene) ring to give the

alkylbenzene,  . Hence, to synthesize ethylbenzene from ethyl alcohol and benzene add an acid to the solution (for example, H_2SO_4 and heat). This results in formation of the ethyl cation ($CH_3CH_2^+$) which now attacks the benzene ring to give the desired product. Hence,

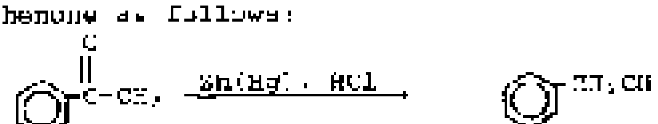


(b) 

Acetophenone

The task in this case is to reduce the carbonyl group (>C=O) to the methylene ($-CH_2-$) group. Such a side chain conversion may be accomplished by Clemmensen or Wolff Kishner reduction. In the former, we have amalgamated zinc and concentrated hydrochloric acid, whereas the latter consists of hydrazine (NH_2NH_2) and a strong base like KOH or potassium tert-butoxide. The reaction may be generalized as:

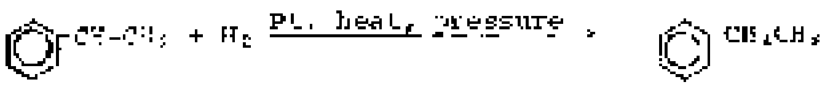
Therefore, we could synthesize ethylbenzene from acetophenone as follows:

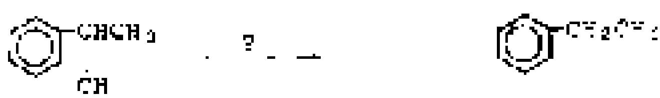


(c) 

Styrene

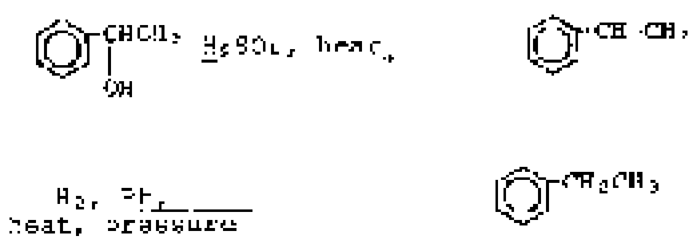
This conversion can readily be made by the addition of hydrogen (H_2) across the carbon-carbon double bond of styrene. This is done by catalytic hydrogenation as shown:

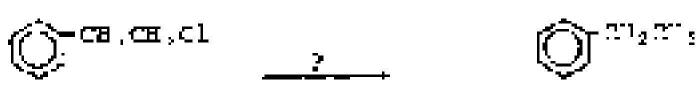


(d) 

α-phenylethyl alcohol

If the alcohol is dehydrated with the use of acid such as H_2SO_4, styrene would be produced. From styrene, we go to ethylbenzene by catalytic hydrogenation as mentioned above. Overall:

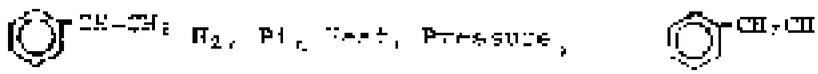


(e) 

β-phenylethyl chloride

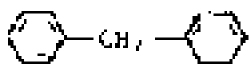
This conversion can be carried out by using the reagent KOH (alc) so that a dehydrohalogenation reaction occurs to yield styrene

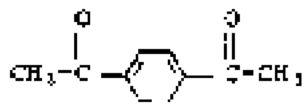
Styrene can now undergo catalytic hydrogenation to produce ethylbenzene.



■ **PROBLEM 12-18**

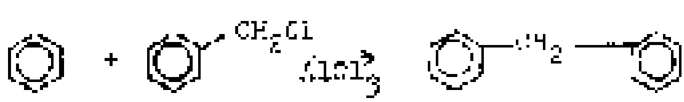
Suggest possible routes for the synthesis of the following compounds:

(a) 

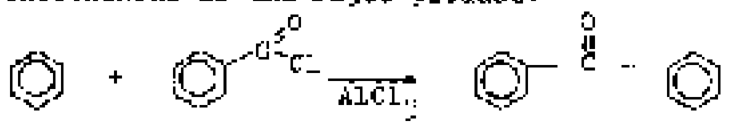
(b) 

(c) 

Solution: (a) Diphenyl methane ($C_6H_5CH_2C_6H_5$) can be prepared by using benzene as our starting material. We would want to add a benzyl group ($C_6H_5CH_2-$) to the benzene ring to get our desired product. A direct method used to accomplish this is the Friedel-Crafts alkylation procedure. In the presence of an alkyl halide (RX) and a Lewis acid (ex: $AlCl_3$) as a catalyst, the benzene ring would become alkylated. Hence the desired product could be synthesized by reacting benzene with benzyl chloride in the presence of $AlCl_3$:

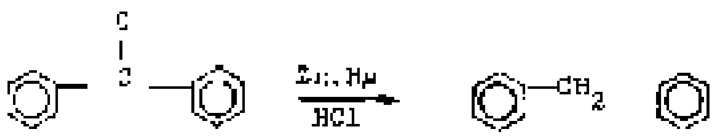


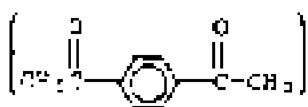
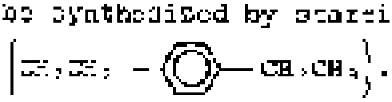
There is a problem associated with the above synthesis. When the benzene ring becomes alkylated, the alkyl group activates the ring. This makes the ring more susceptible to further alkylation; that is, the presence of an activating group on the ring will enhance its susceptibility to alkylation. Therefore, the reaction produces more poly-alkylated than monoalkylated product. One method of synthesis that will not encounter this problem is the Friedel-Crafts acylation. When a benzene ring is treated with an acyl halide $\left(R-\overset{\displaystyle O}{\overset{\|}{C}}-X\right)$ in the presence of a Lewis acid (ex: $AlCl_3$) catalyst, an acyl group $(R-C=O)$ will be added onto the ring. Since an acyl group deactivates an aromatic ring (due to the electron withdrawing carbonyl), diacylation is more difficult than monoacylation. Hence the monoacylated product is the major product in the reaction. When benzene is reacted with benzoyl chloride in the presence of $AlCl_3$, benzophenone is the major product:



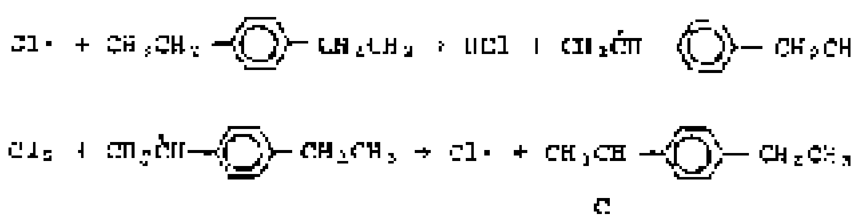
benzoyl chloride benzophenone

To convert benzophenone to our desired product we must reduce the carbonyl $\left(\overset{\text{O}}{\overset{\|}{\text{C}}}\right)$ to a methylene ($-CH_2-$). This can can be done by using the Clemmensen reduction. If there is a carbonyl group attached to a benzene ring, it will be converted into a methylene group when treated with zinc amalgam and hydrochloric acid. When benzophenone undergoes a Clemmensen reduction, diphenylmethane is produced:



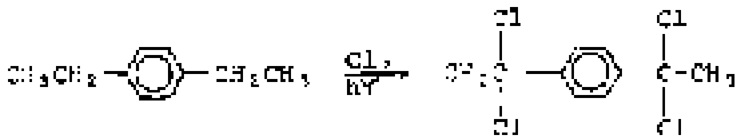
(b) p Diacetylbenzene  can be be synthesized by starting with p diethylbenzene . Free radical chlorination will chlorinate only the methylene groups. This occurs because the reaction proceeds through the most stable benzylic radical:

$$Cl_2 \xrightarrow{h\nu} Cl\cdot + Cl\cdot$$

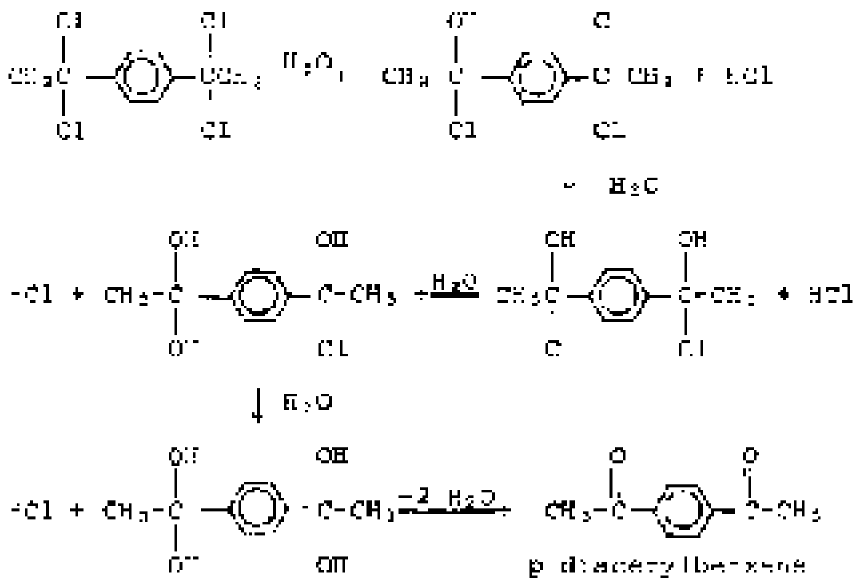


Above: Mechanism of free radical chlorination.

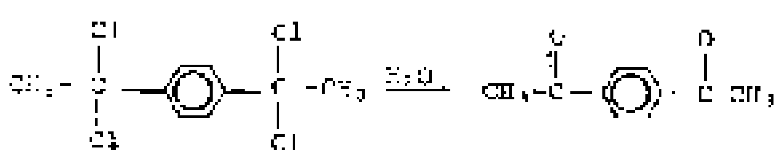
The overall reaction is:

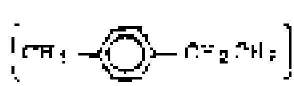


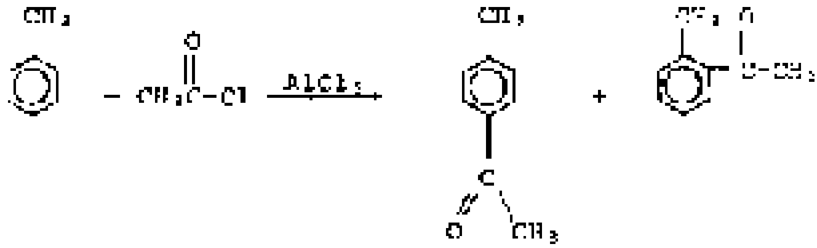
If the chlorinated product is treated with water, a substitution reaction will occur to produce a gem diol [HO-C-OH]. This gem diol will undergo water loss to form the carbonyl:



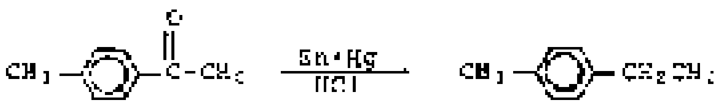
The overall reaction is:



(c) p-Ethyltoluene  can be synthesized from toluene. An ethyl group can be added onto the ring by using a Friedel-Crafts alkylation. There is the problem of polyalkylation in this case. Hence we can use the method described in part (a): Friedel-Crafts acylation followed by a Clemmensen reduction. If toluene is reacted with acetyl chloride (CH_3COCl) in the presence of $AlCl_3$, the acetyl group will add onto the ring. Toluene will be acetylated at its ortho or para position due to the ortho, para directing methyl group. The reaction is:



The product mixture can be separated and the para isomer can undergo Clemmensen reduction to give the desired product:



p-ethyltoluene

• PROBLEM 12-19

tert-Pentylbenzene is the major product of the reaction of benzene in the presence of BF_3 with each of the following alcohols: (a) 2-methyl-1-butanol, (b) 3-methyl-2-butanol, (c) 3-methyl-1-butanol, and (d) neopentyl alcohol. Account for its formation in each case.

Solution: The complicated alkylbenzenes such as tert-pentylbenzene are synthesized by Friedel-Crafts alkylation (attachment of an alkyl group) or by Clemmensen or Wolff-Kishner reduction (conversion of side chain). The fact that the Lewis acid, BF_3, is used in association with benzene and the alcohols in (a)-(d) means the Friedel-Crafts alkylation is taking place.

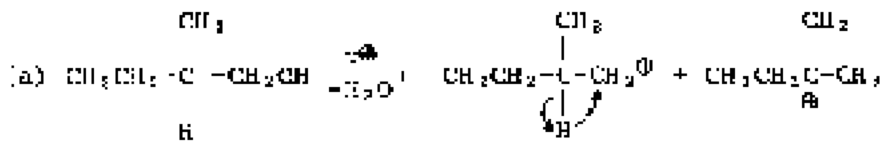
The reaction may be summarized as:

The Lewis acid may be $AlCl_3$, BF_3, HF, etc. RX does not have to be an alkyl halide; it can be an alcohol or alkene, but not aryl halide.

In the mechanism of Friedel-Crafts alkylation, the Lewis acid functions to generate an alkyl carbonium ion. For example:

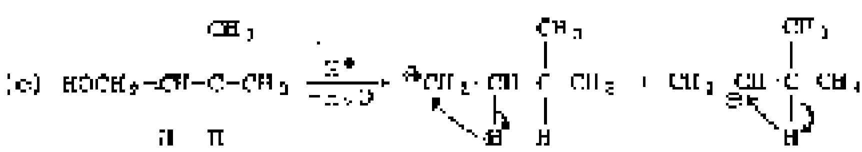
$$ROH + H^{\oplus} \rightleftharpoons ROH_2^{\oplus} \longrightarrow R^{\oplus} + H_2O.$$

This alkyl carbonium ion, an electrophile, attacks the electron rich aromatic ring to give the alkylbenzene. The fact that carbonium ions are involved means it is to be expected they would undergo rearrangement to the most stable carbonium ion. It is this rearrangement of carbonium ions that accounts for the production of tert-pentylbenzene as the major product in (a)-(d). In each case, the tert-pentyl cation $\left(CH_3CH_2-\underset{CH_3}{\overset{CH_3}{C^+}} \right)$ attacks the benzene ring. The formation of this cation occurs by 1,2 hydride and 1,2 methyl shifts as indicated by the arrows below:

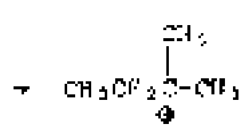


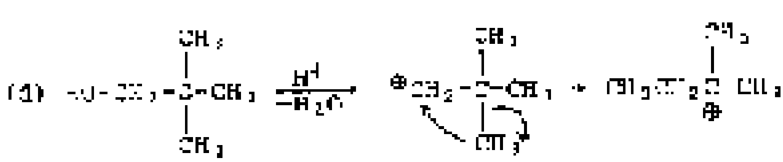
2-methyl-1-butanol 1° cation

3-methyl-2-butanol 2° cation



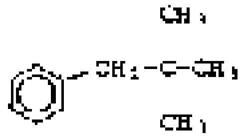
3 methyl 1-butanol 1° cation 2° cation



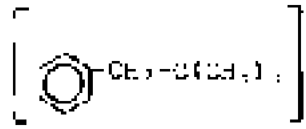


Neopentyl alcohol 1° cation

From available materials outline a synthesis of

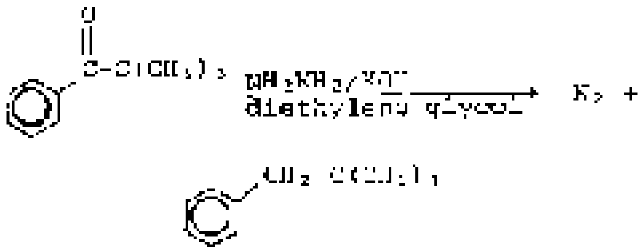


Solution: Neopentylbenzene



can be synthesized by starting with benzene. We must add a neopentyl group $(-CH_2-C(CH_3)_3)$ to the benzene ring to get our desired product. By using a Friedel Crafts alkylation we can alkylate the benzene ring. This method involves the reaction of an aromatic ring with an alkyl halide in the presence of a Lewis acid catalyst ($AlCl_3$). When using this method one encounters the problem of polyalkylation. When an alkyl group adds onto the ring, it activates the ring and makes it more susceptible to further alkylation. Hence the major product will be the polyalkylated product. To produce the monoalkylated product in an acceptable yield, we can use a two step method. First we can acylate the benzene ring by using a Friedel Crafts acylation (differs from Friedel-Crafts alkylation in that an acyl halide is used.) An acyl group $\left(R-\overset{O}{\overset{\|}{C}}-\right)$ will be added onto the benzene ring. If benzene is reacted with trimethylacetyl chloride in the presence of $AlCl_3$, an aromatic ketone will be formed. Polyacylation is not a problem in this reaction. This is because when an acyl group adds onto a benzene ring it will deactivate the ring due to the electron withdrawing carbonyl group. Deactivation makes the ring less susceptible to further acylation. Hence the monoacylated product is the major one. The reaction that forms phenyl-t-butyl ketone is:

To get our desired product we must convert the carbonyl to a methylene group. This is accomplished by employing a Wolff-Kishner reduction. This accomplishes the same thing as the Clemmensen reduction; the difference is that the Wolff-Kishner reduction is carried out in basic solution whereas the Clemmensen reduction is carried out in acidic solution. The aromatic ketone we produced must be reduced by the Wolff-Kishner method and not the Clemmensen method. This is because the ketone is unstable in acidic media (it will undergo a rearrangement). The reagents used in the Wolff-Kishner reduction are hydrazine (NH_2NH_2) and potassium hydroxide (KOH). Nitrogen gas is released as a by-product of the reaction:



neopentyl benzene

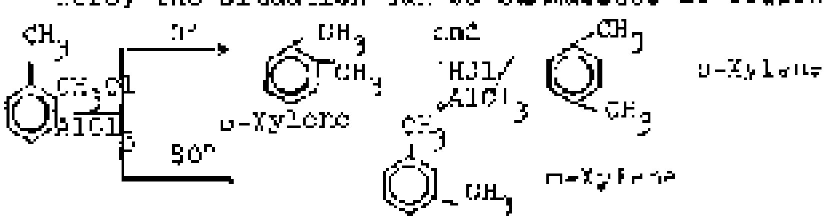
• PROBLEM 12-19

Treatment with methyl chloride and $AlCl_3$ at 0° converts toluene chiefly into o- and p-xylenes; at 80°, however, the chief product is m-xylene. Furthermore, either o- or p-xylene is readily converted into m-xylene by treatment with $AlCl_3$ and HCl at 80°.

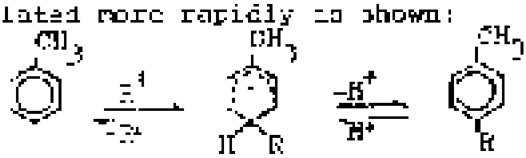
How do you account for this effect of temperature on orientation? Suggest a role for the HCl.

Solution: This problem is similar in nature to that of addition of HBr to 1,3-butadiene ($CH_2=CH-CH=CH_2$) in which both the 1,2 and 1,4 products are obtained, but the proportions in which they are obtained depend on the temperature at which the reaction is carried out. The proportions of products obtained from low temperature addition are determined by the rates of addition, whereas for the high-temperature they are determined by the equilibrium control.

Here, the situation can be summarized as follows:



At the low temperature (0°) addition, rate control is being observed. The o- and p-xylenes are formed faster. At the high-temperature (80°) addition, equilibrium-control is shown: m-xylene is the most stable product. The methyl group of toluene activates the ring for electrophilic aromatic substitution and directs substituents to the ortho and para positions. Just as the methyl group favors alkylation at the ortho and para positions, it also favors dealkylation - via electrophilic attack by a proton - at these same positions. This means that while the ortho and para isomers are formed more rapidly, they are also dealkylated more rapidly as shown:

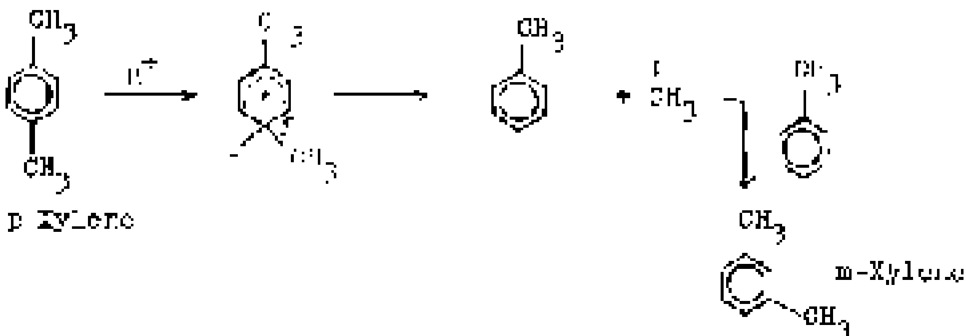


Although the meta isomer forms slowly, it tends to persist (be more stable) once produced.

The function of the HCl is to provide the proton required for the reversal of alkylation:

$$HCl + AlCl_3 \rightleftarrows H^+ + AlCl_4^-$$

It is believed that when the proton attacks the aromatic ring to create an intermediate carbonium ion, the methyl group undergoes a 1,2 shift to give the new orientation. In other words, it is believed the conversion of p-xylene to m-xylene occurs by intermolecular rearrangement (between molecules). A carbon bearing a methyl group in p-xylene is protonated and a methyl cation leaves the ring. This methyl cation attacks another molecule of toluene. This is shown as:



The same process occurs for o-xylene.

CHARACTERIZATION TESTS

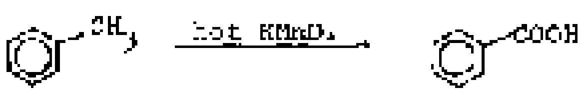
• PROBLEM 12-20

Describe simple chemical tests that would distinguish between: (a) benzene and toluene; (b) bromobenzene and bromocyclohexane; (c) bromobenzene and 3-bromo-1-hexene; (d) ethylbenzene and benzyl alcohol ($C_6H_5CH_2OH$).

Solution: By writing out the structures of the compounds in each case, the functional groups can be identified. In this way, chemical tests can be selected that differentiate between these functional groups.

(a)

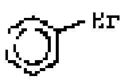
Toluene is classified as an arene; it contains both aliphatic and aromatic units. While compounds such as benzene and alkanes are rather unreactive toward oxidizing agents, arenes are quite susceptible to these agents ($KMnO_4$, $K_2Cr_2O_7$, etc.). It is on this basis that benzene and toluene are distinguished. When the oxidizing agent is added to the arene, the side chain is oxidized down to the ring with only a carboxyl (-COOH) group remaining to indicate the position of the original side chain. Therefore, if hot $KMnO_4$ is added to toluene, benzoic acid results (accompanied by decolorization of $KMnO_4$):



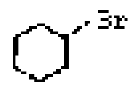
Benzoic Acid

Benzene fails to give this reaction.

(b)

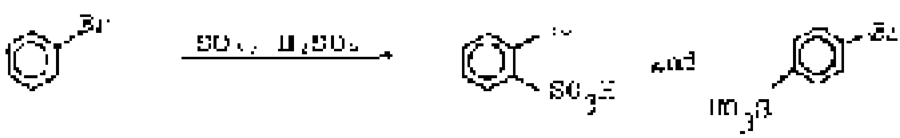


and

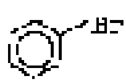


Bromobenzene   Bromocyclohexane

These two compounds are differentiated by the aryl halide's ability to be sulfonated by - and thus dissolve in - cold fuming sulfuric acid. Bromocyclohexane fails to give the sulfonation reaction outlined below for bromobenzene:



(c)

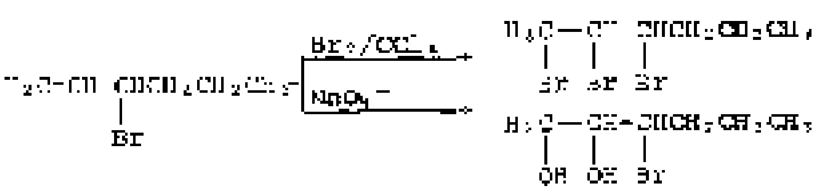


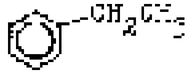
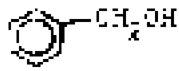
and $H_2C{=}CH-\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$

Bromobenzene

3-bromo-1-hexene

The aryl halide may be distinguished from the alkene by the failure of the former to decolorize bromine in carbon tetrachloride and by the failure to decolorize cold, dilute, neutral permanganate solutions. 3-bromo-1-hexene undergoes a reaction with these reagents as shown below:



(d)  and 

Ethylbenzene Benzyl alcohol

Alkylbenzenes can be distinguished from primary and secondary alcohols by their failure to give a positive chromic anhydride test. Recall, primary and secondary alcohols are oxidized by chromic anhydride, CrO_3, in aqueous sulfuric acid. Within two seconds, the clear orange solution turns blue-green and becomes opaque as shown:

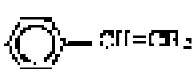
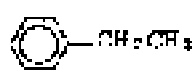
$$\underset{1° \text{ or } 2°}{ROH} + \underset{\text{Clear, orange}}{HCrO_4^-} \rightarrow \text{Opaque, blue green}$$

Benzyl alcohol, a primary alcohol, will give the color change, whereas the ethylbenzene will not.

■ PROBLEM 12-21

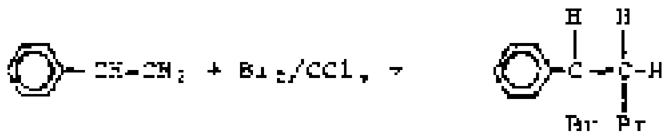
Describe simple chemical tests (if any) that would distinguish between: (a) styrene and ethylbenzene; (b) styrene and phenylacetylene; (c) allylbenzene and 1-nonene; (d) allylbenzene and allyl alcohol (CH_2=CH-CH_2OH). Tell exactly what you would do and see.

Solution: This problem can be solved by writing down the chemical structure to note the particular functional group the compound possesses and then devising characterization tests to distinguish between the functional groups and, as such, the compounds.

(a)  

Styrene Ethylbenzene

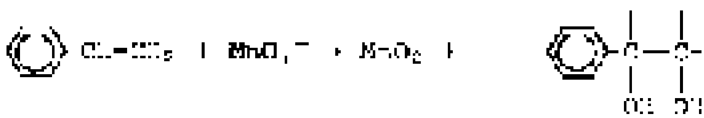
Both of these arenes (compounds containing both an aromatic and aliphatic unit) possess double bonds. However, only styrene has the double bond (for unsaturation) in its side group where it is extremely reactive to reagents that normally add across double bonds as in alkenes. (The double bonds of the aromatic ring are resonance stabilized so that they are not reactive to these reagents). Hence, these two compounds can be distinguished by the ability to decolorize both a solution of bromine in carbon tetrachloride and a cold, dilute, neutral permanganate solution. Styrene will decolorize since the aliphatic portion (-CH=CH_2) behaves as an alkene, whereas ethylbenzene will not (the side chain, -CH_2CH_3, behaves as an alkane so that it is inert to these reagents). The following will be seen:



styrene red colorless

Ethylbenzene + Br_2/CCl_4 → no reaction

red red

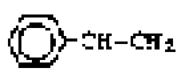


Purple Brown ppt. colorless

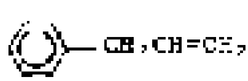
Ethylbenzene + MnO_4^- ⟶ no reaction

(purple) (purple)

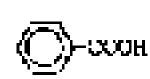
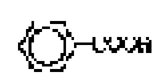
(b) Styrene Phenylacetylene



Phenylacetylene can be distinguished from styrene by the former's ability to form a heavy metal acetylides. The acidic acetylenes such as phenylacetylene react with certain heavy metal ions, chiefly Ag^+ and Cu^+, to form insoluble acetylides. The reaction is indicated by the formation of a precipitate. Styrene will not form this precipitate if placed in a solution such as $Ag(NH_3)_2OH$ or $Cu(NH_3)_2OH$. Hence, detection of a precipitate in either of these solutions is the simple chemical test desired.

(c)  $H_2C{=}CH(CH_2)_6CH_3$

Allylbenzene 1-nonene

These two compounds can be distinguished by physical properties after oxidation. Upon oxidation with hot $KMnO_4$ or $K_2Cr_2O_7$, allylbenzene and nonene yield  and $C_8H_{17}COOH$, respectively. The melting point of  is 122°, whereas the melting point of $C_8H_{17}COOH$ is 16°. This allows one to differentiate between allylbenzene and 1-nonene.

(d)  $CH_2=CH—CH_2OH$

Allylbenzene   Allyl alcohol

Since allyl alcohol is a primary alcohol, it will give a positive chromic anhydride test, whereas allylbenzene will not. Primary and secondary alcohols are oxidized by chromic anhydride, CrO_3, in aqueous sulfuric acid. The clear orange solution turns blue-green and becomes opaque within two seconds in the presence of these alcohols. Hence, allyl alcohol and allylbenzene may be distinguished by the former's ability to give the color change in chromic anhydride.

CHAPTER 13

NUCLEOPHILIC DISPLACEMENT

• PROBLEM 13-1

Explain why $(CH_3)_4N^+$ is neither a nucleophile nor an electrophile.

Solution: An ion or molecule is defined as nucleophilic (nucleus-seeking) if it possesses at least one pair of electrons that it will share with another atom to form a covalent bond. Nucleophiles are therefore Lewis bases. The ion or molecule that accepts electrons is said to be electrophilic (electron-seeking).

In order to fully understand why $(CH_3)_4\overset{+}{N}$ is neither a nucleophile nor an electrophile, all the electrons must be accounted for. The electron dot formula (figure A) shows that $(CH_3)_4\overset{+}{N}$ does not have a lone pair of electrons nor can it accept any electrons. The structure accounts for

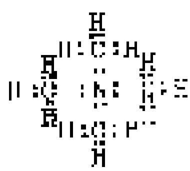


Figure A

all of the electrons and for the charge on the ion.

• PROBLEM 13-2

(a) Draw the structures of ethyl, n-propyl, isobutyl, and neopentyl bromides. These structures can be considered methyl bromide with one of its hydrogens replaced by various alkyl groups (GCH_2Br). What is the group G in each case?

(b) The relative rates of reaction (with ethoxide ion) are roughly: methyl bromide, 100; ethyl bromide, 6; n-propyl bromide, 2; isobutyl bromide, 0.2; neopentyl bromide, 0.00002. What is the effect of the size of the group G attached to carbon bearing the halogen?

Solution: (a) Recalling the nomenclature of the fundamental groups

CH_3CH_2Br	$CH_3CH_2CH_2Br$	$(CH_3)_2CH-CH_2Br$
ethyl bromide	n-propyl bromide	isobutyl bromide

$$CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2Br \qquad \text{neopentyl bromide}$$

The "G" Groups are for ethyl bromide, $-CH_3$, for n-propyl bromide, $-CH_2CH_3$, for isobutylbromide, $(CH_3)_2CH-$, and for neopentyl bromide, $CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-$.

(b) As the G group grows in size, so does the steric hindrance which is the actual physical interference caused by the substituents of a chain. As the interference increases, the likelihood of a reaction decreases hence lowering the rate of reaction.

S_N-2 REACTIONS

• PROBLEM 13-3

Ethyl chloride (0.1 M) reacts with potassium iodide (0.1 M) in acetone solution at 60° to give ethyl iodide and potassium chloride at a rate of 5.44×10^{-7} mole/liter/sec.

(a) If the reaction proceeded by an S_N2 mechanism, what would the rate of the reaction be at 0.01 M concentrations of both reactants? Show your method of calculation.

(b) Suppose the rate were proportional to the square of the potassium iodide concentration and the first power of the ethyl chloride (S_N3). What would the rate be with 0.01 M reactants?

(c) If one starts with solutions initially 0.1 M in both reactants, the rate of formation of ethyl iodide is initially 5.44×10^{-7} mole/liter/sec but falls as the reaction proceeds and the reactants are used up. Make plots of the rate of formation of ethyl iodide against the concentration of ethyl chloride as the reaction proceeds (remembering that one molecule of ethyl chloride consumes one molecule of potassium iodide) on the assumption that the rate of reaction is proportional to the first power of the ethyl chloride concentration and to (1) the zeroth power, (2) the first power, and (3) the second power of the potassium iodide concentration.

(d) What kind of experimental data would one need to tell whether the rate of the reaction of ethyl chloride with potassium iodide is first order in each reactant or first order in ethyl chloride and zero order in potassium iodide?

Solution: The rate of any chemical reaction is always the product of three factors: (1) the collision frequency, (2) the energy factor and (3) probability factor.

In this problem, the effect of the concentration on a given reaction will be examined.

In general, if all other conditions remained uniform, how would changes in concentration affect the rate of a reaction? A change in concentration would have no effect on the energy of the reaction, nor would it influence the percentage of collisions with proper orientation, but a change in concentration would definitely affect the total number of collisions. One can liken the situation to that of a student wishing to breed fruitflies. The greater the number of fruitflies he has in a given space the greater the number of new flies because of the increased number of flies that cross paths. The increase in fruitflies has no effect on the biochemical factors of mating, nor does it increase the fraction of fruitfly collisions which are male female.

The field of chemistry which deals with rates of reactions, and in particular the effects of concentration on the rate of reaction is called kinetics.

(a) The reaction of potassium iodide with ethyl chloride yielding ethyl iodide is an S_N2 reaction.

As can be seen, the reaction proceeds via the interaction of the iodide anion with ethyl chloride; one would reasonably conclude that the rate would be dependent on both the concentration of the nucleophilic anion and ethyl chloride. A doubling of either the iodide anion or ethyl chloride would result in doubling the reaction rate by doubling the number of successful collisions. This proportionality can be expressed in terms of a formula:

$$\text{rate} = k\,[I^{\ominus}][CH_3CH_2Cl]$$

Here, k stands for the rate constant, which is characteristic for a reaction under particular conditions (solvent, temperature, etc.). This rate constant would take into account the effects on the rate of reaction other than the concentration of the reactants.

Given that .1 M ethyl chloride reacts with .1 M potassium chloride in acetone at 60° at a rate of 5.44×10^{-7} mole/liters/sec., the rate constant can be calculated.

$$\text{Rate} = k[CH_3CH_2Cl][I^{\ominus}]$$

Substituting:

$$5.44 \times 10^{-7} = k\,[.1][.1]$$

$$k = 5.44 \times 10^{-5}$$

5.44×10^{-5} is therefore the rate constant of the potassium iodide - ethyl chloride reaction at 60°.

If one were to now change the concentrations of either of the reactants, the rate of reaction could be calculated.

At (.01) M for both reactants the rate would be equal to:

$$\text{rate} = k[CH_3CH_2Cl][I^{\ominus}]$$

$$= 5.44 \times 10^{-5}\,[10^{-2}][10^{-2}]$$

$$\text{rate} = 5.44 \times 10^{-9}$$

(b) The equation

$$\text{rate} = k[I^{\ominus}][CH_3CH_2Cl]$$

is a second order equation which means that the sum of the exponents of its variables are equal to two. Indeed this is the basis of the name S_N2 (in contrast to S_N1) - a nucleophilic reaction of second order.

If the reaction of the iodide anion with ethyl chloride were such that the rate of the reaction were proportional to the square of the potassium iodide concentration it would be termed an S_N3 reaction.

$$\text{rate} = k[I^{\ominus}][CH_3CH_2Cl][I^{\ominus}]$$

or

$$\text{rate} = k[I^{\ominus}]^2[CH_3CH_2Cl]$$

This is termed a third order reaction because basically three molecules are involved in the reaction's transition state and hence the sum of the exponents is equal to three.

In order to calculate the rate constant of this reaction, the initial information provided is employed.

$$\text{rate} = k[I^{\ominus}]^2[CH_3CH_2Cl]$$

$$5.44 \times 10^{-7} = k[10^{-1}]^2[10^{-1}]$$

$$k = 5.44 \times 10^{-4}$$

When the concentrations of both reactants are both .01 M, the rate would be:

$$\text{rate} = 5.44 \times 10^{-4}\ [10^{-2}]^2[10^{-2}]$$

$$\text{rate} = 5.44 \times 10^{-10}$$

(c) If the reaction of ethyl chloride and potassium iodide proceeded in accordance with the mechanism below, it would be termed an S_N1 reaction.

$$CH_3CH_2Cl + I^{\ominus} \rightleftharpoons CH_3CH_2^{\oplus} + Cl^{\ominus} + I^{\ominus}$$

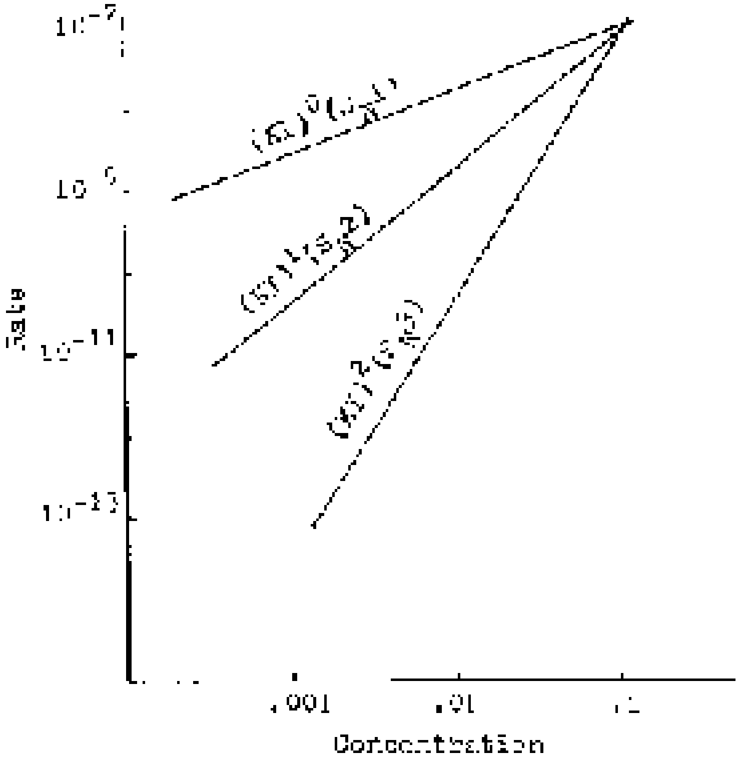
$$\longrightarrow CH_3CH_2I + Cl^{\ominus}$$

This reaction would be independent of the concentration of the iodide ion. No matter how much iodide ion is added it will have no effect on the dissociation of the ethyl chloride. The ethyl chloride would dissociate slowly and would recombine in a second fast step. It is the first step (ionization of ethyl chloride) which is the rate determining step. Therefore the kinetic equation of the reaction is as follows:

$$\text{rate} = k[I^{\ominus}]^0[CH_3CH_2Cl]$$

Since the reaction is a unimolecular, nucleophilic substitution reaction it is termed S_N1.

Plotting the concentration versus the rate for the S_N1, S_N2 and S_N3 reactions:



(3) At this point, the reader must be experiencing some confusion as to whether ethyl chloride and potassium iodide would undergo an S_N1, or an S_N2 reaction. This could be determined by a simple experiment whereby the concentration of only the potassium iodide were changed. If a change in the reaction rate were observed then one could assume the reaction S_N2 and if there is no change in the reaction rate, then the reaction is S_N1.

As it so happens, the reaction of potassium iodide with ethyl chloride proceeds with an S_N2 mechanism. In fact, all nucleophilic attacks on a primary carbon will always proceed through an S_N2 path. S_N1-type reactions are limited to attack upon compounds that will generate particularly stable carbocations (e.g. tertiary, allylic cations).

• **PROBLEM** 13-4

Suppose a water solution was made up initially to be 0.01 M in methyl bromide and 1.0 M in sodium acetate at 50°. In water, the S_N2 rate constant for reaction of hydroxide ion with methyl bromide at 50° is 30×10^{-4} liters/mole/sec, whereas that of acetate ion at 50° is 1.0×10^{-4} liters/mole/sec. The ionization constant of acetic acid at 50° is 1.8×10^{-5}. In the following, assume perfect solutions and neglect the rates of reaction of methyl bromide with water or acetic acid by themselves and any further reactions of methyl acetate:

(a) Calculate the hydroxide-ion concentration in the initial solution.

(b) Calculate the initial rates of formation of methyl acetate and methanol.

(c) What kind of information would be needed to predict what products would be expected from a solution of methyl bromide and sodium hydroxide in methanol? Explain.

Solution: (a) In order to determine the hydroxide ion concentration, the hydrolysis constant must first be obtained. Hydrolysis refers to the action of the salts of weak acids and bases with water to form acidic or basic solutions. Such is the case with sodium acetate.

$$HOAc \rightleftarrows H^+ + OAc^-$$

$$K = \frac{[H^+][OAc^-]}{[HOAc]} = 1.8 \times 10^{-5}$$

$$H^+ + OH^- \rightleftarrows H_2O$$

$$K_w^{-1} = \frac{[H_2O]}{[H^+][^-OH]} = 10^{14}$$

The net equation of the hydrolysis reaction is:

$$HOAc \rightleftarrows H^+ + {}^-OAc$$

$$H^+ + {}^-OH \rightleftarrows H_2O$$

$$HOAc + H^+ + {}^-OH \rightleftarrows H^+ + {}^-OAc + H_2O$$

The equation of the hydrolysis constant is KK_w^{-1}.

$$K = \frac{[H^+][^-OAc]}{[HOAc]} = 1.8 \times 10^{-5}$$

$$K_w^{-1} = \frac{[H_2O]}{[H^+][^-OH]} = 10^{14}$$

$$K_{hyd} = KK_w^{-1} = \frac{[H^+][^-OAc][H_2O]}{[HOAc][H^+][^-OH]}$$

$$= \frac{[^-OAc][H_2O]}{[HOAc][^-OH]} = 1.8 \times 10^{9}$$

$$HOAc + {}^-OH \rightleftarrows {}^-OAc + H_2O$$

In the hydrolysis equation, it will be noted that the concentrations of acetic acid and hydroxide will be identical. Hence if X = the concentration of the hydroxide ion, then $[HOAc][^-OH] = X^2$.

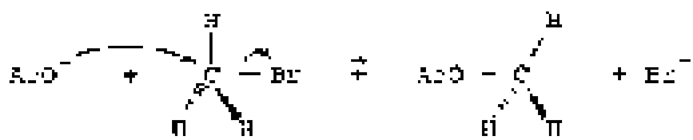
The initial concentration of sodium acetate is 1 M, hence the concentration of sodium acetate at equilibrium is 1 − X; or the initial concentration minus the amount reacted to yield the X moles of hydroxide ion per liter.

Hence, the hydrolysis equation is:

$$\frac{[^-OAc][H_2O]}{[^-OH][HOAc]} = \frac{1 - X}{X^2} = 1.8 \times 10^9$$

Solving for X;

$X = 2.2 \times 10^{-5}$ moles/liter.

(b) 

All S_N2 displacements, as in the above reaction, are second order kinetic reactions. That is, the rate of reaction is dependent on the concentrations of both the reactants. The rate of any second order reaction $A + B \rightarrow C + D$ can be written as

$$\text{rate} = k[A][B],$$

where k is the reaction constant. In the case of the methyl bromide - acetate ion reaction,

$$\text{rate} = k[CH_3Br][^-OAc]$$

Substituting the given values,

$$\text{rate} = 1.0 \times 10^{-4} \times 10^{-2} \times 1.0$$

$$= 1 \times 10^{-6}$$

The rate of the methyl bromide - hydroxide reaction is computed similarly.

$$\text{rate} = k[CH_3Br][OH^-]$$

$$= 3.0 \times 10^{-4} \times 10^{-2} \times 2.2 \times 10^{-5}$$

$$= 6.6 \times 10^{-11} \text{ m/liter/sec.}$$

(c) Three factors are needed in determining the nature of the products expected.

The first would be the position of the equilibrium of the reaction

$$CH_3OH + NaOH \rightleftarrows CH_3O^- Na^+ + H_2O.$$

Secondly, the initial concentration of sodium hydroxide would be needed and thirdly, the rate constants of the reactions:

$$CH_3Br + CH_3OH \rightleftharpoons CH_3OCH_3 + HBr$$

$$CH_3Br + Na(OH) \rightleftharpoons CH_3OH + NaBr$$

$$CH_3Br + CH_3ONa \rightarrow CH_3OCH_3 + NaBr$$

● PROBLEM 13-3

Predict the product(s) of the S_N2 reaction of each of the following nucleophiles with (±)-2-iodooctane.

(a) Br^-

(b) $CH_3C(O)CH_2^-$

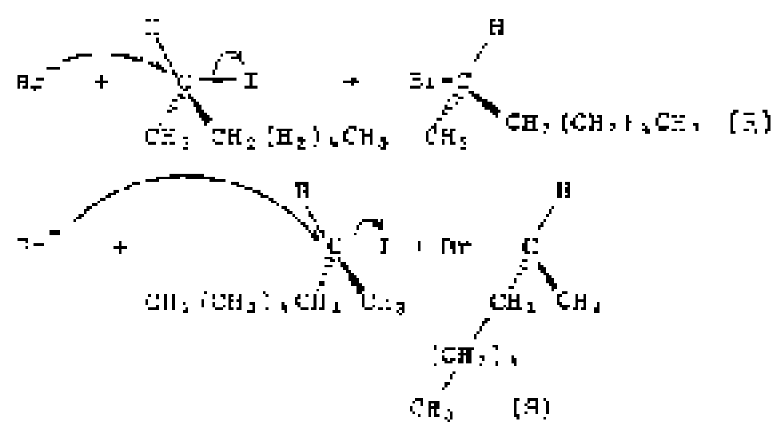
(c) (R)-$CH_3CHCH_2CH_3$ with O^- on C-2

(d) (R,S)-$CH_3CHCH_2CH_3$ with O^- on C-2

Solution: (a) This is an S_N2 displacement reaction with bromide anion acting as a nucleophile and the iodide anion being the leaving group:

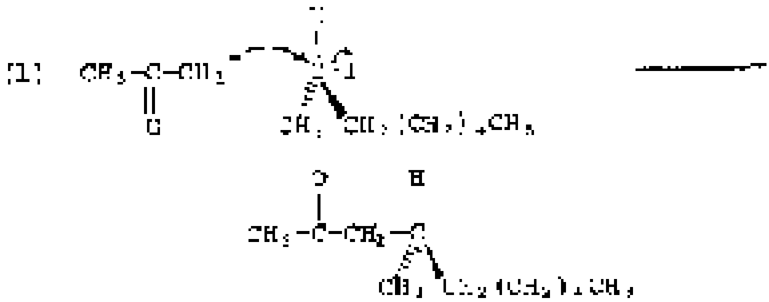
(1)

(2)

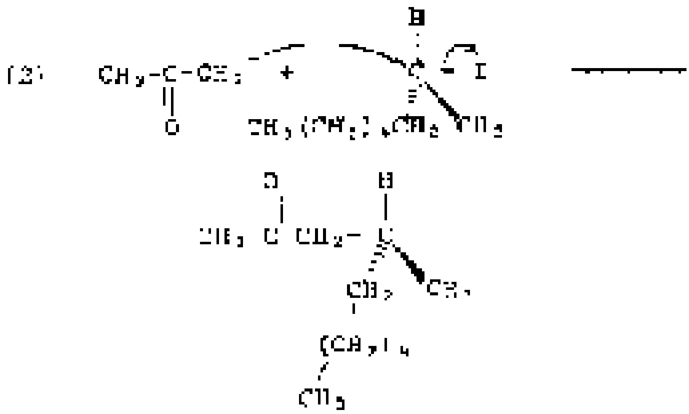


Since equal amounts of the dextrorotatory and the levorotatory 2-iodooctane are present, a racemic product will be obtained. Note that a S_N2 displacement proceeds with inversion of configuration at the chiral carbon.

(b) Here again, the product is a racemic modification.

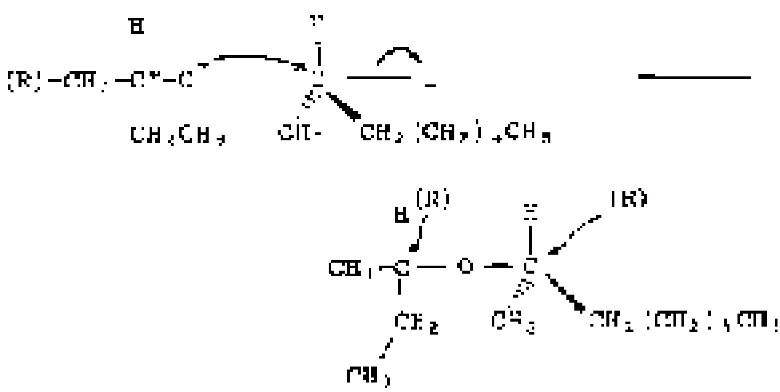


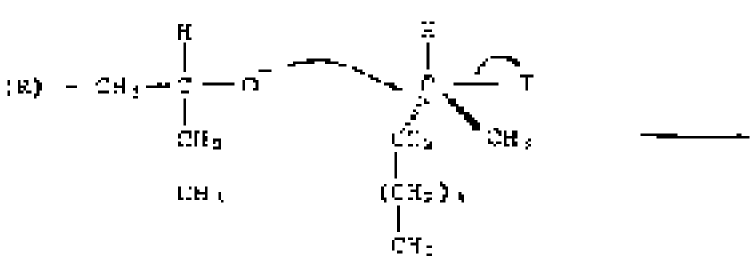
(a)

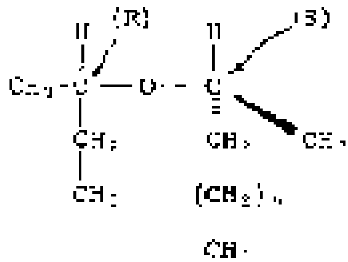


(b)

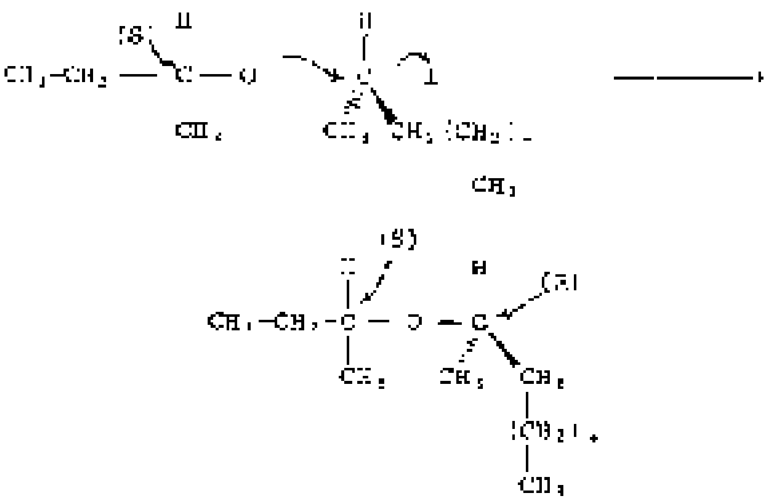
(c) In this problem, the nucleophile contains its own chiral center whose configuration is maintained in the product. Therefore, diastereomers are generated.



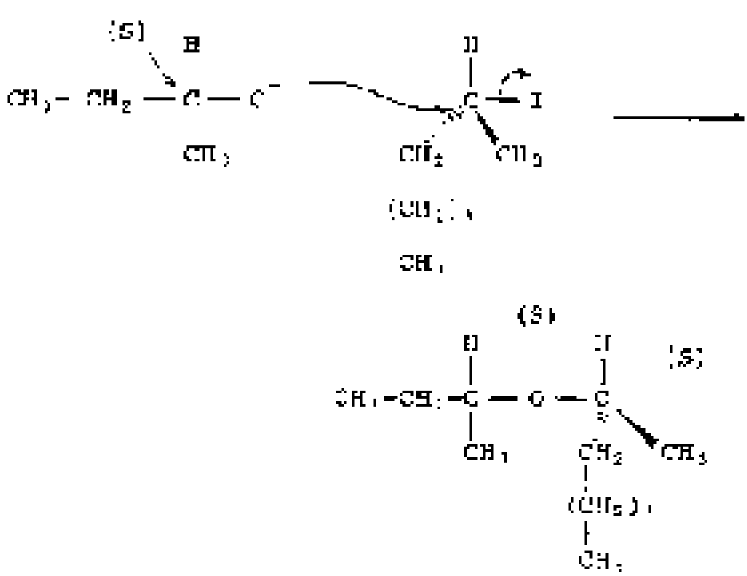




(1) In this displacement, four different stereochemical products would be expected, because the attacking nucleophile is a racemic modification. The stereochemistries of the products are (R, R), (R, S), (S, R) and (S, S). The reaction of the (R) isomer was seen in the last part of this problem.



(d)



S_N1 REACTIONS

■ PROBLEM 13-6

Benzyl bromide reacts with H_2O in formic acid solution to yield benzyl alcohol; the rate is independent of $[H_2O]$. Under the same conditions p-methylbenzyl bromide reacts 58 times as fast.

Benzyl bromide reacts with ethoxide ion in dry alcohol to yield benzyl ethyl ether ($C_6H_5CH_2OC_2H_5$); the rate depends upon both [RBr] and $[OC_2H_5^-]$. Under the same conditions p-methylbenzyl bromide reacts 1.5 times as fast.

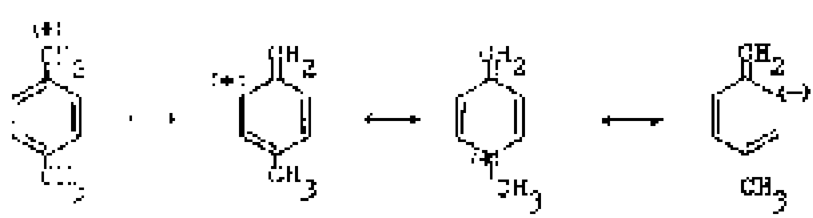
Interpret these results. What do they illustrate concerning the effect of: (a) polarity of solvent, (b) nucleophilic power of the reagent, and (c) electron release by substituents?

Solution: The polarity of a solvent can often determine the mechanism by which a given reaction will occur. Ionization of an alkyl halide occurs only because most of the energy needed to reach the transition state is provided for by the formation of dipole-dipole bonds. The more polar the solvent, the stronger the solution forces and the faster the ionization.

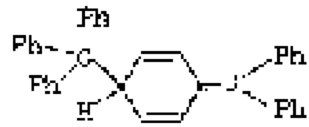
(a) In part a, formic acid is more polar than dry alcohol, and hence favors the S_N1 reaction. The less polar solvent, alcohol, favors the S_N2 reaction.

(b) Water would not be a strong enough nucleophile to undergo and S_N2 reaction and displace bromine. The ethoxide ion, however, is a far stronger nucleophile and is more capable of undertaking an S_N2 displacement.

(c) The electron releasing properties of the methyl group will speed up the S_N1 reaction (by stabilizing the transition state). It will have little effect, however, on the S_N2 reaction.

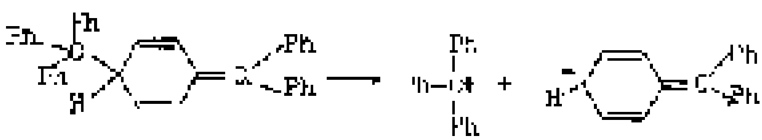


Resonance stabilization of methyl benzyl cation.

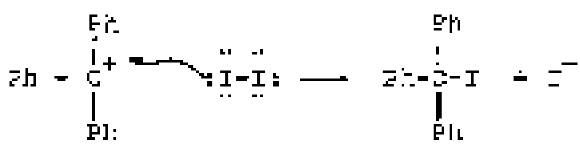


The above dimer decolorizes iodine in the presence of benzene at a rate that is independent of the concentration of iodine, but dependent on the concentration of the dimer. Likewise, if a benzene solution of the dimer is exposed to an NO gas atmosphere, the pressure of the gas drops at a rate independent of the gas but dependent upon the dimer. The rate constants for the above two processes are identical. Account for this.

Solution: Both reactions proceed in an S_N1 manner, where the dissociation of the dimer is the rate determining step.



Subsequent steps are fast and have no effect on the rate of reaction.



The rate of this equation, as well as that of the reaction where nitric oxide is the nucleophile is:

$r = k[\text{dimer}]$

• PROBLEM 13-8

The hydroxyl catalyzed dehydrohalogenation of isopropyl bromide can follow both the E1 or E2 mechanism. Explain with the use of illustrations both types of mechanisms.

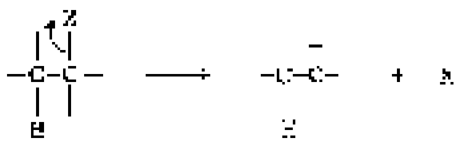
Solution: Elimination reactions may be classified as α eliminations (eliminations of two groups from the same atom) or β eliminations (eliminations of two groups from adjacent atoms yielding unsaturated bonds). Both of these eliminations are catalyzed by bases.

Bimolecular elimination, known as E2, involves the abstraction of a β proton by base attack with the simultaneous departing of the group X. It can be illustrated as follows:

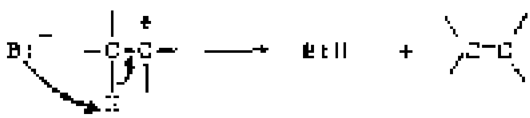
The reaction follows second-order kinetics; the rate of alkene formation depends on the concentrations of both reactants. No rearrangements of the alkyl group are involved in the E2 mechanism.

Unimolecular elimination, known as E1, differs from E2 in that the group X leaves the molecule before the attack of base. As a result, one has an intermediate formation of a carbonium ion. The two step reaction of E1 can be written as:

Step 1: Carbonium ion formation



Step 2: Abstraction of proton by base attack:



Step 1 is the slower and hence, the rate-controlling step, dependent only on the concentration of the alkyl halide.

STEREOCHEMISTRY OF S_N REACTIONS

• PROBLEM 13-8

(1) (+)RO:H + CH_3-C(=O)-O-C(=O)-CH_3 → (+) RO-C(=O)-CH_3 + CH_3-C(=O)-OH

(2) (+) RO:H $\xrightarrow{\text{2 steps}}$ (−) RO-SO_2R

(3) (+) $ROSO_2R$ + CH_3-C(=O)-O^- → (−)$ROCCH_3$ (C=O) + $^-OSO_2R$.

Citing the above three reactions as corroborating evidence, Kenyon and Phillips proposed that the inversion of configuration of an optically active R group accompanies S_N2 nucleophilic displacement reactions. Does their data justify their conclusion?

Solution: Kenyon and Phillips' hypothesis is supported by their data; reaction (3) undergoes an inversion of configuration. However, reaction (3) in itself could not be construed as evidence of configurational inversion. While a change in the sign of rotation occurs, there is no evidence that a change in the optical configuration of the R group occurs. The sign of rotation refers to the rotation of light while passing through an optically active medium: it does not reveal the absolute optical configuration of a molecule.

Reactions (1) and (2), however, do sustain the contention that reaction (3) does undergo inversion of configuration. It is evident that reactions (1) and (2) do not involve a change of configuration of the optically active R group in that in each instance the reaction occurs at the alcohol's oxygen and not at its optically active R group. Hence, the two esters

$$(+)\ RO\overset{\overset{O}{\|}}{C}CH_3 \qquad \text{and} \qquad (+)\ ROSO_2R$$

must have the same optical configurations. Moreover, since

$$(+)\ RO\overset{\overset{O}{\|}}{C}CH_3 \qquad \text{and} \qquad (-)\ RO\overset{\overset{O}{\|}}{C}CH_3$$

have opposite configurations, then

$$(+)\ ROSO_2R \qquad \text{and} \qquad (-)\ RO\overset{\overset{O}{\|}}{C}CH_3$$

must also have opposite configurations. Therefore, reaction (3) proceeds with inversion about the R group.

• PROBLEM 13-10

Under S_N1 conditions, 2-bromo octane, of specific rotation $-20.8°$, was found to yield 2-octanol of specific rotation $-3.96°$. If optically pure 2-bromooctane has a specific rotation of $-34.6°$ and optically pure 2-octanol has a specific rotation of $-9.9°$ calculate: (a) the optical purity of reactant and product; (b) the percentage of racemization and of inversion accompanying the reaction; (c) the percentage of front side and of back side attack on the carbonium ion.

Solution: (a) The optical purity of a compound can be expressed as the fraction $\frac{r_i}{r_p}$, where r_i is the rotation of the impure compound and r_p is the rotation of the pure compound.

In the case of 2-bromooctane, the optical purity is:

$$\frac{20.8}{34.6} \times 100 = 60\%.$$

In the case of 2-octanol:

$$\frac{3.96}{9.90} \times 100 = 40\%.$$

(b) The percentage of racemization and inversion can be obtained by first determining the ratio of the optical purity of the products to that of the reactants. In the case of 2-bromooctane and 2-octanol, this ratio is $\frac{40}{60}$ or $\frac{2}{3}$. If the reaction had proceeded with complete inversion, an optical purity ratio of 1 would have been expected (for every molecule of 2-bromooctane, one molecule of 2-octanol would have formed).

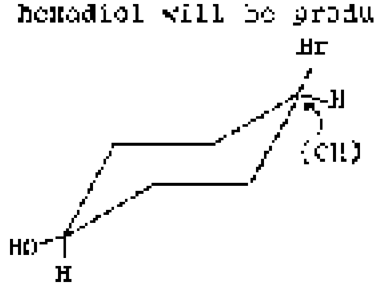
Therefore, if the optical purity ratio is $\frac{2}{3}$, the reaction proceeds with $\frac{2}{3}$ inversion and $\frac{1}{3}$ racemization.

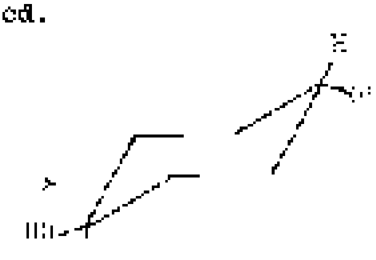
(c) Every molecule that undergoes front-side attack (retention) cancels the optical activity of a molecule that is undergoing back side attack (inversion). In this reaction, $\frac{1}{6}$ front-side attack occurs, cancelling $\frac{1}{6}$ of the back-side attack, giving $\frac{1}{6} + \frac{1}{6}$ or $\frac{1}{3}$ racemization. Therefore, $\frac{1}{6}$ + $\frac{2}{3}$ (inversion) or $\frac{5}{6}$ of the molecules undergo back-side attack.

• PROBLEM 13-11

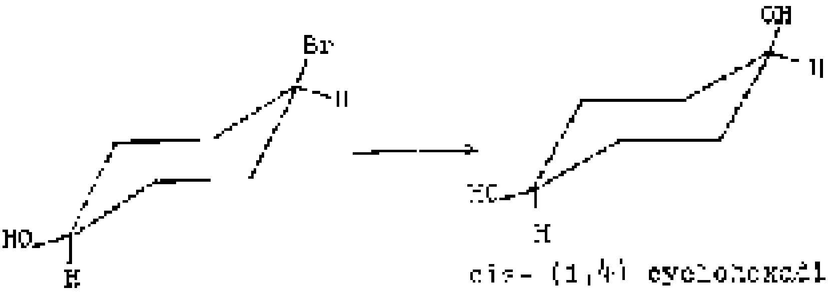
(a) What product would be formed if the reaction of cis-4-bromocyclohexanol with OH^- proceeded with inversion? (b) Without inversion? (c) Is it always necessary to use optically active compounds to study the stereochemistry of substitution reactions?

Solution: (a) If the S_N2 reaction of cis-4-bromocyclohexanol proceeded with inversion, trans(1,4) cyclohexadiol will be produced.





(b) Without inversion (retention):



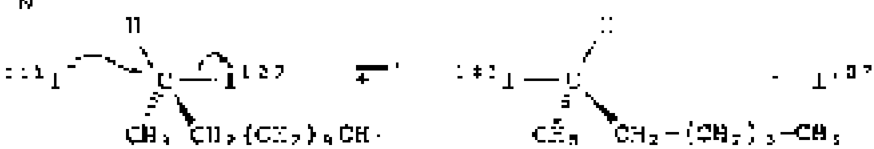
cis- (1,4) cyclohexadiol

(c) It is not necessary to use optically active reactants to study the stereochemistry of substitution reactions. We may use starting materials such as those in this problem which have two chiral centers. Using the proper nucleophile, we can induce the reactants to form diastereomeric products which can be separated by differences in physical properties.

• PROBLEM 13-12

Optically active 2-iodooctane, upon standing in an acetone solution containing NaI^{131}, loses its chirality and exchanges its I^{127} for I^{131}. In addition, while the rate of reaction is dependent on both [RI] and $[I^-]$ racemization proceeds twice as fast as isotopic exchange. Explain.

Solution: The reaction goes as illustrated below: an S_N2 displacement



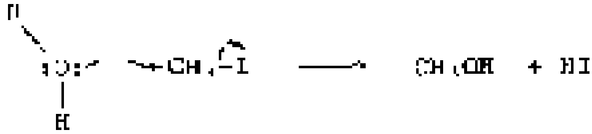
Racemization proceeds at twice the rate of isotopic exchange because for every molecule that is formed, with inverted configuration, one unreacted molecule of opposite configuration is "cancelled", and therefore the rate of racemization should be twice the rate of reaction. For example, if we started with four molecules of bromo-deuteriophenylmethane and introduce iodide anions. The optical purity will decrease by 50% (not 25%) after the initial attack. An additional nucleophilic attack will racemize the mixture completely.

STRUCTURAL AND SOLVENT AFFECTS

• PROBLEM 13-13

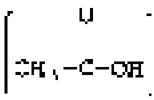
Draw a reaction coordinate diagram for the solvolysis of 2,2,2-triphenylethyl chloride in acetic acid. Pay special attention to the phenonium-ion intermediate. What would be the difference in this diagram if the phenonium ion were a transition state instead of an intermediate?

Solution: Solvolysis refers to the form of nucleophilic substitution where the solvent is the nucleophile. For example, a dilute solution of methyl iodide will always contain methanol

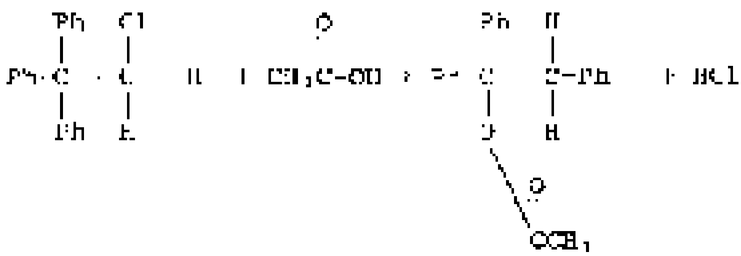


solvent

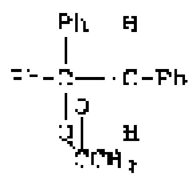
In this particular case, acetic acid



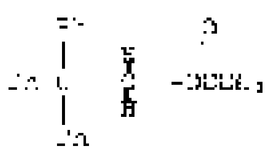
is the nucleophile displacing a chloride anion from 2,2,2-triphenylethyl chloride. The net reaction is



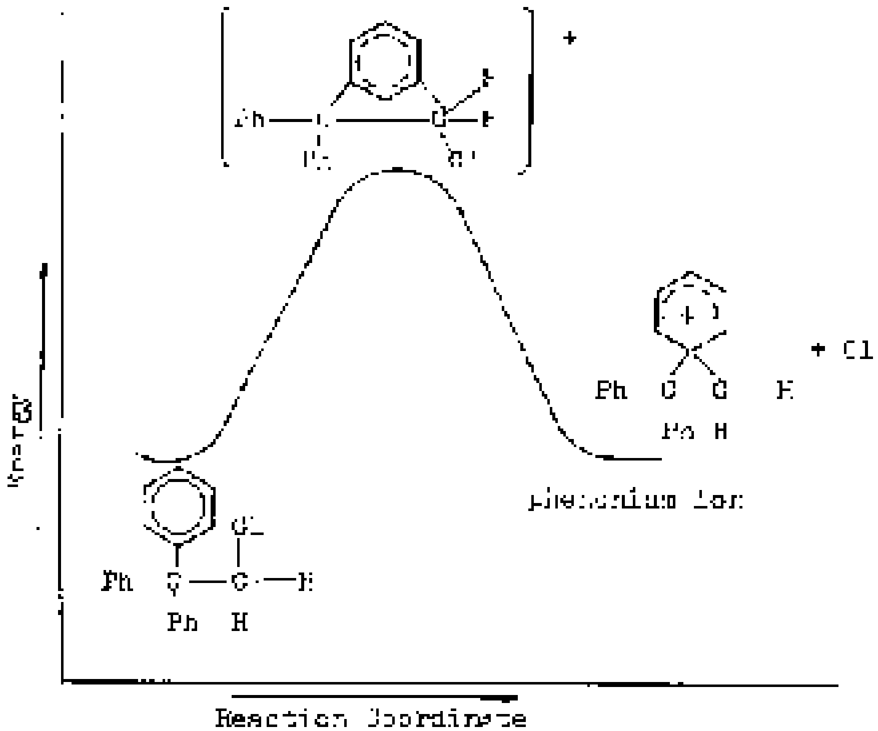
The final product is



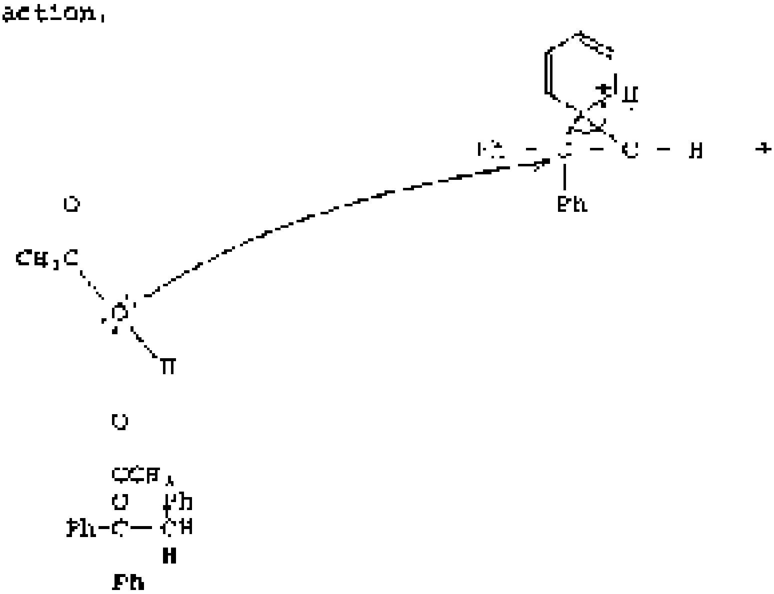
and not



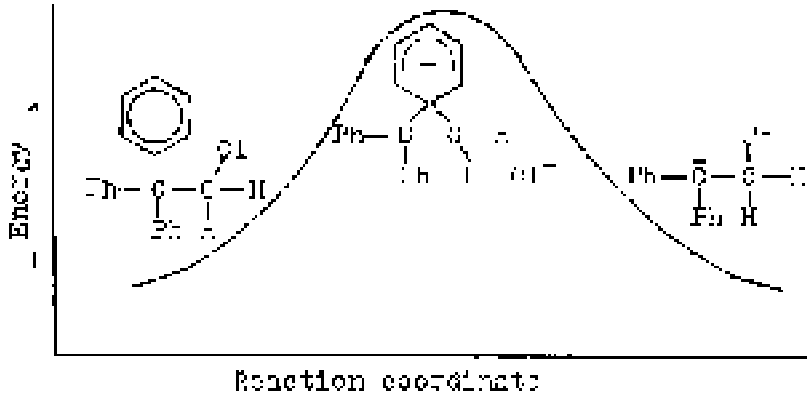
because the latter product would require nucleophilic attack upon a primary carbon. The carbon is too hindered to undergo a S_N2 reaction and the implausibility of a primary cation eliminates the possibility of an S_N1 reaction that does not involve rearrangement. Due to the immense instability of the primary carbocation, 2,2,2-triphenylethyl chloride will undergo an S_N1 solvolysis with migration of a phenyl group to the carbon which is simultaneously losing a chloride ion. This migration, which stabilizes the transition state, is known as anchimeric assistance. The intermediate phenonium ion is very stable due to participation of the aromatic ring in delocalization of the positive charge. The phenonium ion is analogous to the intermediate in electrophilic aromatic substitution. The reaction coordinate for this reaction, assuming the phenonium ion to be an actual intermediate, appears as follows:



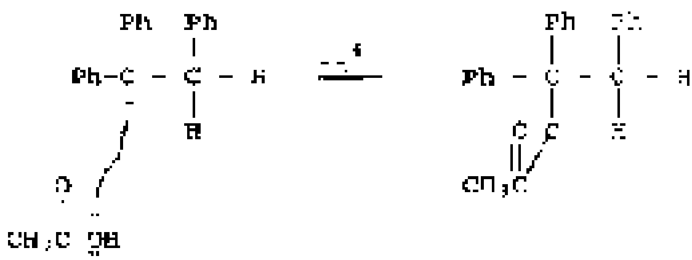
The phenonium ion will be attacked by acetic acid to give the final products in the second part of this reaction.



If the phenonium ion were a transition state instead of an intermediate, the reaction coordinate would be:



The dibenzylic cation intermediate undergoes nucleophilic attack by acetic acid to complete the S_N1 reaction.



• PROBLEM 13-14

Predict either an increase or decrease in the rate of each of the following reactions with an increase in solvent-ionizing power. Specify whether the change would be relatively large or small. Give your reasoning.

(a) $(CH_3)_3CCH_2I \xrightarrow{S_N1} (CH_3)_3\bar{C} + H_2O$

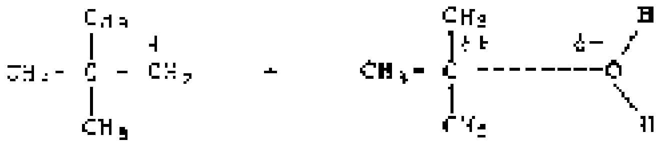
(b) $CH_3OSO_2C_6H_5 + \bar{O}H \xrightarrow{S_N2} CH_3OH + \bar{O}SO_2C_6H_5$

(c) $CH_3\overset{+}{S}(CH_3)_2 + \bar{O}C_2H_5 \xrightarrow{S_N2} CH_3OC_2H_5 + S(CH_3)_2$

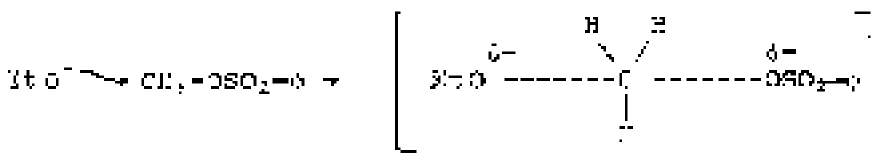
(d) $CH_3CH_2I + (CH_3CH_2)_3N \xrightarrow{S_N2} (CH_3CH_2)_4\overset{+}{N} \quad \bar{I}$

<u>Solution:</u> The polarity of a solvent will often determine by which mechanism a given reaction proceeds. The more polar the solvent, the greater the solvent-ionizing power of the solvent, which in turn increases the S_N1 character of a given reaction. (S_N1 reactions involve the ionization of an alkyl halide.) Hence, an increase in solvent ionizing power will usually serve to increase the S_N1 character of the reaction.

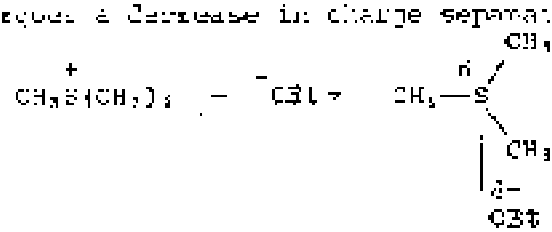
Reaction (a) is an exception to this rule. A decrease in S_N1 character would be expected as the charge is spread out slightly more in the transition state than in the reactant.



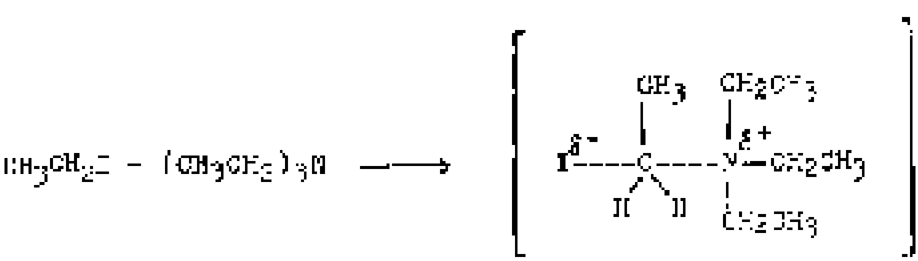
In (b) the S_N2 reaction will also undergo a slight decrease as the transition state has a charge separation only slightly greater than that of the reactant.



(c) In this instance, a large decrease in the S_N2 reaction rate would be expected, as transition state undergoes a decrease in charge separation.



(d) A large increase in the rate would be expected as a large charge separation develops in the transition state. The solvent would help to stabilize the transition state, which would increase the overall rate of the reaction.



solvent. $(CH_3CH_2)_4\overset{+}{N}$ + I^-

Each of the following cations is capable of rearranging to a more stable cation. Limiting yourself to a single 1,2-shift, suggest a structure for the rearranged cation.

(a) $CH_3CHCH_2\overset{+}{C}HCH_3$ (b) $(CH_3)_3C\overset{+}{C}HCH_3$

(c) $CH_3CH_2CH_2\overset{+}{C}HCH(CH_3)C(CH_3)_3$ (d) $CH_2{=}CHCH_2\overset{+}{C}HCH_2CH_3$

(e) $CH_3OCH_2\overset{+}{C}HC(CH_3)_3$

Solution: In solving this problem, one must keep in mind that the order of stability of carbocations is allyl > 3° > 2° > 1°; that is, an allyl carbocation will be more stable than a tertiary cation, which in turn is more stable than the secondary form, which is more stable than the primary. The allyl cation is the most stable carbocation owing to its resonance stabilization.

A molecule that can be represented by two or more viable structural forms which vary only in the arrangement electrons about the same atomic nuclei is said to be in resonance.

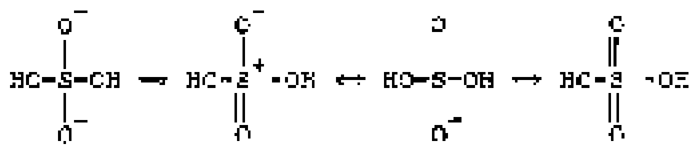
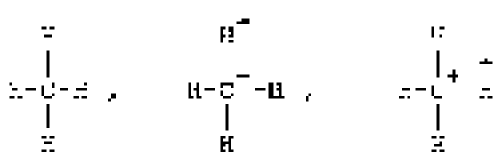


Figure: Resonance forms of Sulfuric Acid (H_2SO_4)

A molecule in resonance cannot be adequately represented by any one of its resonance structures and is viewed as a hybrid of all its resonance structures. The resonance hybrid is more stable than any of its resonance structures. The additional stability of the molecule is its Resonance Energy.

One must keep in mind, however, that only when the contributing structures are of approximately the same energy is resonance important. For example, methane has several resonance forms (A, B, C). However,



(A) (B) (C)

Structure A is of a far more stable energy so as to make the existence of B — C negligible.

In the case of sulfuric acid, where the resonance forms are of nearly the same energy, the electrons are spread over several bonds; this is referred to as delocalization of electrons. Delocalization results in stronger bonds and a more stable molecule.

The relative stabilities of 3° > 2° > 1° can be explained by two factors: Hyperconjugation or the delocalization of electrons in alkyl radicals (see below), and the inductive effect.

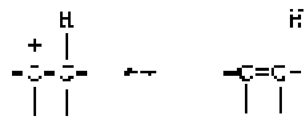


Figure: Hyperconjugation

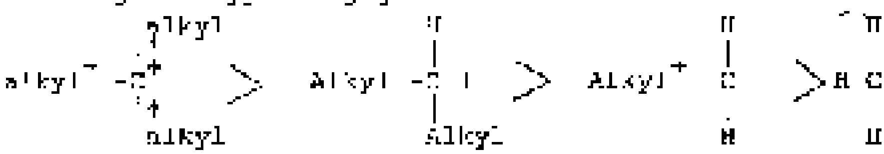
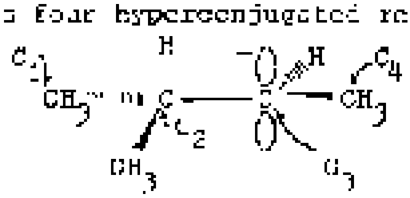


Figure: Inductive Effect

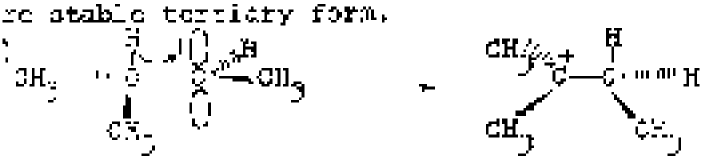
The relative stabilities of 3° > 2° > 1° are explained through hyperconjugation and by the number of resonance contributing structures. t-butyl cation has nine contributing structures; 2 butyl cation has five contributing structures; n-butyl cation has two contributing structures.

The inductive effect relies on the ability of the alkyl group to release electrons along the σ bond to electron deficient atoms. Halogens, because of their high electronegativities, would destabilize the cation. Within the alkyl group sp^3 hybridized alkyls would exert a greater inductive effect than an sp^2 hybridized alkyl which would have a greater inductive effect than sp hybridized alkyls. (NOTE: in decreasing order of electronegativity: $sp > sp^2 > sp^3$).

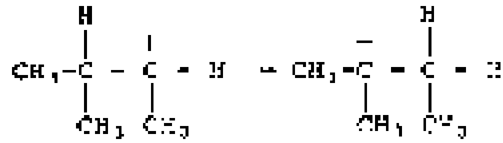
(4) The 3-isobutyl cation is a secondary carbocation, and has four hyperconjugated resonance forms.



In a situation such as the one above, the 3-isobutyl cation will undergo a 1 2 (Whitmore) shift whereby the hydrogen bonded to C_2 and its electrons will migrate to the positively charged π orbital of C_3. This is otherwise known as the hydride shift, to distinguish it from other 1 2 shifts; because both hydrogen and its electron pair migrate, having the net effect of the shift of a hydride ion. This hydride shift places a positive charge on the second carbon, thereby converting the secondary cation into the more stable tertiary form.

(A) 

Figures; 1-2(hydride) shift of the 3-isobutyl cation.

(a) 

Part (b). In the absence of a hydride ion on the tertiary carbon, alkyl groups are capable of undergoing a 1-2 shift.

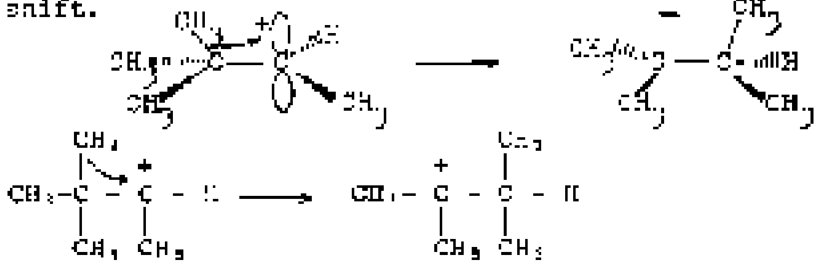
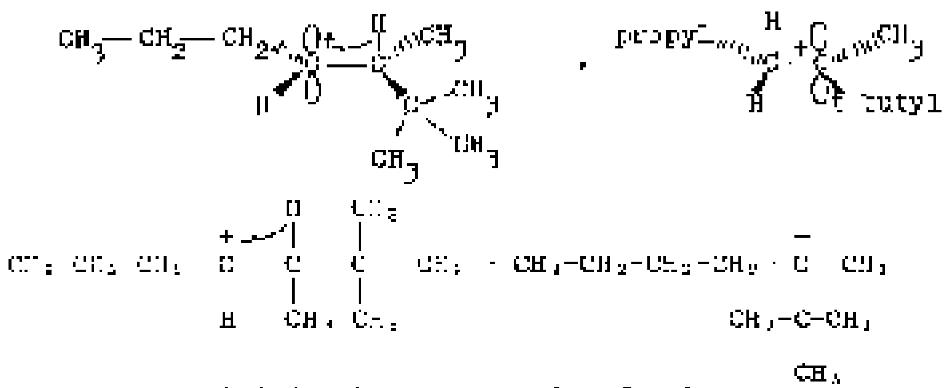
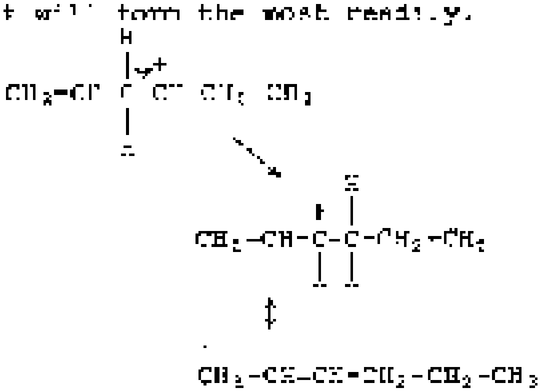


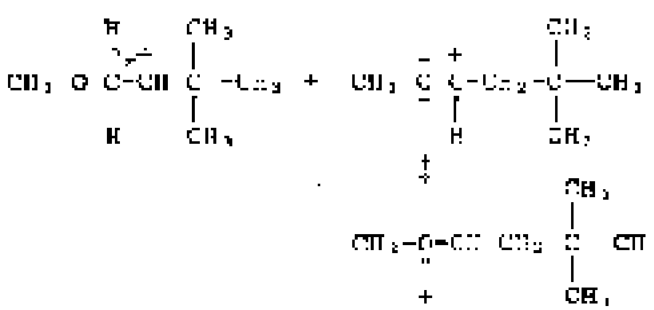
Figure: Migration of methyl group

(c) Simple Hydride Shift



(d) As the allyl is the most stable of all carbocations, it will form the most readily.



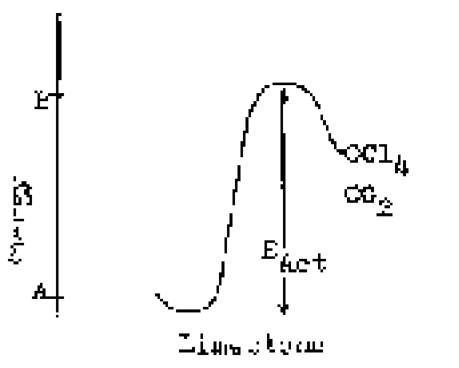
(e) 

NOTE: A methyl shift is not undergone, as the product is not resonance stabilized as is the product of the hydride shift.

• PROBLEM 13-16

Two scientists, working in separate labs, were looking into the properties of limestone. Two months later, both published their results in a highly renowned journal causing a great controversy among the cognoscenti of Organic Chemistry. Said one: "Limestone is quite stable, it is able to withstand centuries of atmospheric exposure." The other said, "Limestone is extremely reactive, dissolving very rapidly in HCl to produce CO_2 and $CaCl_2$." The two statements seem mutually exclusive. Assuming that each scientist is correct, explain.

Solution: These statements are not paradoxical if one considers the conditions each scientist worked under. Under the rather inert conditions used by the first scientist, the energy applied upon the limestone was not enough to cause a reaction, because the energy of activation was too great. In the second scientist's case, the conditions he worked under were quite drastic and the energy of activation was easily overcome.



E_{Act} = Activation energy

Reaction Coordinate

As can be seen from the above diagram, the set of conditions in the first experiment (A) were not sufficient to overcome the energy of activation, whereas the energy in the second experiment (B) were more than enough to affect a reaction.

SPECTROSCOPY

• PROBLEM 13-17

Deduce the structures of the two compounds whose n.m.r. and infrared spectra are shown below. Assign as many of the bands as possible and analyze the n.m.r. spectra in terms of chemical shifts and spin-spin splittings.

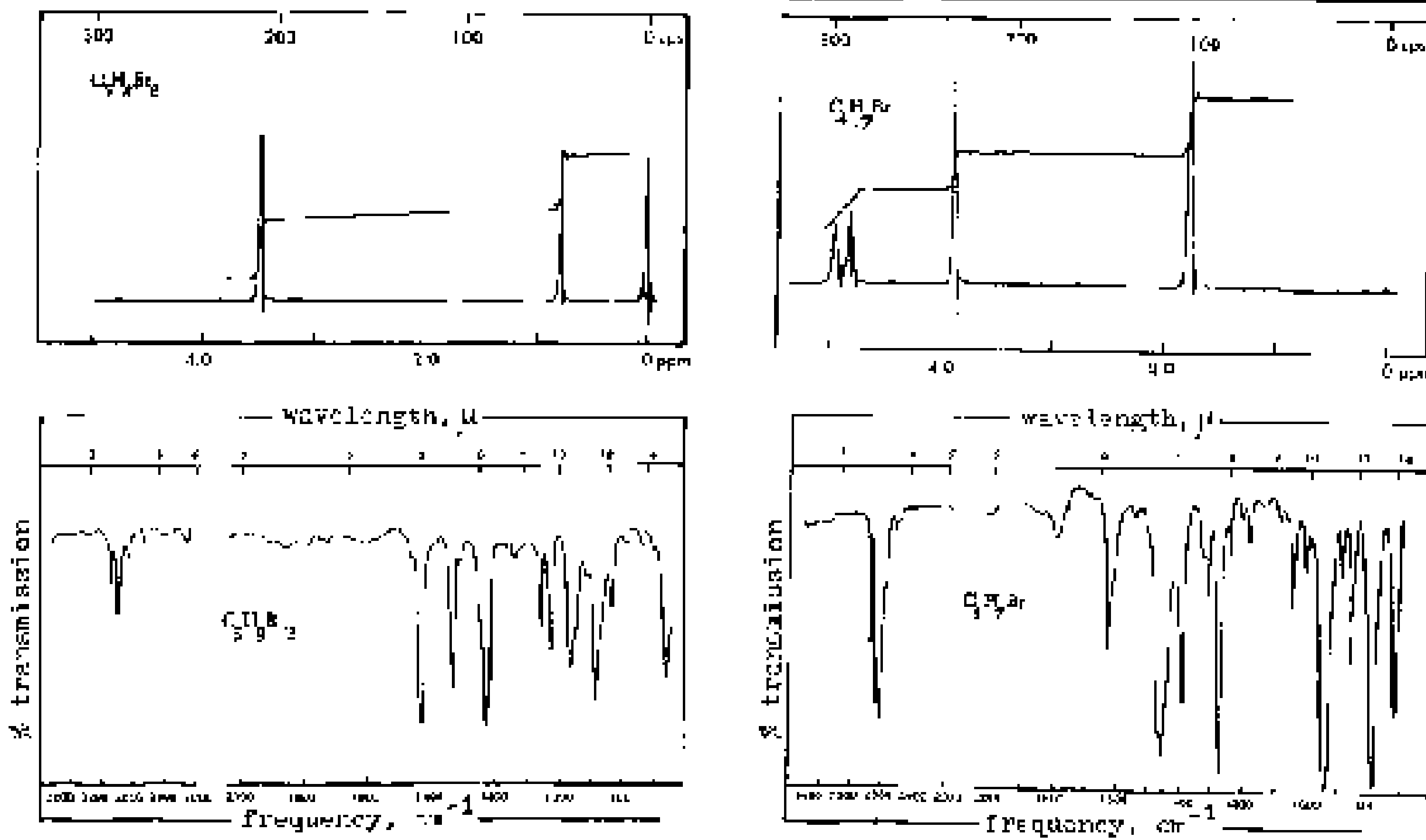


Figure: Infrared and n.m.r. spectra of substance C_4H_7Br and substance $C_5H_8Br_2$.

Solution: (A) Given the empirical formula, C_4H_7Br, and two spectroscopy charts, there is little that can be ascertained immediately. One must piece together all information that can be derived from what is at hand. From the i.r. readout, the characteristic C-H alkane absorption is present at 2800 cm^{-1}. The sharp, symmetric absorption at 1380 cm^{-1} indicates the presence of either a methyl or ethyl but not an isopropyl or t-butyl group. But, the most important piece of information gleaned from an initial observation is the presence of a sharp absorption at 1650 cm^{-1}, which is indicative of a double bond. By consulting Table A, the substitution about the double bond can be established. It will be noted that the i.r. absorptions correspond closely to the

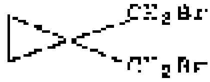
$$\begin{matrix} R \\ & \diagdown \\ & & C=CH_2 \\ & \diagup \\ R \end{matrix}$$

absorptions. This, by itself, is not enough to establish any definite representation. However, by coupling the knowledge already known with the n.m.r. chart, one can be established. The hydrogen absorption ratios are 3 : 2 : 2. The multiplet at 1.85 could be that of $-C-C-CH_3$; the singlet at 3.9 could be that of $C=C-CH_2-X$, and the multiplet at 5.0 is that of the non-equivalent CH_2-protons. Putting everything together,

$$\begin{matrix} & & CH_2Br \\ & \diagup \\ H_2C=C \\ & \diagdown \\ & & CH_3 \end{matrix}$$

can be proposed as a logical structure.

(B) From an initial glance at the i.r. spectra several characteristics of the $C_5H_8Br_2$ molecule become evident. The first is the lack of any significant absorptions between 1500 and 2700 cm^{-1}, which indicates that a double bond is probably not present. The sharp absorption at 1460 is indicative of some form of cyclic component from the n.m.r. It can be seen that there are only two types of hydrogens present, and both present in the ratio of 1 : 1. One group of hydrogens is shifted far downfield, while the other lies at approximately 0.85 ppm which is characteristic of the cyclopropane group. From this information,



can be proposed as a logical structure that would be consistent with the facts given.

	=C-H Stretch	Overtone	C=C Stretch	C-H out of plane Bending
$RCH=CH_2$	3080-3140 (m)	1800-1860 (m)	1645 (m)	990 (s) 910 (s)
$R_2C=CH_2$	3080-3140 (m)	1780-1850 (m)	1650 (m)	890 (s)
(cis) RCH=CHR	3020 (w)		1660 (w)	675-725 (m)
(trans) RCH=CHR	3020 (w)	-	1675 (vw)	970 (s)
$R_2C=CHR$	3020 (w)	-	1670 (w)	790-840 (s)
$R_2C=CR_2$	-	-	1670 (vw)	

s = strong absorption
m = medium absorption
w = weak absorption

All absorptions in cm^{-1}.

Table A: Characteristic absorptions of alkenes.

+ PROBLEM 13-14

(a) In the liquid form, tert-butyl fluoride and isopropyl fluoride gave the following nmr spectra:

tert-butyl fluoride: doublet, δ 1.30, J = 20 Hz
isopropyl fluoride: two doublets, δ 1.23, 6H, J = 23 Hz and 4 Hz
two multiplets, δ 4.64, 1H J = 48 Hz and 4 Hz

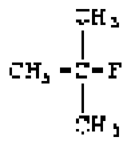
How do you account for each of these spectra?

(b) When the alkyl fluorides were dissolved in liquid SbF_5, the following nmr spectra were obtained:

tert-butyl fluoride: singlet, δ 4.35
isopropyl fluoride: doublet, δ 5.06, 6H, J = 4 Hz
multiplet, δ 13.5, 1H, J = 4 Hz

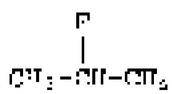
To what molecule is each of these spectra due? (Hint: What does the disappearance of just half the peaks observed in part (a) suggest?) Is the very large downfield shift what you might have expected for molecules like these?

Solution: The fluorine (^{19}F) nucleus, like that of the hydrogen nucleus, possesses magnetic properties. Hence, it too gives rise to nmr spectra, albeit of a different frequency-field strength than that of the proton. However, fluorine nuclei can be coupled with protons (as well as themselves). Splitting by the fluorine proton of the proton signals can be detected, while absorption by fluorine does not appear on a proton nmr spectrum.

(a) 

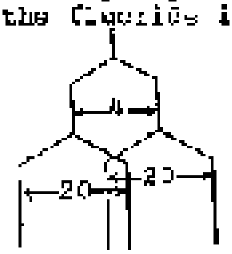
t-butyl fluoride

In t-butyl fluoride, there exists only one species of hydrogen which is the hydrogen on the methyl groups. This hydrogen is split by the fluorine which results in the doublet. The relative downfield position of the doublet (δ 1.30) is due to the electronegative effects of fluorine.



isopropyl fluoride

In this molecule, the splitting of the methyl group's hydrogen by the secondary hydrogen and the fluorine results in the presence of the two doublets at δ 1.23; the hydrogen's splitting of the methyl hydrogen ($J = 4$) followed by the resplitting by the fluoride ion.



Hydrogen splitting

Fluorine splitting

The multiplet at 4.64 is a result of the tri-splitting of the secondary hydrogen by the methyl hydrogens followed by a single splitting by the fluorine. The secondary hydrogen is split seven times by the methyl hydrogens and then split again by the fluorine resulting in a multiplet of fourteen signals.

(b) The disappearance of half of the peaks observed in (a) should suggest that the fluorine is no longer present, and indeed, it no longer is.

This would account for both the presence of only a singlet (from the tert-butyl group) and also the down-field shift (accounted for by the cation and its inductive properties).

This can likewise be seen in the isopropyl cation.

$$CH_3-\underset{F}{\overset{H}{C}}-CH_3 \;+\; SbF_5 \longrightarrow i\text{-}Pr^{+}\;\; SbF_6^{-}$$

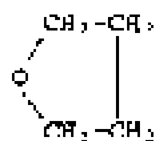
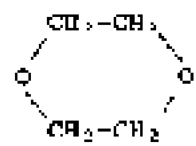
SYNTHESIS

• PROBLEM 13-12

Each of the following might have been synthesized by an S_N2 reaction. Suggest a combination of substrate and nucleophile which could have led to their production.

(a) CH_3OCH_3 (b) $C_6H_5\overset{O}{\overset{\|}{C}}-O-CH_2C_6H_5$

(c) (R) $CH_3CH(OCH_3)CH_2CH_3$ (d) $(CH_3)_4N^+Cl^-$

(e)  (f) 

<u>Solution:</u> (a) The first thing one must do is to look for a suitable nucleophile. In the case of CH_3OCH_3 (Dimethylether), the only possibility is CH_3O^-.

$$\overset{+}{Na}\;{}^{-}OCH_3 \;+\; CH_3I \longrightarrow \overset{+}{Na}\;I^- \;+\; CH_3OCH_3$$

(b) In this problem, two alternatives for the nucleophile

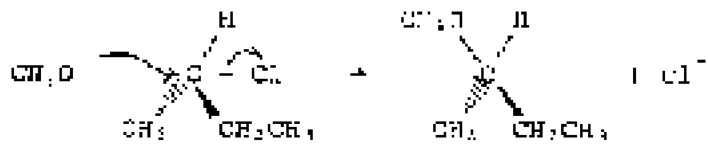
$$\left[\; C_6H_5-\overset{O}{\overset{\|}{C}}-O^- \quad \text{and} \quad C_6H_5CH_2O^- \;\right] \text{ are possible.}$$

$C_6H_5CH_2O^-$, however, is a relatively unstable anion, so that $C_6H_5\overset{O}{\overset{\|}{C}}O^-$ is the nucleophile in this synthesis.

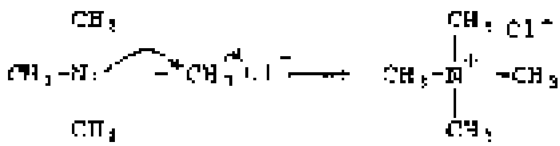
$$C_6H_5CH_2-Br \;+\; {}^{-}O-\overset{O}{\overset{|}{C}}-C_6H_5 \longrightarrow C_6H_5-CH_2-O-\overset{O}{\overset{|}{C}}-C_6H_5$$

(c) The two substituents of this S_N2 reaction are the

Methoxide ion and $CH_3\underset{\underset{L}{|}}{CH}CH_2-CH_3$. (L being any leaving group.) The question then becomes whether the butyl compound is in the (R) or (S) form. Since the product is in the (R) form, and an inversion of configuration always accompanies S_N2 reactions then it can be assumed that the initial butyl compound had an (S) configuration.

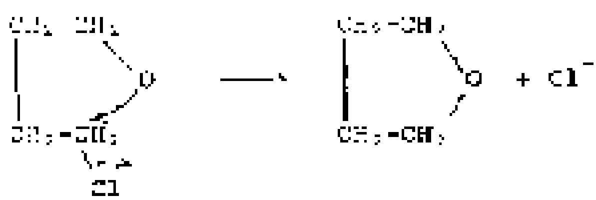


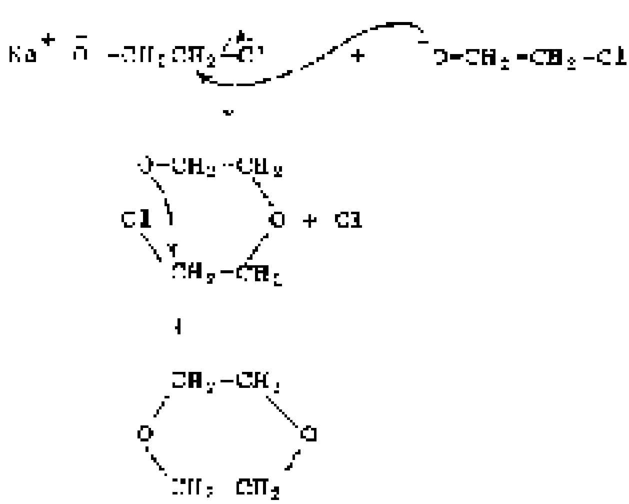
(S) 2-chlorobutane (R) 2-methoxy butane

(d) 

The reader must remember that the lone pairs of electrons on nitrogen and oxygen are capable of acting as nucleophiles.

(e) The cyclic product can only be formed via an intramolecular S_N2.

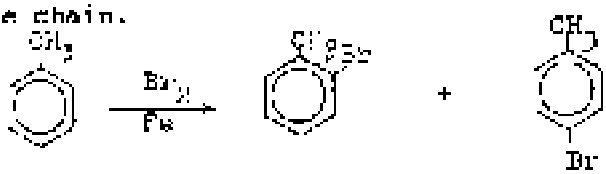


(f) 

Outline all steps in a possible laboratory synthesis of each of the following, using benzene, toluene, and any needed aliphatic or inorganic reagents.

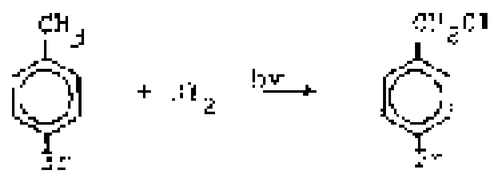
(a) p-bromobenzyl chloride
(b) triphenylchloromethane
(c) allyl iodide
(d) benzal bromide
(e) m-nitrobenzotrichloride
(f) 1,2-dichloro-1-phenylethane
(g) phenylacetylene
(h) phenylcyclopropane

Solution: (a) This reaction involves bromination of the benzene ring followed by the chlorination of the alkyl side chain.



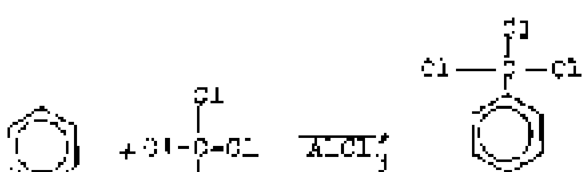
toluene o-bromotoluene p-bromotoluene

The bromination of the benzene ring produces both the ortho and para isomers, which are isolable from each other. After isolating the para isomer, the alkyl side chain is chlorinated.



p-bromotoluene p-bromobenzyl chloride

(b) In this reaction, a variation of the Friedel-Crafts acylation is used with CCl_4 and benzene as the starting products.

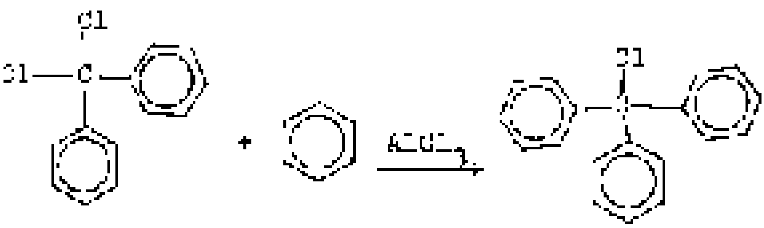


benzene carbon tetrachloride phenyl-trichloro methane

The phenyl-trichloro methane is isolated and reacted with benzene in the presence of $AlCl_3$.

diphenyldichloromethane

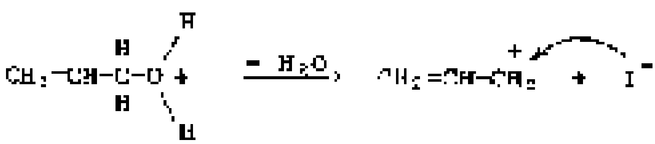
The process is repeated once more with diphenyl-dichloromethane.



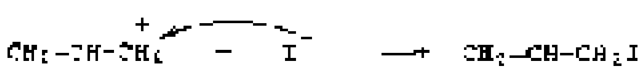
triphenylchloromethane

(c) 

The synthesis begins with the protonation of the hydroxide group. The hydroxide then leaves the molecule as water.

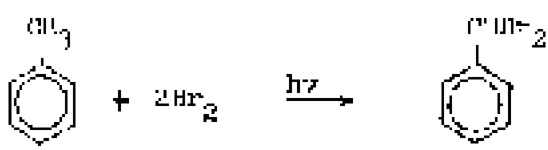


The free iodide anion then attacks the positively charged carbon giving the desired product.



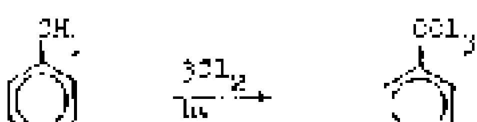
Allyl cation   Allyl iodide

(d) The best approach to this synthesis would be through the bromination of the methyl side chain group of toluene, under controlled conditions.

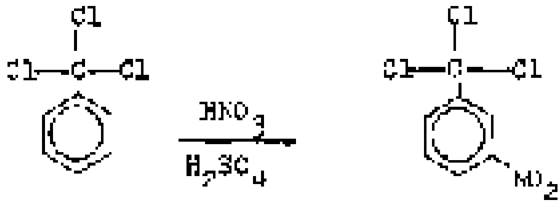


toluene   benzal bromide

(e) The best mode of attack would be to start with toluene, chloronate the methyl side chain and then nitrate.

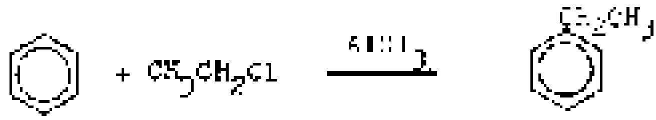


toluene   phenyl trichloromethane



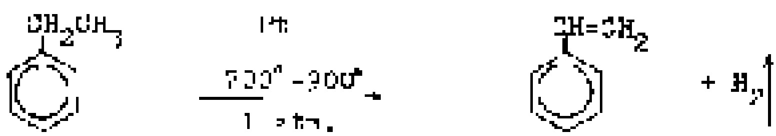
phenyl trichloromethane m-nitrobenzotrichloride

(f) The synthesis of 1,2 dichloro-1 phenylethane can best be affected by starting with benzene and performing a Friedel-Crafts reaction using CH_3CH_2Cl.



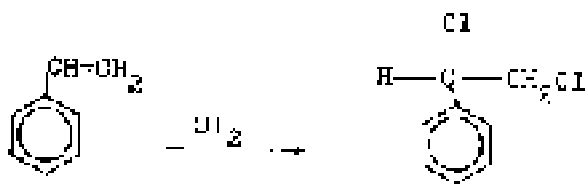
A variety of other substrates, such as ethylene in the presence of hydrogen fluoride, could be utilized.

From this point, a variety of routes may be undertaken, but the best is simply the industrial conversion of the alkane to the alkene.



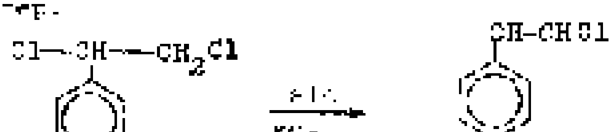
1-phenylethane 1-phenylethylene

From here, the simple chlorination of the double bond will yield the desired product.



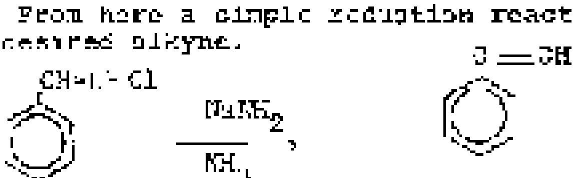
1,2-dichloro-1-phenylethane

(g) Starting with the product formed in (f), an E2 reaction to convert it to an alkene would be the first step.



1-chloro-2-phenylethylene

From here a simple reduction reaction will yield the desired alkyne.

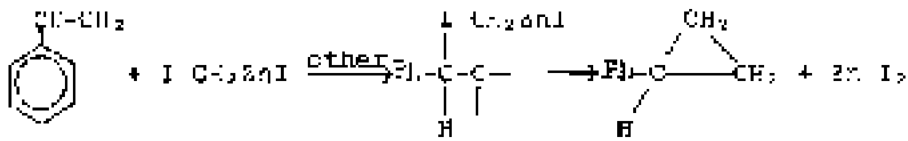


phenylacetylene

(b) The formation of cyclopropane rings is a relatively simple synthetic process.

(1) $CH_2I_2 + Zn(Cu) \longrightarrow I\,CH_2ZnI$

The first step consists of the reaction of methylene iodide with a copper zinc couple. The product then reacts with the appropriate alkene in the presence of ether to yield the desired product.

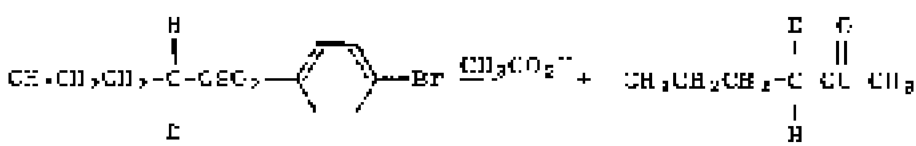


This is a relatively good process which can be carried out in yields ranging from 30 to 70 percent in the laboratory, however, like most organic syntheses, it is far easier to perform on paper.

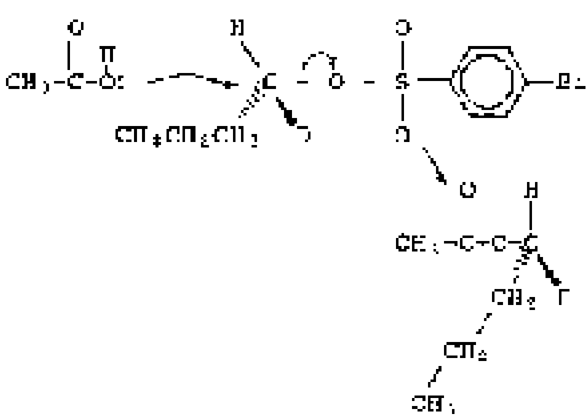
REACTIONS

• PROBLEM 13-21

What can be concluded about the mechanism of the acetolysis of s-butyl derivatives from the following reaction?



Solution: The reaction depicted is an S_N2 displacement. The S_N2 reaction always results in inversion of configuration and this pattern is maintained here. Note that the attacked methylene carbon is a primary carbon and not a secondary one.



HCN has pK_a = 9.21; acetic acid has pK_a = 4.76.

(a) What is the difference in the standard free energies ($\Delta\Delta G^\circ$) for these two acid base equilibria?

(b) What is the equilibrium constant and ΔG° for the reaction

$$HCN + CH_3CO_2^- \rightarrow CN^- + CH_3CO_2H$$

Solution: (a) The general equation for the standard free energy is $\Delta G^\circ = -2.3\ RT \log K_a$.

Therefore $\Delta G^\circ = 2.3\ RT\ pK_a$

To find $\Delta\Delta G^\circ$:

$$\Delta\Delta G^\circ = \Delta G_1^\circ - \Delta G_2^\circ = 2.3\ RT\ pK_{a_1} - 2.3\ RT\ pK_{a_2}$$

$$= 2.3\ RT\ (pK_{a_1} - pK_{a_2})$$

substituting:

$$\Delta\Delta G^\circ = 2.3\ RT\ (9.21 - 4.76)$$

$$= (1.36)(4.45) = 6.05\ \text{Kcal/mole}$$

(b)
$$HCN + CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}O^- \rightarrow CN^- + CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH$$

In order to determine the equilibrium constant and the ΔG° of the reaction, the reaction is broken into its component parts.

$$HCN \longrightarrow CN^- \qquad pK_a = 9.21$$

$$CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^- \rightarrow CH_3{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH \qquad pK_a = -4.76$$

Since the total equation is the sum of these two half-reactions the pK_a must also be the sum of the two component pK_a's.

Hence $9.21 - 4.76 = 4.45$

The K_{eq} is, therefore, the antilog of 4.45, which is 3.5×10^{-5}. The ΔG° is the same as in part a.

$$\Delta G^\circ = 2.3\ RT\ pK_a$$

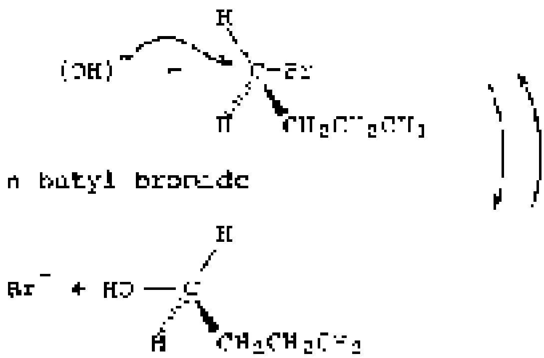
$$\Delta G^\circ = (1.36)(4.45)$$

$$\Delta G^\circ = 6.05\ \text{Kcal/mole.}$$

Give the structures and names of the chief organic products expected from the reaction (if any) of n-butyl bromide with:

(a) NaOH(aq)
(b) KOH(alc)
(c) cold conc. H_2SO_4
(d) Zn, H^+
(e) Li, then CuI, ethyl bromide
(f) Mg, ether
(g) product (f) + D_2O
(h) dilute neutral $KMnO_4$
(i) NaI in acetone
(j) $HC{\equiv}C^-Na^+$
(k) H_2O
(l) NH_3(aq)

Solution: (a) Simple S_N2 displacement



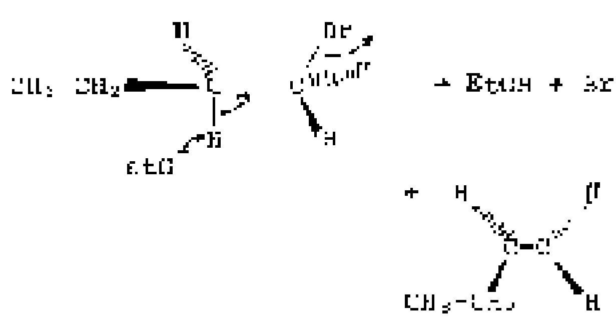
n butyl bromide

1-butanol

(b) In this reaction alcoholic KOH is utilized in order to synthesize oxide ion of an alcohol, usually, methanol or ethanol.

$$CH_3-CH_2OH + (OH)^- \rightleftharpoons CH_3-CH_2-O^- + H_2O$$

The molecule will now undergo an E2 elimination reaction with EtO⁻ acting as a base



1-butene

Note: While in the above reaction the final product has no isomers, this is not always the case. In order that the light isomer be derived, make sure that the bonds being broken in the E2 complex are represented as being anti to each other.

(c) No reaction will be undergone, since n-butyl bromide is not unsaturated.

(d) In the presence of a metal, usually zinc, and acid alkyl halides will be reduced to the corresponding alkane.

$$CH_3CH_2CH_2CH_2Br \xrightarrow[H^+]{Zn} CH_3CH_2CH_2CH_3 \quad \text{n-Butane}$$

(e) This problem is an example of the coupling of alkyl halides with organometallic compounds. This reaction occurs in several steps:

$$CH_3CH_2CH_2CH_2Br + Li \rightarrow CH_3CH_2CH_2CH_2Li + Br^-$$

$$CH_3CH_2CH_2CH_2Li + CuI \rightarrow (CH_3CH_2CH_2CH_2)_2CuLi + I^-$$

$$(CH_3CH_2CH_2CH_2)_2CuLi + CH_3CH_2Br \rightarrow \text{n-hexane}$$

(f) Formation of the Grignard Reagent

$$CH_3CH_2CH_2CH_2Br + Mg \xrightarrow[\text{ether}]{} CH_3CH_2CH_2CH_2MgBr$$

Ether is used as the solvent but it cannot donate a proton. If ever performing a Grignard reaction in the lab make sure that it is carried out in a totally water-free environment. If not, reaction (g) will occur.

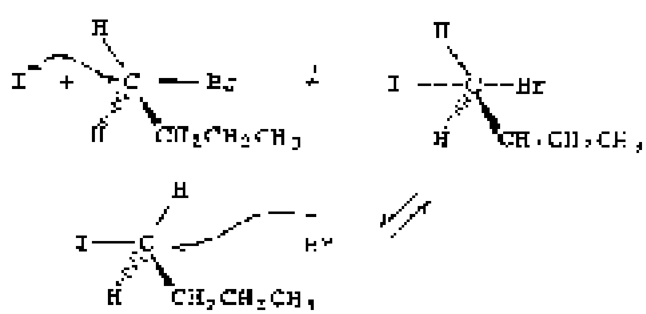
(g) Destruction of the Grignard Reagent

$$CH_3CH_2CH_2CH_2MgBr + D(OD) \rightarrow CH_3CH_2CH_2CH_2D + Mg\begin{matrix} Br \\ OD \end{matrix}$$

This reaction will occur similarly with H_2O.

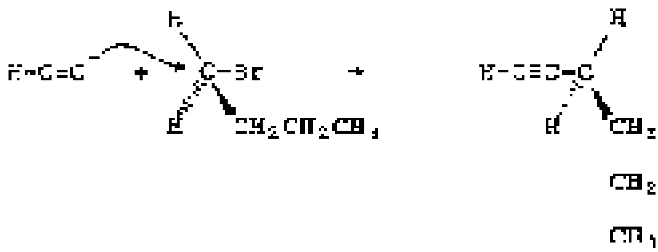
(h) No reaction; the identifying chemical characteristics of alkyl halides are their insolubilities in cold concentrated sulfuric acid (see (c)), their inertness to

(i) S_N2 Displacement



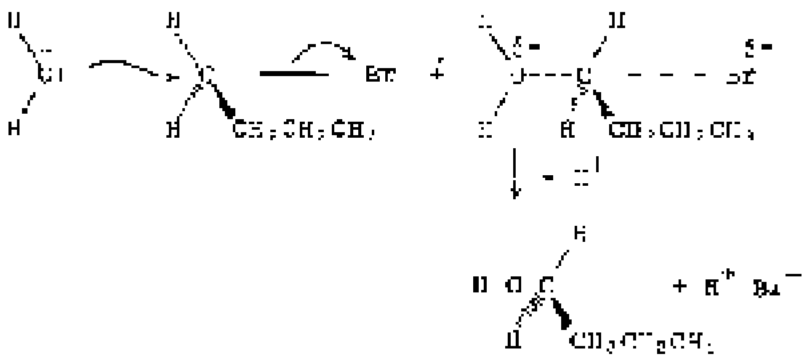
1 iodobutane

(j) S_N2 Displacement



1-Hexyne

(k) In the absence of a stronger nucleophile, the lone pair of electrons on oxygen can act as a nucleophile.



1-butanol

One should note, however, that this reaction is of little practical value as the time of reaction is too slow.

(l) Like the lone pair on oxygen, the electrons on nitrogen can cause it to act as a nucleophile. This is exceedingly important in the synthesis of a class of compounds known as Amines.

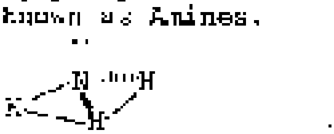
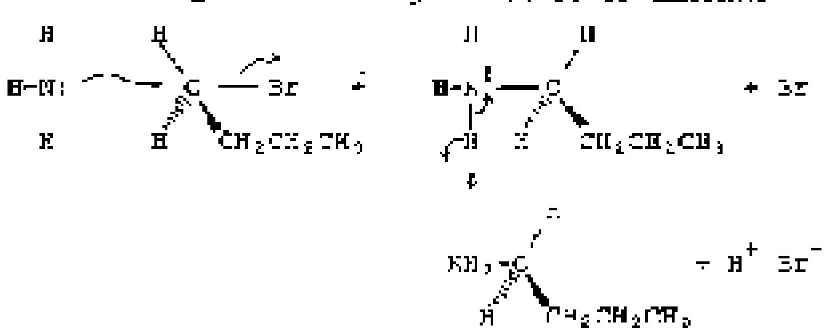


Figure: Bonding structure of ammonia



n-butylamine

• PROBLEM 13-24

A certain graduate student at a great metropolitan university took it to heart to surprise the six students in his lab section by handing them unknowns and requiring them to identify the mysterious compound. As it was still too early in the term for unknowns to be distributed, a great hue and cry was raised. The graduate student relented and agreed to give each student a choice of two possibilities:

(a) Student A was given either $CH_3CH_2CH_2CH_3$ or $CH_3CH_2CH_2CH_2Cl$.

(b) Student B was given either $BrCH{=}CHCH_2Cl$ or $ClCH{=}CHCH_2Br$.

(c) Student C had to choose between $(CH_3)_3CCl$ and $(CH_3)_2CHCH_2Cl$.

(d) Student D: $CH_3CH{=}CHCl$ or $CH_2{=}CHCH_2Cl$

(e) Student E: $CH_3CH_2CH{=}CHCl$ (trans) or $CH_3CH_2CH{=}CHCl$ (cis)

(f) Student F: $CH_3CH_2CH{=}CHCl$ or $CH_2{=}CHCH_2CH_2Cl$.

How would one go about distinguishing chemically between these various compounds?

Solution: (a) n-Butane will not react with alcoholic $AgNO_3$, 1-chlorobutane will, upon warming, yielding AgCl as a precipitate.

$$\underset{\text{n-Butane}}{CH_3CH_2CH_2CH_3} + AgNO_3 \xrightarrow[\text{alc.}]{} \text{No reaction}$$

$$CH_3CH_2CH_2CH_2Br \xrightarrow{Ag^+} CH_3CH_2CH_2CH_2^{\,+} + AgBr$$

This is the reaction used to catalyze S_N1 reactions. Indeed, primary alkyl halides, which will normally undergo S_N2 reactions, will undergo S_N1 reactions in the presence of Ag^+.

(b) Both compounds have halogens in the allylic position, and hence both compounds will react immediately. However, the products will be different.

(1) $BrCH{-}CHCH_2Cl + AgNO_3 \rightarrow Ag^+Cl^- \downarrow + BrCH{=}CH\overset{+}{C}H_2$

(2) $ClCH{-}CHCH_2Br + AgNO_3 \rightarrow Ag^+Br^- \downarrow + ClCH{-}CHCH_2$

All one has to do is isolate the precipitate and test for K_{sp}.

(c) Again, in this reaction, alcoholic $AgNO_3$ is utilized. When Ag^+ cation is reacted with a tertiary chloride, it will react very fast, due to the inductive effect stabilizing the subsequent ion; so that $(CH_3)_3CCl$ will react immediately while $(CH_3)_2CHCH_2Cl$ will react only after heating.

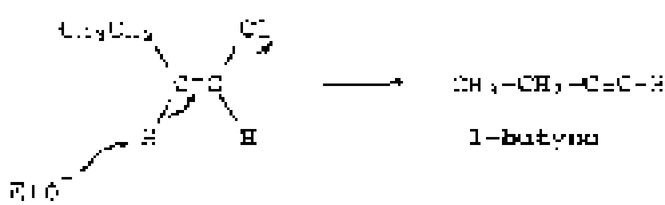
(d) $CH_3CH{=}CHCl$ will not undergo a reaction with alcoholic $AgNO_3$ because the chlorine is not on the allylic carbon. $CH_2{=}CHCH_2Cl$, conversely, will undergo an immediate reaction resulting in the precipitation of AgCl.

$$CH_2{=}CH\,CH_2Cl + AgNO_3 \rightarrow AgCl + CH_2{=}CH{-}\overset{+}{C}H_2$$
$$\updownarrow$$
$$\overset{+}{C}H_2{-}CH{=}CH_2$$

(e) These two isomers can be distinguished by the addition of alcoholic K(OH). The cis isomer will undergo an E2 elimination, while the trans isomer will not.

trans-1-chloro-1-butene   cis-1-chloro-1-butene

As is evident from the illustrations, the hydrogen and the chlorine in the cis isomer are in an anti position to each other, ready to undergo an E2 reaction.



(f) No reaction will occur upon addition of alcoholic $AgNO_3$ to 1-chloro-1-butene (see (d)). Alcoholic $AgNO_3$ will, however, react with 4-chloro-1-butene upon heating.

$Cl{-}CH{=}CH{-}CH_2CH_3$ $CH_2{=}CH{-}CH_2CH_2Cl$

1-chloro-1-butene   4-chloro-1-butene

While the chlorine is not in an allylic position, it is in a primary position, which will allow for a reaction upon heating.

$$CH_3-\underset{|}{CH}-CH_2\ CH_2Cl \xrightarrow[\Delta]{AgNO_3} CH_3-\underset{|}{CH}-CH_2-\overset{+}{C}H_2 + Ag^+\ Cl^-$$

A liquid of boiling point 37-41° was insoluble in water, dilute acids or bases, or concentrated H_2SO_4. It did not react with Br_2/CCl_4 or dilute $KMnO_4$. It was subjected to sodium fusion, and the resulting solution was filtered, acidified with nitric acid, and boiled. Addition of $AgNO_3$ gave a precipitate.

(a) On the basis of the table below what compound or compounds might this have been? (b) Several milliliters of CCl_4 were added to a portion of the acidified solution from the fusion, and the mixture was shaken with chlorine water. A violet color appeared in the CCl_4 layer. Which compound or compounds of (a) are still possible? (c) How would each of the other possibilities have responded in (b)?

Alkyl Halides

Name	Chloride B.p., °C	Chloride Density at 20°C	Bromide B.p., °C	Bromide Density at 20°C	Iodide B.p., °C	Iodide Density at 20°C
Methyl	− 24		5		43	2.279
Ethyl	12.5		38	1.440	72	1.933
n-Propyl	47	.890	71	1.335	102	1.747
n-Butyl	78.5	.884	102	1.276	130	1.617
n-Pentyl	108	.883	130	1.223	157	1.517
n-Hexyl	134	.882	156	1.173	180	1.441
n-Heptyl	160	.880	180		204	1.401
n-Octyl	185	.879	202		225.5	
Isopropyl	36.5	.859	60	1.310	89.5	1.705
sec-Butyl	68	.875	91	1.261	120	1.605
Isobutyl	69	.879	91	1.258	119	1.595
tert-Butyl	51	.840	73	1.222	100d	
Cyclohexyl	142.5	1.000	165			
Vinyl (Haloethene)	− 14		16		56	
Allyl (3-Halopropene)	45	.938	71	1.398	103	
Crotyl (1-Halo-2-butene)	84				132	
Methylvinylcarbinyl (3-Halo-1-butene)	64					
Propargyl (3-Halopropyne)	65		90	1.520	115	
Benzyl	179	1.100	201		93^{10}	
α-Phenylethyl	92^{15}		85^{10}			
β-Phenylethyl	92^{19}		92^{11}		127^{19}	
Diphenylmethyl	173^{19}		184^{20}			
Triphenylmethyl	310		230^{15}			
Dihalomethane	40	1.336	99	2.49	180d	3.325
Trihalomethane	61	1.489	151	2.89	subl.	4.008
Tetrahalomethane	77	1.595	189.5	3.42	subl.	4.32
1,1-Dihaloethane	57	1.174	110	2.056	179	2.84
1,2-Dihaloethane	84	1.257	132	2.180	d	2.13
Trihaloethylene	87		164	2.708		
Tetrahaloethylene	121				subl.	
Benzal halide	205		140^{50}			
Benzotrihalide	221	1.38				

Solution: (a) An inspection of the chemical properties of the liquid unknown reveals it to have the properties of an alkyl halide, namely failure to react with Br_2/CCl_4, dilute $KMnO_4$, or concentrated H_2SO_4. This is confirmed by breaking the unknown into its component elements, via the sodium fusion reaction, and obtaining a precipitate upon reaction with silver nitrate.

An inspection of the table reveals CH_3I (43°), CH_3CH_2Br (38°), and CH_2Cl_2 (40°) as possible compounds.

(b) The addition of CCl_4 to the acidified solution would result in the formation of Br_2 and I_2. The Cl^- ion would be unaffected. The violet color seen in the CCl_4 layer would be clearly indicative of I_2. Therefore, the only compound that the alkyl halide unknown could be is CH_3I.

(c) If the unknown had been CH_3CH_2Br, then a red-brown color indicative of Br_2 would have been observed in the CCl_4 layer. Had the unknown been CH_2Cl_2, no color would have been observed as Cl^- would not have reacted.

• PROBLEM 13-26

An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, etc. Where necessary, make use of the table below.

	b.p., °C		b.p., °C
(a)			
n-decane	174	p-cymene (p-isopropyltoluene)	177
4-methylcyclohexanol	174	limonene (see Problem 17, page 317)	178
1,3-dichloro-2-propanol	175	[illegible]	180
(b)			
1-phenyl-1-propene	[illegible]	n-hexyl iodide	180
benzyl chloride	179	cyclohexylcarbinol	182
2-octanol	179		
(c)			
m-diethylbenzene	192	n-octyl chloride	183
n-butylbenzene	193	trans-decalin (see Problem 8, p. 315)	185
2-ethyl-1-hexanol	194		

Carboxylic Acids

Name	Formula	M.p., °C	B.p., °C	Solub., g/100 g H_2O
Formic	$HCOOH$	8	100.5	∞
Acetic	CH_3COOH	16.6	118	∞
Propionic	CH_3CH_2COOH	−22	141	∞
Butyric	$CH_3(CH_2)_2COOH$	6	164	∞
Valeric	$CH_3(CH_2)_3COOH$	−34	187	3.7
Caproic	$CH_3(CH_2)_4COOH$	−3	205	1.0
Caprylic	$CH_3(CH_2)_6COOH$	16	239	0.7
Capric	$CH_3(CH_2)_8COOH$	31	269	0.2
Lauric	$CH_3(CH_2)_{10}COOH$	44	225^{100}	i.
Myristic	$CH_3(CH_2)_{12}COOH$	54	251^{100}	i.
Palmitic	$CH_3(CH_2)_{14}COOH$	63	269^{100}	i.

Stearic	$CH_3(CH_2)_{16}COOH$	70	383d	i
Oleic	*cis*-9-Octadecenoic	16	223/10	i
Linoleic	*cis,cis*-9,12-Octadecadienoic	−5	230/16	
Linolenic	*cis,cis,cis*-9,12,15-Octadecatrienoic	−11	232/17	
Cyclohexanecarboxylic	*cyclo*-$C_6H_{11}COOH$	31	233	0.20
Phenylacetic	$C_6H_5CH_2COOH$	77	266	1.66
Benzoic	C_6H_5COOH	122	250	0.34
o-Toluic	*o*-$CH_3C_6H_4COOH$	106	259	0.12
m-Toluic	*m*-$CH_3C_6H_4COOH$	112	263	0.10
p-Toluic	*p*-$CH_3C_6H_4COOH$	180	275	0.03
o-Chlorobenzoic	*o*-ClC_6H_4COOH	141		0.22
m-Chlorobenzoic	*m*-ClC_6H_4COOH	154		0.04
p-Chlorobenzoic	*p*-ClC_6H_4COOH	242		0.009
o-Bromobenzoic	*o*-BrC_6H_4COOH	148		0.18
m-Bromobenzoic	*m*-BrC_6H_4COOH	156		0.04
p-Bromobenzoic	*p*-BrC_6H_4COOH	254		0.006
o-Nitrobenzoic	*o*-$O_2NC_6H_4COOH$	147		0.75
m-Nitrobenzoic	*m*-$O_2NC_6H_4COOH$	141		0.34
p-Nitrobenzoic	*p*-$O_2NC_6H_4COOH$	242		0.03
Phthalic	*o*-$C_6H_4(COOH)_2$	231		0.70
Isophthalic	*m*-$C_6H_4(COOH)_2$	348		0.01
Terephthalic	*p*-$C_6H_4(COOH)_2$	300 subl.		0.002
Salicylic	*o*-HOC_6H_4COOH	159		0.22
p-Hydroxybenzoic	*p*-HOC_6H_4COOH	213		0.65
Anthranilic	*o*-$H_2NC_6H_4COOH$	146		0.52
m-Aminobenzoic	*m*-$H_2NC_6H_4COOH$	179		0.77
p-Aminobenzoic	*p*-$H_2NC_6H_4COOH$	187		0.3
o-Methoxybenzoic	*o*-$CH_3OC_6H_4COOH$	101		0.5
m-Methoxybenzoic	*m*-$CH_3OC_6H_4COOH$	110		
p-Methoxybenzoic (Anisic)	*p*-$CH_3OC_6H_4COOH$	184		0.04

Solution: The best way to go about any determination of a compound is by an elimination system of trial and error. We are aided here with a chart of the physical properties of possible unknowns.

The best mode of attack would be to break all the possibilities into subcategories and differentiate between the subcategories.

(a) In any laboratory determination, the key aspect to a successful solution is to use a small amount of the unknown at a time, giving us the ability to perform many tests. Of the six choices in part (a) only n-heptyl bromide and 1,3-dichloro-2-propanol are alkyl halides. It is best to begin with them.

The first step would be to perform a sodium fusion which would break the alkyl halides into their components which include halide anions. After acidification and addition of CCl_4, we shake with Cl_2/H_2O and observe the results. If the unknown is n-heptyl bromide, the bromide anions will be oxidized to Br_2, which will be soluble in CCl_4 layer giving it a distinctive red-brown color. If no color is observed, 1,3 dichloro-2-propanol could still be present, as Cl^- is not converted to Cl_2 under the previous conditions. To test for the dichloro compound, we simply add $AgNO_3$ with a white precipitate, AgCl indicating the presence of chlorine.

If the alkyl halides are eliminated as possibilities, we check for solubility in cold concentrated sulfuric acid since n-decane and p-cymene are insoluble in H_2SO_4. If the unknown is insoluble in cold concentrated sulfuric acid, we test for its solubility in fuming sulfuric acid. n-Decane will not be soluble in fuming sulfuric acid while p-cymene will.

If none of the previous tests have been successful, then either limonene or 4-methyl-cyclohexanol is present. A simple Br_2/CCl_4 test for unsaturation will determine that the unknown is limonene because it will decolorize bromine due to its unsaturation, while the alcohol will not.

It should be noted at this point, that if carrying out this experiment in the lab, one should not be satisfied with one positive test. For best results, a derivative should be synthesized and its melting point should be taken as a confirmatory test.

(b) One would attack the second set of possible compounds in the same manner that the previous six were distinguished. The alkyl halides would be the first to be distinguished.

A sodium fusion test would first be performed on the unknown, breaking it down into its components, and then the unknown would be acidified, mixed with carbon tetrachloride, and shaken with Cl_2. A purple color would be indicative of I_2, which would indicate n-hexyl iodide as the unknown. If no purple color is observed, we would add $AgNO_3$. The formation of a white precipitate (AgCl) would point to benzyl chloride as the unknown.

If the sodium fusion test fails, the Br_2/CCl_4 test for unsaturation would be next. If there is decolorization of the bromine solution, then the unknown would most likely be 1-phenyl 1-propene, which is the only unsaturated compound.

If none of these tests give positive results, then 2-octanol is most likely present. A confirmatory test would be the iodoform reaction ($I_2/(OH)^-$), converting 2-octanol to heptanoic acid.

Once again, once the compound has been identified, a derivative should be synthesized and tested for melting point.

(c) n-octyl chloride can be identified by sodium fusion followed by the addition of $AgNO_3$. The formation of a white precipitate (AgCl) would indicate n-octyl chloride.

The next step would be to test the solubility of the unknown in fuming sulfuric acid, realizing that if it is insoluble then the unknown is trans-decalin.

The rest of the compounds, being alcohols, could be oxidized to their corresponding acids, and their melting points taken.

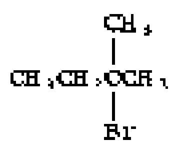
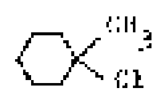
CHAPTER 14

ELIMINATION REACTIONS

E2 REACTIONS

• PROBLEM 14-1

Predict the structure of the major alkene formed in the E2 reactions of the following halides.

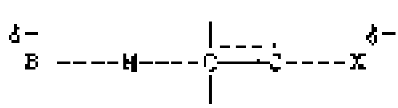
(a)  (b) 

Solution: This problem represents an exercise in applying the Saytzeff and Hofmann rules to the mechanism of an E2 reaction. To understand these rules we will go through the E2 mechanism.

An E2 will be favored over an S_N2 reaction in conditions such as low polar media (an alcoholic solvent is generally used), high temperature, and when a strong base is present. Mechanism (general case): Note: ⟶ represents flow of electrons.

(anionic base)
nucleophile

This reaction, which like an S_N2 is concerted (occurs in one step), has the same activated complex as an S_N2.

activated complex in E2 

The activated complex shows the concerted process of bond making and bond breaking. In the E2 reaction, a nucleophile ($B:^-$) attacks a hydrogen β to the leaving group (X). While this is going on the electron pair of the $H-C_\beta$ bond "swings around" and attacks the carbon (C_α) adjacent to it. C_α, unable to hold ten electrons will simultaneously begin to eject the leaving group along with its two electrons of the $C_\alpha-X$ bond. As the leaving group is ejected, a π bond forms between C_α and C_β, creating a double bond. Note that this process occurs in one continuous step (concerted). A problem arises when there is more than one type of β carbon that bears a hydrogen. For example, in part (a) we are given the compound

$$CH_3CH_2-\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3,$$

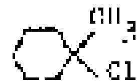
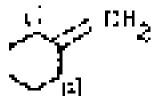
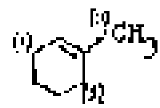
and we are asked to predict the major structure of the alkene formed by an E2 reaction.

$$C_\gamma H_3C_\beta H_2-\underset{\displaystyle Br}{\overset{\displaystyle C_\beta H_3}{\overset{|}{\underset{|}{C_\alpha}}}}-C_\beta H_3$$

One can readily see that the two β-methyl groups have no difference stereochemically, therefore the question is which alkene will form: $CH_3CH=C\begin{matrix} \diagup CH_3 \\ \diagdown CH_3 \end{matrix}$ or $CH_3CH_2-C\begin{matrix} /\!\!/ CH_2 \\ \diagdown CH_3 \end{matrix}$

To answer this we follow Saytzeff's rule for most products. It states that the major alkene produced is the most highly substituted one (i.e., the one with the largest number of alkyl groups bonded to the sp^2-hybridized carbons). In part (a) we readily see that $\underset{(1)}{CH_3CH}=C\begin{matrix} \diagup CH_3\ (2) \\ \diagdown CH_3\ (3) \end{matrix}$ has three substituents bonded to the Csp^2 atoms while with $(2)\ CH_3CH_2-C\begin{matrix} /\!\!/ CH_2 \\ \diagdown CH_3\ (1) \end{matrix}$ we observe only two substituents. According to Saytzeff, $CH_3CH=C\begin{matrix} \diagup CH_3 \\ \diagdown CH_3 \end{matrix}$ is the major alkene compound formed, and it is thus known as the Saytzeff product while $CH_3CH_2-C\begin{matrix} /\!\!/ CH_2 \\ \diagdown CH_3 \end{matrix}$ is the minor alkene formed and is called the Hofmann product.

Hofmann's rule states that the major alkene produced is the least highly substituted one (i.e., the one with the smallest number of alkyl groups bonded to the sp^2-hybridized carbons). Hofmann's rule will usually apply when the leaving group is a positively charged species (e.g. $-\overset{|}{N}(CH_3)_3^+$).

In part (b) we consider which alkene will be produced upon an E2 reaction involving . The major compound will either be  or 

Here, Saytzeff's rule applies since the leaving group is Cl^-, a negatively charged species. Thus the major alkene formed is .

• PROBLEM 14-2

Like Markovnikov, Saytzeff states his rule in terms, not of product stability, but of numbers of hydrogens on carbon atoms. (a) Suggest a wording for this original Saytzeff rule. (b) Predict the major product of dehydrohalogenation of 2-bromo-1-phenylbutane on the basis of the original rule. (c) On the basis of the modern rule.

<u>Solution:</u> (a) To state Saytzeff's rule in numbers of hydrogens on carbon atoms, we consider changes in the number of H-C bonds in a Saytzeff elimination. For example in the elimination reaction

$$CH_3CH_2\overset{Br}{\overset{|}{C}}HCH_3 \xrightarrow[EtOH]{KOH} CH_3CH=CHCH_3 \qquad \text{(Saytzeff product)}$$

the double bond forms between C_2 and C_3 in the Saytzeff product, and not between C_1 and C_2. C_3 has two hydrogens while C_1 has three hydrogens; thus it is safe to assume that "removal of hydrogen occurs from the carbon carrying the fewer hydrogens."

(b) Let us first look at the structure of 2-bromo-1-phenylbutane, $PhCH_2-CHBr-CH_2CH_3$.

We find that both C_1 and C_3 have two hydrogens, but because of our original rule we cannot have any preference in alkene formation since C_1 and C_3 both have two hydrogens.

(c) By using the modern rule which states that the more stable alkene will form in elimination, we clearly see that the emphasis is on stability. In the case of $PhCH_2CH_2CH_2CH_3$, we have a choice of product, upon elimination, between $PhCH=CHCH_2CH_3$ and $PhCH_2CH=CHCH_3$. The key word is stability. $PhCH=CHCH_2CH_3$ is the more stable alkene, because the double bond between C_1 and C_2 is conjugated with the highly stable aromatic, phenyl group. $PhCH_2CH=CHCH_3$ has its double bond between C_2 and C_3 which is too far away for the stabilizing effect that is present in conjugation.

It should be mentioned that among the reasons why conjugation stabilizes a system is the fact that with conjugation usually many important contributing structures can be drawn, indicating great delocalization of charge and thus an increase in stability.

• PROBLEM 14-3

Write the products of the following reactions:

(a) $CH_3CH_2CH_2-OH \xrightarrow[\text{heat}]{H_2SO_4}$

(b) $CH_3CH_2CH_2OH + CH_3CH_2OH \xrightarrow[\text{heat}]{H_2SO_4}$

(c) $CH_3O^{\ominus}Na^{\oplus} + (CH_3)_3C-Br \rightarrow$

Solution: (a) The compound $CH_3CH_2CH_2-OH$ is an alcohol. Alcohols when heated with acid catalysts readily lose a molecule of water to give the corresponding alkene.

The reaction proceeds as follows:

$$(1)\quad \underset{\text{n-propyl alcohol}}{CH_3CH_2CH_2-OH} \xrightarrow[\text{heat}]{H_2SO_4} \underset{\text{propene}}{CH_3CH=CH_2} + H_2O$$

It is also possible by carefully controlling the temperature to convert alcohols to ethers. The general formula of the reaction is as follows:

$$2\ R-OH \xrightarrow{H_2SO_4} R-O-R + H_2O$$

Since a molecule of water is lost for every pair of alcohol molecules, the reaction is a kind of dehydration. Dehydration is generally limited to the preparation of symmetrical ethers, because a combination of two alcohols usually yields a mixture of three ethers. The reaction proceeds as follows:

(2) 2 $CH_3CH_2CH_2-OH \xrightarrow[-H_2O]{H_2SO_4} CH_3CH_2CH_2-O-CH_2-CH_2-CH_3$

n-propyl alcohol n-propyl ether

Summarizing two steps of the reaction we may write the general equation of the reaction outlined in the problem as follows:

$$3\ CH_3CH_2CH_2-OH \xrightarrow[heat]{H_2SO_4} CH_3CH_2CH_2-O-CH_2-CH_2-CH_3 +$$

n-propyl alcohol n-propyl ether

$$+\ CH_3CH=CH_2 + 2\ H_2O$$

propene

The reaction mixture contains 3 major compounds: n-propyl alcohol, propene and n-propyl ether.

(b) The mechanism of the reaction between n-propyl alcohol $CH_3CH_2CH_2-OH$, ethyl alcohol CH_3CH_2OH and hot sulfuric acid is similar to the mechanism outlined above; when alcohols are heated with sulfuric acid they are converted to alkenes. At the same time it is possible by careful control of the temperature to convert alcohols to ethers. The combination of two alcohols usually yields a mixture of three ethers, two symmetrical and one non-symmetrical, and two corresponding alkenes. The reaction outlined in the problem proceeds as follows:

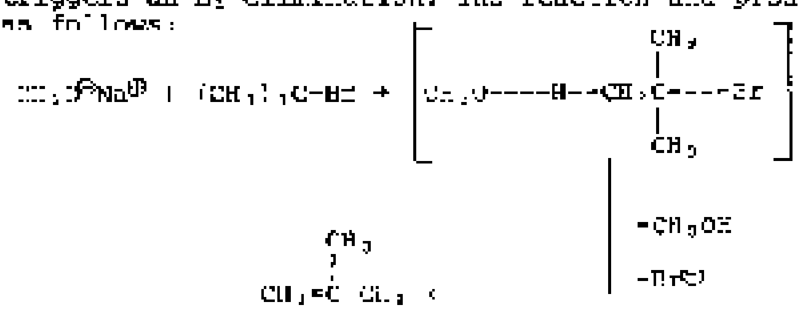
$$CH_3CH_2CH_2OH + CH_3CH_2OH \xrightarrow[heat]{H_2SO_4} CH_3CH_2CH_2OCH_2CH_2CH_3 +$$

n-propyl alcohol ethyl alcohol n-propyl ether

$$+\ CH_3CH_2OCH_2CH_3 + CH_3CH_2CH_2OCH_2CH_3 + CH_2=CH_2 + CH_3CH=CH_2$$

ethyl ether ethyl n-propyl ether ethylene propene

(c) This reaction is the reaction of an alkoxide ion (OR^-) with a tertiary alkyl halide. Two possibilities arise. The reaction can proceed by an S_N1 reaction or it can proceed by an E_2 reaction. The key is that the alkoxide ion $^-OCH_3$ is a much better base than a nucleophile, thus it favors its ability to abstract protons. Its attack on a proton triggers an E_2 elimination. The reaction and products are as follows:



There will also be some substitution so $(CH_3)_3COCH_3$ will be a minor product as well.

Predict the major products, if any, for the reaction of isobutyl n-propyl ether with:

(a) $H_2Cr_2O_7$, room temperature
(b) Dilute, aqueous H_2SO_4
(c) Hot, concentrated HBr.

Solution: Just as alcohols can be protonated by strong acids, ethers too can donate a pair of electrons to a hydrogen ion to form protonated ethers, or oxonium ions. These ions are formed only in concentrated acid. The general equation of the reaction is as follows:

$$R-\ddot{\underset{\cdot\cdot}{O}}-R' + H^{\oplus} \rightleftharpoons R-\underset{\displaystyle H}{\underset{|}{\overset{\oplus}{O}}}-R'$$

oxonium salt

The equation for the reaction outlined in the problem is as follows:

$$\underset{\text{isobutyl n-propyl ether}}{CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}H}-CH_2-O-CH_2-CH_2-CH_3} + \underset{\text{chromic acid}}{H_2Cr_2O_7} \xrightarrow[\text{temperature}]{\text{room}}$$

$$\longrightarrow \underset{\text{oxonium salt}}{CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}H}-CH_2-\underset{\displaystyle H}{\overset{\oplus}{O}}-CH_2-CH_2-CH_3}$$

(b) Ethers can be protonated only by concentrated acids, that is why there will be no reaction between the compounds given in the problem, isobutyl n-propyl ether and dilute, aqueous H_2SO_4.

(c) Ethers react with strong acids to form oxonium ions, as we have seen above. If the acidic solution is heated the reaction proceeds as follows:

(1) The oxonium ion forms:

$$R-O-R' + H^{\oplus} \rightleftharpoons R-\underset{\displaystyle H}{\underset{|}{\overset{\oplus}{O}}}-R'$$

(2) The ether is cleaved upon heating:

$$R-\underset{\displaystyle H}{\underset{|}{\overset{\oplus}{O}}}-R \xrightarrow{X^{\ominus},\ \text{heat}} \underset{\displaystyle R-X}{\underset{+X^{\ominus}}{R^{\oplus}}} + R'-OH$$

where X is a halide (Cl, Br, I or F). If the acid used is excess HCl, HBr or HI, the alcohols formed will also be converted to alkyl halides by the reaction $ROH + HX \rightarrow R\text{-}X + H_2O$. The equation for the reaction outlined in the problem is as follows:

$$\underset{\text{isobutyl n-propyl ether}}{CH_3\text{-}\underset{}{\overset{\displaystyle CH_3}{\overset{|}{C}H}}\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_3} + 2\ HBr \xrightarrow{\text{heat}} \underset{\text{isobutyl bromide}}{CH_3\text{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}\text{-}CH_2\text{-}Br}$$

$$+ \underset{\text{n-propyl bromide}}{CH_3CH_2CH_2Br} + H_2O$$

• PROBLEM 14-6

An alternative mechanism for E2 elimination is the following:

$$CH_3CH_2Cl + OH^{\ominus} \xrightarrow{\text{fast}} \overset{\ominus}{C}H_2CH_2Cl + H_2O \xrightarrow{\text{slow}} CH_2{=}CH_2 + Cl^{\ominus}$$

(a) Would this mechanism lead to a first-order kinetics with respect to the concentrations of OH^- and ethyl chloride? Explain.
(b) This mechanism has been excluded for several cases by carrying out the reaction in deuterated solvents such as D_2O and C_2H_5OD. Explain how such experiments could be relevant to the reaction mechanism.

Solution: To solve part (a) of this problem we must try to determine a rate equation in terms of the concentrations of OH^- and ethyl chloride.

Let us first determine which species are the key ones in a rate equation. For all rate equations we are interested in the species involved in the rate determining step. The rate determining step of a reaction is usually the slow part of the reaction, or if a reaction has several slow steps, the rate determining step is the slowest step.

We now look at the alternative E2 mechanism for this reaction:

$$CH_3CH_2Cl + OH^{\ominus} \xrightarrow{\text{fast}} \overset{\ominus}{C}H_2CH_2Cl + H_2O \xrightarrow{\text{slow}} CH_2{=}CH_2 + Cl^{\ominus}$$

Clearly the species involved in the rate determining step are $\overset{-}{C}H_2CH_2Cl$ (carbanion) and H_2O. We know that the rate equation is dependent upon the concentrations of these two species, so the rate equation can be expressed as follows:

$$\text{Rate} = k[\overset{\ominus}{C}H_2CH_2Cl][H_2O]\ ,$$ where k is a constant of

proportionality. At this point we now try to get this rate equation in terms of $OH^{\ominus}$ and CH_3CH_2Cl. This can be done by creating a new constant, called K, where

$K = [\overset{\ominus}{C}H_2CH_2Cl][H_2O]/[CH_3CH_2Cl][OH^{\ominus}]$. We substitute this into our original equation in the following manner:

$$\text{Rate} = k[\overset{\ominus}{C}H_2CH_2Cl][H_2O]$$

$$K = [\overset{\ominus}{C}H_2CH_2Cl][H_2O]/[CH_3CH_2Cl][OH^{\ominus}]$$

$$[\overset{\ominus}{C}H_2CH_2Cl][H_2O] = [CH_3CH_2Cl][OH^{\ominus}]\,K$$

$$\text{Rate} = kK\,[CH_3CH_2Cl][OH^{\ominus}]$$

From observing this final equation, we can see that this mechanism does lead to first order kinetics with respect to the concentrations of $OH^{\ominus}$ and CH_3CH_2Cl.

(b) To solve this part we must try to involve the deuterated solvents, such as D_2O and C_2H_5OD, in the reaction mechanism. Using the reaction from part (a), as our example, we substitute D_2O for H_2O and $OD^{\ominus}$ for $OH^{\ominus}$. Let us now consider the fast part of this reaction:

$$\overset{\ominus}{C}H_2CH_2Cl + D_2O \xrightarrow[\text{fast}]{} DCH_2CH_2Cl + OD^{\ominus}$$

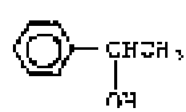
In this reaction (which is reversible), we would expect the carbanion ($\overset{\ominus}{C}H_2CH_2Cl$) to exhibit a deuterated exchange with D_2O when it reverts back to the starting material. If we find some deuterated starting material present after a short time we can conclude that this exchange has taken place, and our mechanism may be correct.

• PROBLEM 14-8

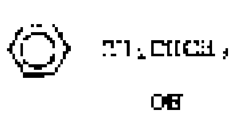
Predict the dehydration product(s) of each of the following alcohols:

(a) $CH_3CH_2CH_2CH_2OH$

n-Butyl alcohol

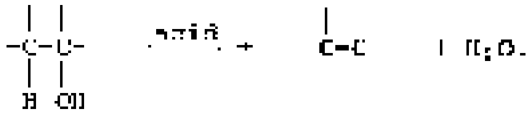
(b) 

1-Phenyl ethanol

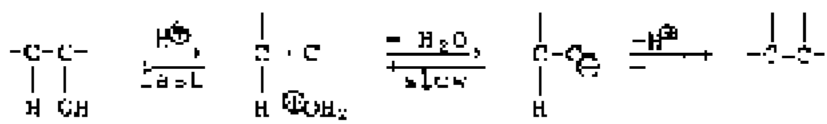
(c) 

1-Phenyl-2-propanol

Solution: A very important reaction of alcohols is that of dehydration, which simply is the transformation of an alcohol into an alkene, e.g.,



According to the commonly accepted mechanism, dehydration involves (1) formation of the protonated alcohol, $ROH_2^{\oplus}$, (2) its slow dissociation into a carbonium ion, and (3) subsequent expulsion of a hydrogen ion from the carbonium ion to form an alkene. Acid is required to convert the alcohol into the protonated alcohol, which dissociates by loss of the weakly basic water molecule - much more easily than the alcohol itself. To illustrate these steps:



Alcohol | Protonated Alcohol | Carbonium Ion | Alkene

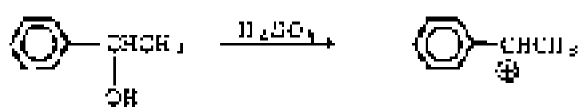
The acid ordinarily used is sulfuric acid (H_2SO_4), but when writing the synthesis the word "acid" is more often used, as H_2SO_4 is understood to be the acid.

Referring to the above general principles and the general reaction, the products of each alcohol can be predicted.

(a) $CH_3CH_2CH_2CH_2OH \xrightarrow{H_2SO_4,\ heat} CH_3CH=CHCH_3$

n-butyl alcohol — 2-butene

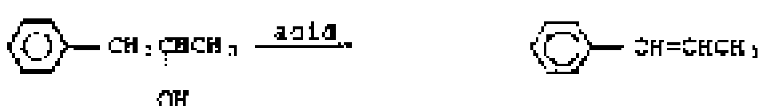
(b)



1-phenylethanol — Carbonium ion intermediate

Styrene

(c)



1 Phenyl-2-Propanol — 1-Phenylpropene

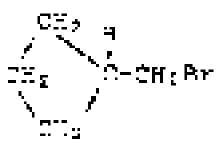
E1 REACTIONS

• PROBLEM 11-7

Predict the products of the following reactions:

(a) $CH_3CH_2CBr(CH_3)CH_2CH_3 \xrightarrow[S_N1,\ E1]{H_2O}$

(b) $(CH_3)_3CCH(CH_3)Cl \xrightarrow[S_N1,\ E1]{H_2O}$;

(c)  $\xrightarrow[S_N1,\ E1]{H_2O}$;

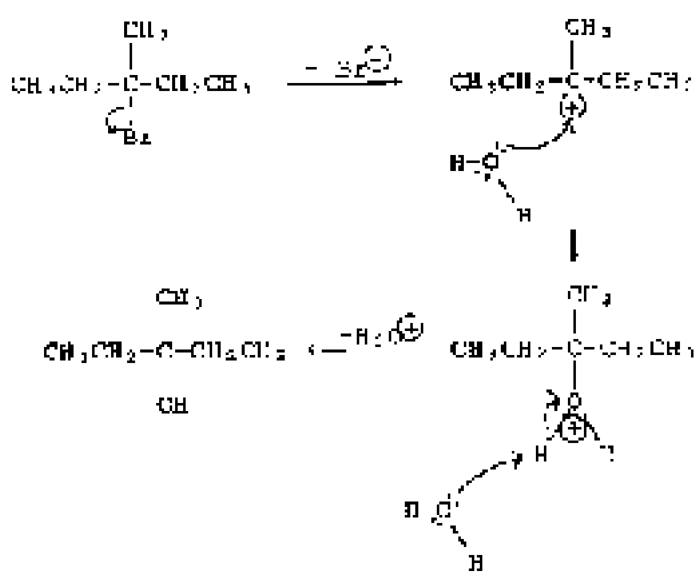
Solution: The systematic way of solving this problem is to follow each reaction through its designated mechanism, while at each step considering rearrangements for increased stability.

For example, in part (a) we are given the following problem:

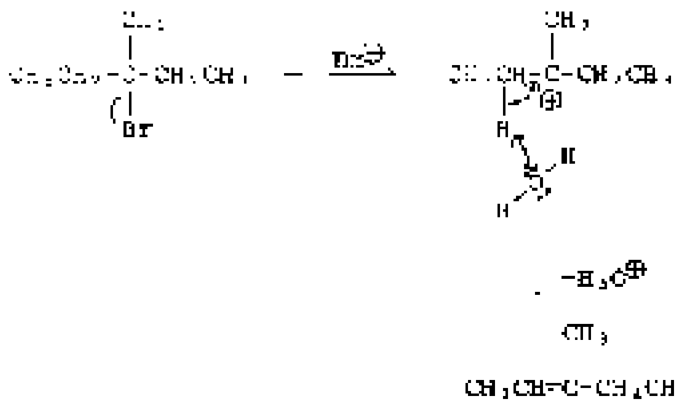
$$CH_3CH_2-\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{C}}-CH_2CH_3 \xrightarrow[S_N1,\ E1]{H_2O} \text{E1 products + }$$

S_N1 products. The mechanism for the E1 and S_N1 reactions are presented below:

S_N1 mechanism:

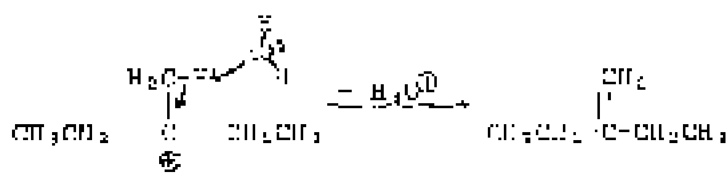


E1 mechanism:



(Saytzeff product)

Looking again at the carbocation we find the mechanism for the Hofmann product to be:



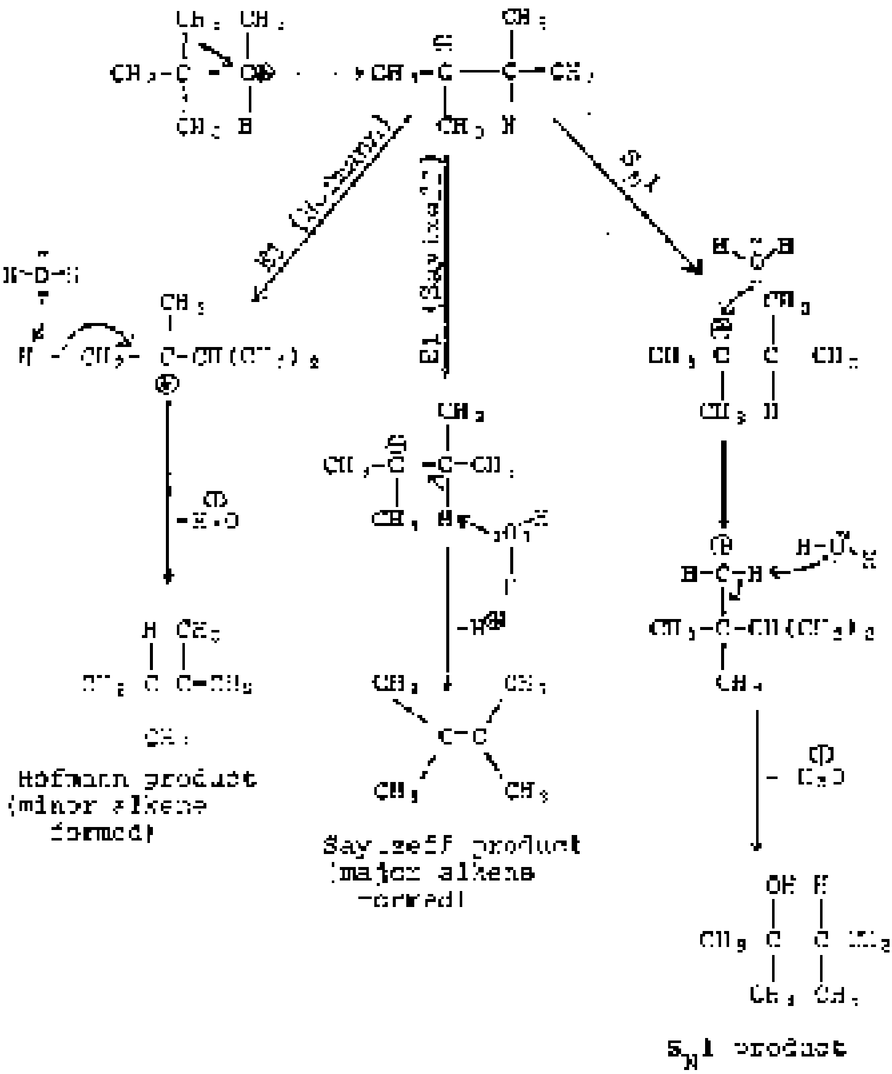
(Hofmann product)

In this case, as in most cases, the Saytzeff product is the major alkene formed.

We follow the same procedure for part (b):

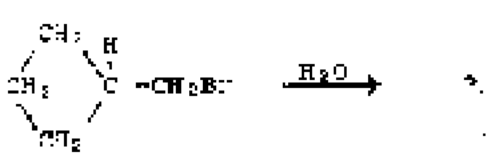
2° carbocation

When this 2° carbocation is formed, something very important happens. Recall that a 3° carbocation is more stable than a 2° carbocation, so it would be nice to be able to form one without the molecule expending too much energy. This formation can be energetically feasible by what is called a methyl shift. A methyl shift occurs when a methyl group attached to a carbon α to the positively charged carbon migrates to the empty orbital in this positively charged carbon thereby making C_{α} the new positively charged carbon. For example, in part (b) the carbocation rearranges in the following manner:

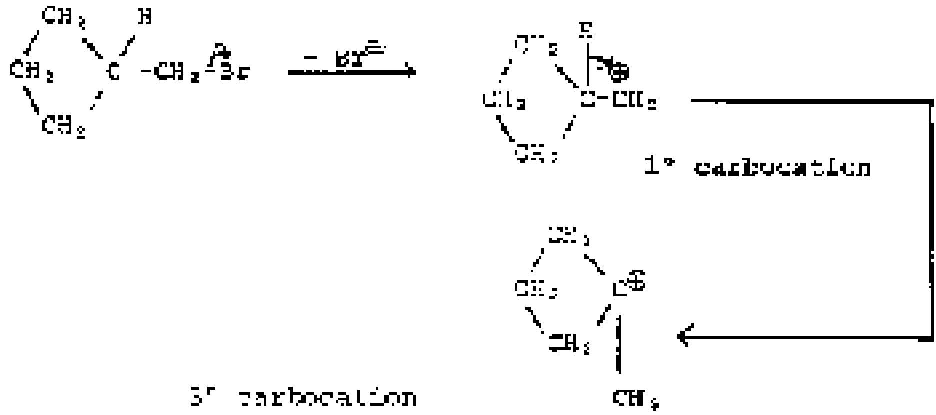


Clearly from this example, and as in our rule, once the methyl shift has taken place the mechanism continues as before.

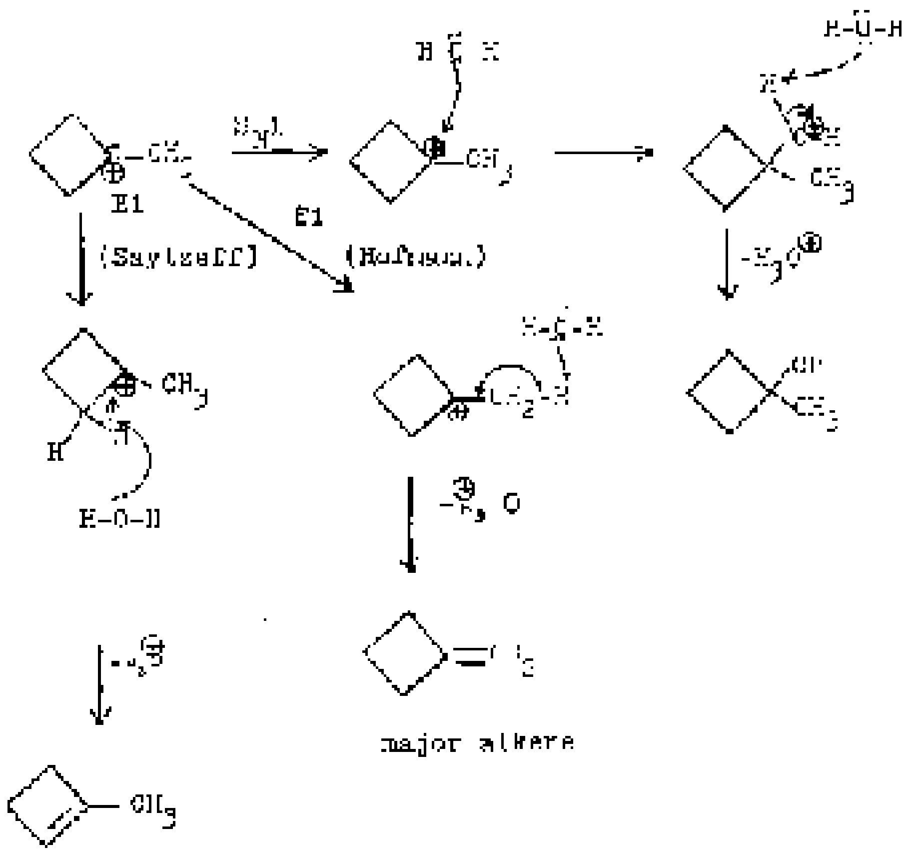
Again we work systematically in part (c):



This reaction will begin in an S_N1 fashion because we are working with an alkyl halide with the potential to form a 3° carbocation. Let us see how this works:

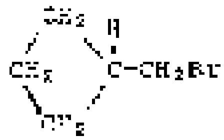


As the methyl group migrated in part (b), the hydrogen migrates here, forming the more stable 3° carbocation. This migration is called a 1,2-hydride shift. We now continue as in part (b) and obtain the expected products:

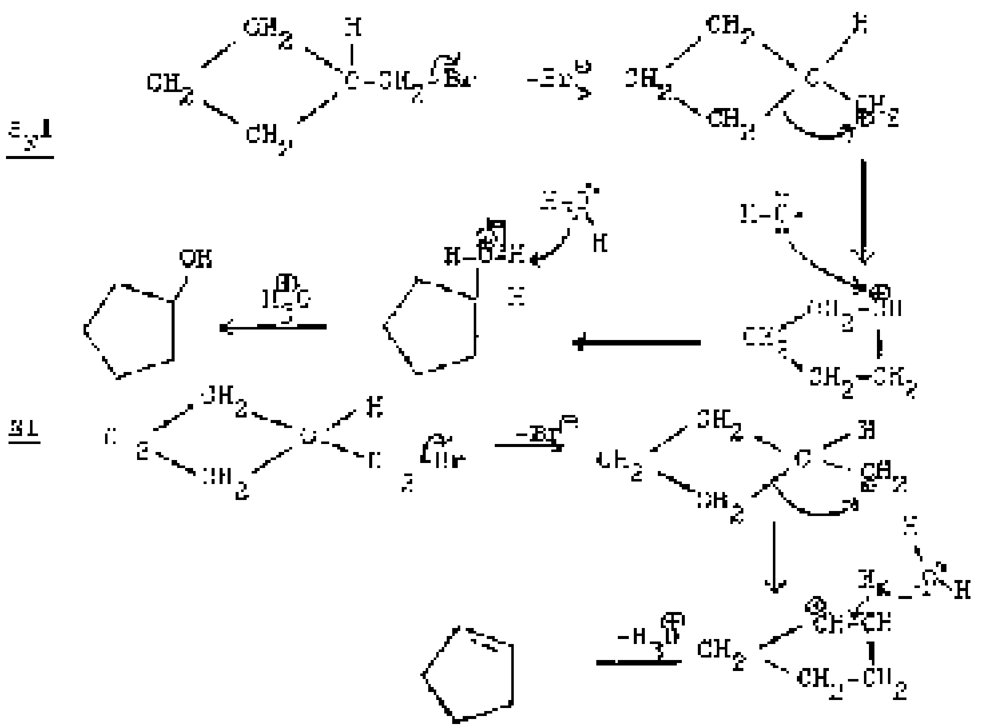


minor alkene (because of ring strain)

These compounds would be all the compounds possibly formed by the indicated E1 and S_N1 reactions if only there was not yet another possible shift, but there is. Let's look at the starting material:



We now, from our study of cycloalkanes, recall that a five membered ring is more stable than a four membered ring. It would be energetically stabilizing if such a five membered ring could be formed. In this case there is a way for this to happen:



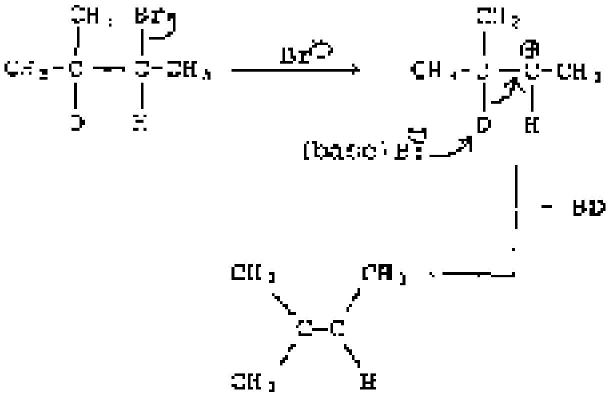
Although this ring shift may seem unlikely, it readily occurs because it increases the molecules' thermodynamic stability. When solving substitution and elimination problems one must always think in terms of stability; the most stable intermediates will form the most often.

• PROBLEM 14-8

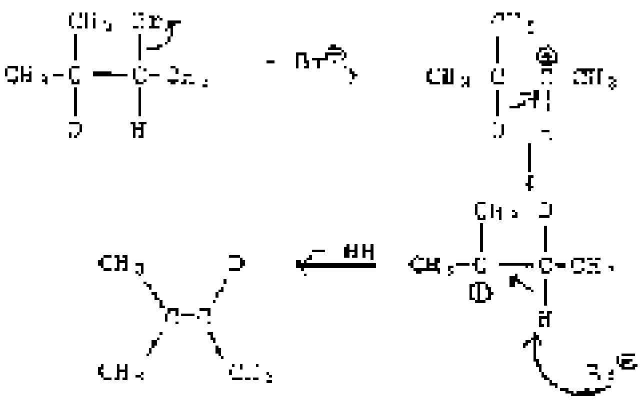
Explain how $(CH_3)_2CDCHBrCH_3$ might be used to determine whether trimethylethylene is formed directly from the bromide in an E1 reaction, or by rearrangement and elimination.

Solution: To solve this problem we simply take $(CH_3)_2CDCHBrCH_3$ and run it through, first a direct E1 reaction, and second a rearrangement and then an E1 reaction. We then compare the results and look for possible differences that can be isolated from the two methods.

Let us now consider the direct E1 reaction of $(CH_3)_2CDCHBrCH_3$:

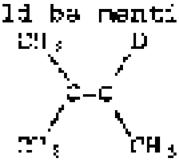
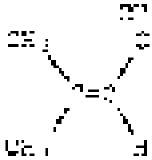


The important thing to note is that no deuterium is found. We now look at the rearrangement and then E1 reaction:

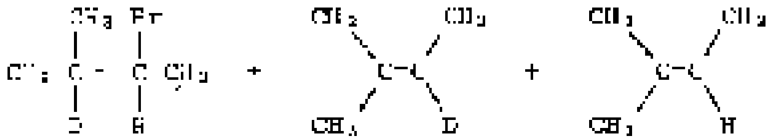


Note: The base ($Br^{\ominus}$) could have pulled off a $D^{\oplus}$ instead of an $H^{\oplus}$.

Looking at this result the answer comes out. We find, in this last reaction, two products are formed in equal yields; one is deuterated while the other one is not. We can conclude from this that if the reaction is a direct E1, then no deuterium should be detected, and if the reaction proceeds via rearrangement and then E1 then about 50% of the product should be deuterated.

It should be mentioned that in the rearrangement and E1 reaction  (product A) will form slightly more than  (product B) because of what is called the kinetic isotope effect. This is the fact that a C-H bond is easier to break than a C-D bond because D has a greater mass than H. In the above example product A has a C-H bond broken in elimination while product B has a C-D bond broken during elimination. For the purposes of this problem this effect should be ignored.

We can summarize the reaction involving rearrangement and then elimination as:

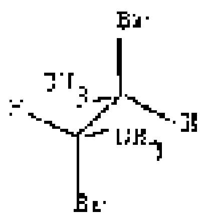


50 % 50 %

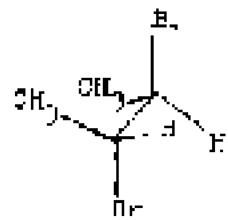
STEREOCHEMISTRY

• PROBLEM 14-2

Write all the possible staggered conformations for each of the isomers of 2,3-dibromobutane shown in (1) and (2).



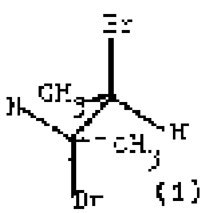
(1)



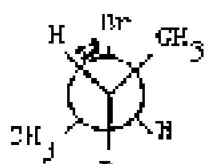
(2)

Show the structures of the alkenes that could be formed from each by a trans E2 elimination of 1 mole of hydrogen bromide with hydroxide ion. Which alkene should more readily eliminate further to form dimethylacetylene? Explain.

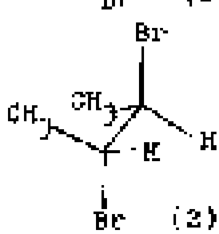
Solution: A staggered conformation is defined as a conformation with a torsional angle of 60° as seen in a Newman projection. Below are the Newman projections for (1) and (2).



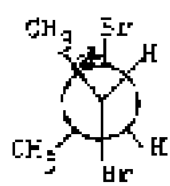
(1) ≡



(1a)

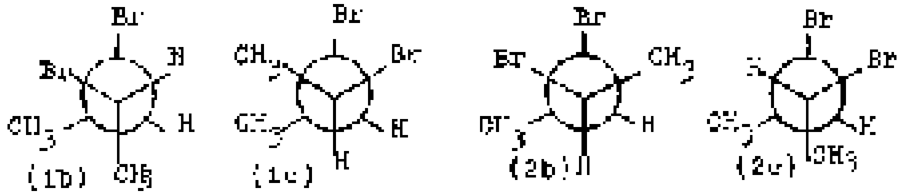


(2) =



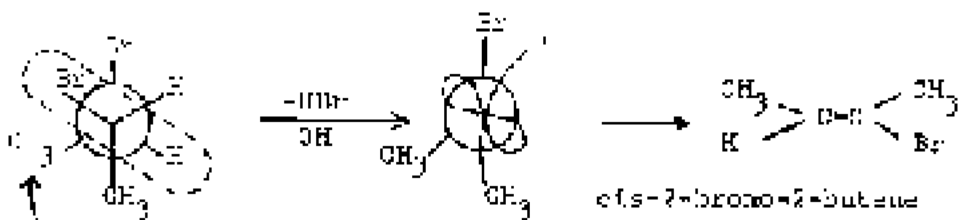
(2a)

For (1) and (2) the only other Newman projections with torsional angles of 60° and thus the only other staggered conformations, are shown below:



(1b) (1c) (2b) (2c)

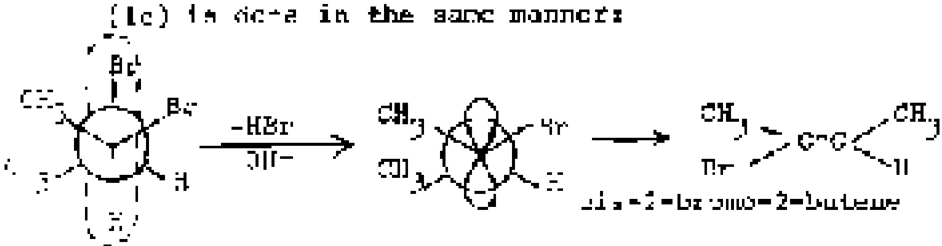
We are now asked to show the structures of the alkenes that could be formed from each by a trans E2 elimination of one mole of hydrogen bromide with hydroxide ion. This requires that in each conformation we look for a hydrogen trans to a bromine and then when making the E2 product, converting the projection to an almost planar figure to judge whether or not the alkene is cis or trans. For example let us consider structure 1b:



cis-2-bromo-2-butene

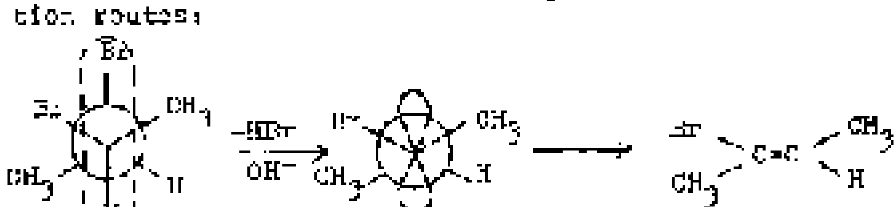
anti conformation between H and Br

(1c) is done in the same manner:



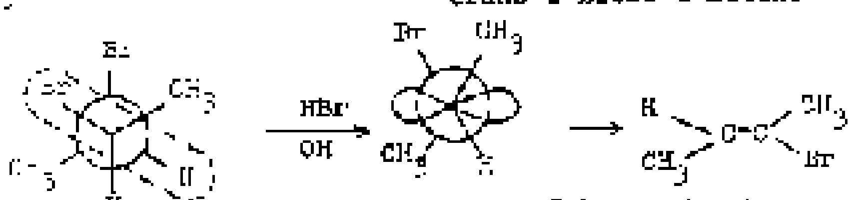
cis-2-bromo-2-butene

Conformations 2a, 2c and 1a will not undergo trans E2 elimination because there are no hydrogens anti to a bromine. Conformation 2b has two possible trans elimination routes:



trans-2-bromo-2-butene

and



trans-2-bromo-2-butene

There is no significance to this since both form the same isomeric alkene, thus the two alkenes that form are trans- and cis-2-bromo-2-butene.

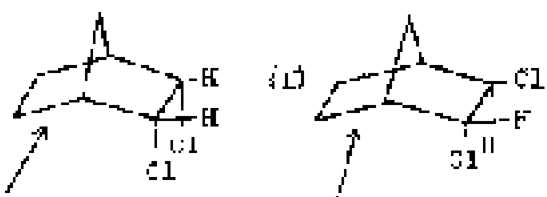
To see which isomer will eliminate more readily we look at the Newman projections for each isomer. Only in the trans isomer is there still another anti H to Br conformation. In the cis isomer H and Br are eclipsed and less stable than the anti conformation. Elimination via an eclipsed conformation is called syn elimination, and it is generally less stable and slower than anti elimination. We conclude the trans isomer (H and Br are anti to each other) will more readily eliminate further to form dimethylacetylene.

• PROBLEM 14-10

Using models, suggest explanations for the following:

(a) On E2 elimination with $t\text{-BuO}^-K^+/t\text{-BuOH}$, both cis- and trans-2-phenylcyclopentyl tosylates give 1-phenylcyclopentene as the only alkene; the cis isomer reacts 14 times as fast as the trans.

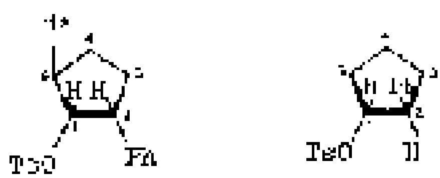
(b) On E2 elimination with $n\text{-C}_5H_{11}O^-Na^+/n\text{-C}_5H_{11}OH$ to give 2-chloronorbornene, II reacts about 100 times as fast as its diastereomer, I.

(I)  (II)

endo-cis-2,3-Dichloronorbornane

trans-2,3-Dichloronorbornane

Solution: (a) Let us look at the structure of both cis- and trans-2-phenylcyclopentyl tosylates:



cis- trans-

For the E2 elimination, the TsO acts as the leaving group in both the cis- and trans-isomers. The question that must be answered is by what mechanisms are the isomers eliminating to form 1-phenylcyclopentene? These mechanisms have one thing in common: they each involve the removal of a leaving group and a hydrogen β to it and the creation of a double bond between C_α and C_β. Sterically it works out that elimination will proceed either with the leaving group anti to the β hydrogen (anti elimination) or with the leaving group eclipsed to the β hydrogen (syn elimination). The anti elimination mechanism is the more energetically stable method because the anti conformation is far more feasible than the eclipsed conformation.

Visually we can determine that the cis isomer will undergo an anti elimination because the leaving group, TsO, has two hydrogens anti to it. Since we are told that only 1-phenylcyclopentene  forms with elimination from both isomers, we can assume that the trans isomer must proceed by syn elimination for that is the only available route (the Ph group is in the anti position to the TsO group). The question is why will the double bond form only on the C_1-C_2 bond? Let us first go through both eliminations.

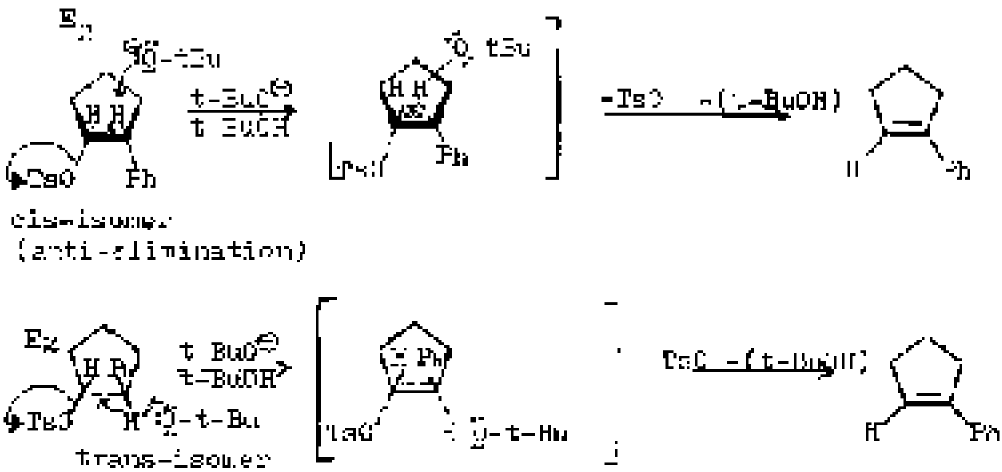


Figure 1

The answer to our question rests with the phenyl group. It greatly controls the orientation of elimination because of the conjugation of the double bond formed by the aromatic, high stable, phenyl group. This drive for the double bond to be conjugated is so energetically favorable that it only forms a double bond between C_1 and C_2.

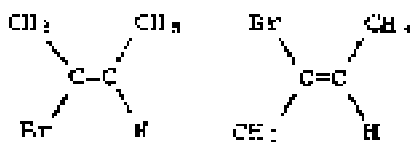
In Figure 1 we see that the cis isomer undergoes the highly favorable trans elimination, thus its elimination reaction goes much faster than that of the trans isomer.

(b) In this part we are dealing with rigid, bicyclic compounds. By rigid we mean that the compound does not readily change conformation. This factor is a key point in dealing with this problem.

Compound I must react via an anti elimination, which can be formed via a change in conformation of the compound. Compound II is already in an eclipsed conformation and will thus react via syn elimination. Normally we would expect the compound using an anti elimination to react faster than a compound using syn elimination but from the data given the reverse is true. The main thing to remember is that the most stable elimination will react the fastest. In this case, for example, the fact that bicycle compounds are rigid makes the anti elimination of I more unstable, thus slower than II. I must change its conformation in order to undergo anti elimination, and the energy needed to change the conformation is relatively large. The result is that II reacts much faster than I.

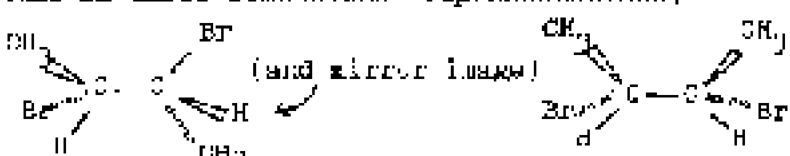
• PROBLEM 14-11

The reaction of (±)-2,3-dibromobutane with ethoxide ion produces trans-2-bromo-2-butene while, under the same conditions, meso-2,3-dibromobutane produces the corresponding cis isomer. With the aid of three-dimensional representations, determine whether this is an anti (trans) elimination. Explain how it is possible for a "trans" elimination to produce both cis and trans product.



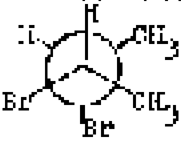
cis trans 2-bromo-2-butene

Solution: To solve this problem we should look at the structures of (±)-2,3-dibromobutane and meso-2,3-dibromobutane in three dimensions representations:



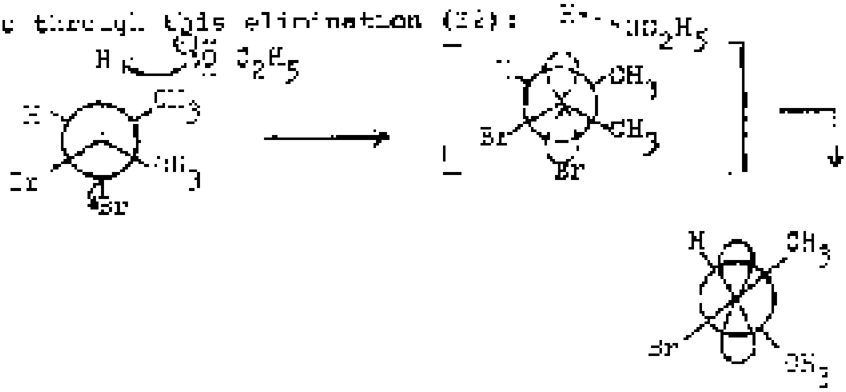
(±)-2,3-dibromobutane meso-2,3-dibromobutane

To make things as clear as possible we will present the meso-2,3-dibromobutane as a Newman projection:



meso-2,3-dibromobutane

We have conveniently rotated this Newman projection so that it is ready to undergo a trans-elimination (the H and Br are anti to each other). The point of this is that if we get a cis product we know that it does undergo a trans-elimination, but if we get a trans product then this meso compound does not undergo a trans-elimination. We now go through this elimination (E2):

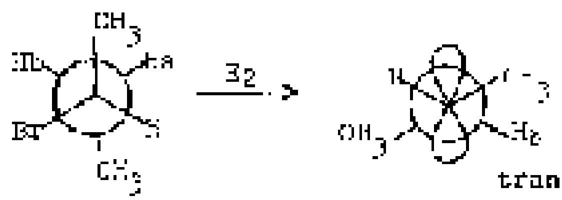


cis-2-bromo-2-butene

We can conclude from this representation that the elimination reaction of meso-2,3-dibromobutane to form cis-2-bromo-2-butene proceeds via a trans-elimination.

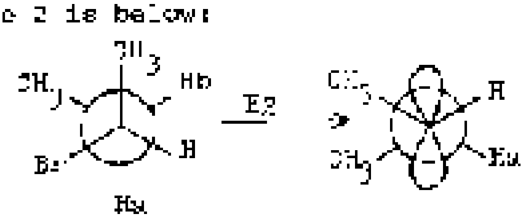
To explain how it is possible for a trans elimination to produce both cis and trans product, let us examine the compound $CH_3CH_2CHBrCH_3$ by using the Newman projection:

Fig. 1



trans product

We labeled the two hydrogens of the methylene group to show two possible routes of anti elimination; figure 1 shows H_a being eliminated and a trans product being formed. Figure 2 is below:



cis product

In this case by labeling the hydrogens to be eliminated we see that there can be both cis and trans products.

ELIMINATION VS. SUBSTITUTION

• PROBLEM 14-12

Consider the reaction of isopropyl iodide with various nucleophiles. For each pair, predict which will give the larger substitution/elimination ratio.

(a) I^- or Cl^- (b) $N(CH_3)_3$ or $P(CH_3)_3$ (c) CH_3S^- or CH_3O^-

Solution: To solve this problem we consider what properties of a nucleophile will increase the substitution to elimination ratio.

A very important difference between elimination and substitution is their emphasis on nucleophilicity and basicity. Nucleophilicity is the affinity of a base for a carbon atom in a displacement reaction transition state. It is measured by the rate of reaction of the nucleophile with a suitable halide. Judging by the first step of an S_n reaction, where a base attacks the back lobate orbital of a suitable carbon, we can state that nucleophilicity is extremely important in S_n reactions.

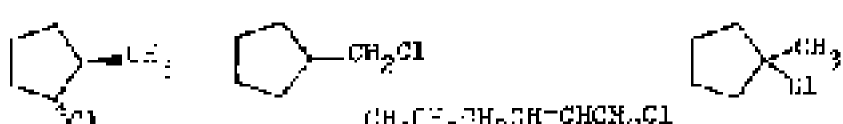
Basicity is the affinity of a base for a proton and is measured by the equilibrium pKa of the conjugate acid in water. Judging by the first step of an elimination reaction, where a base abstracts a proton from a carbon β to a halogen causing a series of electron shifts, basicity is clearly very important in elimination reactions. To summarize then: In S_n reactions nucleophilicity is the key while in elimination reactions basicity is the key.

We want to increase the substitution to elimination ratio; to do this we try to find the nucleophile with the greater nucleophilicity. The question now arises: what factors affect nucleophilicity? What it all boils down to is that the nucleophile with the greater polarizability will also have the greater nucleophilicity. Larger elements have relatively diffuse lone pairs of electrons because the orbitals are larger than in let us say first row elements. These diffuse lone pairs of electrons tend to bond more strongly to the more diffuse state of the p orbital in an S_n2 transition state than to the small, tight 1s orbital of a hydrogen (as if it were acting as a base). From this we can conclude that larger (second and third row) elements are more nucleophilic than smaller (first row) elements.

In part (a) we consider I^- and Cl^-. I^- is the larger element and is thus more polarizable and more nucleophilic, thereby increasing the substitution to elimination ratio. In the same way in part (b), $P(CH_3)_3$ is the correct choice and in part (c), CH_3S^- is the correct choice.

• PROBLEM 14-13

Predict the order of reactivity of the following halides with (a) sodium iodide in acetone; (b) aqueous alcoholic silver nitrate.



Solution: To solve this problem, we consider various techniques used in figuring the relative reactivities of several compounds in S_N reactions.

The first step to solve this problem systematically, is to consider the reaction conditions. In part (a) the reaction conditions are sodium iodide in acetone. This media favors S_N2 over S_N1 reactions. In part (b) the reaction conditions are aqueous alcoholic silver nitrate. This indicates an S_N1 type media.

We now consider what factors affect reactivity in S_N reactions. The most important factor is the degree of alkylation of the carbon α to the halogen (the carbon bonded to the halide), that is whether this alkyl halide is 1°, 2°, or 3°. For review a 1° (primary) alkyl halide follows the form

```
  H
  |
H-C-H
  |
  X
```

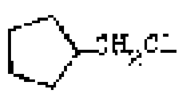
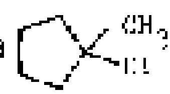
, a 2° (secondary) alkyl halide follows the form

```
  H
  |
R-C-R
  |
  X
```

, and a 3° (tertiary) alkyl halide follows the form

```
  R
  |
R-C-R
  |
  X
```

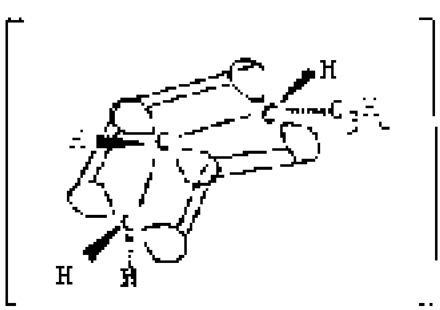
, where X represents a halogen and R represents an alkyl or aromatic group.

is thus a 3° alkyl halide.  is a 1° alkyl halide and 

is a 3° alkyl halide. $CH_3CH_2CH_2CH=CHCH_2Cl$ is a 1° alkyl halide but it is a special case in both S_N1 and S_N2 reactions. In part (a) $CH_3CH_2CH_2CH=CHCH_2Cl$ undergoes an S_N2 reaction as follows: $CH_3CH_2CH_2CH=CHCH_2Cl + I^- \xrightarrow{\text{acetone}} CH_3CH_2CH_2CH=CHCH_2I + Cl^-$. Being an S_N2 reaction the following activated complex is formed:

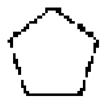
$$CH_3CH_2CH_2CH=CHCH_2Cl + I^{\ominus} \xrightarrow[\text{acetone}]{}$$

π overlap stabilizing the S_N2 activated complex:

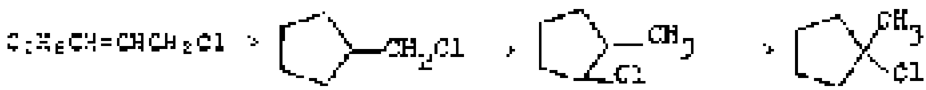


$\longrightarrow C_3H_7CH=CHCH_2I + Cl^{\ominus}$

This activated complex has a π bonding overlap which tends to stabilize and thus decrease the energy content of the activated complex. The net result of all this is that $C_3H_5CH=CHCH_2Cl$ (1°) will have a greater reactivity than


$-CH_2Cl$ because of this effect.

Getting back now to the degree of the alkyl halide, in an S_N2 reaction the order of reactivity is $CH_3X > 1° > 2° > 3°$, while in a S_N1 reaction the order of reactivity is $3° > 2° > 1° > CH_3X$. Thus in part (a) [S_N2 media] the order of reactivity is



In part (b) (S_N1 media) $C_3H_5CH=CHCH_2Cl$ exhibits another very interesting effect. You will note that this compound has an allylic type group: $C_3H_5\diagdown CH=CH\,CH_2Cl$. The compound reacts via an S_N1 path in the following way:

$$C_3H_5CH=CHCH_2Cl \xrightarrow{-Cl^{\ominus}} C_3H_5CH-\overset{\oplus}{C}HCH_2 \xrightarrow{I^{\ominus}} C_3H_5CH-CHCH_2I$$

allylic carbocation intermediate

The allylic carbocation intermediate displays what is called a resonance effect. That is the allylic carbocation can be drawn as two identical arrangements of atoms differing only in their electronic distribution. Each arrangement is called a resonance or contributing structure. These structures have no physical existence and they are not in equilibrium; rather the real allyl cation is a hybrid of the two main contributing structures (hybrid also in electronic distribution):

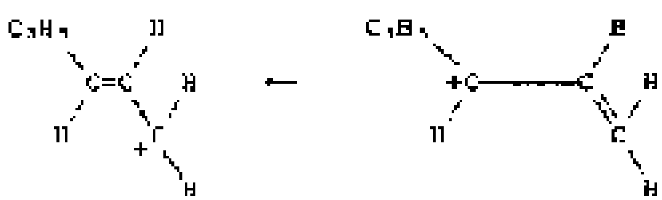
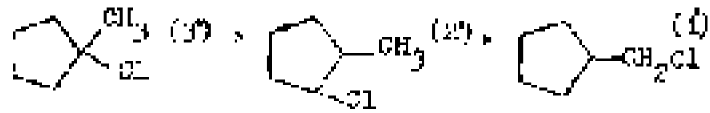


Fig. 1

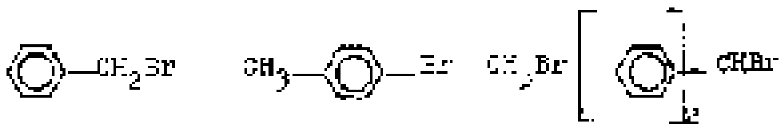
Notice from Fig. 1 that the positive charge is delocalized amongst the contributing structures. This delocalization of charge greatly stabilizes the carbocation, thus creating an effect whereby $C_3H_5CH=CHCH_2Cl$ is more reactive via S_N1 than even t-butyl bromide, a tertiary compound.

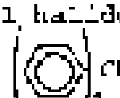
Taking this resonance effect into account, the order of reactivity in part (b) is:

$C_6H_5CH{=}CHCH_2Cl$ > 

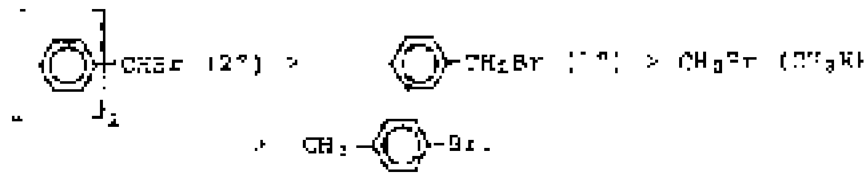
• PROBLEM 14-74

Predict the order of reactivity of the following halides with (a) sodium iodide in acetone; (b) aqueous alcoholic silver nitrate:



Solution: This problem requires an understanding of the techniques used in predicting the order of reactivity of various alkyl halides under S_N1 and S_N2 conditions. Taking a systematic approach in solving this problem we first consider the media in which the reaction takes place. In part (a), we are told that the reaction takes place in a sodium iodide/acetone media. These reaction conditions favor an S_N2 reaction. This means that the compound most favoring an S_N2 reaction will have the greatest reactivity. We know in general the order of reactivity in S_N2 reactions is $CH_3X > 1° > 2° > 3°$. CH_3Br fits the CH_3X brand and is therefore the most reactive species.  is a 1° (primary) alkyl halide and is thus the next most reactive species.  is a 2° alkyl halide and is the third most reactive species. CH_3Br deserves special mention; because the halide (bromine) is attached to the phenyl group the compound is classified as an aromatic halide and because it is so stable it is very unreactive species and it will not easily undergo any type of S_N reaction. Therefore,  is by far the least reactive species in both part (a) and part (b).

By the same method we consider part (b). The reaction media is aqueous alcoholic silver nitrate. This is indicative of S_N1 reaction conditions (aqueous media favors S_N1, while acetone favors S_N2). The order of reactivity by S_N1 for alkyl halides in general, is 3° > 2° > 1° > CH_3X. Taking this into account we find that the order turns out to be



PROBLEM 14-15

The reaction of t-butyl chloride with water is strongly accelerated by sodium hydroxide. How would the ratio of elimination to substitution products be affected thereby?

Solution: To understand the effect of the addition of NaOH to the reaction of t-butyl chloride with water, we should first consider its important chemical properties.

NaOH when placed in water ionizes to a great extent, which causes the pH of the solvent to increase. This increase in pH indicates increased basicity of the water. NaOH ionizes to Na^+ and OH^- ions, with virtually 100 % dissociation in water. Because of this complete dissociation NaOH is a very strong base.

The question is now: what effects does a strong base have on an elimination or substitution reaction? To answer this we consider what a base does. By far the most important use of a strong base is to abstract protons. Thinking now of the mechanisms of elimination and substitution, we see in an E2 reaction the abstraction of a proton β to the halide. Thus we can conclude that the addition of NaOH (a strong base) to the reaction of t-butyl chloride with water would increase the ratio of elimination to substitution.

It should be mentioned that the reason NaOH strongly accelerates the reaction is that it increases the concentration of base present. The reactions of NaOH with t-butyl chloride and water are:

$$NaOH + CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-Cl \xrightarrow[H_2O]{E2} CH_2=C\begin{matrix} CH_3 \\ CH_3 \end{matrix} + NaCl$$

$$NaOH + CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-Cl \xrightarrow[H_2O]{S_N1} CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-OH + NaCl$$

Which compound of each of the following sets would you expect to give the higher yield of substitution product under conditions for bimolecular reaction?

(a) ethyl bromide or β-phenylethyl bromide;
(b) α-phenylethyl bromide or β-phenylethyl bromide;
(c) isobutyl bromide or n-butyl bromide;
(d) isobutyl bromide or tert-butyl bromide.

Solution: To solve this problem we must consider what physical properties will determine the amount of substitution produced from each compound in a nucleophilic bimolecular substitution reaction (S_N2). The properties to be considered are the degree of substitution on the α-carbon (1°, 2°, 3°, or CH_3X), the leaving group, the nucleophile, the reaction conditions (the polarity of the solvent used and the temperature of the reaction), the degree of substitution at the β-carbon, and the substituents themselves at the carbon α and the carbon β. For this problem we do not consider the reaction conditions since we are told they favor S_N2 nor do we consider the nucleophile (which is not given), and the leaving group in each compound is bromine. What we do consider are the degree of substitution of C-α and at C-β, and the substituents themselves at C-α and at C-β. The most favorable conditions for S_N2 arise when C-α is primary

$$\left[\begin{array}{c} R \\ | \\ H-C-H \\ | \\ X \end{array}\right]$$

due to the fact that there is less steric hindrance in the transition state. So therefore the order of reactivity for S_N2 is CH_3X > 1° > 2° > 3°. If both compounds are 1° (primary) we now consider the substituents at C-β. Again, due to the lack of steric hindrance, a primary C-β is the most favorable condition for S_N2. As far as the substituents themselves are concerned, the larger the substituent the less S_N2 is favored. In part (a) we consider CH_3CH_2Br and $PhCH_2CH_2Br$. Usually we can determine that the Ph group at the C-β position causes $PhCH_2CH_2Br$ to be sterically less favorable than CH_3CH_2Br therefore ethyl bromide would give a higher yield than β-phenylethyl bromide under bimolecular reaction conditions. An important note to this problem is that the presence of the highly conjugated Ph group causes E2 (elimination) to easily occur in $PhCH_2CH_2Br$ to produce a conjugated alkene:

(Styrene)

In part (b) we consider $CH_3CH(Ph)Br$ and $PhCH_2CH_2Br$. Here there is the very significant fact that $CH_3CH(Ph)Br$

is secondary at C-α while $PhCH_2CH_2Br$ is primary at C-α. This fact outweighs the point that $PhCH_2CH_2Br$ undergoes a significant E2 reaction because steric considerations are extremely important in terms of reaction rate and yield. In part (c) we consider $Br-CH_2-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{CH}}}}$ and $CH_3(CH_2)_3Br$. Both are primary at C-α site, however, at the C-β site $CH_3CH(CH_3)CH_2Br$ is tertiary while $CH_3(CH_2)_3Br$ is only secondary. This branching in isobutyl bromide creates steric hindrance for an S_N2 but helps stabilize (thermodynamically) the alkene formed by an E2. In part (d) we consider $CH_3CH(CH_3)CH_2Br$ and $CH_3C(CH_3)_2Br$. Using our systematic approach, we immediately see that the C-α of the t-butyl bromide is 3° (tertiary) while the C-α of isobutyl bromide ($BrCH_2CH(CH_3)CH_3$) is 1° (primary). The extreme steric effect exhibited by t-butyl bromide severely inhibits an S_N2 reaction while the primary isobutyl bromide exhibits virtually no steric effects and easily undergoes an S_N2 reaction. Summarizing our answers:

(a) CH_3CH_2Br - (ethyl bromide)

(b) $PhCH_2CH_2Br$ - (β-phenylethyl bromide)

(c) $CH_3CH_2CH_2CH_2Br$ - (n-butyl bromide)

(d) $CH_3\underset{CH_3}{\underset{|}{C}}HCH_2Br$ - (isobutyl bromide)

• PROBLEM 14-17

> Outline a possible laboratory synthesis of each of the following compounds from alcohols and phenols:
>
> (a) methyl tert-butyl ether
> (b) n-propyl phenyl ether
> (c) cyclohexyl methyl ether

Solution: (a) The compound methyl tert butyl ether is an asymmetrical ether with the general formula: R O R'.

Sodium alkoxides $R-\overset{\ominus}{O}\overset{\oplus}{Na}$ are used to obtain ethers. Sodium t-butoxide $(CH_3)_3C-\overset{\ominus}{O}\overset{\oplus}{Na}$ could be reacted with methyl bromide. This reaction gives the desired product methyl tert-butyl ether $(CH_3)_3C-O-CH_3$.

Sodium alkoxides $R-\overset{\ominus}{O}Na^{\oplus}$ are prepared by reacting an alcohol with sodium.

$$R-OH + Na \rightarrow R-O^{\ominus}Na^{\oplus} + H_2\uparrow$$

sodium alkoxide

$$R-O^{\ominus}Na^{\oplus} + R'-X \rightarrow R-O-R' + Na^{\oplus}X^{\ominus}$$

sodium alkoxide   alkyl halide   Asymmetrical ether

$$2\quad CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-O^{\ominus}Na^{\oplus} + CH_3Br \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-O-CH_3 + Na^{\oplus}Br^{\ominus}$$

Sodium t-butoxide   methyl tert-butyl ether

(b) The compound n-propyl phenyl ether is a mixed aliphatic-aromatic ether with the general formula Ar-O-R. It can be prepared from the corresponding alcohol and phenol.

Alcohols can be converted into other kinds of compounds having the same carbon skeleton. Alkyl halides are prepared from alcohols by use of hydrogen halides or phosphorus halides. Phosphorus halides are often preferred because they tend less to bring about rearrangement. The general equation for this reaction is as follows:

$$R-OH + PX_3 \rightarrow RX + H_3PO_3$$

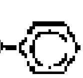
where R represents an alkyl group and X a halide (Cl, Br, I or F). The equation for the reaction outlined in the problem is:

$$3\ CH_3CH_2CH_2OH + PBr_3 \rightarrow 3\ CH_3CH_2CH_2Br + H_3PO_3$$

n-propyl   n-propyl bromide

Phenols are converted into their salts by aqueous hydroxides. The equation for this reaction is as follows:

Phenol   Sodium phenoxide

Sodium phenoxide reacts with n-propyl bromide giving the desired product n-propyl phenyl ether $CH_3CH_2CH_2O-$

n-propyl bromide   Sodium phenoxide   n-propyl phenyl ether

(c) The compound cyclohexyl methyl ether is an asymmetrical ether with the general formula R–O–R'. Ethers can be prepared by the method of synthesis that uses sodium alkoxides and alkyl halides. The general equation for this reaction is as follows:

$$R-O^{\ominus}Na^{\oplus} + R'-X \to R-O-R' + Na^{\oplus}X^{\ominus}$$

a sodium alkoxide   alkyl halide   asymmetrical ether

where R represents an alkyl group and X a halide (Cl, Br, I or F). Sodium alkoxides are made by direct action of sodium metal on dry alcohols:

$$ROH + Na \to RO^{\ominus}Na^{\oplus} + H_2\uparrow$$

a sodium alkoxide

Alkyl halides are commonly prepared from the alcohols by use of phosphorus halides:

$$R-OH + PX_3 \to RX + H_3PO_3$$

alkyl halide

The equations for the reaction outlined in the problem are:

(1) 

cyclohexanol   sodium cyclohexoxide

(2) $3\ CH_3OH + PBr_3 \to 3\ CH_3Br + H_3PO_3$

methyl alcohol   methyl bromide

(3) 

sodium cyclohexoxide   methyl bromide   cyclohexyl methyl ether

CHAPTER 15

ORGANOMETALLIC COMPOUNDS

PREPARATION

• PROBLEM 15-1

Write balanced equations for the preparation of each of the following organometallic compounds by two different reactions starting from suitable alkyl halides and inorganic reagents. Specify reaction conditions and solvents. In each case, indicate which method of preparation you would prefer from standpoints of yield, convenience, etc.

(a) $(CH_3)_2Zn$ (c) $(CH_3CH_2)_4Pb$
(b) CH_3MgCl (d) $(CH_3)_2CHLi$

Solution: Organometallic compounds can be prepared by a direct or an indirect method. The direct method of preparing alkyl organometallic compound is to react an alkyl halide (RX) with the free metal:

$$R—X + 2\ Li \rightarrow Li^+X^- + R—Li$$

The indirect method of preparing organometallic alkanes involves first the formation of an organometallic alkane that differs from the desired product only by the metal. Next, the free metal of the desired product is reacted with the aforementioned alkyl organometallic compound to give the desired product. For example, methyl sodium can be prepared by first forming methylmagnesium chloride. Subsequent reaction with sodium forms methyl sodium, sodium chloride and magnesium:

$$CH_3Cl \xrightarrow[\text{ether}]{Mg} CH_3MgCl$$

$$CH_3MgCl \xrightarrow[\text{n-hexane}]{Na} CH_3Na + Mg + Na^+Cl^-$$

Generally, the direct method of preparing organometallic alkanes is preferred over the indirect method. This is because the direct method involves only one step and will hence give better yields than the indirect method.

(a) A direct method of preparing the organozinc compound $(CH_3)_2Zn$ can be shown as:

$$2\ CH_3I + 2\ Zn \rightarrow (CH_3)_2Zn + ZnI_2$$

An indirect method is as follows:

$$2\ CH_3I + Hg(Na)_2 \rightarrow (CH_3)_2Hg + 2\ NaI$$

$$(CH_3)_2Hg + Zn \rightarrow (CH_3)_2Zn + Hg$$

The direct method (the first one) is preferred because it gives a better yield and it does not proceed through any highly poisonous intermediates ($(CH_3)_2Hg$ is a very poisonous compound). A good solvent for the preparation and reaction of organozinc compounds is diethyl-ether.

(b) The direct method of preparing methylmagnesium chloride is:

$$CH_3Cl + Mg \xrightarrow{\text{ether}} CH_3MgCl$$

Methylmagnesium chloride is an example of a Grignard reagent (organomagnesium compounds); ether is a good solvent for reactions of Grignard reagents. An indirect method of preparing CH_3MgCl is:

$$CH_3Cl + 2\ Li \rightarrow Li^+Cl^- + CH_3Li$$

$$CH_3Li + MgCl_2 \rightarrow CH_3MgCl + Li^+Cl^-$$

The direct method is preferred; it involves only one step and can be carried out at low temperatures due to methylchloride's low boiling point.

(c) Tetraethyl lead $(Pb(C_2H_5)_4)$ is added to automobile fuel to prevent "knocking" in the engine. A direct method of preparing it is:

$$4\ CH_3CH_2Cl + 4\ Pb(Na) \rightarrow (CH_3CH_2)_4Pb + 4\ Na^+Cl^- + 3\ Pb$$

An indirect method of preparation is:

$$2\ CH_3CH_2Cl + Hg(Na)_2 \rightarrow (CH_3CH_2)_2Hg + 2\ NaCl$$

$$2\ (CH_3CH_2)_2Hg + Pb \rightarrow 2\ Hg + (CH_3CH_2)_4Pb$$

The direct method is preferred because it gives a better yield and it does not proceed through any highly poisonous intermediates.

(d) A direct method for preparing isopropyl lithium is:

$$(CH_3)_2CHBr + 2\ Li \rightarrow (CH_3)_2CHLi + Li^+Br^-$$

An indirect method is:

$$(CH_3)_2CHBr + Mg \xrightarrow{\text{ether}} (CH_3)_2CHMgBr$$

$$(CH_3)_2CHMgBr + 2\ Li \rightarrow (CH_3)_2CHLi + Mg + \overset{+}{Li}\overset{-}{Br}$$

The direct method is preferred and ether can be used as a solvent.

• PROBLEM 15-2

When 10.0 g of n-propylchloride is allowed to react with excess sodium in the Wurtz reaction, how many grams of hexane would be produced assuming a 70 % yield?

Solution: The Wurtz reaction is a method used to couple two short chain alkyl groups to form longer chains. The general equation for this reaction is

$$2\ RX + 2\ Na \rightarrow R - R + 2\ NaX$$

where R represents an alkyl group and X a halide (Cl, Br or I).

The equation for the reaction outlined in the problem is:

$$2\ CH_3CH_2CH_2Cl + 2\ Na \rightarrow CH_3(CH_2)_4CH_3 + 2\ NaCl$$

From this equation, it is seen that for every two moles of n-propylchloride that react, one mole of hexane is formed. We must first determine the number of moles of n-propylchloride contained in 10.0 g of the compound. One half of this amount will be the theoretical yield of hexane. The problem states that only 70 % of the theoretical yield is obtained. (MW of $CH_3CH_2CH_2Cl$ = 78.5.)

$$\text{no. of moles of } CH_3CH_2CH_2Cl = \frac{10.0\ g}{78.5\ g/mole}$$

$$= .127 \text{ moles}$$

$$\text{theoretical yield of hexane formed} = (0.5)(0.127 \text{ moles})$$

$$= 6.35 \times 10^{-2} \text{ moles}$$

$$\text{experimental yield} = (0.7)(6.35 \times 10^{-2} \text{ moles})$$

$$= 4.45 \times 10^{-2} \text{ moles}$$

The weight of the hexane formed can now be calculated. (MW of C_6H_{14} = 86.)

$$\text{mass of } C_6H_{14} \text{ formed} = (86\ g/mole)(4.45 \times 10^{-2} \text{ moles})$$

$$= 3.82\ g.$$

• PROBLEM 15-3

What products would you expect to be formed in an attempt to synthesize hexamethylethane from t-butyl chloride and sodium? Write equations for the reactions involved.

Solution: Organosodium compounds are unique in that they are one of the most highly reactive organometallic compounds. Organosodium compounds react rapidly with ethers and alkyl halides. They react with alkyl halides to produce hydrocarbons by either S_N2 and/or E2 reactions. For example, ethylsodium ($CH_3CH_2^-: Na^+$) undergoes S_N2 and E2 reactions with ethyl bromide as shown:

E2 reaction:

$$CH_3CH_2^-: Na^+ + H-CH_2-CH_2-Br \rightarrow CH_3CH_3 + Na^+Br^- + CH_2{=\!=}CH_2$$

S_N2 reaction (Wurtz coupling reaction):

$$CH_3CH_2^-: Na^+ + CH_3CH_2-Br \rightarrow CH_3CH_2CH_2CH_3 + Na^+Br^-$$

When t-butyl chloride is treated with metallic sodium, the organosodium compound (t-butyl sodium) is first formed; sodium chloride is a by product of this reaction:

$$(CH_3)_3C-Cl + 2\ Na \rightarrow (CH_3)_3C^-: Na^+ + Na^+Cl^-$$

As t-butylsodium is formed it reacts with the unconsumed t-butyl chloride to form hydrocarbons. The reaction is strictly E2; there is no Wurtz coupling occurring due to the steric hindrance of the t-butyl groups. Hence the hydrocarbons formed are 2-methylpropane and isobutylene; no hexamethylethane is produced. The reaction can be shown as:

$$(CH_3)_3C^-: Na^+ + H-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-Cl \longrightarrow$$

$$Na^+Cl^- + \underset{\text{2-methyl-propane}}{(CH_3)_3CH} + \underset{\text{isobutylene}}{CH_2{=}C(CH_3)_2}$$

• PROBLEM 15-4

The following projected synthesis for n-butane is not very efficient. Why?

$$CH_3CH_2CH_2Br + CH_3Br + 2\ Na \rightarrow CH_3(CH_2)_2CH_3 + 2\ NaBr$$

Solution: This reaction is an example of the Wurtz coupling reaction. The general equation is

$$2\ R - X + 2\ Na \rightarrow R - R + 2\ NaX$$

where R represents an alkyl group and X a halide (Cl, Br or I).

In the above reaction there is both n-propylbromide and methylbromide in the mixture. According to the equation for the Wurtz reaction, these two compounds can couple to form n-butane. But, at the same time free methyl groups can combine with each other as can free propyl groups, forming ethane and hexane. This leads to a decrease in the production of n-butane. A more efficient reaction mixture would be just ethylbromide and Na. Here, the only coupled product would be n-butane

$$CH_3-CH_2-Br + 2\ Na \rightarrow CH_3(CH_2)_2CH_3 + 2\ NaBr.$$

GRIGNARD REAGENTS

• PROBLEM 15-5

An equilibrium has been suggested to exist between an alkylmagnesium halide (Grignard reagent) and the corresponding dialkylmagnesium in ether solution according to the following equation:

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$

When ether solutions of diethylmagnesium and radioactive magnesium bromide, $\overset{*}{Mg}Br_2$, are mixed and allowed to stand for several hours, the magnesium bromide that is subsequently precipitated (by the addition of dioxane,

```
  CH2-CH2
 /       \
O         O, to the solution) has been reported (with
 \       /
  CH2 CH2
```

Grignard reagents prepared from at least some specimens of magnesium) to contain almost all the initial radioactivity. What can be deduced from such a result?

Solution: If the proposed equilibrium does exist, then the use of radioactive magnesium bromide should incorporate some radioactive magnesium in all the organomagnesium compounds involved in the equilibrium. This equilibrium between diethylmagnesium, radioactive magnesium bromide ($\overset{*}{Mg}Br_2$) and ethylmagnesium bromide is shown as:

$$(CH_3CH_2)_2Mg + \overset{*}{Mg}Br_2 \rightleftharpoons CH_3CH_2MgBr + CH_3CH_2\overset{*}{Mg}Br$$

$$CH_3CH_2MgBr - CH_3CH_2\overset{*}{Mg}Br \rightleftharpoons \tfrac{1}{2}MgBr_2$$

$$\tfrac{1}{2}\overset{*}{Mg}Br_2 + \tfrac{1}{2}(CH_3CH_2)_2Mg + \tfrac{1}{2}(CH_3CH_2)_2\overset{*}{Mg}$$

The fact that most of the initial radioactivity is contained in the magnesium bromide suggests that the proposed equilibrium does not occur.

Excess methylmagnesium iodide and 0.1776 g of compound A of formula $C_4H_{10}O_3$ react to give 84.1 cc of methane collected over mercury at 740 mm and 25°C. How many active hydrogens does compound A possess? Suggest a possible structure for the compound given that the infrared spectrum shows no carbonyl absorption and the n.m.r. spectrum shows only three types of hydrogen with areas in the ratio of 1:2:2.

Solution: To determine the number of active hydrogens (hydrogens that will react with methyl magnesium halide to form methane) in compound A ($C_4H_{10}O_3$), we must employ some organic stoichiometry. The number of active hydrogens will be the same as the number of moles of methane produced per mole of compound A. In the reaction, 0.1776 g of compound A is reacted. The molecular weight of compound A ($C_4H_{10}O_3$) is 4(12) + 10(1) + 3(16) = 106. The number of moles of compound A reacted is calculated as:

$$\# \text{ moles} = \frac{\text{g of compound}}{\text{g/mole or MW of compound}}$$

$$\# \text{ moles} = \frac{0.1776}{106} = 0.00168$$

Hence, the number of moles of compound A reacted is 0.00168. All of the compound reacts because it is treated with an excess of methyl magnesium iodide, CH_3MgI. Now we must determine the number of moles of methane produced. The reaction yielded 84.1 cc of methane collected over mercury at 740 mm and 25° Celsius (298° Kelvin). The first thing we must do is to convert the volume of methane collected to its equivalent volume at STP (standard temperature and pressure, 273° Kelvin and 760 mm). Since a cubic centimeter (cc) is equal in volume to one milliliter (ml), 84.1 ml of methane was collected. To convert the number of milliliters of CH_4 to its STP equivalent, the following calculations are performed:

$$\text{ml } CH_4 \text{ at STP} = \text{ml } CH_4 \text{ collected} \times$$

$$\frac{\# \text{ of mm over mercury}}{760 \text{ mm}} \times \frac{273° \text{ Kelvin}}{\# \text{ of degrees Kelvin}}$$

$$\text{ml } CH_4 \text{ at STP} = 84.1 \times \frac{740}{760} \times \frac{273}{298}$$

$$\text{ml } CH_4 \text{ at STP} = 75.0$$

We can now determine the number of moles of CH_4 collected. Since there are 1000 ml in one liter, and one mole occupies 22.4 liters of space at STP:

$$\# \text{ moles } CH_4 = \frac{\# \text{ ml } CH_4 \text{ collected at STP}}{1000 \text{ ml/liter} \times 22.4 \text{ liters/mole}}$$

$$\# \text{ moles } CH_4 = \frac{75.0}{1000 \times 22.4}$$

$$\# \text{ moles } CH_4 = 0.00335$$

We see that there are two moles of methane produced for every mole of compound A reacted:

$$\frac{\# \text{ moles } CH_4}{\# \text{ moles compound A}} = \frac{0.00335}{0.00168} = 2$$

Hence there are two active hydrogens in compound A.

The problem gives us some infrared (ir) and nuclear magnetic resonance (nmr) spectral data to deduce a possible structure for compound A. The infrared spectrum shows no carbonyl absorption. Since compound A contains oxygens it must be an ether and/or an alcohol. The nmr spectrum shows only three types of hydrogens with relative intensities 1:2:2. Since there are ten hydrogens in compound A, the relative intensities (using the actual number of hydrogens) are 2:4:4. The two active hydrogens in A must be responsible for the relative intensity of "2", since they are different from all the other hydrogens. The only possible structure for compound A that is consistent with all the data is:

$$HOCH_2CH_2OCH_2CH_2OH$$

The two active hydrogens are the alcoholic ones. Compound A reacts with methylmagnesium iodide as follows:

$$HOCH_2CH_2OCH_2CH_2OH + 2\ CH_3MgI_{(excess)} \longrightarrow$$

$$2\ CH_4 + IMgOCH_2CH_2OCH_2CH_2OMgI$$

• PROBLEM 15-7

Unknown Q was analyzed and found to contain one atom of bromine per molecule. When the Grignard reagent prepared from Q was treated with water, ethylbenzene was produced. Draw all the possible structures of Q.

Solution: A Grignard reagent can be prepared from an alkyl or aryl halide by reacting it with solid magnesium in dry ethyl ether.

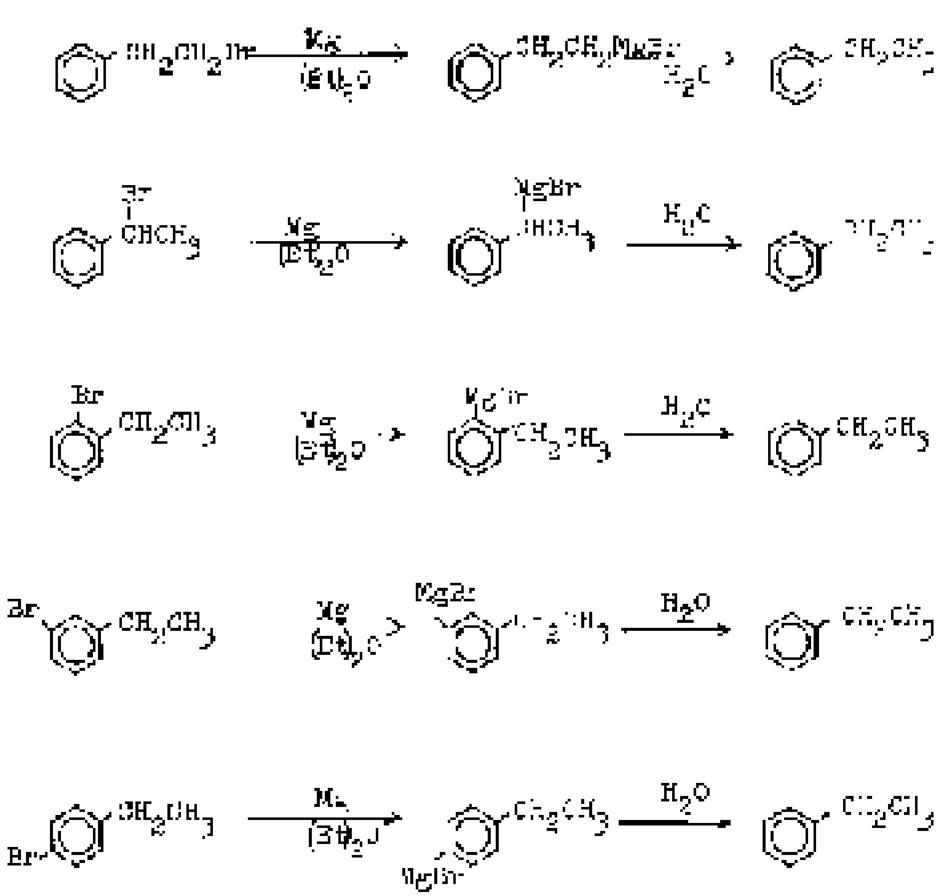
$$\underset{\text{alkyl halide}}{R - X} + Mg \xrightarrow[\text{ether}]{\text{dry}} \underset{\text{Grignard reagent}}{RMgX}$$

A Grignard reagent is a strong nucleophile. It attacks any slightly positively charged species. Thus, when treated with water, very negligibly acidic, it deprotonates the water molecule.

$$RMgX + H_2O \rightarrow RH + MgXOH$$

The unknown C was made into a Grignard reagent. T- deprotonates water to form ethylbenzene. Since Grignard reagent formation and protonation do not change the skeletal structure of a compound, unknown C must be an aryl halide. The possible structures of unknown C are shown below as reactants in the process of ethylbenzene synthesis.

UNKNOWN C ETHYLBENZENE



• PROBLEM 15-8

Convert the following aldehydes into alcohols using the Grignard synthesis method

(a) $CH_3CH_2\overset{H}{C}=O$ Propionaldehyde

(b) $(CH_3)_2CH\overset{H}{\underset{|}{C}}=O$ Isobutyraldehyde

Solution: The Grignard synthesis of alcohols is done with one of the most powerful tools used by the organic chemist, which is the Grignard reagent. The Grignard reagent, as has been shown in previous chapters, has the formula RMgX, and is prepared by the reaction of metallic magnesium with the appropriate organic halide. This halide can be alkyl, allylic, benzylic, or aryl. The halogen may be -Cl, -Br, or I. An example of an aldehyde-Grignard reaction is:

$$\mathrm{H-\overset{H}{\overset{|}{C}}{=}O + RMgX \longrightarrow H-\overset{H}{\overset{|}{C}}-\overset{-}{O}\overset{+}{M}gX \xrightarrow{H_2O} H-\overset{H}{\overset{|}{C}}-OH}$$
$$\mathrm{\qquad\qquad\qquad\qquad\quad \underset{R}{|} \qquad\qquad\qquad\quad \underset{R}{|}}$$

showing formaldehyde reacting with the Grignard reagent. This yields an intermediate that is an organic salt and the addition of water converts the salt into an alcohol.

With the principles above, and using the example as a reference, the aldehydes (a) and (b) can be converted to an alcohol by reacting with the Grignard reagent.

(a) $$\mathrm{CH_3CH_2\overset{H}{\overset{|}{C}}{=}O + CH_3MgBr \rightarrow CH_3CH_2\underset{CH_3}{\underset{|}{\overset{H}{\overset{|}{C}}}}\overset{-}{O}\overset{+}{M}gBr \xrightarrow{H_2O} CH_3CH_2\underset{CH_3}{\underset{|}{CH}}-OH}$$

Propionaldehyde $\qquad\qquad\qquad\qquad\qquad\qquad$ 2-butanol

(b) $$\mathrm{(CH_3)_2CH\overset{H}{\overset{|}{C}}{=}O + CH_3CH_2MgBr \rightarrow (CH_3)_2CH\underset{\underset{CH_3}{|}}{\underset{CH_2}{\underset{|}{\overset{H}{\overset{|}{C}}}}}\overset{-}{O}\overset{+}{M}gBr}$$

Isobutyraldehyde

$$\xrightarrow{H_2O} \mathrm{\begin{matrix} CH_3 \\ \diagdown \\ \end{matrix} CHCHOH \atop \diagup \quad\ \underset{CH_3}{\underset{|}{CH_2}} }$$

$$\mathrm{(CH_3)_2CH\underset{\underset{CH_3}{|}}{\underset{CH_2}{\underset{|}{CH}}}OH}$$

2-methyl-3-pentanol

• PROBLEM 15-9

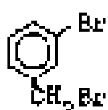
An aromatic dibromide $C_7H_6Br_2$ reacted with aqueous sodium hydroxide. The product of this reaction had lost only one bromo group to give the product C_7H_7BrO. When the dibromide was converted to a Grignard reagent and then hydrolyzed, the product was toluene. Determine the structure of the dibromide.

Solution: It is known that alkyl halides can be converted to alcohols by hydrolysis using a nucleophilic displacement reaction. (Note: this reaction is NOT the same as dehydrohalogenation where the sodium hydroxide is in alcohol. In hydrolysis, the sodium hydroxide is in water.) The overall reaction may be represented by:

$$\underset{\text{(Alkyl halide)}}{R-X} + OH^- \xrightarrow{H_2O} \underset{\text{(Alcohol)}}{R-OH} + X^-$$

The fact that the aromatic dibromide reacted indicates that an alkyl halide group must be attached to the aromatic (or benzene) ring. Since only 1 bromine was lost, the other bromine must be directly bound to the aromatic ring, where NaOH is ineffective in hydrolysis.

The alkyl halide that must be attached to the ring can be deduced from the chemical formula, $C_7H_6Br_2$. The ring is composed of 6 carbons, which leaves only 1 carbon to make up the alkyl halide. Hence, the alkyl halide attached must be CH_2Br. Recalling that the other bromine must be directly attached to the ring, the dibromide can now be written:

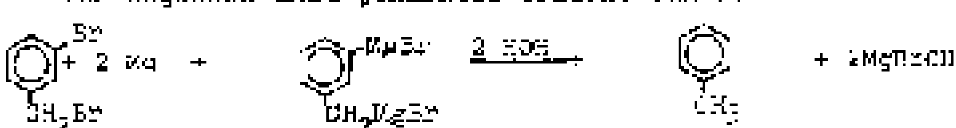


(Note: the dibromide can be ortho, meta or para.) By examining this structure, one can now understand the Grignard reaction which will ultimately lead to toluene.

Alkyl halides and aryl halides can react with magnesium in anhydrous ether to give alkylmagnesium halides, RMgX, which are known as Grignard reagents. The Grignard reagents can then be hydrolyzed by water or acid to the corresponding hydrocarbon as shown:

$$R-MgX + HOH \longrightarrow \underset{\text{(Hydrogen-carbon)}}{R-H} + MgXOH$$

The sequence that generated toluene can now be written:



(Toluene)

● PROBLEM 15-30

Show the product of the following ketones after addition of the Grignard reagent.

(a) $CH_3\overset{O}{\overset{\|}{C}}CH_3$ Acetone

(b) $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ 2 Hexanone

Solution: The Grignard reagent has been shown in many other chapters as an organic magnesium halide, with the structure generally as RMgX. Of course as shown before, the organic group does not necessarily have to be alkyl; it may be allyl, aryl, or arenyl. The halogen (X) may be -Cl, -Br, or -I, and the entire organic magnesium halide reacts with ketones to yield an alcohol.

The general equation for the reaction is

$$-\underset{\underset{O}{\|}}{C}- + RMgX \longrightarrow -\overset{|}{\underset{\underset{\bar{O}\overset{+}{M}gX}{|}}{C}}-R \xrightarrow{H_2O} -\overset{|}{\underset{\underset{OH}{|}}{C}}-R$$

When the Grignard reagent is added to the carbonyl group, the double bond is broken and the intermediate is the magnesium salt of the weakly acidic alcohol and is easily converted into the alcohol itself by the addition of the stronger acid, water. Sometimes a diluted solution of H_2SO_4 or HCl is used instead of water.

With these concepts and by use of the general equation, problems (a) and (b) can be solved.

$$\text{(a)}\quad \underset{\text{acetone}}{CH_3\overset{\overset{O}{\|}}{C}CH_3} + CH_3MgBr \longrightarrow CH_3\overset{\overset{\bar{O}\overset{+}{M}gBr}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3 \xrightarrow{H_2O} CH_3\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3$$

2-methyl-2-propanol

$$\text{(b)}\quad \underset{\text{2-hexanone}}{CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}CH_3} + CH_3MgBr \longrightarrow CH_3CH_2CH_2CH_2\overset{\overset{\bar{O}\overset{+}{M}gBr}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_3$$

$$CH_3CH_2CH_2CH_2\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3 \xleftarrow{H_2O}$$

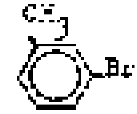
2-methyl-2-hexanol

• PROBLEM 13-11

Synthesize a ketone from each of the following precursors using the reaction of acid chloride with organocadmium compounds.

(a) $CH_3CH_2CH_2CH_2MgBr$

Butyl Magnesium Bromide

(b) 

m-Bromotoluene

Solution: Grignard reagents react with dry cadmium chloride to yield the corresponding organocadmium compounds, which react with acid chlorides to yield ketones. To make this concept clearer, the general equation for the synthesis is:

$$2R'MgX + CdCl_2 \rightarrow R'_2Cd + 2\,MgXCl \qquad \underline{\text{Balanced}}$$

Grignard reagent

$$R'_2Cd \xrightarrow{2RCCl\,(\text{C}=\text{O})} 2R-\overset{\text{O}}{\overset{\|}{C}}-R' + CdCl_2$$

ketone

In this type of synthesis R' must be either aryl or primary alkyl.

Only organocadmium compounds containing aryl or primary alkyl groups are stable enough for use. Inspite of this limitation, the method is one of the most valuable for the synthesis of ketones.

In this ketone synthesis, (1) the Grignard reagent reacts with cadmium chloride to yield an organocadmium compound, plus a magnesium dihalide. (2) The organocadmium is then reacted with an acid chloride to yield a ketone plus cadmium chloride.

Solving problems (a) and (b) to yield a ketone:

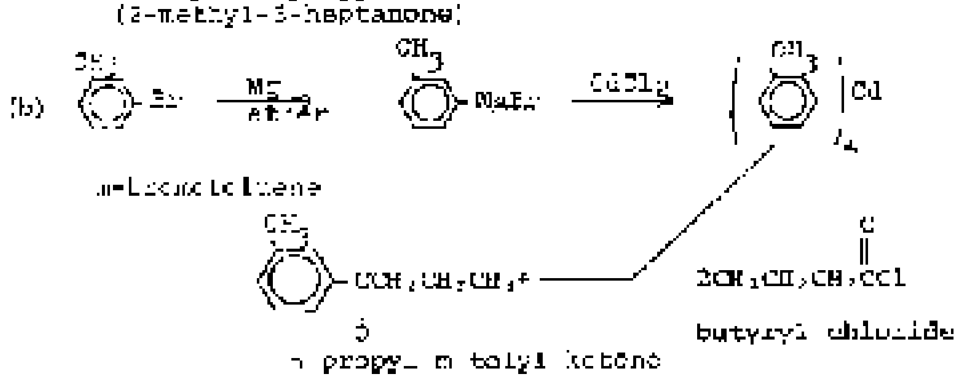
(a) $2CH_3CH_2CH_2CH_2MgBr \xrightarrow{CdCl_2} (CH_3CH_2CH_2CH_2)_2Cd + 2MgBrCl$

butyl magnesium bromide → Di-n-butylcadmium

$$(CH_3CH_2CH_2CH_2)_2Cd + 2CH_3\overset{CH_3}{\overset{|}{C}H}\overset{\text{O}}{\overset{\|}{C}}Cl \rightarrow 2\,CH_3CH_2CH_2CH_2\overset{\text{O}}{\overset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}CH_3$$

Isobutyryl chloride

n-butyl isopropyl ketone
(2-methyl-3-heptanone)



• PROBLEM 15-12

Propose a synthesis for n-butane from n-butylbromide using the Grignard Reaction.

Solution: The Grignard reaction is a common method for synthesizing alkanes from alkyl halides. The general equations for this reaction are as follows:

$$\text{(i)} \qquad R - X \xrightarrow{Mg} RMgX$$

$$\text{(ii)} \qquad RMgX \xrightarrow{HX/H_2O} R - H + MgX_2$$

The Grignard reagent (RMgX) is formed by treating n-butylbromide with clean magnesium in dry ether.

$$\text{(iii)} \quad CH_3(CH_2)_2CH_2Br + Mg \xrightarrow[\text{ether}]{\text{dry}} CH_3(CH_2)_2CH_2MgBr$$

The desired product, n-butane, can then be synthesized by adding HBr and H_2O to the Grignard reagent.

$$\text{(iv)} \quad CH_3(CH_2)_2CH_2MgBr \xrightarrow[H_2O]{HBr} \underset{\text{n butane}}{CH_3(CH_2)_2CH_3} + MgBr_2$$

The intermediate reaction of reaction (iv) is

$$\text{(v)} \quad CH_3(CH_2)_2CH_2MgBr + HOH \rightarrow CH_3(CH_2)_2CH_3 + MgBrOH$$

The bromide ion created by the dissociation of HBr then displaces the OH^- group from MgBrOH to form $MgBr_2$ and water is reformed.

• PROBLEM 15-13

Write structures for the products of the following reactions involving Grignard reagents. Show the structures of both the intermediate substances and the substances obtained after hydrolysis with dilute acid. Unless otherwise specified, assume that sufficient Grignard reagent is used to cause those reactions to go to completion which occur readily at room temperatures.

(a) $C_2H_5MgBr + C_6H_5CHO$

(b) $CH_3MgI + CH_3CH_2CO_2C_2H_5$

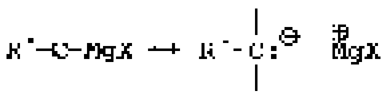
(c) $(CH_3)_3CMgCl + CO_2$

(d) $CH_3CH_2MgBr + ClCO_2C_2H_5$

(e) $CH_3MgI + CH_3COCH_2CH_2CO_2C_2H_5$ (1 mole) (1 mole)

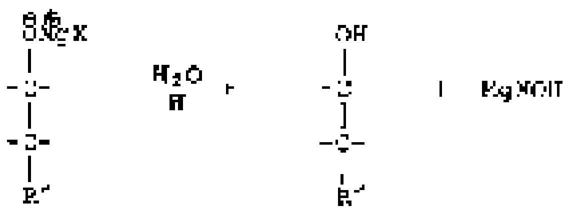
(f) $C_6H_5MgBr + CH_3C{-}\overset{O}{\overset{\|}{C}}{-}CCH_3$

Solution: Grignard reagents are organomagnesium compounds of the general formula R-Mg-X (X is a halogen). The Grignard reagent has two major resonance structures:



In the presence of carbonyl compounds (compounds that have a $-\overset{O}{\overset{\|}{C}}-$ in the molecule), Grignard reagents react to form an alcohol containing a side chain derived from the Grignard. The electron rich Grignard carbon attacks the electron deficient carbonyl carbon (due to oxygen's great electronegativity). The general reaction is written as:

Subsequent acid catalyzed hydrolysis of this intermediate will yield the alcohol:



Note: If the carbonyl carbon has a potential leaving group, the group leaves to form another carbonyl compound; this is subject to further attack by the Grignard. The intermediates and hydrolysis products of reactions (a) through (f) are shown below.

(a) In this reaction there are no potential leaving groups and an alcohol (ROH) will be formed upon hydrolysis of the Grignard salt:

$$C_6H_5MgBr + C_6H_5CHO \rightarrow \underset{\overset{|}{\overset{\ominus}{O}}\overset{\oplus}{MgBr}}{C_6H_5\,CH} - C_6H_5 \xrightarrow[H^+]{H_2O} (C_6H_5)_2CHOH$$

Intermediate (Grignard salt) final product (alcohol)

(b) The ethoxy group ($-OCH_2CH_3$) of the ester ($RCOOR'$) is a potential leaving group. When the Grignard reagent reacts with the ester, the ethoxy group leaves once the Grignard salt is formed. This produces a ketone $\left[R\overset{O}{\overset{\|}{C}}R'\right]$, which will further react with the Grignard reagent. Hydrolysis will lead to a tertiary alcohol.

$$CH_3MgI + CH_3CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \rightarrow CH_3CH_2-\underset{CH_3}{\overset{\overset{\ominus}{O}\overset{\oplus}{Mg}I}{C}}-OCH_2CH_3 \rightarrow CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3$$

intermediate (Grignard salt) intermediate (Ketone)

$$\xrightarrow{CH_3MgI} CH_3CH_2\underset{CH_3}{\overset{\overset{\ominus\ \oplus}{OMgI}}{C}}-CH_3 \xrightarrow[H^+]{H_2O} CH_3CH_2-\overset{OH}{C}(CH_3)_2$$

intermediate (Grignard salt) final product (tertiary alcohol)

(c) The carbon in CO_2 will be attacked by only one molecule of Grignard reagent; the remaining -C=O bond will not be disrupted by any t-butyl Grignard reagents because the subsequent carboxylate anion is inert to further nucleophilic attack.

The intermediate carboxylate salt will be hydrolyzed to a carboxylic acid (RCO_2H):

$$(CH_3)_3CMgCl + CO_2 \rightarrow (CH_3)_3C-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{O}\overset{\oplus}{Mg}Cl \xrightarrow[H^+]{H_2O} (CH_3)_3C-\overset{O}{\overset{|}{C}}-OH$$

intermediate final product (carboxylic acid)

(d) In this reaction there are two potential leaving groups, the ethoxy group ($-OCH_2CH_3$) and the chloro group (-Cl). When the Grignard reagent attacks the carbonyl carbon, the ethoxy group will leave first and not the chloro group; this is because the resulting ethoxide ion is more stable than the chloride ion. Another molecule of Grignard reagent will now react with the acyl chloride $\left[R-\overset{O}{\overset{\|}{C}}-Cl\right]$, and the chloride will leave. A third molecule of Grignard reagent will react with the ketone. Hydrolysis will yield a tertiary alcohol:

$$CH_3CH_2MgBr + Cl-\underset{O}{\overset{}{C}}-OCH_2CH_3 \rightarrow CH_3CH_2-\underset{\overset{\ominus}{O}\overset{\oplus}{Mg}Br}{\overset{Cl}{C}}-OCH_2CH_3 \rightarrow$$

intermediate (Grignard salt)

$$CH_3CH_2-\overset{O}{\overset{\|}{C}}-Cl + CH_3CH_2MgBr \rightarrow CH_3CH_2-\underset{O^{\ominus}MgBr^{\oplus}}{\overset{Cl}{C}}-CH_2CH_3 \longrightarrow$$

intermediate (acyl chloride)

intermediate (Grignard salt)

$$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 + CH_3CH_2MgBr \rightarrow CH_3CH_2-\underset{O^{\ominus}MgBr^{\oplus}}{\overset{CH_2CH_3}{C}}-CH_2CH_3 \xrightarrow[H^+]{H_2O}$$

intermediate (ketone)

intermediate (Grignard salt)

$$(CH_3CH_2)_3C-OH$$

final product (tertiary alcohol)

(e) Since the Grignard reagent is restricted to attacking only one of the two carbonyl groups (since we are reacting one mole of Grignard with one mole of γ ketoester), the Grignard reagent will selectively attack the keto carbon and not the ester carbon. This is because the keto carbon has a greater partial positive charge than the ester carbon. This is due to the fact that the ester portion undergoes electron delocalization (which spreads about the partial charges of the atoms involved) whereas the keto portion cannot. Hence, the nucleophilic Grignard reagent attacks the more positive keto carbon. Hydrolysis will yield the alcohol.

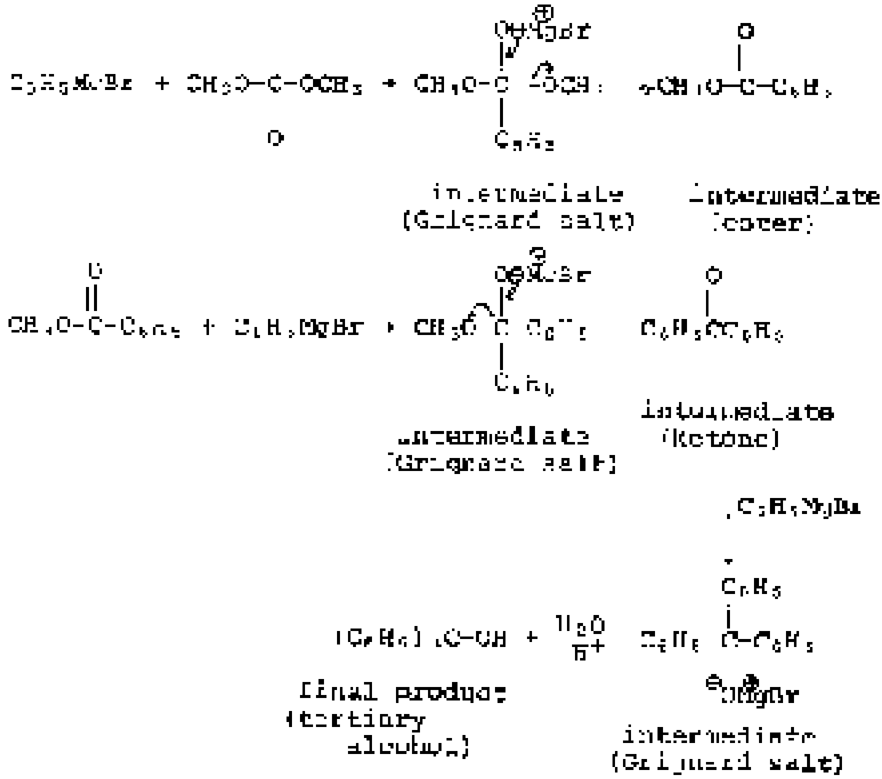
$$CH_3MgI + CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \rightarrow CH_3\underset{O^{\ominus}MgI^{\oplus}}{\overset{CH_3}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[H^+]{H_2O}$$

intermediate (Grignard salt)

$$CH_3\underset{OH}{\overset{CH_3}{C}}-CH_2CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

final product (tertiary alcohol)

(f) Here there are two potential leaving groups of identical structure: $-OCH_3$. When the Grignard reagent attacks the carbonyl carbon, a methoxy group will leave. The carbonyl carbon will again be attacked by another molecule of Grignard reagent and the other methoxy group will leave. This ketone will be attacked by yet another molecule of Grignard reagent. Subsequent hydrolysis will yield a tertiary alcohol.



ORGANOLITHIUM COMPOUNDS

• PROBLEM 15-14

The following experimental observations have been reported:

1. t-Butyl chloride was added to lithium metal in dry ether at 35°. A vigorous reaction ensued with evolution of hydrocarbon gases. After all the lithium metal was consumed, the mixture was poured onto Dry Ice. The only acidic product which could be isolated (small yield) was 4,4-dimethylpentanoic acid.

2. t-Butyl chloride was added to lithium metal in dry ether at −40°. After all the lithium had reacted, the mixture was carbonated and gave a good yield of trimethylacetic acid.

3. t-Butyl chloride was added to lithium metal in dry ether at −40°. After all the lithium was gone, ethylene was bubbled through the mixture at −40° until no further reaction occurred. Carbonation of this mixture gave a good yield of 4,4-dimethylpentanoic acid.

   a. Give a reasonably detailed analysis of the results obtained and show as best you can the mechanisms involved in each reaction.

   b. Would similar behavior be expected with methyl chloride? Explain

c. Would you expect that any substantial amount of 5,5-dimethylheptanoic acid would be found in (3) (above)? Explain.

Solution: Of all the organometallic compounds only organosodium and organolithium compounds will react with ether and have a high reactivity toward alkyl halides. Organolithium compounds react slowly with ether and the reaction can therefore be controlled by varying the temperature.

(a) In part (1) there are a number of reactions that occur. Lithium metal reacts with t-butyl chloride to produce the organolithium compound, t-butyllithium. At 35° this tertiary organolithium compound reacts with ether (the solvent for the reaction) at an appreciable rate by abstracting a methyl hydrogen from the solvent. The hydrocarbon, 2-methylpropane, is emitted as a gas. t-Butyllithium reacts with ethylene to produce 3,3-dimethylbutyllithium in low yield. When this is reacted with Dry Ice (solid CO_2) and worked up with H_2O, the product formed is 4,4-dimethylpentanoic acid. The reaction sequence and its mechanisms are shown as:

$$(CH_3)_3CCl + 2\,Li \xrightarrow[35^\circ]{\text{ether}} (CH_3)_3CLi + LiCl$$

$$(CH_3)_3\overset{-}{C}:\overset{+}{Li} + H\!-\!CH_2CH_2OCH_2CH_3 \rightarrow (CH_3)_3CH + CH_2{=}CH_2 + CH_3CH_2\overset{-}{O}\overset{+}{Li}$$

$$(CH_3)_3\overset{-}{C}:\overset{+}{Li} + CH_2{=}CH_2 \rightarrow (CH_3)_3C\!-\!CH_2CH_2\!-\!Li$$

$$(CH_3)_3C\,CH_2\overset{-}{C}H_2:\overset{+}{Li} + O{=}C{=}O \rightarrow (CH_3)_3C\!-\!CH_2CH_2\!-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-\!\overset{-}{O}\overset{+}{Li} \xrightarrow{H_3O^+}$$

$$(CH_3)_3C\!-\!CH_2CH_2\!-\!\overset{\overset{\displaystyle O}{\|}}{C}OH$$

4,4-dimethylpentanoic acid

In part (2), the reaction was conducted at -40°. At this low temperature, organolithium compounds will not react with ether at an appreciable rate. Hence the initial product is t-butyllithium. Carbonation of this will yield trimethylacetic acid.

$$(CH_3)_3CCl + 2\,Li \xrightarrow[-40^\circ]{\text{ether}} (CH_3)_3C\!-\!Li + LiCl$$

$$(CH_3)_3\overset{-}{C}:\overset{+}{Li} + O{=}C{=}O \rightarrow (CH_3)_3C\!-\!\overset{\overset{\displaystyle O}{\|}}{C}\!-\!\overset{-}{O}\overset{+}{Li} \xrightarrow{H_3O^+} (CH_3)_3C\!-\!\overset{\overset{\displaystyle O}{\|}}{C}OH$$

trimethylacetic acid

In part (1) t-butyllithium is first produced. It is reacted with ethylene and subsequently carbonated to yield 4,4 dimethylpentanoic acid.

$$(CH_3)_3CCl + 2\ Li \xrightarrow[-40°]{ether} (CH_3)_3C\text{-}Li + \overset{+}{Li}\ \overset{-}{Cl}$$

$$(CH_3)_3\overset{-}{C}:\ \overset{+}{Li} + CH_2\text{=}CH_2 \rightarrow (CH_3)_3C\text{-}CH_2\text{-}CH_2\text{-}Li$$

$$(CH_3)_3C\text{-}CH_2\overset{-}{C}H_2:\ \overset{+}{Li} + O\text{=}C\text{=}O \rightarrow (CH_3)_3C\text{-}CH_2CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{-}{O}\overset{+}{Li} \xrightarrow{H_2O}$$

$$(CH_3)_3C\ CH_2CH_2\text{-}\overset{O}{\overset{\|}{C}}OH$$

4,4-dimethylpentanoic acid

(b) If methyl chloride were used in part (1) instead of t-butylchloride, the organolithium compound (methyl lithium) would be formed. Methyl lithium, however, will not react with ether at 35°. The reason why tertiary organolithium compounds will react with ether whereas primary ones will not is because of the greater basicity of the former. Tertiary organolithium compounds are more basic and will be able to remove an ethereal hydrogen. The greater basicity stems from the fact that tertiary carbanions are less stable, hence more reactive, than primary carbanions. Had methyl chloride been used, the main product of part (1) would have been acetic acid.

In part (2) methyl lithium would be formed. Like t-butyllithium, methyl lithium would become carbonated. The product would be acetic acid.

In part (3) methyl lithium will again be initially formed. Unlike t-butyllithium however, methyl lithium will not react with ethylene. This is because methyl lithium is a primary organolithium compound and is less prone to attack ethylene. The product of part (3) would be acetic acid.

(c) Neohexyllithium is a primary organolithium compound and is thus much less prone to attacking ethylene than t-butyllithium. Hence, no substantial amount of 6,6-dimethylheptanoic acid will be formed in part (3).

REFORMATZKY REACTIONS

• PROBLEM 1--15

Give structures of compounds A, B and C: ethyl oxalate + ethyl acetate + sodium ethoxide, then H^+ → A($C_8H_{12}O_5$)
A + ethyl bromoacetate + Zn, then H_2O → B($C_{12}H_{20}O_7$)
B + OH^- + heat, then H^+ → C($C_6H_8O_7$), citric acid.

Solution: When two different esters (one having an α-hydrogen and the other lacking α-hydrogen) are reacted in the presence of a base such as an alkoxide salt ($M^+ {}^-OR$), a crossed Claisen condensation reaction will take place. An ester has the general formula $R-\overset{\overset{O}{\|}}{C}-OR'$. Both ethyl oxalate and ethyl acetate are esters. In basic solution ethyl acetate will lose its α-hydrogen to form a resonance stabilized enolate anion.

$$\underset{\text{ethyl acetate}}{CH_3\overset{\overset{O}{\|}}{C}OCH_2CH_3} + \underset{\text{sodium ethoxide}}{Na^+ {}^-OCH_2CH_3} \rightarrow \underset{\text{enolate anion}}{{}^-CH_2\overset{\overset{O}{\|}}{C}OCH_2CH_3 \leftrightarrow CH_2=\overset{\overset{O^-}{|}}{C}OCH_2CH_3}$$

The enolate anion will attack the partially positively charged carbonyl carbon (due to oxygen's great electronegativity: $-\overset{\overset{\delta- O}{|}}{\underset{\delta+}{C}}-$) of ethyl oxalate. Subsequent treatment with acid will yield compound A ($C_8H_{12}O_5$).

$${}^-CH_2-\overset{\overset{O}{\|}}{C}-OCH_2CH_3 + \underset{\text{ethyl oxalate}}{CH_3CH_2O-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OCH_2CH_3} \rightarrow$$

$$CH_3CH_2O-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OCH_2CH_3 + CH_3CH_2OH$$

$$\downarrow H^+$$

$$\underset{\text{compound A}}{CH_3CH_2O\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OCH_2CH_3}$$

When an α-haloester $\left[R-\overset{\overset{X}{|}}{C}H-\overset{\overset{O}{\|}}{C}OR'\right]$ is in the presence of zinc, an organozinc compound known as a Reformatsky reagent is formed:

$$R-\overset{\overset{X}{|}}{C}H-\overset{\overset{O}{\|}}{C}OR' \xrightarrow{Zn} \underset{\text{Reformatsky reagent}}{R-\underset{\underset{ZnX}{|}}{C}H-\overset{\overset{O}{\|}}{C}OR'}$$

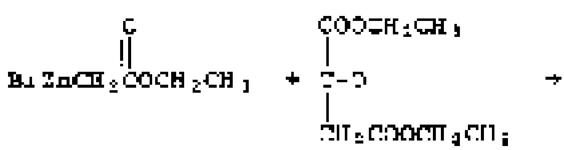
Reformatsky reagents react with aldehydes $\left(R-\overset{O}{\overset{\|}{C}}-H\right)$ and ketones $\left(R-\overset{O}{\overset{\|}{C}}-R'\right)$ to form β-hydroxy esters $\left(R''-\overset{OH}{\overset{|}{CH}}-\underset{|}{\overset{|}{C}}-\overset{O}{\overset{\|}{C}}OR'\right)$

after subsequent hydrolysis. Compound A is a polyfunctional compound and can be viewed as a ketone. When ethyl bromoacetate is in the presence of zinc, the Reformatsky reagent will be formed; it will react with compound A to produce a β-hydroxyester derivative.

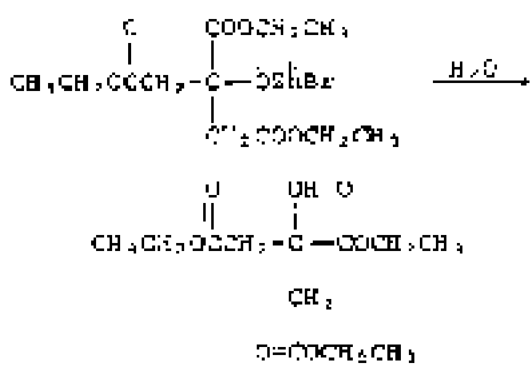
$$Br-CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow{Zn} BrZnCH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3$$

ethyl bromo acetate — Reformatsky reagent

Reformatsky reagents (and organozinc compounds in general) are less reactive than organomagnesium compounds. As a result Reformatsky reagents will not add to esters.



compound A



compound B $(C_{12}H_{20}O_7)$

Compound B has three ester functionalities $\left(-\overset{O}{\overset{\|}{C}}OR\right)$ and one alcohol functionality $\left(-\overset{|}{\underset{|}{C}}-OH\right)$. Esters will undergo base catalyzed hydrolysis to yield the corresponding carboxylic acids (R-COOH).

$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow[H_2O]{^-OH} R-\overset{O}{\overset{\|}{C}}-OH + R'OH$$

ester   carboxylic acid   alcohol

The carboxylic acid will lose a proton in basic solution:

$$R-\overset{O}{\overset{\|}{C}}OH + {}^-OH \rightarrow H_2O + R-\overset{O}{\overset{\|}{C}}-O^-$$

carboxylate ion

Alcohols also become deprotonated in basic solution:

$$R'OH + {}^-OH \rightarrow H_2O + RO^-$$

alkoxide ion

Subsequent acidification will replace all lost protons. Compound B reacts with ^-OH and heat, then with H^+ in the following manner:

$$HO-\underset{CH_2COOCH_2CH_3}{\overset{COOCH_2CH_3}{C}}-CH_2COOCH_2CH_3 \xrightarrow[H_2O]{^-OH} \xrightarrow{H^+}$$

compound B

$$HO-\underset{CH_2COOH}{\overset{COOH}{C}}-CH_2COOH + 3\ CH_3CH_2OH$$

compound C ($C_6H_8O_7$)

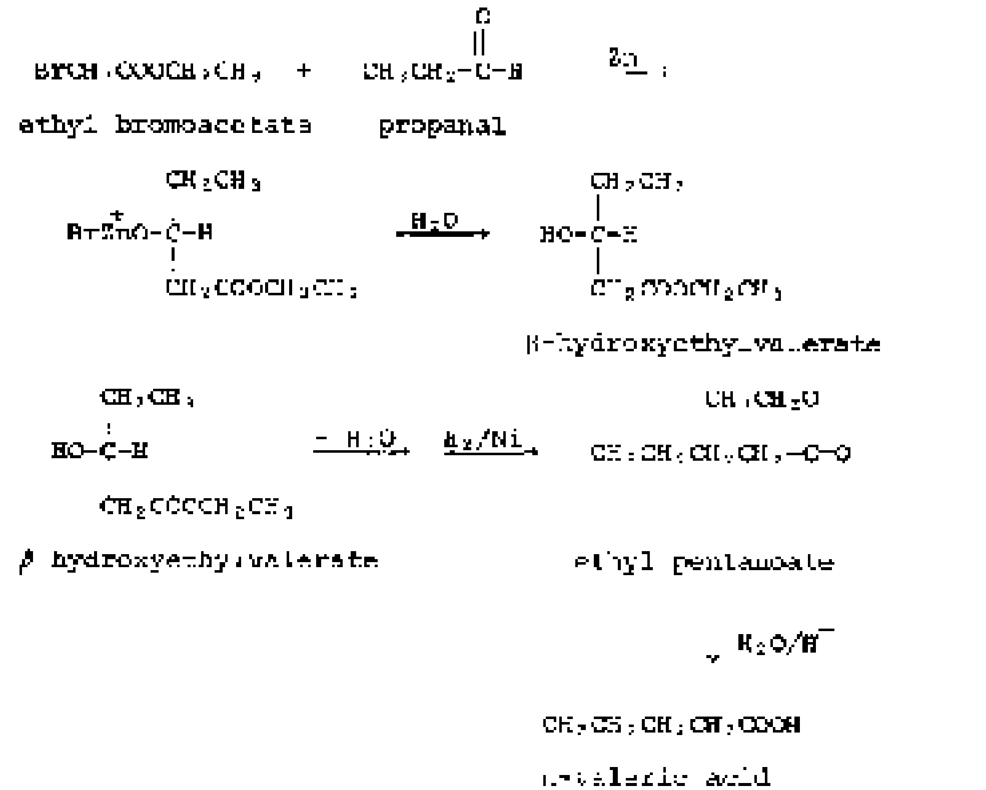
Citric acid

• PROBLEM 13-16

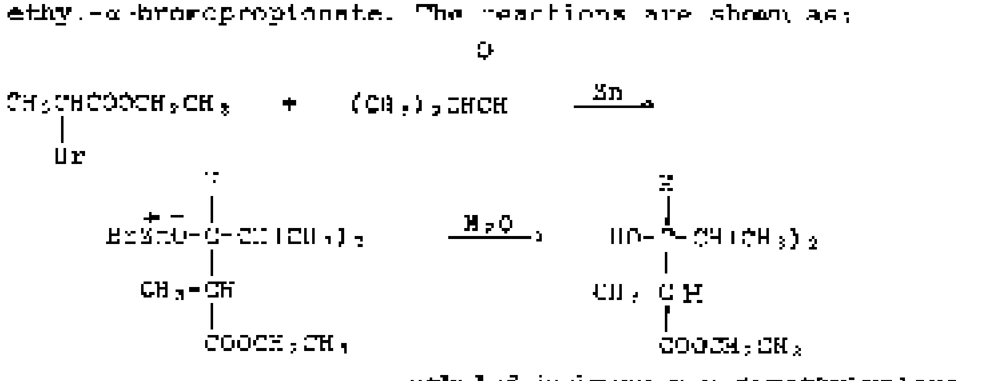
Outline the synthesis of the following acids via the Reformatsky reaction:

(a) n-valeric acid; (b) α,γ-dimethylvaleric acid; (c) cinnamic acid.

Solution: (a) n-Valeric acid has the structure: $CH_3CH_2CH_2CH_2COOH$. The Reformatsky reaction is one that occurs between an organozinc compound derived from an α-haloester and an aldehyde or ketone to form a β hydroxyester. By working backwards, we can devise a method of preparing n-valeric acid by using the Reformatsky reaction. n-Valeric acid can be gotten by the acid catalyzed hydrolysis of ethyl pentanoate, an ester of n-valeric acid. A β-hydroxy-ester of n-valeric acid is β-hydroxyethylvalerate. This can be dehydrated and subsequently hydrogenated to give ethyl-pentanoate. β-hydroxyethylvalerate can be prepared by the Reformatsky reaction between ethyl bromoacetate and propanal. Hence the synthesis of n-valeric acid can be shown as:



(b) α,γ-dimethylvaleric acid has the structure: $\underset{CH_3}{CH_3CH}CH_2\underset{CH_3}{CH}COOH$. Like n-valeric acid, this compound can be synthesized by the sequence: Reformatsky reaction, dehydration, catalytic hydrogenation and hydrolysis. Here the Reformatsky reaction is between 2-methylpropanal and ethyl-α-bromopropionate. The reactions are shown as:



$\downarrow -H_2O$

$\downarrow H_2/Ni$

$(CH_3)_2CHCH_2CHCOOCH_2CH_3$
$\qquad\qquad\quad |$
$\qquad\qquad CH_3$

ethyl-α,γ-dimethylvalerate

$\downarrow H_2O/H^+$

$CH_3CHCH_2CHCOOH$
$\quad | \qquad\quad |$
$\quad CH_3 \quad CH_3$

α,γ-dimethylvaleric acid

(c) Cinnamic acid has the structure $C_6H_5CH=CHCOOH$. By the same reasoning in part (a), we should look for reactants that, in a Reformatsky reaction, would form a β-hydroxyester of 3-phenylpropanoic acid ($C_6H_5CH_2CH_2COOH$). Ethyl-β-hydroxy-β-phenylpropionate is produced by the Reformatsky reaction between ethylbromoacetate and benzaldehyde. As in part (a), and (b), the β-hydroxyester will lose water to form the alkene. Unlike part (a) and (b), however, we will not perform a catalytic hydrogenation because we want to retain the carbon-carbon double bond. Subsequent acid catalysed hydrolysis of the ester will lead to the desired product. The reactions are shown as:

$C_6H_5\overset{O}{\overset{\|}{C}}-H \quad + \quad BrCH_2COOCH_2CH_3 \xrightarrow{Zn}$

$BrZnO-\overset{H}{\overset{|}{C}}-C_6H_5 \xrightarrow{H_2O}$
$\qquad\qquad |$
$\qquad\qquad CH_2COOCH_2CH_3$

$HO-\overset{H}{\overset{|}{C}}-C_6H_5$
$\qquad\ |$
$\qquad\ CH_2COOCH_2CH_3$

ethyl-β-hydroxy-β-phenyl-propionate

$\downarrow -H_2O$

$C_6H_5-CH=CHCOOCH_2CH_3 \xrightarrow{H_2O/H^+}$

$C_6H_5-CH=CH-COOH$

cinnamic acid

CHAPTER 16

ALCOHOLS

NOMENCLATURE AND STRUCTURE

• PROBLEM 16-1

What are alcohols and how are they classified?

Solution: Alcohols are hydrocarbon derivatives in which one or more hydrogen atoms have been replaced by the OH (hydroxyl) group. There are many different alcohols, which are either natural or synthetic derivatives of other hydrocarbons. To be more specific, there are:

I. Monohydroxy Alcohols
  A. Primary
  B. Secondary
  C. Tertiary

II. Dihydroxy Alcohols

III. Trihydroxy Alcohols

IV. Polyhydroxy Alcohols

The monohydroxy alcohols are represented by the general formula R-OH or $C_nH_{2n+1}OH$.

Specific examples of each are:

Primary $CH_3CH_2CH_2CH_2OH$ 1-Butanol (butyl alcohol)

Secondary $\underset{\displaystyle OH}{CH_3CH_2CH\text{-}CH_3}$ 2-Butanol (sec-butyl alcohol)

Tertiary $CH_3\text{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}\text{-}CH_3$ 2-methyl-2-propanol (tert-butyl alcohol)

Dihydroxy and trihydroxy alcohols have two and three hydroxyl groups, respectively, on their hydrocarbon molecule. For example:

(a) $\underset{\displaystyle OH}{\underset{|}{CH_2}}-\underset{\displaystyle OH}{\underset{|}{CH_2}}$ 1,2-ethanediol (ethylene glycol) "Dihydroxy Alcohol"

(b) $\begin{array}{l} CH_2-OH \\ | \\ CH-OH \\ | \\ CH_2-OH \end{array}$ 1,2,3-Propanetriol (glycerol) "Trihydroxy Alcohol"

These alcohols that contain more than one hydroxyl group may be represented by the general formula $C_nH_{2n+2-y}(OH)_y$, where y is two or more. The common polyhydroxy alcohols usually have one "OH" group on every carbon atom in the molecule.

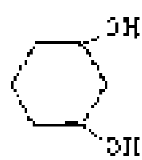
• PROBLEM 16-2

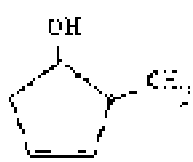
Name the following alcohols using the IUPAC system of nomenclature:

(a) $(CH_3)_2CHCH_2OH$

(b) $CH_2 = CHCH_2\overset{\displaystyle OH}{\overset{|}{C}}H-CH_3$

(c) $CH_3\underset{\displaystyle \overset{\displaystyle CH_2}{|}\atop \displaystyle CH_3}{\underset{|}{C}}H-\underset{\displaystyle CH_3}{\underset{|}{C}}H-\overset{\displaystyle Cl}{C}H-\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH$

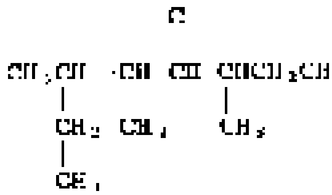
(d) 

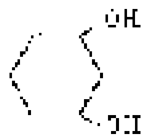
(e) 

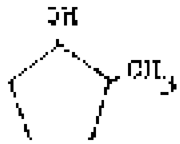
Solution: An alcohol is named as a derivative of the longest continuous carbon chain containing the –OH group. The chain is numbered so as to give the hydroxyl group the lowest number, and the positions of substituents are indicated by number. The -ol ending is used to designate an –OH group. For cyclic compounds, the same rules hold true; thus the first carbon number in the ring is the one which possesses the hydroxyl functional group. With these rules in mind, the alcohol compounds can be named.

(a) $(CH_3)_2CHCH_2OH$ 2-methyl-1-propanol

(b) $CH_2 = CHCH_2\overset{\displaystyle OH}{\overset{|}{C}}H-CH_3$ 4-penten-2-ol

(c)  3-chloro-2,4,5-trimethyl-1-heptanol

(d)  1,3-cyclohexanediol

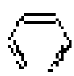
(e)  2-methyl-3-cyclopenten-1-ol

• PROBLEM 16-3

Give each of the following structures IUPAC names:

(a) $(CH_3)_2CHOH$; (b) $(CH_3)_3C-CHOH-CH_3$;

(c) $CH_3CH_2CHOHCH_3$; (d) $CH_3-CH_2COH(CH_3)_2$;

(e) $-CH_2-CH_2-OH$; (f) $Cl-CH_2-CH_2-CH_2-OH$.

Solution: The hydroxyl group -OH is a frequently occurring functional group, both in naturally occurring and in synthetic compounds. When an organic molecule consists of an alkyl group bonded to a hydroxyl group, the compound is called an alcohol.

Complicated alcohols are usually named systematically by the IUPAC system. In the IUPAC system the parent compound name is found by dropping the alkane ending "e" and adding the suffix "ol". In long chain alcohols the position of the hydroxyl group is specified by the appropriate number, just as is done with alkenes.

As an example of the IUPAC system of naming alcohols, the following alcohol (figure A) will be named systematically:

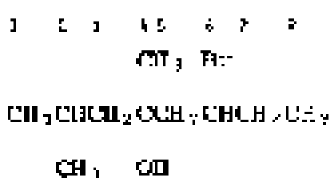


Figure A.

1. The longest chain containing the hydroxyl group has eight carbons; the compound is an octanol.

2. The chain is numbered from either side so that the hydroxyl group is on the lowest possible number; the hydroxyl group is on the 4 position and the parent name is 4 octanol.

3. Substituents are given the number of the carbon to which they are attached; the substituents are 2,4 dimethyl and 6-bromo.

4. Listing the substituents alphabetically, the correct name of the compound is 6-bromo-2,4-dimethyl-4-octanol.

To name the given compounds, first draw the structure of each and then name the compound using the IUPAC system.

(a) $(CH_3)_2CHOH$ is shown in figure B.

```
1 2  3
C-C -C
  |
  OH
```

figure B.

This structure has been drawn without the accompanying hydrogen atoms, however, the name of the compound will not be in any way affected by their deletion. This compound has a three carbon parent chain and the -OH group on the second carbon; thus, the name of this compound is 2-propanol.

(b) $(CH_3)_3C-CHOH-CH_3$ is shown in figure C.

```
  C
  |
C-C-C -C

  C OH
```

figure C.

This compound has a four carbon parent chain with 2 methyl groups on carbon three and the -OH group on carbon 2; thus, the name of this compound is 3,3-dimethyl-2-butanol.

(c) $CH_3-CH_2-CHOH\ CH_3$ is shown in figure D.

```
C-C-C -C
    |
    OH
```

figure D.

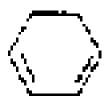
This compound has a four-carbon parent chain with the -OH group on carbon 2; thus, the name of this compound is 2-butanol.

(d) $CH_3-CH_2COH(CH_3)_2$ is shown in figure E.

```
      C
      |
C  C  C  C
      |
      OH
```

figure E.

This compound has a 4-carbon parent chain with the methyl and the OH groups on carbon 2; thus, the name of the compound is 2-methyl-2-butanol.

(e)  $-CH_2-CH_2-OH$ is shown in figure F.

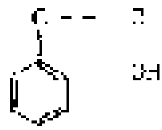


figure F.

This compound has a 2-carbon parent chain with the OH group on carbon 1 and the benzene ring on carbon 2; thus the name of this compound is 2-phenyl-1-ethanol.

(f) $Cl-CH_2-CH_2-CH_2-OH$ is shown in figure G.

```
C  C - C
|      |
Cl     OH
```

Figure G.

This compound has a 3-carbon parent chain with the OH group on carbon 1 and a chlorine atom on carbon 3; thus the name of this compound is 3-chloro-1-propanol.

PROBLEM 16-4

Explain how the following alcohols are named using the IUPAC system of nomenclature:

```
(a)  CH3CH2OH      (b)  CH3CH-CH3     (c)  CH3CH2CH CH-CH3
                            |                     |
                            OH                    CH CH
```

Solution: Alcohols like all other hydrocarbons have a common name, and an IUPAC name which is derived from its parent hydrocarbon chain, its functional groups and their positions. The IUPAC nomenclature for the alcohols replaces the final "-e" of the hydrocarbon name by "-ol" and prefixes a numeral to indicate the position of the hydroxyl group. When there are two or three hydroxyl (OH) groups on the chain, the suffixes di and tri respectively are added before the ol moiety.

(a) CH_3CH_2OH ethanol (ethyl alcohol)

```
(b)    Cl-CH2CHCH3     1-chloro-2-propanol
             |
             OH

(c)    CH3CH2CH CH-CH3  2,3-pentanediol
             |  |
             OH OH
```

PHYSICAL PROPERTIES

• PROBLEM 18-5

How do you account for the fact that, although ethyl ether has a much lower boiling point than n-butyl alcohol, it has the same solubility (8 g per 100 g) in water?

Solution: Examination of the structures of ethyl ether and n-butyl alcohol shows that they are isomers; they are different compounds with the same molecular formula ($C_4H_{10}O$).

$CH_3CH_2CH_2CH_2OH$ — *n*-butyl alcohol

$CH_3CH_2OCH_2CH_3$ — ethyl ether

A consideration of what factors influence boiling points and solubility will aid in the solution to this problem.

Associated liquids are ones whose molecules are held together by hydrogen bonds. It takes considerable energy to break these hydrogen bonds. Hence, the boiling point is raised by hydrogen bonding between like molecules of a compound. It can be seen from the structure of *n*-butyl alcohol, that the alcohol molecules can form hydrogen bonds to each other and to water molecules. The ether can form hydrogen bonds to only the water, however. The situation is depicted below:

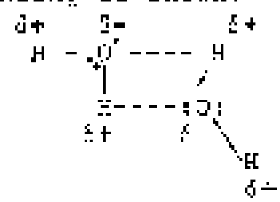
```
                           H
                          /
CH3CH2CH2CH2OH ··· O           ← H-bonding with water
                          \
                           H

                         H
                        /
CH3CH2CH2CH2O ··· OCH2CH2CH2CH3   ← H bonding to each
                                           other

CH3CH2OCH2CH3          ← H bonding with water only.
         :
         :
         H
          \
           O
           |
           H
```

This means the ether must have the lower boiling point. The boiling point is determined, in part, by the hydrogen bonding between (like) molecules, which the ether lacks. This also explains why the alcohol and ether have the same solubility. Solubility reflects and is increased by hydrogen bonding between solute molecules and solvent molecules. In this case, the solute is either the alcohol or ether and the solvent is water. As shown above, both the alcohol and ether may participate in hydrogen bonding with water equally well. Hence, they should possess the same solubility.

• PROBLEM 16-6

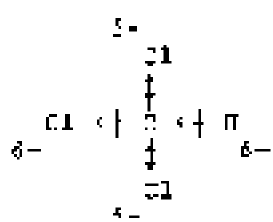
It has been suggested that there is a weak hydrogen bonding: (a) between chloroform molecules; (b) between HCN molecules. How would you account for this?

Solution: Hydrogen bonding generally occurs between an electronegative atom and a hydrogen bonded to another electronegative atom (usually N or O). Hydrogen bonding is actually the electrostatic attraction between the partially positively charged hydrogen and the partially negatively charged electronegative atom. For example, water undergoes hydrogen bonding as shown:

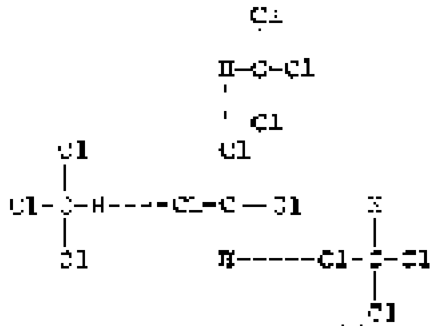


Note: Dotted lines indicate H-bonding.

(a) The inductive effect of the chlorine atoms in chloroform ($HCCl_3$) makes the molecule highly polar. The three electron withdrawing chlorine atoms makes the carbon and hydrogen atoms electron deficient. As a result, the chlorines have a partial negative charge and the carbon and hydrogen have a partial positive charge:



Because the molecule is highly polar, the hydrogen has enough of a positive charge to have a weak electrostatic attraction for the partially negatively charged chlorine of another chloroform molecule. Hence there is weak hydrogen bonding in chloroform. This can be shown as:



(b) The carbon atom of hydrogen cyanide (HCN) is sp-hybridized and this will make the hydrogen more electropositive than an sp^2 or sp^3 hybridized carbon. (Recall that sp-hybridized carbons are more electronegative than sp^2-hybridized carbons, which are more electronegative than sp^3 hybridized carbons.) This plus the fact that nitrogen is an electronegative atom will give hydrogen in HCN a partial positive charge $\left(\overset{\delta-}{N} \equiv C - \overset{\delta+}{H}\right)$. A combination of these two effects will be strong enough for the formation of hydrogen bonding between nitrogen and hydrogen.

The hydrogen bonds will be weak ones because the hydrogen in HCN is not as positively charged as it would have been, had it been bonded to an electronegative atom such as oxygen or nitrogen. The H bonding in HCN can be shown as:

PREPARATION

■ PROBLEM 16-7

What are the various methods of preparing alcohols?

Solution: There are many ways of preparing alcohols through organic reactions, although when one thinks of alcohol preparation, they immediately assume anaerobic sugar fermentation. As yet, it is not possible to introduce hydroxyl groups directly into alkanes, and all synthetic reactions of alcohols start from compounds containing reactive functional groups. The most common methods of preparing alcohols are as follows:

(1) Hydration of olefins in the presence of acid.

(2) Hydrolysis of alkyl halides by water or alkali.

(3) Hydrolysis of ethers in strongly acidic conditions.

(4) Hydrolysis of esters

(a) acid catalyzed hydrolysis
(b) alkaline hydrolysis (saponification)

(5) Reduction or catalytic hydrogenation of aldehydes, ketones, carboxylic acids, and esters.

Each of these methods will be explained in detail with many examples as the chapter progresses.

• PROBLEM 16-8

Predict the products of each precursor by the hydration of olefins method.

(a) $CH_3CH = CH_2$ (b) $CH_2 = CH_2$

Propylene Ethene

Solution: Olefins (alkenes) are readily converted into alcohols either by direct addition of water, or by addition of sulfuric acid followed by hydrolysis. The general reaction for this method of preparation is:

$$RCH = CHR + H_2SO_4 \rightarrow \underset{\displaystyle OSO_3H}{\underset{|}{RCH}}-CH_2R + H_2O \rightarrow \underset{\displaystyle OH}{\underset{|}{RCH}}-CH_2R$$

The addition of H_2SO_4 changes the alkene precursor into alkyl hydrogen sulfate, which is an intermediate in this reaction. This intermediate is hydrated with water which yields an alcohol. From this, the products of precursors (a) and (b) can be obtained by hydration in an acid medium.

$$\text{(a)}\quad CH_3-CH=CH_2 + H_2SO_4 \rightarrow \underset{\displaystyle OSO_3H}{CH_3\underset{|}{C}HCH_3} \xrightarrow{H_2O} \underset{\displaystyle OH}{CH_3\underset{|}{C}HCH_3}$$

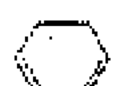
Propylene Isopropanol

$$\text{(b)}\quad CH_2=CH_2 + H_2SO_4 \rightarrow CH_3-CH_2OSO_3H \xrightarrow{H_2O} CH_3CH_2OH$$

Ethylene Ethanol (ethyl alcohol)

• PROBLEM 16-9

Show the product of each compound by hydrolysis of alkyl halides:

(a) $CH_3CH_2CH_2CH_2CH_2Br$ (b)  CH_2Cl

n-Bromopentane Benzyl chloride

Solution: This method of preparing an alcohol can be done by adding a concentrated aqueous alkali to the reactant and reflux the mixture. The alkali usually used is sodium hydroxide (NaOH) or potassium hydroxide (KOH) in which the OH group replaces the halogen on the molecule. The general reaction for this is:

$$\underset{\text{Alkyl Halide}}{RX} + KOH\ (\text{aqueous}) \rightarrow \underset{\text{Alkyl Alcohol}}{R-OH} + K^+X^-.$$

The R shows the alkyl functional group, and the X signifies the halogen (Br or Cl). With the above facts in mind, the products of the two precursors can be derived by hydrolysis.

(a) $$\underset{\text{n-Bromopentane}}{CH_3CH_2CH_2CH_2CH_2Br} \xrightarrow{NaOH\ (\text{aqueous})} \underset{\text{n-Pentanol}}{CH_3CH_2CH_2CH_2CH_2OH} + Na^+Br^-$$

(b) 

Benzyl chloride Benzyl alcohol

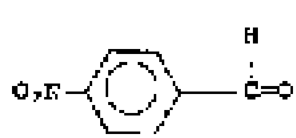
$+ K^+Cl^-$.

• PROBLEM 16-10

Derive an alcohol product from the following aldehyde precursors using any reagents and conditions necessary.

(a) $CH_3CH_2CH(CH_3)CH_2C(H){=}O$ (b) $CH_3C(H){=}O$

3-Methylpentanal Acetaldehyde

(c)  (d) $H-C(H){=}O$

p-Nitrobenzaldehyde Formaldehyde

Solution: Obtaining an alcohol from aldehydes involves aldehyde reduction or catalytic hydrogenation. Reduction involves the use of a strong reducing agent such as lithium aluminum hydride ($LiAlH_4$); alcohols are formed easily and in high yield. Another extremely useful reducing agent is sodium borohydride, $NaBH_4$, but this reagent is limited to the extent that it does not reduce compounds containing carbon-carbon double bonds. Both of these reagents must react in the presence of an acid, either HCl (hydrochloric acid), or acetic acid.

Another method for reducing aldehydes to alcohols is catalytic hydrogenation, which employs the use of hydrogen, and finely divided nickel, palladium, or platinum catalyst.

The general reactions for both of these processes are:

$$\underset{\text{O}}{\text{RC-H}} \begin{cases} \xrightarrow{H_2/\text{Pt, Pd or Ni}} \\ \xrightarrow{\text{LiAlH}_4/H_3O^+} \end{cases} RCH_2OH$$

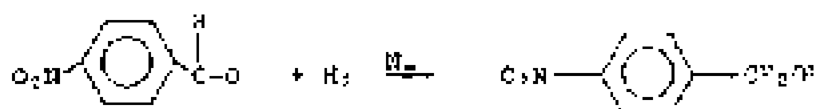
Using the above facts and the general equations, the alcohol products can be derived.

(a) $CH_3CH_2\underset{CH_3}{\underset{|}{C}}HCH_2\overset{H}{C}{=}O + LiAlH_4 \xrightarrow{H_3O^+} CH_3CH_2\underset{CH_3}{\underset{|}{C}}HCH_2CH_2OH$

3-methylpentanal $\qquad$ 3-methyl-1-pentanol

(b) $CH_3\overset{H}{\overset{|}{C}}{=}O + H_2 \xrightarrow{Pt} CH_3CH_2OH$

Acetaldehyde $\qquad$ Ethanol

(c) 

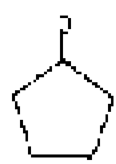
p-Nitrobenzaldehyde $\qquad$ p Nitrobenzyl alcohol

(d) $H-\overset{H}{C}{=}O + NaBH_4 \xrightarrow{H_3O^+} CH_3OH$

Formaldehyde $\qquad$ Methanol

■ PROBLEM 16-11

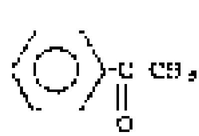
Prepare an alcohol from each ketone precursor using any condition and reagent necessary.

(a) 

Cyclopentanone

(b) $CH_3CH_2\overset{CH_3}{\overset{|}{C}}{=}O$

Methyl ethyl ketone
(2-Butanone)

(c) 

Acetophenone

(d) $CH_3CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$

2-Hexanone

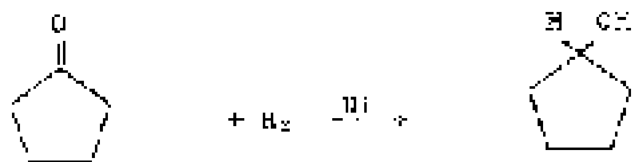
Solution: When preparing an alcohol from a ketone, essentially, the same reaction occurs as with aldehydes. The difference with ketones is that its carbonyl (C=O) moiety or functional group is usually between two groups (alkyl and/or aryl). The reagents used to convert a ketone to an alcohol is $LiAlH_4$ (lithium aluminum hydride), or $NaBH_4$ (sodium borohydride), and both must be used in acidic conditions. The acids used are hydrochloric acid or acetic acid.

Another way to produce an alcohol from a ketone is to reduce the ketone by catalytic hydrogenation. This method involves the use of hydrogen gas with a nickel (Ni), platinum (Pt), or palladium (Pd), catalyst.

The general equations for both methods are:

$$\gt C{=}O \xrightarrow[LiAlH_4,\ \text{or}\ NaBH_4;\ HCl]{H_2\ +\ Ni,\ Pt,\ \text{or}\ Pd} -\underset{\displaystyle H}{\underset{|}{C}}-OH$$

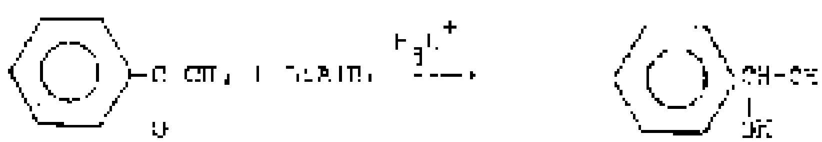
Knowing these facts along with the general equation, the alcohol products can be prepared.

(a) 

Cyclopentanone Cyclopentanol

(b) $$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}O + H_2 \xrightarrow{Pt} CH_3CH_2\overset{\displaystyle CH_3}{CHOH}$$

2-Butanone 2-Butanol

(c) 

Acetophenone α-Phenylethyl alcohol

(d) $$CH_3CH_2CH_2CH_2\overset{\displaystyle O}{C}CH_3 + H_2 \xrightarrow{Pd} CH_3CH_2CH_2CH_2\overset{\displaystyle OH}{\overset{|}{C}H}CH_3$$

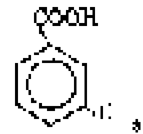
2-Hexanone 2-Hexanol

• PROBLEM 16-12

Prepare an alcohol from each carboxylic acid precursor given, using any condition and/or reagent necessary.

(a) $(CH_3)_3CCOOH$

Trimethylacetic acid

(b) 

m-Toluic acid

Solution: Lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that can reduce a carboxylic acid to an alcohol; the initial product is an alkoxide from which the alcohol is liberated by hydrolysis. The general reaction for this process:

$$4RCOOH + 3LiAlH_4 \rightarrow 4H_2 + 2LiAlO_2 + [(RCH_2O)_4Al]Li \xrightarrow{H_2O} 4RCH_2OH$$

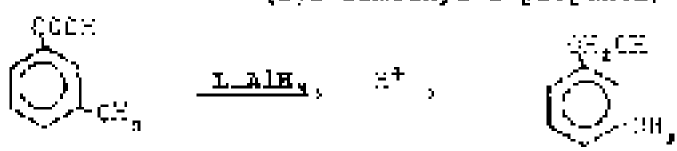
In this type of reaction, the intermediate, an alkyl oxide (alkoxide) is the major product. But as seen above lithium aluminum hydride is oxidized to $LiAlO_2$. The intermediate is then protonated through hydrolysis to yield an alcohol.

From these facts and the general equation the alcohol products of the given carboxylic acid can be prepared.

Trimethylacetic acid

(a) $4(CH_3)_3CCOOH + 3LiAlH_4 \rightarrow [(CH_3)_3CCH_2O]_4AlLi + 2LiAlO_2 + 4H_2 \xrightarrow{H^+} (CH_3)_3CCH_2OH$

Neopentyl alcohol
(2,2-dimethyl-1-propanol)

(b) 

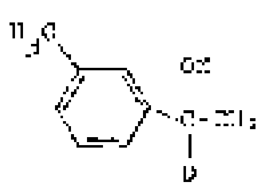
m-Toluic acid — m-Methylbenzyl alcohol

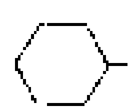
• PROBLEM 16-13

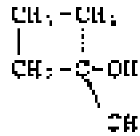
Suggest a Grignard reaction which will produce the following:

(a)
$$CH_3-\underset{CH_3}{\overset{OH}{C}}-CH_2CH_3$$

(b)
CH_2-CH_2
$CH_2-CH-CH_2OH$

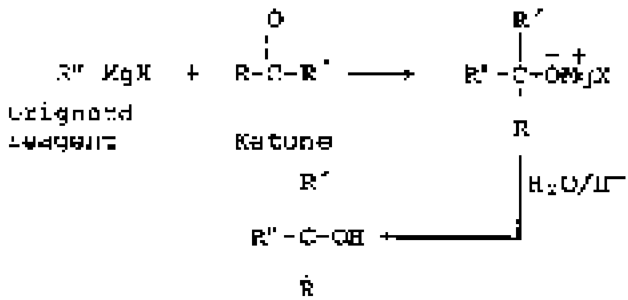
(d) 

(e) $HOCH_2$  $-CH_2OH$ (cis and trans)

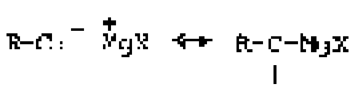
(e) 

(f) $(CH_3)_3CCHOHCH(CH_3)_2$.

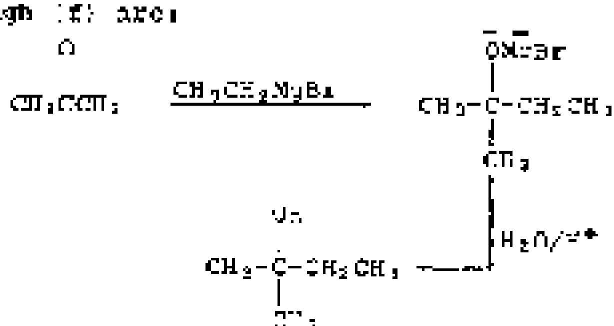
Solution: Grignard reagents (organomagnesium compounds of the general form R-Mg-X, X being a halogen) can react with ketones $\left(R-\overset{O}{\overset{\|}{C}}-R'\right)$ and aldehydes $\left(R-\overset{O}{\overset{\|}{C}}-H\right)$ to form a magnesium halide salt of an alcohol. Subsequent acid catalyzed hydrolysis produces an alcohol. The general reaction is:

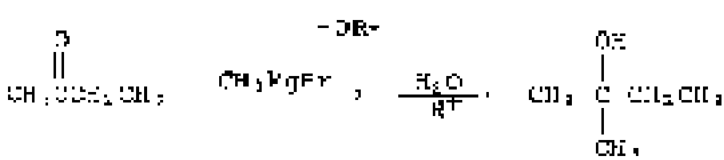


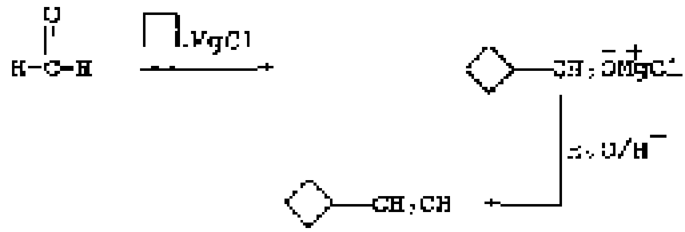
The Grignard reagent has two major resonance forms:

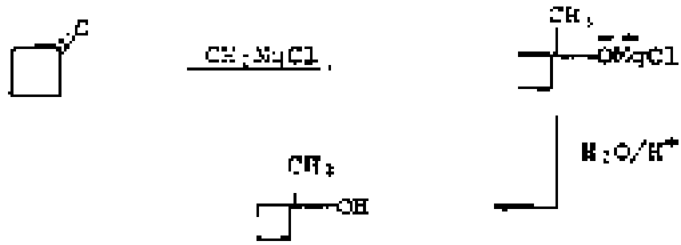


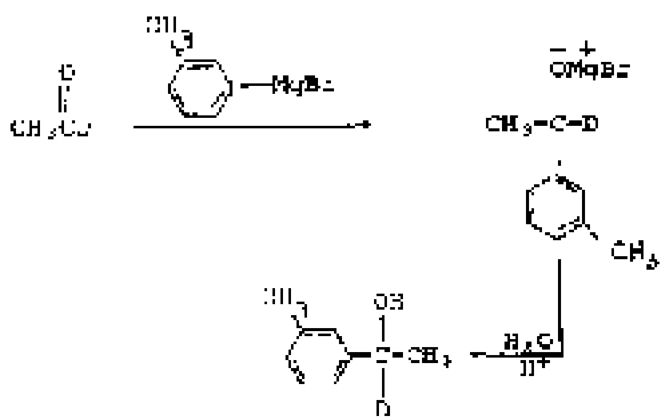
The nucleophilic Grignard carbon attacks the carbonyl carbon to form the magnesium halide salt of the alcohol. The Grignard reactions that will form the compounds (a) through (f) are:

(a) 

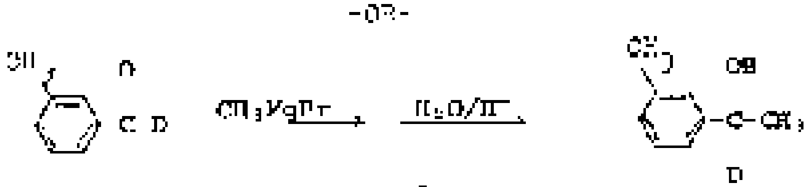


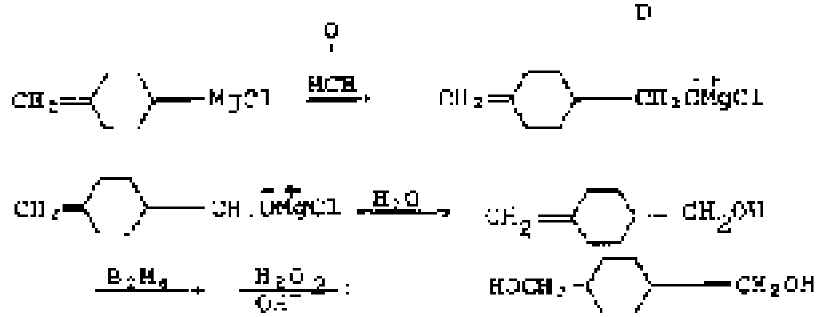
(b) 

(c) 

(d) 

-OR-



(e) 

(cis and trans)

(f) 

-OR

$$(CH_3)_2CH-\overset{\displaystyle O}{\overset{\|}{C}}-H \xrightarrow{(CH_3)_3CMgBr} \xrightarrow[H^+]{H_2O} (CH_3)_3C-\overset{\displaystyle OH}{\overset{|}{C}H}-CH(CH_3)_2$$

• PROBLEM 15-14

> Outline the synthesis of n-butyldimethylcarbinol (2-methyl-2-hexanol) from acetone and n-butylbromide.

Solution: Alcohols are compounds of the general formula ROH, where R is any alkyl or substituted alkyl group.

A general synthesis reaction of alcohols from ketones and aldehydes is the Grignard synthesis. The reaction is:

$$RMgX + R'-\overset{\displaystyle R''}{\overset{|}{C}}=O \rightarrow R'-\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle R''}{\overset{|}{C}}}}-OMgX \xrightarrow{H_2O} R'-\underset{\displaystyle R}{\underset{|}{\overset{\displaystyle R''}{\overset{|}{C}}}}-OH$$

where R can be any alkyl group.

To synthesize n-butyldimethylcarbinol we make use of this important reaction. The structure of n-butyldimethylcarbinol is shown in figure A.

$$n\text{-}C_4H_9-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{C}}}-OH$$

fig. A.

Thus from the general reaction the three R groups are nC_4H_9-, CH_3-, and CH_3- and the reaction is:

$$n\text{-}C_4H_9MgBr + CH_3-\underset{\displaystyle CH_3}{C}=O \rightarrow n\text{-}C_4H_9-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-OMgBr \xrightarrow{H_2O} n\text{-}C_4H_9-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}-OH$$

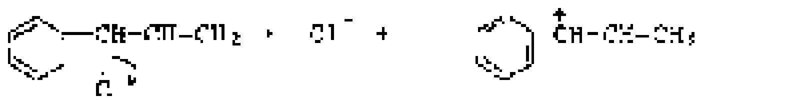
However $n\text{-}C_4H_9MgBr$ must be prepared first. This is done by using n-butyl bromide

$$n\text{-}C_4H_9Br + Mg \xrightarrow{ether} n\text{-}C_4H_9MgBr$$

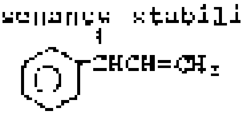
Thus the total sequence of reactions requires only two steps; the production of the Grignard reagent and the addition of acetone to this reagent.

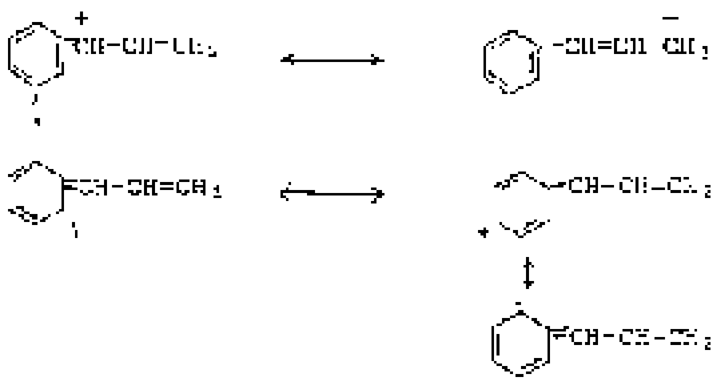
Suggest a mechanism for the conversion of $C_6H_5CHClCH{=}CH_2$ to $C_6H_5CH{=}CHCH_2OH$ in water.

Solution: In order for the double bond to be shifted, the reaction must proceed through a free carbocation stage. This is facilitated by the leaving of the chlorine atom. The carbocation formed is resonance stabilized, and will be hydrolyzed to form an alcohol. The mechanism is shown as:

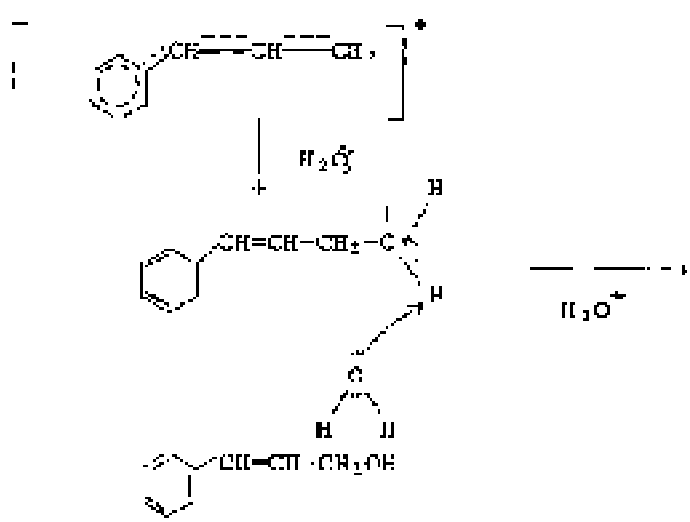


(resonance stabilized)

Resonance stabilization of  :

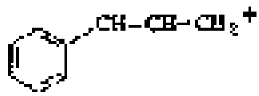


The resonance stabilized carbocation can be represented as:



3-phenyl-2-propenol

The ^{-}OH adds onto the primary carbon because the positive charge is greatest there. This is because the double bond is conjugated with the aromatic ring:



C-OH BOND CLEAVAGE

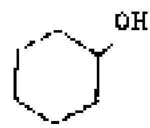
• PROBLEM 16-16

Predict the products of each alcohol if a hydrogen halide were added.

(a)
$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ OH \end{array}$$

t-Butyl alcohol

(b)



Cyclohexanol

(c)
$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_2OH \\ | \\ CH_3 \end{array}$$

Neopentyl alcohol

(d) $CH_3CH_2CH_2CH_2CH_2OH$

n-Pentyl alcohol

Solution: The chemical properties of an alcohol, ROH, are determined by its functional group, -OH, the hydroxyl group.

Reactions of an alcohol can involve the breaking of either of two bonds: the C-OH bond, with removal of the -OH group; or the O-H bond, with removal of -H. Either kind of reaction can involve substitution, in which a group replaces the -OH or -H, or elimination, in which a double bond is formed.

Alcohols react readily with hydrogen halides to yield alkyl halides and water. The reaction is carried out either by passing the dry hydrogen halide gas into the alcohol, or by heating the alcohol with the concentrated aqueous acid. Sometimes hydrogen bromide is generated in the presence of the alcohol by reaction between sulfuric acid (H_2SO_4) and sodium bromide.

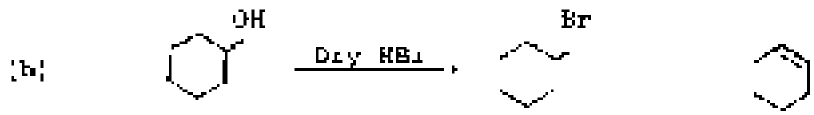
The general formula for this type of reaction is:

$$R-OH + HX \rightarrow RX + H_2O$$

and by using this formula with the above principles, the products of the given reactions may be predicted.

(a) $$CH_3\overset{CH_3}{\underset{OH}{C}}CH_3 \xrightarrow[\text{room temp.}]{\text{conc. HCl}} CH_3-\overset{CH_3}{\underset{Cl}{C}}-CH_3 + CH_2{=}C(CH_3)_2$$

t-Butyl alcohol t-Butyl chloride Isobutylene

(b) 

Cyclohexanol Cyclohexyl bromide Cyclohexene

(c) $$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2OH + HCl \rightarrow CH_3-\overset{CH_3}{\underset{Cl}{C}}-CH_2-CH_3$$

Neopentyl alcohol t-Pentyl chloride

From solution (c) it is seen that the halogen does not always become attached to the carbon that originally held the hydroxyl group. Even the carbon skeleton may be different from that of the starting material. The reason is because compounds during reaction seek their most stable form, and they will rearrange to that form if it is energetically feasible.

Neopentyl alcohol arranged as shown:

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2OH \xrightarrow{H^+} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2\overset{+}{O}H_2 \xrightarrow{-H_2O}$$

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2^+ \rightarrow CH_3\overset{+}{\underset{CH_3}{C}}CH_2CH_3 \xrightarrow{Cl^-} CH_3\overset{Cl}{\underset{CH_3}{C}}CH_2CH_3$$

(d) $$CH_3CH_2CH_2CH_2CH_2OH + HCl \xrightarrow[\text{heat}]{ZnCl_2} CH_3CH_2CH_2CH_2CH_2Cl + H_2O$$

n-Pentyl alcohol n-Pentyl chloride

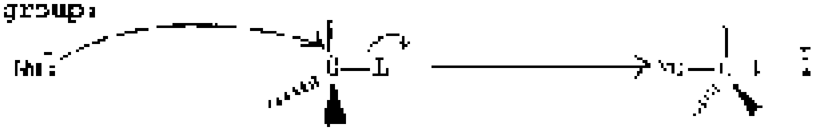
Would you expect optically active 1-deuterioethanol to react with HBr and yield 1-deuterioethyl bromide with inversion of configuration, or with racemization? Explain.

Solution: When an alcohol (ROH) is treated with an acid of the type HX (X being a halogen), a nucleophilic substitution reaction (S_N) will take place. The acid (HX) will ionize to produce the nucleophilic halide ion (X^-) which will replace the hydroxyl (OH) functionality in the alcohol. Before it leaves the molecule, the hydroxyl group is protonated by the proton from the ionization of HX. This occurs because the leaving group is now water (H_2O) and not ^-OH; H_2O is a larger species than ^-OH and is hence a better leaving group. In the problem optically active 1-deuterioethanol reacts with HBr to yield 1-deuterioethyl bromide. The reaction is:

$$CH_3CH(D)(OH) + HBr \rightarrow CH_3CH(D)(Br) + H_2O$$

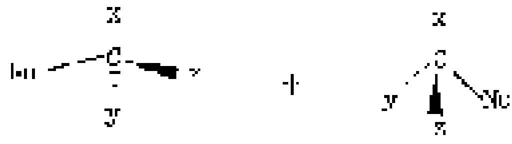
1-deuterio-ethanol   1-deuterioethyl bromide

The problem asks whether the reaction occurs with inversion of configuration or racemization. Inversion of configuration is characteristic of S_N2 (bimolecular nucleophilic substitution) reactions. This is because the reaction proceeds via a concerted mechanism and the nucleophile attacks the chiral carbon on the side opposite the leaving group:



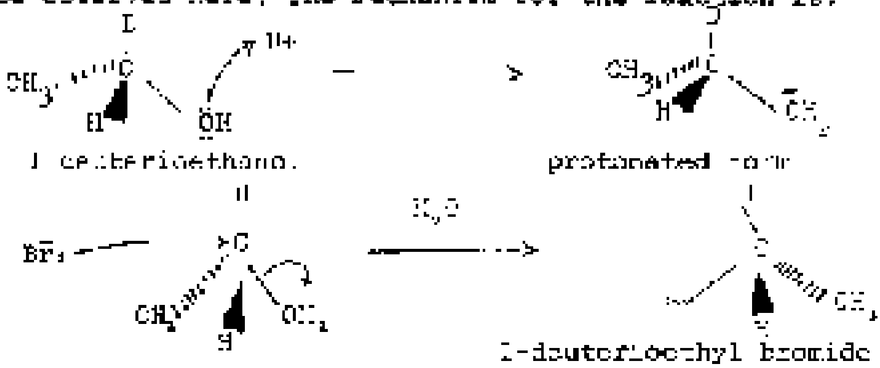
Nu^-: = nucleophile
L = leaving group
C = chiral carbon

The S_N reaction that occurs with racemization is characteristic of an S_N1 reaction (unimolecular nucleophilic substitution). This occurs because the reaction proceeds through a free carbocation stage; the nucleophile attacks either face of the carbocation with equal probability:



50% 50%

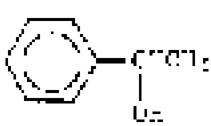
Primary and secondary carbons bearing a potential leaving group will undergo S_N reactions mainly by the bimolecular pathway whereas tertiary carbons will mainly follow the unimolecular pathway. This is due to the relative carbocation stabilities ($3° > 2° > 1° > {}^+CH_3$). Since 1-deuterioethanol is a primary alcohol, it will react with HBr mainly via an S_N2 pathway. Since inversion of configuration is characteristic of S_N2 reactions, it will be observed here. The mechanism for the reaction is:



We can see by this mechanism that 1-deuterioethanol reacts with HBr mainly via an S_N2 pathway and hence proceeds with inversion of configuration.

• PROBLEM 16-18

React the following alcohols with a phosphorus trihalide and show the products.

(a) 

1-Phenylethanol

(b) $CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}H}CH_2CH_2OH$

3-Methyl-1-hexanol

(c) $CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH_2OH$

2,2-Dimethyl-1-butanol

(d) CH_3CH_2OH

Ethyl alcohol

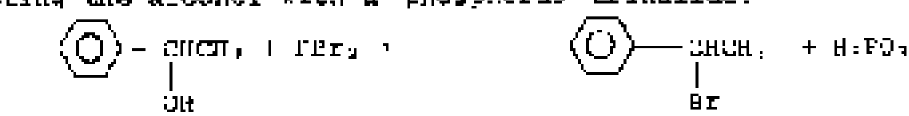
Solution: Alcohols react with phosphorus trihalides to produce alkyl halides with the same carbon skeleton as that of the alcohol. As seen in previous problems, alkyl halides can also be prepared from alcohols with a hydrogen halide, but phosphorus halides are often preferred because they tend less to bring about rearrangement of the carbon skeleton.

The general reaction for this synthesis is:

$$3\ R\text{-}OH + PX_3 \longrightarrow 3\ RX + H_3PO_3$$

$$(PX_3 = PBr_3,\ PI_3,\ PCl_3)$$

This reaction is simple substitution where the halogen, either bromine or iodine will replace the -OH group, and the phosphorus forms the by-product phosphorus acid (H_3PO_3). With the above facts and the general synthesis at hand, the products of each reaction can be obtained after reacting the alcohol with a phosphorus trihalide.

(a) 

1-Phenylethanol 1-Bromo-1-phenylethane

(b) $$CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}H}CH_2CH_2OH \xrightarrow{PBr_3} CH_3CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}H}CH_2CH_2Br + H_3PO_3$$

3-Methyl-1-hexanol 3-Methyl-1-Bromohexane

(c) $$CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH_2OH \xrightarrow{PI_3} CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH_2I + H_3PO_3$$

2,2-Dimethyl-1-butanol 2,2-Dimethyl-1-iodobutane

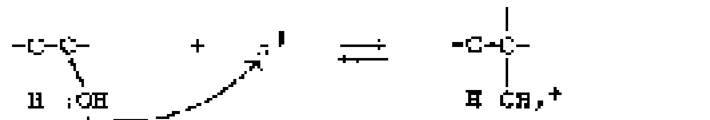
(d) $$CH_3CH_2OH + PCl_3 \longrightarrow CH_3CH_2Cl + H_3PO_3$$

Ethyl alcohol Ethyl chloride

• PROBLEM 16-19

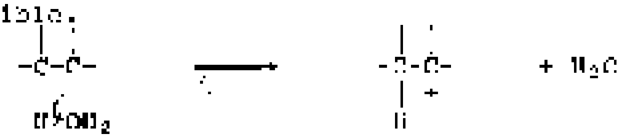
Describe the mechanism for the dehydration of alcohols.

Solution: The dehydration of alcohols begins with the formation of the protonated alcohol. After the dissociation of the acid (H_2SO_4) an H^+ attaches itself to the electronegative oxygen atom. This step is an equilibrium reaction and can go either way depending upon the reaction conditions.

(1) 

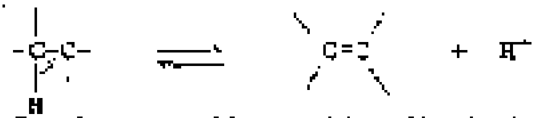
Alcohol — Protonated alcohol

Next, the protonated alcohol loses a molecule of water to form the most stable carbonium ion that is structurally possible.

(2) 

In this step equilibrium lies very far to the left and thus there is a very low concentration of carbonium ions present at any time.

The final step of the reaction is the loss of a proton (or hydrogen ion) from the carbonium ion, restoring the electric neutrality of the molecule and forming a double bond.



In the overall reaction the hydrogen ions are not consumed and are therefore true catalysts.

The dehydration of some alcohols can result in the formation of more than one alkene. 2-butanol, for example, may eliminate in either of two directions to give 1-butene or 2-butene. This can be seen in figure 1.

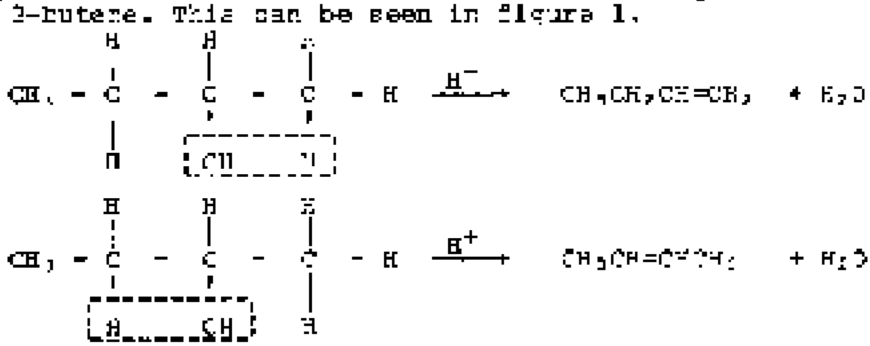
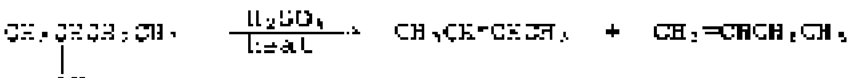


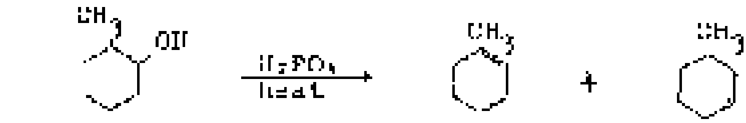
Figure 1

In general when two alkenes can be formed from a single alcohol, the alkene that predominates is the one with more alkyl substituents on the double bond. This generalization, known as the Saytzeff rule, is illustrated by the reactions which follow. In the first reaction 2 butanol gives both 2-butene and 1-butene. 2-Butene is the major product because it has two alkyl substituents (two methyl groups) on the double bond.



major product — minor product

2 butanol



2-methylcyclo-hexanol | 1-methylcyclo-hexene major product | 3-methylcyclo-hexene minor product

1-Butene has only one alkyl substituent (one ethyl group) on the double bond and is therefore the minor product. Similarly, the dehydration of 2-methylcyclohexanol gives as the major product 1-methylcyclohexene (three substituents including the ring carbons) and as the minor product 3-methylcyclohexene (two substituents including the ring carbons).

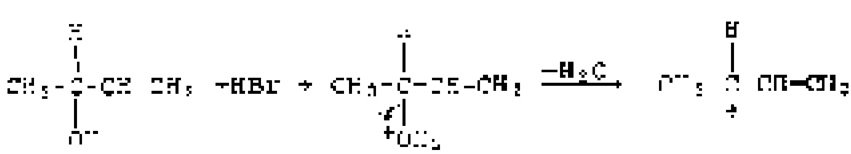
• PROBLEM 16-20

When allowed to react with aqueous HBr, 3-buten-2-ol ($CH_3CHOHCH=CH_2$) yields not only 3-bromo-1-butene ($CH_3CHBrCH=CH_2$) but also 1-bromo-2-butene ($CH_3CH=CHCH_2Br$). (a) How do you account for these results? (b) Predict the product of the reaction between HBr and 2-buten-1-ol ($CH_3CH=CHCH_2OH$).

Solution: (a) These results can be accounted for by the consideration of the allyl cation ($CH_2=CH-CH_2^+$). From inspection of bond dissociation energies, allyl radicals are unusually stable. From this, it is possible to deduce that the allyl cation, too, is unusually stable. This stability is accounted for by delocalization of the electrons in this carbonium ion. It seems that the allyl cation is a resonance hybrid of two exactly equivalent structures:

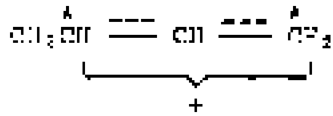
$$[CH_2=CH-CH_2^+ \longleftrightarrow {}^+CH_2-CH=CH_2] \text{ equivalent to } \underbrace{CH_2 \overset{---}{=\!=} CH \overset{---}{=\!=} CH_2}_{+}$$

At this point recall the fact that the dehydration of alcohols with acid (such as HBr) occurs through an intermediate carbonium ion with Markovnikov orientation. Hence, when HBr is added 3-buten-2-ol, a carbonium ion is formed as shown:

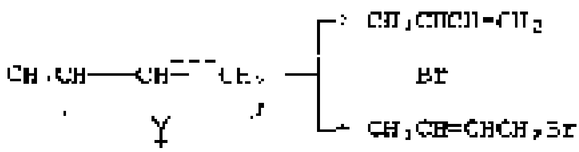


carbonium ion

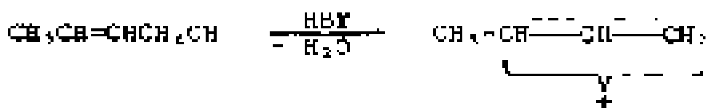
The important thing to see is that this is not just a carbonium ion but an allylic cation. Consequently, the true picture of this structure is:



This hybrid allylic cation formed makes available to the bromide ion (Br^-) two points of attack, which are starred. The result should be two products as indicated:



(b) When HBr is added to 2-buten-1-ol, the same hybrid allylic cation results as shown:

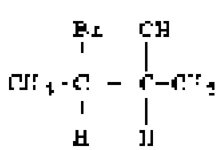


This means that the same two products obtained in (a) will be produced in this reaction.

• PROBLEM 16-31

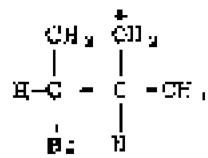
(a) From the reaction of either (2R,3S) or (2S,3R)-3-bromo-2-butanol with HBr, the product is meso-2,3-dibromobutane. Show how this product is formed. Is the intermediate bromonium ion chiral?
(b) Contrast the reaction of (2S,3R)-3-bromo-2-butanol with HBr and the reaction of the same substrate with sodium ethoxide.

Solution: (a) (2S,3R)-3-bromo-2-butanol has the structure shown below (in Fischer projection form):

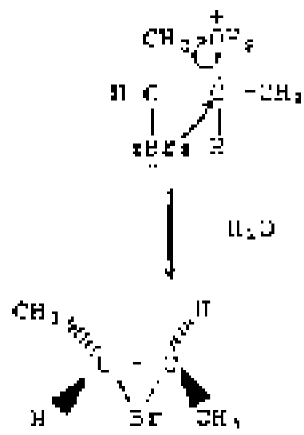


When this is treated with HBr, the hydroxyl group (OH) of the alcohol is protonated by a proton from the ionization of HBr. The presence of a nucleophilic group (bromine) on the carbon adjacent to the carbon bearing the protonated hydroxyl makes it possible for an intramolecular S_N2 reaction to occur. A free electron pair on bromine will attack the carbon bearing the protonated hydroxyl group; water will leave the molecule and a cyclic bromonium ion will be formed. Since this is an S_N2 reaction (because the carbon bearing the leaving group, H_2O, is secondary), the nucleophile (Br) will attack the carbon bearing the protonated hydroxyl group on the side opposite the leaving group:

In order for the bromine to react via an S_N2 pathway, it must be anti to the leaving group (H_2O). The conformation of the protonated alcohol that satisfies this requirement is:

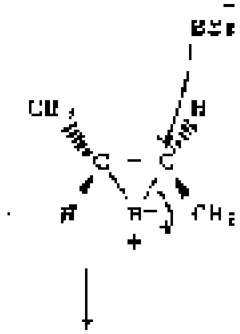


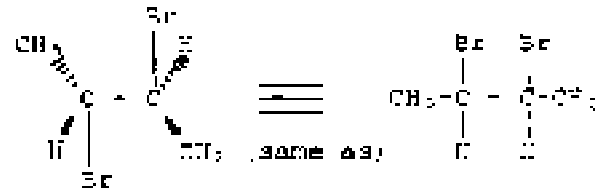
Hence,



cyclic bromonium ion

The cyclic bromonium ion reacts with the bromide ion, Br^-, (from the ionization of HBr) via an S_N2 pathway. The nucleophile bromide ion attacks one of the ring carbons on the side opposite the bromine cation. This results in the formation of meso-2,3-dibromobutane:

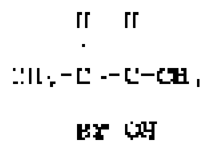




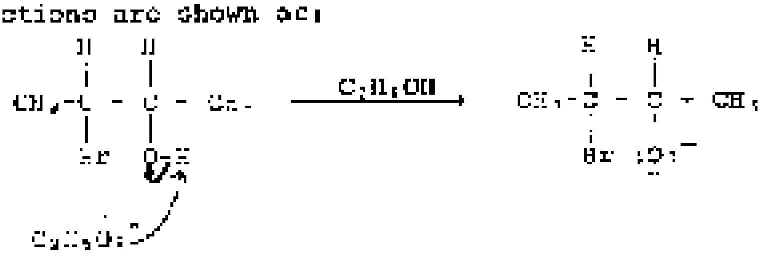
meso-2,3-dibromobutane (Fischer projection)

The cyclic bromonium ion is a chiral molecule. This is because there is no plane of symmetry for the molecule.

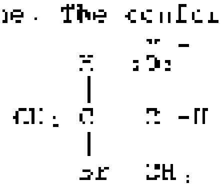
(b) (2R,3S)-3-Bromo-2-butanol has the structure:



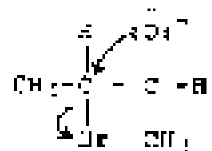
Reaction of this compound with HBr proceeds through a cyclic bromonium ionic intermediate; the final product is meso-2,3-dibromobutane. When the above compound (the alcohol) is reacted with sodium ethoxide ($Na^+\ ^-OC_2H_5$), the mechanism is very similar to that shown in part (a). The ethoxide ion removes a proton from the hydroxyl group. The resulting anionic oxygen attacks the carbon bearing the bromine in an intramolecular S_N2 reaction; this forms a chiral cyclic intermediate (an epoxide). This intermediate reacts with ethoxide ion in an S_N2 reaction to open the ring. The product formed is optically active and is named (2R,3S)-3-ethoxy-2-butanol. The mechanism for these reactions are shown as:

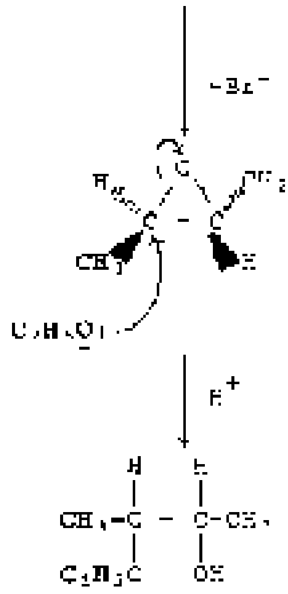


The intermediate must be oriented correctly for an intramolecular S_N2 reaction to occur; the oxygen anion must be anti to the bromine. The conformation that satisfies this requirement is:



Hence,





chiral, cyclic intermediate
[(2R,3R)-2,3-epoxybutane]

(2R,3S)-3-ethoxy-2-butanol

CO-H BOND CLEAVAGE

• PROBLEM 16-22

Sodium metal was added to tert-butyl alcohol and allowed to react. When the metal was consumed, ethyl bromide was added to the resulting mixture. Work-up of the reaction mixture yielded a compound of formula $C_6H_{14}O$.

In a similar experiment, sodium metal was allowed to react with ethanol. When tert-butyl bromide was added, a gas was evolved, and work-up of the remaining mixture gave ethanol as the only organic material.

(a) Write equations for all reactions. (b) What familiar reaction type is involved in each case? (c) Why did the reactions take different courses?

Solution: (a), (b) It is known that alcohols may act as acids. Alcohols may react with active metals to form the alkoxide ion, $RO^{\ominus}$, and hydrogen gas. The reaction may be written as:

$$RO-H + M \rightarrow RO^{\ominus}M^{\oplus} + \tfrac{1}{2}H_2,$$

where M=Na, K, Mg, Al, etc. and the reactivity of ROH is $CH_3OH > 1° > 2° > 3°$. Hence, when sodium metal is added to tert-butyl alcohol and allowed to react, sodium tert-butoxide is formed as shown:

$$CH_3-\underset{OH}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3 + Na \longrightarrow CH_3-\overset{CH_3}{C}-CH_3 + \tfrac{1}{2}H_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad O^{\ominus}Na^{\oplus}$$

t-butyl alcohol   sodium t-butoxide

Alkoxides are useful reagents; they are used as powerful bases (stronger than hydroxide). Sodium t-butoxide and ethyl bromide (CH_3CH_2Br) are mixed together to give $C_6H_{14}O$. This reaction illustrates nucleophilic substitution. Ethyl bromide is an alkyl halide, and nucleophilic substitution is typical of such organic compounds. Nucleophilic substitution may be generalized as

$$R:X \; + \; :Z \; \rightarrow \; R:Z \; + \; :X^{\ominus}$$

A nucleophilic reagent   Leaving group

As mentioned, sodium tert butoxide is a strong base. It is an electron-rich species, so that it may be described as a nucleophile. Consequently, the equation for the reaction with ethyl bromide becomes:

$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-O^{\ominus}Na^{\oplus} + CH_3CH_2Br \rightarrow CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-OCH_2CH_3 \quad (C_6H_{14}O)$$

t-butyl ethyl ether

In a similar experiment, another alkoxide, sodium ethoxide, is obtained when sodium is allowed to react with ethanol. The reaction may be written as follows:

$$CH_3CH_2OH + Na \rightarrow CH_3CH_2O^{\ominus}Na^{\oplus} + \tfrac{1}{2}H_2$$

Ethanol   Sodium ethoxide

Due to the fact that the only organic compound present after tert-butyl bromide is added to sodium ethoxide in ethanol, this reaction cannot be the same as the one discussed above (when ethanol was added to sodium t-butoxide). In fact, this reaction is one of elimination. Recall that in the dehydrohalogenation to produce alkenes, the base ($OH^{\ominus}$) pulled a hydrogen ion away from carbon, and simultaneously a halide ion separated. This is exactly what happens when sodium ethoxide and t-butyl bromide are mixed together, except that in this case the sodium ethoxide replaces OH^{-} as the base. The reaction may be written as:

$$CH_3CH_2O^{\ominus}Na^{\oplus} + CH_3-\underset{Br}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3 \rightarrow CH_3-\overset{CH_3}{C}=CH_2 + CH_3CH_2OH + NaBr.$$

(isobutylene)   Ethanol

Isobutylene, the alkene produced, is a gas and diffuses away. This leaves only NaBr (inorganic) and ethanol.

(c) How can the different courses of the two reactions be explained? Examine the nature of the alkyl halide involved in each case. In the first case, ethyl bromide, a primary alkyl halide, was used. In the second case, tert-butyl bromide, a tertiary alkyl halide, was used. Both nucleophilic substitution and elimination are typical reactions of alkyl halides - they can compete with each other. But note the reactivities for each:

E_1 or E_2 elimination: 3° > 2° > 1°

S_N2 (Substitution nucleophilic bimolecular):

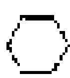
CH_3X > 1° > 2° > 3°.

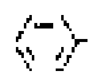
Hence, when the primary alkyl halide is used, S_N2 is favored over elimination. Therefore, nucleophilic (S_N2) substitution occurs when ethyl bromide is added to sodium t-butoxide. However, when the tertiary alkyl halide is employed, the elimination reaction predominates, as seen when t-butyl bromide is added to sodium ethoxide.

• PROBLEM 10-23

Predict the major products of the following reactions:

(a) $(CH_3)_3CBr + CH_3O^{\ominus} \rightarrow$

(b)  — Cl + $(CH_3)_3CO^{\ominus} \rightarrow$

(c)  $CH_2Br + (CH_3)_2CHCH_2O^{\ominus} \rightarrow$

(d) $(CH_3)_2CHCH_2Br + C_6H_5CH_2O^{\ominus} \rightarrow$

<u>Solution:</u> When an alkyl halide (RX) is treated with an alkoxide ($RO^{\ominus}$) the major product will be an alcohol (ROH) and an alkene $\left(\rangle C{=}C\langle \right)$ or an ether (ROR'). The alcohol and alkene are products of an elimination (E) reaction. The ether is the product of a nucleophilic substitution (S_N) reaction. When there are no hydrogens α to the carbon bearing the leaving group, elimination cannot occur and the reaction will yield only S_N products. When the reaction is done in the presence of a strong base, and α hydrogens (relative to C-X) are present, elimination will be favored over substitution. The basicity of alkoxides follows the order: 3° > 2° > 1° > $CH_3O^{\ominus}$. This is because the acidity of their conjugate acids (the alcohols) follow the order: CH_3OH > 1° > 2° > 3°.

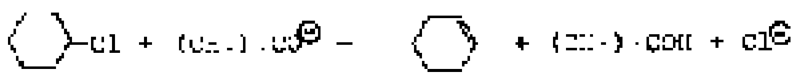
Elimination will also be favored over substitution when the alkyl portion of the alkyl halide can have a fairly stable carbocation (i.e.: tertiary alkyl halides), and if the alkyl portion is a larger group (because of steric considerations, elimination will predominate over substitution). With this in mind, we may predict the major products of reactions (a) through (d).

(a) This is mainly an elimination reaction due to the tertiary alkyl halide; the t-butyl group is a large moiety and it has a fairly stable carbocation.

$$(CH_3)_3C\text{-}Br + CH_3O^{\ominus} \rightarrow (CH_3)_2C{=}CH_2 + CH_3OH + Br^{\ominus}$$

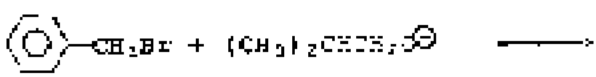
isobutylene methanol

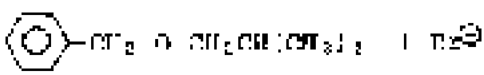
(b) As in part (a) the major reaction will be an elimination; this is because of the relatively strong base, t-butoxide.



cyclohexene t-butanol

(c) Since the alkyl halide has no hydrogens β to the carbon bearing the bromine, elimination cannot occur and the reaction is strictly S_N.





benzyl-isobutyl ether

(d) Elimination will be favored over substitution in this reaction because of the fairly large isobutyl group of the alkyl halide and the good basicity of the benzoxide anion. There will, however, be some substitution because of the nucleophilic nature of the alkoxide and because the alkyl halide is primary.

$$(CH_3)_2CHCH_2Br + C_6H_5CH_2O^{\ominus} \rightarrow (CH_3)_2C{=}CH_2 + C_6H_5CH_2OH + Br^{\ominus}$$

isobutylene benzyl alcohol

There will also be some:

$$(CH_3)_2CHCH_2OCH_2C_6H_5$$

benzyl-isobutyl ether

In the esterification of an acid with an alcohol, how could you distinguish between C-O and O-H cleavage of the alcohol using heavy oxygen (^{18}O) as a tracer?

$$CH_3O \,\vdots\, H + R\overset{\displaystyle O}{\overset{\|}{C}} \,\vdots\, OH \xrightarrow{H^+} RCOOCH_3 + H_2O$$

or

$$CH_3 \,\vdots\, OH + R\overset{\displaystyle O}{\overset{\|}{C}}O \,\vdots\, H \xrightarrow{H^+} RCOOCH_3 + H_2O$$

What type of alcohols might conceivably react by C-O cleavage, and what side reactions would you anticipate for such alcohols?

Solution: We can distinguish between C-O and O-H bond cleavage in the alcohol in Fischer esterification reactions by using ^{18}O-labeled alcohol. In the problem, methanol (CH_3OH) is the alcohol used. If ^{18}O labeled methanol was reacted with a carboxylic acid $\left(R-\overset{\displaystyle O}{\overset{\|}{C}}-OH\right)$, the methyl ester $\left(R-\overset{\displaystyle O}{\overset{\|}{C}}-OCH_3\right)$ would contain heavy oxygen, if the O-H bond was broken and the water would be free of ^{18}O. If the C-O bond was broken, the methyl ester would be unlabeled and the water would contain heavy oxygen. These reactions are shown as:

O-H cleavage

$$CH_3-{}^{18}O \,\vdots\, H + R-\overset{\displaystyle O}{\overset{\|}{C}} \,\vdots\, OH \xrightarrow{H^+} R-\overset{\displaystyle O}{\overset{\|}{C}}-{}^{18}O-CH_3 + H_2O$$

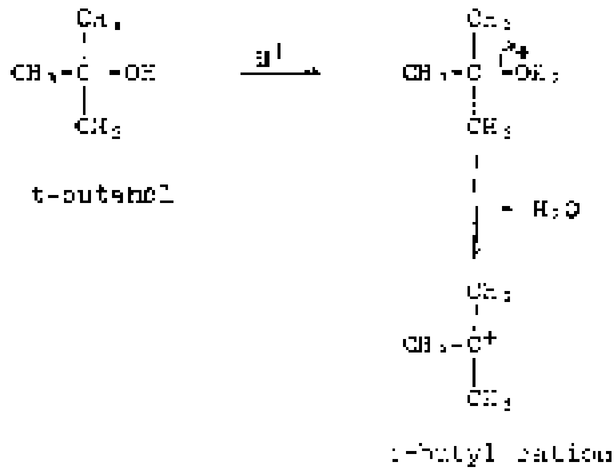
labeled ester unlabeled water

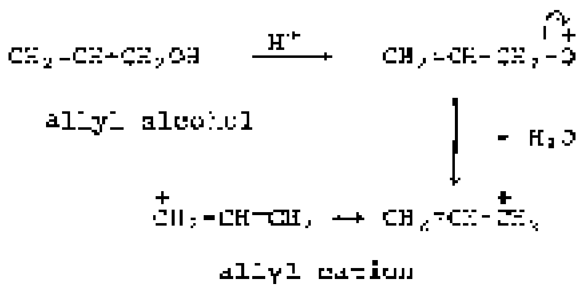
C-O cleavage

$$H_3C \,\vdots\, {}^{18}OH + R-\overset{\displaystyle O}{\overset{\|}{C}}-O \,\vdots\, H \xrightarrow{H^+} R-\overset{\displaystyle O}{\overset{\|}{C}}-O-CH_3 + H_2{}^{18}O$$

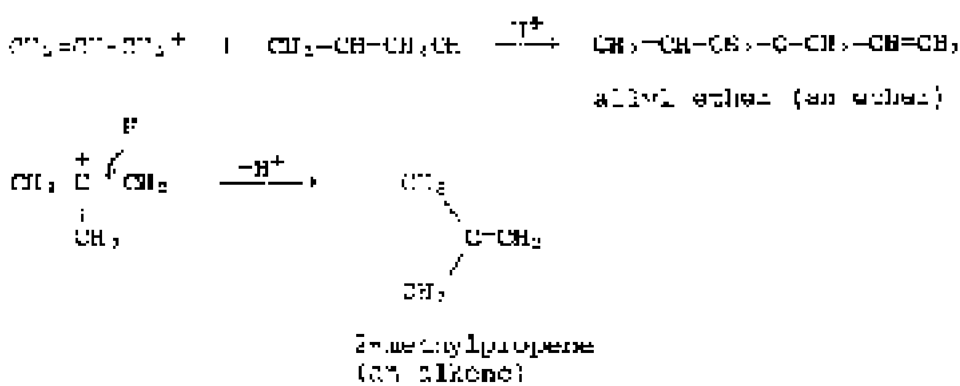
unlabeled ester labeled water

Alcohols that might conceivably react by C-O cleavage are those that can form fairly stable carbocations, such as tertiary or allylic alcohols:





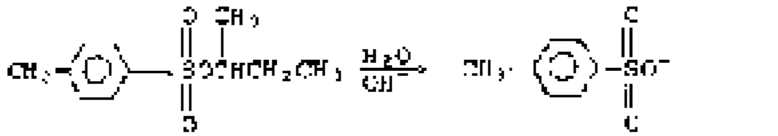
The side reactions expected to occur for such alcohols would be ether and alkene formation as shown:



• PROBLEM 16-25

You prepare sec-butyl tosylate from alcohol of [α] − 6.9°. On hydrolysis with aqueous base, this ester gives sec-butyl alcohol of [α] − 6.9°. Without knowing the configuration or optical purity of the starting alcohol, what (if anything) can you say about the stereochemistry of the hydrolysis step?

Solution: Base catalyzed hydrolysis of a sulfonyl ester ($R'-SO_3R$) will yield an alcohol (ROH) and a sulfonic acid salt ($R'SO_3^-$). Sec-butyl tosylate is a sulfonyl ester and will be hydrolyzed to sec-butanol and the anion of p-methylbenzenesulfonic acid. The reaction is shown as:



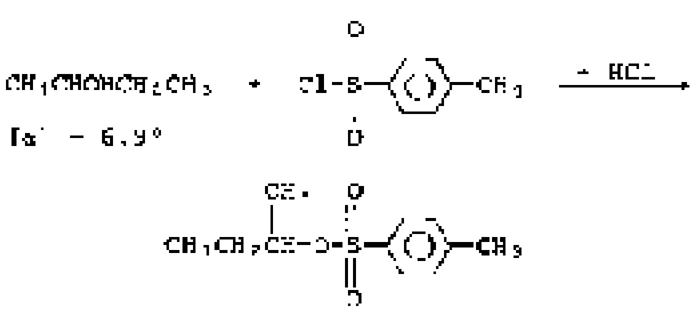
sec-butyltosylate

anion of p-methylbenzenesulfonic acid (tosylate ion)

$CH_3CHOHCH_2CH_3$

sec-butanol

This reaction proceeds via an S_N2 pathway where the hydroxide ion (OH^-) acts as a nucleophile and the tosylate ion acts as the leaving group. As in all S_N2 reactions, this one will proceed with inversion of configuration: that is, if the starting material is optically active, the product will have the same optical rotation as the reactant, only it will have the opposite sign (i.e., if reactant has optical rotation of + 20°, product will have optical rotation of − 20°). The problem states that the sec butyl alcohol produced from sec-butyltosylate has a [α] (optical rotation) of − 6.9°. Since the reaction that produces the sec butyl alcohol is an S_N2 reaction, we may conclude that the sec butyltosylate has a [α] of + 6.9°. Since the sec-butyltosylate was prepared from an alcohol of [α] + 6.9°, we can see that the reaction that produced sec butyltosylate proceeded with retention of configuration. This is explained by the fact that the O-H bond and not the C-OH bond is broken in the alcohol to form the tosylate. The reaction can be written as:



[α] + 6.9°

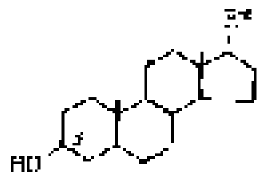
OXIDATION

• PROBLEM 16-20

Give the product of each alcohol below after oxidation with any reagent necessary.

(a) $CH_3CH_2\underset{\displaystyle CH_3}{CH}-CH_2OH$

2-Methyl-1-butanol

(b) 

3-Cholestanol

*R = $CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$

(c) $CH_3CH_2CH_2OH$

n-Propyl alcohol

Solution: The product that is formed by oxidation of an alcohol depends upon the number of hydrogens attached to the carbon bearing the hydroxyl, -OH group, i.e. upon whether the alcohol is primary, secondary, or tertiary. The products formed are aldehydes, ketones and carboxylic acids, and their preparation by the oxidation of alcohols is of great value in organic synthesis.

Some oxidizing reagents (such as $K_2Cr_2O_7$) are highly selective reagents which operate on only one functional group in a complex molecule, and leave the other functional groups unchanged. Of the many reagents that can be used to oxidize alcohols, only the most common ones will be considered here, those containing manganese (Mn), and chromium (Cr).

The general reactions for these oxidations are:

(1) Primary Alcohols

$$R-CH_2OH \xrightarrow{K_2Cr_2O_7} R-\overset{\displaystyle H}{C}=O \xrightarrow[\text{or } K_2Cr_2O_7]{KMnO_4} RCOOH$$

$$R-CH_2OH \xrightarrow{KMnO_4} RCOOH \quad \text{A carboxylic acid}$$

(2) $R-\overset{\displaystyle R}{C}HOH \xrightarrow{K_2Cr_2O_7} R-\overset{\displaystyle R}{C}=O$

Secondary alcohol — A ketone

(3) $R-\underset{\displaystyle R}{\overset{\displaystyle R}{C}}-OH \xrightarrow{\text{neut. } KMnO_4}$ no reaction

Tertiary alcohol

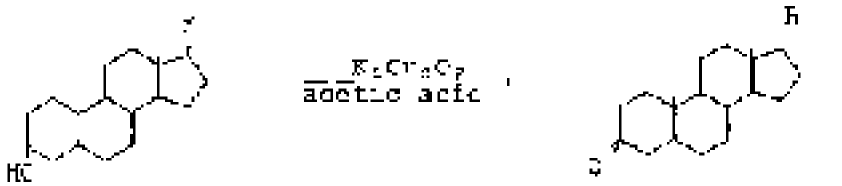
From the general reactions, it can be seen that primary alcohols are oxidized to carboxylic acids either directly or via an aldehyde, depending upon the oxidizing reagent. For example, take problem (a).

$$\underset{\text{2-methyl-1-butanol}}{CH_3CH_2\underset{\underset{CH_3}{|}}{C}HCH_2OH} \xrightarrow{KMnO_4} \underset{\text{2-methylbutanoic acid}}{CH_3CH_2\underset{\underset{CH_3}{|}}{C}HCOOH}$$

or

$$\xrightarrow{K_2Cr_2O_7} \underset{\text{2-methylbutanal}}{CH_3CH_2\underset{\underset{CH_3}{|}}{C}H\overset{\overset{H}{|}}{C}{=}O} \xrightarrow{KMnO_4} \underset{\text{2-methylbutanoic acid}}{CH_3CH_2\underset{\underset{CH_3}{|}}{C}HCOOH}$$

Secondary alcohols are oxidized to ketones by chromic acid or an aqueous solution of potassium dichromate, $K_2Cr_2O_7$ in glacial acetic acid. This will solve problem (b).



3-Cholestanol 3-Cholestanone

In both cases, cholestanol and cholestanone, the alkyl group remains as: R = $CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$.

Problem (c) is also a primary alcohol, and therefore follows the same mechanism as (a).

$$\text{(c)}\quad \underset{\text{n-propyl alcohol}}{CH_3CH_2CH_2OH} \xrightarrow{K_2Cr_2O_7} \underset{\text{propionaldehyde}}{CH_3CH_2\overset{\overset{H}{|}}{C}{=}O}$$

$$\downarrow K_2Cr_2O_7 \text{ or } KMnO_4$$

$$\underset{\text{propionic acid}}{CH_3CH_2COOH}$$

SPECTROSCOPY

• PROBLEM 16-27

(a) Very dry, pure samples of alcohols show spin-spin splitting of the O-H signals. What splitting would you expect for a primary alcohol? a secondary alcohol? a tertiary alcohol? (b) This splitting disappears on the addition of a trace of acid or base. Write equations to show just how proton exchange would be speeded up by an acid (H:B); by a base (:B).

Solution: (a) Proton exchange at the hydroxyl group occurs very slowly in dry, pure samples of alcohol. As a result, a given hydroxyl proton remains bonded to the oxygen long enough for spin-spin splitting to occur (due to the protons of the carbon adjacent to the oxygen). Hence the two protons on the neighboring carbon in primary alcohols $(-CH_2-OH)$ will split the hydroxyl signal into a triplet. The single proton on the carbon in secondary alcohols $\left(-\overset{|}{C}H-OH\right)$ will split the hydroxyl signal into a doublet. The hydroxyl proton will not undergo spin-spin splitting in tertiary alcohols $\left(-\overset{|}{\underset{|}{C}}-OH\right)$ because there are no hydrogens on the carbon adjacent to the oxygen. Hence the hydroxyl signal will occur as a singlet.

(b) When an alcohol is in the presence of a trace of acid or base, proton exchange is speed up as follows:

By Acid:

$$\underset{\text{alcohol}}{R^*OH^*} + \underset{\text{acid}}{H:B} \rightleftharpoons \left[\begin{array}{c} R^*OH^* \\ | \\ H \end{array}\right]^+ + B:^-$$

$$\left[\begin{array}{c} R^*OH^* \\ | \\ H \end{array}\right]^+ + ROH \rightleftharpoons R^*OH + \left[\begin{array}{c} ROH \\ | \\ H^* \end{array}\right]^+$$

$$\left[\begin{array}{c} ROH \\ | \\ H^* \end{array}\right]^+ + B:^- \rightleftharpoons ROH^* + H:B$$

By Base:

$$\underset{\text{alcohol}}{R^*OH^*} + \underset{\text{base}}{B:} \rightleftharpoons R^*O^- + [B:H^*]^+$$

$$R^*O^- + ROH \rightleftharpoons R^*OH + RO^-$$

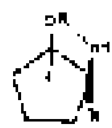
$$RO^- + [B:H^*]^+ \rightleftharpoons ROH^* + B:$$

As a result of this increase in proton exchange, the hydroxyl proton does not remain bonded to the oxygen long enough for spin-spin splitting to occur.

The infrared spectrum of cis-1,2-cyclopentanediol has an O-H stretching band at a lower frequency than for a free -OH group, and this band does not disappear even at high dilution. trans 1,2 Cyclopentanediol shows no such band. Can you suggest a possible explanation?

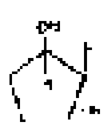
Solution: A consideration of the structure of cis-1,2-cyclopentanediol and the factors that might shift the characteristic absorption band of a group in the infrared spectrum will aid in solving this problem.

It is known that the absorption band of a group may be shifted by various structural features: conjugation, electron withdrawal by a neighboring substituent, angle strain or van der Waals strain, and hydrogen bonding. The structure of cis 1,2 cyclopentanediol (below) reveals an interesting fact.



The hydroxyl groups located on the same face can undergo intramolecular hydrogen bonding, as indicated by the dashed line. This phenomenon is referred to as chelation, the holding of a hydrogen or metal atom between two atoms of a single molecule. Intramolecular hydrogen bonding appears to occur whenever the structure of a compound permits. This phenomenon explains the fact that even at high dilution the shifted absorption band does not disappear. Under high dilution conditions, the chance of intermolecular hydrogen bonding (that is, hydrogen bonding between molecules) is remote, but intramolecular hydrogen bonding still occurs.

At this point, examine the structure of trans-1,2-cyclopentanediol as shown:



Here, the structure of the compound does not permit intramolecular hydrogen bonding. Consequently, there should be no band at high dilution.

The cis-isomer has an O-H stretch band at a lower frequency because the O-H stretch is greater in the cis-isomer than in a free -OH group. This is because the relatively weak intramolecular hydrogen bond pulls the O-H bond further apart; that is the bond is stretched more.

• PROBLEM 16-29

Indicate how you would synthesize each of the following substances from the given organic starting materials and other necessary organic or inorganic reagents. Specify reagents and conditions.

(a) $CH_3CH_2\underset{\underset{\displaystyle O}{\|}}{\underset{|}{CH}}CH_2CH_3$ with $O-C-CH_3$ on the central carbon, from CH_3CH_2OH

(b) $(CH_3)_2CH-CH_2Br$ from $(CH_3)_3COH$

(c) $CH_3CH_2C(CH_3)_2CHO$ from $(CH_3)_2C(OH)CH_2CH_3$

(d) $CH_3OCH_2CH_2OCH_3$ from ethylene

(e) from

(cis) (trans)

Solution: (a) We want to prepare an ester $\left(R-\overset{O}{\overset{\|}{C}}OR'\right)$ from an alcohol (ROH). This esterification reaction can be done by reacting an alcohol with an amide $\left(R-\overset{O}{\overset{\|}{C}}NH_2\right)$, an acid chloride $\left(R-\overset{O}{\overset{\|}{C}}-Cl\right)$, an acid anhydride $\left(R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R\right)$ or a carboxylic acid $\left(R-\overset{O}{\overset{\|}{C}}OH\right)$ with an acid catalyst. The "R" group of the alcohol becomes the ethereal alkyl group of the ester:

$$R'-\overset{O}{\overset{\|}{C}}-Cl \quad + \quad \underline{R}-OH \quad \longrightarrow \quad R'-\overset{O}{\overset{\|}{C}}-O\underline{R} \quad + \quad HCl$$

acid chloride alcohol ester

To prepare our desired product (an ester), we must first synthesize the alcoholic portion of the ester (3-pentanol) from the starting material (ethanol). This can be done by a Grignard reaction. Grignard reagents (organo-magnesium compounds of the type R-Mg-X) will react with carbonyl compounds to produce alcohols upon hydrolysis. The alkyl group of the Grignard reagent adds onto the carbonyl carbon. If the carbonyl carbon bears a potential leaving group, that group will leave to form another carbonyl compound, which will react with another molecule of Grignard reagent. Once 3-pentanol is formed, we can react it with acetyl chloride to produce our desired product. The synthesis is as follows:

First step - an S_N reaction

$$CH_3CH_2OH + HBr \longrightarrow CH_3CH_2Br$$

ethanol $\qquad\qquad\qquad\qquad$ ethyl bromide

Second step - preparation of Grignard reagent

$$CH_3CH_2Br + Mg \xrightarrow{\text{ether}} CH_3CH_2MgBr$$

ethyl magnesium bromide

Third step - reaction with carbonyl compound

$$2\ CH_3CH_2MgBr + H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OC_2H_5 \longrightarrow CH_3CH_2{-}\underset{\underset{\displaystyle CH_2CH_3}{|}}{\overset{\overset{\displaystyle OMgBr}{|}}{C}}{-}H \xrightarrow{H_2O} CH_3CH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_2CH_3$$

3-pentanol

Fourth step - reaction with an acid chloride

$$CH_3CH_2\underset{\underset{\displaystyle OH}{|}}{C}HCH_2CH_3 + CH_3\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl \longrightarrow CH_3CH_2\underset{\underset{\displaystyle O{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}CH_3}{|}}{C}HCH_2CH_3 + HCl$$

3-pentylacetate

(b) We want to synthesize an alkyl bromide (isobutyl bromide) from an alcohol (t-butanol). Since the two compounds have the same carbon skeleton $\left(C{-}\overset{\overset{\displaystyle C}{|}}{C}{-}C\right)$, and the bromine of the alkyl bromide is on a carbon adjacent to the one that holds the hydroxyl group in the alcohol, an elimination reaction must first be performed. Once the alkene is formed we must add a bromine atom in the orientation that will yield the desired product. Elimination reactions occur fastest with a strong base. Tertiary alkoxides are of sufficient basicity so as to yield mainly elimination products. To add a bromine to the alkene (isobutylene) in the orientation that will yield the desired product, we must use a free radical hydrobromination reaction. This reaction proceeds with an anti-Markovnikov addition to the alkene because (1) a bromine radical and not a hydrogen radical reacts first with the π system of the alkene, and (2) the most stable radical is formed most rapidly. Hence the synthesis of isobutyl bromide from t-butanol is:

$$(CH_3)_3C\text{-}OH \xrightarrow[-H_2O]{K^+\ ^-OC(CH_3)_3} (CH_3)_2C{=}CH_2$$

t-butanol isobutylene

$$(CH_3)_2C{=}CH_2 + HBr \xrightarrow[\text{(dibenzoyl peroxide - a radical initiator)}]{C_6H_5\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}C_6H_5}$$

$$\overset{CH_3}{CH_3\text{-}CHCH_2Br}$$

isobutyl bromide

(c) We want to synthesize an aldehyde (R-CHO) from an alcohol. Since the carbon skeleton of the aldehyde

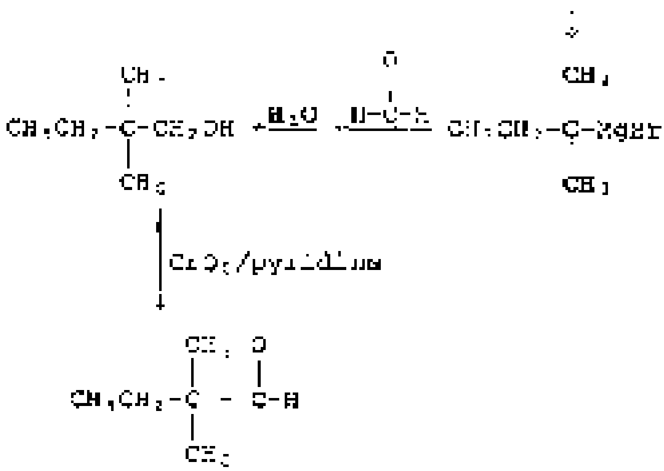
$\left(\begin{array}{c} C \\ C\ C\ C\ C \\ | \\ C \end{array}\right)$ has one more carbon that that of the alcohol

$\left(\begin{array}{c} C \\ | \\ C\text{-}C\text{-}C \\ | \\ C \end{array}\right)$, and that carbon is bonded to the carbon that

bears the hydroxyl group in the alcohol, we can use a Grignard reaction with formaldehyde $\left(H\text{-}\overset{O}{\overset{\|}{C}}\text{-}H\right)$ to bring us closer to our desired product. Subsequent hydrolysis will yield 2,2-dimethylbutanol; our desired product is 2,2 dimethylbutanal. Oxidation of the primary alcohol to the aldehyde can be accomplished with Sarett's reagent, a combination of chromium trioxide (CrO_3) with pyridine. The Grignard reagent can be prepared by first converting the alcohol to the alkyl bromide (R_3I) and then reacting with magnesium in dry ether. The synthesis of 2,2 dimethyl butanal from 1,1-dimethylpropanol is:

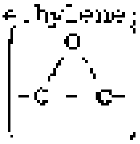
$$CH_3CH_2\text{-}\underset{CH_3}{\overset{CH_3}{C}}\text{-}OH \xrightarrow{HBr} CH_3CH_2\text{-}\underset{CH_3}{\overset{CH_3}{C}}\text{-}Br$$

$$\downarrow Mg/ether$$

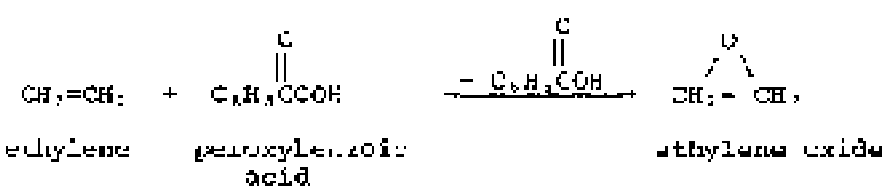


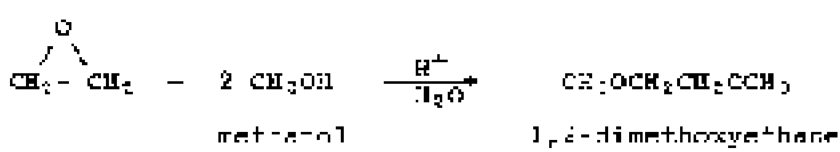
2,2 dimethylbutanal

(d) We want to synthesize 1,2 dimethoxyethane from ethylene; this can be done by proceeding through an epoxide



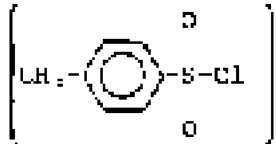
. The desired product is very similar to methyl cellosolve ($CH_3OCH_2CH_2OH$) and is synthesized from ethylene in a similar fashion. Ethylene is converted to ethylene oxide (an epoxide) by reacting with peroxybenzoic acid $\left[C_6H_5\overset{O}{\overset{\|}{C}}-O-OH\right]$. Ethylene oxide will react with two moles of methanol, with an acid catalyst, to produce the desired product. The electron rich oxygen of methanol attacks a carbon of ethylene oxide to form methyl cellosolve. The hydroxyl group becomes protonated and reacts with a second molecule of methanol. The synthesis is:



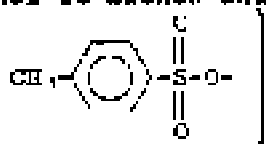


(e) We want to synthesize cis 3 methylcyclopentyl chloride from trans-3-methylcyclopentanol. The inversion of configuration can be accomplished by an S_N2 reaction.

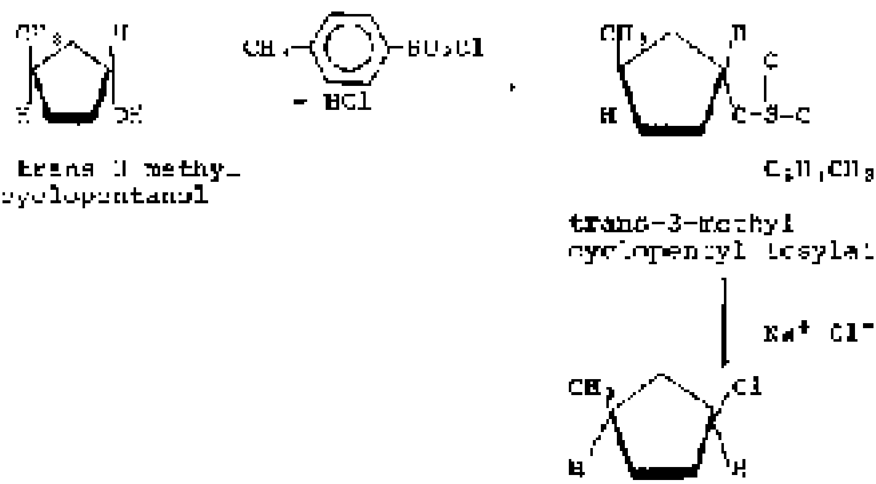
Since the hydroxyl group is a poor leaving group, it will leave only in protonated form; that is, it will leave only as water. If the starting material reacted with HCl, the reaction would be more S_N1 than S_N2; therefore racemization and not inversion of configuration would occur. If the hydroxyl group was replaced by a better leaving group (e.g. chloride ion), the reaction would proceed mainly via an S_N2 pathway. This is accomplished by reacting the starting material with tosyl chloride



, the O-H bond of the alcohol is broken and the product has a tosylate group



in place of the hydroxyl group. The tosylate group has excellent leaving group abilities and will proceed mainly via an S_N2 pathway when the compound is reacted with chloride ion. The synthesis is as follows:



trans-3-methyl-cyclopentanol

trans-3-methyl cyclopentyl tosylate

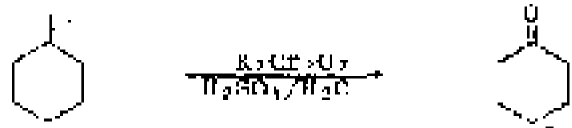
cis-3-methyl-cyclopentyl chloride

• PROBLEM 16-30

Outline all steps in a possible laboratory synthesis of each of the following compounds from cyclohexanol and any necessary aliphatic, aromatic, or inorganic reagents.

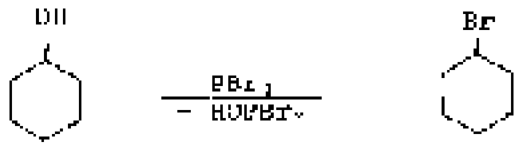
(a) cyclohexanone ($C_6H_{10}O$)
(b) bromocyclohexane
(c) 1-methylcyclohexanol
(d) 1-methylcyclohexene
(e) trans-2-methylcyclohexanol
(f) cyclohexylmethylcarbinol
(g) trans-1,2-dibromocyclohexane
(h) cyclohexanecarboxylic acid
(i) adipic acid $HOOC(CH_2)_4COOH$

Solution: (a) Like most secondary alcohols $\left[\mathrm{R{-}\underset{}{\overset{R'}{|}}{CHOH}}\right]$, cyclohexanol will be oxidized to a ketone $\left[\mathrm{R{-}\overset{O}{\overset{\|}{C}}{-}R'}\right]$ by oxidizing solutions such as potassium dichromate ($K_2Cr_2O_7$) in aqueous sulfuric acid or chromium trioxide (CrO_3) in aqueous acetic acid. The synthesis of cyclohexanone from cyclohexanol is:

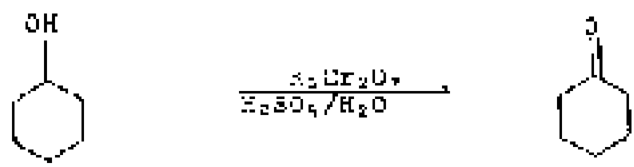


cyclohexanol   cyclohexanone

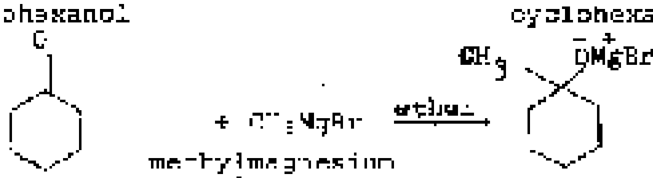
(b) Alcohols will react with phosphorous tribromide to form an alkyl bromide. The hydroxyl group is replaced by a bromine atom and this occurs by an S_N displacement reaction. Bromocyclohexane is prepared from cyclohexanol as shown:



(c) 1-Methylcyclohexanol differs from cyclohexanol in that there is a methyl group bonded to the carbon bearing the hydroxyl group. This extra carbon can be added to cyclohexanol by a Grignard reaction. A Grignard reagent with a one carbon alkyl group (a methylmagnesium halide compound) will react with cyclohexanone to form the Grignard salt of the desired product. Subsequent hydrolysis will lead to 1-methylcyclohexanol. The synthesis is:

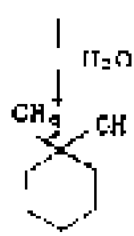


cyclohexanol   cyclohexanone

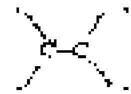


methylmagnesium bromide

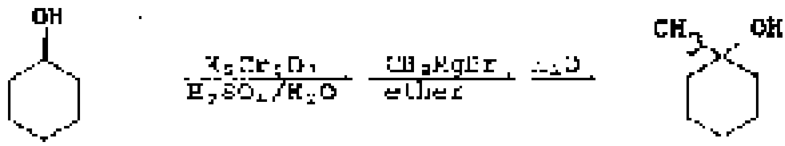
Grignard salt



1-methylcyclohexanol

(d) 1-Methylcyclohexene can be prepared from 1-methylcyclohexanol by a dehydration reaction: in acidic solution an alcohol will have its hydroxyl group protonated and will undergo an elimination reaction to form an alkene  .

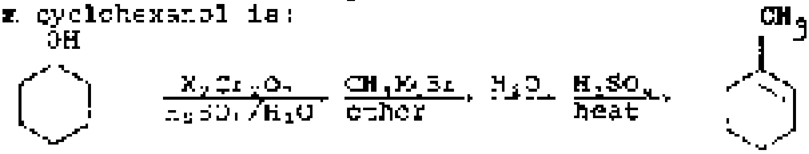
If there is more than one alkene that could possibly be formed (as in our case), the most highly substituted alkene will be the major product because it is the most stable one; this product is called the Saytzeff product. The less substituted alkene (the minor product) is known as the Hofmann product. Hence 1-methylcyclohexene is synthesized from cyclohexanol as follows:



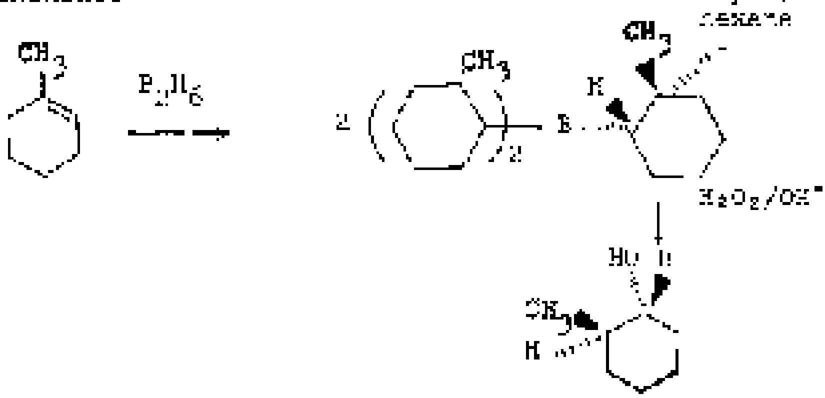
cyclohexanol 1-methylcyclohexanol

1-methylcyclohexene

(e) Trans-2-methylcyclohexanol can be prepared from 1-methylcyclohexene by the hydroboration-oxidation method of synthesizing alcohols from alkenes. This method involves the reaction of an alkene with diborane (B_2H_6); the diborane adds cis to the alkene (the hydrogen and boron atoms add onto the double bond from the same side) and in an anti-Markovnikov fashion. Oxidation of the alkylborane (R_3B) by a basic solution of hydrogen peroxide (H_2O_2) will yield the alcohol. The synthesis of our desired product from cyclohexanol is:



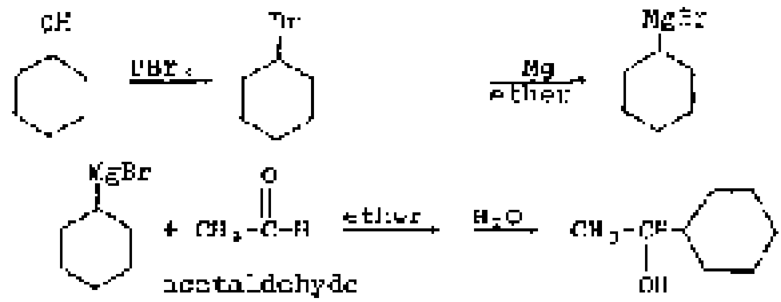
cyclohexanol 1-methylcyclohexene



trans-2-methylcyclohexanol

Note that the hydroxide ion replaces the boron with retention of configuration. Hence the trans configuration in the alkyl borane is retained in the final product.

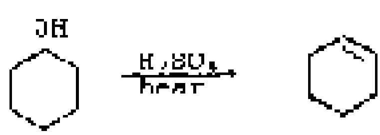
(f) The desired product can be synthesized from cyclohexanol by a Grignard reaction. Cyclohexanol must first be converted to the alkyl halide. We can convert it to an alkyl bromide (cyclohexyl bromide) by reacting it with PBr_3. The Grignard reagent can then be made by reacting cyclohexyl bromide with magnesium in dry ether. Reaction of the Grignard reagent with a carbonyl compound consisting of two carbons (acetaldehyde) will lead to the desired product after hydrolysis. The synthesis of cyclohexylmethylcarbinol from cyclohexanol is:

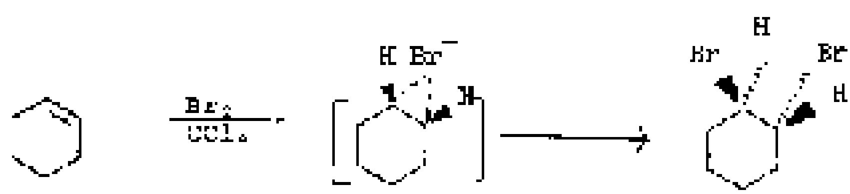


acetaldehyde

cyclohexylmethylcarbinol

(g) Trans 1,2 dibromocyclohexane can be synthesized from cyclohexene by reaction with bromine in carbon tetrachloride. The reaction proceeds through an intermediate cyclic bromonium ion. A bromide ion reacts with the intermediate in a trans fashion to give a trans-product from the alkene. Cyclohexene can be produced from cyclohexanol by a dehydration (elimination) reaction. This is done by heating cyclohexanol with a strong acid.

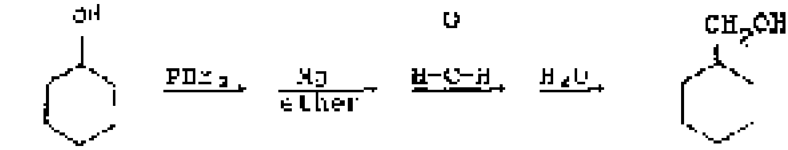




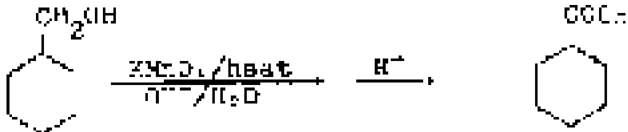
cyclohexene

trans-1,2-dibromocyclohexane

(h) Cyclohexanecarboxylic acid can be prepared by the oxidation of cyclohexylcarbinol by potassium permanganate. Cyclohexylcarbinol in turn can be prepared by the Grignard reaction of cyclohexy magnesium bromide with formaldehyde. Hence we can synthesize cyclohexanecarboxylic acid as follows:

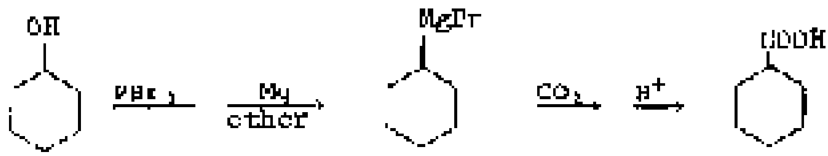


cyclohexanol cyclohexanemethanol

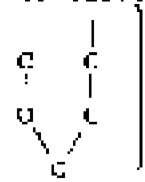


cyclohexanecarboxylic acid

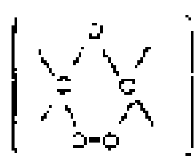
An alternate route of synthesis uses the reaction of cyclohexylmagnesium bromide with carbon dioxide. Subsequent acidification will yield the desired product:



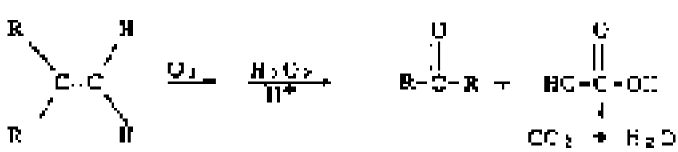
(l) Adipic acid can be synthesized from cyclohexene by an ozonolysis reaction with an oxidative workup. Alkenes react with ozone (O_3) to cleave the σ and π bonds. Upon reaction, a molozonide

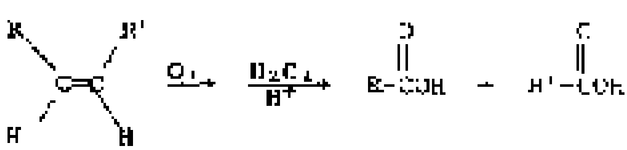


is formed, which spontaneously changes to an ozonide

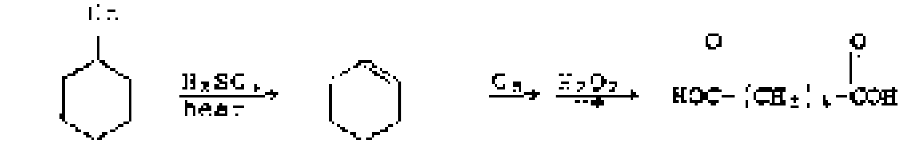


Oxidative workup of the ozonide with an acidic solution of hydrogen peroxide (H_2O_2) will yield ketones and/or carboxylic acids and/or carbon dioxide and water. The oxidation products depend upon the degree of substitution of the alkene. Some examples are:





Cyclohexene will undergo an ozonolysis reaction to yield adipic acid upon oxidative workup. Cyclohexene is produced from cyclohexanol by a dehydration (elimination) reaction. The synthesis of adipic acid from cyclohexanol is:

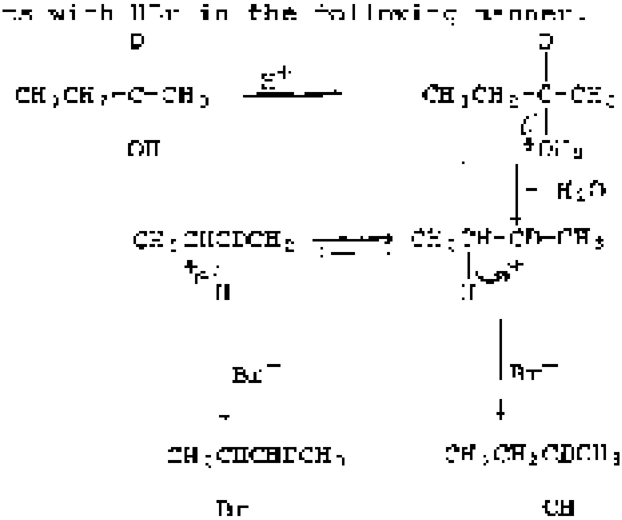


cyclohexanol   cyclohexene   adipic acid

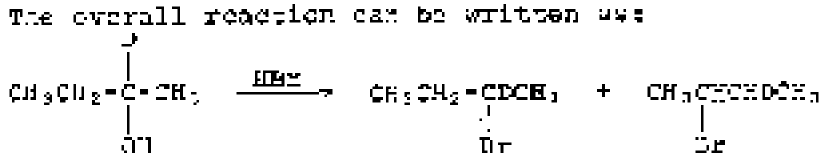
● PROBLEM 16-31

A naive graduate student attempted the preparation of $CH_3CH_2CDBrCH_3$ from $CH_3CH_2CDOHCH_3$ by heating the deuterio-alcohol with HBr and H_2SO_4. He obtained a product having the correct boiling point, but a careful examination of the spectral properties by his research director showed that the product was a mixture of $CH_3CHDCHBrCH_3$ and $CH_3CH_2CDBrCH_3$. What happened?

Solution: In acidic media alcohols will become protonated at their hydroxyl oxygen. Subsequent loss of water will produce a carbocation which will react with bromide ion to produce an alkyl bromide. 2-Deuterio-2-butanol reacts with HBr to form a secondary carbocation; a 1,2-hydride shift might occur to give another secondary carbocation; this type of rearrangement readily occurs because there is no change in stability. Hence 2-deuterio-2-butanol reacts with HBr in the following manner.



The overall reaction can be written as:



Either t-butyl alcohol or isobutylene treated with strong sulfuric acid and hydrogen peroxide gives a mixture of two liquid compounds (A and B), the ratio of which depends on whether the hydrogen peroxide or organic starting material is in excess. Both substances are reasonably stable and A is $C_4H_{10}O_2$, whereas B is $C_8H_{18}O_2$.

Treatment of A and B with hydrogen over a nickel catalyst results in quantitative conversion of each compound to t-butyl alcohol. A reacts with acyl halides and acid anhydrides, whereas B is unaffected by these reagents. Treatment of 1 mole of A with excess methylmagnesium iodide in diethyl ether solution produces 1 mole of methane and 1 mole each of t-butyl alcohol and methanol. One mole of B with excess methylmagnesium iodide gives 1 mole of methyl t-butyl ether and 1 mole of t-butyl alcohol.

When B is heated with vinyl chloride it causes polymerization to occur.

Work out structures for A and B from the above data. Write equations for all the reactions involved, showing the mechanisms and intermediates that are important for each.

Solution: The molecular formula (M.F.) of compounds A and B are of the type $C_nH_{2n+2}O_2$. This indicates that the compounds are saturated (there are no C=O or C=C bonds or rings) and belong to any one of the following classes of compounds:

(1) dialcohol (a diol)

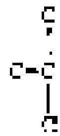
(2) monohydroxy ether

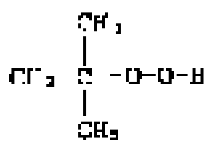
(3) diether (compound with two ether linkages)

(4) peroxide.

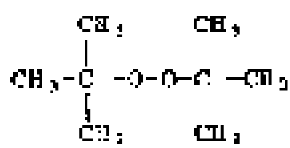
Catalytic hydrogenation of compounds A and B gave the same product: t-butanol. The fact that compounds A and B underwent catalytic hydrogenation indicates that they are peroxide compounds and cannot be any of the other types of compounds listed above. This is because catalytic hydrogenation acts upon π bonds (generally C=O and C=C). Since diols, monohydroxy ethers and diethers do not possess π bonds they will not undergo catalytic hydrogenation. Peroxides also lack π bonds but they will undergo catalytic hydrogenation to yield alcohols:

$$\underset{\text{peroxide}}{R-O-O-R'} \xrightarrow{H_2/Ni} \underset{\text{alcohol}}{R-OH} + \underset{\text{alcohol}}{R'-OH}$$

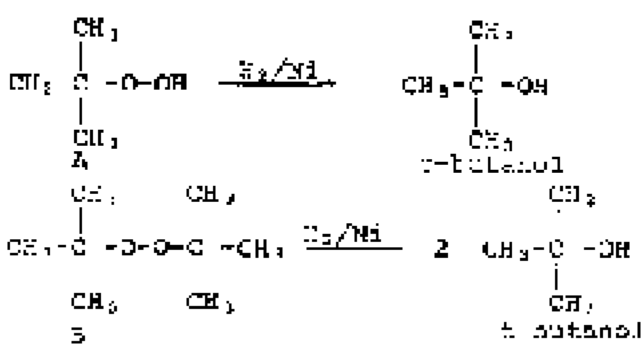
This is because the σ bond between the two oxygens is a relatively weak bond. The strength of this σ bond is closer to a C=C π bond than to a C-C σ bond. Hence the oxygen-oxygen σ bond of peroxides will be broken upon catalytic hydrogenation. t-Butanol ($(CH_3)_3C-OH$) was the sole product of the catalytic hydrogenation of A and B. This means that both A and B have their carbons arranged in the same way that t-butanol is structured; that is, the carbon skeleton of A and B is  . Since the M.F. of compound A is $C_4H_{10}O_2$, this restricts A to four carbons and hence one t-butyl group. The M.F. of compound B ($C_8H_{18}O_2$) restricts B to eight carbons and hence two t-butyl groups. Since A and B are peroxides and their catalytic hydrogenation product is t-butanol (which has the -OH on the tertiary carbon), the peroxide linkage (the -O-O- portion) must be located on the tertiary carbon of the t-butyl group(s). Thus a possible structure for compound A is:

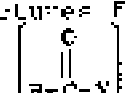
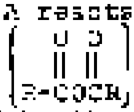


And for Compound B:



The reaction for catalytic hydrogenation of these compounds is:



We will try to explain the other experimental results by referring to our suggested structures for A and B. Compound A reacts with acyl halides  and acid anhydrides  while compound B will not. This can be explained by the fact that A has an -OH functionality whereas B does not. Compounds that have an -OH portion will react with acyl halides and acid anhydrides; the electronegative oxygen will attack the electropositive carbonyl carbon $\left[\begin{array}{c} O^{\delta-} \\ \| \\ -C- \\ \delta+ \end{array}\right]$ to displace a halide ion or a carboxylate anion. Subsequent proton loss from the -OH portion results in water $\left[R-\overset{O}{\overset{\|}{C}}-OR'\right]$ formation. In our case a peroxy ester $\left[R-\overset{O}{\overset{\|}{C}}-O-O-R'\right]$ will be formed. The reaction of A with an acyl halide and an acid anhydride is shown below:

$$\underset{A}{(CH_3)_3C-O-O-H} + \underset{\text{Acyl halide}}{R-\overset{O}{\overset{\|}{C}}-X} \xrightarrow{-X^-} (CH_3)_3C-O-\overset{+}{\underset{H}{O}}-\overset{O}{\overset{\|}{C}}-R$$

$$\xrightarrow{-H^+} \underset{\text{peroxyester}}{(CH_3)_3C-O-O-\overset{O}{\overset{\|}{C}}-R}$$

$$\underset{A}{(CH_3)_3COOH} + \underset{\text{acid anhydride}}{R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R} \xrightarrow{-RCOOH} \underset{\text{peroxy ester}}{(CH_3)_3C-O-O-\overset{O}{\overset{\|}{C}}-R}$$

Grignard reagents (R'-Mg-X) will react with peroxides of the type R-O-O-H to remove the active hydrogen (ROOH) and form a hydrocarbon (R'H) and a Grignard salt (ROO-MgX). If there is excess Grignard reagent, it will react with ROOMgX to form two Grignard salts which will be converted to alcohols upon hydrolysis:

$$ROOH + R'MgX \longrightarrow \underset{\text{hydrocarbon}}{R'H} + ROOMgX$$

$$ROMgX + R'OMgX \xleftarrow{R'MgX} ROOMgX$$

$$\downarrow H_2O$$

$$\underset{\text{alcohols}}{ROH + R'OH}$$

Peroxides of the type ROOR will react with excess Grignard reagent to form an ether and an alcohol (after hydrolysis of the Grignard salt):

$$ROOR + R'MgX \longrightarrow ROMgX + \underset{\text{ether}}{ROR'}$$

$$\downarrow H_2O$$

$$\underset{\text{alcohol}}{ROH}$$

Compounds A and B react with excess methylmagnesium iodide as follows:

$$\underset{A}{(CH_3)_3C\text{-}OOH} + \underset{\text{methyl magnesium iodide}}{CH_3MgI} \longrightarrow \underset{\text{methane}}{CH_4} + (CH_3)_3COOMgI$$

$$(CH_3)_3COOMgI \xrightarrow{CH_3MgI} (CH_3)_3COMgI + CH_3OMgI$$

$$(CH_3)_3COMgI + CH_3OMgI \xrightarrow{H_2O} \underset{\text{t-butanol}}{(CH_3)_3COH} + \underset{\text{methanol}}{CH_3OH}$$

$$\underset{B}{CH_3\text{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}\text{-}O\text{-}O\text{-}\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}\text{-}CH_3} + CH_3MgI \longrightarrow \underset{\text{methyl-t-butyl ether}}{(CH_3)_3C\text{-}O\text{-}CH_3} + (CH_3)_3COMgI$$

$$(CH_3)_3COMgI \xrightarrow{H_2O} \underset{\text{t-butanol}}{(CH_3)_3C\text{-}OH}$$

Peroxides of the type ROOR are often used as radical initiators in free radical polymerization reactions. According to our suggested structures, compound B is a peroxide of the type ROOR. Vinyl chloride will undergo a free radical polymerization to form polyvinylchloride (PVC). Polymerization occurs in a head to tail fashion; the growing end of the polymer chain is the most stable radical possible. Hence the growing end of the PVC chain will be

$$R\text{-}CH_2\text{-}\overset{\overset{H}{|}}{\underset{\underset{Cl}{|}}{C}}\cdot\ .$$

When peroxides are heated, the weak oxygen-oxygen bond is broken and an alkoxy radical $(R\text{-}\ddot{\underset{..}{O}}\cdot)$ is formed. This is the initiation step in free radical polymerization.

Compound B reacts with vinyl chloride to form PVC when heated as follows:

Initiation: $(CH_3)_3C\text{-}\ddot{\underset{..}{O}}\text{-}\ddot{\underset{..}{O}}\text{-}C(CH_3)_3 \xrightarrow{\text{heat}} 2\ (CH_3)_3C\ \ddot{\underset{..}{O}}\cdot$

$$\left[(CH_3)_3C\text{-}\ddot{\underset{\cdot\cdot}{O}}\cdot + CH_2\text{=}CHCl \longrightarrow\right.$$

$$\text{propagation} \left\{ \begin{array}{l} (CH_3)_3C\,O\text{-}CH_2\text{-}\underset{Cl}{\overset{H}{C}}\cdot \quad + \quad n(CH_2\text{=}CHCl) \longrightarrow \\ \\ (CH_3)_3C\text{-}O\text{-}(CH_2\text{-}CHCl)_n\text{-}CH_2\text{-}\underset{Cl}{\overset{H}{C}}\cdot \end{array} \right.$$

$$\left\{ \begin{array}{l} 2\ (CH_3)_3CO\text{-}(CH_2CHCl)_n\text{-}CH_2\underset{Cl}{\overset{H}{C}}\cdot \longrightarrow \\ \\ (CH_3)_3CO\text{-}(CH_2CHCl)_{2n+2}\text{-}OC(CH_3)_3 \end{array} \right.$$

- and/or -

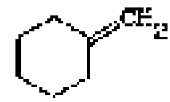
$$\text{termination} \left\{ \begin{array}{l} 2\ (CH_3)_3CO(CH_2CHCl)_n\text{-}CH_2\text{-}\underset{Cl}{\overset{H}{C}}\cdot \longrightarrow \\ \\ (CH_3)_3CO\text{-}(CH_2CHCl)_n\text{-}CH_2CH_2Cl\ + \\ \\ (CH_3)_3CO(CH_2CHCl)_n\text{-}CH\text{=}CHCl \end{array} \right.$$

- and/or -

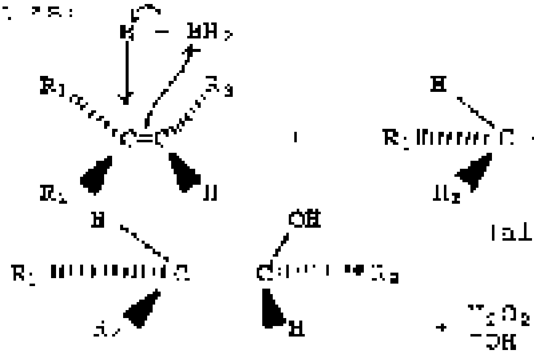
$$\left\{ \begin{array}{l} (CH_3)_3CO\text{-}(CH_2CHCl)_n\,CH_2\underset{Cl}{\overset{H}{C}}\cdot \quad + \quad (CH_3)_3C\ddot{\underset{\cdot\cdot}{O}}\cdot \\ \qquad\qquad\qquad\downarrow \\ (CH_3)_3CO(CH_2CHCl)_{n+1}\text{-}OC(CH_3)_3 \end{array} \right.$$

Since all the reactions of compounds A and B have been accounted for by our suggested structures, compounds A and B must be the ones we suggested.

Identify the alcohol that will be produced by the hydroboration-oxidation of the following:

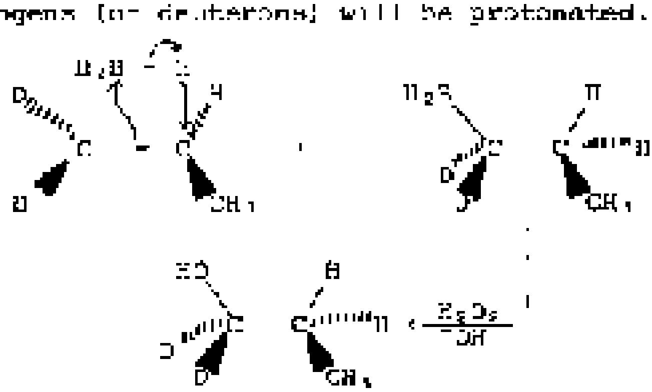
(a) $D_2C{=}CHCH_3$
(b) $CH_3CH{=}CHCH_3$ (Z isomer)
(c) $CH_3CH{=}CHCH_3$ (E isomer)
(d) 

Solution: Alcohols can be synthesized from alkenes by a hydroboration-oxidation procedure. This method involves the reaction of diborane (B_2H_6) with the alkene; subsequent oxidation by a basic solution of hydrogen peroxide (H_2O_2) will yield the alcohol. Diborane adds cis to the alkene and in an anti-Markovnikov fashion. The general reaction is shown as:



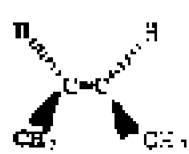
With this information we can predict the hydroboration-oxidation products of alkenes (a) through (d).

(a) Diborane adds to the alkene in an anti-Markovnikov fashion; that is, the carbon bearing the least number of hydrogens (or deuterons) will be protonated. Hence,

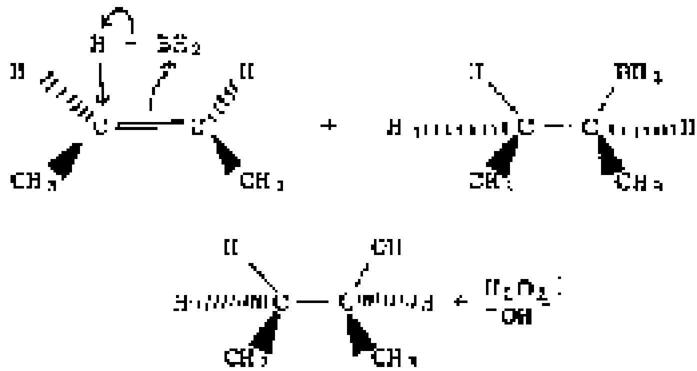


The product is $HO\text{-}CD_2CH_2CH_3$, 1,1-dideuteriopropanol.

(b) The Z isomer of 2 butene is called cis-2-butene; it has the structure:



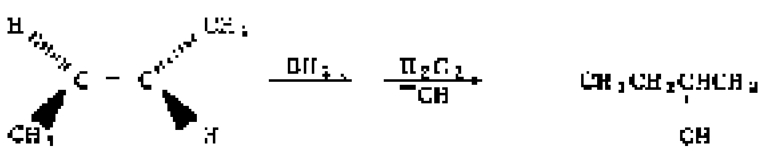
The hydroboration-oxidation of cis-2-butene is shown as:



Either carbon of the alkene can receive the hydrogen since they are equivalent. BH_3 can attack either face of the double bond equally well and hence the product will be a racemic mixture of dextrorotatory and levorotatory 2-butanol. The product is therefore (d,l)-2-butanol.

(c) The E isomer of 2 butene is called trans-2-butene and has the structure:

Either one of the sp^2-hybridized carbons can receive the hydrogen from BH_3 because they are equivalent. Since BH_3 can attack either face of the double bond equally well the product will be a racemic mixture of 2-butanol. This is the same product formed in part (b).



(d,l)-2-butanol

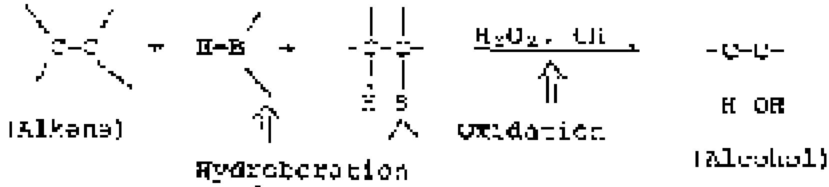
(d) Hydroboration-oxidation of methylene cyclohexane would place the hydroxyl group on the $=CH_2$. Hence the product is cyclohexylcarbinol.

methylene cyclohexane

cyclohexylcarbinol

Predict the products of hydroboration-oxidation of: (a) cis-2-phenyl-2-butene; (b) trans-2-phenyl-2-butene; (c) 1-methylcyclohexene.

Solution: When diborane, $(BH_3)_2$, is added to alkenes, they undergo hydroboration to yield alkylboranes, R_3B. These compounds give rise to alcohols on oxidation. This hydroboration-oxidation may be illustrated as:

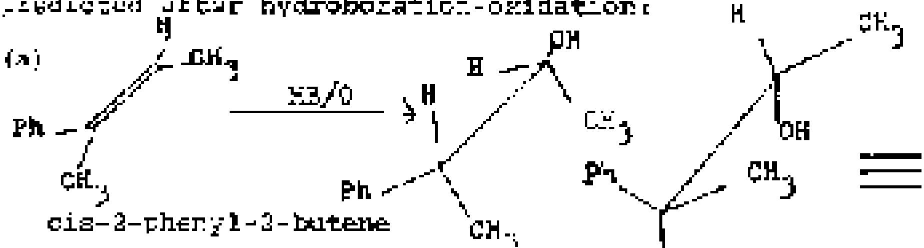


$H-B\langle$ = $H-BH_2$, $H-BHR$, $H-BR_2$

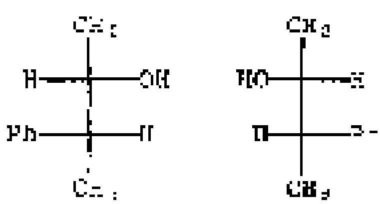
It is important to recognize that this reaction gives products corresponding to anti-Markovnikov addition of water to the carbon-carbon double bond. This behavior evidently results because carbonium ions are not intermediates - rearrangement does not occur in hydroboration. The stereochemistry of this reaction involves syn addition, that is, addition to the double bond is on the same face of the alkene.

With this in mind, the following products can be predicted after hydroboration-oxidation:

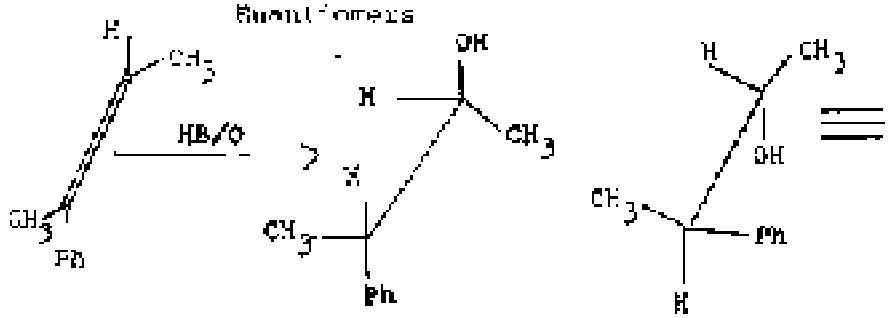
(a)



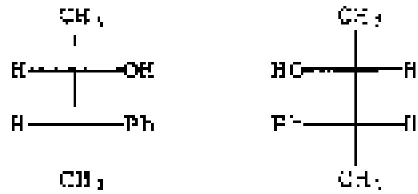
cis-2-phenyl-2-butene



Enantiomers

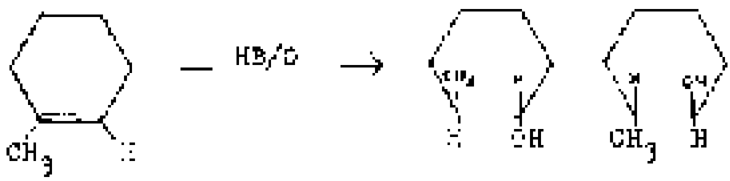


trans-2-phenyl-2-butene



Enantiomers

(c)

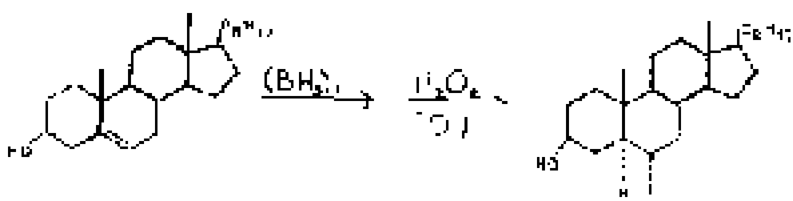


1-methylcyclohexene   Enantiomers

In each case, the reaction proceeds with syn-addition (hydration) and anti-Markovnikov orientation.

• PROBLEM 16-35

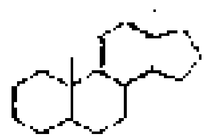
(a) As shown in the diagram below, cholesterol is converted into cholestane-3β,6α-diol through syn-hydration by hydroboration-oxidation. What stereoisomeric product could also have been formed by syn-hydration? Actually, the reaction gives a 78% yield of cholestane-3β,6α-diol, and only a small amount of its stereoisomer. What factor do you think is responsible for this particular stereospecificity?



cholesterol   cholestane 3β,6α-diol

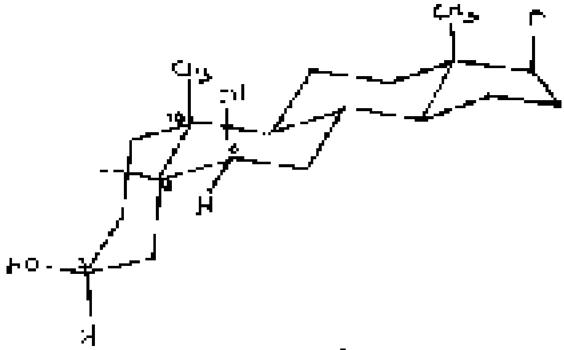
$$C_8H_{17} = -\underset{}{\overset{CH_3}{\overset{|}{CH}}}-CH_2CH_2CH_2CH(CH_3)_2$$

(b) Hydroboration of androst-9(11)-ene gives 90% of a single stereoisomer. Which would you expect this to be?



Androst-9(11)-ene

Solution: (a) Hydroboration-oxidation occurs with cis addition to the alkene in an anti-Markovnikov fashion. Diborane can add onto either face of the alkene. Since the overall hydration process occurs in a cis fashion, hydroboration-oxidation gives syn hydration. Hydration of cholesterol occurs from "beneath" to yield cholestane 3β,6α-diol (β positions are cis to the ring substituents, α positions are trans) and from "above" to yield the stereoisomeric coprostane 3β,6β diol:



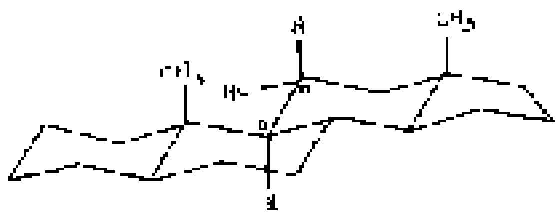
Coprostane-3β,6β-diol

Note:

$R = C_8H_{17}$

Attack from "above" has greater steric hindrance than from "below" because of the substituents projecting "upward", particularly the methyl group at carbon number ten. Hence, the 3β,6α-diol is formed in greater yield than the 3β,6β diol.

(b) Syn-hydration would occur mainly from the side that is less sterically hindered; that is, from "beneath". The main product has an α-OH at carbon number eleven and an α-H at carbon number nine.



CHAPTER 17

ETHERS

NOMENCLATURE AND STRUCTURE

• PROBLEM 17-1

Name each of the following compounds:

(a) $CH_3-O-CH_2-CH(CH_3)_2$

(b) $(CH_3CH_2CH_2)_2-O$

(c) $(CH_3)_2CH-O-CH_2CH_2CH_2CH_3$

(d) $CH_3-O-CH_2CH_2-O-CH_3$

(e) $CH_3CH_2-O-CH_2CH_2CH_2CH_2CH_2-OH$

(f) $\begin{array}{l} \quad\;\; CH_3 \\ \quad\;\;\; | \\ CH_3CHCH_2CH-CH_2 \\ \qquad\qquad \diagdown\;\diagup \\ \qquad\qquad\;\; O \end{array}$

Solution: Ethers have the general formula of R-O-R, where R may represent an alkyl or aryl group. To name many ethers, one usually names the two groups that are attached to oxygen, and follow these names by the word "ether".

(a) The compound $CH_3-O-CH_2CH\begin{array}{l} \diagup CH_3 \\ \diagdown CH_3 \end{array}$ has the oxygen of the ether linkage bonded to methyl and an isobutyl groups. It is called isobutyl methyl ether.

(b) $CH_3CH_2CH_2-O-CH_2CH_2CH_3$ is a symmetrical molecule because the two groups bound to the oxygen are identical. In this compound, the two groups are n-propyls. Thus, it is named dipropyl ether, or n-propyl ether. It is understood that if the name only contains one substituent group, the compound is symmetrical.

(c) The compound $\begin{array}{r} CH_3 \diagdown \\ CH_3 \diagup \end{array} CH-O-CH_2CH_2CH_2CH_3$ contains an isopropyl group and an n-butyl group. It is called n-butyl isopropyl ether.

(d) When an ether contains groups which do not have simple names, the compound may be named as an alkoxy derivative. The alkoxy functional group can be written as RO, where R may be an alkyl group. Since $CH_3-O-CH_2CH_2-O-CH_3$ contains two ether functional groups, which make naming very complicated, one may name the compound as a derivative of ethane. The two substituent groups are both methoxy (CH_3O-) at carbons 1 and 2, respectively. Thus the compound can be named as 1,2-dimethoxy-ethane.

(e) $CH_3CH_2-O-CH_2CH_2CH_2CH_2CH_2OH$ has two functional groups, alkoxy (or ether) and hydroxy (or alcohol). In the IUPAC system, the alcohol functional group takes precedence over the ether in naming. (Exception can be made if the naming is overly complicated when named as an alcohol.)

The compound in question can be named as an alcohol with an alkoxy substitution. The hydrocarbon containing the hydroxy has five carbons. Thus, the compound is a derivative of n-pentanol. The alkoxy substitution is an ethoxy (CH_3CH_2O-) group at the number five carbon (the hydroxyl group is attached to the first carbon). The complete name for the compound is 5-ethoxy-1-pentanol.

Cl

(f) The compound $CH_3CCHCH_2CH-CH_2$ contains a three member ring which includes an oxygen atom. Such compounds are called epoxides. The epoxides are named by numbering the alkyl chain and indicating the two carbons to which the oxygen is attached. The prefix "epoxy" denotes this functional group. Here, the alkyl group contains five carbons: it is a pentane. The epoxide oxygen is attached to carbons 1 and 2, so that the name becomes 1,2 epoxy pentane. The compound also has a chlorine substitution at carbon number four. The full name for

$$CH_3\overset{\overset{\displaystyle Cl}{|}}{C}HCH_2-\underset{\diagdown\,O\,\diagup}{CH-CH_2}$$ is 4-chloro-1,2 epoxypentane.

● **PROBLEM** 17-2

Write structural formulas for:

(a) methyl ether
(b) isopropyl methyl ether
(c) 3-methoxyhexane
(d) 1,2-epoxypentane

Solution: The characteristic functional group in ethers is the oxygen atom single bonded to two carbon atoms. The general formulas for these compounds are R'OR, ROAr and Ar'OAr, where R and R' are either different or identical alkyl groups and Ar and Ar' represent different or identical aryl groups.

When naming simple ethers, both of the attached groups are named in alphabetical order followed by the word 'ether'. For example,

$$CH_3-O-CH_2CH_3$$

is called ethyl methyl ether.

(a) If both of the attached groups are the same, the compound is a symmetrical ether, and only one group need be named. For example, the compound $CH_3CH_2-O-CH_2CH_3$ is usually called ethyl ether. Often to avoid confusion this compound is referred to as diethyl ether. The structure for methyl ether is analogous to this. There is one methyl group on each side of the oxygen. The structure can be written as follows:

$$CH_3-O-CH_3 .$$

This compound is also called dimethyl ether.

(b) Isopropyl methyl ether. This is a simple asymmetrical ether. From its name, one knows that there is a methyl group on one side of the oxygen and an isopropyl group on the other. The structure for this compound is written:

$$\begin{array}{l} CH_3-O-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_3 \end{array}$$

(c) In more complicated ethers, the ether grouping, R-O- (an alkoxy group), may be named as a substituent on a longer chain. A methoxy group is written $-O-CH_3$. In 3-methoxyhexane, the methoxy group is attached to the carbon at the 3 position of the hexane chain.

$$CH_3-CH_2-\underset{\displaystyle O-CH_3}{\underset{|}{CH}}-CH_2-CH_2-CH_3$$

3-methoxyhexane

(d) Epoxides are a class of cyclic ethers in which the ether oxygen is included in a three-membered ring,

$$\overset{|}{-C}-\overset{|}{C}- \text{ (bridged by O)}$$

. Ethylene oxide is drawn as shown: CH_2-CH_2 (bridged by O)

The epoxides are named by numbering the alkyl chain and indicating the two carbons to which the oxygen is attached. The prefix 'epoxy' denotes this functional group. Ethylene oxide can also be called epoxyethane. In 1,2-epoxypentane, the oxygen is bound to the first two carbons of the pentane chain.

1,2-epoxypentane

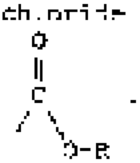
• PROBLEM 17-3

A compound of MW 74 did not react with acetyl chloride, $KMnO_4$, phenylhydrazine, or Schiff's reagent. It dissolved in concentrated H_2SO_4. Suggest three possible structures.

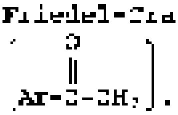
Solution: The molecular weight indicates that it is a small molecule, having at most five carbons. Since it is inert with respect to acetyl chloride, one can make several assumptions.

(1) It contains no amino (NH_2) group, or it would have formed an amide linkage  .

(2) It is not an alcohol because alcohol and acetyl chloride can undergo an esterification reaction to give



(3) It is not aromatic because it does not undergo Friedel-Crafts acylation to give a methyl aryl ketone



Since $KMnO_4$ is an oxidizing reagent for olefins, and the compound is unreactive to $KMnO_4$, it is not an olefin. It does not react with phenylhydrazine or Schiff's reagent; therefore, it is not a carbonyl compound. (Phenylhydrazine can react with the carbonyl group of aldehydes and ketones to form phenylhydrazone; Schiff's reagent is used to identify aldehydes.) Since the compound dissolves in concentrated sulfuric acid, the presence of an oxygen atom is indicated.

Putting all the information together, one obtains a compound with general formula of C_nH_mO. Since oxygen has MW 16, C_nH_m must have MW 58. Keeping in mind the rule C_NH_{2N+2} and the weight limitation of 58, the combination of carbon and hydrogen that fits is C_nH_{2n+2}. (The molecular weights of carbon and hydrogen are, respectively, 12 and 1. Hence, $12(N) + 1(2N + 2) = 58$; $n = 4$.) The molecular formula becomes, therefore, $C_4H_{10}O$. Such a compound may be either an alcohol or ether. Alcohols have already been eliminated by the compounds failure to react with acetyl chloride. Hence, $C_4H_{10}O$ must be an ether. The three possible structures with this molecular formula are as follows:

(1) $CH_3OCH_2CH_2CH_3$ (methyl propyl ether)

(2) $CH_3CH_2OCH_2CH_3$ (diethyl ether)

(3) $CH_3OCH{-}CH_3$ with CH_3 on the CH (isopropyl methyl ether)

PREPARATION

• PROBLEM 17-4

Outline a method of synthesizing α-phenylethyl tert-butyl ether from styrene and tert-butyl alcohol. Any inorganic reagents may be employed.

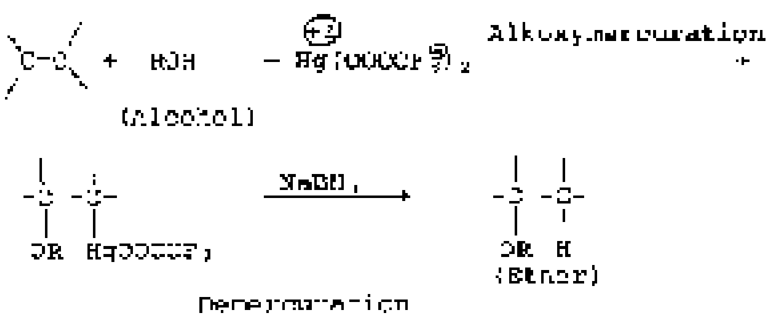
Solution: α-phenylethyl tert-butyl ether

$\left[C_6H_5\underset{OC(CH_3)_3}{\underset{|}{C}H}CH_3\right]$ may be produced from styrene $(C_6H_5CH{=}CH_2)$

and tert-butyl alcohol $((CH_3)_3COH)$ by using the alkoxymercuration-demercuration reaction. In this reaction, alkenes react with mercuric trifluoroacetate

$\left[\overset{+2}{Hg}\ \overset{-}{(OOCCF_3)_2}\right]$ in the presence of an alcohol to give

alkoxymercurial compounds which on reduction yield ethers. Overall, the general reaction may be written as:



This reaction has great utility in that it is fast, convenient, gives good yields, has little or no rearrangement, and has no competing elimination reaction. Therefore, the following equation can be written for the synthesis of α-phenylethyl tert-butyl ether:

$$C_6H_5CH=CH_2 + (CH_3)_3COH \xrightarrow{\overset{\oplus\ \ominus}{Hg(OOCCF_3)_2}} \xrightarrow{NaBH_4} C_6H_5\underset{\displaystyle |\atop \displaystyle OC(CH_3)_3}{C}HCH_3$$

● **PROBLEM 17-5**

> Starting with any alcohols, outline all steps in the synthesis of n-hexyl isopropyl ether, using the Williamson method.

Solution: The Williamson synthesis of ethers is important because of its versatility in the laboratory. This method of synthesis can be used to make unsymmetrical ethers as well as symmetrical ethers. In the Williamson synthesis, an alkyl halide is allowed to react with a sodium alkoxide (or sodium phenoxide).

$$\underset{\text{Alkyl halide}}{R-X} + \underset{\text{Sodium alkoxide}}{R'-O^- Na^+} \rightarrow \underset{\text{Ether}}{R-O-R'} + Na^+X^-,$$

where R represents an alkyl group and X a halide (Cl, Br, I or F). (The yield from RX is: $CH_3>1°>2°$ $(>3°)$.) The sodium alkoxide is made by direct action of sodium metal on dry alcohols:

$$R-OH + Na \rightarrow \underset{\text{Sodium alkoxide}}{R-O^- Na^+} + \tfrac{1}{2} H_2 \uparrow$$

As an example,

$$\underset{\text{Ethanol}}{CH_3-CH_2OH} + Na \rightarrow \underset{\text{Sodium ethoxide}}{CH_3-CH_2-O^- Na^+}$$

Alkyl halides can be prepared from alcohols by use of phosphorus trihalides:

$$R-OH + PX_3 \rightarrow \underset{\text{Alkyl halide}}{RX} + H_3PO_3$$

As an example,

$$\underset{\text{Isobutyl alcohol}}{CH_3-\overset{\displaystyle CH_3\atop \displaystyle |}{C}H-CH_2OH} + PCl_3 \rightarrow \underset{\text{Isobutyl chloride}}{CH_3-\overset{\displaystyle CH_3\atop \displaystyle |}{C}H-CH_2Cl} + H_3PO_3$$

The Williamson synthesis involves nucleophilic substitution of the alkoxide ion for the halide ion.

The compound n-hexyl isopropyl ether is an asymmetrical ether with the formula

$$CH_3(CH_2)_4CH_2-O-\underset{}{\overset{\displaystyle CH_3}{\overset{|}{C}H}}-CH_3$$

and can be prepared from the corresponding alcohols, n-hexyl alcohol and isopropyl alcohol. The complete reactions are:

$$\underset{\text{Isopropyl alcohol}}{CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}H}-OH} + Na \rightarrow \underset{\text{Sodium isopropoxide}}{CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}H}-O^-Na^+}$$

$$\underset{\text{n-Hexyl alcohol}}{CH_3(CH_2)_4CH_2OH} + PBr_3 \rightarrow \underset{\text{n-Hexyl bromide}}{CH_3(CH_2)_4CH_2Br} + H_3PO_3$$

$$\underset{\text{n-Hexyl bromide}}{CH_3(CH_2)_4CH_2Br} + \underset{\text{isopropoxide}}{CH_3-\overset{\displaystyle CH_3}{\overset{|}{C}H}-O^-Na^+} \rightarrow \underset{\text{n-Hexyl isopropyl ether}}{CH_3(CH_2)_4CH_2-O-\underset{\displaystyle CH_3}{\underset{|}{C}H}-CH_3} + NaBr$$

• PROBLEM 17-8

In ether formation by dehydration, as in most other cases of nucleophilic substitution, there is a competing elimination reaction. What is this reaction and what products does it yield? For what alcohols would elimination be most important?

Solution: Ethers have the general formula R-O-R, where R can be aryl and/or alkyl. Ethers can be formed by two alcohols molecules in the presence of strong acid to release a water molecule. This is called acid-catalyzed dehydration of alcohols to form ethers.

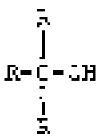
The mechanism of this reaction resembles that of substitution. It involves the protonation of one alcohol and release of a water molecule to form a carbonium ion. A carbonium ion is a strong electrophile. It attacks the electron-rich oxygen of another alcohol, which releases a proton to form an ether.

$$R-O-H \xrightarrow[\text{heat}]{H_2SO_4} R^{\oplus} + H_2O$$

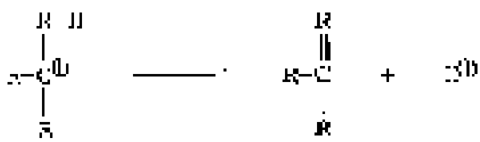
$$R^{\oplus} + \underset{H}{\underset{|}{\ddot{O}}}-R \rightarrow R-O-R + H^{\oplus}$$

Under closer scrutiny, one can see that in the process of strong acid protonation of alcohol, another reaction can occur instead of the substitution attack on another alcohol. A carbonium ion is a highly reactive species. It can participate in a substitution reaction, as in ether formation, or undergo an elimination reaction to form an alkene. The latter reaction is most prominent in tertiary alcohols.

A tertiary alcohol has the general formula of



. It is a bulky molecule. This bulkiness makes the positively charged carbon of the carbonium ion formed less accessible. Therefore, the tertiary carbonium ion can release a proton ($H^{\oplus}$) to obtain the alkene, which will be stabilized by the alkyl substituents.



The dehydration of alcohols to ethers rather than alkenes also reflects the choice of reaction conditions.

• PROBLEM 17-7

> An alkyl bromide, $C_5H_{11}Br$ reacted rapidly with water to give an alcohol $C_5H_{12}O$, but when the alkyl bromide was treated with sodium methoxide in an attempt to convert it to an ether, the only product was an alkene, C_5H_{10}. Ozonolysis of this alkene gave two carbonyl compounds as products, a ketone C_3H_6O and an aldehyde C_2H_4O. What was the structure of the alkyl bromide?

__Solution:__ One method of synthesizing an ether is by reacting sodium alkoxide ($Na^+{}^-O-R'$) with an alkyl halide. Such a preparation is referred to as Williamson synthesis. Since the alkoxide is nucleophilic and a halide is a good leaving group, a substitution reaction may occur. The rate of a substitution reaction depends on the degree of alkylation of the carbon bearing the halide. A primary alkyl halide can undergo a substitution reaction faster than a secondary alkyl halide, which is faster than a tertiary alkyl halide. For a tertiary alkyl halide, the substitution reaction is so slow that the competing elimination reaction begins to predominate. Elimination should be particularly serious when tertiary alkyl halides are present due to the strong basicity of the alkoxide reagent. (Keep in mind that the tendency for alkyl halides to undergo dehydrohalogenation, an elimination reaction, is $3° > 2° > 1°$.)

The fact that the alkyl bromide, $C_5H_{11}Br$, gave an elimination product, an alkene, and not the ether when treated with sodium methoxide strongly suggests it is tertiary, that is,

$$\begin{array}{c} R \\ | \\ R-C-R \\ | \\ Br \end{array}$$

where R represents alkyl groups. Each alkyl group must possess at least one carbon atom, so that the tertiary alkyl halide may be rewritten as:

$$\begin{array}{c} C \\ | \\ C-C-C. \\ | \\ Br \end{array}$$

The molecular formula, $C_5H_{11}Br$, indicates the existence of a total of five carbon atoms, and the above structure accounts for four. The fifth carbon can only be bonded to one of the three available carbon atoms, which are all equivalent. Hence, the carbon skeleton (plus bromine) must be

$$\begin{array}{l} \;\;C \\ \;\;| \\ C-C-C-C. \\ \;\;| \\ \;\;Br \end{array}$$

Filling the hydrogens, the structure becomes

$$\begin{array}{l} \qquad CH_3 \\ H_3C-C\,CH_2CH_3 \\ \qquad Br \end{array}$$

This fits the molecular formula for the alkyl halide and represents the structure in question.

This determination could have been made in another fashion by analysis of the products of ozonolysis. It will be remembered that ozone (O_3) with Zn and H_2O cleaves carbon-carbon double bonds to give aldehydes $\left(\begin{array}{c} O \\ \| \\ R-C-H \end{array}\right)$ and ketones $\left(\begin{array}{c} O \\ \| \\ R-C-R \end{array}\right)$. A doubly bonded oxygen is found attached to each of the originally doubly-bonded carbons. The aldehyde obtained here was C_2H_4O, which can only have the structure:

$$\begin{array}{l} H_3C-C=O \\ \qquad | \\ \qquad H \end{array}$$

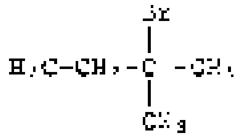
Likewise, the ketone, C_3H_6O, can only be written as:

$$\begin{array}{l} H_3C-C=O \\ \qquad CH_3 \end{array}$$

Working backwards, this means that the alkene originally oxidized was:

$$\begin{array}{l} H_3C-C=O \quad O=C-CH_3 \\ \qquad\;\; H \qquad\quad\;\; CH_3 \end{array} \xleftarrow{O_3} \begin{array}{l} H_3C-C=C-CH_3 \\ \qquad\;\; | \quad | \\ \qquad\;\; H \;\; CH_3 \end{array}$$

Now, recall that the alkyl bromide from which this alkene was obtained must be tertiary. The only way this could happen is if the bromide is positioned on the starred (*) carbon, that is, the structure must be:

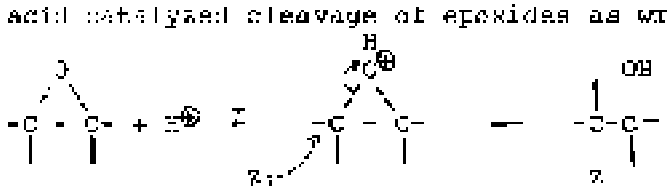


• PROBLEM 17-8

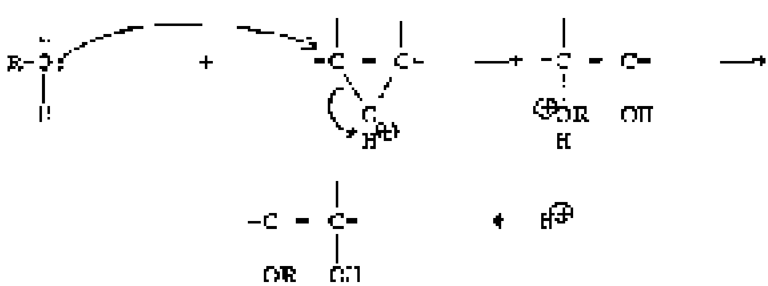
The following compounds are commercially available for use as water soluble solvents. How could each be made?

(a)	$CH_3CH_2-O-CH_2CH_2-O-CH_2CH_2-OH$	Carbitol
(b)	$C_6H_5-O-CH_2CH_2-O-CH_2CH_2-OH$	Phenyl carbitol
(c)	$HO-CH_2CH_2-O-CH_2CH_2-OH$	Diethylene glycol
(d)	$HO-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-OH$	Triethylene glycol

Solution: (a) Carbitol (CH_3CH_2 O CH_2CH_2 O CH_2CH_2 OH) may be synthesized by making use of the chemistry of epoxides. When acid is added to epoxides, they become protonated epoxides which can then undergo attack by any number of nucleophilic reagents. The overall result is acid catalyzed cleavage of epoxides as written below:



, where Z is the nucleophile. Now, the reaction of epoxide with alcohol and acid generates a compound that is both an ether and an alcohol as shown:



An alkoxyalcohol
(A hydroxyether)

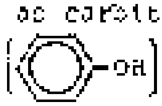
Examination of the structure of carbitol reveals the fact that this compound is both an alcohol and an ether, but with two ether linkages. Hence, the synthesis must be of the same nature as that proposed above.

In the first step of the synthesis, ethanol (CH_3CH_2OH) is taken as the starting material. Ethylene oxide $\left[\underset{O}{CH_2-CH_2}\right]$ is then added in the presence of acid. The product then becomes 2-ethoxyethanol ($CH_3CH_2OCH_2CH_2OH$). The reaction may be written as:

$$CH_3CH_2OH \xrightarrow[\underset{O}{H_2C-CH_2}]{H^{\oplus}} CH_3CH_2OCH_2CH_2OH.$$

At this point, another ethylene oxide must be added (with acid) to synthesize carbitol. ($CH_3CH_2OCH_2CH_2OH$ possesses a hydroxyl (OH) group so that it may act as the nucleophile when the ethylene oxide is protonated by acid.) Consequently,

$$CH_3CH_2OCH_2CH_2OH \xrightarrow[\underset{O}{H_2C-CH_2}]{H^{\oplus}} CH_3CH_2OCH_2CH_2OCH_2CH_2OH.$$

(b) Phenyl carbitol can be synthesized in the same fashion as carbitol, except that the starting material is phenol , not ethanol.

(c) Diethylene glycol is also synthesized in a manner similar to that of carbitol. Here, though, ethanol is replaced by water (HOH).

(d) Triethylene glycol may be readily manufactured if the product from part (c), diethylene glycol, is used as the starting material. Ethylene oxide and acid (H^+) could be added to diethylene glycol to obtain triethylene glycol as illustrated:

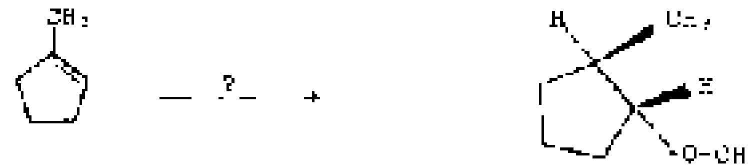
$$HO-CH_2CH_2-O-CH_2CH_2-OH \xrightarrow[\underset{O}{H_2C-CH_2}]{H^{\oplus}}$$

$$HO-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-OH \text{ (triethylene glycol)}$$

• PROBLEM 17-8

Synthesize trans-1-methoxy-2-methylcyclopentane from 1-methylcyclopentene using any needed reagents.

Solution: The problem asks for the following conversion:



1-methylcyclopentene → trans-1-methoxy-2-methyl-cyclopentane

Since the groups participating in the ether linkage are not identical, the ether to be synthesized is asymmetrical. One method of producing asymmetrical ethers is through the Williamson synthesis. In this reaction, an alkyl halide (or substituted alkyl halide) is allowed to react with a sodium alkoxide or a sodium phenoxide as shown:

$$R - X + Na^{\oplus}\ {}^{-}O-R' \rightarrow R\,O\,R' + Na^{\oplus}\ X^{\ominus}$$

(Alkyl halide) (Sodium alkoxide) (Ether)

$$R - X + Na^{\oplus}\ {}^{-}O-Ar \rightarrow R-O-Ar + Na^{\oplus}\ X^{\ominus}$$

(Sodium phenoxide)

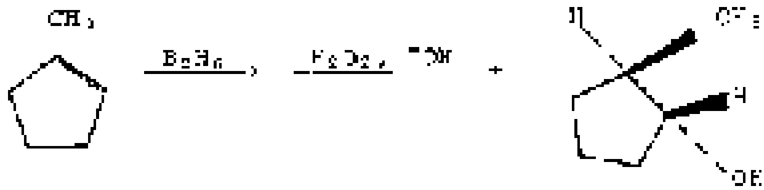
The yield from RX is: $CH_3 > 1° > 2° (> 3°)$. Hence, to produce ether efficiently, a methyl halide or primary halide should be selected. The sodium alkoxides are made by the addition of sodium metal to alcohols: $ROH + Na \rightarrow RO^- Na^+ + \frac{1}{2}H_2$. Due to the appreciable acidity of phenols, sodium phenoxides are made by the action of aqueous sodium hydroxide to phenols:

$$ArOH + NaOH \rightarrow ArO^{\ominus}Na^{\oplus} + H_2O.$$

In this problem, 1-methylcyclopentene, an alkene, is the starting product. This must be converted into the alcohol so that it may be then transformed into the sodium alkoxide for use in the Williamson synthesis. (One does not want to convert 1-methylcyclo-pentene into an alkyl halide because a secondary or tertiary structure would result, and this is not very efficient, as mentioned previously.) Now, there exist a number of ways to synthesize an alcohol from an alkene. The method of choice, however, is the one that provides us with the required stereochemistry. Recall that the final product must be a trans isomer. If hydroboration oxidation of the alkene is used, addition occurs in a cis fashion and the trans isomer will be the net result. That is, the -H and -OH add trans to the methyl group.

Hydroboration-oxidation gives anti-Markownikoff addition of water across the carbon-carbon double bond. The alcohol that results will have the hydroxyl group trans with respect to the methyl substituent on the ring.

Consequently, the following hydroboration-oxidation reaction is performed:



1-methylcyclopentene — trans-2-methyl-1-cyclopentanol

At this point, sodium metal must be added to convert this alcohol into a sodium alkoxide as illustrated:

If a methyl halide, say methyl bromide, is added, the desired product results as shown:

trans-1-methoxy-2-methyl cyclopentane

REACTIONS

• PROBLEM 17-10

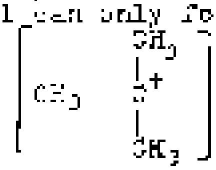
(a) Upon treatment with sulfuric acid, a mixture of ethyl and n-propyl alcohols yields a mixture of three ethers. What are they? (b) On the other hand, a mixture of tert-butyl alcohol and ethyl alcohol gives a good yield of a single ether. What ether is it likely to be? How can the good yield be accounted for?

Solution: (a) Ethers can be synthesized by the acid catalyzed dehydration of alcohols. However, this reaction mechanism is only useful for the synthesis of symmetrical ethers (ROR, where both alkyl or aryl groups are identical). It is inefficient in the synthesis of unsymmetrical ethers (where the alkyl and/or aryl groups are not identical) because it gives a mixture of products. This can be explained by the reaction mechanism.

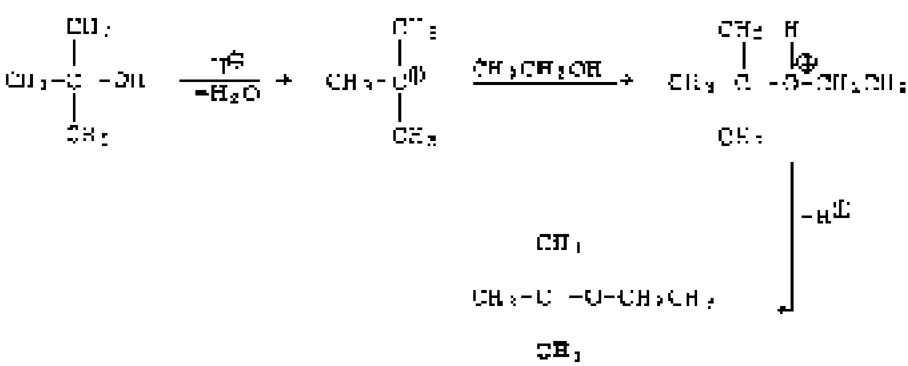
The reaction in question is an acid-catalyzed dehydration. The first step of this reaction is the protonation of alcohol by the acid, H_2SO_4. Since the reaction mixture contains two different alcohols, each one of them can be protonated. This results in two different kinds of carbonium ions after release of water molecules. Each of these two carbonium ions can attack either alcohol to form an ether. If the ethyl cation ($CH_3CH_2^+$) reacts with ethyl alcohol, diethyl ether is formed. If the n-propyl cation ($CH_3CH_2CH_2^+$) reacts with n-propyl alcohol, di-n-propyl ether is formed. And if ethyl cation reacts with n propyl alcohol, or n-propyl cation reacts with ethyl alcohol, ethyl n-propyl ether is formed. Since ethyl and n-propyl cations are formed at the same rate, the product will contain a mixture of diethyl ether, di-n-propyl ether, and ethyl n-propyl ether.

(b) In a mixture of tert-butyl alcohol and ethyl alcohol, the major product is ethyl t butyl ether. This product is in good yield due to the kinetic effect.

As mentioned earlier, the first step of an acid-catalyzed dehydration of alcohol is the protonation of the alcohol. The elimination of a water molecule to form the carbonium ion from the protonated alcohol is the slowest step. Therefore, it is the rate limiting step. The rate at which a carbonium ion forms is dependent on its stability. It can be formed fastest if there are electron-releasing groups to stabilize the positive charge. The rate of carbonium ion formation is: 3°>2°>1°> methyl. This is also the order of stability of carbonium ions. Since tert-butyl alcohol can form a 3° cation, whereas ethyl alcohol can only form a 1° carbonium ion, tert

butyl cation  should form the fastest and predominate over ethyl cation ($CH_3CH_2^+$) in the mixture.

Since the tert-butyl group is bulky, the 3° carbonium ion formed tends to attack ethyl alcohol more often than tert-butyl alcohol in the subsequent substitution reaction. The reactions are shown below:

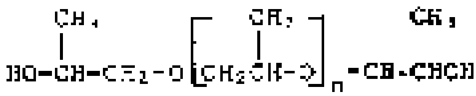


ethyl t-butyl ether

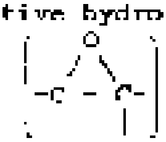
In conclusion, the ethyl t butyl ether should be the predominate ether because of the speed in which t-butyl cation forms and the difficulty of this cation attacking the t-butyl alcohol for steric reasons.

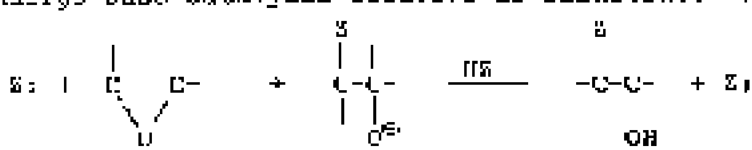
• PROBLEM 17-11

Poly(oxypropylene)glycols,



which are used in the manufacture of polyurethane foam rubber, are formed by the action of base (e.g., hydroxide ion) on propylene oxide in the presence of propylene glycol as an initiator. Write all steps in a likely mechanism for their formation.

Solution: To write the mechanism for the formation of poly(oxypropylene)glycols, two facts must be understood. The first fact to be recognized is that alcohols may act as acids; the polarity of the O-H bond should facilitate the liberation of the relatively positive hydrogen as the ion. The second fact is that epoxides  may undergo base-catalyzed cleavage as illustrated below:



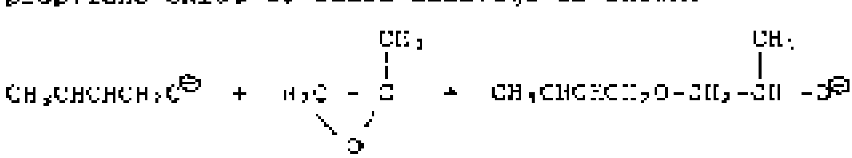
The epoxide undergoes nucleophilic attack by the nucleophile (base), Z:.

With this in mind, the mechanism may be written. When the initiator, propylene glycol, is mixed with base, hydroxide ion, one of the OH groups of the glycol may act as an acid to create an alkoxide-like molecule and water as shown:

$$CH_3CHOHCH_2OH + OH^{\ominus} \rightarrow CH_3CHOHCH_2O^{\ominus} + H_2O$$

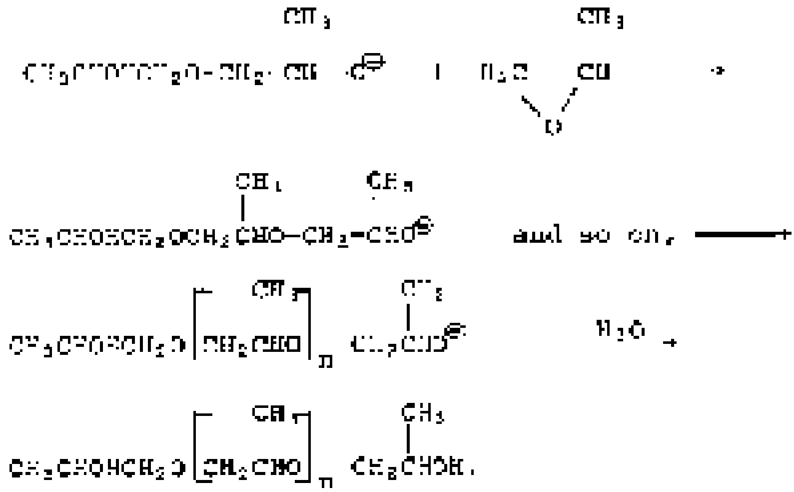
propylene glycol   alkoxide-like ion

The ion formed is sufficiently nucleophilic to attack the propylene oxide to cause cleavage as shown:



propylene oxide

The ion generated in the above reaction can also act as a nucleophile to attack another propylene oxide molecule. This process proceeds on and on until a water molecule is added to form the poly(oxypropylene)glycol. The sequence is written below:



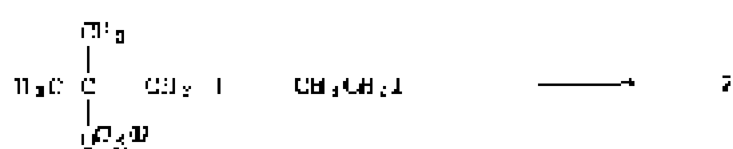
poly(oxypropylene)glycol

• PROBLEM 17-12

Write an equation for each of the following. (If no reaction occurs, indicate "no reaction.")

(a) potassium tert-butoxide + ethyl iodide
(b) tert-butyl iodide + potassium ethoxide
(c) ethyl alcohol + H_2SO_4 (140°)
(d) n-butyl ether + boiling aqueous NaOH
(e) methyl ethyl ether + excess HI (hot)
(f) $C_6H_5OC_2H_5$ + hot conc. HBr
(g) $C_6H_5OC_2H_5$ + HNO_3, H_2SO_4.

Solution: The parts in this problem test understanding of the preparation and reactions of ethers and epoxides.

(a) 

potassium tert-butoxide ethyl iodide

These two reactants illustrate a most versatile method in the preparation of ethers, the Williamson synthesis. In this synthesis, an alkyl halide (or substituted alkyl halide), such as ethyl iodide, is allowed to react with a sodium alkoxide (RO^-Na^+) or a sodium phenoxide (ArO^-Na^+) to produce the ether as shown:

$$\underset{\text{(alkyl halide)}}{R-X} + \underset{(K^+)}{Na^{\oplus}\,{}^{\ominus}O-R'} \rightarrow R-O-R' + Na^{\oplus}X^{\ominus}$$

$$R-X + \underset{(K^+)}{Na^{\oplus}\,{}^{\ominus}O-Ar} \rightarrow R-O-Ar + Na^{\oplus}X^{\ominus}$$

The yield from RX is: $CH_3 > 1° > 2° (> 3°)$. Hence,

$$H_3C-\overset{CH_3}{\underset{CH_3}{C}}-O^{\ominus}K^{\oplus} + ICH_2CH_3 \rightarrow H_3C-\overset{CH_3}{\underset{CH_3}{C}}-O-CH_2CH_3 + K^{\oplus}I^{\ominus}$$

(t-butyl ethyl ether)

$$\text{(b)} \quad H_3C-\overset{CH_3}{\underset{CH_3}{C}}-I + CH_3CH_2O^{\ominus}K^{\oplus} \longrightarrow \; ?$$

These reactants would seem to follow the pattern for Williamson ether synthesis outlined above. After all, an alkyl halide and an alkoxide are again reacting. But note, this time the alkyl halide is tertiary and, as shown above [part (a)], such a halide gives a very low yield. In fact, the use of tertiary halides to produce ethers in this fashion is usually not feasible, for elimination will be favored over substitution (which is what occurs when the ether is generated). Recall that the tendency for alkyl halides to undergo dehydrohalogenation (an elimination reaction) is: 3°>2°>1°. With the strong basicity of the alkoxide reagent, elimination should be particularly serious. Hence, when these two reagents, t-butyl iodide and potassium ethoxide, combine, a dehydrohalogenation reaction occurs as illustrated:

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-I + CH_3CH_2O^{\ominus}K^{\oplus} \rightarrow \underset{\text{(isobutylene)}}{H_3C-\overset{CH_2}{\overset{\|}{\underset{CH_3}{C}}}} + \underset{\text{(ethanol)}}{CH_3CH_2OH} + K^{\oplus}I^{\ominus}$$

$$\text{(c)} \quad CH_3CH_2OH + H_2SO_4 \; (140°) \longrightarrow \; ?$$

Ethyl alcohol

Some symmetrical ethers containing the lower alkyl groups may be prepared by reactions of the corresponding alcohols with sulfuric acid (H_2SO_4). A water molecule is lost for every pair of alcohol molecules so that the reaction is termed dehydration. (Recall that alcohols can be dehydrated also to alkenes. The conditions determine whether the alkene or ether results.) The dehydration to ethers is written below:

$$2ROH \xrightarrow{H_2SO_4,\ heat} R{-}O{-}R + H_2O.$$

This is exactly the reaction that occurs with ethyl alcohol in H_2SO_4 at 140°. Hence,

$$2CH_3CH_2OH \xrightarrow{H_2SO_4,\ 140°} CH_3CH_2OCH_2CH_3 + H_2O$$

ethyl ether

(e) $CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3$ + boiling aqueous NaOH → ?

n-butyl ether

Ethers may be characterized as comparatively unreactive compounds. The ether linkage is quite stable toward oxidizing agents, reducing agents, and bases. Hence, when the boiling aqueous base of NaOH is added to n-butyl ether there is no reaction.

(f) $CH_3OCH_2CH_3$ + excess HI (hot) →

methyl ethyl ether

Under vigorous conditions (high concentration and high temperatures), ethers may be cleaved by acids as shown:

$$R{-}O{-}R' + HX \rightarrow R{-}X + R'OH$$

(Alkyl halide) (Alcohol)

$Ar{-}O{-}R + HX \rightarrow R{-}X + Ar{-}OH.$ The R'OH, in the presence of HX, will proceed to alkyl halide, R-X, also.

The reactivity of HX is: HI > HBr > HCl.

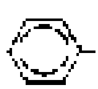
Cleavage by acid involves the nucleophilic attack by halide ion on the protonated ether, with the weakly basic alcohol molecule being displaced as shown:

$$\ddot{R}OR' + HX \rightleftharpoons R\overset{H}{\overset{|}{O^{\oplus}}}R' + X^- \xrightarrow[S_N2]{S_N1 \text{ or}} RX + R'OH.$$

When excess HI (hot) is added to methyl ethyl ether, cleavage of the ether can be expected:

$$CH_3OCH_2CH_3 + \text{excess HI (hot)} \rightarrow CH_3I + CH_3CH_2I$$

methyl iodide   ethyl iodide

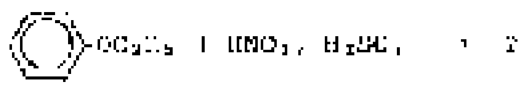
(f) $-OC_2H_5$ + hot conc. HBr ⟶ ?

ethyl phenyl ether

Again, cleavage of the ether can be expected due to the presence of an acid, HBr, with vigorous conditions. The important point to understand is that the cleavage of an aryl alkyl ether yields a phenol and an alkyl halide. This derives from the fact of low reactivity at the bond between oxygen and an aromatic ring, so that it undergoes cleavage at the alkyl-oxygen bond. Therefore,

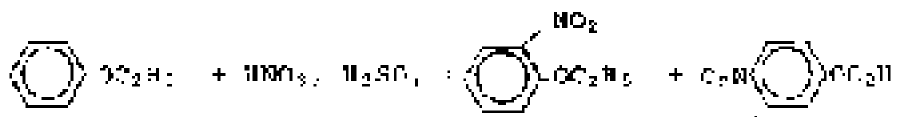
phenol ethyl bromide

(g)



phenyl ethyl ether

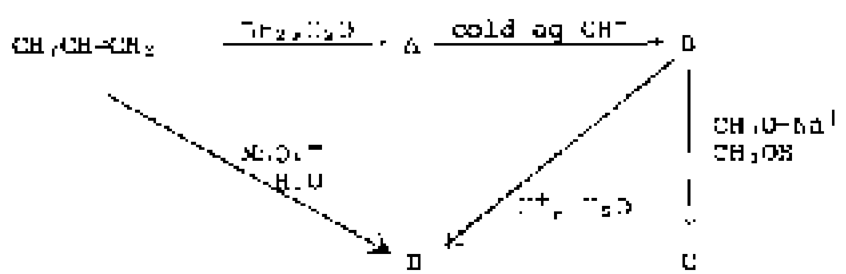
This problem involves electrophilic substitution in aromatic ethers. The alkoxy group, -OR, is moderately activating and so directs ortho, para. Consequently, the nitro group can be expected to be positioned ortho, para to the OC_2H_5 group in phenyl ethyl ether as shown:



o-nitrophenyl ethyl ether p-nitrophenyl ethyl ether

• PROBLEM 17-13

What are the structures of A-D in the scheme shown?



Solution: The sequence commences with propylene, an alkene. When chlorine or bromine is added in the presence of water to alkenes, they yield compounds containing halogen and hydroxy groups on adjacent carbon atoms. Such compounds are called halohydrins. Hence, compound A must be a halohydrin as shown below:

$$CH_3CH=CH_2 \xrightarrow{Br_2, H_2O} \underset{\quad\;\; OH \;\; Br}{CH_3-CH-CH_2}$$

(propylene bromohydrin)

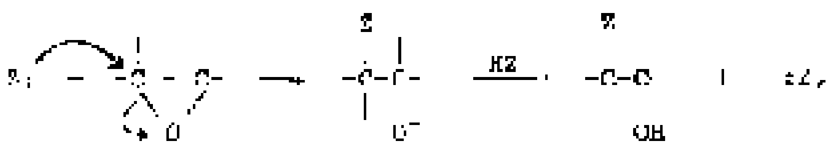
Compound B comes about from compound A by the action of a base, hydroxide ion. This suggests the formation of an epoxide. It is known that halohydrins can be converted into epoxides by the action of base as in the general reaction:

(epoxide)

It can then be said that compound B is an epoxide as illustrated:

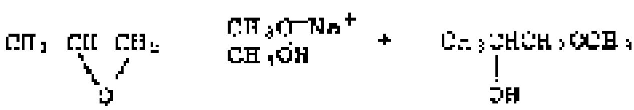
Compound A Compound B

It is possible to cleave epoxides under alkaline conditions. The epoxide undergoes nucleophilic attack by such nucleophilic reagents as alkoxides, phenoxides, and ammonia. The general reaction of this base catalyzed cleavage is written below:



where Z: represents the nucleophile.

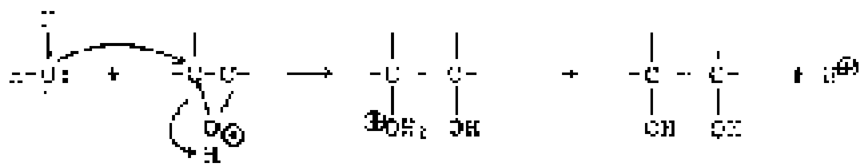
The reagent $CH_3O^-Na^+$ is an alkoxide so that it should cause base-catalyzed cleavage of the epoxide (compound B) as shown:



Compound B Compound C

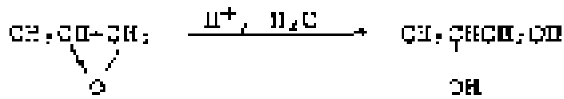
Compound B also generates compound D when H^+, H_2O is added. This reaction denotes acid-catalyzed cleavage of epoxides. An important characteristic of this reaction is the production of compounds with two functional groups. The general reaction is:

Reaction with water generates a glycol as shown:



A Glycol

Compound D must be a glycol. Its formation is depicted in the following equation:



Compound B   Compound D

Propylene also gives rise to compound D when H_2O, MnO_4^- is added. This reaction is typical of alkenes. Certain oxidizing agents (such as $KMnO_4$) convert alkenes into glycols. This is a hydroxylation reaction.

$$CH_3CH{=}CH_2 \xrightarrow{MnO_4^{\ominus},\ H_2O} \underset{\textstyle OH}{CH_3CHCH_2OH}$$

• PROBLEM 17-14

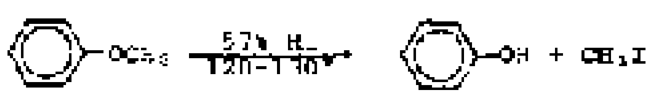
In so far as the ether linkage is concerned, ethers undergo just one type of reaction, cleavage by acids. Discuss this reaction in terms of the mechanism, conditions, and products obtained.

Solution: While the ether linkage (R-O-R) is stable toward bases, reducing agents, and oxidizing agents, they can be cleaved by acids as illustrated:

$$R{-}O{-}R' + HX \rightarrow R{-}X + R'OH \xrightarrow{HX} R'X$$

$$Ar{-}O{-}R + HX \rightarrow R{-}X + Ar{-}OH$$

This reaction will occur only under vigorous conditions (that is, concentrated acids at high temperatures). The alkyl ether reacts with the acid to yield an alkyl halide and an alcohol. The alcohol may continue to react with acid to generate a second mole of alkyl halide. An aryl alkyl ether yields a phenol and an alkyl halide because cleavage occurs at the alkyl-oxygen bond, and not the aryl oxygen due to the latter's low reactivity. For example,



Anisole   Phenol   Methyl iodide

Selection of the acid can be important because of their different reactivities as indicated:

Reactivity of HX: HI > HBr > HCl.

The cleavage of the ether by acid involves nucleophilic attack by halide ion on the protonated ether. This causes displacement of the weakly basic alcohol molecule as illustrated:

$$\mathrm{ROR'} + \mathrm{HX} \rightleftharpoons \underset{\text{(Protonated ether)}}{\mathrm{R\overset{\overset{H}{|}}{\underset{\oplus}{O}}R'}} + X^- \xrightarrow[\mathrm{S_N2}]{\mathrm{S_N1}\ \text{or}} \mathrm{RX} + \underset{\text{(Good leaving group)}}{\mathrm{R'OH}}$$

As mentioned, the reaction may proceed by substitution nucleophilic unimolecular (S_N1) or substitution nucleophilic bimolecular(S_N2). The conditions and structure of the ether will determine which way the reaction goes. S_N1 and S_N2 are outlined below.

S_N1

$$(1)\qquad \mathrm{R\overset{\overset{H}{|}}{\overset{\oplus}{O}}R'} \xrightarrow{\text{slow}} \mathrm{R^{\oplus}} + \mathrm{HOR'}$$

$$(2)\qquad \mathrm{R^{\oplus}} + X^- \xrightarrow{\text{fast}} \mathrm{R\,X}$$

S_N2

$$\mathrm{R\overset{\overset{H}{|}}{\overset{\oplus}{O}}R'} + X^- \longrightarrow \left[\overset{\delta-}{X}\text{---}R\text{---}\underset{\delta+}{\overset{\overset{H}{|}}{O}}R'\right] \longrightarrow \mathrm{RX} + \mathrm{HOR'}$$

Since the S_N1 mechanism proceeds through an intermediate carbonium ion, it might be expected that a tertiary alkyl group undergoes S_N1 displacement, whereas a primary alkyl group undergoes S_N2 displacement.

• PROBLEM 17-15

> A homogeneous solution is known to contain equal parts of diethyl ether and pentane. These liquids have similar boiling points and cannot be separated by fractional distillation. Devise a method for separating them.

Solution: Ethers have the general formula of R-O-R, where the R's stand for alkyl and/or aryl groups. They are unreactive towards most compounds, and are often used as solvents for a wide variety of organic compounds. The solution in question is homogeneous, meaning that diethyl ether and pentane are completely miscible. Since they cannot be separated by fractional distillation, one must look into their differences in properties.

While ethers resemble hydrocarbons (such as pentane) in chemical behavior because of the low reactivity of the functional group, they can be distinguished by the ether's solubility in cold concentrated sulfuric acid through formation of oxonium salts. When diethyl ether is mixed with cold concentrated sulfuric acid, the following takes place:

$$\underset{\text{diethyl ether}}{CH_3CH_2OCH_2CH_3} \xrightarrow[H_2SO_4]{\text{cold concentrated}} \underset{\text{oxonium salt}}{CH_3CH_2\overset{\overset{H}{|}}{\underset{\oplus}{O}}CH_2CH_3 \;\; {}^{\ominus}HSO_4}$$

The hydrocarbon, pentane, fails to produce the oxonium salt.

The oxonium salt formed by diethyl ether is soluble in H_2SO_4. Thus, diethyl ether leaves the homogeneous solution and dissolves in the acid. Pentane does not dissolve in the acid so that a second phase is established. With two phases present, the compounds may be separated by extraction.

• PROBLEM 17-12

The unsaturated cyclic ether furan can readily be made from substances isolated from oat hulls and corncobs; important uses of furan involve its conversion into (a) tetrahydrofuran and (b) 1,4-dichlorobutane. Show how these conversions can be carried out.

Solution: The structure of furan,

```
  HC  CH
  //   \\
 HC     CH ,
   \   /
     O
```

shows it to be a cyclic ether. The preparation and properties of most cyclic ethers do not vary from the other ethers; the ether linkage is basically the same whether it forms part of an open chain or part of an aliphatic ring.

To synthesize tetrahydrofuran,

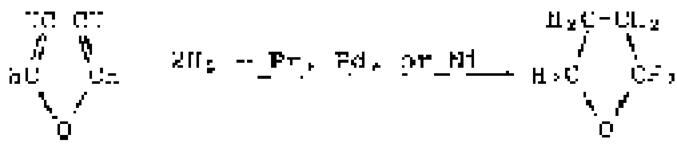
```
  H2C—CH2
  /      \
H2C       CH2 ,
   \     /
      O
```

from furan, hydrogen (H_2) must add across the two carbon-carbon double bonds of furan. Such a reaction is hydrogenation of alkenes as shown:

$$C_NH_{2N} \xrightarrow{H_2,\ Pt,\ Pd,\ or\ Ni} C_NH_{2N+2}$$

Alkene Alkane

Therefore, it can be written:



The ether linkage will remain undamaged in this reaction for it is stable toward reducing agents (and oxidizing agents and bases).

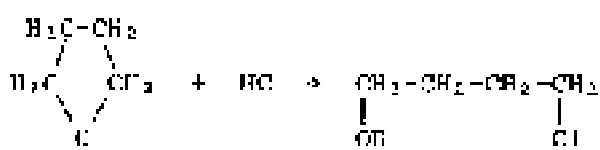
To produce 1,4 dichlorobutane, $ClCH_2CH_2CH_2CH_2Cl$, the starting material should be the tetrahydrofuran synthesized previously. This conversion will take advantage of the fact that cyclic ethers can be cleaved by acid. The general equation for cleavage by acids is shown below:

$$R\text{-}O\text{-}R' + HX \rightarrow R\text{-}X + R'OH \xrightarrow{HX} R'\text{-}X$$

Ether Acid Alkyl halide Alcohol Alkyl halide

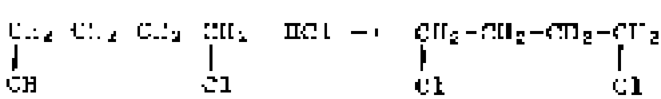
An alkyl ether when mixed with acid (HI>HBr>HCl in reactivity) under vigorous conditions (high concentration and temperature) yields an alkyl halide and an alcohol; the alcohol may react further with acid to yield a second mole of alkyl halide.

Therefore, if HCl is added to tetrahydrofuran in concentration form at high temperatures, the ether linkage should be cleaved as shown:



(4-chloro-1-butanol)

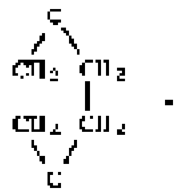
The hydroxyl group and halide end up on the same molecule because of the cyclic nature of the ether. When a cyclic ether is cleaved, it cleaves to one molecule, not two. 4-chloro-1-butanol can continue to react with HCl to produce the desired product, 1,4 dichlorobutane, as indicated:



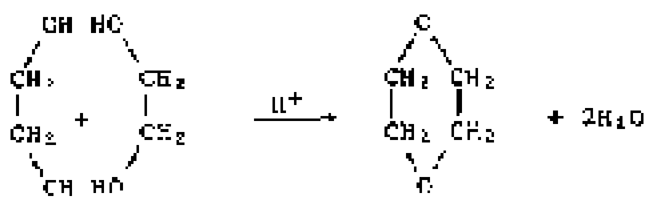
● PROBLEM 17-17

1,4-Dioxane is prepared industrially [for use as a water-soluble solvent] by dehydration of an alcohol. What alcohol is used?

Solution: 1,4 dioxane is a symmetrical cyclic ether containing two oxygens.



Since it is symmetrical, having identical alkyl groups, preparation by dehydration of an alcohol is efficient. Also, since the compound contains two oxygens, a compound with two hydroxyl groups as the main functional groups, a diol, must have been used. The dihydroxy compound having two carbons is called ethylene glycol, $HO-CH_2CH_2-OH$. The reaction is shown below.

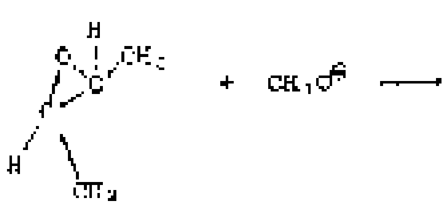


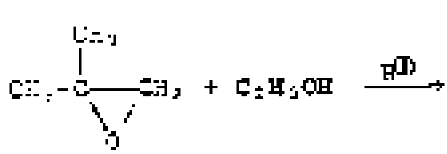
For every two moles of ethylene glycol used, one mole of 1,4-dioxane is formed, and two moles of water are released.

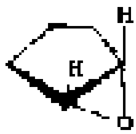
EPOXIDES (OXIRANES)

● PROBLEM 17-18

Draw structures showing stereochemistry where necessary for the products you would expect from the following reactions.

(a) 

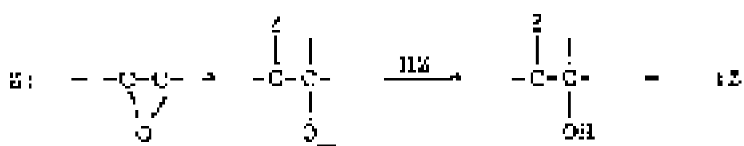
(b) 

(c)  HBr $\longrightarrow$

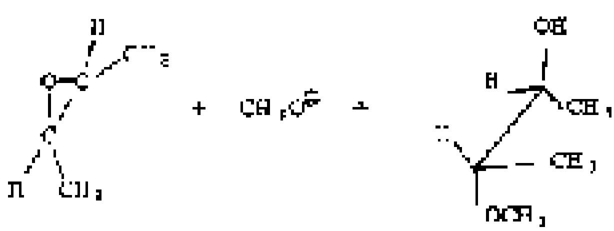
(d) $HOCH_2CH_2CH_2CH_2Cl \xrightarrow{H_2O,\ Na_2CO_3}$

Solution: All the products in (a) - (d) come about as a result of the preparation or reactions of epoxides. Consequently, a knowledge of the chemistry of epoxides is necessary to solve this problem.

(a) Unlike most ethers, epoxides react easily with many strongly nucleophilic reagents. There exists base-catalyzed cleavage of epoxides by such nucleophilic reagents as alkoxides, phenoxides, and ammonia. The reaction may be generalized as:



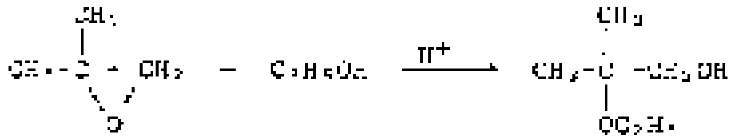
The stereochemistry of the reaction is consistent with an S_N2 mechanism, since inversion of configuration at the site of attack occurs. Here, CH_3O^-, an alkoxide, attacks the epoxide to cause cleavage and gives a trans configuration in the product as shown:



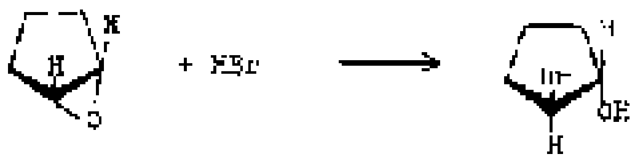
(b) This reaction involves acid catalyzed cleavage of epoxides. The acid converts the epoxide into a protonated epoxide, which is then susceptible to any number of nucleophilic reagents. It may be generalized as shown:

An important feature of this reaction is the fact the compounds formed contain two functional groups. Reaction with water generates a glycol, whereas reaction with an alcohol produces a compound that is both ether and alcohol.

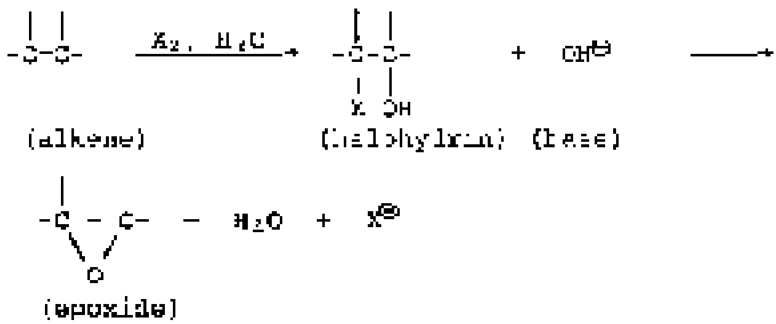
Hence,



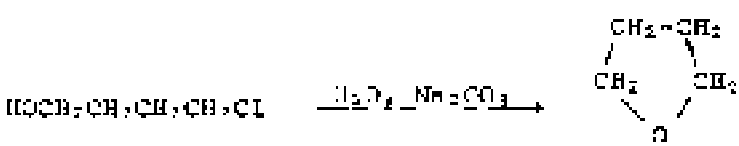
(c) This reaction is also acid-catalyzed cleavage. The only thing that distinguishes this reaction from (b) is that the nucleophile in this instance is bromide (Br^-) ion. It is therefore possible to write the following:



(d) This reaction illustrates a method of preparation of epoxides. Halohydrins may be converted into epoxides by the action of base. This method may be described as an adaptation of the Williamson synthesis. The generalized reaction is depicted below:



The base need not be hydroxide ion. It could be sodium carbonate (Na_2CO_3). Consequently, when Na_2CO_3 is added to the halohydrin $HOCH_2CH_2CH_2CH_2Cl$, one might expect an epoxide to form. But note, the HO and Cl are at opposite ends, so that a cyclic ether forms as shown below:

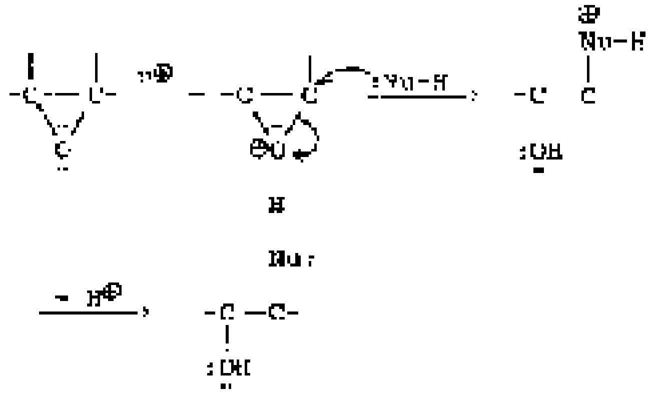


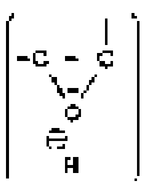
• PROBLEM 17-15

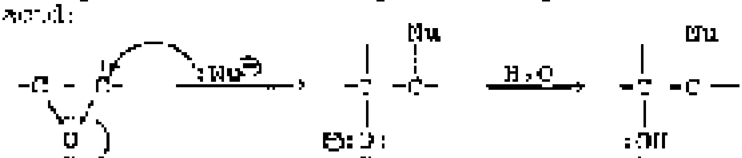
Predict the product(s) of the reaction of ethylene oxide with

(a) $H_3O^{\oplus}$
(b) $OH^{\ominus}/H_2O$, then $H_3O^{\oplus}$
(c) $CH_3S^{\ominus}Na^{\oplus}$
(d) $CH_3CH_2CH_2MgBr$, then $H_3O^{\oplus}$

Solution: This problem focuses on the reactions of epoxides  , which include acid-catalyzed cleavage, base-catalyzed cleavage, and organometallic (e.g. Grignard reagents) cleavage. The general equations for these reactions may be written as follows:

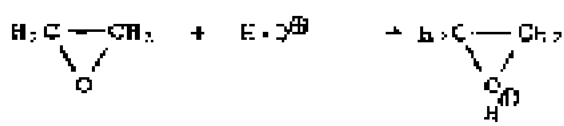
Acid: 

The epoxide is converted by acid ($H^{\oplus}$) into the protonated epoxide  which can then undergo attack by any number of nucleophilic reagents (:Nu H). Absence of acid:

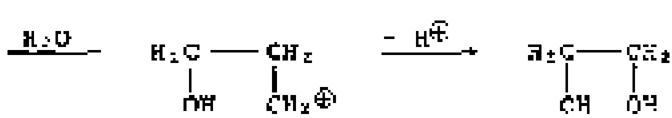


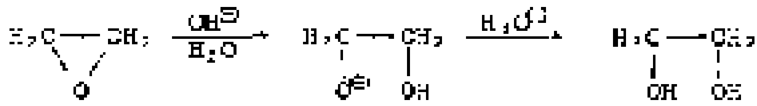
. Here, the epoxide, not the protonated epoxide, undergoes nucleophilic attack.

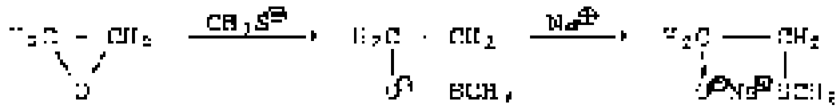
To solve for the products of (a) - (h), substitute into one of the two general equations. The different products reflect the different nucleophilic reagents.

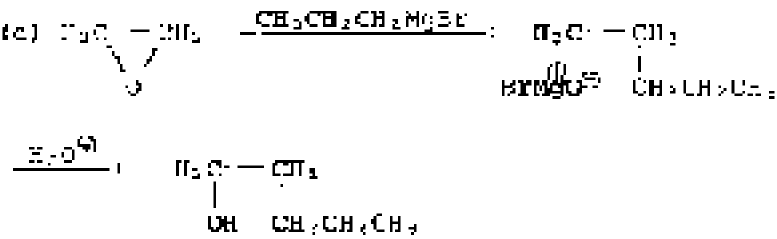
(a) 

Ethylene oxide



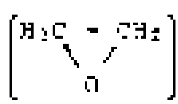
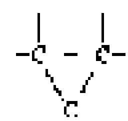
(b) 

(c) 

(d) 

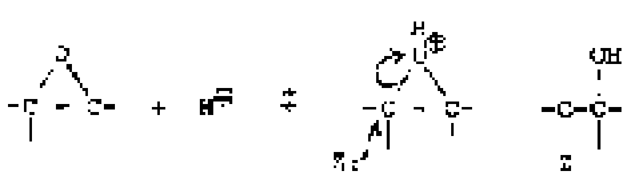
• PROBLEM 17-20

Write equations for the reaction of ethylene oxide with: (a) methanol in the presence of a little H_2SO_4; (b) methanol in the presence of a little $CH_3O^{\ominus}Na^{\oplus}$; (c) aniline.

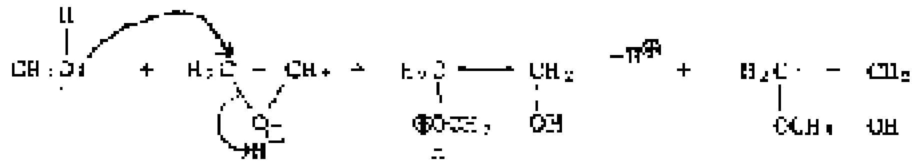
<u>Solution:</u> Ethylene oxide  is an epoxide, a compound containing the three-membered ring  .

Epoxides are highly reactive due to the ease of opening of the highly strained three-membered ring. Epoxides can undergo base and acid-catalyzed cleavage. Reactions in (a) - (c) are examples of such cleavages.

(a) The reaction of ethylene oxide with methanol and H_2SO_4 illustrates the acid-catalyzed cleavage of epoxides. An epoxide when mixed with acid is converted into the protonated epoxide, which can then undergo attack by any of a number of nucleophilic reagents. The general mechanism of the reaction may be written as:



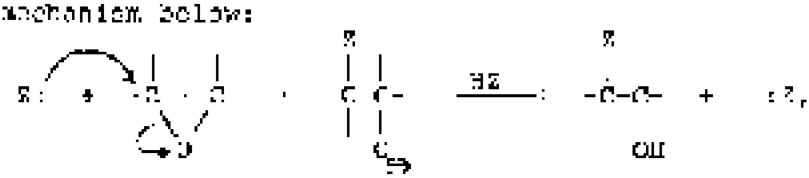
Where Z: represents the nucleophilic reagent. In this problem, methanol is the nucleophilic reagent and attacks the protonated ethylene oxide to produce an alkoxyalcohol (a hydroxyether) as shown:



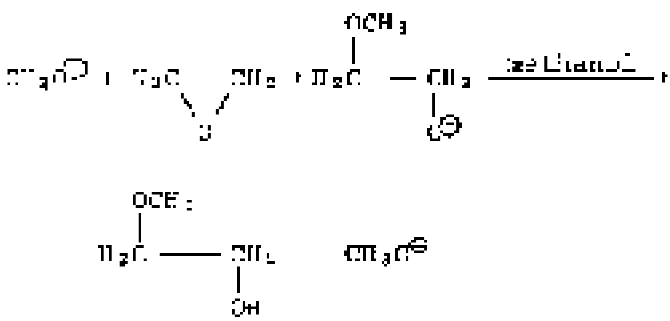
methanol protonated epoxide 2-methoxy-ethanol

Hence, 2-methoxyethanol is the product of the reaction of ethylene oxide with methanol and acid.

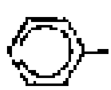
(b) Methanol in the presence of a little $CH_3O^-Na^+$ will react with ethylene epoxide to give the same product in (a), 2-methoxyethanol. However, the product comes about by a different mechanism, base-catalyzed cleavage of epoxides. Here, the epoxide itself, not the protonated epoxide, undergoes nucleophilic attack as indicated in the general mechanism below:

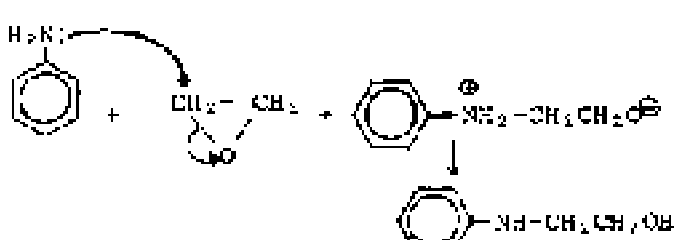


where Z: denotes the nucleophile. Here, CH_3O^- is the nucleophile that attacks ethylene oxide as shown:

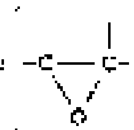


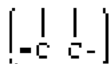
(2-methoxyethanol)

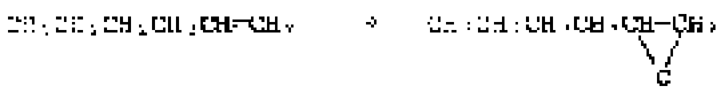
(c) Aniline,  $-NH_2$, is considered to have appreciable basicity due to the pair of non-bonded electrons on the nitrogen atom. Hence, when aniline is added to ethylene epoxide, base-catalyzed cleavage may be expected as shown:



Draw the structure of the epoxide(s) produced by epoxidation of: (a) 1-hexene, (b) 2-hexene.

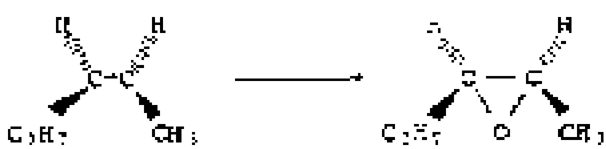
<u>Solution:</u> One method of synthesis of an epoxide 

is by oxidation of an alkene . Peroxyacids are frequently the oxidants used in this epoxidation reaction. It is believed that both carbon-oxygen bonds of the epoxide are formed simultaneously. This means the stereochemistry of the alkene will be retained in the epoxide. Thus, cis alkenes produce cis epoxides and trans alkenes produce trans epoxides. With this in mind, it is possible to draw the structures required.

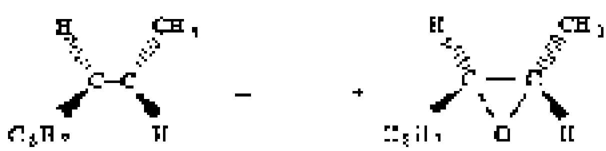
(a) 

(1-hexene)

(b) 2-hexene exists in cis and trans forms. Hence,



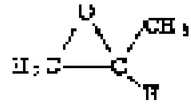
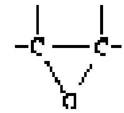
(cis-2-hexene)



(trans-2-hexene)

Note how the cis, trans stereochemistry is retained in each case.

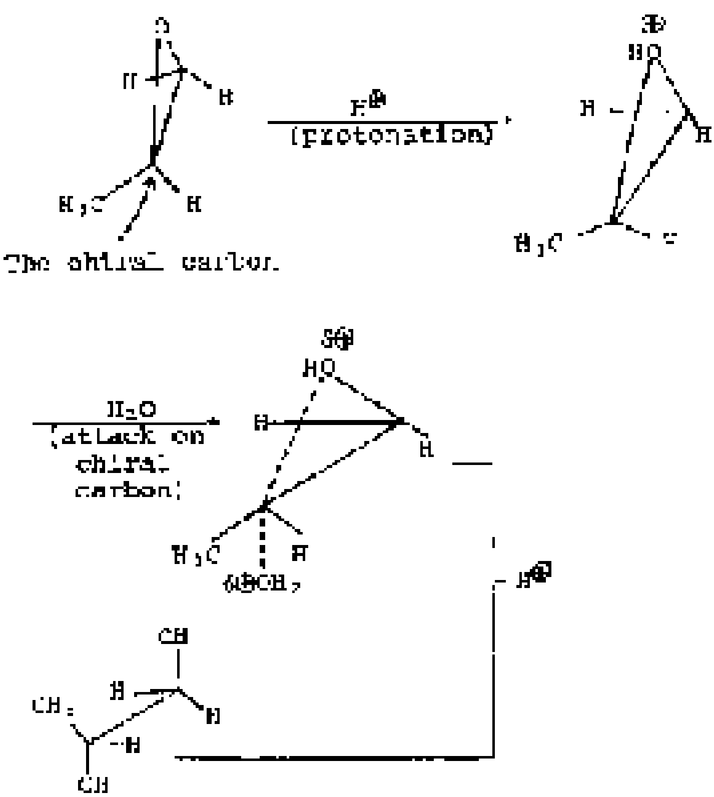
Propylene oxide can be converted into propylene glycol by the action of either dilute acid or dilute base. When optically active propylene oxide is used, the glycol obtained from acidic hydrolysis has a rotation opposite to that obtained from alkaline hydrolysis. What is the most likely interpretation of these facts?

Solution: Propylene oxide, , is an epoxide because it contains the three-membered ring .

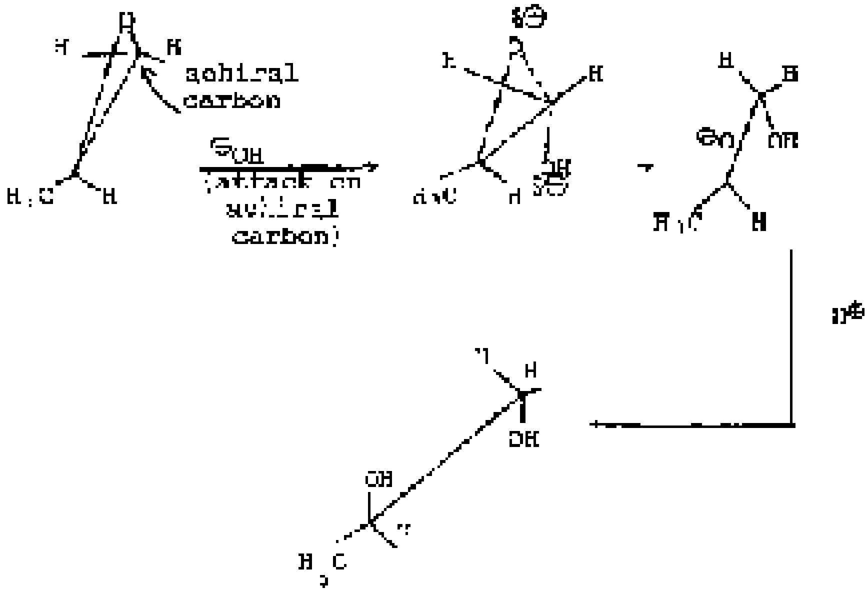
Due to the ease of opening this strained ring, it is highly reactive. Dilute acid or base can hydrolyze it into propylene glycol, $CH_3\underset{OH}{CH}\underset{OH}{CH_2}$.

If optically active propylene glycol is used, depending on the method of hydrolysis, two different enantiomers are formed. Enantiomers are mirror image isomers whose chemical and physical properties are the same, except for the ability to rotate plane polarized light in opposite directions.

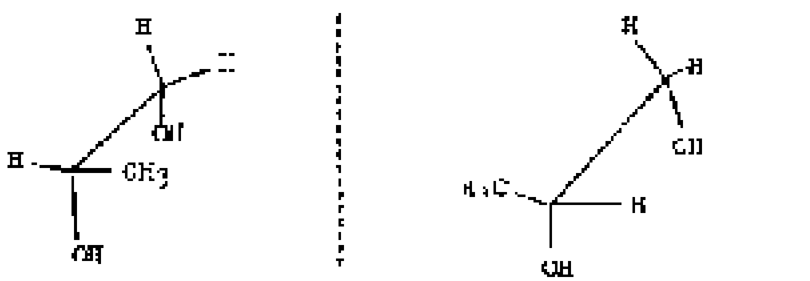
Acid hydrolysis begins with the protonation of the epoxide (see the diagram below). A water molecule then attacks a carbon adjacent to the oxygen. It attacks the more highly substituted carbon. In this case, the carbon attacked is a chiral carbon, that is, a carbon with four different atoms or groups of atoms. Since the water attacks at the chiral carbon, inversion of configuration results to change the rotation of plane polarized light.



Base hydrolysis takes place with retention of configuration. The attack of hydroxide is at the 1° carbon, where no bond to the chiral carbon is broken. Hence, the rotation of plane polarized should not be altered.



The products by base and acid hydrolysis are mirror images of each other. They rotate plane-polarized light in opposite directions.

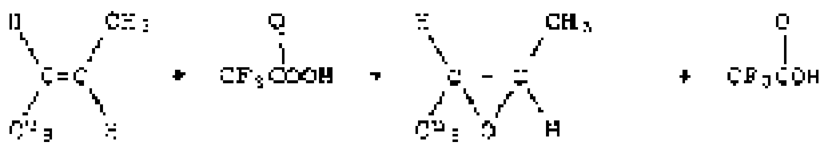


from base hydrolysis from acid hydrolysis

• PROBLEM 17-23

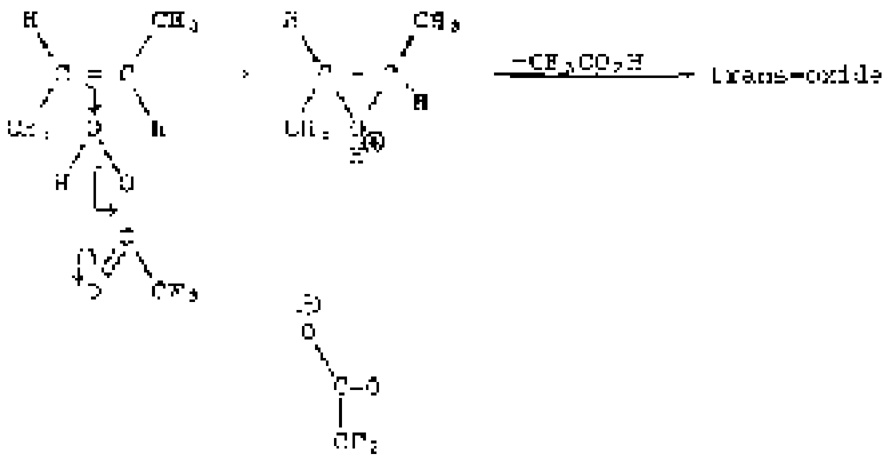
Write a mechanism for the reaction of trans-2-butene with trifluoroperacetic acid which is consistent with the fact that the rate is first order in each participant and gives cis addition.

Solution: One of the most important methods of preparing epoxides or oxiranes involves oxidation or epoxidation of an alkene with a percarboxylic acid, $R\overset{O}{\overset{\|}{C}}OOH$. One such percarboxylic acid is trifluoroperacetic acid, CF_3COOH. The net result of reaction is addition of oxygen across the carbon-carbon double bond. This proceeds only in the cis configuration. Therefore, when trifluoroperacetic acid is added to trans-2-butene, trans-2-butene oxide should result.



trans 2 butene   trans 2 butene oxide

It is believed the peracid furnishes the ^{+}OH to the double bond as shown in the mechanism outlined below:



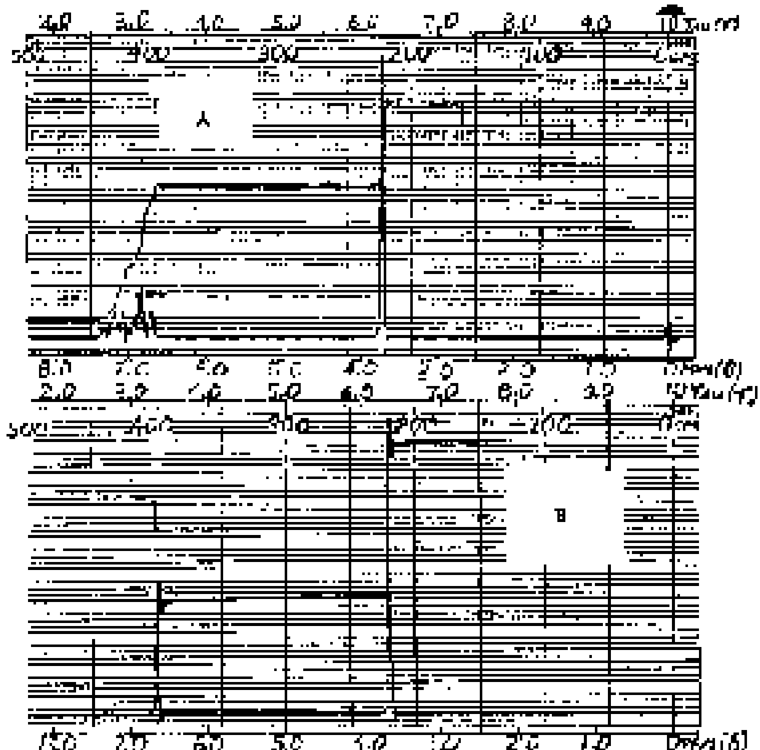
Note: The arrows indicate the shifting of pairs of electrons.

Kinetically, the rate is first order for each participant because all that is needed to produce one molecule of product is one molecule of each reactant.

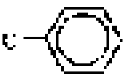
SPECTROSCOPY

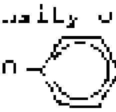
• PROBLEM 17-24

The nmr spectra are those of anisole and p-methoxyanisole. Assign the correct structure to each of these spectra.

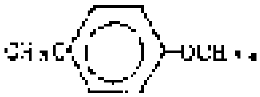


NMR spectrum for ethers

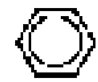
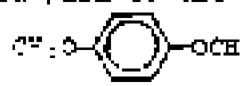
Solution: Spectrum A can be assigned the structure of anisole, CH_3O-  . To see this, consider the hydrogens of the methyl group. Such hydrogens, RO-CH_3, normally have a chemical shift of 3.3-4, where R represents an aryl or alkyl group in the ether linkage. R is aryl, as will be shown below, so that it may be expected that such protons absorb downfield (approximately 3.7 δ) relative to an alkyl R due to the powerful deshielding from the circulation of the π electrons in the aryl ring. Therefore, it may be concluded that the peak at 3.7 δ indicates the existence of RO-CH_3. It is known that aromatic hydrogens absorb between 6 and 8.5 δ. The spin-spin splitting that occurs in this region in spectrum A must signify the hydrogens of the aromatic group. Note that two different chemical shifts are present to illustrate the different electronic environments of the aromatic hydrogens. The hydrogens closest to the ether linkage absorb upfield from the other aromatic hydrogens because of the high electron density of oxygen.

At this point, the structure must be H_3C-O-  . There exist no other peaks, so that it cannot possibly be the other given structure.

Spectrum B can only be p-methoxyanisole,

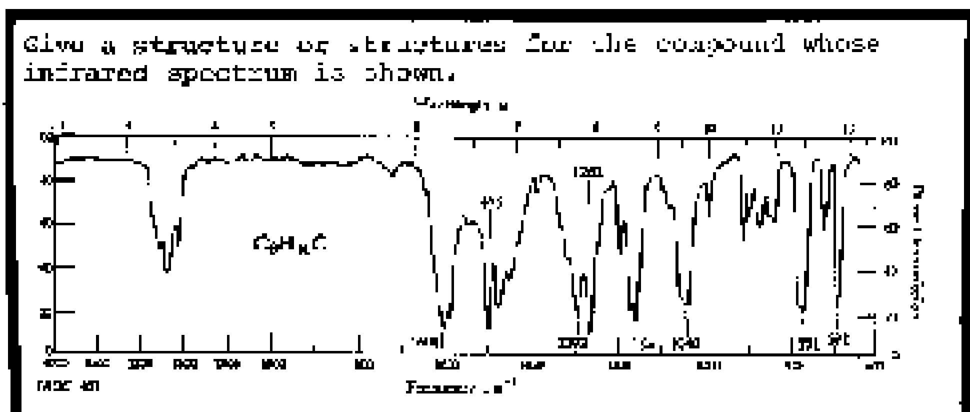


This structure is determined by referring back to spectrum A, anisole. A comparison of the two shows that the only difference is the presence of only one peak in the 6 to 8.5 δ region with no spin-spin splitting. Recall that this region indicated aromatic hydrogens. Now, for spectrum B to have only one peak with no spin-spin splitting indicates that all of its aromatic hydrogens are equivalent; they exist in the same electron environment.

If anisole has the structure CH_3O  with non-equivalent aromatic hydrogens, then the only way to have the same spectrum except for equivalent aromatic hydrogens, is to have another CH_3O linkage located para to the first one, that is, the structure must become , which is p-methoxyanisole.

• PROBLEM 17-25

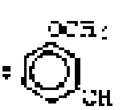
Give a structure or structures for the compound whose infrared spectrum is shown.



Solution: Examination of this infrared spectrum establishes this compound as some kind of aryl ether,  .

The most characteristic feature in the spectroscopic analysis of ethers is the strong band of C-O stretching. It occurs in the 1060-1300 cm^{-1} range. In this region, many bands are present, but this alone does not establish the presence of an ether. For note, alcohols, carboxylic acids, and esters also show C-O stretching. They can be eliminated as possibilities, however, by the fact alcohols would also show the strong and broad O-H stretch in the 3200-3600 cm^{-1}, carboxylic acids $\left[-\overset{O}{\overset{\|}{C}}-OH\right]$ would show carbonyl (C=O) absorption at about 1700 cm^{-1}, and esters $\left[-\overset{O}{\overset{\|}{C}}-O-\right]$, would do the same. The fact that none of these bands is present leaves only the functional group of an ether as one that can exhibit C-O stretching. This ether could be aryl or alkyl. That it must be aryl can be determined by looking at the specific positions of the bands for C-O stretching. Aryl ethers show C-O stretching between 1200 and 1275 cm^{-1} (and, weaker at 1020-1075 cm^{-1}). At 1040 cm^{-1} and approximately 1075 cm^{-1} two bands are present. This fits into the pattern expected for aryl ethers. Note: If it were an alkyl ether, the C-O stretching would have been between 1060-1150 cm^{-1}, and no such band can be detected.

Hence, it is now established that an aryl ether is present. This accounts for, then, 6 carbons (of benzene portion) and one oxygen (the ether linkage). Now subtracting these atoms from the given molecular formula, $C_8H_{10}O$, leaves C_2H_{10}. The two carbons to be accounted for must be part of the substituents on the aromatic ring. This means they will influence the out-of-plane C-H bending for aromatic rings. While out of plane bending gives strong absorption in the 675-870 cm^{-1} region, the exact location will depend upon the number and position of the substituents (mono-substituted, o, m, p-disubstituted). The bands at 771 cm^{-1} and 692 cm^{-1} indicate a m-disubstituted benzene exists, for such a compound shows C-H out of plane bending at 690-710 cm^{-1} and 750-810 cm^{-1}. In summary, it is now known that $C_8H_{10}O$ is an aryl ether with a m-disubstituted benzene. One of the substituents must be linked to the oxygen to establish an ether. Because only C_2H_{10} is available after the aryl ether atoms are considered, the second substituent is an alkyl group.

The question at this point is what other group is the oxygen attached to and what is the specific alkyl group mentioned above. A little thought indicates that if only two carbons (and some hydrogens) are available, methyl (CH_3) groups must be the answer. One methyl group would be attached to the oxygen atom to complete the ether linkage, while the other would be a substituent of benzene in the meta position. The picture becomes 

The two methyls account for two carbons and six hydrogens. Since C_2H_{10} was available, only four hydrogens are still to be determined. They are bonded to the four carbons of the benzene ring that lack a substituent. The structure shown above is, therefore, the compound depicted in the infrared spectrum. It is named m-methylanisole.

• PROBLEM 17-20

Specify a simple chemical test to distinguish the following pairs of compounds. Give the reagent to be used and the observation that you would make.

(a) Diisopropyl ether and diallyl ether
(b) Diethyl ether and methyl iodide
(c) Dibutyl ether and n-butyl alcohol

Solution: A good way to approach this type of problem is to write out the structures of the compounds involved to discern the functional groups present. Then try to select reagents that would distinguish between the compounds on the basis of the functional groups.

$$\text{(a)}\quad \begin{array}{c} \text{H} \quad\quad \text{H} \\ | \quad\quad\ \ | \\ CH_3-C-O-C-CH_3 \\ | \quad\quad\ \ | \\ CH_3 \quad CH_3 \end{array} \qquad\qquad CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}CH{=}CH_2$$

Diisopropyl ether Diallyl ether

The use of reagents that would reveal the presence of an ether would be useless in this case. Both compounds would give a positive test. Note, however, that diallyl ether contains carbon-carbon double bonds. It is unsaturated. An excellent method for characterizing carbon-carbon double bonds is by using a solution of bromine in carbon tetrachloride, which has a reddish color. The bromine will add across the double bond, thereby decolorizing the solution. Since the diisopropyl ether lacks a double bond, it will not decolorize the Br_2/CCl_4 solution. Hence, the two ethers may be distinguished on this basis.

(b) $CH_3CH_2OCH_2CH_3$ CH_3I

Diethyl ether Methyl iodide

Methyl iodide is a primary alkyl halide. It is possible to test for such halides by placing them in aqueous alcoholic silver nitrate. If the alkyl halide exists, a silver halide should precipitate out of solution. Hence, methyl iodide can be expected to produce AgI, the silver halide, slowly after being added to aqueous alcoholic silver nitrate. The ether fails to give a precipitate, so that the compounds are distinguished on this basis.

(c) $CH_3CH_2CH_2CH_2-O-CH_2CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_2OH$

Dibutyl ether N-butyl alcohol

The alcohol may be distinguished from the ether by the fact that the former can act as an acid to form the alkoxide ion, RO^-. The acidity of alcohols is shown by their reaction with active metals (such as sodium, Na) to form hydrogen gas as shown:

$$ROH + Na \rightarrow RO^{\ominus}Na^{\oplus} + \tfrac{1}{2} H_2.$$

Consequently, if sodium pieces are allowed to come into contact with n-butyl alcohol hydrogen gas should be seen bubbling off. The dibutyl ether will fail to liberate hydrogen, so that it is this observation that differentiates the two compounds.

• PROBLEM 17-27

An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, etc. Make use of any needed tables of physical constants.

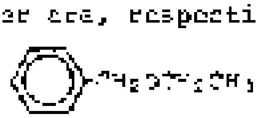
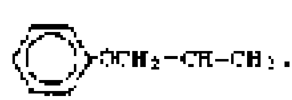
(a) n-propyl ether (b.p. 91°) and 2-methylhexane (b.p. 91°)
(b) benzyl ethyl ether (b.p. 188°) and allyl phenyl ether (b.p. 192°)
(c) methyl p-tolyl ether (b.p. 176°) and methyl m-tolyl ether (b.p. 177°)

Solution: (a) N-propyl ether ($CH_3CH_2CH_2OCH_2CH_2CH_3$) and 2-methylhexane $\left(\begin{array}{l} CH_3CHCH_2CH_2CH_2CH_3 \\ \quad\;\; | \\ \quad CH_3 \end{array}\right)$ may be distinguished on the basis of physical properties, specifically solubility. Since the C-O-C bond angle of ethers is not 180°, there exists a net dipole moment. Ethers possess weak polarity, so that they show solubility in water comparable to that of alcohols. Apparently, the hydrogen bonding between water molecules and ether molecules accounts for the solubility as shown:

$$\begin{array}{ccc} R-O & \cdots & H-O \\ | & & | \\ R & & H \end{array}$$

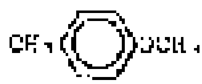
Hence, N-propyl ether should show some solubility in water. Also, it will be soluble in cold concentrated sulfuric acid through formation of oxonium salts. 2-methylhexane, being an alkane, is non-polar. Consequently, it will be insoluble in these same solutions.

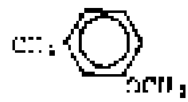
(b) The structures of benzyl ethyl ether and allyl phenyl ether are, respectively,

 and 

The structure of allyl phenyl ether shows a unit of unsaturation. This means that a method of distinguishing the two ethers is by oxidation with the agent $KMnO_4$. The ether linkage, itself, is relatively unreactive. It is stable toward bases, oxidizing agents, and reducing agents. Carbon-carbon double bonds are, however, very reactive, so that when $KMnO_4$ is added, only the allylic ether is oxidized due to the region of unsaturation.

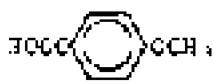
(c) The structures of the two compounds to be differentiated can be written as follows:

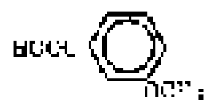




methyl p-tolyl ether   methyl m-tolyl ether

Again, oxidation will distinguish these compounds. Addition of $KMnO_4$ will oxidize the methyl group (CH_3) to the carboxyl group (-COOH) so that the following compounds result:





p-methoxybenzoic acid   m-methoxybenzoic acid

(Recall, the ether group is unreactive toward oxidizing agents such as $KMnO_4$.) These two compounds have significant melting point differences. The melting points of the para and meta compounds are, respectively, 184°C and 110°C. This means a melting point determination should identify which of the two compounds is present. In this way, by working backwards, the correct methyl tolyl ether can be discerned.

CHAPTER 18

ALDEHYDES AND KETONES I

NOMENCLATURE AND STRUCTURE

• PROBLEM 18-1

What is a ketone?

Solution: The main functional group of a ketone is the carbonyl group $\left(\,>C=O\right)$. In a ketone there are two alkyl or aryl groups, attached to the carbonyl carbon. They can either be the same or different groups. The traditional representation of a ketone is

$$R'-\underset{\underset{O}{\|}}{C}-R$$

where R' and R represent alkyl or aryl groups. In general ketones are named by replacing the final "e" of the hydrocarbon name by the suffix "one". For example

$$H_3C-\underset{\underset{O}{\|}}{C}-CH_3$$

is called propanone (its trivial name is acetone) and

$$H_3C-\underset{\underset{O}{\|}}{C}-CH_2CH_2CH_3$$

is called 2-pentanone.

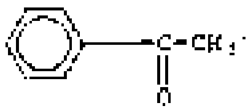
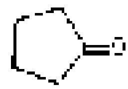
In case there are two or more functional groups present, the suffix takes the form of "dione," "trione," etc. and the 'e' ending remains. For example

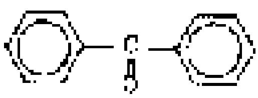
$$H_3C-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

is called 2,5 hexanedione.

Name the following compounds according to an acceptable nomenclature (IUPAC or common):

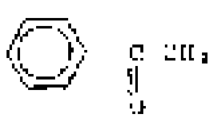
(a) $CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_3$ (d) $CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$

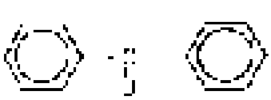
(b)  (e) 

(c) 

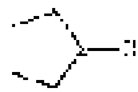
Solution: By looking at the above compounds one can see that they all follow the general formula $R'-\overset{\overset{\displaystyle O}{\|}}{C}-R$, which indicates that they are all ketones. The suffix used to describe ketones is "one". Ketones are named by replacing the "e" of the hydrocarbon name with "one". In cases where there are two or three carbonyl groups ($>C=O$) the suffixes dione and trione are used respectively, and the "e" ending of the hydrocarbon name remains.

(a) $CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_3$ The parent compound is the four carbon alkane, butane. Since two alkyl groups must be attached to the carbonyl group, the carbonyl group must be at C2 or C3. Since these two carbons are equivalent the lower number is used in naming the compound. This compound is named 2-butanone.

(b)  Another method for naming ketones is to place the names of the two alkyl groups as prefixes to the word ketone. Here, one alkyl group is a methyl group and the other is a phenyl group. The groups are named in alphabetical order and the compound is methyl phenyl ketone.

(c)  The two aryl groups are benzene rings (phenyl groups). The compound can be named diphenyl ketone; its trivial name is benzophenone.

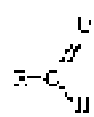
(d) $CH_3-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{|}}{C}\ CH_3$ The parent compound is the five carbon alkane, pentane. Since there are carbonyl groups at both C2 and C4, the suffix used is "dione" instead of "one". The name of this compound is 2,4 pentanedione.

(e)  The parent compound is the cyclic five carbon alkane, cyclopentane. The ketone is named cyclopentanone.

• PROBLEM 16-3

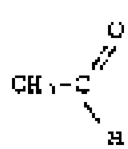
What is an aldehyde?

<u>Solution:</u> The functional group which differentiates an aldehyde from other organic molecules is a carbonyl atom (C=O) joined to another carbon atom and to a hydrogen atom. In general, the formula for an aldehyde is



where R symbolizes an alkyl or aryl group. Aldehydes are named by adding either "al" or "aldehyde" to the end of the name of the parent compound. Substituent groups attached to the alkyl group are taken into account by prefixes before the name of the parent compound.

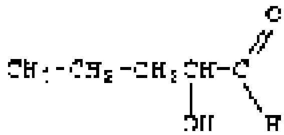
An example of an aldehyde is acetaldehyde which is composed of two carbons. It can be drawn as

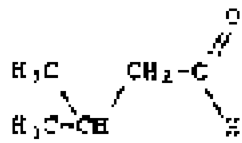


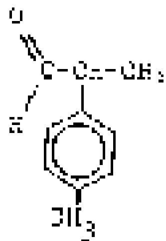
acetaldehyde

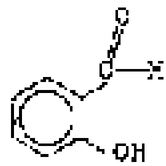
• PROBLEM 16-4

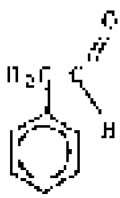
Name the following structures:

(a) 

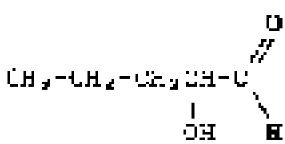
(d) 

(b) 

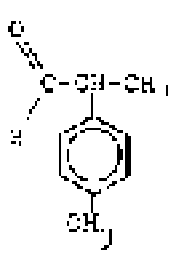
(e) 

(c) 

Solution: First we will determine the parent structure and then the functional groups. The names and locations of the functional groups are added as prefixes to the name of the parent compound. In general the suffix 'al' (IUPAC nomenclature) or aldehyde (common name) is added to the parent names of aldehydes (according to the nomenclature used).

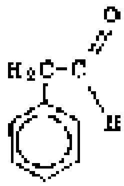
(a) 

The parent compound is the five carbon aldehyde, pentanal or pentaldehyde. There is an alcohol moiety attached to the carbon adjacent to the aldehyde functional group. For aldehydes the carbons beginning with the one attached to the carbonyl carbon are labelled, alpha, beta, gamma (α, β, γ), etc. for the common name and 2,3,4, etc. for the IUPAC name. The name of this compound is therefore 2 hydroxypentanal or α-hydroxypentaldehyde.

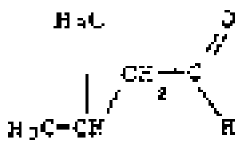
(b) 

Normally in naming the parent compound one determines the longest carbon chain to find the root. The parent compound here would be the three carbon aldehyde propanal or propionaldehyde.

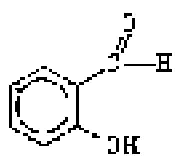
There is a phenyl group with a methyl substituent in the para position attached to the α carbon. The name of this compound is thus 2-p-tolylpropanal or α-p-tolylpropionaldehyde.

(c)  The parent compound is the two carbon aldehyde acetaldehyde

or ethanal. There is a benzene group attached to the α or "2" carbon, which gives the compound the name 2-phenylethanal or 2-phenylacetaldehyde.

(d)  The parent compound is the

four carbon aldehyde, butanal or butyraldehyde. There is a methyl group attached to the "3" or β-carbon. The name of the compound is therefore 3-methylbutanal or β-methylbutyraldehyde.

(e)  The parent compound is the

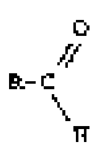
aromatic aldehyde, benzaldehyde. There is a hydroxy group ortho to the aldehyde group. The name of this compound is o-hydroxybenzaldehyde. There is also a trivial name for this compound which is salicylaldehyde.

• PROBLEM 13-5

Give the structural formulas of the following:

(a) Formaldehyde	(d) benzaldehyde
(b) glyceraldehyde	(e) β-aminopropionaldehyde
(c) 3-hydroxybutanal	

Solution: Aldehydes have the general structural formula



(a) Formaldehyde is the simplest aldehyde. It contains only one carbon and can be written as

formaldehyde

(b) The structural formula for glycerol is

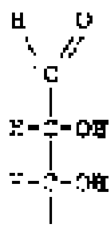
CH_2OH

CHOH

|

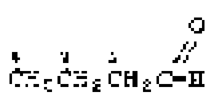
CH_2OH

One of the alcohol functions on the end is oxidized to form the aldehyde, glyceraldehyde.



glyceraldehyde

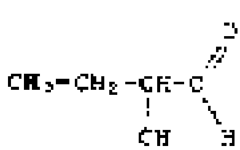
(c) 2-hydroxybutanal. The parent structure is butyraldehyde;



butyraldehyde

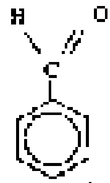
The carbons proceeding from the carbonyl carbon towards the end of the chain are labelled two, three and four.

The hydroxy group is attached to carbon number two.



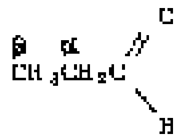
2-hydroxybutanal

(d) Benzaldehyde, as its name implies is a benzene group with an aldehyde function attached.

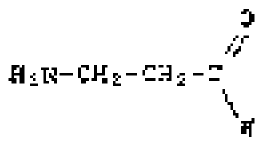


benzaldehyde

(e) β-aminopropionaldehyde The structure of this compound is determined in a manner similar to that used for 2-hydroxybutanal. The parent compound is propionaldehyde.



The carbons are labelled beginning with the first carbon after the carbonyl carbon.



β aminopropionaldehyde

THE CARBONYL GROUP

• PROBLEM 16-6

Arrange the following pairs of compounds in order of expected reactivity toward addition of a common nucleophilic agent such as hydroxide ion to the carbonyl bond. Indicate your reasoning.

(a) $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$ and $CH_3-\overset{O}{\overset{\|}{C}}-CCl_3$

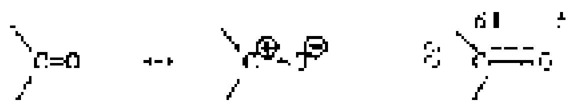
(b) $(CH_3)_3C-\overset{O}{\overset{\|}{C}}-H$ and $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$

(c) $CH_3-\overset{O}{\overset{\|}{C}}-OCH_3$ and $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$

(d)  and 

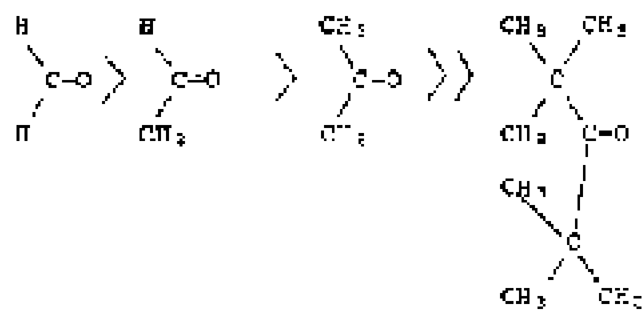
Solution: To solve this problem, we consider what properties of carbonyl compounds favor a reaction with a nucleophilic reagent.

The primary property of carbonyl compounds is the inherent charge separation in the $\rangle C=O$ bond. This charge separation is great enough to lead to a significant contribution of the dipolar resonance form with oxygen negative and carbon positive:

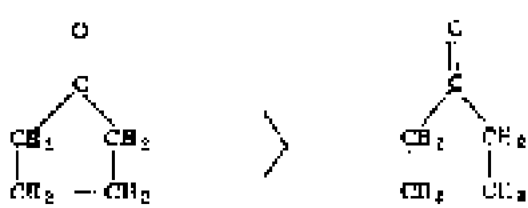


A carbonyl carbon is more susceptible to nucleophilic attack when it is highly electropositive. The nucleophile will more readily contribute its electron pair to a highly electron deficient species in order to relieve the partial positive charge on the carbonyl carbon.

Another important factor in determining reactivity is steric hindrance. The bulkier the substituents on the $\rangle C=O$ group, the less room they have to move freely and thus the less reactive they are, as illustrated in the following comparison:



When comparing cyclic ketones and their open chain analogs in terms of reactivity, the cyclic ketones are almost always more reactive:



This is because the freely rotating alkyl groups on the open chained ketone will often "swing around" and block a nucleophilic attack on the carbonyl group. In a cyclic compound the substituents cannot rotate freely about the $>C-O$ single bonds and the carbonyl carbon is less sterically hindered.

In part a we look at $CH_3-\overset{O}{\overset{|}{C}}-CH_3$ and $CH_3-\overset{O}{\overset{|}{C}}-CCl_3$. The electron withdrawing power of the trichloromethyl group creates a greater electropositive charge on the carbonyl carbon in $CH_3\overset{O}{C}-CCl_3$. This electron withdrawing effect of $-CCl_3$ is called an inductive effect. The compound $CH_3-\overset{O}{\overset{\|}{C}}-CCl_3$ is thus more reactive to nucleophilic attack by $OH^{\ominus}$ than $CH_3-\overset{O}{\overset{\|}{C}}\ CH_3$.

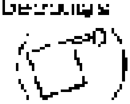
In part b we consider $(CH_3)_3C-\overset{O}{C}-H$ and $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$. The very bulky t-butyl group creates great steric hindrance around the carbonyl carbon thus making a nucleophilic attack by $OH^{\ominus}$ very difficult. For this reason, $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$ is the more reactive compound.

Part c brings an unexpected answer. By considering the inductive effect of $-OCH_3$ we would expect $CH_3-\overset{O}{\overset{\|}{C}}-OCH_3$ to be more reactive. This is not the case. The carbonyl carbon loses some electropositive charge because of the charge stabilization brought about by the following contributing structures:

$$CH_3\overset{O}{C}\ OCH_3 \longleftrightarrow CH_3\overset{O^{\ominus}}{C}=\overset{\oplus}{\ddot{O}}CH_3$$

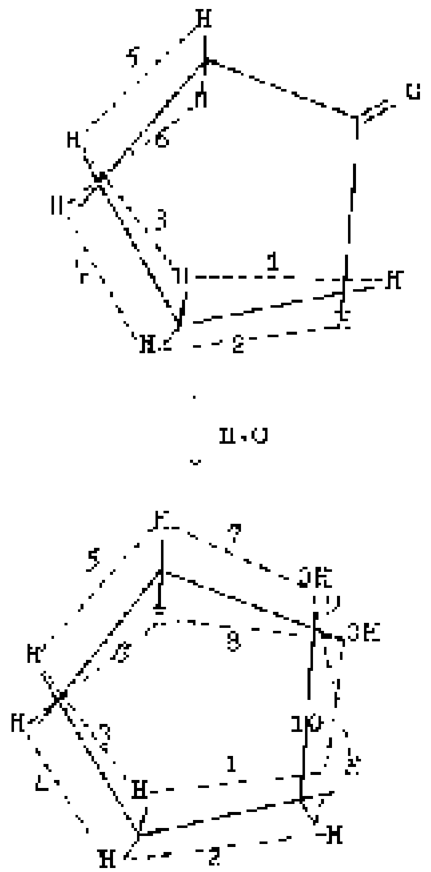
Because of this decrease in electropositive charge and the bulk of the $-OCH_3$ group, the carbonyl carbon of $CH_3-\overset{O}{\overset{|}{C}}-OCH_3$ is less reactive than that of $CH_3-\overset{O}{\overset{\|}{C}}-CH_3$ towards nucleophilic attack.

On this point we should note that the carbonyl carbon is sp^2 hybridized, and that upon nucleophilic attack it becomes sp^3 hybridized. In part d, cyclobutane



has an angle strain of 30° (120° sp^2 bond angle -

90° cyclobutane bond angle = 30° angle strain.) Upon nucleophilic addition the angle strain is reduced to 19.5° (109.5° sp^3 bond angle − 90° = 19.5° angle strain). For cyclobutanone this is a significant reduction of angle strain. In the case of cyclopentanone angle strain is not as important as the eclipsing interactions between non-bonded atoms on adjacent carbons.



six eclipsing interactions

ten eclipsing interactions

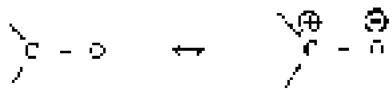
These eclipsing interactions put more energy in the compound's bonds, thus destabilizing the compound. Increasing the number of these interactions will destabilize the compound, thus nucleophilic addition in cyclopentanone is not favorable and cyclobutanone is the more reactive species.

• PROBLEM 18-7

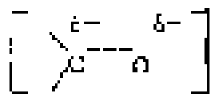
The attack of the nucleophile always occurs at carbon rather than oxygen in a carbonyl compound; this is true when the reaction is kinetically controlled, and it is also true when the reaction is thermodynamically controlled. Explain.

<u>Solution</u>: A carbonyl compound is characterized as having

a -C=O group within it. The C=O bond has a very important
contributing structure which shows the inherent separation of charge between the carbon and oxygen:



A carbonyl is thus more accurately represented with partial charges:



Kinetically this means that the carbonyl carbon is somewhat electrophilic (desires electrons because it is electron deficient) and thus the nucleophile will attack here.

Thermodynamically we could have the following intermediates upon nucleophilic attack:

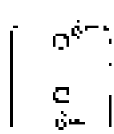
where "B" represents a base.

 is the more stable intermediate because it is more favorable to have the negative charge on the more electronegative atom (oxygen has a greater electronegativity than carbon).

• PROBLEM 10-8

The equilibrium constant for hydration is especially large for formaldehyde, trichloroacetaldehyde, and cyclopropanone. Explain.

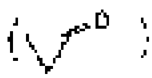
Solution: To solve this problem we must consider what conditions will strongly favor hydration and then see if these conditions are present in the questioned compounds.

Favorable hydrate formation will result when there is a destabilization of charge separation that is inherent in carbonyl groups  caused by a group that is close to it. When there is a steric disadvantage in the carbonyl compound it can sometimes be relieved by formation of the hydrate.

In the case of formaldehyde $\left[\begin{array}{c} O \\ \| \\ H\text{-}C\text{-}H \end{array}\right]$, there is no alkyl group present. Alkyl groups stabilize positively charged centers to which they are bonded, therefore formaldehyde is destabilized, relative to most aldehydes by the absence of these alkyl groups. It exists completely in its hydrated form in aqueous solution.

Trichloroacetaldehyde $\left[\begin{array}{c} O \\ \| \\ CCl_3\text{-}C\text{-}H \end{array}\right]$ has a trichloromethyl group ($-CCl_3$) bonded to the carbonyl carbon. This group induces a significant inductive effect (change in distribution of charge in atoms due to distortions of electron density caused by large electronegativity differences), which destabilizes the charge separation present in the carbonyl group. Chlorine, a very electronegative element, is the cause of this destabilizing inductive effect. The hydrated compound looks like this:

$$\begin{array}{c} OH \\ | \\ CCl_3\text{-}C\text{-}H \\ | \\ OH \end{array}$$

Cyclopropanone  has a large K (equilibrium constant for hydration) value because of steric effects. The bond angle in cyclopropanone is 60°. The carbonyl carbon, being sp^2 hybridized, prefers a bond angle of 120°. The angle strain is thus 60° (120° - 60°). In hydrate form this carbon becomes sp^3 hybridized. The preferred bond angle changes from 120° to 109.5° and the angle strain decreases from 60° to 49.5° (109.5° - 60° = 49.5°).

SYNTHESIS

■ PROBLEM 10-9

Outline all steps in a possible laboratory synthesis of each of the following from alcohols of four carbons or fewer, using any needed inorganic reagents:

(a) $\begin{array}{c} CH_3CH_2\underset{\|}{C}CH_3 \\ \quad O \end{array}$ (b) $\begin{array}{c} CH_3\text{-}\underset{\|}{C}\text{-}CH_3 \\ O \end{array}$

Methyl ethyl ketone Acetone

Solution: Ketones can be prepared by oxidation of secondary alcohols with a variety of reagents, such as CrO_3 (chromium trioxide) or $K_2Cr_2O_7$ (potassium dichromate) with acid. The compound that is formed by oxidation of an alcohol depends upon the number of hydrogens attached to the carbon bearing the -OH group, that is upon whether the alcohol is primary, secondary, or tertiary. For example, in the first problem, to synthesize the product, methyl ethyl ketone, a secondary alcohol is used that has the same number of carbon atoms as the product. In this case sec-butyl alcohol is used as the precursor.

$$\text{(a)}\quad \underset{\text{sec-butyl alcohol}}{CH_3CH_2\overset{\overset{\large OH}{|}}{C}HCH_3} \xrightarrow{CrO_3} \underset{\text{methyl ethyl ketone}}{CH_3CH_2\overset{\overset{\large O}{\|}}{C}CH_3}$$

To obtain the product only requires one step where sec-butyl alcohol is oxidized directly to methyl ethyl ketone with chromium trioxide.

An example of a longer synthesis in preparation of a ketone is producing acetone from a two-carbon alcohol. The only two carbon alcohol is ethanol, so this will be the precursor.

$$\text{(b)}\quad \underset{\text{Ethanol}}{CH_3CH_2OH} \xrightarrow[H^{\oplus}]{K_2Cr_2O_7} CH_3\overset{\overset{\large O}{\|}}{C}H + CH_3MgBr \xrightarrow{H_2O} CH_3\overset{\overset{\large OH}{|}}{C}HCH_3 \xrightarrow{CrO_3} \underset{\text{Acetone}}{CH_3\underset{\underset{\large O}{\|}}{C}CH_3}$$

This synthetic reaction involves oxidation of the alcohol to yield acetaldehyde. To add another carbon atom to this first product, the Grignard reagent methyl magnesium bromide (CH_3MgBr) is added for methylation. Upon hydrolysis this yields a three carbon compound, isopropanol, which is a secondary alcohol. As shown previously, secondary alcohols are oxidized to ketones with chromium trioxide, thus yielding the final product, acetone.

• PROBLEM 18-10

Undecanal is a sex attractant for the greater wax moth (Galleria mellonella). Show how to synthesize this compound efficiently from

(a) 1-nonanol (b) 1-decanol (c) 1-dodecanol

Solution: In a synthetic problem of this type, where one specific compound must be synthesized from various other starting materials, it is a good idea to see what differences there are between the final product and the starting material. The idea is then to synthesize this difference onto the starting material.

For example, in part (a) 1-nonanol ($CH_3(CH_2)_7CH_2OH$), the starting material, must gain two carbons to obtain the carbon skeleton in the final product, undecanal ($CH_3(CH_2)_9CHO$).

Some methods of adding two carbons to the alcohol involve the use of an ethyl Grignard reagent or an acetylene anion. Of these methods, the use of the acetylene anion is the most feasible; it will react with an alkyl halide via an S_N2 mechanism. The alkyne formed can then be converted into the desired product. The synthesis which employs this method is shown below:

$$CH_3(CH_2)_7CH_2OH \xrightarrow{PBr_3} CH_3(CH_2)_7CH_2Br \xrightarrow{HC\equiv C^{\ominus}} CH_3(CH_2)_8C\equiv CH \xrightarrow{B_2H_6} \xrightarrow[OH^{\ominus}]{H_2O_2} CH_3(CH_2)_7CH_2CH_2CHO$$

In part b we follow the same rationale used in part a. In this case we must add one carbon to the starting material. This can be accomplished by a Grignard reagent or through cyanohydrin formation. In this case a Grignard reagent may either react with the ten carbon compound (1-decanol) or be formed from the ten carbon compound. Since 1-decanol will react with a Grignard reagent to produce an alkane and a Grignard salt, we will form the Grignard from the alcohol:

$$CH_3(CH_2)_8CH_2OH \xrightarrow{PBr_3} CH_3(CH_2)_8CH_2Br \xrightarrow[ether]{Mg} CH_3(CH_2)_8CH_2MgBr \xrightarrow{HCHO} \xrightarrow{H^{\oplus}} CH_3(CH_2)_9CH_2OH \xrightarrow[pyridine]{CrO_3} CH_3(CH_2)_8CH_2CHO$$

The last reagent used, CrO_3 with pyridine, is an oxidizing agent that oxidizes a primary alcohol to an aldehyde.

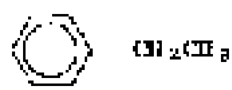
In part c, the starting material must lose one carbon to form the desired product. Some methods of losing one carbon involve the oxidation of a terminal alkene by ozone (followed by a workup) or by hot, basic $KMnO_4$ solution; another method involves the Hoffman degradation of an amide ($RCONH_2$) to an amine (RNH_2). This last method is impractical since the formation of a terminal alkene is much easier than the formation of an amide (from an alcohol). We will use an ozonolysis reaction (followed by reductive workup) to form the desired aldehyde.

$$CH_3(CH_2)_9CH_2CH_2OH \xrightarrow{PBr_3} CH_3(CH_2)_9CH_2CH_2Br$$

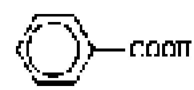
$$CH_3(CH_2)_9CHO \xleftarrow[CH_3COOH]{Zn} \xleftarrow{O_3} CH_3(CH_2)_9CH{=}CH_2 \xleftarrow[\text{alcohol}]{KOH}$$

● PROBLEM 18-11

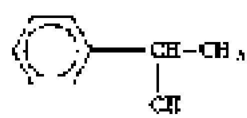
Write equations for all steps in the synthesis of the following from acetophenone, using any other needed reagents:

(a) 

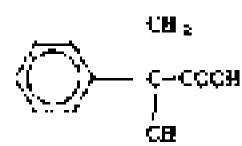
Ethylbenzene

(b) 

Benzoic acid

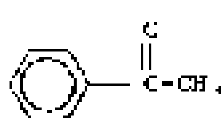
(c) 

1-Phenylethyl alcohol

(d) 

α-Hydroxy-α-phenylpropionic acid

Solution: Reactions involving acetophenone almost exclusively take place at the carbonyl (C=O) moiety of the molecule. To make this concept clearer the chemical structure of acetophenone is illustrated for comparison with the products wanted:



Acetophenone.

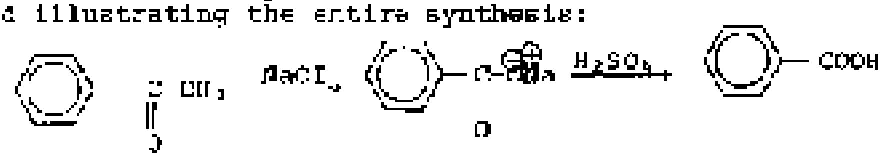
In problem (a), ethylbenzene is synthesized from acetophenone by a process called the Clemmensen reduction, which reduces the ketone to its corresponding hydrocarbon. The carbonyl is reduced to a hydrocarbon by the action of amalgamated zinc [Zn(Hg)] and concentrated hydrochloric acid. The general equation for the reaction is:

$$-\underset{\underset{O}{\|}}{C}- \xrightarrow[\text{conc. HCl}]{Zn(Hg)} -\underset{\underset{H}{|}}{\overset{|}{C}}-H$$, thus solving problem (a).

(a) 

Acetophenone Ethylbenzene

In problem (b), the product desired is benzoic acid which is synthesized by the oxidation of methyl ketones. This reaction involves sodium hypoiodite (NaOI) and sulfuric acid (H_2SO_4) wherein NaOI has the special property of only attacking the methyl group on methyl ketones. The methyl group is then tri-halogenated with the iodine and the CI_3 group is replaced by an $O^{-}\,{}^{+}Na$ portion. This compound formed is known as the intermediate and must be treated with concentrated sulfuric acid to complete the oxidation to a carboxylic acid. Problem (b) can now be solved illustrating the entire synthesis:

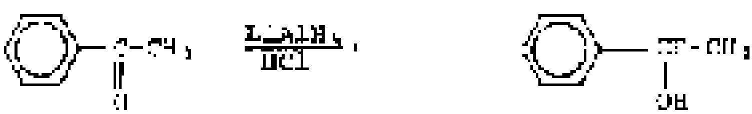
(b) 

Acetophenone + CHI_3 Benzoic acid

Sodium Benzoate

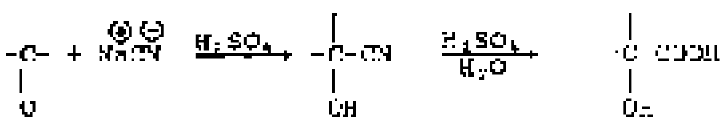
Iodoform

Problem (c) involves the reduction of ketones to yield an alcohol. As shown many times previously most organic compounds can be reduced with hydrogen gas and a metal catalyst such as nickel, platinum or palladium. Even more common, reductions of ketones are done by the use of lithium aluminum hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$), then treating the compound with H_2SO_4 or HCl. The alcohol produced from ketones is a secondary alcohol after reduction and may be illustrated as follows:

(c) 

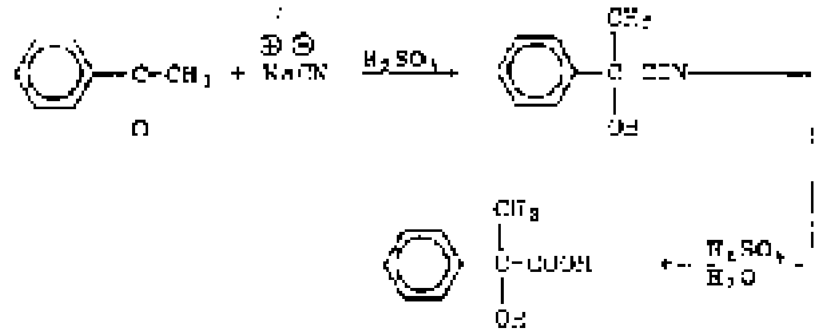
Acetophenone 1-Phenylethyl alcohol

In problem (d), cyanohydrin formation is used. Cyanohydrins are nitriles, and their principal use is based on the fact that, like other nitriles, they undergo hydrolysis; in this case the products are α-hydroxyacids or unsaturated acids. The general equation for this type of reaction is:



Ketone Cyanohydrin α-Hydroxyacid

The hydrocarbon group adjacent to the carbonyl is either aryl(Ar) or alkyl (R) and does not change at all during the synthesis because the reagents used are specific for the carbonyl moiety.

(d) 

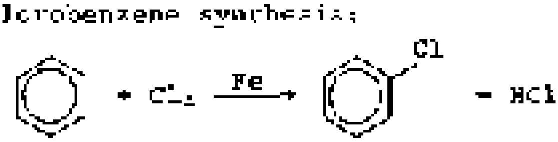
α-Hydroxy-α-phenyl propionic acid

• PROBLEM 18-12

> Propose a reasonable mechanism for the synthesis of benzaldehyde diethyl acetal from benzene.

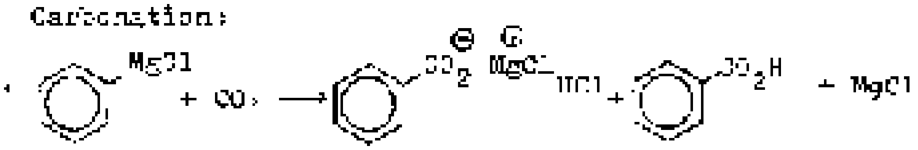
Solution: Benzene can be halogenated in the presence of a catalytic amount of iron (Fe). The halobenzene can form a Grignard reagent, which can be carbonated to give a carboxylic acid. Reduction of a carboxylic acid can give an aldehyde; an acetal is an aldehyde derivative. The complete synthesis is broken down into various steps, and is shown below:

1.) Chlorobenzene synthesis;

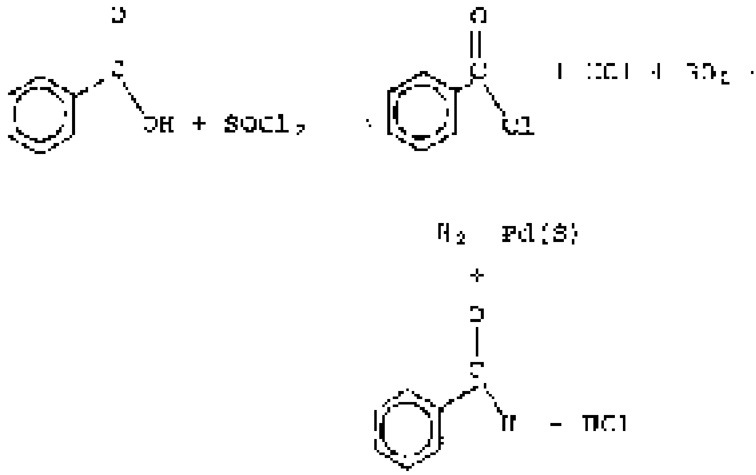


2.) Grignard formation:

3.) Carbonation:



4.) Rosenmund reduction of carboxylic acid;



Benzaldehyde

3.) Acetal synthesis:

Benzaldehyde diethyl acetal

• PROBLEM 18-13

One of the compounds that was initially formed in the primitive atmosphere was formaldehyde ($H_2C=O$). It is one of the precursor molecules that came to make up living organisms. It can be formed photolytically as shown in the following equation:

$$CH_4 + H_2O \xrightarrow{h\nu} H_2C=O + 4H\cdot$$

Propose a mechanism for this reaction.

Solution: When ultraviolet light ($h\nu$) is the energy source for a reaction, free radicals are usually involved.

When methane (CH_4) is exposed to ultraviolet light the following fragmentation will occur.

(a) $CH_4 \xrightarrow{h\nu} \cdot CH_3 + H\cdot$

methyl radical   hydrogen radical

Since there is water in this system, it will also be exposed to the ultraviolet rays, causing it to break up into radicals.

$$\text{(ii)} \qquad 2H_2O \xrightarrow{h\nu} 2HO\cdot \quad + 2H\cdot$$

In designing a mechanism, one attempts to build molecules that look increasingly like the desired products. The system now contains the $HO\cdot$, $H\cdot$ and $CH_3\cdot$ radicals. If $HO\cdot$ and $CH_3\cdot$ combine, a product resembling formaldehyde is made.

$$\text{(iii)} \qquad \cdot CH_3 + HO\cdot \longrightarrow \underset{\text{methanol}}{HO\,CH_3}$$

To produce formaldehyde two hydrogen atoms must be removed from this product; one from the oxygen and one from the carbon.

$$\text{(iv)} \qquad HO\,CH_3 \xrightarrow{h\nu} HO\,\dot{C}H_2 + H\cdot$$

Remember that ultraviolet light will cause the formation of radicals. In the next reaction the other hydrogen will be removed in a different way. An $\cdot OH$ radical will add to the product formed in reaction (iv) and a transition state will form which will lead to the production of one molecule of formaldehyde, and one molecule of water. The brackets indicate the intermediate transition state.

$$\text{(v)} \qquad HO-\dot{C}H_2 + HO\cdot \longrightarrow \left[HO-\overset{\displaystyle OH}{\overset{|}{C}}H_2 \right] \longrightarrow \begin{matrix} H \\ \quad\diagdown \\ \quad\; C=O \\ \quad\diagup \\ H \end{matrix} + H_2O$$

If reactions (i) through (v) are added together one regains the given overall reaction.

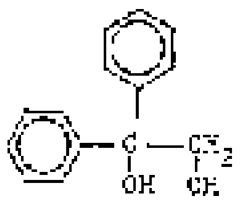
REACTIONS

• PROBLEM 18-11

What are the products from the reaction of 1,1-diphenyl-1,2-ethanediol with strong acid? Propose a reasonable mechanism for the reaction.

Solution: Polyhydric alcohols with hydroxyl groups on different carbons are relatively stable, but in strong acid they tend to dehydroxylate to form carbonium ions. If the alcohol is a 1,2-diol, the carbonium ion can rearrange to give a more stable carbonyl compound.

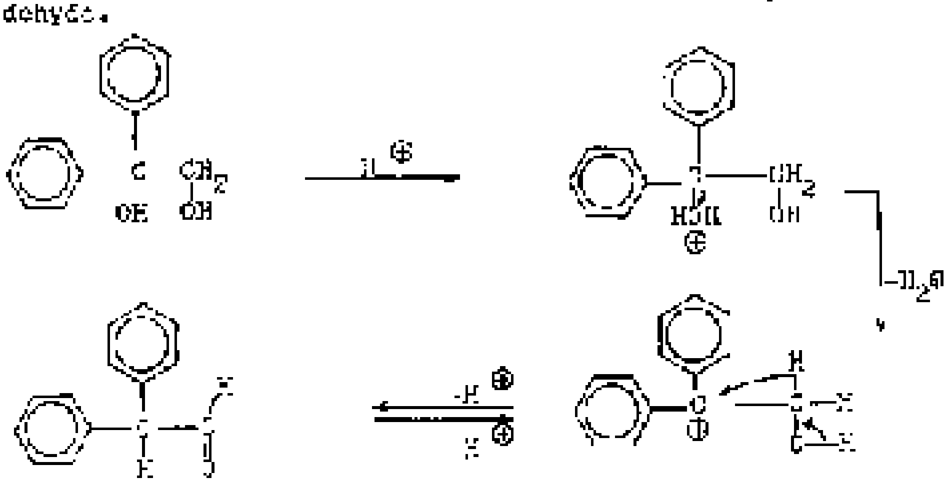
1,1-diphenyl-1,2-ethanediol is a polyhydric alcohol having the structure



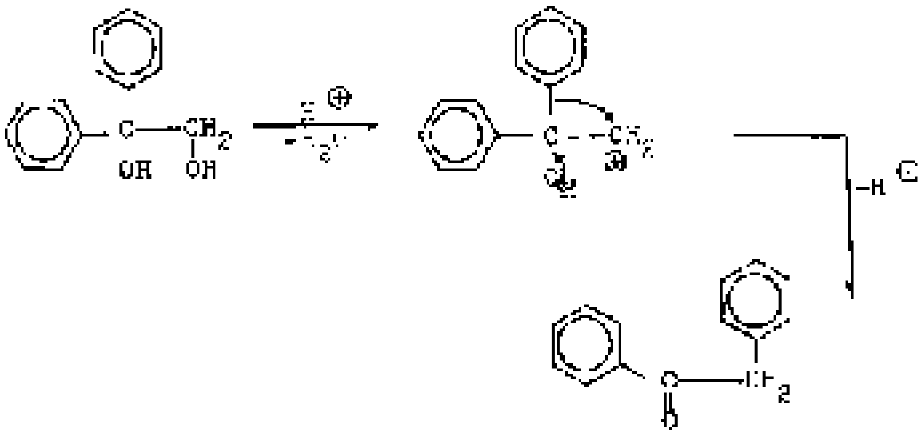
In the presence of strong acid, the carbonium ion can be formed at either carbon, depending upon the method of control employed (kinetic or thermodynamic). If the hydroxyl group at the carbon with the diphenyl is protonated, a benzylic cation is formed. If the other hydroxyl group is protonated, a primary carbocation is formed. The rate of carbocation formation depends upon the stability of the ion formed. The order of stability of carbocations is:

benzylic > tertiary > secondary > primary.

Thus, if kinetic (rate) control is used, the hydroxyl group on the tertiary carbon is protonated to form a tertiary benzylic cation. The loss of water followed by a hydride shift gives the final product, diphenylacetaldehyde.

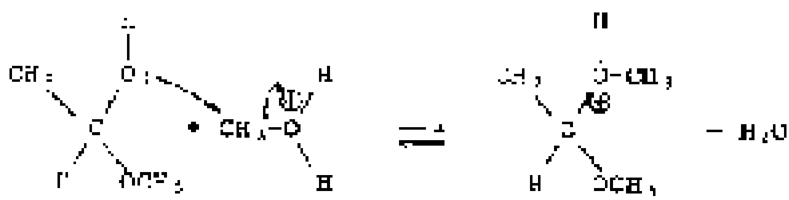


However, if the reaction is left standing for a period of time, a different product is formed. This product is formed slower and is more stable than diphenylacetaldehyde, thus, the pathway of formation is equilibrium-controlled. It occurs at a slower rate because it is formed by protonation of the hydroxyl group on the primary carbon to give a primary carbocation. This primary carbocation undergoes a phenyl shift instead of a hydride shift, in the process of carbonyl formation. This results in a more stable compound because there is more resonance stabilization arising from the carbonyl group being conjugated to a phenyl than lying adjacent to a hydrogen. The final product of this slower equilibrium pathway is benzyl phenyl ketone.



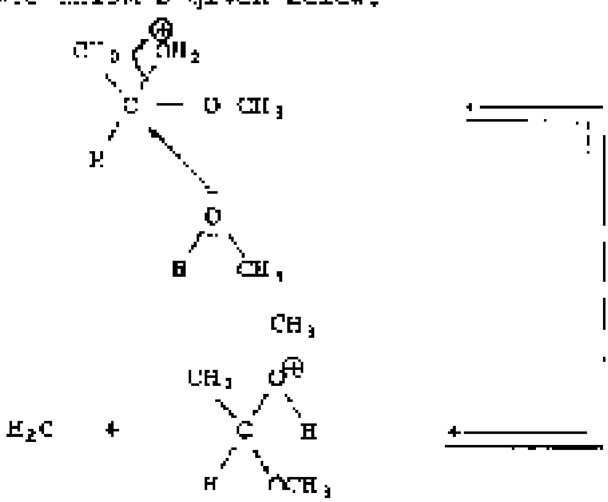
PROBLEM 18-15

The slow step in alternative mechanism A for acetal formation might be as follows:



Mechanism A

How could this mechanism be distinguished experimentally from mechanism B given below?



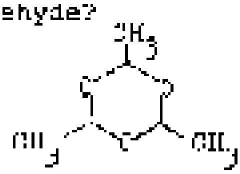
Mechanism B

Solution: The major difference between the two mechanisms lies in the initial step of acetal formation: protonation.

In mechanism A the methanol was protonated whereas in mechanism B the hemiacetal $\left(CH_3-\overset{\overset{OH}{|}}{C}H-OCH_3\right)$ was protonated at the hydroxyl oxygen. Mechanism A shows the cleavage of the C-O bond in methanol; mechanism B shows the cleavage of the C-O bond in the hemiacetal. If we were to use methanol labeled with heavy oxygen (O^{18}), the two mechanisms may be distinguished. If mechanism A was the actual reaction mechanism, heavy oxygen would be found only in the water and methanol, and none of the O^{18} would be incorporated in the acetal. If mechanism B were the actual one, heavy oxygen would be found in the acetal and methanol, and none would be found in the water.

• PROBLEM 18-10

Write a plausible reaction mechanism for the trimerization of acetaldehyde to paraldehyde with a trace of acid. How does this mechanism compare to the acid-catalyzed depolymerization of paraldehyde?

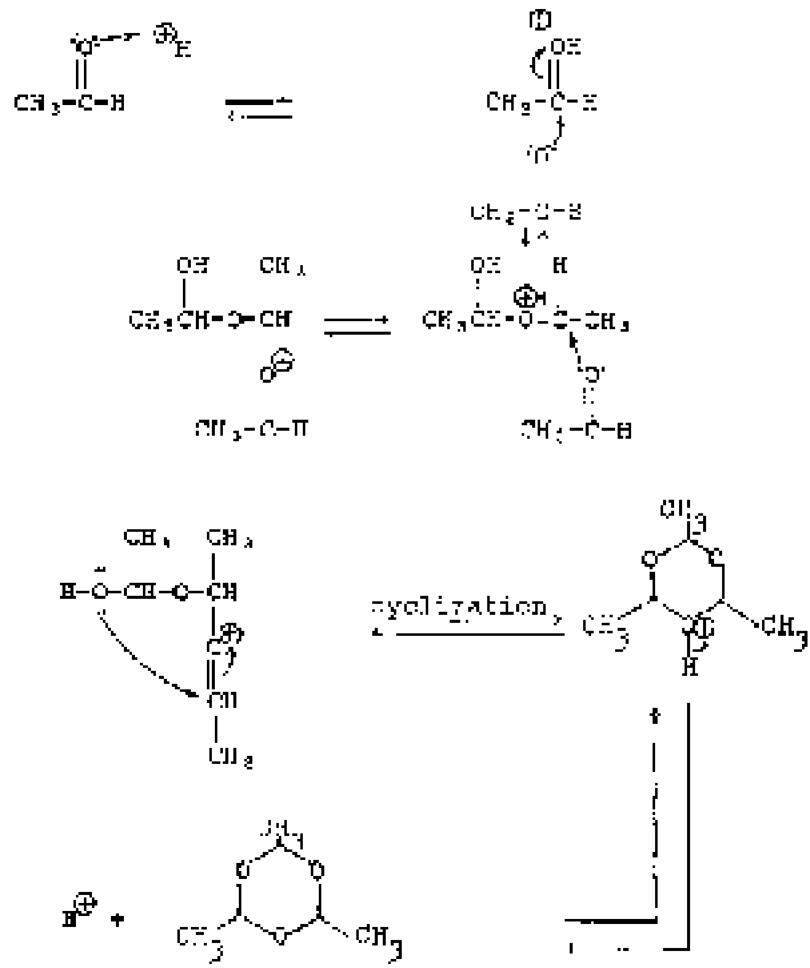


paraldehyde

Solution: In a slightly acidic solution, only some of the acetaldehyde is protonated. A protonated acetaldehyde contains a carbon bearing a positive charge; this species is fairly reactive and will seek out an electron-rich species with which to react. There are four species in this solution: $CH_3\overset{\overset{O}{\|}}{C}-H$, $H^{\oplus}$, $CH_3\underset{\oplus}{\overset{\overset{OH}{|}}{C}}H$ and H_2O.

The protonated acetaldehyde may react with H_2O or $CH_3-\overset{\overset{O}{\|}}{C}-H$.

Reaction with H_2O will yield the initial reactants, $CH_3\overset{\overset{O}{\|}}{C}-H$ and $H^{\oplus}$. Reaction with $CH_3\overset{\overset{O}{\|}}{C}-H$ however, at the cationic carbon, will result in the formation of an acetaldehyde dimer bearing a positive charge. This dimer will react with another $CH_3\overset{\overset{O}{\|}}{C}-H$ molecule to form a trimer of acetaldehyde. This trimer has a cationic carbon on one end and an -OH group on the other end; the electronegative -OH oxygen will bond to the cationic carbon. This cyclization is accompanied by proton loss to stabilize the positive charge. Only the acetaldehyde trimer will undergo cyclization (and not the dimer) because of the stability of the six-membered ring formed. A four membered ring, formed by cyclization of the dimer, is less stable than a six-membered ring due to greater angle strain. The mechanism of paraldehyde formation is shown as:

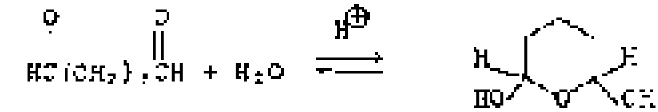


Paraldehyde

Since the polymerization of acetaldehyde to paraldehyde has both forward and reverse directions, the depolymerization of paraldehyde to acetaldehyde follows the reverse mechanism of paraldehyde formation.

■ **PROBLEM 18-17**

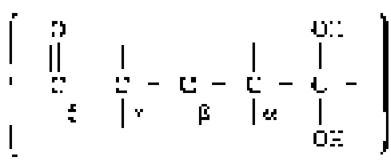
Aqueous solutions of glutaraldehyde are potent biocides, used in hospitals to destroy bacteria, viruses, and spores on environmental surfaces. An nmr investigation has shown that the major component of a 25% solution of glutaraldehyde is a cyclic hydrate. Suggest a mechanism for its formation and reversion to glutaraldehyde.



glutaraldehyde cyclic hydrate

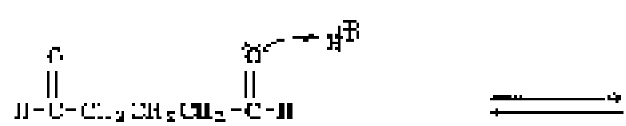
Solution: In acidic solution, glutaraldehyde, like any other aldehyde, will be protonated at one of its carbonyl oxygens. The protonated glutaraldehyde has a positively charged carbonyl carbon which will react with any available nucleophile. A potential nucleophile in this media is water.

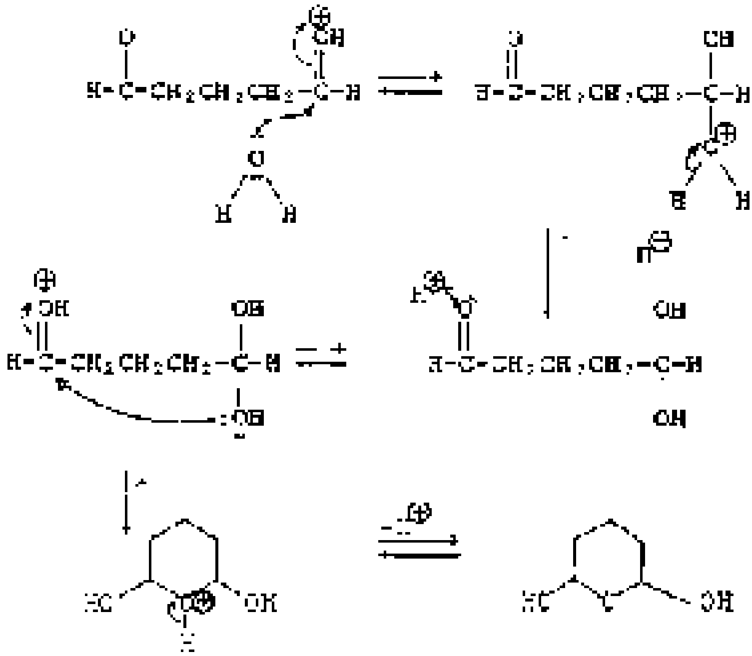
The free electron pair on oxygen causes water to act as a nucleophile upon the positively charged carbonyl carbon. Subsequent proton loss rids the molecule of its charge and forms a δ-oxo-gem diol



The molecule is neutral and is protonated at the remaining carbonyl oxygen. The oxygen of a hydroxyl group will form a bond with the positively charged carbonyl carbon that resulted from the second protonation. This cyclization step is thermodynamically favorable due to the formation of a six-membered ring; six-membered rings consisting of sp^3-hybridized carbons (and one oxygen atom in this case) are fairly stable because they have very little angle strain. The cyclic structure formed thus far has a positively charged ring oxygen; subsequent proton loss will neutralize the molecule and give us the cyclic hydrate of glutaraldehyde.

Reversion of the cyclic hydrate back to glutaraldehyde follows the reverse mechanism of cyclic hydrate formation. This is because all the steps in the mechanism of cyclic hydrate formation are in equilibrium; they have both forward and backward directions. The mechanism of cyclic hydrate formation from glutaraldehyde and its reversion back to glutaraldehyde is shown below:





• PROBLEM 14-18

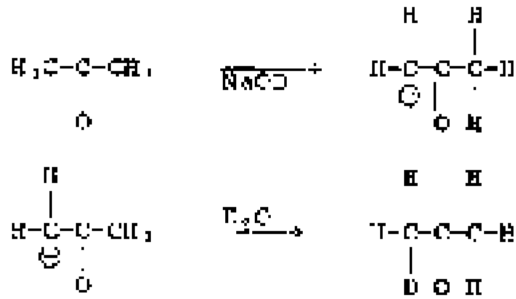
One way we can explore the acidity of hydrogens with an organic molecule is to dissolve the compound in D_2O in the presence of NaOD. If a hydrogen is removed by the base, it will be replaced by deuterium. For example, acetaldehyde, CH_3CHO, in D_2O/NaOD is quickly converted to CD_3CHO. What deuterio compounds would you get from each of the following compounds under these conditions?

(a) acetone (c) cyclohexanone
(b) ethyl alcohol (d) benzaldehyde

Solution: The α-hydrogens of aldehydes, ketones, esters and their derivatives are slightly acidic. The α-hydrogens are those hydrogens joined to the carbon atom which is adjacent to the carbon atom bonded to the oxygen. These α-hydrogens are acidic enough so that small but chemically significant amounts of carbanions are produced simply by dissolving carbonyl compounds in basic solutions.

When an oxygen containing organic compound is dissolved in the basic D_2O/NaOD solution the α-hydrogens are replaced by D. When the compound is placed in the basic solution, these hydrogens dissociate due to their acidities.

(a) In acetone, H_3CCOCH_3, all six hydrogens are positioned on α-carbons and will therefore be replaced with deuterium atoms.

(i) 

(ii)

The above sequence of reactions will occur until all of the α hydrogens are replaced.

(b) In alcohols the most acidic hydrogen is the one bonded to the oxygen atom.

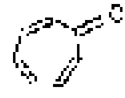
$$C_2H_5-OH \xrightarrow[NaOD]{D_2O} C_2H_5OD$$

The hydrogen attached to the carbon bonded to the oxygen is not acidic enough and will not be replaced. The α-hydrogens will not be replaced either because the negative charge on the oxygen is dispersed by both the hydrogen and the carbon bound to it causing the α-hydrogens to be much less acidic than they are in the presence of a carbonyl group.

(c) There are four α-hydrogens in cyclohexanone, two on each α-carbon. All four of these will be replaced by deuterium.

(d) There are no α hydrogens in benzaldehyde and no deuteric compounds will be formed.

• PROBLEM 18-19

The ketone tropone, , is exceptionally basic in character, forming much more stable salts with HCl than simple ketones. How can this be explained?

Solution: The ability of a compound to accept or release a proton depends on the stability of the resulting compound. Simple ketones are not basic because the protonated compound is too unstable. For example, a protonated acetone has a positively charged oxygen,

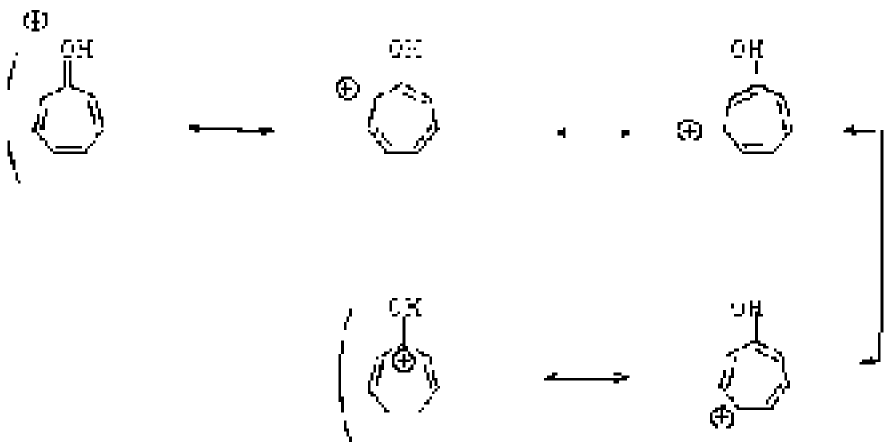
$$H_3C-\overset{\overset{\oplus O-H}{\|}}{C}-CH_3$$

, and no other possible structure. Since oxygen is very electronegative, it tends to lose the positive charge by releasing the proton. Thus, acetone's basicity is negligible.

The ketone tropone is very different from most other ketones. It displays some aromaticity, although it is not a fully aromatic compound. However let us look at its protonated form:

It has six π electrons in a conjugated ring system. It satisfies Hückel's rule and is thus aromatic.

The protonation of tropone creates a positively charged oxygen. However, this positive charge can be shared by all the ring carbons. This is a characteristic property of the aromatic system. The sharing of the positive charge, that is the resonance structures, give extra stabilization to the resulting compound. Thus, tropone is more readily protonated. The resonating protonated tropones are shown below.

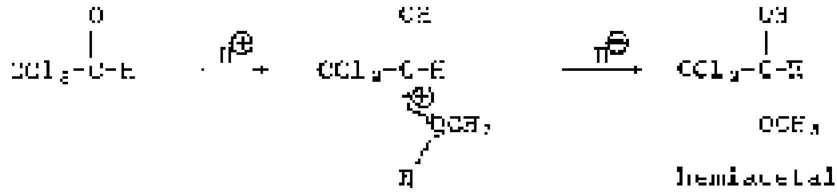


The aromaticity that tropone acquires in its protonated form thus represents a great increase in stability. For this reason tropone forms a much more stable salt with HCl than simple ketones.

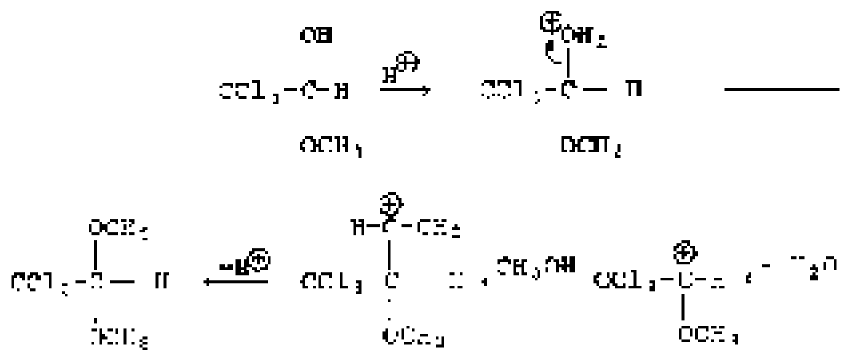
• PROBLEM 18-20

> Chloral (CCl_3CHO) reacts rapidly with methanol to give the hemiacetal but only very slowly to give the corresponding acetal. Explain.

Solution: Chloral (CCl_3CHO) will react rapidly with methanol (CH_3OH) because of the inductive effect of the trichloromethyl group (CCl_3) in chloral. This effect creates a highly electropositive carbonyl carbon, making it very susceptible to nucleophilic attack. In hemiacetal formation the following reaction will occur:



For the acetal to form from the hemiacetal, the following would have to happen:



acetal

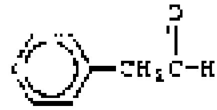
The key to this acetal formation is the protonation of the OH group of the hemiacetal so that dehydration (loss of H_2O) may occur, and the species $CCl_3-\underset{\oplus}{\overset{H}{C}}-OCH_3$ may be formed.

Chloral strongly hydrates in aqueous media because of the inductive effect of the $-CCl_3$ group. In acetal formation we encounter dehydration, which is highly unfavorable. Also, the cation formed, $CCl_3-\underset{\oplus}{\overset{OCH_3}{C}}-H$, will be unstable because of the inductive effect of the CCl_3 group. For these reasons acetal formation will occur very slowly.

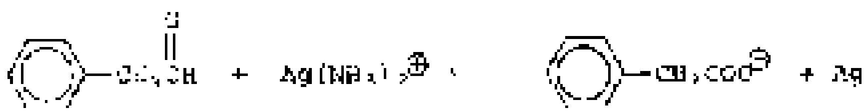
• PROBLEM 18-21

Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetaldehyde with:

(1) Tollens' reagent (5) $NaBH_4$
(2) CrO_3/H_2SO_4 (6) C_6H_5MgBr, then H_2O
(3) cold dilute $KMnO_4$ (7) $NaHSO_3$
(4) $KMnO_4$, H^+, heat (8) CN^-, H^+
(9) 2,4-dinitrophenylhydrazine

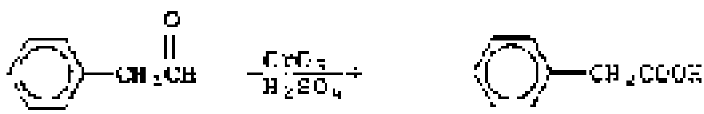
Solution: Phenylacetaldehyde  undergoes these reactions that are typical of aldehydes.

(1) Tollens' reagent contains the silver ammonia ion, $Ag(NH_3)_2^{\oplus}$. Its utility stems from the detection of aldehydes, in particular for differentiating them from ketones. This reagent oxidizes the aldehyde to a carboxylic acid; it is accompanied by reduction of silver ion to free silver (in the form of a mirror under the proper conditions). Hence

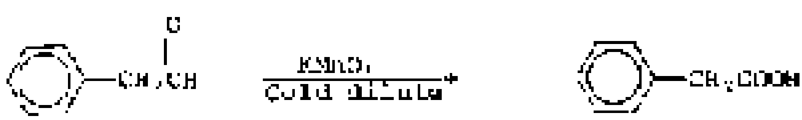


(Silver Mirror)

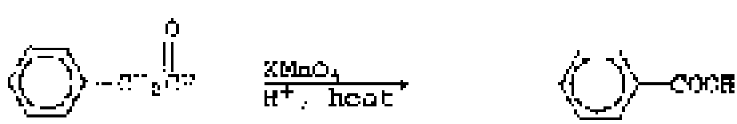
(2) Aldehydes can be easily oxidized to carboxylic acids by chromic acid. Therefore



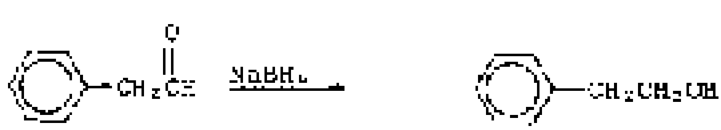
(3) Under the conditions of cold dilute potassium permanganate ($KMnO_4$), the aldehyde is oxidized to the carboxylic acid with the carbon skeleton number unchanged. Hence,



(4) Prolonged hot treatment of a side chain on an aromatic ring with $KMnO_4$ results in its oxidation down to the ring, only a carboxyl group (-COOH) remaining to indicate the position of the original side chain.

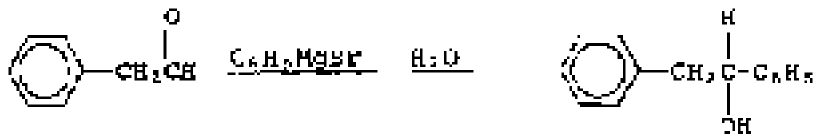


(5) Sodium borohydride, $NaBH_4$, can be used to reduce carbonyl compounds to alcohols. This reagent has the special advantage of not reducing carbon-carbon double bonds, not even those conjugated with carbonyl groups. Consequently, it is useful for the reduction of such unsaturated carbonyl compounds to unsaturated alcohols. Therefore.

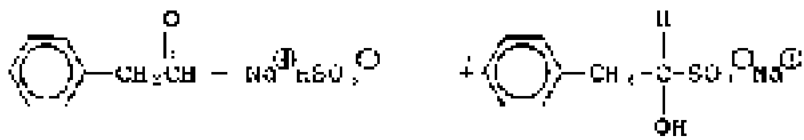


(6) The addition of Grignard reagents to aldehydes is an important route to secondary alcohols (primary alcohols in

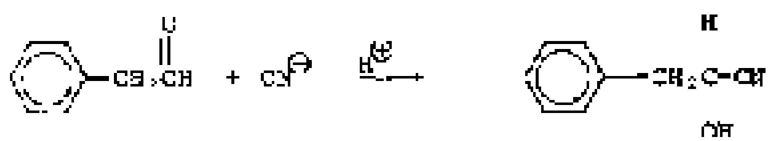
the case of formaldehyde). Thus



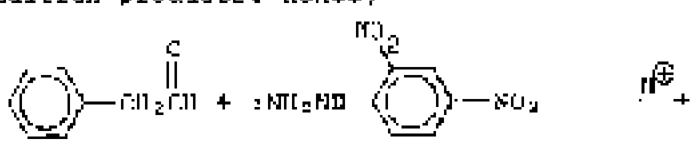
(7) Sodium bisulfite adds to aldehydes (most of them) to form bisulfite addition products. This utility is in separating a carbonyl compound from non-carbonyl compounds. The reaction is illustrated as follows:



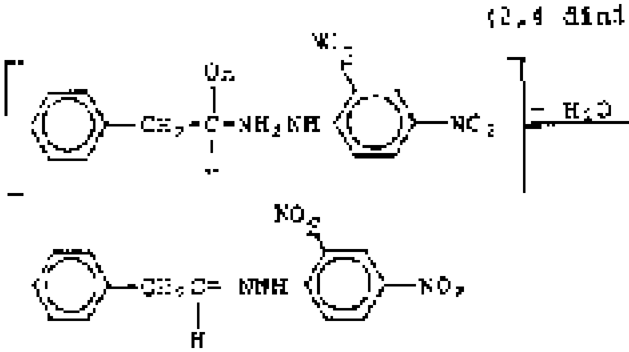
(8) Hydrogen cyanide (HCN) can be added to the carbonyl group of aldehydes and ketones to yield compounds known as cyanohydrins. The reaction is often carried out by adding mineral acid to a mixture of the carbonyl compound and aqueous sodium cyanide. Thus,



(9) Certain compounds that are derivatives of ammonia such as 2,4 dinitrophenylhydrazine add to the carbonyl group to form derivatives useful for the characterization and identification of aldehydes and ketones. The products possess a carbon-nitrogen double bond that was produced from elimination of a molecule of water from the initial addition products. Hence,



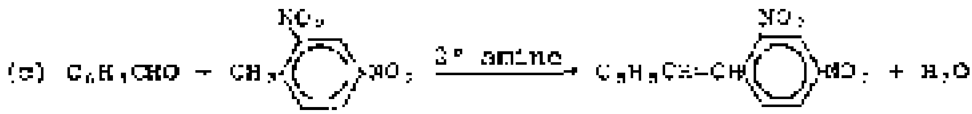
(2,4 dinitrophenylhydrazine)



Account for the following reactions:

(a) $C_6H_5CHO + CH_3NO_2 \xrightarrow{KOH} C_6H_5CH{=}CHNO_2 + H_2O$

(b) $C_6H_5CHO + C_6H_5CH_2CN \xrightarrow{NaOC_2H_5} C_6H_5CH{=}\underset{\displaystyle C_6H_5}{\underset{|}{C}}CN + H_2O$

(c) 

(d) $CH_3CHO + NaC{\equiv}CH \xrightarrow{NH_3(l)} CH_3\underset{\displaystyle ONa}{\underset{|}{C}H}C{\equiv}CH \xrightarrow{NH_4Cl} CH_3\underset{\displaystyle OH}{\underset{|}{C}H}C{\equiv}CH$

(e) A Perkin condensation:

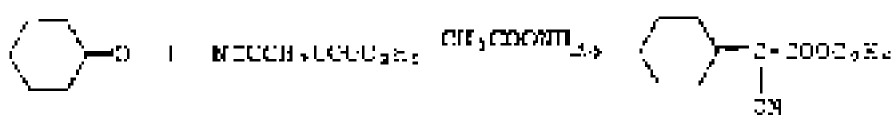
$C_6H_5CHO + (CH_3CO)_2O \xrightarrow{CH_3COONa} C_6H_5CH{=}CHCOOH$

Acetic Anhydride Cinnamic acid

(f) A Knoevenagel reaction:

$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow{2° \text{ amine}} C_6H_5CH{=}C(COOC_2H_5)_2$

(g) A Cope reaction:

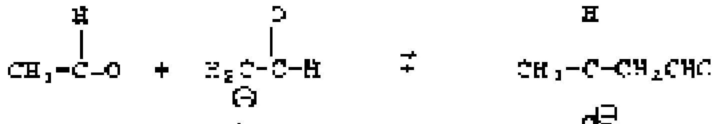


Solution: A consideration of nucleophilic addition to carbonyl compounds (using an aldol condensation as an example) will aid in the solution to this problem.

It is known that under the influence of dilute base two molecules of an aldehyde or a ketone may combine to form a β-hydroxyaldehyde or a β-hydroxyketone. Such a reaction is called an aldol condensation. Using acetaldehyde as an example, the mechanism for the base-catalyzed condensation may be written as follows:

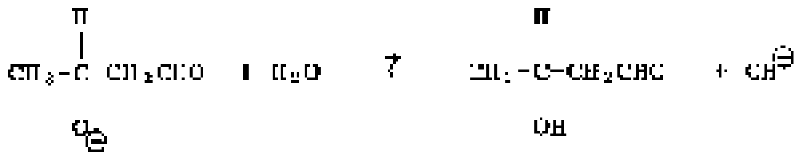
$$(1)\quad \underset{\text{(Acetaldehyde)}}{CH_3CHO} + \underset{\text{(Base Catalyst)}}{OH^{\ominus}} \rightleftarrows H_2O + \underset{\text{(I)}}{H_2\overset{\ominus}{C}-\overset{O}{\overset{\|}{C}}-H}$$

The hydroxide ion ($OH^{\ominus}$) abstracts a hydrogen ion from the α-carbon of the aldehyde to form carbanion I.

(2) 

(I) (Nucleophilic Reagent) (II)

The carbanion I attacks the carbonyl carbon to form carbanion II, an alkoxide.

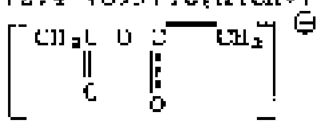
(3) 

(II) (III)

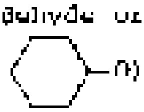
The alkoxide abstracts a proton from water to form the β-hydroxyaldehyde (III), regenerating the hydroxide ion. The purpose of the $OH^{\ominus}$ was to form the carbanion I, which is the actual nucleophilic reagent. The carbonyl group provides the unsaturated linkage at which addition occurs (step 2) and makes the α-hydrogen acidic enough for carbanion formation (step 1) to take place.

With this information, note that in (a) - (g) (except (d)) there exists a base (KOH, $NaOC_2H_5$, 2° amine, NH_3, CH_3COONa, CH_3COONH_4) that abstracts a proton that is alpha to one or more electronic withdrawing groups ($-NO_2$, $-C\equiv N$, $-C=O$, and $2,4-(NO_2)_2C_6H_3-$) to give the following anions: (a) $[CH_2NO_2]^{\ominus}$, (b) $[PhCHCN]^{\ominus}$

(c) $[2,4-(O_2N)_2C_6H_3CH_2]^{\ominus}$ (d) $HC\equiv C^{\ominus}$

(e)  (f) $[CH(COOEt)_2]^{\ominus}$

(g) $[CH(CN)(COOEt)]^{\ominus}$. Hence the bases in (a) - (g) serve the same purpose as the hydroxide ion in the aldol condensation - the production of anions.

At this point, the anions produced add to the aldehyde or ketone present (C_6H_5CHO, CH_3CHO, ) to give an aldol like product, the alkoxy group is protonated, and water is lost. Note that in (e) the hydrolysis of an intermediate anhydride is needed as well.

CARBONYL REACTIONS WITH AMMONIA DERIVATIVES

• PROBLEM 18-23

Find all possible structures of the ketone that reacts with hydroxylamine to form an oxime which contains 13.9% nitrogen.

Solution: Ketones $\left(\begin{matrix} R \\ \quad \diagdown \\ \quad\quad C{=}O \\ \quad \diagup \\ R \end{matrix}\right)$ can undergo a condensation reaction with derivatives of ammonia such as hydroxylamine (H_2NOH) to form stable crystalline solids such as oximes $\left(\begin{matrix}\diagdown \\ C{=}N{-}OH \\ \diagup\end{matrix}\right)$ with the loss of a water (H_2O) molecule.

The reaction of the ketone to be determined with hydroxylamine can be written as:

$$\begin{matrix} R \\ \diagdown \\ \quad C{=}O \\ \diagup \\ R \end{matrix} \quad + \; H_2NOH \longrightarrow \begin{matrix} \\ R{-}C{=}N{-}OH \\ \diagup \\ R \end{matrix} \quad + \; H_2O$$

(Ketone) hydroxylamine (oxime)

The problem indicates that oxime is 13.9% nitrogen (N) and asks that the ketone, specifically the R groups, be found. The percentage of nitrogen in the oxime is a measure of the atomic weight of nitrogen times the number of nitrogen atoms divided by the molecular weight of the oxime times 100:

$$\frac{(\text{AW of N})\ (\text{No. of atoms})}{(\text{MW of oxime})} \times 100 = \%\ \text{of N}$$

One knows the following: No. of N atoms is one, MW of N is 14, MW of carbon is 12, MW of H is 1, and the MW of O is 16. If one represents the total weight of the hydrocarbon R groups by X, then it can be written that:

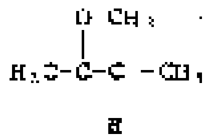
$$\frac{14}{14 + 16 + 1 + 12 + X}\ (100) = 13.9$$

Solving for X, $X = 57.7$.

This means the total weight of the carbon and hydrogen atoms in the R groups is 57.7 Through a little trial and error, one will find this total weight measures a toal of 4 carbon atoms $(4 \times 12 = 48)$ and 10 hydrogen atoms $(10 \times 1 = 10)$. This means the R groups could each be CH_3CH_2, or one could be $CH_3CH_2CH_2$ and the other CH_3. Consequently, the ketone is either diethyl ketone or methyl N-propyl (or isopropyl) ketone as shown:

$$H_3C{-}H_2C{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_2CH_3 \qquad\qquad H_3C{-}\overset{\overset{\displaystyle O}{|}}{C}{-}CH_2{-}CH_2{-}CH_3$$

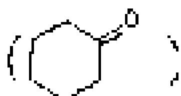
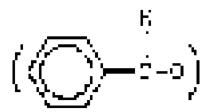
(Diethylketone) (Methyl N-propyl ketone)

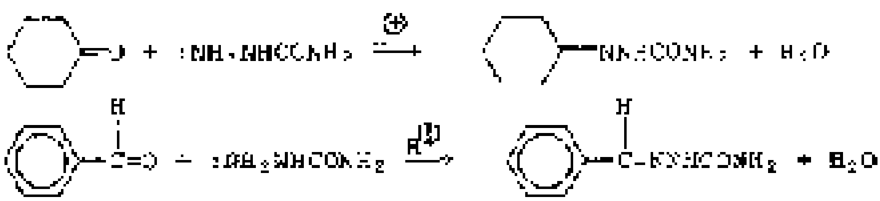


(Methyl isopropyl ketone)

• PROBLEM 18-24

Semicarbazide (1 mole) is added to a mixture of cyclohexanone (1 mole) and benzaldehyde (1 mole). If the product is isolated immediately, it consists almost entirely of the semicarbazone of cyclohexanone; if the product is isolated after several hours, it consists almost entirely of the semicarbazone of benzaldehyde. How do you account for these observations?

Solution: Semicarbazide ($:NH_2NHCONH_2$), a derivative of ammonia, can add to the carbonyl group of aldehydes and ketones to form the derivative semicarbazone. The reactions with cyclohexanone () and benzaldehyde () can be written as follows:



When the product is isolated immediately, most of it consists of the semicarbazone of cyclohexanone, whereas hours later it is mostly the semicarbazone of benzaldehyde. These observations strongly suggest semicarbazide formation is reversible. Cyclohexanone reacts more rapidly, but benzaldehyde gives the more stable product so that it will predominate in time. Initially, one isolates the product of rate control (the compound that reacts with greatest speed). Later, after the equilibrium is established, one isolates the product of equilibrium control (greatest stability).

• PROBLEM 18-25

Calculate the pH which would give the most rapid reaction rate for a carbonyl compound with $K_B = 10^{-14}$ and an RNH_2 derivative with $K_B = 10^{-11}$ assuming 1 M concentrations for the reactants, and the slow step being as in Eq.(1). How many times faster is the rate at this pH than at pH 0? Than at pH 7?

Solution: We approach this problem by trying to find a rate equation for the whole reaction and then, by using the given equilibrium constants, substitute the correct concentrations and by using calculus find the pH value of the maximum reaction rate.

Being that this example involves a great deal of mathematics, we try to simplify as much as possible. Let us now introduce symbols to represent concentrations of various species.

Let $A = [(CH_3)_2CO]$

$B = [RNH_2]$

$H = [H^+]$

$AH = [(CH_3)_2COH^{\oplus}]$

$BH = [RNH_3^{\oplus}]$

$OH = [OH^{\ominus}]$

The rate of reaction (expressed by the symbol v) is equal to the concentration of one reactant multiplied by the concentration of the other reactant times k (constant for reaction rate).

Equation (2) $v = k \cdot AH \cdot B$

We now try to solve for the concentrations of AH and B. We accomplish this by using the equilibrium equation for each of these species. The equilibrium equation that we are speaking of is the equilibrium that occurs when each of the reactant species is isolated in aqueous media. The equilibrium equation for B is:

$$K_B = \frac{BH \cdot OH}{B}$$

This is derived from the chemical equation

$$RNH_2 + H_2O \rightleftarrows RNH_3^{\oplus} + OH^{\ominus}$$

We know that the reactants of Eq. (1) are present in one molar concentrations, thus we can say that $BH + B = 1$ or $BH = 1 - B$. From general chemistry we know that $K_w = OH \cdot H$, thus $OH = \frac{K_w}{H}$. By substitution we can change our equilibrium equation as follows:

$$K_B = \frac{(1 - B) \cdot OH}{B}$$

$$= \frac{(1 - B) \cdot K_w}{B \cdot H}$$

Solving for B we get

$$B = \frac{1}{1 + (K_B/K_w) \cdot H}$$

We now follow the same procedure for expressing AH in terms of its K_B (call it $K_{B'}$):

$$K_{B'} = \frac{AH \cdot OH}{A}$$

Since $AH + A = 1$, then $A = 1 - AH$

$$K_{B'} = \frac{AH \cdot OH}{1 - AH}$$

$$K_w = H \cdot OH, \quad OH = \frac{K_w}{H}$$

$$K_{B'} = \frac{AH \cdot K_w}{(1 - AH) \cdot H}$$

$$AH = \frac{H}{H + (K_w/K_{B'})}$$

We can now express our original rate equation by the following:

$$\text{Eq. (3)} \quad v = k \cdot \frac{H}{H + (K_w / K_{B'})} \cdot \frac{1}{1 + (K_B/K_w) \cdot H}$$

Since K_w is always equal to 10^{-14}, and we are given that $K_B = 10^{-11}$ and $K_{B'} = 10^{-14}$, we can now substitute these values into our rate equation:

$$v = k \cdot \frac{H}{H + (10^{-14}/10^{-14})} \cdot \frac{1}{1 + (10^{-11}/10^{-14}) \cdot H}$$

$$v = k \cdot \frac{H}{H + 1} \cdot \frac{1}{1 + 1000 \cdot H}$$

$$v = k \cdot \frac{H}{1000 \cdot H^2 + 1001 \cdot H + 1}$$

At this point we are interested in finding a value for H that will maximize the reaction rate, v. We find this value by applying a method used in Calculus; the first derivative of the rate equation with respect to H (ex-proceed as $\frac{dv}{dH}$) is calculated. We then solve for H by setting the derivative equal to zero. The value for H is expressed in terms of pH to obtain the final answer. The calculations for this are shown below:

$$\frac{dv}{dH} = k \cdot \left[\frac{(10^3H^2+1001\ H+1)\frac{dH}{dH} - H\ \frac{d(10^3H^2+1001\ H + 1)}{dH}}{(10^3H^2 + 1001\ H + 1)^2} \right]$$

$$\frac{dv}{dH} = k \cdot \left[\frac{(10^3H^2+1001\ H + 1)(1) - H(2000\ H + 1001)}{(10^3H^2 + 1001\ H + 1)^2} \right]$$

$$\frac{dv}{dH} = k \cdot \frac{1 - 1000\ H^2}{(10^3H^2 + 1001\ H + 1)^2}$$

Since k, like all rate equation constants is not equal to zero, when the derivative (dv/dH) is set equal to zero, the equation to be solved is:

$$0 = 1 - 1000\ H^2$$

$$H^2 = .001, \qquad H = \sqrt{.001} = 3.2 \times 10^{-2}$$

$$pH = -\log H = -\log(3.2 \times 10^{-2}) = 1.5$$

We are now asked to compare the rate at this pH to rates at other pH's. To find the rates at this pH and other pH's we substitute the various H values into equation (3). The v values are then compared to each other. The rate equation constant k, should be ignored for it is the same at any pH. The comparisons are shown below:

At pH = 0, H = 1

$$v_1 = \frac{1}{(1+1)(1+10^3)} = \frac{1}{2002} = .0004995$$

At pH = 1.5, H = $\sqrt{.001}$

$$v_2 = \frac{\sqrt{10^{-3}}}{(1+\sqrt{10^{-3}})(1+10^{3/2})} = .0009396$$

At pH = 7.0, H = 10^{-7}

$$v_3 = \frac{10^{-7}}{(1+10^{-7})(1+10^{-4})} = \frac{.0000001}{1.00010001001}$$

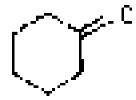
$$v_3 \approx 10^{-7}$$

$$\frac{v_2}{v_1} = 1.88 \approx 1.9 \qquad\qquad \frac{v_2}{v_3} \approx 10^4$$

The reaction at pH = 1.5 will take place 1.9 times faster than the reaction at pH = 0 and 10^4 times faster than the reaction at pH = 7.

• PROBLEM 18-26

Predict the product of each of the following ketone precursors after base-promoted or acid catalyzed halogenation.

(a) 

Cyclohexanone

(b) $CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3$

Acetone

(c) $CH_3\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}-CH_3$

3,3-Dimethyl-2-butanone

Solution: There are two ways to halogenate ketones; one is called base-promoted halogenation and the other is acid-catalyzed halogenation. In essence, acids and bases speed up the halogenation of ketones, thus they are considered to be catalysts in these reactions. The general synthesis for both proceeds as:

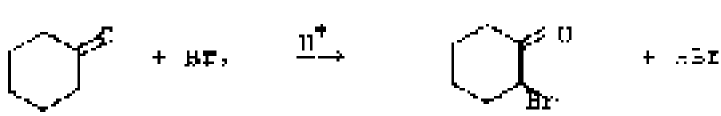
$$-\underset{\underset{\displaystyle H}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}- + X_2 \xrightarrow{H^+ \text{ or } OH^-} -\underset{\underset{\displaystyle X}{|}}{\overset{|}{C}}-\underset{\underset{\displaystyle O}{\|}}{C}- + HX \qquad X_2 = Cl_2,\ Br_2,\ I_2$$

The kinetics of acid catalyzed halogenation show the rate of halogenation to be independent of halogen concentration, but dependent upon ketone concentration and acid concentration.

In both types of halogenation the products are the same, except in acid-catalyzed halogenation racemization can occur; i.e. isomers of the product are formed.

To solve problems a, b, and c the above concepts and the general equation are followed.

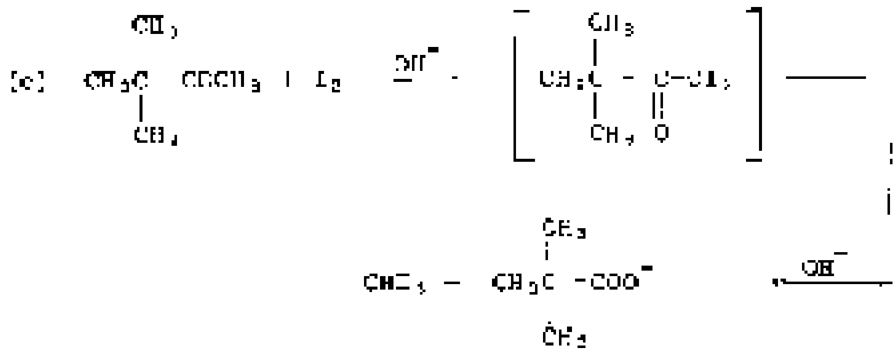
(a)



Cyclohexanone 2-Bromocyclohexanone

(b) $$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + Br_2 \xrightarrow{H^+} CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_2Br + HBr$$

Acetone Bromoacetone



Iodoform Trimethylacetate ion

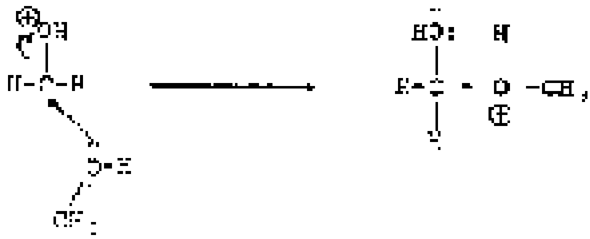
The first product in reaction (e) is an unstable compound so more base is added to take the reaction to equilibrium, thus forming the above product and by-product, trimethylacetate ion and iodoform, respectively.

• PROBLEM 18-27

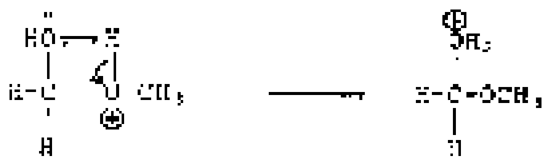
Write a reasonable mechanism for the reaction of hydrogen chloride and methanol with formaldehyde to give methyl chloromethyl ether that is consistent with the fact that the reaction occurs under conditions where neither methylene chloride nor methyl chloride are formed.

$$H-\overset{\overset{\displaystyle O}{\|}}{C}-H + HCl + CH_3OH \rightleftharpoons CH_3OCH_2Cl + H_2O$$

Solution: Both methanol and formaldehyde will become protonated when they are in separate acidic solutions. When a single solution of methanol and formaldehyde is made acidic, only one of these (the stronger base) is protonated. The fact that no methyl chloride was formed indicates that formaldehyde was protonated and methanol was not, that is, formaldehyde is more basic than methanol. This conclusion is based on the fact that methanol must first be protonated in order to undergo a substitution reaction (to form methyl chloride). The protonated formaldehyde will tend to react with a nucleophilic species. There are two available nucleophilic species: $Cl^{\ominus}$ and CH_3OH. Reaction with $Cl^{\ominus}$ would form $ClCH_2OH$; this would undergo a substitution reaction to form methylene chloride faster than CH_3OH would react to form methyl chloride. This is because $ClH_2\overset{\oplus}{C}$ (formed by H_2O loss from $ClCH_2\overset{\oplus}{O}H_2$) is more stable than $CH_3^{\oplus}$ (formed by H_2O loss from $CH_3\overset{\oplus}{O}H_2$) due to resonance. Since no methylene chloride is formed, the protonated formaldehyde must react with CH_3OH rather than $Cl^{\ominus}$. This is shown as:



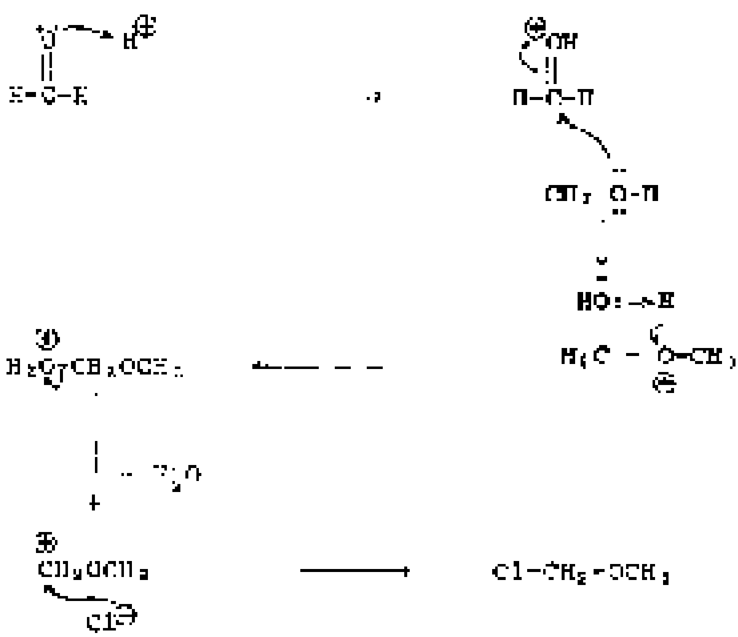
A subsequent proton shift occurs from the CH_3O- to the -OH as follows:



Loss of water will form a resonance stabilized cation of the type:

$$^{\oplus}CH_2-\ddot{O}-CH_3 \longleftrightarrow CH_2=\overset{\oplus}{O}-CH_3$$

Reaction with $Cl^{\ominus}$ forms the desired product. The mechanism of the reaction can be written as:



methylchloromethyl ether

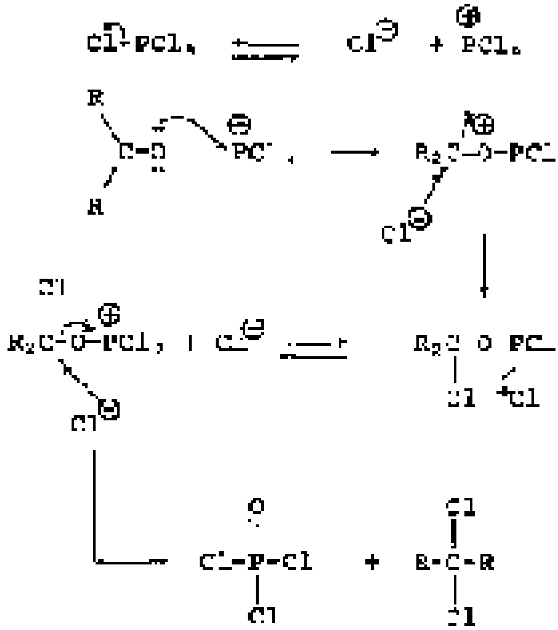
• PROBLEM 18-28

Work out reasonable mechanisms for the reactions of phosphorus pentachloride and sulfur tetrafluoride with carbonyl groups. A reasonable first step with phosphorus pentachloride is dissociation into $PCl_4^{\oplus}$ and $Cl^{\ominus}$.

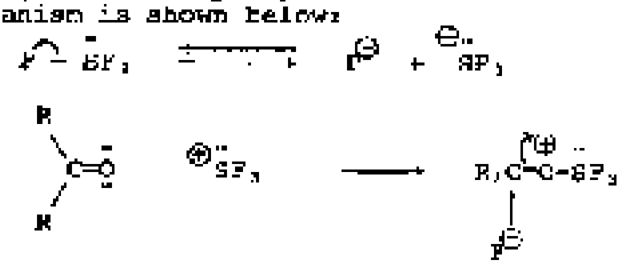
Solution: The reaction of phosphorus pentachloride (PCl_5) with a ketone results in the conversion of the carbonyl group $\left[-\overset{\overset{\displaystyle O}{\|}}{C}-\right]$ to a dichloromethylene group $\left[\overset{\overset{\displaystyle Cl}{|}}{\underset{|}{C}}\,Cl\right]$. We are given the first step:

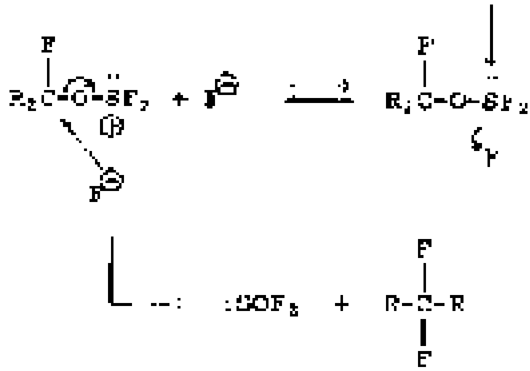
$$PCl_5 \longrightarrow {}^{\oplus}PCl_4 + Cl^{\ominus}$$

The carbonyl oxygen of a ketone is nucleophilic enough to react with the ${}^{\oplus}PCl_4$ species. The resulting cation will react with $Cl^{\ominus}$ to form $R_2\overset{\overset{\displaystyle Cl}{|}}{C}OPCl_4$. The penta coordinated phosphorus will lose a $Cl^{\ominus}$ to form a positively charged species. This will react with $Cl^{\ominus}$ in a S_N type reaction. The mechanism is shown as:



The reaction of sulfur tetrafluoride with ketones is very similar to that of phosphorus pentachloride. Sulfur tetrafluoride will lose a fluoride ion to form the more stable ${}^{\oplus}SF_3$ species (more stable because sulfur now has an octet of electrons). The mechanism of SF_4 with R_2CO is analogous in every aspect to that of PCl_5 and R_2CO. The mechanism is shown below:





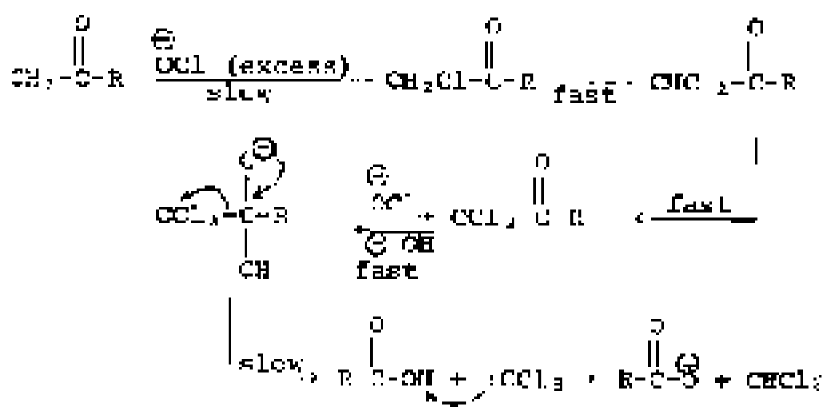
● **PROBLEM 18-25**

> Chloroform was at one time synthesized commercially by the action of sodium hypochlorite on ethanol. Formulate the reactions that might reasonably be involved. What other types of alcohols might be expected to give haloforms with halogens and base?

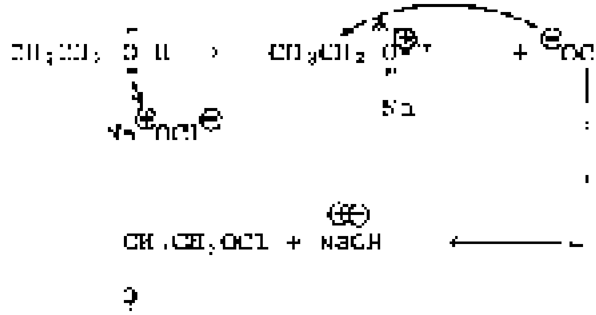
<u>**Solution:**</u> The net reaction that we are interested in is:

$$CH_3CH_2OH \xrightarrow{\overset{\oplus}{Na}\ \overset{\ominus}{O}Cl} CHCl_3$$

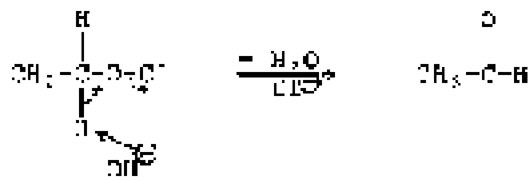
Chloroform ($CHCl_3$) is formed via the base-catalyzed chlorination of a methyl ketone or acetaldehyde by the following reaction sequence:



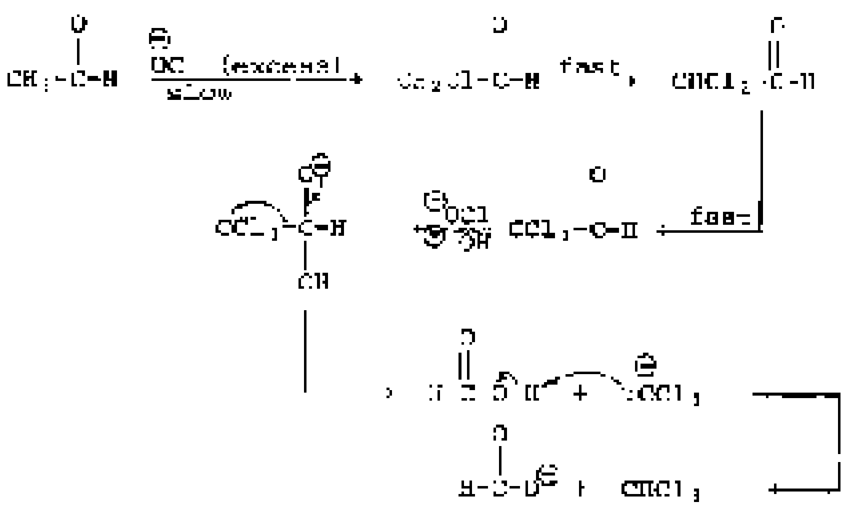
The key then to solving this problem is to create a $CH_3-\overset{O}{\overset{\|}{C}}-$ group from ethanol (CH_3CH_2OH). We also need to create a basic solution with a significant amount of $OH^{\ominus}$ ions present. $OH^{\ominus}$ ions could form if $-OCl$ could be substituted for $-OH$. This could occur by the following mechanism:



The $CH_3\overset{O}{\overset{\|}{C}}-$ group can be formed if $OH^{\ominus}$ were to abstract a proton from the $-H_2C-OCl$ carbon;



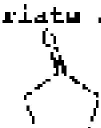
The chloroform can now be formed via the previously discussed base catalyzed chlorination of a $CH_3\overset{O}{\overset{\|}{C}}-$ group:



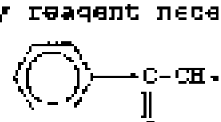
REDUCTION

• PROBLEM 18-30

Reduce the following ketone precursors to their appropriate alcohol product using any reagent necessary.

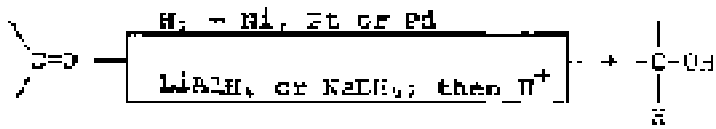
(a) 

Cyclopentanone

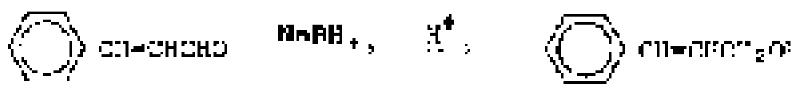
(b) 

Acetophenone

Solution: Ketones can be reduced to secondary alcohols either by catalytic hydrogenation or by use of chemical reducing agents such as lithium aluminum hydride, $LiAlH_4$. Such reduction is useful for the preparation of certain alcohols because of the higher yields than for other methods. The general equation for the reaction is:

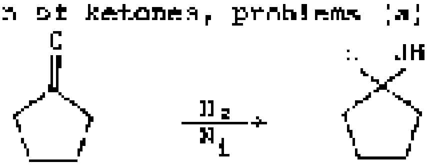


Sodium borohydride, $NaBH_4$, does not reduce carbon-carbon double bonds, not even those conjugated with carbonyl groups, and is thus useful for the reduction of such unsaturated carbonyl compounds to unsaturated alcohols. For example:

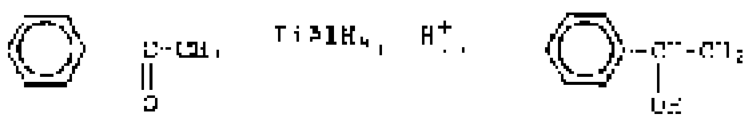


Cinnamaldehyde Cinnamyl alcohol

With the general equation above and the explanation of reduction of ketones, problems (a) and (b) can be solved.

(a) 

Cyclopentanone Cyclopentanol

(b) 

Acetophenone α-Phenylethyl alcohol

● PROBLEM 18-51

Write out the structures of the organic products of the following reactions.

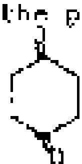
(a) 1,4-cyclohexanedione $\xrightarrow[\text{ether}]{LiAlH_4}$ $\xrightarrow{H^+}$

(b) 2-cyclohexyl-3-pentanone $\xrightarrow[\text{ether}]{LiAlH_4}$ $\xrightarrow{H^+}$

(c) 2-cyclohexenone $\xrightarrow[\text{HCl, } C_2H_5OH]{\text{Pt, } H_2}$

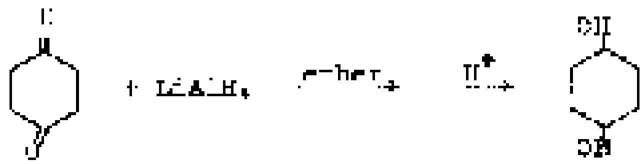
Solution: The three reactions shown above are all reductions, either by catalytic hydrogenation with molecular hydrogen and a platinum, nickel, or palladium catalyst, or by reduction with lithium aluminum hydride ($LiAlH_4$) or sodium borohydride ($NaBH_4$) plus acid.

Ketones are reduced to secondary or tertiary alcohols depending upon the structure of the precursor under reduction. This method of producing alcohols is the most favorable in organic synthesis because of the high yield produced in proportion to the amount of ketone with which was started. To begin solving the problems, the precursors' structure should be drawn:

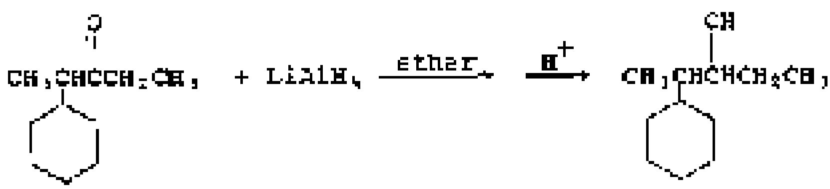


Note that a reduction reagent would react at the carbonyls.

1,4-cyclohexadione

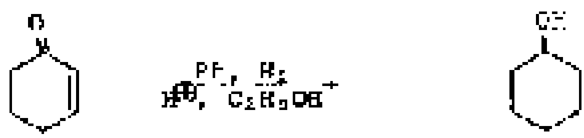
(a) 

1,4-cyclohexadione 1,4-dihydroxylcyclohexane

(b) 

2-cyclohexyl-3-pentanone 2-cyclohexyl-3-pentanol

In both problems (a) and (b) ether is the solvent in which the reaction is carried out. This yields an unstable intermediate that is treated with an acid to obtain an alcohol. In problem (c) the reducing process is changed where hydrogen attacks the carbonyl moiety with the facility of a metal catalyst, platinum. The double bond is also reduced by the addition of hydrogen to yield a cycloalkane. The solvent used to carry out the catalytic hydrogenation is ethanol.

(c) 

2-cyclohexenone cyclohexanol

• PROBLEM 15-32

Reduce the following ketones to their appropriate hydrocarbons by the Clemmensen reduction method.

(a)  (b) $CH_3C(CH_2)_5CH_3$ (with C=O)

n-Butyrophenone — 2-Octanone

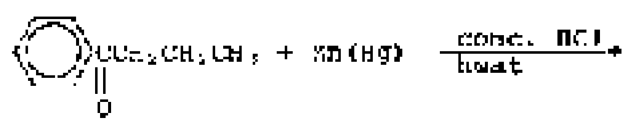
(Phenyl n-propyl ketone)

Solution: The Clemmensen reduction is the reaction used to reduce ketones and aldehydes to their respective hydrocarbons by the action of amalgamated zinc and concentrated hydrochloric acid. This reaction has the general equation of:

$$-\underset{O}{\overset{\|}{C}}- \xrightarrow{Zn(Hg),\ conc.\ HCl} -\underset{H}{\overset{|}{C}}-H$$

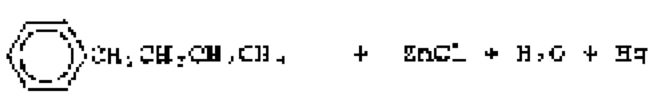
for compounds that are sensitive to base. Amalgamated zinc is an alloy of mercury (Hg) fused with zinc and is used as a catalyst in the reaction. The reaction reduces the carbonyl moiety to a simple one carbon hydrocarbon, thus changing the acyl group in problem (a) to the corresponding aliphatic chain.

The Clemmensen reduction is heterogeneous, involving an organic layer, an aqueous layer containing concentrated hydrochloric acid, and solid amalgamated zinc. Since the reaction is first order in ketone, the rate-determining step cannot be the production of hydrogen atoms, which would react very rapidly if formed. Present evidence indicates that reduction occurs at the surface of the zinc, and that alcohols are not intermediates since they seem to be unreactive under Clemmensen conditions. With the above information and the general equation for the reaction, problems (a) and (b) can be solved as follows:

(a) 

n-Butyrophenone

(Phenyl n-propyl ketone)



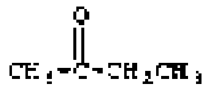
n-Butylbenzene

(b) $CH_3\underset{O}{\overset{\|}{C}}(CH_2)_5CH_3 + Zn(Hg) \xrightarrow[heat]{conc.\ HCl} CH_3(CH_2)_6CH_3 + ZnCl + H_2O + Hg$

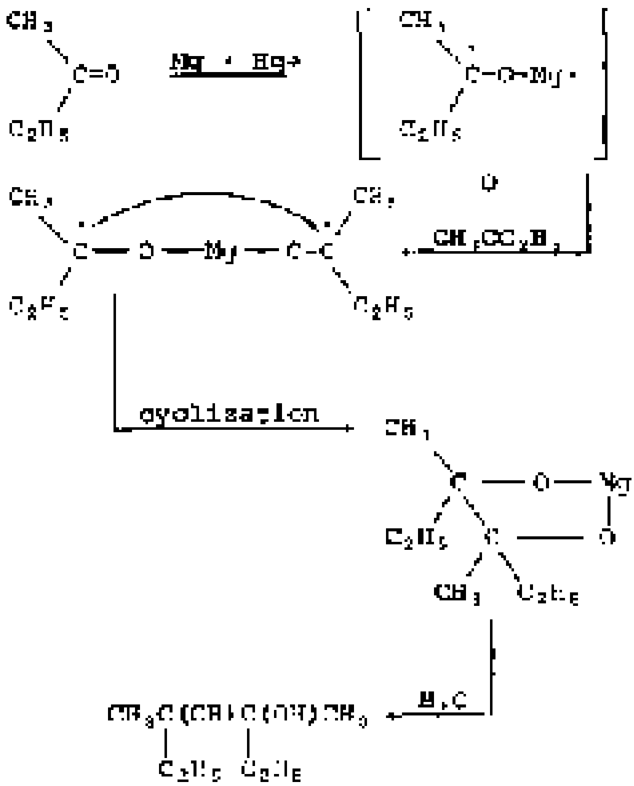
2-Octanone — Octane

The reduction of 2-butanone with magnesium amalgam produces, after hydrolysis, two isomeric glycols. What are their structures?

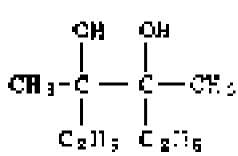
Solution: The structure of 2-butanone is as follows:



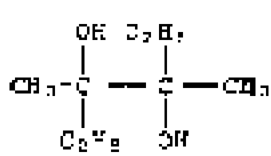
The reaction with magnesium amalgam and water proceeds by the following mechanism:



The compound shown can be formed in two ways, as a meso compound or as a d,l compound:

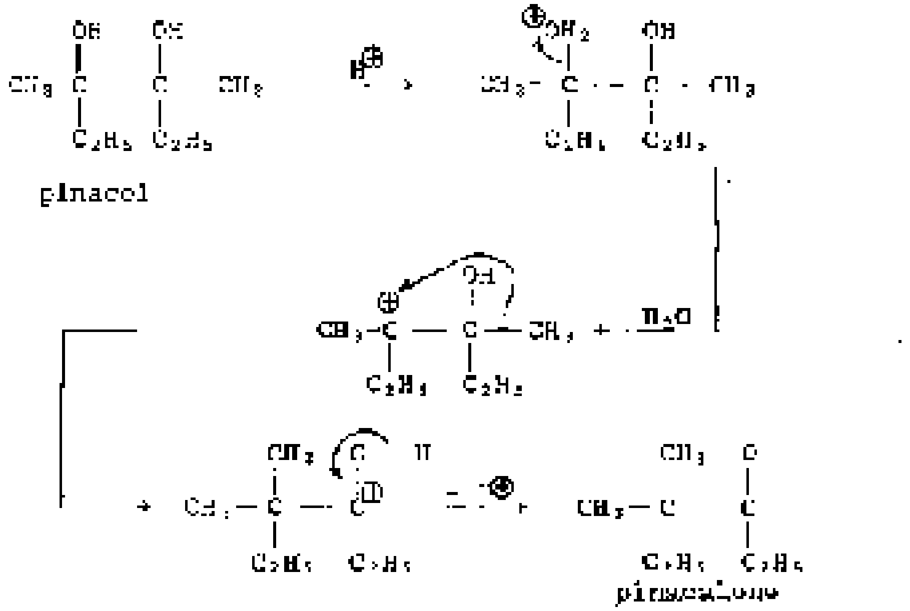


meso compound



d, l compound

Those compounds, which fit the type R R' COH COH R R' where R' may also be R, are known as pinacols. Pinacols, under acidic conditions, form ketones by what is called a "pinacol-pinacolone" rearrangement. This rearrangement is shown in the following reaction:

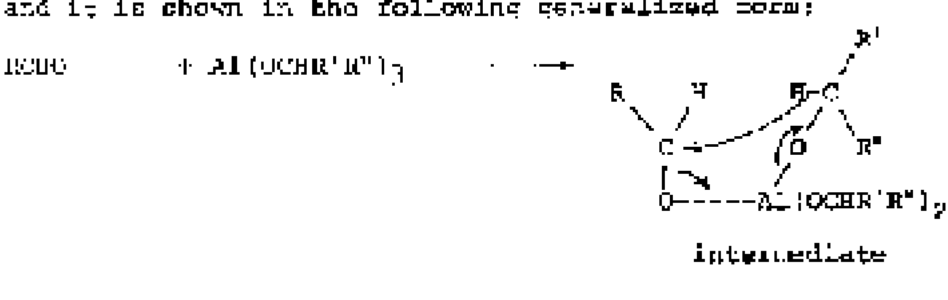


• PROBLEM 18-34

Suppose n-butyraldehyde-1-²H ($CH_3CH_2CH_2CDO$) were reduced with aluminum tri-s-butoxide made from optically active 2-butyl alcohol. Assuming the cyclic reduction mechanism, would you expect the first 10 per cent of n-butanol-1-²H to be optically active? Explain. What would be the products at equilibrium?

Solution: We approach this problem by trying to draw the two different cyclic intermediates formed in the reduction reaction between $CH_3(CH_2)_2CDO$ and aluminum tri-sec-butoxide. Once having done this we see if the intermediates should react equally fast or if one intermediate will react faster than the other.

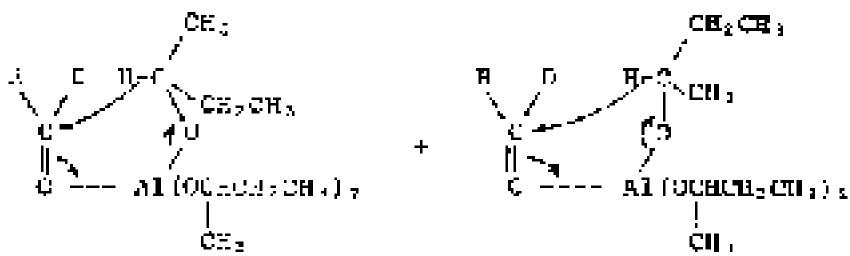
The cyclic reduction mechanism that we are referring to is known as the Meerwein-Ponndorf-Oppenauer-Verley method and it is shown in the following generalized form:



$$R{-}CH_2{-}O{-}Al(OCHR'R'')_2 \; + \; R'{-}\overset{\overset{\large O}{\|}}{C}{-}R'$$

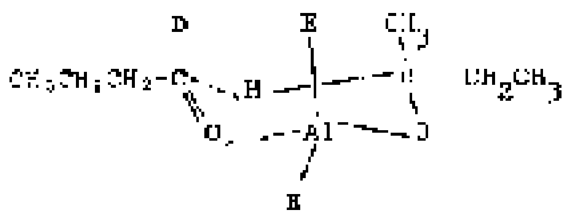
Let us apply this generalized mechanism to our specific case and consider the intermediates:

$$CH_3(CH_2)_2CDO \; + \; Al(O\overset{\overset{CH_3}{|}}{C}HCH_2CH_3)_3 \; \rightarrow$$

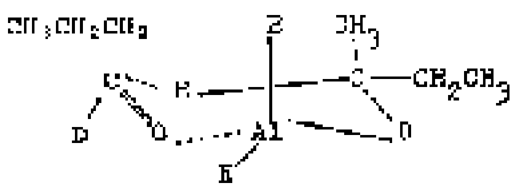


intermediate # 1 intermediate # 2

To show orientation in space and thus bring out the differences between the intermediates, we show them in six membered ring chair conformations:



intermediate # 1



intermediate # 2

In both intermediates shown above, the sec-butoxy group $\left(-O\overset{\overset{CH_3}{|}}{C}HCH_2CH_3\right)$ is represented by "E". Intermediate # 2 has the n-propyl group in an axial position; the n-propyl group and the "E" group are above the ring. Intermediate # 1 has the n-propyl group in an equatorial position; the n-propyl group is further away from the "E" group had it been in an axial position. Hence intermediate # 1 has less steric hindrance than # 2 and the alcohol formed from intermediate # 1 will be produced at a faster rate than that produced from intermediate # 2. Therefore the first 10% of product formed should exhibit some optical activity.

At equilibrium the amount of d- and l-isomers of $CH_3CH_2CH_2CHDCH_3$ are equal, and thus form a racemic mixture which has no optical activity.

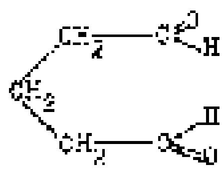
OXIDATION

• PROBLEM 18-35

Write an equation for a reasonable synthesis of 1,5-pentane dialdehyde from cyclopentanone.

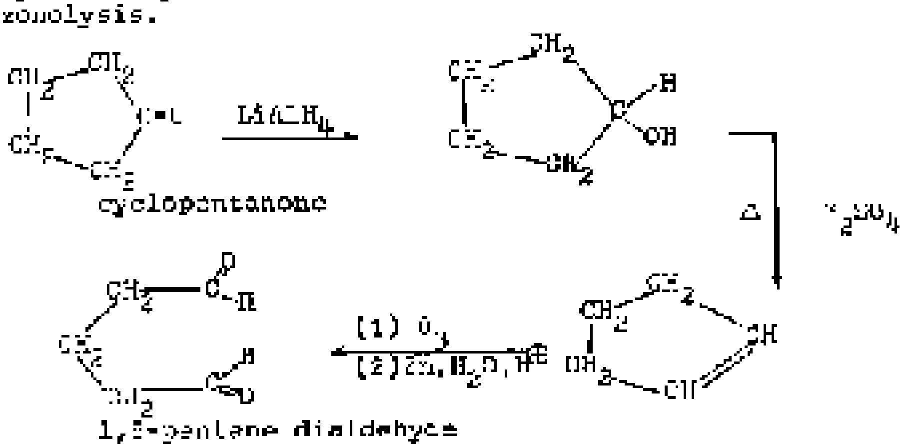
Solution: Cyclopentanone has the structure

and 1,5-pentane dialdehyde has the structure



. The synthesis of 1,5-pentane dialdehyde from cyclopentanone involves the breaking of a carbon-carbon bond to open the ring. In general, cyclic hydrocarbons are resistant to ring opening, thus the C-C bond to be cleaved must be about the carbonyl carbon. Since ketone carbon-carbon bonds are relatively stable, one must modify the keto group first.

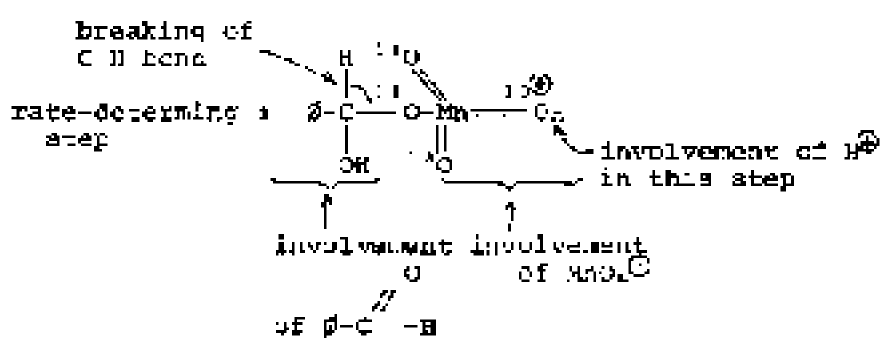
The carbonyl can be reduced to a secondary alcohol, which can be dehydrated to form a cycloalkene. The necessary dialdehyde can be synthesized from the cycloalkene by ozonolysis.



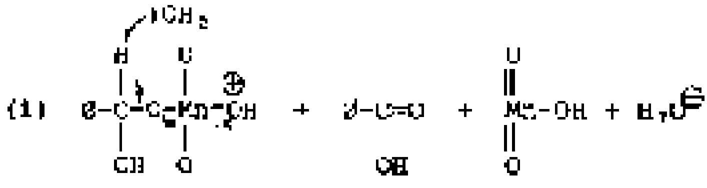
Benzaldehyde (C_6H_5CHO) is oxidized to benzoic acid ($C_6H_5CO_2H$) by acid permanganate. The rate of the oxidation is proportional to the concentrations of $H^{\oplus}$, benzaldehyde, and $MnO_4^{\ominus}$. The reaction is much slower with C_6H_5CDO than with C_6H_5CHO. When the reaction is carried out in $H_2{}^{18}O$ with C_6H_5CHO and $MnO_4^{\ominus}$, the product is $C_6H_5CO_2H$. With C_6H_5CHO, H_2O, and $Mn^{18}O_4^{\ominus}$, the $C_6H_5CO_2H$ contains ^{18}O. Write a mechanism for the reaction which is consistent with all the above facts. (Note that the C_6H_5 group is not involved.) Give your reasoning.

Solution: Since the rate of oxidation is dependent on the concentrations of $H^{\oplus}$, benzaldehyde, and $MnO_4^{\ominus}$, the slow step in the reaction mechanism must involve these species. The slow step or rate-determining step of this mechanism also involves the breaking of a C-H bond of the aldehyde group as evidenced by the isotope effect, that is, the reaction is much slower with $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}D$ than with $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}H$. The next clue gives us the picture for the rate-determining step. That is, the second oxygen of the carboxyl group comes from MnO_4 and not H_2O. This conclusion arises from the fact that when the reaction is carried out in $H_2{}^{18}O$ with $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}H$ and $MnO_4^{\ominus}$, the product is $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}OH$, while the reaction with $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}H$, H_2O, and $Mn^{18}O_4^{\ominus}$ gives $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}OH$ with ^{18}O. With this information, we can now write out the rate-determining step:

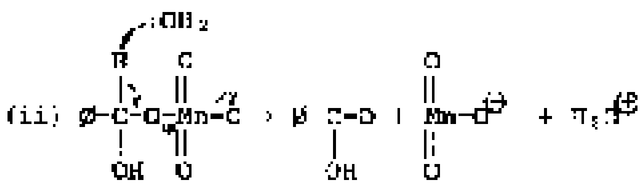
First, we know that $H^{\oplus}$, $\phi\text{-}\overset{O}{\overset{/\!/}{C}}\text{-}H$, and $MnO_4^{\ominus}$ is involved. Second, an aldehydic C-H bond breaks:



Let us now examine this system. In order for $H^{\oplus}$ to play a part in the rate of this step, an O-Mn bond must break. Otherwise the concentration of $H^{\ominus}$ would be irrelevant in this rate-determining step; compare the rate of the following two mechanisms:

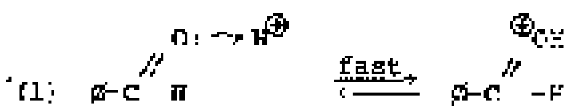


(I)

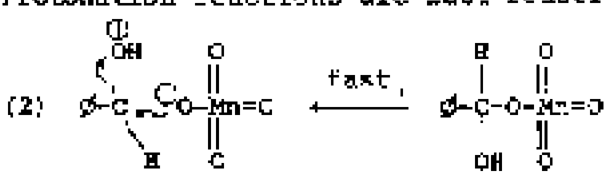


Since mechanism (i) goes from a charged species to a neutral species, it is the faster reaction.

Since this step gives us the desired products, this must be the last step in the reaction mechanism. We can now write out the entire mechanism by writing steps that are much faster than the rate-determining step, and which culminates with species I.

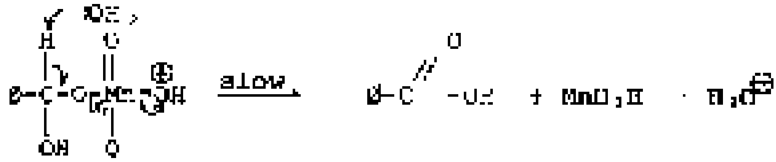


Protonation reactions are fast reactions.



From previous experience we know that nucleophilic attack on $\overset{\oplus OH}{\overset{\|}{-C-}}$ carbon is a fast reaction.

(I)

(4) 

(I)

This mechanism accounts for all experimental data.

■ PROBLEM 18-37

> Certain aldehydes decompose to hydrocarbons and carbon monoxide when heated in the presence of peroxides.
>
> $$(CH_3)_2CHCH_2CHO \xrightarrow[\Delta]{ROOR} (CH_3)_2CHCH_3 + CO$$
>
> Write a reasonable chain mechanism for such reactions.

Solution: Reactions that proceed through a chain mechanism (initiation, propagation, termination) usually involve free radical intermediates. Peroxides will readily decompose to alkoxy radicals ($RO\cdot$) upon heating. This must be the initiating step of the chain mechanism for this reaction.

Carbon monoxide (CO) is formed in the reaction and it must have come from the formyl group $\left(-\overset{O}{\overset{\|}{C}}H\right)$ of the aldehyde. The loss of carbon monoxide from an aldehyde (decarbonylation) has the same mechanism as the loss of carbon dioxide from a carboxylic acid (decarboxylation). The hydrogen of the formyl group is removed by the highly reactive alkoxy radical. This results in the formation of an alcohol and an acylium radical ($R\dot{C}{=}O$). The loss of carbon monoxide from this radical will produce an alkyl radical, which will abstract a hydrogen from another aldehyde molecule to produce an alkane and another acylium ion. These reactions constitute the propagation step of the chain mechanism. Termination can be accomplished by dimerization, disproportionation and/or hydrogen abstraction. The mechanism can be written as:

initiation $$ROOR \xrightarrow{\Delta} 2\ RO\cdot$$

propagation

$$RO\cdot + (CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}H \rightarrow ROH + (CH_3)_2CHCH_2-\overset{O}{\overset{\|}{C}}\cdot$$

$$(CH_3)_2CHCH_2\overset{O}{\overset{\|}{C}}\cdot \rightarrow {}^{\ominus}C{\equiv}O^{\oplus} + (CH_3)_2CHCH_2\cdot$$

$$(CH_3)_2CHCH_2\cdot + (CH_3)_2CHCH_2\overset{O}{\overset{|}{C}}H \rightarrow (CH_3)_2CHCH_3 + (CH_3)_2CHCH_2-\overset{O}{\overset{\|}{C}}\cdot$$

termination:

1 dimerization

$$2(CH_3)_2CHCH_2\cdot \rightarrow (CH_3)_2CHCH_2CH_2CH(CH_3)_2$$

2 disproportionation

$$2(CH_3)_2CHCH_2\cdot \rightarrow (CH_3)_2CHCH_3 + (CH_3)_2C{=}CH_2$$

3 hydrogen abstraction

$$RO\cdot + (CH_3)_2CHCH_2\cdot \rightarrow ROH + (CH_3)_2C{=}CH_2$$

CANNIZZARO REACTION

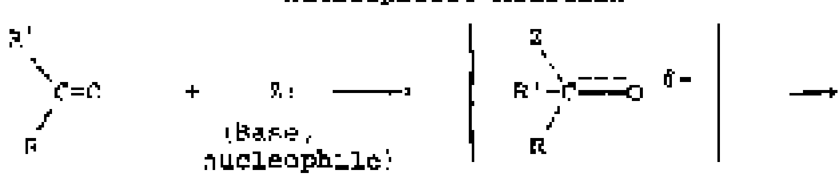
● PROBLEM 15-38

From examination of the mechanism, can you suggest one factor that would tend to make a crossed Cannizzaro reaction involving formaldehyde take place in the particular way it does?

Solution: An investigation into nucleophilic attack on carbonyl compounds and the mechanism of the Cannizzaro reaction will aid in the solution.

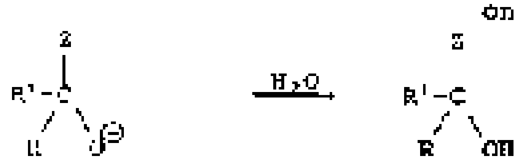
The carbonyl group, C=O, provides a site for nucleophilic addition. The functional group contains mobile π electrons that pull strongly toward oxygen, this makes the carbonyl carbon electron-deficient and the carbonyl oxygen electron-rich. The molecule is flat due to the sp^2 hybridization of the carbon. Consequently, it is open to relatively unhindered attack from above or below. Since the carbonyl carbon is electron-deficient, it is susceptible to attack by electron-rich, nucleophilic reagents such as bases. This typical reaction of aldehydes and ketones may be written as:

Nucleophilic Addition



Reagent, Trigonal shape (Ketone, Aldehyde)

Transition state Becoming tetrahedral, partial negative charge on oxygen



Tetrahedral, negative charge on oxygen

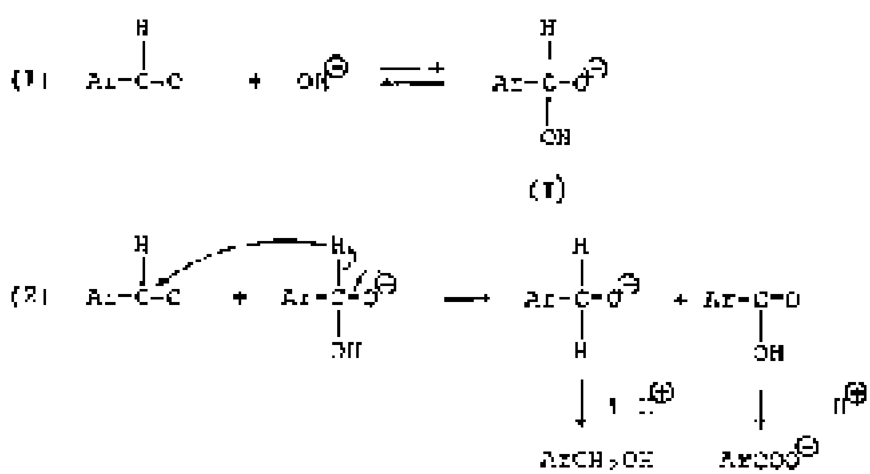
Aldehydes will generally undergo this reaction more readily than ketones. The reason stems from a combination of steric and electronic factors. In the transition state, carbon begins to acquire the tetrahedral configuration; the attached groups are being brought closer together. Hence, one might anticipate moderate steric hindrance. In other words, larger groups will tend to resist crowding more than smaller groups. The hydrogen of aldehydes is the smallest possible group. Therefore, it will not resist the crowding to the same extent as the alkyl or aryl group on the ketone. The electronic factor also comes into play when one considers the fact that an alkyl group releases electrons, and thus destabilizes the transition state by intensifying the negative charge developing on oxygen. This means an aldehyde, which will have less electrons being released, should not destabilize the transition state to the same extent as the ketone.

Consider the Cannizzaro reaction. Here, aldehydes with no α-hydrogens undergo self-oxidation-and-reduction to produce a mixture of an alcohol and a salt of a carboxylic acid. Two aldehydes will generally undergo a Cannizzaro reaction to yield all possible products. However, if one aldehyde is formaldehyde, the reaction almost exclusively yields sodium formate and the alcohol corresponding to the other aldehyde. For example,

$$ArCHO + HCHO \xrightarrow{conc.\ NaOH} ArCH_2OH + HCOO^{\ominus}Na^{\oplus}$$

(formaldehyde) (sodium formate)

The mechanism of the Cannizzaro reaction seems to be the addition of hydroxide (nucleophilic attack) in step 1 (see figure below) to give intermediate I. Then, in step 2, one has addition of a hydride ion to a second molecule of aldehyde. Overall, it may be written (with ArCHO as an example) as:



Formaldehyde should be the most favored aldehyde to undergo the nucleophilic attack by OH^- in step one.

Formaldehyde $\left(H-\overset{\overset{\displaystyle O}{\|}}{C}-H\right)$ contains no alkyl groups, so that electron release does not occur to intensify and, as such, destabilize the negative charge developing on oxygen in the transition state. Also, the two hydrogens are, as previously mentioned, the smallest possible groups, so that any other aldehyde will have larger substituents which means it will resist the crowding that occurs in the transition state.

This means that if step 1 of the Cannizzaro reaction is rate-limiting, HCHO is the chief hydride donor (and not any other aldehyde in solution), since (from the steric and electronic factors discussed) it will react with $OH^{\ominus}$ faster than any other aldehyde. The equilibrium will be positioned farther to the right. Note how the carboxylate salt will derive only from the hydride donor.

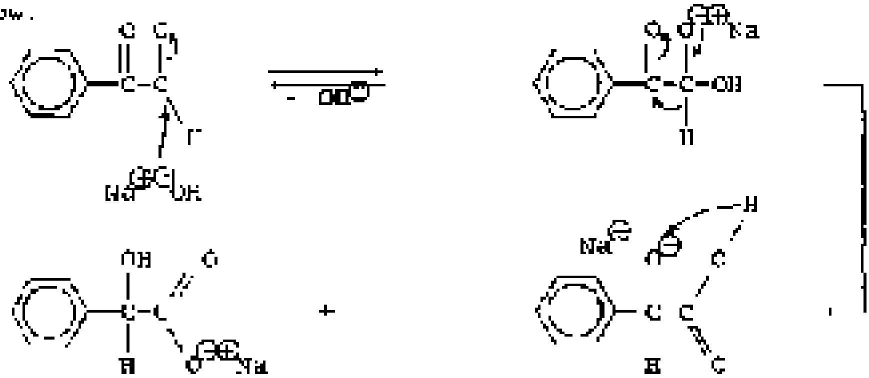
Now, if step 2 is rate-limiting, HCHO is still the chief hydride donor because the equilibrium from step 1 provides more I derived from HCHO than from the other aldehyde. It turns out that kinetic studies indicate step 2 is indeed rate-limiting.

In essence, formaldehyde behaves the way it does because of both steric and electronic factors.

• PROBLEM 18-39

Phenylglyoxal, C_6H_5COCHO, is converted by aqueous sodium hydroxide into sodium mandelate, $C_6H_5CHOHCOONa$. Suggest a likely mechanism for this conversion.

Solution: A characteristic reaction of aldehydes without α-hydrogens is the oxidation-reduction they undergo in the presence of a strong base. This is the Cannizzaro reaction. It involves the attack of a hydroxyl ion upon the aldehyde's carbonyl carbon, followed by a hydride shift to give a carboxyl group. A possible mechanism is illustrated below.



Sodium Mandelate

Assume that an equimolar mixture of formaldehyde and trimethylacetaldehyde (each undergoes the Cannizzaro reaction by itself) is heated with sodium hydroxide solution. Write equations for the various possible combinations of Cannizzaro reactions which might occur. Would you expect formaldehyde used in excess to primarily reduce or oxidize trimethylacetaldehyde? Why?

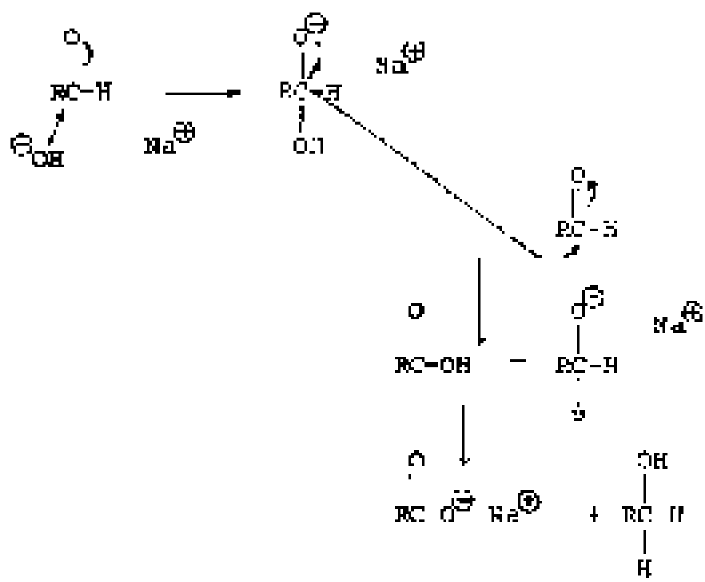
Solution: The Cannizzaro reaction involves treatment of an aldehyde lacking an α hydrogen with concentrated base to produce a primary alcohol and the salt of the corresponding carboxylic acid. This disproportionation (simultaneous reduction and oxidation of the aldehyde) reaction is specific to aldehydes without an α hydrogen because abstraction of such a proton will lead to an aldol condensation instead of a Cannizzaro reaction.

The mechanism for this reaction involves a hydride shift which is a rare occurrence. For example, in the case of the general aldehyde $RCH(=O)$:

net process:

$$2\,RCH(=O) \xrightarrow[\Delta]{NaOH\ (conc.)} RC(=O)O^{\ominus}Na^{\oplus} + RCH_2OH$$

mechanism:



The proton shift that results in the final product occurs because a carboxylic acid is a stronger acid than the alcohol. When two different aldehydes (both lacking α hydrogens) are treated in concentrated base, the reaction is known as a crossed Cannizzaro reaction. In the case at hand, we have four theoretical reactions, of which one does not readily occur.

$$\underset{\text{formal-dehyde}}{\overset{O}{\overset{\|}{HCH}}} + \underset{\text{trimethylacetal-dehyde}}{(CH_3)_3C\overset{O}{\overset{\|}{C}}H} \xrightarrow{OH^{\ominus}} H\overset{O}{\overset{\|}{C}}O^{\ominus} + (CH_3)_3C\overset{OH}{\underset{H}{C}}H \qquad \text{main reaction}$$

$$2H\overset{O}{\overset{\|}{C}}H \xrightarrow{OH^{\ominus}} H\overset{O}{\overset{\|}{C}}O^{\ominus} + CH_3OH \qquad \text{side reaction}$$

$$2(CH_3)_3C-\overset{O}{\overset{\|}{C}}H \xrightarrow{OH^{\ominus}} (CH_3)_3C\overset{O}{\overset{|}{C}}-O^{\ominus} + (CH_3)_3CH_2OH \qquad \text{side reaction}$$

$$H\overset{O}{\overset{\|}{C}}H + (CH_3)_3C\overset{O}{\overset{\|}{C}}H \xrightarrow{OH^{\ominus}} CH_3OH + (CH_3)_3C\overset{O}{C}O^{\ominus} \qquad \text{does not occur}$$

As seen from these equations, formaldehyde will reduce and not oxidize trimethylacetaldehyde. The reason for this can be traced to the fact that the first step of the Cannizzaro reaction involves attack of a carbonyl by the hydroxide ion. The aldehyde which is attacked in this way will eventually be oxidized to the carboxylate salt. Formaldehyde's carbonyl group is more easily attacked than that of trimethylacetaldehyde for both steric and electrostatic reasons. Formaldehyde's carbonyl group does not have trimethylacetaldehyde's bulky t-butyl group and is easily attacked by a nucleophile. Also, formaldehyde has a more intense positive charge on the carbonyl carbon since it lacks the inductively stabilizing t-butyl group.

$$H-\overset{O}{\overset{\|}{C}}-C(CH_3)_3 \longleftrightarrow H-\underset{\oplus}{\overset{O^{\ominus}}{\overset{|}{C}}} \overset{+}{-} C(CH_3)_3$$

For these reasons, formaldehyde will always be converted to its carboxylate ion when it is used in a crossed Cannizzaro reaction.

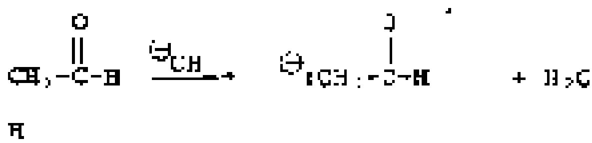
• PROBLEM 18-41

> The compound pentaerythritol, $C(CH_2OH)_4$, used in making explosives, is obtained from the reaction of acetaldehyde and formaldehyde in the presence of calcium hydroxide. Outline the probable steps in this synthesis.

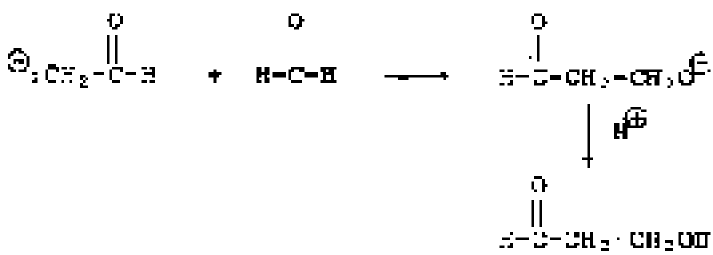
Solution: In the presence of calcium hydroxide, a strong base, two carbonyl compounds with at least one containing α-hydrogens, can undergo an aldol condensation to form a hydroxy-carbonyl compound. This condensation reaction can repeat itself until all three of the α-hydrogens are replaced.

When the reactants are acetaldehyde and formaldehyde, the aldol condensation product is trimethylol acetaldehyde. This compound can undergo a Cannizzaro reaction to give pentaerythritol. The reaction mechanisms are shown in equation form below.

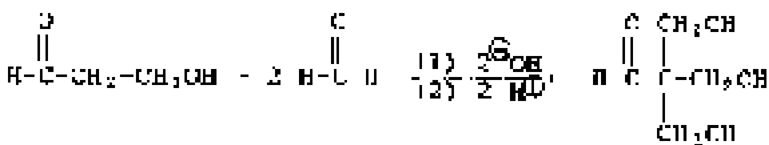
(1) Ionization:



(2) Nucleophilic addition:

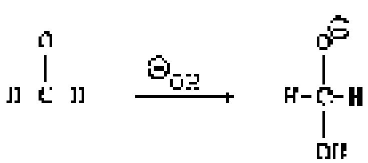


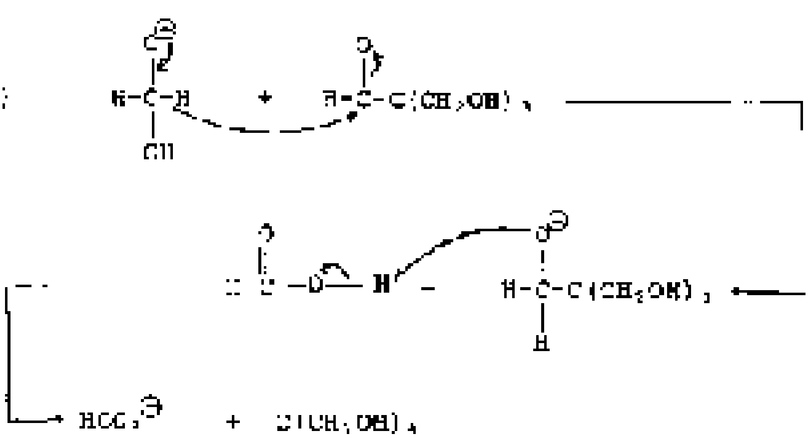
(3) Repeat steps (1) and (2)



Trimethylol acetaldehyde

(4) Cannizzaro reaction:

(a) 

(b) 

formate pentaerythritol

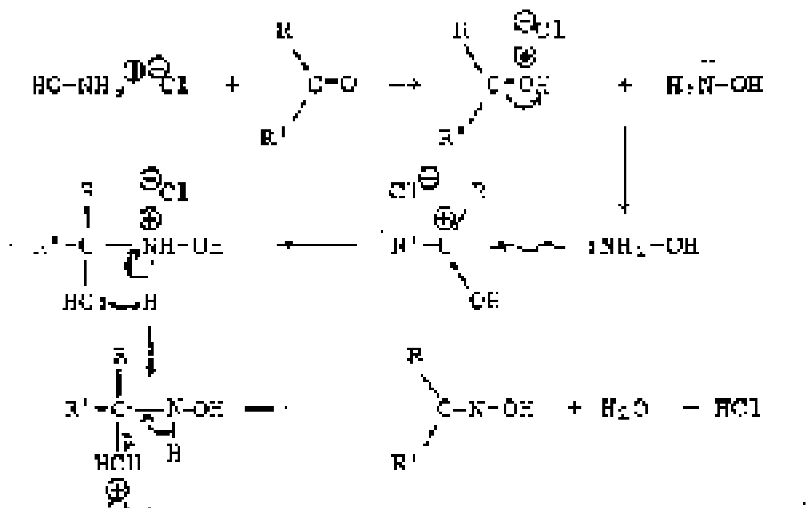
CHARACTERIZATION TESTS

• PROBLEM 18-42

A certain test for aldehydes and most ketones depends upon a color change when the compound is added to a solution of hydroxylamine hydrochloride and an acid-base indicator. Explain the basis of this test.

Solution: A characteristic of both ketones and aldehydes is the carbonyl functional group they possess. Thus, to characterize and identify ketones and aldehydes, reactions with the carbonyls are often done. Since oxygen is more electronegative, (electron-attracting) than carbon, the carbonyl carbon becomes susceptible to nucleophilic attack. Hydroxylamine, derived from its hydrochloride salt, can act as a nucleophilic reagent.

Hydroxylamine hydrochloride ($HO-NH_3^{\oplus}{}^{\ominus}Cl$) is a derivative of ammonia. It can react with the carbonyl carbon to form a carbon-nitrogen double bond. The reaction rate is enhanced by acid. This can be readily seen in the reaction mechanism. The proton attaches itself to the carbonyl oxygen rendering a more positive dipole to the carbon, which is now more susceptible to nucleophilic attack by nitrogen. The mechanism is shown below, R' can be hydrogen or alkyl group.



Oxime

The basis of this test is the pH change of the reaction solution which is manifested by the color change in the acid-base indicator. The pH change is due to the oxime formation which consumes the base hydroxylamine. The initial solution is slightly acidic because some acids are needed to protonate the carbonyl oxygen, facilitating the nucleophilic attack on the carbon. However, the concentration of unprotonated nucleophiles must not be too low, thus, the solution cannot be too acidic. As the reaction proceeds, the bases are being consumed. This lowers the pH of the solution which causes the color change, due to the increase in acidity.

Describe a simple chemical test that would serve to distinguish between:

(a)	n-valeraldehyde	and	ethyl ketone
(b)	propionaldehyde	and	ethyl ether

Solution: To decide on which chemical test to use to distinguish between compounds, one must first look at the structures of the compounds involved, their characteristic functional groups, and their similarities and differences.

(a) n-Valeraldehyde is a five carbon straight chain aldehyde. Ethyl ketone is a five-carbon symmetric ketone. They are both carbonyl compounds, thus, tests involving the carbonyl oxygen, for example, oxime formation, are useless.

Looking at their structures, one can see that the ketone's carbonyl group is situated between two carbons, while the aldehyde's carbonyl group is between a carbon and a hydrogen. This suggests that aldehydes can be further oxidized than ketones and the two compounds can be distinguished by an oxidation test.

Tollen's test is a characteristic criteria for detecting aldehydes by oxidation. The final products include a silver mirror which can be observed as a sign of the aldehyde's presence. If the compound is not an aldehyde, there is no reaction. The reaction mechanism is shown below.

$$(1)\quad CH_3(CH_2)_3CHO \;+\; 2\,Ag(NH_3)_2^{\oplus} \;+\; 3\,{}^{\ominus}OH \;\longrightarrow\; 2\,H_2O + 4\,NH_3 + CH_3(CH_2)_3COO^{\ominus} + 2\,Ag$$

n Valeraldehyde $\qquad\qquad\qquad\qquad$ silver mirror

$$(2)\quad CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 \;+\; 2\,Ag(NH_3)_2 \;\longrightarrow\; \text{no reaction}$$

Ethyl ketone

(b) Propionaldehyde is a three carbon aldehyde and ethyl ether is a four-carbon symmetric ether. Their structures are CH_3CH_2CHO and $CH_3CH_2OCH_2CH_3$, respectively. Since they have different functional groups, they can readily be distinguished by simple chemical tests.

Tollen's test, described previously, can be used to distinguish between the aldehyde and the ether. Also, oxime formation with hydroxylamine, and Schiff test with the fuchsin-aldehyde reagent to form a characteristic magenta color can be used.

$$\underset{\text{propionaldehyde}}{CH_3CH_2\overset{O}{\overset{\|}{C}}H} + \underset{\text{hydroxylamine}}{NH_2OH} \xrightarrow[H^{\oplus}]{-H_2O} \underset{\text{oxime}}{CH_3CH_2CH{=}NOH}$$

$$\underset{\text{ethyl ether}}{CH_3CH_2OCH_2CH_3} + NH_2OH \xrightarrow{H^{\oplus}} \text{no reaction}$$

• PROBLEM 18-44

Describe a simple chemical test which can distinguish between:

(a)	phenylacetaldehyde	and	benzyl alcohol
(b)	diethyl acetal	and	n-propyl ether

Solution: (a) Phenylacetaldehyde ($C_6H_5CH_2CHO$) and benzyl alcohol ($C_6H_5CH_2OH$) have different functional groups, carbonyl and hydroxyl, respectively. They can be distinguished readily by Tollen's test. The appearance of a silver mirror is a positive test for aldehydes.

$$\underset{\text{Phenylacetaldehyde}}{C_6H_5CH_2CHO} + 2\ Ag(NH_3)_2^{\oplus} + 3\ {}^{\ominus}OH \longrightarrow C_6H_5CH_2CO_2^{\ominus} + 2\ H_2O + 4\ NH_3 + \underset{\text{silver mirror}}{2\ Ag}$$

(b) Both n-propyl ether and diethyl acetal are ethers. To distinguish them, modification of either compound into a compound with a different functional group may be used.

Diethyl acetal $\left[\ CH_3-\overset{H}{\overset{|}{C}}-OC_2H_5 \atop \quad\ \ \overset{|}{OC_2H_5}\ \right]$ is a derivative of

of acetaldehyde. It is formed by acid-induced alcoholysis in the following manner.

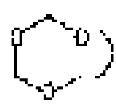
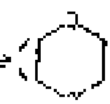
$$\underset{\text{Acetaldehyde}}{CH_3C{\overset{O}{\underset{H}{}}}} + 2\ C_2H_5OH \underset{}{\overset{H^{\oplus}}{\rightleftarrows}} \underset{\text{Diethyl acetal}}{CH_3-\overset{H}{\overset{|}{C}}(OC_2H_5)-OC_2H_5} + H_2O$$

Since the acetals are unstable in presence of acid, addition of acid can reverse the reaction to give acetaldehyde.

Therefore, to distinguish between n propyl ether and diethyl acetal, one can add acid to both compounds and then perform either Tollen's test or Schiff test; both tests are described in previous problems. The appearance of a silver mirror can identify it as acetaldehyde, that is, the compound is diethyl acetal.

• PROBLEM 18-45

Describe a simple chemical test that would serve to distinguish between trioxane and 1,4-dioxane.

Solution: Trioxane () and 1,4-dioxane () have similar chemical names, but they are functionally very different. Trioxane belongs to the family of cyclic aldehydes and dioxane belongs to the family of cyclic ethers. Dioxane is formed by acid-catalyzed dehydration and cyclization of two ethylene glycol molecules. Trioxane is formed by polymerization of three formaldehyde molecules and cyclization.

To distinguish between dioxane and trioxane, one can decyclize trioxane back into formaldehydes by adding acid and heating and then perform the Tollen's test or Schiff test.

CHAPTER 19

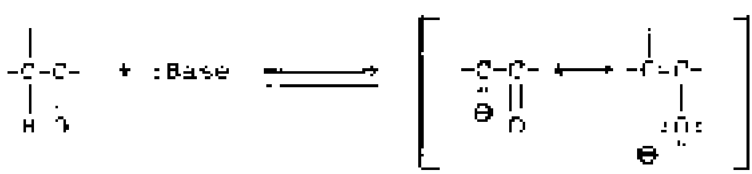
ALDEHYDES AND KETONES II

PROPERTIES AND REACTIONS OF ENOLATE ANIONS

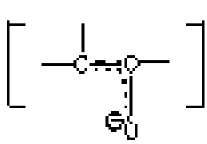
• PROBLEM 19-1

What is a carbanion? How is it formed. Briefly discuss its properties and reactions.

Solution: Carbanion is a compound which contains a carbon with a negative charge due to a nonbonded pair of electrons R–C:$^{\ominus}$. The anion is commonly formed by the ionization of an α-hydrogen of a carbonyl compound. The α-hydrogen is more susceptible to ionization than any other hydrogen in the molecule, with the exception of the carboxylic acid proton. The acidity of the α-hydrogen is enhanced by the resonance stability of the carbanion formed. Formation of carbanion and its resonanization is illustrated below.



The resonance structure is usually written as:



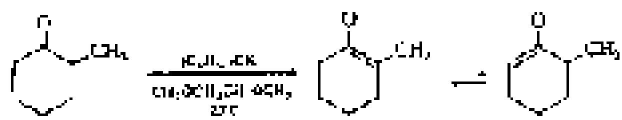
Since oxygen is more electronegative than carbon, most of the negative charge is carried by the oxygen. Thus,

 makes the most contribution to the stability of the carbanion.

Carbon has a normal valence of four. Therefore, having an unbonded electron-pair, the carbanion is exceedingly reactive. It is very basic and behaves like a nucleophile. The carbanion can attack a carbon to form a carbon-carbon bond. Carbanions also participate in halogenation of ketones, aldol condensations, Claisen condensation, and nucleophilic aliphatic substitutions, and various other reactions.

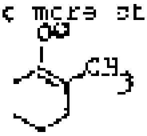
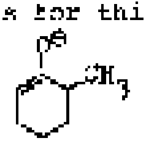
• PROBLEM 19-2

Suggest a reason for the observed stabilities of the two enolates of 2-methylcyclohexanone



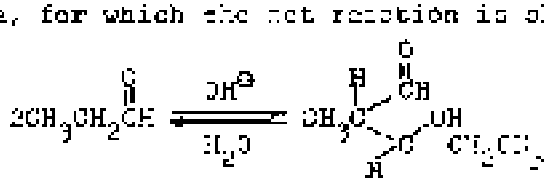
Solution: When in acid media, a carbonyl compound that has no equivalent α-hydrogens can undergo enolization to produce more than one enol. In aprotic basic media non-equivalent α-hydrogens may be extracted to produce more than one enolate anion. 2 Methylcyclohexanone has two types of α-hydrogens in the ratio of 2 : 1. Hence in a solution of potassium triphenylmethide ($(C_6H_5)_3C^{\ominus}K^{\oplus}$) two enolates will be formed; the secondary α-hydrogen may be removed to form one enolate and the tertiary α-hydrogen may be removed to form another enolate.

At equilibrium there will be a greater amount of the more stable enolate. In our problem this means that, at equilibrium, the enolate with the more highly substituted double bond will exist in greater amounts than the enolate with the lesser substituted double bond. This is because thermodynamic stability is directly proportional to the degree of substitution on a carbon-carbon double bond; the greater the substitution, the more stable the compound.

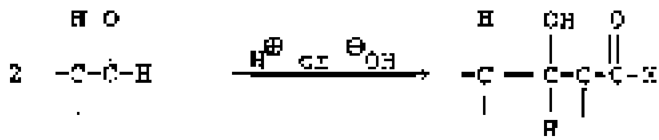
It is for this reason that  is more stable than  .

• PROBLEM 19-3

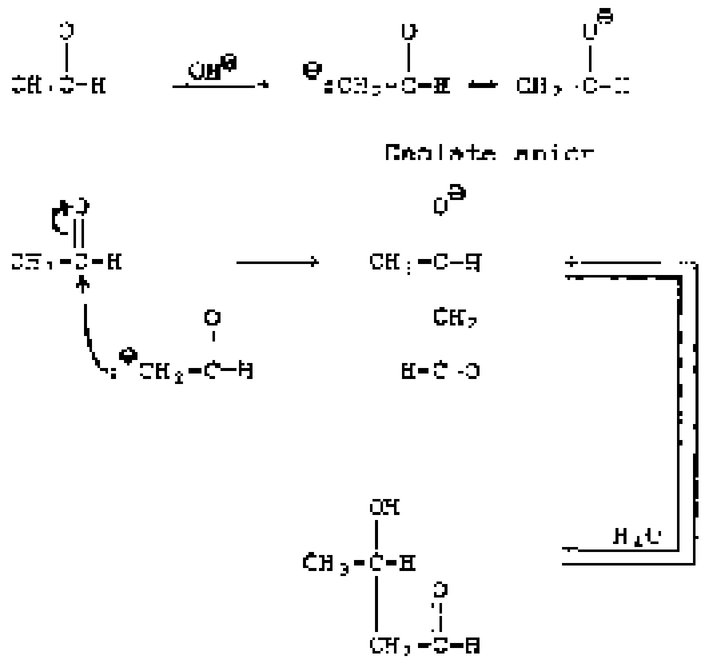
Write the mechanism for the aldol condensation of propionaldehyde, for which the net reaction is shown below.



Solution: The aldol condensation is concerned with the conversion of an aldehyde (not so much a ketone) to a β-hydroxyaldehyde in the presence of acid or base.

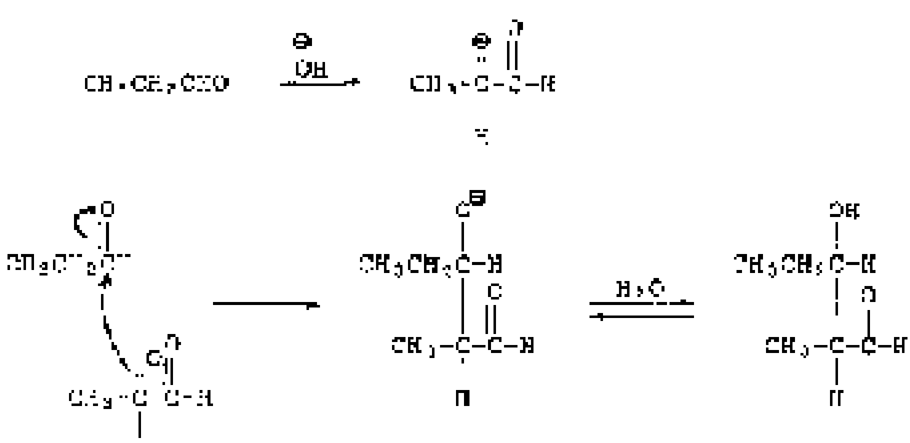


The mechanism for a base catalyzed aldol condensation is shown below. We will use acetaldehyde as our starting material.



The key step in this reaction is the formation of the carbanion.

All that remains is to apply this mechanism to the given starting material, propionaldehyde.



Predict the principal products to be expected in each of the following reactions; give your reasoning:

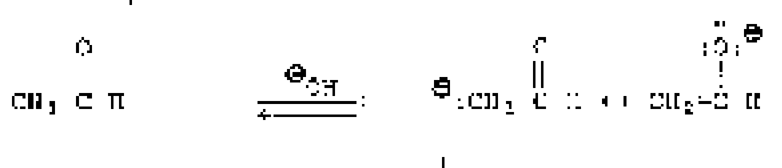
(a) $CH_3CHO + (CH_3)_2CO \xrightarrow{NaOH}$

(b) $(CH_3)_2C(OH)CH_2COCH_3 \xrightarrow{NaOH}$

(c) $CH_2O + (CH_3)_3CCHO \xrightarrow{NaOH}$

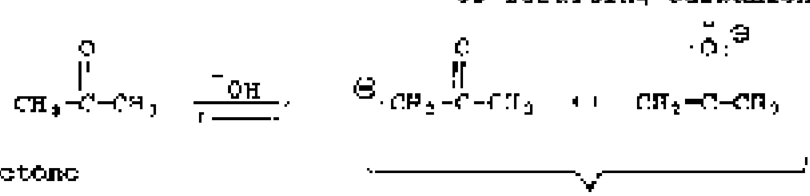
(d) $CH_2O + (CH_3)_2CHCHO \xrightarrow{Ca(OH)_2}$

Solution: (a) Aldol condensation reactions involve the acidity of the α-hydrogens of carbonyl compounds. The degree of acidity depends upon the stability of the subsequently formed carbanion. In a basic solution of acetaldehyde and acetone (two carbonyl compounds possessing α-hydrogens) a hydroxide ion ($OH^{\ominus}$) will remove an α-hydrogen from both compounds. These are acid-base equilibrium reactions where the resulting carbanion is stabilized by resonance:



acetaldehyde

resonance stabilization of resulting carbanion

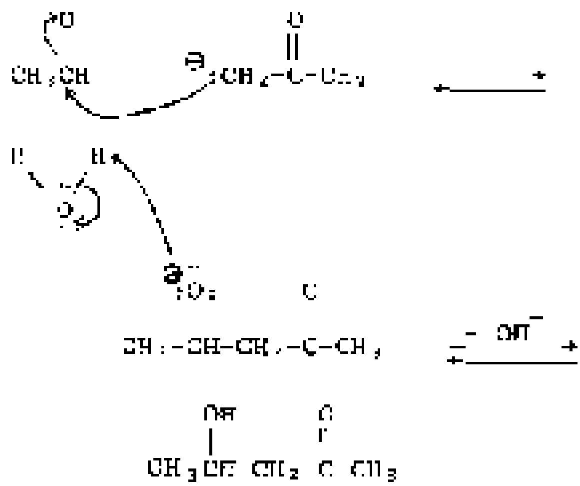


acetone

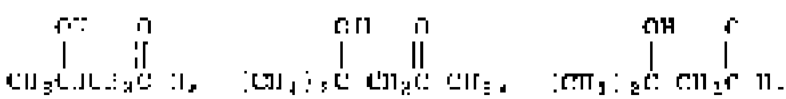
resonance stabilization of resulting carbanion

The acetaldehyde and acetone carbanions will seek an electron deficient species with which to react. The formation of the carbanions is an equilibrium situation which involves the reactant (acetone and acetaldehyde) and the product (the respective carbanions).

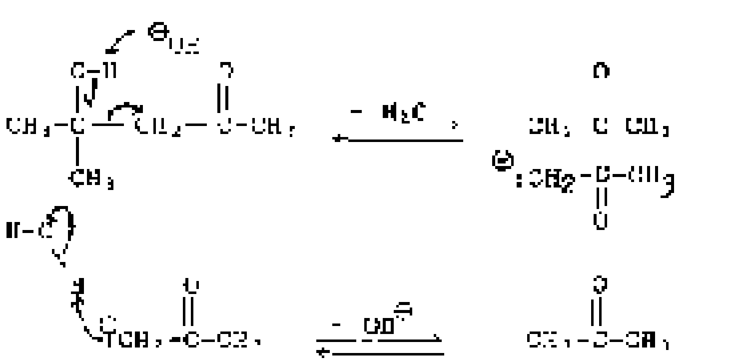
The carbonyl carbons of these reactants are partially positively charged (electron deficient) and may react with any available carbanion. The carbonyl carbon of acetaldehyde has a greater partial positive charge than that of acetone. This is because acetaldehyde has only one electron releasing alkyl group (methyl) whereas acetone has two such groups. Hence the carbanions will react faster with acetaldehyde than with acetone. This occurs also due to the steric reason in that acetone's carbonyl carbon has greater steric hindrance towards carbanion attack than acetaldehyde's carbonyl carbon (two methyl groups in acetone vs. one methyl group in acetaldehyde). The major product will be the one formed by the attack of the acetone carbanion upon acetaldehyde. This is because as acetaldehyde is used up, the equilibrium shifts to the left, hence depleting the acetaldehyde carbanion concentration. The major product is formed by the following mechanism:



Other products formed by the same general mechanism, but in smaller amounts, are:



(b) The reactant, diacetone alcohol, is the product of the base catalyzed aldol condensation of acetone. In basic solution diacetone alcohol will follow the reverse mechanism of its formation to produce acetone. This mechanism is shown as:

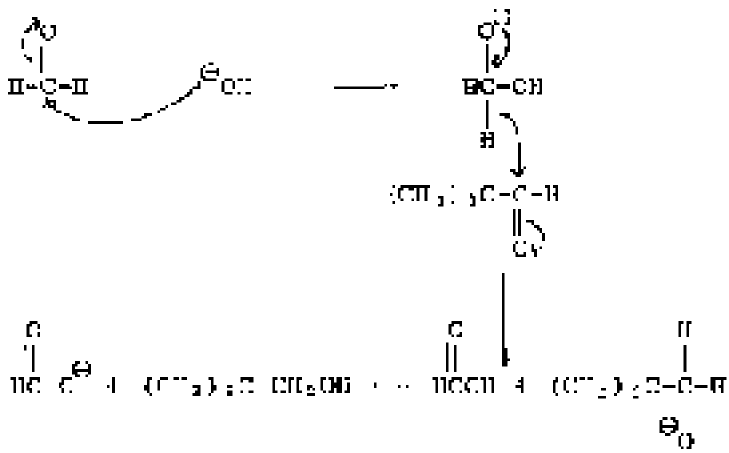


Diacetone alcohol is thermodynamically less stable than acetone and hence the equilibrium for this reaction lies far to the side of the acetone. Another reason why diacetone alcohol formation is difficult is that it involves attack of a ketone upon a ketone

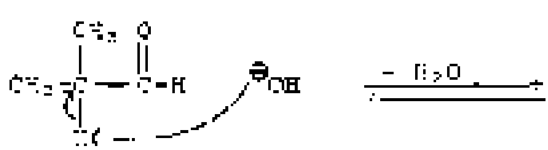
$$\left[{}^{\ominus}:CH_2-\overset{O}{\overset{|}{C}}-CH_3 \quad \text{attacks} \quad CH_3\overset{O}{\overset{\|}{C}}CH_3 \right]$$

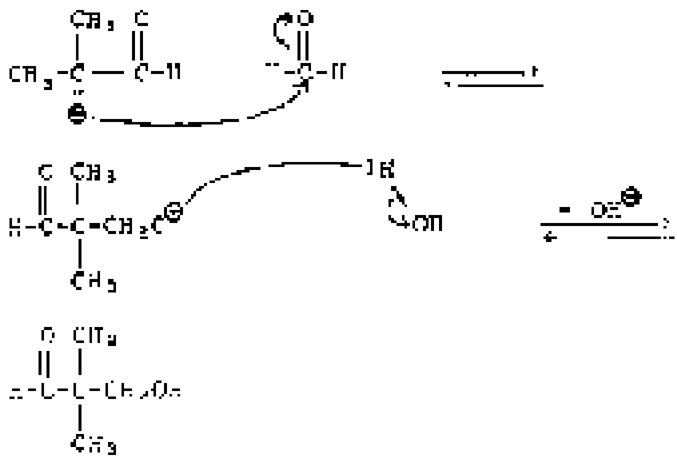
. The steric hindrance from the alkyl groups raises the activation energy. Hence the major product of diacetone alcohol in NaOH is acetone, $CH_3\overset{O}{\overset{\|}{C}}CH_3$.

(c) Aldehydes that lack α-hydrogens will undergo a Cannizzaro reaction in basic solution. This is an oxidation-reduction reaction whereby some of the aldehyde is oxidized to a carboxylic salt and an equal amount is reduced to an alcohol. When two aldehydes that lack α-hydrogens are reacted in basic solution, a crossed Cannizzaro reaction will occur. The more easily oxidized aldehyde will be converted into the carboxylic salt and the other aldehyde will be reduced to the alcohol. Formaldehyde and trimethylacetaldehyde are aldehydes that lack α-hydrogens. In basic solution, formaldehyde is oxidized to the formate salt and trimethylacetaldehyde is reduced to the alcohol. This happens because formaldehyde is more prone to attack by $OH^{\ominus}$ (to form the carboxylic salt) than trimethylacetaldehyde due to steric and electrostatic reasons. The reaction mechanism is shown as:



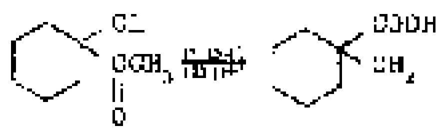
(d) In a basic solution of formaldehyde and dimethylacetaldehyde, the latter will lose its α-hydrogen and undergo an aldol condensation with formaldehyde. The reaction mechanism is shown as:





▼ **PROBLEM 19-5**

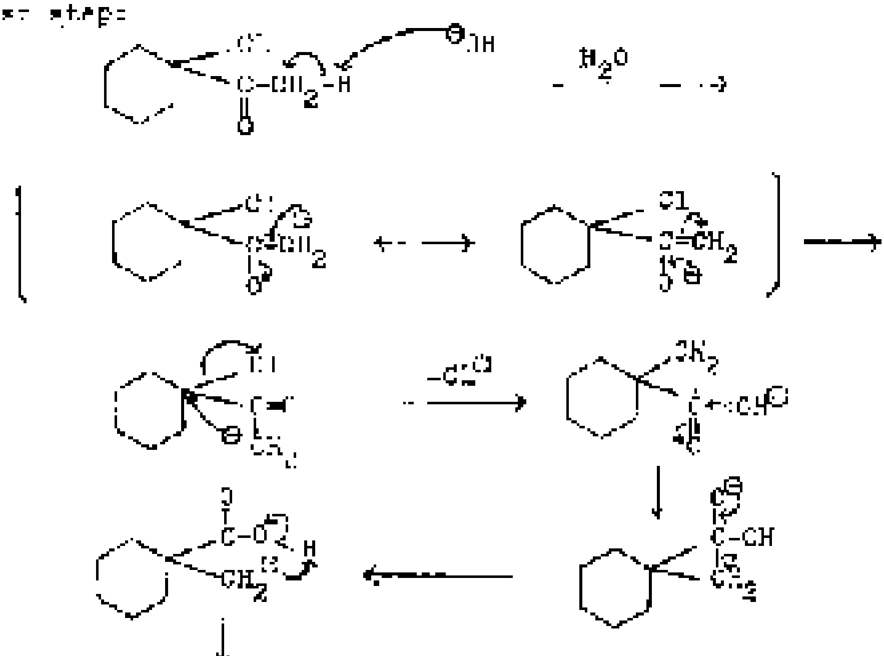
Write a mechanism for the following reaction:



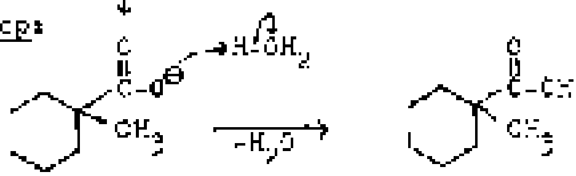
Solution: Ketones that are capable of enolization may be converted to their corresponding enolates by treatment with base in an aprotic media. The enolates may act as nucleophiles in S_N2 reactions in which alkyl chains are added to the reactant. Intramolecular alkylations are possible; being most feasible when ring closure is favorable. For example

An interesting example of such an intramolecular alkylation is the Favorskii rearrangement which involves treating an α-halo ketone with hydroxide and producing a carboxylate salt via a rearrangement of the carbon skeleton. The first step involves the formation of the resonance stabilized enolate ion whose anionic carbon can displace the halide also present in the compound. The intermediate cyclopropanone cannot be isolated because the hydroxide ion will attack the carbonyl group, opening the ring. A proton shift where the newly formed carboxylic acid group transfers a proton to the highly basic carbanion is the final step in this process. The entire process may be depicted as:

First step:



Second step:



● **PROBLEM 19-0**

Pentaerythritol, $C(CH_2OH)_4$, can be obtained by condensing acetaldehyde and formaldehyde together in the presence of sodium hydroxide. Write a mechanism for this reaction.

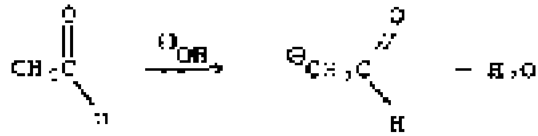
Solution: Pentaerythritol is a quadri-substituted methyl. Therefore, it is reasonable to take acetaldehyde as the main compound and formaldehyde as the substituents.

Since hydrogens alpha to a carbonyl are acidic, in presence of sodium hydroxide, acetaldehyde is ionized to form a carbanion. Carbanions are strong nucleophiles. It attacks the carbonyl carbon of formaldehyde in an aldol condensation reaction to form a hydroxy-carbonyl compound. This series of reactions can repeat until all three α hydrogens are replaced by CH_2OH.

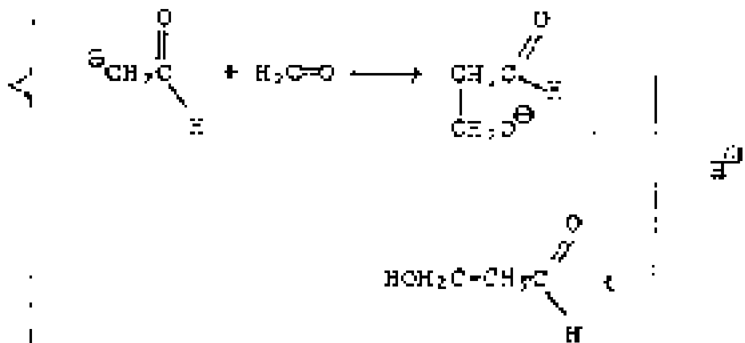
In presence of a strong base, formaldehyde can undergo a nucleophilic addition to form $H_2\underset{\substack{|\\ OH}}{C}-O^{-}$. This compound can react with the tri substituted acetaldehyde in a cross-Cannizzaro reaction to produce pentaerythritol. The reaction mechanisms are shown below:

Aldol condensation

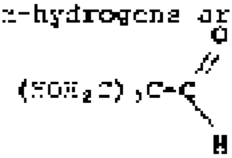
(1) Carbanion formation:



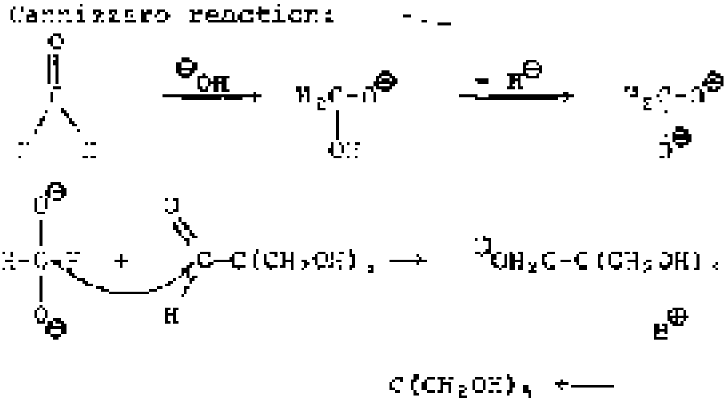
(2) Nucleophilic addition:



(3) Repeat the aldol condensation reactions until all three α-hydrogens are replaced to give



(4) Cannizzaro reaction:



Pentaerythritol

• PROBLEM 19-7

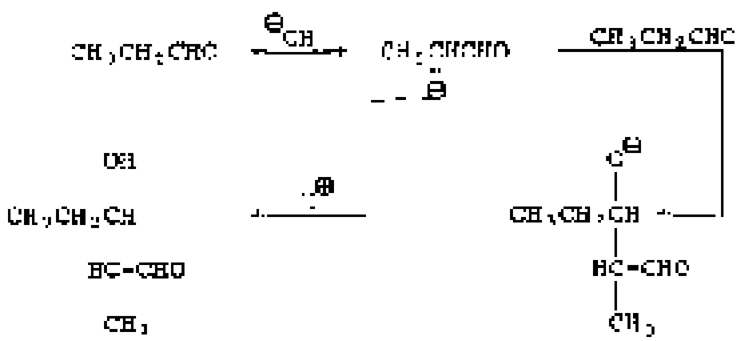
An aldol condensation was carried out on equal amounts of propionaldehyde and butyraldehyde. The reaction gave rise to four distinct products. What were their structures, and how did each arise?

Solution: The aldol condensation is an addition reaction between two carbonyl compounds, at least one of which contains an α hydrogen. It utilizes the fact that an α hydrogen to a carbonyl is acidic. It can be ionized by a strong base to form a carbanion, which is an extremely strong nucleophile. This nucleophile can attack the positively dipoled carbonyl carbon to form an α,β-hydroxy-carbonyl compound.

The determining, or rate-limiting step of an aldol condensation is the ionization of an α-hydrogen from one of the reactants. If both reacting carbonyl compounds are identical, or if only one of them contains an α-hydrogen, the resulting product is pure. But if the reactants are nonidentical and both contain α-hydrogens, the result will be a mixture of products. The reaction in question is of the latter case.

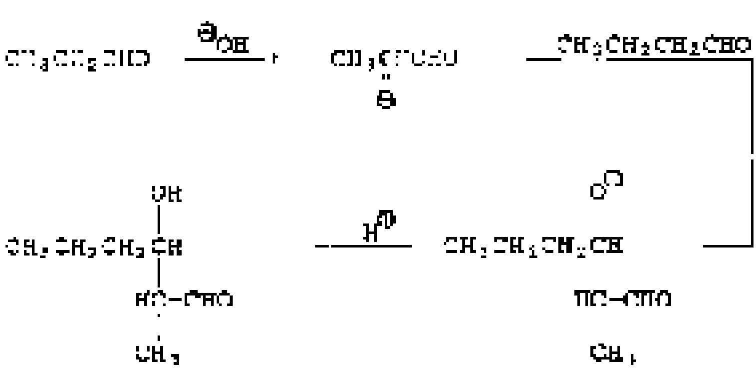
Propionaldehyde, CH_3CH_2CHO, and butyraldehyde, $CH_3CH_2CH_2CHO$, are both carbonyl compounds having α-hydrogens. In the presence of strong bases, both α-hydrogens can be ionized to form carbanions. These carbanions can react with the unionized aldehydes to form aldol compounds. Depending on the reacting carbanion and aldehyde different aldol products are formed. The products and reaction processes are shown below.

(1) Carbanion of propionaldehyde and propionaldehyde:



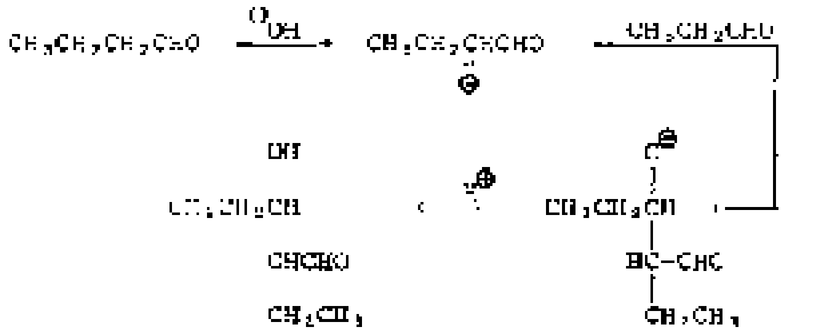
2-Methyl-3-hydroxypentanal

(2) Carbanion of propionaldehyde and butyraldehyde:



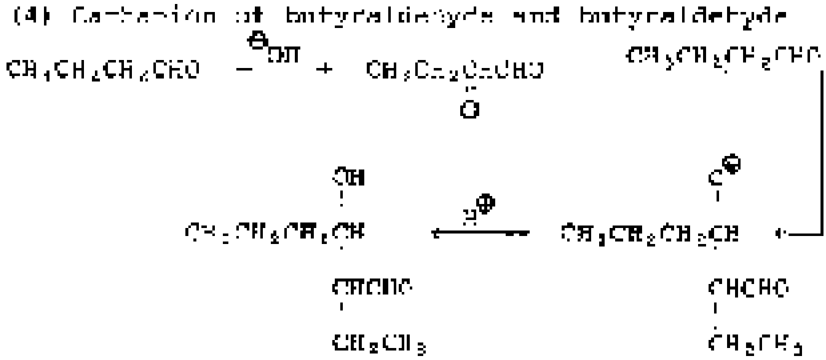
2-Methyl-3-hydroxyhexanal

(3) Carbanion of butyraldehyde and propionaldehyde:



2-Ethyl-3-hydroxypentanal

(4) Carbanion of butyraldehyde and butyraldehyde



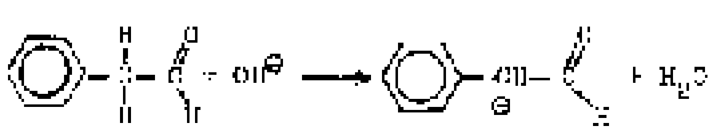
2-Ethyl-3-hydroxyhexanal

• PROBLEM 19-5

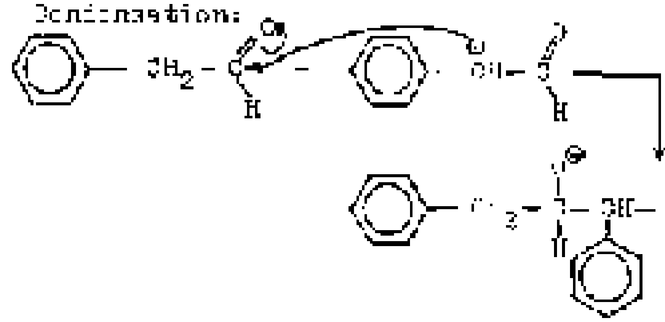
Propose a likely reaction mechanism and name the end-product(s) for the reaction of a solution containing phenylacetaldehyde and dilute sodium hydroxide.

Solution: Phenylacetaldehyde has two potentially reactive functional groups, the carbonyl and the α hydrogens. However, in a dilute sodium hydroxide solution, only the α-hydrogens are readily attacked by the hydroxide ions. The ionization results in a carbanion which is a potent nucleophile. It attacks the positively dipoled carbonyl carbon to form a carbon-carbon bond. The resulting oxide ion is protonated by the water molecules present. The final product is 2,4-diphenyl-3-hydroxy-butyraldehyde. The complete reaction mechanism is called the aldol condensation.

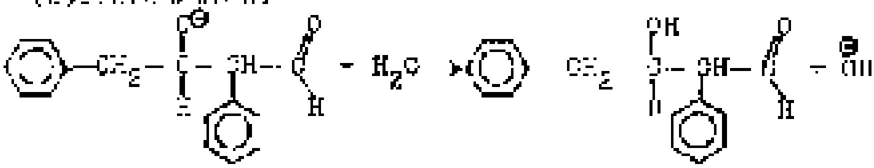
(1) Ionization of α-hydrogen (carbanion formation):



(b) Combination:



(c) Protonation:



2,4-Diphenyl-3-hydroxy-butyraldehyde

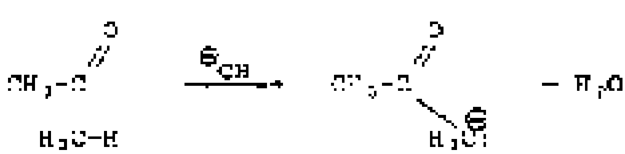
• PROBLEM 19-9

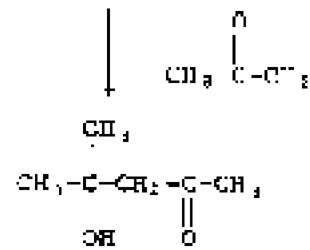
In the manufacturing of methyl isobutyl ketone (MIBK), large quantities of acetone are used. Propose a reasonable mechanism of synthesis for MIBK.

Solution: First, consider the structures of the reactant and product. Acetone is a three-carbon compound, and the product, methyl isobutyl ketone (MIBK) is a six-carbon compound. The three extra carbons in MIBK appear as an isopropyl substituent at the methyl carbon.

Acetone MIBK

From the similarity in structure of the isopropyl substituent to a reduced acetone, one may suggest that the reaction is a condensation between two acetones. The mechanism of an aldol condensation of two acetones is shown below:

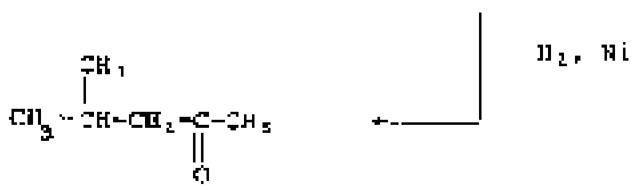




Diacetone alcohol

The aldol condensation of two ketones results in the formation of diacetone alcohol. This compound can be dehydrated, and then hydrogenated to give MIBK.

Diacetone alcohol Mesityl oxide (4-Methyl-3-penten-2-one)



MIBK

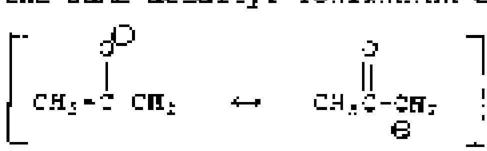
(Methyl Isobutyl Ketone)

• **PROBLEM 19-10**

Determine whether acetylacetone (2,4-pentanedione) or acetone is more acidic. Which are the most acidic hydrogens?

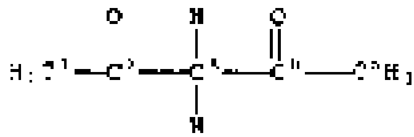
Solution: Acetylacetone and acetone are both carbonyl compounds, the former contains two carbonyl groups while the latter only has one. All hydrogens in both compounds are α-hydrogens, however, their acidities are different. This is so because the carbanions formed have different stabilities.

For acetone, all hydrogens are equivalent, that is, they all have a similar environment, therefore, they are all of the same acidity. Ionization of an α hydrogen will give

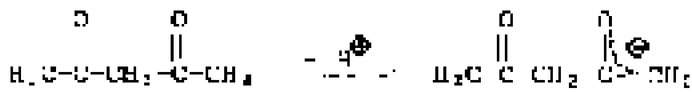


The negative charge is stabilized by the oxygen.

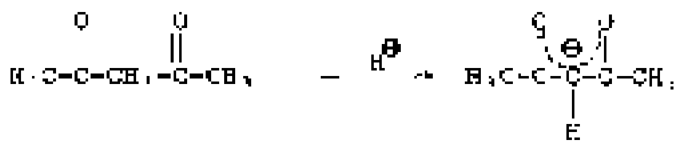
Acetylacetone is considerably different. It has two different groups of equivalent α-hydrogens; one group contains hydrogens attached to carbons 1 and 5, the other contains the two hydrogens at carbon 3.



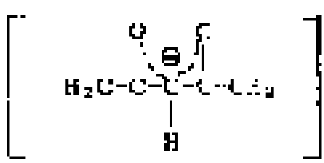
Ionization of different α hydrogens will result in different carbanions with varying stabilities. If a hydrogen from either carbon 1 or 5 is ionized, a primary carbanion is formed.



If the hydrogen is from carbon 3, a secondary carbanion is formed.



In this carbanion, the negative charge is shared by two oxygens. This extra stabilization lowers the energy level of the anion, making the hydrogen more readily released. Thus, for acetylacetone, the hydrogens attached to carbon 3 are more acidic. The carbanion



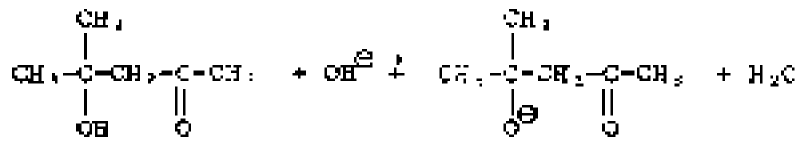
is predominant in an ionized solution.

To compare acid strength between acetone and acetylacetone, one considers the stabilities of the carbanions formed. The carbanion of acetone is similar to the carbanion formed by ionization of a hydrogen from carbon 1 or 5 of acetylacetone. Since the predominant carbanion for acetylacetone is formed by carbon 3 ionization, it is more stable than the acetone carbanion, therefore, more readily formed. This implies that acetylacetone is more acidic than acetone.

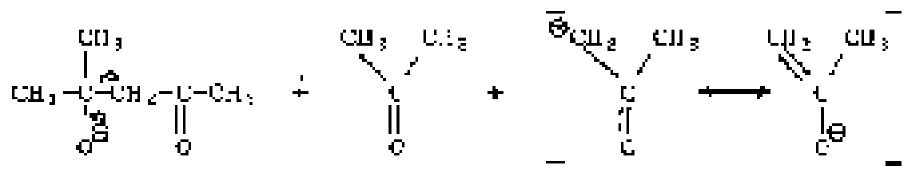
• PROBLEM 19-11

In alkaline solution, 4-methyl-4-hydroxy-2-pentanone is partly converted into acetone. Show all steps of a likely mechanism. What does this reaction amount to?

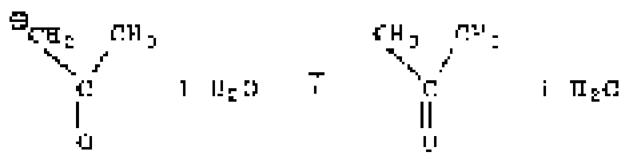
Solution: In alkaline solution, 4-methyl-4-hydroxy-2-pentanone is ionized. The process is shown in equation form below.



The oxyanion formed can undergo an electronic rearrangement; this involves the breaking of a carbon-carbon bond and formation of a carbonyl double bond.



These ions can ionize the water molecules present to form neutral acetone molecules.



Taking all the steps together, one can see that it is a reverse of the aldol condensation of acetone.

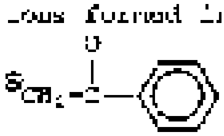
α,β-UNSATURATED ALDEHYDES AND KETONES

• PROBLEM 19-32

Name all the organic products formed in a solution containing benzaldehyde, acetophenone, and dilute sodium hydroxide

Solution: In dilute base, carbonyl compounds tend to combine and form β-hydroxy ketones or aldehydes. This reaction is called an aldol condensation. The mechanism involves ionization of the α-hydrogen to form a carbanion, and the carbanion-attack on carbonyl carbon to form a C-C bond.

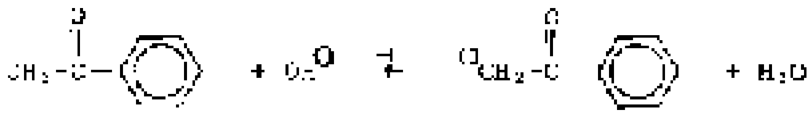
For the two carbonyl compounds given, only acetophenone has an α-hydrogen which is readily ionized. The benzaldehyde α-hydrogen is not acidic due to resonance stabilization of the benzene ring. Thus, the only carbanions formed in significant concentration will be



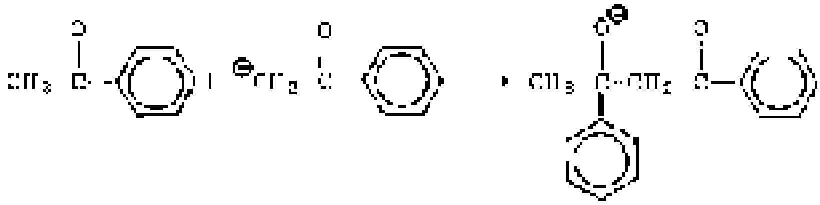
. This ion can react with either carbonyl groups to form the β-hydroxy compound.

If the carbanion reacts with acetophenone, 3-hydroxy 3-phenyl-propyl phenyl ketone is formed. This compound is not stable in alkaline solution because the hydrogens alpha to the carbonyl and the hydroxy are acidic. This β-hydroxy carbonyl compound can undergo an elimination reaction to form a more stable α,β-unsaturated compound. The reaction steps are shown below:

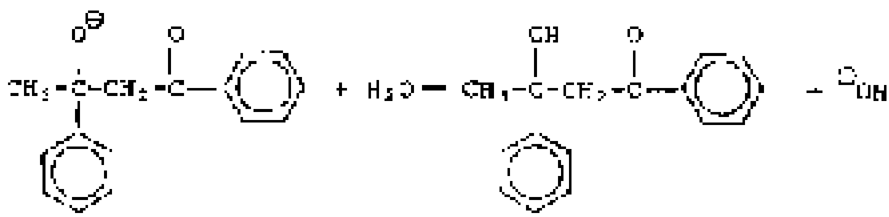
(a) Carbanion formation:



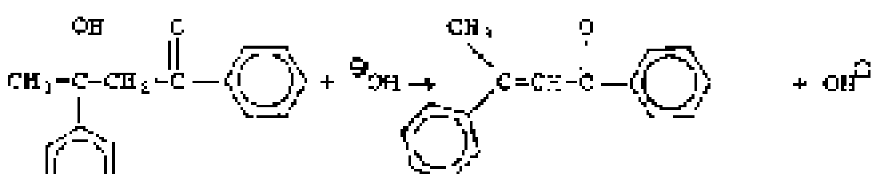
(b) Nucleophilic addition:



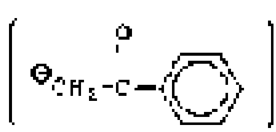
(c) Protonation:

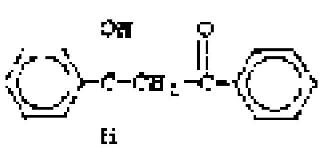


(d) Elimination:



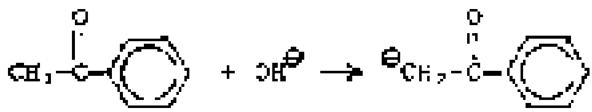
2-Phenylpropenyl
phenyl ketone

If the carbanion  reacts with benzaldehyde, the β-hydroxy carbonyl compound formed has the following structure:

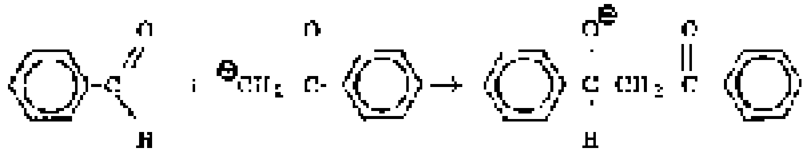


This compound is also very unstable in alkaline solution. It readily undergoes an elimination reaction to form phenylethenyl phenyl ketone. The steps of synthesis are shown below:

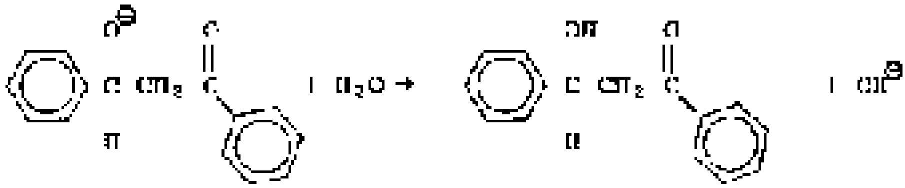
(a) Carbanion formation:



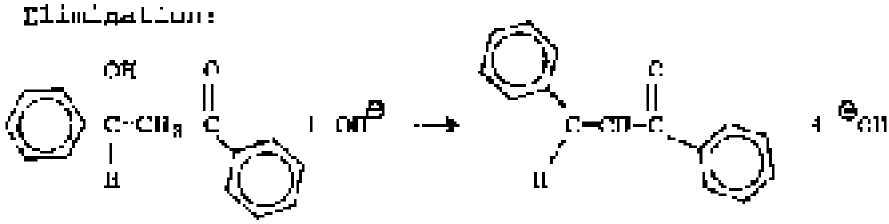
(b) Nucleophilic addition:



(c) Protonation:



(d) Elimination:



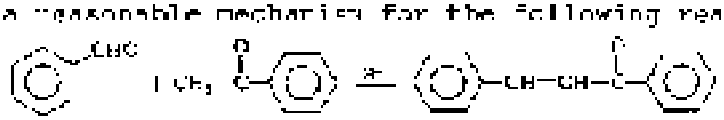
phenylethenyl phenyl ketone

The two reaction mechanisms shown above are both possible, but one of them is more favorable. The predominant product in solution is phenylethenyl phenyl ketone. This can be explained both sterically and thermodynamically.

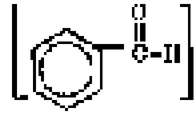
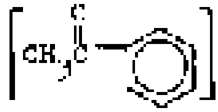
Sterically, acetophenone is bulkier around the carbonyl carbon. This renders the carbon less accessible for nucleophilic addition. Thermodynamically, the ketone-carbonyl bond is stronger, about 3 kcal, than the aldehyde-carbonyl bond. Thus, the addition at the acetophenone carbonyl carbon is much less favorable. Therefore, the predominant product is phenylethenyl phenyl ketone.

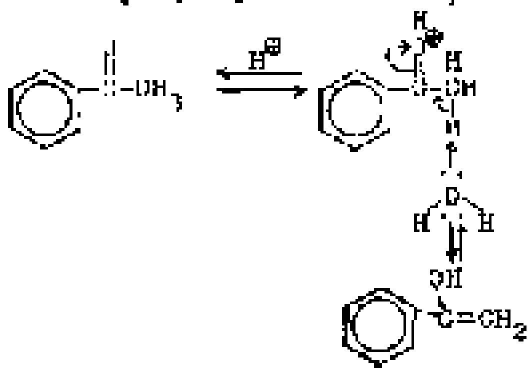
• PROBLEM 19-13

Write a reasonable mechanism for the following reaction:

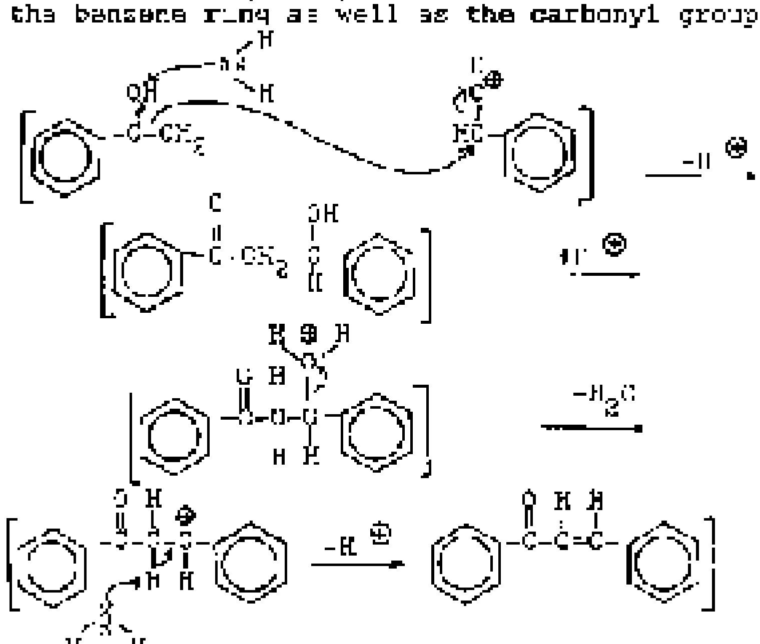


Chalcone
or
Benzalacetophenone

Solution: When the aldehyde, benzaldehyde , and the methyl ketone acetophenone  are mixed in the presence of an acid catalyst, an aldol condensation occurs in which an α,β unsaturated ketone is produced. Such a reaction involves the nucleophilic attack of an enol upon a protonated carbonyl group. We notice here only acetophenone and not benzaldehyde can form the enol and act as a nucleophile. This is because a hydrogen alpha to the carbonyl group is necessary for enolization.



The product isolated after the nucleophilic attack of the enol is an α,β unsaturated ketone and not the intermediate γ hydroxy ketone because the alcohol will spontaneously dehydrate in the acid media to form the conjugated system. The product here is particularly stable because the subsequently formed double bond is conjugated to the benzene ring as well as the carbonyl group.

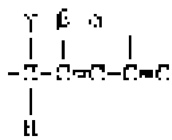


We note that the final product is formed via an E_1 mechanism involving a stable benzylic cation.

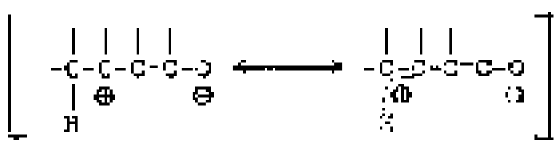
(a) What prediction can be made about the acidity of the γ-hydrogens of α,β-unsaturated carbonyl compounds?
(b) Suggest a pathway for the synthesis of 5-phenyl-2,4-pentadienal, $C_6H_5CH=CH-CH=CH-CHO$.

Solution: (a) The acidity of a proton depends upon the atom to which it is attached, the surrounding environment, and the relative stability of the deprotonated compound. For example, if the proton is attached to a highly electron-withdrawing atom, or an atom having an electronegative surrounding environment, the acidity is enhanced. Also, if the deprotonated compound is relatively stable, ionization is facilitated.

An α,β-unsaturated carbonyl compound, for example, crotonaldehyde has the following skeletal structure:

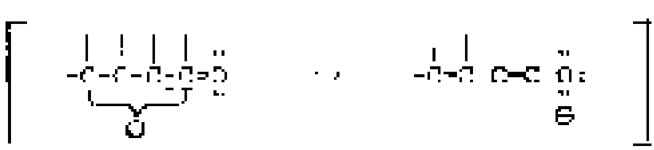


The γ-hydrogen is bonded to a carbon atom which is more electron-withdrawing. Since oxygen is much more electronegative, it tends to shift the molecule's electron density to give the following structures in composite form:

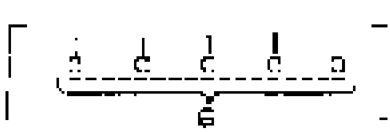


This compound is not stable, thus exists in very small concentration, but, nevertheless, it contributes to the acidity of the γ hydrogen of the α,β-unsaturated carbonyl compound.

Furthermore, there is extra resonance stabilization in the deprotonated compound. As the proton is ionized, the negative charge created can be shared by all the backbone carbon atoms, though the electron density will be highest at the oxygen atom. The ionized compound exists in the following forms:

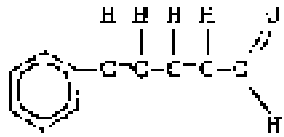


The composite form of these resonance structures is:

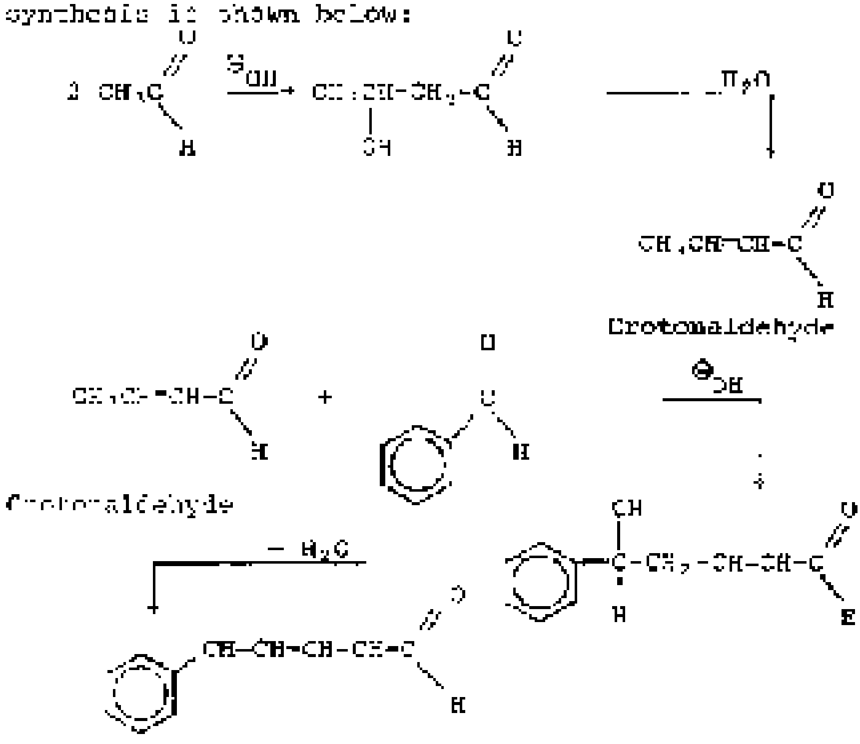


Since the negative charge is shared by five nuclei, the instability created by it is lessened. Thus, with all these contributions, one can conclude that the γ-hydrogens of an α,β unsaturated carbonyl compound are relatively highly acidic.

(b) 5-Phenyl-2,4-pentadienal has the following structure:

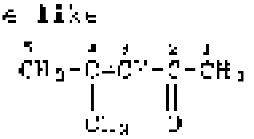


It is an α,β-unsaturated aldehyde with a substitution at the γ carbon. To synthesize this compound, one can begin with an aldol condensation of two acetaldehydes. Dehydration of the product gives crotonaldehyde, which can undergo another aldol condensation with benzaldehyde and then dehydrate to give 5-phenyl-2,4-pentadienal. The total synthesis is shown below:



• PROBLEM 19-15

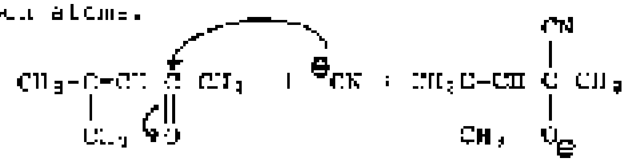
In the reaction of aqueous NaCN with an α,β-unsaturated ketone like



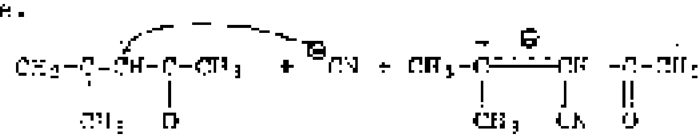
to which carbon will the $CN^{\ominus}$ be added?

Solution: Sodium cyanide ($Na^{\oplus}{}^{\ominus}CN$) is a strong nucleophile. In the α,β-unsaturated ketone, there are three possible sites for nucleophilic attacks: at carbon 2, carbon 3, and carbon 4. The $CN^{\ominus}$ will add to the conjugated system so as to form the most stable carbanion. The stability of an anion depends upon the ability of its atoms to share the negative charge.

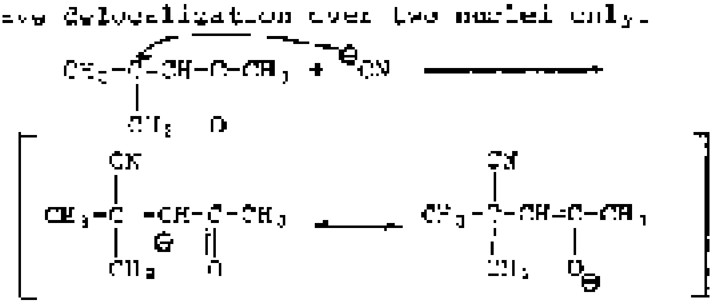
If $CN^{\ominus}$ is added to the carbonyl carbon 2, the negative charge will be carried by the oxygen alone. The contribution from carbanion having negative charge at carbon 3 is negligibly small because it violates the octet rule for carbon atoms.



If $CN^{\ominus}$ is added at carbon 3, the negative charge will be shared by carbon 3 and carbon 4. The carbons are not electronegative enough to remain stable with the extra pair of electrons. This carbanion is less stable than the one above.



If $CN^{\ominus}$ is added at carbon 4, the negative charge can be shared by carbon 3, carbon 2, and oxygen. This anion is more stable than the previous two because the negative charge can delocalize over three nuclei while the other two anions have delocalization over two nuclei only.



I II

Since oxygen is more electronegative than carbon, structure II makes the largest contribution.

• PROBLEM 19-10

Propose an efficient mechanism for the synthesis of glyceraldehyde $\left(\underset{\displaystyle OH}{CH_2}-\underset{\displaystyle OH}{CH}-CHO\right)$ from acrolein ($CH_2=CH-CHO$).

Solution: Looking at acrolein, one might think that this synthesis is a simple hydroxylation reaction, but hydroxylation will not give glyceraldehyde. It will result in oxidation of the aldehyde group. Therefore, the aldehyde functional group must be reversibly modified before hydroxylation. The modified compound has to be stable to hydroxylation of olefin, which can be performed by neutral permanganate in alkaline condition. This can be achieved by acetal formation.

Acetal formation is a characteristic property of aldehydes. It is the addition of two alcohol molecules to the carbonyl carbon under acidic conditions. Acetals are stable to the hydroxylation of olefins by neutral permanganate in alkaline condition. It can be converted back to aldehyde by acid-catalyzed hydrolysis. However, the double bond has to be masked before the acetal formation. This can be done simply by hydrohalogenation which does not affect the aldehyde. Dehydrohalogenation can be accomplished by elimination after the formation of acetal. The complete synthesis of glyceraldehyde is broken down into various steps and shown in equation forms below.

(1) Hydrochlorination of the olefin:

$$CH_2=CH-CHO + HCl \xrightarrow{\text{ethanol}} ClCH_2-CH_2-CHO$$

(2) Acetal formation:

$$ClCH_2-CH_2-CHO + 2\,C_2H_5OH \xrightarrow{H^+} ClCH_2-CH_2-CH(OC_2H_5)_2$$

(3) Elimination (E2-type dehydrochlorination):

$$ClCH_2-CH_2-CH(OC_2H_5)_2 + KOH \rightarrow CH_2=CH-CH(OC_2H_5)_2 + KCl + H_2O$$

(4) Hydroxylation of olefin:

$$CH_2=CH-CH(OC_2H_5)_2 \xrightarrow{KMnO_4} \underset{OH}{\underset{|}{CH_2}}-\underset{OH}{\underset{|}{CH}}-CH(OC_2H_5)_2$$

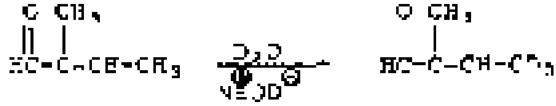
(5) Acidic hydrolysis:

$$\underset{OH}{\underset{|}{CH_2}}-\underset{OH}{\underset{|}{CH}}-CH(OC_2H_5)_2 + H_2O \xrightarrow[\text{mild}]{H^+} \underset{OH}{\underset{|}{CH_2}}-\underset{OH}{\underset{|}{CH}}-CHO$$

Glyceraldehyde

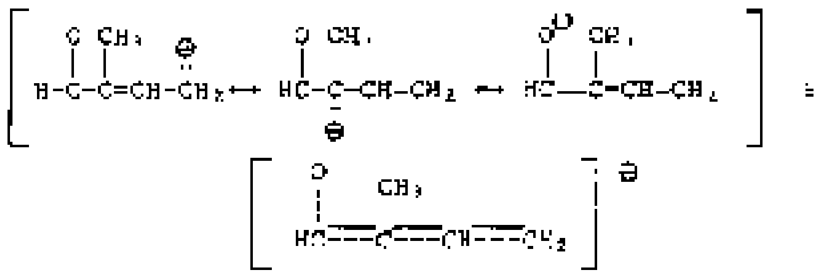
● PROBLEM 19-17

Explain by the use of resonance structures why the following occurs. Why does exchange not occur in the other methyl group?

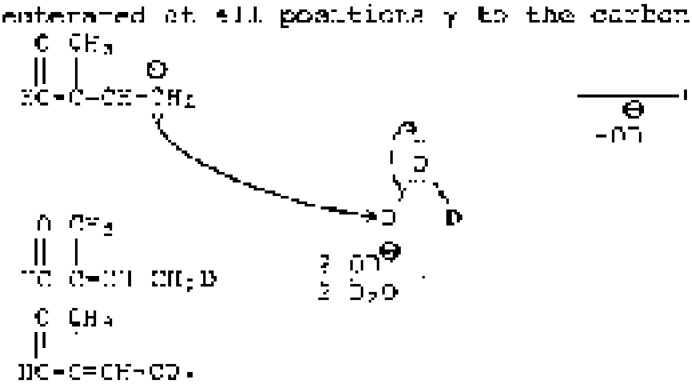


Solution: The primary aspect to note about the reactant in this problem is that it is conjugated. In conjugated systems we often encounter many resonance structures that are created upon carbocation or carbanion formation. In systems where delocalization of charge occurs, resonance structures are used to show this delocalization of charge. Usually in such systems, the greater the degree of delocalization, the more stable the ion.

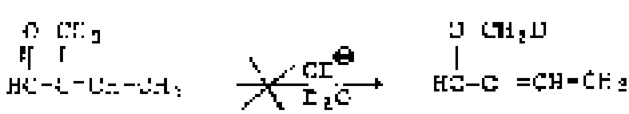
In this problem, we can write three important resonance forms for the carbanion formed by loss of a proton on the carbon γ to the carbonyl group.



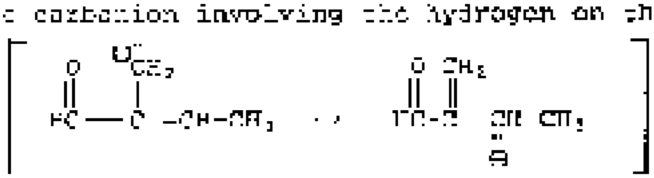
We note that two of the resonance contributing structures give particular stability to the resonance hybrid in that the double bonds present in them are conjugated. Thus, because of stability of the subsequently formed carbanion, the reactant 2-methyl-2-butenal, will be deuterated at all positions γ to the carbonyl group.



Deuterium incorporation does not occur on the carbon β to the carbonyl group.



The carbanion necessary for such incorporation does not have the same degree of resonance stabilization as the carbanion involving the hydrogen on the γ carbon.



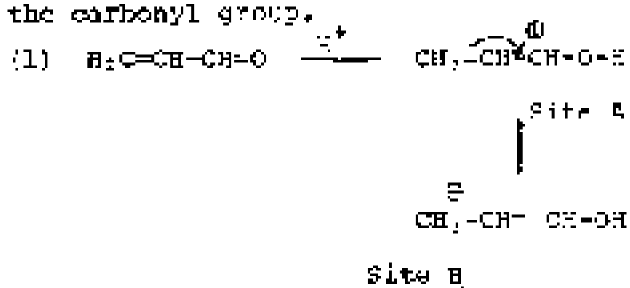
More importantly, as seen from the two major resonance contributing structures, the geometry of the system is such that the free pair of electrons, and both double bonds are not all components of a continuously conjugated system.

■ PROBLEM 19-18

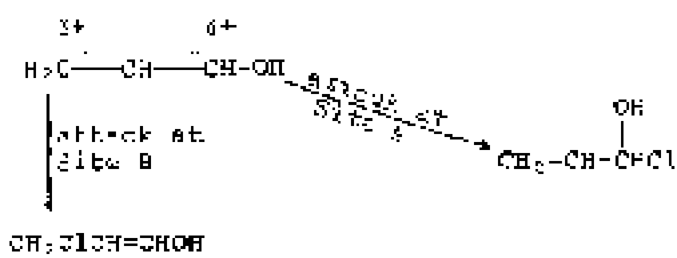
> What product would you expect from the addition of bromine to methyl vinyl ketone? Would you expect this addition to be more or less rapid than the addition of bromine to 1-butene? Why?

Solution: In the addition of bromine to methyl vinyl ketone $\left(CH_3\overset{O}{\overset{\|}{C}}CH{=}CH_2\right)$, we hypothesize two possible products. We can have an addition to the $>C=C<$ bond, called a direct addition, or we can have an addition to the carbon β to the carbonyl group which is known as a conjugate addition.

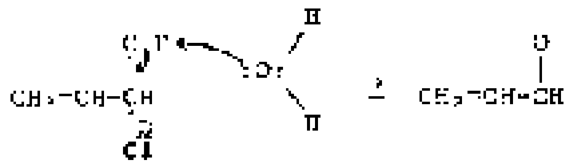
To determine what product is formed, we must look at the possible intermediates in the reaction. For example, we will consider the addition of HCl to acrolein ($CH_2{=}CH{-}CHO$). In the first step, acrolein is protonated at the carbonyl group.



The chloride ion (the nucleophile) can now attack at either Site A or Site B. The resulting structures will allow us to distinguish the actual product.



The adduct produced by attack at site A will revert to the starting material, acrolein.



The other plausible adduct is also unstable and is tautomerized to the actual aldehyde product.

$$CH_2Cl{-}CH{=}CHOH \rightleftharpoons CH_2Cl{-}CH_2{-}\overset{\displaystyle O}{\overset{\|}{C}}H$$

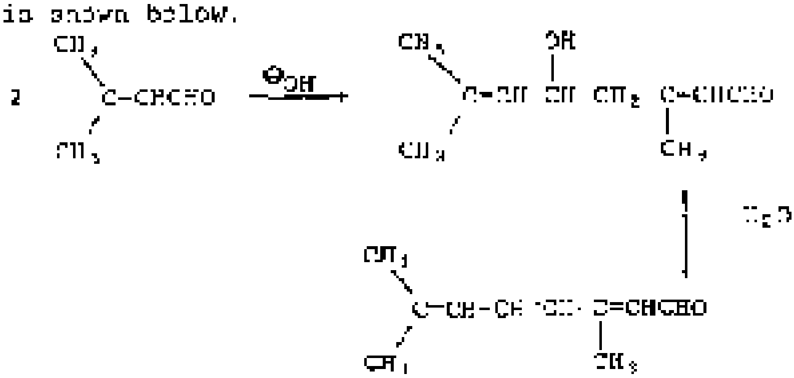
We can now apply our knowledge of conjugate addition to the electrophilic attack of Br_2 upon methyl vinyl ketone. The product is expected to be $CH_3\overset{O}{\overset{|}{C}}{-}CHBr{-}CH_2Br$, with the intermediate cation $CH_3\overset{O}{\overset{\|}{C}}{-}\underset{Br}{CH}{-}CH_2^{\oplus}$.

In comparing the speed of the addition of bromine to 1-butene and methyl vinyl ketone, we realize that the double bond of 1-butene would be attacked more readily because it lacks the electron-withdrawing carbonyl group of methyl vinyl ketone. While methyl vinyl ketone is less reactive in electrophilic additions such as these, it is more reactive toward attack of nucleophiles.

• PROBLEM 18-18

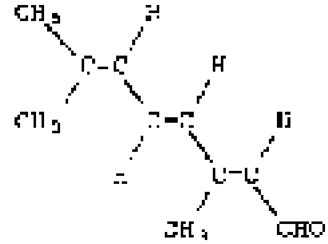
β-Methylcrotonaldehyde, $(CH_3)_2C{=}CHCHO$, when treated with dilute sodium hydroxide, yields a product of formula $C_{10}H_{14}O$, called dehydrocitral. What is a likely structure for this product, and how is it formed?

Solution: β-Methylcrotonaldehyde is an α,β-unsaturated aldehyde, therefore, the γ-hydrogens are relatively acidic. In presence of dilute base, the γ-hydrogen is ionized, and the carbonyl compounds can undergo aldol condensation to form a ten-carbon compound. The proposed reaction mechanism is shown below.

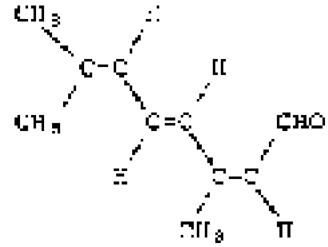


The product of this reaction has a chemical formula of $C_{10}H_{14}O$, dehydrocitral. There are four diastereomers possible for this formula. They are as follows:

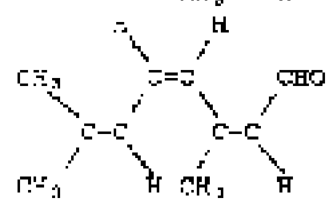
(1)



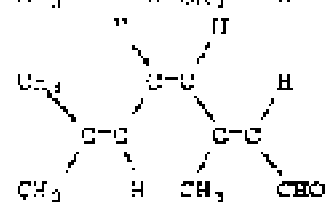
(2)



(3)



(4)



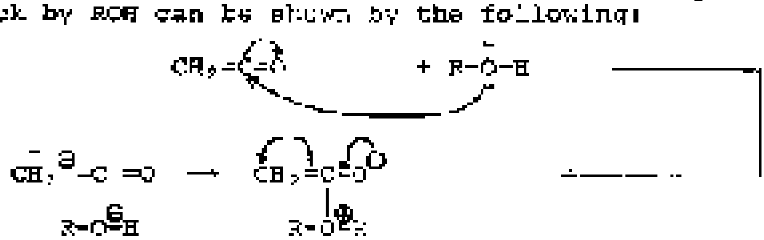
KETENES

• PROBLEM 19-20

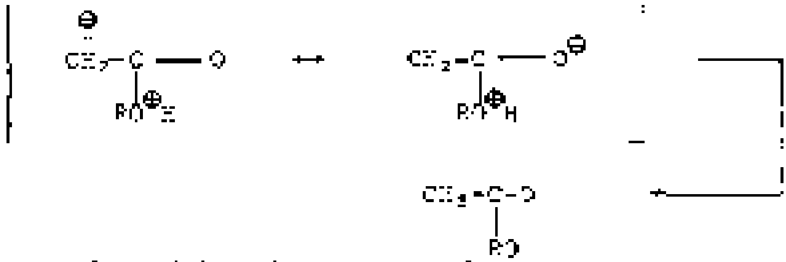
Write reasonable mechanisms for the reaction of ketene with alcohols and amines. Would you expect these reactions to be facilitated by acids and/or bases?

Solution: Ketene ($CH_2=C=O$) is similar to a ketone or an aldehyde in that when it reacts with ROH (alcohol) or RNH_2 (amine) the carbonyl carbon receives the nucleophile. The attack by ROH can be shown by the following:

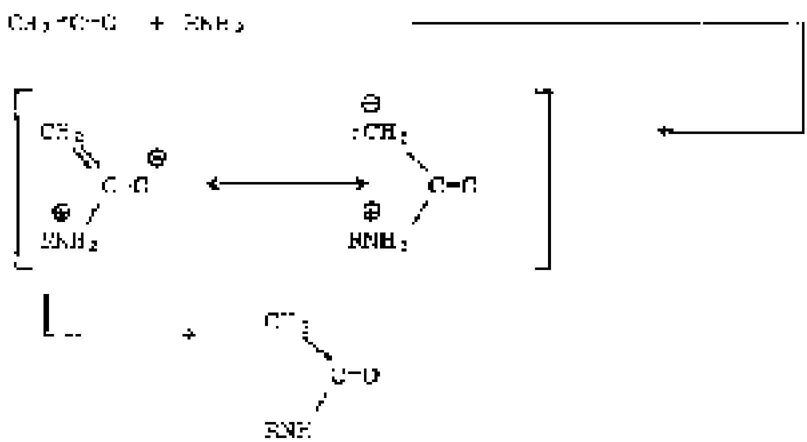
(1)



At this point the hydrogen of $-\overset{\oplus}{O}H$ (with R attached) shifts to the ketene's methylene group forming the final product.

(2) 

The reaction with amines occurs in the same manner.



The question remains how the addition of an acid or a base will affect the rate of the reaction. Let us consider the reaction of an alcohol with ketene. $RO^{\ominus}$ is a better nucleophile than ROH. If base is present it will react with alcohols in the following equilibrium:

$$ROH + OH^{\ominus} \rightleftarrows RO^{\ominus} + H_2O$$

Thus the presence of base will increase the rate of reaction of ketene with an alcohol. The presence of acid also speeds up this reaction because we have the carbonyl oxygen being protonated, making the carbonyl carbon more electropositive.

The effect of bases and acids in the reaction of ketene with RNH_2 is somewhat different. At a low pH, the amine will be tied up as an amine salt ($R\overset{\oplus}{N}H_3 B^{\ominus}$). However, at some intermediate pH, the rate will be optimized by the protonation of the carbonyl oxygen. We can thus conclude that in the reaction of ketene with an amine the rate is pH dependent.

The following reactions represent 'possible' synthetic reactions. Consider each carefully and decide whether or not the reaction will proceed as written. Show your reasoning. If you think side reactions would be important, write equations for each.

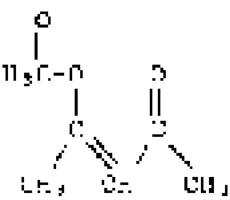
(a) $CH_3COCH_3 + 6\ Br_2 + 8\ NaOH \rightarrow 2\ CHBr_3 + Na_2CO_3 +$

$6\ NaBr + 6\ H_2O$

(b) $CH_3CHO + NaNH_2 + (CH_3)_3CCl \rightarrow (CH_3)_3CCH_2CHO + NH_3 + NaCl$

(c) $(CH_3)_2CHCOCH_3 + CH_2{=}O \xrightarrow{Ca(OH)_2} (CH_3)_2C(CH_2OH)COCH_3$

(d) $CH_3CHO + CH_3CO_2C_2H_5 \xrightarrow{OH^{\ominus}} \underset{\large OH}{CH_3\underset{|}{C}HCH_2CO_2C_2H_5}$

(e) $CH_3COCH_2COCH_3 + CH_2{=}C{=}O \rightarrow$ 

Solution: When given a hypothetical reaction equation, the best mode of attack would be to determine its plausibility by examining the proposed mechanism that would yield the given products. If such a mechanism is not valid, the reaction will not proceed as given.

(a) When halogen and base are reacted with methyl ketones (also acetaldehyde and certain alcohols) a carboxylic acid salt of one less carbon atom is produced. The reaction (haloform reaction) is dependent upon the acidity of the hydrogens alpha to the carbonyl group, and the sufficient stability of $Br-\overset{\displaystyle Br}{\underset{\displaystyle Br}{C}}:^{\ominus}$ to allow it to be a leaving group upon the nucleophilic attack of the hydroxide ion. Examining the stoichiometry of the proposed reaction, we see six moles of bromine are used, implying that both of acetone's methyl groups are brominated completely. This is confirmed by the use of eight moles of hydroxide ions (six used in proton abstraction and two involved in nucleophilic attack) and the two moles of bromoform ($CHBr_3$) produced. It does seem plausible that a monocarboxylic salt will be produced, yielding one mole of bromoform. The inductive effect of bromine allows bromination to occur at one methyl group at a time.

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{OH^{\ominus}} CH_3\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H_2 \longrightarrow CH_3\overset{O^{\ominus}}{\overset{|}{C}}{=}CH_2$$

$$CH_3\overset{O}{\overset{\|}{C}}CH_2^{\ominus} + Br{-}Br \longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2Br + Br^{\ominus}$$

$$CH_3\overset{O}{\overset{\|}{C}}CH_2Br \xrightarrow[2\ OH^{\ominus}]{2\ Br_2} CH_3\overset{O}{\overset{\|}{C}}CBr_3$$

$$CH_3\overset{O}{\overset{\|}{C}}{-}CBr_3 + {}^{\ominus}OH \longrightarrow CH_3\overset{O^{\ominus}}{\underset{OH}{\overset{|}{\underset{|}{C}}}}{-}CBr_3 \longrightarrow$$

$$CH_3\overset{O}{\overset{\|}{C}}{-}OH + :\overset{\ominus}{C}Br_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}{-}O^{\ominus} + CHBr_3$$

The net reaction at this point is:

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + 4\ NaOH + 3\ Br_2 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}O^{\ominus}Na^{\oplus} + 3\ NaBr + CHBr_3$$

The reaction terminates at this point because the acetate ion will not lose a proton to the hydroxide ion. Such a proton loss is unlikely because it will create a dianion, which is unstable and also the resonance stabilization of the carboxyl group interferes with the acidity of the alpha hydrogens. Thus, only one mole of bromoform is produced.

$$CH_3\overset{O}{\overset{\|}{C}}{-}O^{\ominus}\ Na^{\oplus} \xrightarrow{\cancel{\ OH^{\ominus}\ }} :\overset{\ominus}{C}H_2\overset{O}{\overset{\|}{C}}{-}O^{\ominus}\ Na^{\oplus}$$

(b) A condensation reaction is proposed here with the carbanion of acetaldehyde attacking t-butylchloride. Such an addition is not feasible in that the tertiary halide is too sterically hindered to be attacked by a nucleophile in a substitution reaction. The halide will instead undergo an facile elimination reaction to produce an alkene.

$$(CH_3)_3CCl + NaNH_2 \longrightarrow (CH_3)_2C{=}CH_2 + NaCl + NH_3$$

The aldol condensation of acetaldehyde will also be a side reaction

$$2\ CH_3\overset{O}{\overset{\|}{C}}H \xrightarrow{NH_2^{\ominus}} CH_3\overset{OH}{\underset{H}{\overset{|}{\underset{|}{C}}}}CH_2\overset{O}{\overset{\|}{C}}H$$

(c) The combination of a ketone $\left[(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_3\right]$

with an aldehyde lacking an α hydrogen $\left(\overset{O}{\overset{\|}{H C H}}\right)$ seems to be an excellent way of performing a crossed aldol condensation. However, the aldol given as the product would result from the nucleophilic attack of the carbanion,

$(CH_3)_2\overset{\ominus}{C}\overset{O}{\overset{|}{C}}CH_3$, upon formaldehyde. This carbanion would not be generated because the β proton removed to produce it is not as acidic as the α protons of the methyl fragment on the other side of the carbonyl group. This difference in acidity is due to the fact that the more alkyl groups bonding the carbon bearing the negative charge the more unstable the carbanion is.

Thus, the actual aldol product would be:

$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_2CH_2OH$$

$$(CH_3)_2CH\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[-H_2O]{^{\ominus}OH} (CH_3)_2CH\overset{O^{\ominus}}{\overset{|}{C}}=CH_2$$

$$\downarrow CH_2=O$$

$$(CH_3)_2CHCOCH_2CH_2OH$$

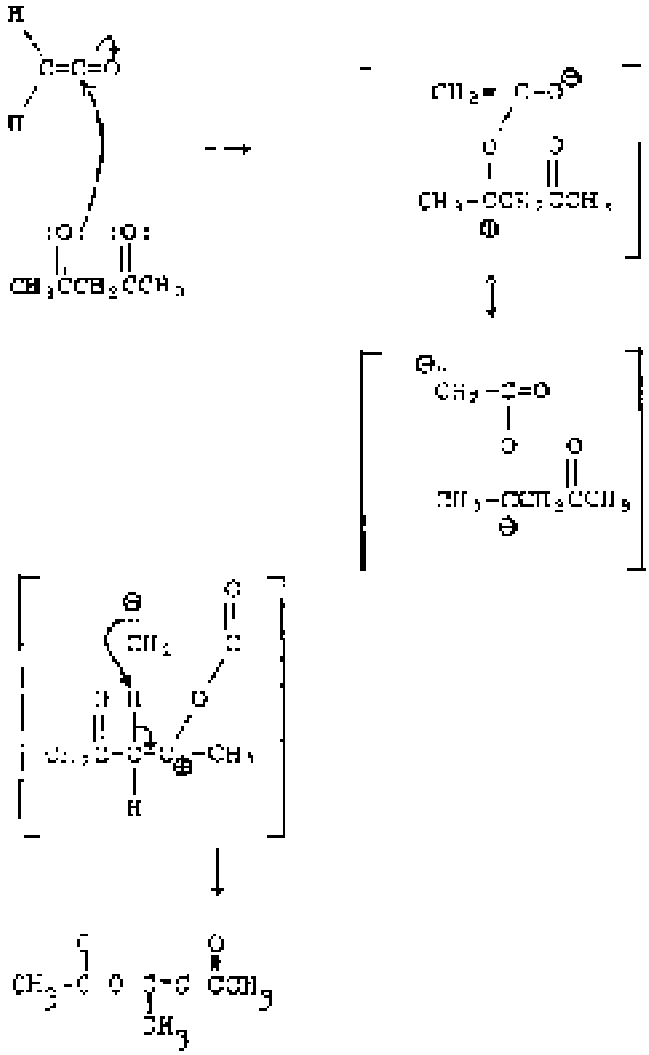
(d) The proposed chemical equation suggests a condensation reaction between the ester ethyl acetate and the aldehyde acetaldehyde. This reaction cannot occur because acetaldehyde can undergo an aldol condensation while the ester is hydrolyzed to a carboxylate salt (saponification).

$$2\ CH_3CHO \xrightarrow{^{\ominus}OH} CH_3CH(OH)CH_2CHO$$

$$CH_3CO_2C_2H_5 + {}^{\ominus}OH \rightarrow CH_3CO_2^{\ominus} + C_2H_5OH$$

We note that even if these side reactions were not present, the reaction would not proceed as written for the α protons of an aldehyde are more acidic than that of an ester.

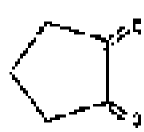
(e) Ketene ($CH_2=C=O$) readily undergoes nucleophilic attack at the electropositive carbon. An oxygen of one of the two equivalent carbonyl groups can attack this carbon and generate an intermediate which simultaneously undergoes a proton shift to give the final product which is correct as written. The conjugation in the product favors its formation.



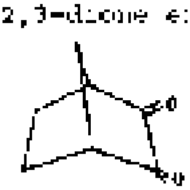
POLYCARBONYL COMPOUNDS

▼ PROBLEM 19-22

1,2 Cyclopentanedione exists primarily as a monoenol whereas biacetyl exists primarily as the keto form. Remembering conformational variances between the two substances: (a) explain this occurrence. (b) To what degree would Bicyclo[2.2.1]heptan-2,3-dione enolize? Explain.

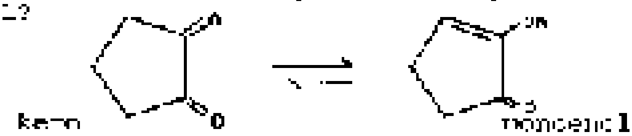


1,2 Cyclopentanedione

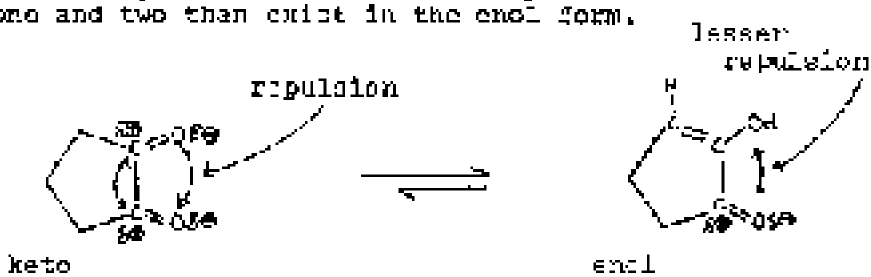


Bicyclo[2.2.1]heptan 2,3,-dione

Solution: (a) Like most carbonyl compounds, 1,2 cyclopentanedione undergoes enolization and is found in equilibrium with its corresponding enol form. The question arises: which is the predominating form, the keto or the enol?

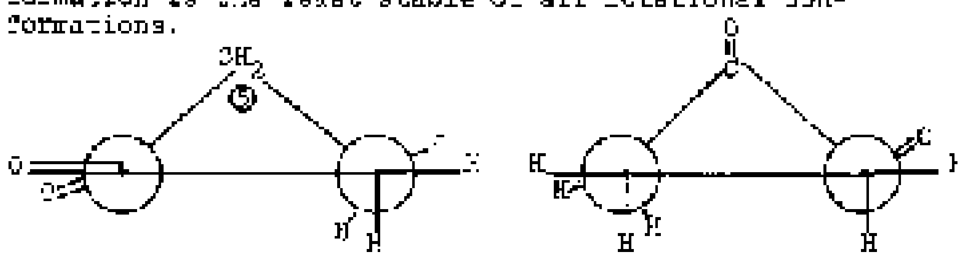


Immediately, one can see that the keto form would exhibit greater electrostatic repulsion between carbons one and two than exist in the enol form.



It should be noted that electrostatic repulsion exists in the enol form. However, this electrostatic repulsion is less in the enol form than in the keto form because the single C-O bond has a smaller polarization gradient than the carbonyl bond, hence lessening the repulsion of the partially positively charged carbons.

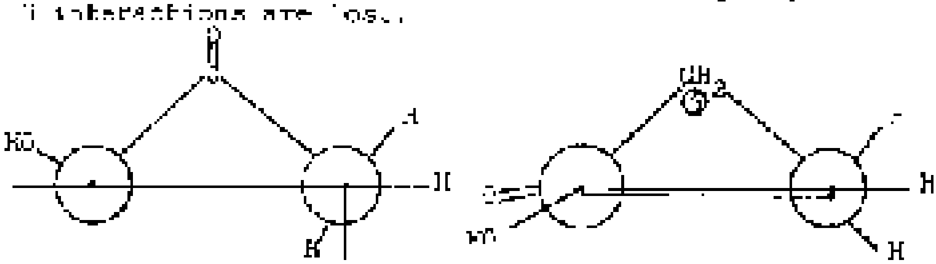
An examination of the Newman projections of the keto and the enol forms reveals that there exist two more eclipsing H-H interactions in the keto form than in the enol form. This lends additional stability to the enol form over the keto form in that the eclipsed Newman conformation is the least stable of all rotational conformations.



Projection along 1-2 and 3-4

Projection along 4-5 and 3-2

In the enol form, two of these four eclipsing H-H interactions are lost.

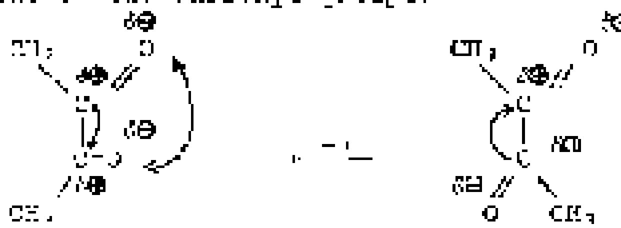


Projection along 3-2 (double bond) and 4-5

Projection along 1-2 and 3-4

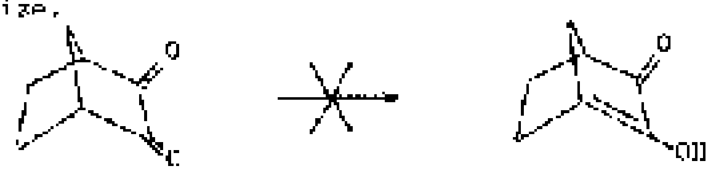
Hence, for conformational, as well as electrostatic reasons the keto form is less favored than the monoenol form.

In biacetyl, the situation is somewhat different from the aforementioned cyclic dione. The presence of a freely rotating bond between the second and third carbons allows the biacetyl to assume the more stable S-trans conformation, thereby reducing the electrostatic interactions of the carbonyl groups.



biacetyl (s-cis conformation) s-trans conformation (no oxygen-oxygen repulsion)

(b) Bicyclo[2.2.1]heptan-2,3-dione would not enolize at all owing to the fact that enolization would require the placement of a double bond at the bridge head, which is a violation of Bredt's rule. This rule states that due to extremely poor overlap of the p orbitals concerned, in π bond formation at a bridge head atom, bicyclic compounds cannot have a double bond at a bridge head position. This does not apply in bicyclic compounds of a large size.



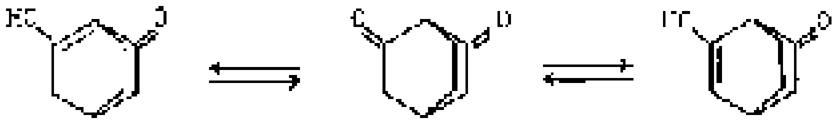
PROBLEM 19-23

2,6-Bicyclo[2.2.2]octanedione [I] exhibits no enolic properties. Explain.

(I)

Solution: The bicyclic dione shown in this problem has its two keto groups in equivalent positions.

The keto groups have two types of α-hydrogens, hence this bicyclo compound can potentially form two enols, C and D:



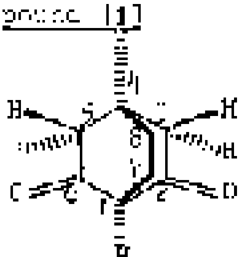
C (1) D

Compound C has a double bond situated at a bridgehead atom. This is a violation of Bredt's rule, which states that bicyclic compounds cannot have a double bond at a bridgehead position due to extremely poor overlap of the p orbitals involved in the π bond. Only very large bicyclic compounds ([5.2.6] and bigger) can have a double bond at bridgehead positions due to a reduction in angle strain. Since compound [1] is a relatively small bicyclo compound ([2.2.2.]), compound C will exist only in negligible amounts.

Compound D has a double bond between carbons number 5 and 6; the numbering scheme for the bicyclo compound is:

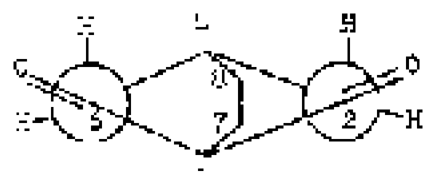
The transition of compound [1] to compound D changes the orbital hybridization of carbon number 5 from sp^3 to sp^2. This transition is extremely difficult primarily because of the creation of eclipsing interactions between the substituents on carbons number 5 and 6. In compound [1] there are no such interactions; the carbonyl oxygen is not eclipsing any substituents on adjacent carbon atoms. In compound D however, the hydroxyl group is eclipsing the hydrogen on carbon number 5. This is illustrated as:

Compound [1]



Fischer projection

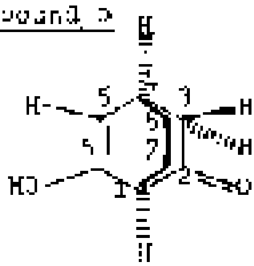
dark lines=toward reader
broken lines=away from reader
normal lines=in the plane of the paper



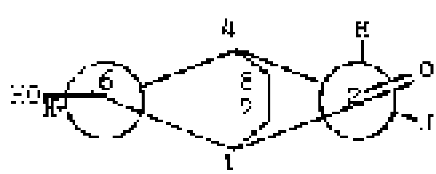
Newman projection

[along carbons 2 and 3 and carbons 1 and 4]

Compound D



Fischer projection



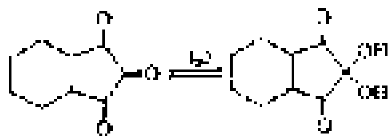
Newman projection

[along carbons 2 and 3 and the double bond of carbons 6 and 5]

Another factor contributing to the instability of compound D is the presence of a carbon-carbon double bond within the ring. A double bond within a bicyclo ring creates further rigidity in the compound's structure and hence generates a greater angle strain. As a result, compound D does not exist in any appreciable amounts and therefore compound [I] shows no enolic character.

• PROBLEM 19-21

Ninhydrin, a reagent used to detect amino acids by a color reaction, is the hydrate of hydrindantrione. Why is the hydrate stable? Why is this the most likely structure for the hydrate?



hydrindantrione ninhydrin

Solution: The hydrate form of a carbonyl compound is stable usually because of one or more of the following reasons:

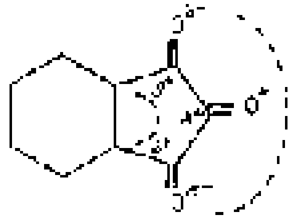
(1) There is a strong inductive effect by an electron withdrawing species placed near the $\diagdown C{=}O$ bond. This tends to destabilize the inherent charge separation present in the C=O bond.

(2) The carbonyl compound has very little alkylation present. Alkyl side groups tend to release electrons to the C=O bond which stabilizes the bond's inherent charge separation.

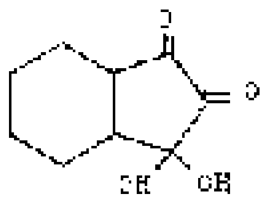
(3) The formation of the hydrate relieves an angle strain. This occurs because the carbonyl carbon goes from being Csp^2 hybridized to Csp^3 hybridized upon hydration.

(4) In cases of poly ketones (compounds with more than one $\diagdown C{=}O$ bond) another factor comes into play. When carbonyl groups are very close together they electrostatically repel each other; hydration of a C=O group relieves this unfavorable repulsion.

In the given example reason four explains the stability of ninhydrin. Let us look at the unfavorable repulsion present in hydrindantrione.



Ninhydrin is the most likely hydrate because this has less electrostatic interactions than the other hydrate form:

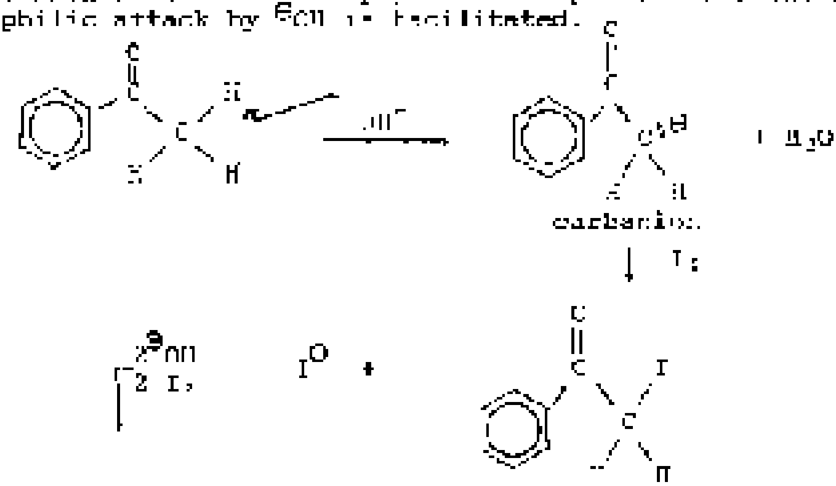


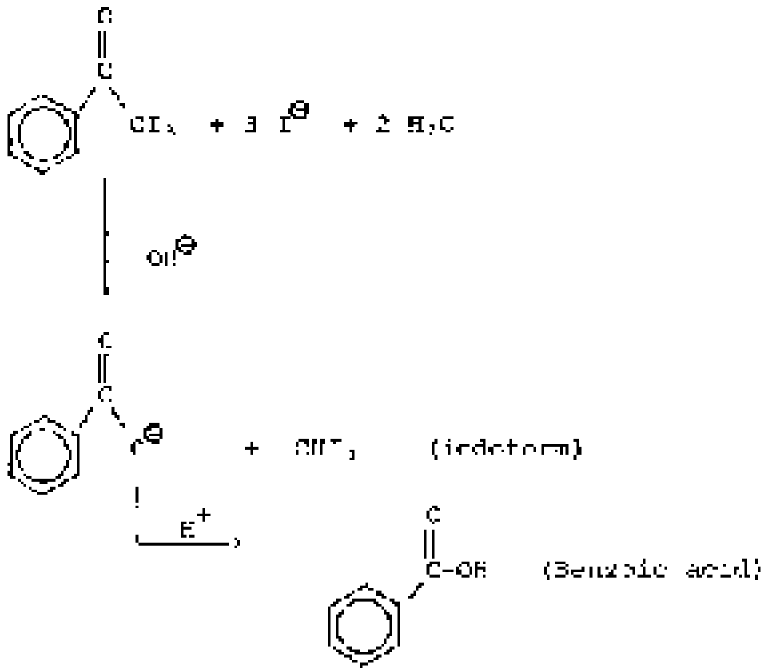
SYNTHESIS AND REACTIONS

• PROBLEM 19-25

Propose a reasonable synthesis for benzoic acid from acetophenone. Write out all the steps in equation form and indicate the involvement of carbanions, if any.

Solution: To synthesize benzoic acid from acetophenone, one needs to remove the methyl group. This can be achieved by using the haloform reaction, which is the halogenation of the acetyl methyl group. The mechanism of this reaction involves a carbanion formation. This can be seen readily by the fact that the haloform reaction is base-catalyzed. The base catalyst ionizes the methyl group to form a carbanion which in turn attacks a halogen. This process repeats until all three hydrogens are substituted by halogens. Tri-halo methyl is a good leaving group in a substitution reaction, also, since the halogens are electronegative, the carbonyl carbon will have a very positive dipole. Thus, the nucleophilic attack by $^{\ominus}OH$ is facilitated.





• PROBLEM 10-26

A lab researcher has supplies of n butyl alcohol, 2-ethyl-1-hexanol and other inorganic reagents. He also has a quantity of mosquitoes flying around in the lab. One day, walking around in a drugstore he looked at a bottle of the insect repellent "6-12" and found that it has the chemical formula name of 2 ethyl 1,3 hexanediol. He realized that he could have synthesized the compound himself. Propose a possible synthesis of "6-12" from the researcher's available materials.

Solution: One of the materials available to him is 2 ethyl 1-hexanol. However, attempts made to synthesize "6-12" from it is impractical, because aliphatic hydrocarbons are not very good substrates for stereoscopic hydrations. Therefore, his only starting material is n butyl alcohol.

Since n-butyl alcohol is a four carbon compound and "6-12" (2-ethyl-1,3-hexanediol) is an eight-carbon compound, it is reasonable to think that the main reaction is a condensation reaction. However, this condensation reaction requires two carbonyl compounds. This can be obtained by oxidizing the alcohol into an aldehyde, subsequently, aldehydes can be combined by aldol condensation to form a hydroxy-carbonyl compound. A reduction of this compound will result in the desired diol.

$$2\ CH_3CH_2CH_2CH_2OH \xrightarrow{K_2Cr_2O_7} 2\ CH_3CH_2CH_2CHO \xrightarrow{OH^-}$$

$$CH_3CH_2CH_2\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle CH_2CH_3}{\underset{|}{CH}}-CHO \xrightarrow{H_2,\ Ni} CH_3CH_2CH_2\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle CH_2CH_3}{\underset{|}{CH}}-CH_2OH$$

"6-12"

(2-Ethyl-1,3-hexanediol)

• PROBLEM 16-27

> Compound K, C_5H_{10}, decolored a solution of Br_2 in carbon tetrachloride. When K was dissolved in cold, concentrated sulfuric acid and then heated with water, L resulted. L, $C_5H_{12}O$, reacted with chromic acid $K_2Cr_2O_7$ to give M, $C_5H_{10}O$. Both L and M gave positive iodoform tests. The reaction mixture of the iodoform test also produced isobutyric acid $(CH_3)_2CHCOOH$. Determine the structure of K, L, and M.

Solution: The fact that compound K decolored Br_2 in CCl_4 means it is unsaturated; an alkene. The solution was decolorized because the deep-red color of bromine is quickly discharged as it adds to the alkene and the dibromide forms:

$$\underset{\text{(Alkene)}}{-\overset{|}{C}=\overset{|}{C}-} \quad + \quad \underset{\text{(reddish)}}{Br_2 \text{ in } CCl_4} \quad \rightarrow \quad -\underset{Br}{\underset{|}{C}}-\underset{Br}{\underset{|}{\overset{|}{C}}}-$$

(colorless dibromide)

When compound K was placed in the sulfuric acid and water, it was hydrated to an alcohol. Alkenes react with concentrated sulfuric acid to give alkyl hydrogen sulfates by Markovnikov addition. The sulfates may then be heated with water to yield the corresponding alcohol as shown:

$$\underset{\text{(Alkene)}}{R-CH=CH_2} + H_2SO_4 \rightarrow R-\underset{OSO_3H}{\underset{|}{CH}}-CH_3 \xrightarrow[\Delta]{H_2O} R-\underset{OH}{\underset{|}{CH}}-CH_3$$

(Alkyl hydrogen sulfate) (Alcohol)

Compound L must, therefore be an alcohol. It is indicated that L reacts with chromic acid to give M. This indicates that L must be either a primary or secondary alcohol since chromic acid is a strong oxidizing agent that readily oxidizes primary and secondary alcohols to aldehydes $\left(\begin{array}{l} H \\ \quad \diagdown \\ \qquad C=O \\ \quad \diagup \\ R \end{array}\right)$ and ketones $\left(\begin{array}{l} R \\ \quad \diagdown \\ \qquad C=O \\ \quad \diagup \\ R \end{array}\right)$, respectively.

This means L must be either a primary or secondary alcohol, while M must be either an aldehyde or ketone.

One can determine the specific functional groups by noting the fact that both give a positive iodoform test. An iodoform test can be used to identify methyl ketones. It will not give a positive reaction with aldehydes. This means M must be a ketone, specifically a methyl ketone. For the ketone to be generated, the precursor of M and L had to have been a secondary alcohol. This can be further proven by the fact that the iodoform reaction can react with secondary alcohols as shown:

$$CH_3\underset{\displaystyle OH}{CH}-R \xrightarrow{I_2/OH^{\ominus}} CH_3\underset{\displaystyle \overset{||}{O}}{C}-R \xrightarrow{I_2/OH^{\ominus}} \text{Positive iodoform test}$$

The problem indicates that isobutyric acid is produced in the iodoform test. The reaction sequence of iodoform is illustrated:

$$\underset{\text{(Methyl ketone)}}{R-\underset{\displaystyle \overset{||}{O}}{C}-CH_3} + 3\ I_2 \xrightarrow{OH^{\ominus}} R-\underset{\displaystyle \overset{||}{O}}{C}-CI_3 + 3\ I^{\ominus}$$

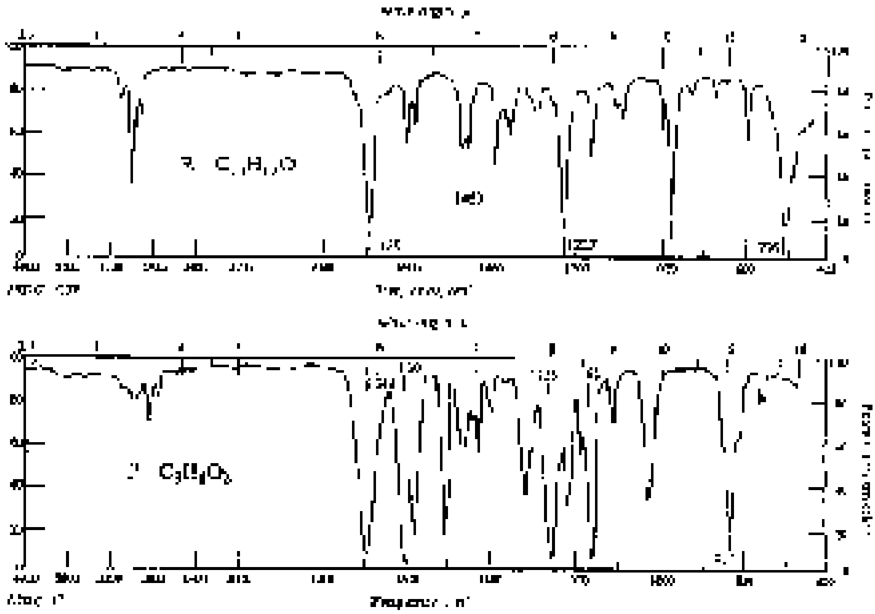
$$R-\underset{\displaystyle \overset{||}{O}}{C}-CI_3 + OH^{\ominus} \rightarrow R-\underset{\displaystyle \overset{||}{O}}{C}-O^{\ominus} + \underset{\text{(Iodoform)}}{HCI_3}$$

In this problem, $R-\underset{\displaystyle \overset{||}{O}}{C}-O^-$ (a carboxylate ion) must be the isobutyric acid obtained, or R is $(CH_3)_2C-$. If one works backward through this sequence, the methyl ketone that generated this acid would have to be $(CH_3)_2CH-\underset{\displaystyle \overset{||}{O}}{C}-CH_3$, which represents the structure of M.

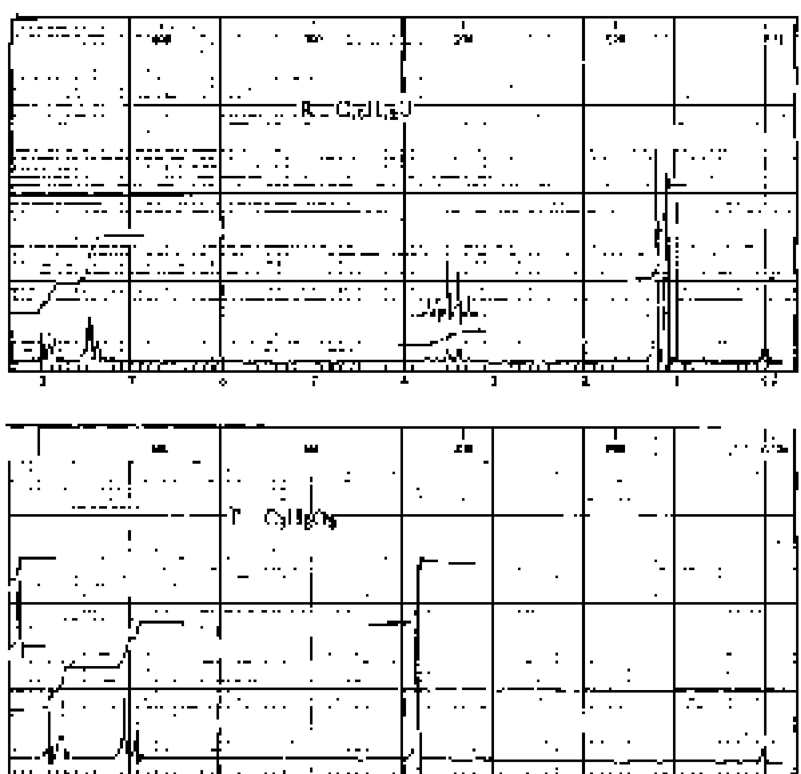
Again, working backwards (and recalling that M comes from the corresponding secondary alcohol L), one obtains $(CH_3)_2CH-\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-CH_3$ for L's structure. A similar process of retracing steps informs one that compound K must be $(CH_3)_2C=\overset{\displaystyle H}{C}-CH_3$.

■ **PROBLEM** 19-29

Give the structures of compounds P and R on the basis of their infrared spectra and their nmr spectra.



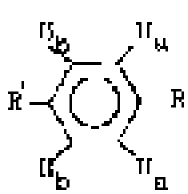
Infrared spectra



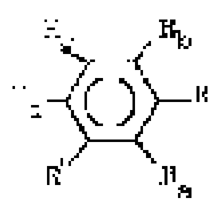
Nmr spectra

Solution: We can use the infrared spectrum of compound P to identify any functional groups that may be present. The most significant feature of the spectrum shown is the strong C=O stretch at 1688 cm^{-1} which is characteristic of aromatic carbonyl compounds (simple saturated carbonyl compounds have a C=O stretch at about 1720 cm^{-1}). The presence of a benzene ring can be confirmed by the moderate to strong bands at 1601, 1585, 1500 and 1450 cm^{-1}. These absorptions are characteristic of the C=C stretch of benzene derivatives. Further spectral evidence supporting the hypothesis of a carbonyl functionality can be seen by the two weak bands at 2750 cm^{-1} and 2825 cm^{-1}. These absorptions are characteristic of the C-H stretch of aldehydes. Another important feature of this spectrum is the moderate band at 1050 cm^{-1}, which is the typical absorption of the C-O stretch of ethers. We now know that compound P is an aromatic aldehyde with a possible ether linkage.

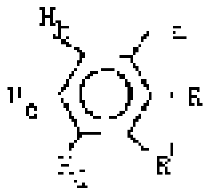
By examining the nmr spectrum of compound P, we see that there are two doublets at 7.0 δ and 7.8 δ. These signals confirm the presence of a benzene ring and suggest a para-disubstituted benzene ring which will be verified later. The singlet that appears as the most downfield signal (greater than 8.0 δ) is given rise to by the aldehyde proton; aldehyde protons generally absorb at 9.5 - 10.0 δ. The singlet at 3.8 δ has a relative intensity of three and is the characteristic signal of a methoxy group ($-OCH_3$). The relative intensities of the signals going from left to right are 1 : 2 : 2 : 3; these are determined by the relative changes in the height of the integration curve at each absorption. The relative intensities indicate the relative abundance of each type of proton. We previously said that the nmr spectrum suggests a para-disubstituted benzene ring. This is indicated by the fact that the aromatic protons' signals occur as two doublets. We know that the two substituents of the benzene ring are not identical (one is a formyl group, $\overset{O}{\overset{\|}{C}}$–H, and the other group has the molecular formula CH_3O). Only a para-disubstituted benzene will have two sets of non-equivalent protons that will occur as two doublets. A meta or ortho orientation will each have four sets of non-equivalent protons. This would result in complex spin-spin splitting patterns.



para - two types of protons

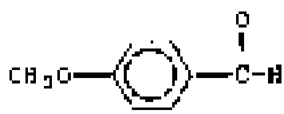


meta - four types of protons



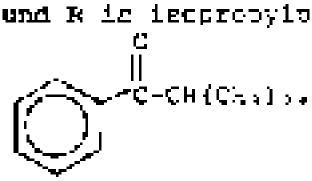
ortho - four types of protons

Proof that compound P is a para-disubstituted benzene comes from the infrared spectrum. The strong band at 834 cm^{-1} is characteristic of the C-H out-of-plane bending of para-disubstituted benzene compounds. Hence compound P is a para disubstituted benzene compound with formyl and methoxy (due to proof of ether linkage in IR) substituents. The compound is p-methoxybenzaldehyde and has the structure:



The infrared spectrum of compound R is similar to that of compound P in that the C=O stretch at 1689 cm^{-1} indicates an aromatic carbonyl compound. The presence of a benzene ring is indicated by the bands at 1600, 1585, 1475, and 1450 cm^{-1}. This is confirmed by the two multiplets at 7.4 δ and 7.9 δ in the nmr spectrum. The presence of a band at 2820 cm^{-1} in itself does not indicate an aldehyde C-H stretch; aldehydes have a band at 2720 cm^{-1} in addition to the one at 2820 cm^{-1}. Hence this suggests that compound R is an aromatic ketone. We have so far accounted for a phenyl and carbonyl group (C_7H_5O); this leaves us with a C_3H_7 group.

The nmr spectrum shows signals with the relative intensities 2 : 3 : 1 : 6, going from left to right. The doublet at 1.1 δ with relative intensity of six must be two equivalent methyl groups. The fact that their signal occurs as a doublet indicates that both methyl groups are split by one proton. Since a C_3H_7 group is all that remains to be identified, it must be an isopropyl group. The multiplet at 3.5 δ with relative intensity of one is the methine proton of the isopropyl group; it is split into a heptet by the six neighboring methyl protons. The isopropyl group must be bonded to the carbonyl group because (1) the methine proton is deshielded by the $-\overset{O}{\overset{\|}{C}}-$ group and hence absorbs relatively downfield (3.5 δ) and (2) the compound is a ketone with a phenyl group on one end; the remaining group must be on the other side of the carbonyl group. Hence compound R is isopropylphenyl ketone and has the structure:



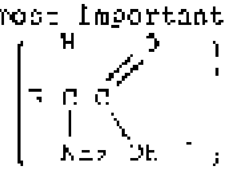
CHAPTER 20

CARBOXYLIC ACIDS

NOMENCLATURE AND STRUCTURE

• PROBLEM 20-1

What are carboxylic acids? Briefly discuss their properties and the system of naming.

Solution: Carboxylic acids are organic compounds which contain one or more carboxyl groups, . As the name implies, these compounds are acidic. In fact, they are the most important acidic organic compounds. This can be readily seen in the variety of substances which contain the carboxyl functional group. The most important examples of these substances are amino acids  building blocks of proteins which are required for animal function and structure.

The carboxyl group has a number of functional properties. They are as follows:

(a) The acidic proton can be released in the presence of a more basic compound, that is, a compound with higher affinity (pK_b) for proton.

(b) This acidic proton can participate in noncovalent hydrogen-bonding, as in protein tertiary and quaternary structures.

(c) The carbonyl oxygen can act as electron donor in hydrogen bonding.

(d) The carbonyl carbon is susceptible to nucleophilic attacks. It participates in various organic reactions, most notably in the amide bond formation in proteins.

In the IUPAC system of naming, the longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the -e of the corresponding alkane with -oic acid.

If there are other substitutions in the chain, they will be classified according to the carbon to which they are attached. The numbering of carbons begins with the carbon immediately attached to the carbonyl carbon, which is called the α-carbon or 2-carbon. The rest of the numbering will follow the Greek letters, β, γ, δ, ε..., etc., which corresponds to 3, 4, 5, 6, ..., respectively,
$\left(\begin{matrix}\delta\ \ \gamma\ \ \beta\ \ \alpha \\ C-C-C-C-COOH\end{matrix}\right)$. For example,

the longest chain contains three carbons; at the α-carbon there is a hydroxy substitution. Thus, the IUPAC name is α-hydroxypropionic acid.

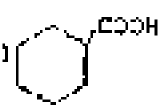
There are also common names for some of the important acids. These are named according to the sources from which they are discovered. The most encountered ones are:

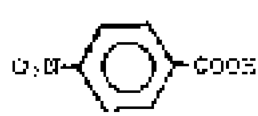
$HCOOH$	Formic acid
CH_3COOH	Acetic acid
$CH_3CH_2CH_2COOH$	Butyric acid

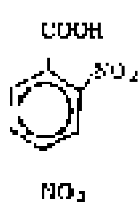
The α-hydroxypropionic acid above is also called lactic acid.

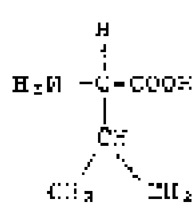
• PROBLEM 20-2

Name the following structures:

(a) 

(b) 

(c) 

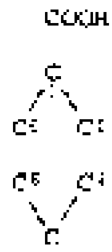
(d) 

(e) $HO_2C\ CH_2\ CH_2-CO_2H$

Solution: Since the carboxyl group takes precedence in naming, all the above structures should have names ending in -oic acid. According to the IUPAC system of naming, the compounds are named as derivatives of the longest carbon chains. Therefore, the nomenclature of the above compounds are:

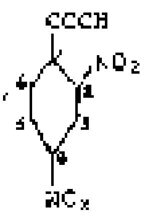
(a) Since the carboxyl group is attached to a cyclohexane ring, the compound is called cyclohexanoic acid. This compound is also called cyclohexanecarboxylic acid.

(b) Substitutions in cyclic compounds are named according to the carbons to which they are attached. These carbons are classified according to their positions with respect to the main functional group. For example,



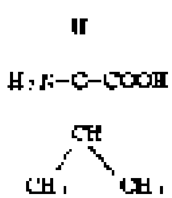
The C2 and C6 carbons are an equal distance from C1 and the carboxyl carbon; they are called ortho-carbons. The C3 and C5 carbons are meta-carbons; the C4 carbon is the para carbon. These three positions are abbreviated as the o, m, and p positions, respectively. Thus, the structure is called para-nitrobenzoic acid, or p-nitrobenzoic acid.

(c) When the cyclic compound has more than two substitutions, instead of using ortho, meta, or para, the carbon numbers are used. Therefore,



is called 2,4-dinitrobenzoic acid.

(d) The longest carbon chain contains 4 carbons. The substitutions are $-NH_2$ at carbon 2 and $-CH_3$ at carbon 3. Thus, the IUPAC name for the compound



is 2-amino, 3-methyl butanoic acid

However, this is also the structure for a natural, essential amino acid. The common name for it is valine.

(c) $HO_2C\,CH_2-CH_2-CO_2H$ contains two carboxyl groups at two equivalent positions. Thus, naming can be from either carboxyl group, taking the other carboxyl as a substitution. The longest carbon chain containing one carboxyl group has three carbons; thus, it is called propionic acid. Since there is a carboxyl substitution at the 3-carbon, the full IUPAC name for the structure is 4-carboxylpropionic acid. The common name for the structure is succinic acid.

• PROBLEM 20-3

Draw structures for the following:

(a) Propionic acid; (b) 2-Chlorobutanoic acid;
(c) m-Nitrobenzoic acid; (d) Trifluoroacetic acid;
(e) 4-Methoxypentanoic acid; (f) α-Bromopropionic acid
(g) Isobutyric acid; (h) 2,2 Dibromoheptanoic acid;
(i) Formic acid; (j) 3-Benzyl-7-cyclopropyl-heptanoic acid.

<u>Solution</u>: The simple carboxylic acids up to five carbons are frequently referred to by their common names as shown below:

$H-COOH$	Formic acid
$CH_3\,COOH$	Acetic acid
CH_3CH_2-COOH	Propionic acid
$CH_3CH_2CH_2-COOH$	Butyric acid
$(CH_3)_2CH-COOH$	Isobutyric acid
$CH_3CH_2CH_2CH_2\,COOH$	Valeric acid

The positions on the chain adjacent to the carboxyl group are specified by Greek letters.

$$\overset{\delta}{C}-\overset{\gamma}{C}-\overset{\beta}{C}-\overset{\alpha}{C}-COOH$$

In the IUPAC system of naming carboxylic acids, the parent compound name is formed by dropping the alkane suffix "e" and adding the suffix "oic" followed by the word "acid." Since the carboxyl group always comes at the end of the chain, it is automatically assigned the number 1, and this number is omitted from the name. For example, H COOH   Methanoic acid

CH_3CH_2-COOH Propanoic acid

$CH_3CH_2CH_2CH_2CH_2CH_2-COOH$ Heptanoic acid

Substituted carboxylic acids are named in the usual way by numbering and listing the substituents as in the following example:

```
6   5   4   3   2   1
        CH3
        |
CH3CH-CH-CH-CH2COOH
   |       |
   CH3     Cl
```

The longest chain has six carbons, and the carboxyl carbon is automatically assigned the number 1. The parent compound is therefore hexanoic acid. The substituents are listed numerically to give the correct name of the compound: 3-chloro-4,5-dimethylhexanoic acid.

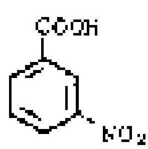
Thus, to draw the above structures, use the given rules:

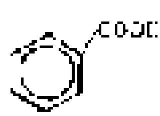
(a) Propanoic acid - one of the carboxylic acids of less than five carbons. Its structure was previously given as CH_3CH_2COOH.

(b) 2-Chlorobutanoic acid - this compound has a four carbon parent chain with the carbon of the carboxyl group being number 1 and the chlorine atom on carbon 2. Thus, its structure is

```
4     3     2   1
CH3-CH2-CH-COOH
            |
            Cl
```

(c) m-Nitrobenzoic acid - this compound has as the parent chain a benzene ring with the carboxyl group on carbon 1 and the nitro group ($-NO_2$) on carbon 3 of the benzene ring. Thus, its structure is



Note: The structure  is called benzoic acid.

(d) Trifluoroacetic acid - this compound has as the parent chain acetic acid whose structure was previously given:

CH_3-COOH

Acetic Acid

Trifluoroacetic acid has the same basic structure as acetic acid except that the hydrogens on the α carbon has been replaced by fluorine atoms. Thus, its structure is:

F_3C-COOH

(e) 4-Methoxypentanoic acid - this compound is both an acid and ether with the methoxy group (CH_3O-) on the fourth carbon of the straight five carbon parent chain. Thus, its structure is

```
5    4    3     2     1
CH3-CH-CH2-CH2-COOH
     |
     OCH3
```

(f) β-Bromopropionic acid - this compound has as its parent chain propionic acid with a bromine atom on the β position. Thus, its structure is:

```
β     α
CH3—CH—COOH
      |
      Br
```

(g) Isobutyric acid - one of the carboxylic acids of less than five carbons. Its structure, given previously, is

```
CH3
   \
    CH-COOH
   /
CH3
```

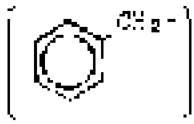
(h) 2,2-Dibromoheptanoic acid - this compound has a seven carbon parent chain with the carbon of the carboxyl group being number 1 and two bromine atoms on carbon 2. Thus, its structure is

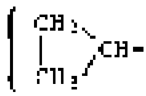
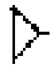
```
                              Br
                              |
CH3-CH2-CH2-CH2-CH2-C-COOH
                              |
                              Br
```

(i) Formic acid - one of the carboxylic acids of less than five carbons. Its structure, given previously, is

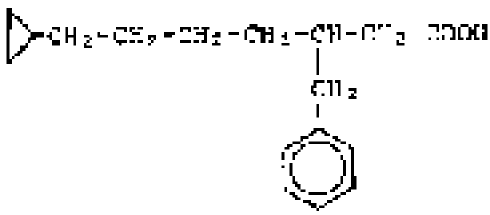
H-COOH

(j) 3-Benzyl-7-cyclopropyl-heptanoic acid - this compound has a seven carbon parent chain with a benzyl group

 on carbon 3, and a cyclopropyl group

 or represented as  on carbon 7. Thus,

the structure is



PROBLEM 20-4

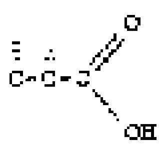
Draw structures for the following compounds.

(a) α-aminopropionic acid (alanine)

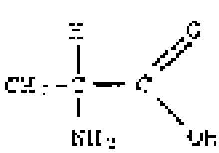
(b) vinylacetic acid

(c) para-methoxybenzoic acid

Solution: (a) Propionic acid consists of three carbons, arranged in the following way:



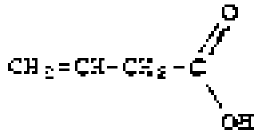
Since the only substitution is an amino ($-NH_2$) group at the α position, the complete structure is:



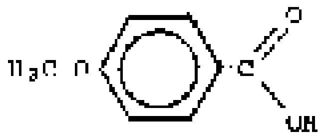
. The common name for this structure is alanine, one of the 20 common amino acids.

(b) Acetic acid has the following structure:

. The vinyl ($CH_2=CH-$) group can only be subsituated at the methyl carbon. Thus, the structure is



(c) Benzoic acid is a derivative of benzene, with a carboxyl group replacing a hydrogen. Since the carboxyl group is the dominant functional group, the carbon to which it is attached is the number one carbon. The para position is at the number 4 carbon. Thus, the structure for para-methoxybenzoic acid is as follows:



CHEMICAL AND PHYSICAL PROPERTIES

• PROBLEM 20-5

(a) How many equivalents of base would be neutralized by one mole of phthalic acid? What is the neutralization equivalent of phthalic acid? (b) What is the relation between neutralization equivalent and the number of acidic hydrogens per molecule of acid? (c) What is the neutralization equivalent of 1,3,5-benzenetricarboxylic acid? Of mellitic acid, $C_6(COOH)_6$?

__Solution:__ (a) Phthalic acid has the structure

. It is a dicarboxylic acid. Hence, for complete neutralization (the conversion by aqueous hydroxides of carboxylic acids into their salts) it will require two equivalents of base, one for each of the COOH groups. For example,

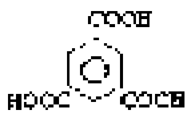
A useful way to identify and prove the structure of acids is by neutralization equivalent: the equivalent weight of the acid as determined by titration with standard base. Since phthalic acid takes two equivalents of base to be neutralized, its equivalent weight must be one half of its molecular weight (166). Therefore, neutralization equivalent

$$= \frac{\text{molecular weight}}{2} = \frac{166}{2} = 83.$$

(b) It can be seen in (a) that the neutralization equivalent was obtained by dividing the molecular weight of the acid by the equivalents of base required for neutralization. The equivalents of base reflect, however, the number of acidic hydrogens (or COOH's) per molecule. Consequently,

$$\text{neutralization equivalent} = \frac{\text{molecular weight}}{\text{number of acidic H per molecule}}$$

(c) The structures of 1,3,5-benzenetricarboxylic acid and mellitic acid, are respectively,



and

The structures indicate that 1,3,5-benzenetricarboxylic acid has 3 acid hydrogens, whereas mellitic acid possesses 6 acid hydrogens. Therefore, the neutralization equivalents must be, respectively, $\frac{210}{3} = 70$ and $\frac{342}{6} = 57$.

• PROBLEM 20-6

Calculate the pH of a solution whose hydrogen ion concentration is 2.7×10^{-6} M.

Solution: The pH of a solution is the negative of the logarithm of the concentration of hydrogen ion in that solution. (In general, pX stands for the inverse logarithm of X.) Thus, the pH of the solution is:

$$pH = -\log [H^+] = \log \frac{1}{[H^+]}$$

$$= -\log (2.7 \times 10^{-6})$$

$$= -\log 2.7 \quad (-\log 10^{-6})$$

$$= -0.43 + 6 = 5.57$$

pH of the solution is 5.57.

• PROBLEM 20-7

The pK_a of aspartic acid is 3.8. What is the aspartic acid concentration of a 1M aspartic acid solution maintained at pH 2.8? What is the aspartate ion concentration if the pH is raised to 3.8?

Solution: Carboxylic acid, in the form of amino acid, is important in biological functions. One of these functions is enzyme catalysis. In catalysis, the carboxyl group can participate in hydrogen bonds to hold the substrate in place. It can also participate in acid-base reactions which are often used by enzymes in catalytic reactions.

Aspartic acid is an amino acid. One of the physical properties of an amino acid is its pK_a, the negative of the logarithm of the acid dissociation constant. The pK_a of an acid also gives the pH, the negative of the logarithm of the hydrogen ion concentration in solution, at which half the acid is dissociated. Thus, at pH 2.8, which is the pK_a of aspartic acid, half the acid is dissociated. Since the starting material has 1M of aspartic acid, at pK_a there is only 0.5 M of undissociated aspartic acid left.

If the pH of the solution is raised to 3.8, one pH unit increase, 90% of the aspartic acid would have been dissociated to form aspartate ions. This can be shown by using an acid-base equilibrium equation, Henderson-Hasselbach equation.

An acid, HA, in equilibrium with its conjugate base in solution can be described by the following equation:

$$HA \rightleftarrows A^- + H^+,$$

where A^- is the conjugate base of acid HA. Since this is an acid dissociation reaction, the equilibrium constant is the same as the acid dissociation constant, $K_{eq} = K_a$. At equilibrium, the above reaction can be represented as

$$K_{eq} = K_a = \frac{[A^-][H^+]}{[HA]}$$

Taking the logarithms of both sides and rearranging,

$$\log K_a = \log \frac{[A^-][H^+]}{[HA]}$$

$$\log K_a = \log \frac{[A^-]}{[HA]} + \log [H^+]$$

$$-\log [H^+] = -\log K_a + \log \frac{[A^-]}{[HA]}$$

Since $pH = -\log [H^+]$ and $pK_a = -\log K_a$, the final equation is in the following form:

$$pH = pK_a + \log \frac{[Base]}{[Acid]}$$

This is the Henderson-Hasselbach equation.

To find the concentration of aspartate ions, the conjugate base of the given reaction, one has to substitute in the known values and manipulate the Henderson-Hasselbach equation. Thus,

Let α = mole fraction of base, aspartate ion

and $1-\alpha$ = mole fraction of acid, aspartic acid

$$pH = 3.8 \qquad ; \qquad pK_a = 2.8$$

$$pH = pK_a + \log \frac{\alpha}{1-\alpha}$$

$$3.8 = 2.8 + \log \frac{\alpha}{1-\alpha}$$

$$1 = \log \frac{\alpha}{1-\alpha}$$

$$10 = \frac{\alpha}{1-\alpha}$$

$$10 - 10\alpha = \alpha$$

$$10 = 11\alpha$$

$$\alpha = \frac{10}{11} \approx 90\%$$

Since the mole fraction of the base, aspartate ion, is 0.9 at pH 3.8 and the starting solution has 1 M aspartic acid, the aspartate ion concentration is 0.9 M.

• PROBLEM 20-8

At 110° and 454 mm pressure, 0.11 g acetic acid vapor occupies 63.7 cc; at 156° and 458 mm, 0.081 g occupies 66.4 cc. Calculate the molecular weight of acetic acid in the vapor phase at each temperature. How do you interpret these results?

Solution: The molecular weight of the acetic acid vapor can be calculated by a determination of the volume the gas would occupy at STP (Standard Temperature (0°C or 273°K) and Pressure (760 mm)). It is known that a mole of vapor (gas) will occupy 22.4 liters or 22,400 cc at STP. Consequently, by comparing the volume occupied by the acetic acid vapor with 22.4 l, the number of moles gas present will be known. From the number of moles of gas present and the mass given in grams, the molecular weight is readily found.

To figure out the volume of acetic acid vapor with mass .11 g at STP, employ the combined gas law which states that for a given mass, the volume is inversely proportional to pressure and directly proportional to the absolute temperature. The law may be written as

$$\frac{P_1V_1}{T_1} = \frac{P_2V_2}{T_2}$$, where P is pressure, V is volume and T is absolute temperature (Celsius plus 273°). The problem indicates that the vapor occupies 63.7 cc at 110°C and 454 mm. Let 63.7 cc = V_1, T_1 = 383°K (110 + 273), and P_1 = 454 mm. Therefore, at STP one can let P_2 = 760 mm, T_2 = 273°K (0 + 273) and V_2 = the unknown. Substituting these values into the combined gas law yields

$$\frac{(454 \text{ mm})(63.7 \text{ cc})}{(383° \text{ K})} = \frac{(760 \text{ mm})(V_2)}{(273° \text{ K})}$$

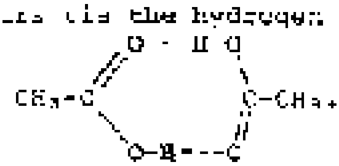
Rewriting and solving, V_2 = volume at STP =

$$63.7 \text{ cc} \times \frac{273}{383} \times \frac{454}{760} = 27.12 \text{ cc}.$$

So, .11 g of acetic acid vapor will occupy 27.12 cc at STP. Recall that if one mole of gas were present, it would occupy 22,400 cc. Hence, the .11 g constitutes only 27.12/22400 = .0012 moles. But a mole is defined as grams/molecular weight. As such, by substitution, one finds molecular weight of vapor at 110°C is grams/moles = .11/.0012 = 91.6.

The same procedure is used to determine the molecular weight of the acetic acid vapor at 156°C. If the calculation is performed, one finds the molecular weight has changed to 71.

These results can be interpreted by noting that the acetic acid monomer has a molecular weight of 60. Consequently, the molecular weights measured must be of acetic acid monomers associated with each other in some fashion. This association occurs via the hydrogen bonds that can be formed. For example,



Association occurs even in the vapor phase, decreasing as the temperature increases (which accounts for the lower molecular weight at 156°C).

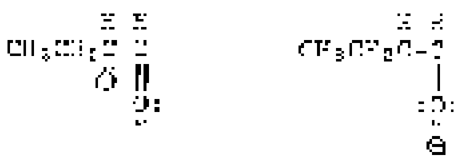
◆ PROBLEM 20 D

How do you account for the fact that the α hydrogens of an aldehyde (say, n-butyraldehyde) are much more acidic than any other hydrogens in the molecule?

γ β α H
$CH_3CH_2CH_2C=O$

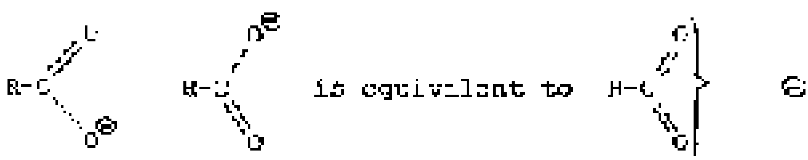
n-Butyraldehyde

Solution: The acidity of the α-hydrogens may be accounted for by the resulting resonance stability of the anion. The carbonyl group affects the acidity of the α-hydrogens by helping to accommodate the negative charge of the anion. Ionization of the α-hydrogen yields a carbanion that is a resonance hybrid of two structures:



These structures are equivalent to the carbanion

Notice how the accommodation of this negative charge is similar in nature to the resonance of the carboxylate ion, which accounts for the acidity of the COOH group:



• PROBLEM 20-10

For each of the following pairs tell which acid is the stronger and why:

(a)	CH_3–COOH	or	H–COOH
(b)	CH_3–COOH	or	Cl–CH_2–COOH
(c)	F–CH_2–COOH	or	Br–CH_2–COOH
(d)	Cl–CH_2–CH_2–COOH	or	CH_3–CHCl–COOH
(e)	C_6H_5–OH	or	CH_3–CH_2–OH
(f)	CH_3–OH	or	CH_3–CH_2–COOH

Solution: Carboxylic acids are acidic in aqueous solutions. The ionization of carboxylic acids proceeds according to the following reaction:

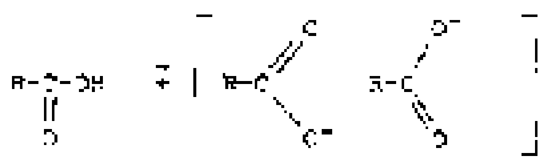
$$R-\underset{\underset{O}{\|}}{C}-O-H \rightleftharpoons R-\underset{\underset{O}{\|}}{C}-O^- + H^+$$

or

$$R-\underset{\underset{O}{\|}}{C}-O-H + H_2O \rightleftharpoons R-\underset{\underset{O}{\|}}{C}-O^- + H_3O^+$$

In general, the equilibrium for this ionization lies to the side of the unionized acid. In fact, the equilibrium constant for most carboxylic acids (called K_a) is approximately 10^{-5}. (K_a is a measure of how strong an acid is.)

The ionization of a carboxylic acid gives a carboxylate anion $R-COO^-$, and this structure is capable of resonance delocalization of charge. That is, there exists contributing resonance structures for the carboxylate anion; the anion is a resonance hybrid of two structures (below), which, being of equal stability, contribute equally.



equivalent to

The resonance delocalization adds to the stability of the carboxylate anion.

A substituent on a carboxylic acid may also assist in stabilizing the carboxylate anion. For example, a carbon-chlorine bond is a polar bond because chlorine is more electronegative than carbon $\left[-\overset{|}{\underset{|}{C}}{}^{\delta+}-Cl^{\delta-}\right]$. When a chlorine substituent is present on a carboxylic acid, the carboxylate ion that results from ionization is further stabilized by the slight positive charge on carbon due to the chlorine.

$$\overset{\delta-}{Cl}-\overset{\delta+}{CH_2}-COOH \rightleftharpoons \overset{\delta-}{Cl}-\overline{\overset{\delta+}{CH_2}-COO^{\ominus}} + H^{\oplus}$$

The added stability of the chlorine substituted carboxylate ions is reflected in the greater acidity of the corresponding chlorine-substituted carboxylic acids. For example, chloroacetic acid is a stronger acid than acetic acid; dichloroacetic acid is even stronger, and trichloroacetic acid is stronger still.

If the electronegative substituent is further down the chain, its stabilizing influence is diminished.

Alkyl groups are more electropositive than hydrogen. Consequently, alkyl substituents decrease the stability of the carboxylate ion relative to hydrogen. Since electropositive substituents donate or release electrons, they decrease the stability of the carboxylate anion.

Substituents that withdraw electrons (such as chlorine) increase the stability of the carboxylate ion.

Thus, (a) HCOOH is a stronger acid than CH_3-COOH

(b) Cl-CH_2-COOH > CH_3-COOH

(c) F-CH_2-COOH > Br-CH_2-COOH

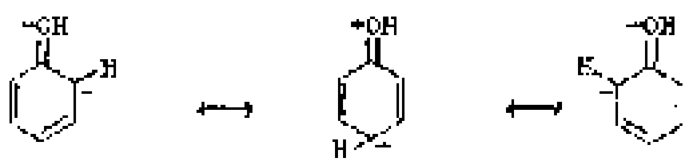
(d) CH_3-CHCl-COOH > Cl-CH_2-CH_2-COOH

(e) C_6H_5-OH > C_2H_5-OH

(f) CH_3-CH_2-COOH > CH_3-OH

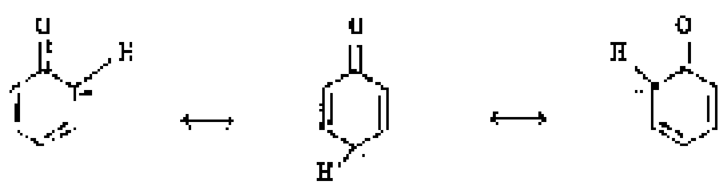
Note: In (c), F is more electronegative than Br, so that the carboxylate anion should be more stable.

In (e), the greater acidity of the phenol (C_6H_5OH) is due to the greater resonance stability of the phenoxide ion as compared to the phenol:



etc.

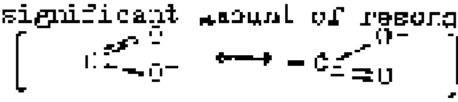
Phenol



etc.

Phenoxide ion

Since energy is required to separate charges, the resonance stability of the phenoxide ion is greater than that of the phenol. There is no corresponding increase in resonance stability for the alkyl alcohol, C_2H_5OH, upon ionization to form the alkoxide ion, $C_2H_5O^-$.

In (f), the carboxylic acid is more acidic than the alcohol because of a significant amount of resonance in the carboxylate anion: 

• PROBLEM 20-11

4-Bromobicyclo[2,2,2]octane-1-carboxylic acid is more acidic than 5-bromopentanoic acid. Explain this observation by considering the transmission of the electrical effect of the C-Br dipole.

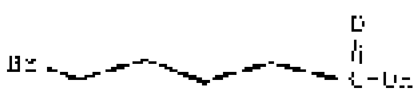
Solution:

According to the Lowry-Brønsted definition, acidity depends on the molecule's tendency to give up a proton. This, in turn, is dependent on the atom to which the proton is attached, and the surrounding electronic environment. Thus, to determine which of the two compounds are more acidic, one has to consider the whole molecular structure with all the electrical relationships between atoms.

4-Bromobicyclo[2,2,2]octane-1-carboxylic acid is a cyclic hydrocarbon with a bromine and a carboxyl substitution. It has the following structure:

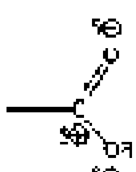
The acidity of this compound is influenced by two groups, the carboxyl oxygens and the bromine: both are more electron withdrawing than the hydrocarbon portion.

5-Bromopentanoic acid is a linear hydrocarbon, also with bromine and carboxyl substitutions. It has the following structure:



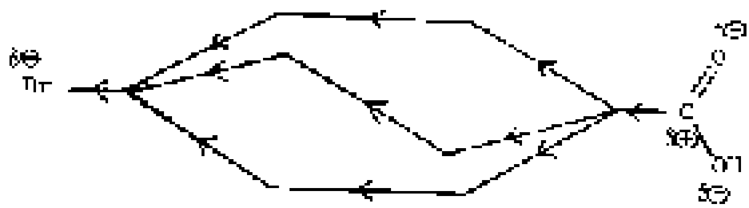
The acidity of this compound is also influenced by bromine and carboxyl oxygens. Thus, the difference in acidities between them must be due to the quantity of electrical effects.

In 5-bromopentanoic acid, the bromine is four carbon atoms away from the carboxyl carbon, which has a partial positive charge, induced by the more electronegative (electron-attracting) oxygens,

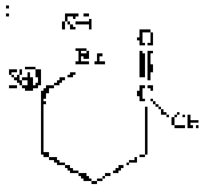
 . Since bromine is more electrone-

attracting than carbon, there is an induced electron flow from carbons to bromine, making the carboxyl carbon even more positive.

In 4-bromobicyclo[2,2,2]octane-1-carboxylic acid, the bromine is also four carbons away from the carboxyl carbon, but there are three paths going from the carboxyl carbon to the bromine. Thus, the inductive electron-withdrawing influence of bromine is amplified. This causes the carboxyl carbon to be more positive than the 5-bromopentanoic acid carboxyl carbon, facilitating the dissociation of the proton. The following is the electrical-effect structure of 4-bromobicyclo[2.2.2]octane-1-carboxylic acid. the arrows indicate the direction of electron flow.



The 5-bromopentanoic acid allows rotation about the C C bonds which permits the molecule to assume the following conformation:



In this conformation, the negative dipole (bromine) is close to the carboxyl oxygens. The resultant electron repulsion renders the oxygen less δ−. Thus, the acid proton is held tighter. This electro-static effect is called the "field effect."

From the field effect and the inductive electron-withdrawing effect, one can understand the observed phenomenon of the greater acidity of 4-bromobicyclo[2,2,2]-octane-1-carboxylic acid.

• PROBLEM 20-12

Use appropriate stabilization energies to show why the enol form of acetyl bromide is likely to be more stable relative to acetyl bromide than 1,1-dihydroxyethylene is relative to acetic acid.

Solution: This problem can be solved by considering the meaning of stabilization energy. The meaning can be seen by comparing the heats of combustion (the heat content change accompanying the complete conversion of a mole of compound into carbon dioxide and water) of benzene and Kekulé's formulation of benzene, 1,3,5-cyclohexatriene. The heat of combustion of Kekulé's cyclohexatriene to liquid water is 827 kcal/mole (from a calculation of average bond energies). The experimental heat of combustion of benzene is 789 kcal/mole, or 38 kcal/mole less than calculated for cyclohexatriene. This 38 kcal/mole is called the stabilization energy of benzene.

At this point, some assumptions must be made. Let us assume the stabilization energies (S.E.) of vinyl alcohol, 1,1-enediol, acyl bromides, and acetic acid are 3 kcal, 6 kcal, 0 kcal, and 18 kcal, respectively. Hence

$$CH_3\overset{\overset{O}{\|}}{C}-Br \rightleftarrows CH_2 = \overset{\overset{OH}{|}}{C} - Br \qquad \text{and}$$

$$\text{S.E.} \sim 3 \text{ kcal}$$

$$CH_3-\overset{\overset{O}{\|}}{C}-OH \rightleftarrows CH_2 = \overset{\overset{OH}{|}}{C} - OH$$

$$\text{S.E.} \sim 18 \text{ kcal} \qquad \text{S.E.} \sim 6\text{kcal.}$$

This indicates enolization of acetyl bromide is more favorable than enolization of acetic acid. Why? The difference in S.E. for acetyl bromide is only 3 kcal, whereas for acetic acid it is 18 − 6 = 12 kcal. Overall, then, the enolization of acetyl bromide is favored by 12 − 3 = 9 kcal over that of acetic acid.

PREPARATION

• PROBLEM 20-13

Starting with ethylene oxide and methyl iodide as the only organic materials, suggest a synthesis of alanine, $CH_3CH(NH_2)CO_2H$, an important amino acid.

Solution: Alanine contains three carbons in its skeleton, so that the starting materials, ethylene oxide $\left(\underset{\diagdown O \diagup}{CH_2 - CH_2}\right)$ and methyl iodide (CH_3I), must unite in some fashion to obtain the correct carbon skeleton.

Now, the reaction of Grignard reagents with ethylene oxide is an important method of preparing primary alcohols. The product contains two carbons more than the alkyl or aryl group of the Grignard reagent. The reaction may be viewed as follows:

$$\underset{\text{(Grignard reagent)}}{R-MgX} + \underset{\diagdown\, O\, \diagup}{CH_2 - CH_2} \rightarrow RCH_2CH_2O^-MgX^+ \xrightarrow{H} RCH_2CH_2OH.$$

The nucleophilic alkyl or aryl group of the Grignard reagent attaches itself to the relatively positive carbon and the electrophilic magnesium attaches itself to the relatively negative oxygen. Here, the Grignard reagent to be used is methylmagnesiumiodide, which can be prepared by reacting Mg with methyl iodide in ether: $CH_3-I + Mg \xrightarrow{\text{ether}} CH_3MgI$.

At this point, the ethylene oxide is added (with subsequent hydrolysis) to obtain n-propyl alcohol:

$$\underset{\diagdown\, O\, \diagup}{CH_2 - CH_2} \xrightarrow{CH_3MgI} \xrightarrow{HOH} CH_3CH_2CH_2OH.$$

This primary alcohol may be oxidized using either $KMnO_4$ or $K_2Cr_2O_7$ to the carboxylic acid of the same carbon skeleton. If this reaction is performed, propionic acid results: $CH_3CH_2CH_2OH \xrightarrow{KMnO_4 \text{ or } K_2Cr_2O_7} CH_3CH_2COOH$

At this point, only an amine (NH_2) group need be added, alpha to the carboxyl group to obtain alanine. To do this, first add a halogen, either Br or Cl, to the alpha position. This can be accomplished using the Hell-Volhard-Zelinsky reaction. This reaction results in α-halo acids. The carboxylic acid is reacted with a halogen (bromine or chlorine) in the presence of catalytic amounts of phosphorus trihalide. Hence,

$$CH_3CH_2COOH \xrightarrow{Cl_2/PCl_3} \xrightarrow{H_3O^+} \underset{\displaystyle Cl}{CH_3\overset{}{C}HCOOH}$$

Finally, ammonia (NH_3) is added to the α-halo acid to obtain amino acid.

$$\underset{\displaystyle Cl}{CH_3CHCOOH} \xrightarrow{NH_3} \xrightarrow{H_3O^+} \underset{\text{(alanine)}}{\underset{\displaystyle NH_2}{CH_3CHCOOH}}$$

• PROBLEM 30-11

In the presence of peroxides, carboxylic acids (or esters) react with 1-alkenes to yield more complicated acids. For example:

$$\underset{\text{1-Hexene}}{n\text{-}C_4H_9CH{=}CH_2} + \underset{\text{n-Butyric acid}}{CH_3CH_2CH_2COOH} \xrightarrow{\text{peroxides}} \underset{\text{2-Ethyloctanoic acid (70\% yield)}}{\underset{\displaystyle C_2H_5}{n\text{-}C_4H_9CH_2CH_2CHCOOH}}$$

(a) Outline all steps in a likely mechanism for this reaction. Predict the products of similar reactions between: (b) 1-octene and propionic acid; (c) 1-decene and isobutyric acid; and (d) 1-octene and ethyl malonate, $CH_2(COOC_2H_5)_2$.

Solution: (a) This problem can be solved by a consideration of the mechanism of free radical addition. The decomposition of peroxides to yield free radicals is a well known reaction. The free radical generated can abstract a hydrogen from, for example, hydrogen bromide as in the mechanism of peroxide initiated addition in anti Markovnikov fashion. Here, the free radical produced abstracts a hydrogen in the alpha position of butyric acid. The loss of the α-hydrogen from butyric acid generates another radical which can add to the double bond of the alkene, 1-hexene. This reaction, in turn, produces another radical which can abstract another α-hydrogen from a different n-butyric acid molecule to produce 2-ethyloctanoic acid and still another radical, which just starts the process over again. Consequently, one sees that the generation of the first radical from peroxide is a chain initiating step, whereas the desired product is produced in chain-propagating steps. Note the similarity to the mechanism of halogenation. Overall, the mechanism may be written as follows:

Chain initiating steps:

(1) $\text{Peroxide} \rightarrow \text{Radical } (Rad\cdot)$

(2) $Rad\cdot + CH_3CH_2CH_2COOH \rightarrow Rad\,H + CH_3CH_2\dot{C}HCOOH$

(3) $n\text{-}BuCH{=}CH_2 + CH_3CH_2\dot{C}HCOOH \rightarrow n\text{-}Bu\dot{C}H{-}CH_2{-}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}{-}COOH$

(4) $n\text{-}Bu\dot{C}HCH_2\underset{\displaystyle C_2H_5}{\underset{|}{CH}}COOH + CH_3CH_2CH_2COOH \rightarrow n\text{-}BuCH_2CH_2\underset{\displaystyle C_2H_5}{\underset{|}{CH}}COOH$ (2-ethyl octanoic acid) $+ CH_3CH_2\dot{C}HCOOH$

Steps (3) and (4) are chain-propagating ones.

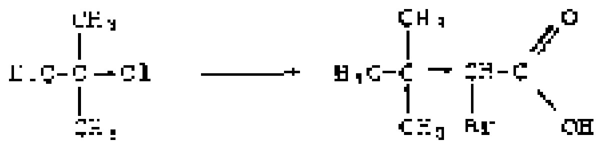
The solution of (b) - (d) is obtained by substituting the appropriate alkene and carboxylic acids (or esters) in the mechanism above and following it through to the product. The following results are obtained:

(b) 2-methyldecanoic acid

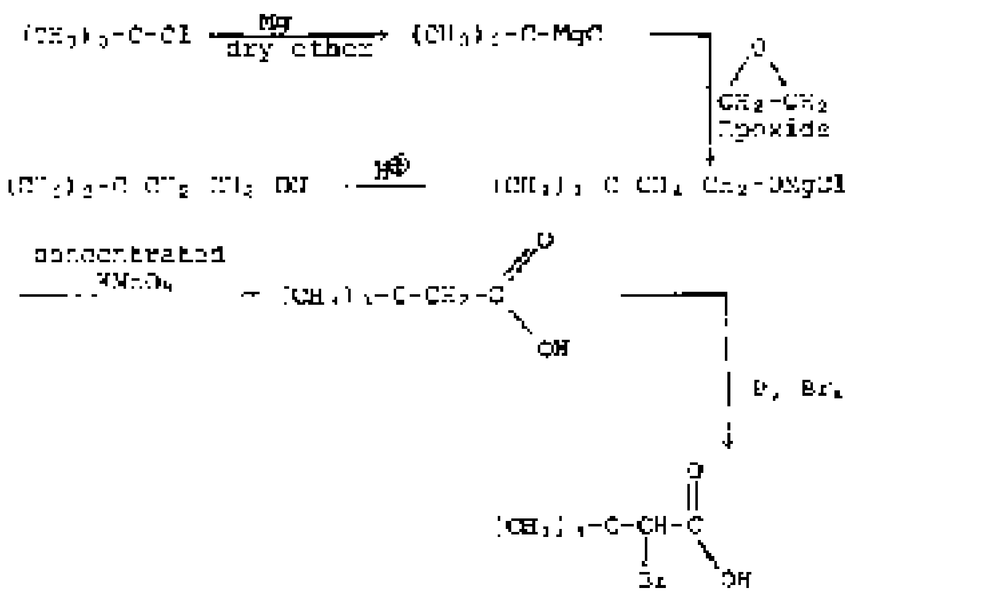
(c) 2,2-dimethyldodecanoic acid

(d) ethyl n-octylmalonate [$n\text{-}C_8H_{17}CH(COOEt)_2$]

Write an equation, with reasonable mechanisms proposed for the appropriate steps, for the synthesis of α-bromo-α-t-butylacetic acid from t-butyl chloride.



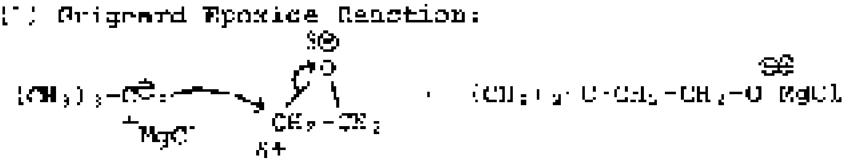
Solution: The synthesis involves an addition of two carbons to an alkyl halide. This can be accomplished by Grignard reaction with epoxide (ethylene oxide). The resulting compound can be oxidized and then brominated to give the final product. The synthesis equation is as follows:



α-bromo α t-butylacetic acid

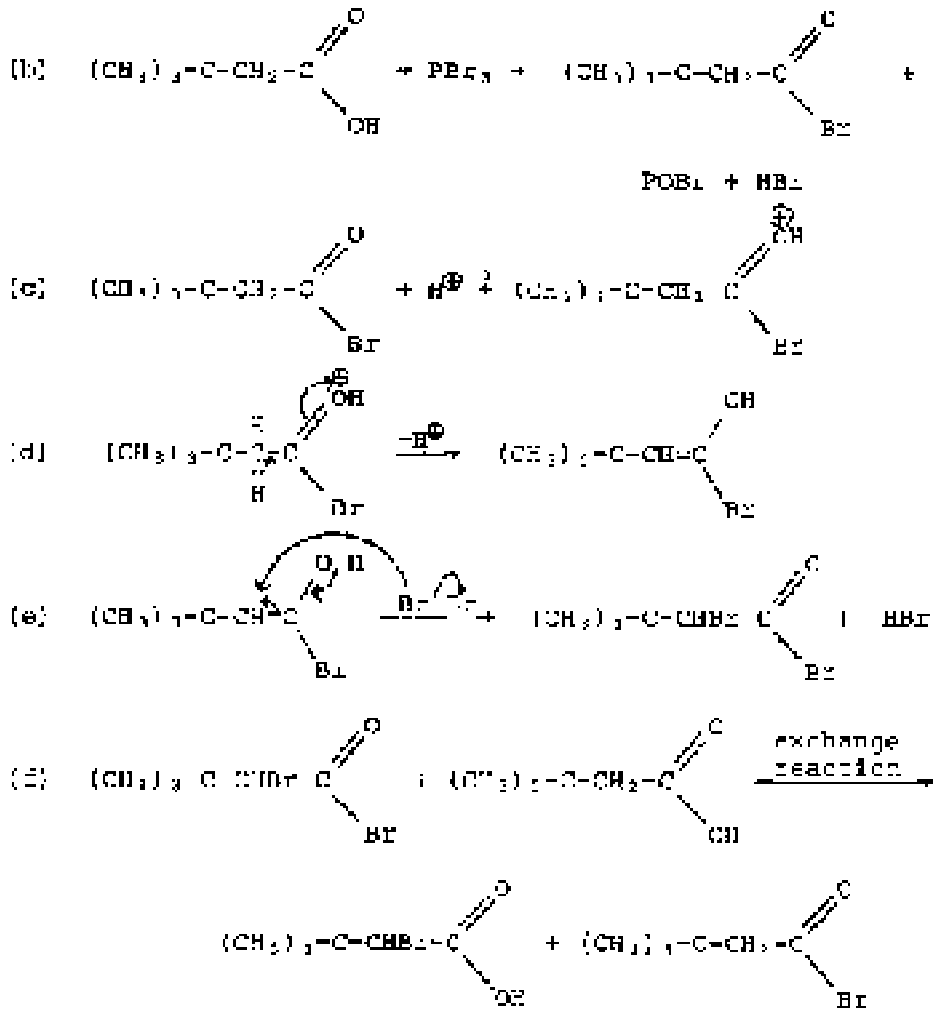
The mechanisms for the Grignard epoxide reaction, and the α-carbon bromination of the carboxylic acid (an example of the Hell-Volhard-Zelinsky reaction) are illustrated below.

(1) Grignard Epoxide Reaction:



(2) α-Carbon Bromination of Carboxylic Acid:

(a) $2P + 3Br_2 \rightarrow 2PBr_3$



[This can go to step (c)]

Note: The Hell-Volhard-Zelinsky reaction works equally well with phosphorus and Cl_2.

• PROBLEM 20-16

Predict the products of the following reactions:

(A) $CH_3CH_2CH_2Br + KCN \to ? \xrightarrow[H^+]{HOH} ?$

(B) $CH_3CH_2CH_2CH_2Br + Mg \xrightarrow[\text{ether}]{\text{anhydrous}} ? \xrightarrow[2.\ HOH]{1.\ CO_2} + ?$

Solution: The reaction sequence of (A) illustrates a method of synthesizing a carboxylic acid which contains one more carbon atom than the initial alkyl halide. The preparation involves 2 steps. In the first step, the alkyl halide $CH_3CH_2CH_2Br$ is converted to its corresponding nitrile in a simple nucleophilic substitution reaction as shown:

$$\underset{}{CH_3CH_2CH_2Br} \quad + \quad KCN \rightarrow \underset{\text{n-propyl cyanide}}{CH_3CH_2CH_2CN} \quad + \quad KBr$$

The cyanide (or nitrile) formed is hydrolyzed to the carboxylic acid in the second step with the aid of a strong acid or base, which acts as a catalyst. It can be illustrated as shown:

$$CH_3CH_2CH_2CN \xrightarrow[H^+]{HOH} \underset{\text{(Butanoic acid)}}{CH_3CH_2CH_2C(=O)-OH} + NH_3$$

In (B), the preparation of carboxylic acid is shown via a Grignard synthesis. The Grignard reagent is first made with the addition of Mg in anhydrous ether to the alkyl halide:

$$CH_3CH_2CH_2CH_2Br + Mg \xrightarrow[\text{Ether}]{\text{Dry}} \underset{\text{(Grignard reagent)}}{CH_3CH_2CH_2CH_2MgBr}$$

The Grignard reagent formed is then reacted with CO_2 in the following sequence:

$$CH_3CH_2CH_2CH_2MgBr \quad + \quad CO_2 \rightarrow CH_3CH_2CH_2CH_2C(=O)-OMgBr$$

Upon addition of dilute acid, the organic acid is liberated by hydrolysis as indicated:

$$CH_3CH_2CH_2CH_2C(=O)-OMgBr \xrightarrow{H^+} \underset{\text{pentanoic acid}}{CH_3CH_2CH_2CH_2C(=O)-OH}$$

• PROBLEM 20-17

Synthesize butyric acid from any organic compound, using inorganic reagents.

Solution: There are numerous ways of synthesizing carboxylic acids. One can oxidize a primary alcohol, or use a Grignard reagent with carbon dioxide. Here, the synthesis of butyric acid will be done by the latter method.

Butyric acid is a four-carbon carboxylic acid ($CH_3CH_2CH_2COOH$). To synthesize this compound, one can begin with propene and add hydrogen bromide in the presence of peroxides to produce 1-bromopropane. 1-bromopropane can react with magnesium in presence of dry ethyl ether to form a Grignard reagent. This Grignard reagent can react with carbon dioxide in acid to form the butyric acid.

The following is the synthesis in equation form:

$$CH_3CH{=}CH_2 \xrightarrow[\text{peroxide}]{HBr} CH_3CH_2CH_2Br \xrightarrow[\text{dry ether}]{Mg} CH_3CH_2CH_2MgBr$$

$$CH_3CH_2CH_2MgBr + CO_2 \longrightarrow CH_3CH_2CH_2COOMgBr \xrightarrow{HBr} CH_3CH_2CH_2COOH + MgBr_2$$

Butyric acid

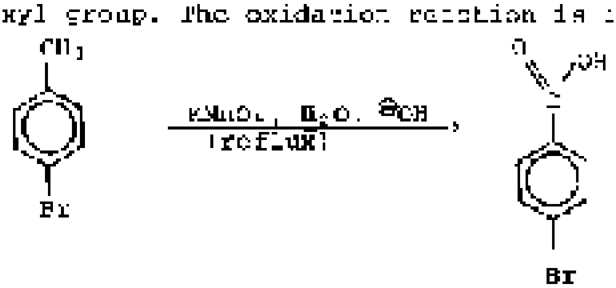
● **PROBLEM** 20-18

What carboxylic acid can be prepared from p-bromotoluene: (a) by direct oxidation? (b) by free-radical chlorination followed by the nitrile synthesis?

Solution: Carboxylic acids can be prepared by a variety of ways. One can employ direct oxidation with potassium permanganate, $KMnO_4$, or potassium dichromate, $K_2Cr_2O_7$, on primary alcohols and aldehydes. $KMnO_4$ may also be used to oxidize alkyl substituents on a benzene ring to the carboxyl group. Carboxylic acids can also be prepared by carbonation of Grignard reagents, and hydrolysis of nitriles.

(a) Direct Oxidation.

p-bromotoluene is an alkylbenzene. Direct oxidation of the compound will change the methyl side chain to a carboxyl group. The oxidation reaction is illustrated below.

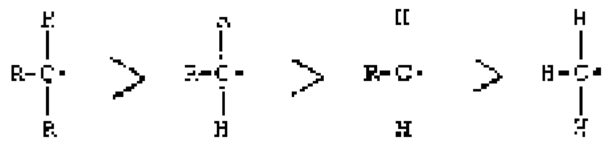


p-bromotoluene p-bromobenzoic acid

(b) Free Radical Chlorination Followed by Nitrile Synthesis:

Alkylbenzenes are susceptible to free-radical halogenation. The halogen is added to the alkyl side chain such that the most stable radical intermediate is formed.

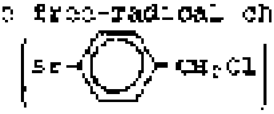
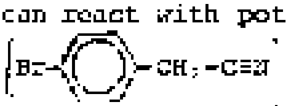
In general, a tertiary radical is more stable than a secondary radical, which is more stable than a primary radical. In equation form, the order of stability is



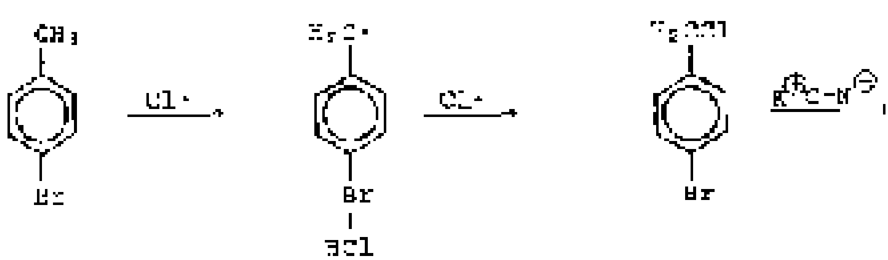
3° 2° 1°

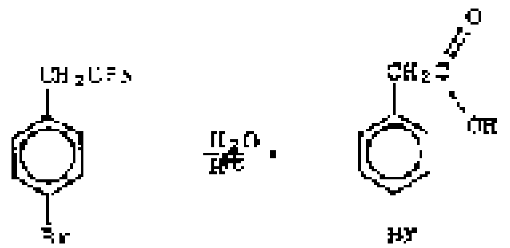
where R stands for alkyl group. In the case of alky benzene, there is extra stability in the benzyl radical (that is, the radical that results from the abstraction of a hydrogen atom attached to the carbon joined directly to an aromatic ring). The stability of the benzyl radical may be accounted for by resonance stabilization. There exist five structures that contribute to the resonance hybrid. The hybrid may be

pictured as follows: 

In this reaction, the free-radical chlorinated product is p-bromobenzyl chloride  . This compound can react with potassium cyanide to form a nitrile  . This reaction occurs because chlorine is a good leaving group, while C≡N is a strong nucleophile. The nitrile formed can be hydrolized to give the carboxylic acid. The complete reaction is illustrated below.

$$Cl{-}Cl \xrightarrow{\text{light}} 2Cl\cdot$$





+ KCl

p-bromophenylacetic acid

The carboxylic acid formed by free-radical chlorination of p bromotoluene, followed by nitrile synthesis and hydrolysis is p-bromophenylacetic acid.

• PROBLEM 20-19

Write equations to show how each of the following can be converted to benzoic acid. Include all reagents and conditions.

(a) Benzyl alcohol (b) Toluene (c) Benzaldehyde

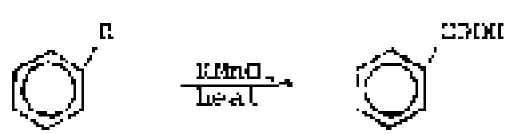
Solution: Carboxylic acids can be prepared from alcohols, ketones, and aldehydes by oxidation. Primary alcohols may be readily oxidized to carboxylic acids by chromic acid. Chromic acid, $H_2Cr_2O_7$, is a strong oxidizing agent prepared by adding sulfuric acid to sodium dichromate. It readily oxidizes primary alcohols to aldehydes, and the aldehydes are, in turn, rapidly oxidized to carboxylic acids.

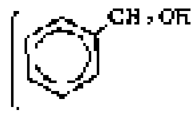
$$R-CH_2OH \xrightarrow{H_2Cr_2O_7} R-\underset{\underset{O}{\|}}{C}-H \xrightarrow{H_2Cr_2O_7} R-\underset{\underset{O}{\|}}{C}-OH$$

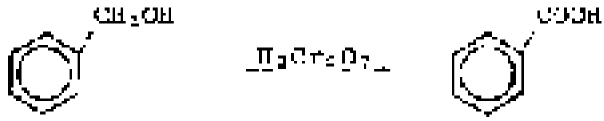
Aldehydes are very easily oxidized to carboxylic acids - even atmospheric oxygen at room temperature will gradually convert aldehydes to acids. For synthetic purposes, chromic acid is a satisfactory reagent for this reaction.

$$R-CHO \xrightarrow{H_2Cr_2O_7} R-COOH$$

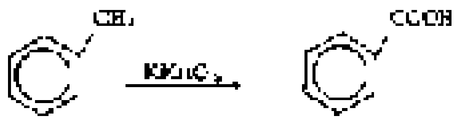
When an alkyl substituent is attached to a benzene ring, the substituent may be oxidized by treatment with hot potassium permanganate. Regardless of the length of the alkyl chain, only one carbon remains attached to the ring in the final product, and this carbon is in the form of a carboxyl group. Any other carbons that were originally present in the chain are converted to carbon dioxide.

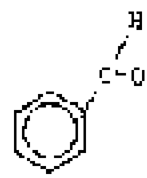


Thus, for (a) Benzyl alcohol  which is a primary alcohol, can be oxidized using $H_2Cr_2O_7$ to benzoic acid as follows:



(b) Toluene is an alkyl substituted benzene ring. It undergoes oxidation with hot $KMnO_4$ to give benzoic acid as follows:



(c) Benzaldehyde, which has the structure  undergoes oxidation with $H_2Cr_2O_7$ to give benzoic acid. Thus,

REACTIONS AT THE CARBONYL GROUP

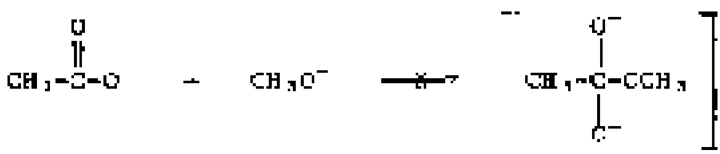
• PROBLEM 20 20

Describe and give examples of base catalyzed nucleophilic addition reactions occurring at the carboxyl carbon.

Solution: Base catalyzed nucleophilic additions with carboxylic acids are rare. Consider the reaction of acetic acid with sodium methoxide. Since the methoxide ion is a strong base and acetic acid is a moderate acid, the acid-base equilibrium lies to the right and is established very rapidly.

$$CH_3-\overset{\overset{O}{\|}}{C}-OH + CH_3O^- \rightleftarrows CH_3-\overset{\overset{O}{\|}}{C}-O^- + CH_3OH$$

In other words, the acetic acid is converted immediately and quantitatively into acetate ion and the methoxide into methanol. Even in the presence of excess methoxide ion no further reaction occurs, since the acetate carboxyl is less electrophilic. That is, nucleophilic addition to the carboxyl would require that two anions combine to give a dianion. Since like charges repel one another, this reaction is unlikely.



does not form

Even so, several base catalyzed nucleophilic additions of carboxylic acids are known. However, these involve special conditions.

The most common reaction of this type is the reaction of carboxylic acid with ammonia or amines to give amides. When ammonia is bubbled through butyric acid at 185°, butyramide is obtained in 85% yield. The reaction involves two stages. At room temperature, or even below, butyric acid reacts with the base, ammonia, to give the salt ammonium butyrate.

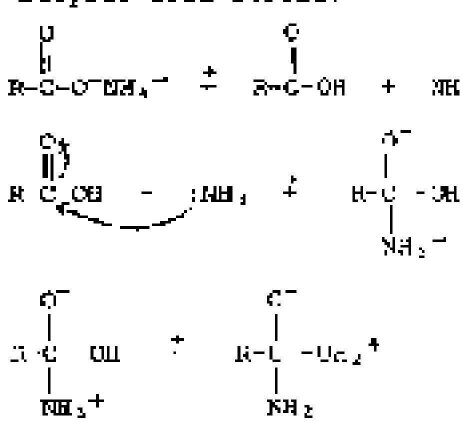
$$CH_3CH_2CH_2CO_2H \quad + \quad NH_3 \xrightarrow{25°C} CH_3CH_2CH_2CO_2^-NH_4^+$$

This salt is stable at normal temperatures. However, pyrolysis of the salt results in the elimination of water and formation of the amide.

$$CH_3CH_2CH_2CO_2^-NH_4^+ \xrightarrow{185°C} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}NH_2 \quad + \quad H_2O$$

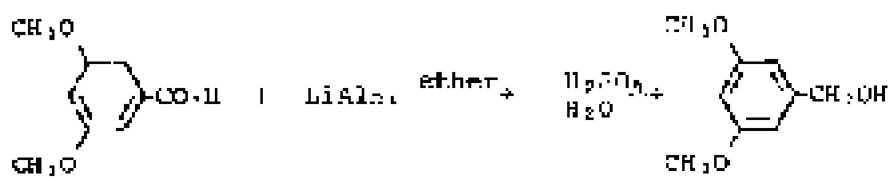
butyramide

The reaction occurs only because ammonium butyrate, being the salt of a weak acid and a weak base, is in equilibrium with a significant amount of ammonia and butyric acid. The actual dehydration step is probably the result of nucleophilic addition of ammonia to the carboxyl group of butyric acid itself.



$$\underset{NH_2}{\overset{O^-}{R-C}}-NH_3^+ \rightleftharpoons R\overset{O}{\overset{\|}{C}}NH_2 + H_2O$$

Another nucleophilic addition to the carboxylate group is in the reduction of carboxylic acids by lithium aluminum hydride.



(93%)

The first step in this reaction is an acid-base reaction, which gives the lithium salt of the acid, hydrogen gas, and aluminum hydride.

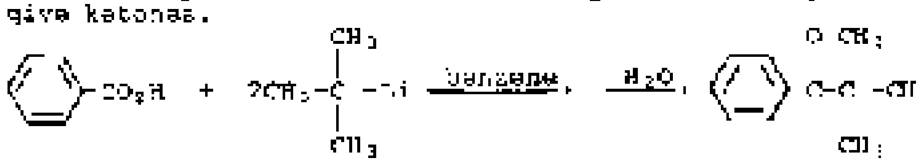
$$RCOOH + LiAlH_4 \longrightarrow RCOOLi + H_2 + AlH_3$$

The lithium carboxylate is then further reduced, eventually to the salt of the corresponding primary alcohol. Tetrahydroaluminate ion, AlH_4^-, is so reactive it reduces even a carboxylate ion:

$$RCO_2^- + AlH_4^- \longrightarrow R-\underset{H}{\overset{O^-}{C}}-O^- + AlH_3$$

The reaction is undoubtedly assisted by the Lewis acid character of aluminum salts which reduce the effective negative charge on oxygen. The remaining steps in the reduction are still more complex but also involve lithium and aluminum salts. For example, further reaction of the bis-alkoxide dianion could involve expulsion of O^{2-} as an aluminum oxide with formation of an intermediate aldehyde. The aldehyde is then rapidly reduced to the alcohol with lithium aluminum hydride.

Carboxylic acids react with alkyllithium reagents to give ketones.



(70%)

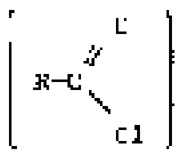
The rationale for this reaction is similar to that given earlier for the reduction of acids by $LiAlH_4$. The first step is reaction with the proton of the carboxylic acid to produce 1 mole of alkene. Alkyllithiums have such high ionic character that they react even with carboxylate ions.

• PROBLEM 20-21

In the formation of an ester, which bond of a carboxylic acid is broken, C-OH or CO-H?

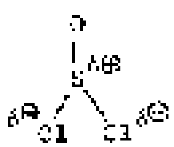
Solution: An ester is a carboxylic acid derivative. It can be formed from carboxylic acid either by heating it directly with alcohol in presence of a little mineral acid, or via the acid or acyl chloride pathway. In both reactions, the same bond of the carboxylic acid is broken. To determine whether it is the C-OH bond or the CO-H bond that is cleaved, one has to know the mechanism of the reaction. Here, ester synthesis via the acid chloride pathway is illustrated.

An acid chloride

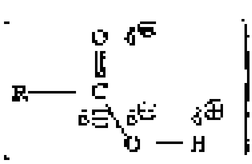


can be formed by reacting carboxylic acid with phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5), or thionyl chloride ($SOCl_2$). Thionyl chloride is used as the chlorinating reagent, here.

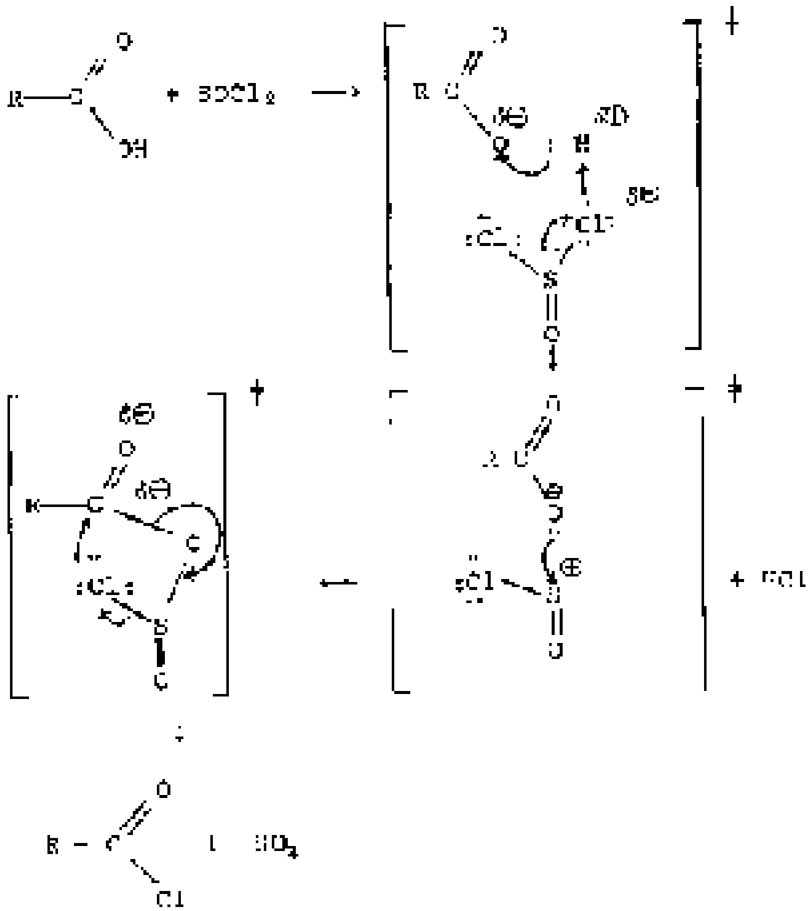
Thionyl chloride has the following structure:



The chlorines are more electronegative (electron-attracting) than the sulfur. Thus, they have negative dipoles (δ^-). The proton and the carbonyl carbon of the carboxyl group of the carboxylic acid have positive dipoles due to the electronegative oxygens

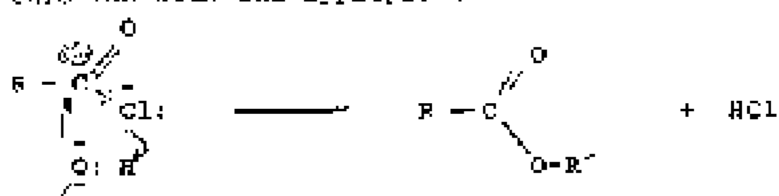


Therefore, in the presence of thionyl chloride, the acidic proton, bonded to oxygen, tends to come off and attach to the electron-rich chlorine, which is not as electronegative as oxygen. This triggers a series of reactions which lead to the formation of acid chloride. The reaction mechanisms are shown below.



acid chloride

To synthesize an ester, one can react the acid chloride with the appropriate alcohol.



ester

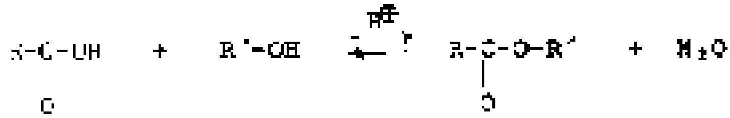
From the mechanism of the acid chloride formation, one can see that it is the C–OH bond of the carboxylic acid that is broken to form the C–Cl bond. Subsequently, the C–Cl bond is cleaved to form the C–OR' bond with the alcohol oxygen.

• PROBLEM 20-32

Explain the mechanism involved in the nucleophilic substitution reaction on carboxylic acids in esterification.

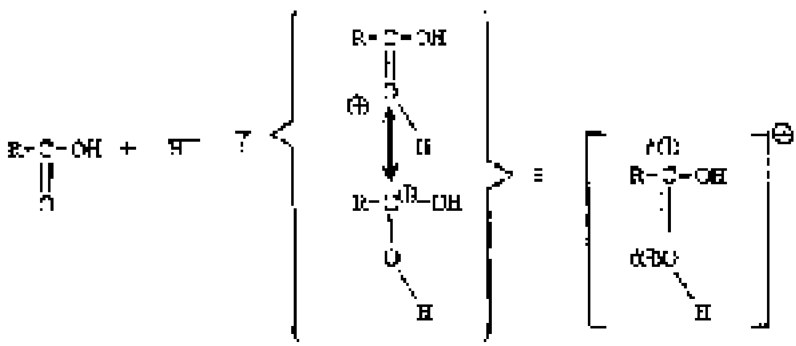
Solution:

The most important example of nucleophilic substitution on carboxylic acids is esterification, in which carboxylic acids react with alcohols to give esters.

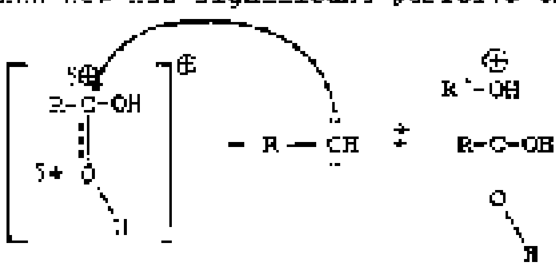


Carboxylic acid   Alcohol   Ester

The esterification reaction requires the presence of a strong acid catalyst. The first step of the reaction is the protonation of the carboxyl group at the double-bonded oxygen.

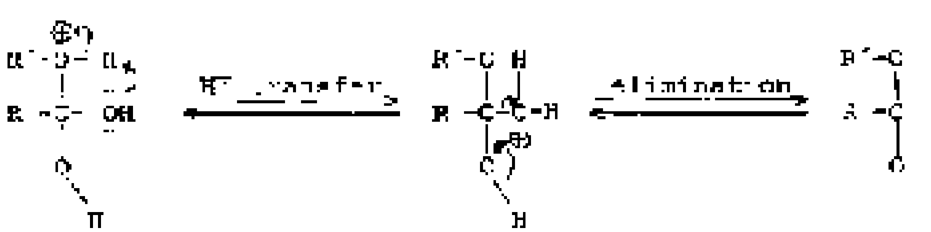


The protonated carboxyl group is readily attacked by nucleophiles (in this case R'-OH) because the carboxyl carbon now has significant positive character.



(Adduct)

The adduct formed by this attack undergoes a hydrogen ion transfer and an elimination to give the final product.

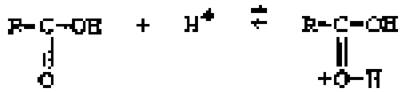


Adduct   Ester

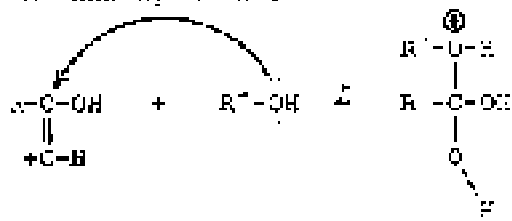
$+H_2O + H^{\oplus}$

To recapitulate, the steps of the mechanism are:

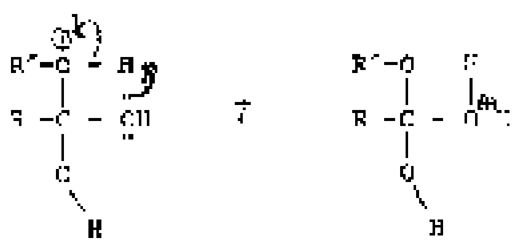
(1) Protonation of the carboxylic acid:



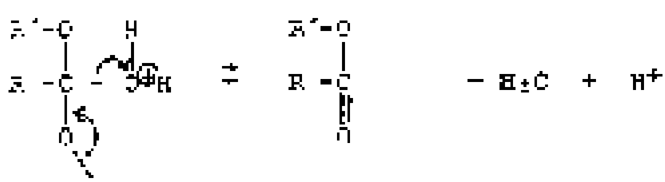
(2) Attack by R'-OH:



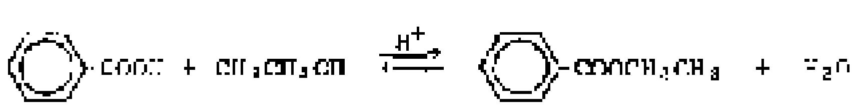
(3) Hydrogen ion transfer:



(4) Elimination of water and H^+:



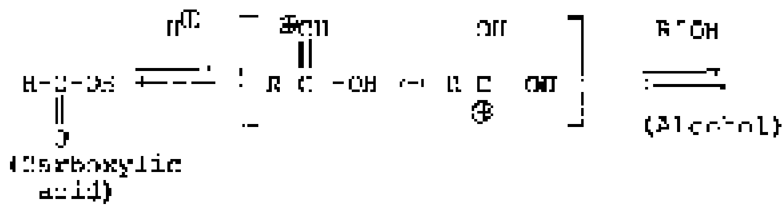
Since every step of the esterification reaction is reversible, the reaction is usually driven to completion by employing either the alcohol or the carboxylic acid in great excess. For example, benzoic acid may be almost completely converted to the corresponding ethyl ester, ethyl benzoate, by using ethanol as the solvent.

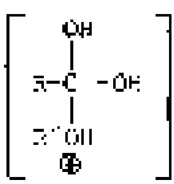


Benzoic acid   Ethanol (excess)   Ethyl benzoate

Predict the outcome of an attempted esterification of acetic acid with t-butyl alcohol in the presence of dry HCl.

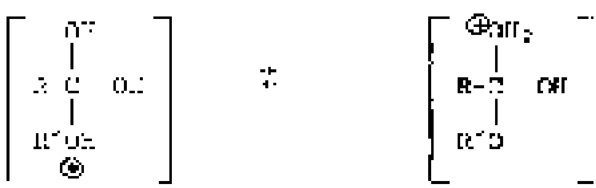
Solution: An examination of the mechanism for acid-catalyzed formation of esters $\left[R-\overset{\overset{O}{\|}}{C}-OR'\right]$ will aid in the solution. The function of the catalyst, HCl, is to protonate the carbonyl carbon so that it becomes more positive and more susceptible to attack by a nucleophilic species, the alcohol in this case.





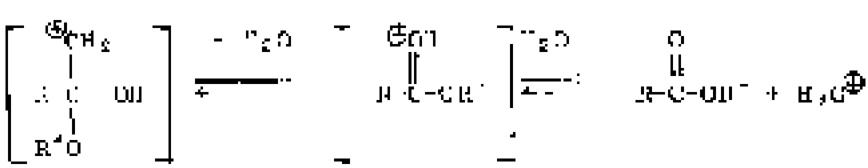
[1]

The product [1] formed can rapidly and reversibly form a second intermediate [2] by proton transfer as shown:



[1] [2]

If [2] loses a molecule and it is followed by transfer of a proton, it gives the ester, [3]



[2] [3]

With this in mind, one might think the outcome of the reaction between acetic acid (CH_3COOH) and t-butyl alcohol

$$\left(\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH_3 \\ | \\ OH \end{array} \right)$$

in dry HCl would be t-butyl acetate

$$\left(\begin{array}{c} \;\;O\;\; CH_3 \\ \;\;\|\;\;\; | \\ CH_3COC-CH_3 \\ \;\;\;\;\;| \\ \;\;\;\;\;CH_3 \end{array} \right)$$

Such thinking is <u>INCORRECT</u>. The reason stems from the fact that if the alcohol is particularly bulky, the reaction will usually not proceed satisfactorily, since the intermediate [1] or [2] is rendered unstable by crowding of the substituent groups. (Bulky groups in the esterifying acid also hinder the reaction.) Hence, no t-butyl acetate is formed due to the bulkiness of the t-butyl alcohol. What actually occurs is the alcohol and the hydrogen halide (HCl) react to form the alkyl halide as shown:

$$\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ OH \end{array} + HCl \longrightarrow \begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ Cl \end{array} + H_2O$$

(t-butyl chloride)

So, the product is t-butyl chloride.

• PROBLEM 20-24

Benzoic acid is not esterified by the procedure that is useful for mesitoic acid because, when benzoic acid is dissolved in sulfuric acid, unlike mesitoic acid, it gives the conjugate acid and no acyl carbonium ion. Explain why the mesitoyl carbonium ion might be more stable relative to the conjugate acid of mesitoic acid than benzoyl carbonium ion is relative to the conjugate acid of benzoic acid. (Among other factors, consider the geometries of the various species involved.)

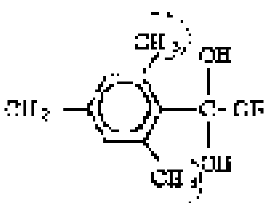
Solution: Bulky groups in the carboxylic acid can hinder the esterification reaction that proceeds through the intermediates

$$\begin{array}{c} ^{+}OH \\ \| \\ R-C-OH \end{array} \leftrightarrow \begin{array}{c} OH \\ | \\ R-C-OH \\ + \end{array} \quad \text{and} \quad \begin{array}{c} ^{+}OH_2 \\ | \\ R-C-OH \\ | \\ R'O \end{array}$$

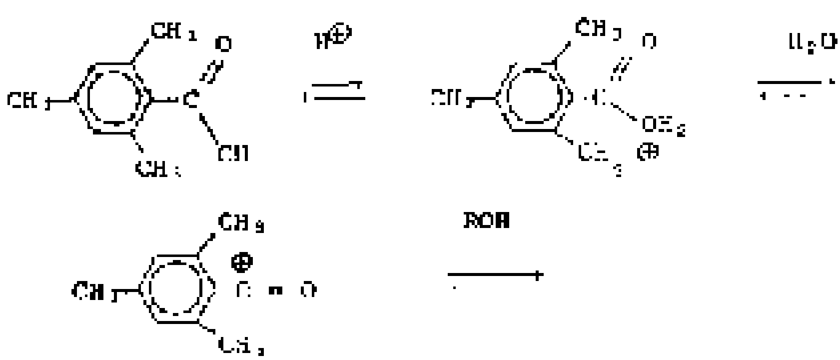
with acid

catalysis. Such is the case with mesitoic acid.

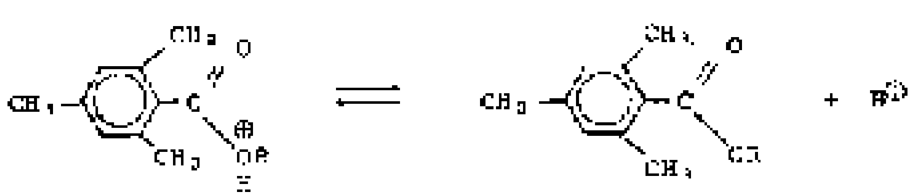
The attached methyl groups in positions adjacent to the carboxyl group block the approach of an alcohol molecule so that the following intermediate is unstable:



Now, mesitoic acid can be esterified through formation of an acyl carbonium ion as indicated:

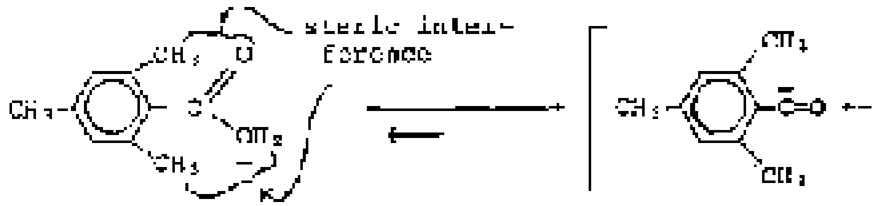


Mesitoyl carbonium ion
(Attack on positive center is unhindered from above or below plane of ring)

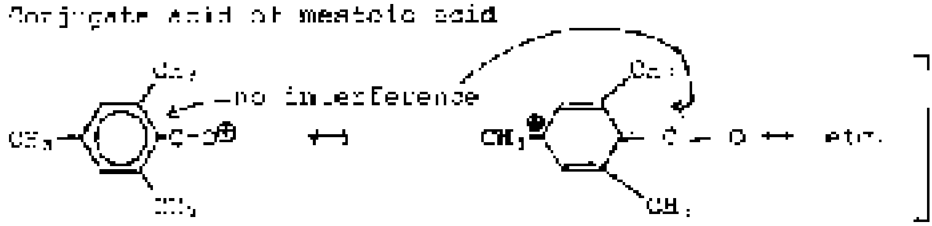


(Ester)

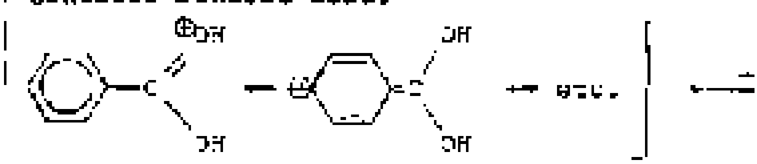
With this information, let us compare the conjugate acid and acyl carbonium ion of benzoic acid and mesitoic acid to determine why they have their respective stabilities.

(1) 

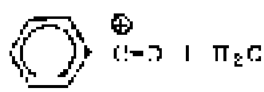
Conjugate acid of mesitoic acid



Notice how the steric interference or congestion in the conjugate acid of mesitoic acid is relieved in the acyl carbonium ion with the linear C ═ C --- O group. Hence, there exists a steric factor that favors the stability of the carbonium ion over the conjugate acid. Also, note that the methyl groups attached possess an electron-donating effect which stabilizes the positive charge of the acyl carbonium ion. In other words, one has an electronic factor that favors acyl carbonium ion stability over the conjugate acid. Consider benzoic acid:

(2) 

Conjugate Acid Form



Carbonium ion

Note that there are neither steric nor electronic factors that operate to favor equation (2). Consequently, the protonation of the carbonyl oxygen of benzoic acid is the favored process, and not an acyl carbonium ion process.

DECARBOXYLATION

• PROBLEM 20-25

Describe the Hunsdiecker reaction.

Solution: Carboxylic acids undergo several reactions in which the carboxyl group is replaced by halogen.

$$RCO_2M \longrightarrow RX$$

Such reactions, in which carbons are lost from a molecule, are called "degradations."

In the Hunsdiecker reaction, the silver salt of a carboxylic acid, prepared by treating the acid with silver oxide, is treated with a halogen. Bromine is the usual reagent, but iodine may also be used. Carbon dioxide is evolved and the corresponding alkyl halide is obtained, usually in fair to good yield.

$$CH_3OOCCH_2CH_2CH_2CH_2COO^-Ag^+ \xrightarrow[CCl_4]{Br_2} CH_3OOCCH_2CH_2CH_2CH_2Br + AgBr + CO_2$$

The reaction appears to proceed by a free radical path, and may be formulated as follows:

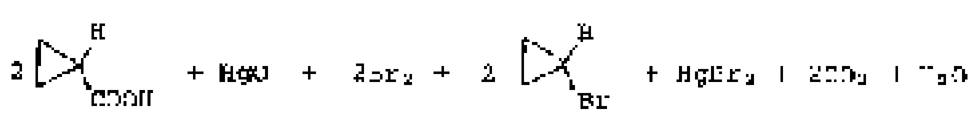
(1) $R{-}COO^-Ag^+ + Br_2 \rightarrow R{-}\overset{O}{\overset{\|}{C}}{-}OBr + AgBr$

(2) $R{-}\overset{O}{\overset{\|}{C}}{-}OBr \longrightarrow R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot + Br\cdot$

(3) $R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot \longrightarrow R\cdot + CO_2$

(4) $R\cdot + R{-}\overset{O}{\overset{\|}{C}}{-}OBr \longrightarrow RBr + R{-}\overset{O}{\overset{\|}{C}}{-}O\cdot$

In a useful modification of the Hunsdiecker reaction, the carboxylic acid is treated with mercuric oxide and bromine.

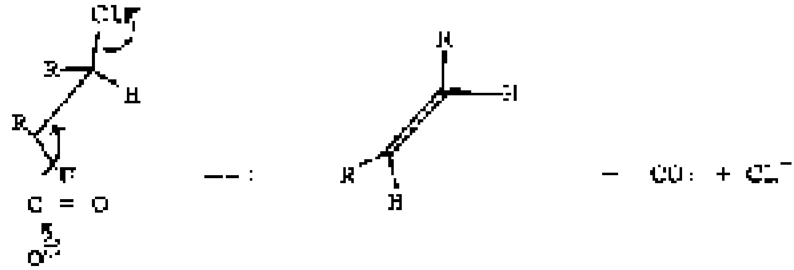


(41-46%)

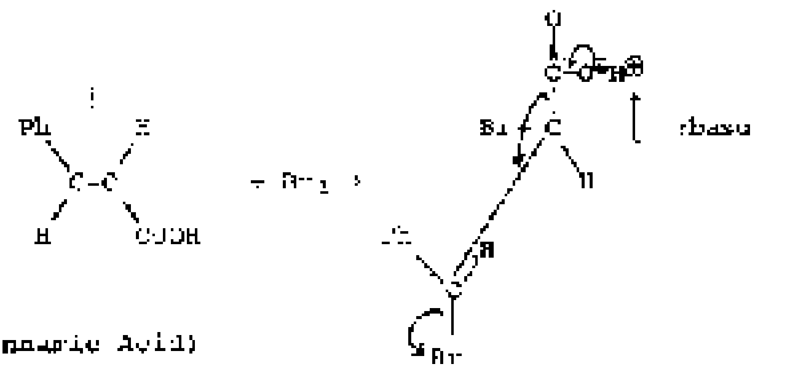
■ PROBLEM 20-20

Outline a synthesis of cis-β-bromostyrene from cinnamic acid (PhCH=CHCOOH). Which isomer of the acid is required, cis or trans.

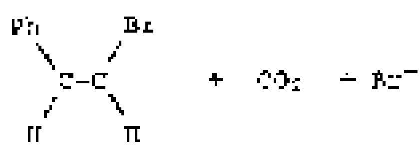
Solution: Cis-β-bromostyrene may be produced from cinnamic acid by decarboxylative elimination. The carboxylate ion is required for this reaction, which has been used for the stereospecific synthesis of alkenes. In addition to the carboxylate ion, a good leaving group such as a halogen is required at the β position. The reaction may be illustrated as follows:



In this problem, the halogen used for a good leaving group will be bromine. Br_2 adds across the double bond of cinnamic acid. At this point, base is introduced to abstract the acidic proton so that the carboxylate ion is created. The molecule is now ready to undergo decarboxylative elimination to produce cis-β-bromostyrene. The trans isomer must be the starting material for the sequence to work as indicated:



(Cinnamic Acid)

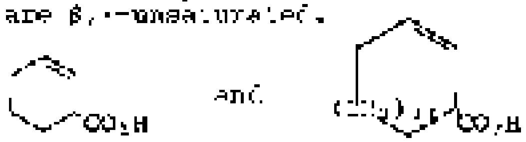


• PROBLEM 20-27

(a) While many α,β-unsaturated carboxylic acids undergo decarboxylation upon heating, the α,β-unsaturated acid shown below is immune to such a reaction. What does this suggest about the mechanism of decarboxylation of α,β-unsaturated acids?

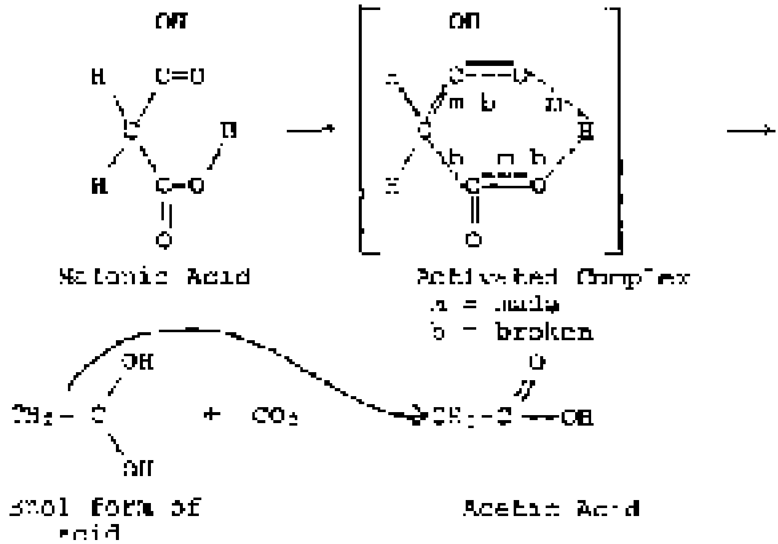
$$\begin{array}{c} CH_3 \\ | \\ CH_3-C-CH=CH-CO_2H \\ | \\ CH_3 \end{array}$$ does not decarboxylate readily

(b) Explain why there should be a difference in the ease of decarboxylation of the following acids, both of which are β,γ-unsaturated.



Solution: (a) Inspection of the structure reveals the fact that the carboxylic acid possesses three methyl groups on the γ carbon. Hence, there exist no protons on the γ carbon. This suggests then, that the mechanism of decarboxylation of α,β-unsaturated acids requires the presence of a γ carbon proton.

(b) The reason for the difference in ease of decarboxylation may be found in the mechanism of decarboxylation of malonic acid, a β-dicarboxylic acid, which is believed to involve a cyclic activated complex. It is believed β,γ-unsaturated acids have a similar method of decarboxylation. The mechanism for malonic acid may be written as follows:

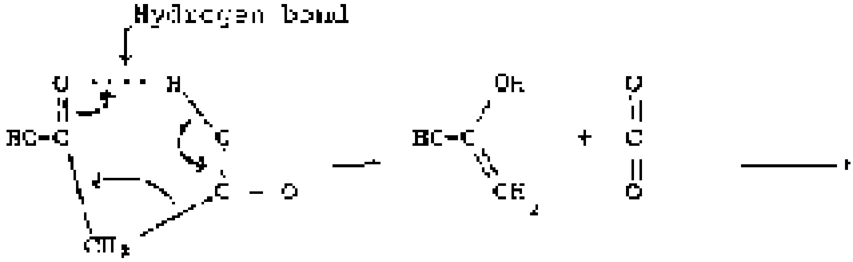


The formation of the activated complex is crucial to the decarboxylation and explains why the smaller ring does not easily decarboxylate. The smaller ring cannot form a cyclic transition state required for decarboxylation, but the larger can.

• PROBLEM 20-28

Explain why decarboxylation of α,α-dimethylacetoacetic acid, $CH_3COC(CH_3)_2CO_2H$, in the presence of bromine gives α-bromoisopropyl methyl ketone, $CH_3COC(CH_3)_2Br$.

Solution: The decarboxylation of carboxylic acids can proceed with some acids by simply heating. While the mechanism of thermal decarboxylation are not the same in all cases, it may (in β,γ-unsaturated acids) be a cyclic process of elimination in which hydrogen bonding plays a role. In the mechanism, an enol form of the molecule exists temporarily as shown in the example with malonic acid decarboxylation:



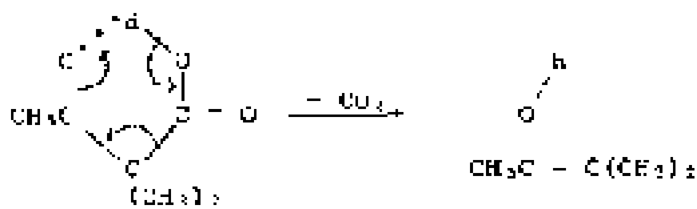
(The arrows indicate shifting of pairs of electrons as heat is applied.)

Enol form of acetic acid

CH_3COOH + CO_2

acetic acid

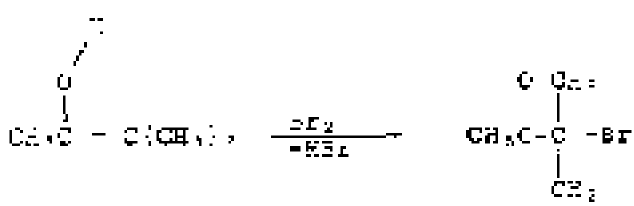
Now, decarboxylation of α,α dimethylacetoacetic acid by the same method (that is, concerted and cyclic) would lead to the enol form of isopropyl methyl ketone as shown:



α,α dimethylacetoacetic acid

Enol form

The enol form of isopropyl methyl ketone is now susceptible to attack by bromine across the double bond to generate the product, α bromoisopropyl methyl ketone as illustrated:



SPECTROSCOPY

• PROBLEM 20-29

Explain why the chemical shift of the acidic proton of a carboxylic acid, dissolved in a nonpolar solvent like carbon tetrachloride, varies less with concentration than that of the OH proton of an alcohol under the same conditions.

Solution: A consideration of hydrogen bonding will explain the changes of the chemical shift.

In alcohols, the hydrogen-oxygen bond of a hydroxyl group gives a characteristic absorption band in the infrared and this absorption is considerably influenced by hydrogen bonding. As an example, examine ethanol. In the vapor state (with no hydrogen bonding), ethanol gives an infrared spectrum with a sharp absorption band at 3700 cm^{-1} (due to the free or unassociated hydroxyl group). However, in a 10% solution of carbon tetrachloride (CCl_4) this band is barely visible at 3640 cm^{-1}. At 3350 cm^{-1}, there is a relatively broad band; this is characteristic of hydrogen bonded hydroxyl groups. The shift in frequency of about 300 cm^{-1} reflects the fact that hydrogen bonding weakens the O-H bond so that its frequency will then be lower.

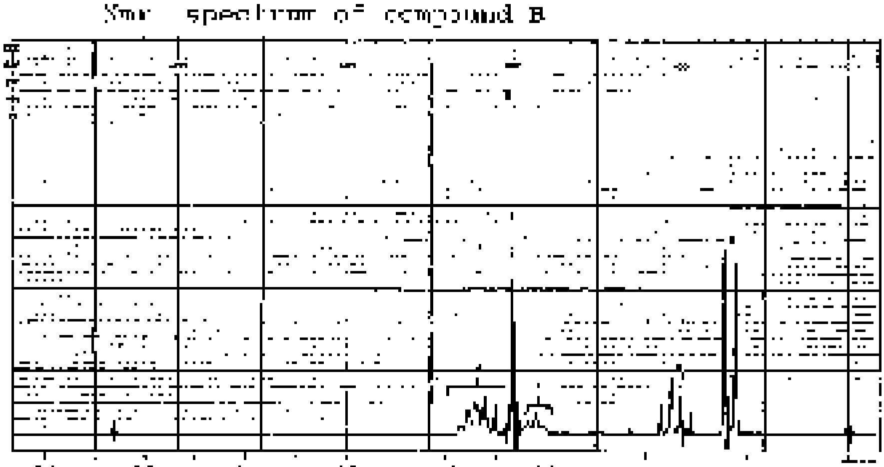
In very dilute solutions of alcohols in nonpolar solvents, the hydrogen bonding is minimized. As the concentration of alcohol increases, more and more molecules become associated and the intensity of the infrared absorption due to associated hydroxyl groups increases at the expense of the free-hydroxyl band.

The OH proton of carboxylic acids fails to show this same variation of chemical shift with concentration. The reason stems from the fact that carboxylic acids are more strongly associated by hydrogen bonding and associate in solution as dimers. Since the dimers are not easily dissociated on dilution, the chemical shift of the OH proton does not change appreciably.

• PROBLEM 20-30

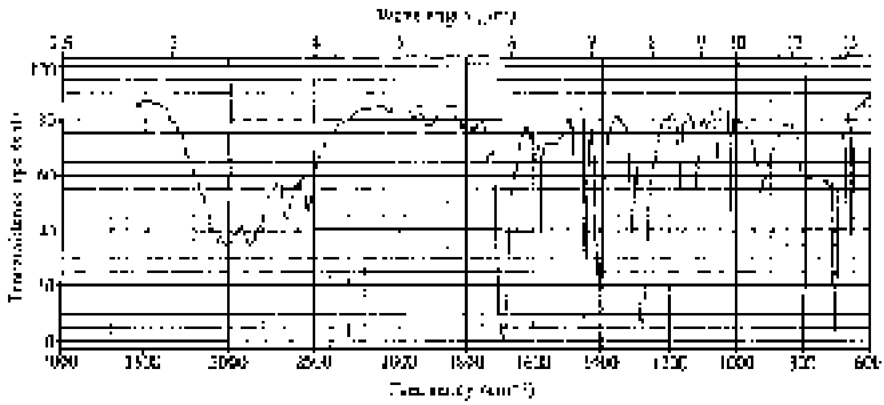
A compound, A, containing only carbon, hydrogen, and oxygen, was insoluble in aqueous base, but on heating in base yielded a new compound, B, which was also insoluble in aqueous base. Compound B was found to have the formula $C_7H_{12}O_2$ and its nmr spectrum is shown.

Nmr spectrum of compound B

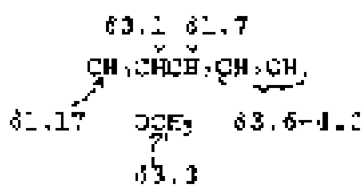


When the aqueous basic solution was made acidic, a new crystalline compound, C, could be filtered from the solution. Compound C was found to have the formula $C_7H_6O_2$ and its infrared spectrum is shown. What are the structures of A, B, and C?

Infrared spectrum of compound C in chloroform solution



Solution: Analysis of the NMR spectrum of compound B reveals the following: The number of signals indicates how many different "kinds" of protons there are in a molecule. Since compound B shows five signals, five different kinds of protons should be expected. The positions of the signals help to tell what kinds of protons they are: aromatic, aliphatic, primary, secondary, tertiary, benzylic, etc. With this in mind, compound B becomes:

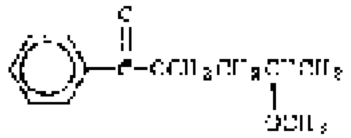


The chemical shifts of the five kinds of protons have been indicated. Notice how the structure written agrees with the formula $C_6H_{14}O$ and the spin-spin splitting. (For example, the methyl signal (δ 1.17) is split into 2 signals by the non-equivalent adjacent hydrogen bound to the carbon atom that participates in the ether linkage.)

Examination of the infrared spectrum for compound C indicates a strong band at 1700 cm^{-1}, which denotes a carbonyl group. This functional could belong to an aldehyde, ketone, carboxylic acid, or ester. However, the strong and broad band between 2500 cm^{-1} and 3000 cm^{-1}, indicates a -COOH group exists. That this is an acid is also confirmed by the C-O stretching at 1250 cm^{-1}. If the formula of compound C is $C_7H_6O_2$ and COOH is accounted for, then C_6H_5 is still to be determined. This formula fits benzene very well,

so that compound C must be benzoic acid. 

Compound A can now be discerned. Compound A must have been the ester between compound B and C, that is



When this compound is heated in the presence of base, hydrolysis of the ester occurs to generate the alcohol (compound B) and the salt of compound C (benzoic acid). With addition of mineral acid, the salt is converted to the carboxylic acid, compound C.

REDUCTION

• PROBLEM 20-31

Write a detailed mechanism for the reduction of acetic acid to ethanol by $LiAlH_4$.

Solution: Lithium aluminum hydride ($LiAlH_4$) is a reagent that can be used to reduce the carboxyl group of acids to the hydroxyl group of alcohols. With the metal hydrides (such as $LiAlH_4$), the key step is transfer of a hydride ion to the carbonyl carbon of the substance being reduced. The acidic hydrogen first reacts to liberate hydrogen gas. The carbonyl group of the carboxylate ion is then attacked by the AlH_4^- ion, and the group is reduced to the primary alkoxide. Overall, the reaction may be written as:

$$4RCOOH + 3LiAlH_4 \rightarrow 4H_2 + (RCH_2O)_4AlLi + 2LiAlO_2 \xrightarrow{H_2O} 4RCH_2OH.$$

The mechanism is as follows:

$$\underset{\text{(acetic acid)}}{CH_3COOH} + LiAlH_4 \rightarrow CH_3\overset{O}{\overset{\|}{C}}-OLiAlH_3 \longrightarrow H^-$$

$$CH_3-\underset{H}{\overset{OLiAl^+}{C}}-OLiAl^+ \longrightarrow CH_3\overset{O}{\overset{\|}{C}}-H + LiAlO^- + H^-$$

$$CH_3\underset{H}{\overset{OLiAl^+}{C}}-H \xrightarrow{H_3O^+} \underset{\text{(Ethanol)}}{CH_3CH_2OH} + Li^+ + Al(OH)_3$$

• PROBLEM 20-32

Outline the synthesis from lauric acid (n-$C_{11}H_{23}COOH$, dodecanoic acid) of the following compounds: (a) 1-bromododecane;

(b) tridecanoic acid (C_{13} acid); (c) 1-tetradecanol; (d) 1-dodecene; (e) dodecane; (f) 1-dodecyne; (g) methyl n-decyl ketone; (h) 2-dodecanol; (i) undecanoic acid; (j) 2-tetradecanol; (k) 2-methyl-2-tetradecanol.

Solution: In synthesis, it is good practice to write out the starting material and desired product to see what functional group changes must be made.

(a) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{11}H_{23}CH_2Br$

Lauric acid — 1-bromododecane

Examination indicates that the carbon skeleton remains intact in this synthesis. All that must be done is to alter the carboxylic acid to the alkyl bromide of the same carbon number. Now, if one had n $C_{11}H_{23}CH_2OH$ (the corresponding alcohol), 1-bromododecane could be produced by reaction with the phosphorus trihalide PBr_3. To obtain the alcohol, use the fact that lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that reduce a carboxylic acid to an alcohol of the same carbon length. Overall, then, the synthesis becomes:

$$n\text{-}C_{11}H_{23}COOH \xrightarrow{LiAlH_4} n\text{-}C_{11}H_{23}CH_2OH \xrightarrow{PBr_3} n\text{-}C_{11}H_{23}CH_2Br$$

(b) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{11}H_{23}CH_2COOH$

Lauric acid — tridecanoic acid

Here, one wants to increase the carbon skeleton of lauric acid by one to obtain tridecanoic acid. Carboxylic acids of the next highest carbon number can be produced from the alkyl halide by two methods:

(1) Make a Grignard reagent from the alkyl halide and carbonate it and subsequently add acid. (2) Produce a nitrile from the alkyl halide and hydrolyze it with acid or base. The alkyl halide synthesized in part (a) of this problem (1-bromododecane) from lauric acid serves as the alkyl halide needed to produce tridecanoic acid. By method (1),

$$n\text{-}C_{11}H_{23}CH_2Br \xrightarrow{Mg} \underset{\text{(Grignard reagent)}}{n\text{-}C_{11}H_{23}CH_2MgBr} \xrightarrow{CO_2;} \xrightarrow{H^+} n\text{-}C_{11}H_{23}CH_2COOH.$$

By method (2),

$$n\text{-}C_{11}H_{23}CH_2Br \xrightarrow{NaCN} n\text{-}C_{11}H_{23}CH_2C{\equiv}N \xrightarrow[\text{Acid or Base}]{H_2O}$$

$n\text{-}C_{11}H_{23}CH_2COOH$

(c) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{11}H_{23}CH_2CH_2CH_2OH$

Lauric acid — 1-tetradecanol

In this part, one is changing the functional group from carboxylic to alcohol and increasing the carbon skeleton by 3. This synthesis is not as complicated as it may seem, for if one takes the Grignard reagent synthesized in part (b) and uses it now, 1-tetradecanol is readily synthesized by the reaction of ethylene oxide. The reaction of Grignard reagents with ethylene oxide is an important method of preparing primary alcohols that contain two more carbons than the alkyl or aryl group of the Grignard reagent. Hence,

$$n\text{-}C_{11}H_{23}CH_2MgBr \xrightarrow{\overset{H_2C-CH_2}{\diagdown\ \diagup}\atop O} \xrightarrow{H^+} n\text{-}C_{11}H_{23}CH_2CH_2CH_2OH$$

(from part (b))

(d) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}CH{=}CH_2$

Lauric acid — 1-dodecene

This synthesis requires the generation of an alkene from a carboxylic acid with the same carbon skeleton. This synthesis can be readily done if one takes the product of part (a), $n\text{-}C_{11}H_{23}CH_2Br$.

This alkyl halide can be dehydrohalogenated by KOH in alcohol to produce 1-dodecene as shown:

$$n\text{-}C_{11}H_{23}CH_2Br \xrightarrow[\text{(alc)}]{KOH} n\text{-}C_{10}H_{21}CH{=}CH_2$$

(e) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}CH_2CH_3$

Lauric acid — dodecane

Dodecane may be produced very quickly if one takes the product from part (d), which ultimately is derived from lauric acid. 1-dodecene can produce dodecane by hydrogenation in the presence of a catalyst such as Pt, Pd, or Ni.

$$n\text{-}C_{10}H_{21}CH{=}CH_2 \xrightarrow[Pt]{H_2} n\text{-}C_{10}H_{21}CH_2CH_3$$

(f) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}C{\equiv}CH$

Lauric acid — 1-dodecyne

This alkyne can be produced from the corresponding alkyl dihalide by dehydrohalogenation. The dehydrohalogenation is carried out in two steps with KOH (alc) that produces a vinyl halide and $NaNH_2$, which is a stronger base, that gives the alkyne. To obtain the dihalide, actually a vicinal dihalide, take the product from part (d), $n\text{-}C_{10}H_{21}CH{=}CH_2$, and perform an addition reaction with halogen. For example, Br_2 in CCl_4. The overall sequence that yields the desired product would then be:

$$n\text{-}C_{10}H_{21}CH{=}CH_2 \xrightarrow[CCl_4]{Br_2} n\text{-}C_{10}H_{21}\underset{Br}{CH}-\underset{Br}{CH_2} \xrightarrow{KOH} \xrightarrow{NaNH_2}$$

$$n\text{-}C_{10}H_{21}C{\equiv}CH$$

(g) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}\underset{\underset{O}{\|}}{C}-CH_3$

Lauric acid — methyl n-decyl ketone

This reaction requires that the carboxyl group be altered to the carbonyl group of a ketone with the carbon skeleton remaining constant. The alkyne produced in part (f), $n\text{-}C_{10}H_{21}C{\equiv}CH$, may be used to synthesize the ketone desired. Addition of water in the presence of H_2SO_4 and $HgSO_4$ results in hydration of the alkyne to a carbonyl compound. Hence,

$$n\text{-}C_{10}H_{21}C{\equiv}CH \xrightarrow[Hg^{++}]{H_2O,\,H_2SO_4} n\text{-}C_{10}H_{21}\underset{\underset{O}{\|}}{C}-CH_3$$

(h) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}CHOH\text{-}CH_3$

Laurie acid — 2-dodecanol

This conversion may be completed by the use of the product from part (g), which stems ultimately from lauric acid. Hydrogenation in the presence of a catalyst can transform a carbonyl (C=O) to a hydroxyl (OH). Since the carbon skeleton does not change in the synthesis, this reaction can be performed as illustrated:

$$n\text{-}C_{10}H_{21}\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow{H_2,\,Pt} n\text{-}C_{10}H_{21}CHOH\text{-}CH_3$$

(i) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{10}H_{21}COOH$

Lauric acid — Undecanoic acid

Undecanoic acid may be obtained from the product of part (g) by use of the haloform reaction followed by treatment with acid. Upon the addition of iodine and sodium hydroxide (to form sodium hypoiodite, NaOI), methyl ketones $\left(-\underset{\underset{O}{\|}}{C}-CH_3\right)$ are converted to carboxylic acids of 1 carbon less. The reaction involves halogenation and cleavage as shown in the example below:

$$\underset{\Large O}{\overset{\parallel}{R-C}}-CH_3 + 3NaOI \rightarrow \underset{\Large O}{\overset{\parallel}{R-C}}-CI_3 + 3NaOH, \quad \underset{\Large O}{\overset{\parallel}{R-C}}-CI_3 +$$

$$NaOH \rightarrow RCOO^-Na^+ + CHI_3$$

The product of part (g) is such a methyl ketone so that undecanoic acid is produced as follows:

$$n\text{-}C_{11}H_{23}\underset{\Large O}{\overset{\parallel}{C}}-CH_3 \xrightarrow{OI^-} \xrightarrow{H^+} n\text{-}C_{11}H_{23}COOH$$

(j) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{12}H_{25}CHOH\text{-}CH_3$

Lauric acid 2-tetradecanol

The alcohol to be produced has an increased carbon skeleton of 2. This synthesis can be performed by selecting the product of part (a), $n\text{-}C_{11}H_{23}CH_2Br$ ($=n\text{-}C_{12}H_{25}Br$). If $n\text{-}C_{12}H_{25}Br$ is converted to the corresponding Grignard reagent, acetaldehyde may be added to obtain the desired product. Addition of aldehydes such as acetaldehyde

$\left(\overset{O}{\overset{\parallel}{H-C}}-CH_3\right)$ to Grignard reagents yields secondary alcohols

$\left(\begin{array}{c} H \\ | \\ R-C-OH \\ | \\ R' \end{array}\right)$ such as 2-tetradecanol. Overall,

$$n\text{-}C_{12}H_{25}Br \xrightarrow{Mg} n\text{-}C_{12}H_{25}MgBr \xrightarrow{CH_3CHO} \xrightarrow{H^+}$$

$$n\text{-}C_{12}H_{25}CHOH\text{-}CH_3$$

(k) $n\text{-}C_{11}H_{23}COOH \longrightarrow n\text{-}C_{12}H_{25}\underset{OH}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3$

Lauric acid 2-methyl-2-tetradecanol

This synthesis is similar to the one in part (j). This time, however, acetone (CH_3COCH_3) will be added to the Grignard reagent made from the product in part (a). Addition of ketones such as acetone to Grignard reagents (with subsequent acid hydrolysis) produces tertiary alcohols

$\left(\begin{array}{c} R \\ | \\ R'-C-OH \\ | \\ R'' \end{array}\right)$ such as 2-methyl-2-tetradecanol. Consequently,

the sequence of reactions is:

$$n\text{-}C_{12}H_{25}Br \xrightarrow{Mg} n\text{-}C_{12}H_{25}MgBr \xrightarrow{CH_3COCH_3} n\text{-}C_{12}H_{25}\underset{OH}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_3$$

CHAPTER 21

CARBOXYLIC ACID DERIVATIVES

• PROBLEM 21-1

What are the carboxylic acid derivatives? Discuss their nomenclature. Give examples.

Solution: The carboxyl group of organic acids may exist in several modified forms. A different entity may replace the hydroxyl portion - such things are called carboxylic acid derivatives.

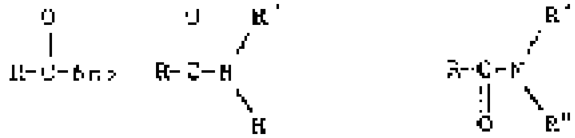
When the hydroxyl is replaced by chlorine, an acyl chloride is obtained: $R-\overset{O}{\overset{\|}{C}}-Cl$. The nomenclature of an acyl chloride is determined from the corresponding acid. The ending "ic acid" is replaced by the ending "yl chloride". For example, propanoic acid (CH_3CH_2COOH) would become propanoyl chloride ($CH_3CH_2\underset{O}{\underset{\|}{C}}Cl$). These substances can also be named, respectively, propionic acid and propionyl chloride.

If an alkoxyl replaces the hydroxyl, an ester is formed: $R-\overset{O}{\overset{\|}{C}}-OR'$. The name of an ester includes two words: the first derives from the alcohol; the second comes from the name of the carboxylic acid by replacing the ending "ic" with the ending "ate". Example:

$$\underbrace{H-\underset{O}{\underset{\|}{C}}}_{\text{Formic acid}}-\underbrace{OCH_3}_{\text{Methyl alcohol}}$$

The ester is derived from methyl alcohol and formic acid. Therefore, its name becomes methyl formate. Similarly, the ester $CH_3\underset{O}{\underset{\|}{C}}-O-CH_2CH_3$ is named ethyl acetate (ethyl ethanoate).

Carboxamides or amides come about when the hydroxyl group is replaced by an amino group. If the amino group has attached to it one or two alkyl or aryl groups, the amide is referred to as N-substituted or N,N disubstituted.



(Simple amide) (N-Substituted amide) (N,N-Disubstituted amide)

The simple amides are named from the corresponding carboxylic acid by dropping the ending "oic acid" or "ic acid" and substituting the ending "amide." For example, acetic acid or ethanoic acid ($CH_3\underset{O}{\underset{\|}{C}}-OH$) becomes acetamide or ethanamide ($CH_3\underset{O}{\underset{\|}{C}}-NH_2$). The N-substituted amides are named by indicating the N-substituents before the name of the parent amide. For example, $CH_3\underset{O}{\underset{\|}{C}}-NH-CH_3$ would be N-methylacetamide.

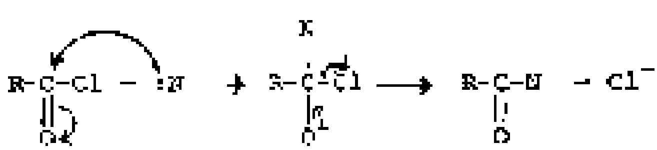
Carboxylic acid anhydrides may be viewed as compounds derived from carboxylic acids by the loss of water; $R-\underset{O}{\underset{\|}{C}}-O-\underset{O}{\underset{\|}{C}}-R$. In naming anhydrides, the word "acid" is dropped from the component carboxylic acid and replaced with "anhydride". For example, $CH_3\underset{O}{\underset{\|}{C}}-O-\underset{O}{\underset{\|}{C}}CH_3$ would be called acetic anhydride or ethanoic anhydride.

ACID CHLORIDES

• PROBLEM 21-2

Describe the nucleophilic substitution reaction of acyl chlorides.

Solution: Acyl chlorides are readily attacked by nucleophiles at the carbonyl carbon. The resulting adduct eliminates the chloride ion, so the overall reaction is a nucleophilic substitution.



Nucleophilic attack — Elimination of chloride — Substitution product

Water, alcohols, ammonia, or amines are the nucleophiles that are usually employed in reactions with acyl chlorides. The products of these reactions are carboxylic acids, esters, or carboxamides according to the following reactions.

$$R{-}\underset{\underset{O}{\|}}{C}{-}Cl \;+\; H_2O \;\rightarrow\; \underset{\text{Carboxylic acid}}{R{-}COOH} \;+\; HCl$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}Cl \;+\; \underset{\text{Alcohol}}{R'{-}OH} \;\rightarrow\; \underset{\text{Ester}}{R{-}\underset{\underset{O}{\|}}{C}{-}OR'} \;+\; HCl$$

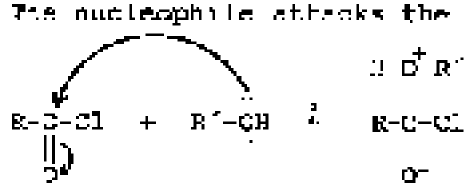
$$R{-}\underset{\underset{O}{\|}}{C}{-}Cl \;+\; 2NH_3 \;\rightarrow\; \underset{\text{Carboxamide}}{R{-}\underset{\underset{O}{\|}}{C}{-}NH_2} \;+\; \overset{+}{N}H_4\overset{-}{Cl}$$

$$R{-}\underset{\underset{O}{\|}}{C}{-}Cl \;+\; \underset{\text{Primary amine}}{2\,R'{-}NH_2} \;\rightarrow\; \underset{\text{N-Substituted carboxamide}}{R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R'} \;+\; R'NH_3^{+}Cl^{-}$$

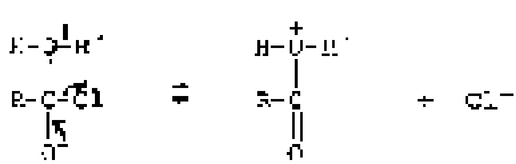
$$R{-}\underset{\underset{O}{\|}}{C}{-}Cl \;+\; \underset{\text{Secondary amine}}{2R'{-}NH{-}R''} \;\rightarrow\; \underset{\text{N,N-Disubstituted carboxamide}}{R{-}\underset{\underset{O}{\|}}{C}{-}N\begin{smallmatrix}R' \\ R''\end{smallmatrix}} \;+\; R'\overset{+}{N}H_2R''\,\overset{-}{Cl}$$

The mechanism of all these reactions follows the general scheme of nucleophilic substitution. As an example, the reaction of an acyl chloride with an alcohol is shown:

(1) The nucleophile attacks the acyl chloride:



(2) The chloride ion is eliminated:



(3) A hydrogen ion is lost to give the ester product:

$$R-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle O}{\|}}{C}-O^{+}}-R' \rightarrow R-\underset{\underset{\displaystyle O}{\|}}{C}-O-R' + H^{+}$$

An ester

Although each step of the reaction is reversible, the reaction by-product is hydrogen chloride gas, which usually escapes from the reaction vessel. Thus, the equilibrium reaction is driven completely in a forward direction.

• PROBLEM 21-3

> Write equations to show the reaction of acetyl chloride with: (a) water, (b) ammonia, and (c) isopropyl alcohol.

Solution: Acyl chlorides such as acetyl chloride are readily attacked at the carbonyl carbon by nucleophiles. The adduct formed will expel chloride ion so that the overall reaction is one of nucleophilic substitution. The reaction may be generalized as:

$$\underset{\underset{\displaystyle O}{\|}}{R-C}-Cl \text{ (acyl chloride)} + :N \text{ (nucleophile)} \rightarrow R-\overset{\overset{\displaystyle N}{|}}{\underset{\underset{\displaystyle O^{-}}{|}}{C}}-Cl$$

$$\rightarrow \underset{\underset{\displaystyle O}{\|}}{R-C}-N + Cl^{-}$$

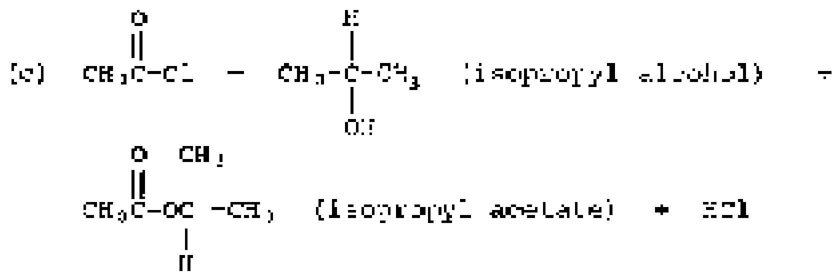
A nucleophilic attack by N: occurs. Chloride ion is eliminated and a substitution product is obtained. Water, ammonia, and alcohols usually serve as the nucleophiles in the reactions with acyl chlorides. The products of these reactions are carboxylic acids, esters, or carboxamides. The following equations can be written now that the general reaction is known:

(a) $$CH_3\overset{\overset{\displaystyle O}{\|}}{C}-Cl \text{ (acetyl chloride)} + H_2O \text{ (water)} \rightarrow$$

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}-OH \text{ (acetic acid)} + HCl$$

(b) $$CH_3\overset{\overset{\displaystyle O}{\|}}{C}-Cl + 2NH_3 \text{ (ammonia)} \rightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \text{ (acetamide)}$$

$$+ \overset{+}{N}H_4\ Cl^{-}$$



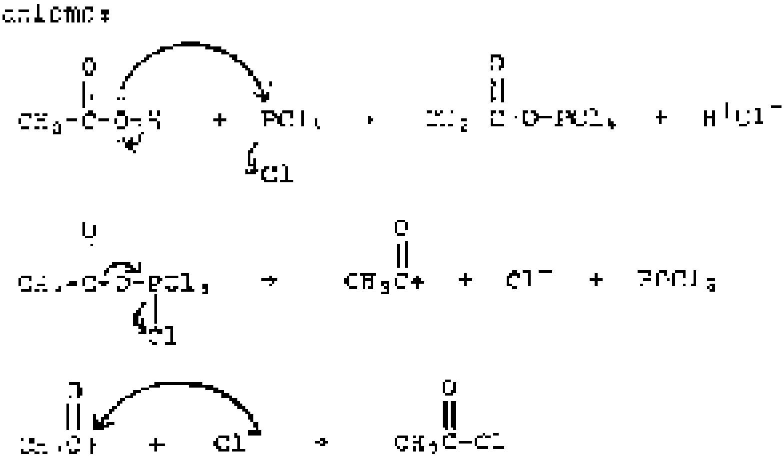
● PROBLEM 21-4

Suggest a mechanism for the reaction of acetic acid with phosphorus pentachloride.

Solution: A carboxylic acid can be converted to an acid chloride by replacing the hydroxyl portion with a chlorine atom. This can be accomplished by using any one of three reagents: PCl_5, PCl_3, or $SOCl_2$. The general reaction can be written as:

Carboxylic acid Acid chloride

The reaction of acetic acid with phosphorus pentachloride (PCl_5) proceeds through the following mechanism:



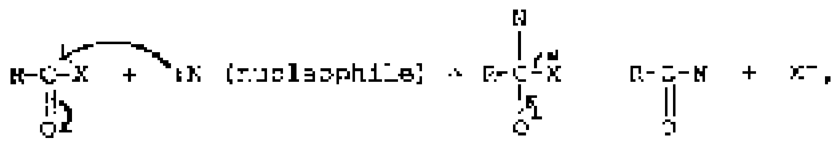
The mechanism accounts for the production of an acylium ion ($R-C\equiv O^+$), which reacts with a chloride anion to give the acid chloride.

ACID ANHYDRIDES

• PROBLEM 21-5

Write equations to show the reaction of benzoic anhydride with: (a) water, (b) ethyl alcohol, and (c) aniline.

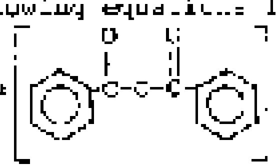
Solution: Carboxylic acid anhydrides such as benzoic anhydride undergo the same type of nucleophilic attack and substitution as acyl halides. It may be represented by



where X may be Cl, NH_2, NHR, NR_2, $\mathrm{O\underset{\underset{O}{\|}}{C}{-}R}$, or OR.

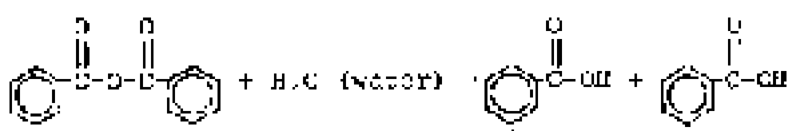
The attack of the nucleophile, which is usually water, ammonia or amines, and alcohols, causes the leaving of X and then gives the substituted compound.

Hence, the following equations for the reaction of benzoic anhydride



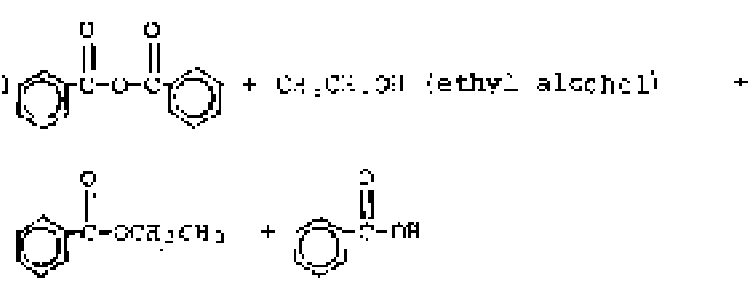
with the various nucleophiles given can be written:

(a)

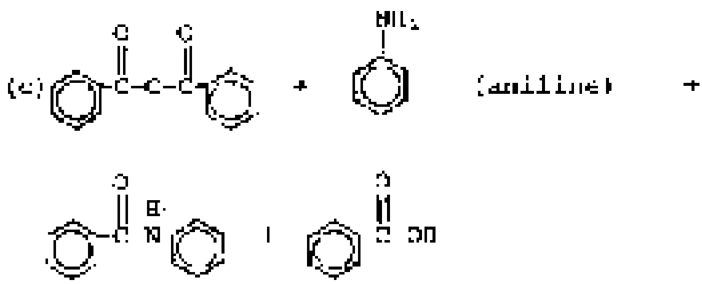


Benzoic acid

(b)



Ethyl benzoate Benzoic acid



N-phenyl benzamide | Benzoic acid

• PROBLEM 21-6

Give structural formulas for compounds A through G.

Benzene + succinic anhydride $\xrightarrow{AlCl_3}$ $\xrightarrow{H_2O}$ $A(C_{10}H_{10}O_3)$

$A + Zn(Hg) \xrightarrow{HCl} B(C_{10}H_{12}O_2)$

$B + SOCl_2 \rightarrow C(C_{10}H_{11}OCl)$

$C \xrightarrow{AlCl_3} D(C_{10}H_{10}O)$

$D + H_2 \xrightarrow{Pt} E(C_{10}H_{12}O)$

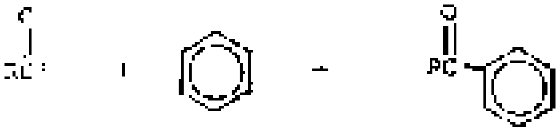
$E + H_2SO_4 \xrightarrow{heat} F(C_{10}H_{10})$

$F \xrightarrow{Pt,\ heat} G(C_{10}H_8) + H_2$

Solution: The sequence of reactions depicted in this problem represents the Haworth synthesis of naphthalene. It commences with the addition of $AlCl_3$ to a mixture of benzene and succinic anhydride to produce $A(C_{10}H_{10}O_3)$. This reaction is an example of a Friedel-Crafts acylation. This is a modification of the Friedel-Craft alkylation, which is the most important method for attaching alkyl side chains to aromatic rings. In Friedel-Crafts acylation, an acyl group (RCO-) is attached to the aromatic ring; this requires the generation of an electrophile, the acylium ion

(R-C≡O). The acylium ion will undergo an electrophilic aromatic substitution reaction with the aromatic ring to form an aromatic ketone. The acylium ion is formed by using a Lewis acid (i.e., $AlCl_3$) as a catalyst. Acid anhydrides will react with $AlCl_3$ to give an acylium ion. The general mechanism of an acid anhydride reacting with an aromatic ring in the presence of $AlCl_3$ is:

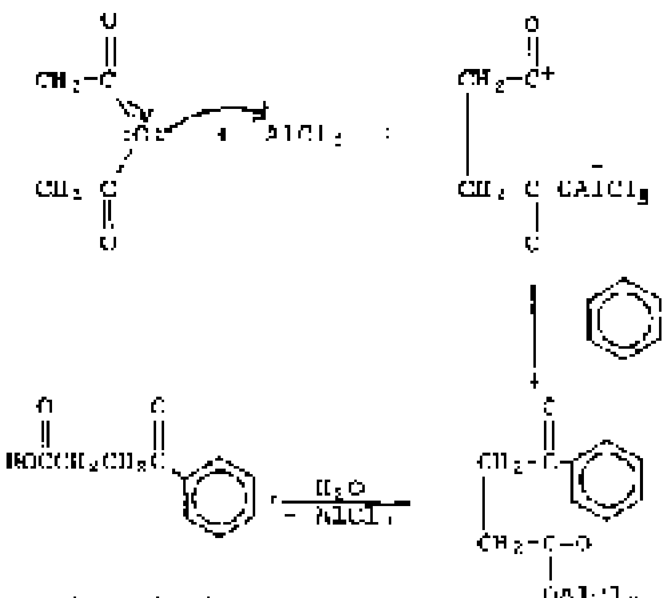
$$\underset{\text{acid anhydride}}{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R'} + AlCl_3 \rightarrow \underset{\text{acylium ion}}{R\overset{O}{\overset{\|}{C}}{}^{+}} + \overset{-}{Cl_3Al}O\overset{O}{\overset{\|}{C}}R'$$



Benzene (aromatic ring) aromatic ketone

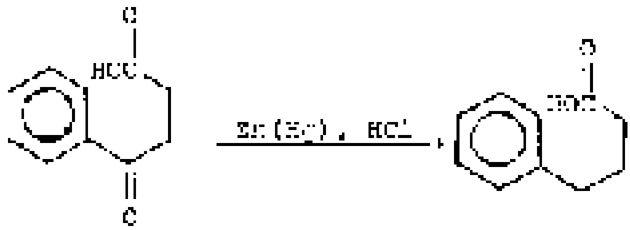
Succinic anhydride,  , is an acid anhydride

and should react with benzene and $AlCl_3$ as depicted above. But note that succinic anhydride is a cyclic acid anhydride; reaction with $AlCl_3$ will open the ring to give the acylium ion and the $-\bar{O}AlCl_3$ portion on the same molecule. This will react with benzene to give an aromatic ketone. Subsequent quenching of the product with water will convert the $-\bar{O}AlCl_3$ to an -OH. The mechanism is:



β-Benzoylpropionic acid (Product A)

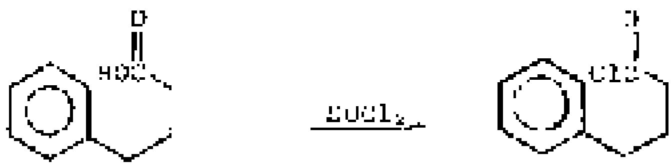
Product A now reacts with Zn(Hg) in the presence of HCl to give B($C_{10}H_{12}O_2$). This reaction is a Clemmensen reduction; it converts an acyl group into an alkyl group. Therefore,



β-Benzoylpropionic acid

γ-phenylbutyric acid (Product B)

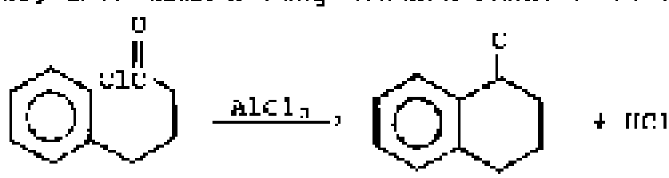
Product B is then reacted with $SOCl_2$ to generate product C ($C_{10}H_{11}OCl$). Thionyl chloride ($SOCl_2$) is a reagent used to convert carboxylic acids into acid chlorides as can be seen below:



γ-phenylbutyric acid

γ-phenylbutyl chloride (Product C)

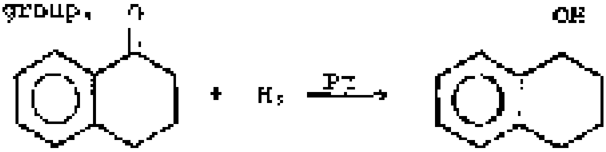
Product C is transformed into product D ($C_{10}H_{10}O$) by $AlCl_3$. This suggests another Friedel-Crafts acylation. However, this time a ring closure results as illustrated:



γ-phenyl butyl chloride

γ-tetralone (Product D)

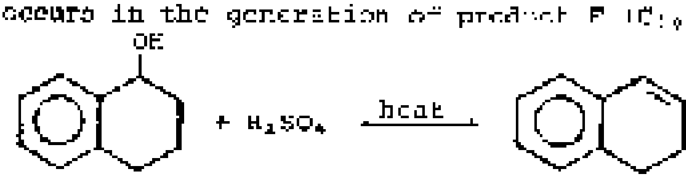
The addition of hydrogen in the presence of Pt to product D indicates product E ($C_{10}H_{12}O$) results from catalytic hydrogenation of the carbonyl group to a hydroxyl group.



α-tetralone

α-tetralol (Product E)

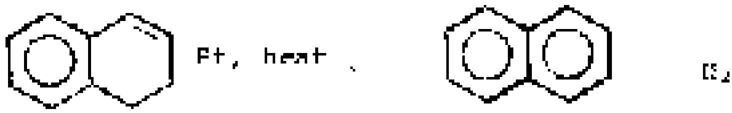
Alcohols in the presence of a mineral acid such as H_2SO_4 can be dehydrated to alkenes. This is exactly what occurs in the generation of product F ($C_{10}H_{10}$) as indicated:



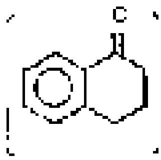
α-tetralol

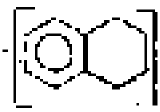
α-tetralone (Product F)

The final reaction in this sequence is aromatization. The addition of Pt and heat results in a dehydrogenation that produces product G, naphthalene.



α-tetralone   Naphthalene

Note: α tetralone  could have been converted to

tetralin  via a Clemmensen reduction. The tetralin could then undergo aromatization to yield naphthalene.

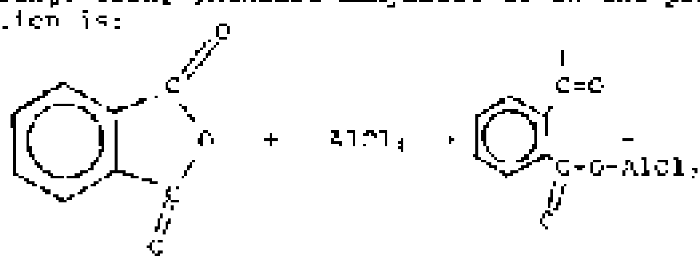
PROBLEM 21-7

> Predict the products of the following reactions: (a) Toluene + phthalic anhydride + $AlCl_3$; followed by H_2O. (b) The product from (a) + Conc. H_2SO_4 + heat.

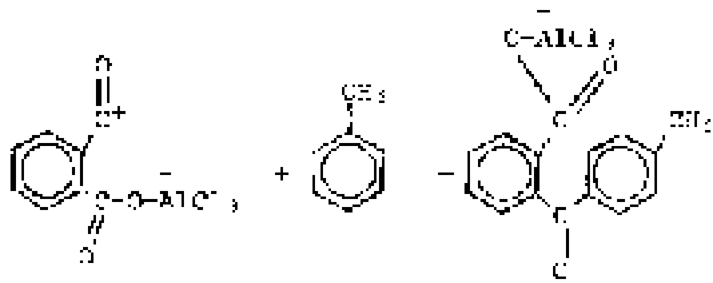
<u>Solution</u>: (a) An acid anhydride will form an acylium ion ($R-\overset{+}{C}=O$) upon treatment with a Lewis acid such as $AlCl_3$. The general reaction is:

$$\underset{\text{Acid anhydride}}{RC(=O)OC(=O)R'} + AlCl_3 \rightarrow \underset{\text{acylium ion}}{R\overset{+}{C}=O} + R'C(=O)-O\overset{-}{Al}Cl_3$$

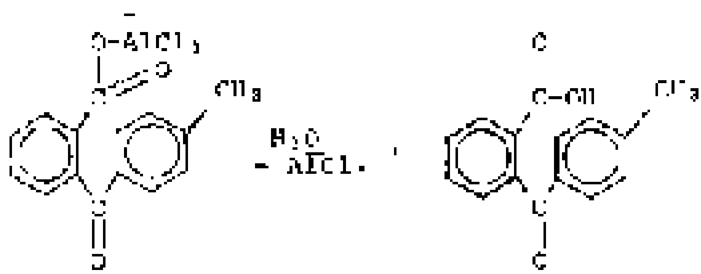
A cyclic acid anhydride will react with $AlCl_3$ to open the ring. Using phthalic anhydride as in the problem, the reaction is:



The resulting acylium ion can undergo an electrophilic aromatic substitution reaction with toluene. Since the methyl group of toluene is an aromatic ring activator, it will direct an electrophile in an ortho, para orientation. The reaction however, will produce almost all para isomer because of the great bulk of the electrophile. The reaction can be written as:

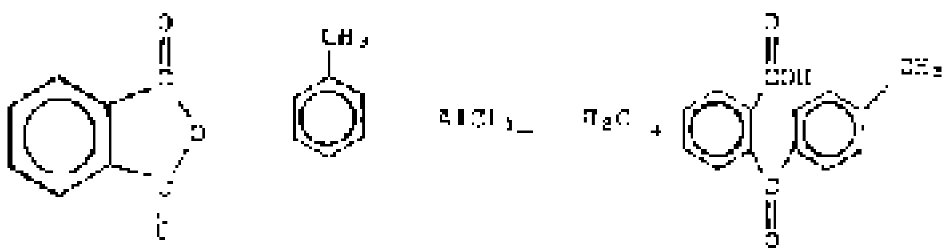


The product can be converted to carboxylic acid by treatment with water. The reaction is:

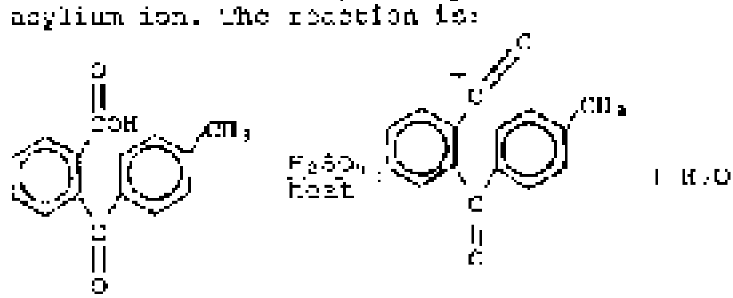


o-(p-Toluyl)benzoic acid

The net reaction can be written as:

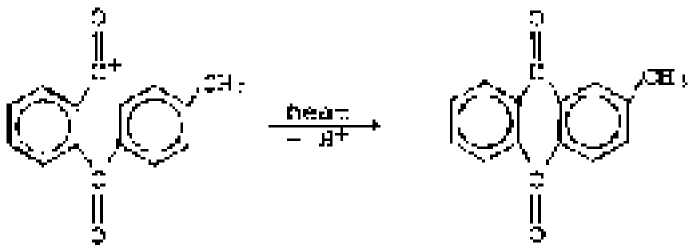


(b) When the product from reaction (a) is heated in concentrated acid, the acylium ion ($R\overset{+}{C}{=}O$) will be formed. This occurs because the concentrated acid is more acidic than the carboxylic acid, and the carboxylic acid will be protonated at the hydroxyl group. It will lose H_2O to form the acylium ion. The reaction is:

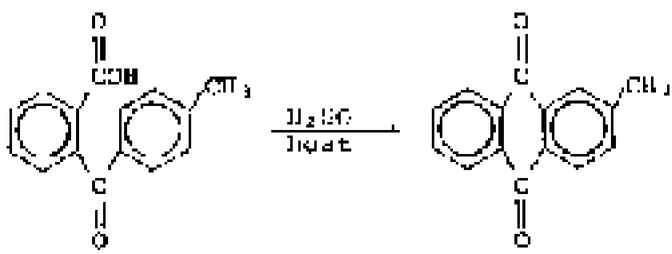


Acylium ion

The acylium ion is oriented in such a way that it can undergo an electrophilic aromatic substitution reaction with the aromatic ring bearing the methyl group. The electrophile will substitute meta to the methyl group, despite the fact that the methyl group is an ortho, para director. This is because the formation of a six-membered ring (by meta substitution) is more stable than the formation of a seven-membered ring (by ortho substitution). Six-membered rings are more stable than seven-membered rings because there is less angle strain on the carbons in a six-membered ring. The ring formation reaction of the acylium ion can be shown as:



The overall reaction can be written as:



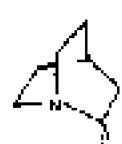
o-(p-Toluyl)benzoic acid

2-Methyl-9,10-anthraquinone

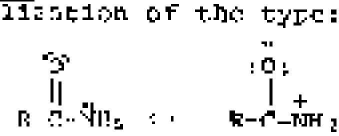
AMIDES

PROBLEM 21-8

Amides with structures like the following are difficult to prepare and are relatively unstable. Explain.

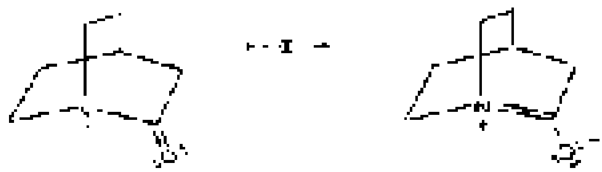


Solution: An amide can be stabilized by electron delocalization of the type:



This type of delocalization is unfavorable in the above structure because of the high strain associated with the double bond at the bridgehead position. This high strain is due to the extremely inefficient overlap of the p-orbitals that form the π bond. This is known as Bredt's Rule and results in loss of stabilization compared to an ordinary amide. Hence, electron delocalization does not occur in the above structure.

DOES NOT OCCUR:



high-energy structure

PROBLEM 21-9

Compound A of molecular formula $C_6H_{12}N_2O_2$ reacts with aqueous nitrous acid to give compound B of formula $C_6H_{10}O_4$. Compound B readily loses water on heating to give C, $C_6H_8O_3$. Compound A can also react with a solution of bromine and sodium hydroxide in water to give D, $C_4H_{12}N_2$, which on treatment with nitrous acid and perchloric acid gives methyl ethyl ketone. Write structures of all compounds and the equations involved.

Solution: The key to this problem is the determination of the structure of compound A. The type of organic compound is indicated by the fact that "A" reacts with a solution of bromine (Br_2) and sodium hydroxide in water. A mixture of Br_2 and NaOH produces $Na^+{-}OBr$, which is the reagent used in the Hofmann degradation of amides to primary amines. Hofmann degradation can be illustrated as:

$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NH_2 + Br_2 + 4NaOH \rightarrow RNH_2 + 2NaBr + Na_2CO_3 + 2H_2O.$$

The fact that compound A, a six carbon molecule, becomes a four carbon molecule, after the degradation indicates A must be a diamide. Consequently, D, the product of the degradation, must be a diamine. The reaction can be written as

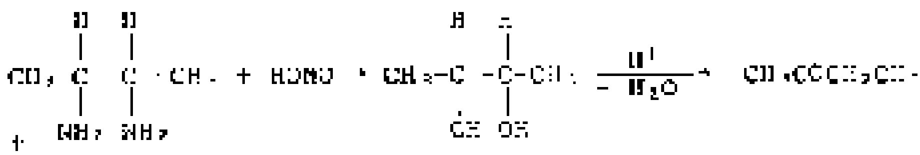
$$[A]\quad C_6H_{12}N_2O_2 \quad C_4H_8\begin{cases}CONH_2\\ CONH_2\end{cases} \xrightarrow[H_2O]{Br_2,\ NaOH} C_4H_8\begin{cases}NH_2\\ NH_2\end{cases}\quad [D]$$

Compound A is reacted with nitrous acid to give $C_6H_{10}O_4$, compound B. This reaction is an example of the fact that unsubstituted amides (such as A) are converted to carboxylic acids by treatment with nitrous acid. Therefore, the equation of the reaction becomes:

$$[A]\quad C_4H_8\begin{cases}CONH_2\\ CONH_2\end{cases} + \underset{\text{(Nitrous acid)}}{HONO} \longrightarrow C_4H_8\begin{cases}COOH\\ COOH\end{cases}\ [B] + 2N_2$$

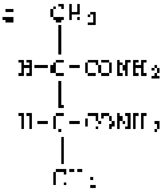
B loses water to yield C, $C_6H_8O_3$. By examining B, one finds that the only way to lose water is for the carboxylic groups to form an anhydride group but B cannot be a straight chain diacid for only β and γ diacids undergo dehydration (2 or 3 carbons between the carboxyl groups). To write C, however, more structural detail is required in B.

This detail can be found by using the last bit of information - the fact that D yields methyl ethyl ketone after nitrous and perchloric acid ($HClO_4$) treatment. When D, the diamine, reacts with these acids it deaminates and undergoes a pinacol type of arrangement as shown:

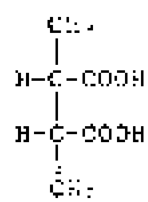


(Structure D) (A pinacol) (methyl ethyl ketone)

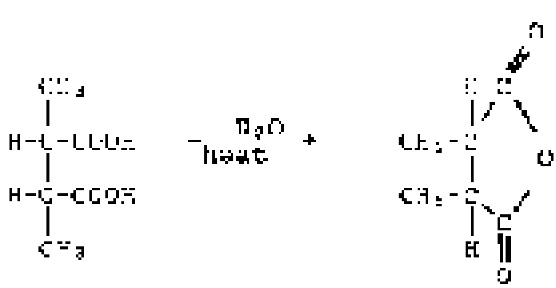
This sequence of reactions indicates that the structural formula of compound A must be the diamide of 2,3 dimethyl-succinic acid or



. This indicates that B can be written as



, which is called 2,3 dimethyl succinic acid. With this structure, the reaction which involves the loss of water becomes:

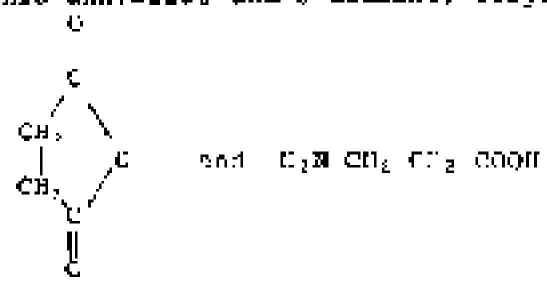


C

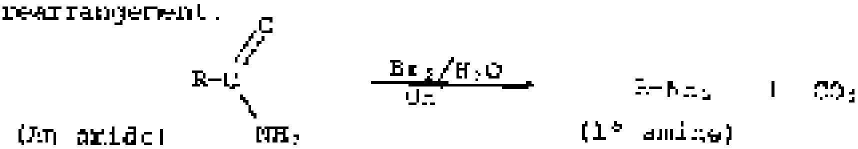
Compound C is, therefore, 2,3-dimethylsuccinic anhydride.

A chemist possesses succinic anhydride and wants to make β-alanine (β-aminopropionic acid). How should the synthesis be performed?

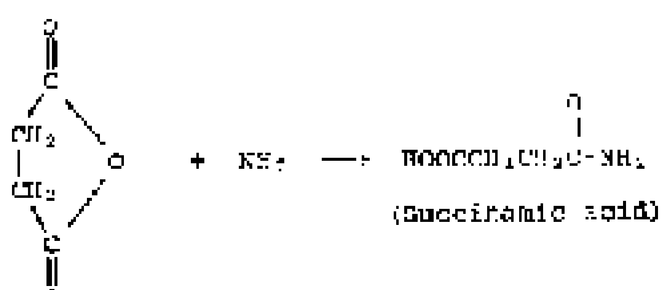
Solution: The following represents the structures of succinic anhydride and β-alanine, respectively:



These structures indicate that β-alanine is an amide of 1 less carbon atom than succinic anhydride. This means the synthesis must employ a reaction that generates an amine of 1 less carbon from succinic anhydride. Such a reaction is the Hofmann degradation of amides. As seen below, the reaction involves the migration of a group from carbonyl carbon to the adjacent nitrogen atom. It is therefore an example of a molecular rearrangement.



This method of generating a 1° amine means that succinic anhydride must be converted to an amide. An ammonolysis reaction can accomplish this task as shown:



Succinamic acid can now undergo Hofmann degradation to yield β-alanine:

$$HOOCCH_2CH_2\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow[OH^-]{Br_2/H_2O} HOOC-CH_2-CH_2-NH_2$$

β-alanine

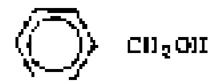
• PROBLEM 21-11

Show how the following alcohols react with carboxylic acids to yield esters.

(a) CH_3CH_2OH

Ethanol

(b)



Benzyl alcohol

Solution: Alcohols react with carboxylic acids in the presence of mineral acid catalysts, to give esters. The general reaction is:

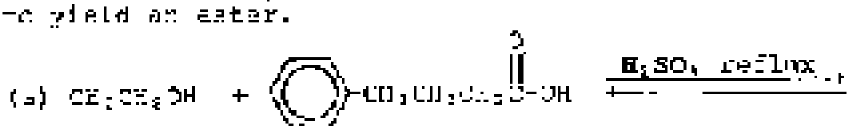
$$R\text{-}OH + R'\text{-}\overset{\overset{\large O}{\|}}{C}OH \xrightarrow{H_2SO_4} R'\text{-}\overset{\overset{\large O}{\|}}{C}\text{-}O\text{-}R + H_2O$$

where the mineral acid is almost always sulfuric acid, H_2SO_4. Also, this type of reaction is completely reversible, in that the same catalyst, hydrogen ion, that catalyzes the forward reaction, esterification, necessarily catalyzes the reverse reaction, hydrolysis. The mechanism by which the forward reaction works is direct esterification where molecules of water are "split out" when the alcohol and carboxylic acid are mixed together. For example:

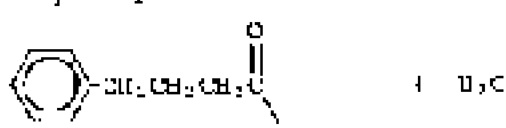
$$RCO\boxed{OH} + \boxed{H}OR' \rightarrow RCOOR' + H_2O.$$

With this principle, the general explanation and reaction, carboxylic acids can be added to each alcohol to yield an ester.

(a)

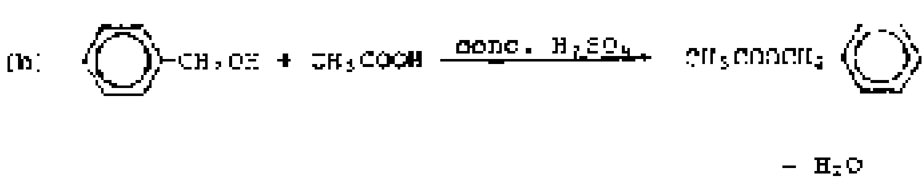


Ethanol γ-Phenylbutyric acid



Ethyl γ-Phenylbutyrate

(b)



Benzyl Alcohol Acetic acid Benzyl acetate

Show and explain how an alcohol can be derived from hydrolysis of the following esters. Give two products from each ester given by:

(1) Alkaline hydrolysis to yield an alcohol

(2) Acid hydrolysis to yield an alcohol

(a) $CH_3\overset{O}{\overset{\|}{C}}-O-CH_2CH_3$

Ethyl acetate

(b)

$CH_2O-\overset{O}{\overset{|}{C}}-(CH_2)_{16}CH_3$

$CH\ O-\overset{O}{\overset{|}{C}}-(CH_2)_{16}CH_3$

$CH_2O-\overset{O}{\overset{|}{C}}-(CH_2)_{16}CH_3$

Tristearin

Solution: Alcohols can be prepared from esters in two ways; by alkaline hydrolysis which is called saponification, and by acid catalyzed hydrolysis.

Considering alkaline hydrolysis first, this reaction is carried out by using a strong base, such as sodium hydroxide (NaOH), mixed with water and the entire reaction mixture heated. The hydrolysis of esters with a concentrated alkaline solution to yield an alcohol is essentially irreversible. The general reaction for this process is:

$$\underset{\text{Ester}}{R-\underset{\underset{O}{\|}}{C}-O-R'} + \underset{\text{Base}}{NaOH} \xrightarrow{aq.} \underset{\text{Salt}}{R-\underset{\underset{O}{\|}}{C}-\overset{-+}{ONa}} + \underset{\text{Alcohol}}{R'OH}$$

The alcohol produced in this type of hydrolysis is the secondary product. The primary product is the sodium salt of the ester which is used in the production of soap. Using the mechanism of the general reaction, the two alkaline hydrolyses can be illustrated.

$$\text{(a)}\ \underset{\text{ethyl acetate}}{CH_3\overset{O}{\overset{\|}{C}}-O-CH_2CH_3} + NaOH \xrightarrow{aq.} \underset{\text{sodium acetate}}{CH_3-\overset{O}{\overset{|}{C}}-\overset{-+}{ONa}} + \underset{\text{ethanol}}{CH_3CH_2OH}$$

(b)

$$\begin{array}{l} CH_2O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \\ | \\ CH\ O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \xrightarrow[aq.]{3\ NaOH} 3Na\overset{+}{O}-\overset{O}{\overset{||}{C}}(CH_2)_{16}CH_3 + \begin{array}{l} CH_2OH \\ CH-OH \\ CH_2OH \end{array} \\ | \\ CH_2O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \end{array}$$

Glyceryl tristearate (Tristearin) — 3X Sodium Stearate — Glycerol

In the second reaction, glyceryl tristearate is known as a triglyceride or triacylglycerol which is nothing more than fat. This molecule is made of glycerol and three long chain fatty acids. When this compound, which is an ester, is heated along with NaOH and water it can be seen that the alcohol (glycerol) is liberated. The salt form of the fatty acid, stearic acid is also liberated as sodium stearate, an ester. The latter product is used in the commercial production of soaps, and the process is called saponification. The problem also calls for a product of acid hydrolysis of esters a & b to yield an alcohol. The reaction in this type of hydrolysis however, is reversible, and the mechanism for hydrolysis is also (taken in the opposite direction) the mechanism for esterification. Hence, the general reaction is:

$$R\overset{O}{\underset{}{\overset{||}{C}}}-OR' + H_2O \underset{}{\overset{HCl}{\rightleftharpoons}} RCOOH + R'OH$$

Ester — Acid — Alcohol

As seen above, when hydrolyzing an ester with an acid, the major product is a carboxylic acid and an alcohol byproduct. Now, using the general reaction, an alcohol product can be derived from precursors (a) and (b).

(a) $$CH_3-\overset{O}{\overset{||}{C}}-OCH_2CH_3 + H_2O \overset{HCl}{\rightleftharpoons} CH_3-\overset{O}{\overset{||}{C}}OH + CH_3CH_2OH$$

Ethyl acetate — Acetic acid + Ethanol

(b)

$$\begin{array}{l} CH_2O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \\ | \\ CH\ O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \quad H_2O \overset{HCl}{\rightleftharpoons} 3\ CH_3(CH_2)_{16}COOH + \begin{array}{l} CH_2OH \\ | \\ CH-OH \\ | \\ CH_2OH \end{array} \\ | \\ CH_2O-\overset{O}{\overset{||}{C}}-(CH_2)_{16}CH_3 \end{array}$$

Gylceryl Tristearate (Tristearin) — 3X Stearic Acid + Glycerol

Acid hydrolysis more or less dissociates the ester precursor into its component parts by adding water. This liberates the ester to yield a carboxylic acid and an alcohol as shown above.

• PROBLEM 21-13

> Indicating the mechanism, show how ethyl propionate may be prepared from propionic acid.

Solution: The structure of ethyl propionate,

$$CH_3CH_2\overset{\overset{O}{\|}}{C}-OCH_2CH_3,$$

indicates that it is an ester. Therefore, the preparation of ethyl propionate from propionic acid (CH_3CH_2COOH) will require an esterification reaction with ethyl alcohol (CH_3CH_2OH). An esterification may be generalized as

$$\underset{\text{(carboxylic acid)}}{R-\underset{\underset{O}{\|}}{C}-OH} + \underset{\text{(alcohol)}}{R'-OH} \overset{H^+}{\rightleftharpoons} \underset{\text{(Ester)}}{R-\underset{\underset{O}{\|}}{C}-O-R'} + \underset{\text{(water)}}{H_2O}$$

The acid H^+ serves as a catalyst as will be seen by the mechanism of esterification, which is an example of nucleophilic substitution.

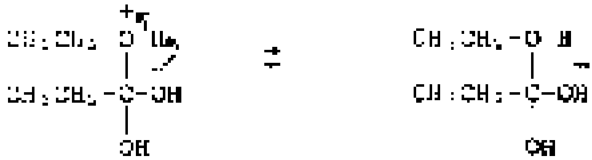
The mechanism begins with the protonation of the carboxylic acid, propionic acid:

$$CH_3CH_2-\underset{\underset{:O:}{\|}}{C}-OH + H^+ \rightleftharpoons CH_3CH_2\overset{+}{C}-OH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad OH$$

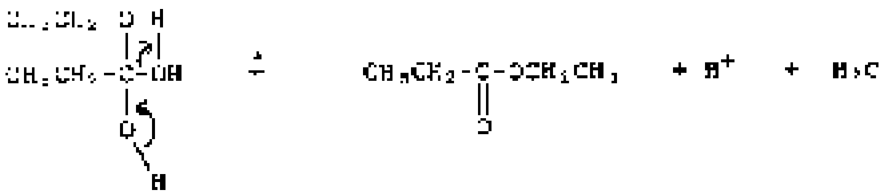
The carbonyl (C=O) is protonated because of its polarization which results in a partially negatively charged oxygen atom. Next, the protonated acid is attacked by a nucleophile, in this case an alcohol (ethyl alcohol) due to the fact that the carboxyl carbon now has significant positive character. It may be illustrated as follows:

$$CH_3CH_2-\overset{+}{C}-OH + CH_3CH_2\ddot{O}H \rightleftharpoons \underset{\text{(Adduct)}}{\begin{array}{c} CH_3CH_2-\overset{+}{O}H \\ | \\ CH_3CH_2-C-OH \\ | \\ OH \end{array}}$$
$$\qquad\qquad OH$$

This adduct then undergoes a hydrogen ion transfer as shown:



The final reaction is the elimination of water and H^+ to obtain ethyl propionate:



The overall reaction then becomes:

$$CH_3CH_2COOH + CH_3CH_2OH \overset{H^+}{\rightleftharpoons} CH_3CH_2\overset{O}{\overset{\|}{C}}-OCH_2CH_3 + H_2O + H^+.$$

■ **PROBLEM 21-16**

> A chemist added water and acid to an unknown ester of formula $C_6H_{12}O_2$ to produce an acid X and an alcohol Y. Oxidation of Y with chromic acid produced X. Determine the structure of the original ester. Write equations for all reactions that occur.

Solution: The structure of any ester may be generalized as $R-\overset{O}{\overset{\|}{C}}-OR'$, where R and R' may be aryl and/or alkyl groups. R and R' may or may not be the same. By a reverse esterification reaction, an ester may be hydrolized to its component carboxylic acid and alcohol by acid and water as follows:

$$R-\overset{O}{\overset{\|}{C}}-OR' + H_2O \overset{H^+}{\rightleftharpoons} R-\overset{O}{\overset{\|}{C}}-OH + R'-CH_2OH$$

(Ester) (Carboxylic acid) (1° Alcohol)

In this problem, $R-\overset{O}{\overset{\|}{C}}-OH$ is represented by X and $R'-CH_2OH$ by Y. The problem indicates Y becomes X upon chromic acid treatment. This is the crux of the problem.

Chromic acid ($H_2Cr_2O_7$) is a strong oxidizing agent. It readily oxidizes primary alcohols to aldehydes, and the aldehydes $\left(\begin{smallmatrix} H \\ & C=O \\ R' \end{smallmatrix} \right)$ are in turn rapidly oxidized to carboxylic acids.

This means that $R'-CH_2OH$ becomes $R'-\overset{\overset{\displaystyle O}{\|}}{C}-OH$ after chromic acid addition. This indicates, therefore, that $R'-\overset{\overset{\displaystyle O}{\|}}{C}-OH$ must be the same as $R-\overset{\overset{\displaystyle O}{\|}}{C}-OH$ for Y to be identical to X. In other words, R must be the same as R'. (They must have the same number of carbon and hydrogen atoms.)

The ester is given as having a molecular formula of $C_6H_{12}O_2$, which indicates each R (R') is made of 3 carbons. Since chromic acid only oxidizes primary alcohols, the alcohol portion of the ester must be from propanol ($CH_3CH_2CH_2OH$). This leaves only the acid propionic $\left(CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OH\right)$ as the carboxylic acid. Therefore, the structure of the original ester must have been $CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_2CH_3$, which is termed n-propylpropionate. If the atoms are counted, one will find they match the molecular formula.

The reactions that must have occurred are indicated as follows:

$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_2CH_3 + H_2O \xrightarrow{H^+} \underset{(X)}{CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OH} +$$

$$\underset{(Y)}{CH_3CH_2CH_2OH} + H^+$$

$$CH_3CH_2CH_2OH \ (Y) + H_2Cr_2O_7 \rightarrow CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-H + H_2Cr_2O_7 \rightarrow$$

$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OH \ (X)$$

• PROBLEM 21-15

Hydrolysis of neutral compound (A), $C_7H_{14}O_2$, gave an acid (B) and an alcohol (C). C reacted with $SOCl_2$ and was then treated with Mg. Addition of CO_2 followed by hydrolysis, yielded an acid identical to (B). Determine the structural formulas of A, B and C.

Solution: Once the nature of the compounds is elucidated (that is, the class of organic compound to which they belong), structural formulas can be written.

Compound A must be an ester, $R-\overset{\overset{O}{\|}}{C}-OR'$, (where R and R' can be the same). That this is so becomes evident from the fact that the hydrolysis of A yields a carboxylic acid (B) and an alcohol (C), which is exactly what one expects when the reverse of the esterification occurs. In addition, esters are neutral substances, which also meets the requirements of this problem. The reverse esterification reaction by acid hydrolysis can be illustrated as follows:

$$\underset{\text{(Ester)}}{R-\overset{\overset{O}{\|}}{C}-OR'} + HOH \xrightarrow{H^+} \underset{\text{(Carboxylic acid)}}{R\overset{\overset{O}{\|}}{C}-OH} + \underset{\text{(Alcohol)}}{R'OH}$$

The alcohol, C, reacted with PCl_3. PCl_3 is one of the reagents which will effect the replacement of the alcoholic hydroxyl group by a halogen atom. The generalized reaction can then be written as:

$$3R-OH + PCl_3 \rightarrow \underset{\text{(Alkyl Chloride)}}{3R-Cl} + H_3PO_3$$

When the alkyl chloride is treated with Mg, the Grignard reagent is produced.

$$R-Cl + Mg \xrightarrow{\text{Dry Ether}} \underset{\text{(Grignard Reagent)}}{R-MgCl}$$

The addition of CO_2 (followed by hydrolysis) illustrates a classical method of producing carboxylic acids. The reaction sequence is shown:

$$R-MgCl + CO_2 \rightarrow R-\overset{\overset{O}{\|}}{C}-OMgCl \xrightarrow[HOH]{H^+} \underset{\text{(Carboxylic acid)}}{R-\overset{\overset{O}{\|}}{C}-OH}$$

The problem indicates this acid formed from the alcohol, C, is identical to B. Note that in the synthesis of the carboxylic acid from C, a carbon atom must be added. (Preparation of carboxylic acids through a Grignard reagent will add one carbon atom to the skeleton.) Consider now the fact that compound A contains 5 carbon atoms. This means the alcohol fragment must be 2 carbons long and the acid portion 3 carbons. The reason for this is the fact that only when the alcohol is 2 carbons long can a carboxylic acid be synthesized from it via a Grignard reagent to yield an acid of 3 carbons that would be identical to the acid portion of the ester.

The only 2 carbon alcohol portion possible is ethyl, which means the acid portion must be n-propyl. (The iso-propyl configuration is not possible since the acid synthesized from the alcohol (ethyl) by carbonation of a Grignard reagent will be a straight chain acid.) Therefore, the structural formula of A becomes:

$$CH_3CH_2\overset{\overset{\large O}{\|}}{C}-OCH_2CH_3$$

(Ethyl Propionate). The sequence of reactions that generates B and C can now be written:

$$CH_3CH_2\overset{\overset{\large O}{\|}}{C}-OCH_2CH_3 \xrightarrow{H^+} \underset{[B]}{CH_3CH_2\overset{\overset{\large O}{\|}}{C}-OH} + \underset{[C]}{HOCH_2CH_3}$$

$$HOCH_2CH_3 + PCl_3 \rightarrow ClCH_2CH_3 + Mg \rightarrow ClMgCH_2CH_3$$

$$+ CO_2 \rightarrow ClMgO\underset{\underset{\large O}{\|}}{C}-CH_2CH_3 \xrightarrow{H^+} \underset{[B]}{HO\underset{\underset{\large O}{\|}}{C}-CH_2CH_3}$$

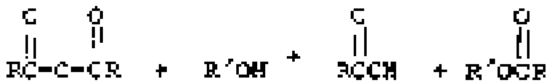
• PROBLEM 21-10

What product do you expect from the following reaction?

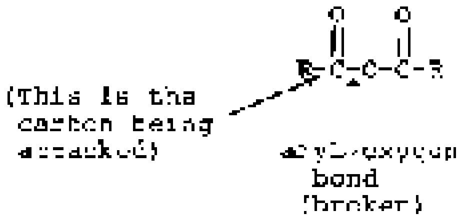
 + CH_3OH →
(1 mole)

The yield of the product is essentially quantitative. Write a mechanism for the reaction.

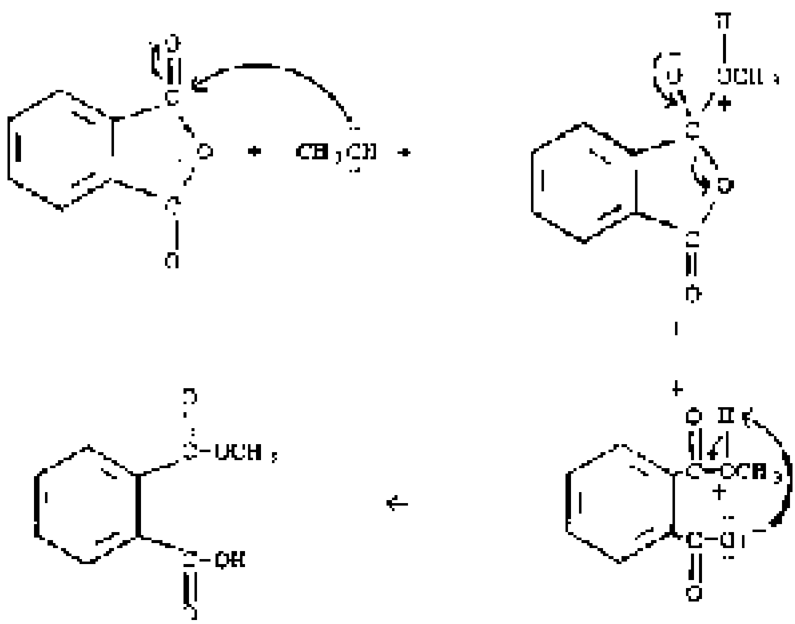
Solution: When an acid anhydride is treated with an alcohol, an esterification reaction occurs. The general reaction is:



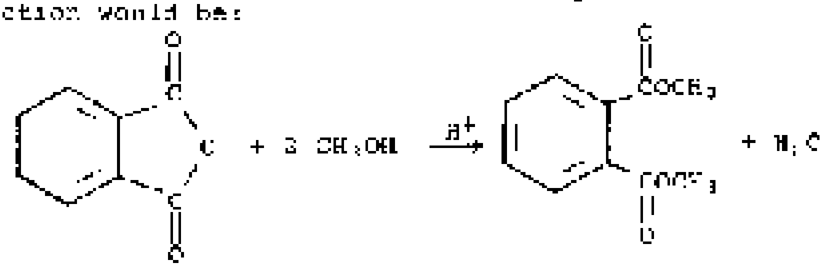
Esterification of this type involve the breaking of the acyl-oxygen bond:



The reaction of a cyclic acid anhydride with an alcohol produces a molecule with both an ester and carboxylic acid functionality. The mechanism for the reaction of phthalic anhydride with methanol is:



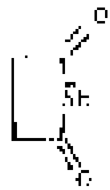
Only one mole of methanol is used in this reaction. If two or more moles had been used in the presence of acid the product would have the methyl diester. The reaction would be:

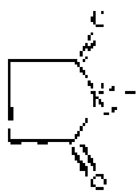


IMIDES

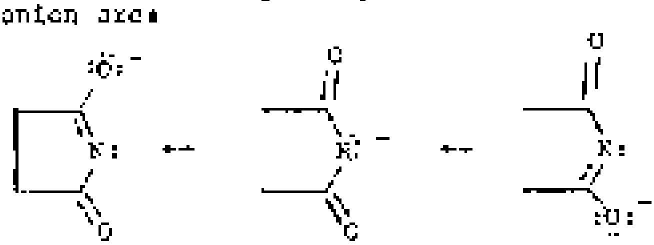
• PROBLEM 21-17

From structural considerations, what can you predict about the acid-base properties of succinimide?

Solution: Succinimide,  , is a fairly acidic compound. This is because the anion produced by proton loss is considerably more stable than the cation produced by protonation.

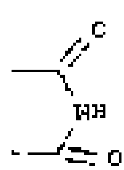
 more stable than 

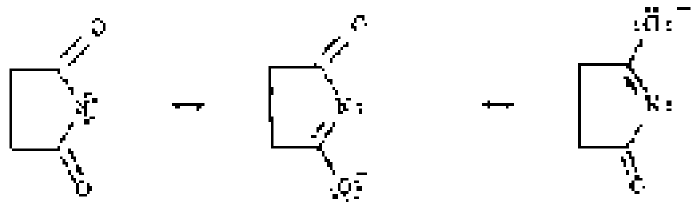
This stabilization of the anion is attributed to electron delocalization involving the carbonyl (C=O) bonds. The cation cannot have this type of electron delocalization. The principal resonance structures for the anion are:



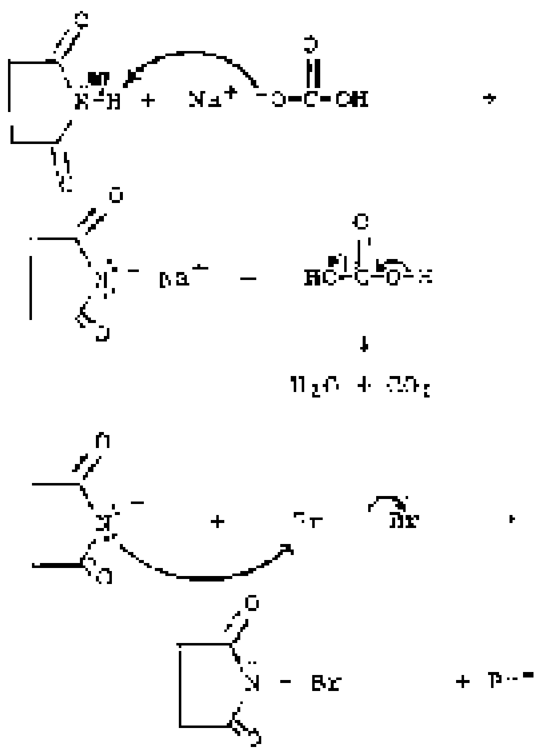
• PROBLEM 21-18

Suggest a mechanism for the reaction of succinimide with bromine and sodium bicarbonate.

Solution: Succinimide,  , acts as an acid because of the large stabilization due to electron delocalization of the anion that results from proton loss. The principal resonance structures for the succinimide anion are:



Sodium bicarbonate ($NaHCO_3$) is a base and will remove a proton from succinimide. The resulting succinimide anion will attack a bromine molecule to produce N-bromosuccinimide (NBS). This mechanism is shown as:



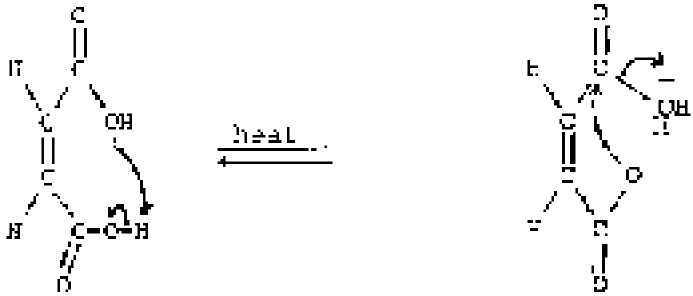
N-bromosuccinimide

DICARBOXYLIC ACIDS

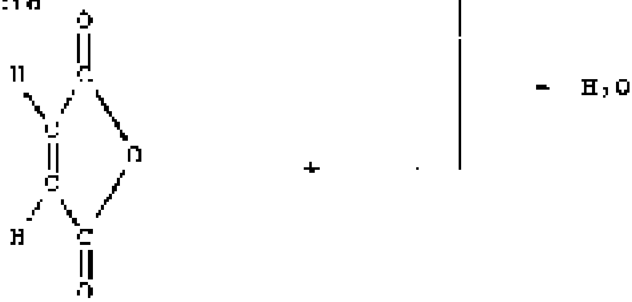
• PROBLEM 21-15

Fumaric and maleic acid give the same anhydride on heating, but fumaric acid must be heated to much higher temperatures than maleic acid to effect the same change. Explain. Write reasonable mechanism for both reactions.

<u>Solution</u>: Maleic acid upon heating undergoes a dehydration reaction to form maleic anhydride. The mechanism involves the formation of a six membered ring in the transition state:

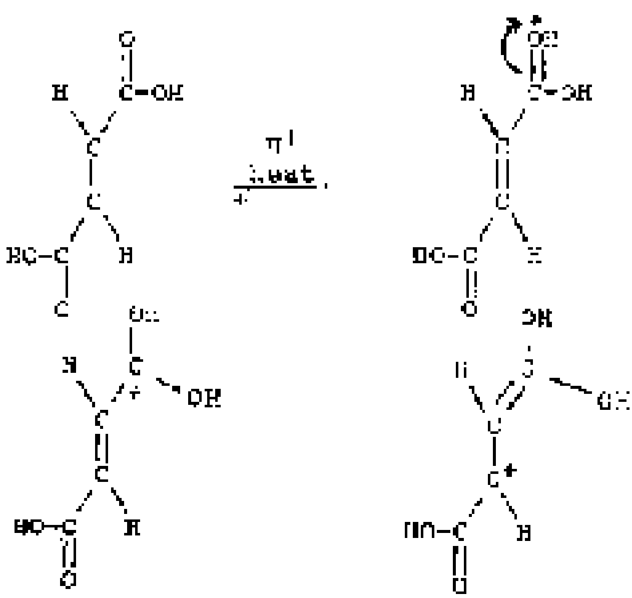


Maleic acid

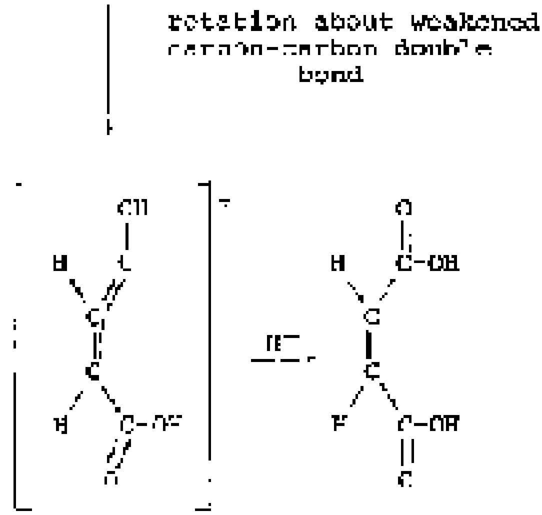


maleic anhydride

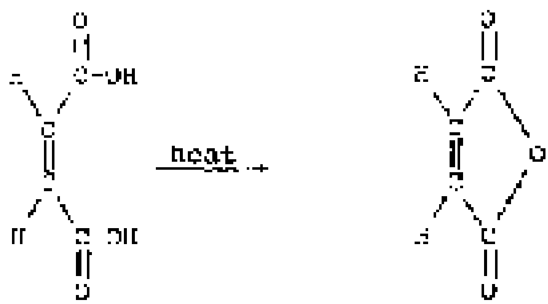
Fumaric acid differs from maleic acid only in that it is in the trans configuration. Upon heating, fumaric acid is isomerized to maleic acid. Continued heating produces maleic anhydride. Fumaric acid is converted to maleic acid by forced rotation around its double bond. The double bond is first weakened by protonation of the carbonyl oxygen. The resultant positive charge is resonance stabilized. The mechanism for conversion of fumaric acid to maleic anhydride is:



resonance stabilized cation



maleic acid



Thus we see that fumaric acid cannot be directly converted to the anhydride since it lacks the cis configuration found in maleic acid. This configuration is necessary for the positively charged carbon of the acylium cation to interact with a carbonyl oxygen of the other carboxyl group.

• PROBLEM 21-20

(a) (−)-Erythrose, $C_4H_8O_4$, gives tests with Tollens' reagent and Benedict's solution, and is oxidized by bromine water to an optically active acid, $C_4H_8O_5$. Treatment with acetic anhydride yields $C_{12}H_{16}O_7$. Erythrose consumes three moles of HIO_4 and yields three moles of formic acid and one mole of formaldehyde. Oxidation of erythrose by nitric acid yields an optically inactive compound of formula $C_4H_6O_6$.

(−)-Threose, an isomer of erythrose, shows similar chemical behavior except that nitric acid oxidation yields an optically active compound of formula $C_4H_6O_6$.

On the basis of this evidence what structure or structures are possible for (−)-erythrose? For (−)-threose?

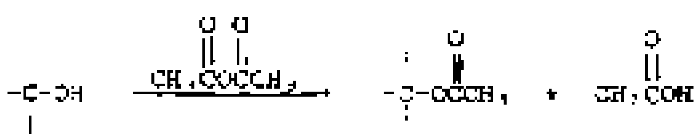
(b) When D-glyceraldehyde, $CH_2OHCHOHCHO$, is treated with cyanide and the resulting product is hydrolyzed, two monocarboxylic acids are formed. These acids are identical with the acids obtained by oxidation with bromine water of (-)-threose and (-)-erythrose.

These acids are identical with the acids obtained by oxidation with bromine water of (-)-threose and (-)-erythrose.

Assign a single structure to (-)-erythrose and to (-)-threose.

Solution:(a) The molecular formula for (-)Erythrose, $C_4H_8O_4$, fits the general formula, $C_n(H_2O)_n$ which is typical of the group of compounds known as carbohydrates. These compounds always have two functional groups - the hydroxyl group and a carbonyl group (either as a ketone or aldehyde). Both ketoses (ketonic carbohydrates) and aldoses give positive tests for Tollens' reagent or Benedict's solution so these oxidations do not give us definitive conclusions. Actually only an aldehyde can be oxidized to a carboxylic acid needed for a positive test. However, under the alkaline reaction conditions, a ketohydroxyl compound will also isomerize to a hydroxy aldehyde, giving a positive test. Bromine water, on the other hand, is specific for aldoses, so therefore (-) Erythrose is an aldose.

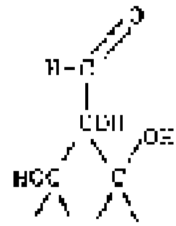
Treatment of (-) Erythrose with acetic anhydride gives a compound with the molecular formula $C_{10}H_{14}O_7$. This shows an addition of six carbons, six hydrogens and three oxygens to (-) Erythrose. A carbon bearing a hydroxyl group upon treatment with acetic anhydride will react to form an ester:



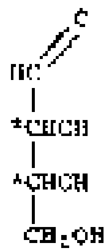
ester acetic acid

This esterification reaction involves the attack of the hydroxyl oxygen upon the carbonyl carbon of the anhydride. Since (-) Erythrose gained six carbons upon treatment with acetic anhydride, and each acetyl group $\left[CH_3\overset{O}{\overset{\|}{C}}-\right]$ has two carbons, there must have been three sites of esterification on (-) Erythrose. That is, there must be three carbons in (-) Erythrose that have a hydroxyl group. At this point the compound looks like:

This has the formula $C_4H_7O_4$.

Note: (-) Erythrose can't be  because there are no chiral centers and no optically active acid could be made from it by oxidation with bromine water.

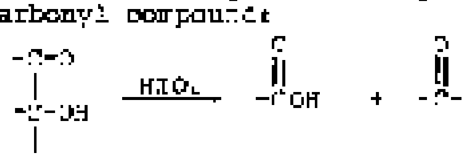
If we filled in the bonding requirements of the carbons by using hydrogens, we would get:



* = chiral carbons

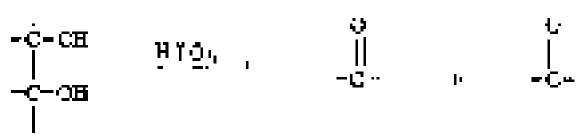
This has the formula $C_4H_8O_4$, which is the formula for (-) Erythrose.

Periodic acid (HIO_4) is a strong oxidizing agent which reacts with α-hydroxycarbonyl compounds to break the carbon-carbon single bond to yield a carboxylic acid and a carbonyl compound:

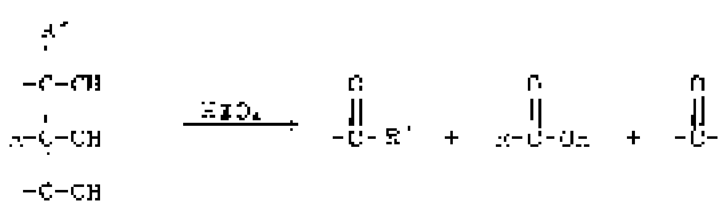


carboxylic acid   carbonyl compound

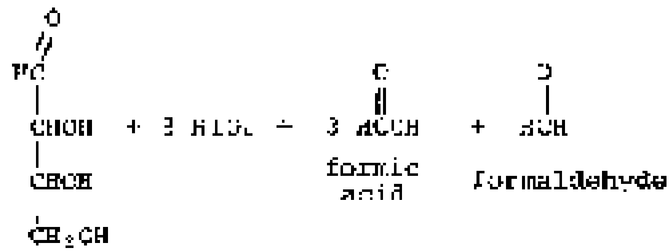
HIO_4 reacts with vic diols to break the carbon-carbon bond and form carbonyls:



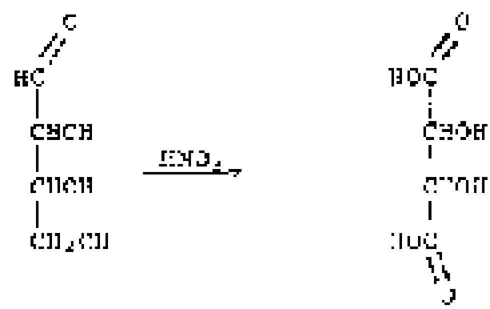
The middle carbon of a triol will be oxidized by HIO_4 to the carboxylic acid:



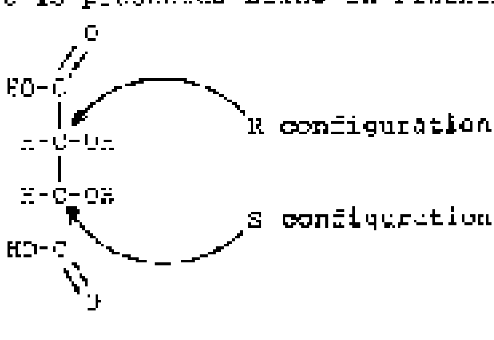
(-) Erythrose reacts with periodic acid to yield three moles of formic acid and one mole of formaldehyde. These results give support to our proposed structure of (-) Erythrose. The overall reaction of (-) Erythrose with three moles of the oxidizing agent is:



The structure of (-) Erythrose has not yet been fully determined; we must derive the orientation about the two chiral carbons. Oxidation of (-) Erythrose by nitric acid yields an optically inactive compound of the formula $C_4H_6O_6$. Nitric acid will oxidize aldehydes and primary alcohols to carboxylic acids. Oxidation of (-) Erythrose by nitric acid would give a dicarboxylic acid:



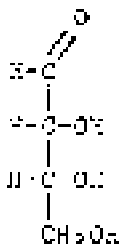
This agrees with the given data because the dicarboxylic acid has the formula $C_4H_6O_6$. Since it is said to be optically inactive, the two chiral carbons must have opposite orientations, and hence opposite relative configurations (one is R, the other is S). The dicarboxylic acid is presented below in Fischer projection form:



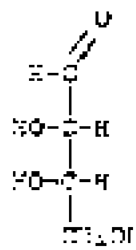
a meso-dicarboxylic acid

By working backwards, we can deduce two possible structures for (-) Erythrose. This is because the configuration about the chiral carbons are influenced by the groups attached to them.

Hence, the two possible structures for (-) Erythrose are shown below in Fischer projection form:

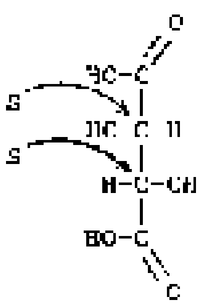


or

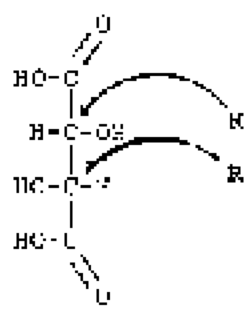


2R, 3R-   2S, 3S-

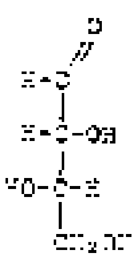
These two structures are enantiomers. (-) Threose is an isomer of (-) Erythrose with similar chemical properties. Oxidation of (-) Threose by nitric acid gives an optically active compound with the formula $C_4H_6O_6$. This compound is a dicarboxylic acid with the chiral carbons having the same configuration (either R or S). The Fischer projections are:



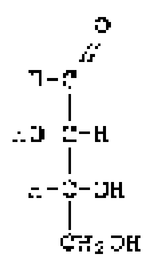
-or-



By working backwards, we can determine the two possible structures of (-) Threose to be:



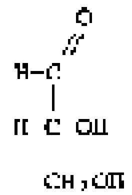
-or-



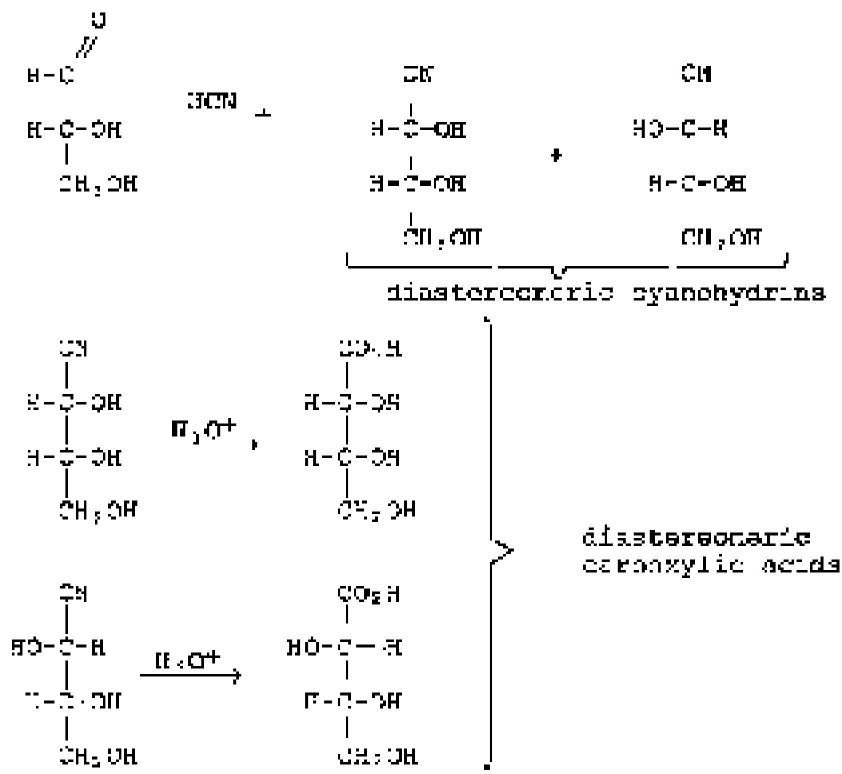
2R, 3S-   2S, 3R-

(-) Erythrose and (-) Threose are diastereomers (non-enantiomeric stereoisomers).

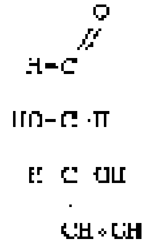
(b) The structure of R-glyceraldehyde is:



When an aldehyde is treated with cyanide, it reacts to form a cyanohydrin. Acid catalyzed hydrolysis will convert the cyano group to a carboxylic acid group. R-glyceraldehyde will form two different carboxylic acids. This is because the cyanide can attack either face of the carbonyl carbon. This results in the formation of two diastereomeric cyanohydrins which are converted to two diastereomeric carboxylic acids. These reactions are shown below:

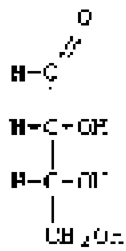


The carboxylic acids formed from R-glyceraldehyde are identical with the acids obtained by oxidation with bromine water of (+) threose and (-) erythrose. This means that of the two possible structures for (-) threose, the correct one is the 2S, 3R structure:



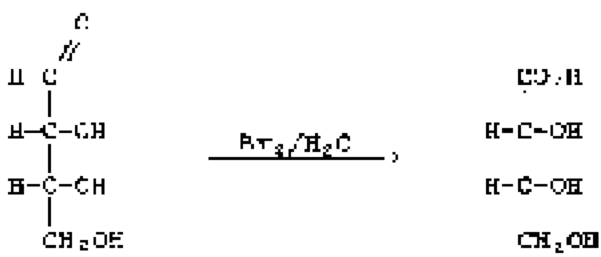
(–) Threose

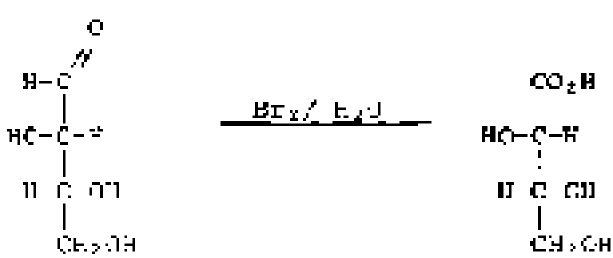
Of the two possible structures for (–) erythrose, the correct one is the 2R, 3R- structure:



(–) Erythrose

Oxidation by bromine water of (–) erythrose and (–) threose will give the same carboxylic acids formed from D-glyceraldehyde:

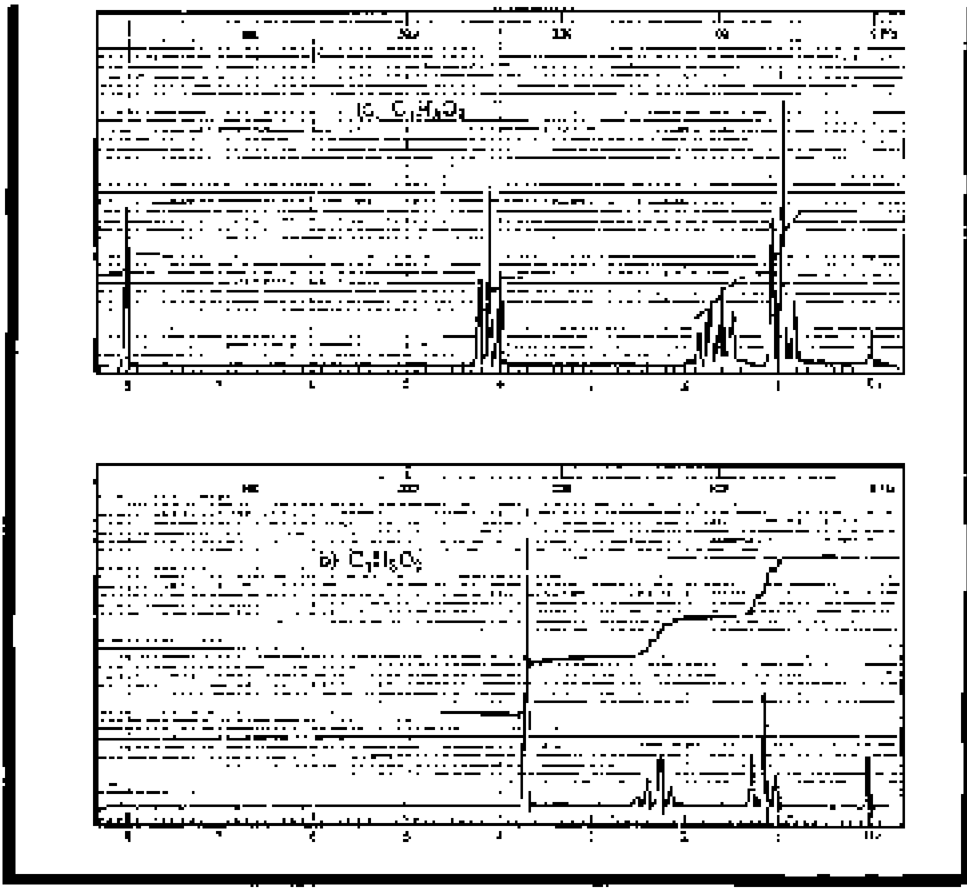




SPECTROSCOPY

• PROBLEM 21-21

Give structure or structures consistent with each of the nmr spectra shown:



Solution: (a) The molecular formula, $C_4H_8O_2$, shows that the compound contains one unit of unsaturation, possibly a double bond. The unsplit peak at δ 8 verifies this in that this chemical shift (the difference between the magnetic field strength at which a proton absorbs and the field strength of an internal standard's absorption) is characteristic of an aldehyde proton $\left(\mathrm{H{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}}\right)$. The compound is further seen to be an ester by the peaks at δ 4.1 which is typical of protons in the alkyl portion of an ester bonded to an oxygen. The δ values can be explained in that the chemical shift of a particular proton is dependent upon the electron density about that proton. Both a carbonyl group $\left(\mathrm{H{-}\overset{\overset{\displaystyle O}{\|}}{C}}\right)$ and oxygen $(\mathrm{-C{-}O-})$ lessen the electron density about a proton and move the proton's absorption downfield (to a higher δ value). The splitting pattern in this nmr spectrum can help us identify the specific alkyl portion of this ester. A proton's magnetic field is directly affected by the protons on adjacent carbons and its absorption pattern is altered. This mutual interaction, called spin-spin coupling, is useful in determining the number and types of protons adjacent to a particular hydrogen atom. In general, n equivalent adjacent protons will split a hydrogen atom into n+1 peaks. Looking at the nmr spectrum we see that the proton(s) next to the oxygen atom are split into a triplet. This means that they are bounded by two equivalent protons and thus we know that the compound contains the fragment

```
  O     H
  ||    |
H-C-O-C-C-
        |
        H
```

Using the molecular formula, we see that one carbon remains and this is shown to be in the form of a methyl group attached to a methylene group (CH_2) from the spectrum, in that there is an absorption at δ 1.0 (typical methyl resonance) which is split into a triplet.

Thus the compound is n propyl formate: $H-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_2CH_3$ whose structure can be checked by seeing the relative intensities on the integration graphs of the absorptions to be 3:2:2 (the intensity of an absorption is indicative of the number of protons giving rise to that absorption). The complex multiplet at δ 1.7 that has at least four peaks can be explained by the fact that these hydrogen atoms are bounded by five non equivalent protons. However, we can identify a distinct quartet among this multiplet whose peaks are sloped toward the methyl triplet. This pattern is typical of the ethyl group found in the molecule.

(b) The appearance of a triplet and a quartet in the spectrum indicates the presence of an ethyl group; the three methyl protons split the methylene into a quartet and the two methylene protons split the methyl into a triplet. The fact that there is only one remaining signal in the spectrum (a sharp singlet near 3.7 δ) and that there are four carbons in the compound (molecular formula $C_4H_8O_2$) suggests that the ethyl group is bonded to a carbon lacking protons, which is bonded to a carbon having protons. This structure

```
      ↗C C  CH2CH3
     /    ↑
has       has no
protons   protons
```

would give the singlet for the carbon with protons. The only possible structures with these restrictions and with the formula $C_4H_8O_2$ are:

$$CH_3-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_3 \qquad\qquad CH_3\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_3$$

methyl propionate $\qquad\qquad$ ethyl acetate

The compound that would account for the given nmr spectrum would be methyl propionate. The protons of CH_3O-

would occur as a singlet and would be downfield from both the CH_3 and CH_2 absorptions of the ethyl group. This is due to the greater deshielding of the CH_3C- by the adjacent oxygen. Ethyl acetate would have the $-OCH_2$ absorption

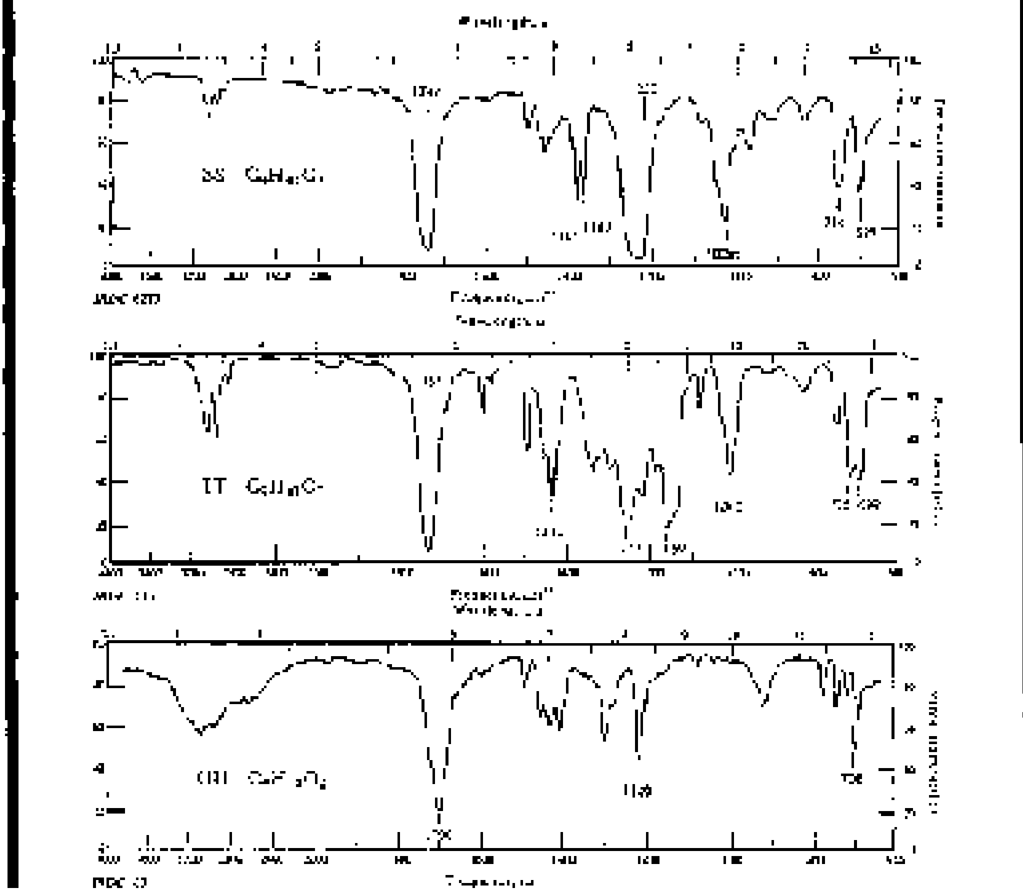
$$\overset{O}{\underset{}{\parallel}}$$

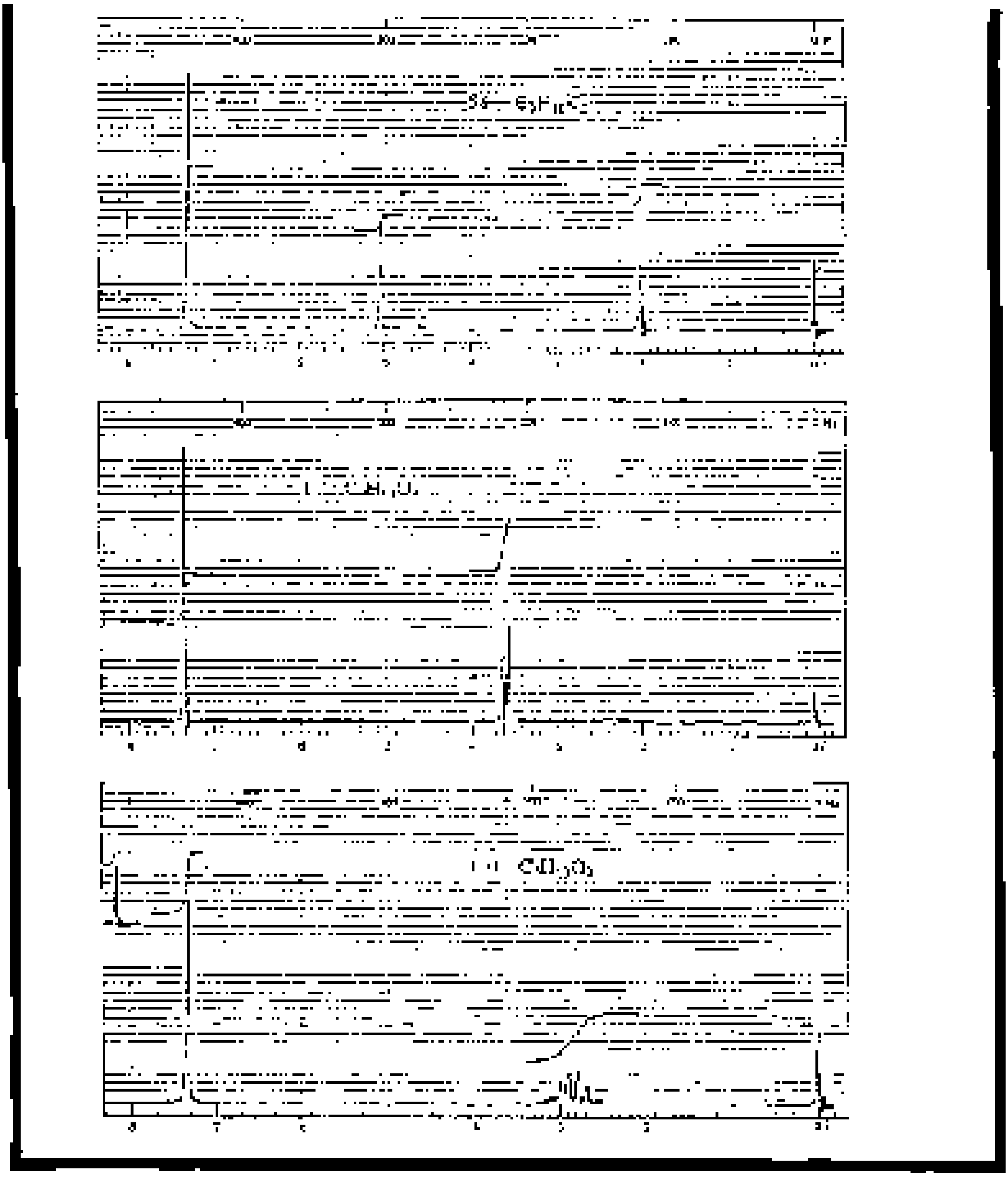
downfield from the $CH_3\overset{O}{\overset{\parallel}{C}}-$ absorption, which is not the case here. Hence the compound is methyl propionate and looks like:

$$CH_3-O-\overset{O}{\overset{\parallel}{C}}-CH_2CH_3$$

• PROBLEM 21-23

Give the structures of compounds SS, TT, and UU on the basis of their infrared spectra and their nmr spectra.





Solution: To identify and differentiate these compounds, we must try to obtain the maximum amount of information from the three sets of data before us: the compounds' molecular formula, their infrared spectrum and their nuclear magnetic resonance spectra. The molecular formula will give scant but useful information on the compounds' identity. The infrared spectrum will verify or suggest the general functionalities within the compounds. The nuclear magnetic resonance spectrum gives details of molecular structure, particularly of the proton arrangement. The molecular formula, $C_9H_{10}O_2$, tells that these are compounds that contain only carbon, hydrogen and oxygen. Thus, aldehydes, ketones, ethers, carboxylic acids, esters and alcohols (phenols) are possible. Also, by removing the oxygens and subtracting this formula from the formula of a saturated compound of the same carbon number we obtain the number of units of unsaturation.

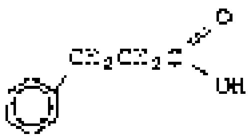
$$\begin{array}{r} C_9H_{20} \\ \underline{C_9H_{10}} \\ H_{10} \end{array} \quad \text{5 units of unsaturation}$$

This high amount of unsaturation is typical of aromatic compounds where there are three double bonds and one ring, each counting as one unit of unsaturation. Before hypothesizing any further, we should look at the compounds' individual infrared spectra. Infrared spectroscopy measures the molecular vibration in terms of the variations along different types of bonds. In an I.R. curve such as these wavelengths is plotted against the percentage transmittance of the sample. Absorptions are given as both frequencies and wavelengths with the former given in units of wave numbers (cm^{-1}). The spectrum of SS has a peak at 754 and 699 cm^{-1} and the two other compounds have similar peaks.

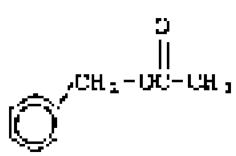
This, together with the weak absorption of SS and TT at 3150 cm^{-1} confirms our hypothesis on the compounds' aromaticity. The peaks 751 and 699 cm^{-1} are particularly typical of monosubstituted benzene compounds. All three compounds have absorptions in the region between 1300 cm^{-1} and 1000 cm^{-1} and these absorptions denote a C-O stretch. This makes the possibility of esters and carboxylic acids more viable. Finally, we examine the very intense peaks in the region 1670 - 1760 cm^{-1} that are found in all the I.R. spectra. Actually, being the most dominant features, these would be noted first and then some of the preceding observations would be made. These peaks represent the presence of carbonyl groups. In addition, UU has a broad peak ranging from 2400 cm^{-1} to 3500 cm^{-1}. This is a typical O-H stretch frequency range. This data, together with the fact that the carbonyl group absorbs at 1700 cm^{-1}, tells us that this compound is a carboxylic acid. In turn, the characteristic carbonyl absorptions of SS and TT show that they are likely esters. After this fairly exhausted study of the I.R., we can now turn to the n.m.r. The n.m.r. of UU shows a peak at a high chemical shift (difference in position of signals due to various intramolecular environments) with a low integration value. (Chemical integration measures the intensity of the peaks which in turn gives the relative number of protons giving rise to a peak.) This is the carboxylic proton confirming what we said about UU's functionality. The sharp, intense peak at 7.7 δ is typical of an aromatic ring. In addition, we see a complex multiplet with at least four distinct peaks. Realizing that this indicates splitting and assuming that the aromatic ring is monosubstituted, (not a bad assumption since an alkyl group and carboxyl group will distort the aromatic peak and what was found in the I.R. spectrum), we can conclude what is the correct structure using chemical arithmetic:

$$
\begin{array}{ll}
C_9H_{10}O_2 & \\
C\ H\ \ O_2 & \text{carboxyl group} \\
\underline{C_6H_5\qquad} & \text{phenyl group} \\
C_2H_4 &
\end{array}
$$

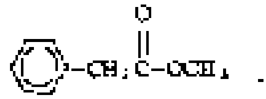
The only carboxylic acid (UU) in conjunction with this data has the structural formula:



The only way the complexity of the multiplet can be explained is that the two sets of methylene protons have similar chemical shifts and have peaks that overlap. In actuality both methylene absorptions are a triplet (following the pattern of n adjacent equivalent protons splitting a proton into n+1 peaks.) The similar chemical shifts can be explained in terms of the fact that both sets of methylene protons have chemical environments that are quite alike. They both have their electron density lowered by the similar electron-withdrawing inductive effects of the phenyl and the carboxyl groups. This lowered electron density in turn results in a higher chemical shift (movement of an absorption downfield). The carboxyl group has a slightly greater inductive effect and therefore the methylene group adjacent to this functionality has an absorption downfield from the other methylene group. Now, let us see if we can differentiate between the two esters SS and TT on the basis of their n.m.r. spectra. The spectrum of SS seems simpler with absorptions at 2.0 δ, 5.1 δ, and 7.3 δ. The relative intensities of these peaks, as seen through the integration curve is 3:2:5, respectively. The unsplit peak at 2.0 δ is typical of a methyl group bordering a carbonyl. The unsplit peak at 5.1 δ is slightly downfield from what chemical shift would be expected of a methylene group bordering an oxygen but it would be expected if the methylene group is also next to a phenyl ring. The structure of SS is therefore



The n.m.r. spectrum of TT contains the aromatic sextet at 7.3 δ and what appears to be two distinct singlets at δ 3.5 and δ 3.6. The peak with the greater intensity (δ 3.6) could be explained as an ethereal methyl group ($-OCH_3$). The methylene group absorption cannot be explained as bordering the phenyl group and the carbonyl group alone but if it borders both of these functionalities, the downfield absorption could be accounted for. The structure of TT is therefore



CHARACTERIZATION TESTS

• PROBLEM 21-23

Describe simple chemical tests that would serve to distinguish between:

(a) propionic acid and methyl acetate
(b) n-butyryl chloride and n-butyl chloride
(c) p-nitrobenzamide and ethyl p-nitrobenzoate
(d) glyceryl tristearate and glyceryl trioleate
(e) benzonitrile and nitrobenzene
(f) acetic anhydride and n-butyl alcohol
(g) glyceryl monopalmitate and glyceryl tripalmitate
(h) ammonium benzoate and benzamide
(i) p-bromobenzoic acid and benzoyl bromide

Tell exactly what you would do and see.

Solution: In solving this problem, consider the functional groups of the compounds and try to devise chemical tests that distinguish between these groups.

(a) propionic acid and methyl acetate

(CH_3CH_2COOH) (CH_3COOCH_3)

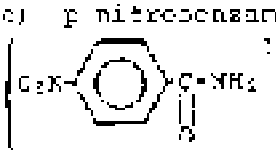
The carboxylic acid may be distinguished from the ester (methyl acetate) by addition of aqueous sodium bicarbonate ($NaHCO_3$). The propionic acid reacts with $NaHCO_3$ to give the sodium carboxylate salt and CO_2, which is detected by the evolution of bubbles.

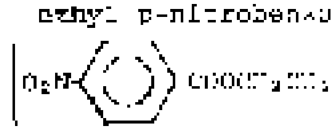
(b) n-butyryl chloride and n-butyl chloride

$\left(CH_3CH_2CH_2\overset{\overset{\large O}{\|}}{C}-Cl\right)$ $(CH_3CH_2CH_2CH_2Cl)$

The addition of sodium bicarbonate can also distinguish the acid chloride from the alkyl chloride by the evolution of CO_2 bubbles. Only the n-butyryl chloride reacts.

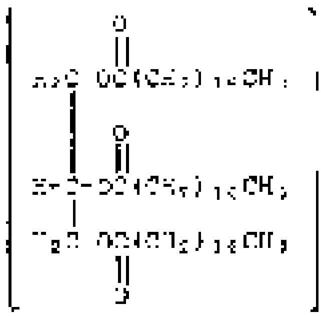
(c) p-nitrobenzamide and ethyl p-nitrobenzoate

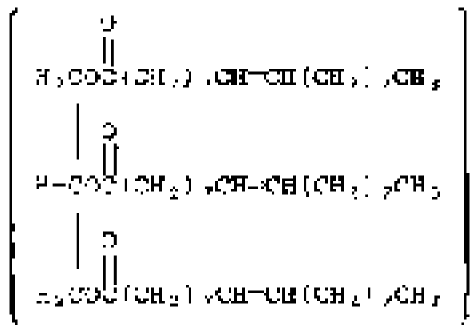




These compounds may be distinguished by the fact that only the amide releases ammonia upon hydrolysis with OH and heat. The addition of NaOH produces ammonia (NH_3) which may be detected by the color change that occurs on litmus paper.

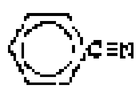
(d) Glyceryl tristearate and glyceryl trioleate

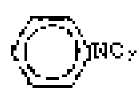




Only the glyceryl trioleate contains carbon-carbon double bonds for unsaturation. Consequently, just as an alkene does, it should decolorize the red solution of Br_2/CCl_4 or the purple color of $KMnO_4$. Glyceryl tristearate will fail to decolorize these solutions so that the compounds may be distinguished on this basis.

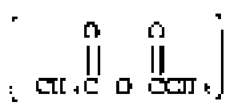
(e) Benzonitrile and nitrobenzene





Nitriles may be hydrolyzed to carboxylic acids with the use of base (or acid). With base, ammonia is also released. Consequently, when NaOH is added to benzonitrile, ammonia is released and can be detected with litmus paper. Nitrobenzene will not give the reaction.

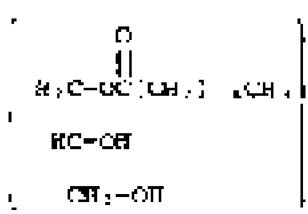
(f) Acetic anhydride and n-butyl alcohol

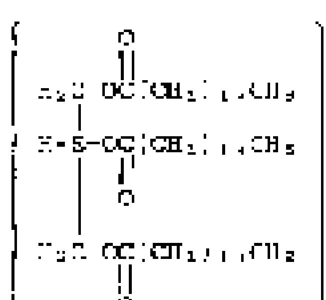


($CH_3CH_2CH_2CH_2OH$)

Addition of warm, aqueous sodium bicarbonate identifies the anhydride. The alcohol will not give a positive reaction.

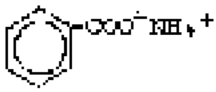
(g) Glyceryl monopalmitate and glyceryl tripalmitate

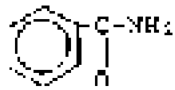




The glyceryl monopalmitate has available a hydroxyl (OH) group that may react with CrO_3/H_2SO_4. This reagent will oxidize the hydroxyl to the carbonyl. The glyceryl tripalmitate fails to give this reaction, which is detected by a color change.

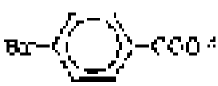
(h) Ammonium benzoate and Benzamide

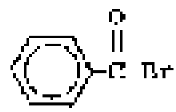




The NH_4^+ salt will evolve ammonia (NH_3) immediately upon the addition of cold, aqueous NaOH. This allows for distinction as the amide gives off no ammonia unless the NaOH is hot.

(i) p-Bromobenzoic acid and benzoyl bromide





Addition of alcoholic $AgNO_3$ can distinguish between these compounds. Benzoyl bromide will react with $AgNO_3$ to form AgBr, which is detected as a precipitate that is insoluble in dilute nitric acid. Halogens attached directly to the benzene ring do not react. Hence, no precipitate is seen with p-Bromobenzoic acid.

• PROBLEM 21-24

(a) What is the saponification equivalent of n-propyl acetate? (b) There are eight other simple aliphatic esters that have the same saponification equivalent. What are they? (c) In contrast, how many simple aliphatic acids have this equivalent weight? (d) Is saponification equivalent as helpful in identification as neutralization equivalent?

Solution: (a) It is known that addition of base can hydrolyze an ester to the alcohol and carboxylate ion. The reaction may be pictured as follows:

$$\underset{\text{(Ester one equivalent)}}{RCOOR'} + \underset{\text{(Base one equivalent)}}{OH^-} \rightarrow \underset{\text{(Carboxylate ion)}}{RCOO^-} + \underset{\text{(Alcohol)}}{R'OH}$$

The hydrolysis of the ester with OH^- is called saponification. If the ester is hydrolyzed in a known amount of base (taken in excess), the amount of base used up can be measured and used to give the saponification equivalent, the equivalent weight of the ester. N-propyl acetate has the structure

$\mathrm{CH_3C(=O)—OC_3H_7\text{-}n}$. The hydrolysis with OH^- produces acetate ion and n-propyl alcohol as illustrated:

$$\mathrm{CH_3C(=O)OC_3H_7\text{-}n + OH^- \rightarrow CH_3COO^- + n\text{-}C_3H_7OH}$$

(acetate ion) (n-propyl alcohol)

From the hydrolysis or saponification, it can be seen that one mole of ester requires one mole of OH^-. This means the saponification equivalent must equal the molecular weight of the ester. N-propyl acetate ($C_5H_{10}O_2$) has M.W. = 102. Therefore, the saponification equivalent of n propyl acetate is 102.

(b) The eight other aliphatic esters must all have the same formula, $C_5H_{10}O_2$, because only this gives the necessary molecular weight or saponification equivalent. Using the formula $C_5H_{10}O_2$ and substituting into the general formula for an ester, RCOOR', one obtains the following combinations:

$\mathrm{HC(=O)\text{-}OCH_2CH_2CH_2CH_3}$ $\mathrm{HC(=O)\text{-}OCH_2CH(CH_3)CH_3}$

$\mathrm{HC(=O)\text{-}OCH(CH_3)CH_2CH_3}$ $\mathrm{HC(=O)\text{-}OC(CH_3)_2\text{-}CH_3}$

$\mathrm{CH_3C(=O)\text{-}OCH(CH_3)\text{-}CH_3}$ $\mathrm{CH_3CH_2C(=O)OCH_2CH_3}$

$\mathrm{CH_3CH_2CH_2C(=O)\text{-}OCH_3}$ $\mathrm{CH_3CH(CH_3)C(=O)\text{-}OCH_3}$

(c) Recalling that carboxylic acids have the formula RCOOH and only $C_5H_{10}O_2$ is available, the R group (aliphatic in this problem) must be a four carbon group. This four-carbon group can be arranged in four ways to obtain four different simple aliphatic carboxylic acids as illustrated:

$\mathrm{CH_3CH_2CH_2CH_2COOH}$ $\mathrm{CH_3CH(CH_3)CH_2COOH}$

$\mathrm{CH_3CH_2CH(CH_3)COOH}$ $\mathrm{CH_3\text{-}C(CH_3)_2\text{-}COOH}$

(c) The saponification equivalent can reveal the equivalent weight of an ester. However, as seen in the parts (a) and (b), there can exist many combinations in the R and R' portions to obtain different substances even though saponification demonstrates they all have the same equivalent weight. Consequently, the saponification equivalent is not as useful due to the great number of possible combinations of R and R' in RCOOR'.

CONDENSATION REACTIONS

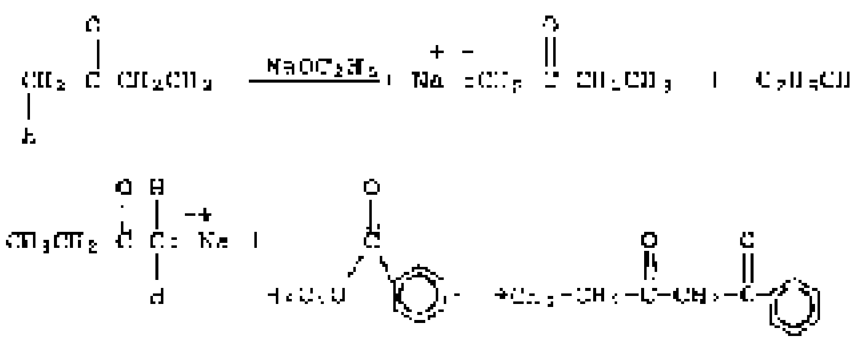
• PROBLEM 21-25

Methyl ethyl ketone can undergo Claisen condensation with a given ester, for example, ethyl benzoate, to yield either of two products, depending upon experimental conditions. What are these two products? How can one tell which product one has obtained?

Solution: Claisen condensation is a reaction involving two carbonyl compounds, one of them must have an α-hydrogen. The condensation reaction is base-induced. The base ionizes the α hydrogen of one compound to give a strong, carbanion nucleophile, which in turn, attacks the carbonyl carbon of the other compound to form a carbon-carbon bond.

Of the two reactants, only methyl ethyl ketone has α hydrogens. Furthermore, methyl ethyl ketone has two different types of α-hydrogen which can be ionized, the methyl hydrogens and the ethyl hydrogens. It is this property that gives the result of two possible products.

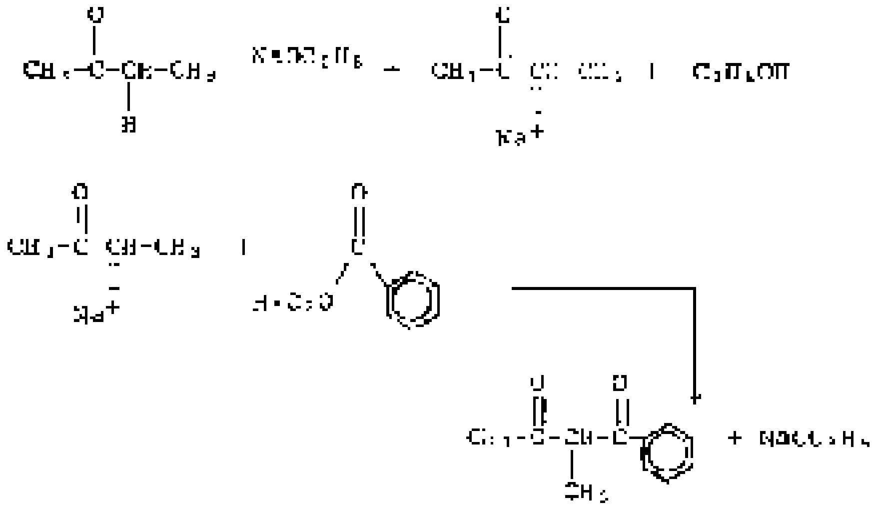
(1) If a methyl hydrogen is ionized, 1-phenyl-1,3-pentanedione is formed:



1-phenyl-1,3-pentanedione

+ $NaOC_2H_5$

(2) If an ethyl hydrogen is ionized, 2-methyl-1-phenyl-1,3-butanedione is formed.

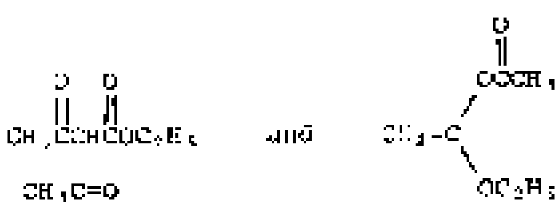


2-methyl-1-phenyl-1,3-butanedione

The two possible products can be distinguished by an iodoform test. A haloform reaction is the base-catalyzed substitution of all three methyl-hydrogens by three halogens. Since 2-methyl-1-phenyl-1,3-butanedione contains an acetyl methyl group, it will readily undergo an iodoform reaction, while 1-phenyl-1,3-pentanedione will not.

• PROBLEM 21-26

Other conceivable products of the Claisen condensation of ethyl acetate are



Explain how these products might be formed and why they are not formed in significant amounts.

Solution: The Claisen condensation takes advantage of the acidic α hydrogen of esters, β-ketoesters and β-diesters.

An alkoxy salt (RO^-Na^+) is basic enough to remove the α hydrogen from an ester. This reaction is shown as:

ester   alkoxide   enolate anion   alcohol

Note that the alkyl group of the alkoxide is the same as the alkyl group of the alcoholic portion of the ester. This is done so that transesterification reactions produce the same ester. A transesterification reaction that results in a different ester is:

$$R'\overset{O}{\overset{\|}{C}}OR'' + RO^- \rightleftarrows R'\overset{O}{\overset{\|}{C}}OR + R''O^-$$

The enolate anion produced in the removal of an α hydrogen by the alkoxide is stabilized by resonance:

$$R'\bar{C}H\overset{O}{\overset{\|}{C}}OR \longleftrightarrow R'\underset{H}{\underset{|}{C}}-\overset{O^-}{\overset{|}{C}}OR$$

The enolate anion is nucleophilic enough to attack the partially positively charged carbonyl carbon of an ester. The acyl oxygen bond of the ester is broken and a β ketoester is produced:

$$R'\overset{O}{\overset{\|}{C}}-O-R$$

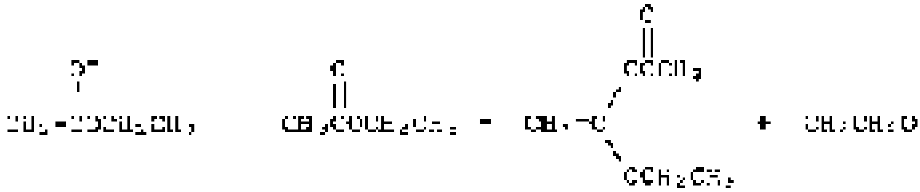
acyl oxygen bond   alkyl oxygen bond

The alkyl oxygen bond will break only if the carbon bonded to the alcoholic oxygen is tertiary, and the reaction conditions are such that the tertiary carbocation can form (acidic conditions are necessary). The reaction of enolate anion with an ester (using ethyl acetate from the problem) is:

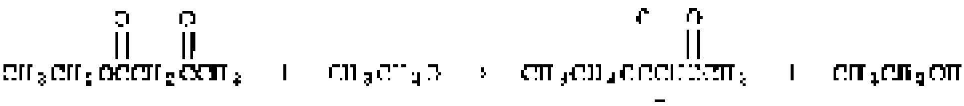
$$^-CH_2\overset{O}{\overset{|}{C}}OCH_2CH_3 + CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3 \rightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OCH_2CH_3 + CH_3CH_2O^-$$

ethyl aceto-
acetate
(a β-ketoester)

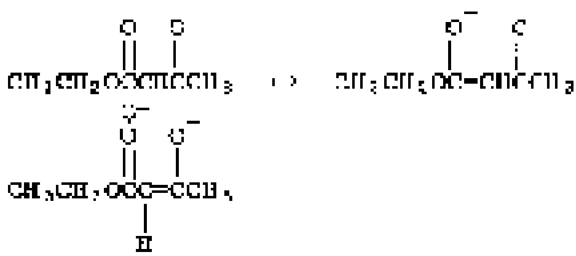
The β-ketoester is not the only product formed. If the enolate anion attacks the ester with its negatively charged oxygen, as depicted in one of the resonance structures, O-acylation will occur. (Remember that the two major resonance structures of the enolate anion do not exist independently; the negative charge is spread between the α carbon and the carbonyl oxygen.) The reaction for O-acylation is less stable thermodynamically than is the reaction that produces the β-ketoester. This means that the O-acylation reaction product accounts for a small portion of the Claisen condensation products. The reaction for O-acylation (again using ethyl acetate from the problem) is:



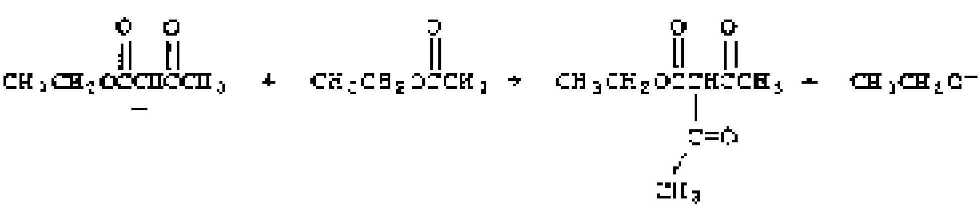
In a solution of an alkoxide salt, the β-ketoester (produced by the Claisen condensation) will give up a hydrogen from the carbon between the two carbonyl carbons. This results in a highly resonance stabilized anion. Using ethyl acetoacetate, we can show how this anion is formed and stabilized:



The principal resonance structures for the resulting anion are:



This anion will not be produced from a β-ketoester that has no hydrogens on the carbon between the two carbonyl groups. Such β ketoesters would result from the Claisen condensation of an ester having only one α hydrogen. Since our problem uses ethyl acetate, the β-ketoester anion is formed. This anion, like the enolate anion, is nucleophilic enough to attack the partially positively charged carbonyl carbon of an ester. Here, O-acylation is much less thermodynamically stable than is C-acylation. Hence, the reaction of the β-ketoester anion with the ester (using ethyl acetoacetate and ethyl acetate as in our problem) is:



The product of this reaction accounts for a small portion of the Claisen condensation products. This is because the β-ketoester anion is less nucleophilic than the enolate anion, and will therefore not attack an ester as fast as the enolate anion will. Another reason that the rate of reaction of β-ketoester anion with ester is very slow is due to the steric hindrance; the β keto ester anion is a large group.

CHAPTER 22

ALIPHATIC AMINES

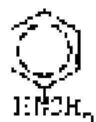
NOMENCLATURE AND STRUCTURE

• PROBLEM 22-1

Discuss the structure, classification, nomenclature and physical properties of amines. Give examples.

Solution: RNH_2, R_2NH or R_3N represents the general formula of amines, where R is any alkyl or aryl group. For example:

CH_3NH_2 (Methylamine)



(N-Methylaniline)

$(CH_3)_3N$ (Trimethylamine)

According to the number of groups attached to the nitrogen atom, amines are classified as primary (1°), secondary (2°), or tertiary (3°). The classifications can be illustrated as follows:

$$\underset{\text{Primary (1°)}}{R-\overset{\displaystyle H}{\overset{|}{N}}-H} \qquad \underset{\text{Secondary (2°)}}{R-\overset{\displaystyle H}{\overset{|}{N}}-R} \qquad \underset{\text{Tertiary (3°)}}{R-\overset{\displaystyle R}{\overset{|}{N}}-R}$$

In the naming of aliphatic amines, the alkyl group or groups attached to the nitrogen is named, and followed by the word -amine. More complicated amines are named by prefixing amino-(or N-methylamino-, N,N-diethylamino-, etc.) to the name of the parent chain. For example:

$$\underset{\text{Isopropylamine}}{CH_3-\overset{\displaystyle H}{\overset{|}{\underset{\underset{\displaystyle NH_2}{|}}{C}}}-CH_3} \qquad \underset{\text{Methylethylamine}}{CH_3CH_2-\overset{\displaystyle H}{\overset{|}{N}}-CH_3}$$

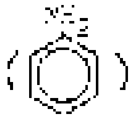
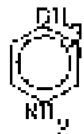
$H_2NCH_2CH_2OH$

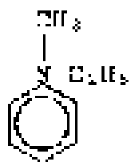
2-Aminoethanol

(Ethanolamine)

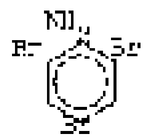
$$CH_3-\overset{\displaystyle H}{\underset{\underset{\displaystyle CH_3}{|}}{N-CH}}(CH_2)_4CH_3$$

2-(N-Methylamino)heptane

When the nitrogen is attached directly to an aromatic ring (to yield an aromatic amine), the compound is generally named as a derivative of the simplest aromatic amine, aniline (). An aminotoluene is given the special name of toluidine ( , p-toluidine). For example:



N-Methyl-N-ethylaniline



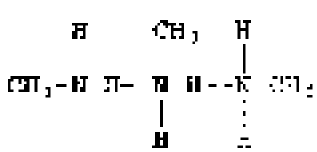
2,4,6-Tribromoaniline

When there is a salt of an amine, the word amine is replaced by -ammonium (or -aniline by -anilinium), and the name of the anion (chloride, nitrate, sulfate, etc.) is added. For example:

$C_6H_5NH_3^+Cl^-$ $(C_2H_5NH_3^+)_2SO_4^{2-}$

Anilinium Chloride Ethylammonium Sulfate

Of the organic compounds that show appreciable basicity, amines are the most important. Amines are polar compounds and, except for 3° amines, can form intermolecular hydrogen bonds as shown:



Amines possess higher boiling points than non-polar compounds (of the same molecular weight), but lower boiling points than alcohols or carboxylic acids. Amines of all types can form hydrogen bonds with water. Consequently, the solubility of amines depends on size; smaller amines are quite soluble in water, with borderline solubility reached at about six carbon atoms. In less polar solvents such as ether, alcohol, and benzene, amines are soluble.

Aromatic amines are often extremely toxic. They are easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

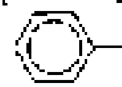
Name the following structures:

(a) $CH_3-NH-C_2H_5$; (b) $C_6H_5-NH-C_2H_5$;

(c) $NH_2-(CH_2)_5-NH_2$; (d) $(CH_3-CH_2-CH_2)_3N$;

(e) $(CH_3)_2CH-NH_2$; (f) NH_2-CH_2-COOH;

(g) $(C_2H_5)_2NCH_3$; (h) $C_6H_5-NH-CH_2C_6H_5$;

(i) $\underset{\displaystyle NH_2}{CH_3-\underset{|}{CH}}-CH_2-\underset{\displaystyle Cl}{\underset{|}{CH}}-COOH$ (j) Cl  NH-CH$_3$

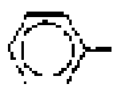
Solution: Aliphatic amines are named by listing the alkyl groups attached to the nitrogen in alphabetical order following them by the suffix "amine." The entire sequence is written as one word as in the following examples.

CH_3-NH_2

Methylamine

$CH_3CH_2-NH-CH_3$

Ethylmethylamine

 $-CH_2-NH-CH_2CH_3$

Benzylethylamine

$$\begin{array}{c} CH_3-N-CH_2CH_3 \\ | \\ CH \\ / \quad \backslash \\ CH_3 \quad CH_3 \end{array}$$

Ethylisopropylmethylamine

If there are two or three identical substituents on the nitrogen, the prefixes "di" and "tri" are used (and they are alphabetized).

$CH_3-NH-CH_3$

Dimethylamine

$$\begin{array}{c} CH_3-N-CH_3 \\ | \\ CH_2CH_3 \end{array}$$

Dimethylethylamine

If the amino group is part of a complicated molecule that contains other functional groups, it may be named as the amino substituent, as in the following examples:

$NH_2-CH_2CH_2-OH$

2-Aminoethanol

$$\begin{array}{c} CH_3CHCH_2COOH \\ | \\ NH_2 \end{array}$$

3-Aminobutyric acid (or 3-aminobutanoic acid)

$$CH_3-\underset{\displaystyle NH_2}{CH}-CH_2-CH_2-CH_2-\overset{\displaystyle CH_3}{CH}-CH_3$$

2-Amino-6-methylheptane

An amino substituent that carries an alkyl group is named as an N-alkylamino group. For example,

$CH_3-NH-CH_2-COOH$

N-Methylamino-acetic acid

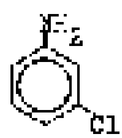
$$\begin{array}{l} CH_3CH-CH_2-CH_2OH \\ \quad | \\ \quad NH-CH_2CH_3 \end{array}$$

3-(N-Ethylamino)-1-butanol

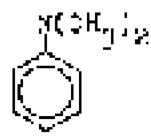
$$\begin{array}{l} (CH_3)_2N-CH-CH_2-CH_2-CH_2-CH_3 \\ \qquad\quad\ | \\ \qquad\quad CH_3 \end{array}$$

2-(N,N-Dimethylamino)-hexane

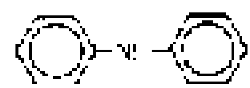
Aromatic amines are usually named as derivatives of the parent compound aniline. The following examples are typical:



m-Chloroaniline



N,N-Dimethylaniline



Diphenylamine

(a) $CH_3-NH-C_2H_5$ has a methyl and an ethyl group attached to the nitrogen, thus the name of this structure is ethylmethylamine.

(b) $C_6H_5-NH-C_2H_5$ has a benzene ring and an ethyl group attached to the nitrogen, thus the name of this structure is ethylphenylamine. This structure can also be named as an aniline: N-ethylaniline.

(c) $NH_2-(CH_2)_3-NH_2$ has two amino groups attached to the first and third carbons of a three carbon parent, thus the name of this structure is 1,3-diaminopropane.

(d) $(CH_3-CH_2-CH_2)_3N$ has three n-propyl groups attached to the nitrogen, thus the name of this structure is tri-n-propylamine.

(e) $(CH_3)_2CH-NH_2$ has an isopropyl group attached to the nitrogen, thus the name of this structure is isopropylamine.

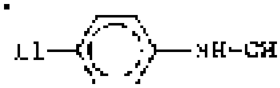
(f) NH_2-CH_2-COOH has an amino group attached to the α carbon of acetic acid, thus the name of this structure is α-aminoacetic acid (or 2-amino-ethanoic acid).

(g) $(C_6H_5)_2NCH_3$ has two benzene rings and a methyl group attached to the nitrogen, thus the name of this structure is diphenylmethylamine.

(h) $C_2H_5-NH-CH_2C_6H_5$ has a benzyl and an ethyl group attached to the nitrogen, thus the name of this structure is benzylethylamine.

(i) $CH_3CHCH_2CH\ COOH$ has a chlorine atom and an amino group
$\quad\quad\ |\quad\quad |$
$\quad\quad NH_2\quad Cl$

attached to pentanoic acid at carbons 2 and 4, respectively. Thus the name of this structure is 4-amino-2-chloropentanoic acid.

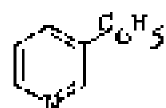
(j)  has a methyl group and p-chloroaniline fragment attached to the nitrogen and thus the name of this structure is N-methyl-p-chloroaniline.

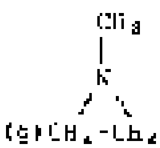
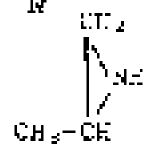
• PROBLEM 22-3

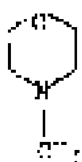
Provide an acceptable name for each of the following. Indicate whether the amino groups in these compounds are primary, secondary or tertiary.

(a) $CH_2{=}CHCH_2NH_2$ (b) $CH_3CH_2CH_2NHCH_3$

(c) $C_6H_5NH_2$ (d) $H_3NCH_2CO_2^-$

(e) $((CH_3)_2C)_3N$ (f) 

(g)  (h) 

(i)  (j) $(CH_3)_3NCH_3$

Solution: Nitrogen appears in a variety of organic compounds. The most common of the monofunctional organic nitrogen compounds are the amines where alkyl groups and/or hydrogens are bonded directly to nitrogen. Amines are designated as primary, secondary or tertiary (1°, 2°, or 3°), depending on the extent of substitution upon the nitrogen. For instance, an amine bearing three alkyl groups (NR_3) would be considered to be a tertiary amine. The amines are named by designating the alkyl groups attached to nitrogen. In amine nomenclature the ordering of substituents is preferably alphabetical and the entire sequence is treated as one word ending with the suffix "amine."

(a) This amine has only the allyl group ($CH_2{=}CH{-}CH_2{-}$) substituted on the nitrogen and is a primary amine named as allylamine.

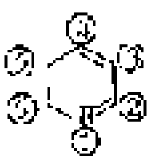
(b) Here, we now have two alkyl groups bonded to the nitrogen, and this secondary amine is called methyl-n-propylamine.

(c) This compound is most appropriately termed a primary aryl amine. It is commonly known as aniline rather than phenylamine.

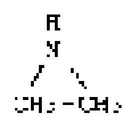
(d) This substituted acetic acid can be unambiguously named as aminoacetic acid since there is only one carbon adjoining the carboxylic acid group. It is a primary amine because it has a single alkyl group derivative on the nitrogen. This compound is also known as glycine.

(e) This tertiary amine is of the general type NR_3 where here R represents a t-butyl group. Thus the compound is tri-t-butylamine.

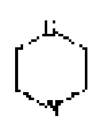
(f) The derivatives of pyridine (C_5NH_5) can be named by the following numbering system.



Treating the benzene ring as a substituent, the compound is named as 3-phenylpyridine. The nitrogen has a double and single bond and is classified as a tertiary amine.

(g) Aziridine has the structure,  . We must designate substitution on the nitrogen by prefixing the substituent with the letter N. The compound in question is named N-methyl-aziridine and is a tertiary amine.

(h) Here the methyl group is substituted on a carbon and since both ring carbons are equivalent, the compound is named methylaziridine. Since the nitrogen still retains a hydrogen, the amine is secondary.

(i) Morpholine has the structure:  .

To show methyl substituent on the nitrogen, we would name the compound N-methyl-morpholine. It is a tertiary amine.

(j) The only structure consistent with five consecutive methylene groups bonded to a nitrogen would be a derivative of the six-membered ring compound piperidine: 

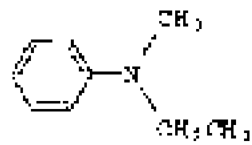
Again, since the substitution occurred on the nitrogen, the desired compound would be named N-methylpiperidine.

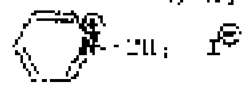
• PROBLEM 22-4

Name the following substances by an accepted system.

(a) $(HOCH_2CH_2)_3N$

(b) $H_2NCH_2CH_2\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$

(c) 

(d) 

Solution: Amines are named by specifying the various substituents on nitrogen as prefixes before the word amine, with the name written as one continuous word. Amine salts where there is a hydrogen bonded to the nitrogen are named similarly except the suffix is now "ammonium" with the anion being listed as a separate word.

(a) This amine has three identical groups attached to nitrogen with the substituent being 2 hydroxyethyl and the compound is named tri-(2-hydroxyethyl)-amine.

(b) This compound is more conveniently named as a derivative of an ammonium salt. Thus, naming the amine portion of the molecule amino, the compound is (2 amino ethyl)ammonium chloride.

(c) If named as an amine, this compound is called ethylmethylphenylamine. Alternatively, we could name the compound as a derivative of aniline, calling it N-ethyl-N-methylaniline with the letter "N" denoting substitution on nitrogen.

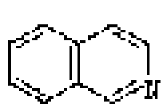
(d) This compound is analogous to an ammonium ion except that this is a derivative of pyridine instead of ammonia. Therefore the name of the compound is N-methylpyridinium iodide.

• PROBLEM 22-5

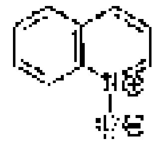
Provide a structure for each of the following.

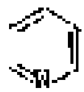
(a) isoquinoline (b) quinoline N-oxide
(c) 1,4-dihydropyridine (d) N-benzylphthalimide
(e) ethyl 5-diphenylamino-2-pentenoate

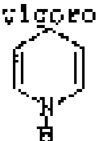
Solution: (a) Isoquinoline is a benzopyridine with weak basic characteristics. It has the structure:



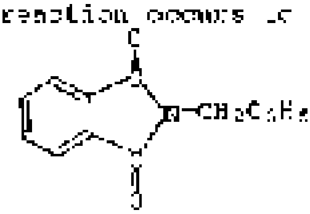
(b) Quinoline, another benzopyridine, can be oxidized like all 3° amines to its N-oxide, quinoline N-oxide:



(c) Pyridine,  will absorb one mole of hydrogen under vigorous conditions to produce 1,4-dihydropyridine:



(d) When phthalimide anion is treated with benzyl iodide, an S_N2 reaction occurs to produce N-benzylphthalimide:



(e) From the suffix of the name of the compound (2-pentenoate), we know that this structure is an ester whose acyl portion contains five carbons and includes a double bond. Ester nomenclature lists the alkyl portion in the first part of the name and here it is an ethyl group.

Realizing that the diphenylamino group is $-N\begin{matrix}^{ph}\\_{ph}\end{matrix}$, we write the entire structure as:

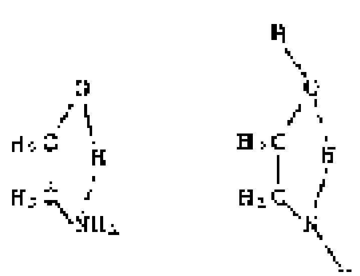
$$C_2H_5O\overset{\overset{\displaystyle O}{\|}}{C}-CH=CHCH_2CH_2-N\begin{matrix}^{ph}\\_{ph}\end{matrix}$$

Note that the carbonyl carbon is termed the #1 carbon.

PHYSICAL PROPERTIES

● PROBLEM 23-6

Ethanolamine, $HOCH_2CH_2NH_2$, can in principle hydrogen-bond to itself in two different ways:

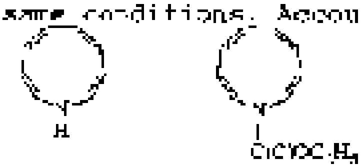


Actually, one of these arrangements is much more important than the other. Explain.

Solution: A hydrogen bonded covalently to an electronegative atom can potentially be electrostatically attracted to another electronegative atom. This interaction in which hydrogen acts as a bridge between the two electronegative atoms is called a hydrogen bond. Of the two possible hydrogen bond arrangements in ethanolamine, the first arrangement in which the hydrogen involved in the hydrogen bond is covalently bonded to the oxygen is the important one. This is because a proton is more apt to be transferred from oxygen as in the first structure than a transfer from nitrogen as is true in the latter arrangement. This difference in acidity is due to the fact that oxygen is more electronegative than nitrogen and can better support the incipient negative charge. By similar reasoning, nitrogen can better accept a proton and the subsequent positive charge.

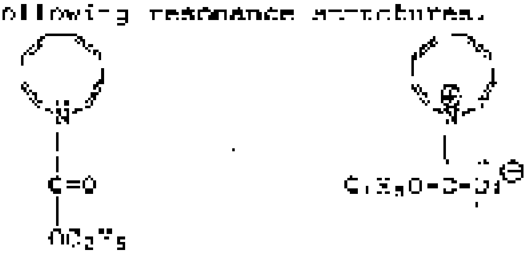
• PROBLEM 22-7

While azanonatetraene is comparatively stable at room temperature, N-carbethoxyazanonatetraene rapidly isomerizes under the same conditions. Account for this difference.



azanonatetraene N-carbethoxyazanonatetraene

Solution: Azanonatetraene contains four double bonds and a nitrogen with its free pair of electrons. We can envision the double bonds' π electrons and the free pair of electrons combining to form a ten electron π system. Hückel's Rule states that a cyclic π system of $4n + 2$ electrons (where n is an integer) will be aromatic. Thus, azanonatetraene is an aromatic compound. N-carbethoxyazanonatetraene differs from azanonatetraene in that the nitrogen borders on an ester group instead of a hydrogen. The carbonyl functionality of the ester will have an electron withdrawing effect on the ring's π electrons. It could remove nitrogen's free pair of electrons, as in the following resonance structures.



Since the nitrogen will contain an empty p orbital when the free electron pair is delocalized toward the carbonyl carbon, the ring will contain eight π electrons and be antiaromatic. Such an antiaromatic structure will be unstable and tend to isomerize.

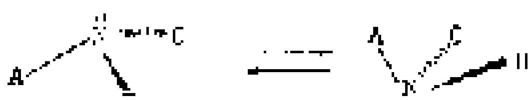
STEREOCHEMISTRY

• PROBLEM 22-8

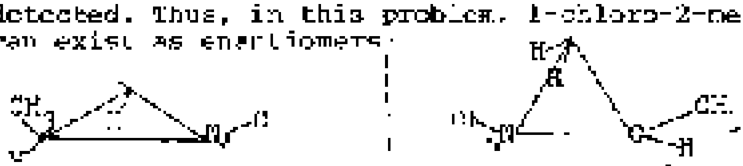
Account for the following, drawing all pertinent stereochemical formulas. (a) 1-Chloro-2-methylaziridine was prepared in two isomeric forms separable at 25° by ordinary gas chromatography. (b) The reaction of $(C_6H_5)_2C=NCH_3$ with R (+) 2-phenylperoxypropionic acid gave a product, $C_{14}H_{13}ON$, with $[\alpha]$ + 12.3°, which showed no loss of optical activity up to (at least) 90°.

Solution: Aziridine differs from cyclopropane in that a nitrogen has replaced a ring carbon. While acylic amines with a nitrogen bonded to four different substituents (including the free pair of electrons) show no optical activity, aziridine derivatives with similarly substituted nitrogens do. This can be explained by nitrogen's stereochemistry in that nitrogen substituted by three different groups should, in principle, exist as enantiomers.

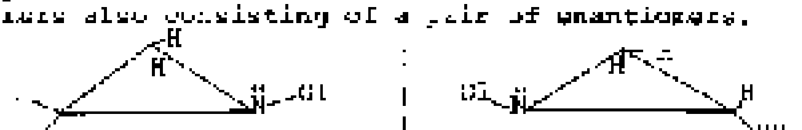
However, acylic amines undergo an inversion process at a rapid rate that involves a planar transition state and no optical activity can be detected.



Aziridine derivatives contain a nitrogen that does not undergo rapid inversion because of an unstable transition state and at lower temperatures, enantiomers can be detected. Thus, in this problem, 1-chloro-2-methylaziridine can exist as enantiomers:



However, we note that nitrogen is sp^3-hybridized and similar to a tetrasubstituted carbon. Therefore this compound can exist as cis and trans isomers with the trans isomers also consisting of a pair of enantiomers.

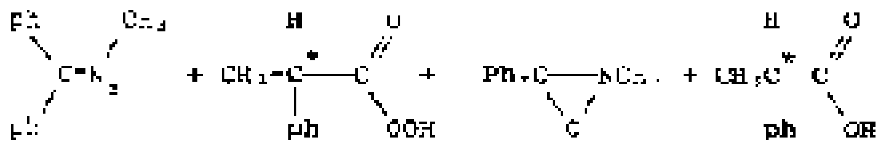


trans-1-chloro-2-methylaziridine.

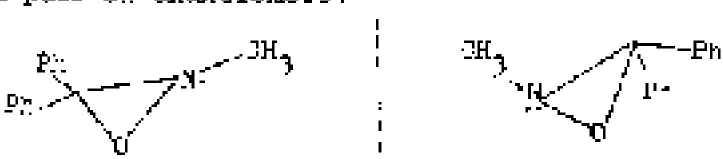
The enantiomers can be classified as stereoisomers that are mirror images of each other while the relationship between a cis isomer and a trans isomer can be termed that of diastereomers-nonenantiomeric stereoisomers. Diastereomers are different compounds with different physical properties and can be separated by a physical technique such as gas chromatography. Enantiomers differ only in their optical activity and cannot be separated by gas chromatography. Therefore only two compounds will be separated by this means - the cis and the trans forms.

(b) When an alkene is treated with a peroxy acid such as peroxyformic acid, HCO_3H, it is converted to an epoxide, containing a ring oxygen.

We note that peroxy acid's corresponding carboxylic acid is also a by-product. If a compound contained a carbon-nitrogen double bond instead of a carbon-carbon double bond, peroxidation would produce a three membered ring that contained both a nitrogen and an oxygen. In this case we are dealing with an optically active peroxy acid which would give an optically active carboxylic acid.



Realizing that the aziridine nitrogen is configurationally stable, we can designate one of the products as a pair of enantiomers:

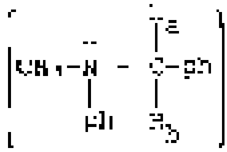


The transition state for this epoxidation contains two chiral centers - that of the optically active peroxy acid and that of the product epoxide. The two possible configurations are diastereomers of each other and therefore they are of different stabilities. Thus, one of these enantiomers will be produced in excess of the other. This accounts for the nitrogen-containing product being optically active. The fact that this optical activity is maintained at temperatures where aziridine compounds lose theirs can be explained by the presence of the oxygen. The oxygen probably makes the ring more rigid and prevents inversion about the nitrogen.

• PROBLEM 22-9

Suggest a means of demonstrating that benzylmethylphenylamine is not configurationally stable at room temperature.

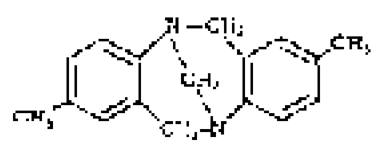
Solution: Amines of the types NRR'R" lack configurational stability in that despite having four different groups surrounding the nitrogen (including the electron pair), the compound cannot exist as a pair of independent enantiomers. Nitrogen cannot maintain a tetrahedron geometry because of the free electron pair and also because the mirror image configurations are interconvertible. Benzylmethylphenylamine,



is a tertiary amine whose nitrogen lacks configurational stability and this can be proven by nuclear magnetic resonance spectroscopy. If the nitrogen were actually configurationally stable, the benzylic protons (H_a and H_b) would be diastereotopic since they would be adjacent to a chiral center and each benzylic proton has a slight different environment. Therefore, in this case, the nonequivalent protons would have different chemical shifts and split each other into doublets. In actuality, the benzylic protons appear as an unsplit single peak (singlet). This is because they are next to a configurationally unstable and achiral nitrogen which renders them equivalent. Thus, a spectral evaluation will verify the nitrogen's configurational instability.

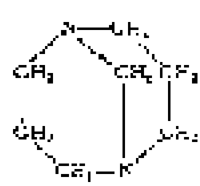
• PROBLEM 28-10

The resolution of Troger's base (1) into stable optically active forms has been achieved by selective adsorption on a column of (+) lactose.



(1)

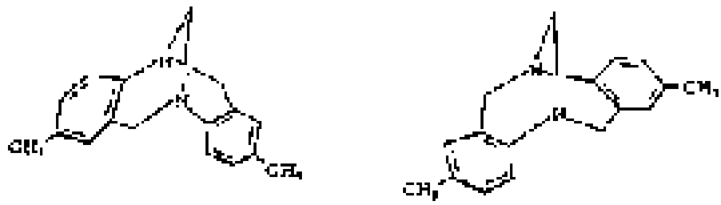
Why is this compound resolvable? Draw clear formulas showing each of the stable stereoisomers which are to be expected for it. Would the base (2) also be resolvable?



(2)

Solution: If an amine has three different groups attached to the nitrogen, the pyramidal geometry would theoretically allow for optical activity, yet in most cases such a mixture of isomers has not been isolated.

This is because the "enantiomers" interconvert by an inversion process about nitrogen, involving a planar transition state. Tröger's base is an unusual nitrogen compound in that it is resolvable. This unique behavior occurs because the nitrogens are incapable of inversion due to the rigid geometry of Tröger's base. The nitrogens are asymmetrical (they possess three unique groups) and the molecule is resolvable into enantiomers.



enantiomers

The geometry of the second compound mentioned in the question is irrelevant since the nitrogens in the eight membered ring are not asymmetrically substituted(N is achiral) in that two of the groups are identical. The molecule is not resolvable despite the fact that inversion is impossible.

ACIDITY AND BASICITY

• PROBLEM 22-11

Explain the feature of amine basicity.

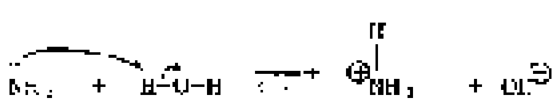
Solution: Ammonia in aqueous solution is weakly basic, and its reaction with water is usually represented by the following equations.

$$NH_3 + H_2O \rightleftharpoons NH_4^{\oplus} \quad OH^{\ominus}$$

or

$$NH_4OH \rightleftharpoons NH_4^{\oplus} + OH^{\ominus}$$

The basic character of ammonia depends on the fact that its unshared pair of electrons can react with a proton from water to form the ammonium ion and liberate the hydroxide ion. This reaction is actually a displacement



reaction.

In fact, any molecule containing an unshared pair of electrons may show basic properties, as in the above example. Like their parent compound ammonia, amines exhibit significant basicity. Their reaction with water is analogous to the reaction with ammonia, as seen in the following figure.

$$R\text{-}\ddot{N}H_2 + H\text{-}\ddot{O}\text{-}H \rightleftharpoons R\text{-}\overset{H}{N^{\oplus}}\text{-}H_2 + OH^{\ominus}$$

This figure was written for a primary amine $R\text{-}\ddot{N}H_2$, but both secondary amines R_2NH and tertiary amine R_3N have an unshared pair of electrons and show basic behavior in water.

The strength of a base is expressed as the equilibrium constant K_b for the protonation reaction. Thus, for the reaction

$$RNH_2 + H_2O \rightleftharpoons \overset{\oplus}{R}NH_3 + OH^{\ominus}$$

The equilibrium constant is:

$$K_b = \frac{[\overset{\oplus}{R}NH_3][OH^{\ominus}]}{[RNH_2]}$$

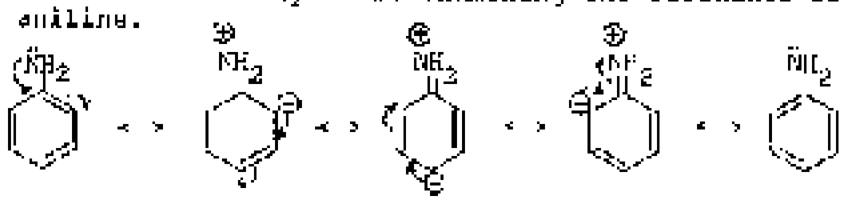
The more the reaction is shifted to the right (towards products) the larger the K_b value; a large K_b indicates a stronger base. For ammonia $K_b = 1.8 \times 10^{-5}$, while for methylamine $K_b = 4.4 \times 10^{-4}$. Methylamine is thus a stronger base than ammonia.

The differences in base strength is due to the availability of the unshared electron pair on the nitrogen of an amine. It is known that methyl groups are electron-donating relative to hydrogen. Thus, when a methyl group is present on an amine, electrons are closer to the nitrogen as compared when nitrogen is bonded to hydrogen.

Thus, there are more electrons close to the nitrogen of the methyl-substituted amine, and the electron pair on this nitrogen is more available to react with the proton from water.

A similar argument predicts correctly that dimethylamine is a stronger base than methylamine.

The base strength of the aromatic amines is significantly lower than that of the aliphatic amines. The K_b of aniline is 4.2×10^{-10}, while that of ethylamine is 4.7×10^{-4}. The relatively low basicity of the aromatic amines can be understood by keeping in mind the notion of electron availability while examining the resonance forms of aniline.



Several of the resonance forms of aniline have the unshared electron pair of the nitrogen in the ring. The electron pair of aniline is thus less available for protonation by water. Since aliphatic amines are not capable of resonance, their electron pair is more available than that of aromatic amines, and the lower basicity of aromatic amines is accounted for.

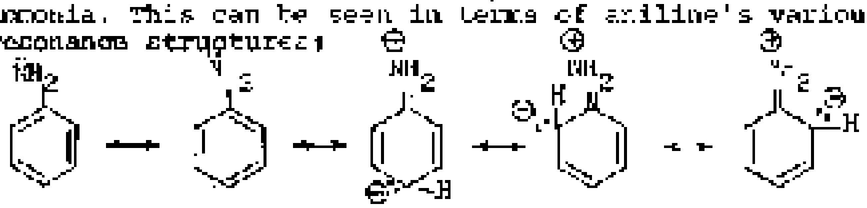
Similarly, there are even more resonance forms for diphenylamine in which the electron pair on the nitrogen is delocalized within the ring. Thus, diphenylamine is a weaker base than aniline.

• PROBLEM 28-12

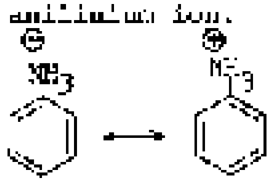
Without referring to tables, arrange the compounds of each set in order of basicity:

(a) ammonia, aniline, cyclohexylamine
(b) ethylamine, 2-aminoethanol, 3-amino-1-propanol
(c) aniline, p-methoxyaniline, p-nitroaniline.

Solution: In order to compare the relative basicities of various compounds, one must understand what factors influence basicity. First of all, aromatic amines such as aniline are less basic than aliphatic amines such as ammonia. This can be seen in terms of aniline's various resonance structures:



The Kekule forms where the double bonds are delocalized around the aromatic ring are found also in the anilinium ion.



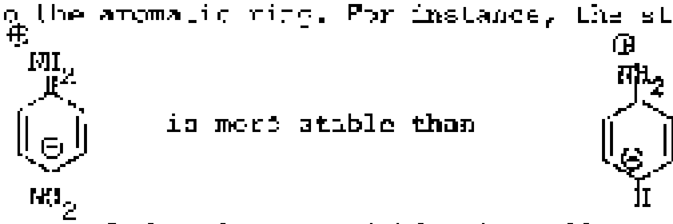
However, while the nitrogen can delocalize its free pair of electrons in aniline to positions ortho and para to the amino group, this delocalization does not occur in the anilinium ion. Therefore, aniline is stabilized by resonance unlike the anilinium ion and the activation energy for protonation is increased by this resonance. In comparison, neither ammonia or the ammonium ion is stabilized by resonance. Thus, aromatic amines are less basic than aliphatic amines. An additional factor that determines basicity is the substituents in the amine. Summarizing, we may say that any substituent that stabilizes the positive charge of the ammonium ion increases the amine's basicity, and anything that destabilizes it, lowers the amines basicity.

(a) We know that the alkyl groups of cyclohexylamine would stabilize the subsequent anilinium ion compared to the unsubstituted ammonia. Also we already know acyclic amines are better bases than aromatic amines. Thus, the order of basicity is:

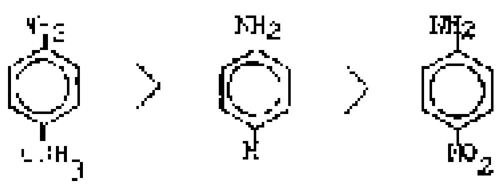
(b) The inductive effect of the hydroxy functionality is that of an electron-withdrawing group while an alkyl group is electron donating. We also note that a group's inductive effect is dependent on the distance from the functionality it is affecting (in this case, the functionality is the amine group). Thus, the basicity sequence is:

$CH_3CH_2NH_2$ > $HOCH_2CH_2CH_2NH_2$ > $HOCH_2CH_2NH_2$

(c) When comparing the basicities of substituted anilines we must consider both the substituent's inductive effect and its interaction with aniline's delocalization into the aromatic ring. For instance, the structure,



because of the electron withdrawing effect of the nitro group. Therefore, the resonance stabilization would be greater for p-nitroaniline and it would be a weaker base than aniline. The methoxy group ($-OCH_3$) is also electron withdrawing but we recall that it also stabilizes positive charge by resonance delocalization and in a similar way it would stabilize the anilinium ion. Therefore, the order of basicity is:



• PROBLEM 22-13

The pK_a of NH_4^+ is 9.24, that of $CH_3NH_3^+$ is 10.64. Is methylamine a stronger or a weaker base than ammonia? How many times stronger or weaker? What do you think this difference is due to?

Solution: Ammonium is in acid-base equilibrium with ammonia as follows:

$$NH_4^{\oplus} \rightleftharpoons NH_3 + H^{\oplus}$$

Likewise, methylammonium is in acid-base equilibrium with methylamine as follows:

$$CH_3\overset{\oplus}{N}H_3 \rightleftharpoons CH_3NH_2 + H^{\oplus}$$

The pK_a's of ammonium and methylammonium can be used to calculate the amounts of dissociation.

$$pK_a \text{ of } NH_4^{\oplus} = -\log \frac{[H^{\oplus}][NH_3]}{[NH_4^{\oplus}]}$$

$$9.24 = -\log \frac{[H^{\oplus}][NH_3]}{[NH_4^{\oplus}]}$$

$$\text{amount of dissociation} = 5.76 \times 10^{-10} = \frac{[H^{\oplus}][NH_3]}{[NH_4^{\oplus}]}$$

$$pK_a \text{ of } CH_3\overset{\oplus}{N}H_3 = -\log \frac{[H^{\oplus}][CH_3NH_2]}{[CH_3NH_3^{\oplus}]}$$

$$10.64 = -\log \frac{[H^{\oplus}][CH_3NH_2]}{[CH_3NH_3^{\oplus}]}$$

$$\text{amount of dissociation} = 2.29 \times 10^{-11} = \frac{[H^{\oplus}][CH_3NH_2]}{[CH_3NH_3^{\oplus}]}$$

The greater the amount of dissociation, the more easily a proton is lost and the stronger the acid. Hence the ammonium cation is a stronger acid than the methylammonium cation because of its greater amount of dissociation. From this we can say that methylamine is a stronger base than ammonia. To find out how much stronger a base methylamine is compared to ammonia, we can use the relative amounts of dissociation of the conjugate acids in our calculations. The amount of dissociation of ammonium compared to the amount of dissociation of methyl ammonium will show us how much stronger an acid ammonium is than methyl ammonium; this is also how much stronger a base methylamine is than ammonia.

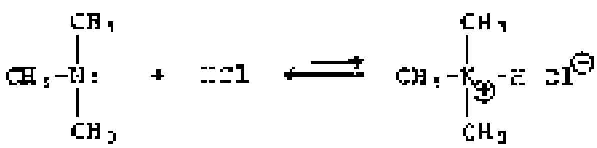
$$\frac{NH_4^{\oplus} \text{ dissociation}}{CH_3NH_3^{\oplus} \text{ dissociation}} = \frac{5.76 \times 10^{-10}}{2.29 \times 10^{-11}} = 25.1$$

Hence methylamine is a stronger base than ammonia by 25.1 times. A reason for this is that the methyl group in methylamine is electron releasing and gives the molecule a greater affinity for protons than ammonia.

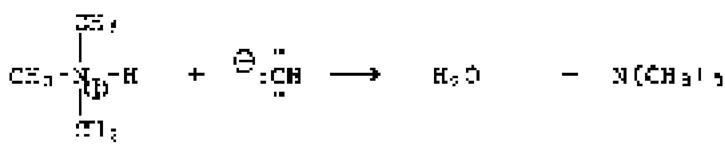
• PROBLEM 22-14

Which is the more strongly basic, an aqueous solution of trimethylamine or an aqueous solution of tetramethylammonium hydroxide? Why?

Solution: When asked to identify the more basic of two solutions, we first distinguish the base in each solution. Trimethyl amine is a base in one of the solutions, being able to abstract a proton to form an ammonium salt.

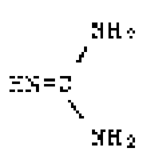


In the other aqueous solution, the nitrogen has no free pair of electrons and the quaternary ammonium cation could not possibly act as a base. The hydroxide anion of this salt, however, can easily accept a proton and is a potent base. Thus, the basicities of the solutions is determined by the relative basicities of the hydroxide anion and trimethyl amine. Hydroxide anion is a much stronger base which can be verified by comparing the relative acidities of their conjugate acids. H_2O, the conjugate acid of $^{\ominus}OH$ is a much weaker acid than the quaternary ammonium cation, trimethyl amine's conjugate acid. In fact, we may write the following reaction:



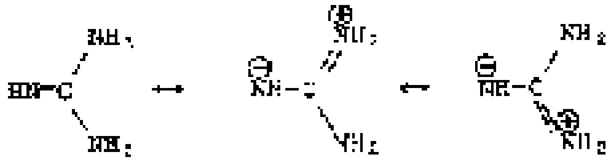
• PROBLEM 22-15

Guanidine (K_b ≈ 1) is a very strong base and an exception to the generalization that unsaturated amines are weaker bases than saturated amines. Consider various ways of adding a proton to a guanidine and the kind of changes in stabilization energies which would be expected for each.

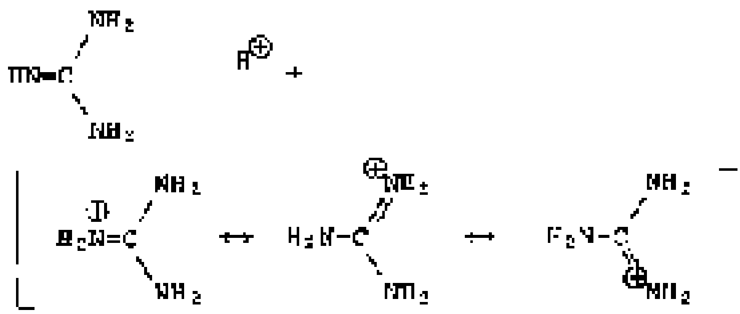


guanidine

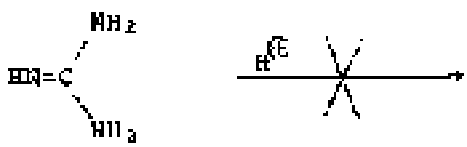
Solution: Protonation of an amine, like any chemical reaction, requires an activation energy, which is equal to the energy difference between reactants and the transition state of the reaction. The latter's energy can be approximated by the stability of the products. We note that the reactant, guanidine, has resonance stabilization where each of the two amino nitrogens bear positive charge.

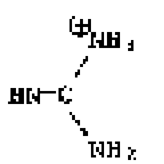


Since the reactant is stabilized by resonance, there must be some factor which further stabilizes the product. Also, the question arises whether the imine function or the amino group will receive the protons. We can account for guanidine's significant basicity and the fact that the imine group is protonated by considering the following resonance structures:



Resonance is more important in the protonated form where there is no charge separation than in guanidine. Also, the amino groups would not be protonated since this would lead to a relatively unstable structure:



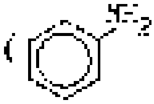
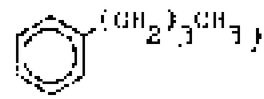


Does not occur.

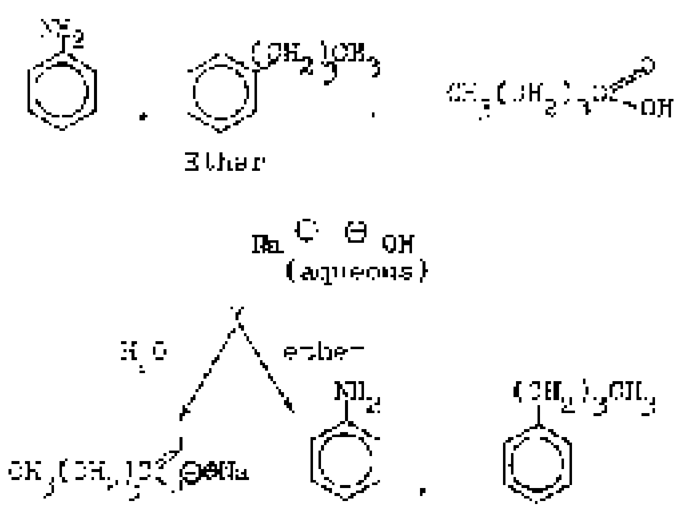
PROBLEM 22-18

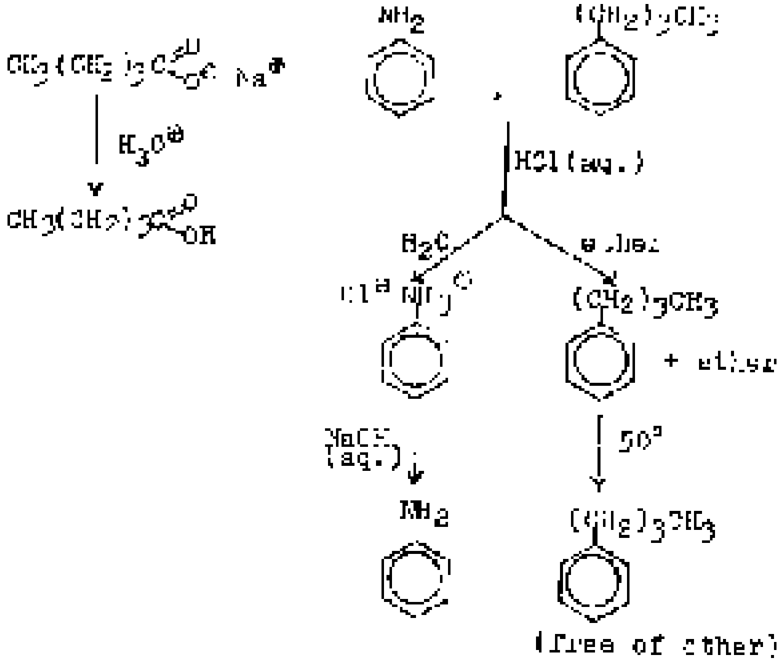
Describe exactly how you would go about separating a mixture of the three water-insoluble liquids, aniline (b.p. 184°), n-butylbenzene (b.p. 183°), and n-valeric acid (b.p. 187°), recovering each compound pure and in essentially quantitative yield. Do the same for a mixture of the three water-insoluble solids, p-toluidine, o-bromobenzoic acid, and p-nitroanisole.

Solution: To perform a separation of particular compounds, an organic chemist usually makes use of the different functional groups within these compounds. Each functionality would undergo its own set of reactions, some of which would allow the compound to be transformed temporarily to a compound which can be separated from the mixture and from which the original compound may be regenerated. In the first case, we have the water-insoluble liquids,

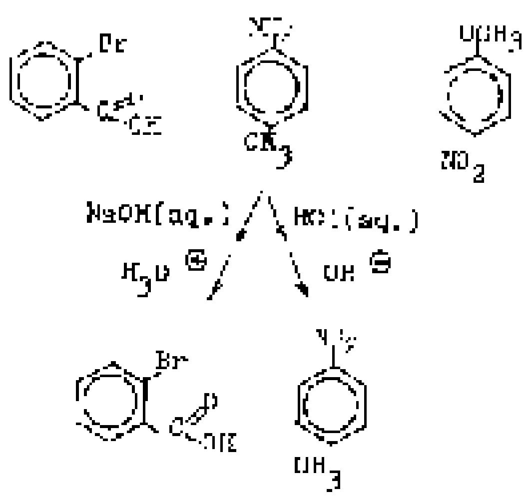
aniline (), n-butylbenzene (),

and n-valeric acid $\left(CH_3(CH_2)_3C(=O)OH \right)$. Their similar boiling points leaves us no choice but to take advantage of their differing functionalities. N-valeric acid is a carboxylic acid whose carboxyl functionality $-C(=O)-OH$ has the prime reaction of acidity, i.e., losing a proton to form a carboxylate salt. This salt, unlike the other two compounds, is soluble in aqueous solution. Aniline is an amine whose amino group ($-NH_2$) gives it the characteristic reaction of gaining a proton, i.e. basicity. The resulting anilinium salt is soluble in aqueous solution. By virtue of these two compounds' reactions, we do not have to have the arene, n-butylbenzene, undergo any particular reaction. To facilitate separation by taking advantage of the compounds' insolubility in water, we initially dissolve the mixture of compounds in ether. A "flow scheme" for this separation would be:





We may separate the solids p-toluidine, o-bromobenzoic acid, and p-nitroanisole in a way similar to the way we separated the liquids. The major difference is that the original mixture need not be dissolved in ether and can be treated directly. We remove the carboxylic acid (o-bromobenzoic acid) and the amine (p-toluidine) by converting them again to their water-soluble salts. The ether (p-nitroanisole) is too weak a base to be protonated by the dilute acid. A flow scheme for this separation is:



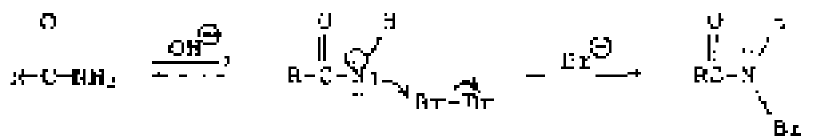
• PROBLEM 32-17

Synthesize n-pentylamine from any alcohol using the process of

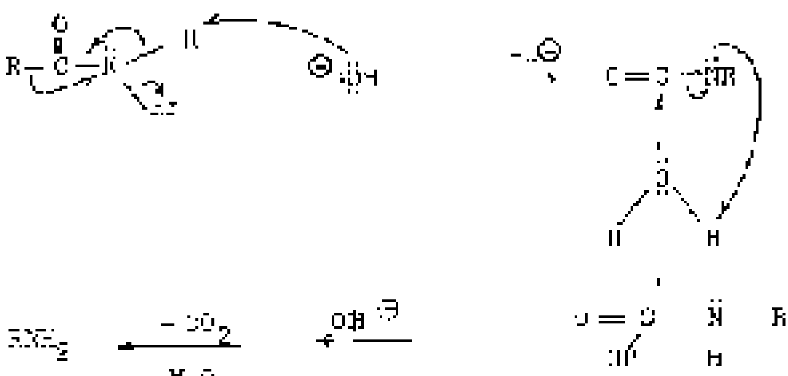
(a) Hofmann degradation
(b) nitrile reduction
(c) reductive amination

Solution: In this problem we are asked to synthesize n-pentylamine ($CH_3(CH_2)_4NH_2$) from alcohols in a variety of ways. The general method for solving a synthesis problem is to begin with the product and work backwards to the reactants. In this case, we are told to achieve the transformation by a particular route so we need to use specific intermediates in each case.

(a) The Hofmann degradation involves the conversion of an amide, $Ar(R)\overset{O}{\overset{\|}{C}}NH_2$, to an amine, $Ar(R)NH_2$. The amide is treated with alkaline solutions of bromine, chlorine or iodine. The mechanism is controversial but an N-haloamide, an isocyanate, and an unstable carbamic acid are known to be intermediates.



N-bromoamide



amine

carbamic acid

This rearrangement proceeds with complete retention of configuration in relation to the chiral center of the migrating moiety. Also, this "migration" does not involve the generation of a free particle such as a carbanion. This concurs with the stereochemistry of the process in that a free particle would mean the loss of configuration and an optically inactive product would be formed which is not the case. It has been proposed that the carbonyl carbon attaches itself to the nitrogen before it leaves the chiral center. Various groups have different migratory aptitudes with a phenyl group migrating faster than an alkyl group. Returning to our problem of synthesizing, n-pentylamine via the Hofmann degradation, and realizing that this process reduces a carbon chain by one carbon, we would start with an amide of six carbons. The amide can be derived from an acid chloride of equal length which would in turn be synthesized from its corresponding carboxylic acid. Oxidation of our starting material, n-hexanol, would yield the carboxylic acid. Summarizing this synthetic route:

$$CH_3(CH_2)_5OH \xrightarrow[OH^-/H_2O]{KMnO_4/\Delta} \xrightarrow{H^+} CH_3(CH_2)_4COOH$$

$$CH_3(CH_2)_4COOH \xrightarrow{PCl_3} CH_3(CH_2)_4C(=O)-Cl$$

$$CH_3(CH_2)_4C(=O)-Cl + NH_3\ (\text{excess}) \rightarrow CH_3(CH_2)_4C(=O)-NH_2$$

$$CH_3(CH_2)_4C(=O)-NH_2 \xrightarrow[Br_2]{OH^-} CH_3(CH_2)_4NH_2$$

Phosphorus trichloride is just one agent that would achieve our desired transformation to the acid chloride $-RCOCl$ ($SOCl_2$, PCl_5 are others). Also, we used an excess of ammonia because the subsequently produced HCl would destroy the amide.

(b) Nitriles with the general formula $R-C\equiv N$ can be converted to a primary amine, $R-CH_2NH_2$, by a variety of ways, including hydroboration, use of lithium aluminum hydride, and catalytic hydrogenation. The last method has the disadvantage that the newly formed amine will react with the intermediate imine, $RCH=NH$ to give a symmetrical secondary amine, $RCH_2-NH-CH_2R$. This loss of yield can be circumvented by converting the amine to an amide and its salt while carrying out the reduction. The final product is liberated by alkaline hydrolysis. The cyanide anion has nucleophilic capabilities and we use this to produce the five carbon nitrile, $CH_3(CH_2)_3CN$, from the four carbon alkyl halide via a nucleophilic displacement of the S_N2 type. Subsequent reduction of the nitrile will yield the desired amine while treatment of n-butanol, our starting material with the brominating agent, PBr_3, will yield the alkyl halide. Summarizing this sequence:

$$CH_3(CH_2)_3OH \xrightarrow{PBr_3} CH_3(CH_2)_3Br$$

$$CH_3(CH_2)_3Br \xrightarrow{CN^-} CH_3(CH_2)_3CN$$

$$CH_3(CH_2)_3CN \xrightarrow[\text{dioxane}]{B_2H_6} CH_3(CH_2)_3CH_2NH_2$$

(c) The process of reductive amination involves reacting a carbonyl compound in the presence of an amine and a reducing agent. Reductive amination has the synthetic advantage of being able to produce 1°, 2° and 3° amines by picking the appropriate amine-carbonyl compound combination. Since treating a carbonyl compound with ammonia does not affect the number of carbons, we would start with n-pentanol and oxidize it selectively to its corresponding aldehyde which would be treated with ammonia in the presence of hydrogen and a catalyst. The sequence would be as follows:

$$CH_3(CH_2)_4OH \xrightarrow[\text{pyridine}]{CrO_3} CH_3(CH_2)_3\overset{\overset{O}{\|}}{C}-H$$

valeraldehyde

$$CH_3(CH_2)_3\overset{\overset{O}{\|}}{C}-H \xrightarrow[Pt/H_2]{NH_3} \left[CH_3(CH_2)_3\overset{\overset{\overset{H}{|}}{N}}{\overset{\|}{CH}} \right] \xrightarrow{\text{reduction}} (CH_3(CH_2)_3)CH_2NH_2$$

• PROBLEM 22-18

> Isopropylamine and n-pentylamine are to be synthesized. In the laboratory synthesis, outline all the steps from alcohols of four carbons or less, using any needed inorganic reagents.

Solution: These organic compounds can be prepared by employing reductive amination and reduction of nitriles, two ways of preparing amines.

Isopropylamine Synthesis: Many aldehydes $\left[R-\overset{H}{\overset{|}{C}}=O \right]$ and ketones $\left[\begin{matrix} R' \\ & \diagdown \\ & & C=O \\ & \diagup \\ R \end{matrix} \right]$ can be converted to amines (of the same carbon number) by reductive amination: reduction in the presence of ammonia. This reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. The reaction can be generalized as follows:

$$R-\overset{\overset{R'}{|}}{C}=O + NH_3 \rightarrow \left[R-\overset{\overset{R'}{|}}{C}=NH \right] \xrightarrow[\text{or } NaBH_3CN]{H_2,\ Ni} R-\underset{\underset{H}{|}}{\overset{\overset{R'}{|}}{C}}-NH_2$$

(Ketone) (Imine) (2° Amine)

Note: A similar sequence can be written for an aldehyde, with a 1° amine being formed.

This reaction means that if acetone $\left[CH_3-\underset{\displaystyle O}{\underset{\|}{C}}-CH_3 \right]$

were present, isopropylamine $\left[CH_3-\underset{\displaystyle NH_2}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}-CH_3 \right]$ could be

synthesized by reductive amination. Acetone can be obtained

from isopropyl alcohol $\left[CH_3-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}-CH_3 \right]$ by oxidation with CrO_3

in glacial acetic acid. CrO_3 oxidizes 2° alcohols (such as isopropyl alcohol) to the ketone. Note that isopropyl alcohol is allowed as the starting material since it is less than four carbons, as the problem demands. The sequence of reactions can therefore be outlined:

$$\underset{\text{(Isopropyl Alcohol)}}{CH_3-\underset{\displaystyle OH}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}-CH_3} \xrightarrow{CrO_3} \underset{\text{(Acetone)}}{CH_3-\underset{\displaystyle O}{\underset{\|}{C}}-CH_3} + NH_3 \xrightarrow{H_2,\ Ni} \underset{\text{(Isopropyl Amine)}}{CH_3-\underset{\displaystyle NH_2}{\underset{|}{\overset{\displaystyle H}{\overset{|}{C}}}}-CH_3}$$

N-Pentylamine Synthesis: N-Pentylamine's structure ($CH_3CH_2CH_2CH_2CH_2NH_2$) indicates it is composed of 5 carbon atoms. Since the starting material cannot have over 4 carbon atoms, the synthesis of the amine must include an increase in the carbon skeleton of the starting material. Synthesis via reduction of nitriles ($-C\equiv N$) has the special feature of increasing the length of a carbon chain, producing a primary amine that has one more carbon atom than the alkyl halide from which the nitrile was made.

Reduction of a nitrile will be used in the synthesis of N-pentylamine. This necessitates, therefore, that an alkyl halide of 4 carbon length be produced. (Addition of the nitrile ($-C\equiv N$) will increase the length to the desired number of 5 carbon atoms.)

Since the structure of N-pentylamine is a straight chain carbon sequence, the alkyl halide should be a straight chain. The alkyl halide can be made from an alcohol, using a catalyst, PX_3:

$$\underset{\text{(Alcohol)}}{R-OH} + \underset{(X = I,\ Cl,\ Br)}{PX_3} \rightarrow \underset{\text{(Alkyl halide)}}{RX} + H_3PO_3$$

Hence, one needs an alcohol of 4 carbons that possesses a straight carbon chain. N-butyl alcohol fits this description. N-butyl alcohol is reacted with a phosphorus trihalide, say PBr_3.

$$CH_3CH_2CH_2CH_2OH + PBr_3 \rightarrow CH_3CH_2CH_2CH_2Br + H_3PO_3$$

(N-butyl alcohol) (N-butyl bromide)

The nitrile is then formed by a nucleophilic reaction

$$CH_3CH_2CH_2CH_2Br + NaCN \rightarrow CH_3CH_2CH_2CH_2CN$$

(N-butyl nitrile)

Reduction of this compound produces the desired product:

$$CH_3CH_2CH_2CH_2CN \xrightarrow[\text{catalyst}]{2\ H_2} CH_3CH_2CH_2CH_2CH_2NH_2$$

(N-pentylamine)

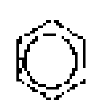
The overall synthesis can be written as:

$$\text{N-BuOH} \xrightarrow{PBr_3} \text{N-BuBr} \xrightarrow{CN^-} \text{N-Bu CN} \xrightarrow{H_2,Ni} \text{N-BuCH}_2NH_2$$

• PROBLEM 22-18

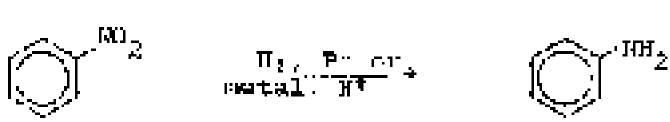
Synthesize m-chloroaniline from benzene. Any inorganic reagents may be used.

Solution: The structures of m-chloroaniline and benzene

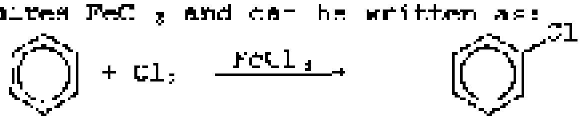
may be written, respectively, as  and 

These structures indicate that a chlorine atom and an amino group must be attached to benzene in a 1,3 (or meta) position.

Amino groups can often be placed on a benzene ring by reduction of the corresponding nitro compound. Reduction of nitro compounds is a key step in what is probably the most important synthetic route in aromatic chemistry. The nitro compounds can be reduced in two general ways: (1) by catalytic hydrogenation using molecular hydrogen or (2) by chemical reduction, usually by a metal and acid. The two methods of reduction can be illustrated as follows:

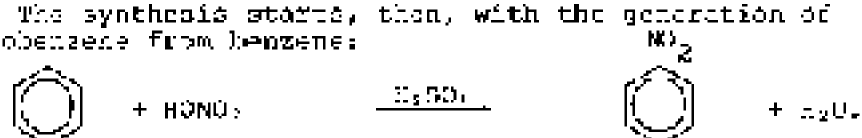


To place chlorine on the ring, an electrophilic aromatic substitution reaction must be used. The reaction requires $FeCl_3$ and can be written as:



The problem at this point is how to obtain the meta orientation on the ring. It is known that a nitrogroup on a ring deactivates the ring strongest at the ortho and para positions by destabilizing the carbocation formed in electrophilic aromatic substitution that occurs in halogenation of aromatic compounds. This means, therefore, that the meta position is least deactivated by the nitro, so that it will direct the chlorine to the meta position as desired. Hence, the benzene should have the nitro group on the ring before halogenation. After halogenation, the nitro group can then be reduced to the amino group. (The amino group cannot be formed before halogenation because NH_2 directs para and ortho, not meta in electrophilic aromatic substitution.)

The synthesis starts, then, with the generation of nitrobenzene from benzene:

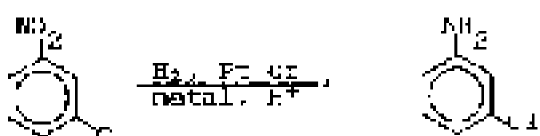


(Benzene) (Nitric Acid) (Nitrobenzene)

Nitrobenzene is now halogenated to obtain m-nitrochlorobenzene:

(m-nitrochlorobenzine)

The product can be reduced to the amino group to obtain the desired m-chloroaniline:



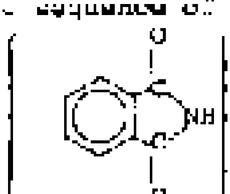
(m-chloroaniline)

REACTIONS

• PROBLEM 22-20

The following sequence of reactions is performed:

phthalimide



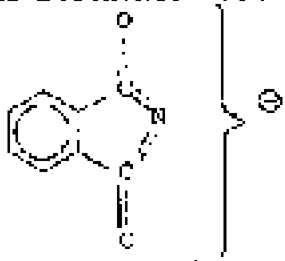
+ KOH (ale.) → A($C_8H_4O_2NK$),

A + $CH_3CH_2CH_2Br$, heat → B($C_{11}H_{11}O_2N$), B + H_2O, OH^-, heat → $C(C_3H_9N)$ + D.

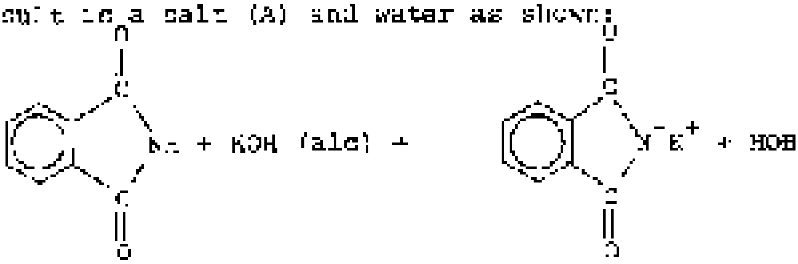
Give structural formulas of compounds A through D in this sequence that illustrates the Gabriel synthesis.

Solution: The hydrogen on the nitrogen of phthalimide is very acidic.

The reason for this stems from the fact that a stable resonance form can come about as a result of the adjacent carbonyls helping to accommodate the negative charge of the anion. The resonance form can be pictured as

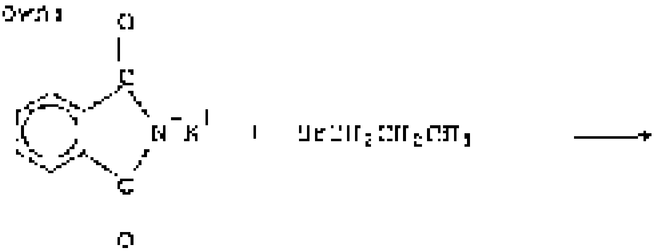


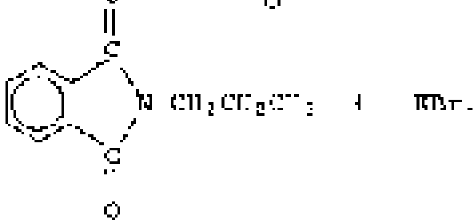
Since the hydrogen is acidic, an acid-base reaction occurs when the base KOH is added to phthalimide. The result is a salt (A) and water as shown:



(A) (salt of imide)

The next step in the sequence has "A" reacting with an alkyl halide, $CH_3CH_2CH_2Br$. The alkyl halide reacts in a similar manner to reaction of halides with ammonia or amines as shown:



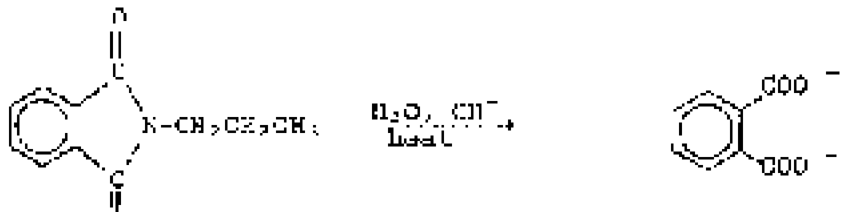


Imides such

(B)

as "B" can undergo hydrolysis with H_2O and base (OH^-) to yield carboxylic acid, just as amides can. This is exactly what happens when H_2O and base is added to "B".

The reaction can be written as:



(D)

$+ H_2NCH_2CH_2CH_3$

(C)

The Gabriel synthesis has great utility in that it produces pure primary amines (such as "C"), free from contaminating secondary or tertiary amines.

■ PROBLEM 22-21

Explain why in the Ritter reaction with hydrogen cyanide and t-butyl alcohol, the product is t-butylamine and not t-butyl cyanide (or trimethylacetic acid).

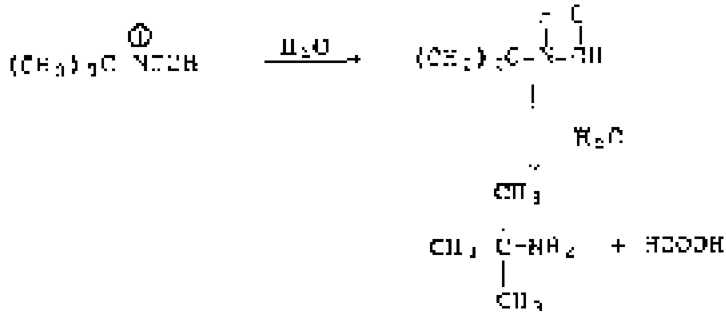
Solution: Primary amines having the general formula R_3CNH_2 cannot be synthesized via a substitution route because an S_N2 reaction would be sensitive to the steric hindrance caused by the t-butyl group.

$$NH_3 + R_3CX \not\longrightarrow R_3CNH_2 + HX$$

Amines of this type can be prepared by the Ritter reaction in which an alkene or alcohol is reacted with hydrogen cyanide or a nitrile in the presence of sulfuric acid. In the case of t-butyl alcohol and hydrogen cyanide, the carbocation that is formed coordinates the nitrogen of the cyano group forming a new C-N bond. A C-N bond is formed rather than a C-C bond because it is the nitrogen that has a free pair of electrons and not the carbon. Therefore, only the nitrogen will attach to the electropositive carbon.

$$H-C\equiv N: \quad \overset{\oplus}{C}(CH_3)_3 \longrightarrow H-C\equiv\overset{\oplus}{N}-C(CH_3)_3$$

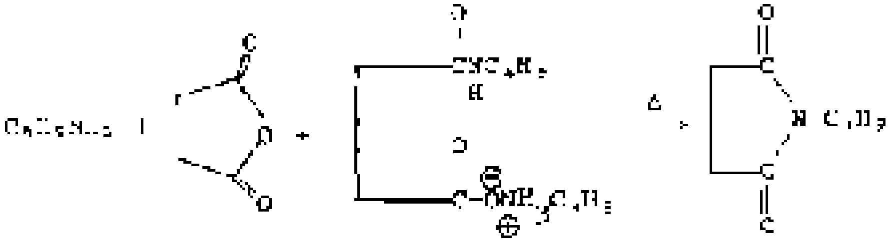
If the carbon did actually attach, t-butyl cyanide and its hydrolysis product would be formed. What does happen is that the nitrile intermediate is hydrolyzed to an amine, passing through an amide stage.

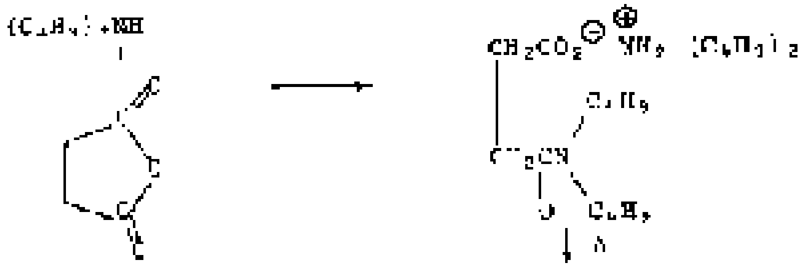


▶ PROBLEM 22-22

Show how a mixture of n-butylamines prepared from n-butyl bromide and an excess of n butylamine might be resolved into its components by reaction with succinic anhydride, separation of the products through advantage of their solubility properties in acid or base, and regeneration of the corresponding amines. Write equations for the reactions involved.

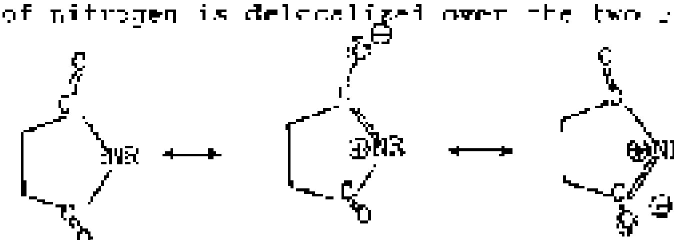
Solution: When an excess of alkylamine is reacted with an alkyl halide, several products of varying degrees of alkylation are expected. This is because the initial substitution product is still a nucleophile and can further attack the alkyl halide. Thus, n-butyl bromide and n-butylamine will produce mono-, di-, and tri-n-butylamines as well as a sparse amount of tetra-n-butylammonium bromide. We may separate the amines by having them react with succinic anhydride. The tertiary amine will not readily react with the anhydride and it can be isolated via an extraction in which the amine is first protonated and then regenerated by aqueous base. When the primary amine reacts with the cyclic anhydride, a compound containing a salt and amide linkage is formed. Dibutylamine forms a similar type of structure but only the intermediate formed by butylamine will cyclize when heated strongly, forming an imide. This is because only the primary amine retains a hydrogen on the nitrogen, after attacking the anhydride.





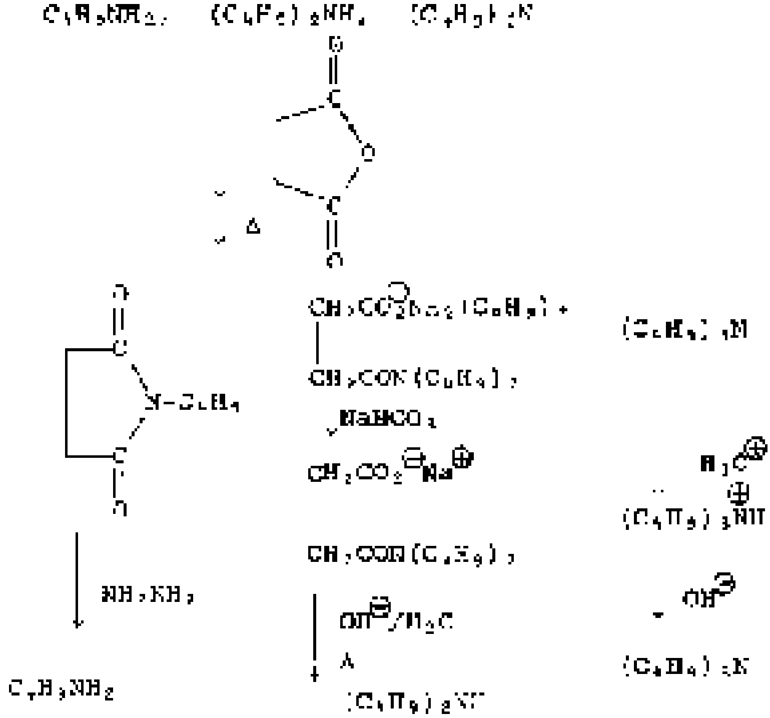
No reaction

Thus after addition of the anhydride and heating, the mixture of amines will be converted to a combination of N-butyl-succinimide, tri-n-butylamine, and the amido salt. The amine may be removed in the aforementioned way because neither the salt nor the succinimide is basic. The succinimide is actually neutral because the electron pair of nitrogen is delocalized over the two carbonyl groups



After tri-n-butylamine is removed from the mixture, we may use the salt's acidity to isolate it in solution. The succinimide will remain in the organic layer and the primary amine may be produced from it by reacting the imide with hydrazine. Similarly, we may regenerate the secondary amine from the amide by alkaline hydrolysis. The entire separation sequence is summarized below, using ether as the organic phase:

$C_4H_9NH_2$, $(C_4H_9)_2NH$, $(C_4H_9)_3N$



Choline, a constituent of phospholipids (fat like phosphate esters of great physiological importance), has the formula $C_5H_{15}O_2N$. It dissolves readily in water to form a strongly basic solution. It can be prepared by the reaction of ethylene oxide with trimethylamine in the presence of water.

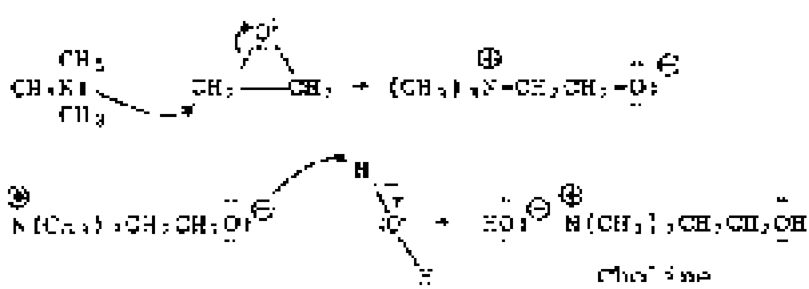
(a) What is a likely structure for choline?
(b) What is a likely structure for its acetyl derivative, acetylcholine, $C_7H_{17}O_3N$, important in nerve action?

Solution: Amines have the general formula NR_3 where R may be an alkyl group, an aryl group or a hydrogen. The nitrogen's free pair of electrons allow them to participate in reactions involving nucleophilic attack. The three membered epoxide ring of ethylene oxide is highly strained and is an excellent site for such an attack. In this case, the tertiary amine, trimethyl amine, will attack the epoxide to give a charge separated form. This amine has no hydrogen directly attached to the nitrogen and thus proton transfer cannot occur. If we do some chemical arithmetic, we see that a molecule of H_2O has been added to this charge separated form.

C_3H_9N	trimethylamine
C_2H_4O	ethylene oxide
$C_5H_{13}ON$	

$C_5H_{15}O_2N$	Choline
$C_5H_{13}ON$	
H_2O	

This can be explained by a proton transfer from water to the alkoxide oxygen and with the subsequent product being a quaternary ammonium hydroxide solution. This solution, like any containing the hydroxide ion, is strongly basic. Thus choline is prepared as follows:



(b) The nitrogen in choline is attached to four groups and does not have a free pair of electrons. It cannot, therefore, attack an acylating agent such as acetic anhydride. However, the uncharged oxygen of choline still has two pairs of free electrons and can participate in such a nucleophilic attack. We can verify that choline's hydroxyl group was acetylated by using chemical arithmetic:

$$\begin{array}{ll} C_5H_{15}O_2N & \text{choline} \\ \underline{\quad -H \quad} & \text{hydroxyl proton lost in acetylation} \\ C_5H_{14}O_2N & \end{array}$$

$$\begin{array}{lll} C_7H_{17}O_3N & \text{acetylcholine} & \\ \underline{C_5H_{14}O_2N} & & \\ C_2H_3\ O & \text{acetyl group} & \left[CH_3-\overset{O}{\overset{\|}{C}}- \right] \end{array}$$

Thus the structure of acetylcholine is:

$$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2\overset{\oplus}{N}(CH_3)_3 \quad :\ddot{O}H^{\ominus}$$

• PROBLEM 22-24

Novocaine, a local anesthetic, is a compound of formula $C_{13}H_{20}O_2N_2$. It is insoluble in water and dilute NaOH, but soluble in dilute HCl. Upon treatment with $NaNO_2$ and HCl and then with β-naphthol, a highly colored solid is formed.

When Novocaine is boiled with aqueous NaOH, it slowly dissolves. The alkaline solution is shaken with ether and the layers are separated.

Acidification of the aqueous layer causes the precipitation of a white solid A; continued addition of acid causes A to redissolve. Upon isolation A is found to have a melting point of 185-6° and the formula $C_7H_7O_2N$.

Evaporation of the ether layer leaves a liquid B of formula $C_6H_{15}ON$. B dissolves in water to give a solution that turns litmus blue. Treatment of B with acetic anhydride gives C, $C_8H_{17}O_2N$, which is insoluble in water and dilute base, but soluble in dilute HCl.

B is found to be identical with the compound formed by the action of diethylamine on ethylene oxide.

(a) What is the structure of Novocaine? (b) Outline all steps in a complete synthesis of Novocaine from toluene and readily available aliphatic and inorganic reagents.

CARBOXYLIC ACIDS

Name	Formula	M.p. °C
o-Nitrobenzoic	$o\text{-}O_2NC_6H_4COOH$	147
m-Nitrobenzoic	$m\text{-}O_2NC_6H_4COOH$	141
p-Nitrobenzoic	$p\text{-}O_2NC_6H_4COOH$	242
Phthalic	$o\text{-}C_6H_4(COOH)_2$	231
Isophthalic	$m\text{-}C_6H_4(COOH)_2$	348
Terephthalic	$p\text{-}C_6H_4(COOH)_2$	300 subl.
Salicylic	$o\text{-}HOC_6H_4COOH$	159
p-Hydroxybenzoic	$p\text{-}HOC_6H_4COOH$	213
Anthranilic	$o\text{-}H_2NC_6H_4COOH$	146

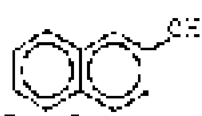
m-Aminobenzoic	$m\text{-}H_2NC_6H_4COOH$	179
p Aminobenzoic	$p\text{-}H_2NC_6H_4COOH$	187
o-Methoxybenzoic	$o\text{-}CH_3OC_6H_4COOH$	101
m-Methoxybenzoic	$m\text{-}CH_3OC_6H_4COOH$	110
p Methoxybenzoic(Anisic)	$p\text{-}CH_3OC_6H_4COOH$	184

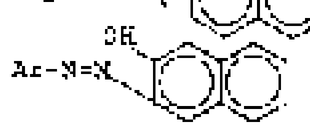
Solution: (a) When solving this problem where we are given certain experimental data and are told to determine certain structures, it would be most helpful to analyze each piece of information and see what it will tell us about the structure we are trying to find. From just Novocaine's formula, we see that it is highly unsaturated in that there is a low ratio of hydrogen to carbon in the molecule, after we account for the presence of the compound's heteroatoms.

$$\begin{array}{ll} C_{13}H_{20}O_2N_2 & \\ \underline{\quad - O_2} & \text{no change in H's} \\ C_{13}H_{20}\ N_2 & \\ \underline{\quad - N_2} & \text{subtract 2 H's} \\ C_{13}H_{18} & \end{array}$$

$$\begin{array}{ll} C_{13}H_{28} & \\ \underline{C_{13}H_{18}} & \text{saturated 13 Carbon compound} \\ \quad H_{10} & \text{5 units of unsaturation} \end{array}$$

The high amount of unsaturation would indicate the presence of an aromatic ring. The fact that Novocaine is insoluble in H_2O indicates that this is an organic molecule of some size and not great polarity. Its insolubility in base indicates that Novocaine cannot contain an acidic functionality such as a carboxylic acid group and it cannot be a phenol for the same reason. Novocaine must be a compound with significant basicity such as an amine because it is soluble in dilute acid. The reaction of Novocaine with $NaNO_2$ and HCl tells us a great deal in that the compound must be a primary aromatic amine because only such a compound will form a diazonium cation ($Ar\text{-}N_2^{\oplus}$) when treated with nitrous acid $-HONO(NaNO_2 + HCl)$. This cation will react with

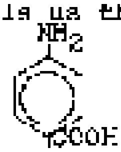
the activated β-naphthol () to form a colored

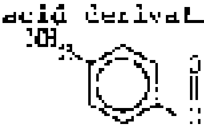
azo compound (). The fact that

Novocaine dissolved eventually when boiled in aqueous base shows that this compound can undergo hydrolysis and therefore is an acid derivative. We also know that the "acid part" of this compound will exist as a salt ($RCOO^{\ominus}Na^{\oplus}$). If Novocaine were an amide, the other hydrolysis product would be an amine and if it were an ester the other product would be an alcohol. The carboxylate anion would be separated into the aqueous layer since it is polar and the other product (amine or alcohol) would dissolve in the non-polar ether layer. Each part of Novocaine can be analyzed individually as a result. Precipitation of the aqueous layer upon addition of acid is not surprising since we have just converted the carboxylate anion to its carboxylic acid. ($RCOO^{\ominus} \xrightarrow{H^{\oplus}} RCOOH$). However, the fact that further acidification dissolves the acid (A) indicates that this substance has a basic functionality. Compound A is amphoteric in that it may accept as well as donate a proton. Chemical arithmetic can now tell us the structure of A in that we know it contains a carboxyl group (COOH) and the high amount of unsaturation in the remainder of compound A is indicative of an aromatic ring. Since the six carbons are contained in the ring and only the remaining heteroatom is the nitrogen, this must be a disubstituted aromatic compound, specifically an aminobenzoic acid. This is summarized by:

Compound A' molecular formula	$C_7H_7O_2N$
the carboxyl group	$-\ COOH$
	$C_6H_6\ N$
disubstituted aromatic ring	C_6H_4
the amino group	H_2N

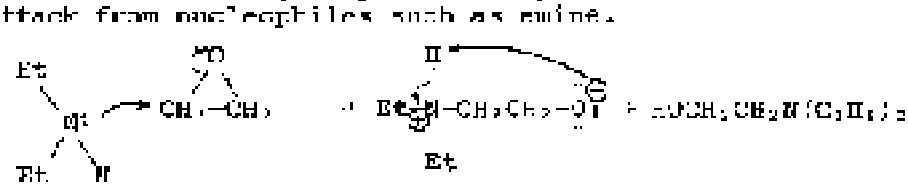
The exact orientation about the ring is given to us by the physical data. The accompanying table of melting points tells us that compound A must be p aminobenzoic acid.



Since Novocaine is an acid derivative, we know that it must contain the fragment  from compound A.

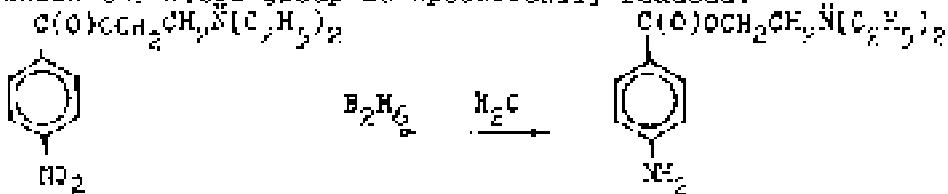
$C_{13}H_{20}O_2N_2$	Novocaine
$C_7\ H_6\ O\ N$	contribution from compound A
$C_6\ H_{14}O\ N$	undetermined part of Novocaine

We do not yet know the nature of the nitrogen in compound B but this may be found by examining the hydrolysis product in the ethereal layer. Compound B is basic and this basicity is not altered by its treatment with acetic anhydride. Therefore, B must be an amine and in fact a tertiary amine since they do not readily form amides. Thus, it is an oxygen and not a nitrogen that is attached to the carbonyl group in Novocaine. Furthermore, it is the oxygen of the alcohol that attacks the anhydride. Novocaine is an ester and the alcohol part can be found from the reaction of diethylamine and ethylene oxide. Ethylene oxide is a strained three-membered ring compound (an epoxide) and is prone to attack from nucleophiles such as amine.

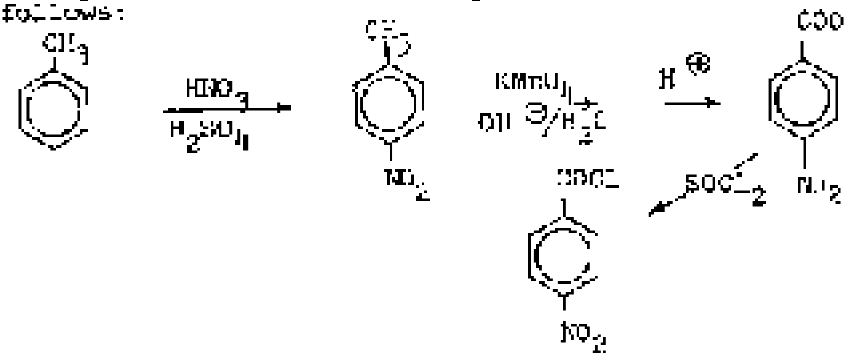


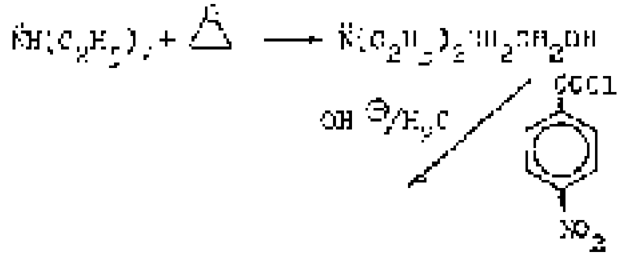
Hence, Novocaine has the structure:

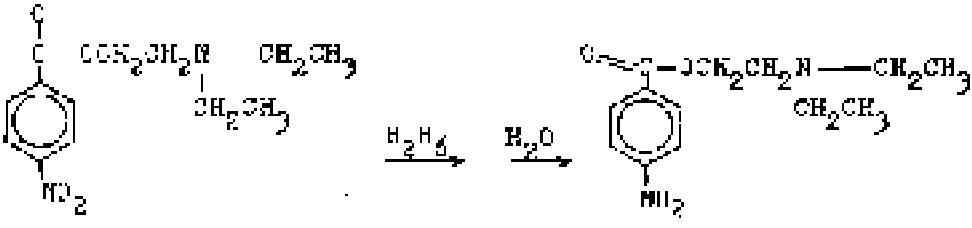
(b) If we examine Novocaine's structure, we see that the product contains an amino group. This group is sensitive to many processes and therefore it is synthetically feasible not to create this group until the last step where the nitro group is specifically reduced.



The nitro compound is also an ester which can be derived from an alcohol and an acid derivative. In this case, it would be best to synthesize the ester from the acid chloride, p-chlorobenzoyl chloride, and the amino alcohol in the presence of base. The base will prevent protonation of the amino group by the subsequently formed HCl. The nitro group can be given its proper para orientation by directly nitrating toluene. Subsequent oxidation of the methyl group and treatment with thionyl chloride will yield the acid chloride. The alcohol portion of the ester can be derived from the reaction of diethylamine with ethylene oxide. Thus, the synthetic scheme would be as follows:







Write balanced equations, naming all organic products, for the following reactions:

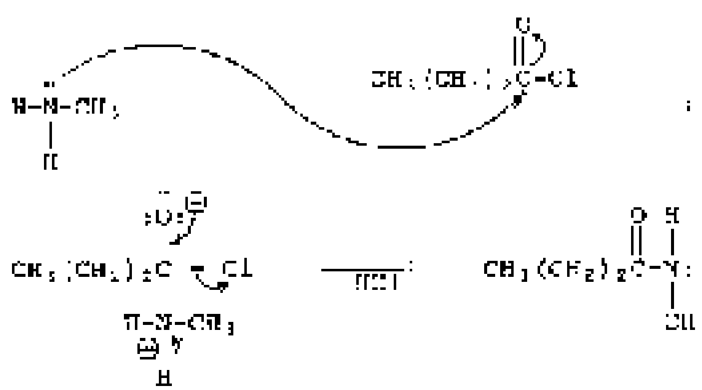
(a) n-butyryl chloride + methylamine
(b) acetic anhydride + N-methylaniline
(c) tetra-n-propylammonium hydroxide + heat
(d) tetramethylammonium hydroxide + heat
(e) N,N-dimethylacetamide + boiling dilute HCl
(f) benzanilide + boiling aqueous NaOH
(g) m-$O_2NC_6H_4NHCH_3$ + $NaNO_2$ + H_2SO_4
(h) p-toluidine + $Br_2(aq)$ in excess
(i) p-toluidine + $NaNO_2$ + HCl
(j) p-$CH_3C_6H_4NHCOCH_3$ + HNO_3 + H_2SO_4
(k) benzanilide + Br_2 + Fe

Solution: Nitrogen takes a variety of forms in organic chemistry, of which many are biologically important. This problem involves the reactions of amines and their related compounds. It is best to examine the reactants and see what type of reaction is involved. For example, if given the reactants ammonia and acetic acid, we know that this is an acid base reaction involving a proton transfer. The reaction would be designated as:

$$NH_3 + CH_3COOH \rightarrow CH_3COO^{\ominus}\,{}^{\oplus}NH_4$$

Other general reactions of amines would be nucleophilic displacement, electrophilic aromatic substitution in anilines and substitution via diazonium salts.

(a) The reactants are an acid chloride and an amine. The reaction may be seen as nitrogen's free pair of electrons attacking the electropositive carbon of the carbonyl group in an addition-elimination reaction with the chloride anion leaving.



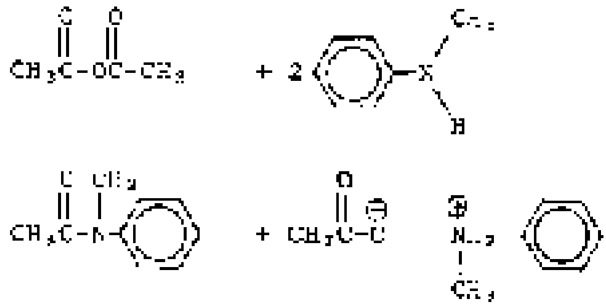
The HCl that is generated will protonate the unreacted amine to give a salt.

$$HCl + NH_2CH_3 \rightarrow {}^{\oplus}NH_3CH_3\ Cl^{\ominus}$$

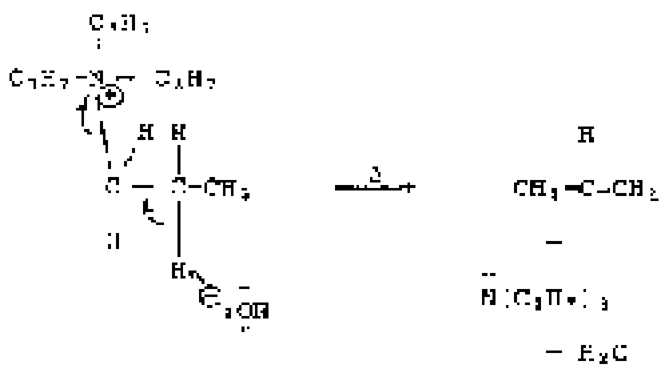
The balanced equation for the entire reaction is:

$$2NH_2CH_3 + CH_3(CH_2)_2\overset{O}{\overset{\|}{C}}-Cl \rightarrow CH_3(CH_2)_2\overset{O}{\overset{\|}{C}}-NHCH_3 + \overset{\oplus}{N}H_3CH_3Cl^{\ominus}$$

(b) In this reaction, the amine will attack the anhydride to yield an amide with the carboxylate anion acting as a leaving group. The other product is the salt of the amide.

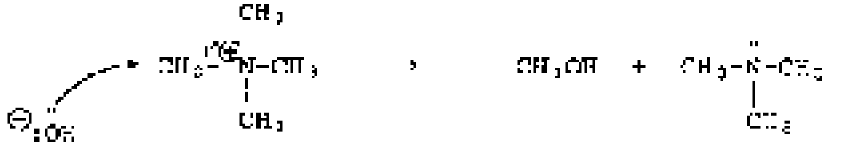


(c) In this problem, we have tetra-n-propylammonium hydroxide as a reactant. This salt belongs to the general class of compounds known as quaternary ammonium hydroxides with the formula $R_4N^{\oplus}\,OH^{\ominus}$. When these compounds are heated strongly, they undergo an elimination reaction of the E2 variety in which the hydroxide ion acts as a base and a tertiary amine leaves. In this case:

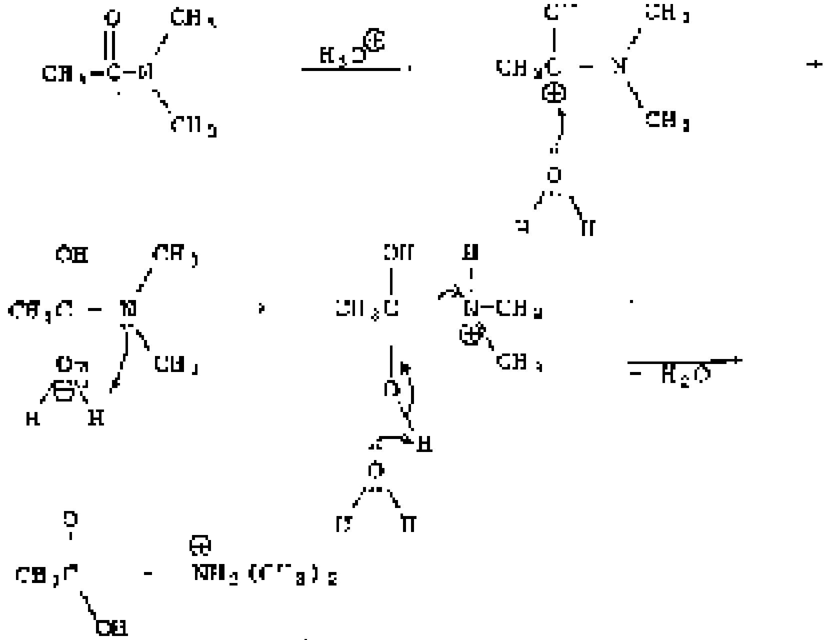


This Hofmann elimination follows an anti-orientation of leaving groups with the less-substituted alkene product predominating.

(d) Tetramethylammonium hydroxide is a quaternary ammonium hydroxide that cannot possibly undergo an elimination reaction. Hofmann eliminations usually have substitution reactions as side reactions but in this case substitution is the only feasible route. The substitution is of an S_N2 variety with the relatively unhindered methyl moiety being an excellent site for such attack. Here the hydroxide ion is acting as a nucleophile instead of a base.



(e) When acid derivatives such as esters, amides and acid chlorides are subject to aqueous acid, they undergo a hydrolysis reaction forming a carboxylic acid and another molecule. In this case, hydrolysis of the amide yields the acid and a protonated amine by the following mechanism:

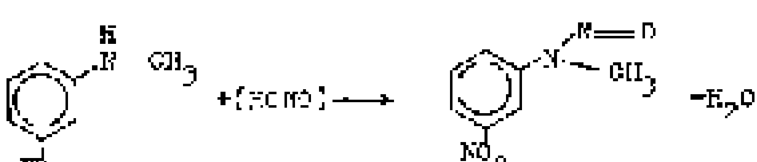


The net reaction is:

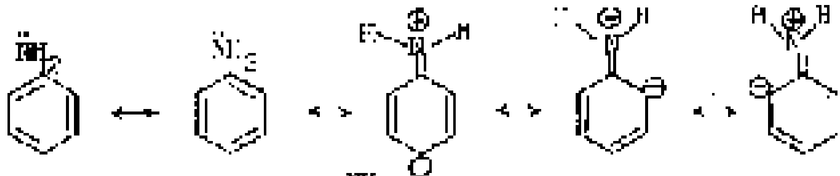
$$H_3O^{\oplus} + CH_3\overset{O}{\overset{\|}{C}}-N(CH_3)_2 \rightarrow CH_3\overset{O}{\overset{\|}{C}}-OH + \overset{\oplus}{N}H_2(CH_3)_2$$

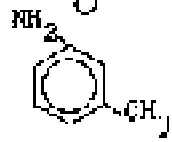
(f) Hydrolysis of a carboxylic acid derivative may be undertaken under alkaline conditions as well as acidic conditions. Benzanilide, which is the condensation product of benzoyl chloride and aniline, will yield aniline and the anion of benzoic acid when subjected to alkaline hydrolysis. The mechanism involves the nucleophilic attack of the hydroxide ion upon the carbonyl group.

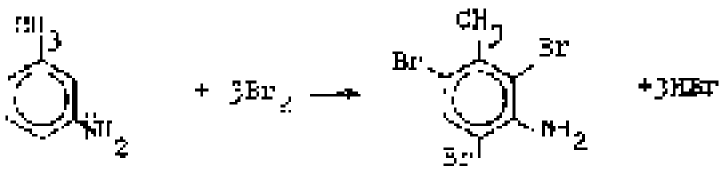
(g) When sodium nitrite ($NaNO_2$) and H_2SO_4 are mixed, nitrous acid is generated. This short-lived reagent reacts with secondary amines, both alkyl and aryl, to form an N-nitroso compound. We note that this reagent is specific to amino group and the nitro group is unaffected.



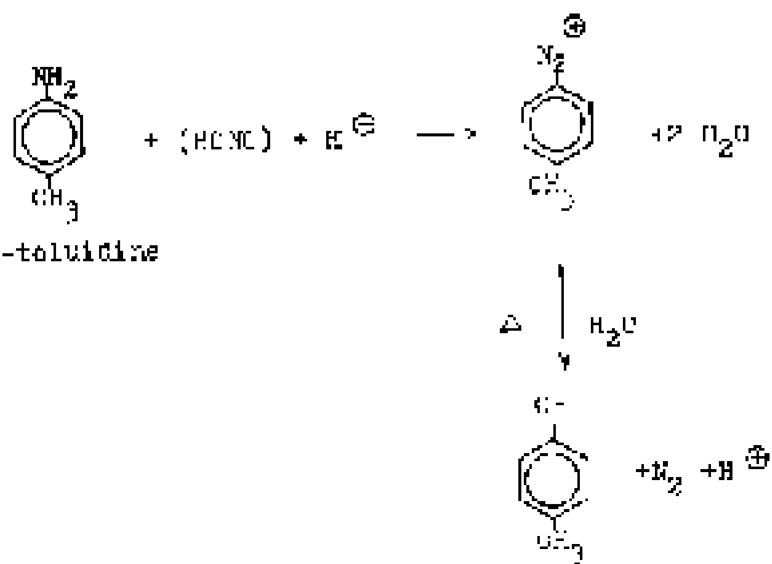
(h) When located directly on an aromatic ring, the amino group is an activating ortho-para director. This activation and orientation in electrophilic aromatic substitution can be seen in terms of aniline's resonance structures which include forms where the negative charge is delocalized to positions ortho and para to the amino group.



m-toluidine, () contains both the amino group and the methyl group, both of which are activators. However, the amino group is the stronger activator of the two and the incoming bromines are directed ortho and para to it. We can see the aniline's great reactivity by the fact that no catalyst was needed and that all positions ortho and para to the amino group were brominated.



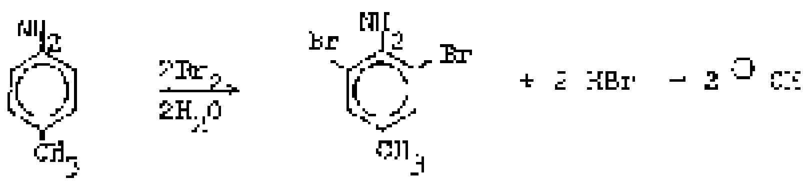
(i) When an aromatic or aliphatic amine is reacted with nitrous acid, they form a diazonium salt $R(Ar)-N_2^{\oplus}X^{\ominus}$. While the alkyl diazonium salt is unstable and loses nitrogen to form a variety of alkenes and alcohols, the aryl type is stable and has synthetic importance. When an aniline such as p-toluidine is converted to its diazonium salt, the temperature is kept low to avoid formation of the phenol.

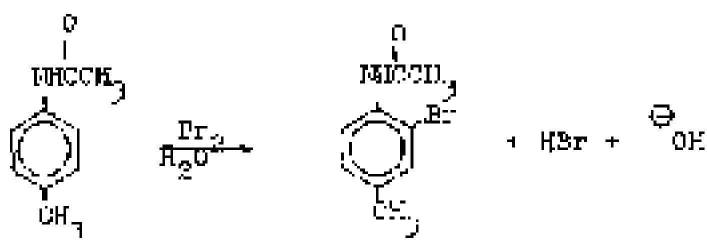


p-toluidine

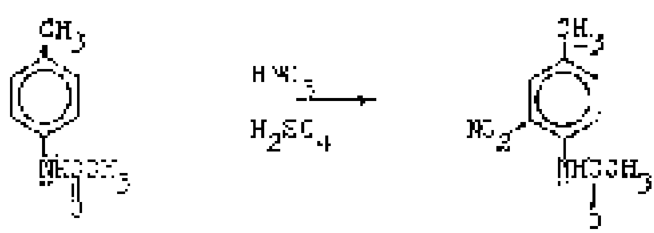
p-cresol

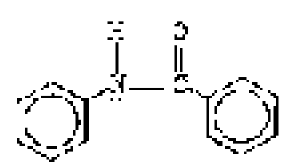
(j) We note that aceto-p-toluidide contains an acetyl group attached to the amino group. The carbonyl carbon is electropositive and lessens the adjacent nitrogen's tendency to delocalize the electrons within the aromatic ring. Hence, the reactivity to electrophilic substitution of aceto-p-toluidide is less than its corresponding aniline, p-toluidine. This can be seen in the comparable bromination reactions of these compounds in which only the aniline will undergo polysubstitution.

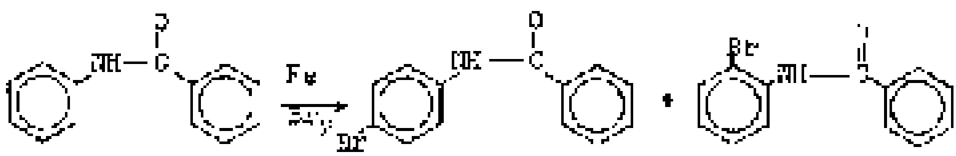




Thus when Aceto p toluidide is treated with the nitrating mixture, nitration occurs only at a single ortho position. We note that we may remove the acetyl group by alkaline hydrolysis. It is a useful synthetic procedure to protect the amino group by acetylating it and removing it after undertaking the desired reaction. Besides reducing the activity of the aniline, acetylation protects the amine group from protonation or oxidation during the nitration reaction.



(k) Benzanilide,  contains two aromatic rings, one of which is bounded by the amide nitrogen and the other is bounded by a carbonyl group. The nitrogen can delocalize its free electron pair less than an amine group can but it activates the adjacent ring nevertheless. The carbonyl group, on the other hand, is electron withdrawing and the aromatic ring bounded by it is deactivated toward electrophilic aromatic substitution. Thus, when benzanilide undergoes a bromination reaction, the electrophile is more likely to attack the more activated aromatic ring which is the one bounding the nitrogen. We note that the amide nitrogen is an ortho-para director and we get both ortho and para products.



• PROBLEM 22-26

Predict the products expected in the reactions of the following amines with nitrous acid (prepared from $NaNO_2$ + HCl in aqueous solution):

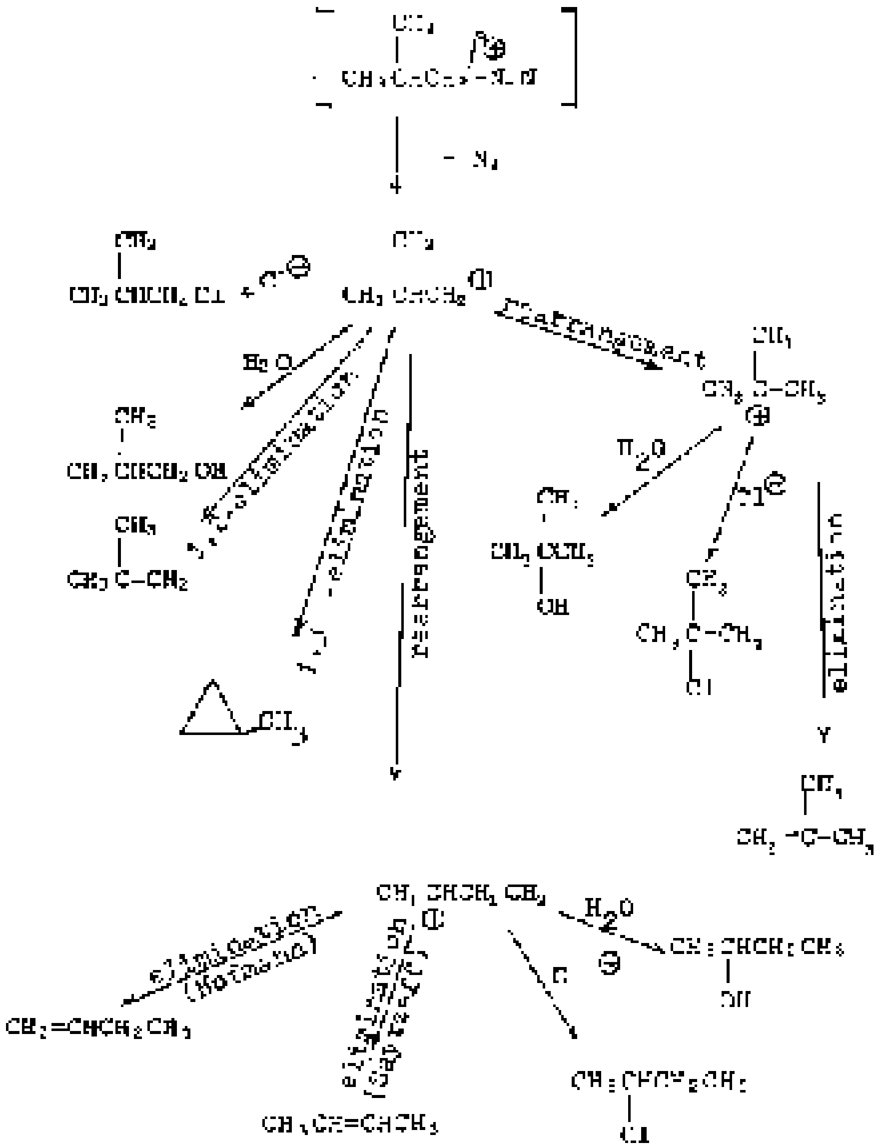
(a) $CH_3-\underset{H}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2NH_2$

(b) 

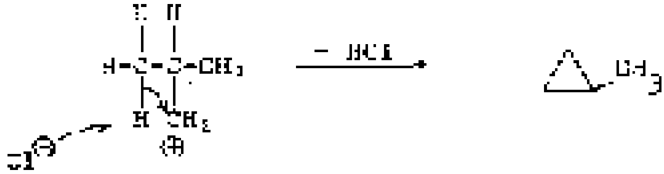
(c) $CH_3-\underset{NH_2}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-\underset{OH}{\overset{CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3$

<u>**Solution:**</u> Nitrous acid is generated by a mixture of sodium nitrite and HCl at 0°C. This unstable reagent is useful in differentiating amines of various degrees of substitution.

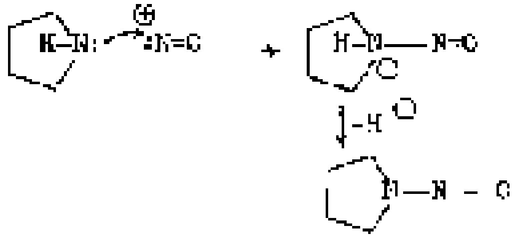
(a) Primary alkyl amines of this type form diazonium salts ($R-\overset{\oplus}{N_2}X^{\ominus}$), which decompose spontaneously, losing the the stable molecule nitrogen, to form a variety of products. The products can be explained in terms of intermediate carbocations which can undergo rearrangement, substitution and elimination.

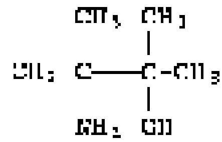


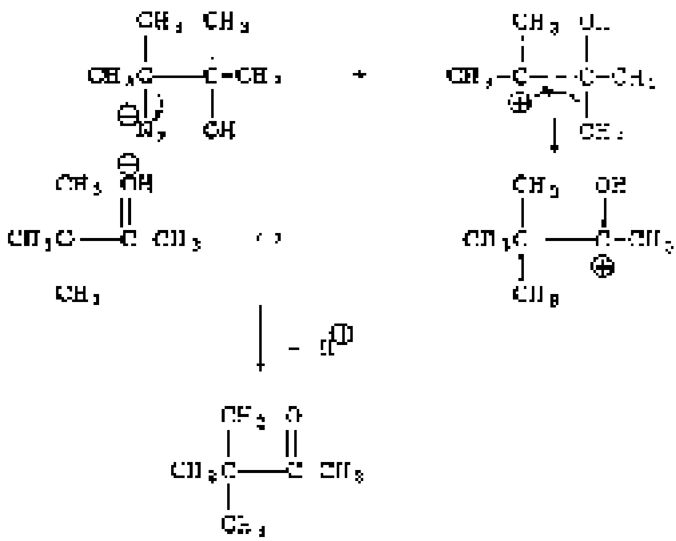
Methylcyclopropane results from a 1,3- or γ-elimination where the proton is removed from a carbon not adjacent to the positively charged carbon.



(b) A secondary amine, whether aryl or alkyl, will be converted to an N-nitroso compound, which are usually yellow in color. They result from the electrophilic attack of the nitrosium ion upon the nitrogen.



(c) The compound , is analogous to the corresponding vic diol and the diazonium salt undergoes a reaction similar to the vic-diol's pinacol rearrangement where there is a methyl shift and subsequent formation of a ketone.



Note that the intermediate cation is resonance stabilized by the adjacent oxygen.

• PROBLEM 22-27

An amine of unknown structure has the molecular formula $C_7H_{11}N$. Benzenesulfonyl chloride was added to this amine. The result was a precipitate which was soluble in sodium hydroxide. If the amine had been treated with nitrous acid at 0°C, a reaction would have occurred. A gradual warming to room temperature in the presence of water would have caused a gas to be evolved. Write a possible structure of the amine.

Solution: The reaction of benzenesulfonyl chloride indicates the Hinsberg test as being used. This test is employed to determine the class of an amine. If the amine is primary or secondary, a reaction occurs. Tertiary amines fail to react. The fact that a precipitate formed means the amine of formula $C_8H_{11}N$ is either 1° or 2°.

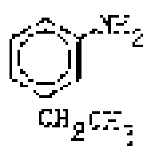
Primary and secondary amines can be distinguished by the fact that the benzenesulfonamide of a 1° amine can dissolve in sodium hydroxide, while the 2° amine cannot. Since the precipitate did dissolve in this substance, the unknown amine can be classified as primary.

The next bit of information about the structure of $C_8H_{11}N$ comes from the fact that it reacts with nitrous acid at 0°C. Both aliphatic and aromatic primary amines react with nitrous acid to form diazonium compounds as illustrated:

$$R\text{-}NH_2 \xrightarrow{HNO_2} R\text{-}N{\equiv}N^{\oplus}\ , \quad R = \text{alkyl or aryl group.}$$

The problem now is to determine whether R is alkyl or aryl. It is known that primary aliphatic amines yield an stable diazonium compounds that immediately decompose to give nitrogen (N_2) gas and a carbonium ion. The problem indicates that nitrogen gas is formed but only after a gradual warming to room temperature. It is known that primary aromatic amines (that have formed the diazonium compound) will yield the phenol under such conditions with the evolution of nitrogen gas. Hence, the only conclusion is that the unknown amine must be aromatic, since the reaction of the diazonium is gradual, not immediate.

To this part, the structure of the unknown compound must be a primary aromatic amine. An example of such a compound would be:



(m-ethyl aniline)

• PROBLEM 23-28

Compound A, $C_{10}H_{21}N_2$, was soluble in dilute acid, but did not react with benzenesulfonyl chloride. Upon addition of excess methyl iodide, Compound A reacted. It was then treated with silver oxide, and the resulting product heated. thus B, C_8H_{14}, was formed. B was treated with ozone and the ozonide decomposed with dilute acid in the presence of zinc dust. One of the two products isolated was

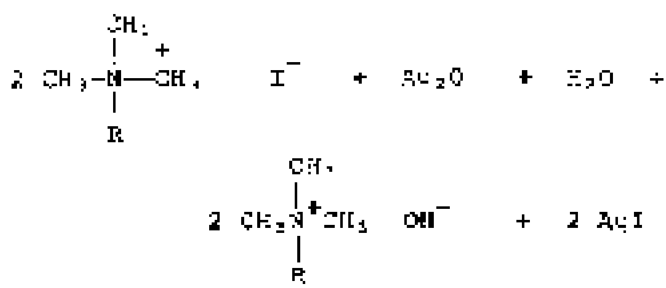
$$\begin{array}{ccccc} & CH_3 & CH_3 & CH_3 & \\ & | & | & | & \\ O{=} & C & \text{—} C \text{—} & C & {=}O. \\ & & | & & \\ & & H & & \end{array}$$

Write structures for A and B with the equations of all reactions.

Solution: Since compound A does not react with benzenesulfonyl chloride, it must be a tertiary amine. This fact is known for benzene sulfonyl chloride (and excess sodium hydroxide) are used in the Hinsberg reaction, which provides a means for differentiating primary, secondary and tertiary amines. The amide formed from the reagent and primary amine is soluble in sodium hydroxide solution, the sulfonamide from the secondary amine is not, and the tertiary amine does not react.

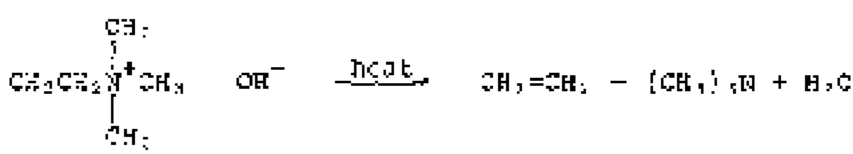
Once the fact that compound A is a tertiary amine is recognized, the reactions that lead to the formation of compound B should be seen as the formation of a quaternary ammonium salt with subsequent decomposition by heat (Hofmann elimination). The formation of quaternary ammonium salts can be generalized as follows:

$$R-NH_2 + 3CH_3I \xrightarrow{2NaOH} CH_3CH_2\overset{+}{N}(CH_3)_3I^- + 2NaI + 2H_2O.$$



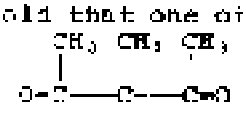
(Quaternary Ammonium Hydroxide)

After treatment with CH_3I and Ag_2O, one can say that compound A is now a quaternary ammonium hydroxide. The problem indicates this compound is heated to obtain B. This reaction is an example of the decomposition of quaternary ammonium hydroxides to alkenes, tertiary amines and water. A typical reaction would be:

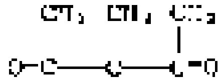


The compound B formed must be, then, either a tertiary amine or an alkene. Its molecular formula does not contain "N" (for nitrogen), which means it must be an alkene. In addition, the fact that B was cleaved into two products by ozone, acid, and zinc indicates the presence of a double bond, for these reagents are the basis for the ozonolysis reaction, which cleaves compounds with double bonds into aldehydes and ketones.

One is told that one of the two products of the ozonolysis is

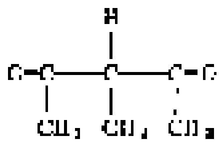


. This compound has 6 carbons

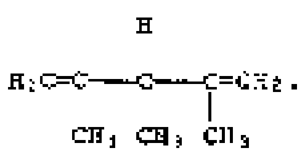
and 12 hydrogens, which means that the second product isolated may have only 1 carbon and two hydrogens. This is explained as follows:  contains two carbonyls which means B has two double bonds, a diene. But because only two kinds of product are obtained after ozonolysis, and three species are possible, (a diene will always yield three species on ozonolysis, since

$$R_1{=}R_2{=}R_3 + O_3 \xrightarrow[H^+]{Zn} R_1{=}O + O{=}R_2{=}O + R_3{=}O\ ,$$

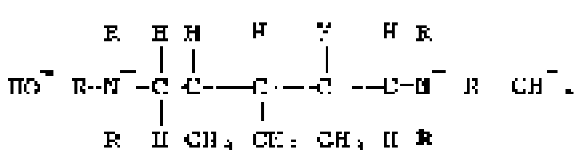
two of the species must be the same compound. Since the molecular formula of B contains 8 carbons and 14 hydrogens

and  has 6 carbons and 10 hydrogens, the two species must contain a total of 2 carbons and 4 hydrogens. But if each is the same compound, it must contain half these numbers, or 1 carbon and 2 hydrogens. The only such aldehyde (in this case no ketone can be formed) that has this carbon and hydrogen molecular formula is formaldehyde

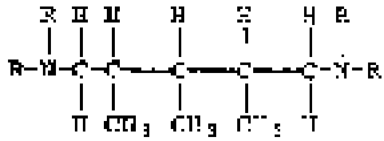
 Note that an examination of compound A's molecular formula eliminates the possibility of a cyclic structure so the second ozonolysis product is $H\overset{O}{\overset{\|}{C}}H$ and not $H{-}\overset{O}{\overset{\|}{C}}{-}\overset{O}{\overset{\|}{C}}{-}H$. Thus compound B must be



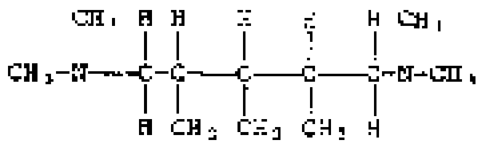
As stated previously, compound B was the alkene (actually a diene) that resulted from the decomposition of the quaternary ammonium hydroxide. Hence, the hydroxide had to have the formula of:



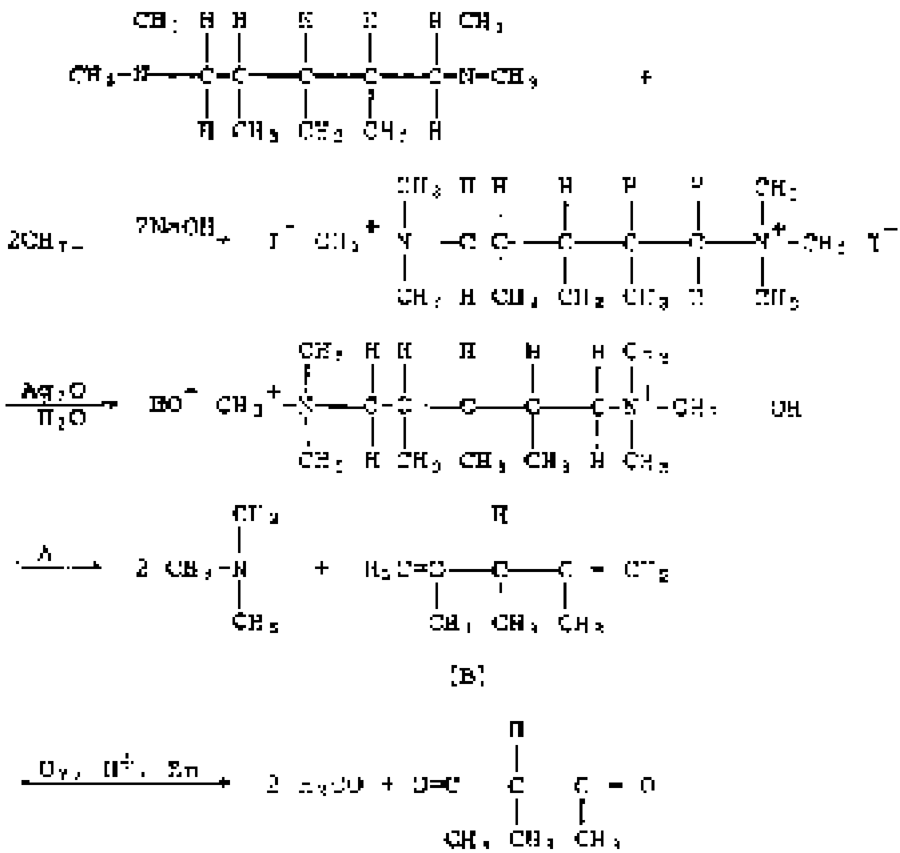
From the reactions which indicate the method of synthesis of the hydroxide from the original amine, compound A must have a structure of



which agrees nicely with the Hinsberg test for tertiary amines. To determine R, consider the molecular formula of A, $C_{13}H_{28}N_2$. The structure above includes all of these atoms, except for 4 carbons and 12 hydrogens. Since four alkyl groups are required, only methyl (CH_3) can be used as the alkyl group. The formula of compound A becomes:

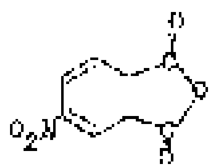


The sequence of reactions can now be written:

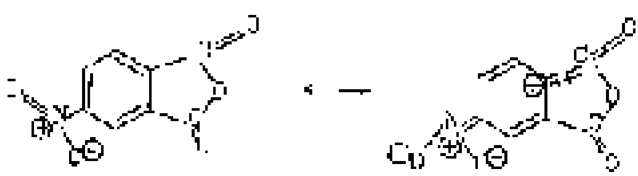


What will be the major product of the reaction of 4-nitrophthalic anhydride with n-butylamine? Explain.

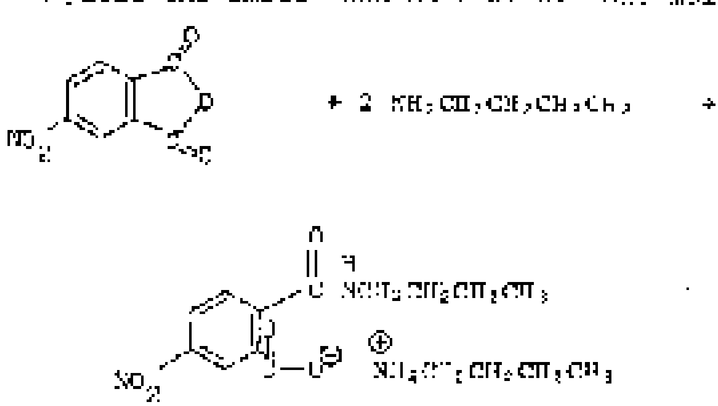
Solution: An amine will react with an anhydride to produce an amide and its salt. The basis for this reaction is that the amine has a free pair of electrons on nitrogen and it can act as a nucleophile, attacking one of the two electrophilic carbonyl carbons. In this case, the orientation of the product is made more complex in that it becomes questionable which of the anhydride's carbonyl groups will be attacked, due to their different orientation towards the nitro group of 4-nitrophthalic anhydride.



The carbonyl group whose carbon is most electrophilic, or more aptly electron-deficient, would be the site of the nucleophilic attack. The attack would have to occur at the carbonyl group para to the nitro substituent since only here will the nitro functionality exert its electron-withdrawing resonance effect as well as its inductive effect. This resonance effect can put positive charge on the carbon para to the nitro group. This positively charged carbon will make the adjacent carbonyl carbon more electrophilic.

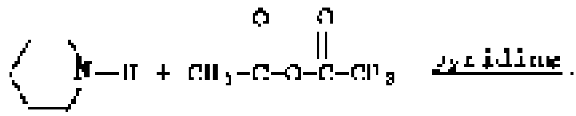


Attack of the amine, n-butylamine, upon the anhydride would yield the amide and salt within one molecule.

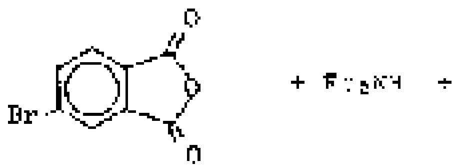


Complete the following:

(a) $CH_3CH_2\underset{\displaystyle CH_3}{\overset{|}{N}} - Ph + CH_3I \rightarrow$

(b) 

(c) $(CH_3)_3N + CH_3-C(=O)Cl \rightarrow$

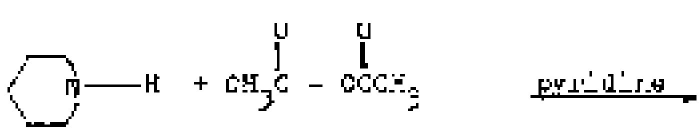
(d) 

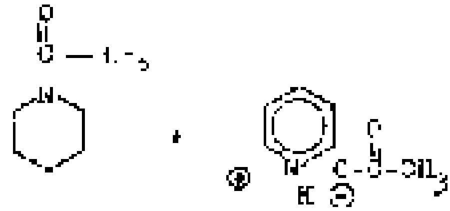
Solution: Amines contain a nitrogen with a free pair of electrons which make them potent nucleophiles. They can attack various sites of positive charge, such as the carbonyl groups of carboxylic acid derivatives.

(a) Amines may be alkylated by an S_N2 displacement upon a primary or secondary halide. This, however, is a poor way of converting a primary amine into a secondary one, or a secondary amine into a trisubstituted type. This is because the product thus is more nucleophilic than the reactant amine and further substitution may take place. The action of an amine may become synthetically feasible if a large excess of the amine is used or, as in the present case, a trisubstituted amine is converted to a quaternary ammonium salt.

$$CH_3CH_2-\underset{\displaystyle CH_3}{\overset{}{N}}-Ph \quad CH_3-I \longrightarrow CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{\overset{\oplus}{N}}}Ph \;\; I^{\ominus}$$

(b) When an amine is reacted with an anhydride, an amide and its salt is formed. To increase the concentration of the amide, a "scavenger" base is also put in the reaction mixture to combine with the subsequently formed acid which would otherwise react with the amine. In this case, we would form the acetamide of piperidine and a pyridium salt.

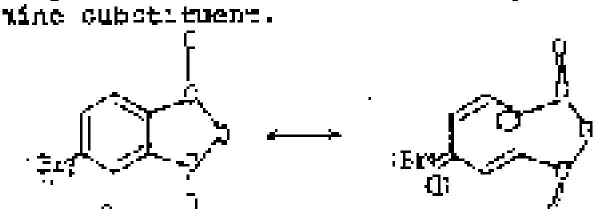


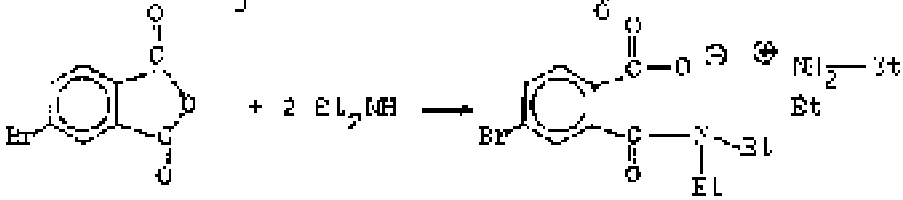


(c) When a tertiary amine is placed together with an acyl halide it appears not to react in that the amine is recovered unchanged after workup with aqueous base. Actually, they do react to form salts which are effective acylating agents. In the presence of water they form an acid and the protonated amine.

$$(CH_3)_3N + CH_3\overset{O}{\overset{\|}{C}}\text{-}Cl \rightarrow CH_3\overset{O}{\overset{\|}{C}}\overset{\oplus}{N}(CH_3)_3\ \overset{\ominus}{Cl} \xrightarrow{H_2O} CH_3\overset{O}{\overset{\|}{C}}\text{-}OH + \overset{\ominus}{Cl}\ \overset{\oplus}{H}N(CH_3)_3$$

(d) When an amine is reacted with an unsymmetrical anhydride, it will attack the anhydride carbonyl group that is most electron-deficient. In this case, we know that bromine can delocalize its electrons onto the aromatic ring and put a negative charge on the carbon para to the bromine, making the adjacent carbonyl carbon less electropositive. Thus, the nucleophilic amine will attack the carbonyl (which is next to the ring carbon meta) to the bromine substituent.

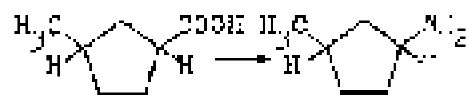




■ **PROBLEM 22-31**

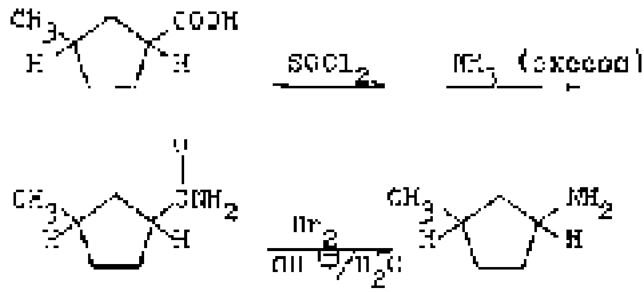
Show how the following conversion can be carried out. Use

(a) Hofmann degradation
(b) Curtius degradation.
(c) Schmidt reaction.

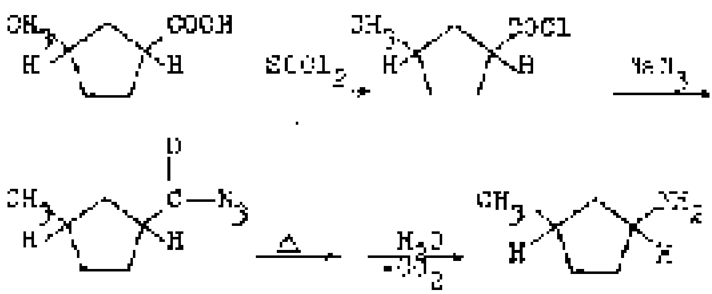


Solution: The Hofmann degradation, Curtius degradation and the Schmidt reaction all lessen the carbon skeleton of the reactant by one carbon, producing an amine. They all involve a rearrangement about nitrogen with the migrating group maintaining its relative configuration.

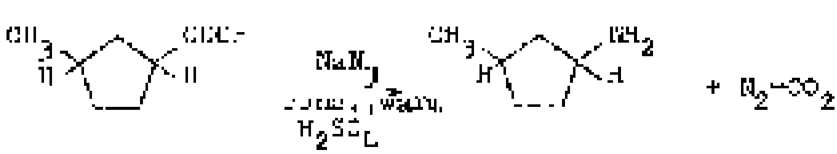
(a) The Hofmann degradation acts upon amides, and the necessary reagents are halogen and base. The mechanism involves abstraction of an amide proton, formation of an N-bromo amide and simultaneous migration of the group on the carbonyl carbon to nitrogen and expulsion of the halogen. In this migration, a double bond is formed between nitrogen and the carbonyl carbon. The intermediate isocyanate (R-N=C=O) forms a carbamic acid which decarboxylates to the amine. The synthetic sequence would be carried out as follows:



(b) The Curtius degradation differs from the Hofmann degradation in that the intermediate is an acyl azide ($RCON_3$) which undergoes the rearrangement to the isocyanate upon heating. After treatment with water, there is a decarboxylation to the amine.

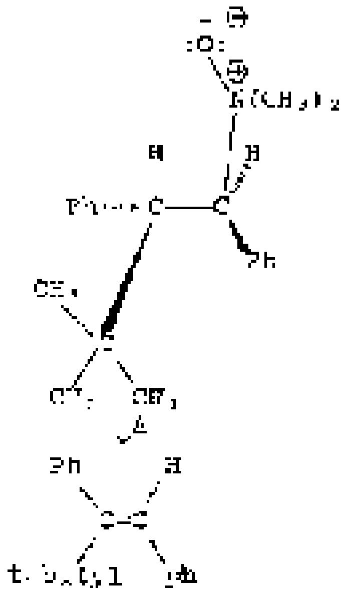


(c) The Schmidt reaction has the synthetic advantage over the Hofmann and Curtius degradation in that the carboxylic acid can be directly converted to the amine without isolating any intermediates.

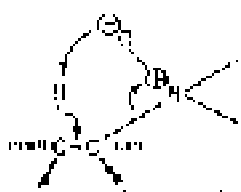


Why is the Cope elimination called a syn elimination?

Solution: When a tertiary amine is treated with an oxidant (hydrogen peroxide), an N-oxide is formed. When



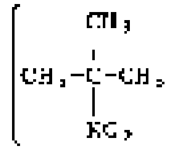
such an N-oxide contains a β hydrogen (in relation to the nitrogen) it will undergo a thermal decomposition to an alkene and a hydroxylamine derivative. This elimination follows a syn orientation in that both leaving groups (the proton and the nitrogen fragment) leave from the same face of the molecule.

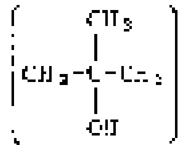


Note that a syn orientation refers to the mechanism of elimination and not the stereochemistry of the subsequently formed alkene. A syn elimination can result in a trans product, as was shown earlier. The Cope elimination differs from the Hofmann elimination of quaternary ammonium salts which is a trans elimination.

• PROBLEM 22-33

Show how 2-methyl-2-nitropropane might be synthesized from (a) t-butyl alcohol, (b) trimethylacetic acid.

Solution: Both 2-methyl-2-nitropropane 

and t-butyl alcohol  have the t-butyl carbon skeleton and the basic problem is how to convert the hydroxyl group to the nitro functionality. This could be best accomplished through the intermediate 2-amino-2-methylpropane. The amino compound can be synthesized via the Ritter reaction by treating t-butanol with sulfuric acid and hydrogen cyanide and hydrolyzing the intermediate to the amine.

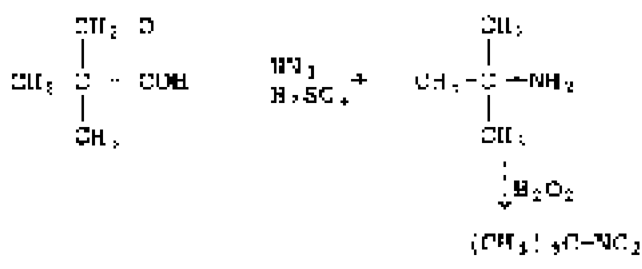
$$(CH_3)_3COH \xrightarrow[HCN]{H_2SO_4} (CH_3)_3C\overset{\oplus}{N}{=}C{-}H \xrightarrow{H_2O} \xrightarrow{-H^{\oplus}}$$

$$(CH_3)_3CNH\overset{O}{\overset{\|}{C}}H \xrightarrow{H_2O} (CH_3)_3CNH_2$$

T-butylamine, like any primary amine, can be oxidized to the corresponding nitro compound. One possible oxidizing agent is hydrogen peroxide.

$$(CH_3)_3CNH_2 \xrightarrow{H_2O_2} (CH_3)_3CNO_2$$

(b) By examining the structure of the starting material, we realize that we must degrade the compound by one carbon and then synthesize the intermediate t-butylamine. This can be done conveniently through the Schmidt Reaction where the reactant carboxylic acid is converted directly into a rearrangement of an azide which never need be isolated. The amine produced is oxidized to 2-methyl-2-nitropropane.



● PROBLEM 22-34

Show how one could synthesize and resolve methylethylallylamine oxide from allylamine, with the knowledge that amine oxides are somewhat basic substances having K_B values at about 10^{-11}.

Solution: Tertiary amine oxides may be prepared by the oxidation of tertiary amines with hydrogen peroxide or a peroxycarboxylic acid (RCO_3H). A tertiary amine may be prepared from a primary amine by S_N reactions. The free electron pair of nitrogen makes the primary amine nucleophilic enough to displace the halide in an alkyl halide to form a secondary amine. This secondary amine can act as the nucleophile in another S_N reaction.

Allylamine will react with ethylbromide to form ethylallylamine; this will be accompanied by loss of hydrogen bromide. An excess of allylamine must be used in order to avoid polyalkylation of the amine. Methyl iodide will react with an excess of ethylallylamine to form methylethylallylamine with loss of hydrogen iodide. Subsequent reaction of the tertiary amine with hydrogen peroxide will produce the tertiary amine oxide, methylethylallylamine oxide. The reaction sequence can be shown as:

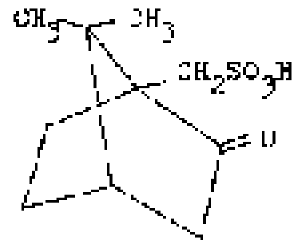
$$\underset{\text{allyl amine}}{CH_2{=}CH{-}CH_2{-}NH_2}\ (ex) + CH_3CH_2Br \rightarrow HBr + \underset{\text{ethylallylamine}}{CH_2{=}CH{-}CH_2{-}\overset{H}{\overset{|}{N}}{-}CH_2CH_3}$$

$$CH_2{=}CH{-}CH_2{-}\overset{H}{\overset{|}{N}}{-}CH_2CH_3\ (ex) + CH_3I \rightarrow HI + \underset{\text{methylethylallylamine}}{CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\overset{|}{N}}{-}CH_2CH_3}$$

$$CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\overset{|}{N}}{-}CH_2CH_3 + H_2O_2 \rightarrow \underset{\text{methylethylallylamine oxide}}{CH_2{=}CH{-}CH_2{-}\overset{CH_3}{\underset{O^-}{\underset{\downarrow}{N^+}}}{-}CH_2CH_3}$$

The tertiary amine oxide above is chiral and will be expected to be optically active. On the contrary, we find that the reaction product has no optical activity. This is explained by the fact that the reaction produces a racemic mixture of the tertiary amine oxide; the d- (dextrorotatory) and l (levorotatory) isomers are produced in equal amounts and as a result there is no optical activity observed.

The d- and l- isomers of a compound are enantiomers and have identical physical properties. A mixture of d- and l- isomers can be resolved by forming diastereomeric salts with a neutralization reaction using an optically active acid or base. Since we know that amine oxides are slightly basic, we should react the mixture with an optically active acid. If we use the d- acid, we will produce two diastereomeric salts; one composed of a d acid and a d base, the other composed of a d-acid and a l-base. Diastereomers are different compounds and can therefore be separated by a number of methods, one of the most common being crystallization. Hence a racemic mixture of methylethylallylamine oxide can be resolved by reacting it with a strong, optically active acid (because the amine oxide is only slightly basic, $K_B \approx 10^{-11}$) such as d-camphor-10-

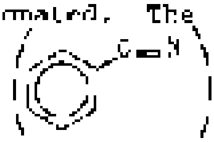
sulfonic acid: 

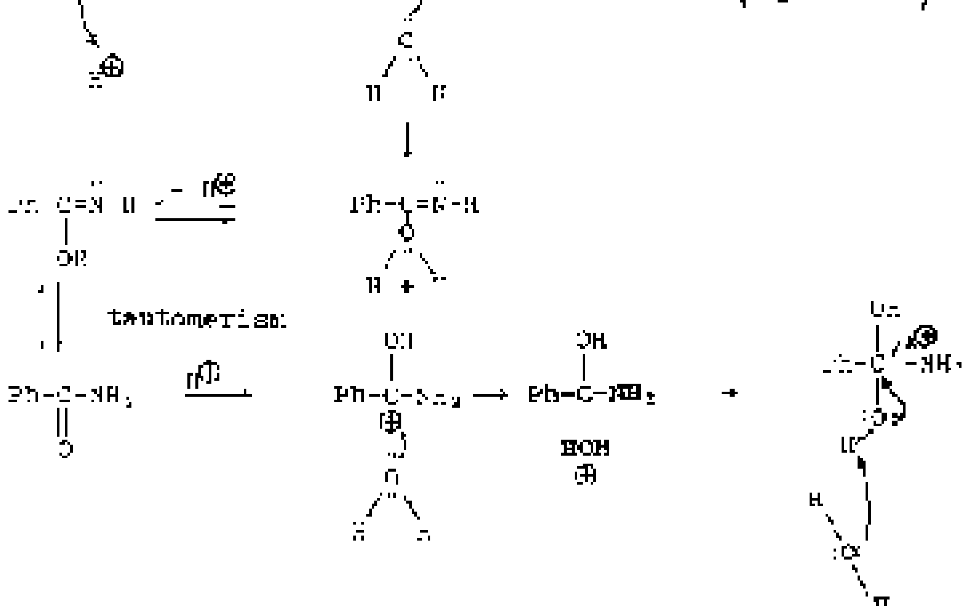
NITRILES

PROBLEM 22-35

Write the mechanisms for the acidic and basic hydrolyses of benzonitrile.

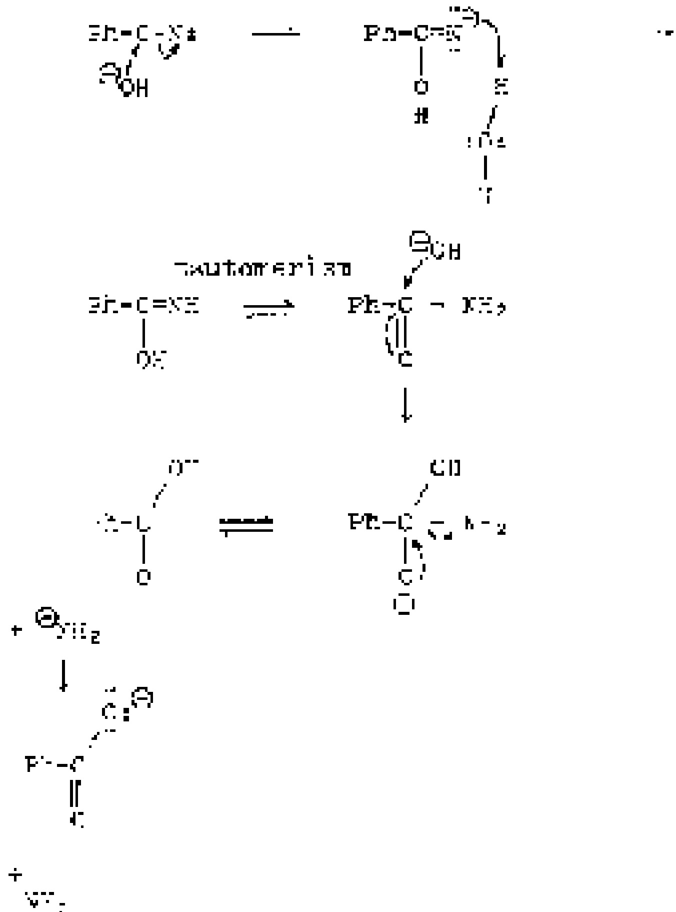
Solution: (a) When treated with aqueous acid, a nitrile is converted to a carboxylic acid. The mechanism essentially involves the addition of two molecules of water to the triple bond between carbon and nitrogen. The initial protonation puts a positive charge on the atom that can best afford it - carbon.

Tautomerism after the addition of water yields the intermediate amide whose carbonyl undergoes protonation to add another water molecule. In the acid media, the ammonia that acts as a leaving group is protonated. The mechanism is as follows, using benzonitrile ()



$H_3O^{\oplus} + PhCOOH + NH_3 \rightarrow NH_4^{\oplus} + H_2O + PhCOOH$

(b) In alkaline hydrolysis of nitriles, the hydroxide anion acts as a nucleophile, attacking the electropositive cyano carbon. After tautomerization to the amide, the hydroxide will attack the carbonyl group in an addition-elimination mechanism. In the basic media, the carboxylic acid will lose a proton to form the anion. The mechanism is demonstrated in the case of benzonitrile.



◆ PROBLEM 29-36

An unknown compound C_7H_5N on catalytic hydrogenation gave $C_7H_{15}N$. Hydrolysis of the unknown compound converted it into an acid which on fusion with NaOH yielded C_6H_6. On catalytic hydrogenation this hydrocarbon gave C_6H_{12}. Suggest a suitable structure for the unknown.

<u>Solution:</u> The formula C_7H_5N, implies that the compound is multi-unsaturated. This is seen by the following chemical arithmetic.

$$\begin{array}{r} C_7H_5N \\ -\ N- \\ \hline C_7H_4 \end{array}$$ adjustment for nitrogen's trisubstitution

$$\begin{array}{r} C_7H_{16} \\ C_7H_4 \\ \hline H_{12} \end{array}$$ seven carbon saturated compound

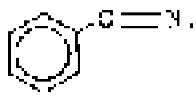
6 units of unsaturation

Upon catalytic hydrogenation, two hydrogens are added. Therefore, the compound has five double bonds, or their equivalent.

Conversion into acid by hydrolysis is a characteristic reaction for nitriles, $R-C\equiv N$. The basic formula for the unknown becomes $C_6H_5C\equiv N$.

The acid derivative of the unknown yields a hydrocarbon (C_6H_6) in a sodium hydroxide fusion reaction. Since sodium hydroxide fusion is a decarboxylation mechanism for aromatic carboxylic acid, the acid derivative is benzoic acid. This is confirmed by the fact that catalytic hydrogenation of C_6H_6 yields C_6H_{12}, which is the formula for cyclohexane.

From all the informations above, one can determine that the unknown having formula of C_7H_5N, is a phenyl nitrile,



• PROBLEM 22-37

Nitriles of the type RCH_2CN undergo an addition reaction analogous to the aldol addition in the presence of strong bases such as lithium amide. Hydrolysis of the initial reaction product with dilute acid yields a cyanoketone,

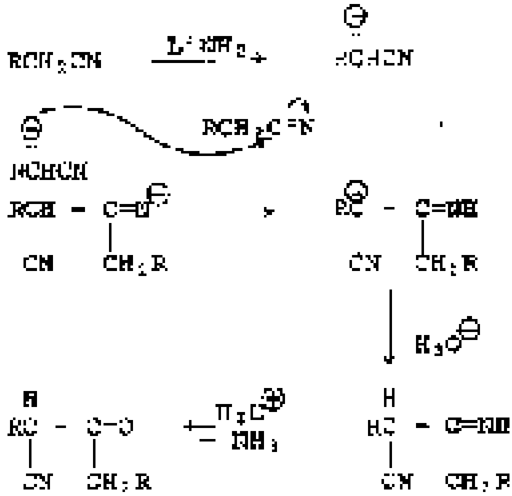
$$RCH_2-\overset{\overset{O}{\|}}{C}-\overset{\overset{CN}{|}}{CH}-R.$$

Show the steps that are involved in the mechanism of the over-all reaction and outline a scheme for its use to synthesize large-ring ketones of the type $(CH_2)_nC{=}O$ from dinitriles of the type $NC(CH_2)_nCN$.

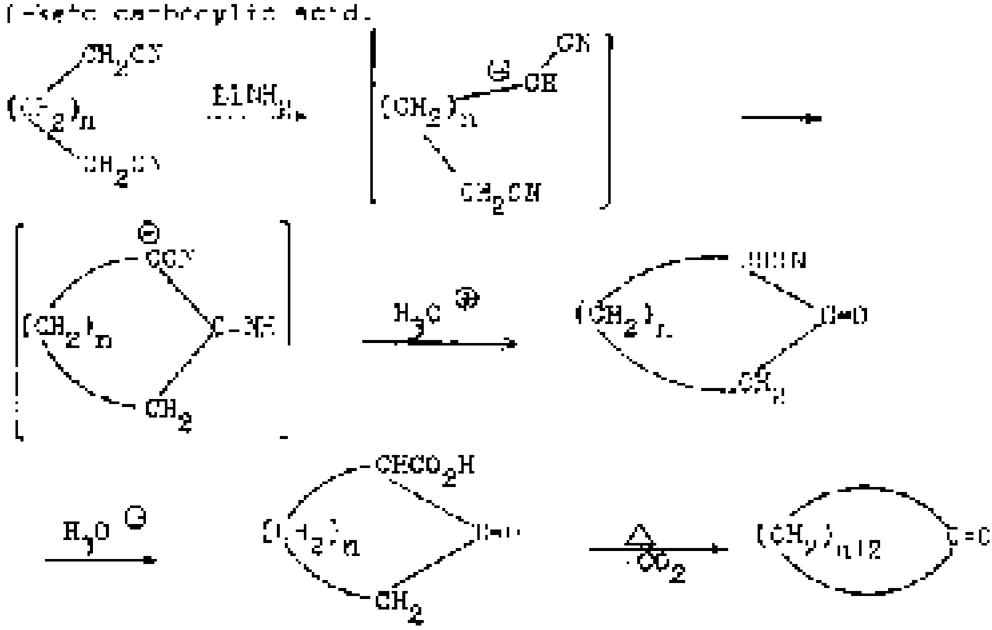
Solution: The cyano group has an sp-hybridized carbon bonded to a nitrogen and therefore this electronegative atom will stabilize negative charge on the carbon α to the nitrile function. Besides this inductive effect, negative charge on the α carbon will be stabilized by resonance involving the cyano group:

$$R\overset{\ominus}{\underset{H}{C}}C\equiv N: \longrightarrow R\underset{H}{C}=C=\ddot{N}:^{\ominus}$$

Thus, in the presence of a strong base, nitriles of the type RCH_2CN will lose a proton and undergo a reaction analogous to an aldol condensation in which a carbanion will attack the electropositive carbon of the cyano group. There is a proton transfer to yield another stable carbanion which is hydrolyzed in acid media to the α-cyanoketone.

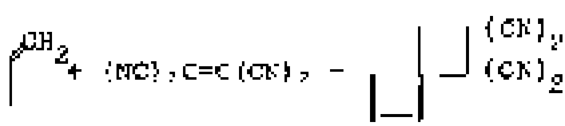


We can utilize this reaction to create large-ring ketones by beginning the sequence with a compound that contains two cyano groups that are separated by a number of carbons. The cyano group can be removed from the intermediate by hydrolysis and decarboxylation of the β-keto carboxylic acid.

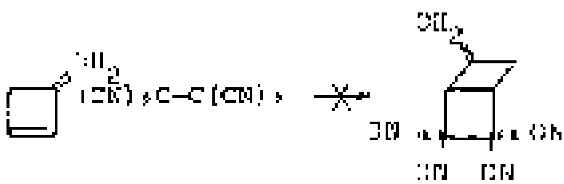


• **PROBLEM 22-33**

Explain how and why the following reaction takes the observed course.



Solution: In a cycloaddition reaction, two molecules containing unsaturated functional groups combine to form a cyclic compound. The most common type of cycloaddition is the Diels-Alder reaction in which a molecule of four π electrons cyclizes with a molecule of two π electrons. Tetracyanoethylene, $((NC)_2C{=}C(CN)_2)$ is often used as the two π electron system or dienophile. However, methylenecyclobutene cannot act here as a diene in a Diels-Alder reaction because of the geometry required in the reaction. The Diels-Alder reaction requires the diene to be in the s-cis conformation in that both termini of the diene must react with the ends of the dienophile's double bonds simultaneously. Methylenecyclobutene cannot assume such an s-cis conformation because of the ring and the Diels-Alder reaction cannot occur. What actually occurs is a 1,2-addition of tetracyanoethylene to the exocyclic double bond (the double bond not in the ring), forming a cyclobutane ring. Addition to the endocyclic double bond would not occur in that such an addition would form a strained [2.2.0] hexene compound.

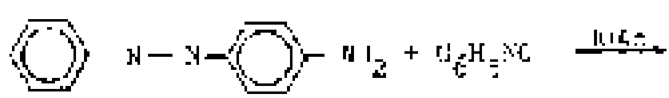


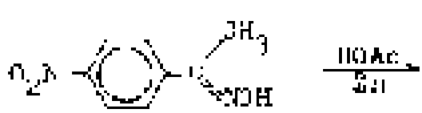
ISOCYANIDES AND ISOCYANATES

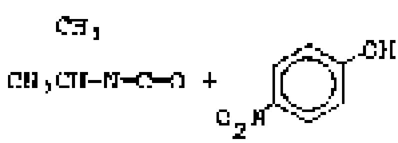
• PROBLEM 22-39

Complete the following:

(a) $PhCHO + CH_3CH_2NO_2 \xrightarrow{NaOH}$

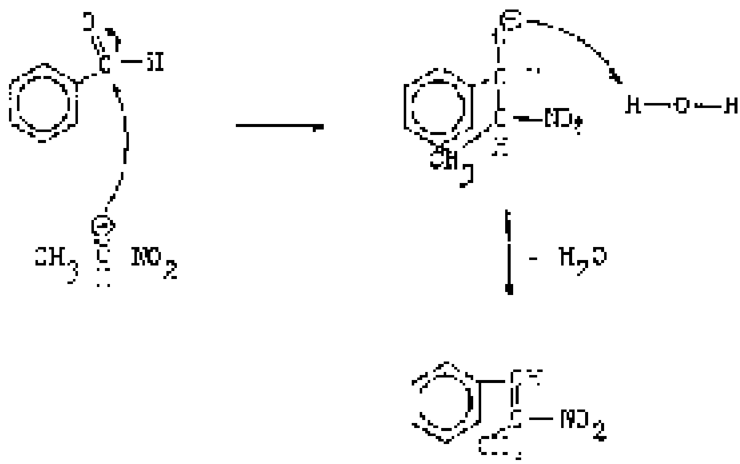
(b) 

(c) 

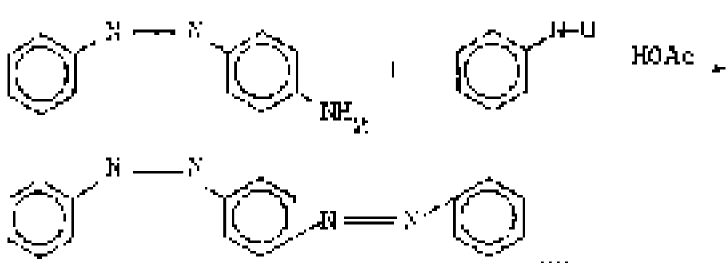
(d) 

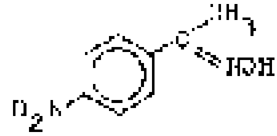
Solution: (a) The nitro group is electron withdrawing and it will stabilize negative charge. Therefore, the carbon alpha to a nitro group has an acidic hydrogen. Such carbanions are stabilized by resonance involving the nitro group.

This carbanion may attack the aldehyde carbonyl of benzaldehyde to give an alcohol which readily dehydrates to give a double bond which would be conjugated to the aromatic ring. The mechanism is analogous to that of an aldol condensation.

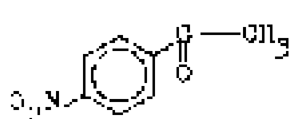


(b) When an aryl nitroso compound is reacted with an aniline derivative, the product is an azobenzene derivative. This procedure, catalyzed by acid, is useful in synthesizing unsymmetrical azobenzenes as in the case here with 4-aminoazobenzene and nitrobenzene. The weak acetic acid will not cleave the azo linkage in the reactants.

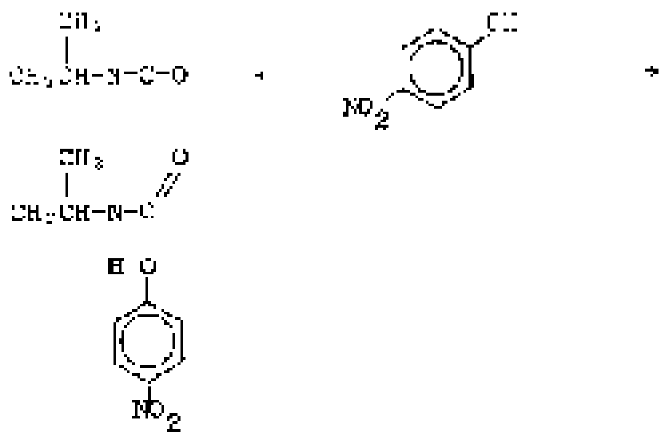


(c) The compound  is made from

the reaction of hydroxylamine (NH_2OH) and the carbonyl

compound  in acid. The product forms may be reduced to its corresponding amine by the action of zinc in acetic acid, noting that both the nitro group and the carbon nitrogen double bond linkage are reduced.

(d) Isocyanates have a carbon double bonded to both nitrogen and oxygen and is thus highly electropositive. Thus, isocyanates are susceptible to attack by nucleophiles such as alcohols. Here p-nitrophenol reacts with the isocyanate to produce a urethane.



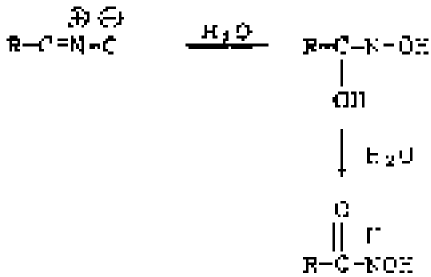
• PROBLEM 22-40

Nitrile oxides, $R-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$, are isomeric with isocyanates. What kind of physical and chemical properties would you expect them to have? Show your reasoning in detail.

Solution: Nitrile oxides have charge separation inherent in their structures and therefore they possess a large dipole moment. As a result of this, they are most soluble in polar solvents. Also, the presence of dipole-dipole interactions make them have high boiling points. The resonance structures that represent the nitrile oxides charge separation are:

$$\left[R-\overset{\oplus}{C}=N-\overset{\ominus}{\ddot{O}}: \longleftrightarrow R-C\equiv\overset{\oplus}{N}-\overset{\ominus}{\ddot{O}}: \longleftrightarrow R-\overset{\ominus}{\ddot{C}}=\overset{\oplus}{N}=O \right]$$

The partial negative charge on the oxygen relates some basic properties to the nitrile oxides. They are significantly reactive with water, yielding a hydroxamic acid via a hydroxyoxime.

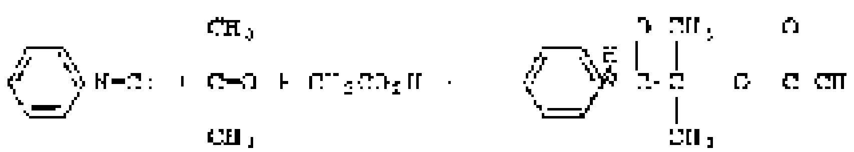


They may act as oxidizing agents, regenerating the progenitor nitrile (R-C≡N).

• PROBLEM 22-41

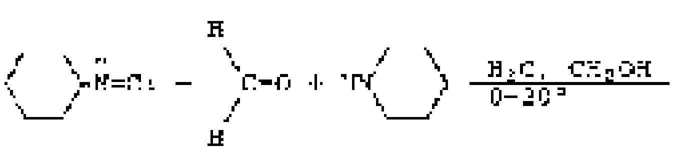
(a) Show how the reaction given in Eq. A, the Passerini reaction proceeds if $CH_3\overset{O}{\overset{\|}{C}}\overset{\oplus}{O}C(CH_3)_2$ is assumed to be an intermediate. How could this intermediate be formed?

(b) Work out a similar mechanism for Eq. B noting that an important early step is addition of the amine to the carbonyl compound.

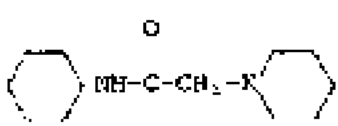


(A)

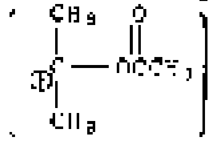
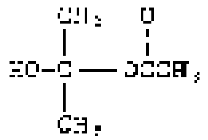
phenyl isocyanide

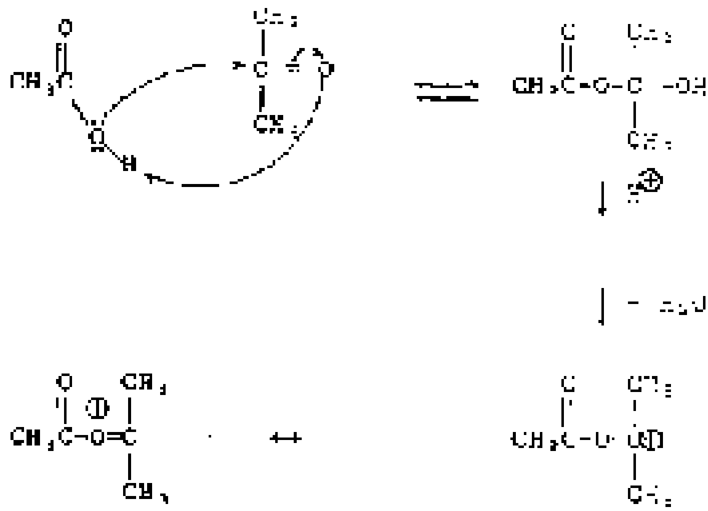


cyclohexyl isocyanide　　piperidine

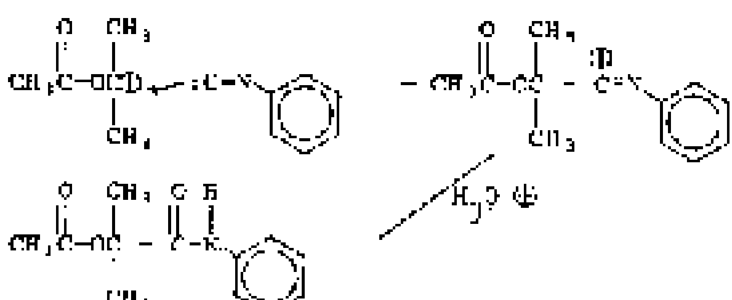


78%　　　　(B)

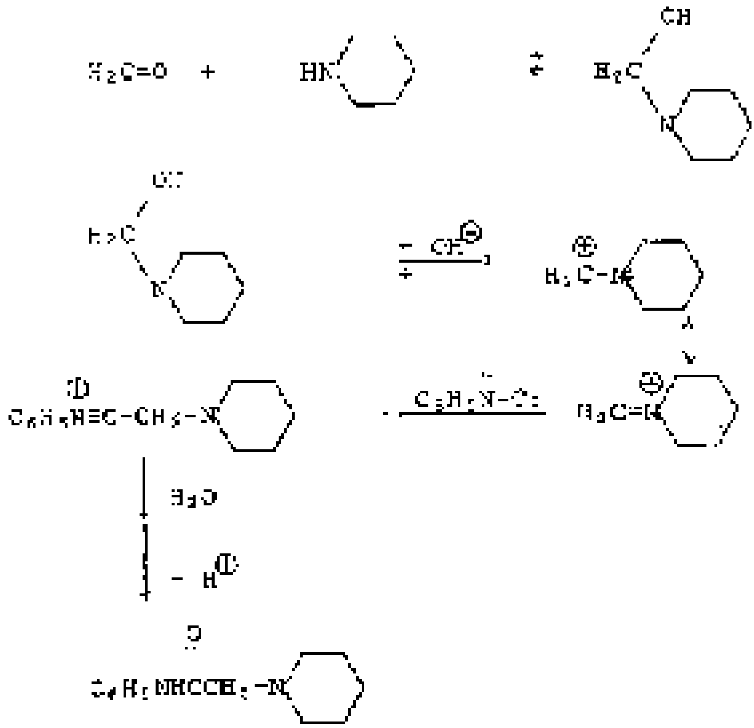
Solution: The Passerini reaction involves the combination of a carbonyl compound with a carboxylic acid and an isocyanide. Isocyanides are reactive compounds with a carbon-nitrogen double bond analogous to a nitrogen-nitrogen triple bond. The given intermediate  seems to be derived from  which would lose water in the acid media to form the cation. We could envision the condensation product of the carboxylic acid and carbonyl compound being the source of the intermediate.



The isocyanide has a free pair of electrons on a carbon and this is the basis for the nucleophilic attack upon the cation. The nitrile-type product can be hydrolyzed to an amide.



(b) When a carbonyl compound is reacted in the presence of an amine and an isocyanide, a process occurs which is analogous to the Passerini reaction. The amine attacks a carbonyl compound to yield an aminoalcohol. Since the reaction occurs in alkaline media, the leaving group in the cation formation must be the hydroxide ion. This step of the sequence, unlike in the Passerini reaction, is reversible. Nucleophilic attack by the isocyanide, followed by hydrolysis will yield the amide. The sequence would be as follows:



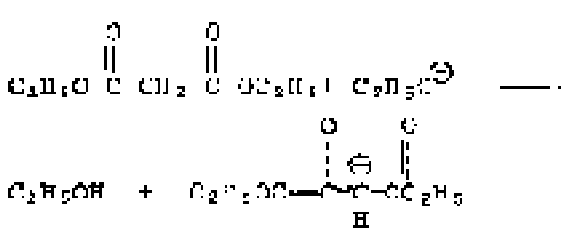
Further hydrolysis would yield an α-amino carboxylic acid and aniline.

NITRO AND NITROSO COMPOUNDS

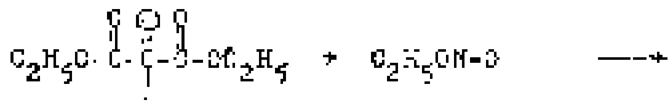
• PROBLEM 22-42

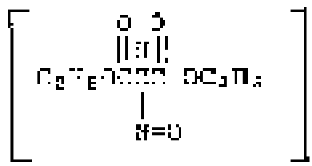
Predict the product formed by the reaction of diethyl malonate with sodium ethoxide and ethyl nitrite in ethanol solution. Write a mechanism for the formation of this product.

Solution: In the presence of base, diethyl malonate will lose a proton between the ester carbonyls to give a resonance stabilized carbanion.



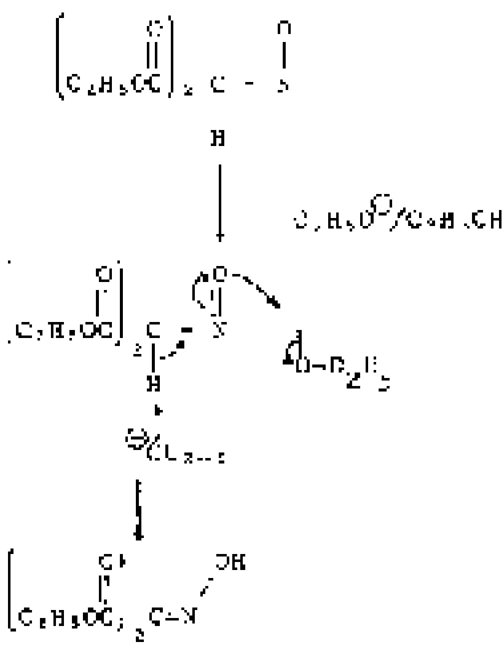
The carbanion can attack ethyl nitrite in a displacement upon nitrogen.





nitroso compound - unstable in acid or base

The subsequently formed nitroso compound has a proton alpha to the nitroso group and, like all of its type, it can be isomerized to an oxime by either acid or base.

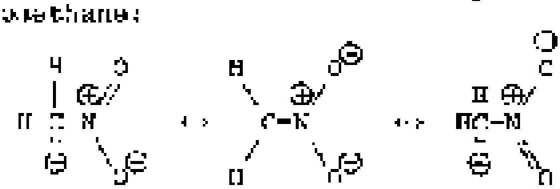


• PROBLEM 22-43

Show how the following compounds might be prepared from the commercially available nitroalkanes obtained from the nitration of propane.

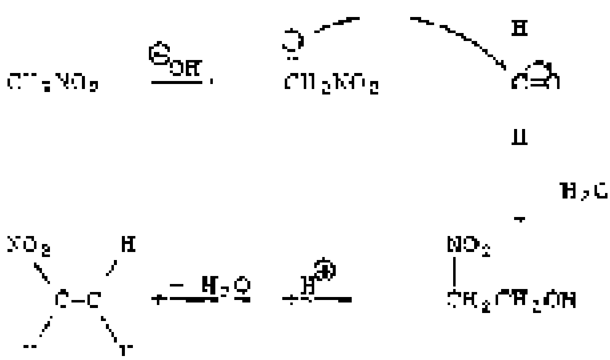
(a) $CH_2=CHNO_2$ (c) $HOCH_2C(CH_3)_2NH_2$
(b) $(O_2NOCH_2)_3CNO_2$ (d) $H_2NCH_2CH_2C(CH_3)_2NH_2$

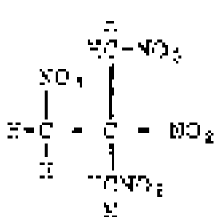
Solution: When alkanes are mixed with nitric acid at high temperatures, a variety of nitroalkanes are produced. The mechanism is uncertain but is believed to be of a free radical nature. The distribution of products is dependent upon the reaction conditions, including the types of catalysts. Nitration of propane yields 1 and 2-nitropropane as well as nitromethane and nitroethane. Using the nitroalkanes derived from propane, we can create compounds with longer carbon chains by utilizing the acidity of the hydrogen on the carbon α to the nitro group. This acidity can be seen by the subsequent carbanion's stabilization by the adjacent nitro group, both by resonance and induction. For example, in the case of nitromethane:



The carbanion is a nucleophile which can attack some source of positive charge, such as a carbonyl group, in a reaction similar to an aldol addition.

(a) Nitroethene ($CH_2{=}CHNO_2$) may be derived from 2-nitroethanol via an acid catalyzed dehydration reaction. The alcohol may be synthesized from the carbanion of nitromethane together with formaldehyde.



(b)  contains a fragment that seemed to originate from nitromethane. If nitromethane is treated in base, together with an excess of formaldehyde, we form a triol. To convert the triol into the nitrate, we treat the reactant in the dilute nitric acid.

The reaction is a dehydration process with the nitrate anion acting as the nucleophile on the cation. The process would occur as follows:

$$CH_3NO_2 + 3\ CH_2{=}O \xrightarrow[H_2O]{OH^{\ominus}} (HOCH_2)_3CNO_2 \xrightarrow{3\ HNO_3}$$

$$-3\ H_2O + CH_2NO_3\text{–}\underset{\displaystyle CH_2NO_3}{\overset{\displaystyle CH_2NO_3}{\underset{|}{\overset{|}{C}}}} - NO_2$$

(c) By examining the desired product, we see that it contains an amino group ($-NH_2$), which can be derived from a nitro functionality. The desired nitro compound may be synthesized by reacting 2-nitropropane with formaldehyde in alkaline media. Reduction yields the final product.

$$(CH_3)_2CHNO_2 + CH_2{=}O \xrightarrow[H_2O]{OH^{\ominus}}$$

$$\underset{\displaystyle OH}{\overset{}{}}CH_2\text{–}\underset{\displaystyle CH_3}{\overset{\displaystyle NO_2}{\underset{|}{C}}} - CH_3 \xrightarrow{LiAlH_4} \xrightarrow{H_2O} (CH_3)_2\underset{\displaystyle CH_2OH}{\underset{|}{C}}NH_2$$

(d) Starting with 2-nitropropane, we can create a carbanion which can attack nitroethene in a Michael addition reaction in which a nucleophile attacks a conjugated system. The adduct formed by this addition has two nitro groups, both of which may be reduced to an amine functionality.

$$H\text{–}\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}} - NO_2 + CH_2{=}CHNO_2 \xrightarrow[H_2O]{OH^{\ominus}}$$

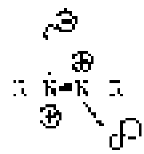
$$O_2NCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}NO_2 \xrightarrow{LiAlH_4} \xrightarrow{H_2O} H_2NCH_2CH_2\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{C}}NH_2$$

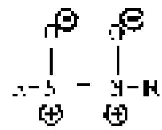
• PROBLEM 22-44

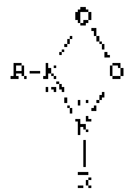
Consider possible ways of formulating the electronic structures of nitroso dimers with the knowledge that X-ray diffraction studies indicate the presence of nitrogen-nitrogen bonds.

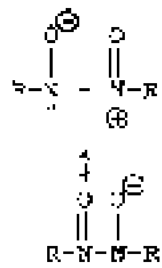
__Solution:__ Aliphatic nitroso compounds exist in the solid phase as dimers which is their most stable form. Resonance stabilization allows N,N dimethylaniline to remain as a monomer.

Realizing that the dimer contains at least one nitrogen-nitrogen bond, we may formulate four possible structures for it.

(A) 

(B) 

(C) 

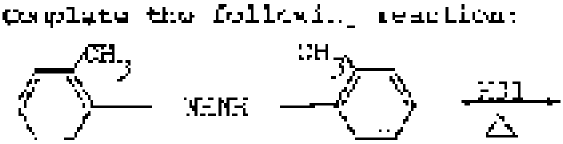
(D) 

Structures (A) and (B) can be eliminated immediately because they are not electrostatically feasible. These two structures are cis and trans forms of the same compound which juxtaposes positive charges - an unlikely occurrence. The peroxide linkage (O-O) has low thermodynamic stability and makes structure (C) improbable as the arrangement of the dimer. Structure (D) seems to be the correct form for the dimer in that it has resonance stabilization and is electrostatically feasible. The electron arrangement, however, does not make the geometry of the molecule clear.

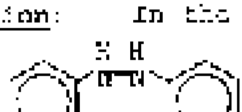
HYDRAZINES

• PROBLEM 22-45

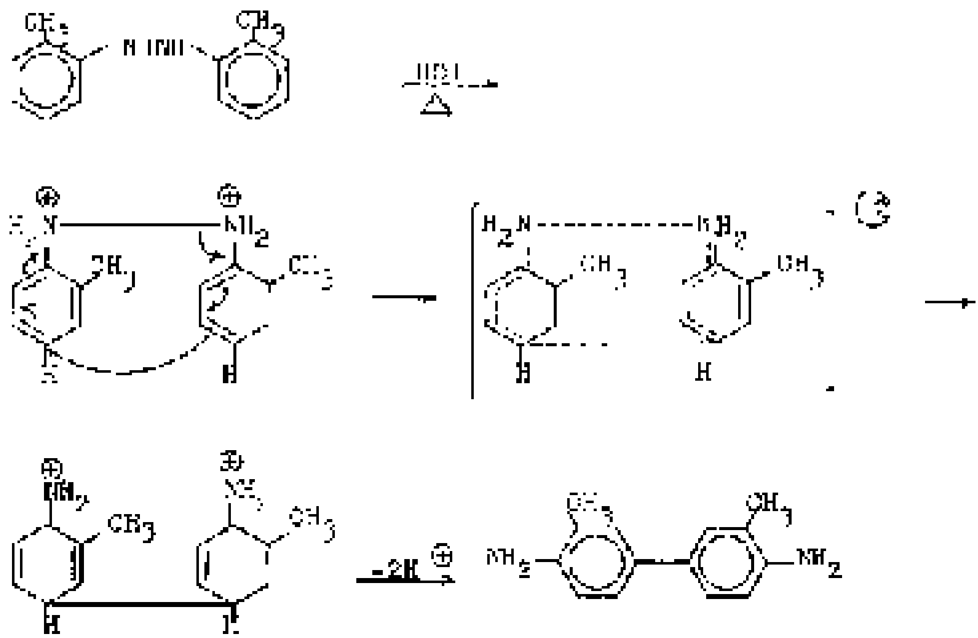
Complete the following reaction:



Solution: In the presence of acid, hydrazobenzene



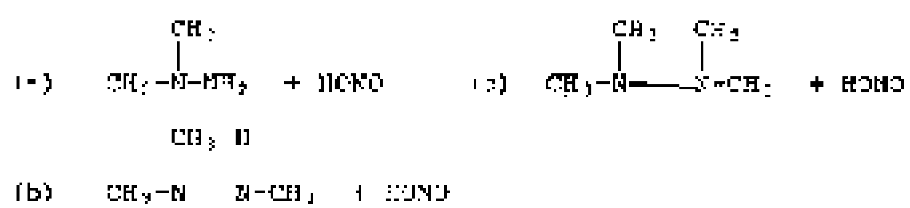
undergoes a rearrangement to a derivative of 4,4'-diaminobiphenyl (benzidine). The mechanism is controversial with one proposal involving a diprotonated intermediate. The orientation for this benzidine rearrangement supports the proposed mechanism.



benzidine derivative

• PROBLEM 22-46

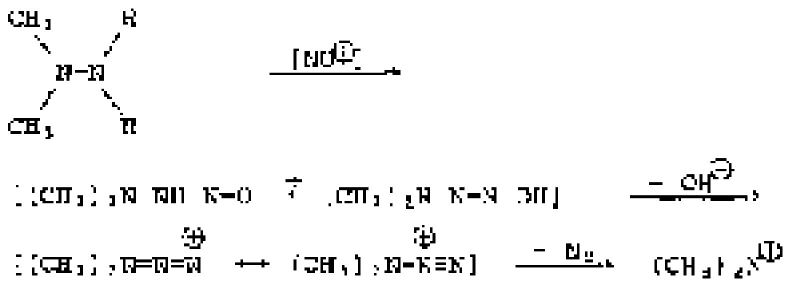
Arguing on the basis of mechanistic principles and knowledge of related reactions, work out products which might be expected for the following reactions:



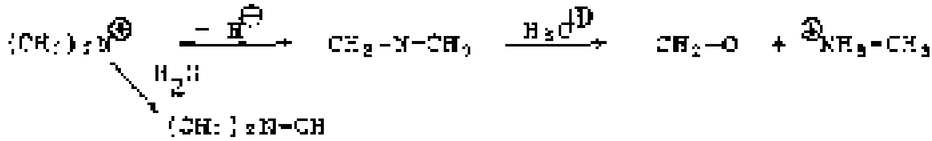
Solution: Nitrous acid (HONO) can be prepared from the combination of sodium nitrite and a protic acid at a low temperature. The actual reagent is the nitrosium ion, $[NO]^{\oplus}$. The following compounds that are reacted with nitrous acid are hydrazine (NH_2NH_2) derivatives and they give similar products as amines would. For example, primary amines react with nitrous acid to give diazonium salts. The analogous reaction with a monosubstituted hydrazine would yield an azide as an intermediate.

$$R\text{-}\overset{H}{N}\text{-}NH_2 + HONO \rightarrow R\text{-}N{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H_2O$$

(a) N,N-dimethylhydrazine is attacked at the nitrogen that bears the hydrogens to yield a product that tautomerizes to a structure which loses an hydroxide ion to give a resonance stabilized species analogous to a diazonium ion.

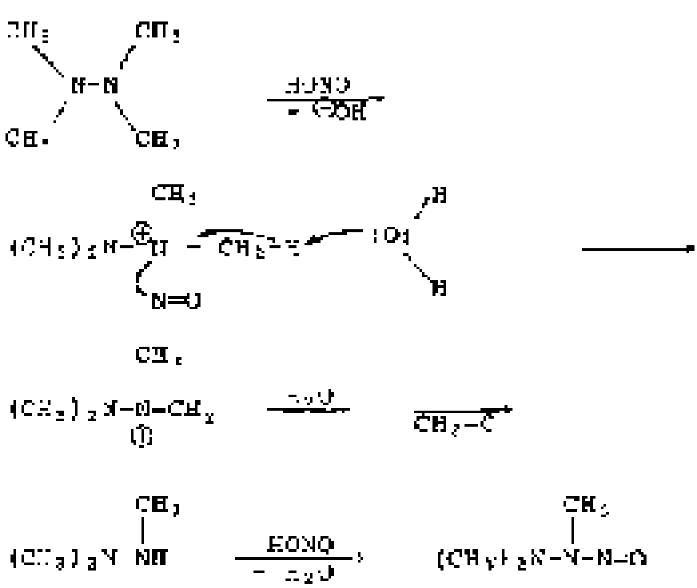


Nitrogen (N_2) is a stable molecule and it is easily lost to give a cation which has a positive charge on nitrogen. This cation, like a carbocation may either undergo elimination or be attacked by a nucleophile such as water. The imine formed by elimination is hydrolyzed in the acid media.



(b) Like a secondary amine, N,N,N' trimethylhydrazine yields a N-nitroso compound upon treatment with nitrous acid.

(c) The reaction of N,N,N',N' tetramethylhydrazine with nitrous acid is analogous to similar treatment of tertiary amines. Following this pattern, the nitrosium ion attacks one of the nitrogens. This is followed by an elimination reaction in which the nitrosium ion leaves. Hydrolysis and reaction of nitrous acid with the trisubstituted hydrazine yields the final product.

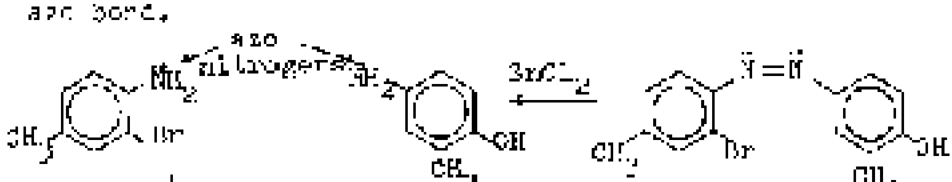


AZO COMPOUNDS

• PROBLEM 22-47

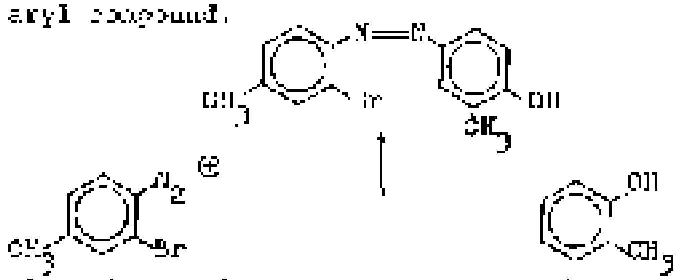
An azo compound is cleaved at the azo linkage by stannous chloride, $SnCl_2$, to form two amines. (a) What is the structure of the azo compound that is cleaved to 3-bromo-4-aminotoluene and 2-methyl-4-aminophenol? (b) Outline a synthesis of this azo compound, starting with toluene.

Solution: (a) Azo compounds (Ar-N=N-Ar) are formed by the electrophilic aromatic substitution of a diazonium cation ($Ar-N_2^{\oplus}$) onto a highly activated aromatic ring. When such an azo compound is treated with stannous chloride, $SnCl_2$, it is cleaved at the azo linkage to give two aniline derivatives. Since the azo nitrogens are converted to amino nitrogens we may determine what azo compound gave rise to particular anilines by linking the amino nitrogens in an azo bond.



3-bromo-4-aminotoluene 2-methyl-4-aminophenol azo compound

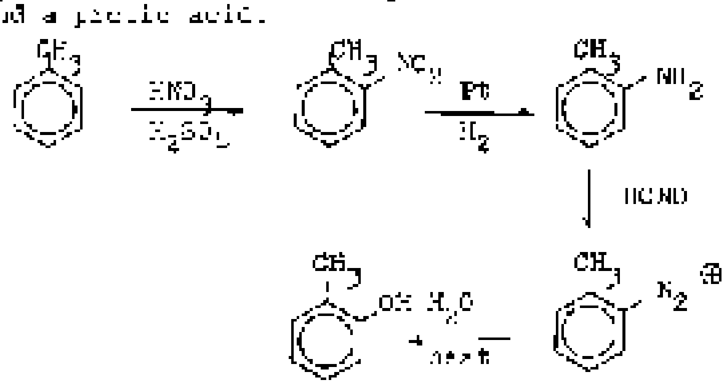
(b) To synthesize this azo compound, we must first synthesize each of the two components from which it was derived - the diazonium cation and the highly activated aryl compound.



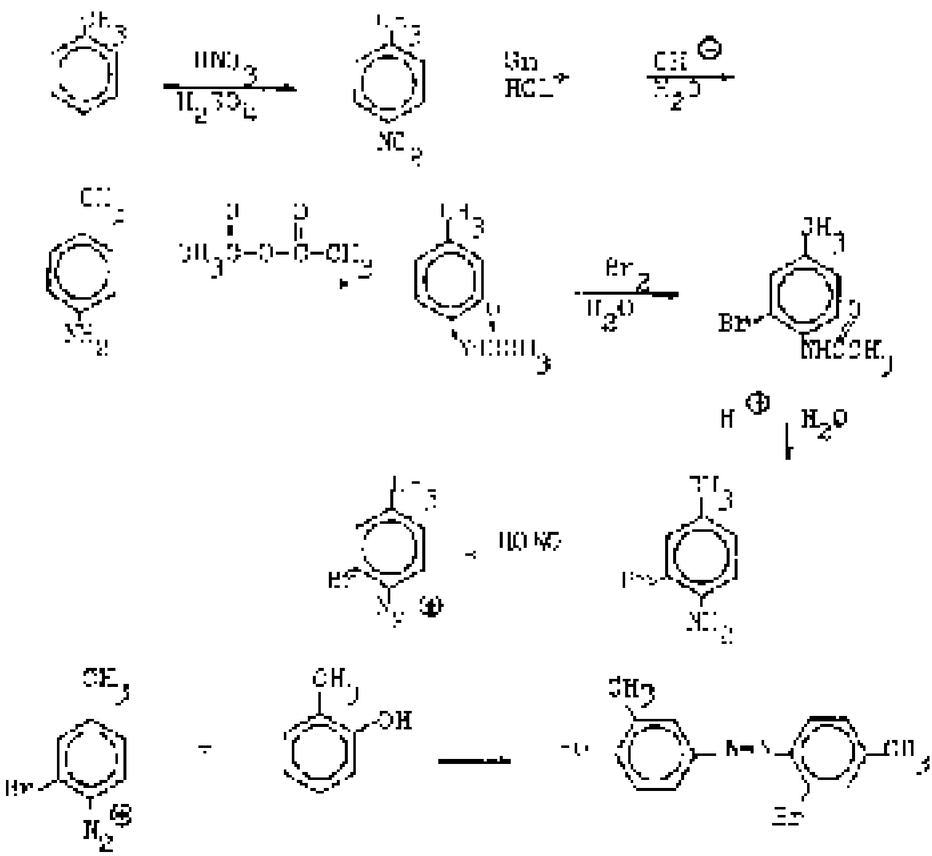
azo compound

diazonium cation activated aryl compound

The phenol we desire may itself be synthesized from a diazonium salt which was made in the typical sequence of nitration, reduction and diazotization. The diazotizing agent, nitrous acid, was generated from sodium nitrite and a protic acid.

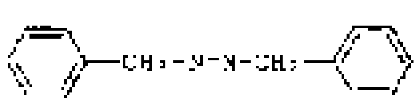


The other component of the azo compound is synthesized by using the orientational effect of the amino nitrogen. Only one position ortho to the amino is brominated when the amino group is acetylated. Nitration and reduction creates the amino group itself. Summarizing the synthesis of the diazium salt:

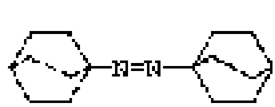


● PROBLEM 22-48

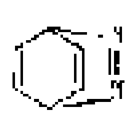
Arrange the following azo substances in order of their expected rates of thermal decomposition to produce nitrogen. Give your reasoning.

(a) 

(b) $(CH_3)_3C-N=N-C(CH_3)_3$

(c) 

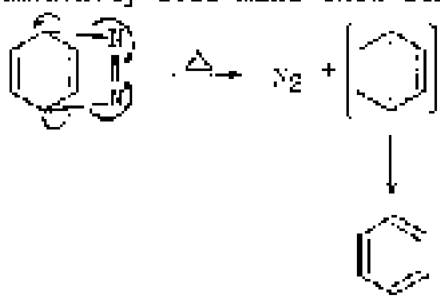
(d) $CH_3N=NCH_3$

(e) 

Solution: Azo compounds have the $-N=N-$ linkage and substances of this type decompose into radicals and nitrogen when heated to a particular temperature. The temperature needed for the decomposition is dependent upon the stability of the radical generated

$$R-N=N-R \rightarrow 2R\cdot + N_2$$

In this question, we consider if such factors as resonance and induction will stabilize the radical and the relative magnitudes of this stabilization. Careful examination shows that Compound E would yield benzene upon thermal decomposition and the gain of stability as a result of aromaticity will make this structure decompose most easily.



Structure A's decomposition rate is second, because it forms a resonance stabilized benzyl radical.

Structures B and C decompose next most easily and at about equivalent rates because they both form tertiary radicals of the type $R_3C\cdot$. The radical from structure C's decomposition may be slightly more stable due to greater inductive stabilization. However structure B's subsequent radical has more hyperconjugation stabilization. Structure D decomposes most slowly because the radical formed ($CH_3\cdot$) is neither resonance nor inductively stabilized.

DIAZO COMPOUNDS

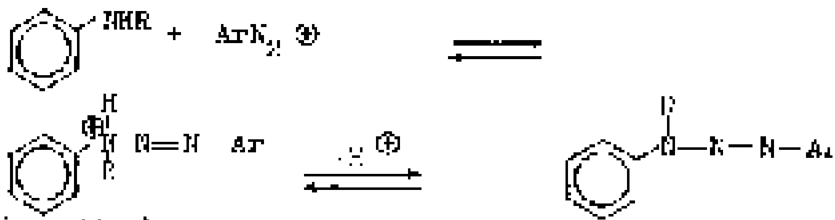
• PROBLEM 22-49

(a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid, suggest a possible structure for this by-product.

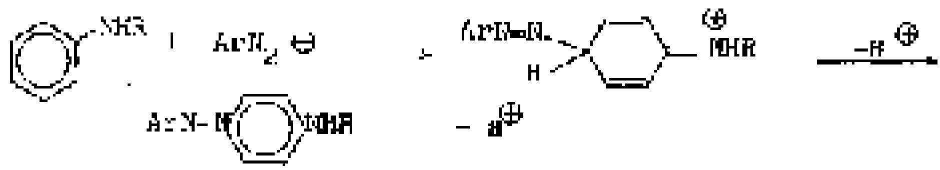
(b) Upon treatment with mineral acid, this by-product regenerates the original reactants which recombine to form the azo compound. What do you think is the function of the acid in this regeneration?

Solution: (a) The diazonium cation ($Ar-N_2^{\oplus}$) is an extremely weak electrophile which is sensitive to sites of high electron density. An aromatic amine has two such electron-rich sites - the amino nitrogen and the aromatic ring. The electrophilic diazonium cation may attack either of these two sites. If attack occurs at the nitrogen of a primary or secondary amine, the intermediate can lose a proton to form a diazoamino compound. We note that a tertiary aromatic amine lacks a proton and cannot form such a compound. Alternatively, the diazonium cation will attack the aromatic ring to give a C-coupling product via an intermediate benzenonium ion.

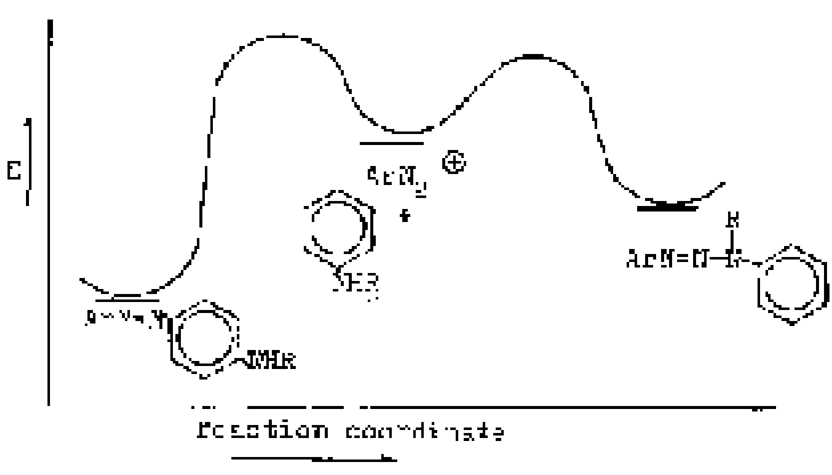
Nitrogen attack:



Ring attack:



(b) It turns out that the N-coupling product is formed more easily than the C coupling product, but it is less stable of the two. As a result of this, the formation of the diazoamino compound is reversible while the azo compound does not revert to the starting materials. The addition of the mineral acid increases the solution's proton concentration and reverts the diazoamino compound back to the reactants which may irreversibly form the azo compound. Summarizing, the N-coupling product is kinetically favored while the C-coupling product is thermodynamically favored.



• **PROBLEM 22-50**

What product is obtained from reaction of diazomethane with each of the following?

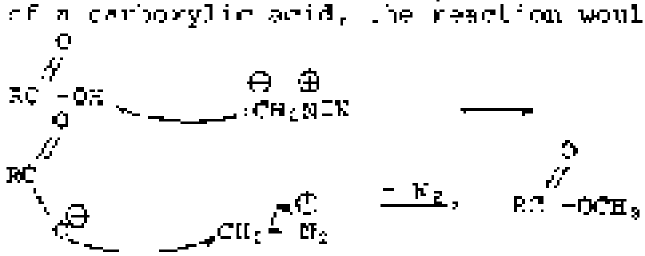
(a) Benzoyl chloride
(b) m-Hydroxybenzoic acid

Solution: (a) Diazomethane (CH_2N_2) can be represented as a charge separated form $\left[H_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv N \right]$ and the anionic carbon may attack the electropositive carbonyl group of the acid chloride to yield a terminal α-diazo ketone. A tertiary amine may be added to trap the HCl produced.

$$Ph\overset{O}{\overset{\|}{C}}Cl + CH_2N_2 + NR_3 \rightarrow H\overset{\oplus}{N}R_3\,Cl^{\ominus} + Ph-CO-CHN_2$$

The α-diazo ketone produced in this case has the name α-diazoacetophenone.

(b) Diazomethane reacts with carboxylic acids and phenols (alcohols also in presence of base) to yield methyl esters and anisoles, respectively. The reaction involves the basic properties of diazomethane as well as the nucleophilic capabilities of the subsequently produced anion. In the case of a carboxylic acid, the reaction would be as follows:

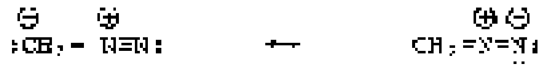


In the case of m-hydroxybenzoic acid, both the carboxylic acid and phenolic substituents will be methylated to give methyl m-methoxybenzoate.

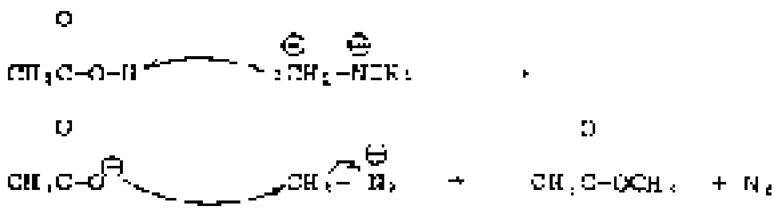
• **PROBLEM 22-51**

Write the important resonance structures which contribute to the resonance hybrid of diazomethane and show how these can be used to rationalize the formation of methyl acetate from diazomethane and acetic acid.

Solution: Diazomethane is a versatile reagent that can be pictured as a hybrid of two resonance forms in which a negative charge is shared between carbon and nitrogen. This can be illustrated in terms of diazomethane's two important resonance structures:

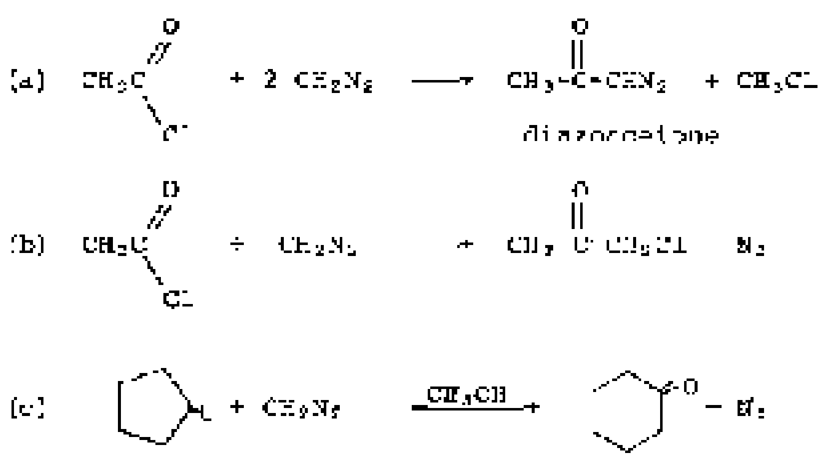


The negative charge on carbon allows diazomethane to act as a base toward acetic acid. After the proton transfer, the acetate ion may act as a nucleophile upon the newly formed methyl moiety. This sequence can be diagrammed as:



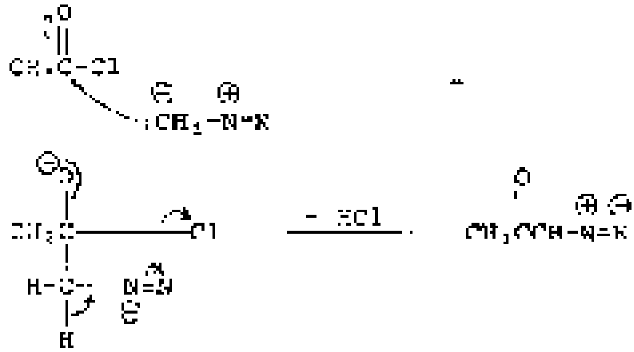
• PROBLEM 22-33

Write reasonable mechanisms for the following reactions:



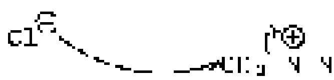
Solution: Diazomethane is a useful reagent that is potentially both a nucleophile and a base. In addition, it introduces a nitrogen fragment in the newly formed adduct that may leave the molecule as nitrogen gas (N_2), an excellent leaving group.

(a) In this reaction diazomethane acts as a nucleophile upon the carbonyl group of the acid chloride. The excess diazomethane acts as a base, consuming the HCl that is produced by the reaction.

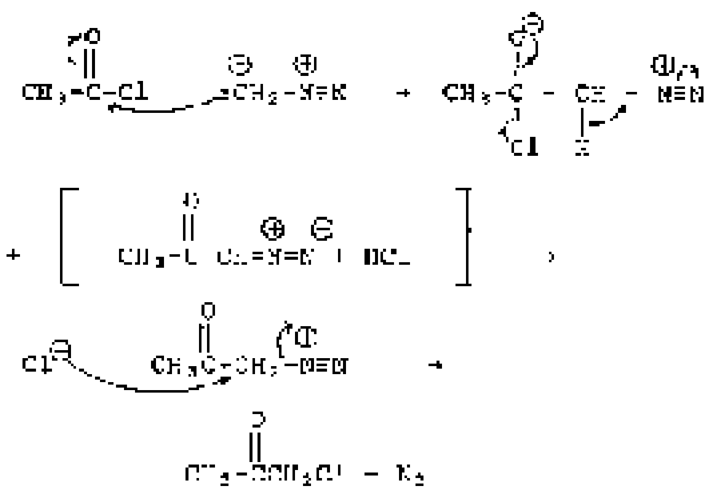


$$HCl + CH_2N_2 \rightarrow CH_3Cl + N_2$$

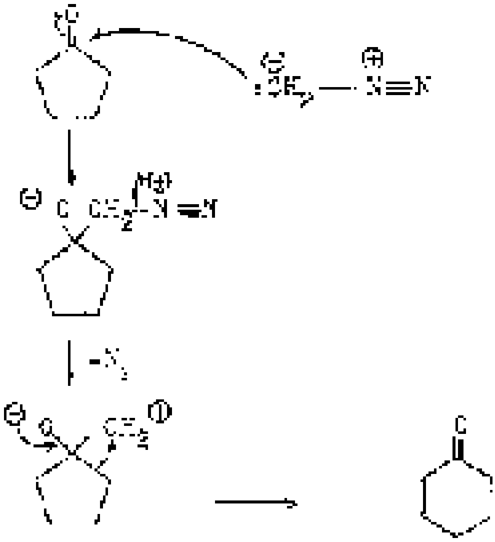
The methyl chloride is formed by a nucleophilic attack on the protonated diazomethane:



(b) In this question, an equimolar mixture of diazomethane and acetyl chloride are mixed to initially yield an α-diazoketone. In the absence of a more electrophilic species, the chloride will attack the carbon that bears the nitrogen fragment in an S_N2 displacement.



(c) Diazomethane may act as a nucleophile toward the carbonyl group of cyclopentanone. The adduct form contains positive charge on a primary carbon, which is relatively unstable. This species, like any carbocation, may rearrange to a more stable carbocation. This shift involves the formation of a secondary carbocation as a result of a ring shift. The transition from the five membered ring to a cyclohexane ring is entropically favored. The entire sequence occurs as follows:



AZIDES

• PROBLEM 22-53

What is a good method (an easy method that gives a pure product in good yield) for carrying out the following transformation?

$$R-CH_2-Br \rightarrow R-CH_2-NH_2$$

Solution: An alkyl halide can readily be converted to its corresponding azide by employing the azide anion (N_3^-) in a nucleophilic displacement reaction.

$$:\overset{\ominus}{N}-\overset{\oplus}{N}-\overset{\ominus}{N}: \quad R-CH_2-Br \xrightarrow{-Br^{\ominus}} RCH_2-N_3$$

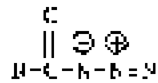
The azide may be reduced to an amine by a variety of reagents including zinc and acid.

$$RCH_2-N_3 \xrightarrow[N_2]{Zn/H^{\oplus}} RCH_2NH_3^{\oplus} \xrightarrow[H_2O]{OH^{\ominus}} RCH_2NH_2$$

This method of converting the intermediate azide into an amine is preferable to adding ammonia to the bromide because the latter sequence will have elimination as a side reaction.

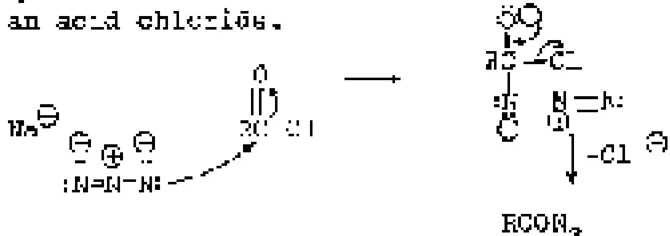
• PROBLEM 22-54

Reaction of acid chlorides with sodium azide, NaN_3, yields acyl azides, $RCON_3$. When heated, these undergo the Curtius rearrangement to amines, RNH_2, or, in a non-hydroxylic solvent, to isocyanates, RNCO. Using the structure



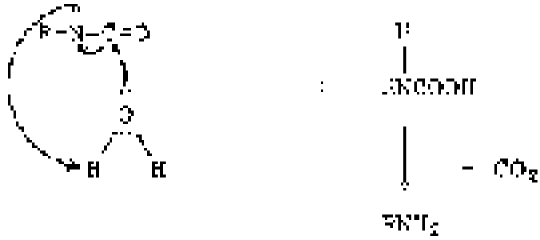
for the azide, suggest a mechanism for the rearrangement.

Solution: The Hofmann rearrangement involves the conversion, $RCONH_2 \rightarrow RNH_2$, degrading the compound by one carbon. The Curtius rearrangement gives a similar degradation but through an intermediate azide instead of an amide, ($RCON_3 \rightarrow RNH_2$). The azide may be synthesized via an addition-elimination in which the azide anion acts as a nucleophile upon an acid chloride.



Once the intermediate acyl azide is synthesized, it may be converted to a variety of products, depending on the reaction conditions. For instance, if the azide is heated, it is converted to an isocyanate. Like the Hofmann degradation, this involves a rearrangement in which there is a 1,2 shift to the electronegative nitrogen. The alkyl or aryl group that was originally attached to the carbonyl group will attach to this nitrogen but probably did not migrate as a free reactive particle.

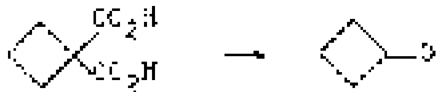
This reaction is enhanced by the fact that N_2, a very stable molecule, is lost. Water will react with the intermediate isocyanate to form an unstable carbamic acid which decarboxylates to the amine.



• **PROBLEM 22-55**

Show how the following transformations might be achieved with the aid of azide derivatives.

(a) $CH_3-CHCH_2CH_2OH \rightarrow CH_3-CHCH_2CH_2NH_2$

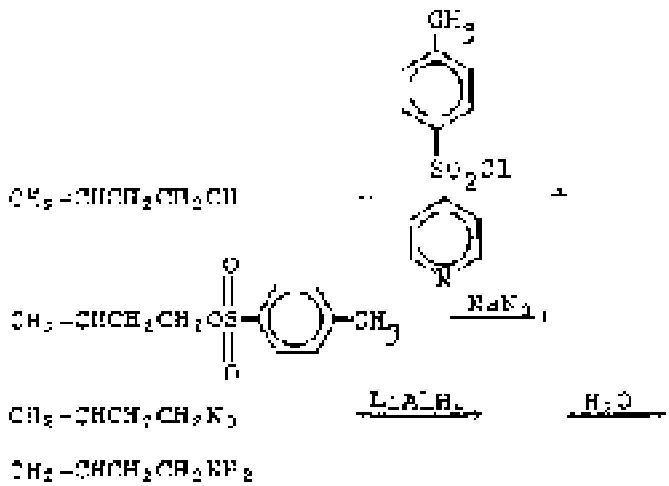
(b) 

Solution: The reduction of an azide to its corresponding amine compound is a reasonable route to the synthesis of amines.

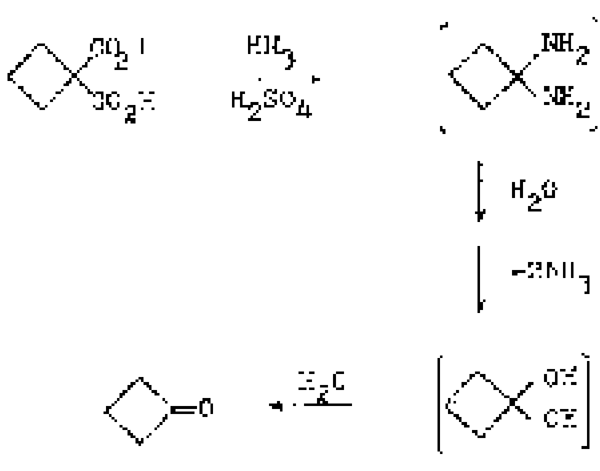
$$R-N_3 \xrightarrow[N_3]{[H]} R-NH_2$$

The azides are conveniently made through nucleophilic displacement reactions.

(a) The alcohol is activated toward nucleophilic displacement reactions by converting it to its corresponding tosylate through the use of p-tolyl sulfonylchloride. The azide ion will displace the tosylate ion in a substitution reaction and the amine is produced by reduction.

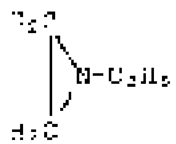


(b) The reactant dicarboxylic acid differs from the product, cyclobutanone, in that it contains two additional carboxyl groups. We may eliminate these groups through the use of the Schmidt reaction where we treat the carboxylic acid with hydrazoic acid (HN_3) together with sulfuric acid. The process involves a rearrangement of an intermediate acyl azide. The diamine is easily hydrolyzed to the ketone.

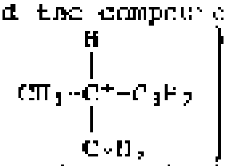


• PROBLEM 23-55

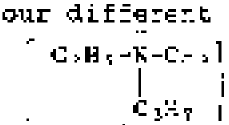
At room temperature, the nmr spectrum of 1-ethylaziridine shows the triplet-quartet of an ethyl group, and two other signals of equal peak area. When the temperature is raised to 120°, the latter two signals merge into a single signal. How do you interpret these observations?



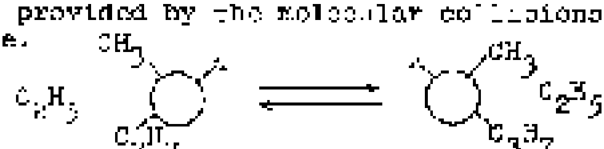
Solution: This question involves the discussion of two topics - the stereochemistry of nitrogen compounds and proton equivalence as determined by spectroscopy. A carbon atom surrounded by four different substituents as in 3-methylhexane is chiral and the compound as a whole will possess optical activity



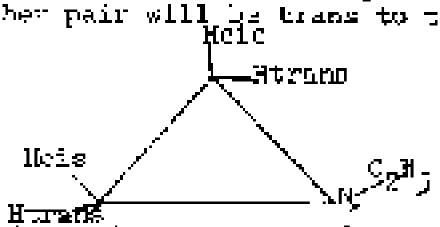
. However, the amine butylethylpropylamine does not show optical activity despite being attached to four different entities which include the free electron pair



. This lack of optical activity is a result of configurational instability, which in turn is due to amine inversion. Amines, like ammonia itself, undergoes inversion which involves the amine turning inside out from one pyramidal arrangement to another equivalent one. The energy barrier for this conversion is very low and is provided by the molecular collisions at room temperature.



Unlike a tetrasubstituted carbon which assumes a tetrahedral configuration, the amine nitrogen is configurationally unstable because the free pair of electrons will be oriented in one manner at a certain moment and oriented in the opposite manner at the next instant. We note that each of these configurations are enantiomers of each other and their interconversion is known as racemization. Configurational instability is not restricted to amines in that the trisubstituted carbanions also lack optical activity. In this question, we are confronted with the compound, 1-ethylaziridine, which is a cyclopropane derivative. It differs from acyclic amines in that it shows some degree of configurational stability. This was shown by the compound's nuclear magnetic resonance spectrum which contained two signals of equal peak area besides the familiar triplet-quartet pattern of the ethyl fragment. Since pyramidal inversion changes the molecular environment of the four ring protons, both their chemical shift and splitting pattern will be varied. At room temperature, 1-ethyl aziridine undergoes very slow inversion and two of the ring protons will differ in environment from the other two ring protons. One set of protons will be cis to nitrogen's ethyl substituent while the other pair will be trans to the ethyl group.

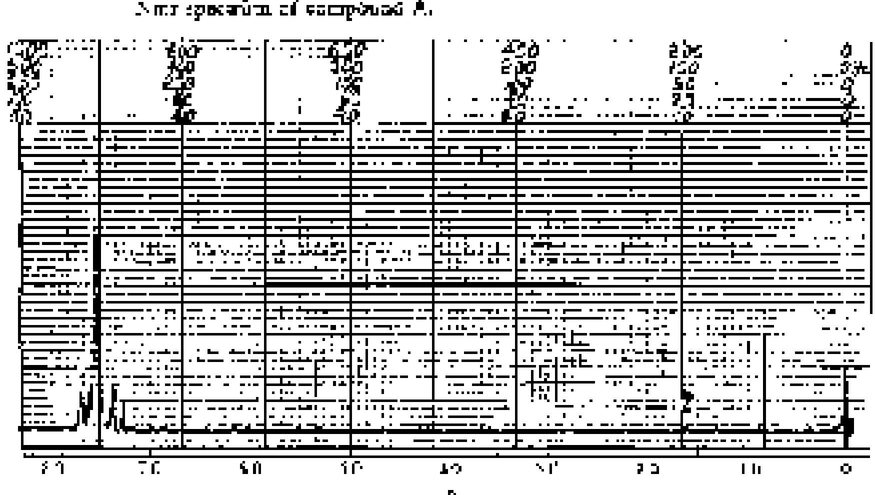


Thus, at room temperature, we find two equally sized peaks that represent the ring protons. The transition to a single peak can best be explained by the fact that the n.m.r. spectrometer, like any instrument, has only a certain degree of resolution and that at higher temperatures, the "cis" protons and the "trans" protons appear to the instrument as a smear in which each proton seems to be in the same average environment. This temperature dependence is a result of the increased rate of inversion at the higher temperature. Since the ring protons appear to be equivalent to the spectrometer, they are recorded as a single peak. The question now arises why inversion is slower in aziridine derivatives than in most acyclic amines. The answer lies in the fact that for amines to undergo inversion they pass through a planar sp^2 hybridized transition state. While acyclic amines can make this $sp^3 \rightarrow sp^2$ transition fairly easily, aziridine derivatives have significant ring strain in their transition states when they undergo inversion. The high activation energy for aziridine inversion is easily overcome at a high temperature.

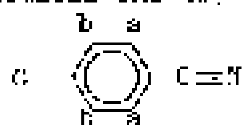
• PROBLEM 22-57

A neutral compound, C_7H_4NCl (A), gave the nmr spectrum shown. Reaction of A with $LiAlH_4$ afforded a basic product C_7H_8NCl (B), a solution of which in cold dilute H_2SO_4 reacted immediately with sodium nitrite to give a neutral substance C_7H_7OCl (C). After the original compound (A) was refluxed with 30 percent aqueous KOH and the resulting solution was acidified, an acidic solid $C_7H_5O_2Cl$ (D) was obtained. Write structures for compounds A – D.

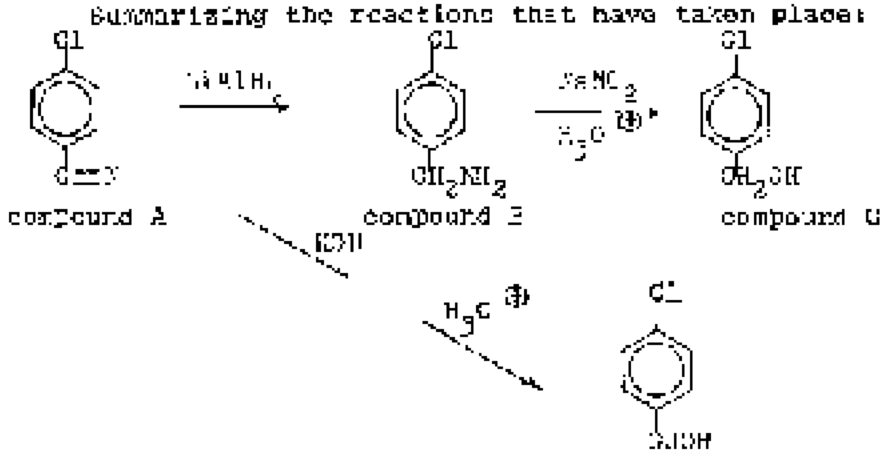
Nmr spectrum of compound A.



Solution: Compound A contains nitrogen but is neutral so it cannot be an amine. The high amount of unsaturation suggests the possibility of an aromatic ring and this is verified by its nmr spectrum. Treatment with $LiAlH_4$ adds four hydrogens to compound A's molecular formula to give the basic compound B which is most probably an amine since it diazotizes to the compound C. The amino group must not have been on the ring since compound C is not a phenol, with acidic properties, as would be expected of hydrolysis after diazotization. The fact that compound A yields a carboxylic acid, free of nitrogen when acidified after alkaline hydrolysis, suggests that the original compound is a nitrile. This hypothesis concurs with the molecular formula change of compound A upon reduction. Note that chlorine remains in the molecule after treatment with hydroxide ion and therefore the chlorine was not involved in any substitution or elimination reaction. Hence, chlorine is on the aromatic ring. Accounting for the six carbons of the aromatic ring and the nitrile carbon, the original compound must be one of the three chlorobenzonitriles. The compound is determined to be the para isomer by its n.m.r. spectrum, which is fairly symmetrical. The ortho and meta isomers would have unsymmetrical patterns due to the different orientation of the ring protons toward the substituents. In contrast, p-chlorobenzonitrile has two sets of protons, each with similar chemical shifts, accounting for the symmetrical pattern.

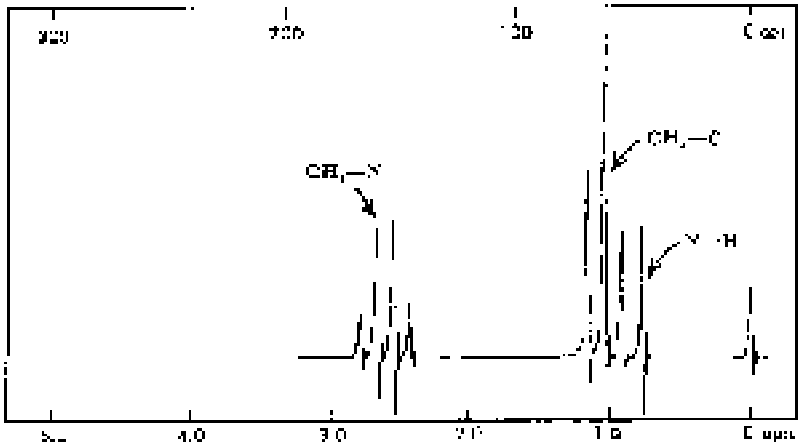


Summarizing the reactions that have taken place:



*** PROBLEM 22-58**

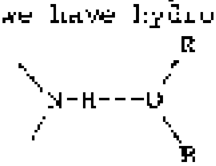
How could one show with certainty that the peak at 47 cps with reference to tetramethylsilane in the n.m.r. spectrum of diethylamine is actually due to the N-H resonance?



N.m.r. spectrum of diethylamine at 60 Mc/s relative to tetramethylsilane (0.00 ppm).

Solution: As seen in the nuclear magnetic resonance spectrum of diethylamine, the chemical shift of the proton bonded to nitrogen is quite similar to the chemical shift of the C-CH_3 protons. This proves quite irksome in interpreting the spectra of certain amines. However, there are several ways to differentiate between these two absorptions. If we add D_2O to the solution containing diethylamine, the intensity of the N-H absorption will decrease. This is because deuterium, unlike hydrogen, will not give rise to a signal in an n.m.r. spectrum. The deuterium incorporation occurs because the proton on the nitrogen is fairly acidic, as opposed to a hydrogen on carbon.

In addition, we may vary the chemical shift of the proton on nitrogen by changing the concentration of the amine in a solvent that is capable of hydrogen bonding. For example, in an ether, we have hydrogen bonding of the type

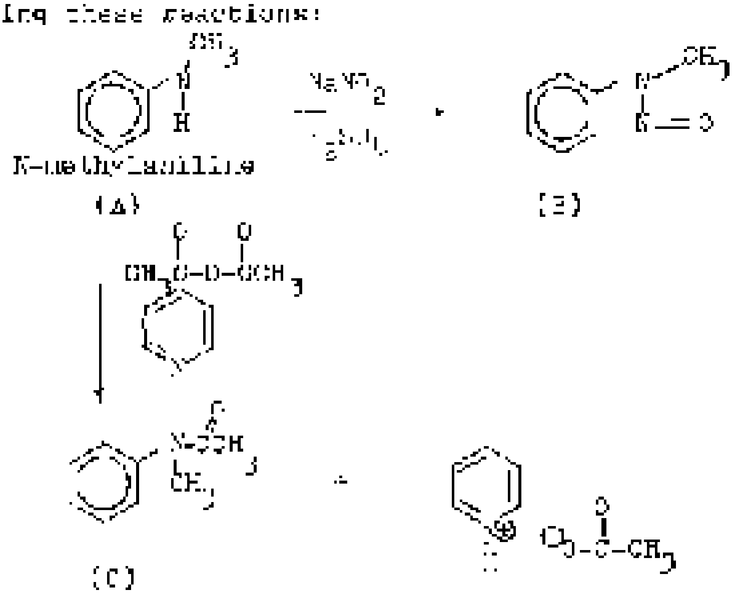


If we increase the amount of hydrogen bonding, we will shift the N-H resonance downfield because the proton will spend more time on the nitrogen and be subject to its electron-withdrawing inductive effect. The C-CH_3 fragment is not involved in hydrogen bonding and its proton's chemical shift will not be altered by changes in concentration.

• PROBLEM 22-30

A colorless basic liquid C_7H_9N (A) reacts immediately with sodium nitrite in cold dilute sulfuric acid to give a neutral yellow oil (B). Reaction of A with acetic anhydride in pyridine solution gives a neutral white solid (C), the nmr spectrum of which shows a singlet at δ 1.9, a singlet at δ 3.5, and a multiplet at δ 7.3 with intensities of 1 : 1 : 1.67, respectively. Assign structures to A, B, and C.

Solution: The reagent nitrous acid is generated when sodium nitrite and a cold protic acid are combined ($NaNO_2$ + H_2SO_4). Reaction with nitrous acid (HONO) is a common method of differentiating various nitrogen compounds. In this case, a yellow, neutral oil as a nitrosation product is characteristic of both aliphatic and aromatic secondary amines. This oil (Compound B) would be an N-nitroso compound which is probably aromatic due to the high amount of unsaturation evident in the molecular formula of the compound B. The fact that compound A reacts with acetic anhydride verifies that it is a secondary amine since tertiary amines do not readily react with anhydrides and primary amines would be eliminated as a possibility for compound A by the nitrosation product. The acetylation product (Compound C) has a multiplet at δ 7.3 and this confirms that Compound A is an aromatic, secondary amine since this represents the aromatic protons. The peak at δ 1.9 is characteristic of a methyl group bonding a carbonyl, which would be expected from an acetyl compound. Since we know that an acetyl group adds three hydrogens to a compound's molecular formula, we must multiply the given intensities by three to get the right number of protons (eleven) in the ratio 3 : 3 : 5. Hence Compound A contains a methyl group which must be on the nitrogen since it is a secondary amine. This methyl group would correspond to the peak at δ 1.5 which is relatively downfield (at a higher δ value) because of the inductive effect of the adjacent nitrogen. Summarizing these reactions:



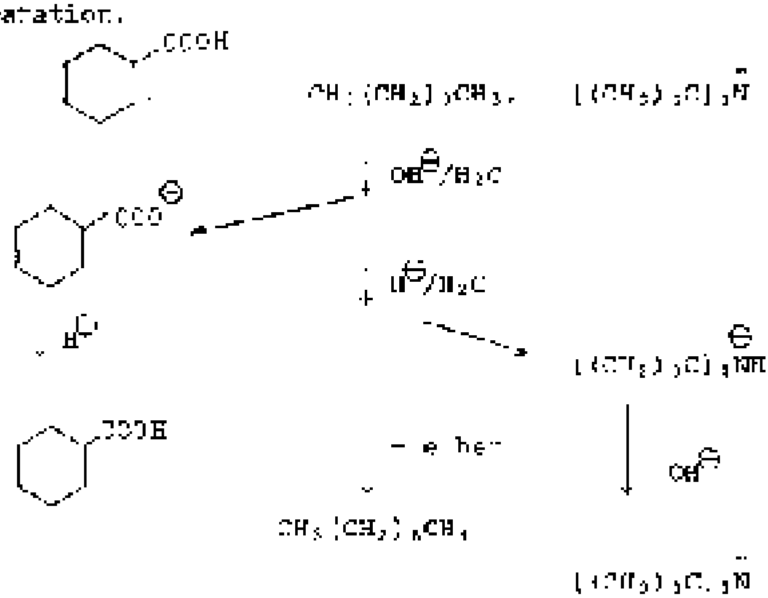
CHARACTERIZATION TESTS

• PROBLEM 23-60

Propose a method for separating a mixture of cyclohexanecarboxylic acid, tri-t-butylamine, and decane.

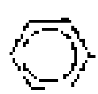
Solution: To achieve the separation of various organic materials, we must determine which general class of compounds that each of the substances belong to, and then which properties are characteristic of each general class.

Cyclohexanecarboxylic acid, $C_6H_{11}C(=O)OH$, is a carboxylic acid whose carboxyl group can lose a proton to form the corresponding anion. Tri-t-butylamine, $[(CH_3)_3C]_3N$ has a free pair of electrons and therefore it can act as a base to form an ammonium cation. Decane is a neutral compound. Thus, we can treat the mixture with base and only the acid will dissolve in the alkaline solution since it is the only substance that ionizes. We can employ the same reasoning to separate the amine from the alkane. The basic amine will be soluble in a solution of aqueous acid whereas the neutral alkane will not dissolve. The organic solvent (e.g. ether) that contains the alkane after sequential treatment with base and acid, can be evaporated and we will have achieved the separation.



■ PROBLEM 22-61

What simple chemical tests could be employed to distinguish one compound from the other in each of the following?

(1) $CH_3(CH_2)_4CH_2NH_2$ and  NH_2

(2) $CH_3CH_2C(=O)NH_2$ and $CH_3CH_2CH_2NH_2$

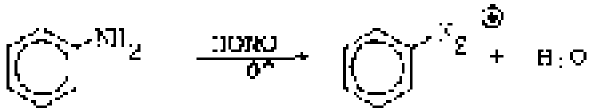
Solution: (1) Here we want to differentiate between primary aliphatic and primary aromatic amines. They can be distinguished by their reaction with nitrous acid (HONO) at 0°C. When treated with nitrous acid at 0°C, the primary aliphatic amine, but not the primary aromatic amine, will liberate bubbles of nitrogen gas. If no gas is liberated at 0°C, and the solution is then warmed to room temperature with the evolution of bubbles, then one possesses a primary aromatic amine. The reactions with nitrous acid can be written as:

$$CH_3(CH_2)_4CH_2NH_2 \xrightarrow[0°]{HONO}$$

$$CH_3(CH_2)_4CH_2^{\oplus} + N_2 + H_2O$$

$\downarrow$

alkenes and alcohols



(2) In this part of the problem, we must distinguish between a primary amide and a primary amine. The amide, like any acid derivative, can undergo hydrolysis. When refluxed in alkaline solution, the amide will yield ammonia and the salt of a carboxylic acid. The ammonia evolved can be detected through the use of litmus paper.

$$CH_3CH_2\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow[H_2O]{NaOH}$$

$$CH_3CH_2\overset{O}{\overset{\|}{C}}-O^{\ominus}\ Na^{\oplus} + NH_3\uparrow$$

The amine would be unaffected by the aqueous base.

PROBLEM 23-62

Give for each of the following pairs of compounds a chemical test, preferably a test tube reaction which will distinguish between the two compounds.

(a) $(CH_3)_3CNH_2$ and $(CH_3)_2NC_2H_5$
(b) $CH_3CH_2NO_2$ and CH_3CONH_2
(c) CH_3CH_2CN and $CH_3CH_2NO_2$
(d) CH_3CH_2NHCl and $CH_3CH_2NH_3Cl$
(e) $CH_3NHCOCH_3$ and $CH_3NHCO_2CH_3$

Solution: (a) We must distinguish between t-butylamine $(CH_3)_3CNH_2$, a primary amine, and dimethylethylamine which is a tertiary amine. The simplest way to do this would be to treat both compounds with nitrous acid (HONO) for only the primary amine will yield nitrogen upon these conditions. The tertiary amine undergoes a complex process, eventually yield-but an N-nitroso compound which would be a yellowish oil or solid.

(b) Acetamide $\left(CH_3\overset{O}{\overset{\|}{C}}NH_2\right)$, unlike nitroethane $(CH_3CH_2NO_2)$ is an acid derivative and can be hydrolyzed to yield an carboxylic anion and ammonia. This is done by the addition of aqueous base to the solution and using wet litmus to test for the evolved ammonia.

$$NaOH + CH_3\overset{O}{\overset{\|}{C}}NH_2 \xrightarrow[H_2O]{} CH_3\overset{O}{\overset{|}{C}}O^{\ominus}\ Na^{\oplus} + NH_3$$

The nitro compound will not react similarly.

(c) Of propanenitrile and 2-propynylamine, only the amine has a terminal carbon-carbon triple bond and thus a hydrogen of significant acidity. Because of the acetylene's acidity, we may precipitate an acetylide salt when we treat the compound with ammoniacal silver nitrate. The nitrile will not yield such a salt.

$$HC \equiv C - CH_2NH_2 + Ag(NH_3)_2^{\oplus}\ NO_3^{\ominus} \rightarrow$$

$$AgC \equiv C - CH_2NH_2 + NH_4^{\oplus}\ NO_3^{\ominus} + NH_3$$

By an alternate method, we could have both compounds undergo alkaline hydrolysis where only the nitrile's hydrolysis will evolve ammonia.

(d) We differentiate between the N-chloroamine and the ammonium salt by realizing that aqueous hydrogen chloride will produce chlorine gas from the N-chloroamine. The salt would be unaffected.

$$CH_3CH_2N\begin{matrix} Cl \\ H \end{matrix} + HCl \rightarrow CH_3CH_2NH_2 + Cl_2$$

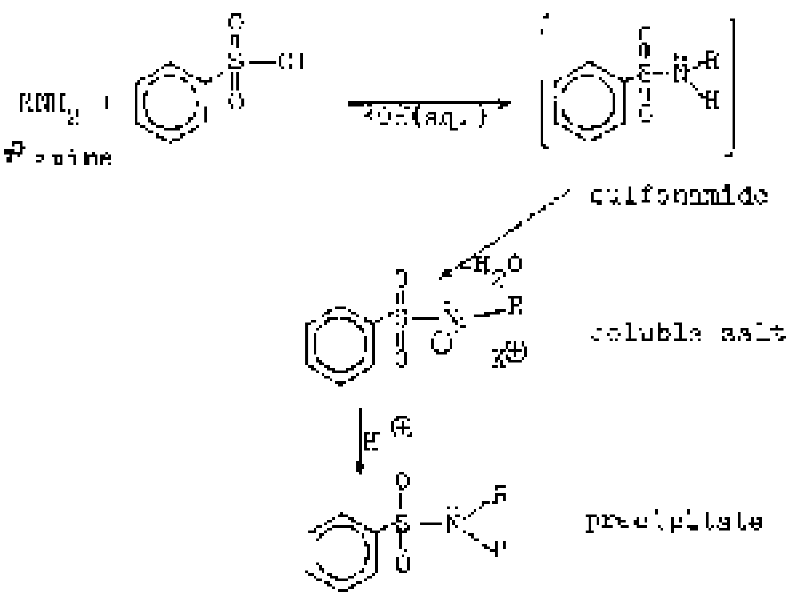
(e) Here we are confronted with a carbamate $(CH_3NHCO_2CH_3)$ and an amide $(CH_3NHCOCH_3)$. When subjected to acid hydrolysis, the amide will yield an amine and a carboxylic acid. The carbamate is transformed to an intermediate carbamic acid which immediately decarboxylates to an amine and the easily detectable carbon dioxide.

$$CH_3-\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{H_3O^{\oplus}} CH_3\overset{\oplus}{N}H_3 + CH_3\overset{O}{\overset{\|}{C}}-OH$$

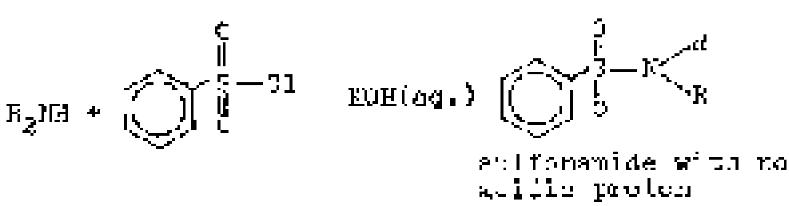
$$CH_3\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-OCH_3 \xrightarrow[-\,CH_3OH]{H_3O^{\oplus}} \left[CH_3NH\overset{O}{\overset{\|}{C}}-OH\right] \rightarrow CH_3NH_2 + CO_2$$

The sulfonamides of big primary amines are only partially soluble in aqueous KOH. (a) In the Hinsberg test, what incorrect conclusion might you draw about such an amine? (b) How might you modify the procedure to avoid this mistake?

Solution: Amines are usually differentiated from other organic compounds by their basicity, but once they are identified as amines, it becomes necessary to classify them as either primary, secondary, or tertiary. This classification is based on the degree of substitution on nitrogen. The Hinsberg test can differentiate between 1°, 2°, and 3° amines by treating the amine in benzenesulfonyl chloride in the presence of excess base. The test is based upon the nucleophilic attack of the amine's nitrogen upon the sulfonyl chloride and the differing properties of the subsequently formed sulfonamide. A primary amine would form a sulfonamide that would immediately lose a proton to give a salt that is usually soluble. The sulfonamide may be regenerated by the addition of acid. This is seen experimentally by the dissolution of the amine and the appearance of a precipitate upon acidification.



A secondary amine forms a sulfonamide that is inert to both acid and base.



Finally, tertiary amines yield a compound that is insoluble (the unreacted amine) but upon protonation it forms a quaternary amine salt which is soluble.

(a) In this question, we are confronted with a large primary amine that forms an only slightly soluble sulfonamide salt. This can be best explained by the fact that the R group in the primary amine ($R-NH_2$) is a large non-polar moiety such as an extensive hydrocarbon chain. Being the most significant part of the molecule because of its size, this chain would dominate the compound's physical properties, and render it insoluble in the polar solvent, H_2O. The appearance of a precipitate when treating the amine under the conditions of the Hinsberg test is not typical of primary amines but of secondary and tertiary amines. In this case, the experimental observation would be incorrect.

(b) We can eliminate the presence of a secondary amine by adding acid to the solution and seeing a newly formed precipitate. Reprecipitation at this point eliminates the presence of secondary amines which would not have been in the original solution. The same argument holds for tertiary amines.

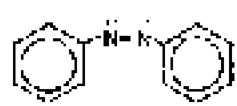
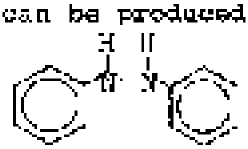
SYNTHESIS

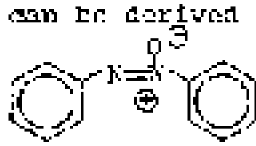
• PROBLEM 22-64

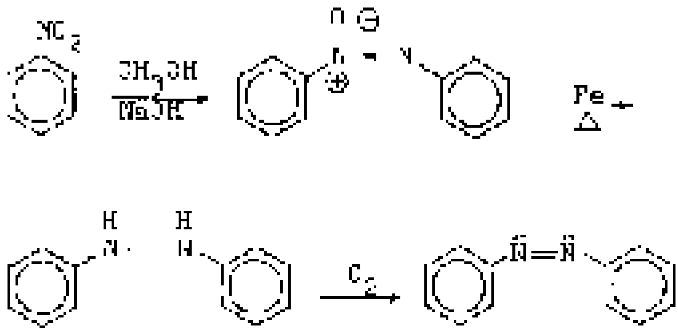
Suggest a synthesis for each of the following, using nitrobenzene and any other necessary reagents.

(a) $C_6H_5N=NC_6H_5$ (c) $p-CH_3C_6H_4NH_2$
(b) C_6H_5NHOH (d) $C_6H_5NH_2$

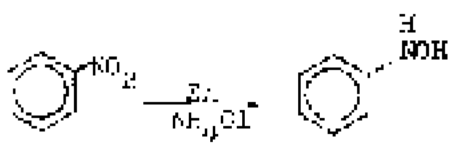
Solution: Nitrobenzene can be reduced to various different products depending on the nature of the reducing mixture. In acidic media, the reduction proceeds directly to aniline while in analogous basic and neutral media, certain intermediates can be isolated.

(a) Azobenzene,  , can be produced by the mild oxidation of hydrazobenzene  .

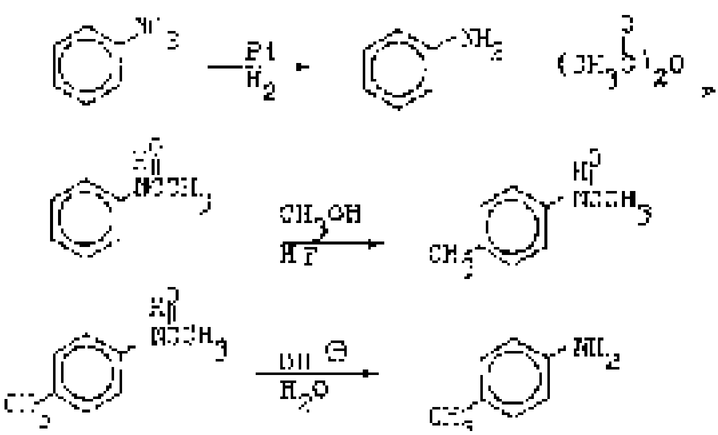
Hydrazobenzene can be derived from a catalytic reduction of azoxybenzene (). Nitrobenzene may act as as oxidant towards methanol in alkaline solution and in turn be reduced to azoxybenzene. The final product is predominantly transazobenzene. The synthesis is as follows:



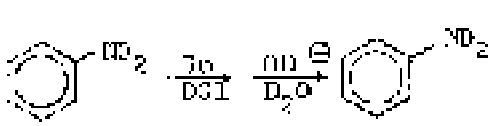
(b) In the mildly acidic media of zinc dust and aqueous ammonium chloride, nitrobenzene would be reduced to N-phenylhydroxylamine.



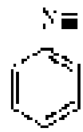
(c) The product, p-methylaniline, has an amino group transformed from a nitro group. The methyl group is para to this amino and can be put on by a Friedel-Crafts reaction. We lessen the overreactivity of the amino group and its susceptibility to oxidation by the process of acylation. We may recover the final product by alkaline hydrolysis.

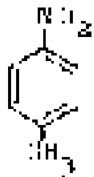


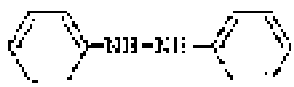
(d) We may make the conversion from nitrobenzene to the dideuteric aniline by a catalytic reduction using a deuterated acid.



Complete and balance the following reactions:

(a)  $+ SO_3^{2-} + H_2O \rightarrow$

(b)  $+ SnCl_2 + HCl \rightarrow$

(c)  $+ OBr^- \rightarrow$

Solution: In balancing these organic oxidation-reduction (redox) reactions, we are concerned with two concepts - that of realizing what action a particular oxidizing (or reducing) agent will take on an organic compound and also how to balance the reaction itself. Organic redox reactions are balanced in the same way that inorganic redox reactions are balanced and may be done by simple inspection.

We may represent the overall process as a set of two half-cell reactions, as long as we conserve charge. We may balance the charge by inserting $H^{\oplus}$ and $OH^{\ominus}$, depending on the particular media.

(a) We know that the benzenediazonium cation can be reduced by the action of sodium sulfite (Na_2SO_3) to phenyl hydrazine. We will need three protons to balance the number of hydrogens and four electrons to balance the charge.

$$C_6H_5N_2^{\oplus} + 3\,H^{\oplus} + 4\,e^{\ominus} \rightarrow C_6H_5NHNH_2$$

Since this is a reduction, the other reaction must be an oxidation. The sulfite ion will be oxidized to the sulfate ion with the sulfur atom losing two electrons (sulfur's oxidation number changes from +4 to +6). Two protons and two electrons balance the equation

$$SO_3^{\ominus} + H_2O \rightarrow SO_4^{\ominus} + 2\,H^{\oplus} + 2\,e^{\ominus}$$

We must double the oxidation reaction to balance the electron loss ($2\,e^{\ominus}$) and electron gain ($4\,e^{\ominus}$). The sum of these reactions will give us the total process:

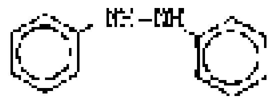
$$\begin{array}{rcl} 2\,SO_3^{\ominus} + 2\,H_2O & \rightarrow & 2\,SO_4^{\ominus} + 4\,H^{\oplus} + 4\,e^{\ominus} \\ C_6H_5N_2^{\oplus} + 3\,H^{\oplus} + 4\,e^{\ominus} & \rightarrow & C_6H_5NHNH_2 \\ \hline C_6H_5N_2^{\oplus} + 2\,SO_3^{\ominus} + 2\,H_2O & \rightarrow & C_6H_5NHNH_2 + 2\,SO_4^{\ominus} + H^{\oplus} \end{array}$$

(b) We know that reduction of nitroarenes in acid media will proceed to the corresponding aniline. We use water to balance the oxygens, and protons to balance the hydrogens. This reduction is accompanied by the oxidation of tin to the +4 oxidation state. Again, we balance charges to get the final equation.

$$3 \times [Sn^{2+} \rightarrow Sn^{4+} + 2e^{-}]$$

$$\underline{CH_3C_6H_4NO_2 + 6H^{+} + 6e^{-} \rightarrow CH_3C_6H_4NH_2 + 2H_2O}$$

$$CH_3C_6H_4NO_2 + 3Sn^{2+} + 6H^{+} \rightarrow CH_3C_6H_4NH_2 + 3Sn^{4+} + 2H_2O$$

(e) Hydrazobenzene () and azobenzene

are easily interconverted when treated with the proper reagents.

In the presence of the oxidizing agent, the hypobromite ion, hydrazobenzene is oxidized to azobenzene. The reaction can be balanced by inspection, using one H_2O molecule

$$C_6H_5NHNHC_6H_5 + OBr^{-} \rightarrow$$

$$C_6H_5N{=}NC_6H_5 + H_2O + Br^{-}$$

CHAPTER 23

PHENOLS

NOMENCLATURE AND STRUCTURE

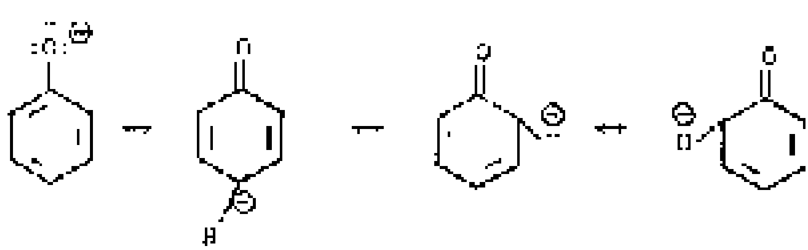
PROBLEM 23-1

Write structural formulas for substances (one for each part) that fit the following descriptions:

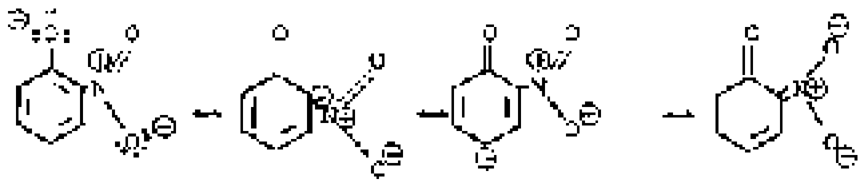
(a) a phenol that would be a stronger acid than phenol itself
(b) that isomer of dichlorophenol that is the strongest acid
(c) the Claisen rearrangement product from a α-methylallyl-2,6-dimethylphenyl ether
(d) a quinone which does not undergo Diels-Alder addition
(e) a quinone that would be a better charge-transfer agent than quinone itself.

Solution: The best way to solve this problem is to find what general structural features would give the compound the desired properties and then deduce the specific structure.

(a) The key point to realize is what affects the acidity of phenols. The answer lies in terms of the resonance structures of the subsequent phenoxide anion. For phenol itself, the major contributing forms for the phenoxide anion are:

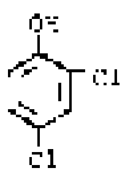


We note that oxygen's free pair of electrons are delocalised within the aromatic ring causing the negative charge to reside on the carbons ortho and para to the hydroxyl group. The negative charge and consequently the resonance structures bearing it may be stabilized by substituents that inductively withdraw the charge toward themselves or have significant resonance contributing structures that stabilize the charge. Realizing this, we see that such stabilizing effects are greatest when the substituents are ortho and/or para to the hydroxyl group. The nitro group is a substituent that stabilizes negative charge both by resonance and induction. The nitrogen of the nitro group is sp^2 hybridized and highly electronegative. This group is also an electron-withdrawing substituent by resonance as shown in ortho nitrophenol:



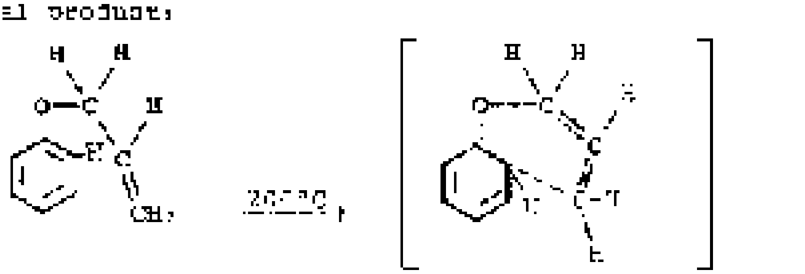
Thus, the phenoxide anion of o-nitrophenol has greater stability than the phenoxide anion, and therefore o-nitrophenol is a stronger acid than phenol.

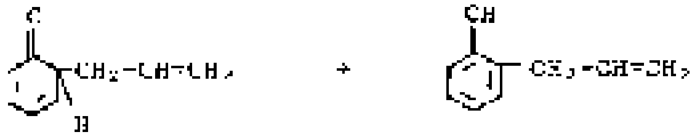
(b) As previously stated, the effect of a substituent upon a phenoxide anion's stability and the phenol's acidity is maximized when the substituent is ortho and/or para to the hydroxyl group. In this problem, we are dealing with dichlorophenols, i.e. phenols with two chlorine substituents. Chlorine is a group that will stabilize negative charge and the effect of two chlorines will logically be even more stabilizing, and therefore dichlorophenols are stronger acids than chlorophenols. The dichlorophenol isomer that has the greatest acidity would be 2,4-dichlorophenol:



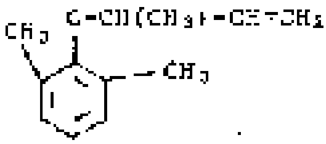
since there is a chlorine in one ortho position and one in the para position. Both would have a direct stabilizing effect on the negative charge that may reside in these positions. By similar reasoning 2,6-dichlorophenol will also have a significant acidity.

(c) Phenyl allylether is unusual among O-alkylated phenols in that it is thermally unstable and at high temperatures it isomerizes to o-allylphenol. This rearrangement proceeds through a cyclic transition state to form a tautomer of the final product:

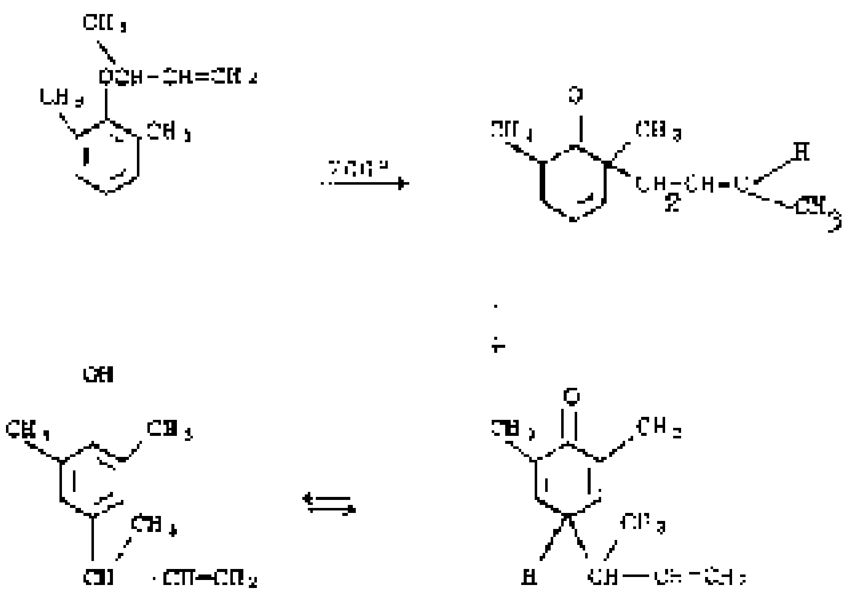




In our compound, α-methylallyl-2,6-dimethylphenyl ether:

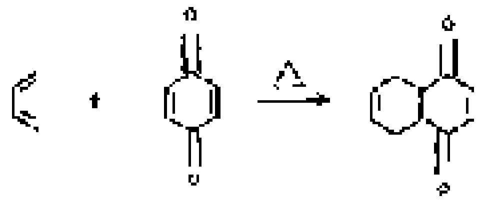


The ortho position is blocked in the sense that there is no ortho proton whose removal is necessary for the tautomerization to the phenol. In this special case of the Claisen rearrangement, isomerization continues and the allyl group is put in the para position as a result of a similar cyclization process.



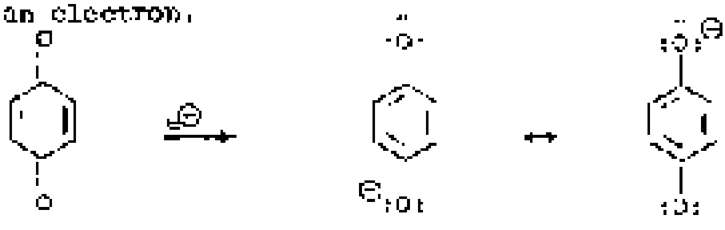
4 (1-methyl-2-propenyl)-2,6,-dimethylphenol

(d) A cycloaddition reaction involves the cyclization of two unsaturated molecules as a result of formation of two new σ bonds from π electrons. These may be initiated by heat or ultraviolet light depending on the number of π electrons involved in the cyclization. The Diels-Alder reaction is a specific cycloaddition in which a total of six π electrons are involved with four belonging to a conjugated diene and two to an alkene (dienophile). Dienophiles are most reactive when the double bonds are conjugated to an electron withdrawing group. Quinones such as benzoquinone are potent dienophiles.

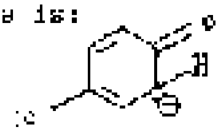


On the other hand, quinones such as 9,10 anthraquinone made from the oxidation of anthracene contains double bonds that are part of an aromatic system and therefore it could not act as a dienophile in a Diels-Alder reaction. This is because the disruption of the double bond loses the extra stability of aromatic compounds.

(c) A charge-transfer complex is a compound whose resonance structures include a complex where an electron-rich donor transferred an electron to an electrophilic acceptor molecule. Quinone is a charge transfer agent in that it may be reduced to an anionic radical by transfer of an electron.



We note that the resonance structure for this compound, though an unimportant one is:



The substitution on the ring will directly determine the stability of such structures and the ability of quinones to bear negative charge in general. Electron-withdrawing groups like the cyano group will provide this stabilization and therefore compounds bearing these substituents will better be able to bear negative charge. Thus, a compound like tetracyanobenzoquinone will be a better charge transfer agent than quinone.

■ **PROBLEM 23-2**

Write structures for each of the following names;

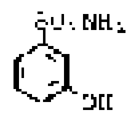
(a) m-cresol
(b) 3-hydroxybenzenesulfonamide
(c) 3-chloro-1,2-benzoquinone
(d) o methoxyphenol
(e) p-(p-tolyl)azophenol
(f) benzyl phenyl ether
(g) 3-(o-hydroxyphenyl) pentanoic acid
(h) 2-methoxy-1,4-naphthoquinone

Solution. (a) Cresols are phenols with methyl substituents. Meta-cresol has a methyl group in the "3" position with the hydroxyl group in the "1" position.

The structure of this compound is:  .

(b) This compound, 3-hydroxybenzenesulfonamide, is a derivative of benzenesulfonic acid: 

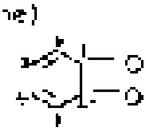
3-hydroxybenzenesulfonic acid has an alcohol functionality in the "3" position 

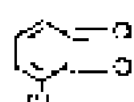
The amide derivative of this substituted sulfonic acid is the compound we desire:  .

(c) 1,2-benzoquinone is a dicarbonyl compound, derived from the oxidation of the polyhydric phenol catechol:

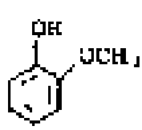
catechol

1,2 benzoquinone
(o-benzoquinone)

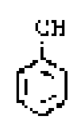
The numbering scheme for 1,2 benzoquinone is: 

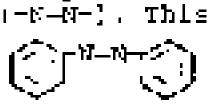
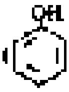
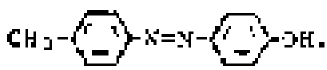
A chlorine substituent in the "3" position gives us the compound 3-chloro-1,2-benzoquinone 

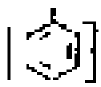
(d) The methoxy group is $-OCH_3$. In this substituted phenol, the methoxy group is ortho or adjacent to the alcohol functionality. The structure of this compound is:

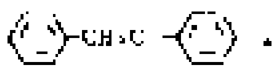


o-methoxy phenol
(2-methoxy phenol)

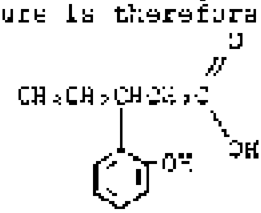
(e) The substituent, p-tolyl, is derived from toluene: 

It is in the para position where the attachment is made to the azo group $(-N{=}N-)$. This compound is a derivative of azobenzene:  with the two substituted benzene rings being p-tolyl:  and phenol with the substitution occurring at the para position . The compound which is named as a substituted phenol has the structure: .

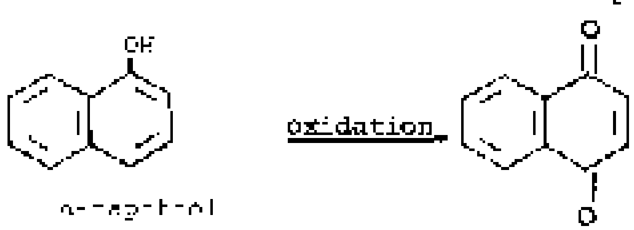
(f) As seen from its name, this is an ether with the general formula ROR'. Here, R is a benzyl substituent  and R' is a phenyl group . The structure is:

.

(g) This compound is a substituted carboxylic acid. The acid contains five carbons (pentanoic acid) and is substituted on the third carbon from the carboxyl group. The substituent on the carboxylic acid is a phenol with substitution occurring ortho to the hydroxyl group. The structure is therefore:

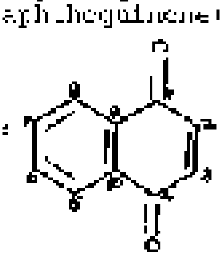


(h) 1,4 naphthoquinone is a dicarbonyl aromatic compound. It is derived from the oxidation of α naphthol:

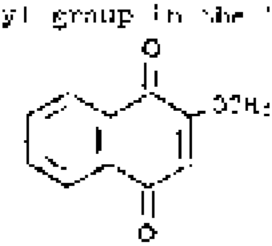


1,4 naphthoquinone (α-naphthoquinone)

α-naphthol

The numbering scheme for 1,4 naphthoquinone is: 

Here the substituent is the methoxyl group in the "2" position. The structure is therefore:

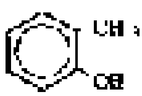


PHYSICAL PROPERTIES

• PROBLEM 23-3

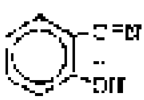
In which of the following compounds would you expect intramolecular hydrogen bonding to occur: o-nitroaniline, o-cresol, o-hydroxybenzoic acid (salicylic acid), o-hydroxybenzaldehyde (salicylaldehyde), o-fluorophenol, o-hydroxybenzonitrile.

__Solution:__ A hydrogen bond is an attraction between a hydrogen atom covalently bonded to an electronegative element and a second electronegative element. These electronegative elements are usually nitrogen, oxygen and fluorine. If both electronegative elements and the proton are in the same molecule, it is called intramolecular hydrogen bonding. O-cresol cannot have intramolecular hydrogen bonding because it has only one electronegative element. (Carbon is not electronegative enough for hydrogen bonding.)

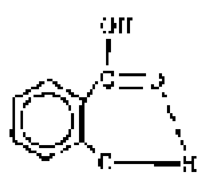


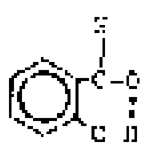
o-cresol

O-hydroxybenzonitrile cannot have hydrogen bonding either but for a different reason; the linear geometry of the nitrile group prevents significant interaction between the nitrogen and the hydroxyl proton.

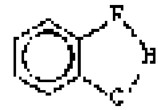


o-hydroxybenzonitrile

In both salicylic acid 

and salicaldehyde:  the proton involved

in hydrogen bonding is between two oxygen atoms. In o-nitroaniline:  It is between nitrogen and oxygen.

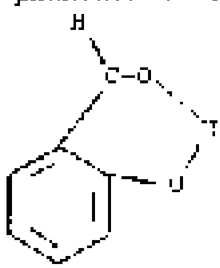
In o-fluorophenol  the proton is

between fluorine and oxygen.

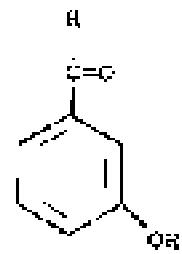
• **PROBLEM** 23-4

How much difference in physical properties would you expect for o- and p-cyanophenol isomers? Explain.

Solution: Hydrogen bonding can account for differences between the physical properties of ortho, meta, and para isomers of substituted phenols. For instance, o-salicylaldehyde has a significantly lower boiling point than m-salicylaldehyde. This can be accounted for by the intramolecular hydrogen bonding found in o-salicylaldehyde, not possible in the meta isomer.



o-salicylaldehyde
intramolecular H- bonding



m-salicylaldehyde
intermolecular H bonding only

The intramolecular hydrogen bonding in the ortho isomer causes greater intramolecular attraction with a corresponding decrease in intermolecular attraction, accounting for its lower boiling points (increased volatility) than its meta and para isomers. This provides an efficient way to separate the o-isomer from the m and p isomers-steam distillation. In comparing the ortho and para cyanophenols, one might first suppose that intramolecular H-bonding in o-cyanophenol will cause it to have a lower boiling point than its p-isomer. This is shown not to be true if one examines the geometry of o-cyanophenol. The carbon and nitrogen of the cyano group are both sp-hybridized and therefore must lie in the same plane. This will prevent proper overlap between the hydroxyl hydrogen and the cyano nitrogen.

linear

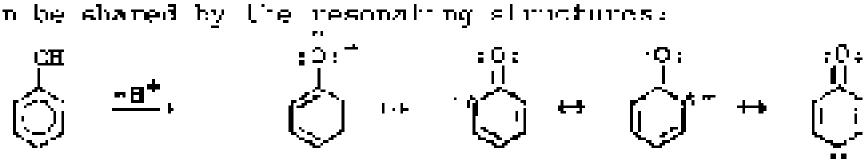
Thus, intermolecular hydrogen bonding is the only type of hydrogen bonding possible in both o and p-cyanophenol. Therefore, the two compounds will have very similar physical properties.

• PROBLEM 23-5

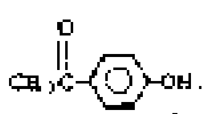
> (a) Why is phenol C_6H_5OH a stronger acid than an alcohol? (b) Would para-acetylphenol be a stronger or weaker acid than phenol? (c) Would 2,4-dinitrophenol be a stronger or weaker acid than p-nitrophenol? Draw contributing structures to support the answers.

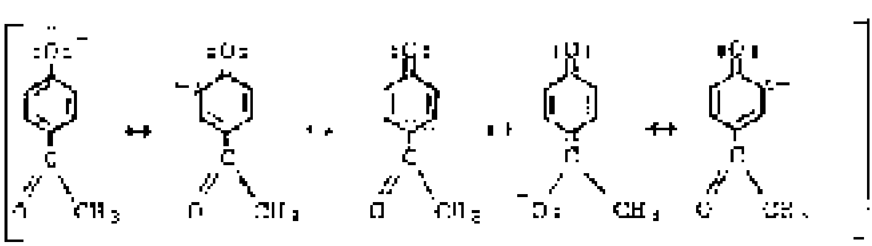
<u>Solution</u>: Acidity, the tendency of a compound to release a proton, depends on the compound's surrounding environment and its stability after deprotonation. If it is in a non-polar environment, therefore, not having a compound ready to accept the proton, it tends to be less acidic. If it is in a basic environment, surrounded by proton-acceptors, it tends to release the proton more readily.

(a) Phenol is more acidic than simple alcohols because the negative charge created by deprotonation can be distributed in phenol by resonance. This lowers the energy level of the deprotonated compound, thus, stabilizes it. For an alcohol, deprotonation leads to RO^-. For phenol, the negative charge can be shared by the resonating structures:



Therefore, phenol can release its proton more readily, and is thus a stronger acid than an alcohol.

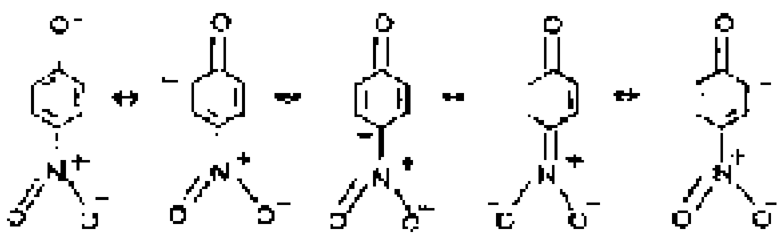
(b) Para-acetylphenol,  is more acidic than phenol. The acetyl group, $CH_3\overset{O}{\overset{\|}{C}}-$, can delocalize the negative charge. It adds an extra contributing structure, thus further stabilizes the deprotonated compound. The contributing structures are:



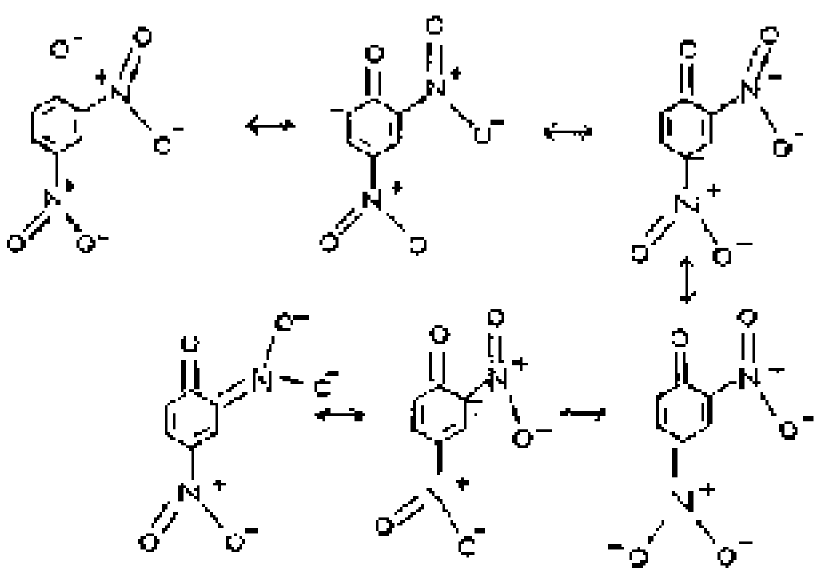
(c) 2,4-dinitrophenol and p-nitrophenol have the following structures, respectively.

As can be seen from the previous answers, conjugated double bonds are essential for charge delocalization, which is the essence of extra stabilization. From the structures shown, one can see that 2,4-dinitrophenol has one more conjugated double bond than p-nitrophenol. This implies that 2,4-dinitrophenol has more contributing structures than p-nitrophenol, therefore it is more acidic. The contributing structures for both deprotonated compounds are shown.

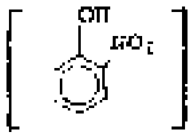
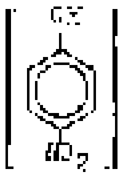
(1) p-nitrophenol (five major contributing structures)



(2) 2,4 dinitrophenol (six major contributing structures)

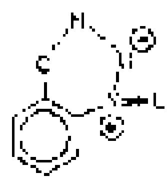


• PROBLEM 23-6

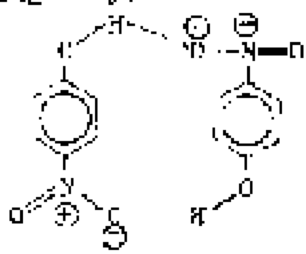
Ortho nitrophenol  and para-nitrophenol  have different acidities, melting points, and boiling points. In all cases, the ortho nitrophenol has lower values in these areas. Why?

Solution:

In solution, ortho-nitrophenol is capable of <u>intramolecular</u> hydrogen bonding, while the para isomer <u>intermolecular</u> hydrogen bonding only.



ortho-nitrophenol



para-nitrophenol (2 molecules)

Since intramolecular hydrogen bonding is possible, it is favored entropically over intermolecular hydrogen bonding for the ortho isomer. Because the proton is held by two oxygens in the ortho isomer, it is harder to deprotonate the ortho isomer than the para isomer. Consequently, the ortho isomer has a lower acidity.

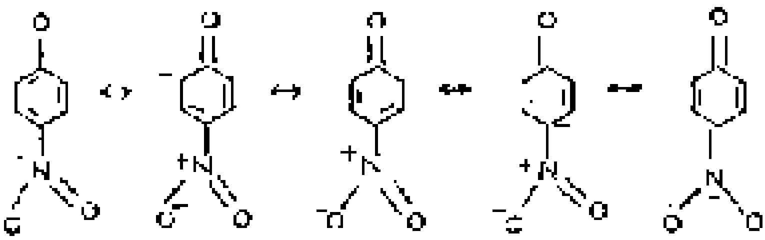
Since there is much intermolecular hydrogen bonding in the para isomer, there is greater attraction between molecules in the para isomer as opposed to the ortho. Therefore more energy is required to break these attractive forces in the boiling process. This results in the ortho isomer having a lower boiling point.

The lower melting point of the ortho isomer is due to its lack of symmetry as compared to the para isomer. Since the latter is more symmetric, it can fit better in the crystal lattice. This necessitates that more energy be required to break the para crystal lattice than the less ordered ortho crystal lattice. Thus, the ortho isomer has a lower melting point.

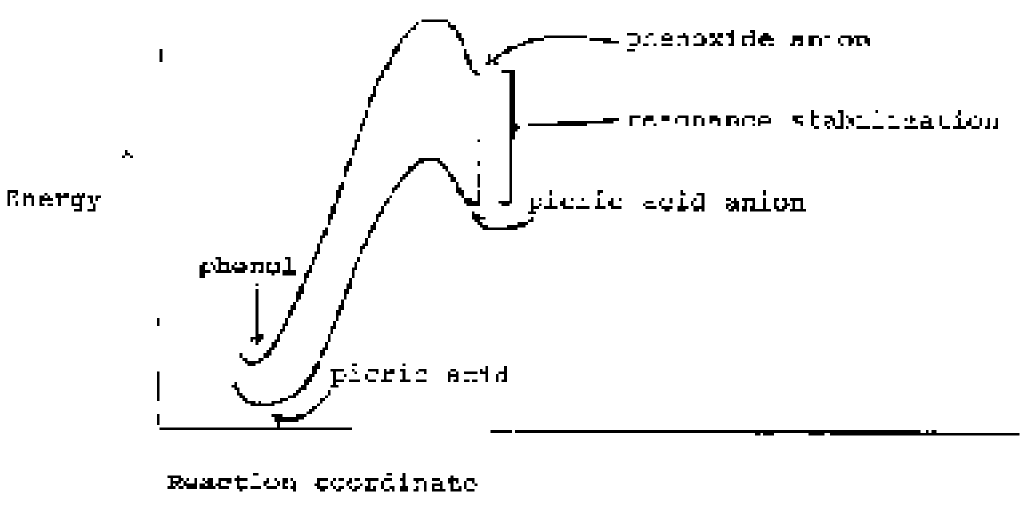
• PROBLEM 23-7

How do you account for the fact that, unlike most phenols, 2,4-dinitrophenol and 2,4,6-trinitrophenol are soluble in aqueous sodium bicarbonate?

Solution: Substituted phenols acidities are directly dependent upon the substituents on the benzene ring. This is because the negative charge on the oxygen of the phenoxide anion can be delocalised into the ring and the substituents will determine how important this delocalization will be. The nitro group, because of the electronegativity of sp^2-hybridized nitrogen and resonance effects, will stabilize negative charge in the benzene ring. The stabilization will be greatest when the nitro groups are ortho and/or para to the hydroxyl group, because this is when the resonance effect is maximal in these cases. For instance, in the case of p-nitrophenol, the following resonance structures are possible for its anion:

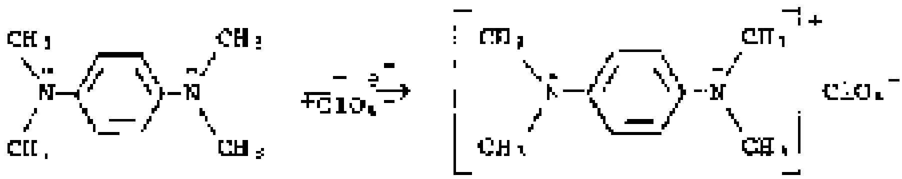


It is important to see that the negative charge can only be delocalized onto the ortho and para positions. Thus while a nitro stabilizes the negative charge only by induction (due to nitrogen's electronegativity), a nitro group in the ortho or para will stabilize the negative charge both by induction and resonance. The unsubstituted phenol is a weaker acid than 2,4 dinitrophenol because the latter's corresponding anion has greater resonance stabilization than phenol. $NaHCO_3$ is a weak base and useful in separating phenols from the stronger carboxylic acids. Only the carboxylic acids will ionize and dissolve in the aqueous phase. However both 2,4 dinitrophenol and 2,4,6-trinitrophenol (picric acid) are comparable to the carboxylic acids and will dissolve in aqueous $NaHCO_3$. The latter has nitro groups on all its ortho and para positions and its anion is particularly resonance stabilized.



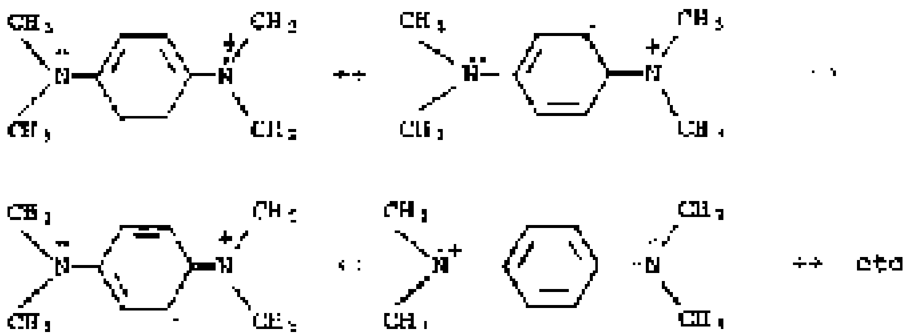
Write resonance structures that account for the stability of the cation of Wurster's salts. Explain why octamethyl-p-phenylenediamine does not form a similarly stable cation radical.

Solution: N,N,N',N'-tetramethyl-p-phenylenediamine undergoes a mild oxidation to produce a Wurster salt which contains a stable cation radical.

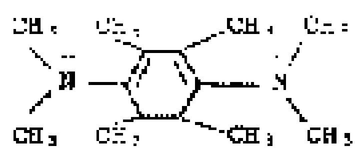


Wurster salt

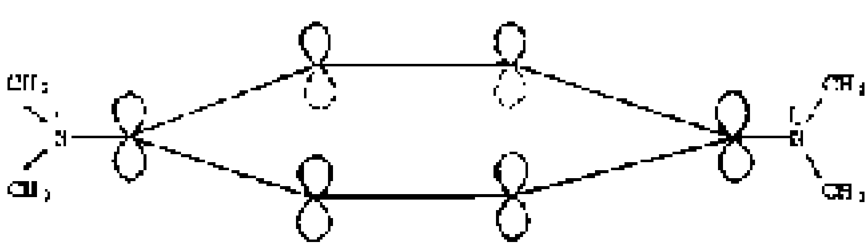
This cation is stabilized, similar to the way aniline is, by delocalization of the odd electron on nitrogen. Several resonance structures may be written as a result of this delocalization:



Octamethyl-p-phenylenediamine:



does not form a resonance stabilized cation as does the previously mentioned Wurster salt cation and one must examine the geometry of the molecule to see why this is so. The Wurster salt cation has the following molecular geometry:



The nitrogen bearing the free electron is sp^2 hybridized and has a p orbital which accounts for the various resonance structures in which the free electron and the rings π system interact.

The methyl groups on the ring in octamethyl-p-phenylene interfere with this interaction by affecting the molecular geometry. Thus there is no resonance stabilization as in the Wurster salt cation and it is not as stable.

PREPARATION

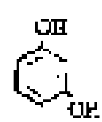
• PROBLEM 23-9

4-n-Hexylresorcinol is used in certain antiseptics. Outline its preparation starting with resorcinol and any aliphatic reagents.

4-n-Hexylresorcinol

Solution: 4-n-Hexylresorcinol has the structure:

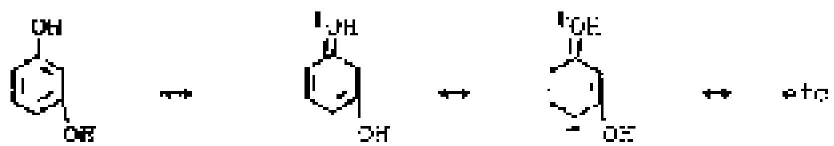
To synthesize this compound from the polyhydric alcohol resorcinol



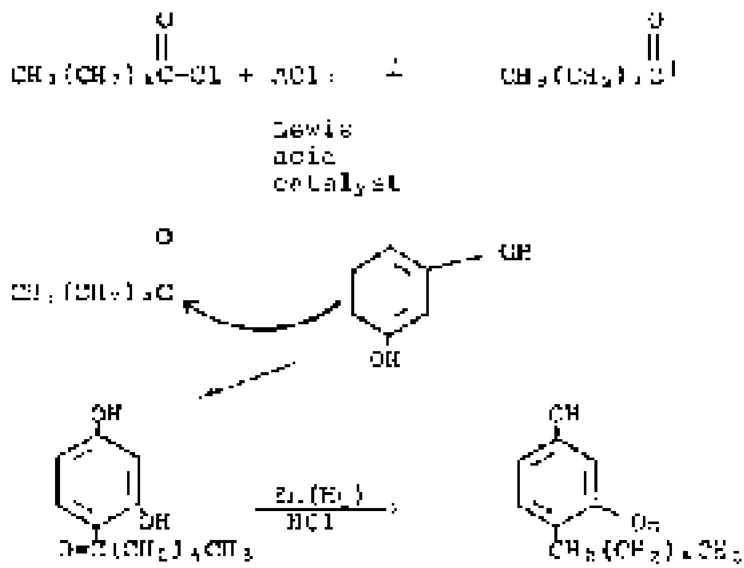
, one would have to add a straight six-carbon chain to the aromatic ring by an electrophilic addition. This is best done through a Friedel-Crafts acylation reaction in which a resonance stabilized acylium cation, here the hexanoyl cation

$$\left[CH_3(CH_2)_4\overset{+}{C}{=}\ddot{O}: \longleftrightarrow CH_3(CH_2)_4C{\equiv}\overset{+}{\ddot{O}} \right]$$

acts as an electrophile upon the electron system of an aromatic ring. Following this addition, the carbonyl group is reduced specifically by the Clemmensen reduction which involves treating the carbonyl compound with zinc amalgam in the presence of acid. It should be noted that Friedel-Crafts alkylation would be inadequate for this procedure because an alkyl cation (desired from an alkyl halide, etc.) will undergo rearrangement unlike the acylium ion and also in Friedel-Crafts alkylation, there is the significant danger of polysubstitution upon the aromatic ring. This is particularly relevant in this case since resorcinol, even to a greater extent than phenol itself, is activated toward electrophilic attack. This can be seen in resorcinol's resonance structures if oxygen donates a pair of electrons to the benzene ring to give a negative charge within the ring:



The carbonyl group acts as a deactivating group when substituted directly on a ring and therefore polyacylation is rare. The synthesis of 4-n-Hexylresorcinol proceeds as follows:

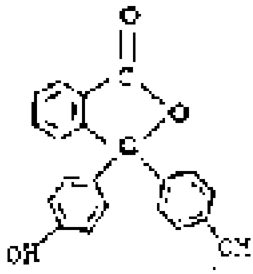


It should be noted that the hydroxyl group is an ortho-para director. Also, there is very little substitution between the hydroxyl groups of resorcinol for steric reasons.

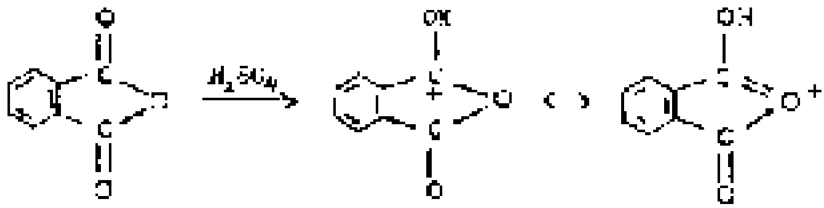
• PROBLEM 23-10

Suggest a mechanism for the steps in the synthesis of phenolphthalein.

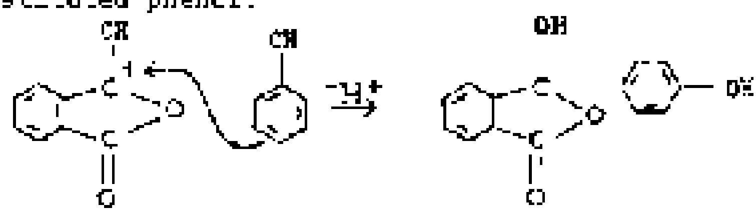
Solution: Phenolphthalein, a pH indicator, has the structure:



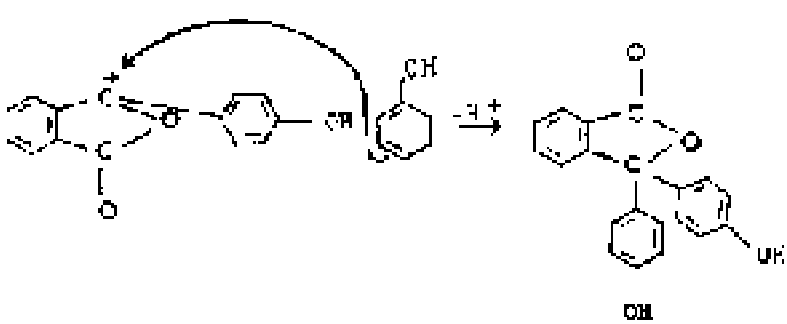
It is synthesized by reacting one mole of phthalic anhydride with two moles of phenol in the presence of a strong acid (i.e. H_2SO_4). The mechanism involves the sequential formation of two resonance stabilized cations. The first is formed by the protonation of one of phthalic anhydride's carbonyl groups. The subsequent cation is resonance stabilized by the adjacent oxygen atom:



This cation is an electrophile which may attack the electron rich aromatic ring of phenol to give a para substituted phenol.



This substituted phenol still has a hydroxyl group which may be protonated to give a resonance stabilized cation. Protonation occurs at this hydroxyl because of the dibenzylic cation produced. This may act as an electrophile upon phenol's aromatic system to give phenolphthalein containing two parasubstituted phenols.

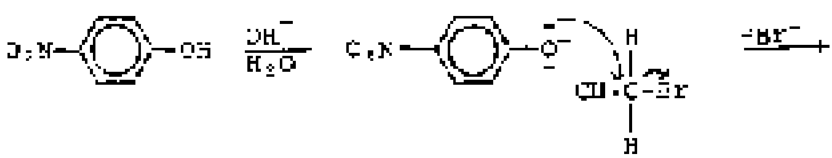


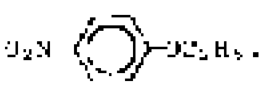
• PROBLEM 23-11

Give structures of all compounds below:

(a) p-nitrophenol + C_2H_5Br + NaOH(aq) → A($C_8H_9O_3N$)
A + Sn + HCl → B($C_8H_{11}ON$)
B + $NaNO_2$ + HCl, then phenol → C($C_{14}H_{14}O_2N_2$)
C + ethyl sulfate + NaOH (aq) → D($C_{16}H_{18}O_2N_2$)
D + $SnCl_2$ → E($C_8H_{11}ON$)
E + acetyl chloride → phenacetin ($C_{10}H_{13}O_2N$), an analgesic ("pain-killer") and antypyretic ("fever killer")
(b) 2-(o-hydroxyphenyl)ethyl alcohol + HBr → F(C_8H_9OBr)
F + KOH → coumarane (C_8H_8O), insoluble in NaOH.

Solution: Treating a phenol with base in the presence of an alkyl halide is representative of the Williamson synthesis. The reaction produces phenolic ethers by an S_N2 (substitution nucleophilic bimolecular) with the phenoxide anion acting as a nucleophile and the halide as the leaving group. In this case, the displacement results in the formation of p-nitrophenylethylether.

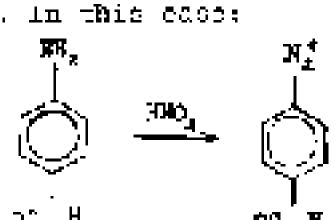




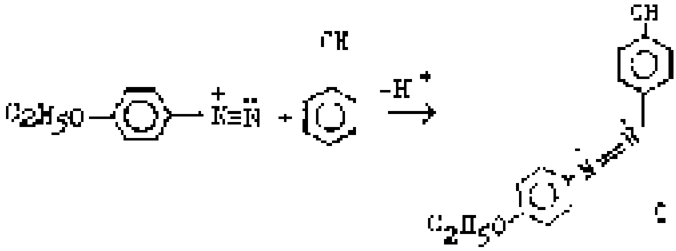
A

In a useful reaction, aromatic nitro compounds are reduced to their corresponding aniline derivatives. The reduction involves treating the nitro compound with a metal catalyst. Usually base is needed to isolate the final product.

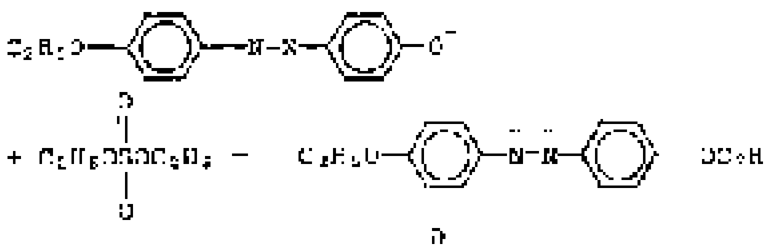
When sodium nitrite ($NaNO_2$) is treated with acid, nitrous acid (HNO_2) is produced. This is the reagent in the mixture that converts the aniline derivative to its diazonium salt. In this case:



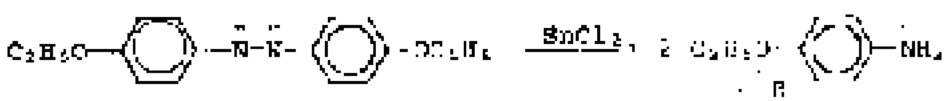
This diazonium cation is a very weak electrophile that may react with aromatic rings but with only very highly activated ones, such as phenol. The final product is an azo compound.



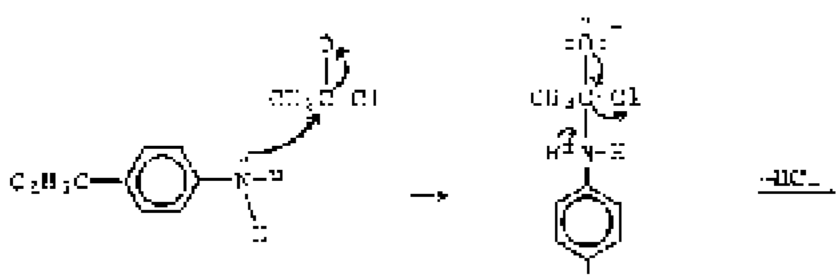
This azo compound contains a phenolic hydroxyl group and therefore it may undergo a Williamson synthesis. Ethyl sulfate is an alkylating reagent which reacts with the phenoxide ion to produce an ethyl ether.

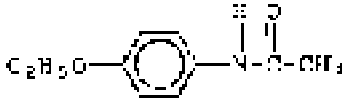


The final product retains its azo linkage which can be cleaved into two aniline derivatives, which in this case are equivalent.



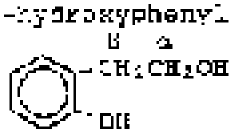
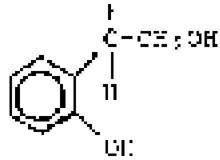
This compound, like any amine, can undergo an acylation reaction in which the pair of electrons on nitrogen attacks the partially positively charged carbonyl carbon of an acylating agent (i.e. acetyl chloride) to give an amide.



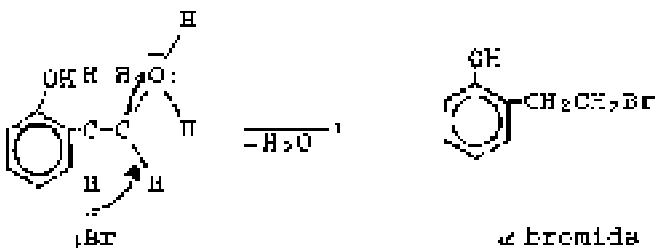


phenacetin

(c) β-(o-hydroxyphenyl)ethyl alcohol has the structural

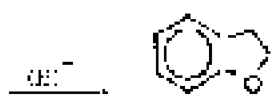
formula:  with the β carbon of ethanol being the one that does not bear the hydroxyl group. The question arises whether the bromine would be on the α or β carbon upon treatment with HBr. Any mechanism that involves a cation would rearrange to give the stable benzylic cation,  and therefore give the β bromide.

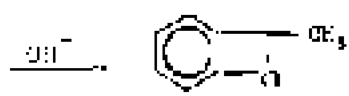
On the other hand, a concerted mechanism (S_N2 displacement) would have the α bromide formed by the following mechanism:



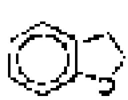
α bromide

Whichever compound is formed will react with base to form another compound with the loss of HBr. This is typical of a Williamson synthesis but since the alcohol and the halide are in the same molecule, this is an intramolecular reaction. Looking at the possible products if the α and β bromide undergo an intramolecular Williamson synthesis we see that the ethereal ring contains five and four carbons respectively.

α bromide 

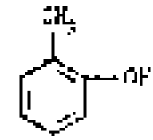
β bromide 

The ether containing the five-membered ring is more stable entropically and therefore it is the α-bromide that underwent the Williamson reaction. The fact that the α-bromide used its phenol group in the reaction is verified by the product's insolubility in base. Had this not been true, the hydroxyl group would lose its proton to form the anion and therefore dissolve. The product, coumarane, is therefore:



• **PROBLEM** 23-12

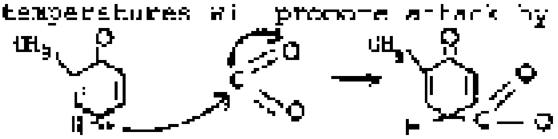
Write the principal reaction product or products, if any, of o-cresol with CO_2, K_2CO_3, 240°.

Solution: The phenol o-cresol,  in the presence of the base, K_2CO_3, ionizes to the phenoxide anion. This anion can be written as several resonance forms as a result of oxygen contributing a pair of electrons to the aromatic ring:

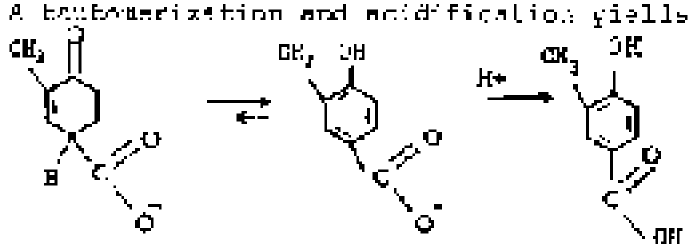
Note that the negative charge on the ring appears only ortho and para to the hydroxyl group. In the presence of CO_2, the phenoxide anion will attack the positively charged carbon

$$\left[\overset{\delta-}{O} = \overset{\delta+}{C} = \overset{\delta-}{O}\right]$$

to give a salicylic acid after acidification (Kolbe reaction). While it is the ortho carbon of the phenol that attacks CO_2 at moderate temperatures, higher temperatures will promote attack by the para carbon.



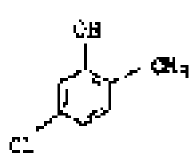
A tautomerization and acidification yields the final product.



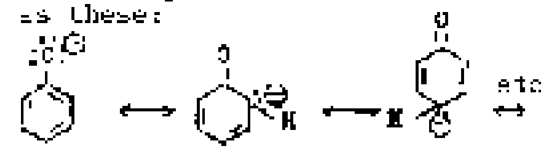
4-hydroxy-3-methylbenzoic acid

■ **PROBLEM 25-13**

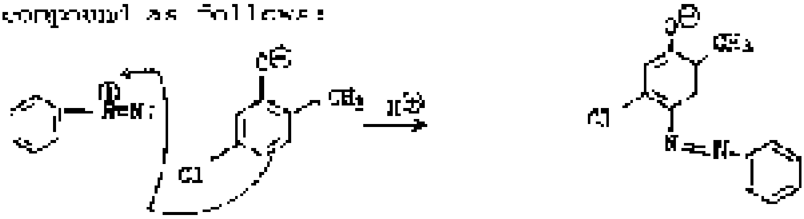
What is the principal organic product of the following sequences:

 $\xrightarrow[OH^-]{C_6H_5N_2^{\ominus}}$, $\xrightarrow[HCl]{SnCl_2}$, $\xrightarrow{FeCl_3}$

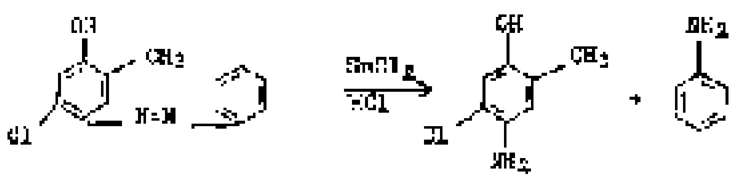
Solution: $C_6H_5N_2^{\oplus}$, the benzene diazonium cation is a weak electrophile that may undergo a reaction with highly activated aromatic rings (aniline, phenol, phenoxide anion). In this case, the phenoxide anion is the substrate for the electrophilic attack. Its reactivity can be traced to resonance structures such as these:

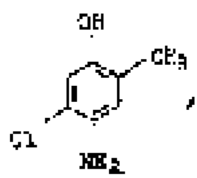


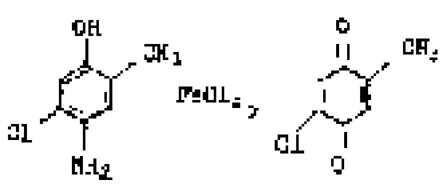
in which a negative charge is distributed throughout the aromatic ring. The product of such an electrophilic attack is an azo compound. In this case, the benzene diazonium cation reacts with 5-chloro-2-methylphenoxide to form an azo compound as follows:



Note that the electrophile is directed para to the hydroxyl group, the most powerful activating group on the ring. The product, like any azo compound, can be cleaved to two aniline derivatives by a mixture of stannous chloride and acid. In this case, they are aniline and 4-amino-5-chloro-2-methylphenol.



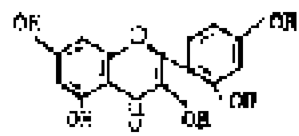
The compound,  , contains two oxidizable functional groups: the amine and the hydroxyl group. Oxidation of this compound yields a parabenzoquinone derivative. One such oxidizing agent is ferric chloride.



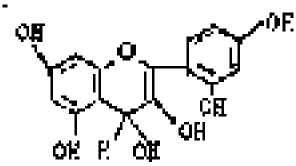
2-chloro-5-methyl-
parabenzoquinone

Reduction of the carbonyl group of quercitin gives a substance that loses water readily to give a brilliant-violet compound, which, when treated with hydrochloric acid, is converted reversibly to a red salt. Consider possible ways that the reduction product might dehydrate to give a violet substance and show how addition of a proton to this substance could occur in such a way as to give a substantial color change.

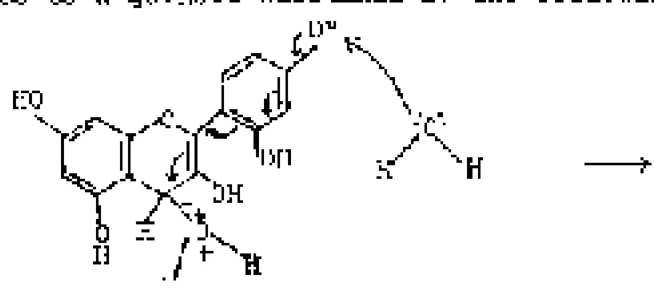
Solution: Quercitin



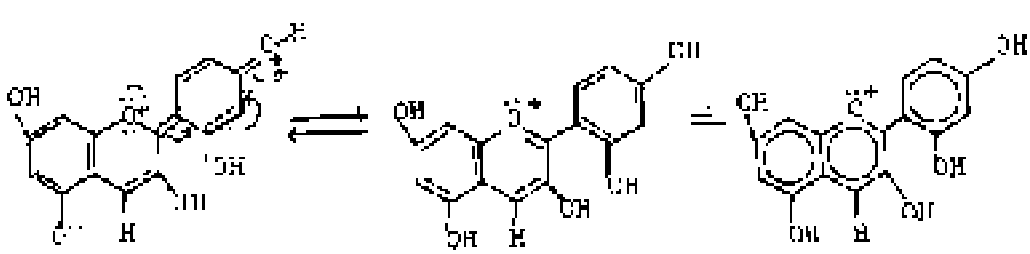
has only one carbonyl group which may be reduced to the corresponding alcohol:



In the presence of dilute acid, this alcohol de-hydrates to a quinoid substance by the following mechanism:



In the presence of HCl, this substance undergoes a reduction reaction:



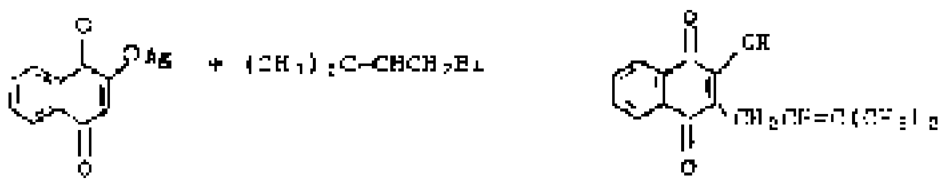
Violet red

The difference in color can be best explained by seeing the greater amount of conjugation in the product of dehydration compared with the starting material. The product has all three rings in conjugation which is not the case in the reactant. These two compounds differ in the wavelengths (distance between two peaks) of radiation that they absorb. The quinoid reactant absorbs in the violet region of the electromagnetic spectrum while the salt absorbs in the red region. The higher wavelength for the red product corresponds to the increased conjugation in this compound. Increasing conjugation also increases the wavelength of absorption. This is useful in ultraviolet spectroscopy (absorption in ultraviolet region as a result of electron excitation).

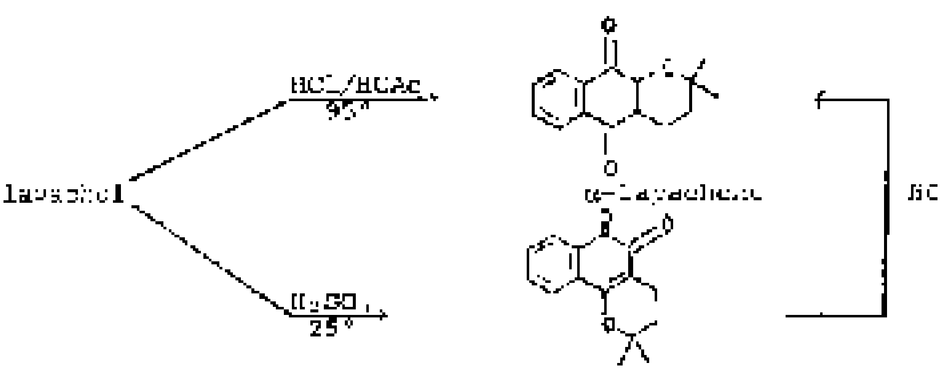
QUINONES AND QUINOLINES

• PROBLEM 23-16

Lapachol occurs in the grain of some woods, including the South American lapacho. This yellow material can be prepared, in vitro, by the sequence shown below. Suggest a mechanism for this synthesis and for the interconversions of lapachol and α- and β-lapachone. Which of the latter two is more stable? How would you rationalize this?



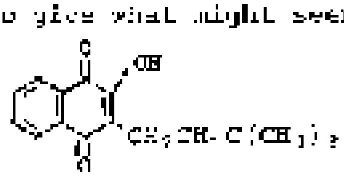
Lapachol



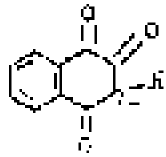
β-Lapachone

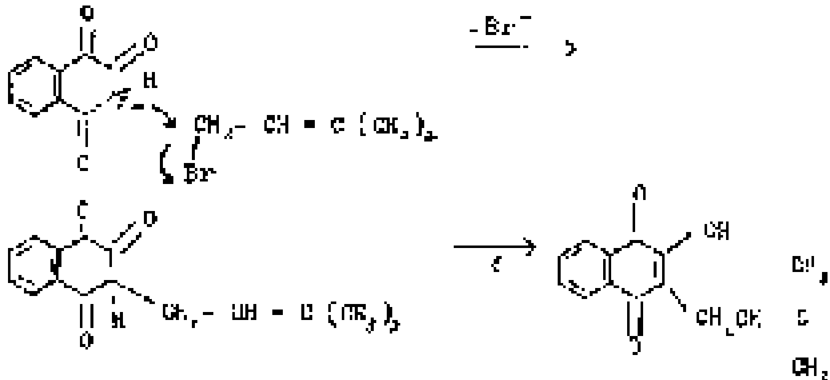
Solution: Quinones are carbonyl compounds that are derived from oxidation of phenols. The structure,

, is a salt of a quinoid derivative which reacts with a derivative of allyl bromide [$(CH_3)_2C{=}CHCH_2Br$] to give what might seem to be an unlikely product, lapachol:

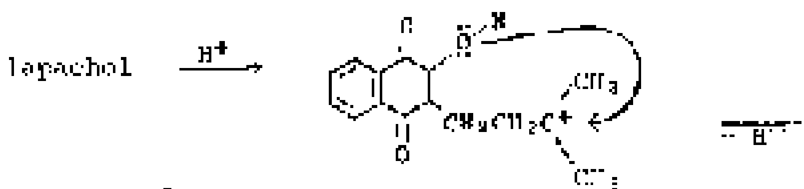


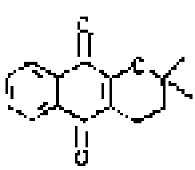
. The reaction actually involves

the carbanion  which acts as a nucleo-phile in an S_N2 displacement in which the bromide acts as leaving group and the C alkylated product is formed after tautomerization. The anionic intermediate is stabilized by its delocalization of the negative charge.



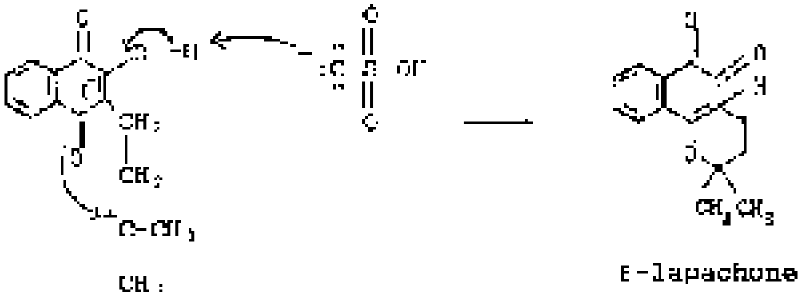
At 95° C in HCl/HOAc, lapachol is converted to α-lapachone by a mechanism that is typical of an addition of an alcohol to an alkene.





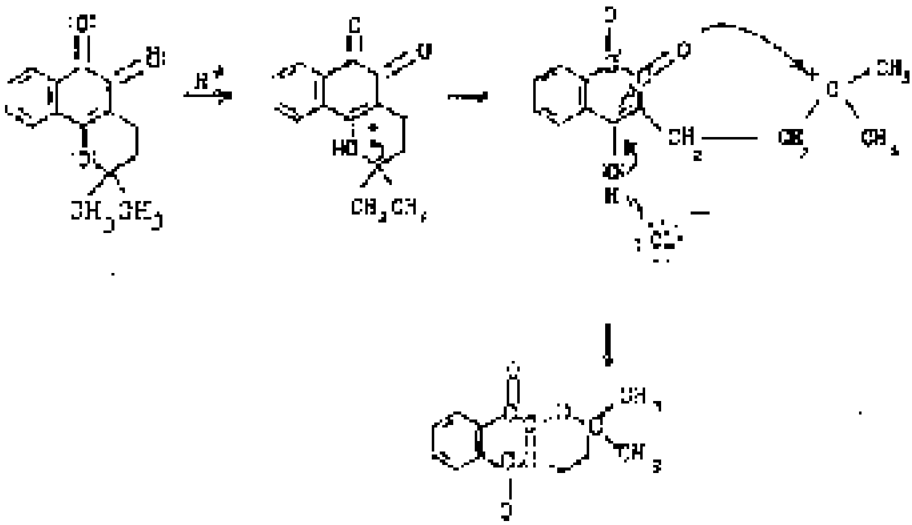
α-lapachone

β-lapachone is formed at 25°C in H_2SO_4 from the same cation.



β-lapachone

β-lapachone is converted to α-lapachone through treatment of HCl by the following mechanism. The lesser stability of β lapachone could be traced to the mutual repulsion of the adjacent carbonyl groups.

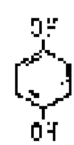


α-lapachone

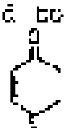
● PROBLEM 23-15

(a) Hydroquinone is used in photographic developers to aid in the conversion of silver ion into free silver. What property of hydroquinone is being taken advantage of here?
(b) p-Benzoquinone can be used to convert iodide ion into iodine. What property of the quinone is being taken advantage of here?

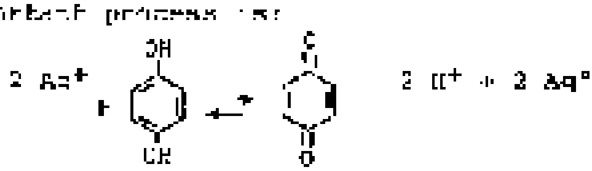
Solution: (a) Parabenzoquinone and hydroquinone are in a rapid and reversible equilibrium as are all quinones and phenols. Hydroquinone,



, has the ability to convert silver ion to metallic silver by reducing it, i.e., by donating electrons to the cation. While Ag^+ is reduced to $Ag°$, the phenol is oxidized to the quinone

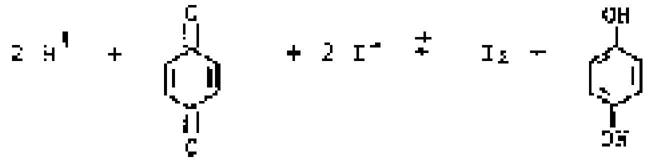


. The net reaction for this commercially important process is:



Thus, it is the ability of hydroquinone to be oxidized that we are using here.

(b) As mentioned, the phenol-quinone equilibrium is reversible and parabenzoquinone may be easily reduced by a suitable electron source such as the iodide ion (I^-). The products of this process where we use p-benzoquinone's ability to be reduced are hydroquinone and iodine.

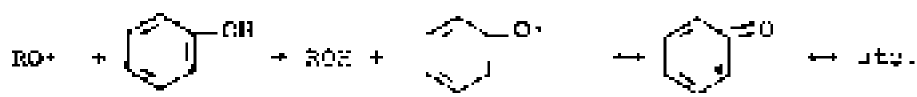


• PROBLEM 23-17

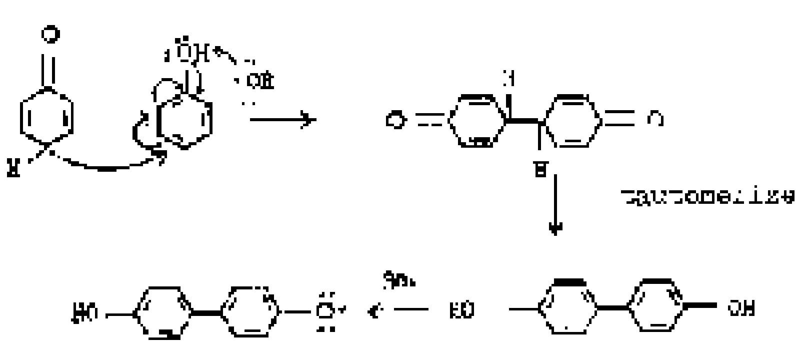
Phenol samples that have been allowed to stand in air always possess a pink or red color because of oxidation. Write a mechanism for the oxidation of phenol by oxygen that could lead to one or more products that might be expected to be colored.

Solution: Colored impurities are characteristic when dealing with phenols. They are oxidation products, usually conjugated quinoid compounds. One possible mechanism involves free radicals and may be catalyzed either by oxygen or peroxide. One possible mechanism is as follows:

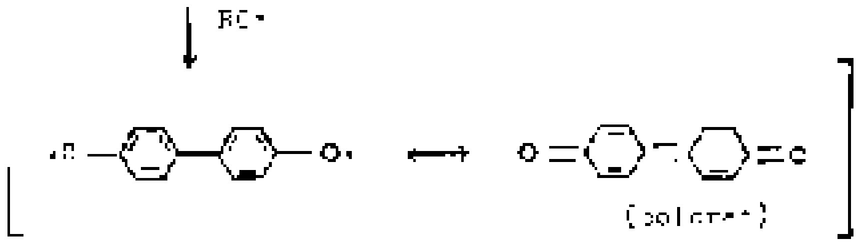
$ROOR \rightarrow 2\ RO\cdot$.



Note that the phenoxide radical has several resonance structures including those which contain the free radical inside the benzene ring. This radical may attack phenol to form a dimer which quickly tautomerizes to give 4,4'-dihydroxybiphenyl, which in turn will repeat the previous sequence to form a more complex quinoid structure or it may react with the peroxide catalyst to form a two ringed quinone. Summarizing:

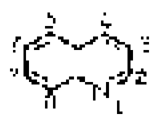


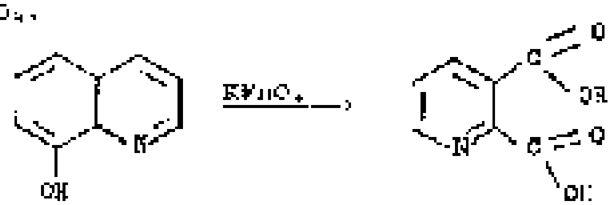
complex quinone (colored) 4,4' dihydroxybiphenyl



• PROBLEM 23-18

Many foot powders contain 8-hydroxyquinoline, a mild bactericide and fungicide. What is its structure? When oxidized with alkaline potassium permanganate, it is converted to quinolinic acid, $C_7H_5NO_4$. Suggest a structure for quinolinic acid.

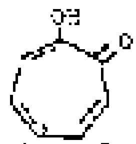
Solution: Many alkaloid derivatives of quinoline are found in the plant kingdom. The numbering system for this weak base is . Therefore, 8-hydroxyquinoline has the structure, . If we examine this polynuclear compound closely, we see that it consists of a phenolic aromatic ring fused onto a pyridine ring. The phenolic ring is activated due to the potential delocalization of oxygen's free pair of electrons with the ring. On the other hand, the heterocyclic nitrogen ring is deactivated because the sp^2 hybridized nitrogen will pull the π electrons toward it, making it less reactive to electrophilic attack. In other words, the nitrogen will theoretically contribute one π electron to the six electron π system of the pyridine ring but nitrogen has a significantly greater electronegativity than carbon and therefore there will be disproportionate sharing of electrons in the π system. In such polynuclear compounds, the more highly activated aromatic ring will be attacked by an electrophile. Oxidation is similar with only the more highly activated aromatic ring being cleaved by the oxidant. Thus, the activated phenolic ring will be cleaved by $KMnO_4$ to a nitrogen derivative of phthallic acid with the formula $C_7H_5NO_4$.



TROPOLONES

• PROBLEM 23-19

Tropolone (I, $C_7H_6O_2$) has a flat molecule with all carbon-carbon bonds of the



I, Tropolone

same length (1.40 Å). The measured heat of combustion is 20 kcal lower than that calculated by the method of summing bond energies. Its dipole moment is 3.71 D; that of 5-bromotropolone is 2.07 D.

Tropolone undergoes the Reimer-Tiemann reaction, couples with diazonium ions, and is nitrated by dilute nitric acid. It gives a green color with ferric chloride, and does not react with 2,4-dinitrophenylhydrazine. Tropolone is both acidic ($K_a = 10^{-7}$) and weakly basic, forming a hydrochloride in ether.

(a) What class of compounds does tropolone resemble? Is it adequately represented by formula I? (b) Using both valence-bond and orbital structures, account for the properties of tropolone.

(c) In what direction is the dipole moment of tropolone? Is this consistent with the structure you have proposed?

(d) The infrared spectrum of tropolone shows a broad band at about 3150 cm⁻¹ that changes only slightly upon dilution. What does this tell you about the structure of tropolone?

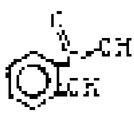
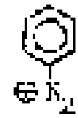
Solution: Tropolone is a seven carbon ring compound with several distinct properties whose analysis will allow us to give a more detailed structural formula than the one given

as:  The planar geometry of this compound,

together with equally long carbon-carbon bonds suggest that tropolone is aromatic.

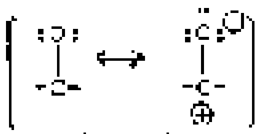
(a) The unusual stability of a compound of such structure verifies its aromaticity (thermodynamic stability is usually associated with aromaticity) and suggests that this structure may not accurately describe tropolone.

The Reimer-Tiemann reaction is particular to phenols and involves treating these compounds in alkaline chloroform and forming a salicylaldehyde derivative after pro-

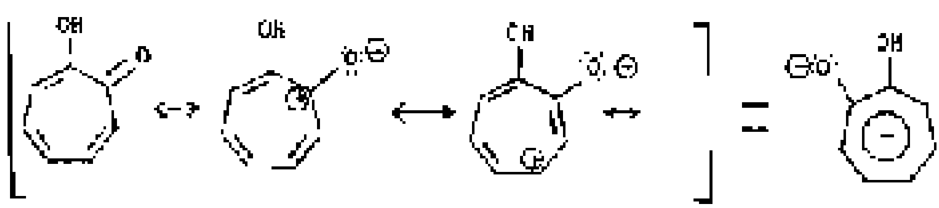
tonation.  Diazonium cations  react

only with highly activated aromatic compounds (phenols, phenoxide anion, anilines) in an electrophilic aromatic addition reaction. Nitration is also an electrophilic aromatic substitution that involves the attack of the nitronium ion upon an aromatic system. The nitronium ion is generated usually by a mixture of nitric and sulfuric acid with the latter acting as a protonating catalyst. Only a very activated aromatic compound could react in the absence of this catalyst. Dilution also reduces the effectiveness of nitration. All this information plus the fact that this compound gives a positive ferric chloride ($FeCl_3$) test (phenols react with $FeCl_3$ to give a colored complex) tells us tropolone is a phenol. Thus, we now know tropolone is aromatic and, in particular, is a phenol. In addition, we know that tropolone cannot contain a carbonyl group since it does not undergo the 2,4 dinitrophenylhydrazine addition reaction typical of ketones and aldehydes.

(b) We can account for tropolone's aromaticity, if we consider the polar nature of the carbonyl group resulting from the great disparity between the electronegativities

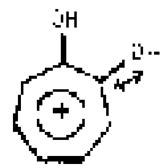
of carbon and oxygen.  Using this

and the previous data, we may hypothesize a resonance hybrid which includes seven dipolar structures which seem to delocalize the positive charge within the ring. This theoretical delocalization does not determine aromaticity however. Huckel's Rule states that a cyclic system which contains a delocalized π electron system above and below the molecule's plane and which contains a total of 4n+2 π electrons in the electron system is aromatic. Tropolone fits this qualification and can be represented as:

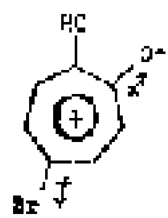


This aromatic compound has 6 π electrons and is analogous to a cycloheptatrienyl cation. We note the dipolar nature of this compound and this would account for the high dipole moment. If the negatively charged oxygen gains a proton, the aromaticity would not be interrupted and in fact the subsequent tropylium ion is an actual cation and the resonance structures do not contain any charge separation, constituting a more stable molecule. Tropolone is weakly basic forming a compound which also has aromatic resonance structures.

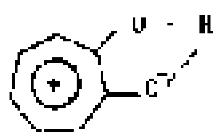
(c) Consistent with the dipole structure proposed for tropolone, this structure is directionally charged in the direction of the carbonyl oxygen.



In 5-bromotropolone, the dipole moment is significantly less than tropolone and this indicates that the C-Br bond moment is roughly in the opposite direction of the carbonyl polarization.



(d) The typical infrared frequency range for an O-H stretch is 2800 - 3500 cm^{-1}. It is a broad peak which is usually dependent on concentration because of intermolecular hydrogen bonding. Since the frequency of tropolone's O-H stretch is unaffected by dilution, there must be no intermolecular interactions of this type. Only intramolecular hydrogen bonding would account for this lack of a dilution effect.

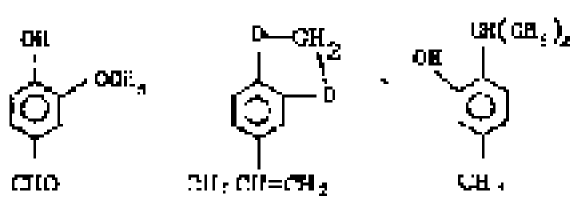


Intramolecular hydrogen bonding in tropolone.

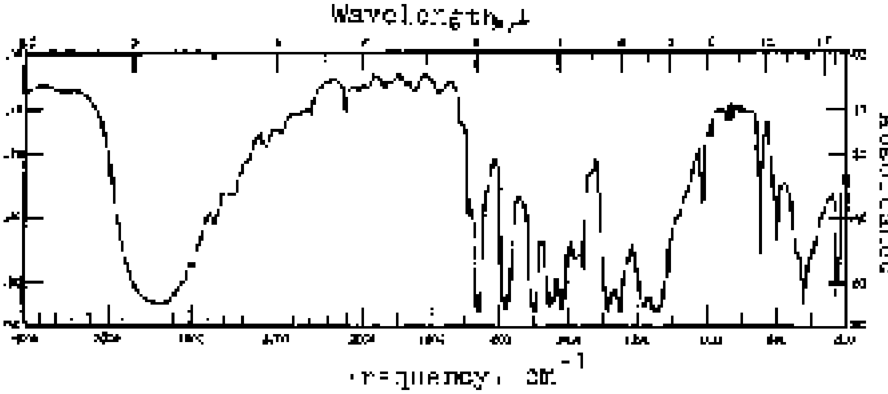
SPECTROSCOPY

• PROBLEM 33-30

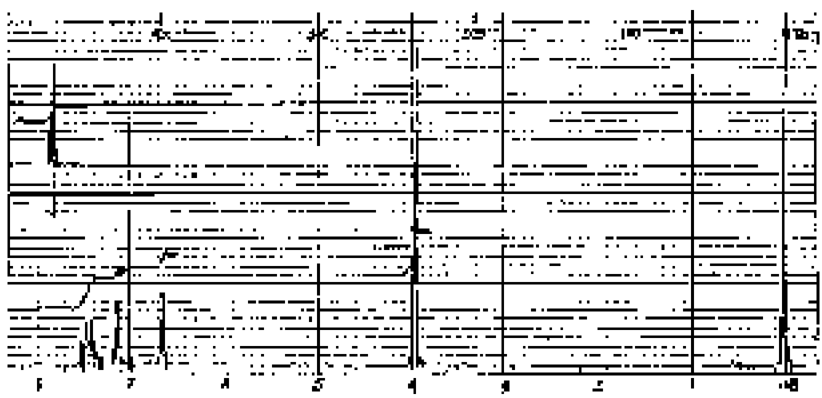
Assign one of the listed structures to each set of i.r. and/or n.m.r. spectra and identify major spectral features, noting their source.



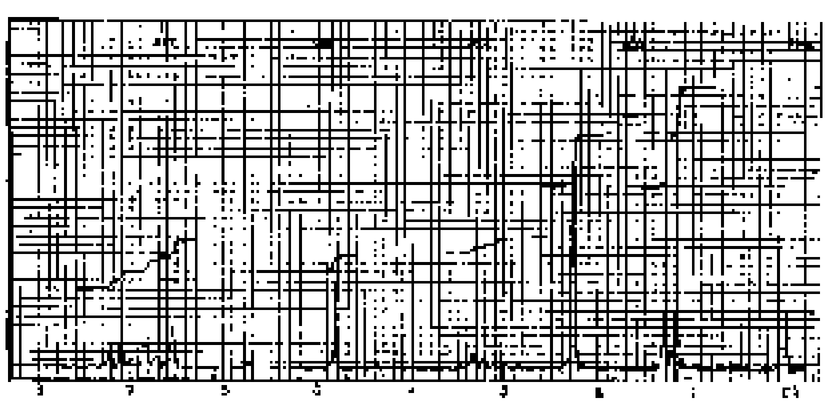
vanillin safrole thymol



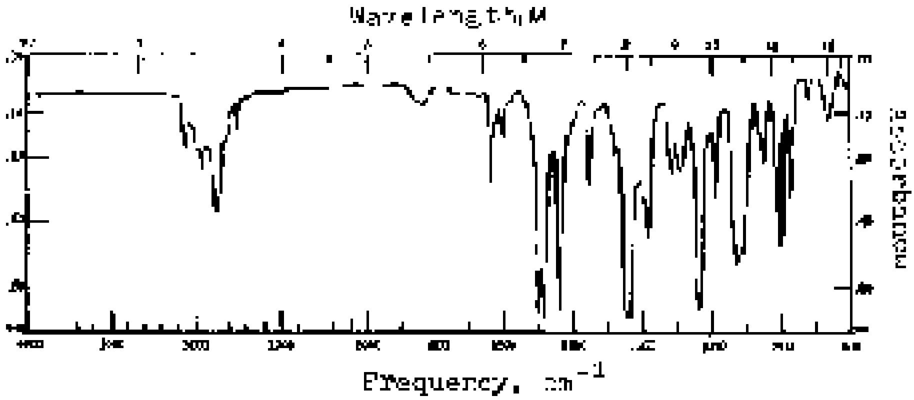
Infrared spectrum of A



Nmr spectrum of A



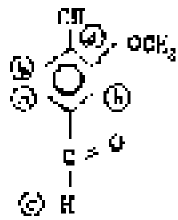
Nmr spectrum of B



Infrared spectrum of C

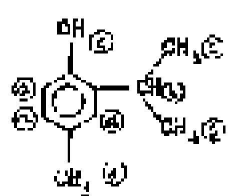
Solution: In this problem, we will make use of nuclear magnetic resonance spectra and infrared spectra to differentiate among the compounds vanillin, safrole and thymol, which are phenols or related compounds. Since the compounds have distinct differences, the task of distinguishing them would not be an overwhelming one and this demonstrates how an organic chemist would make use of spectra to differentiate compounds of similar composition. However once tentative structural determination has been achieved, the proposed structure is analyzed in comparison to its spectra, particularly noting the key spectral features and whether there are corresponding structural properties. Infrared spectroscopy is useful in identifying the major functional groups in a molecule by measuring the molecular vibration of most bonds within the compound, when absorbing radiation of the infrared frequency. Turning to the i.r. spectrum of A, we first notice an intense absorption band at a frequency of 1695 cm^{-1} which represents a carbonyl group. This alone, may allow us to label compound A as vanillin but we must examine the remainder of its spectra. The absorption frequency for an aldehyde carbonyl is 1725 cm^{-1} but a carbonyl's frequency is lowered by 30 cm^{-1} when conjugated with a double bond as is the case in vanillin. Other features of compound A's i.r. spectra include strong peaks in the region of 1000 cm^{-1} to 1300 cm^{-1} which indicates a C-O bond and a complicated absorption pattern in the region 700-1000 cm^{-1} that is characteristic of a 1,2,4 trisubstituted benzene derivative. The broad band that ranges from 2800 to 3400 cm^{-1} seems to be vanillin's O-H stretch (a particular kind of molecular motion).

Nuclear magnetic resonance is based upon the molecule's proton's absorptions of radiation of the radiofrequency range. These absorptions are directly dependent upon a proton's environment, including adjacent protons. Examining the n.m.r. spectrum of A, we note the sharp singlet at 4.4 δ which denotes the unsplit (no adjacent protons) methyl group. The peak is fairly downfield, i.e., has a high chemical shift (the absorption of a proton as compared to an absorption of a standard) because it borders on an electronegative element, oxygen, which lowers the electron density around the methyl protons. A proton's electron density determines the delta value of absorption. The complicated multiplet that is the furthest downfield from the methyl resonance represents the three protons directly attached to vanillin's aromatic ring. Its complexity is typical of benzene derivatives with electronegative substituents. The singlet at 6.? is representative of a hydroxyl proton. This peak is not easily seen here and is not useful but brings out the point that the (O-H) proton's chemical shift is variant, depending on such factors as concentration, and also the fact that the hydroxyl proton is usually un split. Another feature of vanillin's n.m.r. is the offset, downfield singlet. This is the aldehyde proton that is so downfield because the positively charged carbonyl carbon reduces the electron density about this hydrogen. Summarizing vanillin's n.m.r.:



δ value	
(a)	4.4
(b)	[illegible]
(c)	[illegible]
(d)	[illegible]

Turning now to the n.m.r. spectrum of compound B, we note that the most downfield multiplet is slightly upfield from where benzene would undergo absorption. This is characteristic of benzene derivatives containing electron-donating substituents such as alkyl groups. At 3.3 δ, we see a multiplet of at least three peaks which integrates (integrators run off a curve above the n.m.r. spectrum that measures intensity of absorptions and in turn the number of protons giving rise to a particular absorption) for the same value as the singlet at 4.8 δ but less than that of the singlet at 2.3 δ and the doublet at 1.3 δ. The combination of a downfield multiplet (actually a heptet) of low integration and an upfield doublet of higher integration is typical of a isopropyl group in which the heptet represents the methine proton and the doublet represents the methyl protons. The methine proton is downfield from its characteristic value because it borders a benzene ring and the phenyl group is inductively electron-withdrawing, decreasing the proton's electron density. Thus we know that the compound contains an isopropyl group and therefore the compound is thymol. The sharp singlet at 2.3 δ must be the methyl group and its chemical shift does coincide with that of a benzylic proton. The low integration singlet is the hydroxyl proton whose chemical shift falls in the range for this type of proton. Thus assigning chemical shifts to thymol's protons:



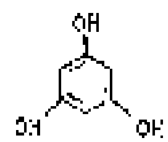
δ value	
(a)	6.9
(b)	3.3
(c)	1.3
(d)	2.3
(e)	4.8

By elimination, we know that safrole is compound C, but let's confirm this hypothesis by examining its infrared spectrum. The spectrum contains C-O stretch bands but not an O-H stretch band therefore the spectrum fits an ethereal compound such as safrole. The weak band at 1650 cm^{-1} shows the presence of an unconjugated double bond (not part of a benzene ring) and the C-H bands would be characteristic of a terminal methylene group ($-CH_2$) to a knowledgeable observer. All this is found in safrole.

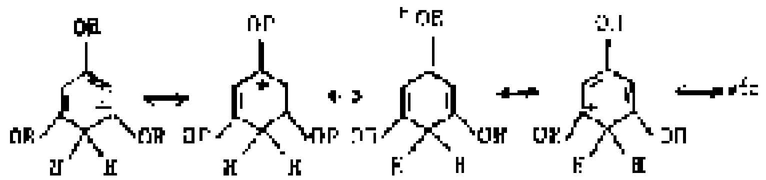
• PROBLEM 23-31

When phloroglucinol, 1,3,5-trihydroxybenzene, is dissolved in concentrated $HClO_4$, its nmr spectrum shows two peaks of equal area at δ 6.12 and δ 4.15. Similar solutions of 1,3,5-trimethoxybenzene and 1,3,5-triethoxybenzene show similar nmr peaks. On dilution, the original compounds are recovered unchanged. Solutions of these compounds in D_2SO_4 also show these peaks, but on standing the peaks gradually disappear.

How do you account for these observations? What is formed in the acidic solutions? What would you expect to recover from the solution of 1,3,5-trimethoxybenzene in D_2SO_4?

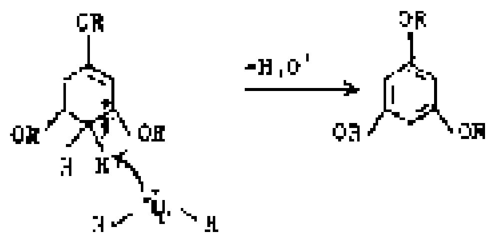
Solution: When 1,3,5-trihydroxybenzene, ,

is treated with $HClO_4$, we get a structure which has a nmr (nuclear magnetic resonance spectrum) consisting of two peaks of equal area (the intensity or area of a peak reflects the number of equivalent protons giving rise to that peak). These data tell us that there are two different types of protons, each of the same number. We note that $HClO_4$ is a good source of protons, a potential electrophile. Both the trihydroxy and trialkoxybenzene compounds are good substrates for electrophilic aromatic substitution since the free pair of electrons on the oxygens may be delocalized to ortho and para positions in relation to the hydroxyl (alkoxy) group. It is for this reason that the incoming electrophile is directed to these positions. The intermediate of this reaction is a benzenonium cation whose structure fits the desired spectrum with two equivalent protons at the site of attack. The reason for both types of protons being fairly downfield (high delta value - high chemical shift) can best be explained by the presence of the positive charge of the benzenonium cation. The peak with the lower chemical shift represents the two allyl protons while the other peak is indicative of the vinyl protons. The cation is a highly stabilized form with three resonance forms containing a positively charged oxygen. Its structure can be represented as:

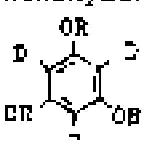


R = H, CH_3, C_2H_5

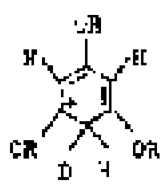
On dilution, water acts as a base to gain a proton and the starting material is recovered.



D_2SO_4, like its protic analogue, is a strong acid and a good source of a deuteron (D^+). This deuteron may undergo electrophilic attack on the activated aromatic ring of the trihydroxy (trialkoxy) compound. Since there are three sites for electrophilic attack, a moderate concentration of D_2SO_4 with 1,3,5-trimethoxybenzene will yield 2,4,6 trideuterio-1,3,5 trimethoxybenzene.



This product will be formed because the deuterium substituted on the ring, like a proton, will not diminish the activation of the aromatic ring. One of the intermediate benzenonium ions would be:



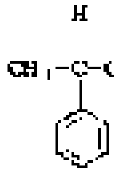
The heavy isotope deuterium has a different net nuclear spin and will not give rise to a nmr signal, explaining the absence of peaks in the spectrum of 2,4,6-trideutero-1,3,5-trimethoxybenzene. Note that we are ignoring any protons of the R groups.

SYNTHESIS

• PROBLEM 28-22

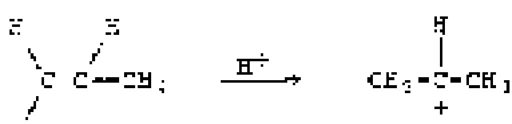
Outline a synthesis of cumene from cheap, readily available hydrocarbons. Then synthesize phenol from cumene.

Solution: One way to synthesize cumene (isopropyl benzene):

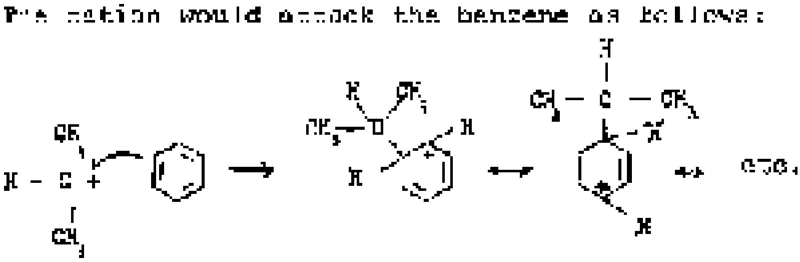


is to use a Friedel-Crafts alkylation reaction involving propylene, benzene and H_3PO_4. The Friedel-Crafts alkylation reaction refers to the attack of the weak electrophile, the alkyl cation, upon the pi system of benzene. In this case, we desire to produce the isopropyl cation. This may be formed in several ways: (1) alkyl halide with a Lewis catalyst (isopropyl bromide with $AlCl_3$), (2) alcohol with a strong protic acid (isopropanol with HF) or (3) alkene with strong acid. In this case, the last method has the advantage that propylene can readily be made in satisfactory yield from the industrial process of cracking. In this process a long chain alkane undergoes pyrolysis, breaking carbon-carbon bonds at random places and forming smaller alkyl radicals. Propylene would be formed from the disproportionation reaction of the propyl radical and another alkyl radical:

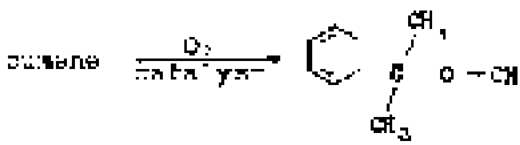
The more stable isopropyl cation (secondary rather than the primary propyl cation) would be generated by treating propylene with acid:



The cation would attack the benzene as follows:



Note that the benzenonium ion contains resonance structures putting the positive charge on carbons ortho and para to the incoming electrophile. This intermediate will lose a proton to form the desired product, cumene. Cumene, itself, is the starting material in an useful synthesis of phenol. This process involves the air oxidation of cumene to cumene hydroperoxide:

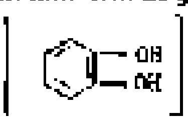


This, when treated with aqueous acid, gives phenol and acetone, another useful byproduct.

• PROBLEM 23-23

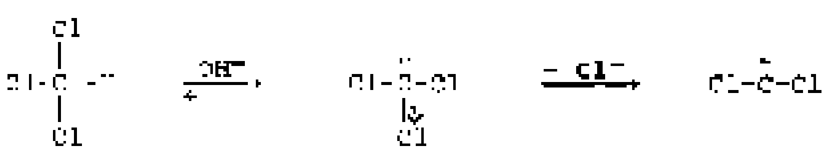
A component of urushiol, the active constituent of the irritating oil of poison ivy, is 3-pentadecyl-1,2-dihydroxybenzene. Synthesize this compound from catechol.

Solution: A feasible way of introducing the fifteen carbon straight-chain ortho to a hydroxyl group in catechol

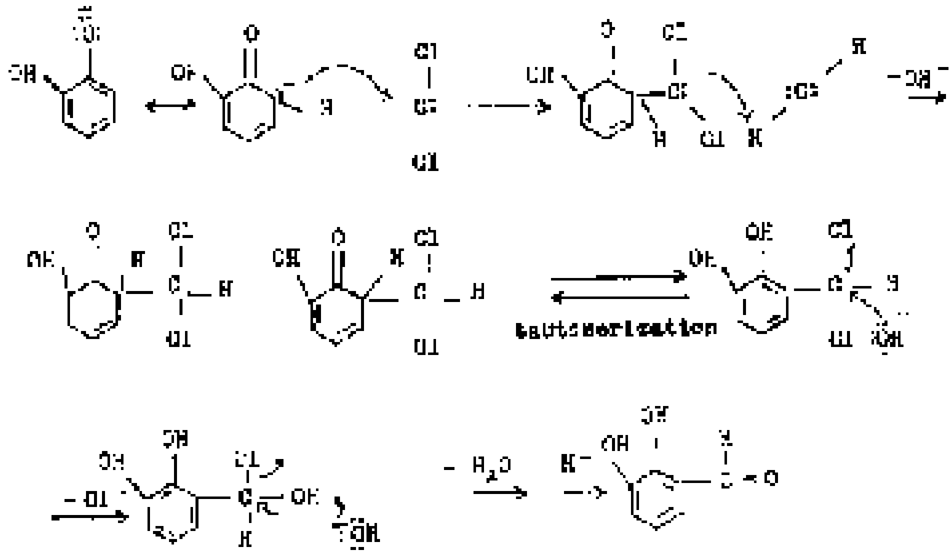


is to first introduce a formyl group in that position and make the appropriate fourteen chain Grignard reagent to form an alcohol which through a sequence of reactions can form the desired product, 3-pentadecyl-1,2-dihydroxybenzene:

The best way to introduce the formyl group in the proper position is through a Reimer-Tiemann reaction. This involves treating a phenol with chloroform in the presence of base. Under these conditions, chloroform sequentially loses a proton and a chloride anion in an α-elimination (elimination with both leaving groups on same carbon) to form a dichlorocarbene.

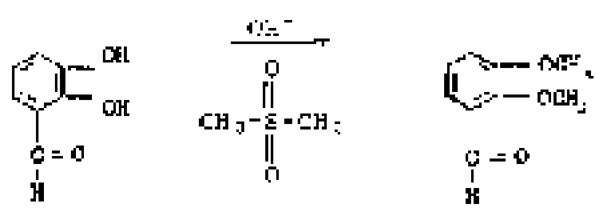


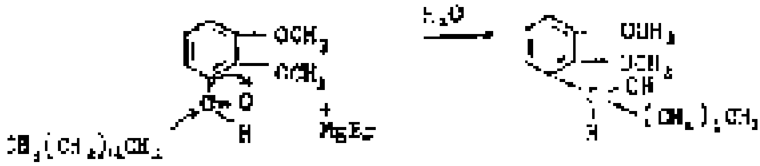
The carbene is an electron-deficient species which may be attacked by a nucleophile such as a phenoxide anion. The resultant adduct is hydrolyzed and then it enolizes to a dichloro phenolic compound which further reacts with base to give the final hydroxybenzaldehydic product after acidification.



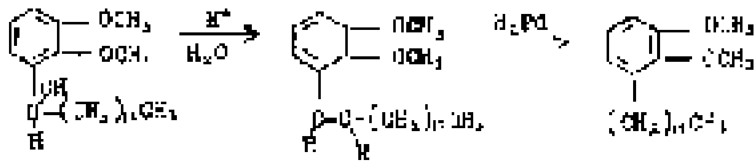
The newly formed carbonyl group has a carbon with a partial positive charge that is susceptible to attack by nucleophiles such as a Grignard reagent. Such an attack followed by work-up with H_2O will yield an alcohol. However, the situation is usually more complicated than this in that the Grignard reagent may react with a variety of compounds other than the carbonyl group. The Grignard reagent is a potent base as well as a nucleophile. Therefore, a Grignard reagent can potentially react with the following functional groups: OH, NH_2, CN, NO_2, $\overset{O}{\overset{\|}{C}}$H, $\overset{O}{\overset{\|}{C}}$OH, C≡C H, $\overset{O}{\overset{\|}{C}}$R, etc. In the compound synthesized by the Reimer-Tiemann reaction, we have both an aldehydic and a hydroxyl functional group. If we reacted this compound with a Grignard reagent, we actually would get the alkane, pentadecane and a phenoxide anion. To avoid this proton transfer, the hydroxyl groups are converted into other linkages. This is best done by treating the polyhydric alcohol in base and the alkylating agent, dimethyl sulfate. The methylating occurs by a substitution-nucleophilic-bimolecular-mechanism and the resultant compound can form the desired alcohol since the ether linkages are inert to base. The Grignard reagent itself, can be made from the corresponding alkyl halide.

$$CH_3(CH_2)_{13}CH_2Br \xrightarrow[\text{ether}]{Mg} CH_3(CH_2)_{13}CH_2MgBr$$

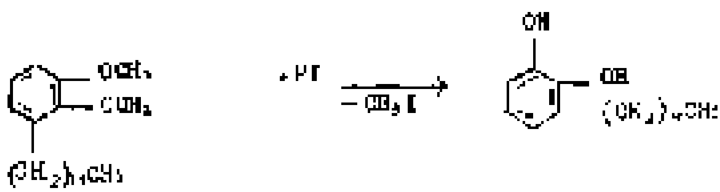




The resultant alcohol is easily dehydrated to an alkene in the presence of acid since the subsequent double bond is in conjugation with the benzene ring. The ether linkages are probably maintained if dilute acid is used. The newly formed double bond can be catalytically hydrogenated since under mild conditions such as this the extra stability of the aromatic system will not be lost by reducing the ring's double bonds.

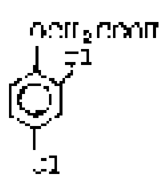


If they still remain, the ether linkages may be removed by treatment with the strong protic acid HI.



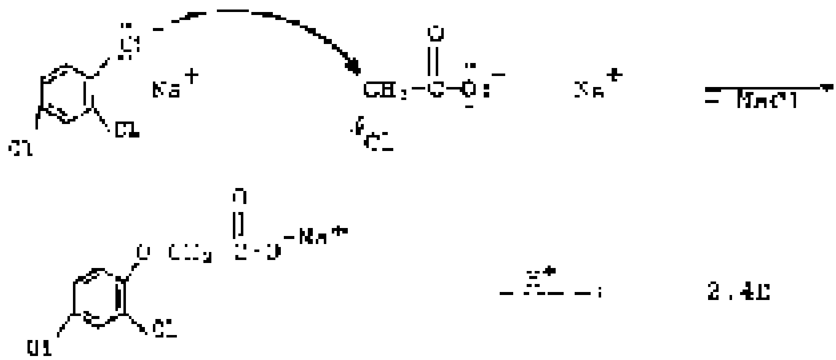
• PROBLEM 23-24

2,4-Dichlorophenoxyacetic acid is the important weed-killer known as 2,4 D. Outline the synthesis of this compound starting from benzene or toluene and acetic acid.



2,4-Dichlorophenoxyacetic acid
(2,4 D)

Solution: Examination of 2,4 Dichlorophenoxyacetic acid (2,4-D), the compound we wish to synthesize, shows that it contains a 2,4 dichlorophenoxy fragment and it is logical to synthesize this part of the compound because reaction of 2,4-dichlorophenoxide anion with sodium (α chloroacetate) will yield 2,4 D after working up the product with acid. The reaction is an S_N2 displacement which takes advantage of the nucleophilic potential of the phenoxide anion. We note that the substrate for this nucleophilic attack is the salt of acetic acid and not acetic acid itself so as to avoid proton transfer between the acid and the phenoxide anion. Also notice that the carbonyl group of the carboxylate anion is virtually inert to nucleophilic attack because of the anion's resonance stabilization. The reaction can be written as:

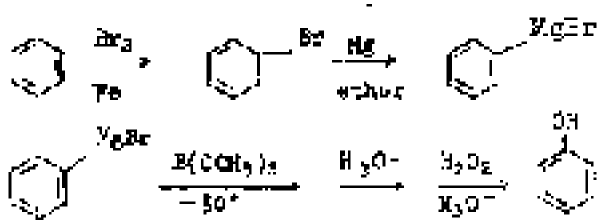


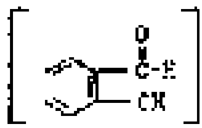
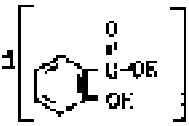
The question remains now how to synthesize the two starting materials (the salts). Sodium (α-chloroacetate) can be made by treating the corresponding α-chloroacid in the presence of sodium hydroxide and this in turn is made by treating acetic acid with chlorine and the chlorinating agent PCl_3. These conditions are specific for chlorination of the alpha carbon of a carboxylic acid. Outlining this sequence:

$$CH_3COOH \quad Cl_2 \quad \xrightarrow[PCl_3]{\Delta} \quad CH_2ClCOOH$$

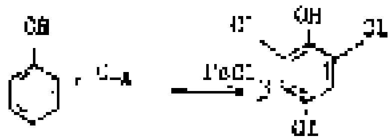
$$CH_2ClCOOH \xrightarrow{NaOH} CH_2ClCOO^-Na^+$$

The phenoxide anion is slightly more difficult to make and seems to be derived most easily from phenol. There are a variety of ways, both industrial and experimental, to synthesize phenol. Phenol can be made in reasonable yields from benzene via a Grignard reagent. This involves treating the Grignard reagent with trimethyl borate, followed by acidification and then reacting the phenylboronic acid in dilute, acidic hydrogen peroxide.

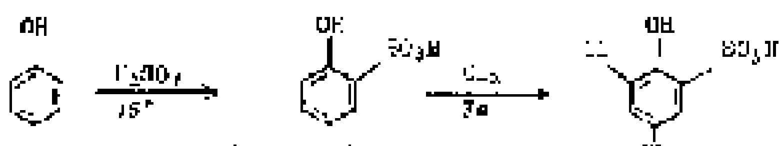


We note that the usual considerations remain when synthesizing the Grignard reagent and any substituted phenol containing a center for nucleophilic attack or an acidic proton cannot be made from this route. These would include salicylaldehyde  and salicylic acid .

To synthesize 2,4 dichlorophenol from phenol, we run into the difficulty of overreactivity of phenol in which treatment of this compound with chlorine and a Lewis acid catalyst will result in 2,4,6 trichlorophenol.

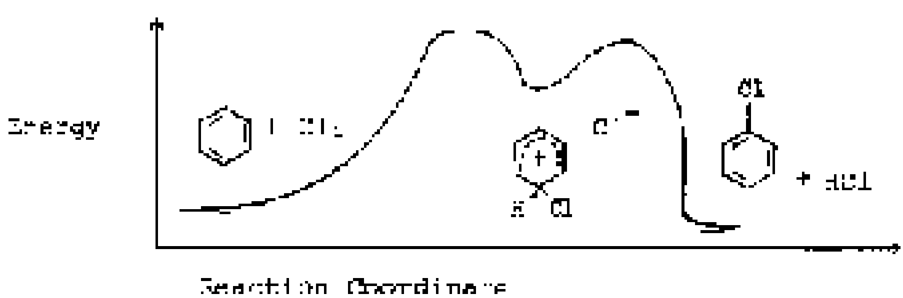


This is because the hydroxyl group is an activating, ortho-para director. To solve this difficulty we may temporarily block one of the ortho positions by putting a particular group there and removing it after chlorination. A useful blocking group is the sulfonic acid group (SO_3H). Sulfur trioxide, the actual electrophile in sulfonation (the substitution of SO_3H on an aromatic ring) is less reactive than the halonium ion in chlorination and polysubstitution is less likely. However, to ensure mono substitution, temperatures are kept low and fuming sulfuric acid (the usual sulfonation mixture which contains SO_3) is not used. The subsequent o-hydroxybenzenesulfonic acid that is generated is isolated and catalytically chlorinated.

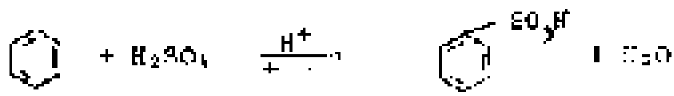


+ para isomer

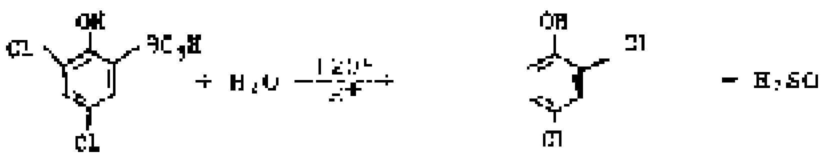
Now we can remove the "blocking group" SO_3H and next form the final product 2,4-D. To do this we treat 2-hydroxy 3,5-dichlorobenzenesulfonic acid with steam at 120°C with a trace of acid catalyst. This is essentially the reverse of sulfonation, or "desulfonation." We note that sulfonation is the only one of the common electrophilic aromatic substitutions that is reversible and the question arises why this is so. This calls for an analysis of the general mechanism of electrophilic aromatic substitution. The idealized energy profile for such a reaction (chlorination) is:



The energy profile shows that the first peak is the higher one and therefore it represents the rate determining step which represents the electrophiles disruption of the aromatic system. The second and smaller peak represents the removal of a proton to restore the aromaticity. That, in chlorination, the intermediate benzenonium ion (sigma complex) has a tendency to travel over the lesser energy barrier and form the product chlorobenzene, rather than to return to starting materials. In sulfonation, on the other hand, the energy barriers are of similar heights and the reaction can potentially go either to products or reactants once the benzenonium ion is formed. Under certain conditions (such as those in desulfonation there is an excess of H_2O and the sulfonated product) the reaction is shifted back to starting materials. Summarizing:



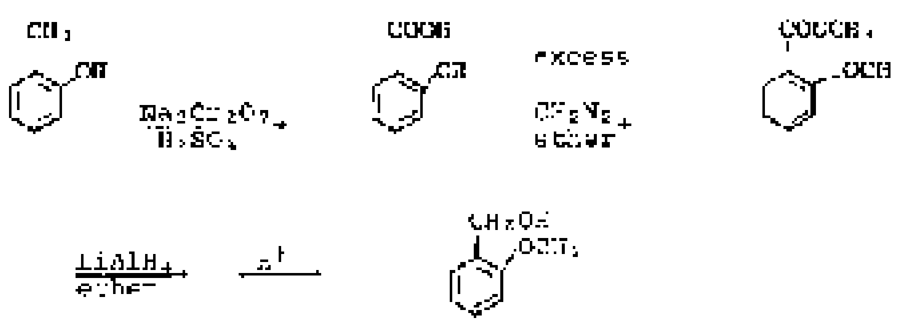
Using the proper condition, we now use the desulfonation in our synthesis to get 2,4 dichlorophenol.



This can be treated with NaOH to get our desired anion which will react with $CH_2ClCOO^-Na^+$ to give us the final product.

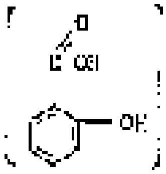
• PROBLEM 23-25

A student attempted the following synthesis of o-methoxybenzyl alcohol from o-cresol, but got essentially no yield. What went wrong?



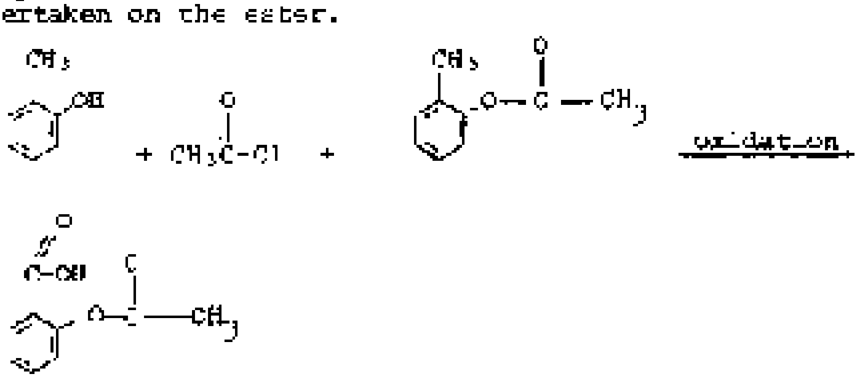
Solution: Reactive aromatic compounds, such as phenol and aniline are sensitive to oxidation. The oxidation products for both compounds is parabenzoquinone:

, a conjugated diketone. Such oxidations may be undertaken by a variety of reagents including the potent oxidant $H_2Cr_2O_7$ whose use involves the reduction of Cr^{+6} to Cr^{+3}. Experimentally, $H_2Cr_2O_7$ is generated by mixing H_2SO_4 with $Na_2Cr_2O_7$. Any phenol or aniline derivative would be oxidised to a quinone by this mixture. Thus, although the outlined synthesis is correct once salicylic acid



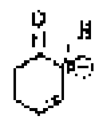
is produced, this compound would never be produced in the outlined synthesis shown because the phenolic starting material would be oxidized to its corresponding quinone.

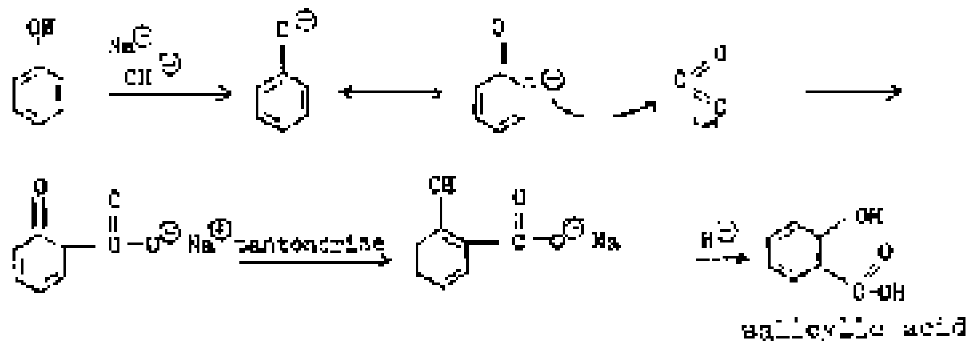
We have now encountered one of the synthetic difficulties when working with phenols: their sensitivity to oxidation. Another is their overreactivity where electrophilic aromatic substitution would lead to polysubstituted products. This is because the hydroxyl group is a highly activating substituent; all the available ortho and para positions will be attacked by the incoming electrophile. Both these problems can be handled by temporarily altering the hydroxyl group by attaching a protecting group to it. For example, in our synthesis, the starting material may be reacted with acetyl chloride and the desired oxidation may then be undertaken on the ester.



An alternate way of protecting the hydroxyl group is to change it to an ethereal linkage instead of an ester linkage. The ester linkage is removed by acidic hydrolysis, while the ethereal linkage is broken by a protic acid.

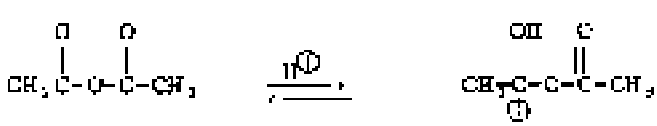
Aspirin is acetylsalicylic acid (o-acetoxybenzoic acid, o-$CH_3COO-C_6H_4COOH$); oil of wintergreen is the ester, methyl salicylate. Outline the synthesis of these two compounds from phenol.

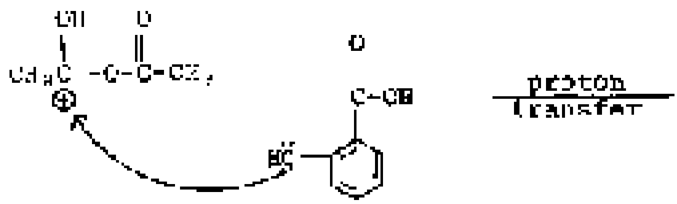
Solution: The easiest way to isolate the two esters, acetylsalicylic acid and methyl salicylate, is to first produce salicylic acid (o-hydroxybenzoic acid). This, in turn, is made through the Kolbe reaction of phenol. This reaction involves the nucleophilic attack of the phenoxide anion upon the weak electrophile CO_2. The phenoxide anion is produced by treating phenol with base and the final product is acidified to give salicylic acid. Note that the phenoxide anion exists in several resonance forms and it is the form that contains a negatively charged carbon ortho to the hydroxyl group  that attacks CO_2 at moderate temperatures. The sequence of the Kolbe reaction is as follows:

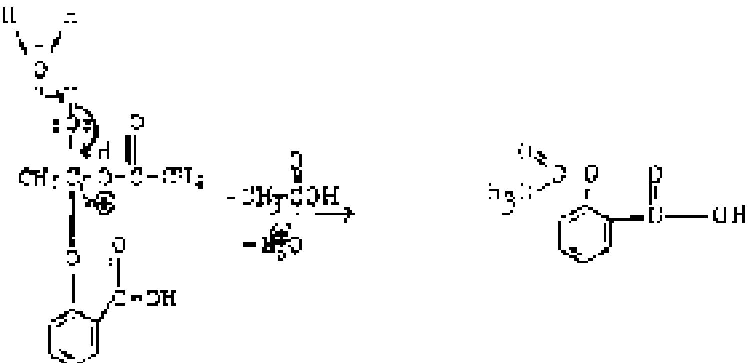


salicylic acid

Salicylic acid is a bifunctional compound, containing both a hydroxyl group and a carboxyl group. The hydroxyl group contains a free pair of electrons which would allow salicylic acid to act as a nucleophile upon a positive source. Such positive sources include the carbonyl carbons of methyl acetate, acetic anhydride, and acetyl chloride. The hydroxyl group would attack the carbonyl carbon of acetic anhydride in the presence of an acid catalyst to give acetylsalicylic acid (aspirin), one of our desired products. The mechanism is as follows:

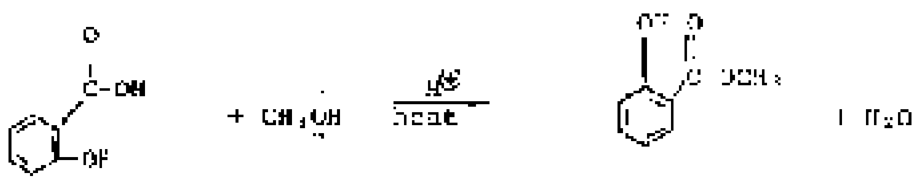






acetylsalicylic acid
(aspirin)

Salicylic acid, however, also contains a carboxyl group which undergoes its own characteristic reactions. By a mechanism similar to that of the formation of aspirin, methanol attacks salicylic acid again in the presence of acid, to form methyl salicylate, our other desired product. Note here, however, that salicylic acid is the acylating agent, forming the intermediate cation and methanol is the nucleophile:

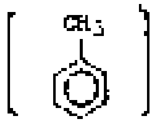
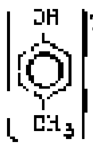


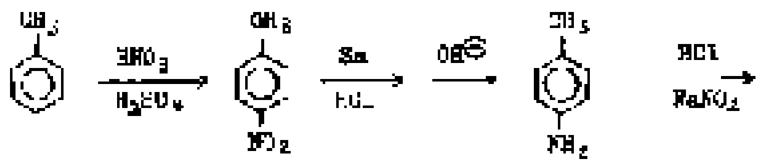
• PROBLEM 23-27

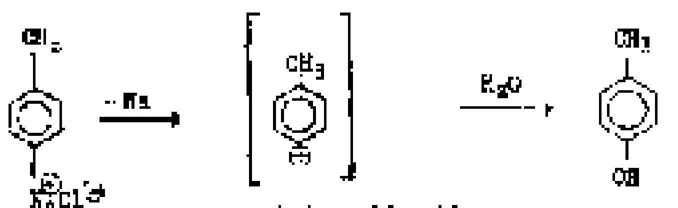
Outline all steps in the synthesis from toluene of: (a) p-cresol via diazotization; (b) p-cresol via sulfonation; (c) and (d) m-cresol via each route.

Solution: (a) Synthesizing phenols via diazonium salts is a popular synthetic route that usually begins with a relatively easy and inexpensive nitration reaction. The nitro compound is catalytically reduced to an amine which is then converted to the versatile diazonium salt which can be converted to a variety of aromatic compounds. If the diazonium salt is heated in the presence of water at moderate temperatures, a phenol is formed. The reaction is often a wasteful side reaction in diazonium syntheses and this is why the reaction temperature of such reactions is kept at a minimum.

A phenyl cation which is quite unusual is one proposed intermediate for the hydrolysis of diazonium salts. Note that this cation contains an empty sp^2 orbital, perpendicular to the π system.

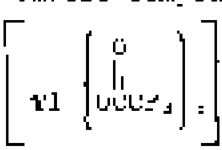
Thus, toluene,  can be converted to p-cresol, , by first putting a nitro group para to the methyl group and carrying out the aforementioned conversions.



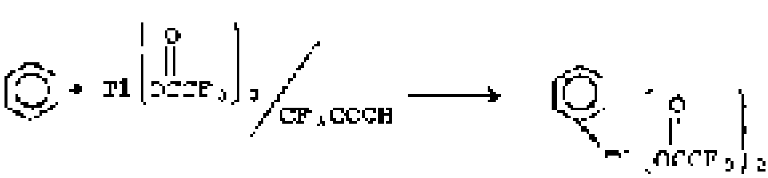


no delocalization in this phenyl cation p cresol

(b) An alternate, shorter, more recent route to p-cresol from toluene is thallation which involves treating an aromatic compound with thallium trifluoroacetate,

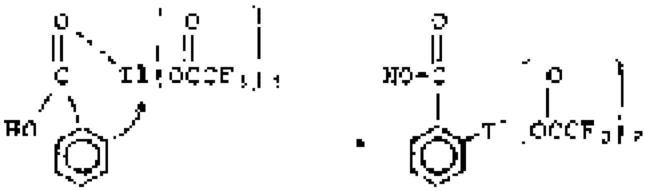
 in trifluoroacetic acid 

solution. The product of such treatment is a crystalline thallium ditrifluoroacetate aromatic compound.



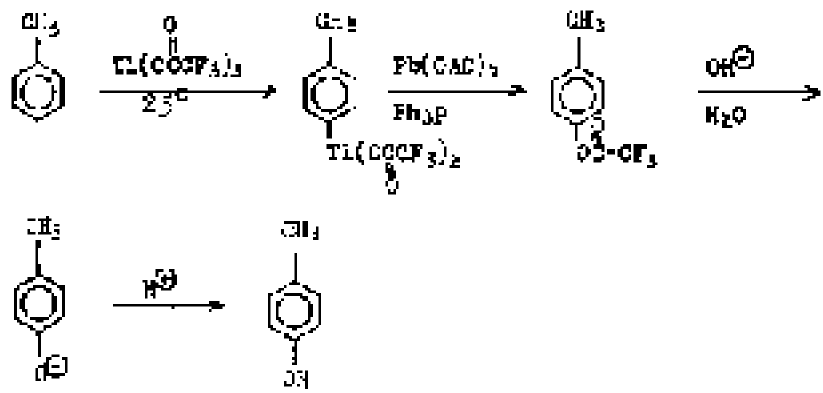
phenylthallium di-trifluoroacetate

The major advantage of thallation is orientational specificity. While thallation is essentially all para to alkyl groups, halides and alkoxy substituents, orientation is almost all ortho to a carboxyl or an ester substituent. We see that such orientation to ester and carboxyl substituents is unusual in that these groups are typically meta-directing in electrophilic aromatic substitution. This behavior can be attributed to an intramolecular interaction involving the electrophilic thallium and the carbonyl group which allows for facile ortho substitution.

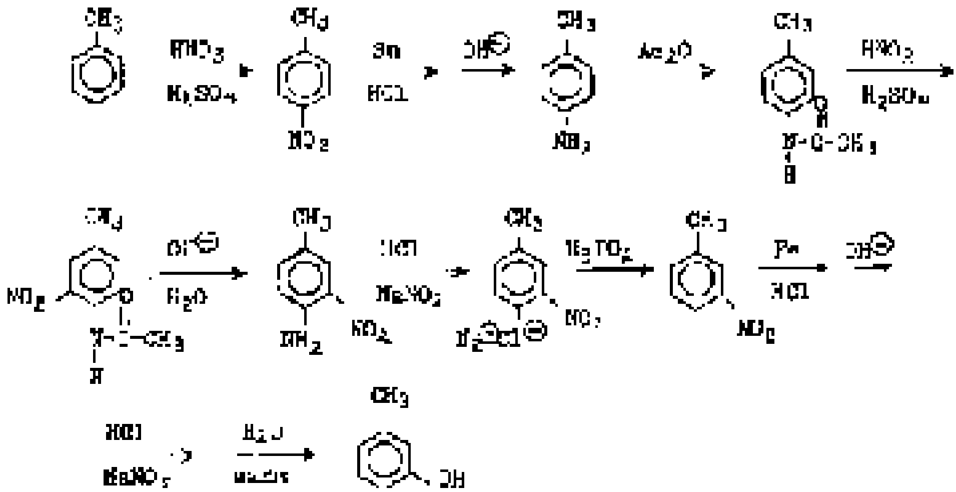


benzoic acid

When an arylthallium compound is treated with the oxidant lead tetraacetate [$Pb(OAc)_4$] together with triphenylphosphine [$P(Ph)_3$], it is oxidized to an aryl trifluoroacetate, which, when hydrolyzed, yields the phenol after subsequent acidification. To obtain p-cresol by thallation, we would use the following sequence.

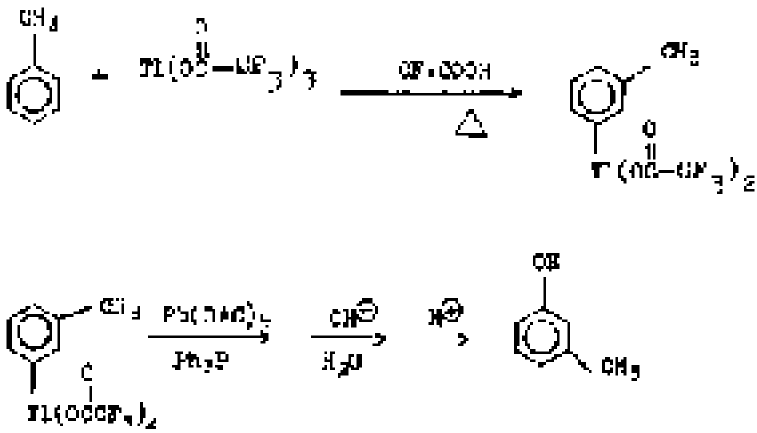


(c) Both thallation and diazotization can be used to synthesize m-cresol as well as p-cresol from toluene. Both, however, involve complications with m-cresol. The difficulty with diazotization is that the methyl group is an ortho para director and a nitro group cannot be put directly in the meta position. However, an ortho-para director that is stronger than the methyl group and is removable can be temporarily located para to the methyl group. This can be accomplished sequentially by nitration, reduction, acetylation (for protection against overreactivity and protonation), nitration, alkaline hydrolysis, diazotization of the amino group, and reduction of the diazotized salt by the specific reagent hypophosphorous acid (H_3PO_2). The subsequently formed nitro compound can be converted to the final product by reduction, diazotization and hydrolysis. Outlining this in the synthesis of m-cresol:



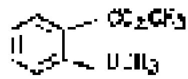
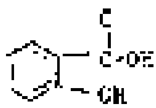
m cresol

(C) The complication of synthesizing m-cresol from toluene through thallation is that it involves the temperature dependence and reversibility of the process. At lower temperatures (25°) the para tolylthallium ditrifluoroacetate is the predominant product while the meta isomer is the main product at higher temperatures. This is best explained by the interpretation that the para isomer is kinetically favored and is formed the fastest. The meta product has a higher thermodynamic stability (lower energy content). Therefore at higher temperatures, the reaction would occur in both directions at a significant rate and the more stable meta isomer would tend to be the major product. Using this phenomenon, we can synthesize m-cresol by the following steps.

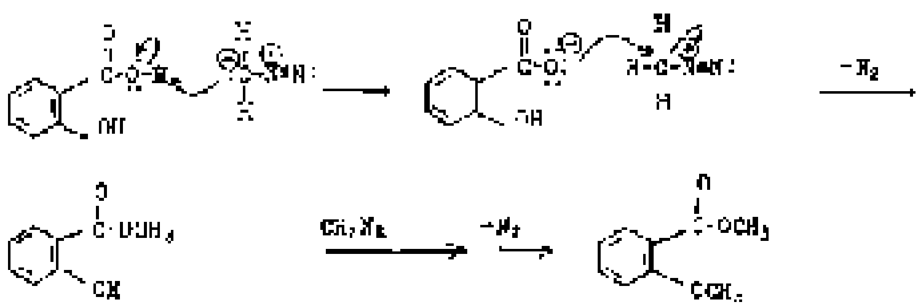


Show by means of equations how each of the following substances might be synthesized, starting from the indicated materials. Specify reagents and approximate reaction conditions.

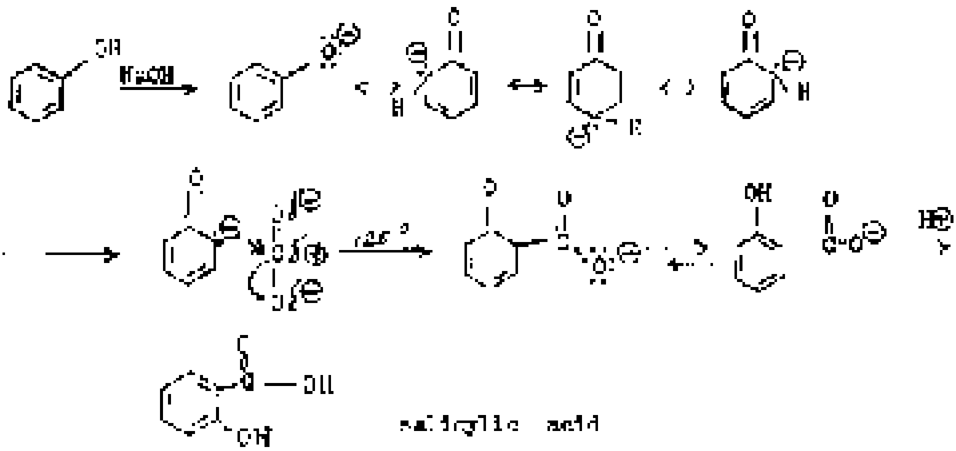
(a) methyl 2-methoxybenzoate from phenol.
(b) 2,6-dibromo-4-t-butylanisole from phenol.
(c) 4-cyanophenoxyacetic acid from phenol.
(d) cyanoquinone from hydroquinone.

Solution: (a) Methyl 2-methoxybenzoate is an ester with the structure  . Since both the ester and the ether linkage contain a methyl group, it would appear that it is best derived from the hydroxybenzoic acid, salicylic acid: 

The conversion from salicylic acid to methyl 2-methoxybenzoate could best be carried by treating salicylic acid with a quantitative amount of diazomethane (CH_2N_2). This versatile reagent reacts with both carboxylic acids and phenols to give methyl esters and methyl ethers respectively. The mechanism of these conversions is based upon the acidity of carboxylic acids and phenols. (Alcohols normally do not react with diazomethane.)



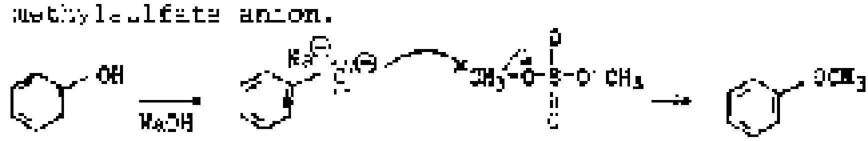
Continuing our technique of synthesis elucidation by working backwards, we will attempt to produce salicylic acid from phenol. Surprisingly, this conversion can be brought about by a single reaction: the Kolbe reaction. This reaction involves the attack of a phenoxide anion on the electron-deficient carbon of carbon dioxide. The phenoxide anion, generated by treating phenol with base, can be depicted as several resonance forms in which the negative charge is located ortho and para to the original hydroxyl group. At 125°C, the final product seems to result from attack at the ortho position, perhaps because of initial attachment to the phenoxide oxygen. Summarizing:



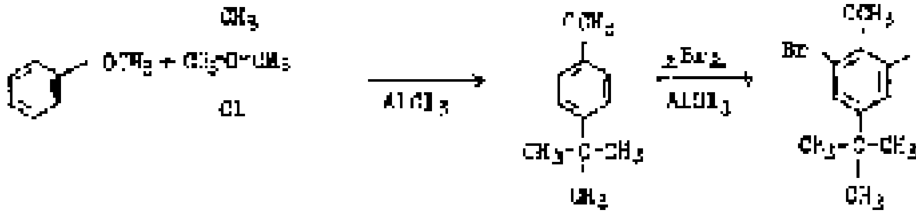
salicylic acid

Salicylic acid may be reacted with diazomethane as proposed to give the final product.

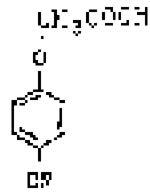
(b) In this problem, we are asked to synthesize 2,6-dibromo-4-t-butylanisole from phenol. The major difficulty is not any of the individual steps but in what order to carry them out. The methyl ether linkage can be created by treating the phenol with the alkylating agent, dimethyl-sulfate. Both the two bromines and the t-butyl group, ortho and para to the original hydroxyl group respectively can be put on the aromatic ring by electrophilic aromatic substitution. It seems vital to our synthesis to first put on the ether linkage by the alkylation reaction because reaction of phenol with bromine produces 2,4,6-tribromophenol and the reaction of phenol with t-butyl chloride and a Lewis catalyst (conditions for an electrophilic aromatic substitution reaction) will create t-butylphenyl ether as a major side product. The alkylation reaction involves an S_N2 mechanism and takes advantage of the good leaving group, the methylsulfate anion.



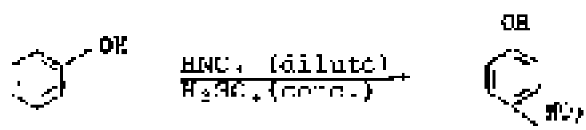
Of the two stages remaining, bromination and substitution of the t-butyl group onto the ring, the latter should be carried out first since the electrophilic attack will proceed almost exclusively in the para position because of steric factors; (the transition state of the reaction would be of higher energy for ortho attack) and for the same reason, polysubstitution is unlikely. Thus once the para position is occupied, exhaustive bromination will yield the final product. Note that the methoxy group (OCH_3) like the hydroxyl group is an activating substituent and an ortho-para director for the same reasons as the hydroxyl group: the ability to delocalize oxygen's free pairs of electrons to the ortho and para positions. Thus, once we generate methylphenyl ether, the synthesis may be completed by the following steps:



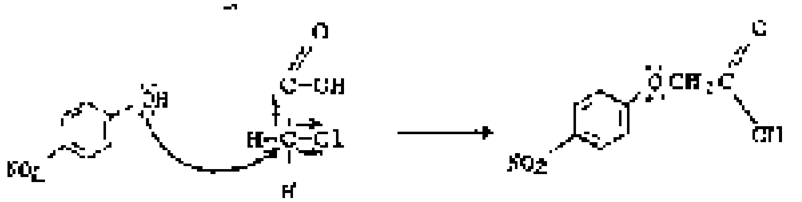
(c) The product we wish to synthesize, 4-cyanophenoxy

acetic acid, 

, has the feature of having a cyano group (CN) directly attached to an aromatic ring. This is most practically carried out via the use of aryl diazonium salts ($Ar-N_2^{\oplus}Cl^{\ominus}$) which are derived from aryl amines ($Ar-NH_2$) which are themselves produced by the catalytic reduction of aryl nitro compounds ($Ar-NO_2$). Thus, we would seem to need to put a nitro group para to the original hydroxyl group. We must be aware of phenol's immense reactivity and the subsequent danger of polynitration. To avoid this danger, we treat phenol with dilute nitric acid instead of with concentrated nitric acid and with concentrated sulfuric acid as the catalyst.

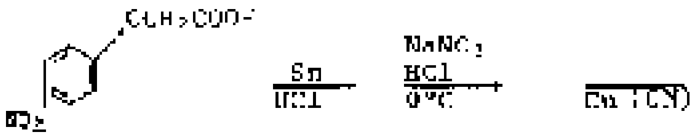


We may now deal with putting on the other fragment of the final product ($-CH_2COOH$). This fragment seems to be derived from acetic acid and may be added to 4-nitrophenol through the nucleophilic attack of the phenol on α-chloroacetic acid. We see that both chlorine and the carboxyl group are inductively electron-withdrawing and this creates a partially positively charged α carbon which makes a good source for nucleophilic attack by the phenoxide oxygen. The carbonyl carbon of the carboxy group is also partially positively charged but a nucleophilic displacement involving the carboxyl group requires that the hydroxide anion act as a leaving group which is an unlikely event. What actually occurs is an S_N2 attack on the α carbon.



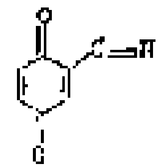
4-nitrophenoxyacetic acid

At this point, we may carry out the reduction of the nitro compound to its amine derivative, the amine's diazotization and the replacement of the azo group with a nitrile group by treatment with cuprous cyanide. We note that the reduction is specific for the nitro group, not altering the double bonds or the carboxyl group. Summarising:

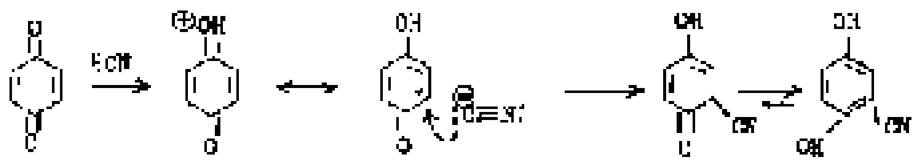


4 cyanophenoxyacetic acid

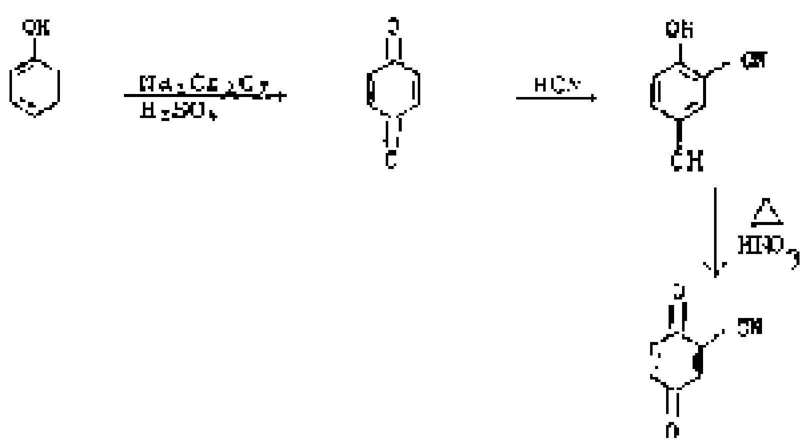
(c) Cyanoquinone with the structure



is a derivative of a quinone, specifically parabenzoquinone which in turn is derived from the oxidation of phenol. The oxidation can be brought about by a variety of means with one way using $H_2Cr_2O_7$ generated by a mixture of $Na_2Cr_2O_7$ and H_2SO_4. This quinone, like any 1,4 unsaturated ketone can undergo addition reactions such as the electrophilic attack of HCN.

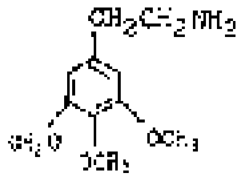


We note that this is a reduction of sorts converting the quinone to a hydroquinone derivative. The oxidation to the final product is carried out by HNO_3. Therefore, the sequence of steps is:



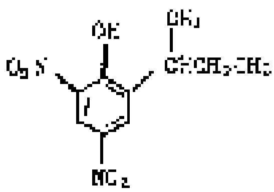
Each of the following phenol or quinone derivatives has the common or trivial name shown and is a compound of some significance. Provide the IUPAC name and synthesize each from the starting material given.

(a)



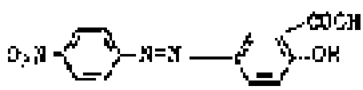
Mescaline the active ingredient in peyote. Prepare from gallic acid.

(b)



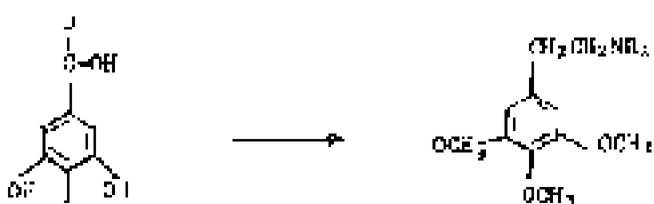
The ester of this phenol with 3-methyl-but-2-enoic acid is binapacryl, which is used as a fungicide and miticide. Synthesize the phenolic portion shown from phenol.

(c)



Alizarine Yellow R is used as an indicator in alkaline solutions. The color changes from yellow to red over the pH range from 10 to 12. Synthesize from aniline.

Solution: (a) Gallic acid (I) must have its hydroxyl groups transformed to methyl ether linkages in its conversion to Mescaline (II).



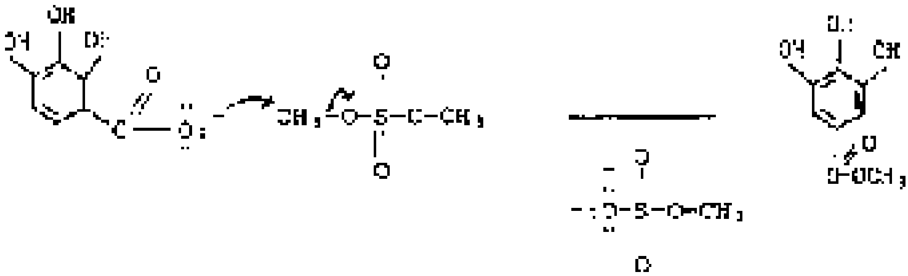
I II

This is best done by treating gallic acid with the alkylating agent, dimethyl sulfate

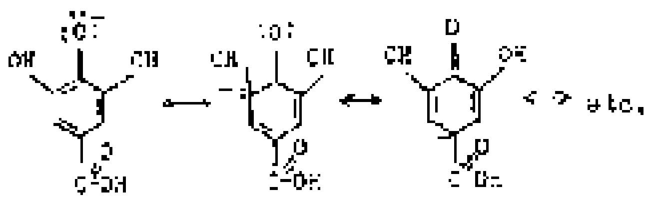
$$\left[CH_3-O-\overset{\displaystyle O}{\underset{\displaystyle O}{\overset{\|}{\underset{\|}{S}}}}-O-CH_3 \right]$$

, in the presence of base. The starting

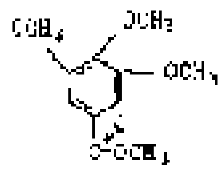
material loses its acidic carboxylic proton easily and the subsequent carboxylate anion can undergo a nucleophilic reaction with dimethylsulfate to form a methyl ester.



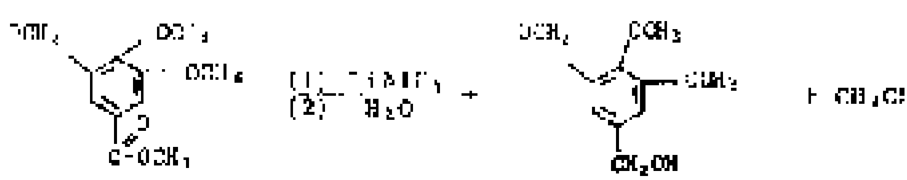
The hydroxyl groups also lose their protons to form resonance stabilized phenoxide anions in which the hydroxyl group and the carbonyl group both stabilize the negative charge within the ring by an inductive effect. For example



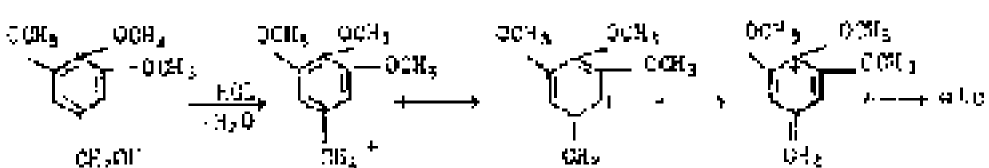
Thus treatment of gallic acid with dimethyl sulfate in base will yield the compound:

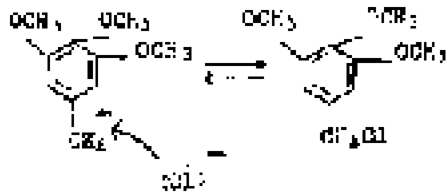


Mescaline differs from this compound in that it contains one more carbon and has an amine functionality in place of the ester linkage. This change is best achieved by first reducing the ester to an intermediate benzylic alcohol by the potent reducing agent, $LiAlH_4$. This can be represented as:

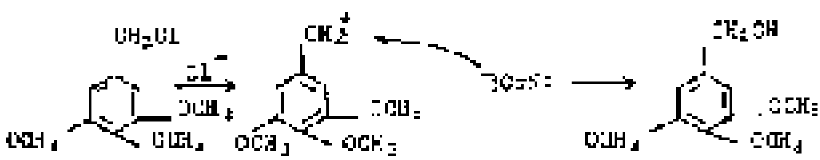


The alcohol can be converted to the benzylic chloride by addition of aqueous HCl. The latter is much more reactive to nucleophilic displacement. This reaction has a benzyl cation as its intermediate.

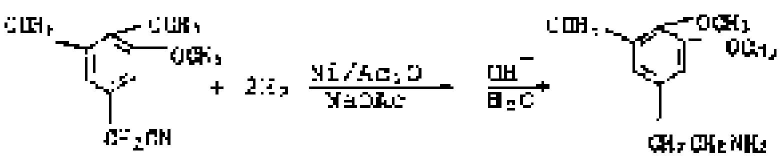




The chloride can be converted to a compound containing one more carbon by use of the nucleophile, the cyanide anion. The reaction probably occurs by an S_N1 mechanism because of the stability of the benzylic cation.

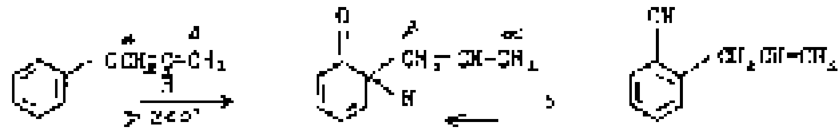


This compound, like any nitrile can be catalytically reduced to its corresponding amine compound. To prevent the formation of any byproducts, the nitrile is treated with the catalyst, hydrogen and a mixture of sodium acetate in acetic anhydride. This protects the primary amine and the final product is isolated by alkaline hydrolysis. Summarising:



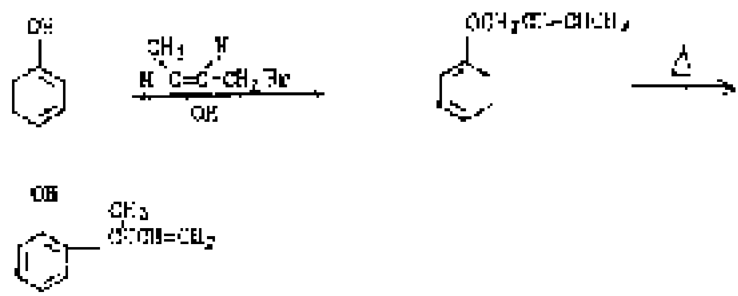
Like any substituted arene, this compound may be named as a substituted alkyl chain, which in this case is an amine. On the aromatic ring itself, the "3", "4", and "5" positions contain methoxy groups ($-OCH_3$). Thus the IUPAC name of mescaline is 2-(3,4,5-trimethoxyphenyl)ethylamine.

(b) The compound we wish to synthesize here has a simple alkyl side chain on the aromatic ring and may be named as a substituted phenol. The substitution on the alkyl chain occurs on the second carbon of an n-butane chain and thus this dinitro compound has the IUPAC name 4,6-dinitro-2-sec-butylphenol. It may at first seem difficult to put the sec-butyl chain on the aromatic ring, but this may occur via a reaction sequence that is unique to phenols - the Claisen Rearrangement. This reaction involves the thermal instability of allylphenyl ether and its subsequent formation of o-allyl phenol. This isomerisation of O and C alkylated products occurs via a cyclic transition state. The immediate product is a dienone which tautomerises to the phenol.

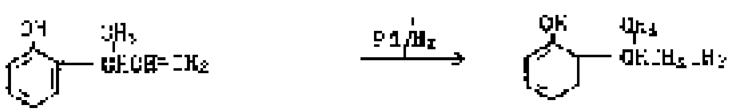


O-allyl ether dienone o-allylphenol

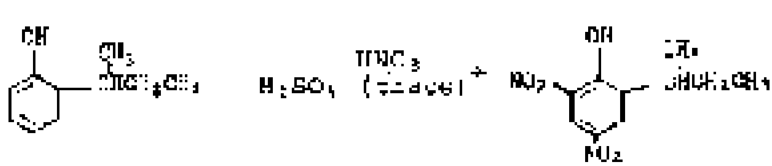
In terms of our synthesis, we see that our product actually has an additional methyl group on the benzylic carbon (carbon adjacent to the aromatic ring). This can be made by altering the original allyl-phenyl ether. The ether, in turn, can be made in a reaction between a phenol and 3-methylallyl bromide in the presence of base. This reaction probably occurs by an S_N2 mechanism and is facilitated since the alkyl halide is not an ordinary halide but is an allyl bromide. The sequence of reactions may be outlined as



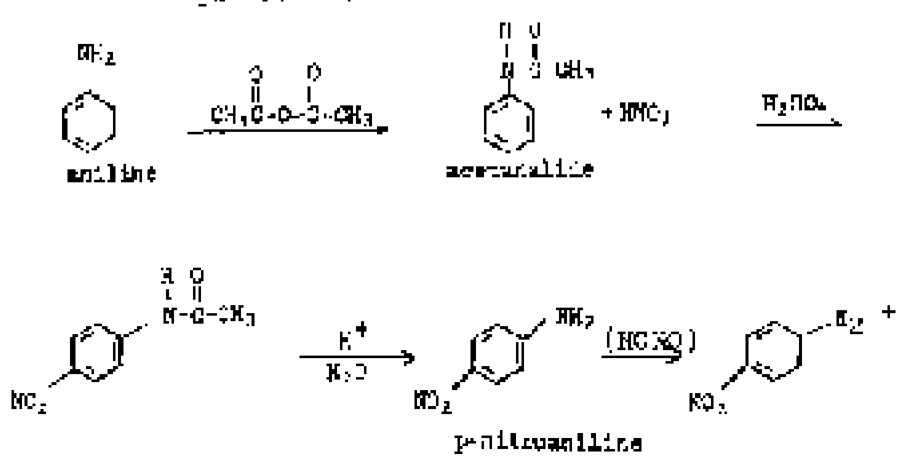
To obtain the desired sec-butyl side chain, a simple catalytic hydrogenation is sufficient. We note that as usual mild reductions of this type do not affect any of the aromatic ring's double bonds which if were reduced, the stability of aromaticity would be lost.



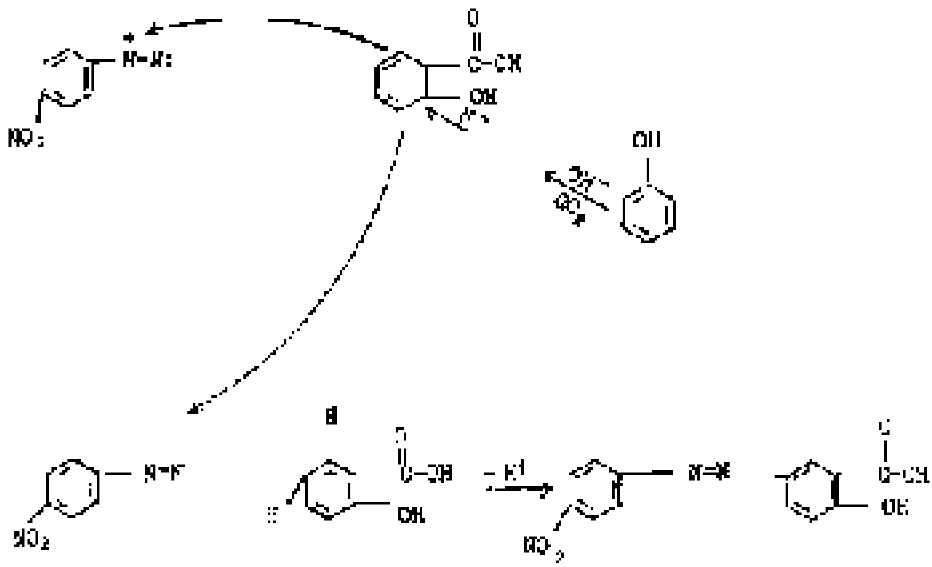
This alkylated phenol can have the nitro group put in the remaining ortho and para position (in relation to the hydroxyl group) that are in the final product by a nitration reaction that involves treating the starting materials with "mixed acid" - a mixture of concentrated HNO_3 and H_2SO_4. The actual reagent is the nitronium cation, $[NO_2]^+$. We note that both the hydroxyl group and the alkyl group are activating ortho-para substituents but the hydroxyl group is the more powerful one and therefore directs the incoming nitro groups ortho and para to itself.



(c) This is an azo compound that contains the -N=N- linkage and the compound is most easily named as a derivative of the substituted benzoic acid rather than as a nitrobenzene derivative. The name of the compound is therefore 5-(p-nitrophenyl)azo-2-hydroxybenzoic acid. We note the IUPAC system favors naming this compound as a substituted carboxylic acid rather than a substituted phenol. This compound is typical of many compounds called azo dyes which have special coloring properties and contain the azo linkages. They are made by the electrophilic attack of a diazonium cation upon a highly activated aromatic ring (phenol, phenoxide, aniline). The weak electrophile, the diazonium cation, can be made in turn from an aniline derivative. In this case, the aniline derivative is p-nitroaniline which can be made from aniline. However, this procedure involves more than simply treating the amine with the nitrating reagents (mixed acid). Such an action would have severe consequences with very little of the desired product formed. Aniline is a fairly potent base and will be protonated to an anilium salt where $-NH_3^+$ is deactivating and meta directing. Also, oxidation to parabenzoquinone is possible. To avoid these difficulties, we "protect" the amino group by acetylating with acetic anhydride. After the nitration has occurred the protecting acetyl group may be removed by acidic hydrolysis. The resulting p-nitroaniline may now form the diazonium cation through the reagent, nitrous acid: (HONO) which is generated in situ from a mixture of sodium nitrite ($NaNO_2$) and a protic acid. The reaction sequence is:



The diazonium cation may now undergo a typical electrophilic aromatic substitution upon salicylic acid to give us the final product. We note that salicylic acid contains both a carboxyl and a hydroxyl functionality and the product is directed para to the latter substituent since the hydroxyl group is an ortho, para activating group while the carboxyl substituent is deactivating and meta directing. Salicylic acid, itself, can be made through the Kolbe reaction of phenol. Summarizing this:

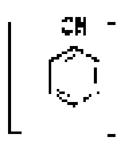
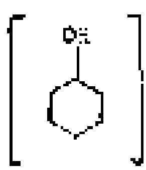


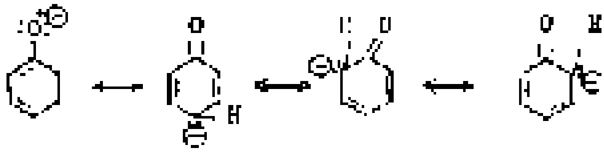
CHARACTERIZATION TESTS

• PROBLEM 23-30

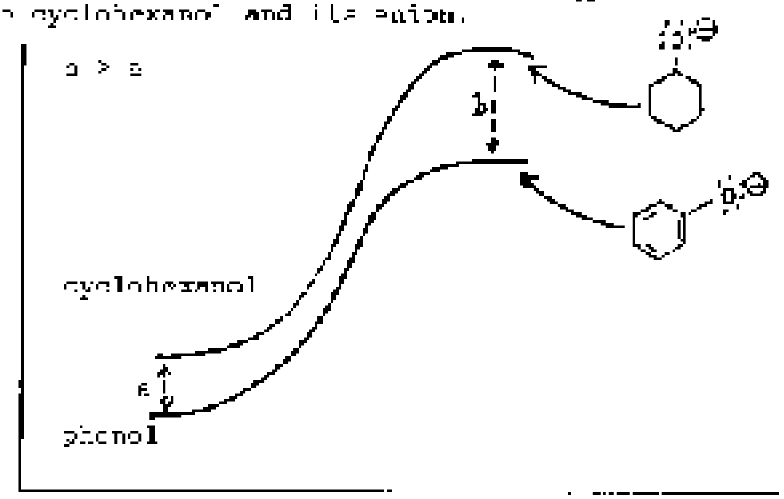
Give for each of the following pairs of compounds a chemical test, preferably a test-tube reaction, that will distinguish between the two compounds. Write a structural formula for each compound and equations for the reactions involved.

(a) phenol and cyclohexanol.
(b) methyl p-hydroxybenzoate and p-methoxybenzoic acid.
(c) 9,10-anthraquinone and 1,4-anthraquinone.

Solution: (a) Both alcohols and phenols contain the hydroxyl group (-OH) but the group is directly attached to an aromatic ring in phenols and this causes a drastic change in their properties. Phenol  is a significantly stronger acid than cyclohexanol  and this difference can be related to phenol's aromaticity. Aromaticity stabilizes phenol in comparison to cyclohexanol, but the stability difference is even greater for the phenoxide anion in relation to the cyclohexanol anion. The stability of the phenoxide anion lies in its ability to delocalize its negative charge as seen in its various resonance structures.

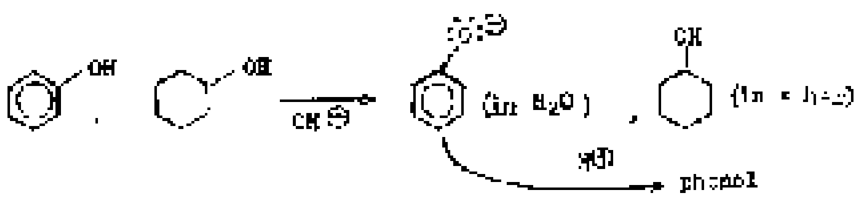


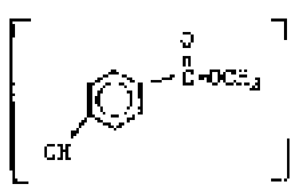
The reason that phenol is a stronger acid than cyclohexanol is that the energy difference between phenol and the phenoxide anion is less than the energy difference between cyclohexanol and its anion.

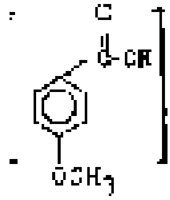


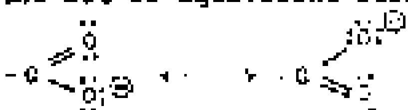
Reaction Coordinate

Another way of explaining this difference in acidity is to say that the activation energy (the energy differential between the reactants and the transition state of the reaction) for phenol's ionization is less than that of cyclohexanol's loss of a proton. NaOH is a base that will receive a proton from phenol but not from the weaker acid cyclohexanol. Experimentally, this means that the phenoxide salt will be in the aqueous layer of an ethereal-aqueous mixture and will easily be removed. Subsequent protonation will yield phenol.

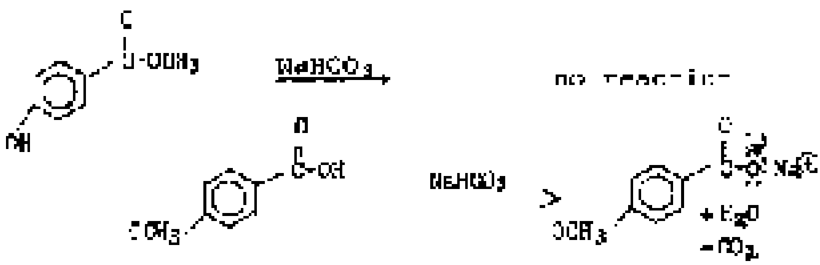


(b) methyl-p-hydroxybenzoate  is

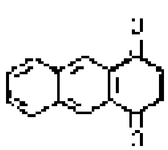
an ester whose acyl portion contains a phenolic functionality. p-Methoxybenzoic acid  is a carboxylic acid with a phenolic ether (anisole) attached to the carboxyl group. Both the carboxylic acid and the ester have acidic functionalities and both would form their corresponding anions when treated with the potent base NaOH. However, when the weaker, more selective base $NaHCO_3$ is used, separation is achieved only because p-methoxybenzoic acid will ionise and have its salt separated into the aqueous phase. Thus a carboxylic acid is more acidic than a phenol. This can be explained by the different activation energies for ionisation. The key difference is that the delocalization in the carboxylate anion stabilizes this species more relative to the reactant carboxylic acid than delocalization stabilizes the phenoxide anion in relation to the starting phenol. The delocalization in the carboxylate anion is significant as seen in the set of equivalent resonance structures.



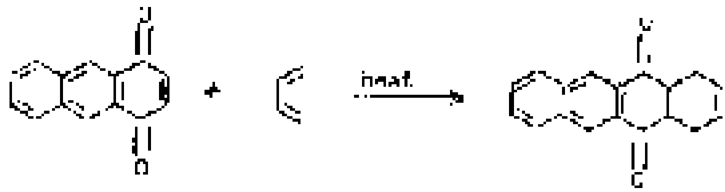
Thus while the phenolic ester, methyl p-hydroxybenzoate does not react with $NaHCO_3$, the carboxylic acid p-methoxybenzoic acid will and this is the basis of their separation.



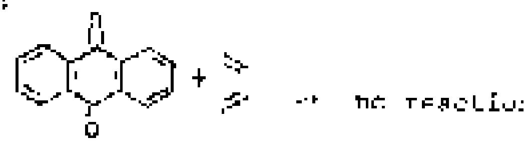
(c) The Diels-Alder reaction involves the 1,4 addition of an alkene to a conjugated diene. It is often named as a [4+2] cycloaddition because a four π electron system (the diene) adds to a two-π electron system (the alkene or dienophile) to form a cyclic compound. In this heat induced process two π bonds are converted to two σ bonds. The mechanism is believed to be concerted. Reactive dienophiles have electron-withdrawing groups in conjugation with the double bond. One class of compounds that fit this description are quinones, the oxidation products of phenols. For example, the quinone 1,4-anthraquinone,



has a "reactive" or "alkene"-type double bond which will react with a diene such as 1,3-butadiene to form a tetracyclic compound.



On the other hand, 9,10 anthraquinone will not react with 1,3 butadiene:



The reason for this is that 9,10 anthraquinone has no reactive double bonds and each double bond is, in fact, part of an aromatic system. Disrupting a double bond would destroy the extra stability of the aromatic system and therefore this compound cannot act as a dienophile.

CHAPTER 24

ORGANOSULFUR COMPOUNDS

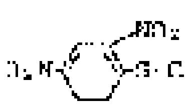
NOMENCLATURE AND STRUCTURE

• PROBLEM 24-1

Write the structural formulas for the following substances:

(a) di-t-butyl thioketone
(b) ethylene sulfide
(c) methyl thioacetate
(d) β,β' dichloroethyl sulfide (mustard gas)
(e) tris-(methylsulfonyl)-methane
(f) cis 1,4 dithiacyclohexane dioxide
(g) trimethylene disulfide
(h) 5-thia-1,3-cyclopentadiene (thiophene)

Typical Organosulfur Compounds

Compound	Oxygen analog	Common name	IUPAC name
		A. Divalent sulfur	
CH_3SH	ROH	methyl mercaptan	methanethiol
$C_2H_5SC_2H_5$	ROR	diethyl sulfide diethyl thioether	ethylthio-ethane
$C_6H_5SSC_6H_5$	R-O-O-R	diphenyl disulfide	phenyldithio-benzene
$(CH_3)_3\overset{\oplus}{S}\ \overset{\ominus}{Br}$	$R_3\overset{\oplus}{O}\ \overset{\ominus}{X}$	trimethylsulfonium bromide	
$(C_6H_5)_2C{=}S$	$R_2C{=}O$	thiobenzophenone	
	ROCl	2,4-dinitrobenzene-sulfenyl chloride	2,4-dinitro-benzenesulfenyl chloride
$C_2H_5O{-}\overset{\overset{S}{\parallel}}{C}{-}SCH_3$	$RO{-}\overset{\overset{O}{\parallel}}{C}{-}OR$	O-ethyl S-methyl xanthate	

B. Sulfur greater than bivalent

$C_2H_5-\overset{O}{\overset{\|\|}{S}}-OH$	ethanesulfinic acid	ethanesulfinic acid
$CH_3-\underset{O}{\underset{\|\|}{\overset{O}{\overset{\|\|}{S}}}}-OH$	methanesulfonic acid	methanesulfonic acid
$CH_3-\underset{O}{\underset{\|}{\overset{O}{\overset{\|}{S}}}}-Cl$	methanesulfonyl chloride	methanesulfonyl chloride
$CH_3-\overset{O}{\overset{\|\|}{S}}-C_2H_5$	ethyl methyl sulfoxide	methylsulfinylethane
$C_6H_5-\underset{O}{\underset{\|}{\overset{O}{\overset{\|\|}{S}}}}-C_6H_5$	diphenyl sulfone	phenylsulfonylbenzene

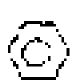
Figure 1

<u>Solution</u>: The nomenclature of organosulfur compounds is analogous to that of the previous organic compounds. Divalent sulfur derivatives (organosulfur compounds with two bonds attached to sulfur) are structurally similar to oxygen compounds, and they are often named by using the prefix thio in conjunction with the name of the corresponding oxygen compound.

For example:

(1) $CH_3-\overset{S}{\overset{\|\|}{C}}-CH_3$ dimethyl <u>thio</u>ketone

(2) CH_3-CH_2-SH ethane<u>thiol</u>

(3) -SH <u>thio</u>phenol

The replacement of a methylene or methine group with sulfur are often named by using the term "thia" in conjunction with the name of the corresponding hydrocarbon.

For example:

(1) CH_3CH_2–S–CH_3 2-thiabutane

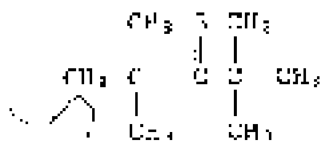
(2)  2,5-dithiahexane 2,5-dioxide

Other typical sulfur compounds with their common and IUPAC names are listed in Fig. 1.

(a) di t-butyl thioketone:

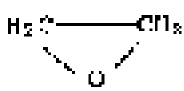
Since the prefix "thio" is inserted before "ketone", we know that the oxygen of a regular ketone is replaced with sulfur:

The di t-butyl tells us that there is a tert-butyl group on each side, therefore the structural formula is:

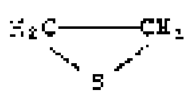


(b) ethylene sulfide:

By analogy with ethylene oxide:

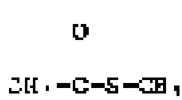


This compound has the "oxi" replaced with "sulfi", therefore the oxygen in ethylene oxide should be replaced with sulfur:



(c) methyl thioacetate:

Since there is a prefix "thio" in front of "acetate," we replace the oxygen in O–CH_3 with S–CH_3 to get:



(d) β,β'-dichlorodiethyl sulfide:

This compound is analogous to the ethers:

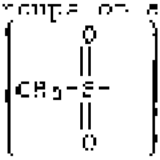
Ether	Sulfur Compound
diethyl ether	diethyl sulfide
$C_2H_5-O-C_2H_5$	$C_2H_5-S-C_2H_5$

In fact, another common name for β,β'-dichloroethyl sulfide is β,β'-dichloroethyl thioether. The β refers to the second carbon away from the sulfur. The prime ("'") on the second β refers to the second chloroethyl group. More specifically, the chlorine on the second chloroethyl group is also on a β carbon. Therefore, the structural formula is:

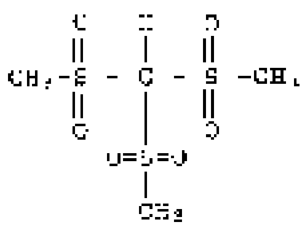
$$Cl\ CH_2CH_2\ S\ CH_2CH_2\ Cl$$

(e) <u>tris-(methylsulfonyl)-methane</u>:

The nomenclature used here involves the naming of substituent groups on a methane molecule. The methyl sulfonyl group



is derived from methylsulfonic acid (See Fig. 1). The <u>tris</u> tells us that there are three of these groups, therefore:



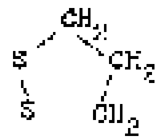
(f) <u>cis-1,4-dithiacyclohexane dioxide</u>:

The "thia" tells us that sulfur has replaced carbon in cyclohexane at the 1,4 positions. The dioxide tells us that an oxide linkage (-O) is on each sulfur. The <u>cis</u> tells us that the oxide linkages is on the same side of the cyclohexane molecule. Remember that the

$-\ddot{S}\rightarrow O$ group is not planar, unlike its carbonyl counterpart. The reason for this is that the π bond formed here is not a $p_\pi-p_\pi$ overlap (as it is in the $>C=O$ π bond). This type of π bond is a $p_\pi-d_\pi$ overlap, which involves the vacant d orbitals of sulfur. The S-O bond is a hybrid of two resonance structures: $^{\oplus}:\ddot{S}-\ddot{O}:^{\ominus}$ and $:\ddot{S}=\ddot{O}:$, and both these resonance structures are important. Therefore, the structural formula is:

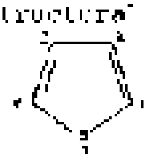
(g) trimethylene disulfide:

This name indicates that a disulfide, -S-S-, is bonded to a trimethylene group: $CH_2CH_2CH_2$. Therefore, the structural formula is:



(h) 5-thia-1,3-cyclopentadiene:

The prefix "5-thia" tells us that a carbon is replaced with sulfur at the 5 position of 1,3-cyclopentadiene. Therefore the structural formula is:



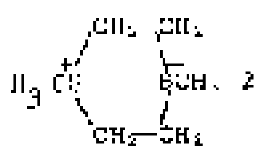
Remember that in simple cycloalkenes, the double-bonded carbons are considered to occupy positions 1 and 2.

• PROBLEM 24-2

How many and what kind of stereoisomers would you expect for each of the following compounds?

(a) methylethyl-n-butylsulfonium bromide

(b) $[CH_3(C_2H_5)SCH_2CH_2S(CH_3)(C_2H_5)]^{2+}$ $2\,Br^-$

(c)  $2Br^-$

Solution: Stereoisomers are isomers that are different from each other only in the way the atoms are oriented in space. Two stereoisomers are classified as either enantiomers, if they are nonsuperimposable mirror images of each other, or diastereomers, if they are not mirror images of each other. A carbon atom with four different groups attached to it is a chiral center. A meso compound is a compound whose molecules are superimposable on their mirror images even though they contain chiral centers. A meso compound is often recognized by a plane of symmetry in the compound.

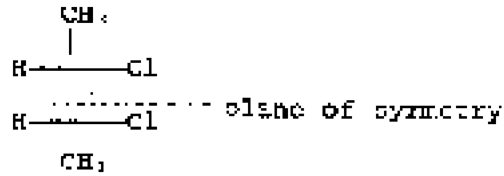


Fig. 1 - Fischer Projection of 2,3-dichlorobutane.

However, the absence of a plane of symmetry does not necessarily mean that a molecule is chiral. (e.g. trisubstituted nitrogen compounds).

(d) methylethyl-s-butylsulfonium bromide:

The method that was used here is the one where the compound is named as a substituted methane, therefore we have a methyl, an ethyl, and a sec-butyl group attached to the sulfonium ion. Using the Fischer projection, we have:

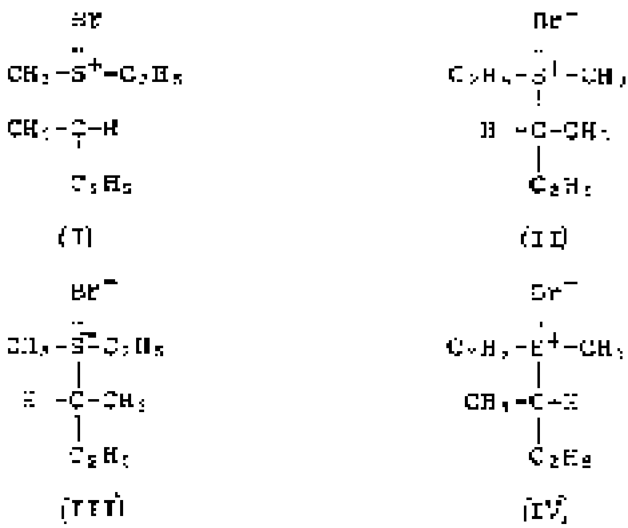


Fig. 2

Therefore, there are four optical isomers, with isomers I and II, and III and IV being enantiomers.

The possibility of four optical isomers is due to the nonplanarity of the bonds formed by the sulfonium ion, as opposed to the planar carbonium ion:

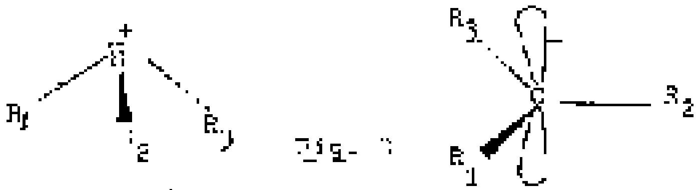


Fig. 3

The sulfonium ion configuration shown in Fig. 3 is quite stable, as opposed to the configurational instability of ammonia derivatives, which undergo rapid inversion.

Optically active forms of sulfonium ions are stable and have been isolated.

The method used to draw stereoisomers of this type is to first draw one isomer in the Fischer projection. Then we draw its mirror image and see if they are superimposable. If they are not, they are stereoisomers, specifically enantiomers (see structures I and II of Fig. 2). Then we switch the first left hand group with the first right hand group and compare it with the original structure to see if they are superimposable. If they are not superimposable, they are stereoisomers (compare structure I with structure III in Fig. 2). We continue this process with all the chiral centers until we reach the other end of the molecule.

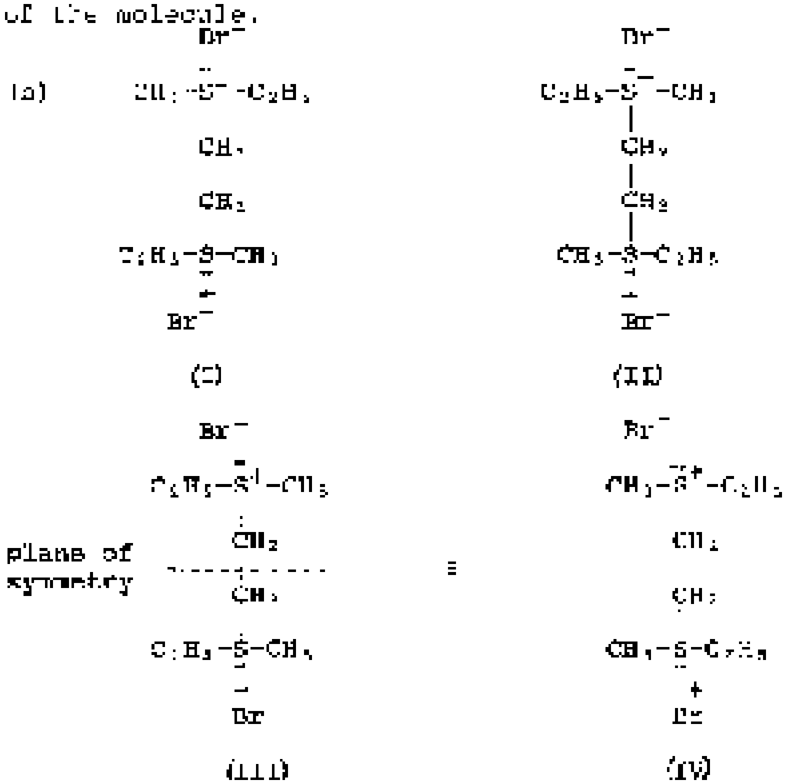
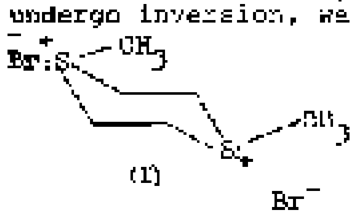


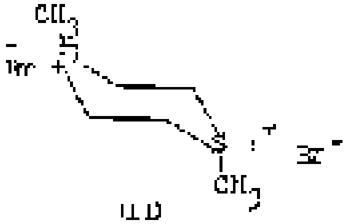
Fig. 4

Therefore, there are three stereoisomers. Isomers I and II are enantiomers, while isomers I and III are diastereomers. Note that isomer III has a plane of symmetry, therefore it has no enantiomers. Structure III is called a meso compound.

(c) Since the configuration of a sulfonium ion does not undergo inversion, we have the following stereoisomers:



cis



(II)

trans

Fig. 5

Remember that "cis" in a cyclic compound tells us that the two substituent groups are on the same side of the ring; trans tells us that they are on opposite sides. The mirror images of both structures, I and II, in Fig. 5, are superimposable on their respective mirror images, therefore there are no enantiomers.

THIOLS

• PROBLEM 24-3

The sulfhydryl group of coenzyme A plays an important role in the biosynthesis of fatty acids from units of acetic acid. The key steps are suggested to be carboxylation with carbon dioxide of acetyl coenzyme A (which is a thioester abbreviated as $CH_3\overset{O}{\overset{\|}{C}}-S-CoA$) to give malonyl coenzyme A ($HO_2CCH_2\overset{O}{\overset{\|}{C}}-S-CoA$), followed by condensation of the malonyl coenzyme A with acetyl coenzyme A, or a molecule of an acyl coenzyme A, to produce an acyl malonyl coenzyme A ($HO_2C-\underset{COCH_2R}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-S-CoA$). This is followed by decarboxylation and reduction to an acyl coenzyme A with two more carbon atoms than the starting acyl coenzyme A. Each repetition of the process gives a fatty acid (or thioester of a fatty acid) with an additional two carbons. All the steps are of course controlled by specific enzymes.

5'(adenosine 3' phosphate) $OP(O)(OH)OP(O)(OH)OCH_2C(CH_3)_2$

$-CH(OH)-CONH(CH_2)_2CONH(CH_2)_2SH$

coenzyme A (CoA-SH)

(a) Write out the complete structure of coenzyme A as corresponds to the above condensed formula; what products would you expect coenzyme A to give on vigorous hydrolysis?

(b) Work out the steps for synthesis of hexanoic acid from acetic acid with the aid of coenzyme A, using the abbreviation CoA-SH and indicating the general nature of each step in terms of the kind of reagents that might be used to achieve it in ordinary laboratory operations. What advantages would you expect to accrue from CoA-SH as compared to CoA-OH as the acyl carrier?

(c) Suppose the enzymic synthesis of hexanoic acid to be carried on in the presence of radioactive carbon dioxide; would the postulated course of the reaction be precluded if the hexanoic acid produced were completely devoid of radioactivity? Explain in detail.

Solution: (a) To write out the complete structure of coenzyme A (using the condensed formula in the question), we must first learn the structure of ribose (a 5-carbon sugar), and examine the numbering of its constituent carbons:

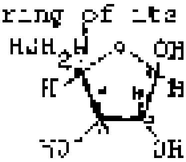


Fig. 1 - Ribose

The structure of adenine (6-aminopurine - a nitrogenous base) is:

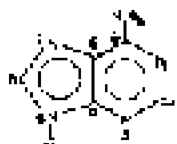


Fig. 2 - Adenine

When the 1-carbon of ribose is connected to the 9-nitrogen of Adenine, the combined structure is called adenosine, which is a nucleoside (a base-sugar unit):

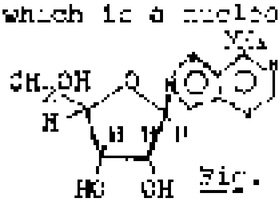


Fig. 3 - Adenosine.

The primes (') on the numbers in the condensed formula refer to the carbons on the ribose molecule. The 3'-phosphate indicates that a phosphate molecule replaces the OH group located on the 3' carbon of the ribose molecule. The 5' implies that the rest of the structure is connected to the 5' carbon of ribose. Now that we have reviewed the structure of the constituents of coenzyme A, we can write out the complete structure:

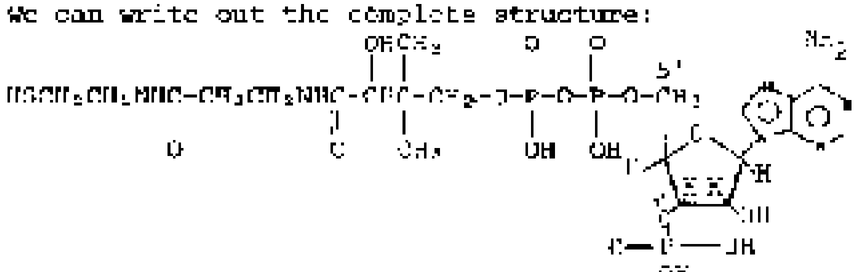
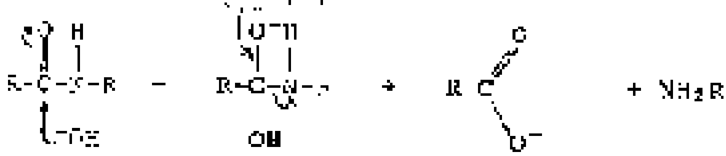
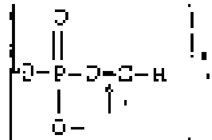


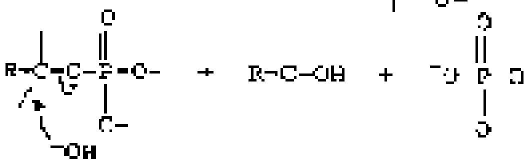
Fig. 4 Coenzyme A

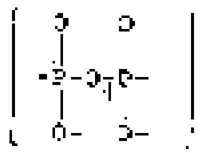
Upon vigorous hydrolysis, the following bonds would be hydrolyzed:

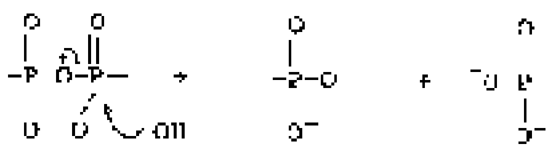
(1) amide bonds  :

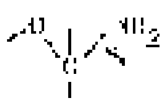


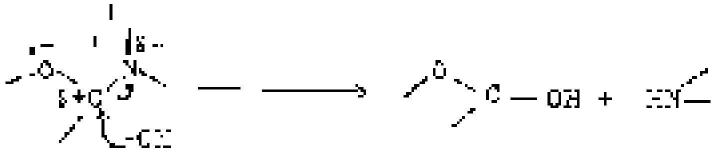
(2) Phosphate ester bonds  :



(3) Pyrophosphate bonds  :



(4)  bonds:



hemiacetal

Therefore, looking at the total molecule, the bonds that would break would be:

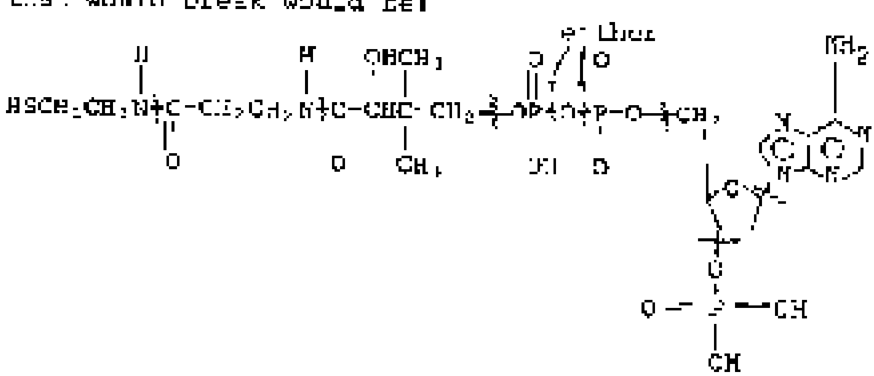


Fig. 5 - Coenzyme A

The products upon hydrolysis are:

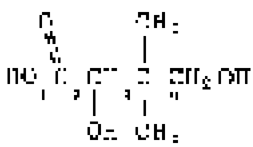
(1) 2-aminoethanethiol:

$HSCH_2CH_2NH_2$

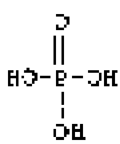
(2) β-aminopropionic acid:

$NH_2CH_2CH_2\overset{O}{\overset{\|}{C}}-OH$

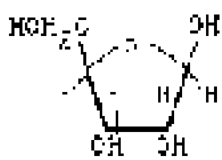
(3) 2,4-dihydroxy-3,3-dimethylbutanoic acid:



(4) Phosphoric acid:

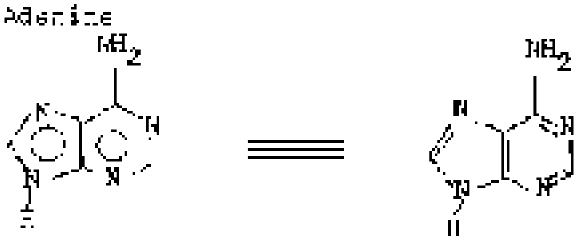


(5) D-ribose:



The prefix "D" tells us that D ribose belongs to the same optical family as D-glyceraldehyde. The other stereoisomer, L-ribose, would be related to L-glyceraldehyde. Note that the symbols D and L refer to configuration, and not to sign of rotation.

(6) Adenine



(b) The general steps to this synthesis are:

(1) $CH_3-\overset{O}{\overset{/\!/}{C}}-OH + CoA-SH \rightarrow CH_3\overset{O}{\overset{\|}{C}}-S-CoA + H_2O$

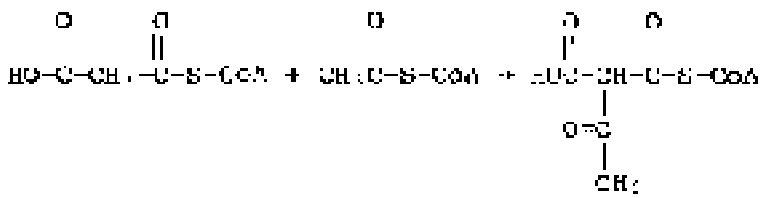
acetic acid+coenzyme A→acetyl coenzyme A

This step is a thiol-carboxylic acid reaction to yield a thioester, acetyl coenzyme A.

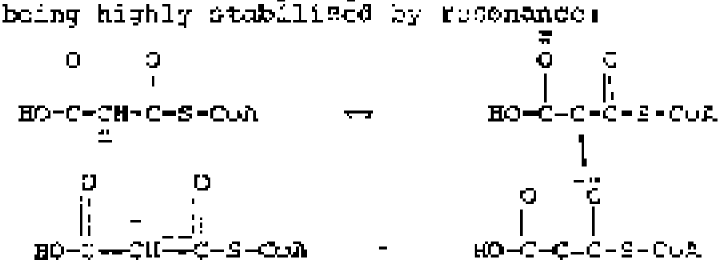
(2) 

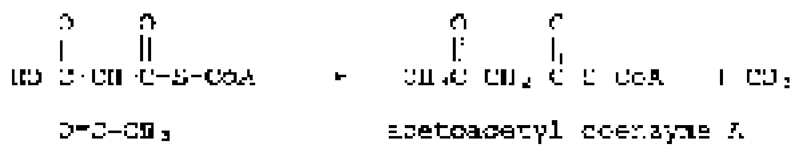
Malonyl coenzyme A

This step is a carboxylation reaction. This step is possible due to the acidity of the α-hydrogen (the hydrogen on the carbon next to —C(=O)—).

(3) 

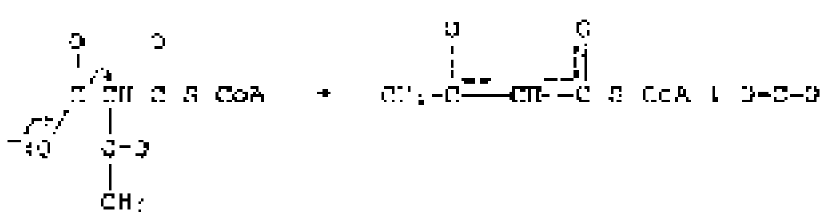
This step is a Claisen-type condensation with $CH_3C(O)SCoA$ being attached. Malonyl coenzyme A is a β-keto thioester, therefore the α-hydrogen is acidic, with the resultant anion being highly stabilized by resonance:

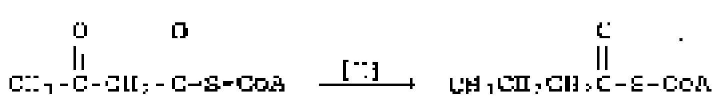


(4) 

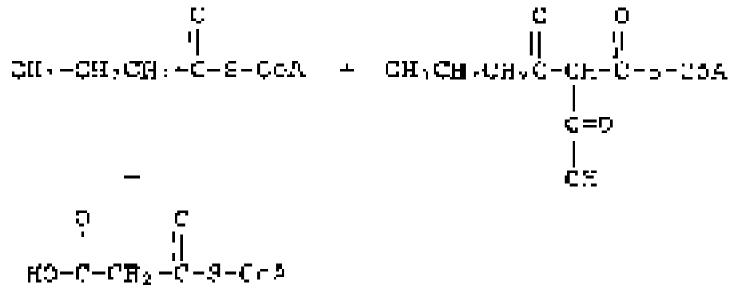
acetoacetyl coenzyme A

This step is a decarboxylation reaction. This reaction is again possible due to this β-keto thioester's ability to accommodate a negative charge on the α-carbon common to all the carbonyls.

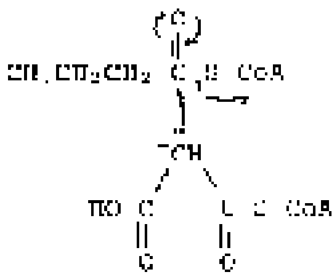


(5) 

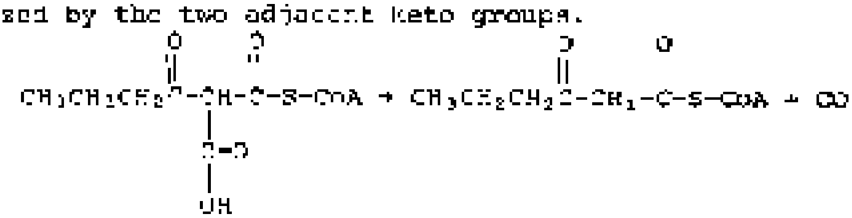
This step is a reduction reaction (reduction of a ketone) resulting in a thiol ester ([H] = reducing agent; usually [H] = NADPH + H⁺).

(6) 

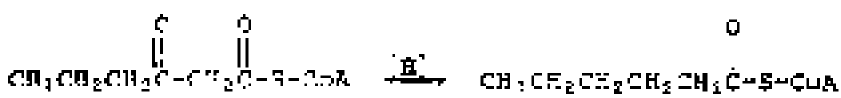
This step is Claisen-type condensation, with ⁻S-CoA as the leaving group:



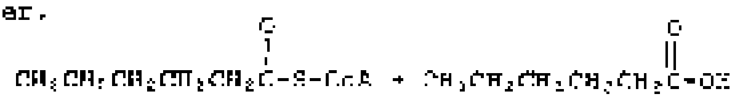
Remember that the negative charge on the carbon is stabilized by the two adjacent keto groups.

(7) 

This step is a decarboxylation reaction.

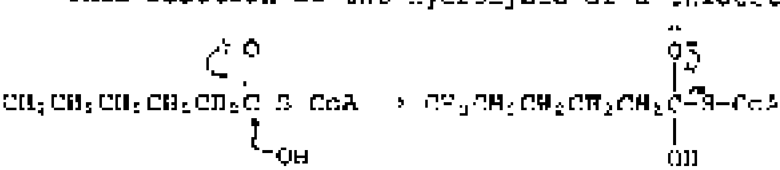
(8) 

This step is a reduction reaction (reduction of a ketone to a methylene group: $-CH_2-$), resulting in a thiol ester.

(9) 

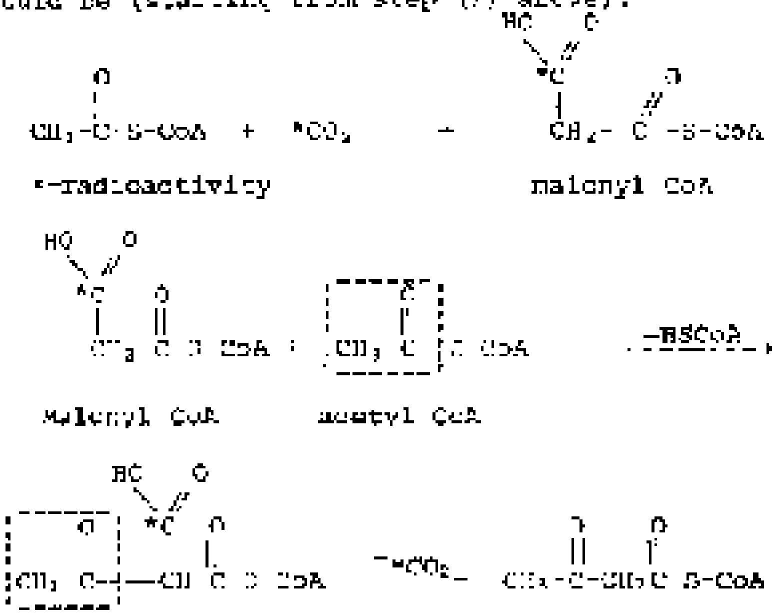
+ ⁻OH hexanoic acid

This reaction is the hydrolysis of a thioester:



The advantage of CoA-SH over CoA-OH is that ^-SH is a better leaving group than ^-OH. Also, C-S bonds are weaker than C-O and C-N bonds: 65, 81, and 73 kcal-mole^{-1} respectively; therefore, of the three types of bonds, the C-S bond is the easiest to break.

(c) If radioactive CO_2 were used and the hexanoic acid produced was devoid of radioactivity, this would not necessarily preclude the postulated course of reaction because the decarboxylation step may involve loss of only the carboxyl group that was initially formed from the radioactive CO_2. A possible pathway for CO_2 incorporation in the synthesis of fatty acids which would show this would be (starting from step (2) above):



*-radioactivity

malonyl CoA

Malonyl CoA

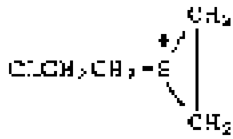
acetyl CoA

As we can see from the above mechanism, elimination of only the carboxyl group that was initially formed from the radioactive CO_2 is a possible event. In fact, in fatty acid synthesis of E. Coli, it is the carboxyl group from the $^*CO_2$ that is eliminated. This was determined by using $^*CO_2$ as explained in the problem, therefore the role of CO_2, in the biosynthesis of fatty acids, is similar to that of a catalyst.

ALKYL SULFIDES

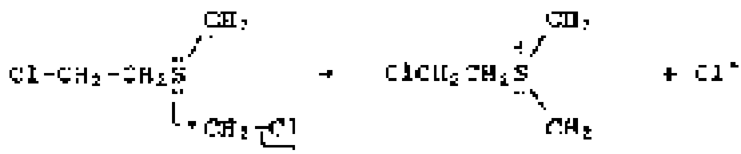
• PROBLEM 24-4

Mustard gas or bis-(β-chloroethyl) sulfide, $(ClCH_2CH_2)_2S$, is an oily liquid that was used extensively as poison gas in World War I. It is a deadly vesicant that causes blindness and numerous other effects. The active agent is actually the cyclic sulfonium salt

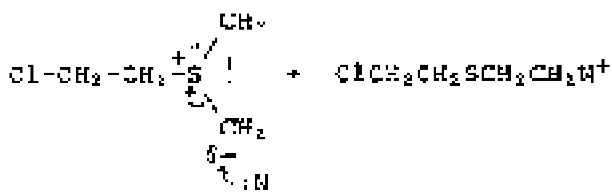


which reacts with nucleophilic materials in the body. The formation of the cyclic sulfonium salt can be regarded as an internal or intramolecular S_N2 displacement reaction. Write out this reaction mechanism. What mechanism does this process suggest for the subsequent reaction of the cyclic sulfonium salt with nucleophilic reagents?

Solution: Sulfides are good nucleophiles because they contain sulfur with its free pair of electrons. They readily undergo S_N2 displacements. This problem involves an intramolecular displacement:



The cation contains a three member ring. This ring is similar to cyclopropane, or ethylene oxide, and so are their properties. A combination of angle strain and positive charge on the carbons in the ring make the cyclic carbons susceptible to nucleophilic reagents. Therefore, the mechanism is:



Note that this reaction with nucleophiles is the reverse of the formation of the cyclic sulfonium salt.

• PROBLEM 24-5

Methionine is the active agent for many biological methylations, particularly of nitrogen. Transmethylation involving methionine is activated by ATP. Suggest a mechanism for the transfer of a methyl group from methionine to an amine in which ATP would combine with methionine in such a way as to make the methyl group of the methionine readily reactive toward nucleophilic agents.

Solution: Adenosine triphosphate, ATP, is the key compound which serves as the reservoir of chemical energy in all living systems. Its structural formula is:

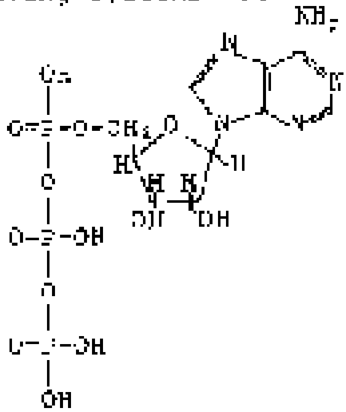
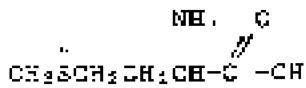
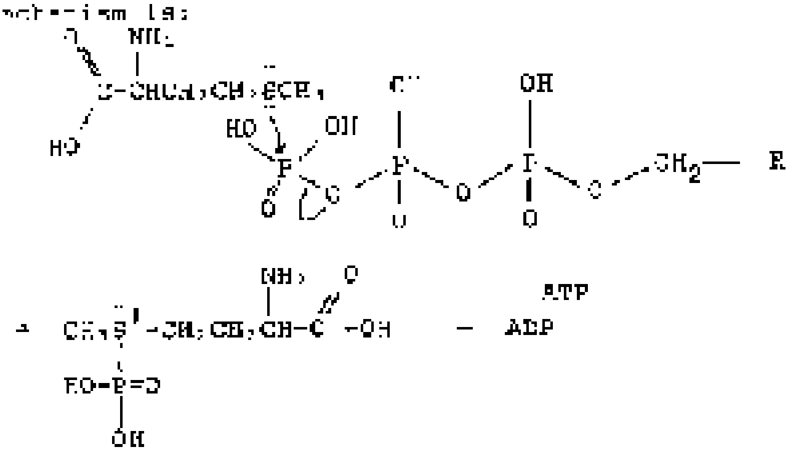


Fig. 1. Adenosine Triphosphate (ATP)

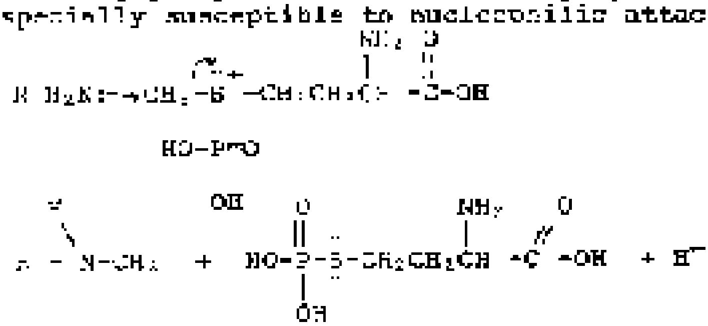
The structural formula for methionine is:



Sulfur compounds are strong nucleophiles and pyrophosphate bonds are weak, therefore the reaction mechanism is:



This reaction results in the formation of a sulfonium ion attached to the methyl group. The sulfonium ion is a good leaving group, and makes the methyl group attached to it especially susceptible to nucleophilic attack:

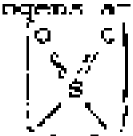


SULFOXIDES AND SULFONES

• PROBLEM 24-8

(a) Methyl chloromethyl sulfone reacts with strong alkali to yield ethylene and sodium sulfite. Write a mechanism for this reaction which is in accord with the reagents and the products. (b) Butadiene when heated with sulfur dioxide undergoes 1,4-addition with formation of an unsaturated cyclic sulfone. How might this sulfone (in conjunction with the reaction which gives an alkene from an α-halosulfone) be used in a synthesis of cyclobutadiene?

Solution: (a) Hydrogens attached to a carbon next to a sulfonyl group



are acidic; this is analogous to the acidity of α-hydrogens in carbonyl compounds. The stability of the resultant anion is due to resonance with oxygen:

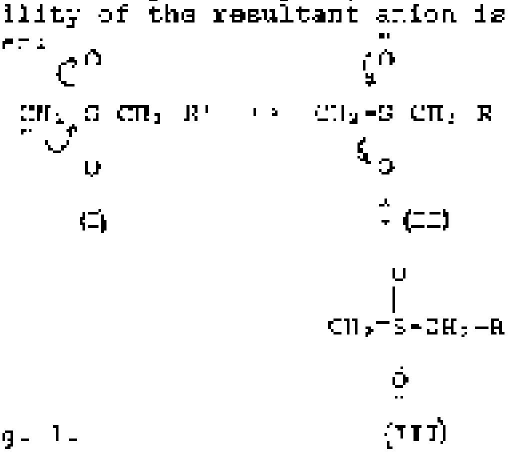
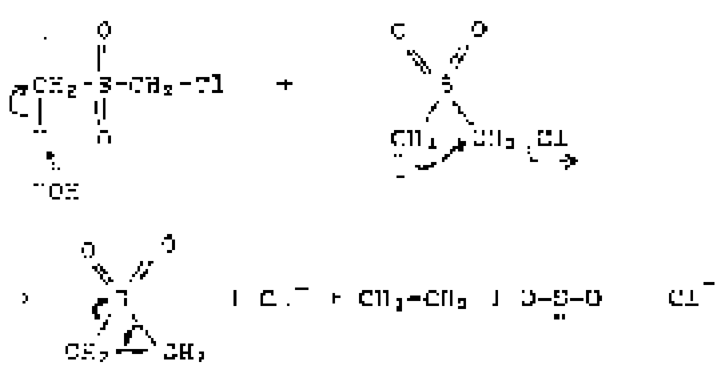


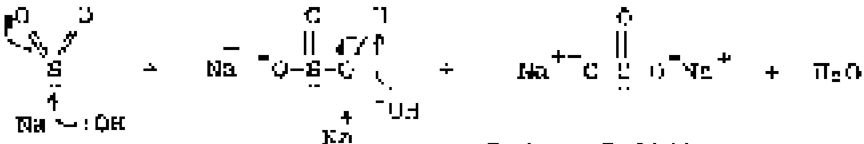
Fig. 1.

Structures II and III are particularly good resonance structures because the negative charge is on oxygen, the atom which is most able to accommodate the charge (compare the stabilities of ^-OH and $^-CH_3$).

The mechanism for this reaction is:

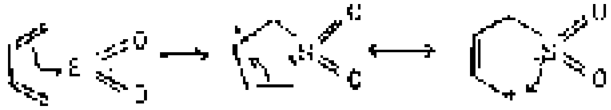


episulfone   ethylene

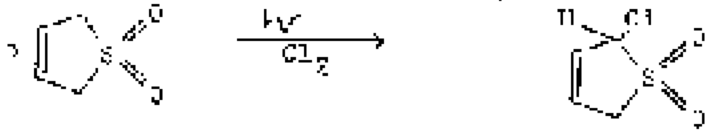


Sodium Sulfite

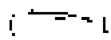
(b) Alkenes are electron rich, therefore we would expect the butadiene electrons to attack sulfur:

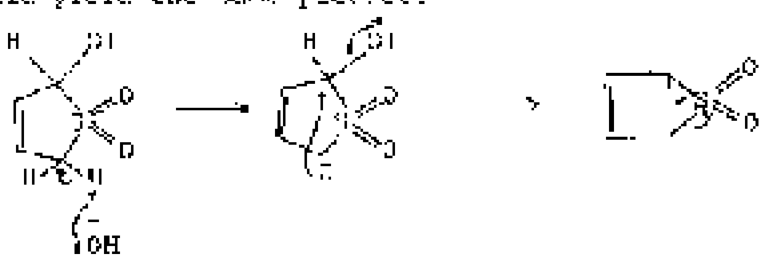


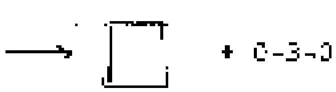
butadiene 1,4 addition



unsaturated cyclic sulfone

Note that in this last step, the photochemical chlorination is a good reaction because: (1) Vinyl hydrogens () are hard to abstract while allylic hydrogens () are easy to abstract; (2) all four allylic hydrogens in the unsaturated cyclic sulfone are equivalent, therefore substitution at any allylic hydrogen would yield the same product.





The last step of this reaction, the elimination of sulfur dioxide to give an alkene, we saw in part a of this problem. However, this reaction does not seem to work in the laboratory.

• PROBLEM 24-7

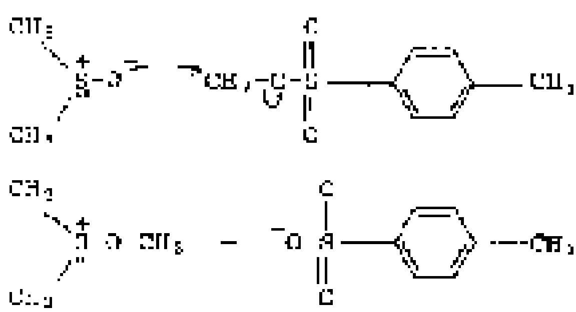
Methyl p-toluenesulfonate reacts with dimethyl sulfoxide to yield a solution whose n.m.r. spectrum shows, besides the methyl resonances of the solvent and ring methyl substituent, two kinds of methyl resonances in the ratio of 2:1. Evaporation of the solvent gives a solid which has an elemental analysis corresponding to combination of one molecule of methyl p-toluenesulfonate with one molecule of dimethyl sulfoxide. In contrast, methyl iodide reacts with dimethyl sulfoxide to give a product which shows only one kind of methyl group in its n.m.r. spectrum and which, when treated with silver p-toluenesulfonate, produces an isomer of the compound made directly with methyl p-toluenesulfonate. What are the structures of these compounds? Write equations for the reactions involved and suggest a possible reason for the difference in the kind of compound formed by methyl iodide and methyl p-toluene sulfonate

<u>Solution</u>: The $\rangle S=O$ "double bond" is the result of a $p_\pi - d_\pi$ overlap between oxygen and sulfur. This overlap is not as good as a $p_\pi - p_\pi$ overlap, therefore there is a greater $\rangle \overset{+}{S}-\overset{-}{O}$ character in this bond than there is in a carbonyl double bond. Both resonance structures of the $\rangle S=O$ bond are important:

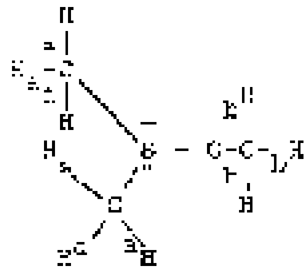
$$\rangle \overset{+}{S}-\overset{-}{O} \longleftrightarrow \rangle S=O$$

As a result, both these resonance structures play a vital role in the chemistry of sulfoxides.

<u>dimethyl sulfoxide - Methyl p-toluenesulfonate reaction</u>:



We can see from this reaction that the greater $\rangle \overset{+}{S}-\overset{-}{O}$ character makes oxygen a potent nucleophile, enabling the oxygen to execute a S_N2 displacement (compare this with the chemistry of carbonyl compounds). Disregarding the ring methyl substituent, we can see that there are 2 sorts of methyl groups in the product:

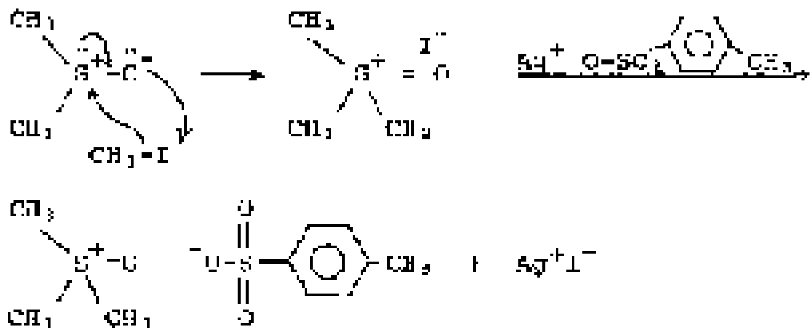


Product I

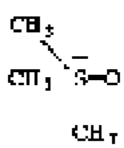
This structure will give us an n.m.r. with two kinds of methyl resonances, in the ratio of 2:1 (6 "a" hydrogens to 3 "b" hydrogens).

<u>dimethyl sulfoxide - Methyl iodide reaction:</u>

The greater dipolar structure of the $\rangle$S=O bond plays an even more significant role in this reaction which involves a nucleophilic attack on a halide:



This product has only 1 set of methyl groups:

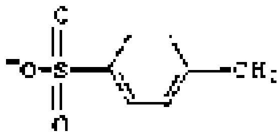


Product II

If we compare product I with product II, we see that they are isomers:

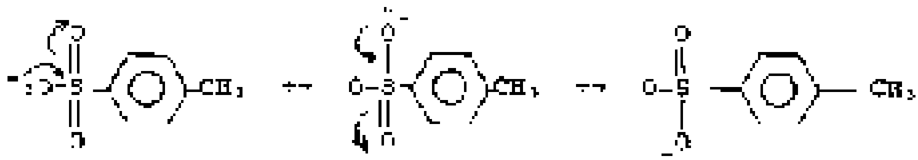
I II

The reason for the two different products has to do with the nature of the group attached to the methyl group, specifically, the resultant anion:

 vs ^-I

Anion III Anion IV

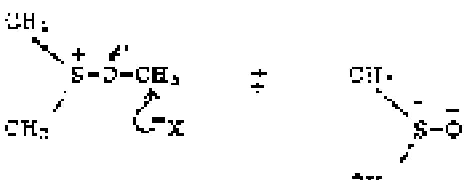
Anion III is not a good nucleophile due to resonance of the negative charge:



The iodide ion is a good nucleophile.

If we call the group attached to the methyl group X, and then analyze the situation, we will understand why we get two products:

This is a fast reaction but it is reversible if X^- is a good nucleophile:

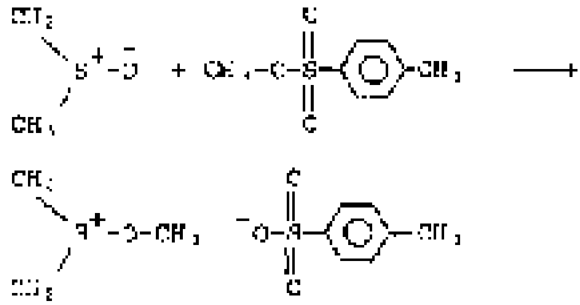


V VI

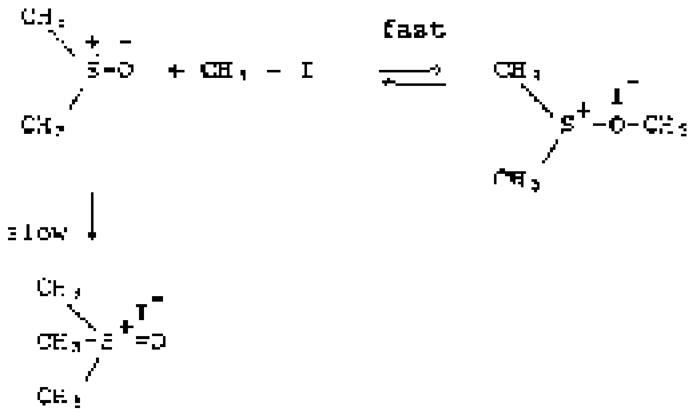
This is the case with the second reaction (with CH_3I). Because of this the solution will be in equilibrium between the two states (structures V & VI). For the first reaction, this is not the case and it is essentially an irreversible reaction under the given conditions. The reversible reaction will yield a different product because there is a slow reaction which can occur under these conditions:

This reaction, although slow, is the favorable product because it is thermodynamically more stable, that is, its total bond energies are greater than the other product, yielding a compound lower in energy and therefore more stable.

In summary, the first reaction will go the faster route, and being irreversible, will not be able to undergo the slower reaction to yield the more favorable product:



The second reaction, which is reversible, will eventually yield the more favorable product:



This is an example of a rate-controlled vs. equilibrium-controlled reaction. If the rate controlled product is reversible, and sufficient time is allowed for the equilibrium-controlled reaction to occur, the more stable product will be the result.

SULFENIC, SULFINIC AND SULFONIC ACIDS

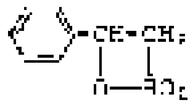
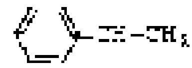
• PROBLEM 24-6

Show how you would synthesize the following compounds from the indicated starting materials and any desired inorganic reagents.

(a) di-n-octyl sodium sulfosuccinate, $CH_3(CH_2)_7O_2CCH_2CH(SO_3Na)CO_2(CH_2)_7CH_3$ ("Aerosol" detergent) from maleic anhydride and n-octyl alcohol.

(b) $(CH_2)_3(SO_3H)_2$ from $(CH_2)_3Br_2$

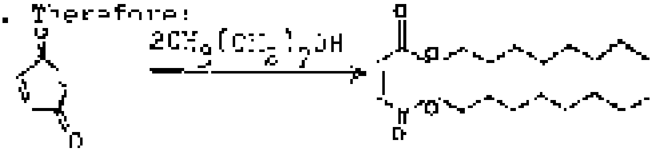
(c) methyl 1-butanesulfonate from n-butyl bromide

(d)  from 

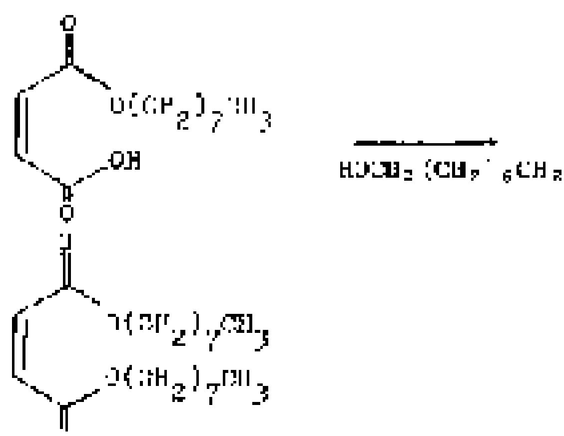
(e) optically active ethyl benzenesulfinate from optically active 2-octyl-benzenesulfinate.

Solution: (a) The compound to be synthesized is di-n-octyl sodium sulfosuccinate:

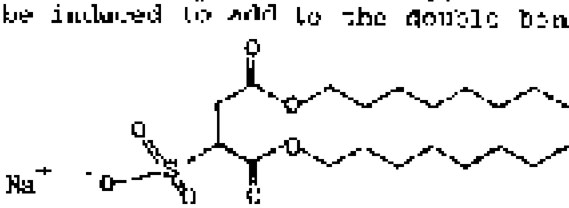
We can think of this compound as being a maleic anhydride with three substituents in it: the 2 "a" group we recognize as being n-octyl alcohol; the "c" group as sodium sulfite with "b" being the backbone-maleic anhydride. Therefore:



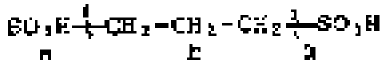
The addition of alcohol to the anhydride will initially create a carboxyester, which in acid media, will be converted to a diester:



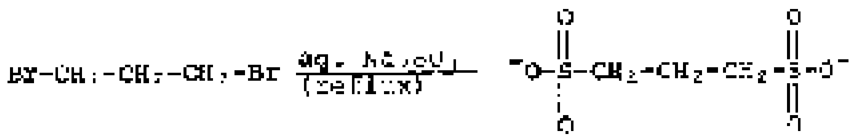
In the presence of oxygen, sodium bisulfite will be induced to add to the double bond to form the product,



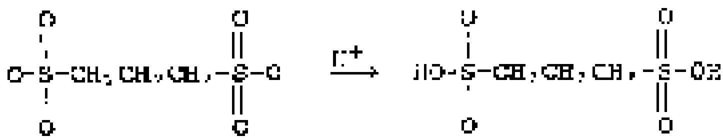
(b) We think of the product as a derivative of $(CH_2)_3Br_2$:



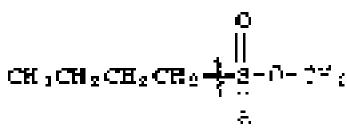
We see that this is just a substitution of SO_3H for Br in the original molecule. Therefore, we have a S_N2 displacement with the sulfite ion being the nucleophile:



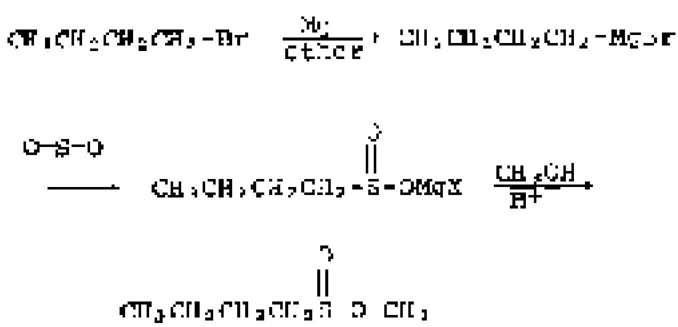
Now we must acidify this compound:



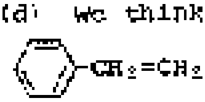
(c) We think of the product as a derivative of n-butyl bromide:

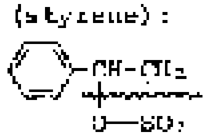


Substituent "a" is an ester of the sulfinic acid. To get the sulfinic acid, we use a Grignard reagent:

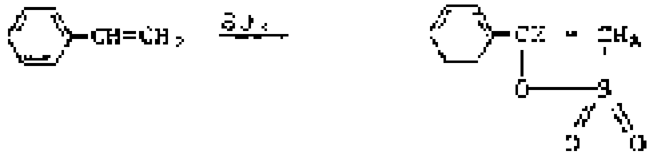


(d) We think of the product as a derivative of

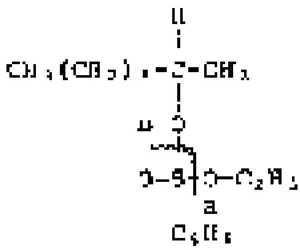
 (styrene):



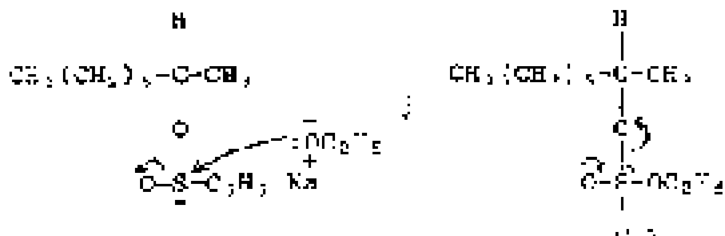
Therefore this compound has SO_3 inserted in place of the π bond:



(e) We think of the product as a derivative of optically active 2-octyl-benzenesulfinate:

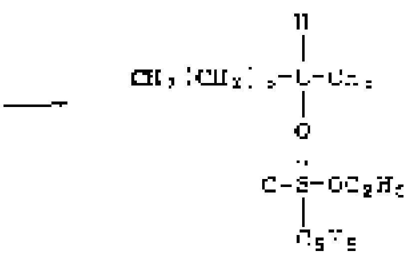


To get the product, we add group "a", an ethoxide, and break off group "b". Therefore:



(optically active)

(opt. active)
(separate diastereomers)

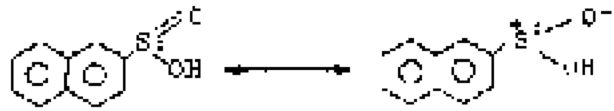


(optically active)

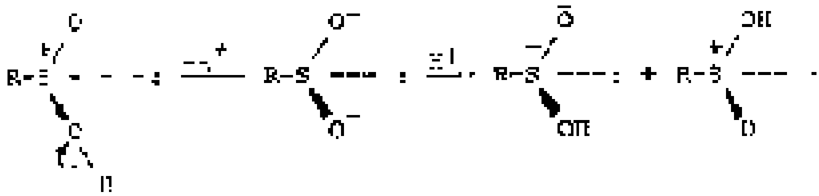
♦ PROBLEM 24-8

"All attempts to prepare and study optically active 2-naphthalenesulfinic acid are doomed to failure." What possible justification could be made for this prediction?

Solution: The structure of 2 naphthalenesulfinic acid is:



Although sulfur is a chiral center because the molecule does not undergo inversion, rapid racemization occurs by formation of the sulfinate anion, making all attempts to prepare and study optically active 2-naphthalenesulfinic acid doomed to failure. (Remember that a racemic modification is a mixture of equal parts of enantiomers, and is therefore optically inactive):



chiral achiral racemic

This is comparable to deuterium exchange in carboxylic acids:

where D = deuterium.

CHARACTERIZATION TESTS

• PROBLEM 24-10

Give each of the following pairs of compounds a chemical test, preferably a test-tube reaction, which would serve to distinguish one from the other.

(a) CH_3CH_2SH and CH_3SCH_3
(b) $(CH_3CH_2S)_2$ and $(CH_3CH_2)_2S$
(c) $CH_3S(O)OCH_3$ and $CH_3CH_2SO_3H$
(d) $CH_3S(O)OCH_3$ and $CH_3S(O)_2CH_3$
(e) $CH_3SCH_2CH_2OH$ and $CH_3OCH_2CH_2SH$

Solution: (a) Thiols, like hydrogen sulfide, react with certain heavy metals; the reaction of thiols with mercury to form a precipitate is a classical test for thiols.

Thioethers (sulfides) do not react with mercury:

$$CH_3CH_2SH \quad Hg^{+2} \rightarrow (CH_3CH_2S)_2Hg\downarrow + 2H$$

(b) Reduction of disulfides occur much more readily than sulfides to give thiols:

$$CH_3-CH_2-S-S-CH_2-CH_3 \xrightarrow{Zn,\ C_2H_5OH} 2\ CH_3CH_2SH$$

(c) Ethanesulfonic acid -- $CH_3CH_2SO_3H$ is a very strong acid, comparable in strength to sulfuric acid. The ester --

$CH_3\overset{\overset{O}{\|}}{S}-OCH_3$ is neutral. Therefore we can distinguish the acid from the ester by using litmus paper or by testing for salt formation.

(d) $CH_3\overset{\overset{O}{\|}}{S}-OCH_3$ is an ester while $CH_3\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-CH_3$ is a sulfone.

Therefore, we can test for the ester by seeing which compound gets hydrolyzed to CH_3OH; a positive result would indicate the ester.

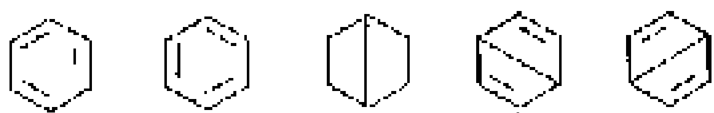
(e) $CH_3SCH_2CH_2OH$ is a thioether-alcohol while $CH_3-O-CH_2CH_2SH$ is an ether thiol. To test for the thiol, we react it with mercury. If there is a precipitate, it is a thiol (see part A). Alcohol, ether, and thioether groups do not precipitate as mercury salts.

CHAPTER 25

NONBENZENOID AROMATIC COMPOUNDS

• PROBLEM 25-1

A beginning student in organic chemistry writes the following resonance structures for benzene:



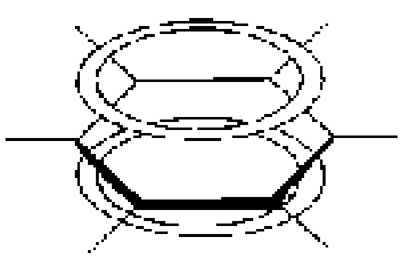
1 2 3 4 5

(a) Explain why resonance structures 1 and 2 are equal in stability.

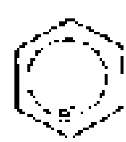
(b) Why are structures 3, 4 and 5 significantly more unstable than the first two?

Solution: (a) The first two resonance structures are energetically equivalent and in fact, neither exists in preference to the other.

This is because in these structures, known as Kekulé forms, π electrons are shared, not only by the two carbon atoms of each bond, but between atoms adjacent to bonds as well. This results in the delocalization of the π electrons around the ring (aromaticity). We can visualize the π orbital system of an aromatic ring as a circuit of electrons. All adjacent pairs of carbon atoms have the same characteristic, with an equivalence of 1 ½ bonds between each pair.



or



It must be emphasized that although separate resonance structures (1 and 2) are drawn, this should not be taken to mean that benzene will sometimes exist in the one form, and sometimes in the other. The equal stability of the two structures indicates that benzene will exist at any given time as a hybrid between them.

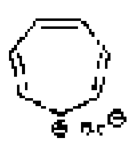
(b) If resonance structures 3, 4, and 5 were as stable as the other two, then the benzene hybrid would of course reflect their characteristics as well.

Bonds such as those between $C_1 - C_4$, $C_2 - C_5$, and $C_3 - C_6$ are sometimes known as formal bonds. Further consideration, however, would convince us that such a bond is highly unstable. This is due to the fact that atoms of a formal bond are physically too far apart (> 2Å) for stable bond formation. Therefore the formal bond is expected to be highly energetic, and resonance structures involving formal bonds would be so unstable as to be insignificant.

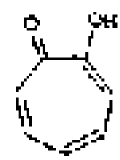
HÜCKEL'S RULE

• PROBLEM 35-2

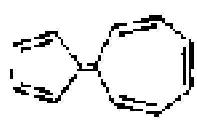
Predict which of the following compounds may have some aromatic character. Give your reasons.

(a) 

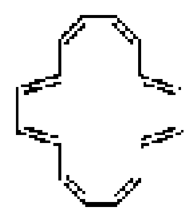
tropylium bromide

(b) 

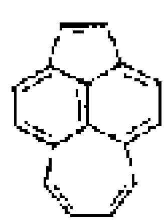
tropolone

(c) 

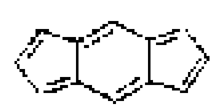
sesquifulvalene

(d) 

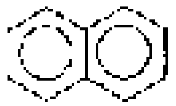
[16] annulene

(e) 

acepleiadylene

(f) 

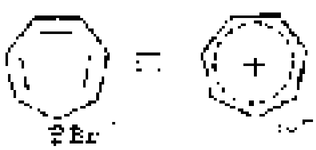
Solution: The criterion for aromaticity in a compound is the satisfaction of Hückel's rule, which states that 'only monocyclic carbocycles containing $(4n + 2)$ π electrons (where n is an integer) in a closed, planar, conjugated circuit are capable of enhanced thermodynamic stability.' Actually, this rule can also be applied to heterocycles and polycyclic carbocycles. For instance, naphthalene,



, a fused bicyclic carbocycle, is aromatic because of the presence of $10 (4n + 2, n = 2)$ π electrons. The enhanced thermodynamic stability mentioned in Hückel's rule is characteristic of all aromatic compounds and is ascribed to π electron delocalization within the aromatic ring.

Compounds that possess some measure of aromatic character typical of benzene, but are themselves not benzene rings, are known as nonbenzenoid aromatic compounds.

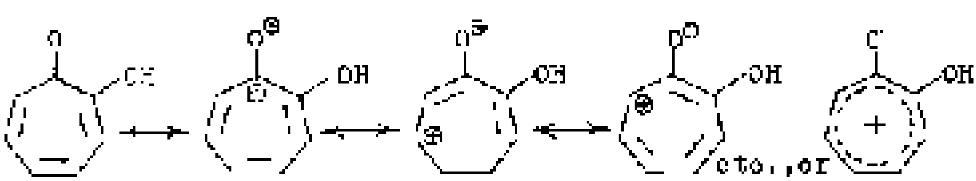
(a)



Tropylium bromide is a nonbenzenoid aromatic compound. It is aromatic because of delocalization of $6 (4n + 2, n = 1)$ π electrons about seven carbon atoms. Also, the repulsion between the electrons within the ring is low because of their electrostatic interaction with the positive charge.

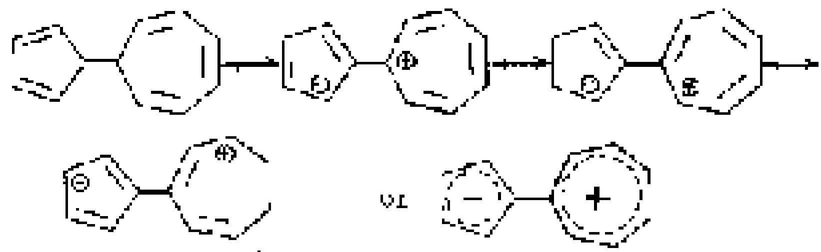
However, a certain degree of instability is expected in this structure due to angle strain. It is found that in order to be planar this compound must carry with it 12° of angle strain at each corner of its structure.

(b) We can write the following resonance structures for tropolone:



As we can see, this structure can be viewed as a substituted form of the tropylium cation discussed in (a). $6\ \pi$ electrons are spread over seven carbon atoms, and the electrons are held together by the carbon nuclei as well as by the positive charge. Thus tropolone will have aromatic properties.

(c) Some resonance structures of this compound are:

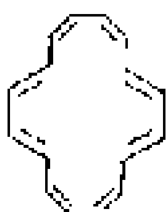


etc.,

Hence there is a dipole moment with the five-membered ring at the negative end and the seven-membered ring at the positive end.

Although theoretically we can view this hydrocarbon as a cyclopentadienate anion substituted on a tropylium ring, experimentally this structure has not been isolated. It appears that it polymerizes readily, due either to low stability or to a more favorable polymerized structure.

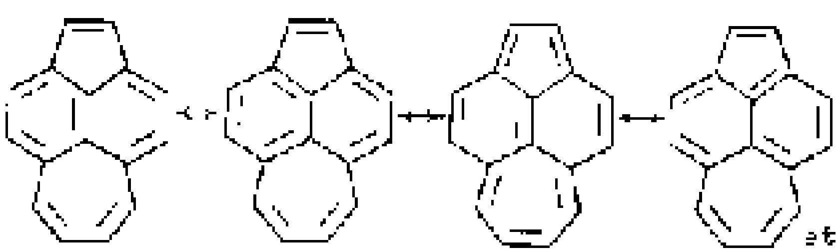
(d)



[16] annulene

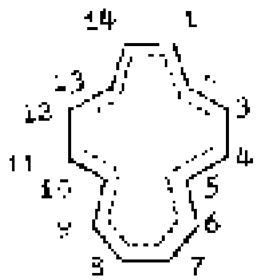
This is a 16-membered conjugated polyene, with 16 π electrons spread over the carbons of the ring. Since its number of π electrons does not satisfy Hückel's rule, and there is a considerable amount of instability due to crowding of hydrogens inside the system, this hydrocarbon will not be aromatic.

(e) The principle resonance structures of acepleiadylene without formal bonds are:



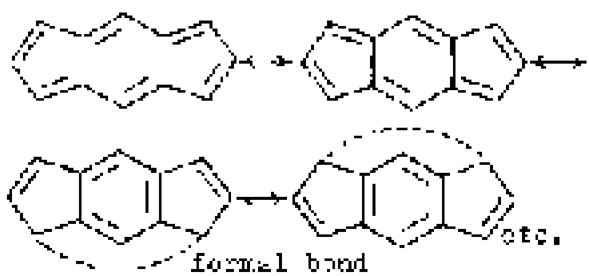
etc.

The 14 π electrons on the periphery of the ring system are delocalized to form a continuous current of electrons, which can be visualized thus:



The 14 π electrons satisfy Hückel's Rule for aromaticity (4n + 2, n = 3). Also, note that in acepleiadylene there are no hydrogens crowded in the center of the ring system, and so the structure will be considerably stable. This aromatic compound has actually been made, and is a red solid that is stable enough to form a mononitro compound.

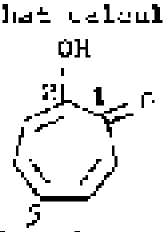
(c).



There are only 12 π electrons spread over this ring system. In addition, Kekulé forms cannot be written for the central benzoid ring without formal bonds between atoms of the neighboring rings. Because of the long distance separating the atoms of the formal bond, it will not be stable. Thus this hydrocarbon will not be sufficiently stabilized by resonance and is not expected to be aromatic.

■ **PROBLEM 25-3**

Tropolone has a measured heat of combustion that is 20 kcal lower than that calculated.



Tropolone

Its dipole moment is 3.71 D; that of 5-bromotropolone is 2.07 D. Tropolone is both acidic ($K_a \approx 10^{-7}$) and weakly basic, forming a hydrochloride in ether.

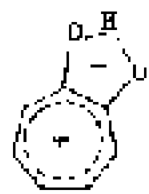
(a) What class of compounds does tropolone resemble? Is it adequately represented by the formula given?

(b) Use valence-bond structures to account for the properties of tropolone.

(c) In what direction is the dipole moment of tropolone or 5 bromotropolone? Account for the difference in their dipole moments.

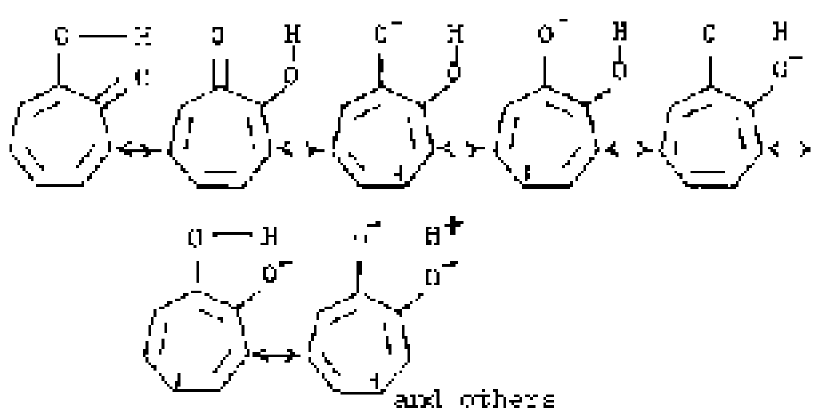
(d) The infrared spectrum of tropolone shows a broad band at about 3150 cm^{-1} which changes only slightly upon dilution. What does this tell you about the structure of tropolone?

Solution: (a) Tropolone belongs to the class of nonbenzenoid aromatic compounds. It is not adequately represented by the structural formula given in the problem. A significant number of other resonance structures can be written for tropolone, which are given in (b). Tropolone is a hybrid of all its resonance structures and is believed to look like the following:



As we can see, the ring has cationic properties and 6 π electrons capable of delocalization. Thus tropolone is defined as an aromatic substance by Hückel's rule.

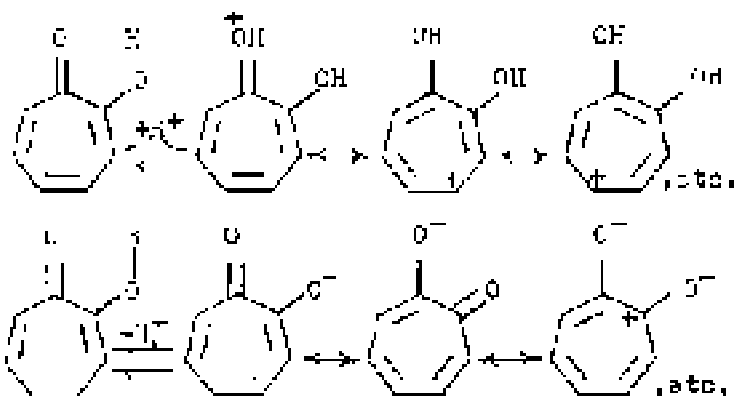
(b)



The many valence bond structures we can draw for tropolone indicate that a great deal of resonance exists in this molecule. This resonance is responsible for the thermodynamic stability of tropolone, which is revealed in the lower than expected heat of combustion of tropolone. The 20 kcal energy of stabilization is better known as conjugation energy.

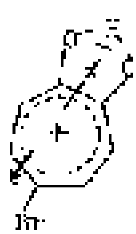
The ionic property of the resonance structures indicates the existence of polarity in tropolone. Because of the strong electronegativity of oxygen, and the stability of the ring as an aromatic cation, tropolone has a dipole moment of 3.71 D.

Both the protonated and deprotonated forms of tropolone are stabilized by resonance. This explains why tropolone is both acidic (proton-donating) and basic (proton-accepting).



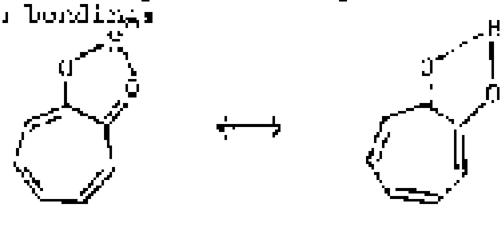
(c) The direction of tropolone's dipole moment is

. The dipole moment of 5-bromotropolone has the same direction but is opposed by a smaller C-Br dipole, which is due to the strong electronegativity of bromine.



The net moment of 5-bromotropolone (2.07 D) therefore is smaller than the dipole moment of tropolone (3.71 D).

(d) The broad band at 3150 cm^{-1} corresponds to intramolecular hydrogen bonding. Inspection of its structure reveals that tropolone is capable of intramolecular hydrogen bonding:

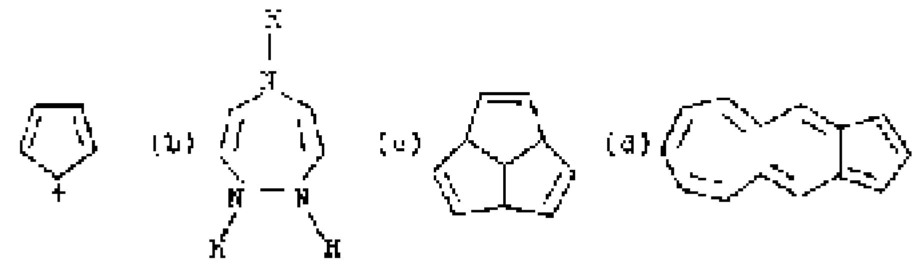


Since this type of H-bonding occurs within and not between molecules, we can expect the infrared band to stay reasonably constant around 3150 cm^{-1} despite dilution of the tropolone sample.

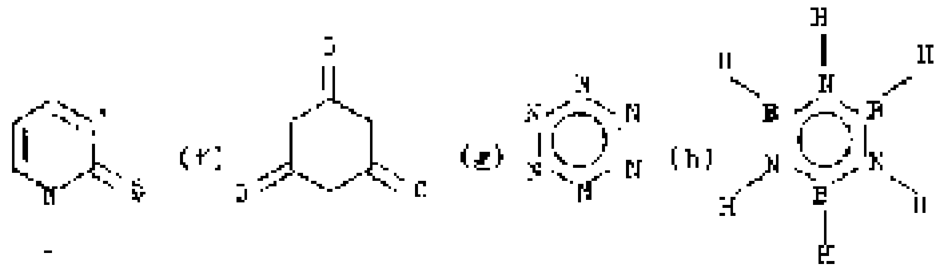
• PROBLEM 25-4

Discuss the aromaticity or lack of it for the following:

(a) (b) (c) (d)

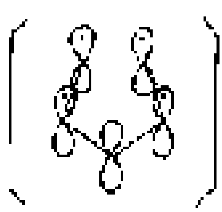


(e) (f) (g) (h)



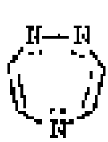
Solution:

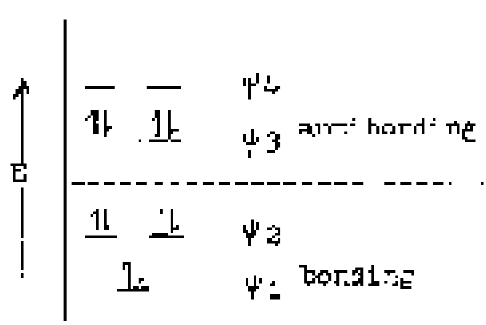
(a)



The above orbital picture indicates that only 4 π electrons occupy the π orbital system of the ring. The ring is therefore, according to Hückel's rule, not aromatic.

(b)



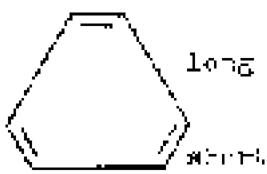


Configuration of π electrons

If we look at the electron configuration of the π system of this structure, we will find that although 10 π electrons are present (three pairs are from the nitrogen atoms), 4 are actually located in antibonding orbitals.

Since electrons in an antibonding orbital tend to force the atoms apart, thus resulting in an energetically unfavorable state, the formation of a circular π system in this molecule is not favored. What aromatic stabilization the molecule can hope to gain by forming a π system is lost by having electrons in high-energy antibonding orbitals and by the angle strain which accompanies planarization. Instead, the molecule will probably not be planar, and will have the lone-pair electrons of the nitrogens in sp^3 orbitals (nonbonding orbitals). This will give the molecule two bonding π orbitals and three nonbonding sp^3 orbitals with an accompanying relief of angle strain. Therefore, this molecule is probably not aromatic.

(c) This compound can be pictured as a benzene-type ring with three "long" and three "short" bonds:

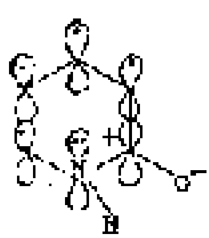


Although 6 π electrons are present the "long" bonds are actually too long for effective orbital overlapping. Little conjugation is hence possible. The ring is more correctly a triene with distinct double and single bonds. It is not aromatic.

(d) The periphery of this fused ring system can be looked at as a 14-membered, 14 π-electron cycle. Hückel's rule is satisfied ($4n + 2$, $n = 3$) if the structure is planar. Conjugation stabilization probably is sufficient to dictate coplanarity. This structure therefore is expected to be aromatic.

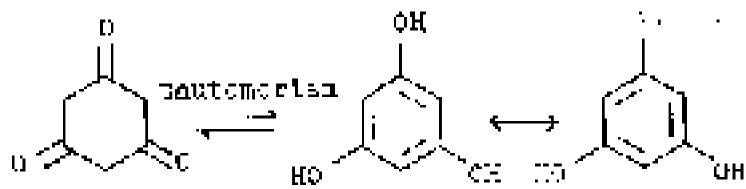
(e) This is the stable tautomer of 2-hydroxypyridine,

whose orbital structure is given below:



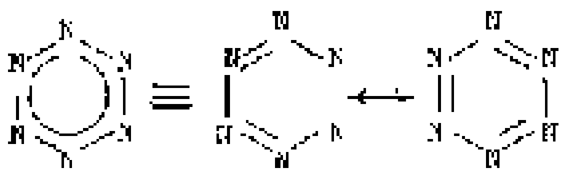
The nitrogen in this structure is sp^2 hybridized, and its lone pair of electrons occupies a p orbital. There are thus a total of 6 electrons in the π orbital system, and the compound will have aromatic character.

(f)



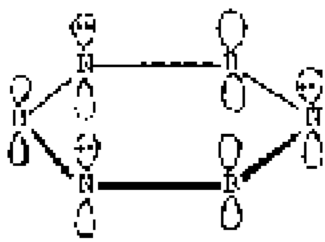
The tautomer (1,3,5-hydroxy benzene) of this structure has two Kekule forms which are important resonance structures. The compound will resemble benzene in being aromatic.

(g)

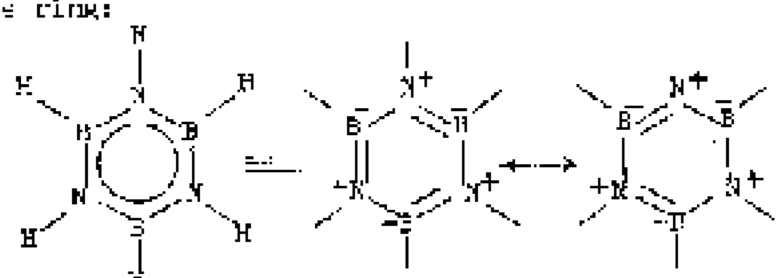


The nitrogen atoms are sp^2 hybridized. Two sp^2 orbitals bond with two other sp^2 orbitals of the adjacent nitrogens. The third sp^2 orbital is occupied by a lone pair of electrons. Since the valence of nitrogen is 5, a fifth electron is located in a p orbital. The p orbitals of the six nitrogen atoms are capable of overlapping, and the 6 π electrons are thus delocalized. The molecule is aromatic although it tends to dissociate readily to 3 N_2.

(h) The electron contribution for this molecule is shown below:

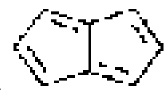


Thus, Boron with its empty p orbitals does not contribute any electron to the π system. As such, the molecule should be highly ionized when the electrons are delocalized about the ring:



Since charge separation requires much energy, the aromatic stabilization which accompanies 6 π electrons in a planar ring is highly reduced. Therefore, the aromaticity of this compound is very much less than that of benzene.

• **PROBLEM** 25-5

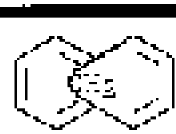
Do you anticipate that pentalene () will be a stable aromatic system? Why?

Solution: Examination of the ring system of pentalene indicates a total of 8 π electrons, which does not meet Hückel's requirement for aromaticity ($8 \neq 4n + 2$). If two electrons were added to pentalene, forming a dianion,

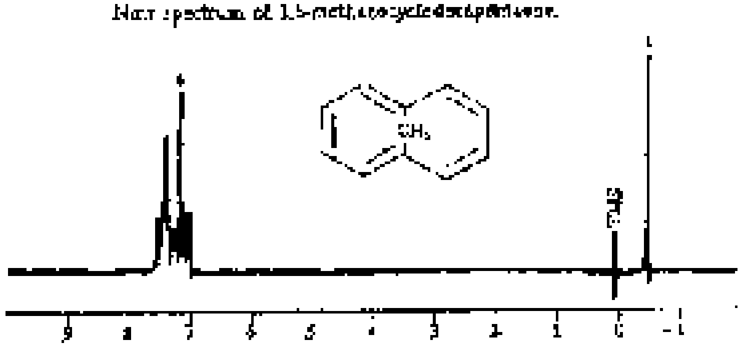
some degree of aromaticity would be expected due to the presence of 10 ($4n + 2$, where $n = 2$) π electrons, in accordance with Hückel's rule. Therefore pentalene will not be a stable aromatic system.

SPECTROSCOPY

• **PROBLEM** 25-6

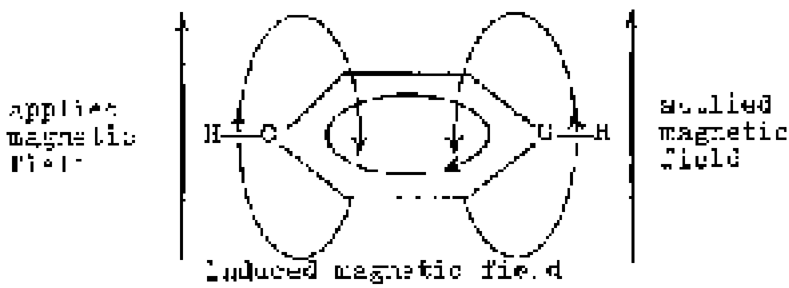
The nmr spectrum of  is shown. What conclusions can you draw from this spectrum.

Nmr spectrum of 1,6-methanocyclodecapentaene.



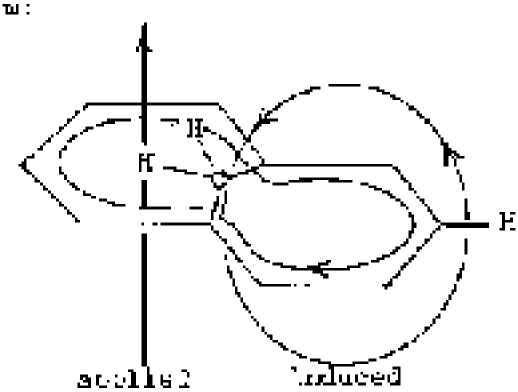
Solution: By the presence of 10 π electrons that are capable of delocalization, this compound is confirmed to be aromatic in accordance with Hückel's rule. The compound consists of two types of protons which differ with respect to their environment, the aromatic protons and the CH_2 protons.

Earlier it was mentioned that the π electrons of an aromatic system are capable of delocalization. A magnetic field applied to the aromatic ring would induce a flow of these electrons around the ring in the same way that an electric field would introduce a current in a loop of wire. This ring current would in turn generate an induced magnetic field which tends to reinforce the applied field felt by the protons, as illustrated below:



The aromatic protons would experience an enhanced net magnetic field (applied + induced) and be "deshielded". Deshielded protons have a larger δ value and thus a low field position in the nmr.

The CH_2 protons are not coplanar with the ring. Since they are in the center of the ring, the magnetic field induced by the aromatic current would oppose rather than reinforce the applied magnetic field felt by them, as shown below:



The two CH_2 protons are equal and, unlike the aromatic protons, are shielded from the applied magnetic field by the induced magnetic field. They would experience a smaller net field (applied - induced). They have a smaller δ value and a high field position in the nmr.

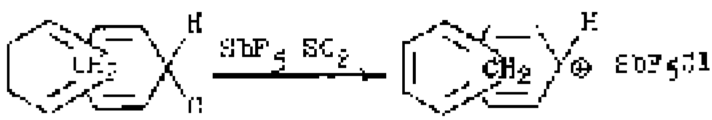
Therefore, in the nmr spectrum given, the peak in the high field region (δ - 0.5) reflects absorption of the CH_2 protons and the one in low field (δ 7.0 - 7.5) indicates absorption of the aromatic protons. The peak size ratio 1 : 4 indicates the ratio of the number of the two types of protons: 2 high field protons (of CH_2) to 8 low field protons (which are aromatic).

• PROBLEM 25-1

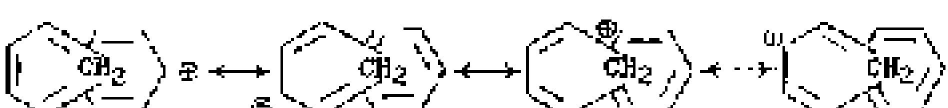
If  were to be dissolved in SbF_5-SO_2, what compound would you expect to form? How might you show whether or not it did form?

Solution: One driving force of a reaction is the stability of the product. The more stable the product, the more readily will the reaction proceed.

in the presence of SbF_5SO_2, will readily liberate a chloride ion to give a positively charged product:



Comparing the stabilities of the reactant and the product will explain to us why the forward reaction is favorable. The product is, as we can see, stabilized by a considerable degree of π electron delocalization. This is evidenced by the many resonance structures that we can draw for the cation product:



etc.

or 

This cation is actually aromatic. 10 π electrons are delocalized about 11 atoms, causing a considerable amount of resonance stabilization.

For the neutral reactant, we can write only resonance structures involving separation of charges (such as

which are highly unstable.

In addition, this compound lacks a planar structure, and the p-orbital overlapping is interrupted at the tetrahedral carbon which bears the chlorine. Thus, although it contains 10 π electrons, the π orbital system is not planar and closed, and the compound is therefore non-aromatic. It will tend to lose the chlorine, become planar and aromatic, and be stabilized by resonance.

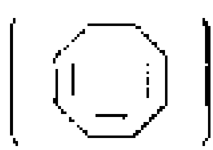
The hydrogens of the cation product are attached via σ bonds to an aromatic ring. They are for convenience called aromatic protons. The hydrogens of the neutral form are nonaromatic. Aromatic protons characteristically show a considerably larger δ value (and are thus more downfield) than those found for regular conjugated polyene protons (see previous problem). They can thus be distinguished from the latter by the nmr spectrum. Therefore, studying the nmr spectra of a pure sample of the compound, and of the same compound dissolved in SbF_5-SO_2, will reveal to us whether the cationic product was indeed formed.

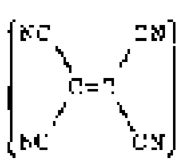
REACTIONS

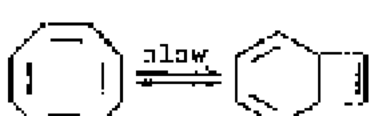
• PROBLEM 25-8

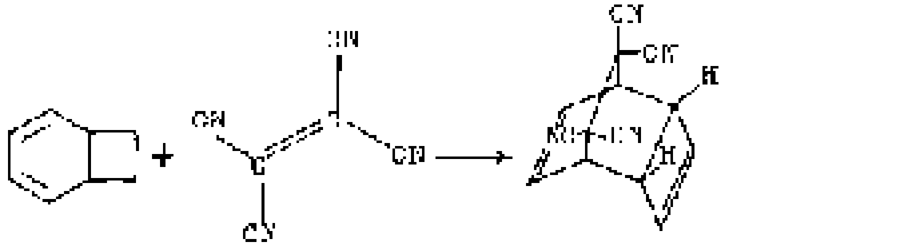
The rate of the Diels-Alder addition between cycloöctatetraene and tetracyanoethylene is proportional to the tetracyanoethylene concentration $[C_2(CN)_4]$ at low concentrations of the addende but becomes independent of $[C_2(CN)_4]$ at high concentrations. Write a mechanism which accounts for this behavior.

Solution: The Diels-Alder addition reaction between

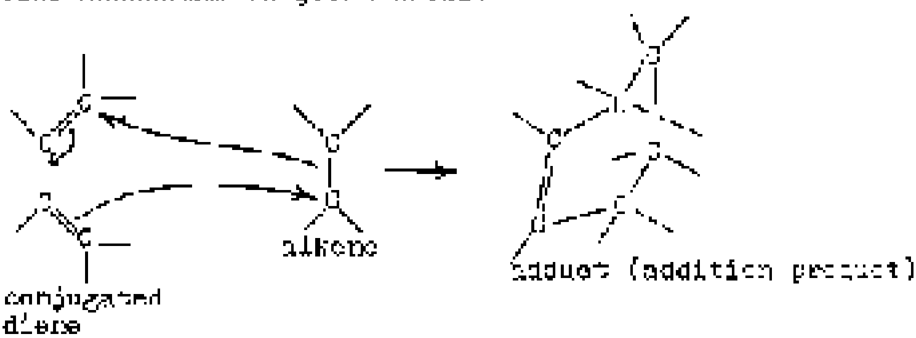
cycloöctatetraene  and tetracyanoethylene

 proceeds via the following mechanism:

1. 

2. 

In the first step, cyclooctatetraene undergoes slow valence tautomerism to form a bicyclooctatriene. Due to similar thermodynamic stability, these two isomers will exist in equilibrium. In step 2, in the presence of $C_2(CN)_4$, the bicyclooctatriene undergoes addition to yield a three ringed product. This type of addition, involving the 1,4 addition of an alkene to a conjugated diene, is the Diels-Alder reaction. A simple scheme for the Diels-Alder mechanism is given below:

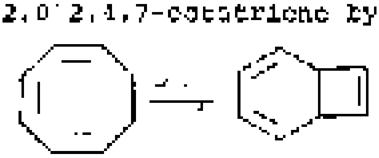


Hence when $C_2(CN)_4$ is at a low concentration, it becomes the limiting factor and step 2 will therefore be rate-determining. As $C_2(CN)_4$ is raised in concentration, the rate of step 2 is enhanced. Step 2 in this case proceeds faster than step 1, and the limiting factor is now the bicyclooctatriene. Step 1 hence becomes rate-determining. The rate of the reaction therefore is independent of the amount of $C_2(CN)_4$ present.

• PROBLEM 25-0

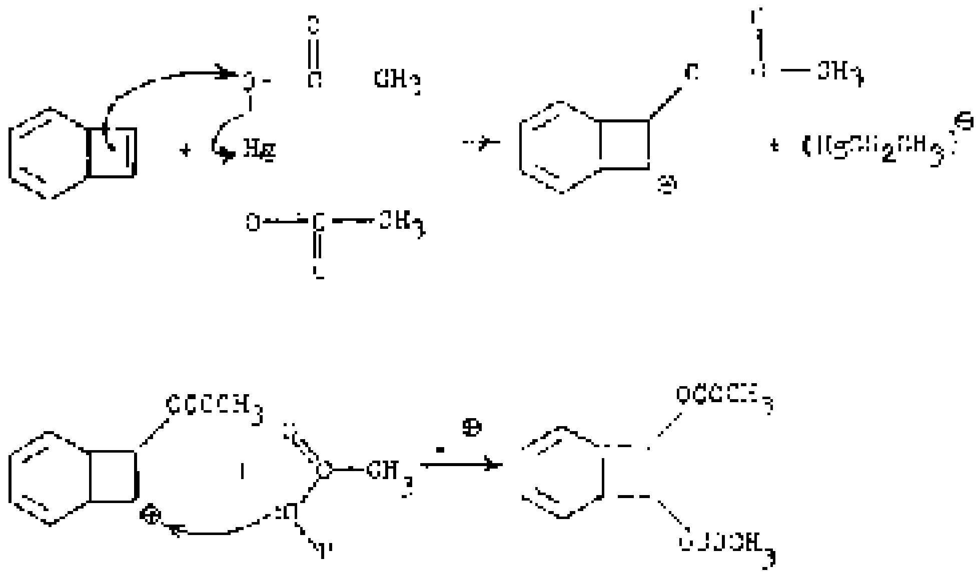
Write reasonable mechanisms for the different oxidation reactions of cyclooctatetraene with mercuric acetate in acetic acid, methanol, and water solutions. Note that compounds of the type $Hg(OR)_2$ appear to act in some cases as ^+OR-donating agents and also that the oxide produced from the cyclooctatetraene and peracids rearranges readily to phenylacetaldehyde in the presence of acids.

Solution: Cyclooctatetraene isomerizes slowly to bicyclo[4.2.0]2,4,7-octatriene by valence tautomerism.

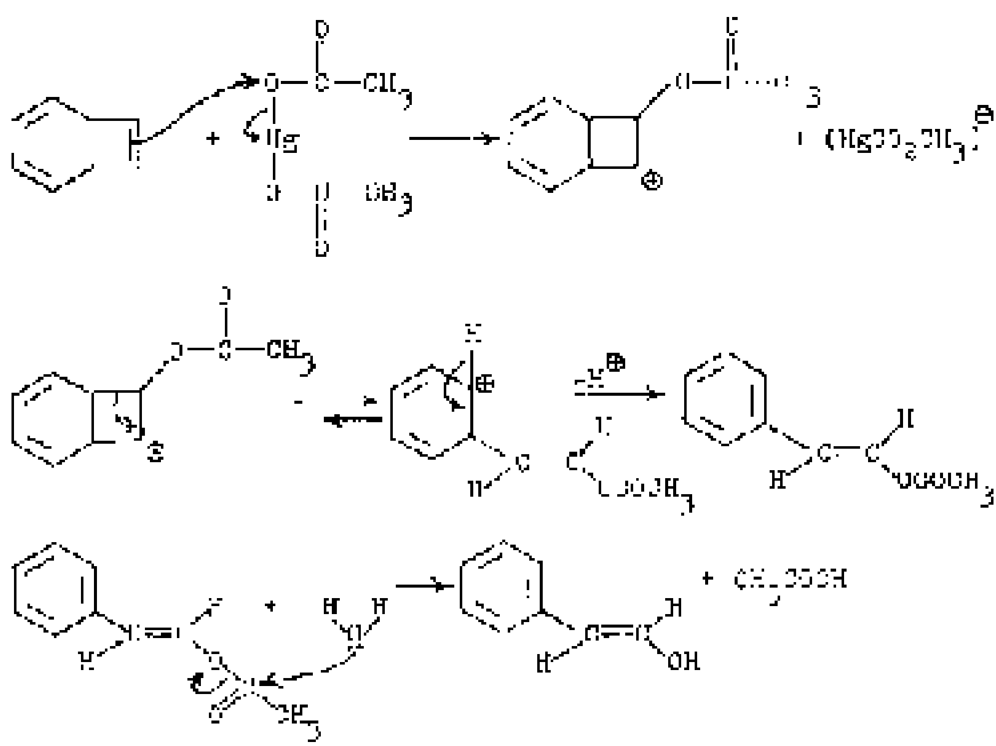


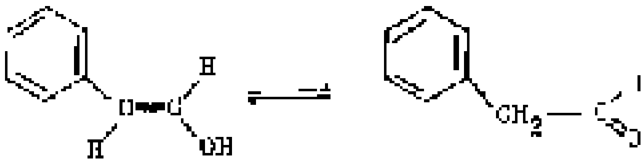
Because of instability of the cyclobutene of the bicyclic isomer, the double bond is the site of attack. Mercuric acetate can donate $^{+}O_2CCH_3$ to the double bond to initiate addition reaction.

(a) Addition of acetic acid



(b) Addition of water

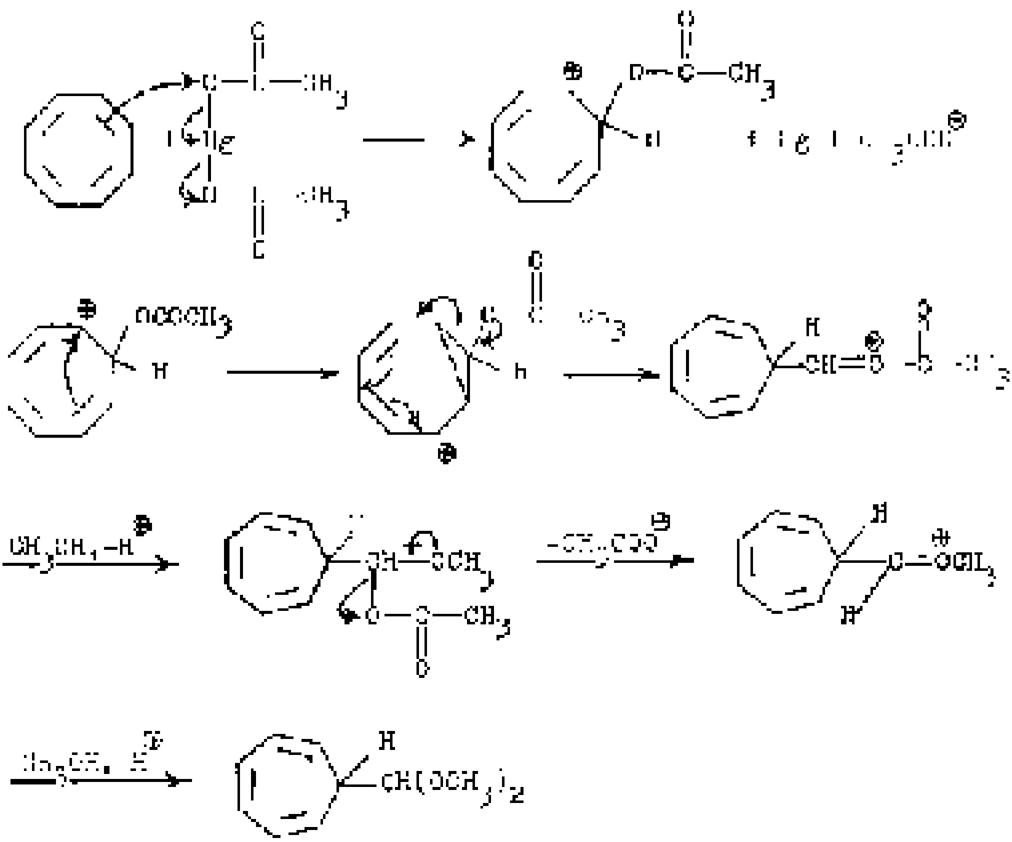




tautomerism

(c) Addition of methanol

The mechanism for this reaction differs from the previous two in that addition directly occurs at one of the double bonds of cyclooctatetraene and not of its isomer.



CHAPTER 26

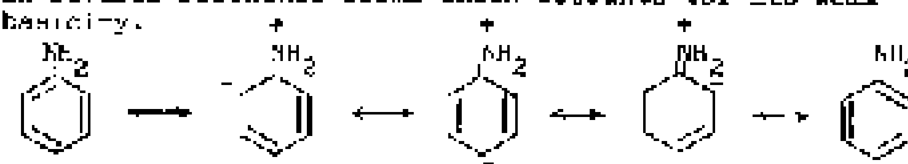
AROMATIC AMINES

AROMATIC NITRO COMPOUNDS

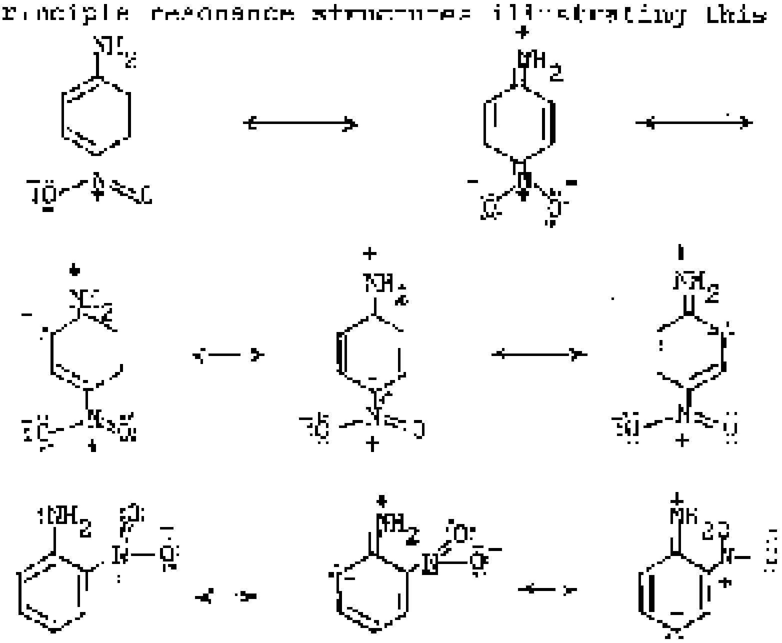
• PROBLEM 26-1

(a) Besides destabilizing the anilinium ion, how else might a nitro group affect basicity? (b) Why does the nitro group exert a larger base-weakening effect from the para position than from the nearer meta position?

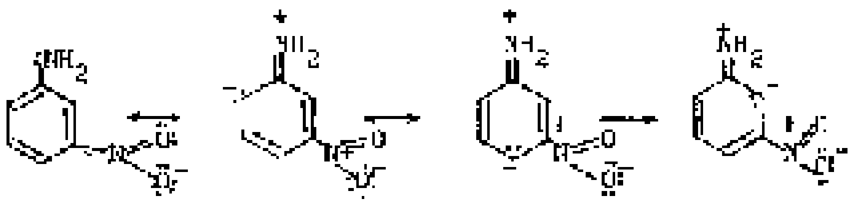
Solution: (a) The basicity of an aromatic amine is often dependent on the ability of the substituent groups to stabilize the amine through resonance. Aniline itself exists in several resonance forms which accounts for its weak basicity.



In the ortho and para positions, the nitro group stabilizes the amine and hence, decreases its basicity. The principle resonance structures illustrating this are:

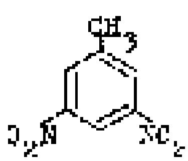


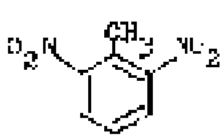
(b) The nitro group exerts a smaller base-weakening effect from the meta than from ortho or para because no nitro stabilized resonance forms are possible. Thus, only three resonance forms show unavailability of electrons when the nitro is meta compared with four when it is para or ortho.

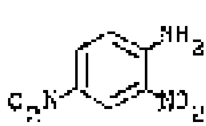


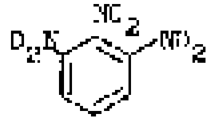
■ PROBLEM 26-2

Show how the following compounds could be synthesized from the indicated starting materials.

(a)  from toluene

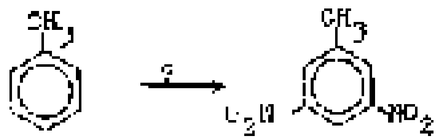
(b)  from p-toluenesulfonic acid

(c)  from chlorobenzene

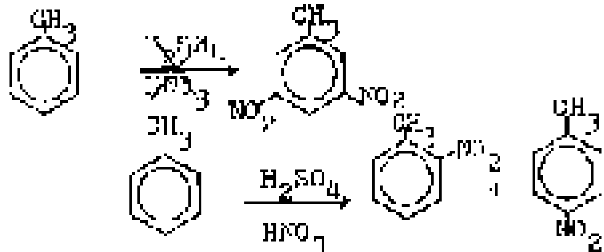
(d)  from p-chlorobenzenesulfonic acid

Solution:

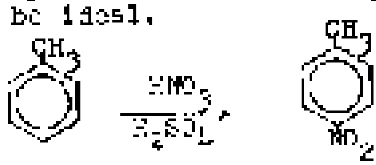
(a)



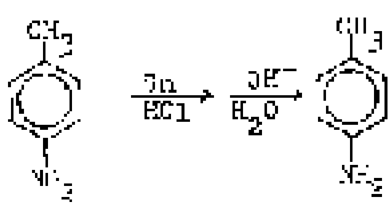
Direct nitration of toluene would not yield the desired meta-dinitro product, it would yield an ortho-para substituted nitro toluene.



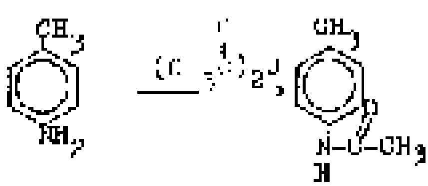
The best way to place the nitro groups in a position meta to the methyl group would be to introduce a group at the para position which is a stronger ortho-para director than the methyl and can be later hydrolyzed. The amino group would be ideal.



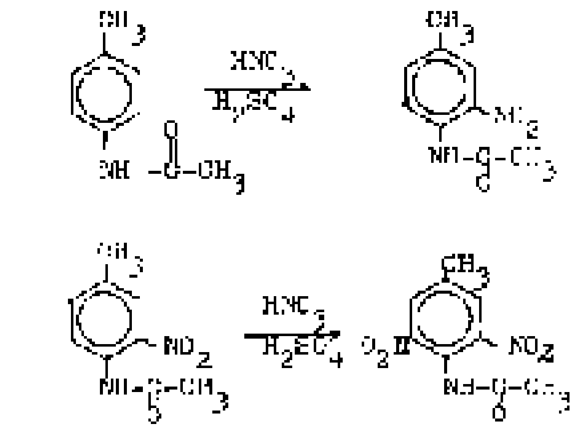
The first step is the nitration of toluene to p-nitrotoluene from which p-amino toluene may be obtained by reduction.



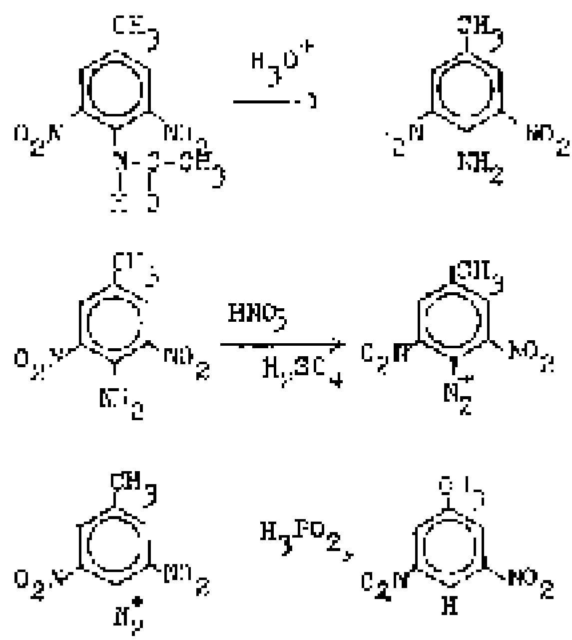
Since the amino group is a reactive functionality, its presence on benzene may lead to multiple substitutions. In addition, the $-NH_2$ group is easily oxidized. This means that reactions involving unprotected amino groups often give undesired products. Therefore, the amino group is protected by acetylation in the second step.



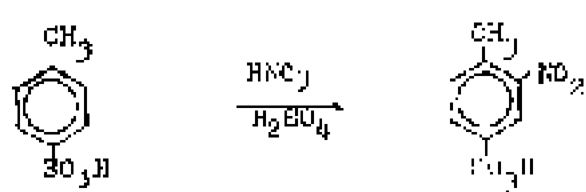
The aceto-toluidide is then nitrated twice. Since the aceto amino group is a stronger ortho-para director than the methyl group, substitution should occur at the two ortho positions.

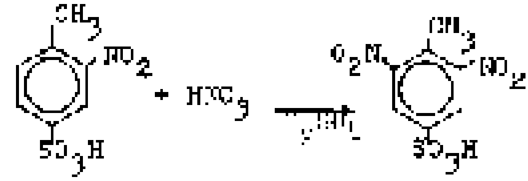


From this point, the deamination process will yield the desired product.

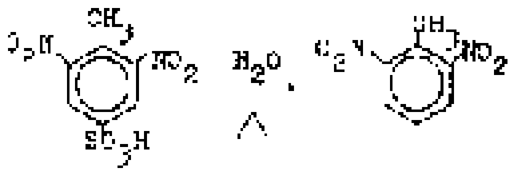


(b) The synthesis of ortho dinitrotoluene from p-toluenesulfonic acid can be achieved by simple nitration. The methyl group is a stronger director than the SO_3H group and will direct the nitro groups exclusively to the two ortho positions since the para position is conveniently blocked.

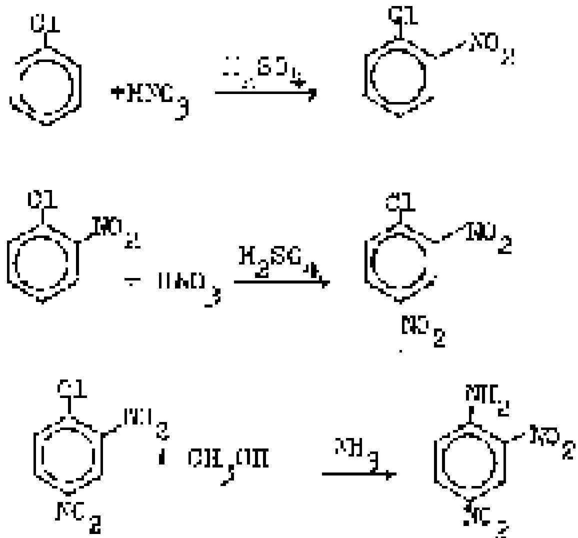




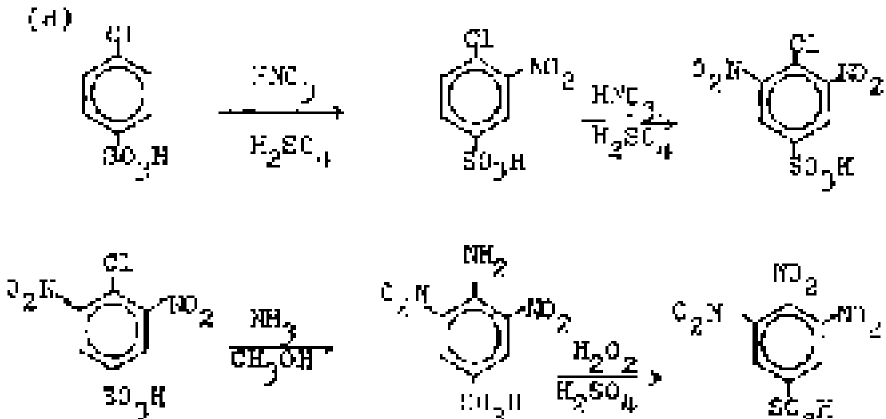
The SO_3H group can be removed from an aryl group by adding water and heating.

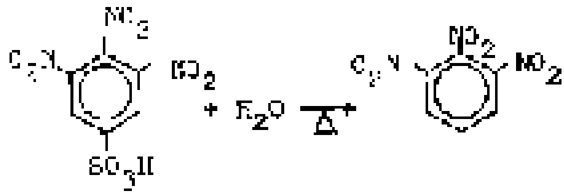


(c) This synthesis can be achieved by the nitration of chlorobenzene followed by the replacement of the chloro group by an amino group. The presence of two nitro groups (electron withdrawers) facilitates the last step.



(d)

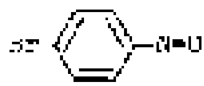


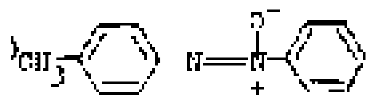


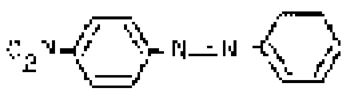
Note: For your own sake, as well as the sake of others, don't try the above synthesis in the laboratory.

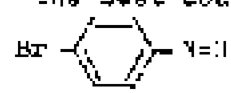
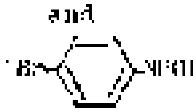
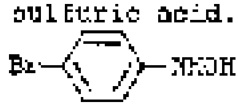
• PROBLEM 20-3

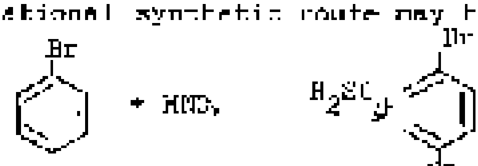
Show how the following substances may be synthesized from benzene, nitrobenzene, and halogenated or alkylbenzenes:

(a) 

(b) 

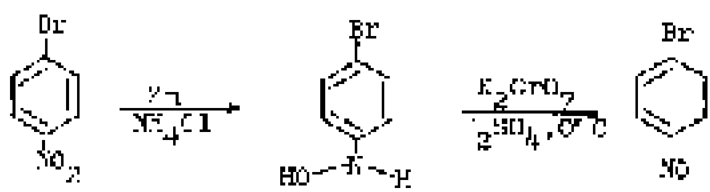
(c) 

Solution: (a) In approaching organic syntheses of rather complex molecules, it is best if one approaches them from a reverse route. For example, in "a" the best course of action would be to look first at  and realize that it is obtained through the oxidation of  with $K_2Cr_2O_7$ in cold sulfuric acid. Continuing to work backwards, we see that  can be obtained via the reduction of  with NH_4Cl/Zn. p-nitrobromobenzene is easily obtainable from the starting materials. Hence a rational synthetic route may be proposed.



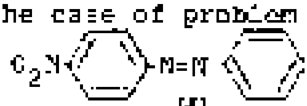
bromobenzene

p-bromobenzene

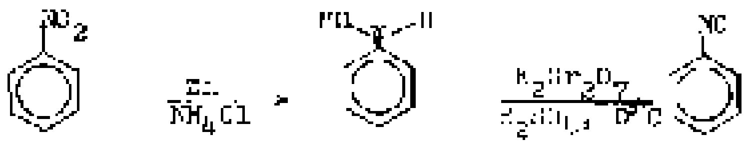


p-bromo N phenylhydroxylamine p-bromonitrosobenzene

(b) An asymmetrically substituted azo compound should immediately suggest the pyridine catalyzed condensation of an amine with a nitroso compound, both of which can be synthesized from simpler aryl compounds.

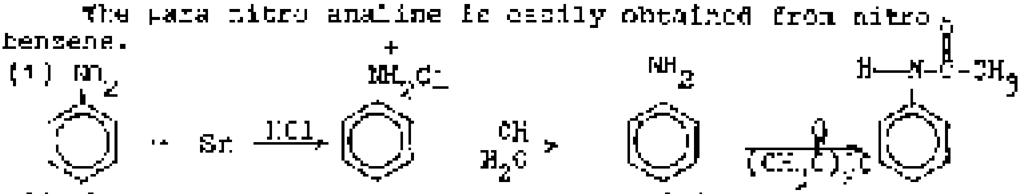
In the case of problem (b), the asymmetrical azo compound  can be synthesized from

The nitroso compound can be synthesized as in (a).

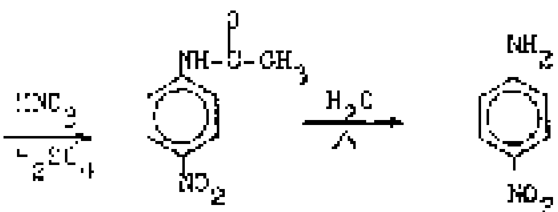


The para nitro analine is easily obtained from nitrobenzene.

(1)



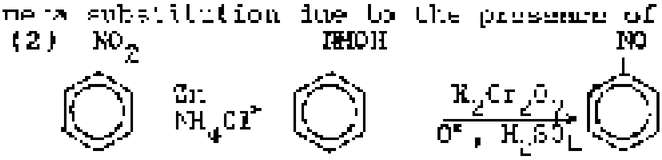
nitrobenzene aniline acetanilide



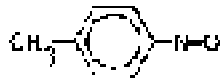
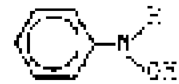
p-nitroaniline

The importance of the acetylation of aniline cannot be overemphasized. Acetanilide is always a preferred route not only because aniline is easily oxidized, but also because a reaction with aniline would lead to extensive meta substitution due to the presence of 

(2)

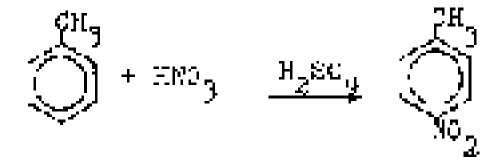


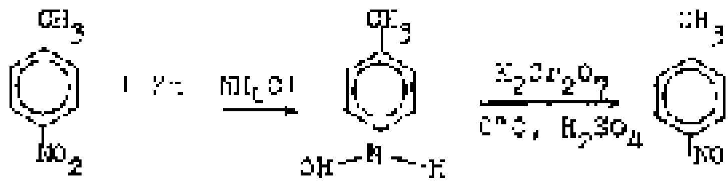
(c) An azoxybenzene is usually obtained via the reaction of an azobenzene with a phenylhydroxylamine, in the presence of sodium hydroxide.

In reaction (c) the two reactants required to yield the azoxybenzene would be  and 

both of which were synthesized in earlier parts of the problem.

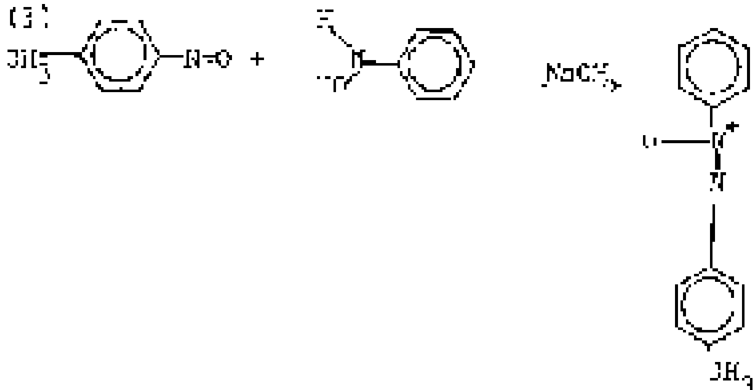
(1)





(2)

(3)



AROMATIC AMINES

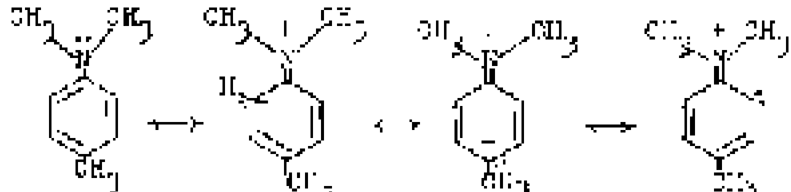
• PROBLEM 21-4

N,N,4-Trimethylaniline has K_B of 3×10^{-9}, quinuclidine has $K_B = 4 \times 10^{-4}$, and benzoquinuclidine has $K_B = 6 \times 10^{-7}$.

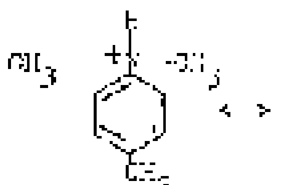
What conclusions may be drawn from these results as to the cause(s) of the reduced base strength of aromatic amines relative to saturated aliphatic or alicyclic amines? Explain.

K_B = [illegible] K_B = [illegible] K_B = [illegible]

Solution: Aromatic amines are less basic (indeed, they are acidic) because of the delocalization of the lone pair of nitrogen's electrons over the aromatic ring. The delocalization of the lone pair hinders its action as an electron pair donor.

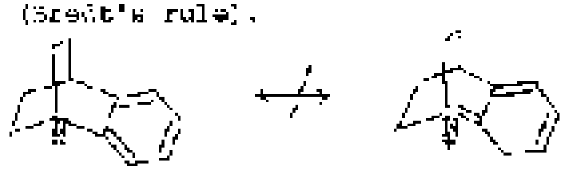


Were the aromatic amine to gain a proton, then the stabilization gained through the resonance forms would be lost.

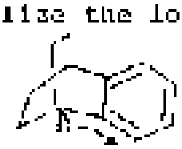


No important resonance forms.

Aliphatic amines cannot display any stabilization of the lone pair, hence the lone pair is free to exhibit its basic properties. Such would explain the relative basicities of quinuclidine and N,N,4-trimethylaniline, but what of benzoquinuclidine? Why is its relative basicity 10^{3} times smaller than that of quinuclidine? There can be no resonance stabilization of the lone pair of electrons on nitrogen (Bredt's rule).

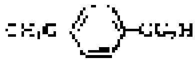
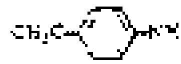
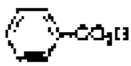
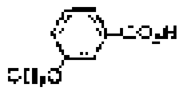
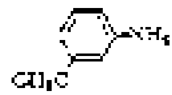
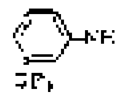
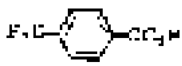
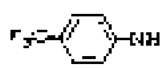


However, while resonance stabilization may not be permissible, the inductive effect of the phenyl group may serve to stabilize the lone pair.



This would decrease the basic properties of the lone pair, while not resulting in the resonance stabilization of the system.

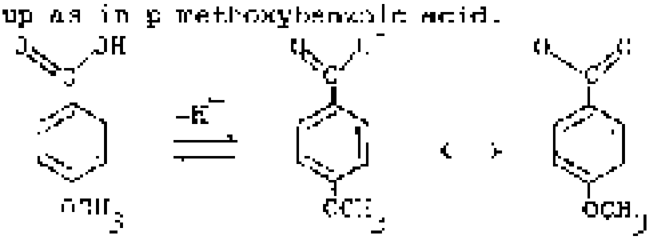
The Following data are relative strengths of some aromatic carboxylic acids and aromatic amines, with benzoic acid and aniline taken as standards:

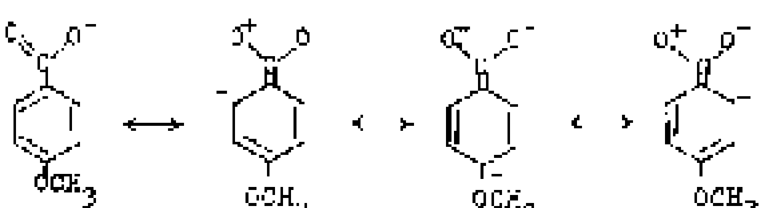
Relative acid strengths		Relative base strengths	
	0.84		5.5
	1.0		1.0
	1.2		0.5
	2.6		0.032
	3.4		0.0012

(a) Explain the general features of the observed orders of the acid and base strengths and why the effect of substituents is greater on the anilines than on the acids.

Solution: (a) The relative strengths of aromatic acids and amines are readily explained by comparing the stability of the ions resulting from proton loss (acids) or addition (bases). The compound's substituents will determine the stability of these anions (acids) and cations (bases).

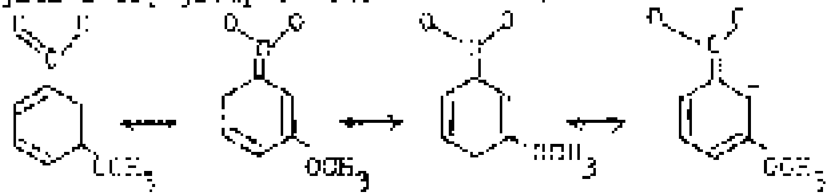
For instance, using benzoic acid as a standard, one can readily see the destabilizing effects of a methoxy group as in p methoxybenzoic acid.





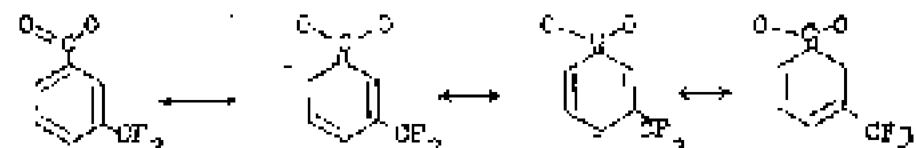
(1) (2) (3) (4)

The position of the methoxy group in the para position greatly destabilizes the resulting anion in resonance form (3) because the effect of electrostatic repulsion far outweighs any stability that results from the inductive effect. In other words, the methoxy group draws electrons toward itself because of oxygen's electronegativity and tends to stabilize the CO_2^- to some extent. However, this effect is much smaller than the one resulting from oxygen's tendency to donate electrons to the ring and destabilize the already negative CO_2^- group of the dissociated acid.



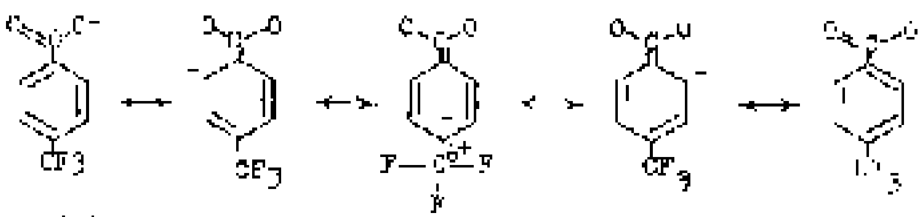
(1) (2) (3) (4)

When the methoxy group is in the meta position, there is no electrostatic repulsion because there are no resonance forms showing the negative charge on the methoxy bearing carbon. Indeed, the anion is stabilized by the inductive effect of the methoxy group. This gives m-methoxy benzoic acid greater acidity than unsubstituted benzoic acid.



(1) (2) (3) (4)

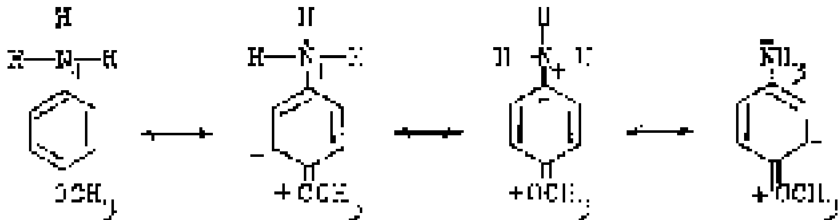
In the case of meta-trifluoromethyl benzoic acid, the great increase in the relative acidity is due not to any resonance stabilization, but to the strong inductive effects of the highly electronegative fluorines. This stabilizes the free negative charge of the π-cloud.



(1) (2) (3) (4) (5)

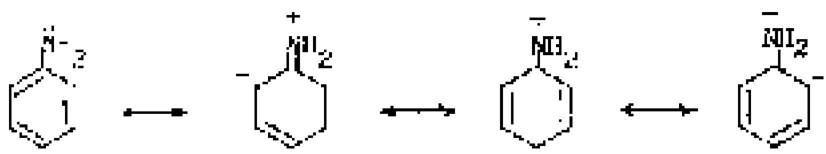
Para-trifluoromethyl benzoic acid would be expected to exhibit strong acidic properties in that it is stabilized by both resonance and induction. Structure (3) is a stable one because the negative charge is stabilized by the positively charged carbon.

In the case of the amines, the reverse holds. Para-methoxyaniline is the most basic because the electron releasing ability of the methoxy group stabilizes the cation.



(1) (2) (3) (4)

Aniline is not as basic as an aliphatic amine due to the presence of the aromatic group. Resonance structures can be drawn for aniline that show the electron pair of



nitrogen unavailable for bonding with protons.

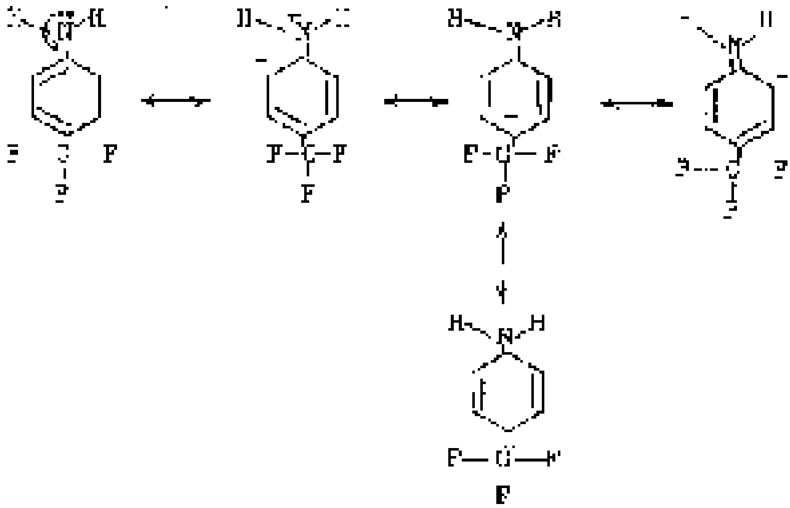
Meta-methoxy aniline destabilizes the cation through its inductive properties. The pull of the electrons toward

the methoxy group results in a slightly positive charge on the carbon bonded to the nitrogen. The slightly positive charge leads to a slight repulsion between the carbon and the nitrogen.

This effect is even more pronounced in meta trifluoro aniline, as the fluorine results in a greater inductive pull

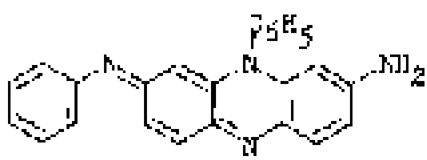
This greater inductive pull results in a greater positive charge at C, and hence a greater repulsion between the carbon and the nitrogen.

The basic properties of p-trifluoromethyl aniline are almost non-existent because of the resonance interactions of amino group with the trifluoromethyl group.



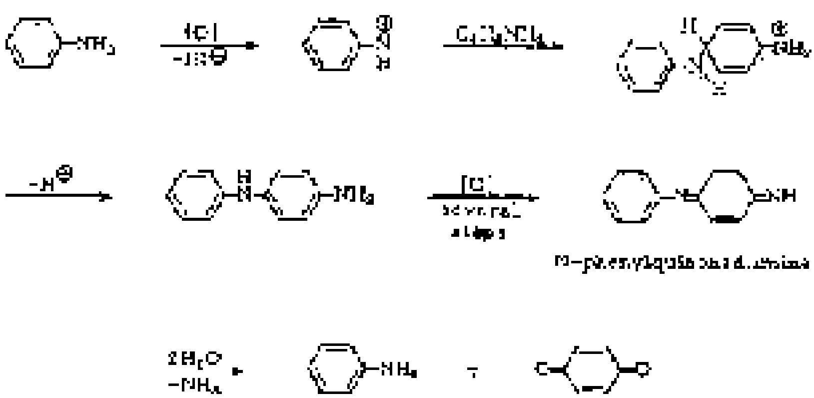
• PROBLEM 26-6

Show how oxidation of aniline by a sequence related to Eq. (1) might lead to the brilliant red-purple dye "pseudomauveine," which has a structure related to Aniline Black.

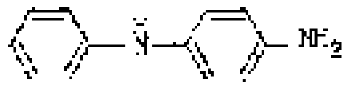


pseudomauveine

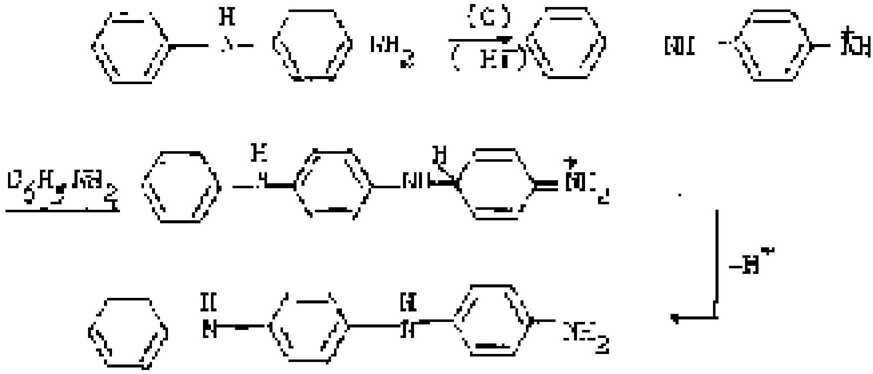
Equation (1) is shown below.

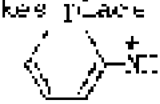


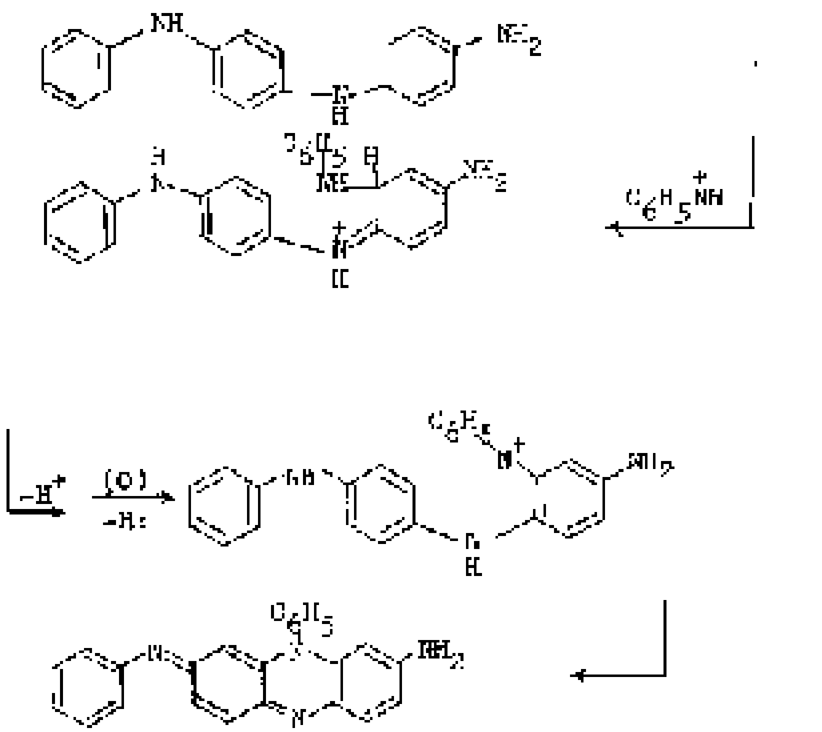
Solution: The oxidation, shown by equation (1) is initiated by a hydride-ion abstraction. The resulting N-phenylamino cation then adds para to another aniline molecule, which after removal of the proton and complete oxidation, yields, N-phenylquinonediimine. The final structure of pseudomauveine is synthesized via two such oxidation sequences, and then a slight rearrangement to form six membered ring. Beginning from



let's go through the reactions.



The next oxidation takes place after an attack by the N-phenylamino cation,  meta to the amino group. After this oxidation takes place there is a hydride ion abstraction whereby the resulting positive charge in the nitrogen is relieved by its electrophilic attack on



the adjacent benzene ring.

L720

It will be noted here that the substituents exert a greater influence on the amides than on the acids because they are closer to the unshared electron pair on nitrogen than to the carbonyl group of the carboxyl function.

DIAZONIUM SALTS

• PROBLEM 20-7

For the diazonium ion-diazotate ion equilibrium expressed as

$$ArN_2^+ \underset{}{\overset{K}{\rightleftharpoons}} ArN_2O^- + 2H^+$$

Some values of pK for substituted benzenediazo compounds at 25° are as follows: p-NO_2, 9.44; p-Cl, 10.70; H, 11.90; m-CH_3, 12.12. Plot these values against the appropriate σ values and calculate ρ for this equilibrium. Does ρ have the sign you would have expected?

Hammett Substituent Constants

Group	σ_m	σ_p
CH_3	-0.069	-0.170
$C(CH_3)_3$	-0.10	-0.197
C_6H_5	0.06	0.01
CF_3	0.43	0.54
CN	0.56	0.660
$COCH_3$	0.376	0.502
NH_2	-0.16	-0.66
NO_2	0.710	0.778
OCH_3	0.115	-0.268
OH	0.121	-0.37
F	0.337	0.062
Cl	0.373	0.227
Br	0.391	0.232
I	0.352	0.18

Solution: When given two equilibrium constants, K_i and K_H (where K_i is the equilibrium constant of a substituted aromatic ring, and K_H is the equilibrium constant of the unsubstituted ring) there exists a linear relation between their two logarithms in accordance with Professor L.P. Hammett's equation.

$$\log \frac{K_i}{K_H} = \rho\sigma_i$$

This equation can also be expressed as

$$\log K_i = \log K_H + \rho\sigma_i$$

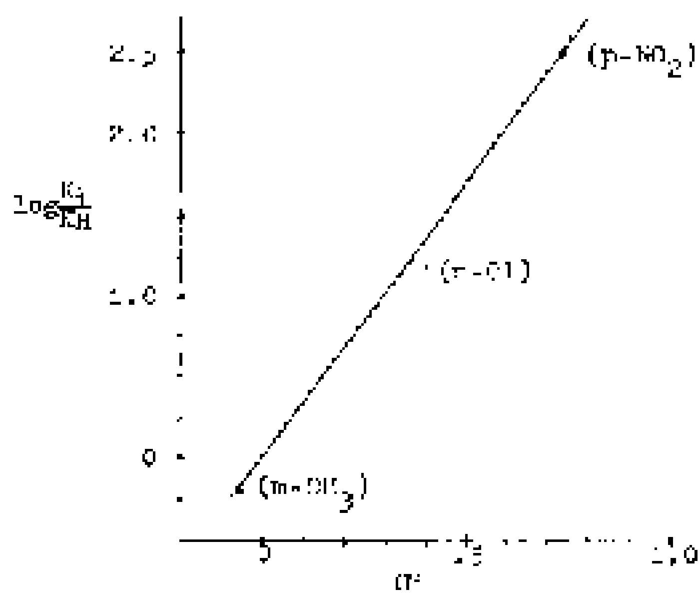
$$pK_i + pK_H = \rho\sigma_i$$

$$pK_H - pK_i = \rho\sigma_i$$

where ρ (rho) is defined as the unity constant, and σ (sigma) is defined as the Hammett Substituent Constant.

A geometric interpretation using the values given will lead to an understanding of the chemical implications.

Substituent	$\log\left(\frac{K_i}{K_H}\right)$ [pK_H pK_i]	σ_i
$p\text{-}NO_2$	11.9 − 9.44 = 2.46	.778
$m\text{-}Cl$	11.9 −10.70 = 1.20	.373
$m\text{-}CH_3$	11.9 −12.12 − 0.22	−.069



It should be noted that a negative σ signifies an electron releasing group while a positive σ is indicative of an electron attracting group, and that the larger the magnitude of σ, the larger the effect of the substituent. The unity constant, ρ (rho), is indicative of the relative need of a particular reaction for electron withdrawal or release. A positive ρ value signifies that the equilibrium is aided by electron attracting substituents, while a negative ρ would be indicative of an equilibrium aided by electron releasing substituents.

Referring back to the graph of the diazonium equilibrium, the calculated ρ values are all positive, hence the diazonium equilibrium is aided by the presence of electron withdrawing groups.

$$\log\left(\frac{K_i}{K_H}\right) = \rho\sigma_i$$

For $p\text{-}NO_2$: $2.46 = \rho\,(.778)$

$\rho = 3.16$

For m-Cl: $1.20 = .373\,\rho$

$\rho = 3.22$

For m CH_3: $0.22 = -.069\,\rho$

$\rho = 3.19$

The significance of Hammett's linear relation is that it can be used to compare the effect of electron withdrawing groups on various reactions quantitatively and geometrically.

Since Hammett's equation is in the general form of $y = mx + b$, (where $y = \log\frac{K_i}{K_H}$, $\rho = m$ and $\sigma_i = x$), the greater the electron withdrawing effects the greater the ρ value and consequently the greater the slope of the line.

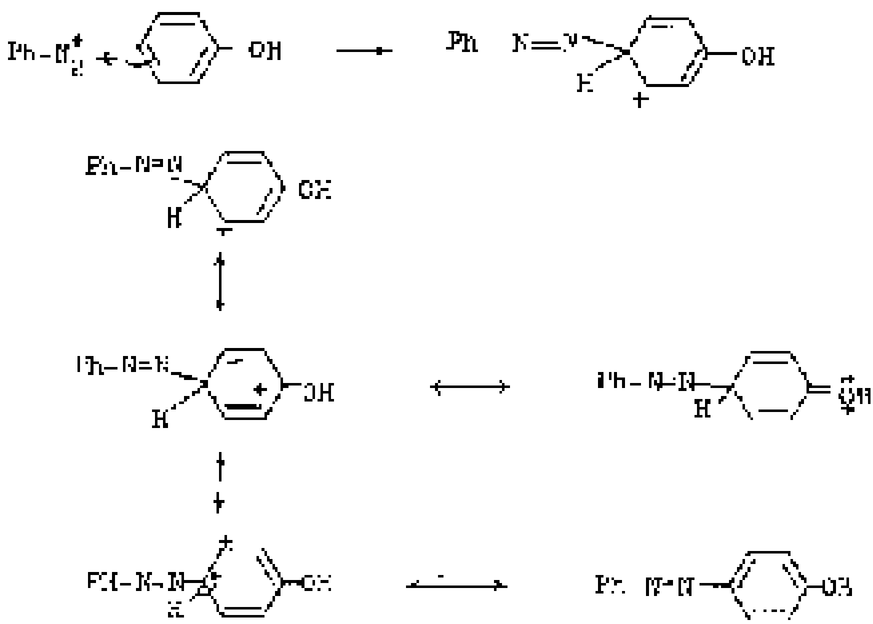
One can see that the diazo reaction would be helped by electron withdrawing substituent as it would increase the electrophilicity of the diazo group.

• PROBLEM 25-8

Benzenediazonium chloride couples with phenol, but not with the less reactive anisole. 2,4-Dinitrobenzenediazonium chloride, however, couples with anisole; 2,4,6-trinitrobenzenediazonium chloride even couples with the hydrocarbon mesitylene (1,3,5-trimethylbenzene).

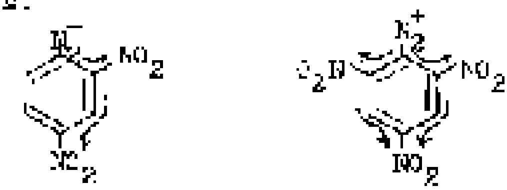
(a) How can you account for these differences in behavior? (b) Would you expect p-toluenediazonium chloride to be more or less reactive as a coupling reagent than benzenediazonium chloride?

Solution: Diazo coupling results from the attack of a diazonium salt on a benzene ring containing highly activating substituents, (e.g. $-O^-$, $-N(CH_3)_2$, $-OH$). The coupling reaction proceeds through an electrophilic aromatic substitution mechanism whereby the electron releasing activating group serves to stabilize the positive charge placed on the ring by the reaction with the electrophilic diazonium salt.



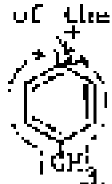
The methoxy group on anisole is not as strong an electron releasing group as the hydroxy group on phenol hence, it will not activate the aromatic ring sufficiently to allow a reaction with benzene-diazonium chloride.

The presence of the nitro groups on the diazonium salt, however, serves to increase the electrophilicity of the diazo group, due to its electron withdrawing properties.



The increase in the electrophilicity of the diazo group permits it to couple with benzene rings substituted with substituents of relatively low activating energy. Thus, two nitro groups on a benzene diazonium salt will allow it to react with anisole, three with 1,3,5-trimethyl benzene.

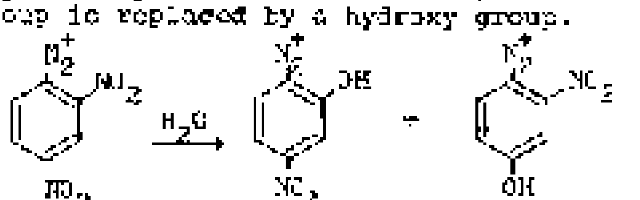
(b) Conversely, the presence of an electron releasing group on the diazonium salt would serve to decrease the electrophilicity of the azo group. This, in turn, would decrease



the diazo coupling ability of a particular compound. Hence, one would expect benzenediazonium chloride to be more reactive than p-toluene diazonium chloride which possesses an electron releasing methyl.

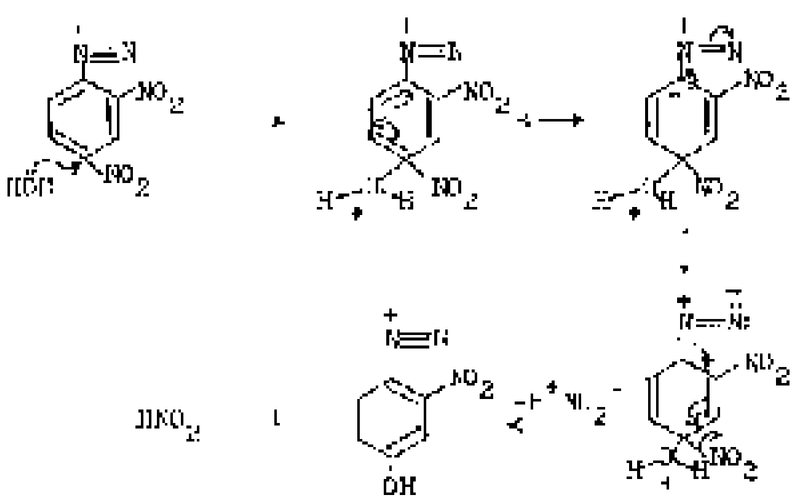
• PROBLEM 26-9

Diazotization of 2,4-dinitroaniline in aqueous solution is accompanied by some conversion to phenols in which a nitro group is replaced by a hydroxy group.

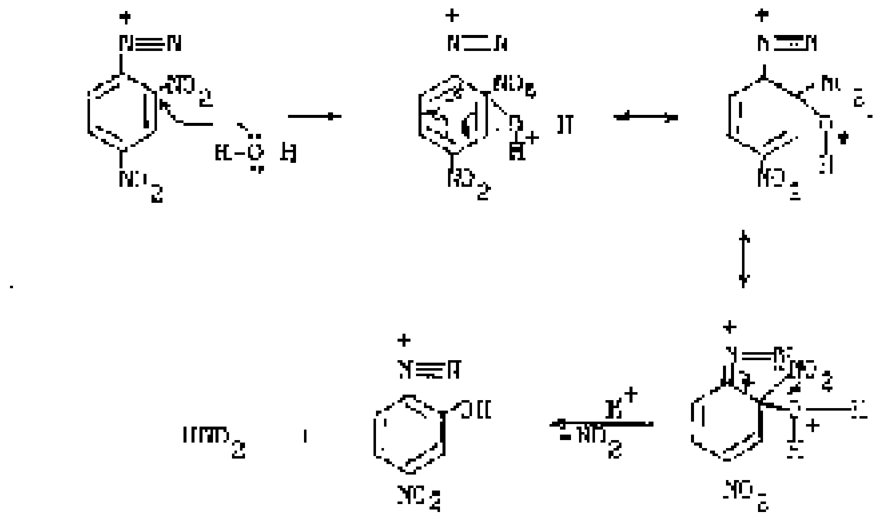


Give a reasonable mechanism for this reaction.

Solution: The conversion of small amounts of 2,4-dinitroaniline to phenol can be accounted for by a nucleophilic aromatic substitution mechanism in which the diazo group acts as an activating group.

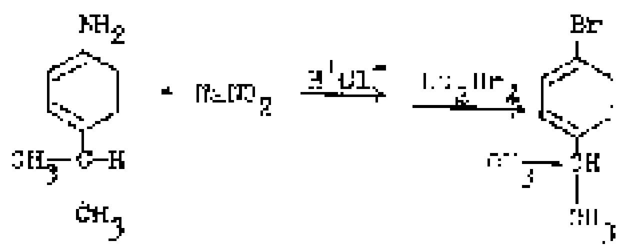


The production of the ortho phenol will proceed by an identical mechanism.



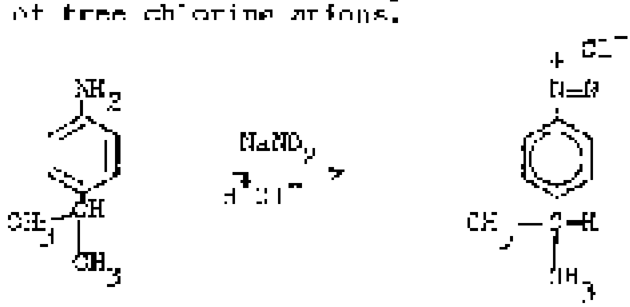
■ **PROBLEM 26-10**

During the heat of an important Organic Chemistry examination, a student proposed the following route for the synthesis of p-bromocumene from p-aminocumene.



The professor, upon seeing the student's synthesis, laughed and gave the chagrined student half credit, promising full credit if the student could carry out the experiment in good yield in the lab. Try as he might, the student continued to obtain a mixture of products. What went wrong, and what is the nature of the mixture?

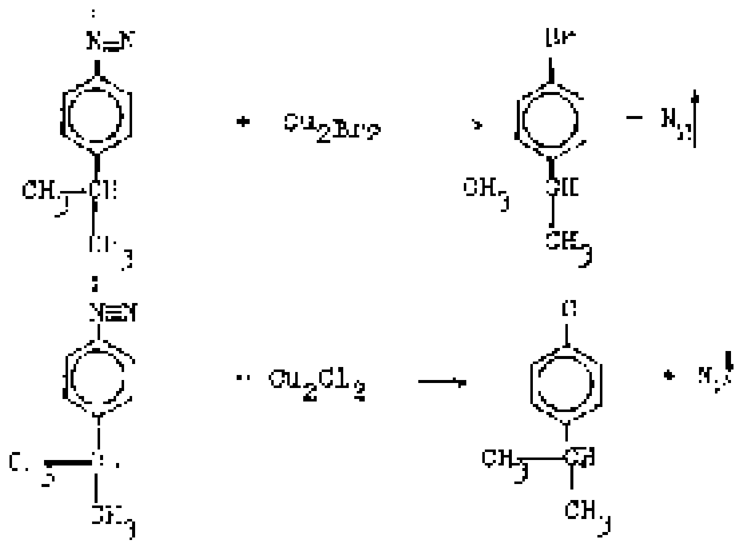
Solution: The mixture consists of p-bromocumene and p-chlorocumene. The student forgot to account for the presence of free chlorine anions.



The first step results in the formation of diazonium salt. To this point the student's reasoning was correct. However, when he added the Cu_2Br_2 he failed to take into account the equilibrium reaction between CuBr and Cl^-.

$$Cu_2Br_2 + 2Cl^- \rightleftarrows Cu_2Cl_2 + 2\,Br^-$$

Hence, the last step of the reaction proceeds with Cu_2Br_2 and Cu_2Cl_2 both reacting with the diazonium salt.



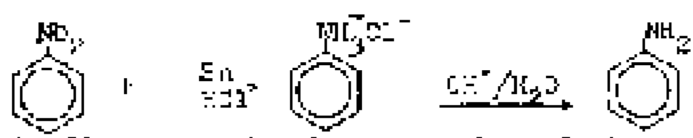
This unfortunate mixture could have been avoided if the student had used HNO_2, H_2SO_4 and H_2O at 25°C. This route would have alleviated the problem of free Cl^- anions.

• PROBLEM 26-11

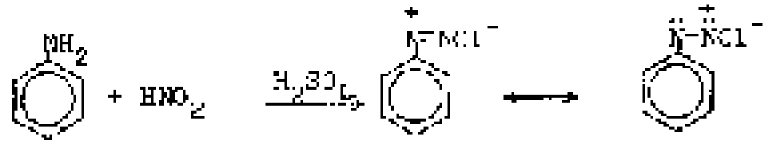
Beginning with nitrobenzene, how would you synthesize the following compounds?

(a) Bromobenzene
(b) Benzonitrile

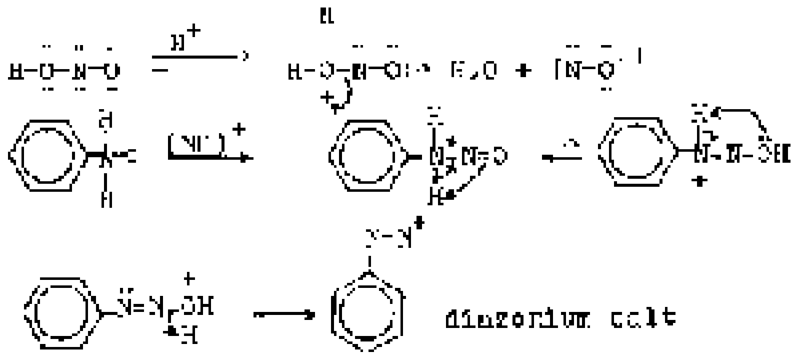
Solution: Both bromobenzene and benzonitrile can be synthesized through reactions with the diazonium salt, which is easily obtained from nitrobenzene.



The first step in the conversion of nitrobenzene to the diazonium salt involves the formation of aniline. To aniline, HNO_2 in the presence of sulfuric acid, is added resulting in the diazonium salt.

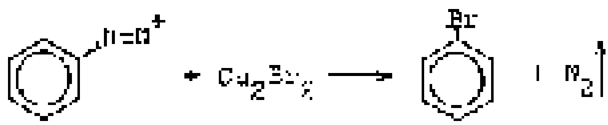


The mechanism of diazonium salt formation involves the N-nitrosation of aniline.



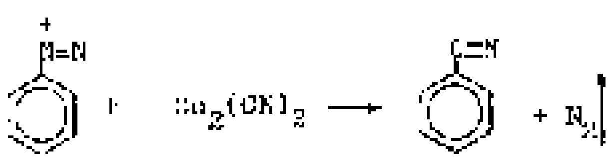
diazonium salt

(a) Once the diazonium salt has been synthesized, bromobenzene can be obtained via the Sandmeyer reaction.



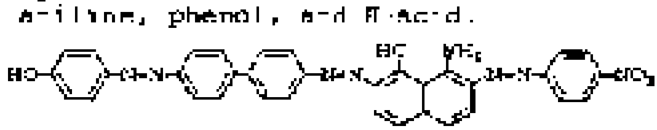
bromobenzene

(b) The Sandmeyer reaction is also useful in obtaining cyano compounds.

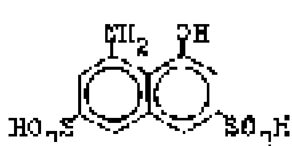


• PROBLEM 26-12

Devise a synthesis of "Diamine Green B" based on nitrobenzene, aniline, phenol, and H-acid.

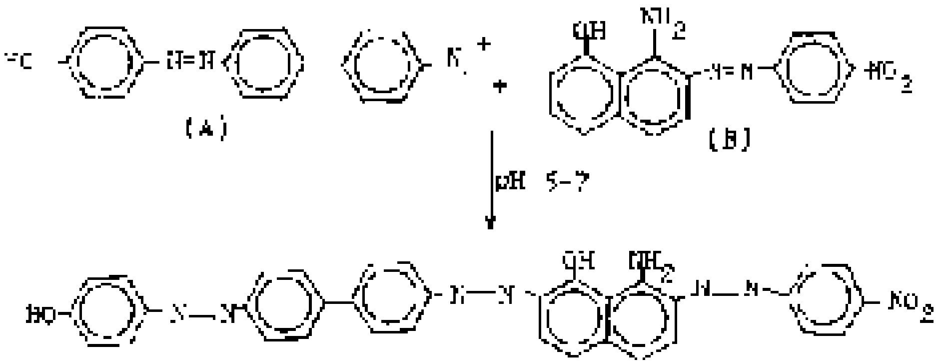


Diamine Green B



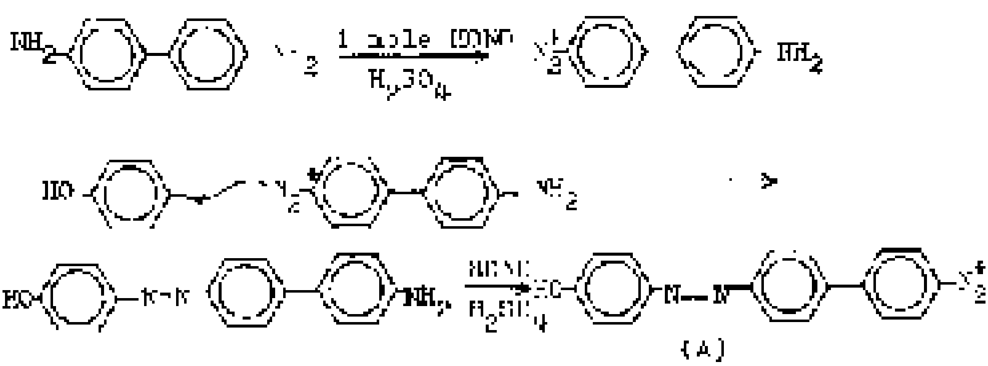
H-acid

Solution: The only way to approach a problem which calls for the synthesis of a complex molecule is to go about solving the problem backwards. If Diamine Green B is broken down into component parts, the synthesis proves to be nothing more difficult than a series of successive diazo linkages. The last diazo linkage in the series involves the coupling of A with B at a pH of 5 - 7.

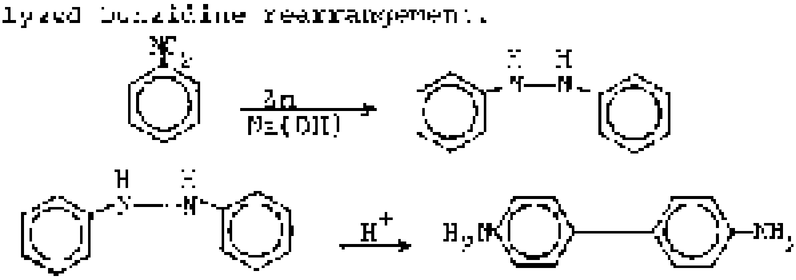


Diamine Green B

Molecule A can easily be formed from the corresponding amino compound (via diotization with HONO and H_2SO_4), which in turn may be obtained via the diazo coupling of benzidine and phenol.

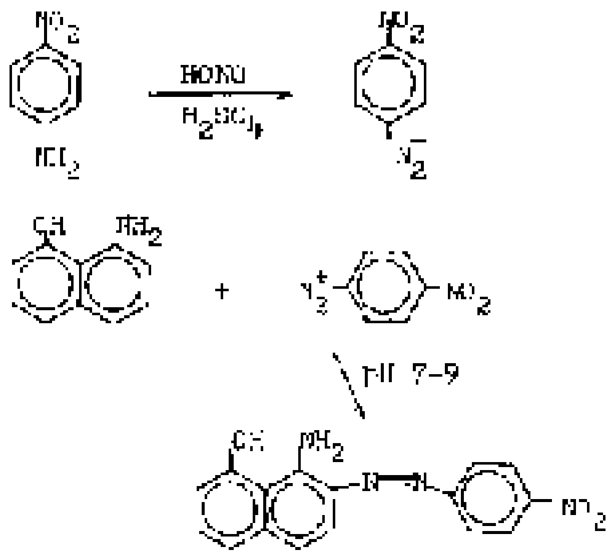


Benzidine, in turn, can be prepared via the reduction of nitrobenzene with Zn/Na OH followed by the acid catalyzed benzidine rearrangement.



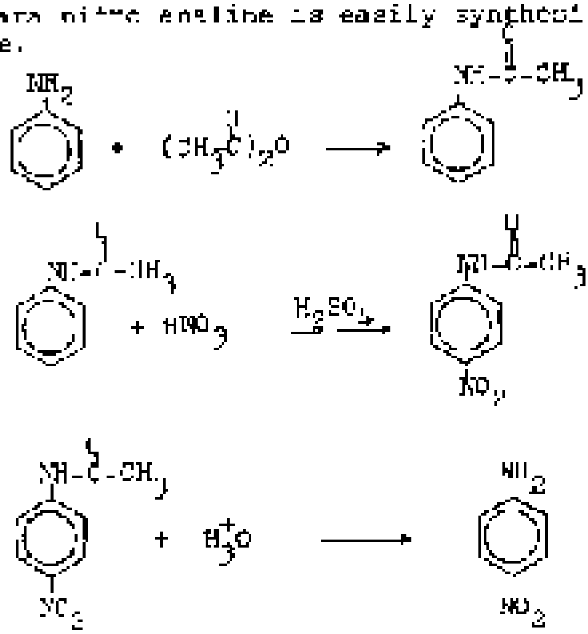
The mechanism of the benzidine rearrangement is still unclear, and the subject of much controversy among chemists.

Molecule B can be obtained through the diazo coupling of H-acid with the diazo salt of p-nitro aniline at pH 7 - 9.



(B)

Para nitro aniline is easily synthesized from aniline.



And there it is, starting from nitrobenzene, aniline, phenol and H acid a route for the synthesis of Diamine Green B has been devised.

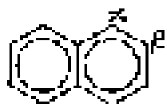
Suggest the syntheses of

(a) β-naphthol from naphthalene

(b) Orange II from β-naphthol and sulfanilic acid.

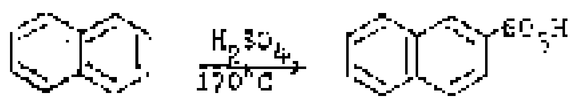
β-naphthol   sulfanilic acid   orange II

Solution: (a) Substitution in a free ringed system is always a problem because one is never sure whether substitution will occur at the α or β position.



However, at normal temperatures (25°C) the α substituted form, due to energetic considerations, will predominate. At higher temperatures, the β form will predominate; hence, substitution on a fused ring system can be controlled.

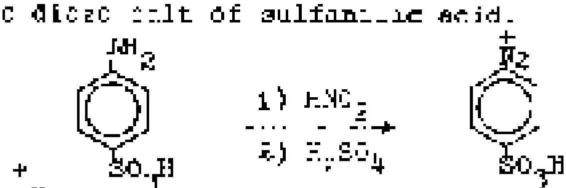
naphthalene

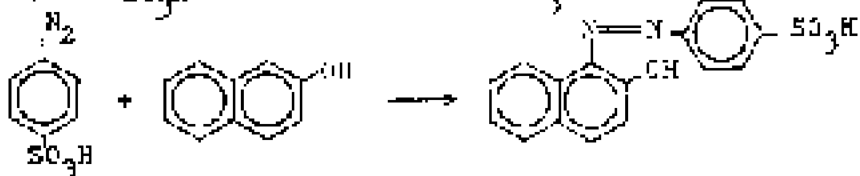


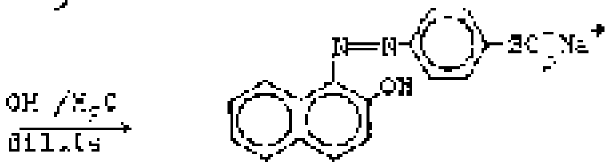
β-naphthol can now easily be synthesized through a simple sodium hydroxide fusion.

β-naphthol

(b) The reaction of β naphthol and sulfanilic acid will proceed via a diazo coupling reaction of β naphthol with the diazo salt of sulfanilic acid.





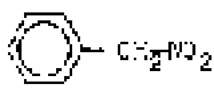


• PROBLEM 26-14

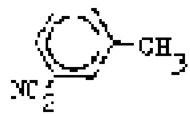
Give for each of the following pairs of compounds a chemical test, preferably a test-tube reaction, that will distinguish the two compounds. Write a structural formula for each compound and equations for the reactions involved:

(a) m-nitrotoluene and phenylnitromethane
(b) p-nitrotoluene and benzamide
(c) hydrazobenzene and benzidine
(d) p-methoxyazobenzene and p-methylazoxybenzene
(e) aniline and cyclohexylamine.

Solution: (a)

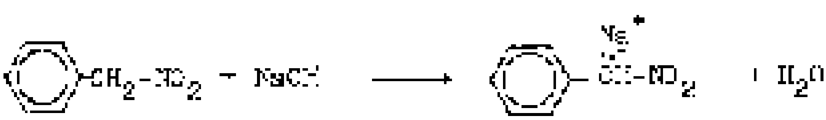


phenylnitromethane

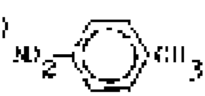


m-nitrotoluene

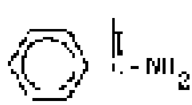
The important difference between these two compounds is that the methyl protons of m-nitrotoluene are far less acidic than the methylene protons of phenylnitromethane. The reason that toluene's protons are less acidic is because the NO_2 group, which is electron withdrawing, is vicinal to the methylene protons in phenylnitromethane, while in m-nitrotoluene the nitrogroup has no effect upon the methyl hydrogens. Thus, an excellent way to distinguish these two compounds is to test for their solubility in base. The phenylnitromethane should be moderately soluble while the m-nitrotoluene is completely insoluble.



(b)

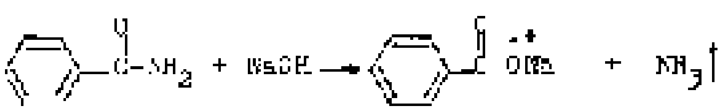


p nitrotoluene



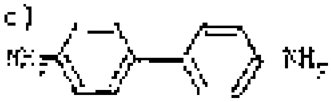
benzamide

Benzamide, an ammonia derivative, yields ammonia upon hydrolysis in basic solution:

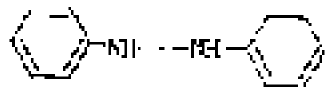


p-Nitrotoluene will not readily hydrolyze under the above conditions.

(c)

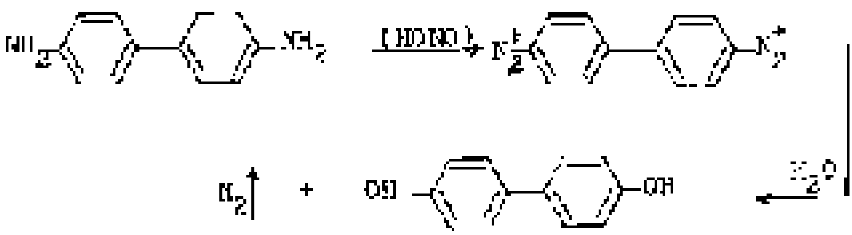


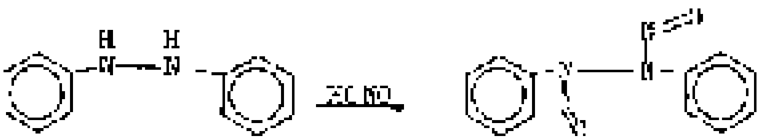
benzidine



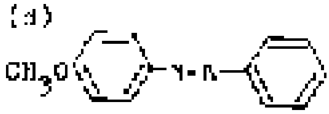
hydrazobenzene

The amino group of the benzidine molecule can form a diazonium salt which, upon hydrolysis, will yield nitrogen gas (N_2). Hydrazobenzene will react with HONO to give a nitroso compound.

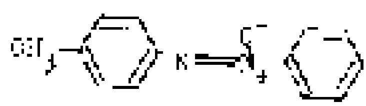




(d)

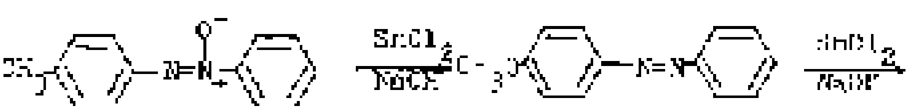


p-methoxyazobenzene



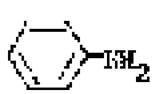
p-methylazoxybenzene

The compound, p-methoxyazobenzene can be formed by reduction of p-methylazoxybenzene; however, most reducing agents will reduce it further, some to hydrobenzene others to aniline. There is, nevertheless, one reducing agent that will reduce p-methylazoxybenzene to only p-methoxyazobenzene and no further: and that one is $SnCl_2$ in base.

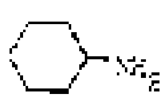


no reaction

(e)

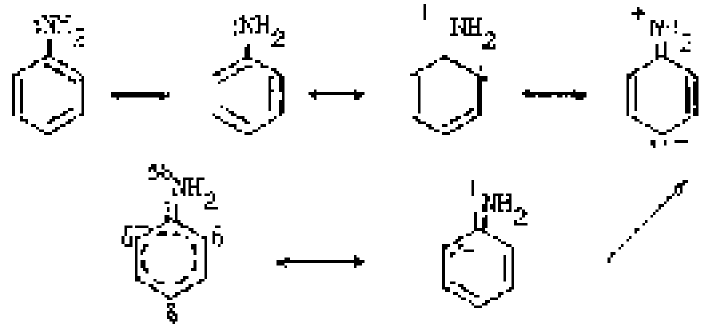


aniline

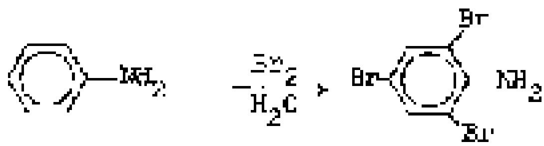


cyclohexyl amine

The aniline molecule has important resonance structures:



From these structures we can see that the aromatic ring in aniline will readily undergo electrophilic attack. In particular aniline reacts very quickly with aqueous Br_2 to form 2,4,6-tribromoaniline, whereas cyclohexyl amine does not react with Br_2 under these conditions.

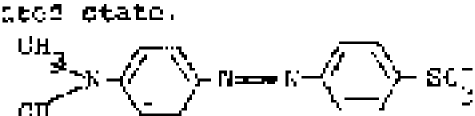


CHEMICAL PROPERTIES

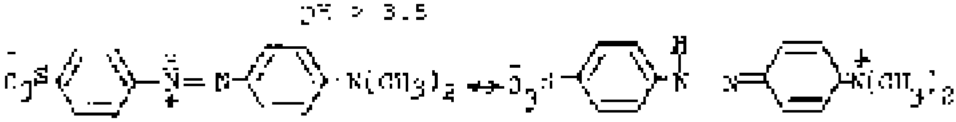
• PROBLEM 20-15

A small amount of Methyl Orange is added to a solution containing equimolar amounts of acetic acid and sodium acetate. Is this solution yellow or red?

Solution: Methyl Orange, an important azobenzene dye, is employed as an indicator for solutions of pH less than 3.5; that is, at a pH of greater than 3.5 Methyl Orange will exist in its yellow unprotonated state. At a pH of less than 3.5, Methyl Orange will exist in its red, protonated state.



nonprotonated (yellow) Methyl Orange
$pH > 3.5$



protonated (red) Methyl Orange
$pH \leq 3.5$

To determine which state Methyl Orange would be in an equimolar solution of acetic acid and sodium acetate, the pH of such a system must be obtained.

$$AcOH \rightleftarrows AcO^- + H^+$$

$$K_a = \frac{[AcO^-][H^+]}{[AcOH]} = 1.8 \times 10^{-5}$$

$$\text{Since } [AcO^-] = [AcOH],\ K_a = \frac{[\cancel{AcO^-}][H^+]}{[\cancel{AcOH}]}$$

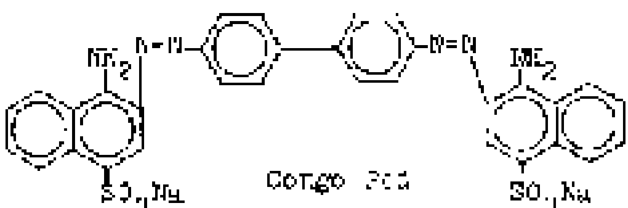
$K_a = K_H = [H^+] = 1.8 \times 10^{-5}$ which means

$$pK_a = pH = -\log [H^+] = 4.74$$

Hence, the color of the solution will be yellow.

• PROBLEM 20-10

Many common pH indicators are azo dyes, for example Congo Red, which is red in basic or neutral solution, and blue in acid solution. The neutral (red) form of the dye is shown.



Congo Red

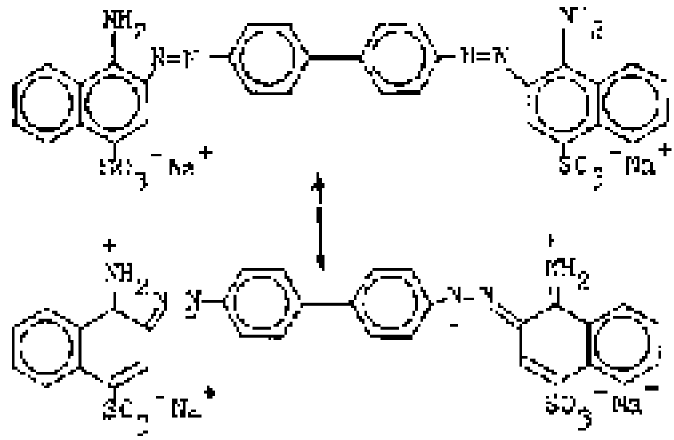
Suggest a structure for the blue form of the dye, assuming that it is a dication.

Solution: Azo dyes are commercial water soluble pigments of a yellow or orange yellow color. Deeper shades of color in azo dyes result from the presence of more highly conjugated systems.

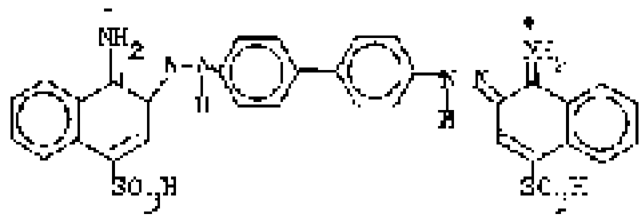
Azo dyes are more than just simple pigments in that they are adsorbed by the fiber being dyed. Polar substituents such as SO_3Na are of utmost importance in binding the dye to a polar surface.

Most azo dyes have substituents known as auxochromes which can deepen the color of the given compound by increasing conjugation. The most common auxochromes are: $-\ddot{N}R_2$, $-\ddot{N}HR$, $-\ddot{N}H_2$, $-\ddot{O}H$, halogen$-\ddot{X}:$, and $-\ddot{O}R$, which all have unshared pairs of electrons that can participate in resonance interaction with the azo system.

For instance, Congo red can be represented as being in resonance with a quinonoid contributor.



In an acidic media, the free protons will neutralize the negative charges on the quinonoid contributor yielding the blue quinonoid salt.



SPECTROSCOPY

• PROBLEM 26-17

A compound A has the molecular formula C_7H_4BrClO. Treatment of A with diazomethane gave B, which upon heating with silver oxide and water was converted to another compound, C, $C_8H_7BrO_2$. The NMR spectrum of C is as follows: δ 3.7 singlet, A = 2; δ 7.2 multiplet, A = 4; δ 12.0 singlet, A = 1. What are the structures of compounds A, B and C?

Solution: A $(C_7H_4BrClO) + CH_2N_2 \rightarrow$ B

$$B \xrightarrow[\Delta,\ H_2O]{AgO} C\ (C_8H_7BrO_2).$$

Any reaction involving diazomethane followed by silver oxide is classifiable as an Arndt-Eistert synthesis. This reaction converts an acid chloride into the next higher homolog in the series. Realizing this, partial structures can be proposed for structures A, B and C.

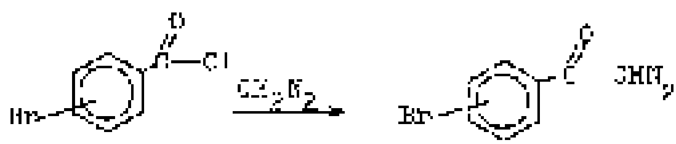
$$A\ \left[(C_6H_4Br)-\overset{\overset{O}{\|}}{C}-Cl\right] \xrightarrow{CH_2N_2} B\ \left[(C_6H_4Br)-\overset{\overset{O}{|}}{C}-CHN_2\right]$$

$$(C_6H_4Br)-\overset{O}{\overset{\|}{C}}-CHN_2 \xrightarrow[H_2O,\ \Delta]{AgO} [C_6H_4Br]-CH_2-\overset{O}{\overset{\|}{C}}-OH] \qquad C$$

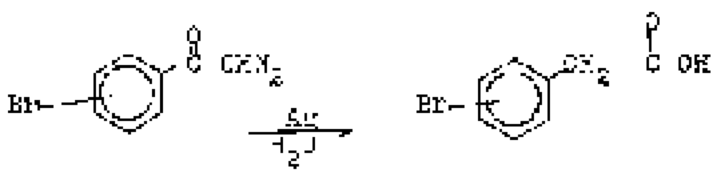
Inspection of the nmr data provided is of definite help in determining the structure of the C_6H_4Br group. The multiplet at δ 7.2 (A = 4) should be indicative of an aromatic group; and indeed, this would account very well for the C_6H_4 group. The δ 2.7 singlet (A = 2) and the singlet at δ 12.0 (A = 1) are confirmatory of the

$-CH_2-\overset{O}{\overset{\|}{C}}-OH$.

The presence of a multiplet δ 7.2 and not a singlet would reveal that five hydrogens are not present. The multiplet would be more indicative of four hydrogens; however from the information given, it cannot be determined whether the benzene is substituted ortho, meta or para.



(A) (B)

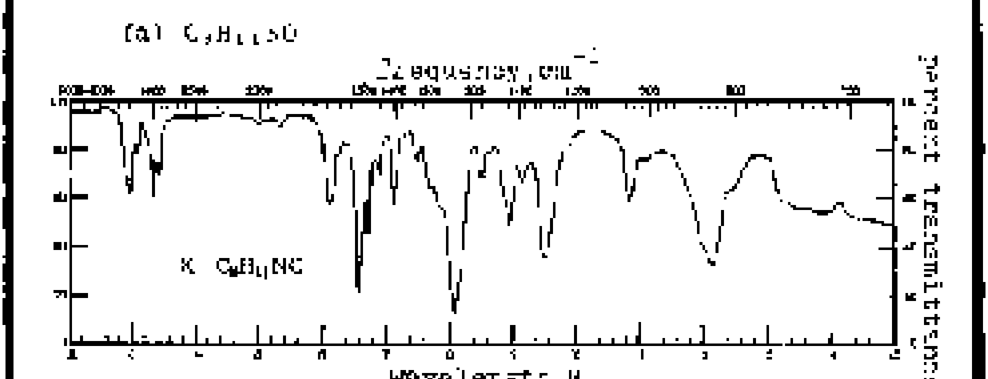


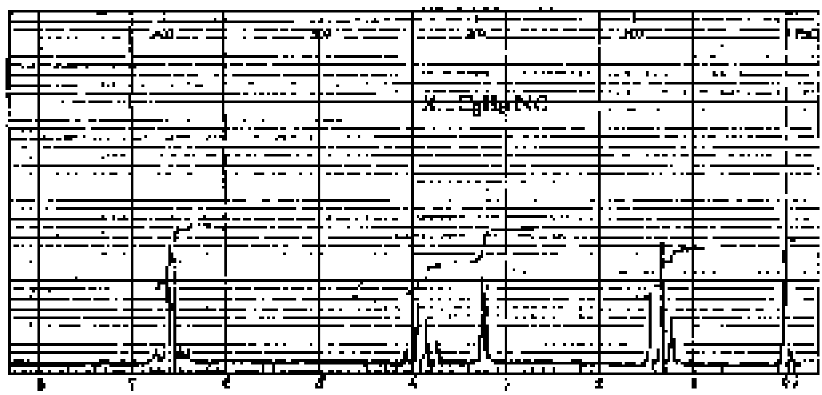
(C)

• PROBLEM 26-18

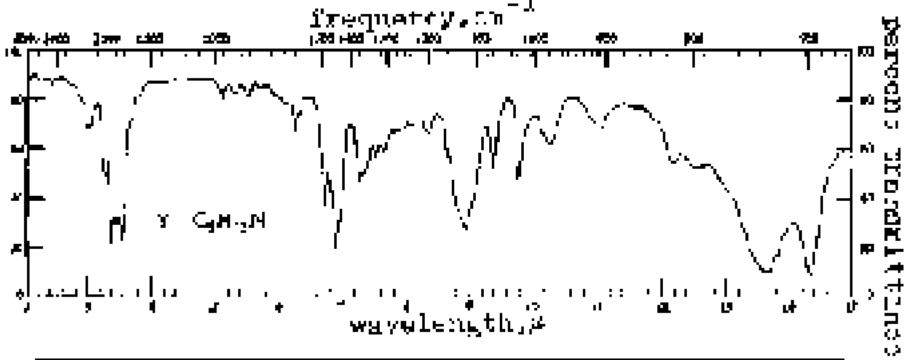
Identify the structures below, given their molecular formulae, infrared and nmr spectra.

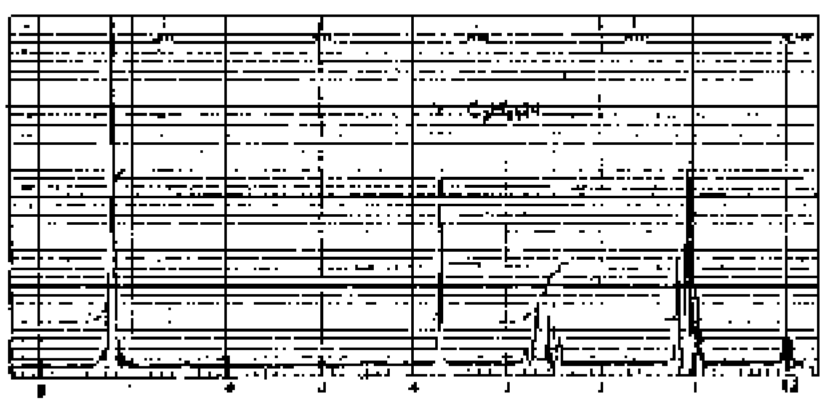
(a) $C_9H_{11}NO$



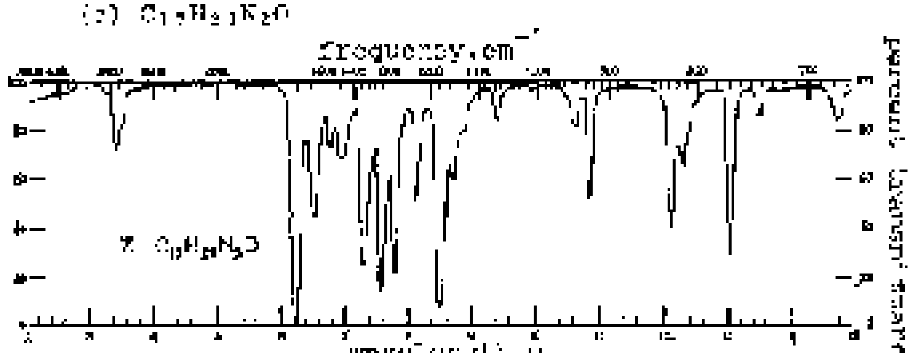


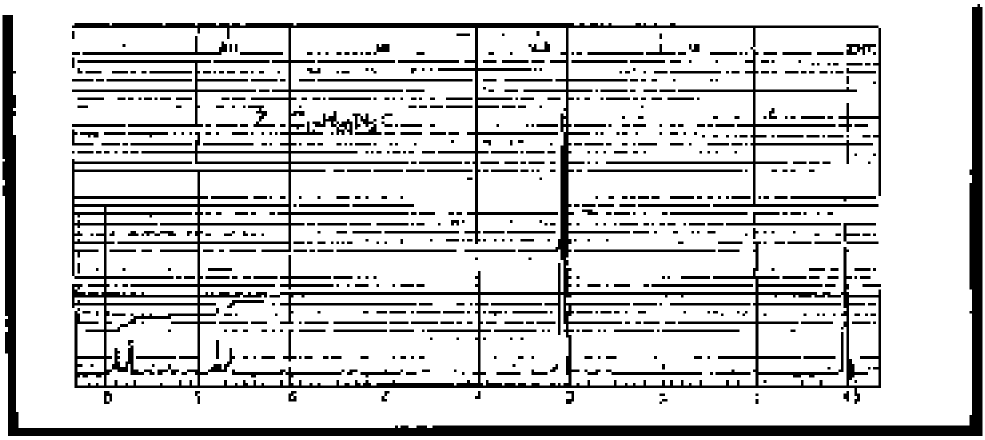
(b) $C_5H_{13}N$





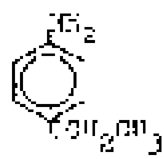
(c) $C_{13}H_{21}N_2O$



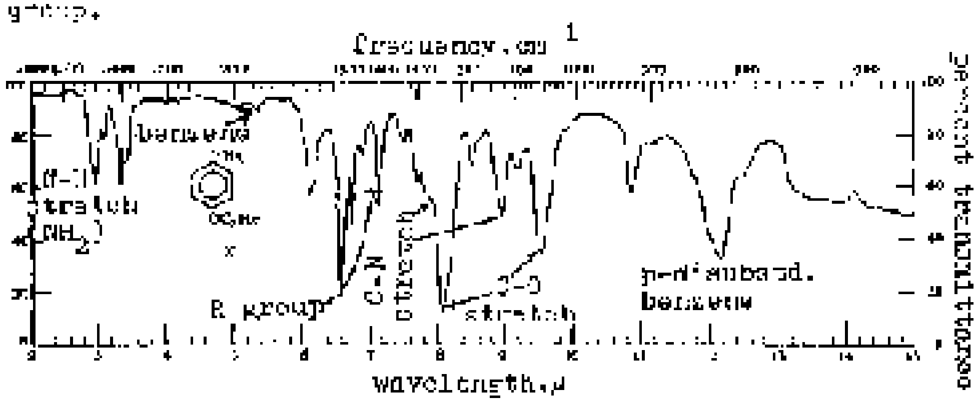


Solution:

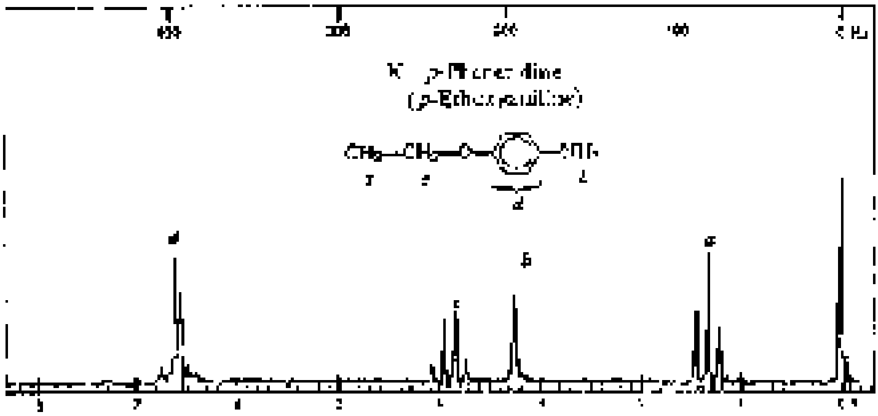
(a)



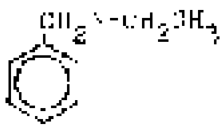
In glancing at the infrared spectra, there are several immediately noticeable bands of absorptions. The sharp absorption at approximately 1070 should be indicative of the carbon-oxygen single bond stretch. The weak doublet at 3400 would be indicative of a double bond. The medium peak at 830 could be indicative of a para-substituted benzene; the presence of benzene is indicated by the weak finger-like absorptions between 1700 and 2000 cm^{-1}. The absence of a sharp absorption at 1710 cm^{-1} would be indicative of the absence of a carbonyl group, while the absorption at approximately 1380 would indicate the presence of a methyl, isopropyl, ethyl or t-butyl group.



An examination of the nmr data would provide the last needed clues in the determination of the structure of $C_8H_{11}NO$. The doublet at δ 6.7 would be confirmatory of a para-substituted benzene ring. The triplet at δ 1.3 would be indicative of a group split by a $-CH_2$ group. Indeed, pairing this with the quintet at δ 4.0, a CH_3-CH_2-O group can be proposed, the oxygen causing the downfield shift. The singlet at δ 3.2 could be accounted for by the presence of an amino group.

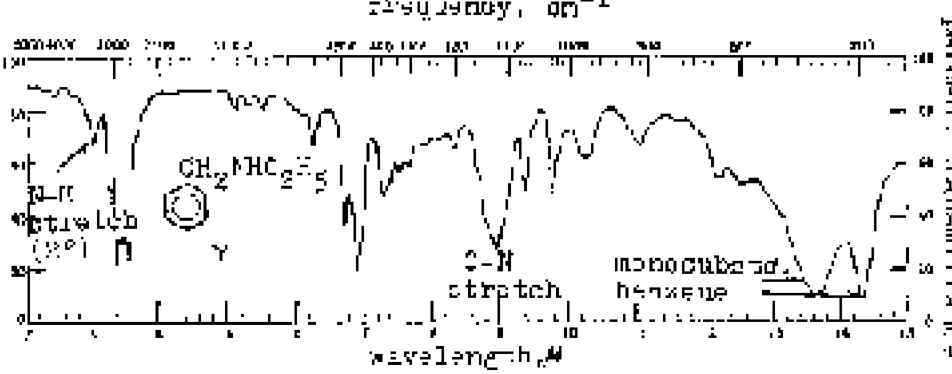


(b)



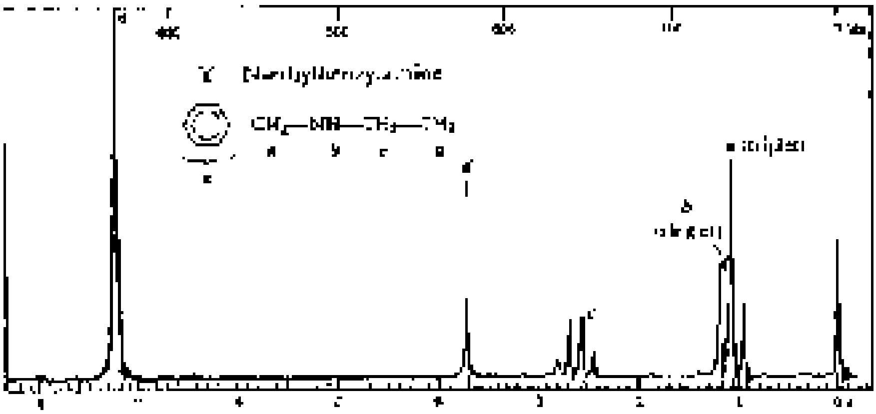
n-ethylbenzylamine

The weak absorption at 3040 cm^{-1} in the infrared spectrum would be indicative of the N-H stretch of secondary amines. The absorption at 1380 would be indicative of an ethyl, methyl, isopropyl or t-butyl group. The broad absorption at 1120 would be indicative of a C-N stretch, while the broad absorptions at 750 cm^{-1} and 700 cm^{-1} would be indicative of a monosubstituted benzene ring. Unfortunately one can only interpret infrared spectra if one is familiar with the various group characteristic peaks. There are no "easy" ways of interpreting IR spectra.

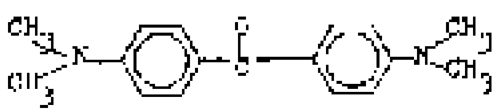


The nmr spectra of the problem is misleading at first glance. The triplet at δ 1.2 is comprised of three peaks not in the 1 : 2 : 1 ratio. However this can be explained if the -N-H absorption is kept in mind. The hydrogen of a secondary amine will absorb at a position of 1.2 ppm. This would cause an overlap and produce a disproportionate triplet. The sharp singlet at δ 7.2 confirms the presence of a monosubstituted benzene alluded to by the compound's infrared spectra. The peak at δ 3.8 with a relative area of two would be indicative of a methylene group situated next to electron withdrawing substituents.

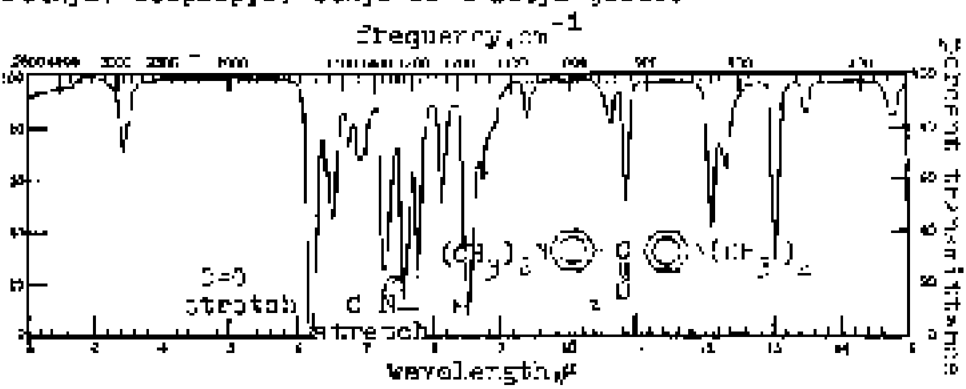
The quartet at δ 2.7 of relative area two indicates a methylene group situated next to a methyl group. By integrating this data, one can propose the following structure with reasonable certainty.



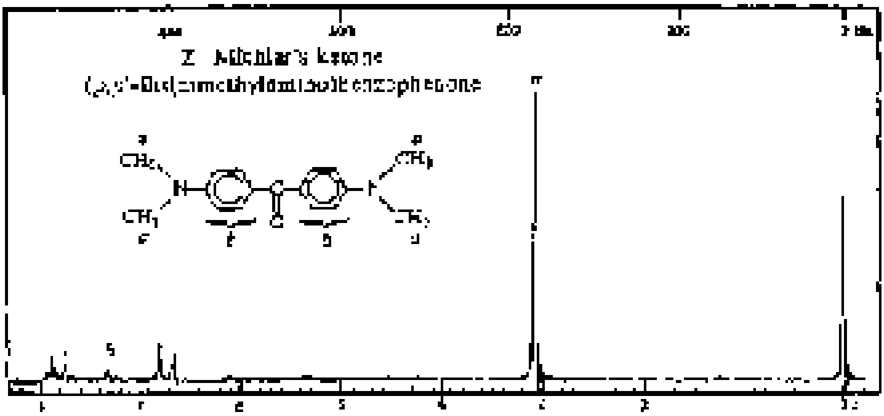
(c)



The most evident clue to the structure of the above compound is given by the infrared spectra's very strong absorption at 1665 cm^{-1}. This is characteristic of the C=O stretch, and specifically at 1665, of a carbonyl substituted on both sides by phenyl groups $\phi-\overset{O}{\overset{\|}{C}}-\phi$. The strong peaks at 1310 cm^{-1} and 1160 cm^{-1} would indicate the presence of a C-N bond linkage, as these absorptions are characteristic of the C-N stretch. However, there is no absorption above 3000 cm^{-1}, which indicates the absence of an N-H bond. This would imply that the nitrogen group present exists in the form of a tertiary amine. The strong absorption at 1380 cm^{-1} would indicate the presence of either a methyl, isopropyl, ethyl or t-butyl group.

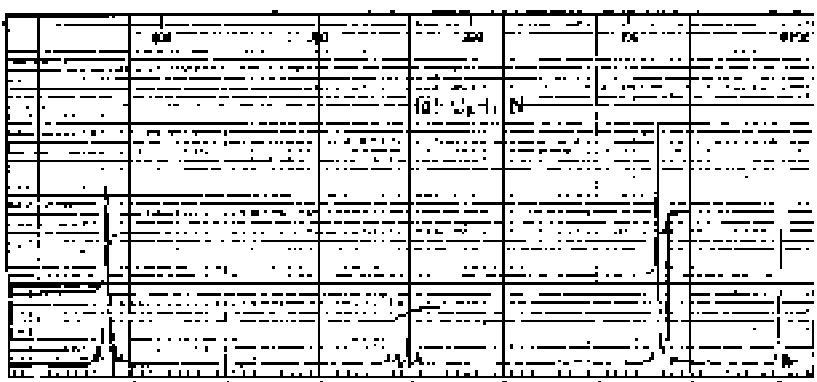


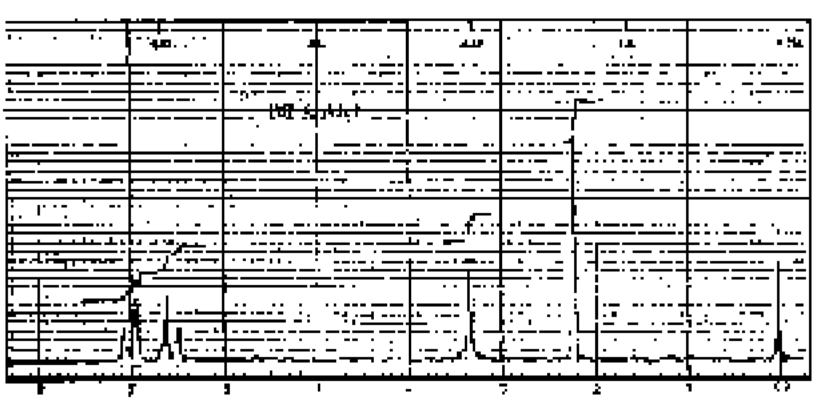
The nmr spectra of the unknown compound is interesting in its lack of peaks. In fact, there are only two: a sharp singlet at δ 3.1 of relative area six and a symmetric multiplet of broad absorption from δ 6.7 - δ 8.1. Close inspection of this absorption shows it to be similar to the absorption characteristic of a para-substituted benzene ring. However, the existence of two of these absorptions is confirmatory of the presence of two phenyl groups, each substituted in the para position.



■ PROBLEM 20-19

Give a structure or structures consistent with each of the nmr spectra shown.





Solution: (a) The nmr spectrum has a singlet at δ 7.3 which indicates the presence of a benzene ring. By subtracting the molecular formula of a phenyl group (C_6H_5) from the molecular formula of the compound ($C_8H_{11}N$), we are left with a C_2H_6N portion.

The relative intensities of the signals (going from left to right) are 5 : 1 : 5. The signal near δ 1.3 is actually two signals that overlap each other. This conclusion is reached by noticing that the two peaked signal at δ 1.3 is asymmetrical; one peak is taller than the other. If the signal resulted from only one type of proton causing splitting, the doublet would appear symmetrical, that is both peaks would have the same height. Since the more downfield peak (δ 1.35) is taller than the other peak (δ 1.25) of the signal, it is logical to assume that a second type of proton gives rise to a singlet at δ 1.35. This makes the δ 1.35 peak of the doublet taller than the δ 1.25 peak. From the relative intensities we know that five protons were responsible for the signals at δ 1.3 (doublet centered at δ 1.3 and singlet at δ 1.35). The quartet at δ 4.0 has a relative intensity of one. This indicates that a single proton underwent spin-spin splitting by three non-equivalent protons to give rise to the four peaked signal. We now have identified a phenyl group and a methine group. The unidentified portion has the molecular formula CH_5N. Since the methine carbon is bonded to only one hydrogen, it must be also bonded to the phenyl group:

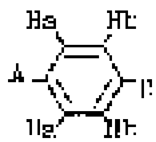
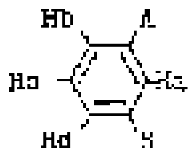
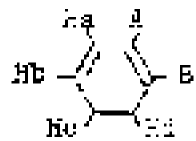
$$C_6H_5-\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}-$$

. The two remaining bonds must be to the carbon and nitrogen of the CH_5N portion. The only structural formula that is consistent with these requirements is that of α-Phenylethylamine.

$$C_6H_5-\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_3 .$$

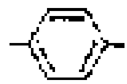
The chemical shift of the methine proton is fairly downfield due to the deshielding effects of the proximal phenyl ring and amino group. The methine proton signal is split into a quartet by the three equivalent methyl protons. The methyl protons are split into a doublet (occurs at δ 1.3) by the lone methine proton. The amino protons occur as a singlet at δ 1.35. It is the overlap of the amino and methyl signals that give the nmr signal at δ 1.3 a relative intensity of five (the two amino protons and the three methyl protons).

(b) The nmr spectrum shows two doublets at δ 7.0 and δ 6.6. These doublets are equivalent with respect to their integration curve, that is, the relative intensities of the doublets are equal. The relative intensities of the signals at δ 7.0, δ 6.6, δ 3.3 and δ 2.2 are 2 : 2 : 2 : 3, respectively. The fairly downfield chemical shift of the two doublets coupled with the fact that the two doublets are the only signals that show spin-spin splitting indicates a para disubstituted benzene ring. Each doublet arose from spin-spin splitting by one non-equivalent proton. A para-disubstituted benzene ring has two sets of two non-equivalent protons and would give rise to two doublets in the range of δ 6.5 – δ 7.5. Meta- and ortho-disubstituted benzene rings (where the two substituents are not identical) have four sets of non-equivalent protons and would give rise to very complex signals (overlapping multiplets).

para - two types of protons

$\underbrace{\text{meta} \qquad\qquad\qquad \text{ortho}}_{\text{four types of protons}}$

Hence there is a  or $-C_6H_4-$ portion in the compound. This leaves us with a CH_5N portion to be identified. Since the benzene ring bears two substituents, and it cannot be hydrogen atoms, the substituents must be methyl and amino. The compound is p-toluidine and has the structure:

ture: .

The singlet at δ 3.3 has a relative intensity of two and hence must be the amino protons' signal. It occurs relatively downfield due to the deshielding effects of the benzene ring and the nitrogen. The singlet at δ 2.2 is the methyl signal and has a relative intensity of three. Again, the signal is relatively downfield due to the deshielding effects of the benzene ring.

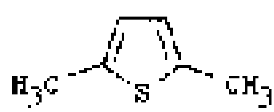
CHAPTER 27

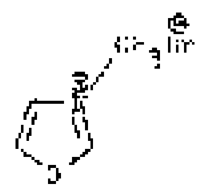
HETEROCYCLIC AROMATIC COMPOUNDS

NOMENCLATURE AND STRUCTURE

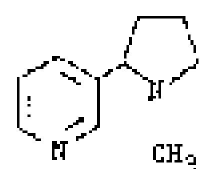
• PROBLEM 27-1

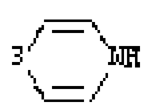
Name the following compounds by an accepted system.

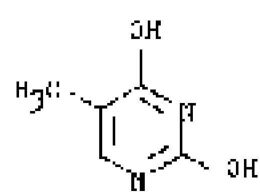
a. 

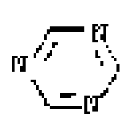
e. 

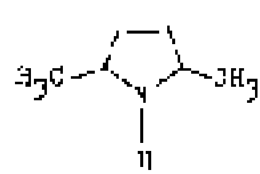
b. 

f. 

c. 

g. 

d. 

h. 

Solution: Many heterocyclic compounds have acquired common names that are unlikely to be replaced by more systematic names. However, some rules have been adopted by IUPAC for the naming of monocyclic and polycyclic ring systems possessing one or more heteroatoms. We will briefly discuss the nomenclature for monocyclic rings (nomenclature for polycyclic rings is discussed in the next problem), and then we will name compounds (a) - (h). The method is to add the appropriate suffix and prefix to a given stem according to the following rules:

(1) The ring size is denoted by the stem (see Table 1).

(2) The heteroatom is denoted by the prefix: oxa = oxygen; thia = sulfur; aza = nitrogen. The presence of two oxygens, sulfurs, or nitrogens is indicated by dioxa, dithia, or diaza respectively. If there are two or more different heteroatoms in the ring, they are written in order of preference: oxygen before sulfur before nitrogen.

(3) The degree of unsaturation is usually indicated by the suffix, which differs for nitrogen and non-nitrogen compounds (see Table 1).

(4) The numbering system starts with the heteroatom and proceeds around the ring so as to give substituents (or other heteroatoms) the lowest numbered positions. If there are two or more different heteroatoms, oxygen has priority over sulfur, and sulfur over nitrogen for the number one position.

(5) Partially reduced ring compounds are either referred to as dihydro or tetrahydro derivatives of the parent compound, or else they are indicated by attaching H with the number denoting position of saturation to the name of the parent compound.

Table 1:

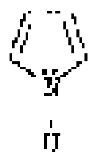
Stems, Suffix, and Ring Size of Heterocyclic Compounds

		Stem – suffix			
		Ring contains nitrogen		Ring contains no nitrogen	
Ring size	Stem	Unsaturated[a]	Saturated	Unsaturated[b]	Saturated
3	-ir-	-irine	-iridine	-irene	-irane
4	-et-	-ete	-etidine	-ete	-etane
5	-ol-	-ole	-olidine	-ole	-olane
6	-in-	-ine	b	-in	-ane
7	-ep-	-epine	b	-epin	-epane
8	-oc-	-ocine	b	-ocin	-ocane
9	-on-	-onine	b	-onin	-onane
10	-ec-	-ecine	b	-ecin	-ecane

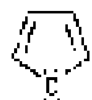
[a]Corresponding to maximum number of double bonds, excluding cumulative double bonds.

[b]The prefix "perhydro" is attached to the stem and suffix of the parent unsaturated compound.

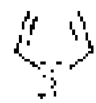
Note that the systematic names are usually not used with the common heterocyclic compounds. Examples of these are (systematic names are in parentheses):



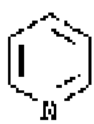
pyrrole
(azole)



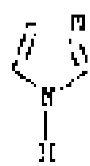
furan
(oxole)



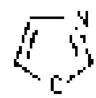
thiophene
(thiole)



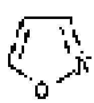
pyridine
(azine)



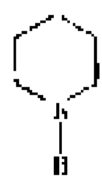
imidazole
(1,3-diazole)



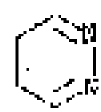
oxazole
(1,3-oxazole)



isoxazole
(1,2-oxazole)



piperidine
(perhydroazine)

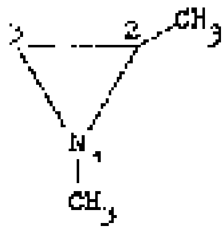


pyridazine
(1,2-diazine)

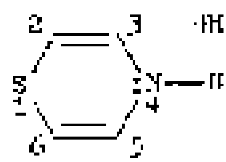
With this in mind, let us name compounds (a) - (q):

(a) The parent compound is a thiophene, with two methyl substituents at positions 2 and 5, therefore its name is 2,5-dimethylthiophene.

(b) The parent compound is aziridine; az (the "a" drops out when it is followed by another vowel) because it is a nitrogen compound, and iridine because it is a 3-membered saturated ring that contains nitrogen. The two methyl substituents are at positions 1 and 2, therefore its name is 1,2-dimethylaziridine.

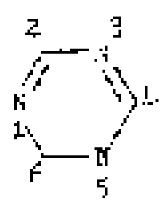


(c) The parent compound is 1,4-thiazine. The "1" indicates the position of the sulfur, the "4" indicates the position of nitrogen, and ine indicates an unsaturated six-membered ring that contains nitrogen. Since the nitrogen is hydrogenated, we must indicate this by using the prefix 4H, where the "4" indicates that hydrogenation is at the "4" position:

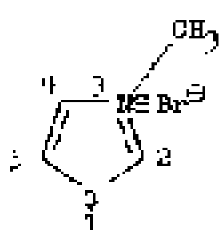


4H 1,4-thiazine

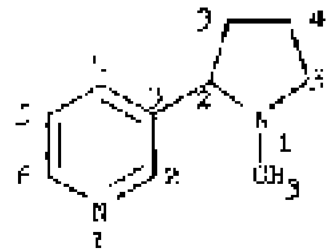
(d) This heterocyclic compound has three nitrogens at positions 1, 3, and 5 of an unsaturated six-membered ring that contains nitrogen, therefore its name is 1,3,5-triazine.



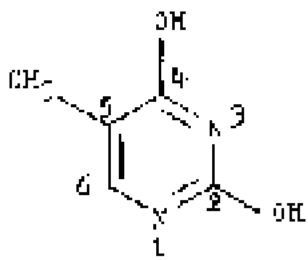
(e) The parent structure is 1,3-oxazole. The methyl group is at position 3. Since this oxazole has a positive charge, it is called an oxazolium. The associated anion is bromide, therefore its name is 3-methyl-1,3-oxazolium bromide:



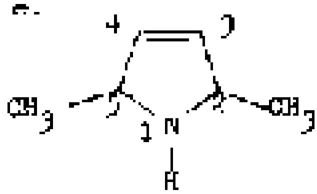
(f) The parent structure is pyridine, with a substituent at position 3. The substituent itself is a heterocyclic compound whose parent structure is azolidine (nitrogen → aza, olidine → five-membered saturated ring that contains nitrogen). The azolidine substituent has a methyl group at the 1 position, therefore the substituent is called 1-methylazolidine and the compound is 3-(1-methyl-azolidin) pyridine. Its common name is nicotine.



(g) The parent structure is pyrimidine with hydroxy groups at positions 2 and 4 and a methyl group at position 5. Therefore its name is 2,4-dihydroxy-5-methylpyrimidine. Its common name is thymine, one of the four bases in DNA.

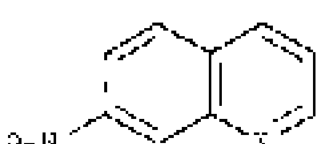


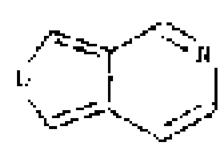
(h) The parent structure is pyrrole. It is partially reduced with hydrogens at positions 2 and 5, and methyl groups at positions 2 and 5. Its name is 2,5-dihydro-2,5-dimethylpyrrole.



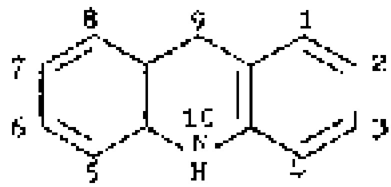
PROBLEM 27-2

Name the following structures by an accepted system. Note that the numbering given in part (b) constitutes an exception to the rules; here the system resembles that for anthracene.

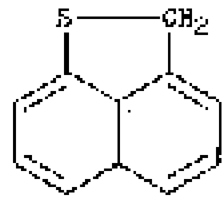
a. 

c. 

b.



d.



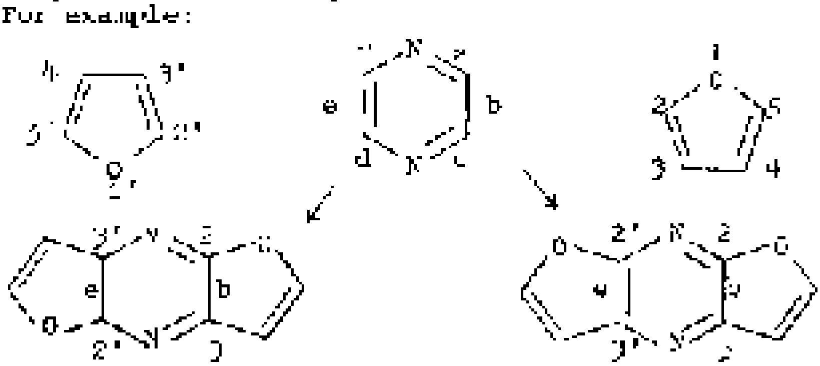
Solution: Polycyclic rings with heteroatoms are named according to the following rules:

(1) The name of the hetero ring is used as the parent compound and the name of the fused ring is attached as a prefix.

(2) In the selection of the parent ring, when two or more hetero rings are present, the ring containing nitrogen has priority over the ring containing oxygen (and oxygen over sulfur). However, in the numbering system for the polycyclic compound, oxygen has priority over sulfur, and sulfur over nitrogen for the number one position (see Rule 5 for numbering system).

(3) Preference is given to the largest hetero ring system which has a common name.

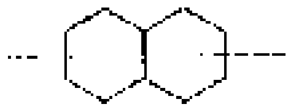
(4) To indicate the position of the ring junction, the sides of the parent ring are lettered a, b, c, etc., starting clockwisely with the 1,2-bond; substituent fused rings that are not symmetrical are indicated by numbers. For example:



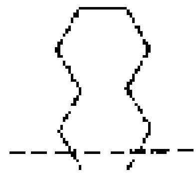
difuro[2,3-b:2',3'-e]pyrazine   difuro[2,3-b:3',2'-e]pyrazine

(5) In numbering the periphery of a polycyclic compound, the structure must be oriented according to the following rules:

(a) The greatest number of rings must lie along a horizontal axis:

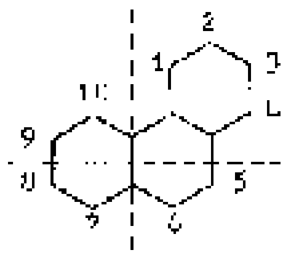


correct

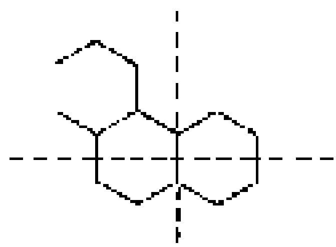


incorrect

(b) Of the other rings, a maximum must lie uppermost to the right above the horizontal axis (the first quadrant):



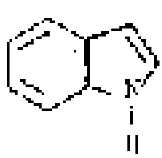
correct



incorrect

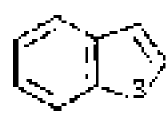
Numbering starts with the uppermost ring farthest to the right and proceeds in a clockwise direction, omitting ring junctions. Other things being equal, the orientation of the rings should be such as to lead to the lowest possible number for the heteroatoms.

Common names for some polycyclic compounds are:

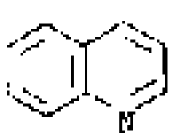


indole

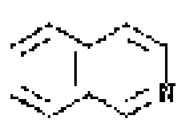
benzofuran



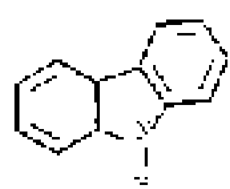
benzothiophene



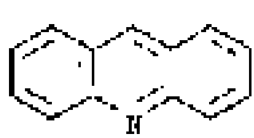
quinoline



isoquinoline



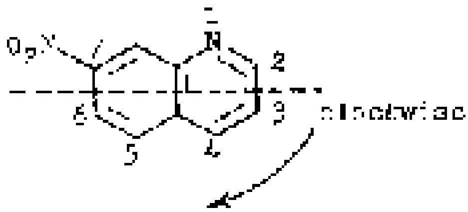
carbazole



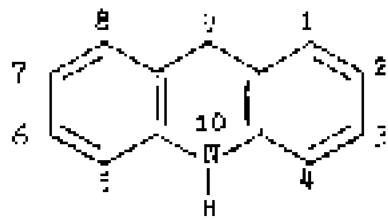
acridine

With this in mind, let us name compounds (a) - (d).

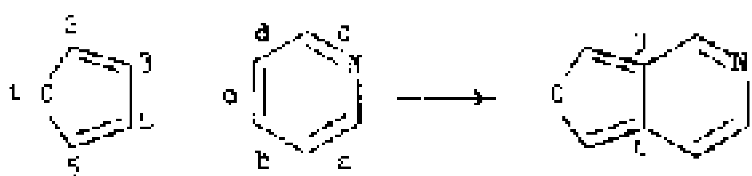
(a) The parent structure is quinoline. There is a nitro substituent at position 7, therefore its name is 7-nitroquinoline.



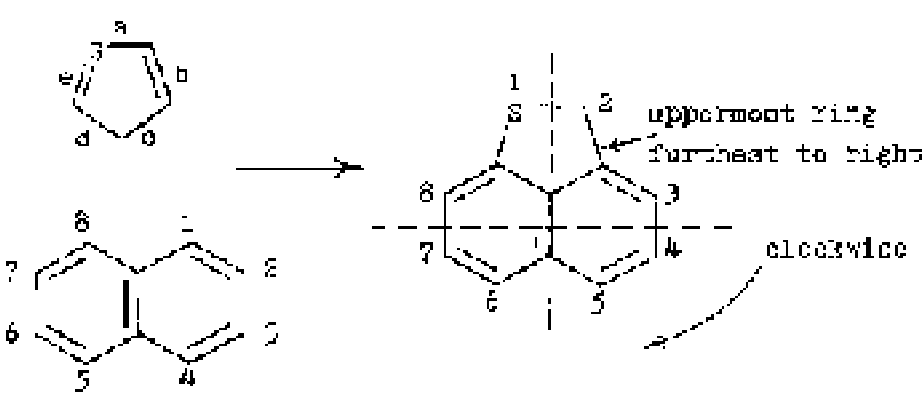
(b) The parent structure is acridine. It is partially reduced, with hydrogens at positions 9 and 10. Therefore its name is 9,10-dihydroacridine.



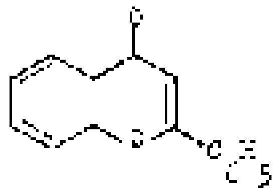
(c) The parent structure is pyridine. It has a furan ring fused to it. The position of this fusion is on side c of pyridine and between C_3 and C_4 of furan, therefore its name is furo[3,4-c]pyridine.



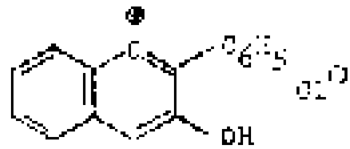
(d) The parent structure is thiophene. The ring fusion is on sides b and c of thiophene, and C_1 and C_8 of naphthalene. The thiophene is partially reduced, with the hydrogen on C_2, of the polycyclic compound. Therefore, its name is 2H-naphtho[1,8-bc]thiophene.



Many of the beautiful colors of butterflies' wings, autumn leaves, and flowers are due to the presence of flavone derivatives called anthocyanins. When anthocyanins are hydrolyzed in hydrochloric acid (to remove sugar residues), they produce aromatic oxygen-containing salts. One of these is delphinidin chloride. Explain why delphinidin chloride is aromatic. What is the hybridization of the heterocyclic oxygen in this compound?

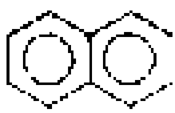


flavone

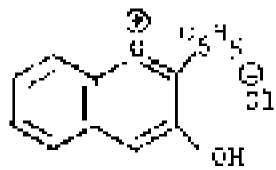


delphinidin chloride

Solution: Delphinidin chloride is aromatic for the same reason that naphthalene is aromatic: two overlapping aromatic sextets of π electrons that have a pair of electrons in common.



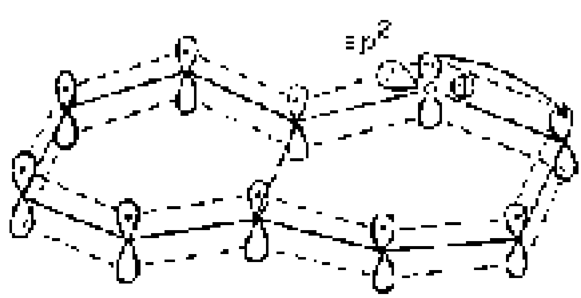
naphthalene



delphinidin chloride

From another point of view, their periphery contains 10 π electrons, which satisfy Hückel's rule for aromaticity ($4n+2$ for $n=2$).

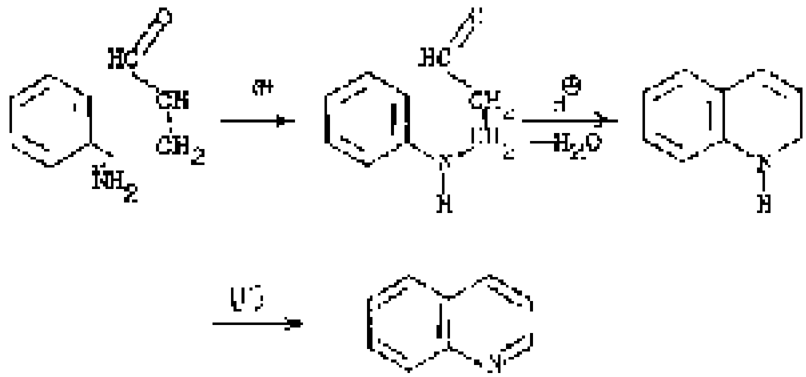
The hybridization of the heterocyclic oxygen in delphinidin chloride is sp^2, as is the hybridization of the carbons in the compound. Thus, a pair of electrons from oxygen is in a p orbital, which allows them to participate in the π cloud. The other lone-pair electrons of oxygen are in a sp^2 orbital, with the other two sp^2 orbitals forming σ bonds with two carbon atoms. Since oxygen contributes two electrons to the π cloud, it has a formal charge of +1.



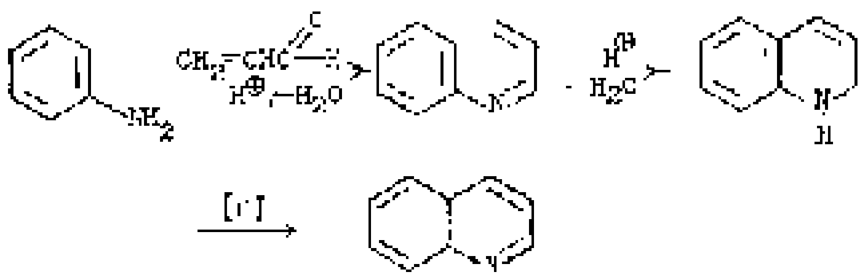
• PROBLEM 27-4

Two mechanisms for the Skraup synthesis are:

1.



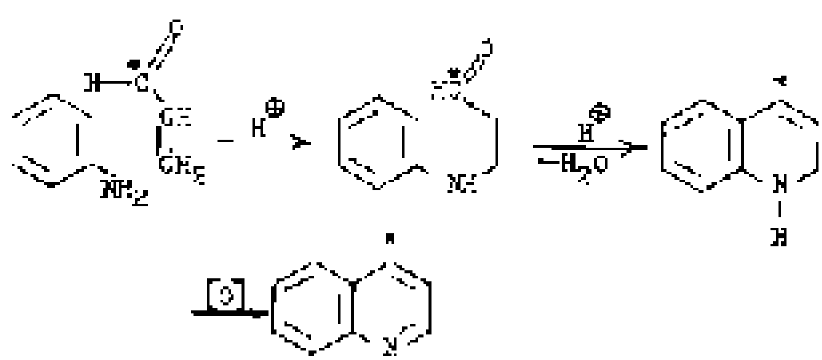
2.

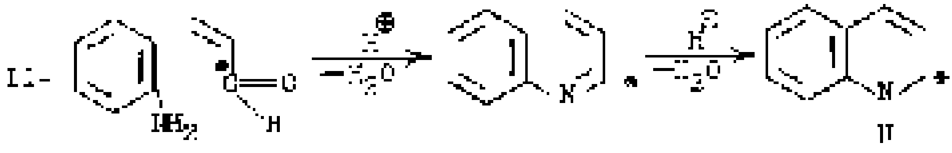


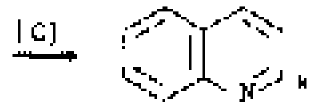
Devise an experiment whereby we can tell which is the actual mechanism.

Solution: The difference between the two mechanisms is the place of attack by the nucleophilic nitrogen atom. The first mechanism involves attack on the β-carbon of the α,β-unsaturated aldehyde. The second mechanism involves attack at the aldehydic carbon. By using ^{14}C labeled acrolein, we can deduce the actual mechanism by the position of the label in the product:

1.





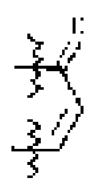


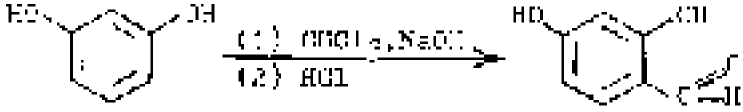
• PROBLEM 27-5

Umbelliferone is a coumarin derivative present as a glucoside in many plants, for example, in several species of japonica. It is used commercially as a sun-screen in lotions. Show how it may be synthesized from resorcinol.

Solution: Umbelliferone has the structure:

We see that this is just a derivative of resorcinol.

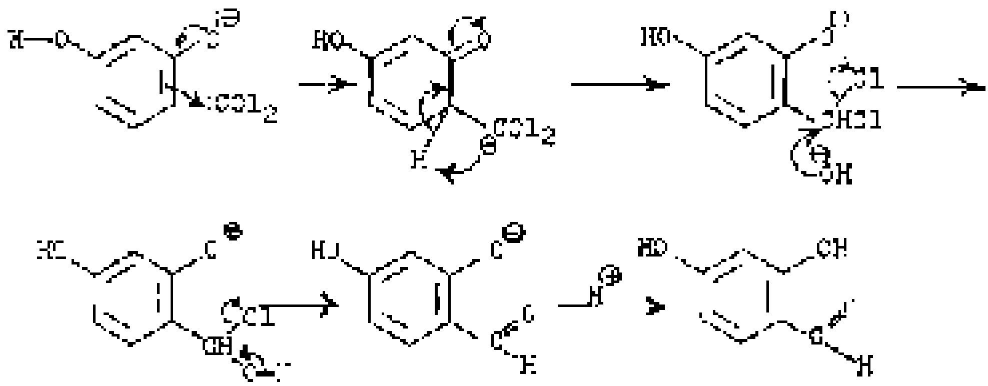
One way in which we can attach the  group to resorcinol is by first attaching an aldehyde group to position 4 via the Reimer-Tiemann reaction:



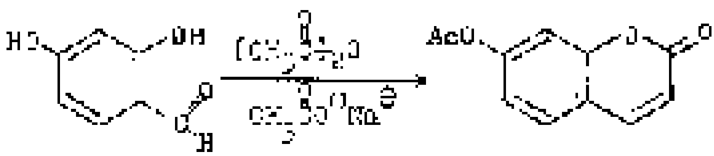
The reactive intermediate of Reimer-Tiemann reactions is the dichlorocarbene.

$$OH^{\ominus} + CHCl_3 \rightleftharpoons H_2O + {}^{\ominus}\!:CCl_3 \longrightarrow Cl^{\ominus} + :CCl_2$$

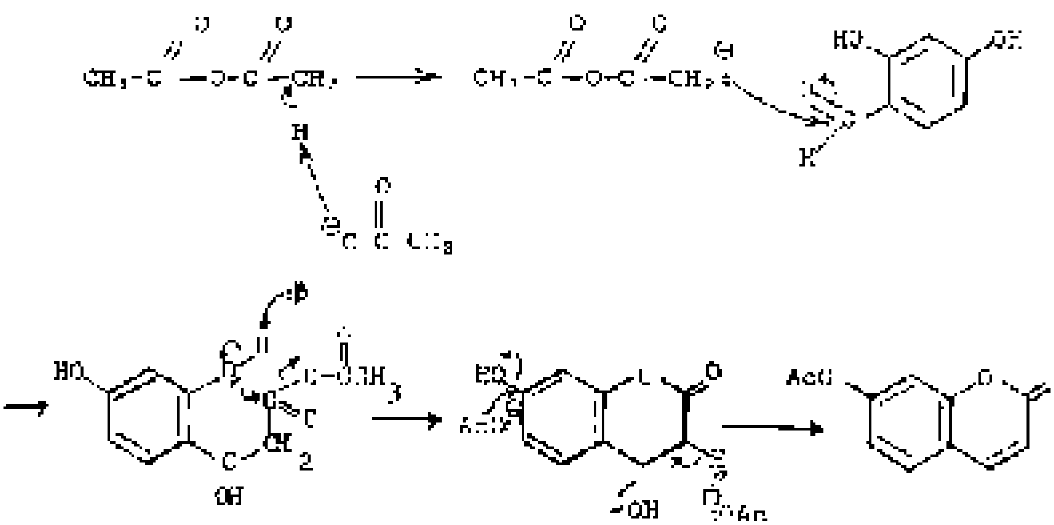
dichlorocarbene



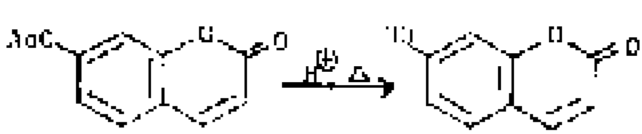
Next, we use the Perkin condensation to form the fused ring:



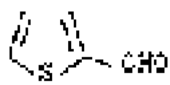
The mechanism for the Perkin Condensation is:



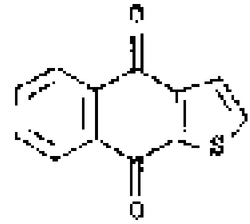
By acidifying and heating, we can replace the acetyl group with the hydroxyl group, thereby getting the product.



Suggest a feasible synthesis of each of the following compounds from the indicated starting material:

a. 

from thiophene

b. 

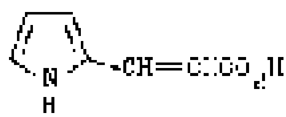
from thiophene

c. 

from benzothiophene

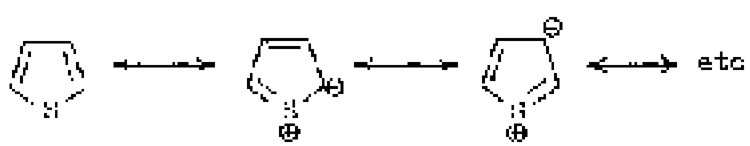
d. 

from furan

e. 

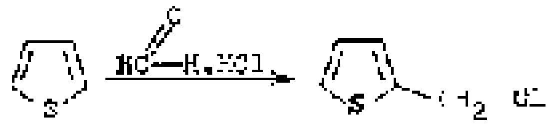
from pyrrole

Solution: (a) Before we answer this question, let us review some of the chemical properties of thiophene. Thiophene is an aromatic compound with a resonance energy of about 29-31 kcal/mole, as calculated from heats of combustion data. Although this is less than that of benzene (36.0 kcal/mole), it is almost the same per ring atom. Therefore thiophene resembles benzene in many of its reactions, except it is more reactive and less stable. The resonance structures for thiophene are:

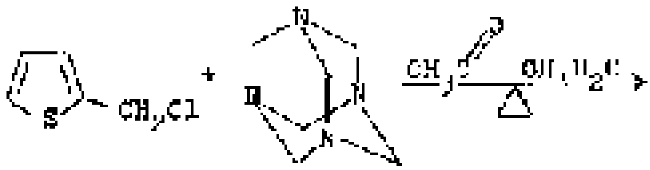


Calculations of the π-electron distribution in the ground state of thiophene show that electron distribution is greater at C_2 and C_5, therefore electrophilic substitution should occur at C_2 and C_5, as it is in actuality.

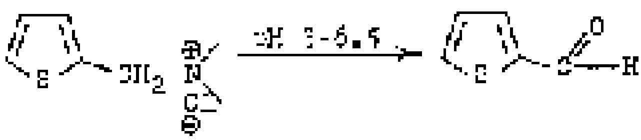
The given compound has a $-\overset{O}{\overset{\|}{C}}-H$ group attached to thiophene at position 2. One method of achieving this is by chloromethylation via electrophilic substitution, followed by the Sommelet reaction:



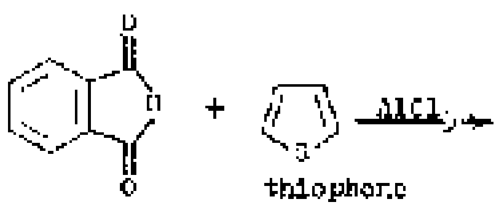
thiophene



hexamethylene
tetramine

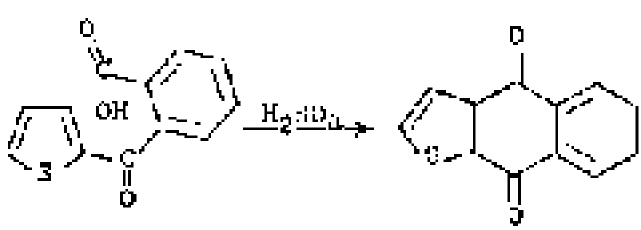


(b) This compound has a phthalic group attached to side "b" of the thiophene. One method of achieving this is by reacting thiophene with phthalic anhydride in $AlCl_3$ in an electrophilic substitution, followed by ring closure, this time via intramolecular electrophilic substitution:

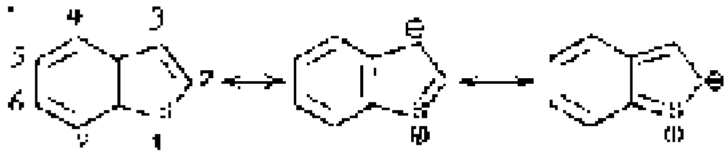


phthalic
anhydride

thiophene



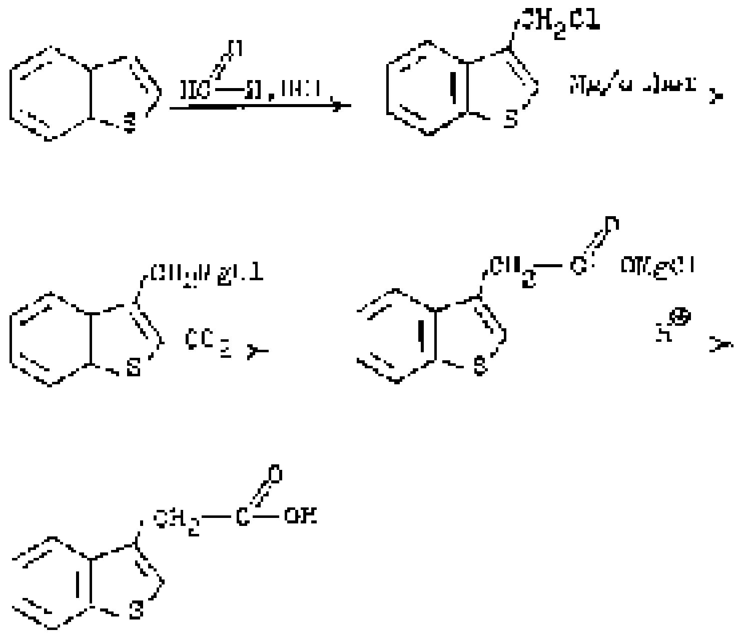
(c) Benzothiophene (specifically benzo[b]thiophene) is more stable and less reactive than thiophene. Benzothiophene is best represented as a resonance hybrid of structures I, II, and III in order of decreasing importance.



I II III

Since there is a greater electron density at C_3, electrophilic substitution occurs mainly at C_3.

The given compound has an acetic acid group $\left[-CH_2-\overset{O}{\overset{\|}{C}}-OH\right]$ attached to benzothiophene at C_3. This can be achieved by chloromethylation of benzothiophene via electrophilic substitution, followed by a Grignard reaction, and subsequent carbonation:

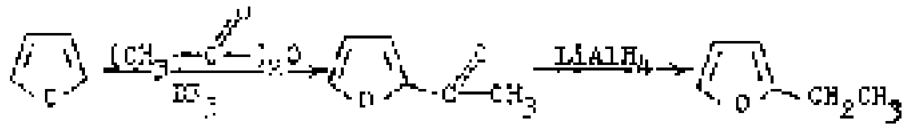


(c) Furan is an aromatic compound with a resonance energy of 23.7 - 26.54 kcal/mole, as calculated from heats of combustion data. This value is considerably less than that for benzene (36.0 kcal/mole). The resonance structures for furan are:

IV V VI VII VIII

The bond lengths data suggest that structure IV is the major contributor to the resonance hybrid. Structures V and VI are also of importance. The energy required to separate the charges is lower in these structures than in VII and VIII, as the distance involved is less. Therefore electrophilic attack greatly favors substitution at positions 2 and 5. Since oxygen is more electronegative than sulfur or nitrogen, it shares its electrons less readily; therefore furan is less aromatic than pyrrole or thiophene.

This compound has an ethyl group attached to furan at position 2. The best method for attaching an alkyl group to furan is by acylation followed by reduction:



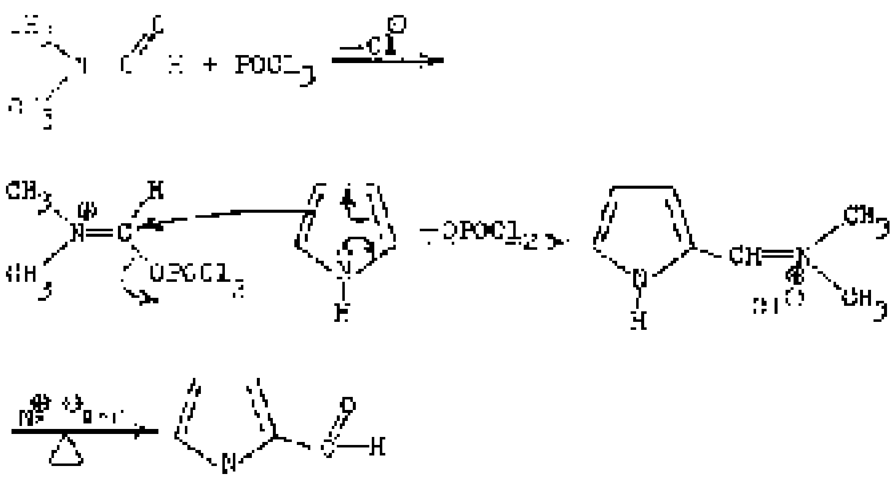
(e) Pyrrole is an aromatic compound with a resonance energy of 21-24 kcal/mole. The resonance structures for pyrrole are:

IX X XI XII XIII XIV

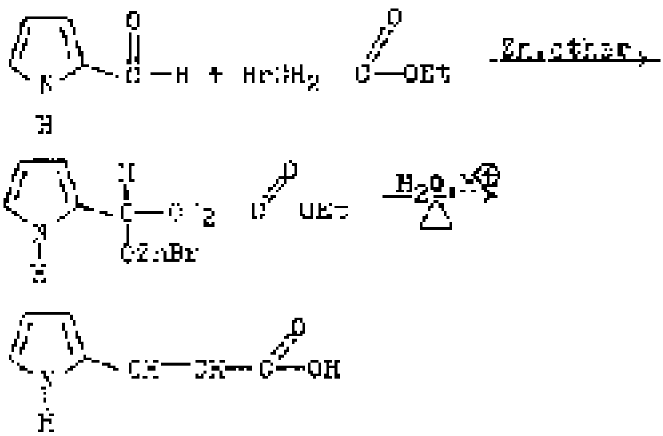
Electrophilic substitution of pyrrole occurs preferentially at positions 2 and 5, as in the case of thiophene and furan.

This compound has a $-CH=CH-\overset{O}{\overset{\parallel}{C}}-OH$ group attached to pyrrole at position 2. The best method of achieving this is by the Vilsmeier reaction to form pyrrole-2-carbaldehyde, followed by the Reformatsky reaction to form the given product:

Vilsmeier reaction:



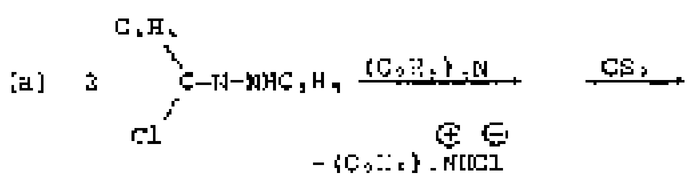
This reaction is basically an electrophilic substitution, followed by hydrolysis. The Reformatsky reaction, which follows, is an organometallic reaction which yields a β-hydroxy ester or acid. Upon heating, we get the corresponding α,β-unsaturated product:

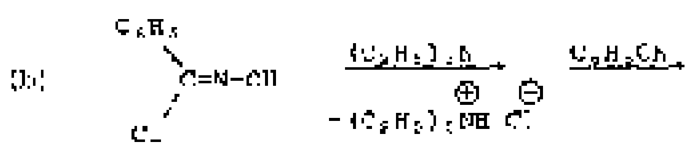


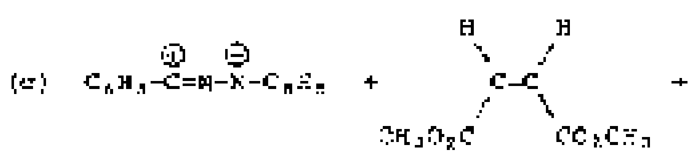
It is the carbanion character of the organozinc compound that allows this reaction to proceed. The formation and reaction of the organozinc compound is similar to that of a Grignard reagent. Zinc is used in place of magnesium because organozinc compounds do not react with the ester function, but only with the aldehyde or ketone. Hydrolysis of the ester yields the corresponding acid.

• PROBLEM 27-7

Write structures for the products of the following reactions:



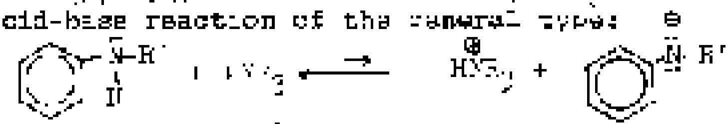




Solution: The above reactions all involve the addition of 1,3-dipolar compounds to compounds possessing double or triple bonds. Each is a 1,3 cycloaddition reaction that occurs in the same manner as a Diels-Alder reaction - it is stereospecific and is usually concerted. These 1,3-cycloaddition reactions result in the formation of polyhetero ring systems that contain at least one five-membered ring.

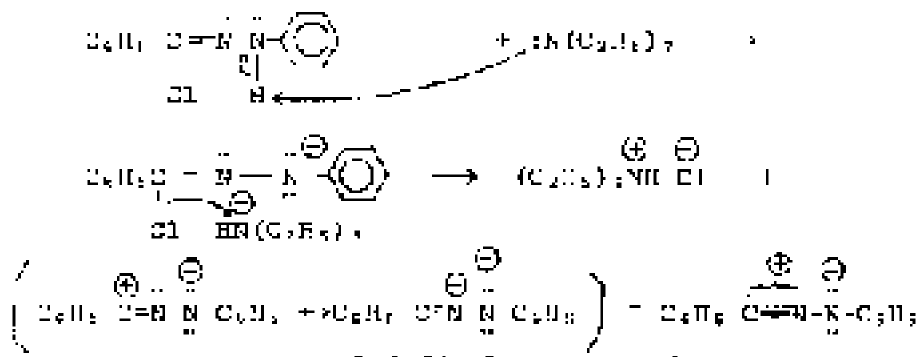
For reactions (a) and (b) the 1,3-dipolar compound will be found in the first step, whereas in reaction (c) it is given. 1,3-cycloadditions are syn addition reactions; they add cis to the multiple bond due to stereochemical restrictions.

(f) The formation of the 1,3-dipole involves an acid-base reaction of the general type:



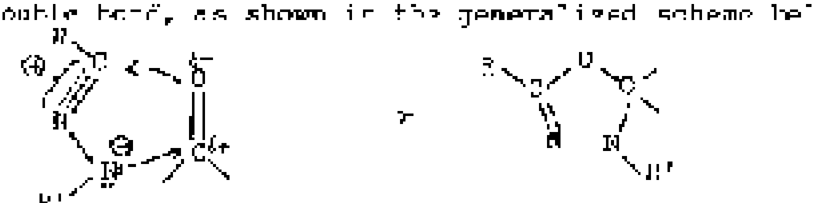
aromatic amine   3° amine

The phenyl group of the aromatic amine is electron withdrawing and renders the nitrogen less basic than its aliphatic analog. The tertiary aliphatic amine is an even stronger base relative to the aromatic amine due to the electron donating power of its three alkyl groups. However, the equilibrium of this acid-base reaction lies far to the left. This is because the conjugate base of the aromatic amine is unstable due to the inability of the negative charge to be delocalized about the aromatic ring (the electron pairs of nitrogen are in sp^3 orbitals, not p orbitals). If the conjugate base of the aromatic amine could somehow be stabilized, the acid-base equilibrium would be shifted to the right. Note that the aromatic amine given in (f) has a chlorine atom on the carbon beta to the acidic nitrogen. Loss of the chlorine ion from the conjugate base of the aromatic amine would form a stable 1,3-dipolar compound, as shown below:



1,3-dipolar compound

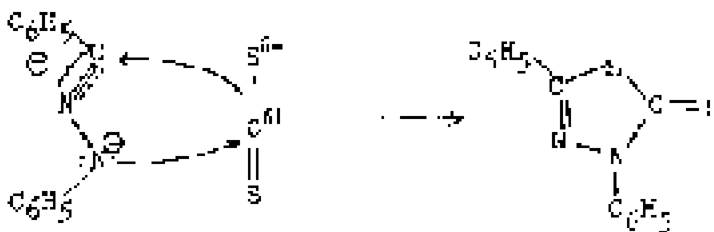
The 1,3-dipolar compound is a nitrilimine and is resonance stabilized. In the second part of the reaction, the nitrilimine is reacted with carbon disulfide. In general, a nitrilimine will react with a carbon-sulfur double bond in the same way it would with a carbon-oxygen double bond, as shown in the generalized scheme below:



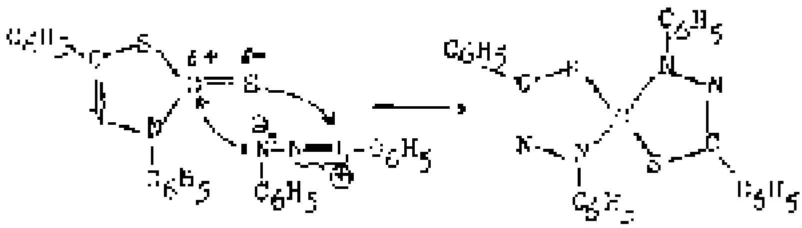
a nitrilimine   a 1,3,4-oxadiazoline

The electrophilic carbon of the nitrilimine forms a bond with the electron-rich oxygen, and the electron rich nitrogen of the nitrilamine forms a bond with the electron-deficient carbonyl carbon.

Since there are two carbon-sulfur double bonds in carbon disulfide, two moles of the nitrilimine can react with one mole of carbon disulfide. The reaction will proceed as follows to form the sulfur analog of a 1,3,4-oxadiazolidine:



Nitrilimine   Carbon disulfide



(b) This reaction is similar to reaction (a) in that it initially involves an acid-base reaction with triethylamine serving as the base, followed by abstraction of Cl^- by the conjugate acid formed:

$$\underset{Cl}{\overset{C_6H_5}{\diagdown}}C{=}N{-}OH \xrightarrow{:N(C_2H_5)_3} (C_2H_5)_3\overset{\oplus}{N}H\ \overset{\ominus}{Cl} + C_6H_5{-}\overset{\oplus}{C}{=}N{-}\ddot{O}:^{\ominus}$$

nitrile oxide

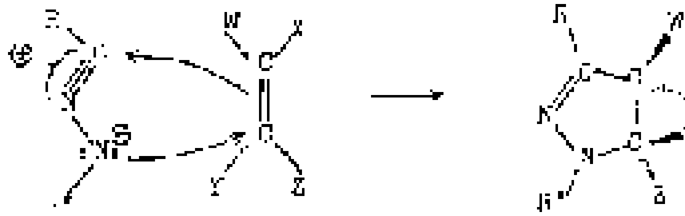
The 1,3-dipole formed is a nitrile oxide which has resonance stabilization:

$$\left(C_6H_5{-}\overset{\oplus}{C}{=}N{-}\ddot{O}:^{\ominus} \longleftrightarrow C_6H_5{-}C{\equiv}\overset{\oplus}{N}{-}\ddot{O}:^{\ominus}\right) = C_6H_5{-}C{\equiv}\overset{\oplus}{N}{-}\ddot{O}:^{\ominus}$$

The nitrile oxide will add to the triple bond in benzonitrile in a manner similar to the one depicted in reaction (a).

Nitrile oxide   Benzonitrile

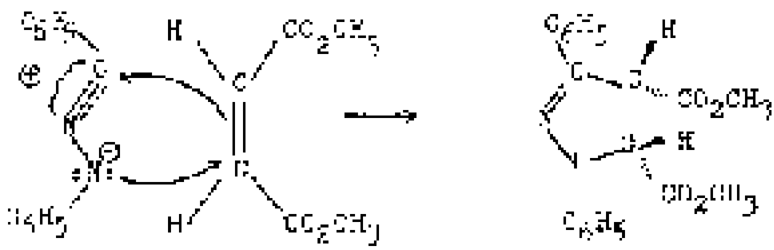
(c) In this reaction we are given the 1,3-dipolar compound, a nitrilimine. The nitrilimine is reacted with a compound possessing a carbon-carbon double bond as well as carbon-oxygen double bonds; it will preferentially react with the carbon-carbon double bond. In general, addition of this type will yield a pyrazoline as shown:



a pyrazoline

Note that the reaction is a syn addition; the orientation about the carbon-carbon double bond is retained in the pyrazoline (substituents W and Y remain cis to each other as do substituents X and Z, due to inhibition of free rotation about the single bond).

We can now show the reaction of the given nitrilimine with the methyl ester of maleic acid as follows:

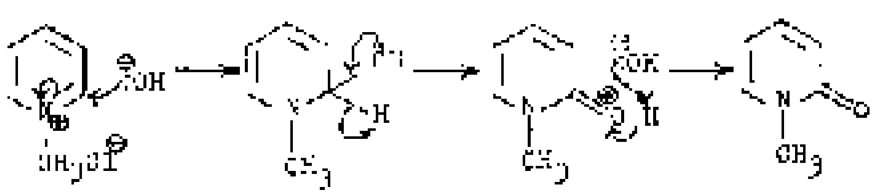


DEDUCTION OF STRUCTURAL FORMULA

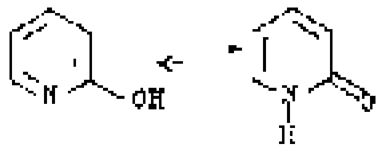
• PROBLEM 27-8

Pyridine methochloride is converted by aqueous alkali and a mild oxidizing agent (ferricyanide) to a solid compound of formula C_6H_7NO, which shows no hydroxyl absorption in the infrared. What is a likely structure for this substance and how is it formed? Would you expect a similar reaction with pyridine?

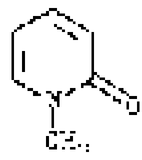
Solution: A nucleophilic substitution reaction will occur:

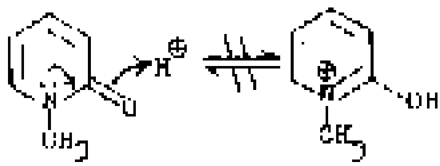


This structure is consistent with the molecular formula and infrared data. With pyridine, a similar reaction will occur at high temperatures with KOH. The product, however, will be a tautomeric system of 2-pyridone with 2-pyridinol:



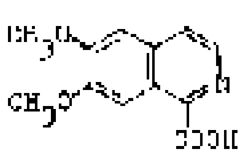
2-pyridinol 2-pyridone

Note that  will not exist in the hydroxyl form because that would put a positive charge on the molecule.



• PROBLEM 27-9

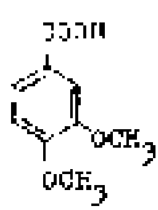
Papaverine, $C_{20}H_{21}O_4N$, is an alkaloid present in opium and is used as a muscle relaxant. It is nonaddicting but is classified as a narcotic. Reaction with excess hydriodic acid gives 4 moles of CH_3I and shows the presence of 4 CH_3O groups (Zeisel determination). Oxidation with $KMnO_4$ gives first a ketone, $C_{20}H_{19}O_5N$, which on continued oxidation gives a mixture from which the compounds shown below were isolated and identified. Deduce the structure of papaverine and interpret the reactions described.



I

II

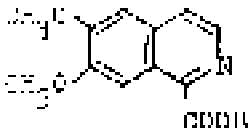
III



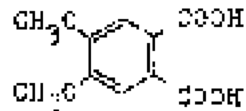
IV

Solution: By Zeisel determination, we know that the compound papaverine contains four CH_3O substituents. Hence a partial formula of papaverine can be written as $C_{16}H_9N(OCH_3)_4$. By the observation that there are more carbons than hydrogens, we can expect some cyclic character in the structure of papaverine.

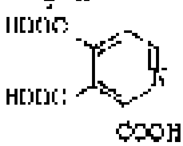
Oxidation of papaverine with $KMnO_4$, we are told, results first in a ketone, $C_{15}H_7N\overset{O}{\overset{\|}{C}}(OCH_3)_4$. This ketone can undergo further oxidation, whose products have been identified and are given.



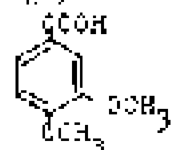
I $C_9H_4N(COOH)(OCH_3)_2$



II $C_6H_2(COOH)_2(OCH_3)_2$



III $C_5H_2N(COOH)_3$



IV $C_6H_3(COOH)(OCH_3)_2$

Inspection of the structures of the products convinces us that I and IV must be the earliest products of the prolonged oxidation process. Their ring carbons add up to 15, which agrees with the number of ring carbons in $C_{15}H_7NCO(OCH_3)_4$, the initial oxidation product. Also, their summed number of nitrogen atoms, 1, agrees with that in the ketone. Furthermore, they have the lowest number of COOH groups among the four, and thus should be the earliest oxidation products formed.

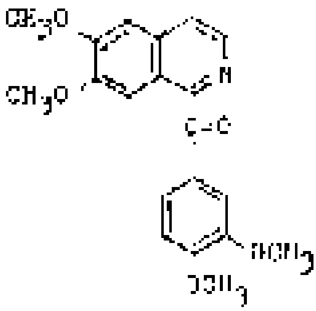
Based on these observations, we can deduce the steps of the entire oxidation process in sequence:

$$C_{15}H_7N(CH_2)(OCH_3)_4 \xrightarrow{[O]} C_{15}H_7NCO(OCH_3)_4 \xrightarrow{[O]} \begin{array}{ccc} I & - & IV \\ \downarrow & & [O] \\ II & & III \end{array}$$

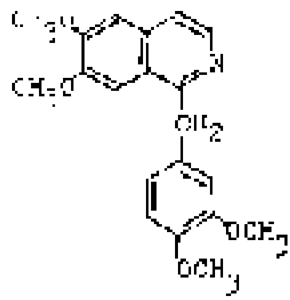
Because I and IV are the primary products, the structure of the ketone of papaverine can be derived from them. Moreover, the COOH of both I and IV must come from the same ketone carbonyl as shown in the generalized scheme below:

$$R{-}COOH \ + \ R'COOH \xleftarrow{[O]} \begin{array}{l} R \\ \quad \diagdown \\ \quad\ \ C{=}O \\ \quad \diagup \\ R' \end{array}$$

So the structure of the ketone and of papaverine must be:



Ketone



Papaverine

• PROBLEM 27-10

The alkaloid hygrine is found in the coca plant. Suggest a structure for it on the basis of the following evidence:

Hygrine ($C_8H_{15}ON$) is insoluble in aqueous NaOH but soluble in aqueous HCl. It does not react with benzenesulfonyl chloride. It reacts with phenylhydrazine to yield a phenylhydrazone. It reacts with NaOI to yield a yellow precipitate and a carboxylic acid ($C_7H_{13}O_2N$). Vigorous oxidation by CrO_3 converts hygrine into hygrinic acid ($C_6H_{11}O_2N$).

Hygrinic acid can be synthesized as follows:

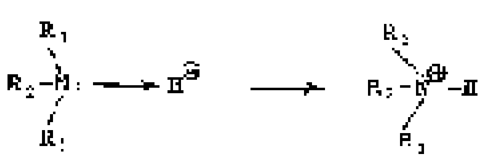
$$BrCH_2CH_2CH_2Br + CH(COOC_2H_5)_2^{\ominus}Na^{\oplus} \rightarrow A\ (C_{10}H_{17}O_4Br)$$

$$A + Br_2 \rightarrow B\ (C_{10}H_{16}O_4Br_2)$$

$$B + CH_3NH_2 \rightarrow C\ (C_{11}H_{19}O_4N)$$

$$C + aq.\ Ba(OH)_2 + heat \rightarrow D \xrightarrow{HCl} E \xrightarrow{heat} \text{hygrinic acid} + CO_2$$

Solution: Alkaloids are natural compounds of vegetable origin that contain nitrogen. They usually have heterocyclic ring systems and one or more basic nitrogen atoms. Since hygrine is insoluble in aqueous NaOH but soluble in aqueous HCl, it must be basic:

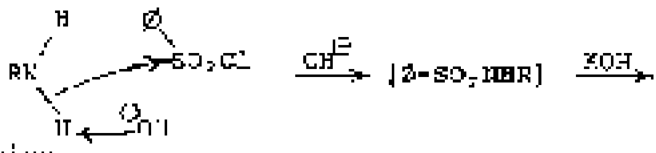


(insoluble in water) ionic (soluble in water)

$OH^{\ominus}$

no reaction (remains non-polar — insoluble in water)

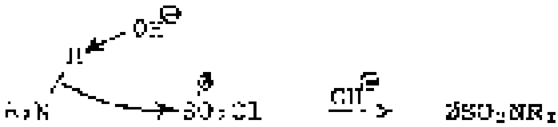
It does not react with benzene sulfonyl chloride, therefore it is a tertiary amine. This analysis is known as the Hinsberg test:



1° amine

ϕ-$SO_2NR^{\ominus}K^{\oplus}$

clear solution



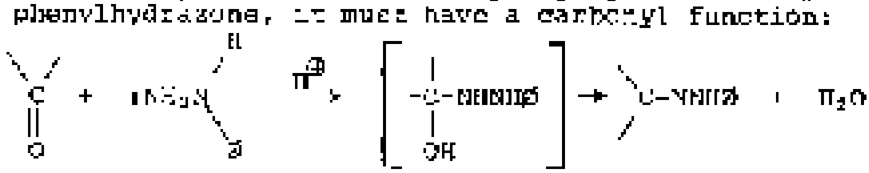
2° amine insoluble

$R_3N + \phi SO_2Cl \xrightarrow{OH^{\ominus}}$ no reaction

3° amine

The tertiary amine does not react because there are no hydrogens attached to nitrogen.

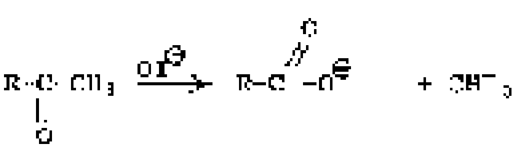
Since tygerine reacts with phenylhydrazine to yield a phenylhydrazone, it must have a carbonyl function:



phenylhydrazone

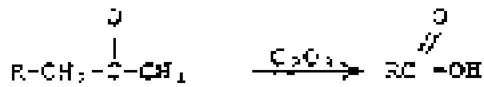
phenyl hydrazine

This fact together with the subsequent iodoform test tells us that the carbonyl function is a methyl ketone:



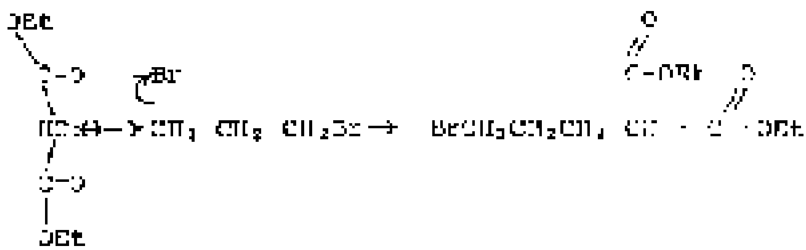
A Yellow precipitate

Structure A has the molecular formula of $C_7H_{13}O_2N$. Vigorous oxidation by CrO_3 removes one more carbon and two more hydrogens than the iodoform reaction, therefore a tentative conclusion is a $-CH_2\overset{O}{\overset{\|}{C}}-CH_3$ group attached to a resistant group:

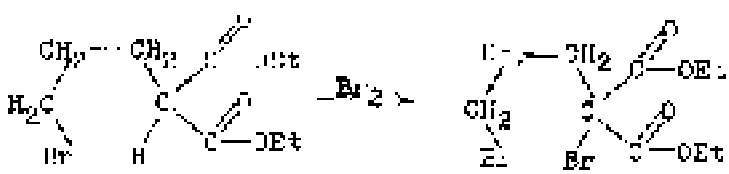


hygrine hygrinic acid

By following the synthesis for hygrinic acid, we can deduce the structure of hygrine. The first step is the malonic ester synthesis:

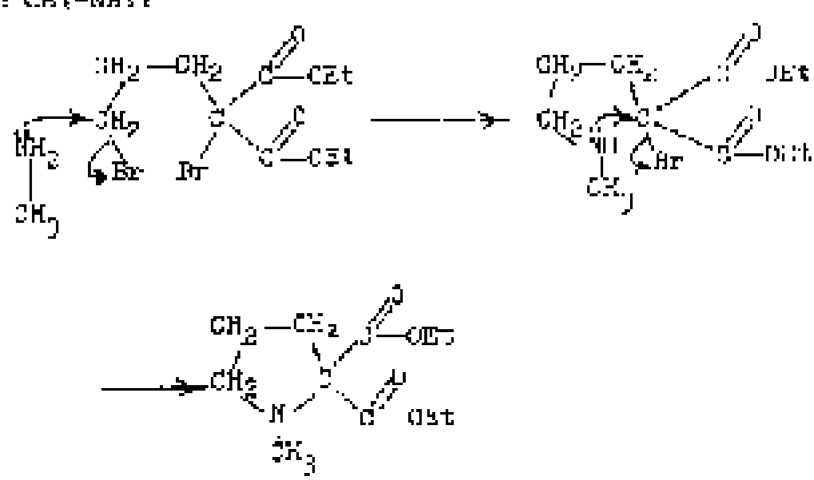


The next step is alpha-halogenation of the diester, known as the Hell-Volhard-Zelinsky reaction:



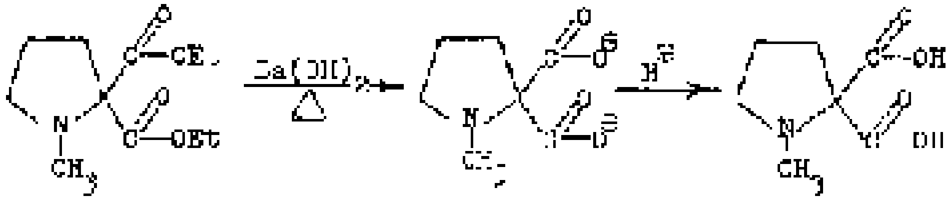
A B

The next step is an S_N2 displacement by the nucleophile CH_3-NH_2:



C

The next step is hydrolysis of the diester, and subsequent acidification:

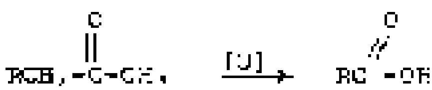


C D E

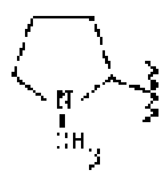
The next step is decarboxylation by heat to form hygrinic acid:

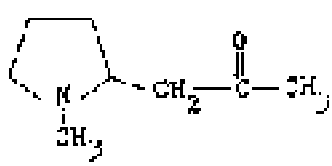
E hygrinic acid

From our previous conclusion, we know:



hygrine hygrinic acid

Therefore, R =  and the structure for hygrine is:



CHAPTER 28

POLYMERS

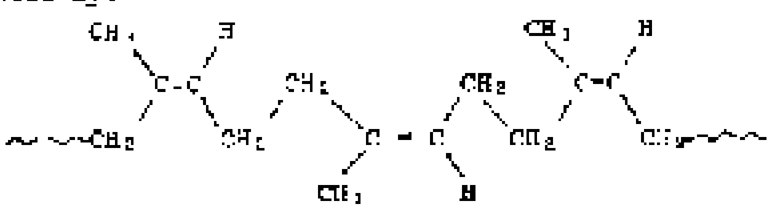
POLYMERS AND POLYMERIZATION

• PROBLEM 28-1

Explain how natural rubber can be made durable for use in hot and cold weather.

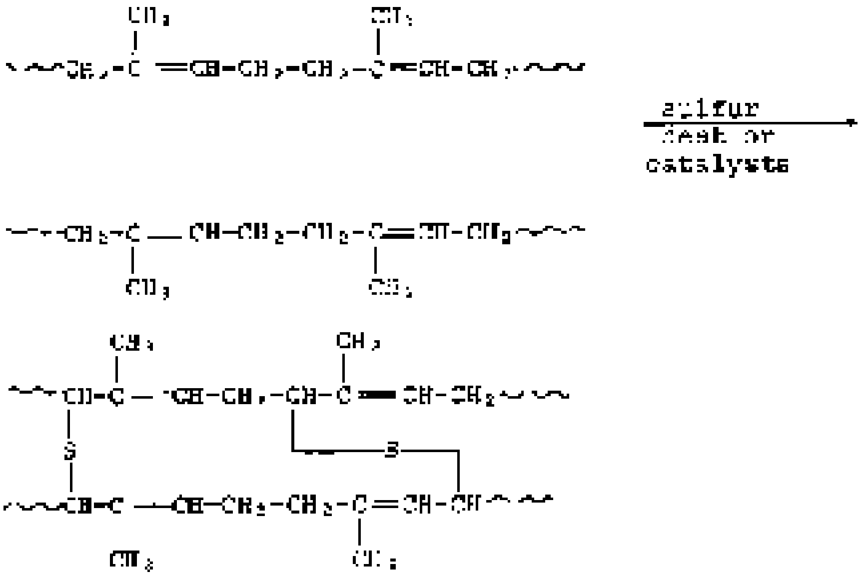
Solution: Before the nineteenth century rubber had limited use because of its tendency to become sticky in warm weather and brittle in cold weather. This problem was alleviated by the discovery of a process known as vulcanization. Charles Goodyear discovered that if the natural latex was heated with sulfur it was converted to a more useful elastomer.

Natural rubber (grown in Malaya, etc.) is mainly cis-1,4-polyisoprene whose structural formula could be represented by:



This structural arrangement suggests that it is composed of long flexible chains, with weak intermolecular forces - ideal for use as an elastomer. Due to these properties it can undergo a great deal of deformation and yet return to its original shape. Another requirement for a good elastomer is that these long polymeric chains should occasionally be connected by cross links, such that it does not hinder extension but prevents the slipping of molecules past one another.

This type of cross linking could be readily brought about by vulcanization. This process requires the heating of natural rubber with sulfur, thus forming sulfur bridges between different chains. This is possible because the double bonds in the rubber molecule provide reactive allylic hydrogens.

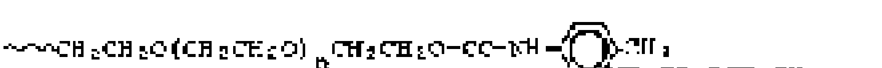


These sulfur crosslinks make the rubber harder and stronger. This vulcanized rubber has a wide range of uses from tires to toys. An increase in temperature causes natural rubber to fuse individual chains together; this makes the rubber sticky. Because of sulfur crosslinks in vulcanized rubber, temperature changes will not create either a fusion of separate chains or make it brittle. The sulfur crosslinks keep the chains at a fixed distance.

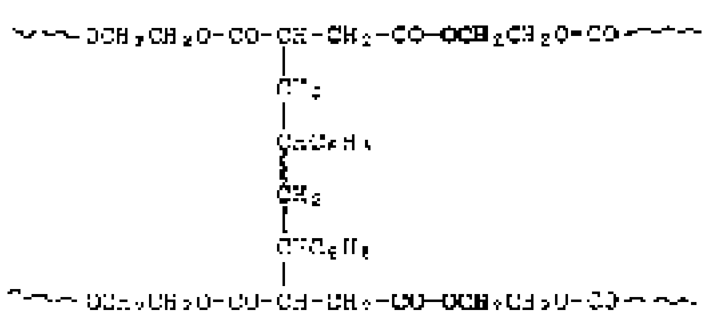
• PROBLEM 28-2

Outline all steps in a possible synthesis from non-polymeric starting materials of each of the following polymers.

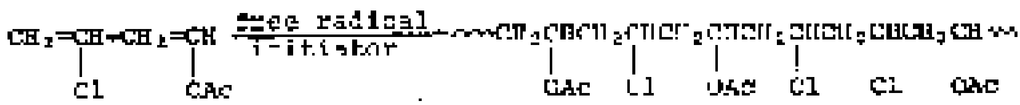
(a) Elastic fibers, used in girdles and bathing suits (Spandex, Lycra).



(b) A polyester resin, used in making pipe, boats, automobile bodies, etc.

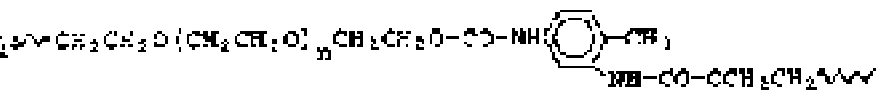


(c) A surface-active polymer.

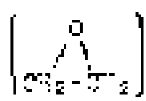


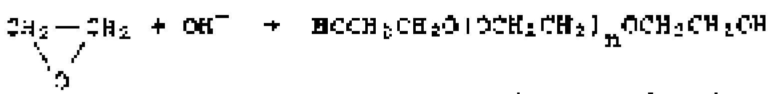
IV

Solution:



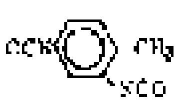
There are two monomers in the repetitive unit and therefore polymerization will have to take place via a step reaction or condensation polymerization. The first monomer itself is a subpolymer having the repetitive unit ethylene

oxide  . In this case chain reaction polymerization is necessary:

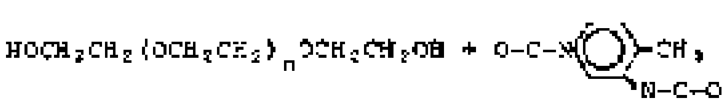


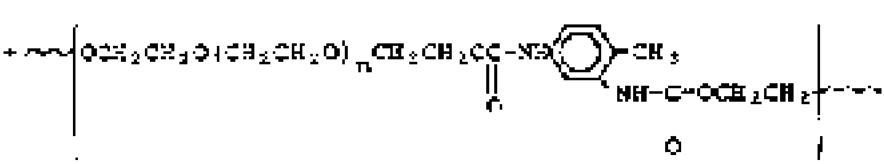
The initiator or original reactive species is the hydroxy group (as the anion), which adds onto ethylene oxide, one after another until the reaction is terminated to provide a suitable number of ethylene oxide groups in the polymer with terminal -OH groups.

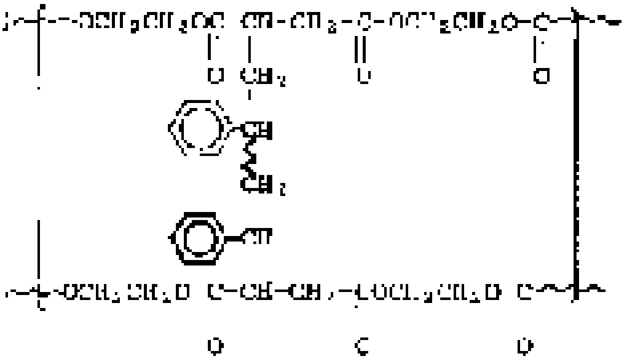
The other monomer in the chain is a diisocyanate

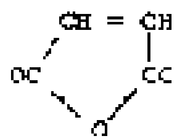
 . Reaction of this compound with the original

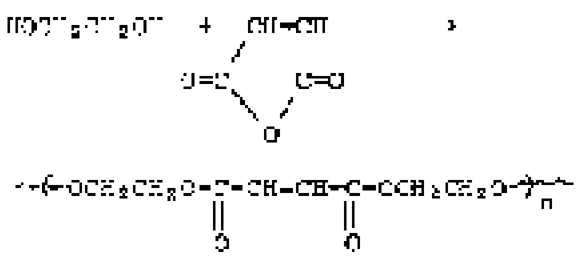
polymer yields the needed polymer:





(b) 

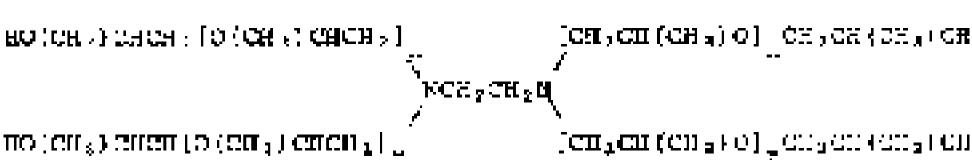
The two polymer units (linear polyesters) that are joined together, by a polymer whose repetitive unit is styrene, $CH_2=CH$–, are identical and are also formed by two monomer units implying step reaction or condensation polymerization. The first polymer can be produced from an esterification involving an alcohol and an electrophilic compound. For this purpose  an anhydride is used.



Step reaction of the above with styrene leads to the polymer required

In this reaction styrene is free to react with either itself or the other polymer. Therefore there could be more than one styrene group joining the two identical polymer units.

(c)

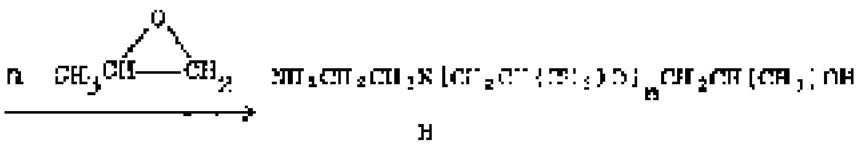


The repetitive unit is $-O(CH_3)CH\ CH_2-$. It is possible to derive this structure from CH_3CH-CH_2 (with O bridging) (propylene oxide).

The polymeric growth has initiated from $H_2NCH_2CH_2NH_2$.

This can be viewed as a case of an anionic chain reaction polymerization. The mechanism for this reaction could be structurally represented in the following manner:

$NH_2CH_2CH_2\overset{+}{N}H_2CH_2\overset{O^-}{C}H(CH_3) \rightarrow NH_2CH_2CH_2NHCH_2\overset{OH}{\underset{H}{C}}-CH_3$



This is basically an S_N2 mechanism, typical of nucleophilic attack upon an epoxide. However, we still have not synthesized the required product. If only a trace (a very limited quantity) of $NH_2CH_2CH_2NH_2$ is made available in the reaction then addition of $-\!\!(CH_2CH(CH_3)O)\!\!-$ would occur at all the N-H linkages.

The final compound is:

$HO(CH_3)CHCH_2[O(CH_3)CHCH_2]_n \qquad [CH_2CH(CH_3)O]_nCH_2CH(CH_3)OH$

$\qquad \qquad NCH_2CH_2N$

$HO(CH_3)CHCH_2[O(CH_3)CHCH_2]_n \qquad [CH_2CH(CH_3)O]_nCH_2CH(CH_3)OH$

• PROBLEM 28-3

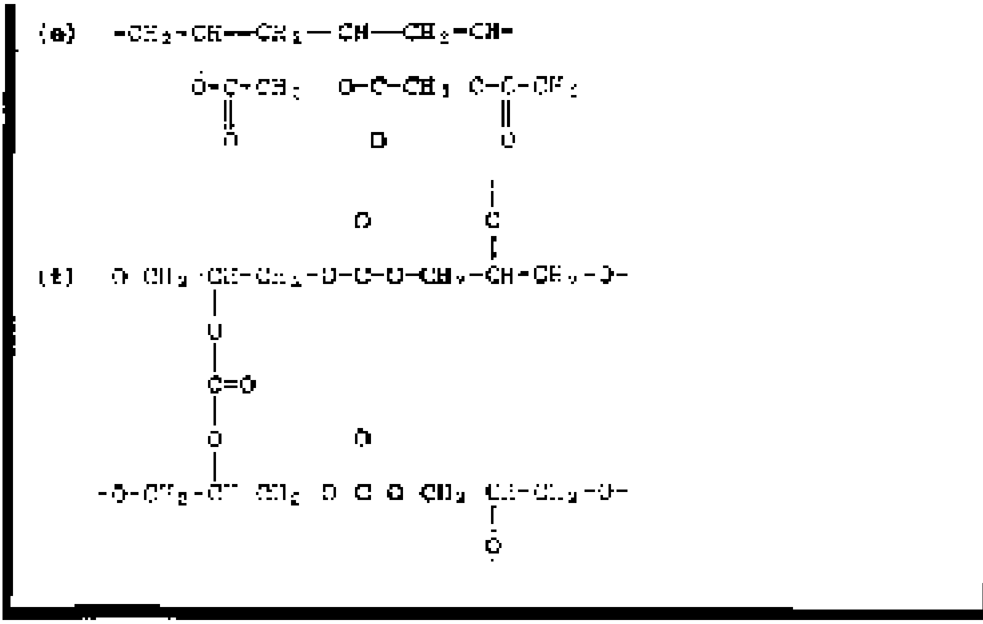
Show how each of the following polymer structures might be obtained from suitable monomers by either addition or condensation. More than one step may have to be involved.

(a) $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$ (three ways)

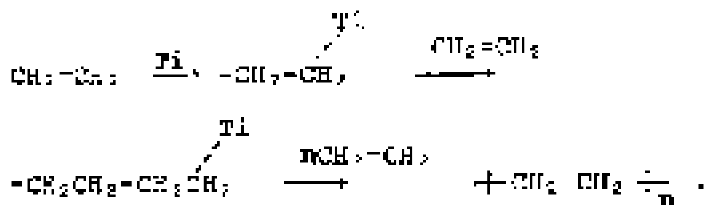
(b) $-N-CH_2-CH_2-N-CH_2-CH_2-N-CH_2-CH_2-$ with CH_3 on each N

(c) $-CH-CH-CH-CH-CH-CH-$ with CH_3 on each CH

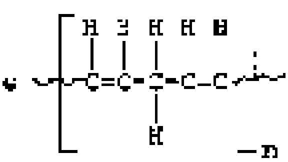
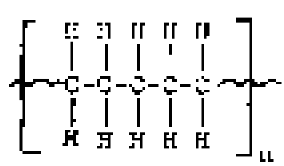
(d) $-O-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-C-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-O-CH_2-CH_2-\overset{O}{\overset{\|}{C}}$



Solution: (a) $-CH_2-CH_2-CH_2-CH_2-$ Polyethylene can be prepared by the coordination polymerization of ethylene with titanium or aluminum as catalysts.



Titanium behaves as an electrophilic agent and the growing chain end is transferred to the monomer as an anion.

Polyethylene can also be prepared by the hydrogenation of poly-1,4-pentadiene  . This is similar to the hydrogenation of pentadiene. The double bond is replaced by two hydrogen atoms throughout the entire chain and the final product is polyethylene 

Polyethylene can be made in a third way by the polymerization of $:CH_2$ from diazomethane $CH_2=\overset{+}{N}=\overset{-}{N}:$, a yellow gas. Diazomethane reacts with light to produce the carbene $:CH_2$ and under the presence of a catalyst the $:CH_2$ group will react with others of its kind to produce the required polymer $\sim\!CH_2-CH_2-CH_2-CH_2\!\sim$.

(b) $\quad N\!-\!CH_2\!-\!CH_2\!-\!N\!-\!CH_2\!-\!CH_2\!-\!N\!-\!CH_2-$ (with CH_3 on each N)

The repetitive unit of this polymer is $\left[\begin{array}{c}-N-CH_2-CH_2-\\ |\\ CH_3\end{array}\right]$;

since it has been produced from just one monomer an addition polymerization must take place. The monomer is the aziridine derivative (N-methylaziridine, CH_3 on N) which polymerizes by a nucleophilic reaction in which the ring breaks.

(c) $\sim\!CH-CH-CH-CH-CH-CH\!\sim$ (with CH_3 on each carbon)

Since the polymerization of 2-butene cannot be brought about easily, the polymerization and eventually hydrogenation of $CH_3CH-C=C-CHCH_3$ (with CH_3 on each of the two doubly bonded carbons) would be required to produce the desired compound. Since there is only one monomer involved, this reaction must be a chain or addition reaction.

$CH_3CH-C=C-CHCH_3$ (with CH_3 on each doubly bonded carbon) $\xrightarrow{\text{Monomer}}$

$CH_3CH_2-C=C-CH-CH-C=C-CHCH_2CH-C=C\!\sim$ (with CH_3 side groups)

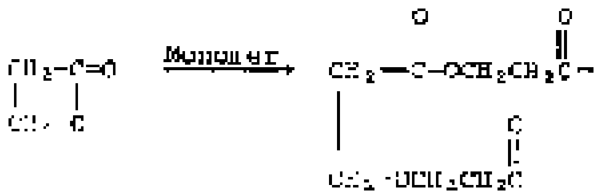
Hydrogenation of this compound would lead to

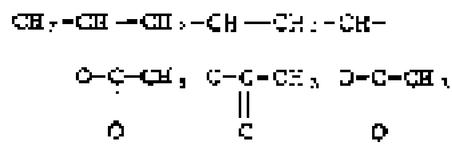
$\sim\!C-C-C-C-C\!\sim$ (with CH_3 side groups)

(d) $\quad C-CH_2-CH_2C-OCH_2CH_2-C-C-CH_2-CH_2C-$ (with O on the carbonyl carbons)

Note that the repetitive unit in this polymer is

$[CH_2CH_2C(=O)O]$. In the addition (chain reaction) polymerization of $\left|\begin{array}{l}CH_2-C=O\\ |\\ CH_2-O\end{array}\right|$, the ring is broken as illustrated by the following reaction;

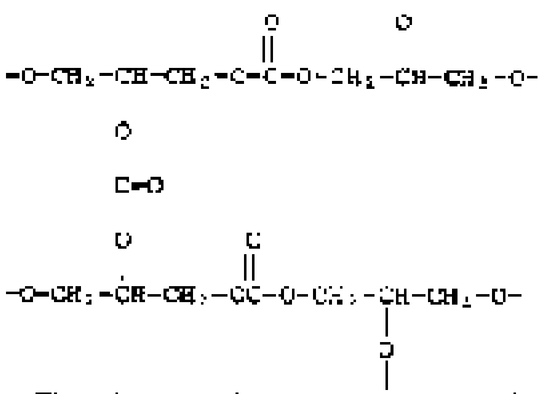


(g) 

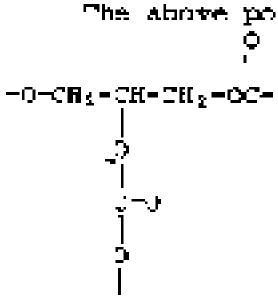
The clue in outlining a synthesis for a certain polymer lies primarily in detecting the repetitive unit. In this case it can be seen that the repetitive unit is $-CH_2-CH-$

$O-\underset{O}{\underset{\|}{C}}-CH_3$

The addition polymerization of $CH_2=CH-O\overset{O}{\overset{\|}{C}}-CH_3$ would give the above polymer.

(f) 

The above polymer has a repetitive unit consisting of



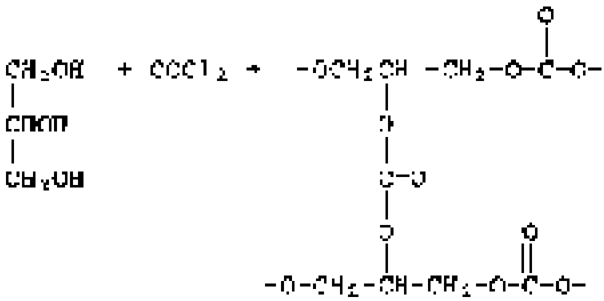
. Each of the 3 carbon atoms is joined to an oxygen so we can consider using glycerol as one of the monomers. This has the structural formula CH_2OH, Phosgene

$CHOH$

CH_2OH

$(COCl_2)$ reacts with any alcohol and this can be represented by this equation: $COCl_2 + 2\,ROH \rightarrow RO\overset{O}{\overset{\|}{C}}OR + 2\,HCl$.

The reaction between phosgene and glycerol would give us the necessary polymer called for i.e.



Cross links are easily formed in this case because of the protruding $-C-O-\underset{\underset{O}{|}}{C}$ arising from the middle carbon of glycerol. This is a condensation reaction, splitting out the small molecule, HCl.

• PROBLEM 28-4

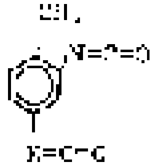
Suggest reasonable chemistry associated with the fact that the first drops of rain in a big industrial city sometimes causes nylons to weaken and run.

Solution: Nylon 6.6 (fibers) has a structural formula $\sim\underset{\underset{O}{\|}}{C}(CH_2)_4\underset{\underset{O}{\|}}{C}NH(CH_2)_6NH\sim$. This compound is classified as an amide because it contains the $-\overset{O}{\overset{\|}{C}}NH$ group.

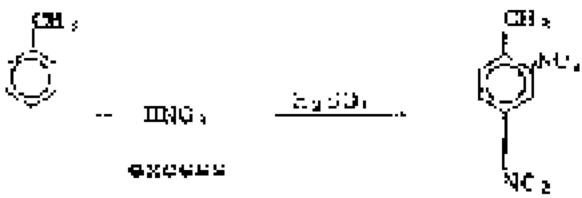
In an industrial city there is a relatively high concentration of sulfur trioxide which is formed by the combustion of fuels with high sulfur content. Sulfur trioxide is highly soluble in water, and rain dissolves most of the SO_3 from the atmosphere producing H_2SO_4 ($SO_3 + H_2O \rightarrow H_2SO_4$). As amides are basic they undergo reactions with all acids, in this case sulfuric acid. The sulfate ion will then displace the amide group which combines with hydrogen to produce ammonia. Some units will thus become contaminated and the bonds between the monomers will decrease and damage the nylon.

Outline a synthesis of 2,4 tolylene diisocyanate from toluene.

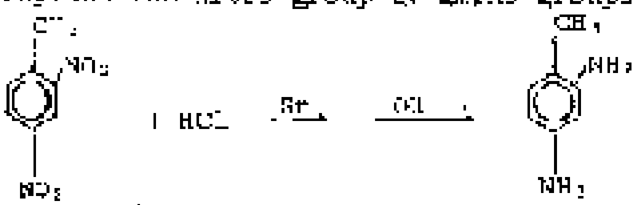
Solution: 2,4-tolylene diisocyanate has the structure



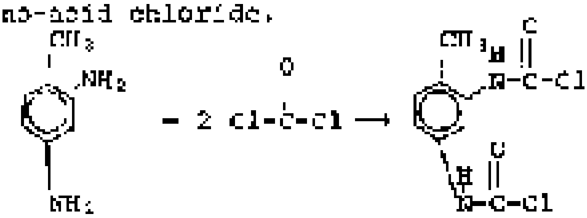
Judging from the structure toluene has been nitrated on its second and fourth carbon on the ring. Since the methyl group is activating and an ortho, para director; direct nitration will add these groups in the required positions.

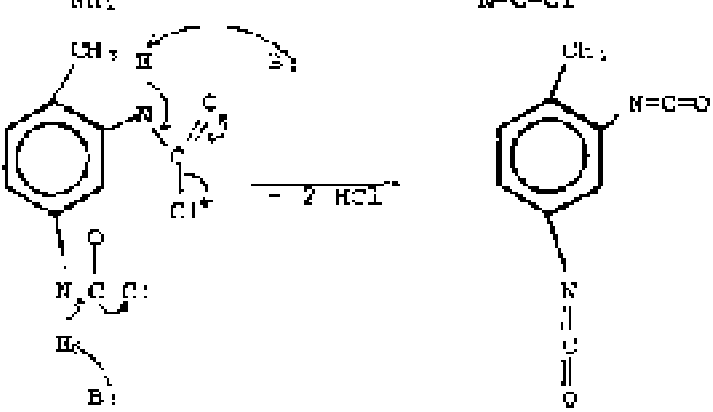


As an isocyanate group is to be added, it is necessary to replace the nitro group by amino groups.



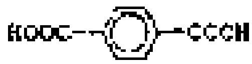
The diisocyanate is obtained by reacting the diamine with phosgene ($COCl_2$) at moderate temperatures. The conversion involves the elimination of HCl from the unstable amino-acid chloride.

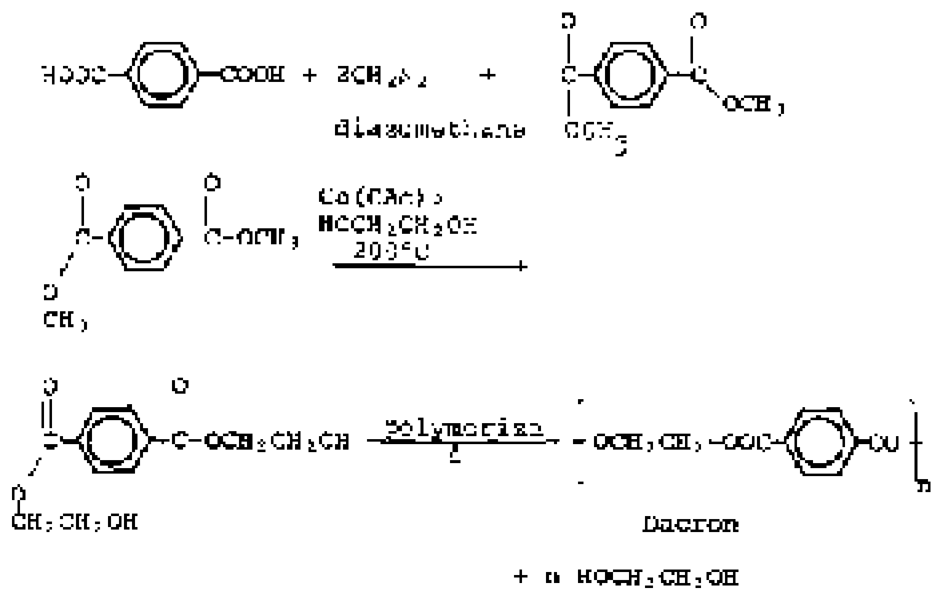




• PROBLEM 20-6

What commercial chemical reactions of terephthalic acid would be used to give a common polyester?

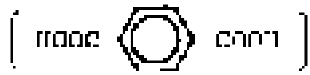
Solution: Terephthalic acid has the following structural formula: . Polyesters can be formed by the condensation of this acid, with an ester or a transesterification reaction. Base $\left[Ca(-O\overset{O}{\overset{\|}{C}}-CH_3)_2\right]$ at high temperatures catalyzes the alcohol interchange. We note that transesterifications can be catalyzed by base but esterifications cannot because the carboxylic acid will protonate the catalyst and the resultant carboxylate anion is inert to nucleophilic attack. Thus terephthalic acid can easily be converted to its methyl diester by the versatile reagent, diazomethane. This ester can be transesterified to the diester of ethylene glycol which in turn is transesterified (when heated) to a copolymer. The sequence of reactions is as follows:

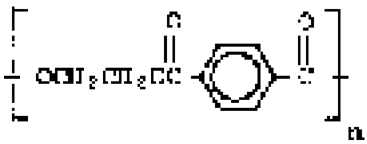


• PROBLEM 20-7

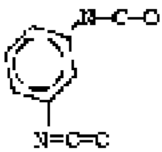
Write the structures for the following common polymeric materials:

(a) Mylar (b) Polyurethan
(c) Bakelite (d) Saran
(e) Lucite (f) Orlon

Solution: (a) Mylar is a polymer formed by the condensation of terephthalic acid  and ethylene glycol $\begin{bmatrix} CH_2OH \\ | \\ CH_2OH \end{bmatrix}$. It is a low molecular-weight polymer and basically is fabricated as a tough film with the structure:



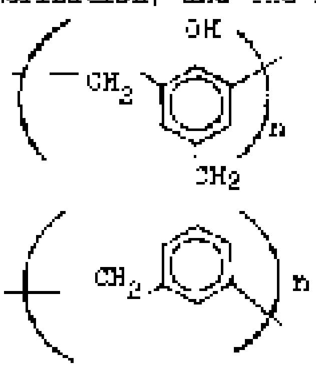
(b) Polyurethans contain amide groups together with many ester groups. It is normally made from diisocyanate



and an alcohol. Thus it is a condensation polymer, prepared by a repetitive mechanism. Polyurethan is a long, linear molecule without any linkages interconnecting the individual strands. The structure is represented by

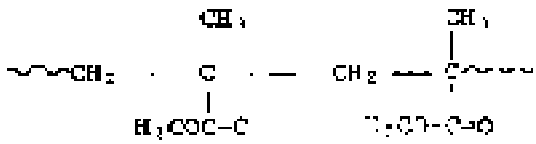
$$-NH\left[RNHC{-}O{-}CH_2CH_2{-}O{-}\overset{\overset{O}{\|}}{C}{-}NH \right]_n$$

(c) Bakelite is a phenol-formaldehyde resin, consisting of a highly cross-linked structure which produces a three dimensional structure. This is also formed by condensation polymerization, and the basic structure is denoted by

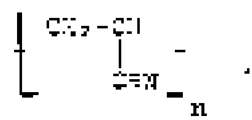


(d) Saran is a common polymer (used as wrappers) formed by suspension polymerization. Vinylidene chloride and vinyl chloride $\left(CH_2{=}CCl_2 \;,\; \underset{\displaystyle Cl}{CH_2{=}\overset{|}{CH}} \right)$ are mixed together and the molecules add together randomly to produce a copolymer (polymer of two different monomers). The structure of Saran is $-(CH_2{\cdot}CCl_2\ CH_2\ CHCl)_n$.

(e) Lucite is prepared by the free radical polymerization of methyl methacrylate $CH_2=C(CH_3)-C(=O)-OCH_3$ producing a homopolymer (an addition polymer which is prepared from only one kind of monomer). It is generally used for clear window panes and contact lenses because it is stiff and transparent; the structure of Lucite is:



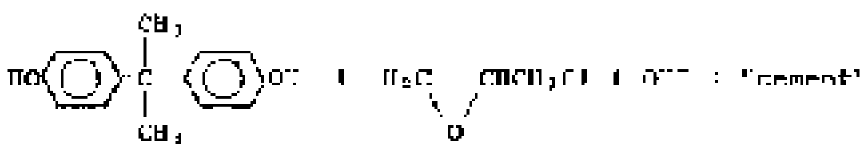
(f) Orlon: Free radical polymerization of acrylonitrile $CH_2=CHCN$ in aqueous solution gives a polymer which is spun to produce the textile Orlon. The structure of the addition polymer i.e. polyacrylonitrile is:



CORRELATION OF POLYMER PROPERTIES WITH STRUCTURE

• PROBLEM 26-8

To use an epoxy cement, one mixes the fluid "cement" with the "hardener," applies the mixture to the surfaces being glued together, brings them into contact, and waits for hardening to occur. The fluid cement is a low-molecular weight polymer prepared by the following reaction:



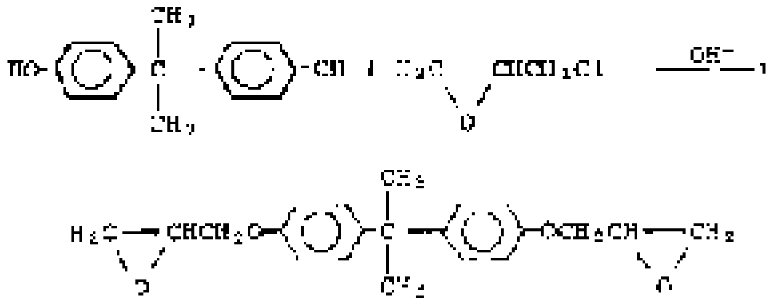
2,2-Bis(p-hydroxyphenyl) propane ("Bisphenol A") — Epichlorohydrin excess — Contains no chlorine

The hardener can be any of a number of things: $NH_2CH_2CH_2NHCH_2CH_2NH_2$, diethylenetriamine, for example.

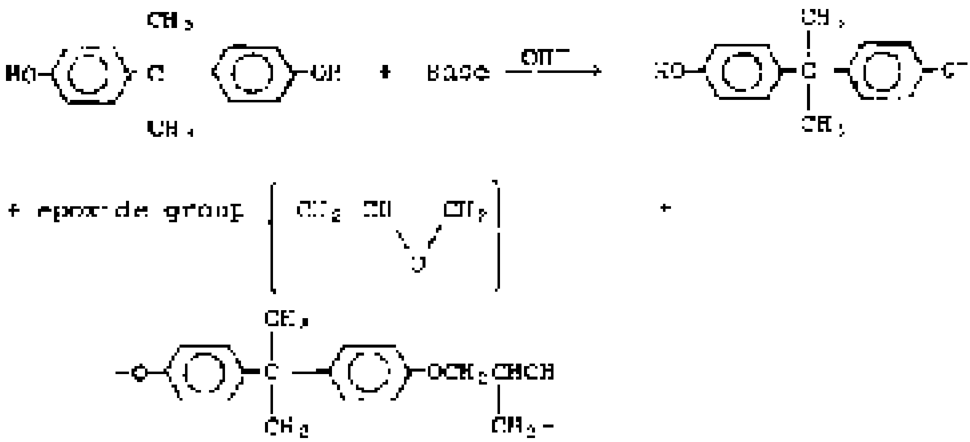
(a) What is the structure of the fluid cement, and how is it formed? What is the purpose of using excess epichlorohydrin? (b) What happens during hardening? What is the structure of the final epoxy resin? (c) Suggest a method of making Bisphenol A, starting from phenol.

Solution: The prepolymer (fluid cement) for epoxy resins are made from salts of "Bisphenol A" and epichlorohydrin. A reagent such as diethylenetriamine $(NH_2CH_2CH_2NHCH_2CH_2NH_2)$ is used for cross linking and the final polymer contains a network of cross linked chains.

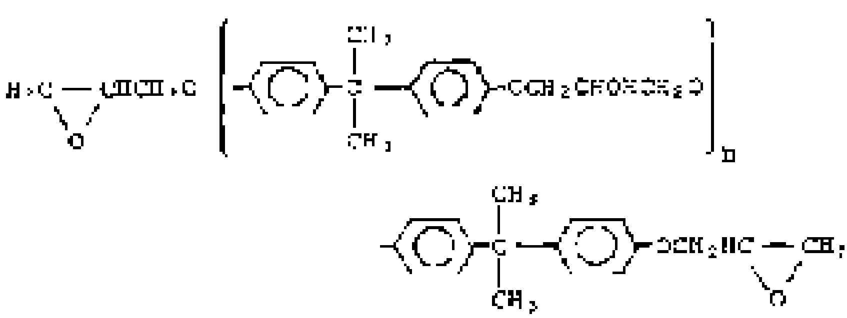
The cement is first manufactured by reacting the 2,2-Bis-(p-hydroxyphenyl)propane and epichlorohydrin in the presence of base to form the condensation polymer. In this Williamson synthesis, the chlorine anion acts as a leaving group and the phenoxide anion is the nucleophile. This reaction, like any S_N2 displacement is facilitated by the lack of steric hindrance in the attacked compound. In general, primary halides are more reactive than secondary or tertiary halides in such displacements. The equation for this reaction is:



The epoxide group reacts with a phenoxide anion under alkaline conditions in a sequence that also follows an S_N2 pattern. Typical of such reactions, the phenoxide anion attacks the primary carbon.



The final cement which is usually of low molecular weight has the following structure:



Excess epichlorohydrin is used, thus assuring the availability of unreacted epoxide groups at the ends of the chain. This is absolutely necessary in order for the cement to undergo a productive reaction with the hardener, which will be explained in part (b).

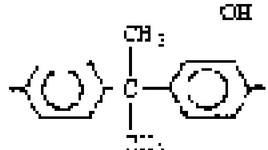
(b) The hardener chosen is $NH_2CH_2CH_2NHCH_2CH_2NH_2$, diethylenetriamine. During hardening the amine groups react with the epoxide and causes the $-\underset{\diagdown\ \diagup}{C - C}$ ring to break and
O

hydrogen is added to the oxygen forming a $\underset{|}{C}$ bond, whereas
OH

the other carbon atom joins with the amine. The final epoxy resin is represented by:

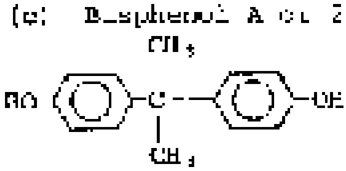
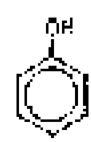
$$\sim\sim NHCH_2CH_2\underset{\displaystyle \wr}{N}-CH_2CH_2NHCH_2\underset{\displaystyle |\atop OH}{C}HCH_2O\,[A-OCH_2CHOHCH_2O]_n A -$$

$$OCH_2\underset{\displaystyle OH}{C}HCH_2NH\sim\sim$$

where A is given by  .

The amine has three distinct sites where it can react with the epoxide thus generating cross-linkages and forming a space-network polymer.

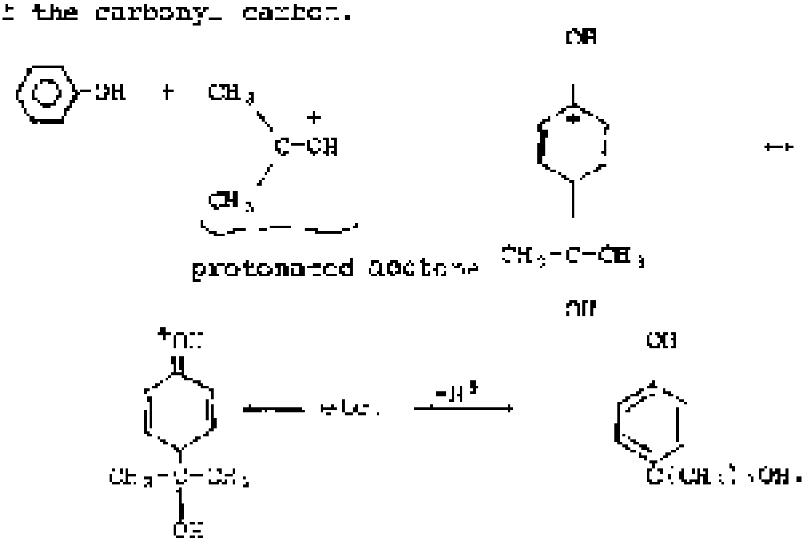
(c) Bisphenol A or 2,2-bis(p-hydroxyphenyl)propane

 can be prepared from phenol 

in the following steps outlined below:

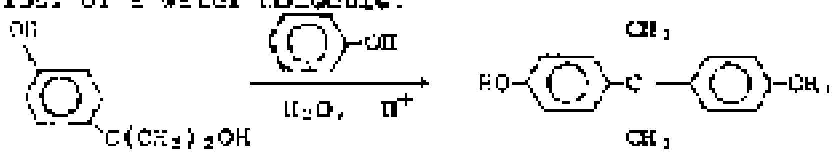
Phenols react with formaldehyde $\left[\begin{matrix} H \\ & \diagdown \\ & & C{=}O \\ & \diagup \\ H \end{matrix}\right]$ and ketones $\left[\begin{matrix} R \\ & \diagdown \\ & & C{=}O \\ & \diagup \\ R \end{matrix}\right]$ to produce macromolecules and the same technique could be applied here. Since the two phenol groups are joined by $CH_3-\overset{|}{\underset{|}{C}}-CH_3$, we could use acetone $\left[\begin{matrix} CH_3 \\ & \diagdown \\ & & C{=}O \\ & \diagup \\ CH_3 \end{matrix}\right]$

for this process. In the presence of an acid catalyst the reaction proceeds in a number of steps. The reaction involves an electrophilic attack on the aromatic ring by the electron deficient carbon of protonated acetone, in which the phenol acts as a nucleophile. The acid catalyzes the reaction by protonating acetone and increasing the electron deficiency of the carbonyl carbon.



protonated acetone

The initial adduct reacts with another phenol molecule giving the desired product (Bisphenol A) along with the loss of a water molecule.



The ortho-isomer of bisphenol will not be formed because of excessive steric hindrance due to the presence of the fairly large electrophile.

A practical method to attain this reaction is by gradually dripping acetone into a container of phenol.

• PROBLEM 28-9

Linseed oil and tung oil, important constituents of paints, are esters derived from acids that contain two or three double bonds per molecule: 9,12-octadecadienoic acid, for example. On exposure to air, paint forms a tough protective film; oddly enough, after the initial rapid evaporation of solvent, this "drying" of paint is accompanied by a gain in weight. What kind of process do you think is involved? Be as specific as you can be.

Solution: Linseed oil and tung oil, major constituents in paints, contain a fair amount of the esters derived from linoleic acid or 9,12 octadecadienoic acid. This has the structure: $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$.

The ester derived from this acid will be

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7\overset{O}{\overset{|}{C}}OR''$$, where R"

represents any alkyl group. This compound, in the presence of the oxygen diradical, will lose a hydrogen atom to form an extremely stable allyl radical that undergoes delocalization involving both double bonds.

$$\sim\!\!\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}-\underset{\cdot}{\overset{H}{\overset{|}{C}}}-\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}\!\sim \longleftrightarrow \sim\!\underset{\cdot}{\overset{H}{\overset{|}{C}}}-C{=}\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{C}}{=}C\!\sim \longleftrightarrow \sim\!\overset{H}{\overset{|}{C}}{=}\overset{H}{\overset{|}{C}}-\overset{H}{\overset{|}{C}}{=}C-\underset{\cdot}{\overset{H}{\overset{|}{C}}}\!\sim$$

Letting R· represent the entire radical and R' the remainder of the carbon chain not bearing the free electron, the mechanism can be represented as follows:

$$\ddot{O}{::}\ddot{O} \longleftrightarrow \cdot\ddot{O}{:}\ddot{O}\cdot$$

$$\cdot\ddot{O}-\ddot{O}\cdot + RH \rightarrow R'-O-O\cdot + \cdot O-OH$$

This radical that was formed on exposure to air can polymerize as follows:

$$R'-O-O\cdot \longrightarrow \overset{R'}{C} \quad + \quad ROOR + O_2$$

(arrows represent movement of one electron)

The ester has two allylic hydrogens and the dimer could react with another molecule of ester forming cross linkages and liberating oxygen.

$$CH_3(CH_2)_4CH{=}CH\overset{\wr}{\overset{|}{C}}-CH{=}C(CH_2)_7\overset{O}{\overset{\|}{C}}-OR'$$

$$\begin{array}{c} O \\ | \\ O \end{array}$$

$$CH_3(CH_2)_4CH-CH\overset{|}{\underset{|}{C}}-CH-C(CH_2)_7\overset{O}{\overset{\|}{C}}-OR''$$

$$\begin{array}{c} O \\ | \\ O \\ \wr \end{array}$$

Above: polymer with oxygen cross linkages.

The increase in weight is due to the addition of the oxygen molecules as the ester polymerizes and the paint dries.

METHODS OF POLYMERIZATION

• PROBLEM 28-10

Give an example of coordination polymerization. Name the chemists responsible for the discovery of this method of polymerization.

Solution: Coordination Polymerization is a type of addition polymerization. It differs from free radical polymerization in that it produces linear polymers and permits stereochemical control in their formation. In these reactions organometallic catalysts such as triethylaluminum-titaniumtrichloride are employed. This catalyst adds on a monomer and then adds another one between itself and the other monomer and the process is then repeated. Therefore the reaction is restricted near the catalyst and branching is prevented. Thus only linear molecules are formed. For example, in the polymerization of ethylene:

$$\underset{\diagdown CH_2=CH_2}{M-CH_2CH_3} \rightarrow \underset{\diagdown CH_2=CH_2}{M-CH_2CH_2CH_2CH_3} \rightarrow M-CH_2CH_2CH_2CH_2CH_2CH_3 \rightarrow \text{etc.}$$

Karl Ziegler and Guilio Natta jointly received a Nobel Prize in 1963 for their work in developing these catalysts.

$$\text{Eq.} \quad CH_2=CHCH_3 \xrightarrow{Al(C_2H_5)_3 \cdot TiCl_4} \left[CH_2-\overset{CH_3}{\underset{H}{C}} \right]_n .$$

• PROBLEM 28-11

How does a condensation polymer differ from an addition polymer? Give an example of each.

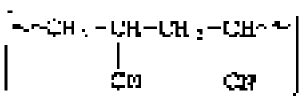
Solution: Polymers are macromolecules which are made by joining together many small molecules to form a few very large molecules. The simple compounds from which polymers are formed are called monomers.

Addition polymers are produced by molecules of a single monomer being added together. This is caused by a chain reaction, where a reactive particle joins with a monomer to produce another reactive particle. The original particle could be a radical, a cation, or an anion. For example, in the polymerization of ethylene:

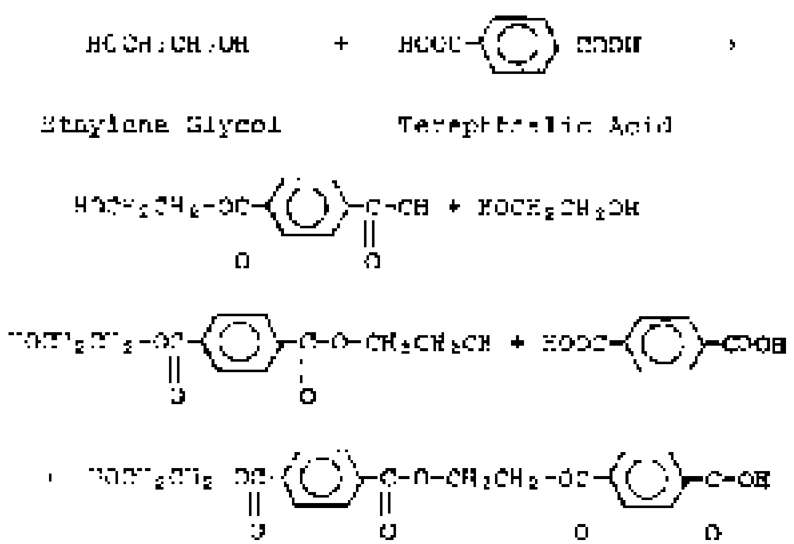
$$Rad* + CH_2=CH_2 \rightarrow Rad\ CH_2CH_2* \xrightarrow{CH_2=CH_2} Rad\ CH_2CH_2CH_2CH_2*$$

$$\xrightarrow{nCH_2=CH_2} Rad\ (CH_2)_{n-1}CH_2* \quad \text{(* represents the active particle)}$$

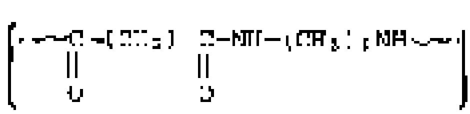
This reaction comes to an end when all the monomer molecules are either depleted or used up in chain termination steps. Polyethylene (~ $CH_2CH_2CH_2CH_2$~) is the final product. Other examples of addition polymers are polyvinyl chloride ~CH_2-CH-CH_2-CH~ (with Cl on each CH) and orlon i.e. polyacrylonitrile



Condensation polymers originate under step-reaction polymerization. In this case there is more than one kind of monomer. A series of reactions take place which are totally independent of preceding reactions. For example, a glycol and a dicarboxylic acid can react with each other to form an ester which can link itself to another ester linkage thus creating a complex molecule.



This goes on until one of the monomers is used up.

Nylon , where

$HOOC(CH_2)_4COOH$ and $NH_2(CH_2)_6NH_2$ are the two monomers, can be an example of condensation polymerization.

• PROBLEM 28-12

High-pressure polyethylene differs from polyethylene, made with the aid of Ziegler catalysts, in having a lower density and lower T_m. It has been suggested that this is due to branches in the chains of the high-pressure material. Explain how such branches might arise in the polymerization process and how they would affect the density and T_m.

Solution: Polyethylene can be made under high pressure by using peroxide catalysis in a free radical polymerization. The peroxide initiates the reaction by producing a free radical to which other ethylene molecules react.

$$R:\ddot{O}:\ddot{O}:R \rightarrow 2R:\ddot{O}\cdot \qquad \text{Initiation}$$

$$R:\ddot{O}\cdot + CH_2{=}CH_2 \rightarrow R:\ddot{O}:CH_2{-}CH_2\cdot$$

$$R:\ddot{O}:CH_2CH_2\cdot + n\,CH_2{=}CH_2 \rightarrow \qquad \text{Propagation}$$

$$RO\left(CH_2{-}CH_2\right)_n CH_2CH_2\cdot$$

$$\rightarrow RO\left(CH_2{-}CH_2\right)_n CH_2{-}CH_2\cdot$$

This growing chain could react with another polyethylene group such as $\left(CH_2\right)_m CH_2\left(CH_2\right)_n$ producing:

$$RO\left(CH_2{-}CH_2\right)_n CH_2CH_2\cdot + \left(CH_2\right)_m CH_2\left(CH_2\right)_n$$

$$\rightarrow RO\left(CH_2{-}CH_2\right)_n CH_2CH_2H + \left(CH_2\right)_m \dot{C}H\left(CH_2\right)_n$$

middle of chain radical

$$\xrightarrow{CH_2=CH_2} \left(CH_2\right)_n \underset{CH_2-CH_2\cdot}{\underset{|}{CH}} \left(CH_2\right)_m$$

An ethylene molecule could interact with the 'middle of chain radical' and react to form a branched polymer. A number of such branches occurring at random will destroy the linear arrangement of the polymer and the macromolecules will not be able to arrange themselves compactly. Thus the density of such a branched polymer will decrease and because of lower crystallinity the T_m (similar to melting point in crystalline compounds) will be lowered as compared to linear compounds.

Polyethylene made by using Ziegler catalysts, on the other hand, will not form branched polymers. This method is known as Coordination polymerization and certain organometallic catalysts such as triethylaluminum-titanium chloride $(C_2H_5)_3Al-Ti\ Cl_4$ are employed. This catalyst forms a bond with ethylene and keeps adding other monomer. near the catalyst preventing any branching and therefore permits a great deal of stereochemical control.

$$M = Al(C_2H_5)_3 \quad Ti\ Cl_4.$$

$$M - CH_2CH_3 \rightarrow M - CH_2CH_2CH_2CH_3$$

$$\quad CH_2 = CH_2 \qquad\qquad CH_2 = CH_2$$

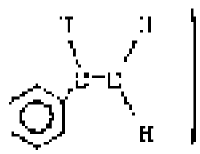
$$\rightarrow M - CH_2CH_2CH_2CH_2CH_2CH_3.$$

Since only linear molecules are generated it is possible for the various macromolecules to arrange in a minimum volume and thereby cause high crystallinity leading to a high T_m and density. Branching will decrease intermolecular attractions between these macromolecules and thus lower these physical constants.

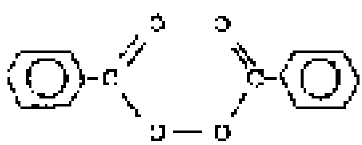
• PROBLEM 28-13

The rate of free radical polymerization of styrene, induced by benzoyl peroxide in mixtures of carbon tetrachloride and benzene, is independent of the concentration of carbon tetrachloride. At high concentrations of carbon tetrachloride, the average molecular weight of the polymer is greatly reduced and chlorine is found in the polymer. Explain.

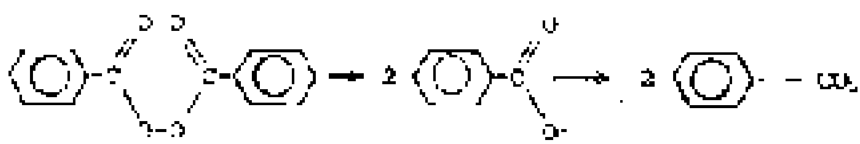
Solution: Polystyrene (composed of the monomer styrene:

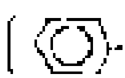


is produced by free radical polymerization initiated by a catalyst (normally a peroxide). In this case, it is benzoyl peroxide:

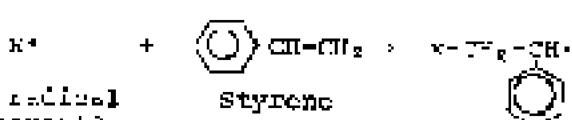


The mechanism of this reaction in the presence of a low concentration of carbontetrachloride, CCl_4 is:

(1) 

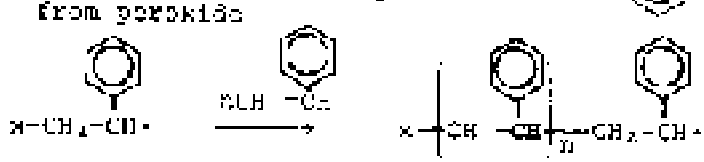
Thermal decomposition of benzoyl peroxide leads to the formation of free radicals ( to be designated as $X\cdot$). $X_2 \rightarrow 2X\cdot$.

[Initiation]

(2) 

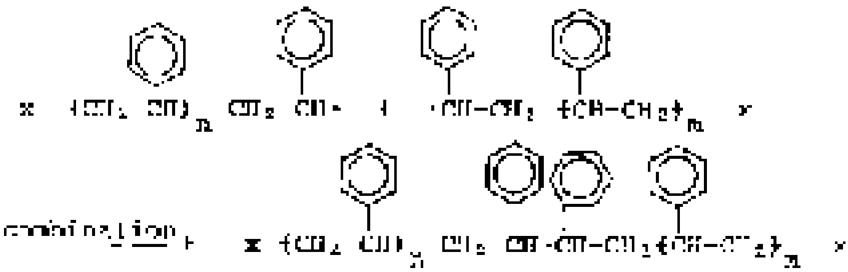
Free radical from peroxide

Styrene



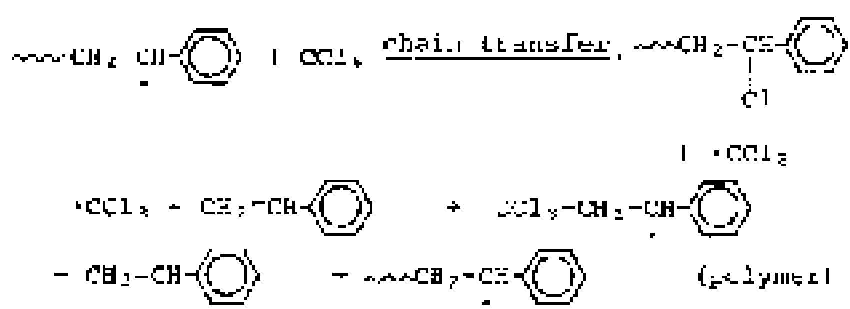
[Propagation]

This growing chain can be interrupted by various means. Chain termination can occur by combination of radicals or by disproportionation of radicals. Two growing chains can combine with formation of a carbon-carbon bond, or disproportionation could lead to a hydrogen atom being transferred from one chain to the other.



Polystyrene terminates primarily by combination of radicals.

A totally different way by which a chain could be terminated is by chain transfer. In this case the chain transfer reagent is carbon tetrachloride. At very large concentrations CCl_4 competes against further polymerization and results in the formation of polymers containing CCl_3 and Cl groups. The interaction of the growing polymer chain with carbon tetrachloride produces a polymer and a CCl_3 radical. The growth of the former chain is transferred to the $\cdot CCl_3$ group which starts adding to styrene monomers.



A transfer agent thus competes with the monomer for the growing chains. It does not use up the initiator radicals but lowers the average molecular weight of the polymer by reducing the number of propagation steps in the reaction sequence. Certain industrial transfer agents are used specifically for this purpose.

PROBLEM 28-14

When formaldehyde is polymerized to a linear polymer in heptane solvent, with $(C_6H_5)_3P$ or a proton as a catalyst, it yields a thermally unstable material (A) that unzips readily to re-form formaldehyde. However, if the end of the polymer is "capped", the product is a highly crystalline, tough polymer. The example below, B, is called Delrin and is already replacing nylon as a molding resin. Suggest a reason for the stability gained by capping the polymer.

$$HO-[CH_2O]_n-CH_2OH \qquad CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O-(CH_2O)_n-CH_2-O-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3$$

(A) (B)

Solution: Polymeric products of formaldehyde, known for over 100 years, are quite unstable for commercial use. Thermal stability could be improved by acetylation of the hydroxyl end groups using acetic anhydride.

$$-CH_2OCH_2OH + CH_3COO^- \rightarrow -CH_2OCH_2O^- + CH_3COOH$$

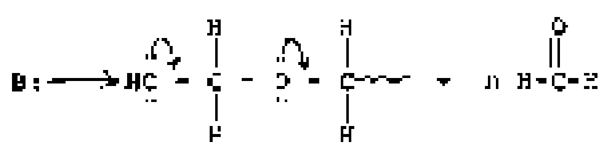
$$\xrightarrow{(CH_3CO)_2O} -CH_2OCH_2OCOCH_3 + CH_3COO^-.$$

By "capping" the two ends of formaldehyde we produce acetyl linkages at the two ends; the structure of which would be given by

$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-O(CH_2O)_n\,CH_2O\overset{\overset{\displaystyle O}{\|}}{C}-CH_3.$$

The rise in stability is remarkable. Polyformaldehyde is insoluble in the reaction mixture and is removed as a slurry while capped polyformaldehyde is about 75 % crystalline and has a definite melting point. The reason is that both are held by acetal type bonds, except that polyformaldehyde reacts with base (unlike acetals) to reverse the polymerization. Capped paraformaldehyde lacks a terminal hydroxyl hydrogen and cannot react so easily with base. The reactions can be summarized as:

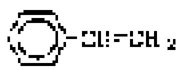
$$n\,H-\overset{\overset{\displaystyle O}{\|}}{C}-H \xrightarrow{H^+} HOCH_2(OCH_2)_{n-1}OH$$



• PROBLEM 28-15

A sample of styrene is polymerized with the help of a little azoisobutyronitrile as initiator. Hydrolysis of the resulting polymer releases 6 g of ammonia from 10 kg of polymer. If all the end groups are derived from the initiating radical (α-cyanoisopropyl), what is the average number of styrene units in the chain?

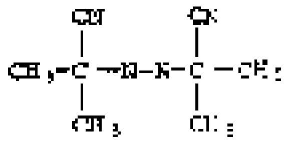
Solution: Styrene has the structural formula



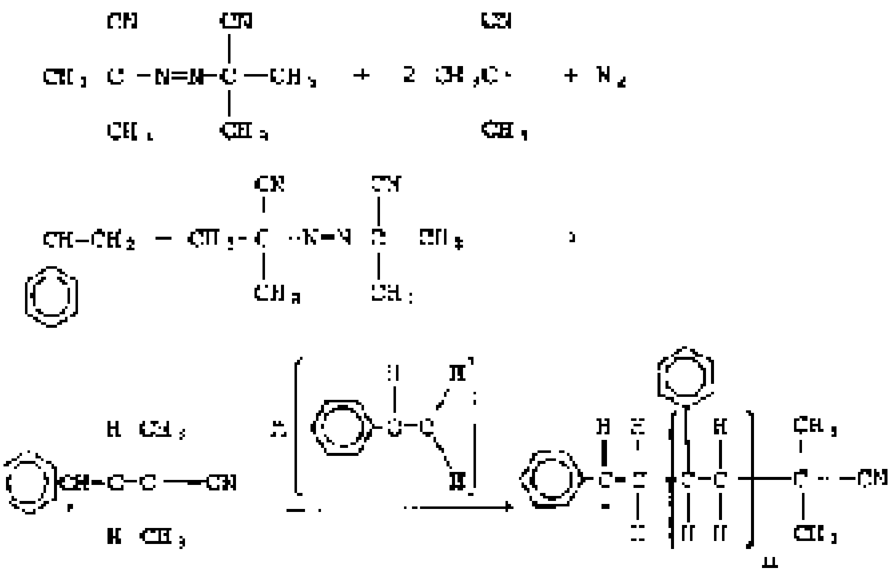
(Molecular weight = 77+24+3=104).

When azoisobutyronitrile is used as the initiator, addition chain reactions take place and the formation of polymer continues until all of the monomer (styrene) has been depleted. Azoisobutyronitrile has the chemical struc-

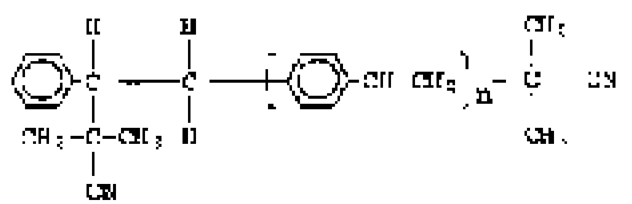
ture of



The initiator joins with styrene and nitrogen is evolved:



chain termination:



(A)

Hydrolysis of the resulting polymer produces ammonia and polystyrene.

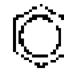
Six grams of ammonia is evolved from 10 kg [10 kg × 1000 gms/kg = 10,000 gms] of the polymer A. The molecular weight of ammonia NH_3 is 14 + 3 = 17. Therefore, the number of moles of ammonia produced is equal to the number of grams of ammonia divided by its molecular weight, i.e. $\frac{6}{17}$ = .353 moles. Since there are two groups in polymer A that produce ammonia, one mole of polymer produces two moles of ammonia upon hydrolysis. Therefore the number of moles of polymer present is $\frac{.353}{2}$ = .1765 moles.

So .1765 moles corresponds to 10,000 gms of polymer A. The average molecular weight is given by $\frac{10,000}{.1765}$ = 56,657.

The molecular weight of the individual chains vary so an average is chosen. The molecular weight of the two end

groups, i.e. $-\underset{CH_3}{\overset{CH_3}{|}}\!\!\!\!C-CN$ is equal to [4(12) + 14 + 6]2 = 136.

So by subtracting the molecular weight of the end chains from the polymer (A) would give the molecular weight of polystyrene.

The molecular weight of the whole polystyrene chain is 56,657 - 136 = 56,521. One molecule of styrene  $-CH=CH_2$ has a molecular weight of 104. Therefore, the average number of styrene units in one chain is the molecular weight of the whole polystyrene chain divided by the molecular weight of one styrene unit which is equivalent to

$\frac{56,521}{104}$ = 543.5 styrene units in one polystyrene chain.

SYNTHETIC POLYMERS

• PROBLEM 28-16

Examine the structure of each of the following synthetic polymers. Tell what class of compound it belongs to and give structures of the most likely monomers.

(a) nylon 6,6 (fibers) $\sim\sim\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH(CH_2)_6NH\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}NH(CH_2)_6NH\sim\sim$

(b) nylon 6 (fibers) $\sim\sim\overset{O}{\overset{\|}{C}}CH_2(CH_2)_4NH\overset{O}{\overset{\|}{C}}CH_2(CH_2)_4NH\sim\sim$

(c) Carbowax (water-soluble wax) $\sim\sim OCH_2CH_2OCH_2CH_2OCH_2CH_2\sim\sim$

(d) Neoprene (oil-resistant elastomer),

$$\sim\sim CH_2\underset{Cl}{\underset{|}{C}}=CHCH_2CH_2\underset{Cl}{\underset{|}{C}}=CHCH_2\sim\sim$$

(e) Saran (packaging film, seat covers) $\sim\sim CH_2CCl_2CH_2CCl_2\sim\sim$.

Solution: (a) In the structure of nylon 6,6 (fibers)

$$\sim\!\sim C(=O)(CH_2)_4C(=O)NH(CH_2)_6NHC(=O)(CH_2)_4C(=O)NH(CH_2)_6NH\sim\!\sim \;,$$ it is

recognizable from the $\left(\begin{array}{c} O\quad H \\ \| \quad | \\ -C-N- \end{array}\right)$ group that the above could be classified as a polyamide. Amides are synthesized when a carboxylic acid reacts with an amine in the presence of a drying agent and heat. However, when an acid contains two or more $-COOH$ groups and reacts with an amine containing more than one $-NH_2$ group, polyamides are formed. The acid used for the above polymer unit contains two $-COOH$ groups, both attached to $-(CH_2)_4-$, while the amine contains two $-NH_2$ groups which are joined together by $-(CH_2)_6-$.

The structural formulas are $COOH(CH_2)_4COOH$ (adipic acid) and $H_2N(CH_2)_6NH_2$. This polymer was brought about by condensation polymerization with the loss of a small molecule (H_2O), which is a characteristic of all condensation polymerizations.

(b) $$\sim\!\sim C(=O)CH_2(CH_2)_4NHC(=O)CH_2(CH_2)_4NH\sim\!\sim$$

This polymer unit is also characterized by an $-\left(\begin{array}{c} O \\ | \\ NHCO \end{array}\right)$ group. Thus it falls under the category of amides.

By observing the polymer unit two identical monomers $\sim C(=O)CH_2(CH_2)_4NH-$ are paired to build the required polymer.

This is a case of addition polymerization having no by-products. The most likely monomer is $COOH\,CH_2(CH_2)_4NH_2$; ε-aminocaproic acid.

(c) Carbowax: $\sim\!\sim OCH_2-CH_2O-CH_2CH_2O\;CH_2CH_2\sim\!\sim$

The repeating unit in this polymer is $-CH_2CH_2O-$. This polymer fits under the category of ethers with the general formula ROR'.

This is also a case of addition polymerization (without any by-products) and only a single kind of monomer namely the epoxide, ethylene oxide $\left[\begin{array}{c} O \\ / \quad \backslash \\ CH_2-CH_2 \end{array}\right]$.

(d) Neoprene; $\sim\!\sim CH_2C(Cl)=CH-CH_2CH_2C(Cl)=CHCH_2\sim\!\sim$

The repeating unit can be recognized as $\left[-CH_2C{=}CHCH_2-\right]$ with Cl on the second carbon

implying addition polymerization and due to the double bond will come under the classification of chloroalkenes. The most likely monomer will have a structural formula $CH_2{=}C(Cl){-}CH{=}CH_2$ which undergoes 1,4 addition in polymerization.

(c) Saran $\quad \sim CH_2{-}CCl_2{-}CH_2{-}CCl_2 \sim$

This structure is unsaturated, having chlorine atoms attached to a carbon atom and could be classified as a chloroalkane. This is a case of addition reaction and the monomer is $CH_2{=}C(Cl){-}Cl$.

ION-EXCHANGE RESINS

• PROBLEM 28-17

Show how the successive use of cation- and anion-exchange resins could be used to remove sodium chloride from water.

Solution: Polymers are insoluble in H_2O but may form soluble inorganic salts. This is the basis for the use of ion-exchange resins. Such a method could be implemented whereby NaCl can be removed from sea water hence replacing the traditional purification by expensive distillation.

In aqueous solution, sodium chloride dissociates to form sodium and chlorine ions.

$$NaCl \rightarrow Na^+ + Cl^-.$$

The sodium cation could be displaced by a cation exchange resin. Let R^+A^- represent a cation exchange resin and B^+OH^- an anion-exchange resin. The cation-exchange resin reacts with sodium chloride and the sodium ion is displaced by the insoluble resin.

$$\underline{H^+A^-} + Na^+Cl^- \rightarrow \underset{\text{insoluble}}{\underline{Na^+A^-}} + H^+ + Cl^-.$$

The chlorine ion is then displaced by an anion-exchange resin.

$$H^+ + \underline{B^+OH^-} + Cl^- \rightarrow \underset{\text{insoluble}}{\underline{B^+Cl^-}} + H_2O.$$

The two insoluble compounds precipitate and are removed from the water by filtration. Thus by the successive usage of cation and anion-exchange resins sodium chloride could be removed from water. An example of a cation exchange resin is sulfonated styrene-divinyl-benzene polymer and an anion-exchange resin can be made by chloromethylating styrene-divinyl copolymer and replacing the chlorines with trimethylamine.

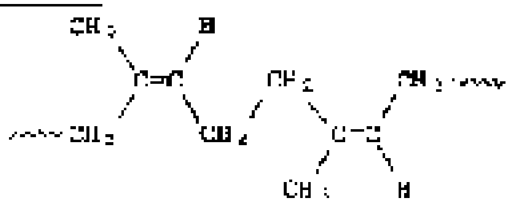
NATURALLY OCCURRING POLYMERS

• PROBLEM 28-18

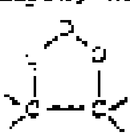
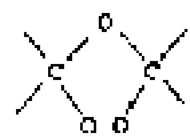
Natural rubber is attacked readily by ozone. If the resulting material is treated with H_2O_2 in acetic acid, the major product isolated is levulinic acid ($C_5H_8O_3$).

(a) What is the structure of levulinic acid?
(b) If a rubber plant is fed radioactive sodium acetate labeled only at the acetate methyl ($^*CH_3CO_2Na$), radioactive rubber can be obtained from the latex of the plant after a short time. Degradation of this rubber by ozone yields radioactive levulinic acid. Which specific carbon atoms of the levulinic acid would you expect to be radioactive?

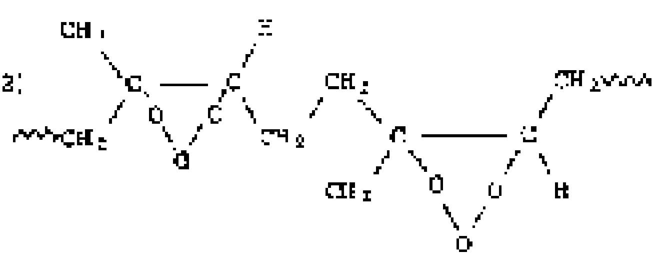
Solution: The structure of natural rubber is

(1) 

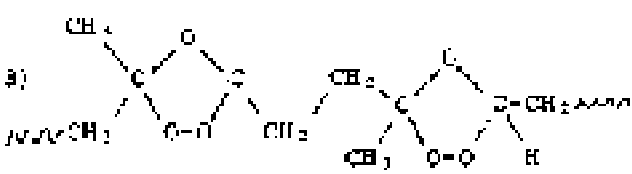
Ozone (O_3) readily oxidizes unsaturated compounds. For example, with alkenes, ozone reacts to produce a molozonide

 which rearranges to an ozonide 

Thus the double bond is replaced by 3 oxygen atoms. The reaction of ozone with natural rubber is very similar and the product could be represented by

(2) 

This compound will then readily rearrange and form

(3) 

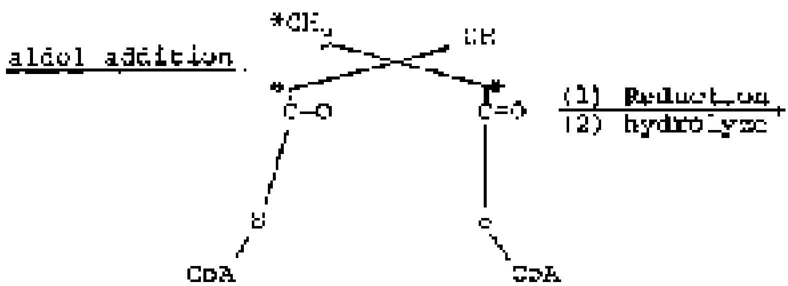
By allowing this product to react with hydrogen peroxide (O_3) and acetic acid (CH_3COOH) the polymer breaks up into several molecules. The final material contains a carboxylic group. The ozonides are decomposed by reduction to produce:

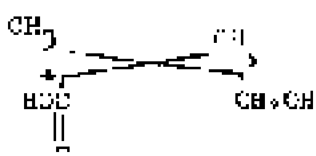
$$CH_3\underset{\displaystyle O}{\underset{\|}{C}}-CH_2CH_2\underset{\displaystyle O}{\underset{\|}{C}}OH \quad \leftarrow \quad \text{Levulinic acid}$$

(b) To find the specific radioactive carbon atoms in levulinic acid it is necessary to show the synthesis of natural rubber starting from radioactive sodium acetate ($^*CH_3CO\bar{O}\overset{+}{Na}$) where * represents the radioactive atom. CoA stands for a coenzyme A.

$$^*CH_3C\bar{O}_2\overset{+}{Na} \xrightarrow{CoASH} {}^*CH_3CO-S\ CoA.$$

$$2\ \overset{*}{C}H_3CO\ S-CoA \xrightarrow{Base} {}^*CH_3\overset{O}{\overset{\|}{C}}-\overset{*}{C}H_2-\overset{O}{\overset{\|}{C}}—SCoA$$



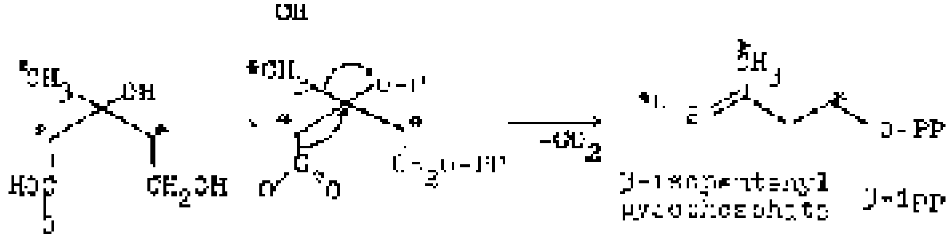


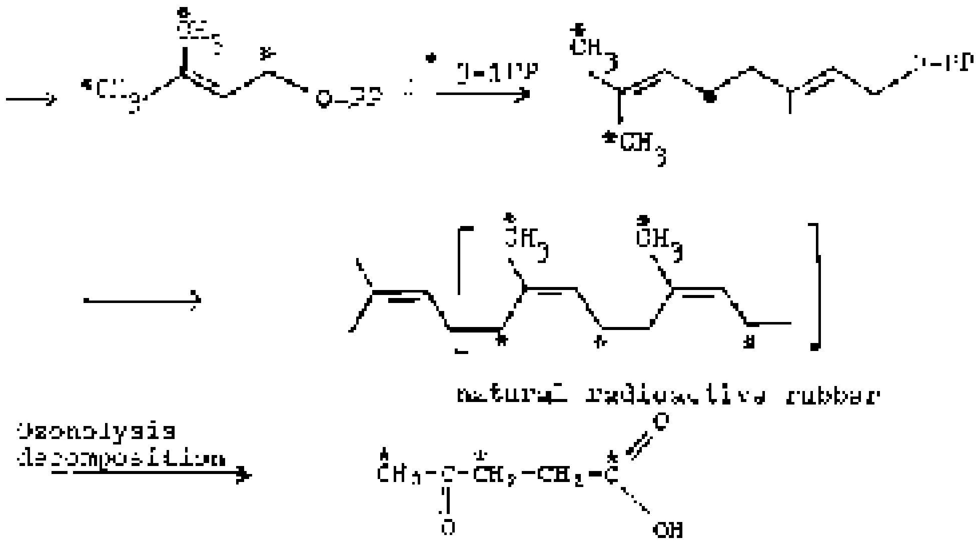
Mevalonic acid

Mevalonic acid is activated by phosphorylation in the biosynthesis of polyisoprene:

P stands for the phosphate ion $-\overset{O}{\overset{\|}{P}}(OH)_2$ whereas

PP represents $-\underset{OH}{\overset{O}{\overset{|}{P}}}-O-\overset{O}{\overset{|}{P}}(OH)_2$, pyrophosphate ion.

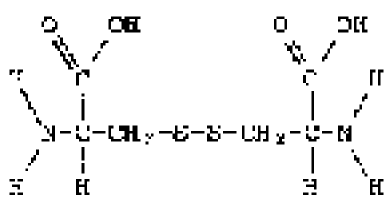




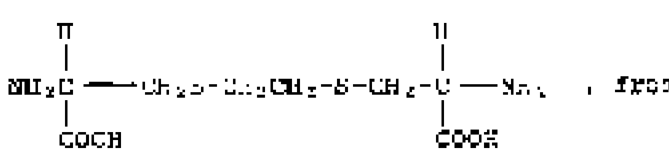
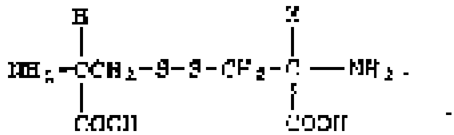
■ PROBLEM 23-19

Apparently the economically important chain reaction, wool + moths → holes + more moths, has, as a key step, scission of the disulfide linkages of cystine in the polypeptide chains by the digestive enzymes of the moth larva. Devise a method of mothproofing wool which would involve chemically altering the disulfide linkages.

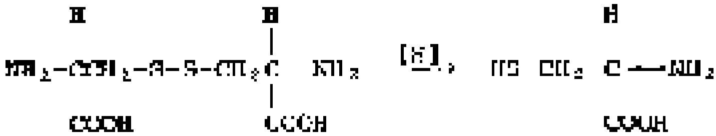
Solution: A major component in the structure of wool (also insulin) is the compound cystine:



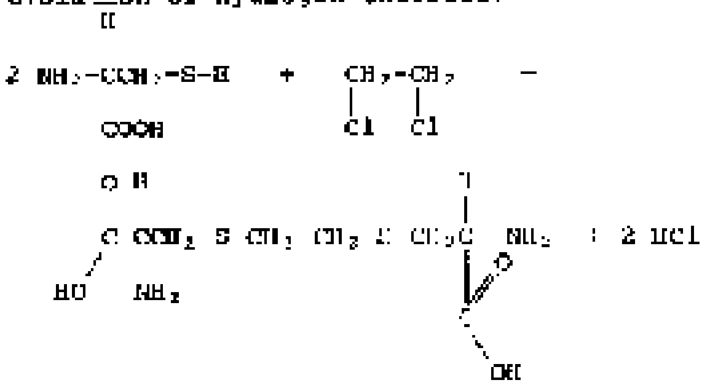
The digestive enzymes of the moth larva cleave the cystine chain at the -S-S- bond and therefore cause damage to the molecular structure of wool (cystine). The disulfide cross linkages between the peptide chains play a major role in determining the mechanical properties of wool fibers. Therefore their removal will make wool pliable. However if an intermediate group is attached between the two sulfur atoms (CH_2 CH_2), then the disulfide linkage cannot be broken by the digestive enzymes of the larva. We therefore have to

synthesize  , from cystine, 

Hydrogenation breaks the S-S bonds and produces:



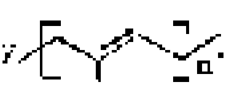
By reacting the product with 1,2-dichloro ethane $\underset{Cl}{CH_2}-\underset{Cl}{CH_2}$, nucleophilic substitution takes place with the evolution of hydrogen chloride.

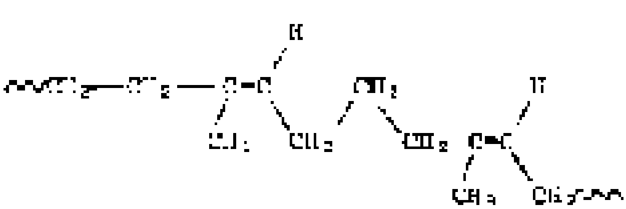


The final product was altered to prevent scission of the disulfide linkages.

• PROBLEM 28-20

> Balata is a natural occurring polymer, similar in physical properties to polyethylene. What is its structure?

Solution: Balata is the name of the rubber grown in South America. The chemical name is poly-trans-isoprene and the structural formula is represented by . The natural polymer is useful for many consumer products such as golf ball covers and as an impregnant for textile belting and may extend to hundreds of molecules i.e.



CHAPTER 29

ORGANOSILICON, PHOSPHORUS AND BORON COMPOUNDS

ORGANOSILICON COMPOUNDS

• PROBLEM 29-1

Name the following compounds according to the nomenclature used in the table below:

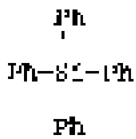
(a) $(C_6H_5)_4Si$ (d) $(CH_3)_3SiOSiH_3$
(b) $(C_3H_7)_3SiBr$ (e) $CH_3SiH_2NH_2$
(c) $(C_6H_5)_2Si(OH)_2$ (f) $C_6H_5CONHSi(CH_3)_3$

Principal Types of Organosilicon Compounds and Their Carbon Analogs

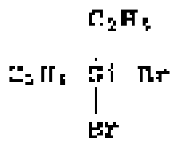
Organosilicon Compound		Carbon Compound	
silanes and organosilanes:		alkanes:	
$H_3Si-SiH_3$	disilane	CH_3-CH_3	ethane
CH_3-SiH_3	methylsilane	CH_3-CH_3	ethane
$(CH_3)_4Si$	tetramethylsilane	$(CH_3)_4C$	neopentane
organosilyl halides (halosilanes):		alkyl halides (haloalkanes):	
$(CH_3)_3SiCl$	trimethylsilyl chloride	$(CH_3)_3CCl$	t-butyl chloride
H_2SiCl_2	dichlorosilane	CH_2Cl_2	dichloromethane
CH_3SiCl_3	methylsilyl trichloride	CH_3CCl_3	1,1,1-trichloroethane
silanols:		alcohols:	
H_3SiOH	silanol	H_3COH	methanol (carbinol)

$(CH_3)_3SiOH$	trimethylsilanol	$(CH_3)_3COH$	trimethylcarbinol (t-butyl alcohol)
$(CH_3)_2Si(OH)_2$	dimethylsilanediol	$(CH_3)_2C(OH)_2$	acetone hydrate (unstable)
$CH_3Si(OH)_3$	methylsilanetriol	$CH_3C(OH)_3$	orthoacetic acid (unstable)
siloxanes and alkoxysilanes:		ethers:	
$(CH_3)_3SiOSi(CH_3)_3$	hexamethyldisiloxane	$(CH_3)_3COC(CH_3)_3$	di-t-butyl ether
$(CH_3)_3SiOCH_3$	trimethylmethoxysilane	$(CH_3)_3COCH_3$	methyl t-butyl ether
$(CH_3)_2Si(OCH_3)_2$	dimethyldimethoxysilane	$(CH_3)_2C(OCH_3)_2$	acetone dimethyl ketal
$CH_3Si(OCH_3)_3$	methyltrimethoxysilane	$CH_3C(OCH_3)_3$	methyl orthoacetate
silyl esters:		alkyl esters:	
$(CH_3)_3Si{-}O\overset{O}{\overset{\|}{C}}CH_3$	trimethylsilyl acetate	$(CH_3)_3C{-}O\overset{O}{\overset{\|}{C}}CH_3$	t-butyl acetate
silazanes (silylamines):		amines:	
$(CH_3)_3SiNH_2$	trimethylsilazane (trimethylsilylamine)	$(CH_3)_3CNH_2$	t-butyl amine
$(H_3Si)_2NH$	disilazane (disilylamine)	$(CH_3)_2NH$	dimethylamine
$(H_3Si)_3N$	trisilylamine	$(CH_3)_3N$	trimethylamine

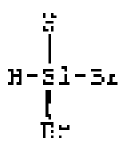
Solution: Organosilicon compounds are named as derivatives of the various classes of these compounds. Examples of this are shown in the above table.

(a) 

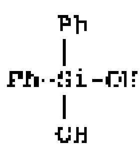
This compound belongs to the class of silanes. There are four phenyl groups attached to the silicon, therefore its name is tetraphenylsilane.

(b) 

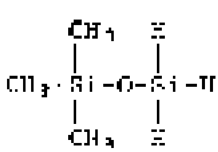
This compound belongs to the class of organosilyl halides. There are two ethyl groups and two bromides attached to the silicon, therefore its name is diethylsilyl dibromide. Note that if the two ethyl groups were hydrogens:



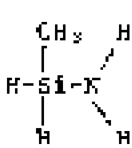
its name would be derived from the term halosilane, and its corresponding name would be dibromosilane.

(c) 

This compound belongs to the class of silanols, specifically silanediols. There are two phenyl groups attached to this silanediol, therefore its name is diphenylsilanediol.

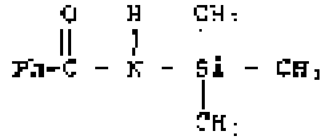
(d) 

This compound belongs to the class of siloxanes. There is a trimethylsilane group attached to the siloxy group, therefore its name is siloxytrimethylsilane.

(e) 

This compound belongs to the general class of silazanes. There is one methyl group attached to this compound, therefore its name is methylsilazane.

(f)

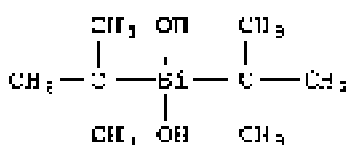


This compound belongs to the general class of silazanes. There is a benzoyl group [Ph–C(=O)–] attached to the nitrogen, therefore we must use an "N" prefix to denote this. There are three methyl groups attached to the silicon, therefore its name is N-benzoyltrimethylsilazane.

• PROBLEM 29-2

Di-t-butylsilanediol is stable to heat and acid. It will not lose water, even with dehydrating agents above 400°C. Offer an explanation.

Solution: The structure of di-t-butylsilanediol is:



If we compare this silicon compound to its analogous gem diol, di-t-butylketone hydrate, we might expect the silanediol to lose water to form a compound with a Si–O bond. Also, silicone formation seems possible as it is a property of many silanediols. However, neither occurs as seen in the following:

(1)

This reaction will not occur due to the reluctance of silicon to form $p_\pi - p_\pi$ Si=O bonds, that is, the π overlap of a 3p silicon orbital with a 2 p oxygen orbital.

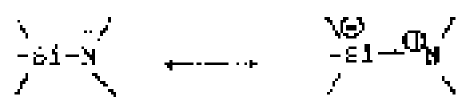
(2)

This reaction is not possible due to steric hindrance; the bulky t-butyl groups would make such a polymer impossible. Usually, a silanediol would polymerize to a silicone because of the stability of the Si–O bond. (Note: Do not confuse silicone with silicon.)

• PROBLEM 29-3

Since silicon is more electropositive than carbon, silylamines reasonably might be expected to be more basic than the corresponding organic amines. They are, in fact, much weaker bases. Offer an explanation.

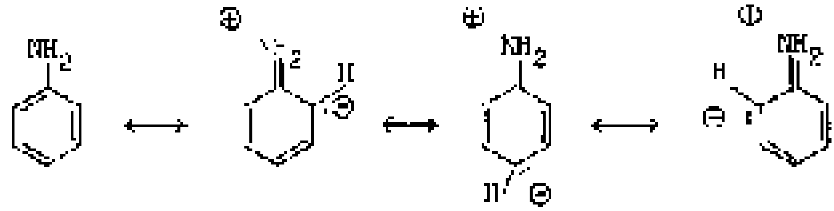
Solution: Silicon, like phosphorus and sulfur, can expand its valence shell to accommodate ten electrons by using its 3d orbitals. Nitrogen, like other second row elements, is not able to do this. In compounds of the type $-\overset{|}{\underset{|}{Si}}-X$, where X is a molecule having electrons in p orbitals, the p electrons of X can overlap with an empty 3d orbital of silicon. The result is an Si–X bond with partial double bond character of the $d_\pi - p_\pi$ type. This is the case with silylamines. The lone-pair electrons of nitrogen are involved in $d_\pi - p_\pi$ overlap with silicon. This lowers the electron density on nitrogen, thereby reducing the basicity of silylamines:



(I) (II)

From another point of view, we can say that protonation of silylamines destroys resonance structure II, that is, resonance energy stabilizes silylamines in a manner that is not possible with protonated silylamines. In essence, resonance lowers the energy content of silylamines more than it lowers the energy content of the corresponding cation. The net effect is to shift the equilibrium in the direction of less ionization. Therefore, silylamines are weaker bases than the corresponding organic amines, in spite of the fact that silicon is more electro-positive than carbon. In this case, the inductive effect is off-set by the resonance effect — $d_\pi - p_\pi$ overlap.

An analogous case is the basicity of aniline with respect to the corresponding aliphatic amines. Aliphatic amines have K_b's of about 10^{-3} to 10^{-4}, while aromatic amines have K_b's of 10^{-9} or less (note: the larger the K_b, the stronger the base). The reason for this phenomenon is similar to that of silylamines. The $-NH_2$ group shares electrons with the ring, yielding resonance structures III, IV, V, and VI:



(III) (IV) (V) (VI)

This decreases the basicity of anilines with respect to the aliphatic amines, as seen from both viewpoints that we discussed earlier.

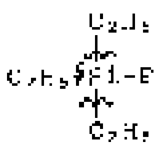
• PROBLEM 20-4

Work out a synthesis of each of the following compounds based on one of the available silicon compounds SiF_4, $SiCl_4$, $HSiCl_3$, H_2SiCl_2, $(CH_3)_2SiCl_2$, $(CH_3)_3SiCl$.

(a)	$(C_2H_5)_3SiF$	(d)	$Cl_3SiCH_2CH_2CH{=}CH_2$
(b)	$(C_6H_5)_2SiClH$	(e)	$Cl_3SiCH_2CH_2SiCl_3$
(c)	$(n\text{-}C_4H_9)Si(CH_3)_2H$	(f)	$(C_2H_5)_3SiCH_2CH_2CH_2Si(CH_3)_3$

Solution: The method for synthesizing a compound is to look at the product and dissect it in a manner such that it can be synthesized as a derivative of one of the starting reagents.

(a)



As we can see from the above figure, we can synthesize this compound from SiF_4 by substituting three ethyl groups for three flourines.

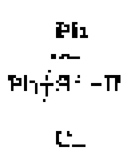
One method of doing this is through a Grignard reagent:

$$F_3Si\text{-}F + BrMgCH_2CH_3 \rightarrow F_3Si\text{-}CH_2CH_3 + BrMgF$$

Three such substitutions will give us the product:

$$SiF_4 + 3\ C_2H_5MgBr \rightarrow (C_2H_5)_3SiF$$

(b)



We substitute two phenyl groups for two chloro groups in $HSiCl_3$. One method of synthesis is through a Grignard reagent:

$$HSiCl_3 + 2\ C_6H_5MgBr \rightarrow (C_6H_5)_2SiHCl$$

(d)

$$CH_3CH_2CH_2CH_2 \overset{}{\underset{b}{+}} \overset{CH_3}{\underset{CH_3}{Si}} \underset{a}{+} H$$

We can synthesize this compound by: (1) reducing $(CH_3)_2SiCl_2$ to $(CH_3)_2SiH_2$, then (2) substituting an n-butyl group for one of the hydrogens by using n-butyllithium:

(1)

$$CH_3-\overset{Cl}{\underset{CH_3}{Si}}-Cl \xrightarrow{LiAlH_4} CH_3-\overset{H}{\underset{CH_3}{Si}}-H$$

(2)

$$CH_3-\overset{H}{\underset{CH_3}{Si}}-H \xrightarrow{n-C_4H_9Li} CH_3-\overset{H}{\underset{CH_3}{Si}}-CH_2CH_2CH_2CH_3$$

(e)

$$Cl-\overset{Cl}{\underset{Cl}{Si}} + CH_2CH_2-\overset{H}{C}=\overset{H}{C}-H$$

We can synthesize this compound by substituting

$$-CH_2CH_2\overset{H}{C}-CH_2$$

for a hydrogen in Cl_3SiH. This may be achieved through addition of the silicon hydride to the appropriate alkene:

$$CH_2=CH-CH=CH_2 + Cl_3SiH \xrightarrow{(C_6H_5CO_2)_2} Cl_3SiCH_2CH_2CH=CH_2$$

The mechanism is a free-radical chain reaction:

$$\left.\begin{array}{l}(PhCO_2)_2 \rightarrow 2\ Ph\cdot + 2\ CO_2 \\ Cl_3Si-H + R\cdot \rightarrow Cl_3Si\cdot + RH\end{array}\right\}\ \text{initiation}$$

$$\left.\begin{array}{l}Cl_3Si\cdot + CH_2=CH\ CH=CH_2 \rightarrow \\ [Cl_3SiCH_2\dot{C}HCH=CH_2 \leftrightarrow Cl_3SiCH_2CH=CH\dot{C}H_2] \\ \text{more stable} \\ Cl_3SiCH_2\dot{C}HCH=CH_2 + Cl_3Si-H \rightarrow Cl_3SiCH_2CH_2CH=CH_2 \\ \qquad + Cl_3Si\cdot\end{array}\right\}\ \text{propagation}$$

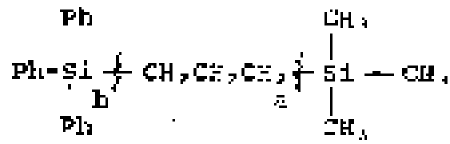
(e) $Cl_3Si\text{-}CH_2CH_2\text{-}SiCl_3$

This compound can be synthesized by substituting a $CH_2=CH_2$ group for hydrogen in Cl_3SiH and then continuing the reaction so that $Cl_3Si-CH=CH_2$ can further react with $HSiCl_3$. The reaction can be catalyzed by ultraviolet light:

$$Cl_3SiH + HC\equiv CH \xrightarrow{h\nu} Cl_3SiCH=CH_2$$

$$Cl_3SiCH=CH_2 + Cl_3SiH \xrightarrow{h\nu} Cl_3Si-CH_2-CH_2-SiCl_3$$

(f)



This compound can be synthesized by (a) substituting $-CH_2CH=CH_2$ for hydrogen in $(CH_3)_3SiH$ and then (b) reacting this with $(C_6H_5)_3SiH$. Therefore, a method of synthesis would be:

$$(CH_3)_3SiCl + CH_2=CH-CH_2MgBr \rightarrow (CH_3)_3Si-CH_2CH=CH_2 \xrightarrow{(C_6H_5)_3SiH} (CH_3)_3Si-CH_2CH_2CH_2Si(C_6H_5)_3$$

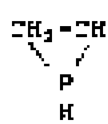
ORGANOPHOSPHORUS COMPOUNDS

• PROBLEM 29-5

Name the following compounds:

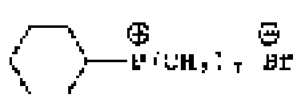
(a) $CH_3PHCH_2CH_3$

(b) $CH_3\underset{\underset{O}{\|}}{P}(C_6H_5)_2$

(c) 

(d) $P(OC_2H_5)_3$

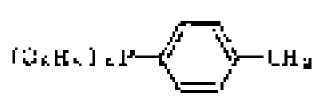
(e) $O=P(OC_2H_5)_3$

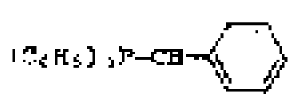
(f) 

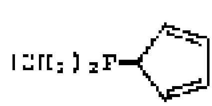
(g) $(C_6H_5)_2P-N(C_2H_5)_2$

(h) CH_3PHCl

(i) $(CH_3)_2CH\overset{O}{\overset{\|}{P}}Br_2$

(j) 

(k) 

(l) 

Solution: Organophosphorus compounds are named as derivatives of phosphorus hydrides, oxyacids, and oxides. The parent compounds (some of which are unstable) are:

(1) Phosphine - H_3P:

Ex.:

$$\begin{array}{c} C_2H_5 \\ | \\ CH_3P: \\ | \\ H \end{array}$$

methylethyl<u>phosphine</u>

(2) Phosphorane - H_5P

Ex:

$$\begin{array}{c} Ph \\ | \\ Ph-P-Ph \\ / \quad \backslash \\ Ph \quad\quad Ph \end{array}$$

pentaphenyl<u>phos</u><u>phorane</u>

(3) phosphinous acid - $\begin{array}{c} OH \\ | \\ H-P: \\ | \\ H \end{array}$

The esters of phosphinous acid, H_2POR, are phosphinites.

Ex:

$$\begin{array}{c} CH_3 \\ | \\ CH_3-P-OCH_3 \end{array}$$

methyl dimethylphosphinite.

(4) Phosphonous acid - $\begin{array}{c} H-P-OH \\ | \\ OH \end{array}$

The corresponding esters, $HP(OR)_2$, are phosphonites.

Ex:

$$\begin{array}{c} OCH_3 \\ / \\ CH_3-P: \\ \backslash \\ OCH_3 \end{array}$$

dimethyl methyl<u>phosphonite</u>.

(5) Phosphine oxide - $\begin{array}{c} H \\ H-P=O \\ H \end{array}$

Ex:

$$\begin{array}{c} C_2H_5 \\ | \\ CH_3-P=O \\ | \\ H \end{array}$$

methylethyl<u>phosphine oxide</u>.

(6) Phosphinic acid -

$$R-\underset{\displaystyle H}{\overset{\displaystyle OH}{P}}=O$$

Ex:

$$C_2H_5-\underset{\displaystyle Cl}{\overset{\displaystyle C_2H_5}{P}}=O$$

diethyl phosphinic chloride

Note that compounds having phosphorus halogen bonds or phosphoric-nitrogen bonds are considered to be acid chlorides or amides. More specifically, halogens and amines replace -OH groups, not hydrogens. Therefore, the above compound is diethylphosphinic chloride, with the chlorine replacing an -OH group and not diethylchlorophosphine oxide, with chlorine replacing a hydrogen.

(7) Phosphonic acid

$$H-\underset{\displaystyle OH}{\overset{\displaystyle OH}{P}}=O$$

The corresponding esters are phosphonates.

Ex:

$$H-\underset{\displaystyle OCH_3}{\overset{\displaystyle OCH_3}{P}}=O$$

dimethyl phosphonate

(8) Phosphorous acid -

$$HO-\overset{\displaystyle OH}{P}-OH$$

The corresponding esters, $P(OR)_3$, are phosphites.

Ex: $CH_3CH_2O-P(O-CH_2CH_3)(O-CH_2-CH_3)$ triethyl phosphite

(9) Phosphoric acid -

$$HO-\underset{\displaystyle OH}{\overset{\displaystyle OH}{P}}=O$$

The corresponding esters, $OP(OR)_3$, are phosphates.

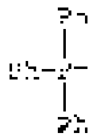
Ex:

$$CH_3-O-\underset{\displaystyle OH}{\overset{\displaystyle O}{\overset{\|}{P}}}-OH$$

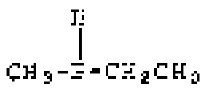
methyl phosphate

Note that there are two types of phosphoranes:

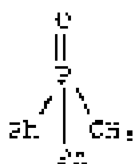
the simple variety (R_5P) is called a 'phosphorane,' while those that have pentacovalency through $d_\pi - p_\pi$ overlap are called alkylidenephosphoranes.

Ex:  ethylidenetriphenylphosphorane

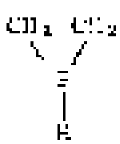
Now that we have reviewed the nomenclature, we can start to name the compounds.

(a) 

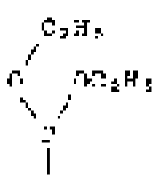
This is a phosphine derivative with two alkyl groups replacing two hydrogens, therefore, its name is methylethylphosphine.

(b) 

This compound is a phosphine oxide derivative, with a methyl group replacing a hydrogen and two phenyl groups replacing two hydrogens. Its name is diphenylmethylphosphine oxide.

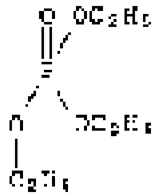
(c) 

This compound is a phosphine derivative, with an ethylene group replacing two hydrogens; this is analogous to the naming of ethylene oxide . Therefore, its name is ethylenephosphine. It is also sometimes called phosphirane.

(d) 

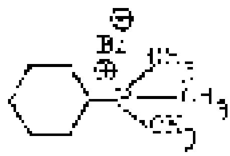
This compound is a phosphite derivative, with three ethyl groups replacing three hydrogens in the -OH groups. Therefore, its name is triethyl phosphite.

(e)



This is a phosphate derivative, with three ethyl groups replacing three hydrogens in the -OH groups. Therefore, its name is triethylphosphate.

(f)

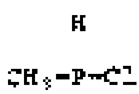


This is a phosphonium halide. There are three methyl groups and a cyclohexyl group attached to it, and therefore its name is trimethylcyclohexylphosphonium bromide.

(g)

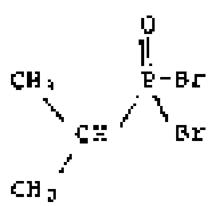
This is a phosphinous acid derivative, with an amino group replacing an -OH group, and two phenyl groups replacing two hydrogens. The amide group is a diethylamide, therefore its name is diphenylphosphinous diethylamide.

(h)



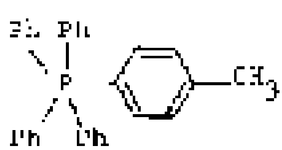
This is a chloride derivative of phosphinous acid, with a methyl group replacing a hydrogen, therefore its name is methylphosphinous chloride.

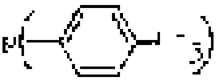
(i)



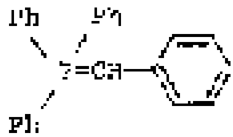
This compound is a dibromo derivative of phosphonic acid, with an isopropyl group replacing a hydrogen, therefore its name is isopropyl phosphonic dibromide.

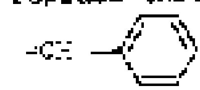
(j)



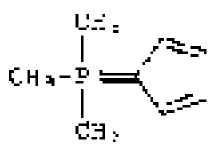
This compound is a phosphorane derivative. Four phenyl groups replace four hydrogens and a p-tolyl group () replaces the fifth hydrogen. Its name is tetraphenyl-p-tolylphosphorane.

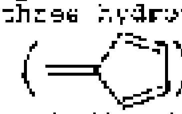
(k)



This compound is an alkylidenephosphorane derivative. Three phenyl groups replace three hydrogens and a doubly bonded benzyl group  replaces two hydrogens. Its name is benzylidenetriphenylphosphorane.

(l)



This compound is an alkylidenephosphorane derivative. Three methyl groups replace three hydrogens and a doubly bonded cyclopentadiene group () replaces two hydrogens. Its name is cyclopentadienylidenetrimethylphosphorane.

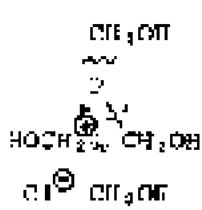
• PROBLEM 29-6

Phosphine reacts with formaldehyde in the presence of hydrochloric acid to produce tetrakis(hydroxymethyl)-phosphonium chloride, THPC. This material is used in flame-retardant finishes for cotton fabric. Suggest a mechanism for its formation.

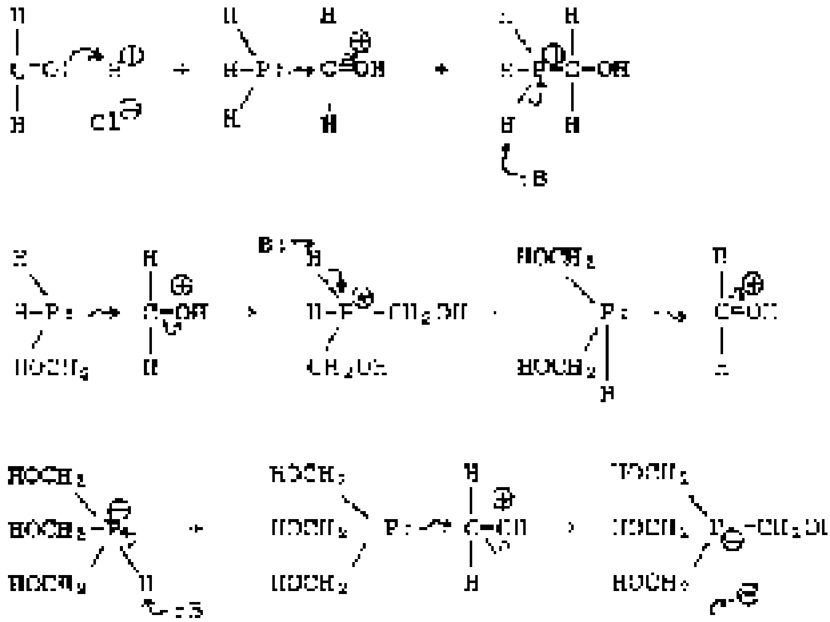
$$P^{\oplus}(CH_2OH)_4Cl^{\ominus}$$

THPC

Solution: The structure for tetrakis(hydroxymethyl) phosphonium chloride (THPC) is



We can see that this compound has four $-CH_2OH$ groups and a chlorine atom attached to phosphorus. The method for adding CH_2-OH groups is to react formaldehyde with phosphine:

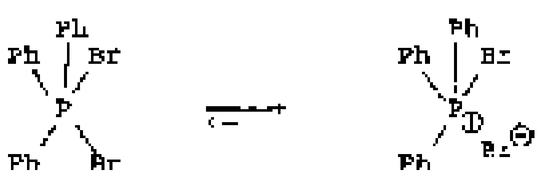


Note that this is just repeated reactions of nucleophilic phosphorus attacking the electrophilic carbonyl carbon of formaldehyde. As this sequence demonstrates, there is an analogy between amines and organophosphorus compounds in that both classes of compounds have a free pair of electrons that confer nucleophilicity. Phosphines are, in fact, better nucleophiles than amines because phosphorus is larger and more electropositive than nitrogen.

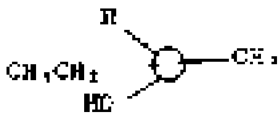
• PROBLEM 29-7

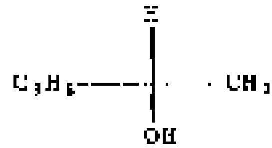
Predict the product of the reaction of (R)-2-butanol with triphenylphosphorus dibromide.

Solution: Triphenylphosphorus dibromide in solution exists mainly in the ionized form:



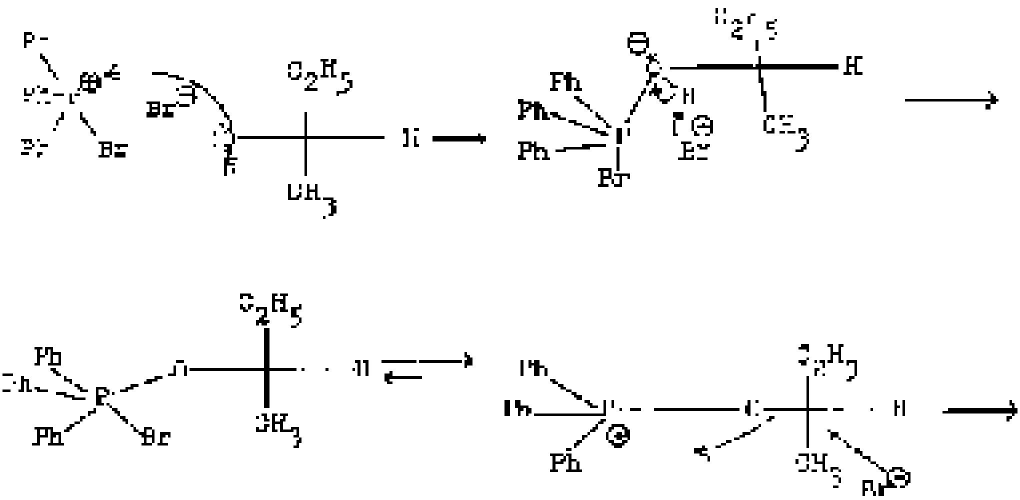
The configuration for (R)-2-butanol is:

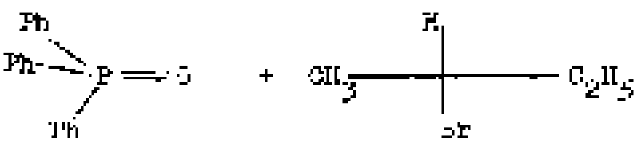




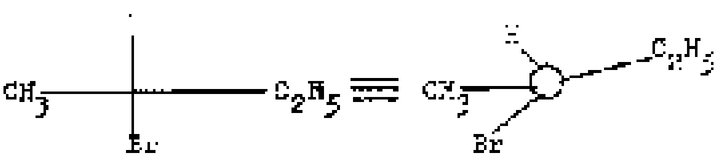
pictorial model   Fischer projection

Alcohols are good nucleophiles, while the phosphorus compound is a good electrophile, especially in the ionized state, therefore the reaction should proceed as follows:



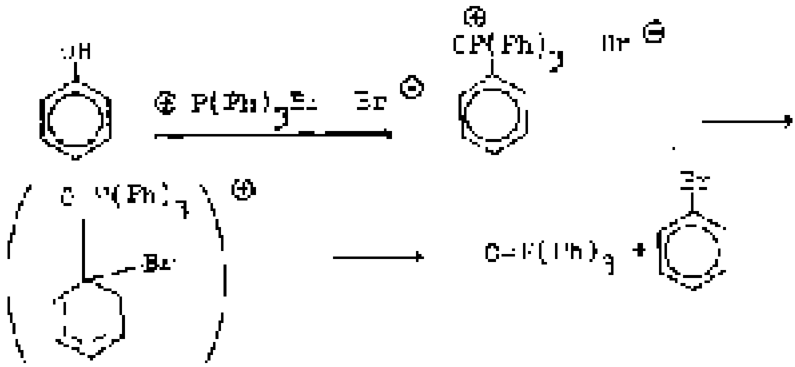


triphenylphosphine oxide   (S) - 2 - bromobutane



(S) -2 - bromobutane

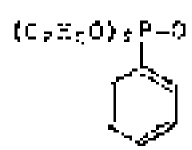
Inversion occurs when the bromide ion displaces the tetraphenylphosphine oxide group in an S_N2 displacement. The reaction is a useful method for converting alcohols to alkyl bromides. The driving force for this process is the immense stability of the P=O in the phosphine oxide product. This stability is the basis of the following reaction where we make the unusual conversion of phenol to aromatic halide.



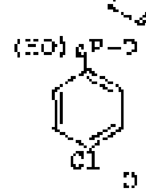
• PROBLEM 29-[illegible]

On the basis of the electronic structure of the phosphoryl group, predict the course of the following reactions.

(a) $(C_2H_5O)_2P{=}O$ + HNO_3 (fuming) $\xrightarrow{30-35°}$

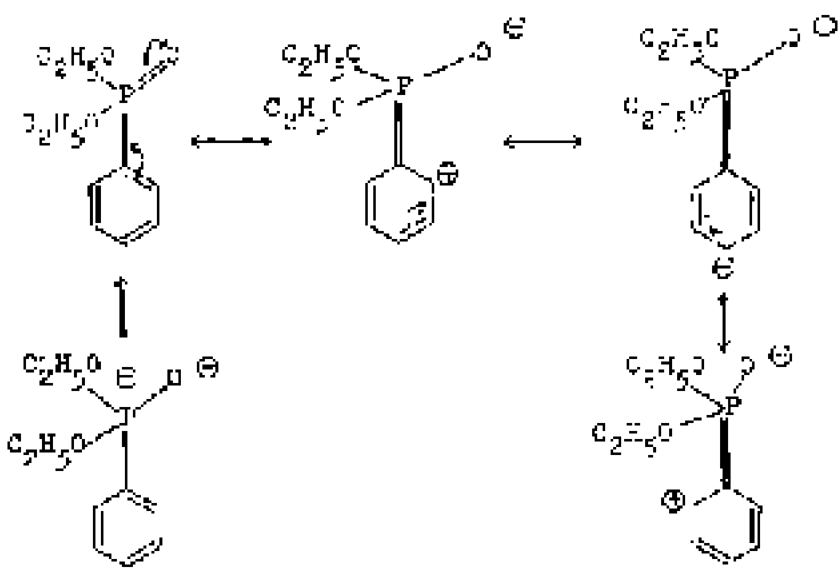


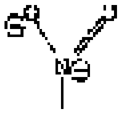
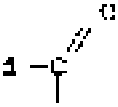
(b) $(HO)_2P{=}O$ + NH_3 $\xrightarrow[150°]{Cu_2O}$



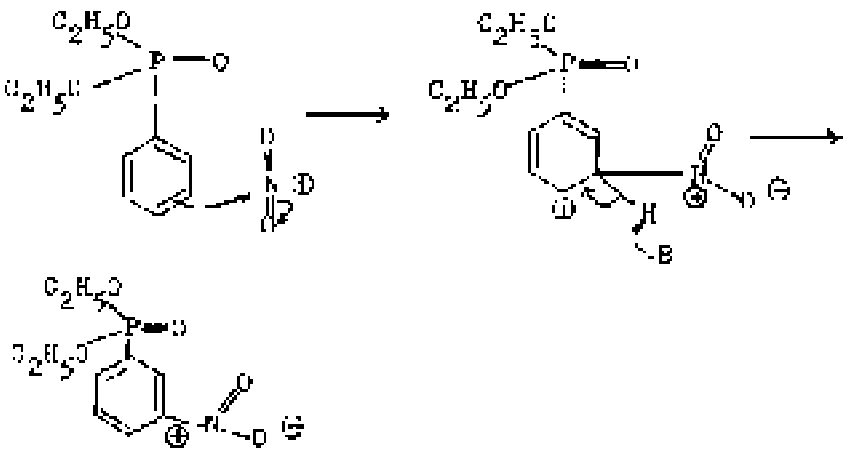
(c) $CH_2{=}CH{-}P(OC_2H_5)_2$ + $CH_2(CO_2C_2H_5)_2$ $\xrightarrow{NaOC_2H_5}$

Solution: The resonance structures for this compound are:



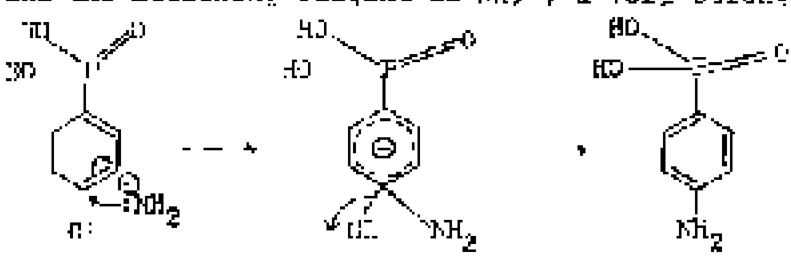
As we can see from the above figure, the phosphoryl group is an electron-withdrawing group (like  and ). When an electron withdrawing group is on a benzene ring, the effect on electrophilic aromatic substitution is deactivation and meta orientation. However, the effect on nucleophilic aromatic substitution is activation when the electron-withdrawing group is ortho or para to a potential leaving group.

This is an electrophilic aromatic substitution reaction and therefore the orientation should be meta:

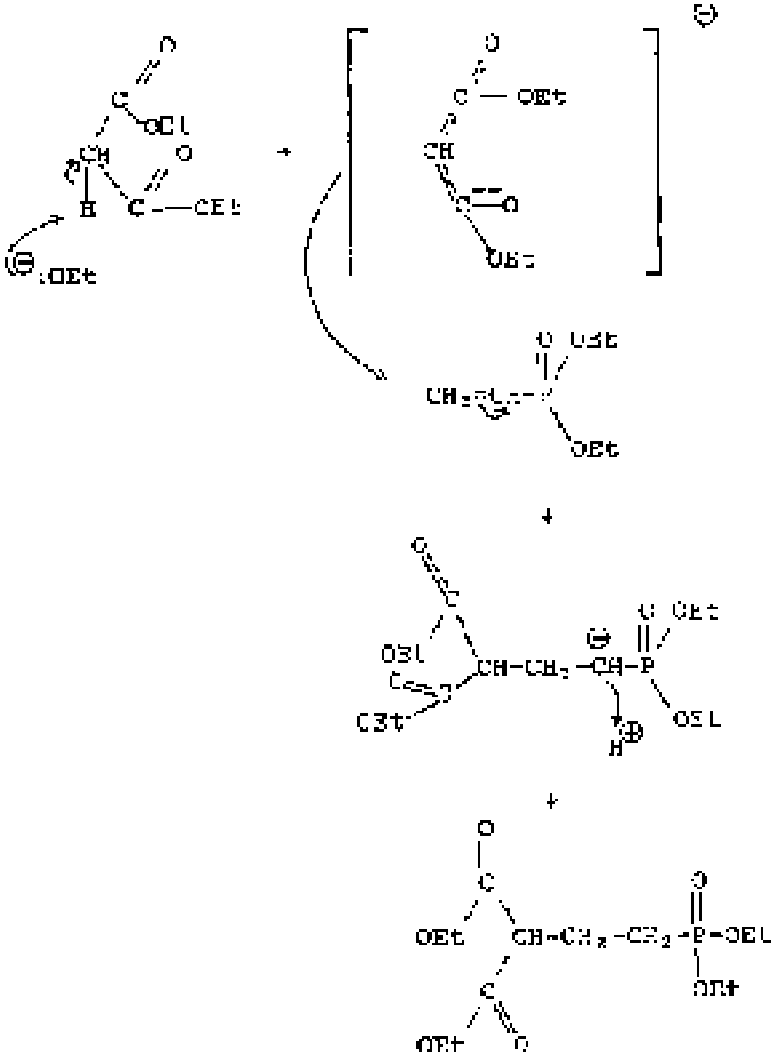


Notice that the attacking reagent is $NO_2^{\oplus}$.

(b) This reaction is a nucleophilic aromatic substitution reaction. The phosphoryl group is again electron-withdrawing and the attacking reagent is $NH_2^{\ominus}$, a very strong base:



(c) This reaction is a Michael-type addition. (Recall that a Michael addition is the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds.) The phosphoryl group acts like a carbonyl group. Therefore, the reaction is:



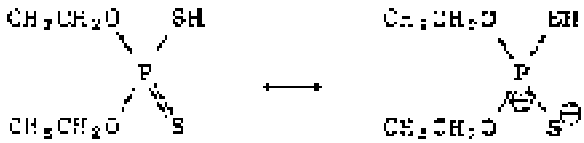
PROBLEM 28-8

Malathion, an insecticide of low toxicity to humans, is made by a Michael addition. Given the structure of malathion, suggest the immediate precursors for its synthesis.

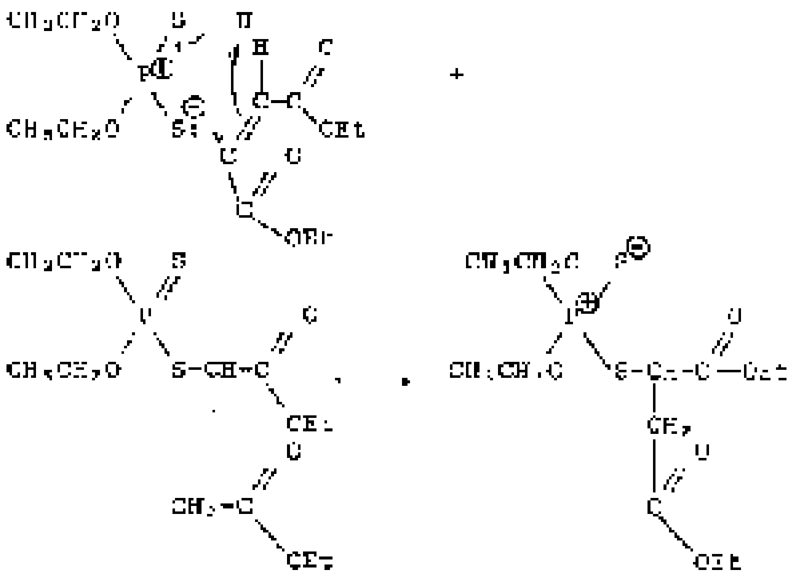
$$(CH_3CH_2O)_2\underset{\underset{S}{\|}}{P}-S-\underset{\underset{CH_2-CO_2Et}{|}}{CH}-CO_2Et$$

Solution: Michael additions involve the nucleophilic addition of carbanions to α,β-unsaturated carbonyl compounds.

The compound $(CH_3CH_2O)_2P(=S)SH$ has two important resonance structures:



The importance of the dipolar structure is due to the inherent weakness of the $p_\pi - d_\pi$ bond between phosphorus and sulfur. This bond is formed by the overlap of a 3d phosphorus orbital with a 3p sulfur orbital. The orbital overlap is poor and this bond has much dipolar character. The reaction to form malathion is:

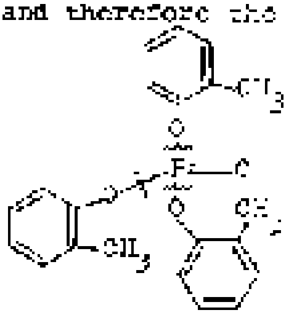


• PROBLEM 20-10

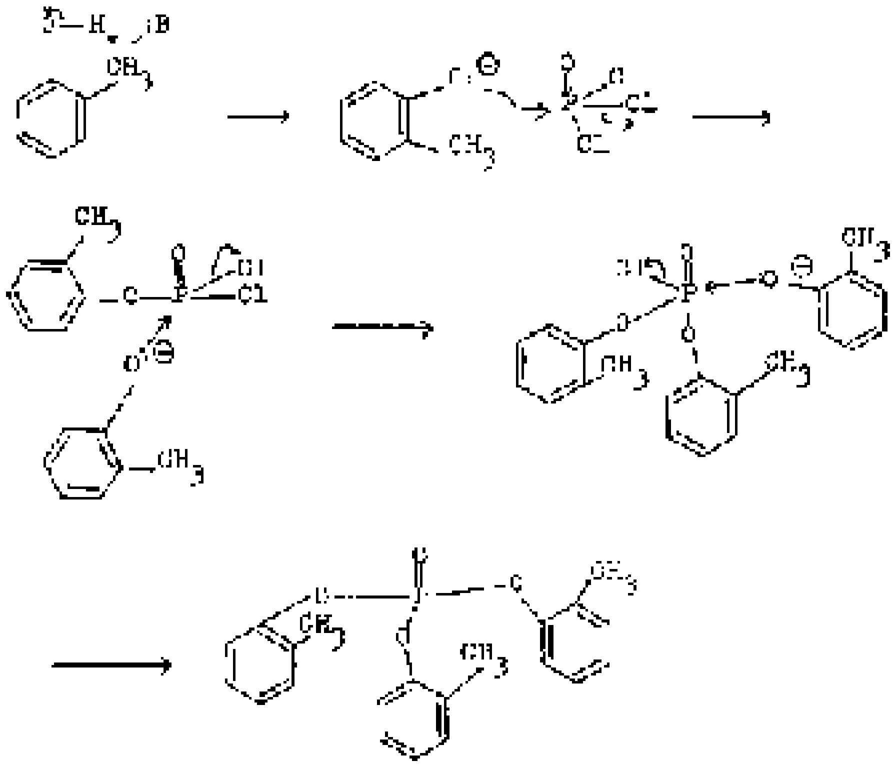
Tri-o-cresyl phosphate, $(o\text{-}CH_3C_6H_4O)_3PO$, is used as a gasoline additive. Suggest a preparation.

Solution: The structure for o-cresol is: 

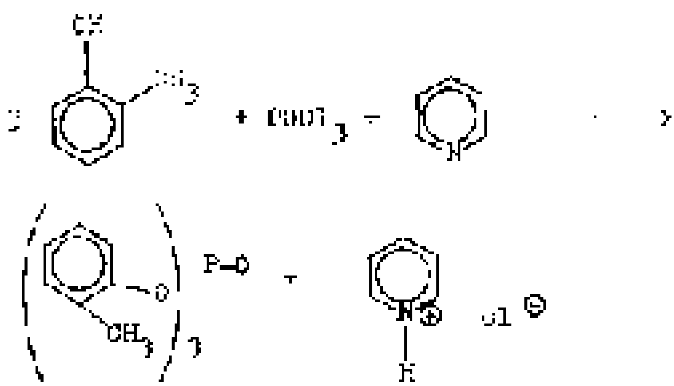
and therefore the structure for tri-o-cresyl phosphate is:



We see that this is a tri-substituted phosphoric acid. By using phosphorus oxychloride, we can make phosphorus an excellent electrophilic center since chloride ions are excellent leaving groups. This is analogous to the use of acid chlorides instead of the corresponding carboxylic acids in substitution reactions. Therefore, the reaction is:



The base used in this reaction produces the phenoxide anion which is more nucleophilic than the phenol itself. It also consumes the HCl produced which may cause side reactions such as hydrolysis of product. The net reaction is:



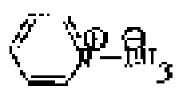
ORGANOBORON COMPOUNDS

• PROBLEM 29-11

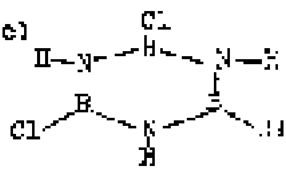
Write names for the following compounds.

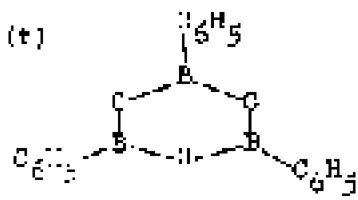
(a) $CH_2=CH-CH_2-B(CH_3)_2$

(b) $(C_2H_5)_2BHBH_2$

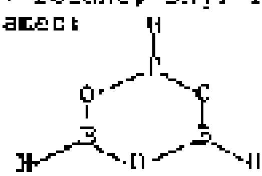
(c) 

(d) $(CH_3)_2N-B(CH_3)_2$

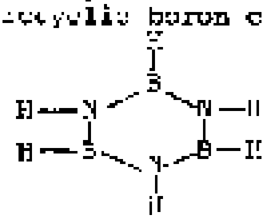
(e) 

(f) 

Solution: Organoboron compounds are named as derivatives of borane, BH_3. Two heterocyclic boron compounds have special names:

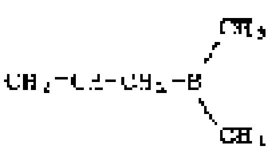


Boroxine

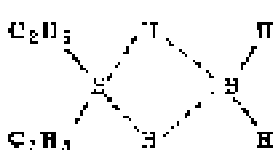


Borazine

However, many boron-oxygen compounds are still named as derivatives of boric acid, $B(OH)_3$; boronic acid, $HB(OH)_2$; and borinic acid, $(H_2B(OH))$. We will not use this method for naming boron-oxygen compounds.

(a) 

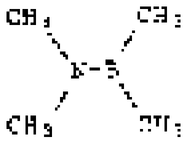
Two methyl groups replace two hydrogens and an allyl group ($-CH_2-CH=CH_2$) replaces the third hydrogen. Its name is allyldimethylborane.

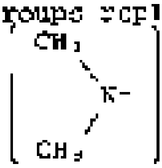
(b) 

There are two ethyl groups replacing two hydrogens on the first boron of this diborane molecule. Its name is 1,1-diethyldiborane.

(c) 

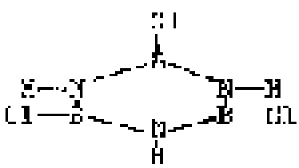
A pyridine is bonded to a borane molecule, therefore its name is pyridine borane.

(d) 

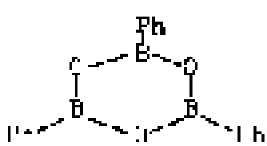
Two methyl groups replace two hydrogens while a dimethylamino group  replaces the third hydrogen.

Its name is dimethylaminodimethylborane.

(e)



Three chlorines replace the three hydrogens on the three borons of the borazine molecule. Notice that the hydrogens on the nitrogens can be replaced as well, therefore we must use B's to indicate that the chlorines are attached to the boron. Its name is B,B,B-trichloroborazine.

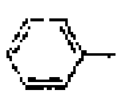
(f) 

Three phenyl groups replace three hydrogens on three borons. The oxygens have no hydrogens to be replaced, therefore the use of the B-prefix to indicate that the phenyl groups are on the borons is not necessary. Its name is triphenylboroxine.

• PROBLEM 29-12

Write structures for the principal products of the following reactions:

(a) $(CH_2=CH)_4Sn + BCl_3 \rightarrow$

(b)  $MgCl + BF_3 \rightarrow$

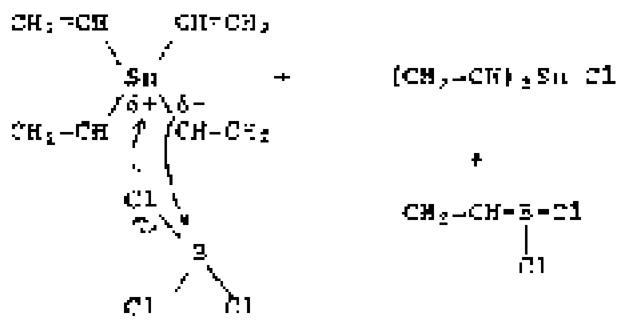
(c) $Br(CH_2)_4Br$ $\xrightarrow[\text{ether}]{Li}$ $C_4H_8BF_2$

(d) $(n\text{-}C_4H_9O)_3B + n\text{-}C_3H_7MgBr \rightarrow$

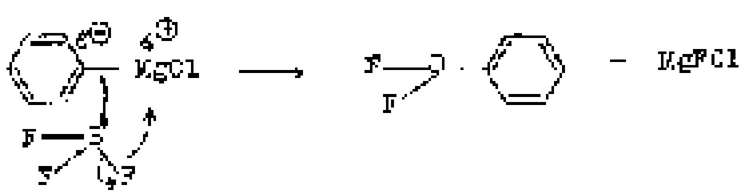
(e) $B(OC_2H_5)_3 + Al(C_2H_5)_3 \rightarrow$

Solution: Boron has three valence electrons, therefore it uses sp^2 bonding orbitals to form compounds of the type BX_3. Since boron, in these compounds, has only 6 electrons in three bonding orbitals, one bonding orbital is empty and boron is said to be "electron deficient." It is for this reason that boron has a high tendency to accept a pair of electrons, thereby filling this empty bonding orbital and thus attaining an octet of electrons. Since these boron compounds are accepting electron pairs, they are called Lewis acids. The chemistry of boron is best understood if we remember that boron compounds of the type BX_3 are usually Lewis acids.

(a) The alkyl groups in $(CH_2{=}CH)_4Sn$, like all alkyl groups in organometallic compounds, have considerable carbanion character, thus we would expect the alkyl group, in this case ethylene, to attack the electrophilic boron:

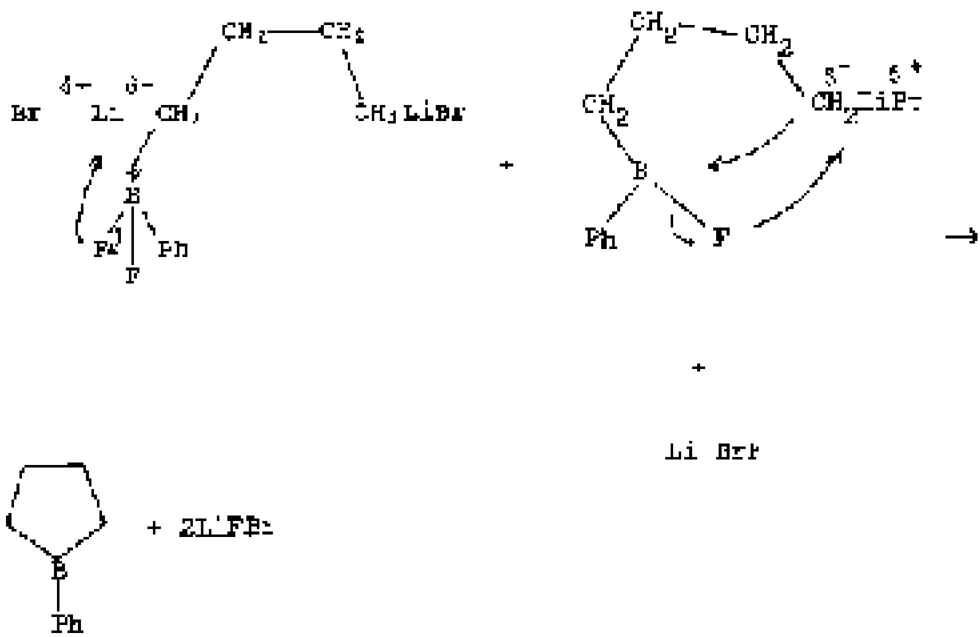


(b) The phenyl group of the Grignard reagent is again electron rich, therefore we would expect it to attack the electron deficient boron:

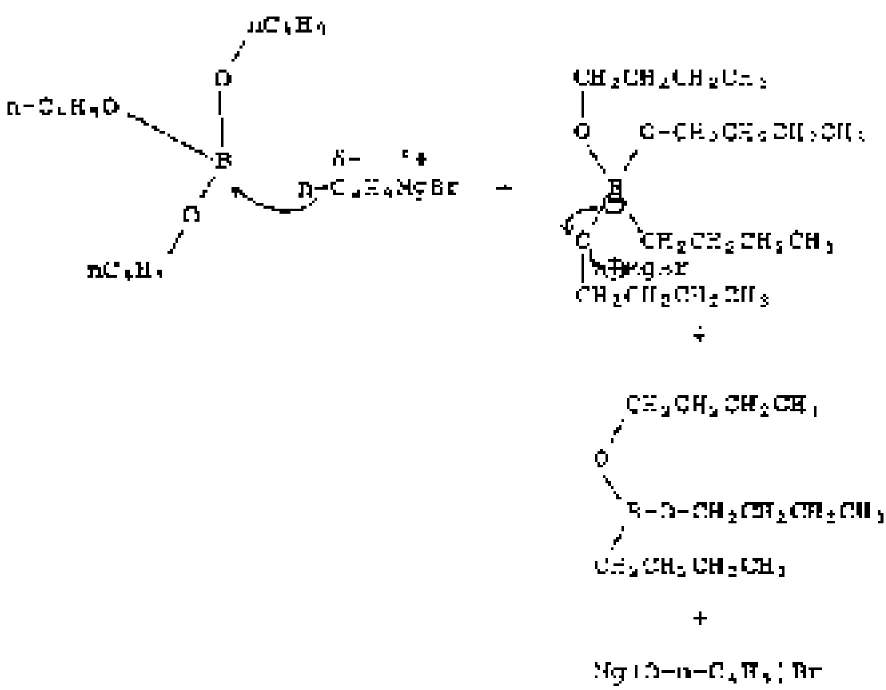


(c) The reaction of an alkyl halide with lithium yields an alkyllithium compound. This compound, like all organometallic compounds, has an electron rich alkyl group, which can attack the electron deficient boron:

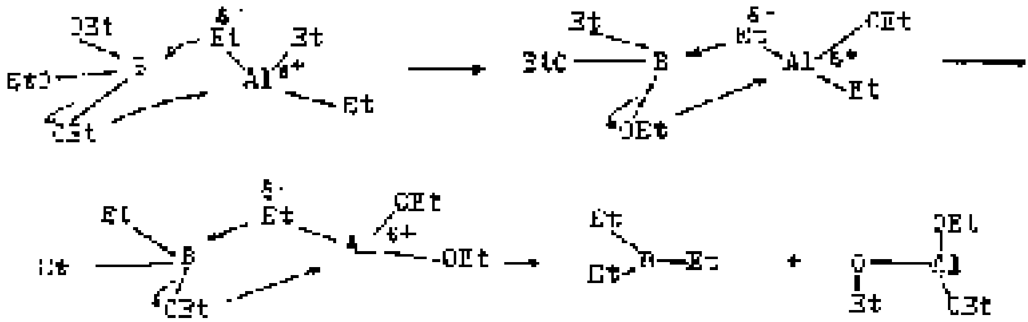
$$Br{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}Br \;+\; Li \xrightarrow{C_6H_5BF_2}$$



(d) This is again a reaction between an organometallic compound and a substituted borane. This time, the leaving group is an alkoxide:



(c) This again is a reaction involving an organometallic reagent and a substituted borane. The reaction is:



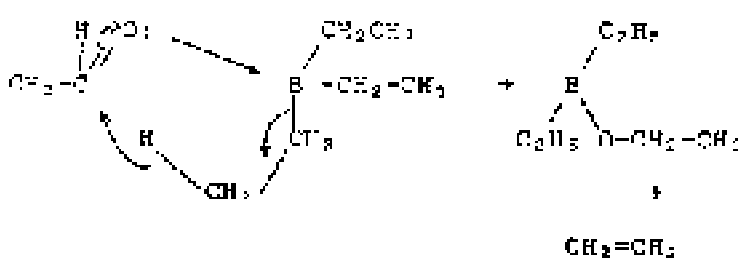
Note that whether one, two or three X groups are displaced depends on the amount of organometallic reagent used, on the nature of X and R, and on the reaction temperature. Alkyl aluminum compounds are useful for the synthesis of trialkylboranes, while organostannous compounds usually result in monosubstitution products.

• PROBLEM 25-13

Formulate a reasonable mechanism for the reduction of acetaldehyde by triethylborane to give ethoxydiethylborane.

$$CH_3CHO + B(C_2H_5)_3 \rightarrow CH_3CH_2OB(C_2H_5)_2 + CH_2{=}CH_2$$

Solution: From our knowledge of borane chemistry, a probable reaction between acetaldehyde and triethyl borane would be an attack by electron-rich oxygen on electron-deficient boron, with the subsequent expulsion of an ethyl anion. However, this is very unlikely due to the instability of the ethyl anion. But if a hydride ion can be transferred from the ethyl group, then the resultant ethylene molecule can be easily displaced. By looking at the arrangement of the atoms in the transition state, we will be able to see how this displacement can occur:



Notice that the arrangement of the molecules is such that the end hydrogen of the ethyl group is very close to the carbonyl carbon, allowing a hydride shift to occur.

• PROBLEM 29-14

The nuclear magnetic resonance spectrum of tetramethylsilane appears as a singlet at δ 0.00. Offer an explanation that accounts for the high field strength necessary to observe this resonance.

Solution: In a nuclear magnetic resonance spectrum (nmr), a molecule is placed in a magnetic field. This causes the electrons to circulate, thereby generating a secondary magnetic field. This induced magnetic field about the proton opposes the applied field, therefore the field which the proton "feels" is diminished and the proton is said to be shielded. The more electronegativity an atom that is attached to hydrogen has, the greater is the pull of the electrons away from the hydrogen; this effect increases the field felt by the proton and the proton is said to be deshielded. Compared with a naked proton, a shielded proton requires a higher applied field strength, while a deshielded proton requires a lower applied field strength, in order for the proton to "feel" a particular field strength at which absorption occurs. Therefore shielding shifts the absorption upfield, while deshielding shifts the absorption downfield. The magnetic field value where a proton does absorb is its chemical shift.

A high field strength is necessary to observe the resonance of tetramethylsilane (TMS) because silicon is electropositive relative to hydrogen, therefore the protons in TMS are shielded: $\overset{\delta+}{Si}\ \overset{\delta-}{H}$. Silicon, in fact, is more electropositive than carbon, nitrogen, oxygen and most other atoms that are associated with organic chemistry. The reason for silicon's high electropositivity is due to silicon's position in the periodic table; it occupies a position on the border between metals and non metals (metals are electropositive relative to non-metals). In essence, TMS protons absorb upfield relative to most other organic molecules. All twelve TMS protons are equivalent, therefore only a single peak is seen in its nmr spectrum. This is the reason why the signal from TMS protons is used as the reference point (δ 0.00) from which chemical shifts are measured.

• PROBLEM 29-15

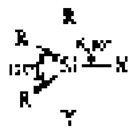
Pentacovalent phosphorus compounds normally have trigonal-bipyramidal structures. In such structures the more electronegative substituents show a strong preference for the apical positions. With these facts in mind, suggest an explanation for the following data obtained by nuclear magnetic resonance studies.

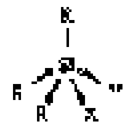
CH_3PF_4: one kind of methyl
one kind of fluorine

$(CH_3)_2PF_3$: one kind of methyl
two kinds of fluorines in the ratio 2:1

$(CH_3)_3PF_2$: one kind of methyl
one kind of fluorine

Hint:


Trigonal bipyramid

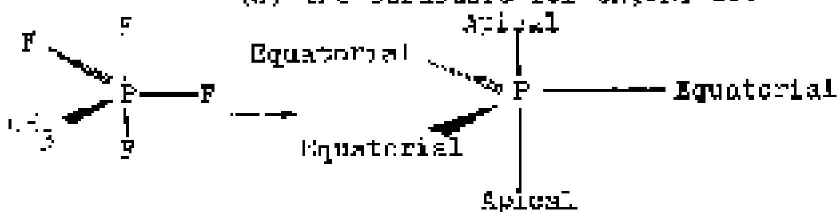

Tetragonal pyramid

Interchange of Apical and Equatorial Substituents: As a reaction of a given molecule proceeds along the reaction coordinate, the nuclei (and electrons) assume positions corresponding to the minimum possible free energy. These positions must be the same in the forward and reverse reactions; that is, both the forward and reverse reactions must occur by the same mechanism. This is called the principle of microscopic reversibility. Note that in the trigonal bipyramid shown, the leaving and entering groups (X and Y) do not occupy like positions; X is in an equatorial position and Y is in an apical position. If this were the transition state it would imply that in the forward reaction a group Y would enter from the apical direction and in the reverse reaction a similar group X would enter from the equatorial direction. Such a situation is unlikely to obtain. We can get out of this dilemma by suggesting that a process termed pseudo-rotation occurs. By pseudo-rotation, a trigonal-bipyramid molecule is transformed by deforming bond angles in such a way that the molecule appears to have been rotated by 90°. In the following illustration the group toward the observer remains fixed while the apical (vertical) groups are pushed backwards (transforming a 180° bond angle to a 120° bond angle) and the remaining two equatorial groups are pulled forward and apart slightly (transforming a 120° bond angle to a 180° bond angle).

Note that this process of pseudo rotation results in an interchange of apical and equatorial substituents. Because of the principle of microscopic reversibility, a trigonal bipyramid with an entering and leaving group occupying unlike positions is not likely to represent a transition state, but more probably represents a metastable intermediate of sufficient lifetime to undergo pseudo-rotation.

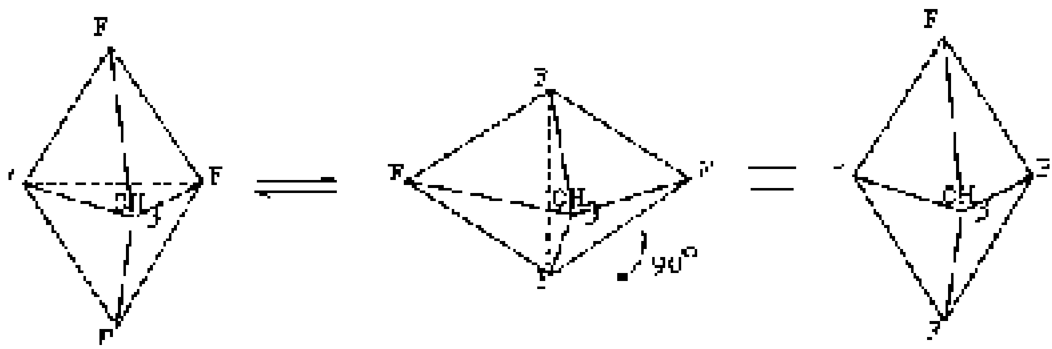
Solution:

(a) The structure for CH_3PF_4 is:



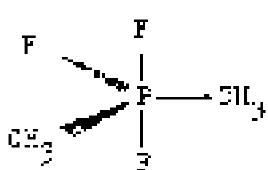
Trigonal bipyramid

Although there appears to be two sets of fluorine atoms (one set at the apical positions, the other set at the equatorial positions), this is not the case; pseudo-rotation converts the apical fluorines into equatorial fluorines in a rapid equilibrium. Using the method described in the information above, we can see that the methyl group, being less electronegative than fluorine, is not involved in this pseudo-rotation. That is, it stays at the equatorial position:

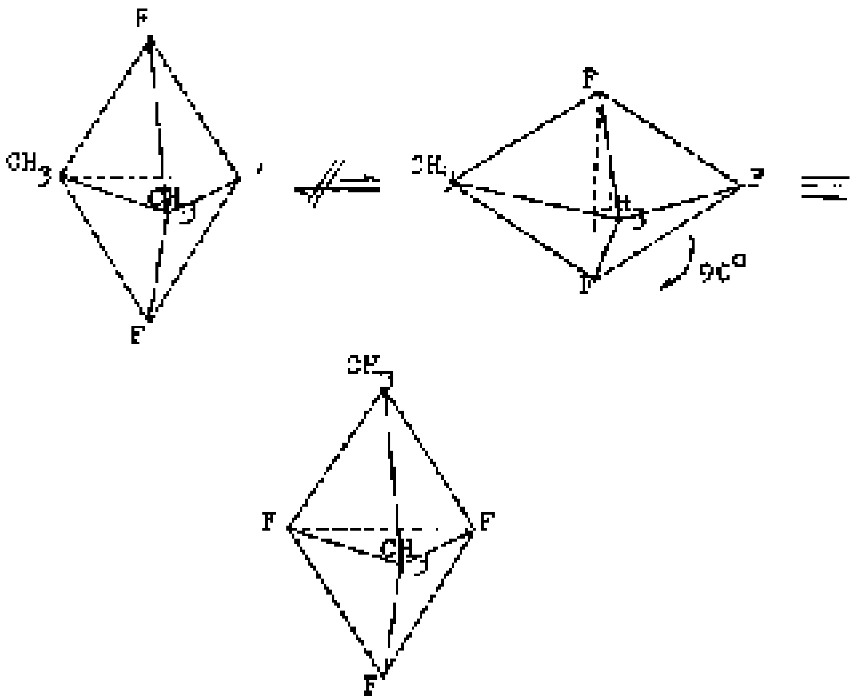


Since this interconversion of the fluorines is rapid, the nmr spectrum signals show only one kind of fluorine and one kind of methyl group.

(b) In $(CH_3)_2PF_3$, both methyl groups are equatorial, while two fluorines are apical and one fluorine is equatorial:

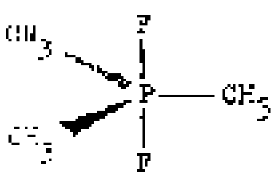


Pseudo-rotation, in this case, would require placing at least one methyl group in the apical position; placing methyl groups in the apical position instead of the more electronegative fluorines is not favored. Therefore pseudo-rotation is inhibited:



Therefore interconversion of apical fluorines with the equatorial fluorine is not possible. The result is one kind of methyl and two kinds of fluorine in the ratio of 2:1 on the nmr spectrum.

(c) In $(CH_3)_3PF_2$, all three methylgroups are equatorial, and both fluorines are apical:



No pseudo-rotation occurs for the same reasons as in part (b) of this question, therefore there is one kind of methyl and one kind of fluorine in the nmr spectrum.

CHAPTER 30

FATS

• PROBLEM 30-1

Trimyristin is a white crystalline fat, m.p. 54-55°, obtainable from nutmeg, and is the principal constituent of nutmeg butter. Hydrolysis of trimyristin with hot aqueous sodium hydroxide gives an excellent yield of myristic acid, m.p. 52-53°, as the only fatty acid. What is the structure of trimyristin?

Solution. Fats are triacylglycerols, that is, they are carboxylic esters derived from glycerol, $HOCH_2CHOHCH_2OH$. Fats have the general structure:

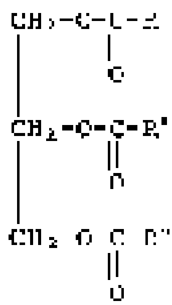
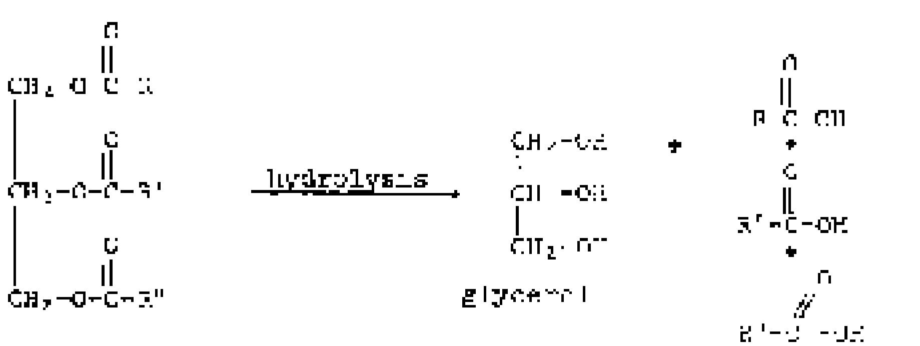


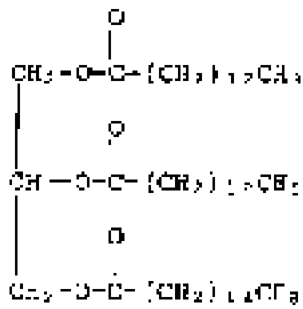
Fig. 1 - A triacylglycerol (glyceride)

Hydrolysis of a fat will yield the three corresponding fatty acids, and a molecule of glycerol:



three fatty acids

In trimyristin, hydrolysis yields myristic acid as the only fatty acid, therefore all three fatty acids in trimyristin must be myristic acid:



trimyristin

FATTY ACID BIOSYNTHESIS AND OXIDATION

• PROBLEM 30-8

In 1904, Franz Knoop outlined a scheme for the biological oxidation of fatty acids that was shown - 50 years later - to be correct. In his key experiments, he fed rabbits fatty acids of formula $C_6H_5(CH_2)_nCOOH$. When the side chain (n + 1) contained an even number of carbons, a derivative of phenylacetic acid, $C_6H_5CH_2COOH$, was excreted in the urine; an odd number, and a derivative of benzoic acid was excreted. What general hypothesis can you formulate from these results?

Solution: We will use fatty acids with side chains of three and four carbons, to answer this question:

For a fatty acid with four carbons in its side chain, we must cleave off two carbons to get the product:

$$Ph\,CH_2\,CH_2 \wr CH_2\,\overset{O}{\overset{/\!/}{C}}-OH \longrightarrow Ph\,CH_2\,\overset{O}{\overset{/\!/}{C}}-OH$$

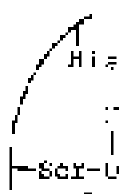
For a fatty acid with three carbons in its side chain, we again must cleave off two carbons to get the product:

$$Ph-CH_2 \wr CH_2-\overset{O}{\overset{/\!/}{C}}-OH \longrightarrow Ph-\overset{O}{\overset{/\!/}{C}}-OH$$

By extending this argument to five, six, seven, eight, and an n number of carbons in its side chain, we can conclude that the biological oxidation of fatty acids removes two carbons at a time, starting at the carboxyl end. This is called beta-oxidation. Our conclusion is reasonable considering that the biosynthesis of fatty acids is by acetic acid units, that is, fatty acids are built up two carbons at a time.

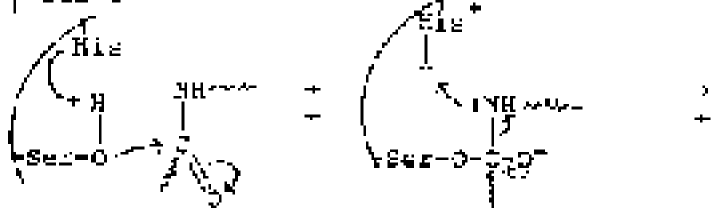
Carbon dioxide is required for the conversion of acetyl CoA into fatty acids. Yet when carbon dioxide labeled with ^{14}C is used, none of the labeled carbon appears in the fatty acids that are formed. How do you account for these facts?

Solution: The role of carbon dioxide in the conversion of acetyl CoA into fatty acids is that of a catalyst, in that it is regenerated at the end of the reaction. We must remember that every reaction in this synthesis is catalyzed by a specific enzyme. Enzymes enable an organism to carry on reactions that are otherwise impossible under physiological conditions. Enzymes are stereospecific, therefore reactions can occur at one reactive center without affecting another reactive center. The manner in which enzymes work is very complex, however, an example of an enzyme catalysis will help to illustrate the organic chemical principles by which enzymes work:



active site of the enzyme chymotrypsin

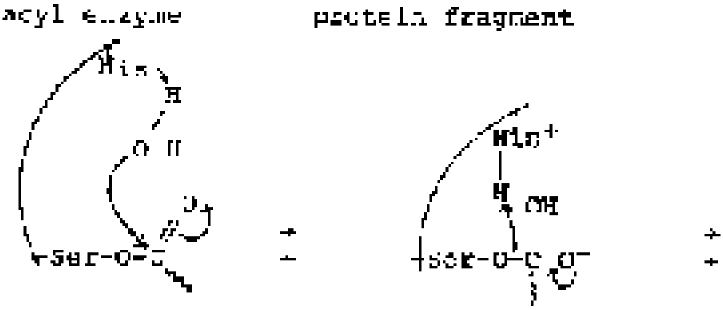
(a)



enzyme protein

acyl enzyme protein fragment

(b)



acyl enzyme

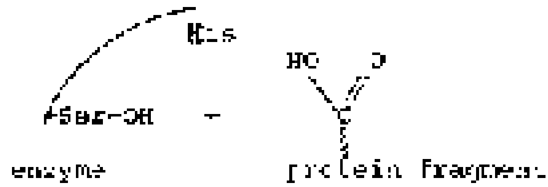


Fig. 1 – Catalysis by the enzyme chymotrypsin of the cleavage of one peptide bond in a protein.

This proposed mechanism shows:

(a) cleavage of protein with histidine and protonated histidine acting as base and acid, respectively, in two successive nucleophilic substitution reactions;

(b) hydrolysis of acyl fragment with regeneration of the enzyme.

$$(1)\quad CH_3\overset{O}{\overset{\|}{C}}OH + CoA{-}SH \rightarrow CH_3\overset{O}{\overset{\|}{C}}{-}S{-}CoA + H_2O$$

acetic acid coenzyme A acetyl CoA

This step is a thiol-carboxylic acid reaction to yield a thioester.

$$(2)\quad CH_3{-}\overset{O}{\overset{\|}{C}}{-}S{-}CoA + \overset{*}{C}O_2 \xrightarrow{base} \xrightarrow{H^+} \overset{*}{C}(=O){-}OH \;\; CH_2{-}\overset{O}{\overset{\|}{C}}{-}S{-}CoA$$

malonyl CoA

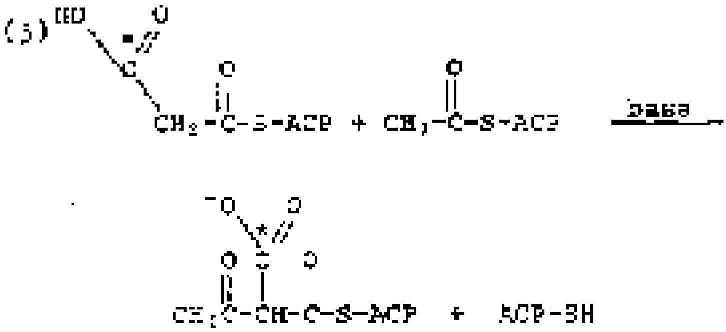
This step is a carboxylation reaction. It is made possible by the acidity of the α-hydrogen (the hydrogen on the carbon next to $-\overset{O}{\overset{\|}{C}}-$).

In the remaining steps the carrier, CoA, is replaced by an acyl carrier protein (ACP). ACP is a small protein with a prosthetic group quite similar to CoA.

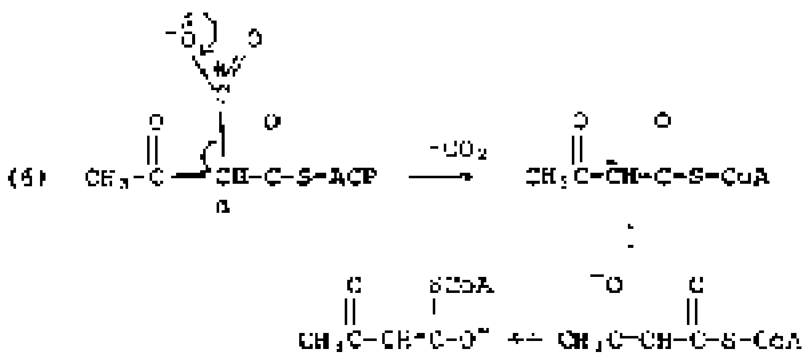
$$(3)\quad CH_3{-}\overset{O}{\overset{\|}{C}}{-}S{-}CoA + ACP{-}SH \rightarrow CH_3\overset{O}{\overset{\|}{C}}{-}S{-}ACP + CoA{-}SH$$

$$(4)\quad HO{-}\overset{O}{\overset{\|}{C}}{}^{*}{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}S{-}CoA + ACP{-}SH \rightarrow \underset{HO}{\overset{O}{\overset{\|}{{}^{*}C}}}{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}S{-}ACP + CoA{-}SH$$

These last two reactions are transesterification reactions where ACP replaces CoA.



This is a Claisen-type condensation.



This is a decarboxylation reaction. This reaction is possible due to the β-keto thioester's ability to accommodate a negative charge on the α carbon. The initial $^*CO_2$ is regenerated in this step, therefore no labeled carbons will appear in the fatty acids that are formed.

DETERGENTS

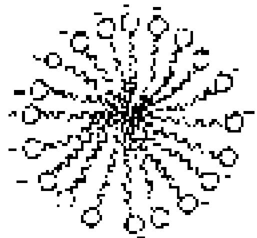
• PROBLEM 30-4

Which of the following compounds would exhibit detergent properties?

(a) $CH_3(CH_2)_{10}CH_2\overset{+}{N}(CH_3)_3Cl^-$
(b) $CH_3(CH_2)_{13}CH_2COO^-$
(c) $CH_3(CH_2)_{10}CH_2SO_3^-Na^+$

<u>Solution</u>: Soaps and detergents are composed of molecules that contain large hydrocarbon groups (non polar or hydrophobic) and one or more polar groups (hydrophilic). This type of molecule is called amphipathic; it has both polar and non polar ends. Since "like dissolves like", the non-polar ends stay together while the polar ends project into the polar solvent, water. This system is called a micelle:

Fig. 1: A soap or detergent micelle



a soap or detergent molecule

Dirt is contained in oil or grease; the non polar ends of the detergent molecules dissolve in the oil droplet, while the polar ends project into the surrounding water. Repulsion between similar charges of the polar ends prevents the oil droplets from coalescing; the result is a stable emulsion of oil and water. Since the cleansing property of detergents is completely dependent on its amphipathic properties, a detergent molecule must therefore be amphipathic. The only molecules that are amphipathic are (a) and (c):

(a) $$\underbrace{CH_3(CH_2)_{10}CH_2}_{\text{non-polar end}}\;\underbrace{\overset{CH_3}{\underset{CH_3}{N^+}}-CH_3\;Cl^-}_{\text{polar end}}$$

(c) $$\underbrace{CH_3(CH_2)_{10}CH_2}_{\text{non-polar end}}\;\underbrace{SO_3^-Na^+}_{\text{polar end}}$$

Note that the polar end of an ester (b) is not charged, therefore micelle formation is not possible.

LIPIDS

• PROBLEM 30-6

From saponification of cerebrosides, lipids found in the membranes of brain and nerve cells, there is obtained nervonic acid. This acid rapidly decolorizes dilute $KMnO_4$ and Br_2/CCl_4 solutions. Hydrogenation in the presence of nickel yields tetracosanoic acid, $n\text{-}C_{23}H_{47}COOH$. Vigorous oxidation of nervonic acid yields one acid of neutralization equivalent 156 ± 3 and another acid of neutralization equivalent 137 ± 2. What structure or structures are possible for nervonic acid?

Solution: Since nervonic acid rapidly decolorizes dilute $KMnO_4$ and Br_2/CCl_4 solutions, we know that this compound contains carbon carbon double bonds.

Hydrogenation in the presence of nickel yields tetracosanoic acid, $n\text{-}C_{23}H_{47}COOH$, with a molecular weight (MW) of 368. Since the vigorous oxidation of nervonic acid yields two different carboxylic acids, there must have been only one carbon-carbon double bond in nervonic acid. This is because a carboxylic acid possessing n carbon-carbon double bonds will be oxidized into n + 1 carboxylic acids:

$$C_x\text{-}C{=}C\text{-}C_y\text{-}C{=}C\text{-}C_z\text{-}COOH \xrightarrow{[O]} C_x\text{-}COOH + HOOC\text{-}C_y\text{-}COOH +$$

$$HOOC\text{-}C_z\text{-}COOH$$

Note: x, y and z may or may not be equal.

Nervonic acid must be a straight chain monocarboxylic acid because its hydrogenation product is also straight chained. Hence nervonic acid is oxidized to a straight chained monocarboxylic acid and a straight chained dicarboxylic acid. The MW of tetracosanoic acid ($n\text{-}C_{23}H_{47}\text{-}COOH$) is 368; nervonic acid must have a molecular formula of $n\text{-}C_{23}H_{45}\text{-}COOH$ with a MW of 366. This is because it contains only one carbon-carbon double bond. The MW of a dicarboxylic acid is twice its neutralization equivalent (NE). If the dicarboxylic acid produced by the oxidation of nervonic acid has an NE = 156 ± 3, its MW = 312 ± 6. The MW of a monocarboxylic acid is equal to its NE. Hence the MW of the monocarboxylic acid produced by oxidation of nervonic acid would be 137 ± 2. Addition of the MW's of the two acids should give us the MW of nervonic acid plus 64 (four times the weight of oxygen):

$$n\text{-}C_a\text{-}\overset{\overset{\large H}{|}}{C}{=}CH\text{-}C_b\text{-}COOH \xrightarrow{[O]} n\text{-}C_a\text{-}COOH + n\text{-}HOOC\text{-}C_b\text{-}COOH$$

nervonic acid

Note: a + b = 21.

MW nervonic acid + 64 = MW mono-acid + MW di-acid

$$366 + 64 = (312 \pm 6) + (137 \pm 2)$$

$$430 \neq 449 \pm 8$$

We find that an inequality (above) arises and hence the dicarboxylic acid must have the NE of 137 ± 2. The MW of the dicarboxylic acid would be 274 ± 4. The MW of the monocarboxylic acid would be 156 ± 3. Applying these values to our equation gives us:

$$366 + 64 = (274 \pm 4) + (156 \pm 3)$$

$$430 = 430 \pm 7$$

This equality confirms our conclusions: the di carboxylic acid has a MW of 274 ± 4 and the monocarboxylic acid has a MW of 156 ± 3. We will now figure out the molecular formula of the acids:

Monocarboxylic acid: $C_mH_{2m+1}COOH$

MW = 12(m) C + 1(2m+1) H + 45 (1) COOH

MW = 14 m + 46

156 ± 3 = 14m + 46

m = 8

Monocarboxylic acid: n-$C_8H_{17}COOH$, n-nonanoic acid;

NE = MW = 158.

Dicarboxylic acid: $C_mH_{2m}(COOH)_2$

MW = 12(m) C + 1(2m) H + 45 (2) COOH

MW = 14 m + 90

274 ± 4 = 14 m + 90

m = 13

Dicarboxylic acid: n-HOOC-$C_{13}H_{26}$-COOH, n-pentadecanedioic acid;

NE = $\frac{1}{2}$ MW = 136.

Since the oxidation of nervonic acid cleaved its lone carbon-carbon double bond to yield two carboxylic acids, the joining of these two acids should give us the structure of nervonic acid. In joining these acids, we must remove four oxygens to give us the carbon carbon double bond of nervonic acid.

n-C_8H_{17}COOH   HOOC-n$C_{13}H_{26}$-COOH

$\downarrow$

n-C_8H_{17}—CH=CH-n$C_{13}H_{26}$-COOH

Nervonic acid (cis and trans)

As we can see, both the cis and trans structures are possible; it is actually the trans isomer that is called nervonic acid. The hydrogenation and oxidation reactions were as follows:

$$CH_3(CH_2)_7-CH=CH-(CH_2)_{13}-COOH$$

nervonic acid

$$\xrightarrow{H_2/Ni} CH_3(CH_2)_7-CH_2-CH_2-(CH_2)_{13}-COOH$$

tetracosanoic acid

$$\xrightarrow{[O]} CH_3(CH_2)_7COOH \quad +$$

nonanoic acid

$$HOOC-(CH_2)_{13}-COOH$$

pentadecanedioic acid

• PROBLEM 30-6

Spermaceti (a wax from the head of the sperm whale) resembles high-molecular weight hydrocarbons in physical properties and inertness toward Br_2/CCl_4 and $KMnO_4$; on qualitative analysis it gives positive tests only for carbon and hydrogen. However, its infrared spectrum shows the presence of an ester group, and quantitative analysis gives the empirical formula $C_{16}H_{32}O$.

A solution of the wax and KOH in ethanol is refluxed for a long time. Titration of an aliquot shows that one equivalent of base has been consumed for every 475 ± 10 grams of wax. Water and ether are added to the cooled reaction mixture, and the aqueous and ethereal layers are separated. Acidification of the aqueous layer yields a solid A, m.p. 62-3°, neutralization equivalent 260 ± 5. Evaporation of the ether layer yields a solid B, m.p. 48-9°. Reduction by $LiAlH_4$ of either spermaceti or A gives B as the only product. B is normal alcohol. What is the structure of spermaceti?

Solution: Spermaceti is inert toward Br_2/CCl_4 and $KMnO_4$, therefore there are no carbon-carbon double bonds. From the infrared spectrum, we know that there is an ester group $\left(\begin{array}{c} O \\ \| \\ C-OR \end{array}\right)$.

Its empirical formula is $C_{16}H_{32}O$; for saturated mono-esters, the empirical formula is $C_{\frac{n}{2}}H_nO$ (where n is the number of carbons); therefore we know that this compound is a monoester. Monoesters have two oxygens, therefore the molecular formula is twice its empirical formula: $C_{32}H_{64}O_2$.

Upon hydrolysis of spermaceti with KOH in ethanol, we get two compounds, A and B. Upon extraction with water and ether, compound A is found in the aqueous layer, while compound B is found in the ether layer. Since esters hydrolyze to form an acid and an alcohol:

$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow{KOH} \xrightarrow{H^+} R-C\begin{matrix}\nearrow O \\ \searrow OH\end{matrix} + R'OH$$

Compound A must be the acid, which is polar, and compound B must be the long-chained alcohol, since it is nonpolar. Reduction of compound A by $LiAlH_4$ yields compound B, therefore the backbone of B and C must be the same. By dividing the number of carbons by two, we get the molecular formula of A and B:

$$C_{15}H_{31}-C\begin{matrix}\nearrow O \\ \searrow OH\end{matrix} \qquad\qquad C_{15}H_{31}-CH_2-OH$$

A B

Since we know that B is a straight chain alcohol, A must be a straight chain acid. Using this information, we get the structure of spermaceti:

$$n-C_{15}H_{31}-\overset{O}{\overset{\|}{C}}-OH \quad (A) \quad \underset{\xleftarrow{KOH}}{\xrightarrow{H^+}} \quad n-C_{15}H_{31}-\overset{O}{\overset{\|}{C}}-O-CH_2-C_{15}H_{31}-n$$

Hexadecanoic acid
(Palmitic acid)
M.p. 63°
N.E. = M.W.=256

spermaceti
n Hexadecyl hexadecanoate
M.E. = M.W. = 480

+

$n-C_{15}H_{31}-CH_2OH$ (B)

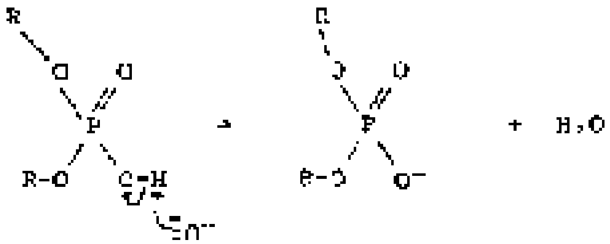
1-Hexadecanol

$$n-C_{15}H_{31}-\overset{O}{\overset{\|}{C}}OH \xrightarrow{LiAlH_4} n-C_{15}H_{31}-CH_2OH$$

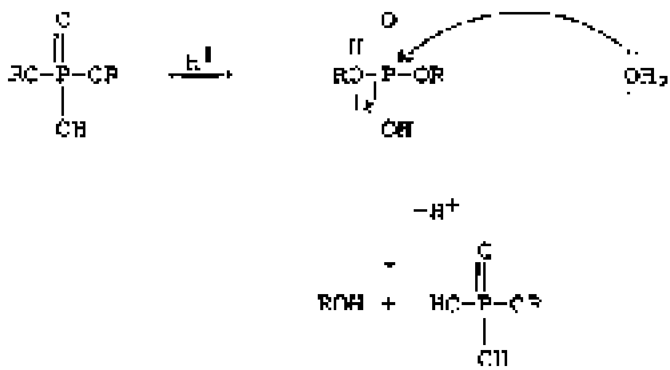
• **PROBLEM** 30-7

Consider hydrolysis of $(RO)_2PC(OH)$ by aqueous hydroxide, and grant that for electrostatic reasons attack by ^-OH cannot occur. Even so, why does not attack by the nucleophile water lead to hydrolysis? After all, water is the successful nucleophile in acidic hydrolysis.

Solution: Before we can answer this question, let us look at the structure of $(RO)_2PO(OH)$ in basic solution:



The diester of phosphoric acid, like phosphoric acid, is an acid. In basic solution, it will lose a proton to form an anion. Therefore, this negatively charged species would repel the negatively charged hydroxide ion. Attack by the nucleophilic water would not lead to hydrolysis because alkoxides are poor leaving groups. Water is a successful nucleophile in acid hydrolysis because the leaving group, in that case, is an alcohol, which is a good leaving group.

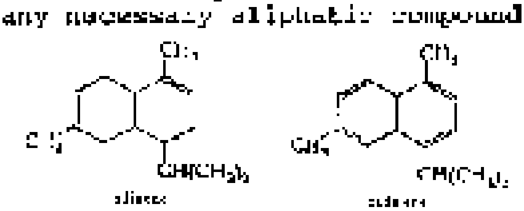


OILS

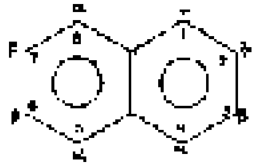
• PROBLEM 30-8

Cadinene, $C_{15}H_{24}$, is a sesquiterpene occurring in the essential oils of junipers and cedars. Dehydrogenation gives the naphthalene hydrocarbon cadalene.

(a) What is the IUPAC name for cadalene.
(b) Give a rational synthesis of cadalene from toluene and any necessary aliphatic compounds.

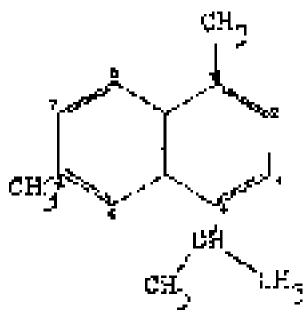


Solution: Cadalene is a naphthalene derivative. The numbering system for naphthalene is:



Naphthalene

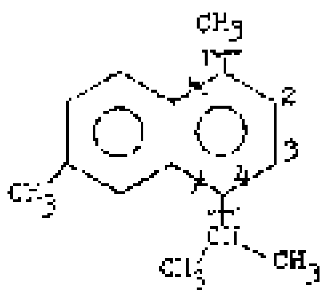
Two isomeric monosubstituted naphthalenes are differentiated by the prefixes 1- and 2-, or α- and β-. For more highly substituted naphthalenes, the arrangement of the substituents is indicated by numbers. Since there are three substituent groups on the naphthalene ring of cadalene, we must use the number system:



cadalene

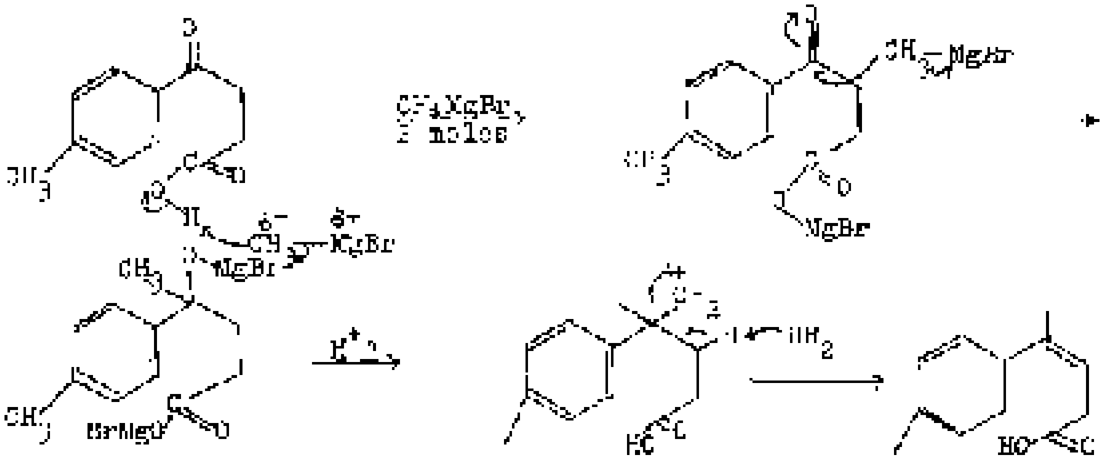
Therefore, the IUPAC name for cadalene is 1,6-dimethyl-4-isopropylnaphthalene.

(b) In order to synthesize cadalene from toluene, we must attach a second ring to toluene. This can be accomplished by adding a four-carbon compound to toluene.

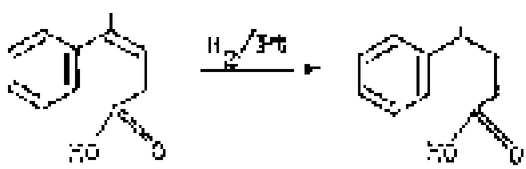


This four-carbon compound must maintain reactive groups at positions one and four after substitution, in order to attach the corresponding substituents on these carbons. A possible four-carbon compound is succinic anhydride:

This step is a Friedel-Crafts acylation reaction, with toluene acting as the nucleophile.



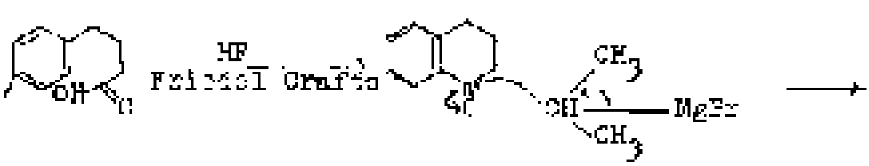
Note that in this Grignard reaction, the first mole of methyl magnesium bromide reacts with the carboxylic acid to form $-\overset{O}{\overset{\|}{C}}-OMgBr$, which is inert to further attack by CH_3MgBr. Acidification of the salt yields the corresponding acid. This process also protonates the alcohol, resulting in an elimination reaction.

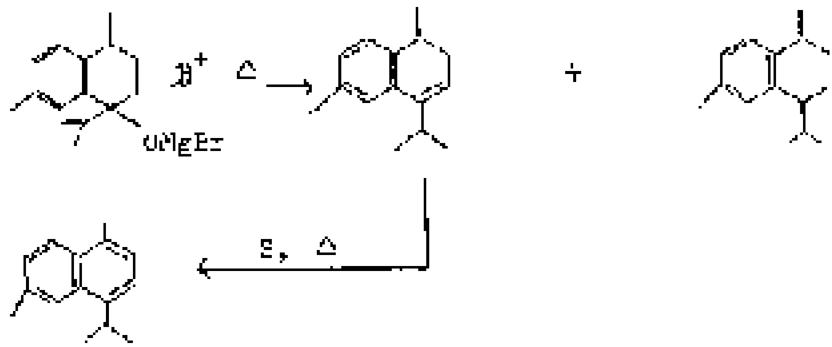


Note that hydrogenation at this point is important. If we did not hydrogenate before ring closure, we would obtain a substituted naphthol, instead of a ketone:

Fig. 1 - The phenol is the favored product (instead of the ketone), due to the stability of the aromatic ring.

A ketone is required in order to attach an isopropyl group to the corresponding carbon via a Grignard reagent:



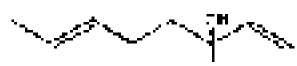


cadalene

The last step of this synthesis is aromatization, accomplished in this case by sulfur.

• PROBLEM 30-9

Suggest a plausible mechanism for the biosynthesis of linalool(A).

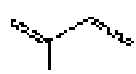
(A) 

Linalool

(lavender oil)

Solution: Linalool is a terpene, therefore it is separable into isoprene units:

linalool



isoprene

Therefore, our goal is to synthesize an isoprene-like compound, and then combine two molecules of it in a "head-to-tail" orientation. As in the case of fatty acid biosynthesis, we start with acetyl-CoA:

$$(1)\quad 2\ \underset{\alpha}{CH_3}\overset{O}{\overset{\|}{C}}-S-CoA \longrightarrow CH_3-\underset{\beta}{\overset{O}{\overset{\|}{C}}}-\underset{\alpha}{CH_2}-\overset{O}{\overset{\|}{C}}-S-CoA$$

Acetyl-CoA $\qquad$ Acetoacetyl-CoA

This is a Claisen-like condensation, that is, two thioesters condense to form a β-keto thioester. (Recall that a thioester is the sulfur analog of esters: $-\overset{O}{\overset{\|}{C}}-O-R$ vs. $-\overset{O}{\overset{\|}{C}}-S-R$). Claisen condensations are dependent on the acidity of the α-hydrogen. As in the case of other biochemical reactions, the basis of this reaction can be understood by general organic chemical concepts:

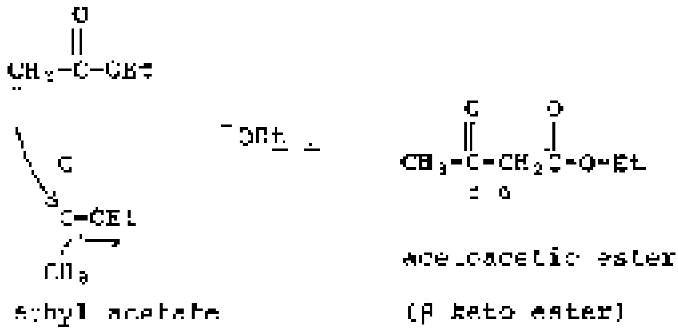
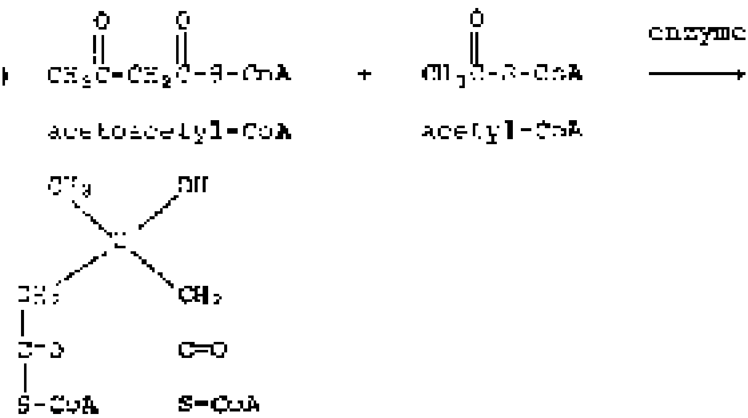


Fig. 1 Claisen Condensation (Et = $-C_2H_5$)

(2)



This is an aldol condensation. An aldol condensation involves two molecules of a carbonyl compound which combine to form a β hydroxy carbonyl:

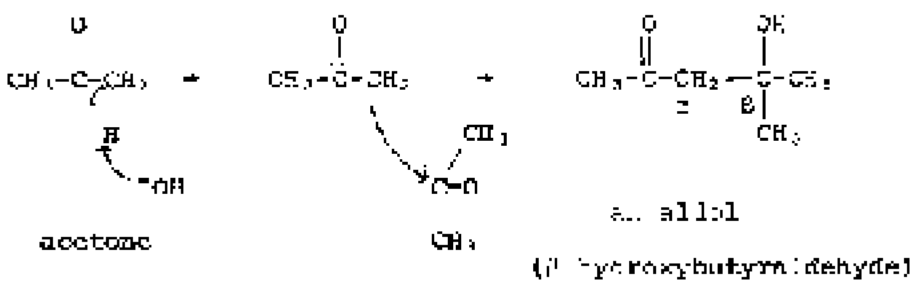
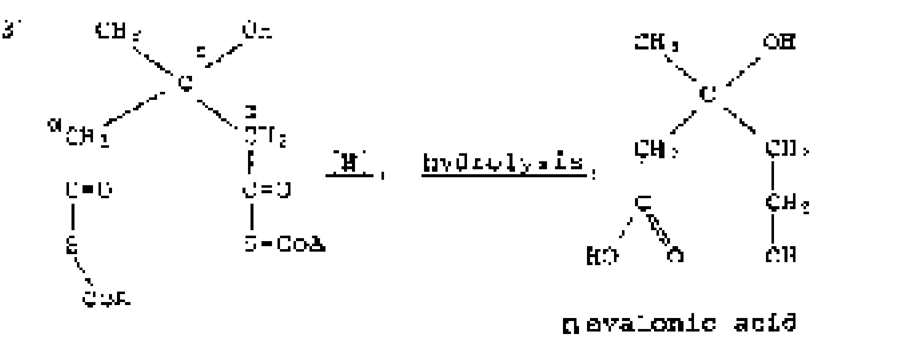
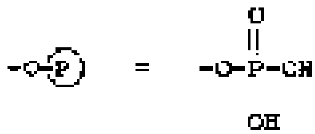


Fig. 2 - Aldol Condensation

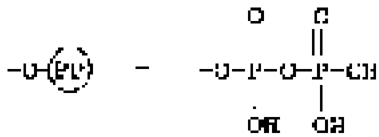
(3)



Mevalonic acid is the universal precursor of all terpenes. At this point, we must introduce two symbols that are used extensively in biochemistry:



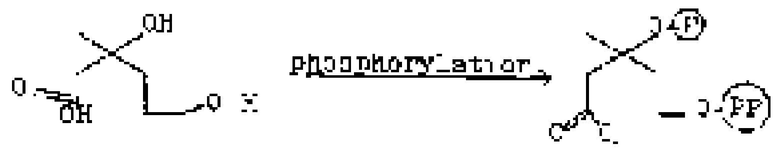
(phosphate)



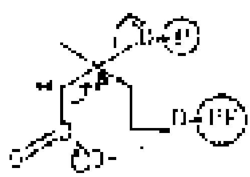
(pyrophosphate)

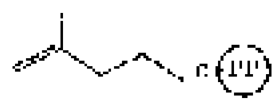
Nature uses phosphate and pyrophosphate as good leaving groups, just as organic chemists use sulfonate esters and halides as good leaving groups. In the next step of this biosynthesis, mevalonic acid is phosphorylated:

(4)



(5)





3 isopentenyl pyrophosphate
(3-IPP)

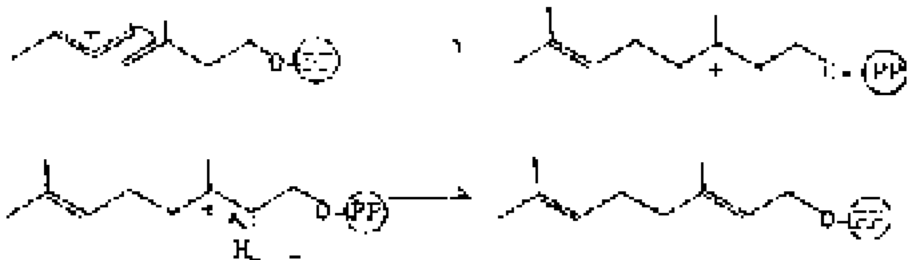
This step is a decarboxylation reaction made possible by the good leaving group, phosphate, on the β-carbon. The compound 3-isopentenyl pyrophosphate, is an isoprene unit attached to a pyrophosphate. We must dimerize the isoprene units in an orientation consistent with linalool; to accomplish this, 3-IPP must isomerize to 2-IPP:

3-IPP

2-IPP

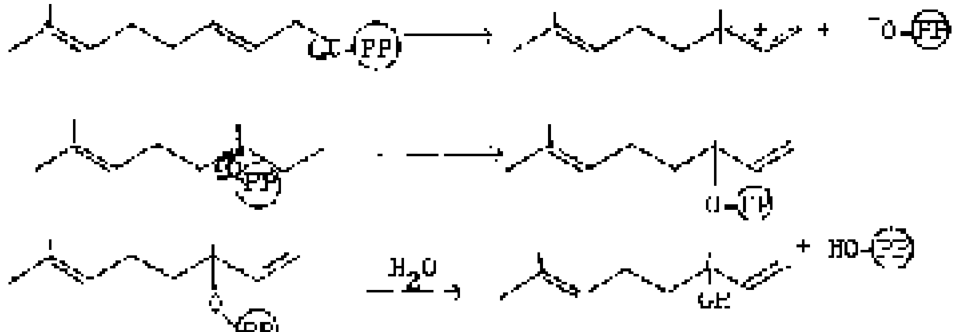
Since pyrophosphate is a good leaving group, it leaves to form the resonance stabilized allylic cation:

This allylic cation then reacts with 3-IPP to form geranyl pyrophosphate:



geranyl pyrophosphate

Again, pyrophosphate leaves to form the corresponding allylic cation. Reattachment of the pyrophosphate at the tertiary position, followed by hydrolysis will yield linalool:

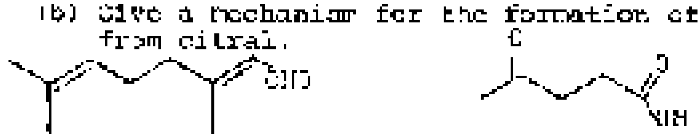


linalool

• PROBLEM 30-10

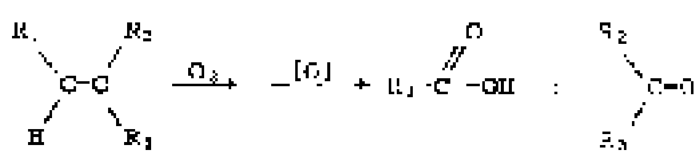
Citral is the major constituent of lemon grass oil. When citral is heated for some hours with dilute aqueous alkali, it is converted into a neutral oil ($C_8H_{14}O$). Ozonolysis of this oil, followed by oxidative workup, yields acetone and levulinic acid.

(a) What is the structure of the alkali transformation product from citral?
(b) Give a mechanism for the formation of this compound from citral.



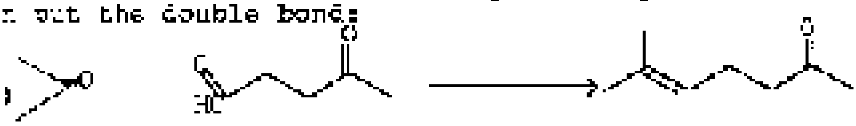
Citral   levulinic acid

Solution: Ozonolysis followed by oxidative workup cleaves double bonds to form ketones and carboxylic acids:

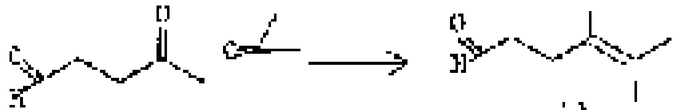


R≠H

Since ozonolysis, followed by oxidative workup of the alkali transformation product yields levulinic acid and acetone, we need only connect two carbonyl carbons with double bonds to get the structure of the transformation product. However, there are two possible places where we can put the double bond:

(1) 

acetone   levulinic acid   (A)

(2) 

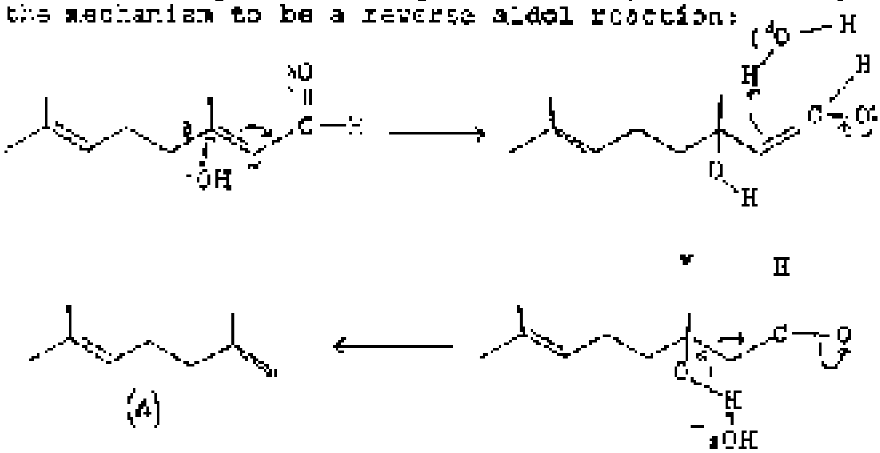
(B)

Note that if there was an aldehyde group on the transformation product, it would be oxidized to an acid after ozonolysis, followed by oxidative workup.

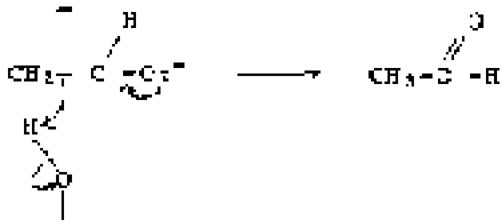
Looking at the structure of citral, we can eliminate structure B. Therefore, the structure of the transformation product is:

(A)

(d) Comparing the structure of citral with A, we see that citral (an α-β unsaturated carbonyl compound) is the product of a condensation reaction of A with acetaldehyde, specifically, an aldol condensation, followed by acid dehydration. Therefore, in order to transform citral to compound A in aqueous alkali, we would expect the mechanism to be a reverse aldol reaction:

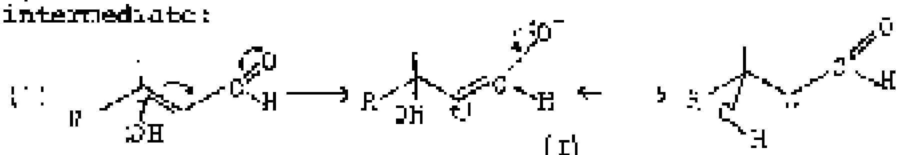


(A)



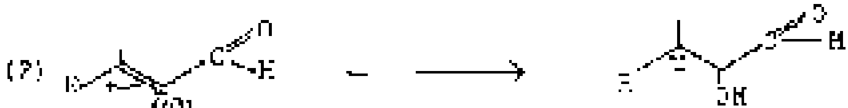
Note that attack by OH^- occurs at the β-carbon, instead of the α carbon; attack at the end of a conjugated system (β-carbon in this case) yields the most stable intermediate:

(1)



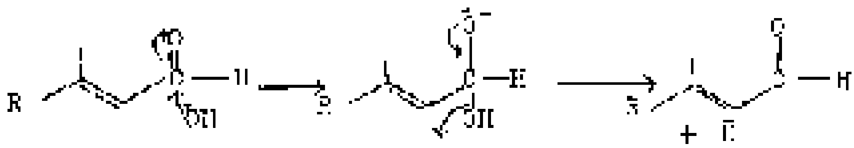
(I)
resonance stabilized intermediate

(2)



(II)
bad intermediate

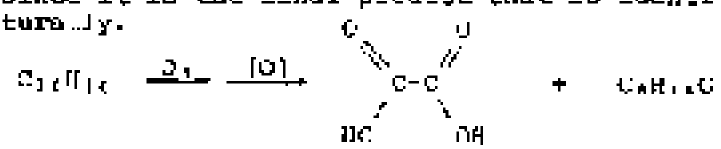
Not only is intermediate I resonance stabilized, but its negative charge is on oxygen; oxygen is able to accommodate a negative charge better than carbon. Attack at the carbonyl carbon would yield the initial reactant since hydride ions are very poor leaving groups:



• PROBLEM 30-11

An oil with the pleasant odor of lemons, α-terpinene, has been isolated from the marjoram plant. It has the formula $C_{10}H_{16}$. Upon ozonolysis, followed by an oxidative workup, it yielded two compounds: oxalic acid and a neutral compound having the formula $C_8H_{14}O_2$. When oxidized with sodium hypochlorite, the latter was converted to an acidic compound having the formula $C_7H_{12}O_3$. This acidic compound was identified as 5-methyl-4-oxo hexanoic acid. What is the structure of α-terpinene?

Solution: In doing problems of this type, it is best to outline the general synthesis, then work backwards, since it is the final product that is identified structurally.



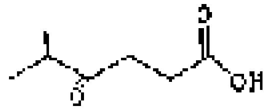
α-terpinene Oxalic acid B

$\downarrow$ NaOCl

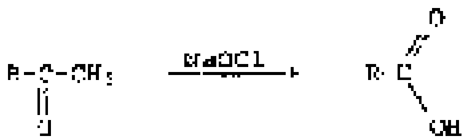
$C_7H_{12}O_3$

5-methyl-4-oxo-hexanoic acid

The structure of 5-methyl-4-oxo-hexanoic acid is:



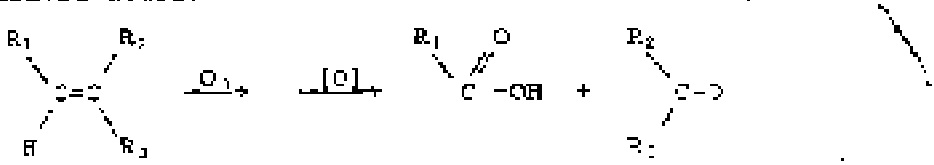
In order to get this compound, we reacted D with NaOCl, which is a hypohalite. Hypohalites oxidize methyl ketones in the general reaction:



Applying this reaction to our compound, we get the structure for compound D:

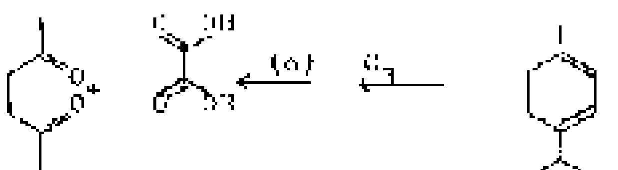
D

In order to get compound B, α-terpinene had to undergo ozonolysis, followed by oxidative workup. This reaction cleaves double bonds to form ketones and carboxylic acids:



Ref!

Since the dicarboxylic acid and compound B are the products of α-terpinene ozonolysis, we can put double bonds where the carbonyl carbons are, to get the structure of α-terpinene. Notice that all the oxygens in oxalic acid and compound B are the result of ozonolysis because α-terpinene is a hydrocarbon (there are no oxygens in α-terpinene). Oxalic acid is a symmetrical molecule, therefore there is only one way that we can put in the double bonds:



α-terpinene

As we can see, α terpinene belongs to the class of terpenes, specifically monoterpenes (monoterpenes are isomeric hydrocarbons of the composition $C_{10}H_{16}$; they are found in the essential oils of many plants). Like all terpenes, α-terpinene follows the isoprene rule, that is, it is formally into isoprene units:

isoprene (C_5H_8)

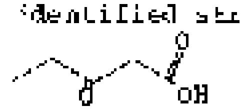
α-terpinene ($C_{10}H_{16}$)

The dashed lines show isoprene units.

• PROBLEM 30-12

A compound named γ-terpinene, an isomer of α-terpinene, is isolated along with the α isomer from the oils of a number of plant products. Upon ozonolysis, followed by an oxidative workup, γ-terpinene yields two compounds, one of which is 4-methyl-3-oxopentanoic acid. The second compound is an acid which decarboxylates upon heating and gives acetone. Two structures consistent with the data are possible for γ-terpinene. What are they? On the basis of the isoprene rule, one of them can be discarded as highly improbable. What is the structure of γ-terpinene?

Solution: In doing problems of this type, it is best to outline the general synthesis, then work backwards, since it is the final product that is identified structurally.

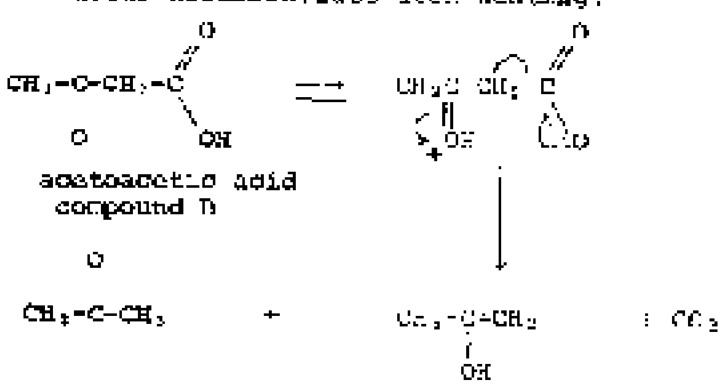
γ-terpinene $\xrightarrow{O_3}$ $\xrightarrow{[O]}$ 

4-methyl-3-oxopentanoic acid

+

B (an acid) $\xrightarrow[-CO_2]{\Delta}$ $CH_3\overset{O}{\overset{\|}{C}}-CH_3$

Since decarboxylation of compound B yields acetone, compound B must be acetoacetic acid. This is because β-keto acids decarboxylate upon heating:



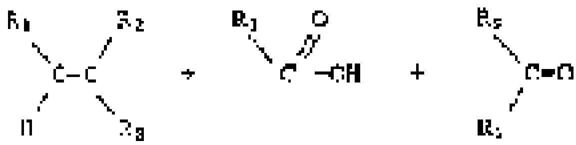
acetoacetic acid compound B

acetone tautomerization enol-intermediate

1159

Decarboxylation of acetoacetic acid involves transfer of the acidic hydrogen to the keto group. Note that compound E must be acetoacetic acid because that is the only possible manner in which we can attach a carboxyl group to acetone.

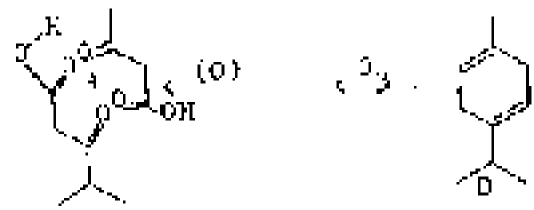
In order to get compound B, γ-terpinene had to undergo ozonolysis, followed by oxidative workup. This process cleaves double bonds to form ketones and carboxylic acids in the general reaction:



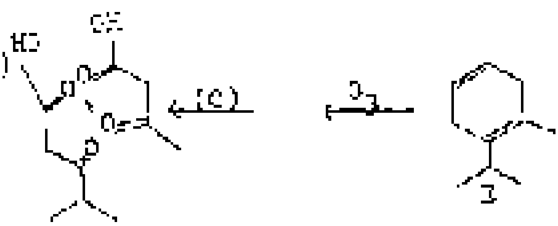
R≠H

Therefore, we need only connect two carbonyl carbons with double bonds to get the structure of γ-terpinene. Two structures are possible, however, due to the asymmetry of both acetoacetic acid and 4-methyl-3-oxopentanoic acid:

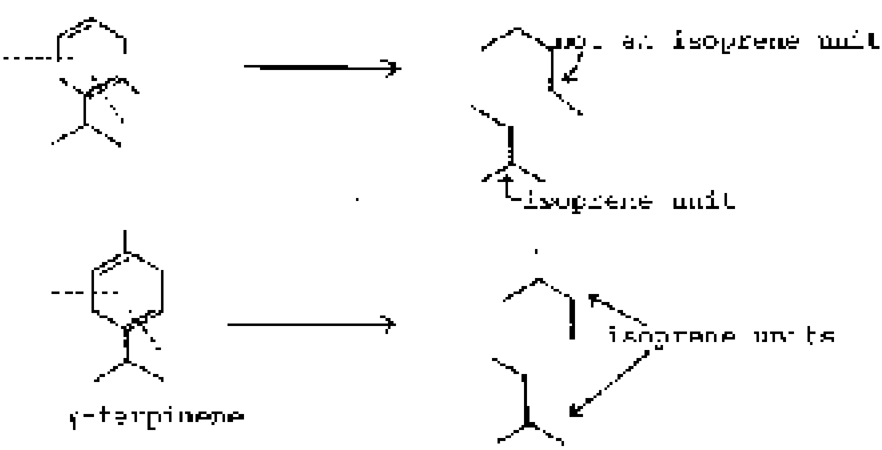
1)



2)



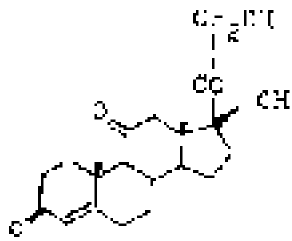
On the basis of the isoprene rule, which states that all terpenes are formally divisible into isoprene units, we can discard structure B. Therefore D is the correct structure for γ-terpinene:



The dashed lines show isoprene units.

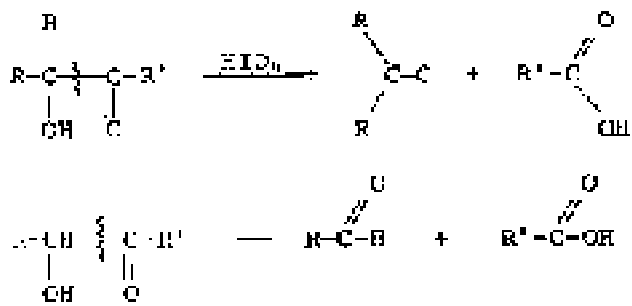
• PROBLEM 30-13

Predict the structure of the neutral crystalline compound formed when cortisone reacts with excess periodic acid.

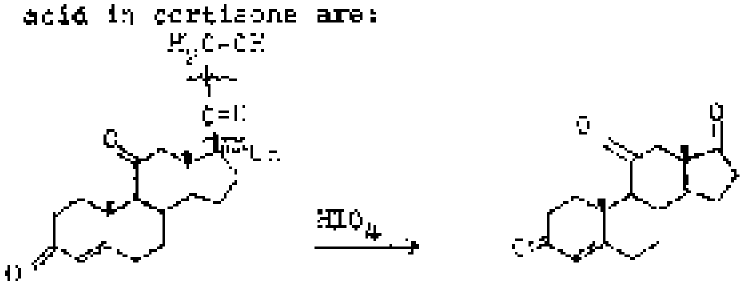


Cortisone
(an anti-inflammatory steroid)

Solution: Compounds containing two or more -OH or =O groups on adjacent carbon atoms are oxidized by periodate, HIO_4, with cleavage of carbon-carbon bonds:



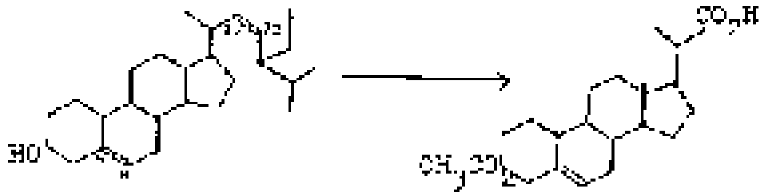
Therefore the bonds that should be cleaved by periodic acid in cortisone are:



Treatment with periodic acid will lead to formation of formic acid (HCOOH), water, carbon dioxide and the above ketone.

• PROBLEM 30-14

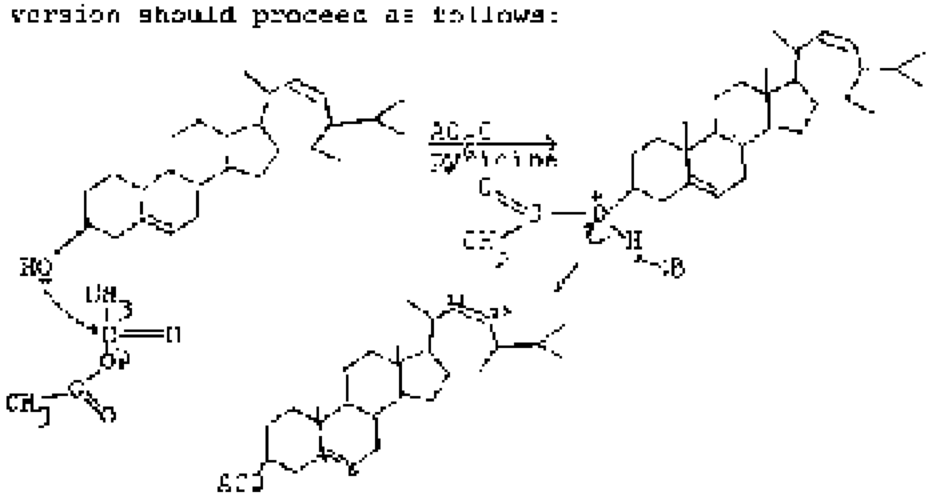
The plant steroid stigmasterol is readily available on a commercial scale from soybeans. Suggest a method for its conversion into the acid shown here, a compound that has been used as a starting material for the production of pharmaceutically valuable steroids.



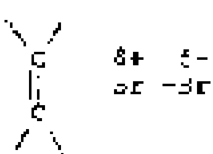
Stigmasterol

(HINT: Trisubstituted double bonds are usually more reactive toward electrophiles than are disubstituted double bonds.)

Solution: Comparing the structures of stigmasterol with that of the acid, we see two major changes: (1) Substitution of the -OH group with an acetate; (2) cleavage of the C_{22}-C_{23} double bond with oxidation of the 22nd carbon. The conversion should proceed as follows:



But before we can cleave the corresponding double bond by ozonolysis, we must protect the C_5-C_6 double bond. One method of protecting a double bond is by bromination. A problem arises at this point: how do we brominate the C_5-C_6 double bond without brominating the C_{22}-C_{23} double bond at the same time? If we compare the two double bonds, we will see that the C_5-C_6 double bond is trisubstituted, while the C_{22}-C_{23} double bond is disubstituted. To see how this will help us selectively brominate the C_5-C_6 double bond, we must look at the mechanism for addition of halogens to alkenes. When a halogen molecule is near a double bond, it becomes polarized:



This polarization occurs because the dense negatively charged electron cloud of the double bond repels the similarly charged electron cloud of the halogen molecule. With this in mind, let us now look at the mechanism for addition of halogens to alkenes:

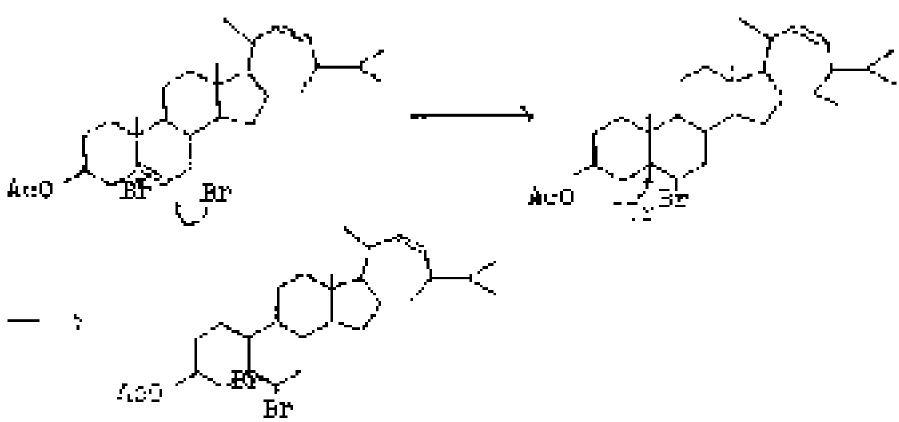
II

Looking at intermediate II, we see that a trisubstituted alkene would stabilize this carbonium ion more than a disubstituted alkene:

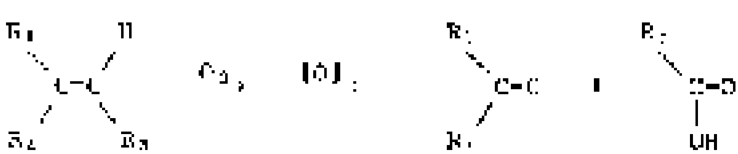
I-more stable   II-less stable

Fig. 1 - Alkyl groups are electron releasing, therefore I is more stable than II.

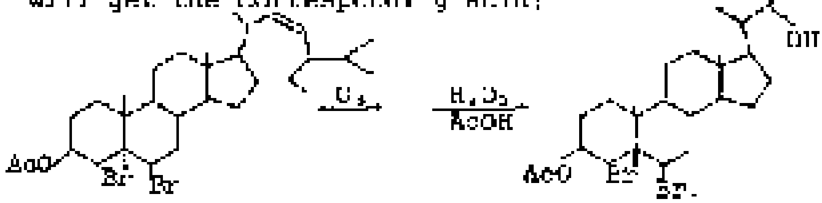
The more stable the carbonium ion, the more easily it is formed, therefore the rate of bromination for the trisubstituted double-bond is faster than that of the disubstituted double-bond. By controlling reaction conditions, we can selectively brominate the C_5-C_6 double bond:



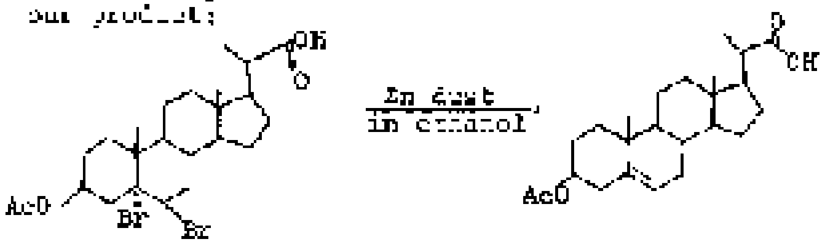
Now we can form the acid by ozonolysis followed by oxidative workup. This process cleaves double bonds to form the corresponding acids and ketones:



Since the C_{22}-C_{23} double bond is disubstituted, we will get the corresponding acid;



Dehalogenation of the vicinal dibromide will give us our product;



CHAPTER 31

CARBOHYDRATES

NOMENCLATURE AND STRUCTURE

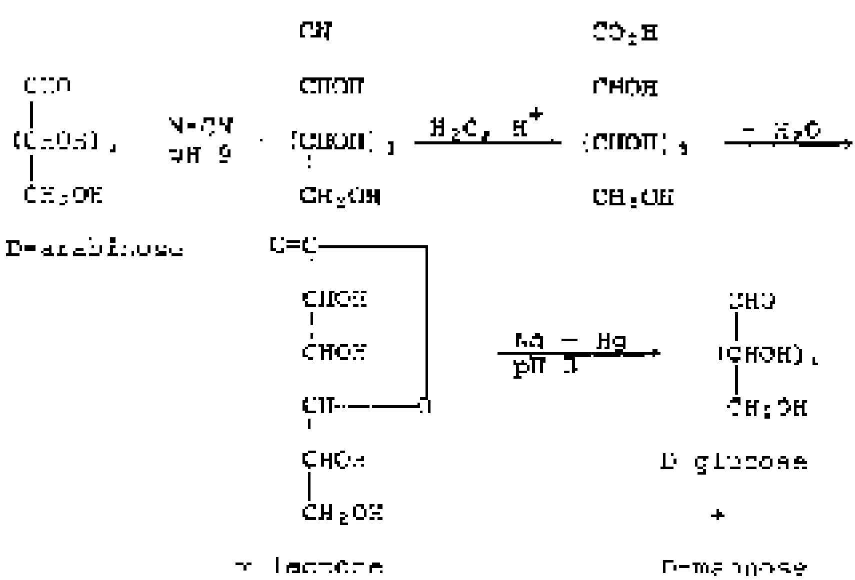
■ PROBLEM 31-1

Answer the following as Fischer did in his famous monosaccharide structure determination.

(a) Write projection formulas for all the theoretically possible D-aldopentoses, $HOCH_2(CHOH)_3CHO$.

(b) One of the D-aldopentoses is the naturally occurring D-arabinose, enantiomeric with the more abundant L-arabinose. Oxidation of D-arabinose with nitric acid gives an optically active five-carbon trihydroxydicarboxylic acid. Which of the D-aldopentoses could be the D-arabinose?

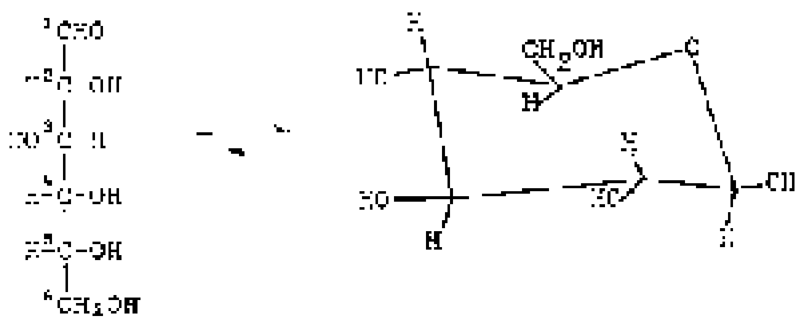
(c) D-Arabinose is converted by the following transformations into D-glucose and D-mannose. (This is the classic Kiliani-Fischer cyanohydrin synthesis of sugars.) What do these transformations tell about the relationship between the configurations of mannose and glucose?



(d) Oxidation of D-glucose and D-mannose gives the six-carbon, tetrahydroxydicarboxylic acids, glucaric and mannaric acids, respectively. Both are optically active. What then are the configurations of the D and L-arabinoses?

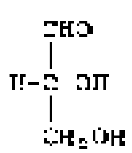
(e) D-Glucaric acid can form two different γ-monolactones, whereas D-mannaric acid can form only one monolactone. What then is the configuration of D-glucose and D-mannose?

Solution: Carbohydrates are a group of extremely important naturally occurring compounds. They have the general structural formula $C_n(H_2O)_n$ with n being an integer greater than or equal to three. The most basic type of carbohydrates are the sugars (saccharides) which are polyhydroxyaldehydes or polyhydroxyketones which exist almost exclusively in cyclic form. D-glucose, the ubiquitous natural product, is a diastereomer of 2,3,4,5,6 pentahydroxylhexanal.



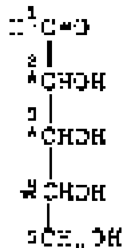
D-glucose

Note the numbering system of the monosaccharides in which the carbonyl carbon (or the terminal carbon nearest the carbonyl group in a ketose) is considered carbon number one. Also note that the "D" configuration refers to the stereochemistry about the chiral center furthest from the carbonyl group. The D-family of sugars is based upon the three-carbon sugar D-(+)glyceraldehyde:

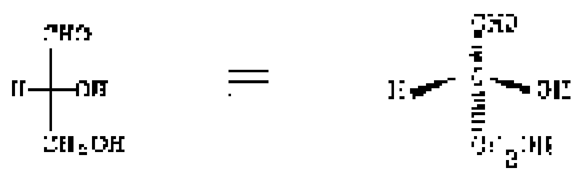


Actually, Fischer did not know the absolute configuration of this carbohydrate and was lucky in designating this compound correctly as a D-sugar.

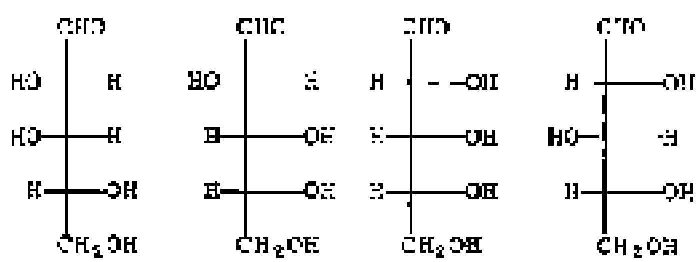
(a) Carbohydrates are classified in two general ways by designating the number of carbons in the sugar and the type of carbonyl group it possesses (ketone or aldehyde). Thus a five-carbon sugar with an aldehyde carbonyl is termed an aldopentose. The general structural formula for an aldopentose is:



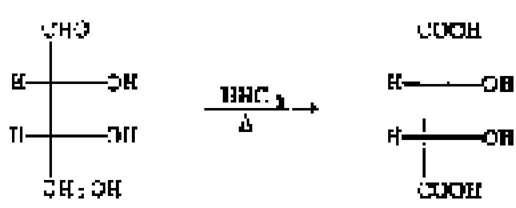
Three of the carbons are asymmetric (bonded to four different groups) and therefore they are chiral centers, allowing for the existence of eight (2^n where n = number of chiral carbons = 3) different stereoisomers. We can denote the stereochemistry of these different isomers through the use of Fischer projection formulas, remembering its convention of horizontal lines representing bonds coming out of the plane of the paper and vertical lines representing bonds behind this plane. For example, in D (+)-glyceraldehyde



We are asked to list all the possible D-aldopentoses which requires that the stereochemistry at C_4 be fixed. This means that there are only four different D-aldopentoses. The diastereomers are:

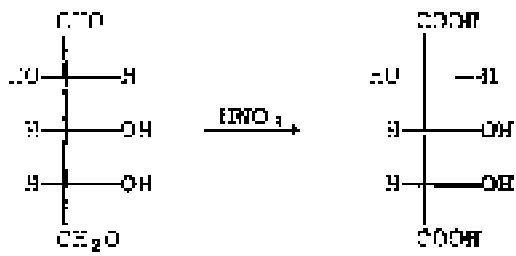


(b) Nitric acid is a potent oxidizing agent which will oxidize both the terminal carbonyl and hydroxyl group to carboxylic acid functionalities. The product is a dicarboxylic acid which is termed an aldaric acid.

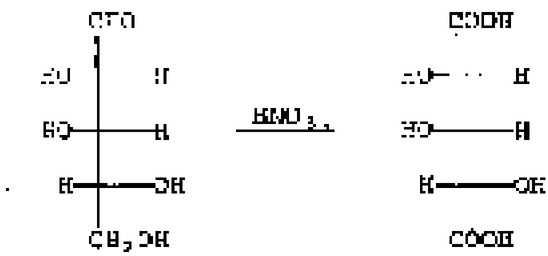


D-erythrose D-erythric acid

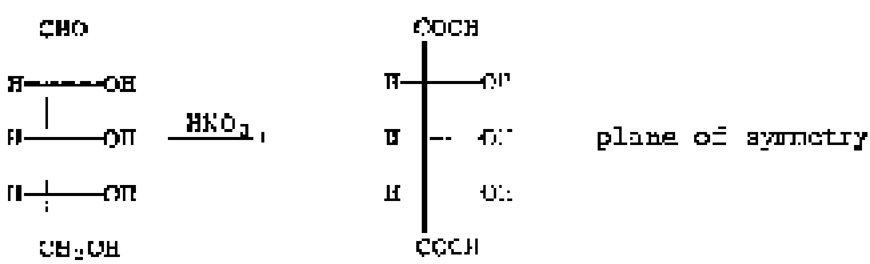
The two terminal groups of an aldaric acid are identical and if the acid possesses a plane of symmetry, it will be an optically inactive meso compound. Two of the D-aldopentoses will give meso aldaric acids while two will yield optically active aldaric acids.



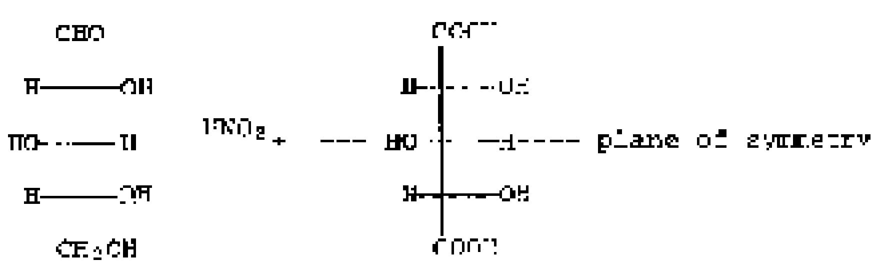
optically active



optically active



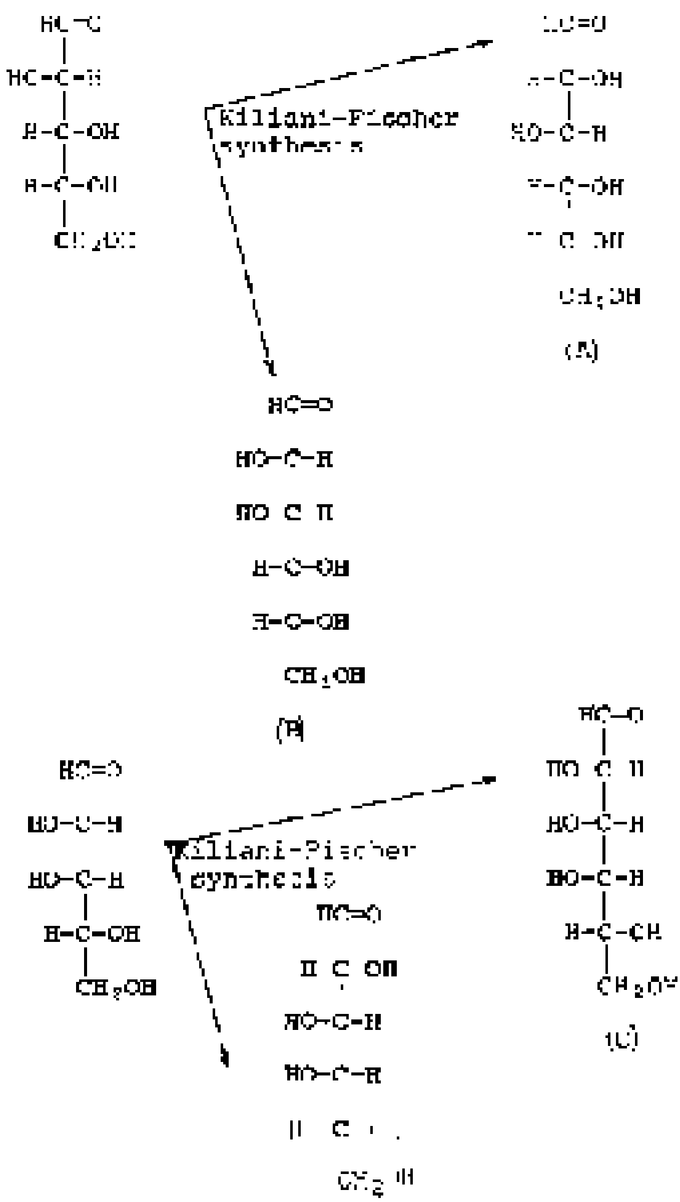
optically inactive



optically inactive

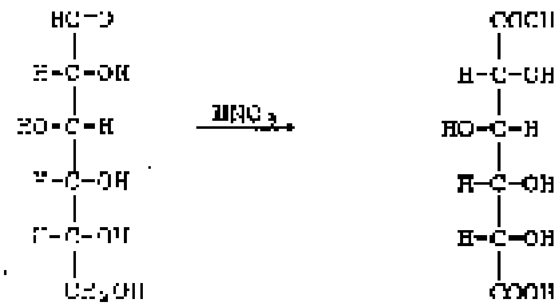
The two optically active products are the only structural possibilities for D-arabinose.

(c) In the Kiliani-Fischer cyanohydrin synthesis, a cyanide ion attacks the carbonyl group to form an intermediate cyanohydrin which is hydrolyzed to its corresponding α-hydroxy carboxylic acid. This acid will be esterified to the γ-lactone. The lactone is reduced by sodium amalgam to form the diastereomeric sugars. We note that none of the chiral centers in the starting material were altered. Also, only one new chiral center was generated by attack of the nucleophile. Therefore, D-glucose and D-mannose differ in configuration only at C_2. Compounds such as these which differ in configuration at only one chiral center are termed epimers. Combining this information with our data from the aldaric acid, we can propose four possible structures (A-D) for D-glucose and D-mannose.

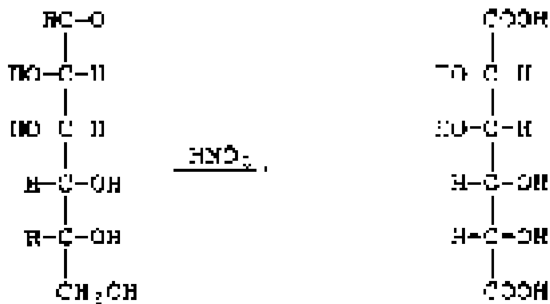


(A) (B) (C) (D)

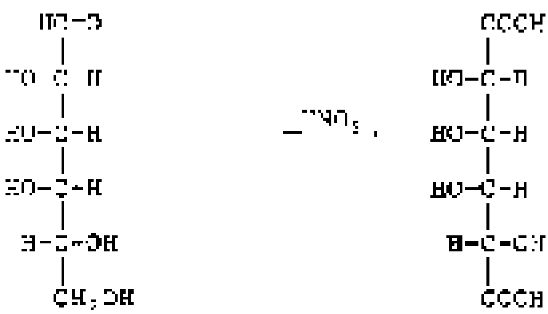
(d) Nitric acid will oxidize a carbohydrate to an aldaric acid. Realizing that a dicarboxylic acid with a plane of symmetry lacks optical activity, we can limit the structural possibilities for the aldohexoses to two Fischer projections.



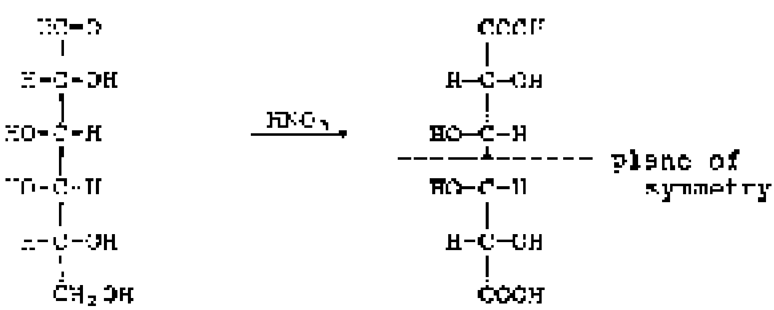
(A) optically active



(B) optically active

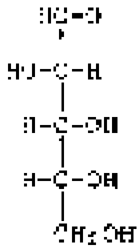


(C) Optically active

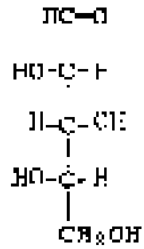


(D) optically inactive

Compound C yields an optically active aldaric acid upon treatment with HNO_3, but it can be eliminated as a possible structure for D glucose or D-mannose because it is an epimer of compound D which yielded a meso aldaric acid. We recall that D glucose and D mannose are epimers, differing only at C-2. However, examining the configurations of C_3, C_4, C_5 of the aldohexoses A and B, we can depict D-arabinose and its enantiomer L-arabinose.



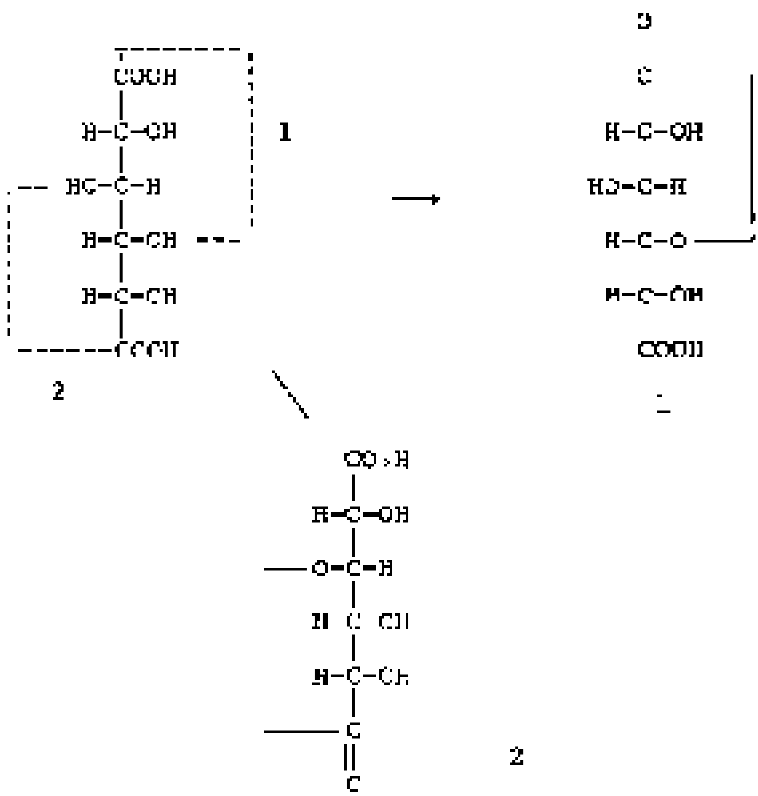
D arabinose



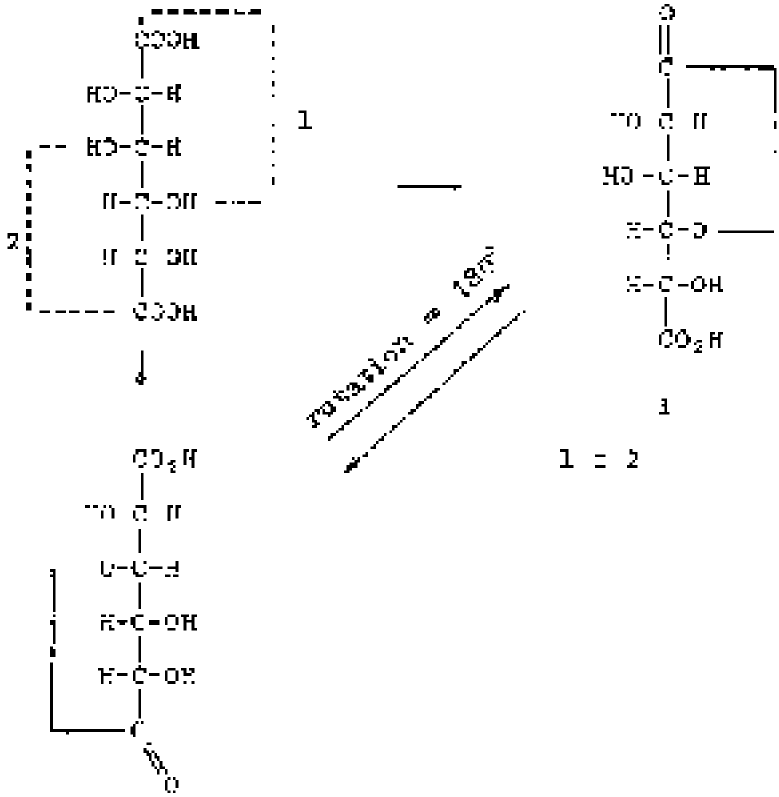
L arabinose

Thus Compounds A and B must be differentiated as D glucose and D-mannose.

(e) Examining the aldaric acid of compound A, we see that two distinct γ-monolactones can be derived from it.



On the other hand, Compound 3's aldaric acid can form only one lactone. This can be verified by rotation of the Fischer projections by 180°.

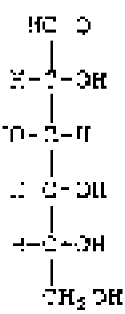


3

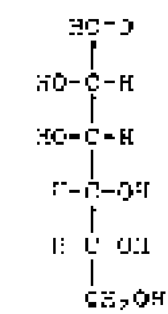
1 = 2

2

Therefore, we can now designate the correct structures for D-glucose and D-mannose. These are:



D-glucose



D-mannose

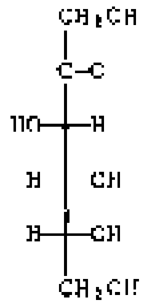
CONFIGURATION

• PROBLEM 31-2

(a) How many chiral centers are there in (+)-fructose?

(b) How many stereoisomeric 2-ketohexoses should there be?
(c) Draw a "cross" formula of one enantiomer of each pair, placing C=O near the top, and -OH on the right on the lowest chiral center (C-5).

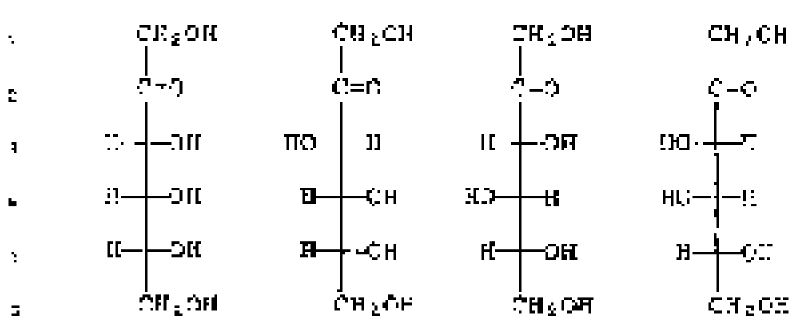
<u>Solution</u>: (a) (+)Fructose is a ketohexose with the structural formula



It possesses three asymmetric carbons which have four different groups attached to them. These carbons are termed chiral centers and may allow the molecule as a whole to be optically active. (-) Fructose is optically active and has three chiral centers located at C_3, C_4, and C_5.

(b) If a molecule possesses n chiral centers, it may have a maximum of 2^n stereoisomers. Meso compounds have chiral centers but are not optically active due to the presence of an internal plane of symmetry. Fructose is seen to lack such symmetry and has 2^3 (2^n, where n=3) or 8 sterioisomeric 2-ketohexoses.

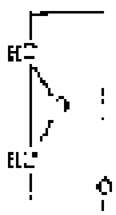
(c) We may write the various stereoisomers of 2-ketohexose just by exchanging the hydrogen and hydroxyl groups about each chiral center. Such an exchange will produce the enantiomer of the first compound. Hence, the four following compounds cannot be converted to each other by such a single exchange and therefore are diastereomers of each other with each diastereomer possessing a non-superimposable mirror image (enantiomer).



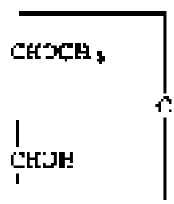
Psicose Fructose Sorbose Tagatose

(a) A certain sugar and its methyl glycoside can be isolated in both α and β anomeric forms. Also, the ring structure of the glycoside is known to be present in the pyranose form. How could you ascertain from rotation data whether or not the parent sugar also exists in the pyranose form?

(b) A D-glucose derivative with a 1,2-epoxide ring gives a methyl β-D-glucoside on solvolysis with methanol.



partial structure of 1,2-anhydro-α-D-glucopyranose 3,4,6-triacetate



partial structure of methyl β-D-glucopyranoside 3,4,6-triacetate

Explain how this reaction helps to establish the configuration of the α- and β-anomers of D-glucose.

<u>Solution:</u> (a) When the geometric arrangement of a molecule is such that it is nonsuperimposable on its mirror image, it is said to possess optical activity. Experimentally, the degree of optical activity of a compound can be designated in terms of its specific rotation [α], which is related to the degree that the compound polarizes light under certain set conditions. The specific rotation can be converted to the more useful molecular rotation [M] by the following equation:

$$[M]_{\lambda}^{t^{\circ}} = \frac{[\alpha]_{\lambda}^{t^{\circ}} M}{100}$$

t° - temperature

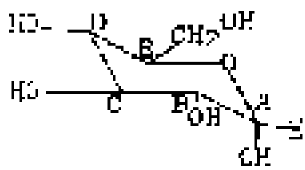
λ - wavelength of light

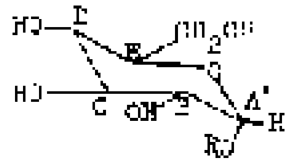
M - molecular weight of optically active compound which is in solution.

A sugar and its derivatives contain several chiral centers. The molecular rotation of these compounds is the sum of each of the individual rotations of the asymmetric carbons. For instance in α-D-glucose, the rotations of the five chiral carbons can be designated A, B, C, D, E. If A represents the rotation of the anomeric carbon,

$$[M]_{\alpha} = A + B + C + D + E \quad \text{and} \quad M_{\beta} = -A + B + C + D + E.$$

The difference between the molecular rotations of the two anomers is 2A and their sum is 2B + 2C + 2D + 2E. The α glycoside will have each of its asymmetric carbons contribute an amount to its molecular rotation that is equivalent to the donation made by the corresponding asymmetric carbons in its parent sugar with the exception of the anomeric carbon. For example, we can compare the molecular rotations of α D glucose and its glucoside,





$$[M] = A + B + C + D + E \qquad [M] = A' + B + C + D + E$$

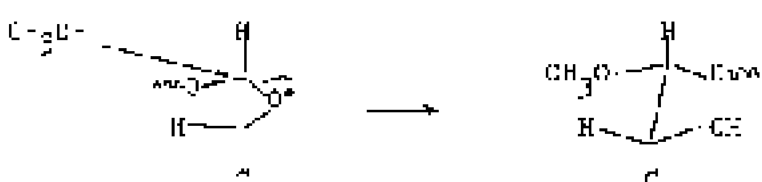
$$A \neq A'$$

Similarly, the rotations of the asymmetric carbons of β-D-glucose and its glucoside should differ only at the anomeric carbon. Therefore, if the α and β-anomeric forms of the methyl glycosides and their parent sugars are all in the pyranose forms, the sum $[M]_\alpha + [M]_\beta$ will be the same for the sugars and their glycosides.

	Sugar	Glycoside
	$[M]_\alpha = A + B + C + D + E$	$[M]_\alpha = A' + B + C + D + E$
	$[M]_\beta = -A + B + C + D + E$	$[M]_\beta = -A' + B + C + D + E$
$[M]_\alpha + [M]_\beta =$	$2(B + C + D + E)$	$= 2(B + C + D + E)$

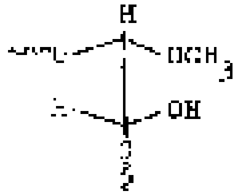
We must note that any change in the configuration about the anomeric carbon will not appreciably alter the rotatory contributions of the rest of the molecule.

(b) In the ring opening reactions of oxiranes, the attacking nucleophile undergoes a backside attack at carbon, typical of S_N2 displacements, forming a product with a trans arrangement of the nucleophile and leaving group. Thus, attack on the α anomer of the glucose with the 1,2 epoxide ring gives a methyl glycoside with a β configuration, and a trans relationship of the methoxyl group and the hydroxyl group on C_2.



α configuration β-configuration

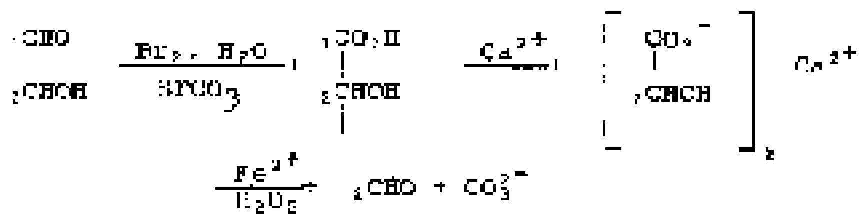
The β anomer of the epoxide would yield a glycoside of β-configuration.



Thus, if we know the configuration of the epoxide, we can predict the structure of the product of its ring-opening.

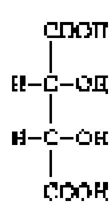
• PROBLEM 31-4

D-Arabinose and D-ribose give the same phenylosazone. D-Ribose is reduced to the optically inactive pentahydric alcohol, ribitol. D-Arabinose can be degraded by the Ruff method, which involves the following reactions:

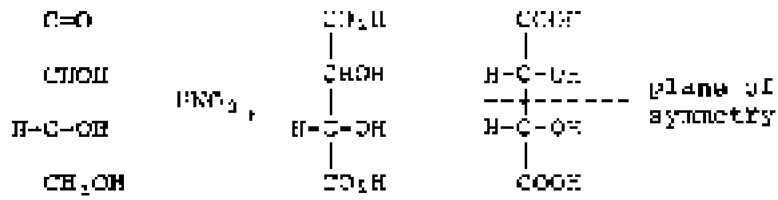


The tetrose, D-erythrose, so obtained can be oxidized with nitric acid to mesotartaric acid. What are the configurations of D-arabinose, D-ribose, ribitol, and D-erythrose?

Solution: In an identification problem such as this, it is most advisable to work backwards from the last piece of data given us. Meso-tartaric acid is a four-carbon (it is derived from a tetrose sugar) dicarboxylic acid which has the structure:

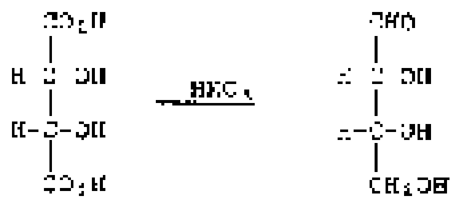


We deduce this from the fact that: 1 - nitric acid will oxidize the terminal hydroxyl group and the carbonyl group of the sugar to carboxylic acid functionalities, and 2 - it is a D-sugar that lacks optical activity in that it has a plane of symmetry (meso compound). This reasoning can be outlined as follows:



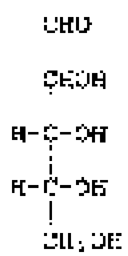
D-sugar D-tartaric acid meso-D-tartaric acid

We now know the structure of D-erythrose from its oxidation product, tartaric acid:



D-erythrose

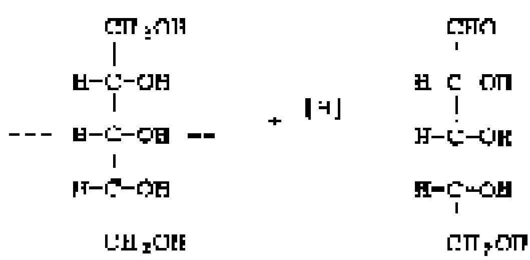
D-erythrose is the product of the Ruff degradation of D-arabinose, which significantly did not alter the stereochemistry about the C-3 and C-4 carbons of the pentose. Thus, still ignorant of the stereochemistry of C-2, we depict the structure of D-arabinose as:



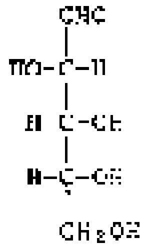
D-arabinose

Since phenylosazone formation also does not affect the stereochemistry about C_3 and C_4 of the pentose, the above structure also represents D-ribose whose structure differs only at the C-2 chiral center. Such compounds, differing in stereochemistry only about one carbon, are termed epimers. D-ribose is reduced to an optically inactive alditol, ribitol, and therefore we can determine the structure of D-ribose and its epimer, D-arabinose.

plane of symmetry



(optically inactive alditol of D-ribose) ribitol D-ribose



D-arabinose

DERIVATIVES OF GLUCOSE

• PROBLEM 31-8

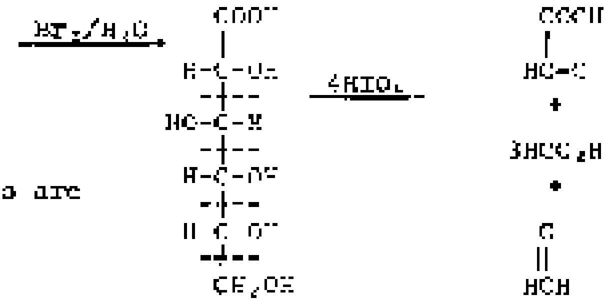
Identify each of the following glucose derivatives:

(a) A + $4HIO_4$ → 3HCOOH + HCHO + OHC–COOH
(b) B + $5HIO_4$ → 4HCOOH + 2HCHO
(c) C + $3HIO_4$ → 2HCOOH + 2OHC–COOH
(d) D + $4HIO_4$ → 4HCOOH + OHC–COOH

Solution: Periodic Acid (HIO_4) is an oxidizing agent that is specific for α-hydroxyl carbonyls, vic-diols, and oxalyl $\left(\begin{matrix} O\;\;O \\ \|\;\;\| \\ -C-C- \end{matrix}\right)$ compounds. Under mild conditions, HIO_4 will oxidize an α-hydroxyacid functionality bonded to a carbon bearing an oxidizable group, i.e., –C(OH)–C(OH)–C(=O)OH to yield $\overset{O\,O}{\overset{\|\;\|}{HCCOH}}$ as a product. By examining the oxidation products and the number of moles of oxidant consumed, we can decipher the structure of each of the glucose derivatives.

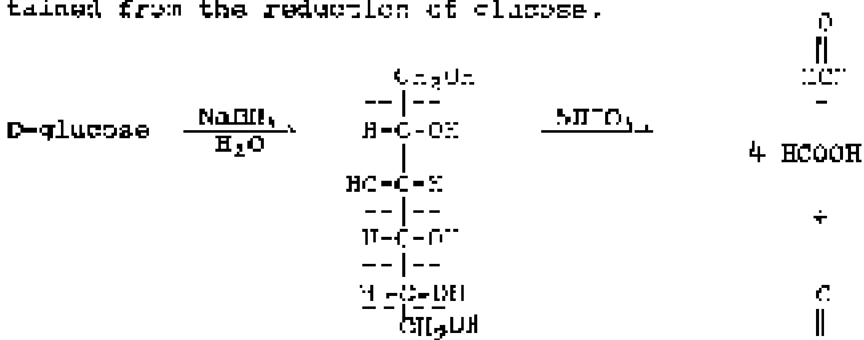
(a) This glucose derivative gives one mole of $\overset{O\;O}{\overset{|\;\;\|}{HC\,C\,OH}}$ while consuming four moles of the oxidizing agent, HIO_4. Hence, we now know that the compound contains four "oxidizable" bonds and has a $-CHOH-\overset{O}{\overset{\|}{C}}OH$ functionality as one terminus. The other terminus is $-CH_2OH$ as evidenced by the formaldehyde formed. A hydroxyl group adjacent to two oxidizable functions will be oxidized to formic acid by HIO_4. Thus compound A has three such hydroxyl groups and is gluconic acid which is derived from glucose after treatment with bromine water.

Note: ---- indicates which bonds are broken



D-gluconic acid

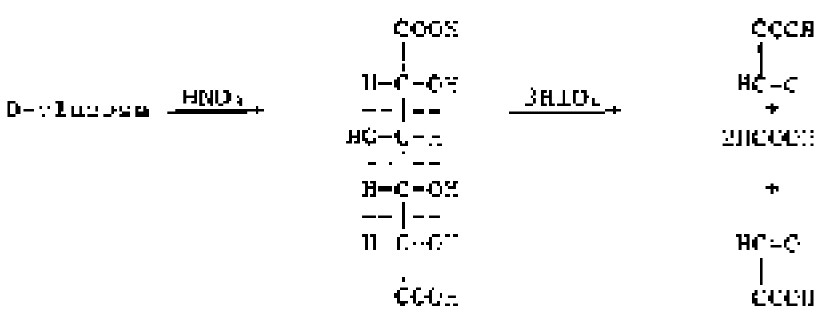
(b) The two moles of formaldehyde denote that the two termini are $-CH_2OH$ groups while the four moles of formic acid tell us that the rest of the carbons also bear a hydroxyl group. Therefore compound B is glucitol obtained from the reduction of glucose.



D-glucitol

(c) Compound C has only three bonds that are oxidized by periodic acid. The two moles of HC(=O)–COOH represent the oxidation of the terminal –CH(OH)–C(=O)–OH groups while the formic acid molecules are derived from the –CHOH– groups.

Thus Compound C is glucaric acid, obtained by HNO_3 action on glucose.

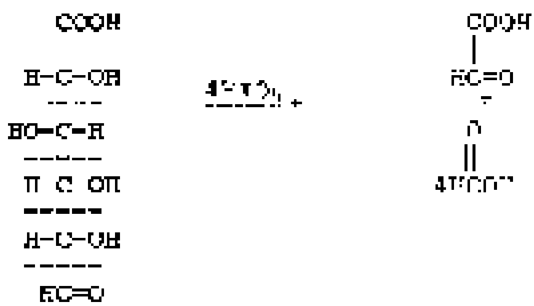


D-glucaric acid

(d) Compound D must have one terminal $-\underset{\displaystyle OH}{\underset{|}{CH}}-COOH$ group

(as seen from the oxidation product $\underset{\displaystyle O}{\underset{||}{HC}}-COOH$), and one

terminal -CHO (the source of one of the molecules of $\overset{\displaystyle O}{\overset{||}{HCOH}}$ formed). Therefore Compound D is glucuronic acid with the structure:



D-Glucuronic acid

GLYCOSIDES

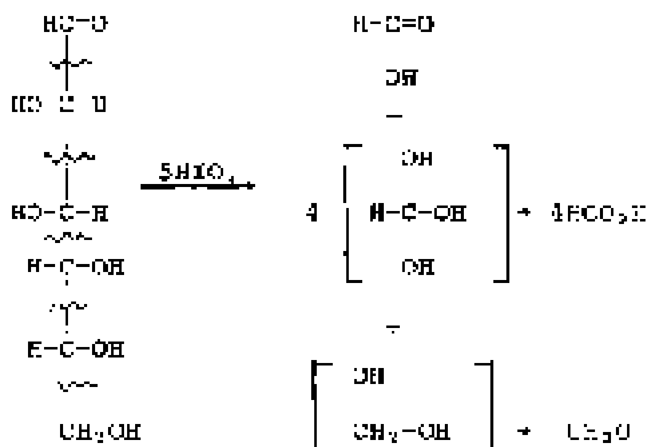
• PROBLEM 31-6

From the following information deduce the ring structures of the sugars listed:

Sugar (as methyl glycoside)	Moles of IO_4^- consumed	Moles of HCO_2H formed	Moles of HCHO formed
(a) methyl α-D-mannoside	2	1	0
(b) methyl α-D-riboside	1	0	0
(c) a methyl glycoside of an aldohexose	3	2	0
(d) a methyl glycoside of an aldohexose	2	0	1

Solution: Periodic acid, HIO_4, is an oxidizing agent that specifically oxidizes vic-diols, α-hydroxycarbonyl compounds and oxalyl compounds. This reagent may allow us to make structural determinations by analyzing the oxidation products and the number of moles of HIO_4^- consumed.

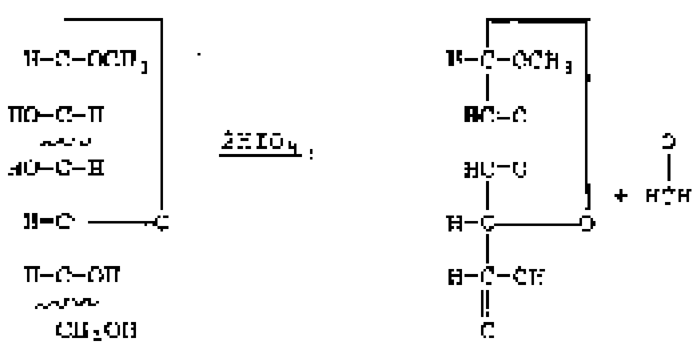
(a) Methyl α-D-mannoside, like any glycoside, is an acetal that does not mutarotate, which means the compound does not possess a free carbonyl group. This is important in context of the action of periodic acid in that if the carbonyl structure was present, even in a minute quantity, it will be acted upon by the oxidant. For example, treatment of D-mannose with periodic acid yields five moles of formic acid and one mole of formaldehyde, consuming five moles of HIO_4. The straight chain aldehyde is in equilibrium with the α and β cyclic forms but it is acted upon by the oxidant despite its relatively low stability. We may formulate the products by substituting hydroxyl groups for each cleaved bond and analyzing the fragments.



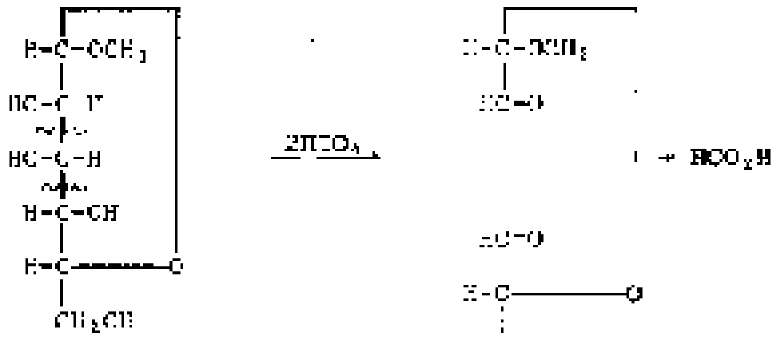
D Mannose

Alternatively, one may consider the oxidation level of each fragment in the reactant, determining the oxidation products by considering the number of adjacent bonds cleaved and the degree of oxidation. Following the oxidation sequence of alcohol → aldehyde → carboxylic acid, a $-CH_2OH$ moiety will be oxidized to formaldehyde and a

H-C-OH fragment will be oxidized to formic acid. There are only two feasible structures that will consume two moles of HIO_4 and only the pyranose form will yield the proper products.

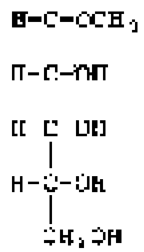


methyl-α-D-mannofuranose

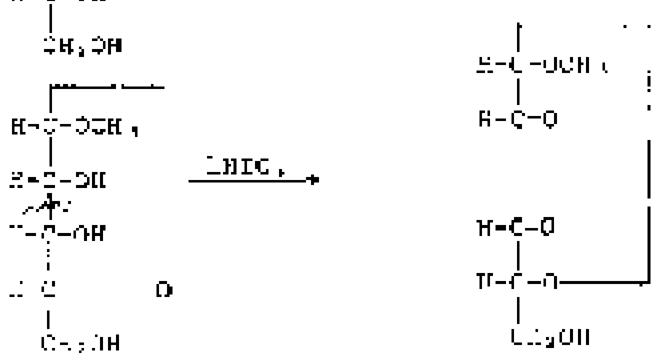


methyl-α D pyranose

(b) Prior to determining its ring size we may represent methyl α-D-ribose as:

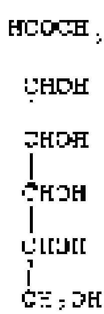


The only structure that fits the data is the furanose form.

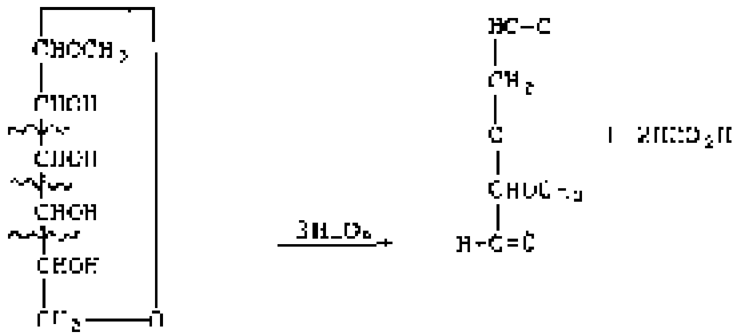


Note that a four-membered ring will also consume only one mole of the oxidant but will produce formaldehyde as an oxidation product as well as being unstable itself.

(c) The methyl glycoside of the aldohexose may be depicted as the following before oxidation:

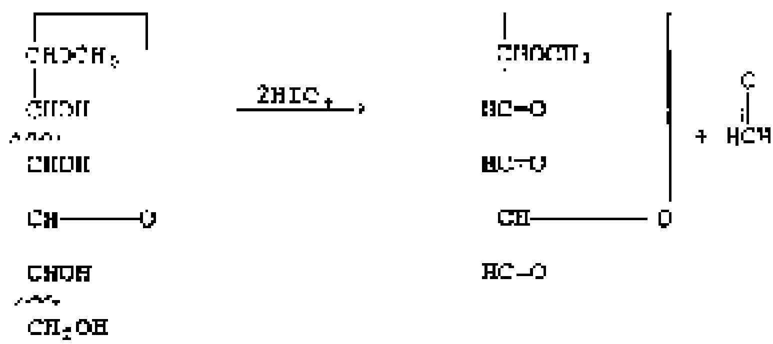


Only the seven membered ring structure will consume three moles of HIO_4 and produce two moles of HCO_2H.



Note that we cannot specify the stereochemistry about any of the chiral carbons including the anomeric carbon.

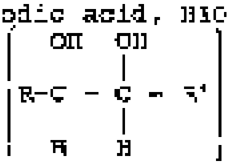
(d) The furanose form of the methyl glycoside of the aldohexose is consistent with the given information which requires the use of two moles of oxidant and produces a mole of formaldehyde.



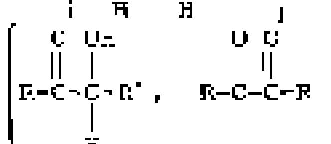
• PROBLEM 31-7

When methyl α-D-glucoside was treated with HIO_4, it yielded 1 mole of formic acid, plus a product (A). Write the structure of A. When a methyl glycoside of unknown structure (B) was similarly treated with HIO_4, only 1 mole of HIO_4 was consumed, and no formic acid was produced, but the same product (A) was obtained. Draw the configurational structure of B.

Solution: Periodic acid, HIO_4, is an oxidant specific to vicinal diols



and their carbonyl derivatives

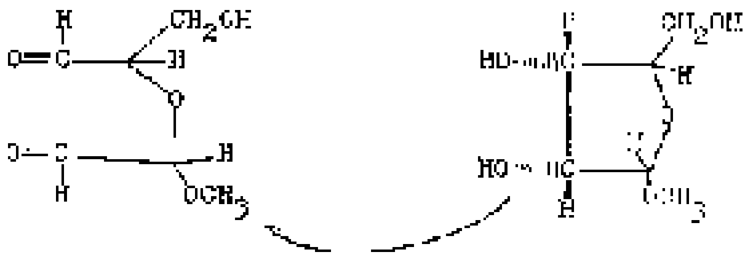


. Methyl α-D-glucoside

yields formic acid in addition to a fragment, A, that is found by examining the action of the oxidant,

(A)

To find the unknown structure, B, one must convert the carbonyl groups of the dialdehyde, A, and put oxidizable functional groups on these terminal carbons. In this way, we know that the methyl glycoside will be cleaved at only one bond and only one product will be formed.



(A) 1 HIO_4 (B)

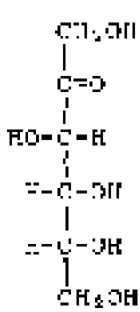
Note that we do not know the configurations of the carbons bearing the hydroxyl groups in structure B.

PROBLEM 21-8

Predict how many moles of formaldehyde and how many of formic acid would be obtained from methyl α-D-fructoside upon treatment with HIO_4

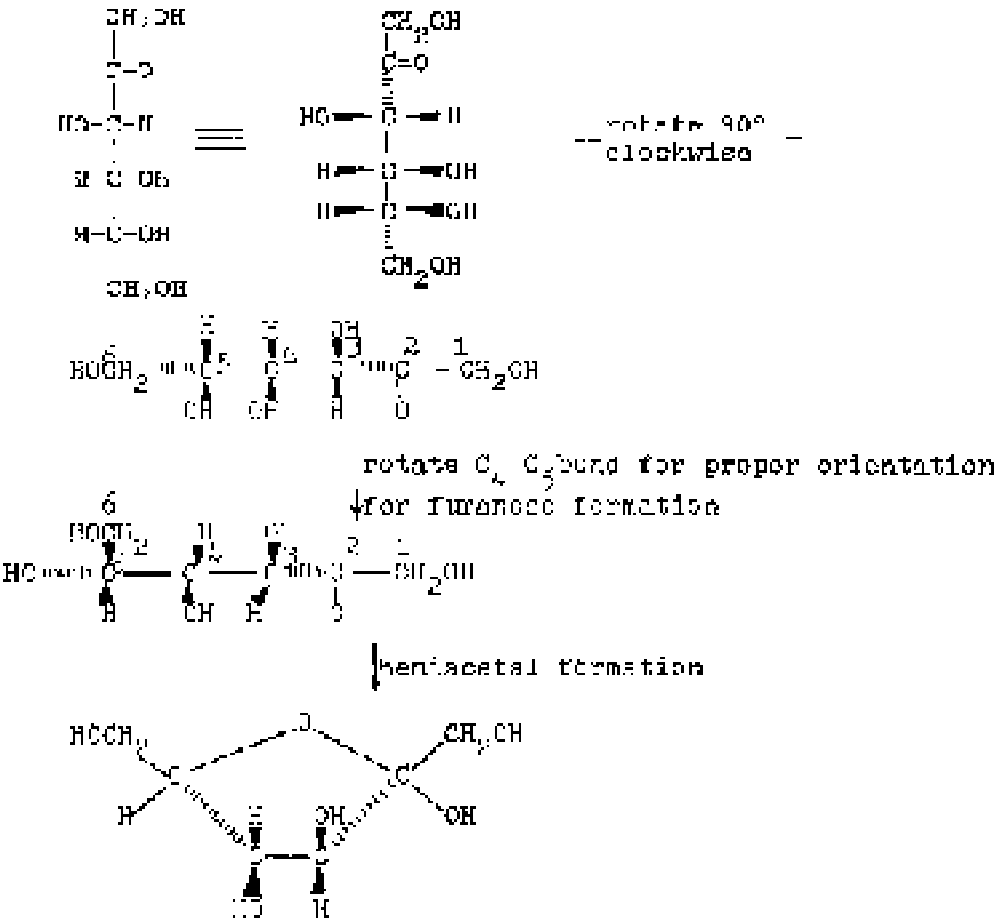
(a) If the furanose form were present.
(b) If the pyranose form were present.

Solution: The monosaccharide, D-fructose, has the open chain form of:

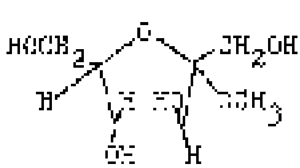


different products will be yielded when methyl α-D-fructoside is treated with periodic acid, depending on whether a furanose or pyranose ring is formed.

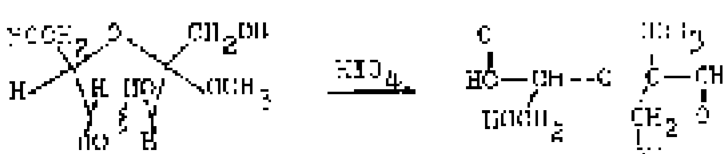
(c) The following sequence will demonstrate how one can deduce the Haworth structure for α-D-fructofuranose:



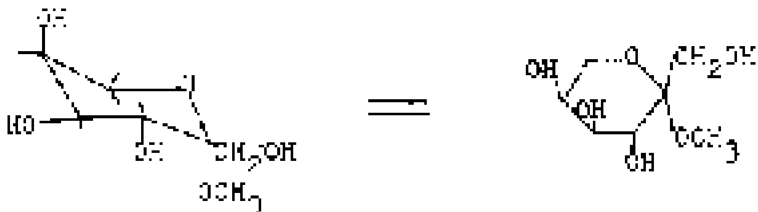
Thus, the Haworth structure for methyl α-D-fructofuranoside is:



Upon treatment with HIO_4, the glycoside consumes one mole of oxidant but yields neither formaldehyde nor formic acid.



(b) Methyl α-D-fructopyranoside has the structure:



Periodic acid action on this compound involves the consumption of two moles of the oxidant and the production of a mole of formic acid.

DISACCHARIDES

• PROBLEM 31-9

Show how the structure of maltose can be deduced from the following evidence:

(a) The sugar is hydrolyzed by yeast α-D-glucosidase to D-glucose.

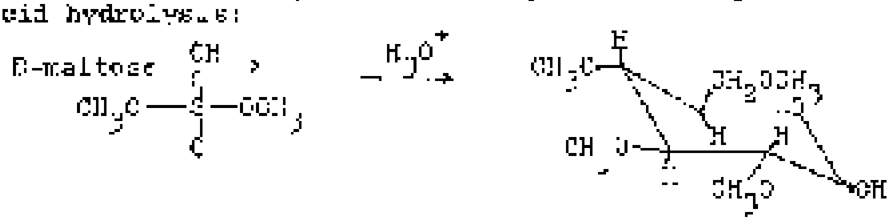
(b) Maltose mutarotates and forms a phenylosazone. Methylation with dimethyl sulfate in basic solution followed by acid hydrolysis gives 2,3,4,6-tetra-O-methyl-D-glucopyranose and 2,3,6-tri-O-methyl-D-glucose.

(c) Bromine oxidation of maltose followed by methylation and hydrolysis gives 2,3,4,6-tetra-O-methyl-D-glucopyranose and a tetramethyl D-gluconic acid which readily forms a γ-lactone.

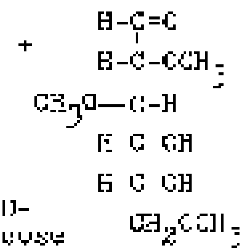
Solution: Maltose is obtained by the partial hydrolysis of starch in aqueous acid. By examining each fragment of information and trying to use this data to determine maltose's constitutional characteristics, we will be able to deduce its structure.

(a) Enzymes are specific in that some will act only on certain glycosidic linkages while others will only take action with their anomeric counterparts. Here, the enzyme (α-D-glucosidase), is specific in hydrolyzing only α glycosidic linkages. Thus maltose consists only of D-glucose monosaccharide units and has an α configuration at the anomeric carbon.

(b) Both mutarotation (change in optical rotation upon dissolution of the crystalline compound) and phenylosazone formation (incorporation of two molecules of phenylhydrazine) are characteristic of carbohydrates with a free aldehyde or ketone carbonyl group. Since maltose possesses these two properties, it has a free carbonyl group and therefore both anomeric carbons are not involved in the acetal formation as is the case with a disaccharide such as D-sucrose. We can examine the products of sequential methylation and acid hydrolysis:



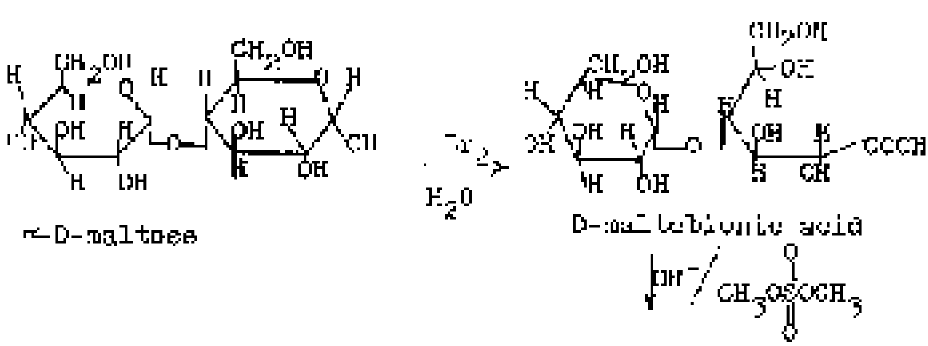
2,3,4,6-tetra-O-methyl-D-glucopyranose

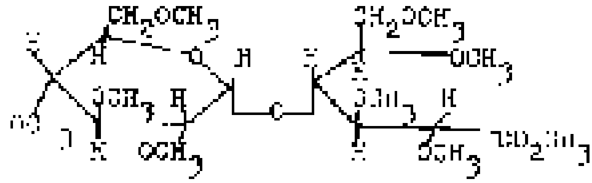


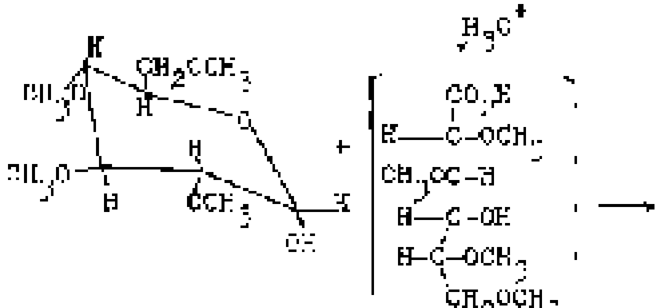
2,3,6-tri-O-methyl-D-glucose

From this information, we know immediately that at least one of the glucose units was in the pyranose form as seen from the glucopyranose product. The trimethyl glucose infers that the second glucose unit has either its C_4 or C_5 hydroxyl involved in the glucoside formation while the other forms the intramolecular hemiacetal.

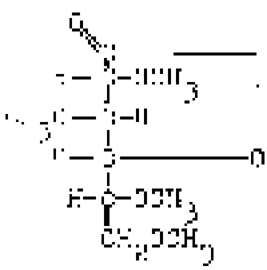
(c) γ-lactone formation after bromine oxidation, methylation, and hydrolysis informs us that C_4 of the second glucose unit was involved in the glucoside linkage. A γ-lactone has three ring carbons besides the carbonyl group which tells us which of the hydroxyl groups was not methylated and therefore was involved in the glucoside formation.







2,3,4,6 tetra O methyl-L glucopyranose 2,3,5,6-tetramethyl-D-gluconic acid



(easily formed)

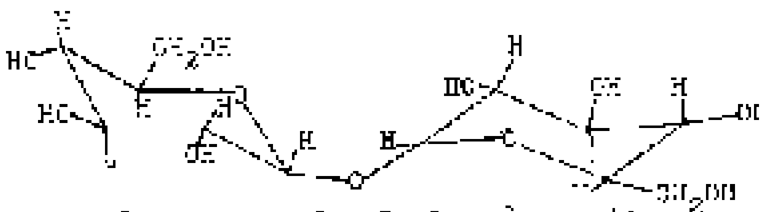
δ-Lactone of 2,3,5,6-tetramethyl D gluconic acid

• PROBLEM 31-10

(a) (+)-Trehalose, $C_{12}H_{22}O_{11}$, a non-reducing sugar found in young mushrooms, gives only D-glucose when hydrolyzed by aqueous acid or by maltase. Methylation gives an octa-O-methyl derivative that, upon hydrolysis, yields only 2,3,4,6-tetra-O-methyl-D-glucose. What is the structure and systematic name for (+)-trehalose?

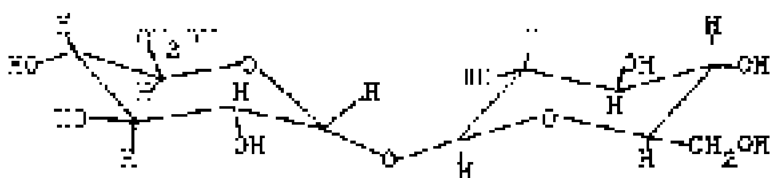
(b) (+)-Isotrehalose and (+)-neotrehalose resemble trehalose in most respects. However, isotrehalose is hydrolyzed by either emulsin or maltase, and neotrehalose is hydrolyzed only by emulsin. What are the structures and systematic names for these two carbohydrates?

Solution: (a) (+)-Trehalose is a disaccharide since it can be formed by the condensation of two monosaccharide units ($2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}$). (+)-Trehalose is a non-reducing sugar which means that it does not have a free carbonyl group and therefore does not mutarotate or react with Benedict's or Fehling's solutions. Furthermore, the disaccharide has each monosaccharide unit's anomeric carbon linked in a glycosidic bond. Acid hydrolysis yielding only D-glucose infers that this is the mono-saccharide. Maltase is an enzyme that hydrolyses only α linkages as in maltose. C_1 is part of a formyl group and C_5 has a free hydroxyl group after methylation and hydrolysis. Therefore, (+) Trehalose consists of α D glucopyranose rings. Its systematic name and structure is:



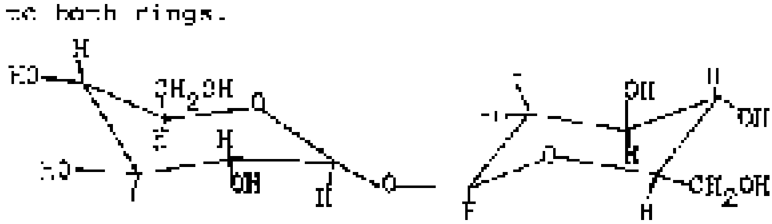
α D glucopyranosyl-α-D-glucopyranoside

(b) (-)-Isotrehalose differs from (+)-Trehalose only in that it is hydrolysed by either emulsin or maltase. Therefore, one ring will have an α glycosidic linkage while this linkage will be β to the other ring. The systematic name and formula of (-)-Isotrehalose is:



α-D-Glucopyranosyl-β-D-glucopyranoside

Similarly, (+)-neotrehalose is hydrolysed only by emulsin and therefore the glycosidic linkage is β to both rings.

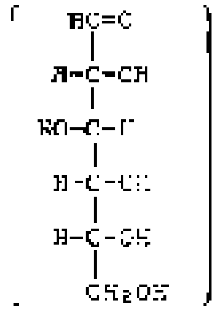


β-D-glucopyranosyl-β-D-glucopyranoside

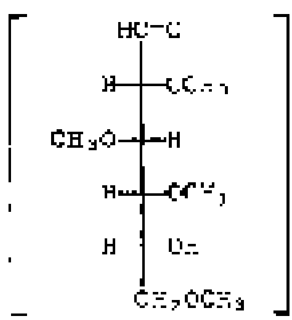
• PROBLEM 31-11

A disaccharide, G, $C_{11}H_{20}O_{10}$, is hydrolyzable by α-glucosidase, yielding D-glucose and a D-pentose. The disaccharide does not reduce Fehling's solution. Methylation of G with dimethyl sulfate in NaOH yields a hepta-methyl ether, H, which upon acid hydrolysis yields 2,3,4,6 tetra-O-methyl D glucose and a pentose tri-O-methyl ether, (I). Oxidation of I by bromine water yields 2,3,4-tri-O-methyl-D-ribonic acid. Assign structures to compounds G through I compatible with these data.

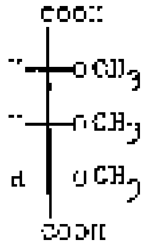
Solution: To solve an identification problem such as this one, it is most beneficial to analyze each fragment of data and deduce how each will aid in finding the desired structures. A disaccharide is a carbohydrate consisting of two monosaccharide units. Here, the two monosaccharide units in

compound G are D-glucose  and D-pentose

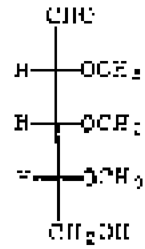
(five carbon sugar). The fact that compound G does not reduce Fehling's solution (tartrate ion complexed with Cu^{++}) indicates that the carbohydrate does not possess a free carbonyl group. This is because the free carbonyl group would have reduced the cupric ion to cuprous ion ($Cu^{++} \rightarrow Cu^{+}$) while being oxidized to a carboxylic acid functionality. We can further infer that the anomeric carbons of each sugar are linked to one another through an acetal oxygen and neither sugar will contain a hemiacetal linkage. Since compound G is hydrolyzed specifically by α-glucosidase, the anomeric oxygen is bonded axially in reference to the glucose ring. The disaccharide is exhaustively methylated to compound H which is then hydrolyzed to its component methylated sugars. We note that the carbons bearing hydroxyl groups in each of the methylated sugars after hydrolysis were the ones involved in the intramolecular hemiacetal linkages. The hydrolysis products are

2,3,4,6-tetra-O-methyl-D-glucose  and

a pentose tri-O-methyl ether (compound I). Since there is a hydroxyl group on carbon number five of the glucose, the glucose sugar exists as a pyranose ring in the disaccharide. Compound I's structure can be deduced by examining its oxidation product 2,3,4,-tri-O-methyl-D-ribonic acid:



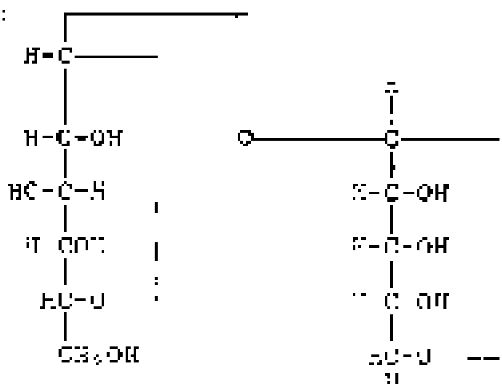
The only tri-O-methyl ether that this



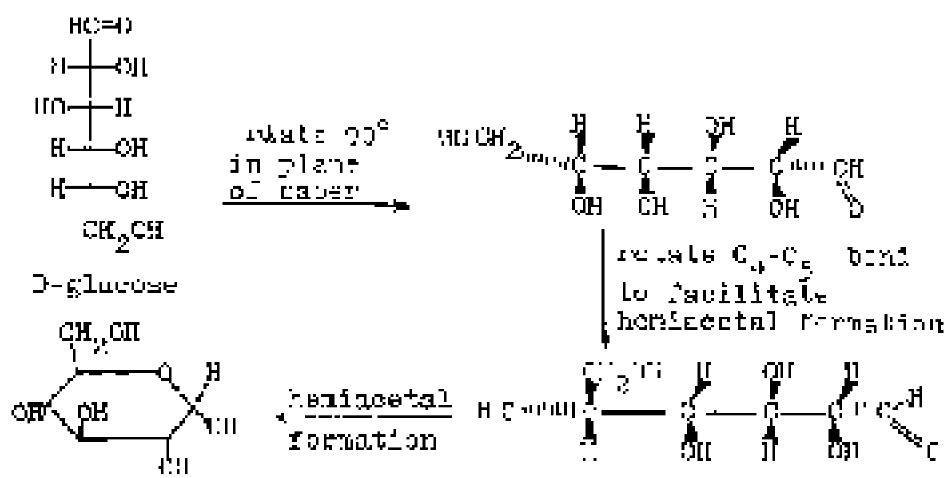
aldonic acid could be derived from is:

(Compound I)

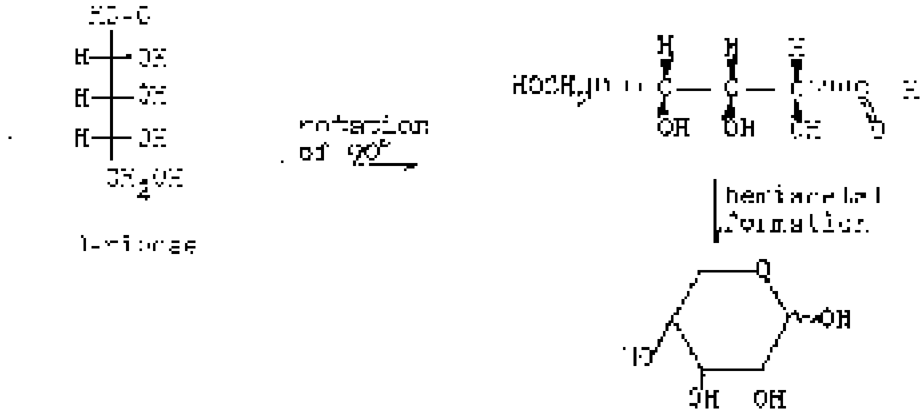
Since the carbon number five bears a hydroxyl, it is involved in hemiacetal formation and the aldopentose also is in pyranose form when linked to glucose. Using the previous data, the Fischer projection for compound C may be written as:



Note the α-glucosidase action will not allow us to specify the stereochemistry at the anomeric carbon of the pentose. Manipulation of the Fischer projection will allow us to draw the Haworth structure of the disaccharide:

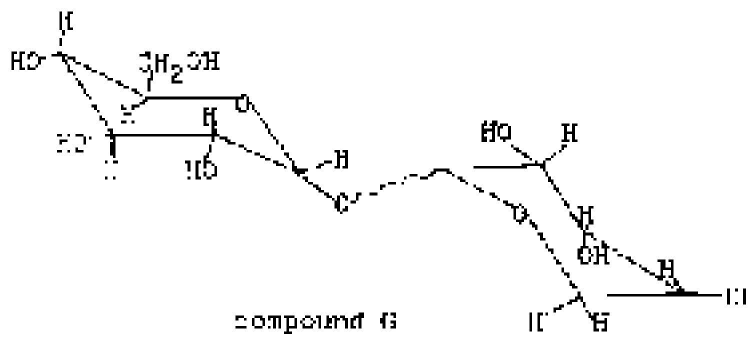


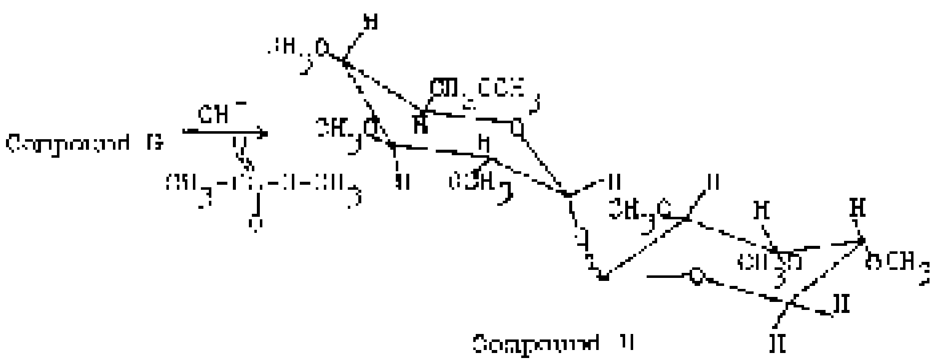
α-D-glucopyranoside

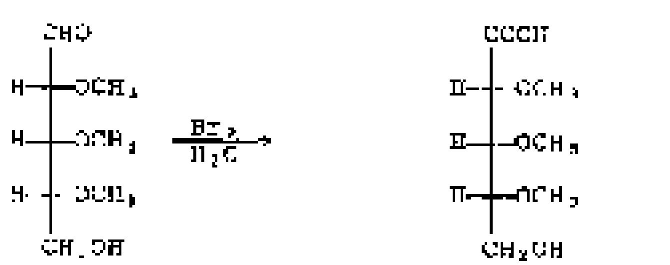


D-ribopyranose

Compound G may also be depicted as a combination of cyclohexane chair forms.





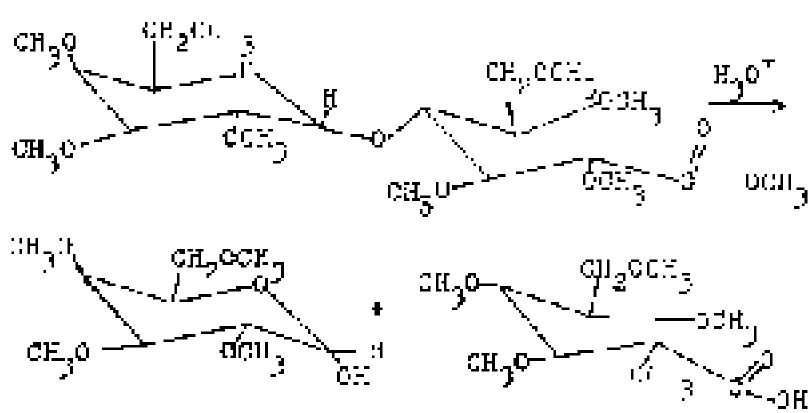


Compound I

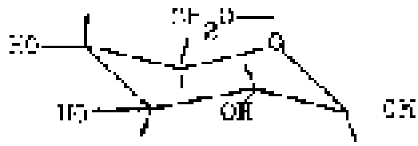
2,3,4-tri-O-methyl-D-ribonic acid

The disaccharide melibiose is hydrolyzed by dilute acid to a mixture of D-glucose and D-galactose. Melibiose is a reducing sugar and is oxidized by bromine water to melibionic acid, which is methylated by sodium hydroxide and dimethyl sulfate to octa-O-methylmelibionic acid. Hydrolysis of the latter gives a tetra-O-methylgluconic acid (A) and a tetra-O-methylgalactose (B). Compound A is oxidized by nitric acid to tetra-O-methylglucaric acid. Compound B is also obtained by the acidic hydrolysis of methyl 2,3,4,6-tetra-O-methylgalactopyranoside. Melibiose is hydrolyzed by an α-galactosidase from almonds. What is the structure of melibiose?

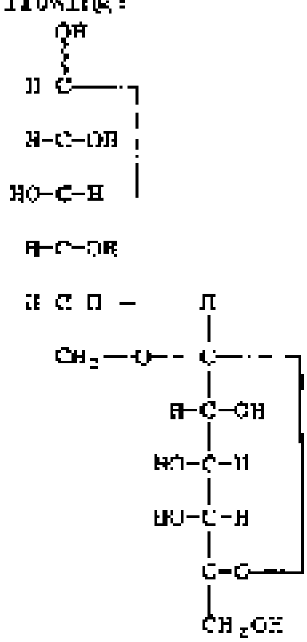
Solution: In a carbohydrate identification problem such as this, one first finds general characteristics of the unknown compound. Utilizing this broad data, we can discover more specific properties of the carbohydrate, eventually deducing the complete structure of the compound. A disaccharide is a carbohydrate that has two monosaccharide components. Here, we know that the monosaccharides making up the disaccharide are glucose and galactose. We are also informed that the disaccharide melibiose is a reducing sugar. This infers that one of the monosaccharides retains a hemiacetal linkage. This means that melibiose, unlike a disaccharide such as sucrose, will be in equilibrium with a carbonyl compound. However, the important questions remain to be answered: (1) Which sugar (glucose or galactose) will contain the hemiacetal linkage? (2) What is the respective sizes of each of the monosaccharide rings (furanose or pyranose)? (3) What is the nature of the acetal linkage between the monosaccharides (α or β)? Bromine water is a reagent which specifically oxidizes the carbonyl group of a reducing sugar to a carboxylic acid functionality. The subsequently formed carboxylic acid (an aldonic acid) is exhaustively methylated in a Williamson reaction. We note that the methyl groups attached to the hydroxyl oxygens will not be disrupted by hydrolysis, since these are part of ether linkages. However, the acetal linkage between the two sugars will be broken and the carboxylic acid functionality will be regenerated. For example, in the hydrolysis of the methyl ester of methylated maltobionic acid:



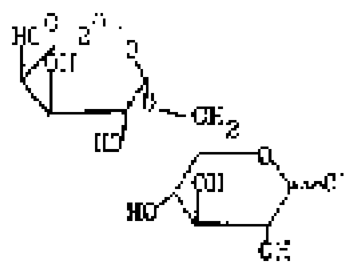
Hydrolysis of the methylated melibiose yields a tetra-O-methylgluconic acid (A) and a tetra-O-methylgalactose (B). Since the carboxylic acid is derived from glucose, it is glucose that has the hemiacetal linkage. Nitric acid is a potent oxidizing agent and it will convert any unprotected (unmethylated) hydroxyl group to a carboxylic acid functionality. Thus, since nitric acid transforms the gluconic acid into the glucaric acid, it is the hydroxyl group on carbon number six that is involved in the acetal bond with galactose. At this point we can depict the glucopyranosyl fragment of the carbohydrate as:



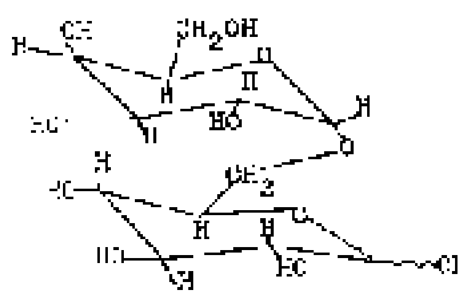
As seen previously, the acid hydrolysis of a methyl pyranoside will convert only the acetal linkage to a hydroxyl group. Since the hydroxyl group on carbon number five is not methylated, it must be involved in the intramolecular hemiacetal linkage and thus the galactose component of melibiose is a pyranose, bonding to glucose at carbon number one. Enzymes may promote the hydrolysis of carbohydrates. Since melibiose is hydrolyzed by an enzyme specific to α anomeric linkages (axial hydroxyl group at the anomeric carbon, which is the carbon involved in the hemiacetal formation), the acetal bond must be an α linkage. We designate melibiose in its Fischer projection form, Haworth projection and cyclohexane chair form in the following:



Fischer projection of melibiose

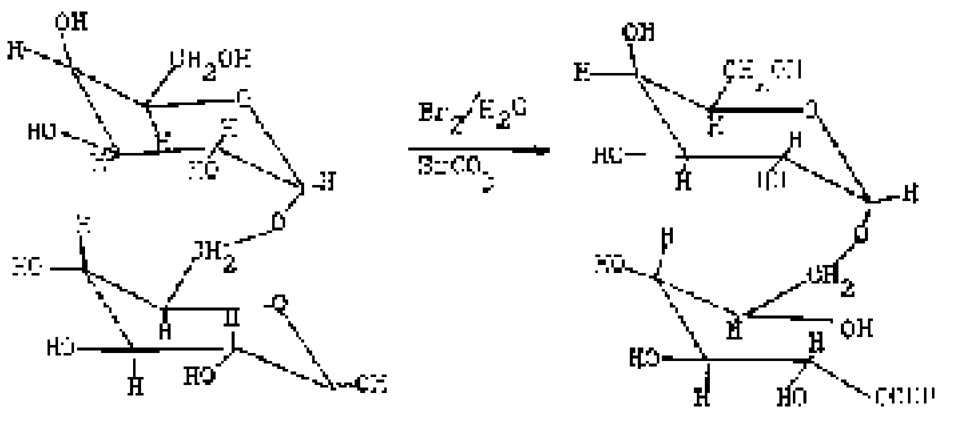


Haworth structure of melibiose

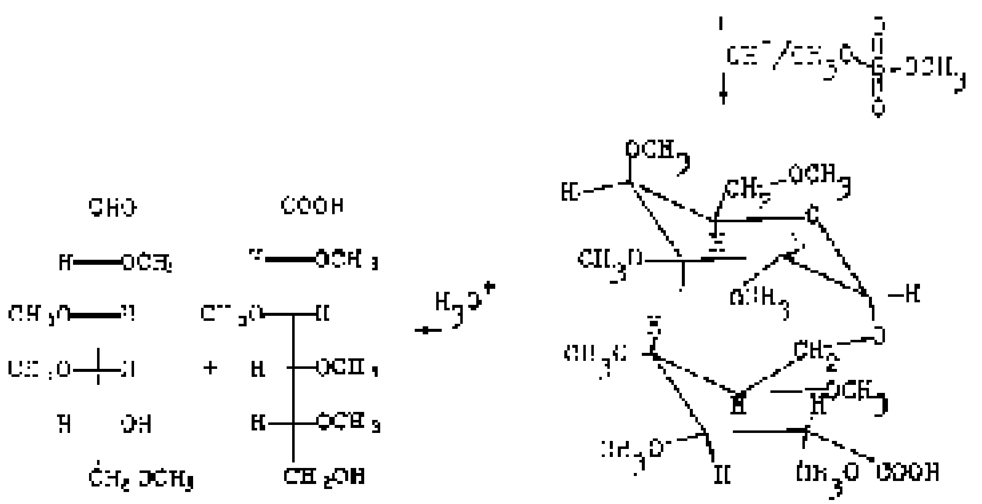


Cyclohexane conformation of melibiose

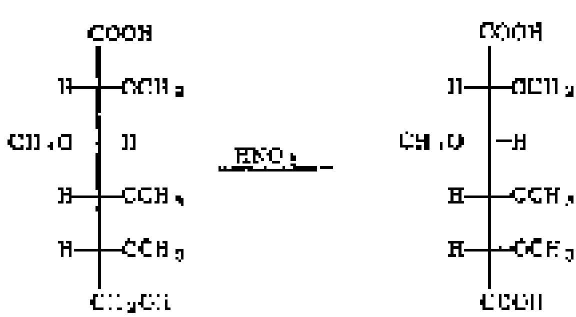
Note the various ways in which the α anomeric linkage is designated in the different types of structures. Utilising the structure of melibiose we can deduce compounds A and B and their related products.



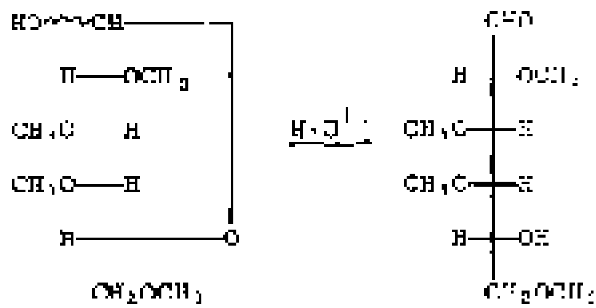
melibiose   melibionic acid



Compound B   Compound A   octa-O-methyl-melibionic acid



Compound A   tetra-O-methyl-glucaric acid



2,3,4,6 tetra O methyl-galactopyranoside

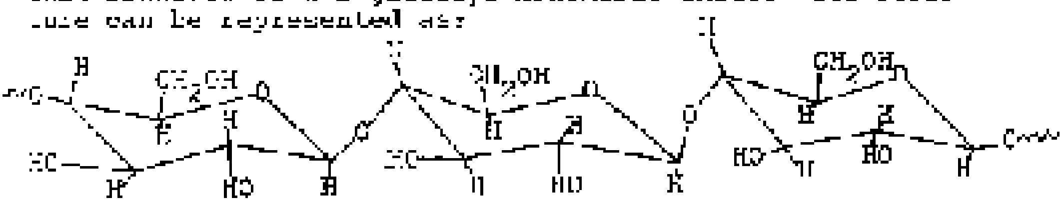
Compound B

POLYSACCHARIDES

• PROBLEM 31-13

Paper napkins, tissues, and similar items are composed largely of cellulose. What is the structure of cellulose? At one time there was a television commercial that showed how "concentrated stomach acid" (hydrochloric acid) could rapidly destroy such paper articles. What chemical reaction was occurring during this dissolution?

Solution: Cellulose is a large polymer found in nature that consists of β D glucosyl monomeric units. Its structure can be represented as:



Cellulose, like all glycosides, can be hydrolyzed in acid to its component sugars. Assuming complete hydrolysis, we depict this hydrolysis which is identical with the chemical reactions that destroy the paper articles as follows:

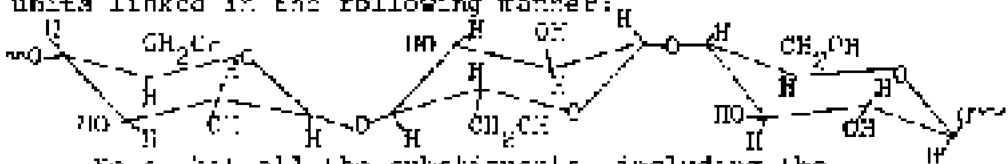
$\xrightarrow[H_2O]{HCl}$ n glucose units (both α and β)

We should note that this is a chemical reaction that would occur in a beaker as well as a human stomach. The human stomach does not have β-glucosidase unlike the termite which can readily digest wood, a cellulose by-product.

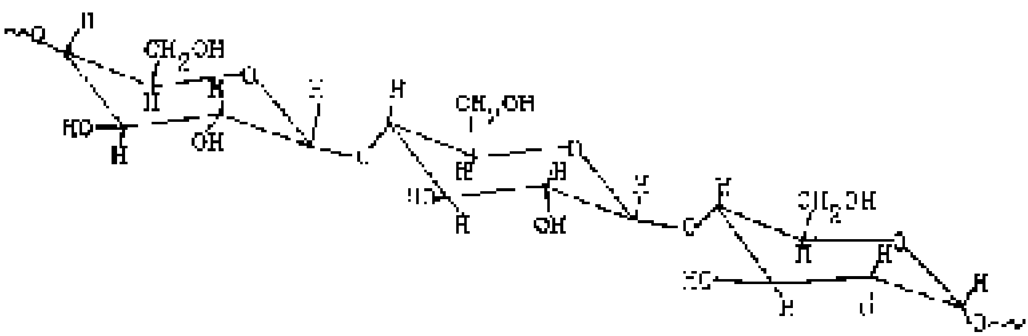
• PROBLEM 31-14

How can the D-glucoside units of cellulose produce a polymer with a stronger, more compact physical structure than the D-glucoside units of starch?

Solution: The polymer cellulose consists of glucose units linked in the following manner:



Note that all the substituents, including the anomeric oxygens are equatorial, creating a minimum of steric interaction. Thus, we see the basis for the prevalence of β-D-glucose in such natural compounds as cellulose. Starch contains α-D-glucosyl units and in its most stable conformation, the anomeric oxygens are axial. The slight diaxial steric interaction is destabilizing and accounts for the difference in the physical properties of starch and cellulose.

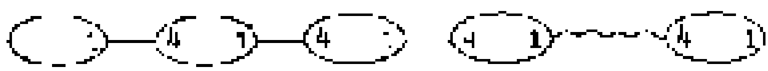


amylose
(a major constituent of starch)

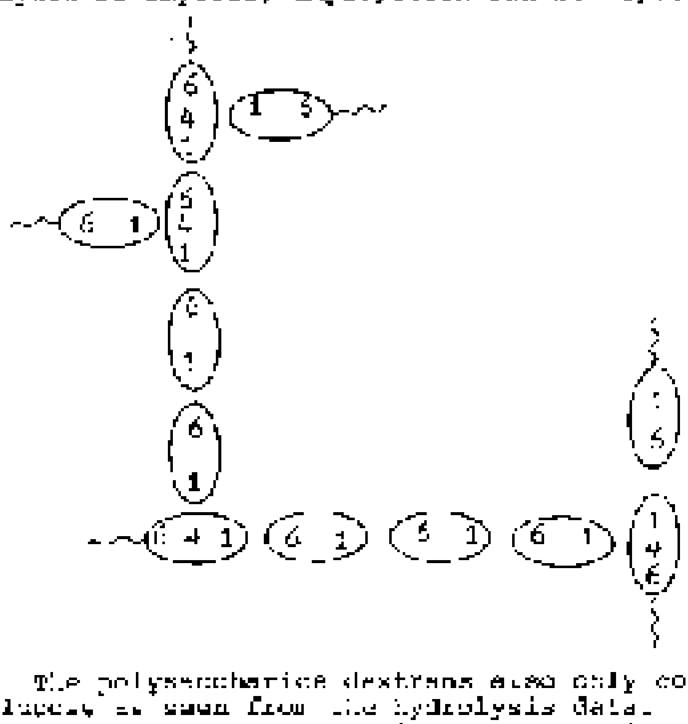
• PROBLEM 31-15

Polysaccharides known as dextrans have been used as substitutes for blood plasma in transfusions; they are made by the action of certain bacteria on (+)-sucrose. Interpret the following properties of a dextran: Complete hydrolysis by acid yields only D-(+)-glucose. Partial hydrolysis yields only one disaccharide and only one trisaccharide, which contain only α-glycosidic linkages. Upon methylation and hydrolysis, there is obtained chiefly 2,3,4-tri-O-methyl-D-glucose, together with smaller amounts of 2,4-di-O-methyl-D-glucose and 2,3,4,6-tetra-O-methyl-D-glucose.

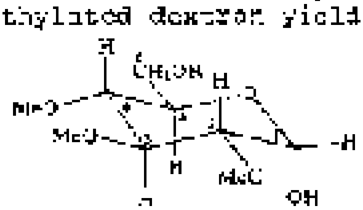
Solution: Polysaccharides are compounds that may contain thousands of monosaccharide units in a single molecule. The common polysaccharide, starch, contains two carbohydrate fractions which are named respectively as amylose and amylopectin. Both contain D-glucosyl monosaccharide units but amylopectin is a branched molecule while amylose consists of long straight chains. The structures of the two can be differentiated by the analytical method of end group analysis which involves a sequential methylation and hydrolysis of the compound. Hydrolysis of methylated amylose yielded 2,3,4,6-tetra-O-methyl-D-glucose in minute amounts with the remainder of the product being 2,3,6-tri-O-methyl-D-glucose. Since the free hydroxyl groups are involved in glycoside formation, the first fragment represents the initial monosaccharide unit of an amylose chain while the second moiety depicts the additional monosaccharide units of amylose. Thus, amylose consisted of D-glucosyl units linked at C_1 and C_4.



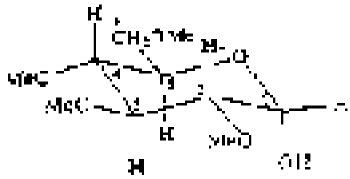
Hydrolysis of methylated amylopectin yielded 2,3,6-tri-O-methyl-D-glucose, 2,3,4,6-tetra-O-methyl-D-glucose and 2,3-Di-O-methyl-D-glucose in the approximate respective ratio of 90 : 5 : 5. Following the approach in the analysis of amylose, amylopectin can be depicted as:



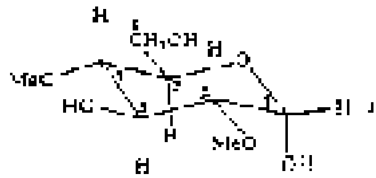
The polysaccharide dextrans also only contains D-glucose as seen from the hydrolysis data. Hydrolysis of the methylated dextran yields 2,3,4-tri-O-methyl-D-glucose



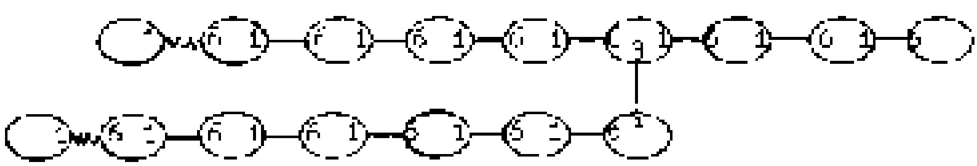
in large amounts and smaller, equal amounts of 2,3,4,6-tetra-O-methyl-D-glucose



and 2,4-di-O-methyl-D-glucose respectively.



We can determine the structure of dextran, a poly-α-D-glucopyranoside, by noticing how these fragments reveal the points of attachments, or in other words, what carbons are involved in glycoside linkages. 2,3,4-tri-O-methyl-D-glucose, the most common unit, is the chain forming unit with attachments at C_1 and C_6. 2,3,4,6-tetra-O-methyl-D-glucose with an attachment only at C_1 represents the terminal unit. 2,4-di-O-methyl-D-glucose has attachments at C_1, C_3 and C_6 and is the source of the chain-linking. Note that the latter two of the mentioned units must occur in equal amounts since they form the branch. Thus, we may depict dextran schematically as:



A dextran

CHARACTERIZATION TESTS

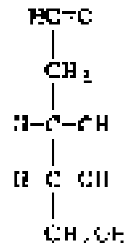
• PROBLEM 31-10

Will 2-deoxyribose form an osazone? Why?

Solution: A useful reaction of carbohydrates is their formation of osazones (bisphenylhydrazones) on treatment with excess phenylhydrazine. The mechanism is debatable but probably involves the tautomerization of the initially formed imine to the enol of a carbonyl group that also reacts with phenylhydrazine. The net reaction for this process is:

$$\begin{array}{l} CHO \\ | \\ CHOH \\ | \\ R \end{array} + 3C_6H_5NH_2 \xrightarrow[-NH_3]{-H_2O} \begin{array}{l} HC{=}N{-}NHC_6H_5 \\ | \\ C{=}N{-}NHC_6H_5 \\ | \\ R \end{array} + C_6H_5NH_2$$

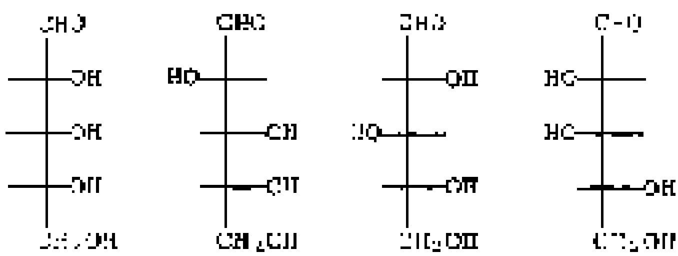
2-deoxyribose has the structure:



The methylene group at C_2 will not be oxidized to a carbonyl (or a hydroxyl) and the sugar will form a phenyl hydrazone but not an osazone. Osazone formation is specific to α-hydroxy carbonyl compounds.

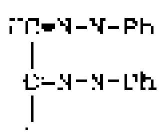
• PROBLEM 31-17

Which of the four D-aldopentoses shown below will form identical osazones?



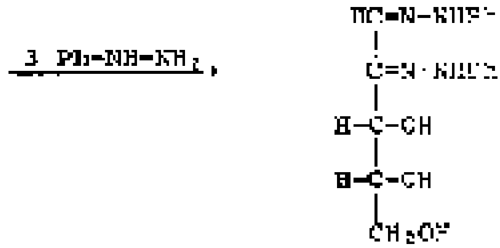
Ribose   Arabinose   Xylose   Lyxose

Solution: The reaction of α-hydroxyl carbonyl compounds with excess phenylhydrazine produces osazones of the general structural formula:

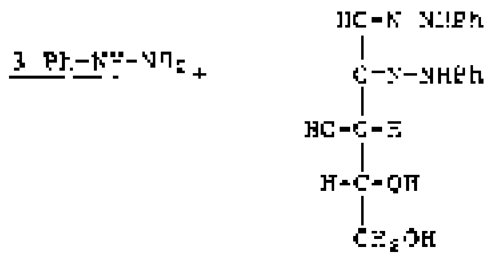


. Since chirality is lost at the C_2 carbon which bears the hydroxyl group, epimers at C_2 (compounds differing in configuration at only C_2) will yield identical osazones. Thus, D-glucose and D-mannose give the same osazone. D-fructose also produces the osazone of these sugars because all three monosaccharides have identical configurations at C_3, C_4, and C_5. In this problem, D-ribose will give the same osazone as D-arabinose because of their identical configurations at C_3 and C_4. For the same reason, D-xylose gives the same osazone as D-lyxose.

D-Ribose
and
D-Arabinose



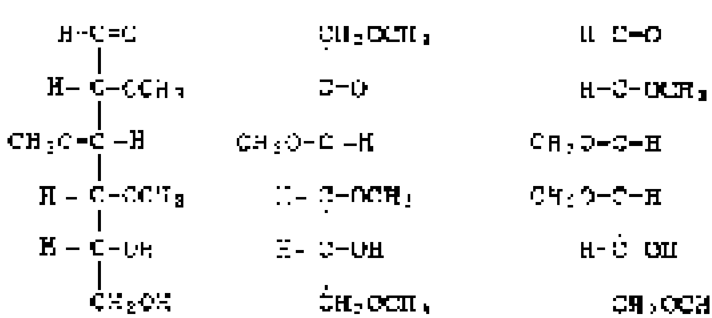
D-Xylose
and
D-Lyxose



• PROBLEM 31-18

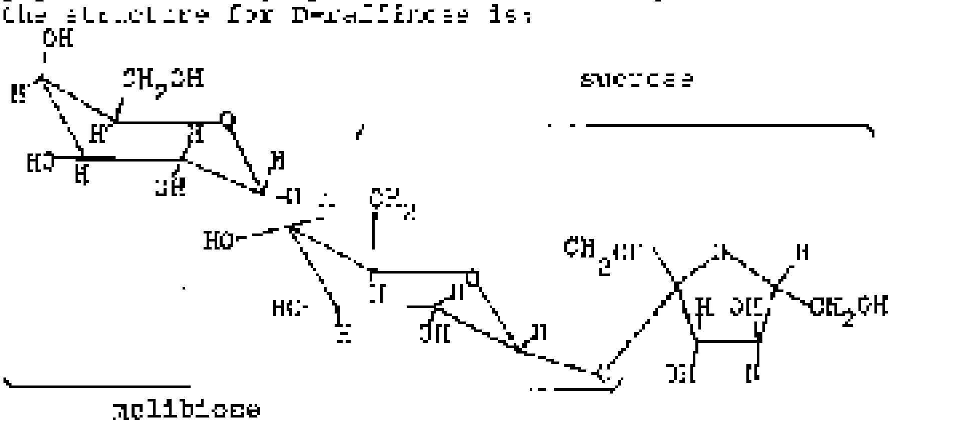
D-Raffinose is a trisaccharide that does not react with Fehling's solution. Upon hydrolysis it produces D-glucose, D-galactose, and D-fructose. Completely methylated raffinose is hydrolyzed to 2,3,4-tri-O-methylglucose, 1,3,4,6-tetra-O-methylfructose, and 2,3,4,6-tetra-O-methylgalactose. What structures for raffinose are consistent with these data? What further information, if any, is required to identify completely the structure of raffinose?

Solution: A trisaccharide is a carbohydrate that consists of three monosaccharides. Hydrolysis breaks the glycosidic bonds between the monosaccharides and we note that D-raffinose is made up of D-glucose, D-galactose and D-fructose. We can determine the ring size and the order of the component sugars by examining the products of D-raffinose's methylation and hydrolysis. These compounds are:



2,3,4-tri-O-methylglucose　　1,3,4,6-tetra-O-methylfructose　　2,3,4,6-tetra-O-methylgalactose

Since the free hydroxyls on the methylated sugars were involved in the intramolecular hemiacetal formation, they inform us of the ring size of each monosaccharide. The D-glucose and D-galactose exist in D-raffinose as pyranoses while D fructose is a furanose. Since D glucose possesses a free hydroxyl on C_6 as well as C_1, it is located between D-galactose and D-fructose. Fehling's solution tests for the presence of a free aldehyde with the appearance of the red precipitate Cu_2O. It involves the reduction Cu^{++} to Cu^{+}. Since Fehling's solution gives a negative result for D-raffinose, this carbohydrate has no free carbonyl group and does not mutarotate. From this data, the sequence of sugars is galactose-glucose-fructose. However, we cannot determine whether fructose or galactose is linked to the anomeric carbon of glucose. In addition, we don't know if the glycosidic linkages are α or β. Suppose we are given the additional information that hydrolysis induced by an enzyme specific for a certain glycosidic linkage yields fructose and melibiose (6-O-α-D-galactopyranosyl-(1,6)-D-glucopyranose). An enzyme specific for another type of glycosidic linkage produces sucrose and galactose. Thus, the structure for D-raffinose is:



CHAPTER 32

AMINO ACIDS AND PROTEINS

AMINO ACIDS: STRUCTURE, PROPERTIES AND PREPARATION

• PROBLEM 32-1

> In quite alkaline solution, an amino acid contains two basic groups, $-NH_2$ and $-COO^-$. Which is the more basic? To which group will a proton preferentially go as acid is added to the solution? What will the product be?

Solution: An amino acid is any compound containing both an acid group and an amino group; however, it is generally used to mean an α-amino carboxylic acid of the general formula:

$$R-\underset{\displaystyle NH_2}{\underset{|}{C}H}-COOH$$

Their physical and chemical properties include

(a) They are non-volatile crystalline solids that do not melt until they decompose at fairly high temperatures.

(b) They are insoluble in non-polar solvents and are appreciably soluble in water.

These properties suggest that they are salt-like molecules, and therefore exist as zwitterions (dipolar ions) of the form:

$$R-\underset{\displaystyle {}^{+}NH_3}{CH}-\overset{\displaystyle O}{\overset{\|}{C}}-O^-$$

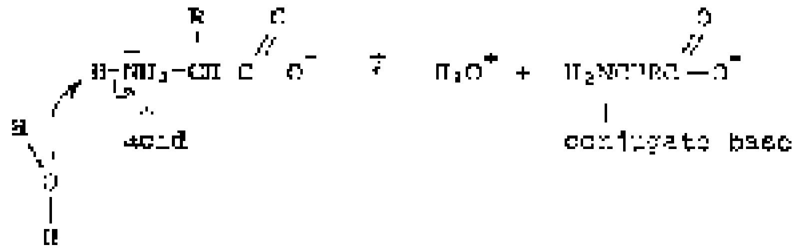
We can quantitatively conclude from this that the $-NH_2$ group is more basic than the $-\overset{O}{\overset{\|}{C}}-O^-$ group;

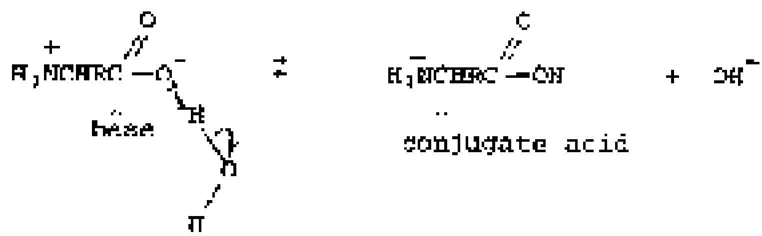
$$(1)\quad R-\underset{\substack{|\\ NH_2\\ +\\ \text{stronger base}}}{CH}-\overset{O}{\overset{\|}{C}}-\underset{\substack{\uparrow\\ \text{stronger acid}}}{OH} \rightleftharpoons R-\underset{\substack{{}^{+}NH_3\\ +\\ \text{weaker}\\ \text{acid}}}{CH}-\overset{O}{\overset{\|}{C}}-\underset{\text{weaker base}}{O^-}$$

Experimental data is necessary to obtain their respective K_b's. Using glycine as an example, it has

$K_a = 1.6 \times 10^{-10}$ and $K_b = 2.5 \times 10^{-12}$.

Looking at the acid-base equations:

(2) 

(3) 

We see that the measured K_a actually refers to the acidity of the ammonium ion $(-\overset{+}{N}H_3)$, while the K_b refers to the basicity of the carboxylate ion $\left[-C{\overset{O}{\diagup\!\!\diagup}}\!\!-O^-\right]$, which is 2.5×10^{-12}. In order to get the K_b of the $-NH_2$ group, we must use the expression: $K_a \times K_b = 10^{-14}$; that is, in aqueous solution, the acidity and basicity of an acid and its conjugate base are related by the expression

$$K_a \times K_b = K_w = 10^{-14}.$$

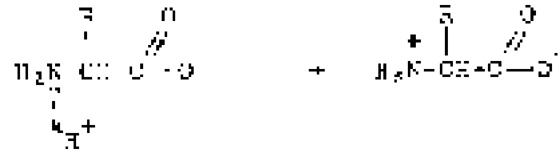
From Equation (2), we see that the conjugate base of $-\overset{+}{N}H_3$ is NH_2, therefore using the K_a value of 1.6×10^{-10} for $-\overset{+}{N}H_3$,

$$K_b = \frac{10^{-14}}{1.6 \times 10^{-10}} = 6.3 \times 10^{-5}$$

we can conclude that NH_2 is more basic than $\overset{O}{\overset{\diagup\!\!\diagup}{C}}\!-O^-$:

$$K_{b(NH_2)} = 6.3 \times 10^{-5} >> K_b\left[C{\overset{O}{\diagup\!\!\diagup}}\!-O^-\right] = 2.5 \times 10^{-12}$$

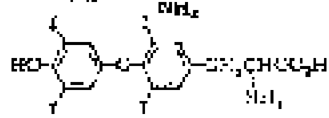
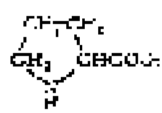
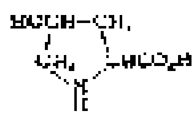
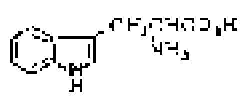
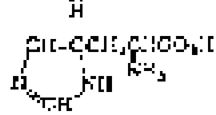
As acid is added to the solution, the proton will preferentially go to the stronger base, $-NH_2$. The product will be the zwitterion:



◆ PROBLEM 32-2

Which of the amino acids in the table shown are "acidic" amino acids and which "basic" amino acids? Which of the structures shown would have the most basic nitrogen? The least basic amino nitrogen? The most acidic and least acidic carboxyl group? Give the reasons for your choices.

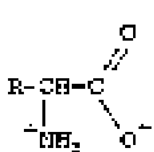
Name	Abbreviation	Formula	Isoelectric point, pH units	Water solubility at isoelectric point,[b] g/100 g/25°C
glycine	Gly	$NH_2CH_2CO_2H$	6.0	22.5
alanine	Ala	$CH_3CH(NH_2)CO_2H$	6.0	15.8
valine*	Val	$(CH_3)_2CHCH(NH_2)CO_2H$	6.0	6.8
leucine*	Leu	$(CH_3)_2CHCH_2CH(NH_2)CO_2H$	6.0	[illegible]
isoleucine*	Ileu	$CH_3CH_2CH(CH_3)-CH(NH_2)CO_2H$	6.0	2.1
phenylalanine*	Phe	$C_6H_5CH_2CH(NH_2)CO_2H$	[illegible]	2.7
serine	Ser	$HOCH_2CH(NH_2)CO_2H$	5.7	4.3
threonine*	Thr	$CH_3CH(OH)-CH(NH_2)CO_2H$	[illegible]	1.6
lysine*	Lys	$NH_2(CH_2)_4CH(NH_2)CO_2H$	9.6	very sol.
δ-hydroxylysine	Lys-OH	$NH_2CH_2CH(OH)(CH_2)_2CH(NH_2)CO_2H$	9.15	very sol.
arginine	Arg	$(NH_2)_2C{=}N(CH_2)_3CH(NH_2)CO_2H$	11.2	very sol.
aspartic acid	Asp	$HO_2CCH_2CH(NH_2)CO_2H$	2.8	0.4

asparagine	Asp-NH_2	$NH_2COCH_2CHCO_2H$ (NH_2 on the α-carbon)	5.4	2.4
glutamic acid	Glu	$HO_2C(CH_2)_2CHCO_2H$ (NH_2 on the α-carbon)	3.2	[illegible]
glutamine	Glu-NH_2	$NH_2CO(CH_2)_2CHCO_2H$ (NH_2 on the α-carbon)	5.7	[illegible]
cysteine	CySH	$HSCH_2CHCO_2H$ (NH_2 on the α-carbon)	5.[illegible]	very sol.
cystine	CyS CySS	[illegible] $S-CH_2CHCO_2H$ (NH_2 on the α-carbon) | $S-CH_2CHCO_2H$ (NH_2 on the α-carbon)	5.0	[illegible]
methionine[b]	Met	$CH_3S(CH_2)_2CHCO_2H$ (NH_2 on the α-carbon)	[illegible]	3.3
tyrosine	Tyr		5.[illegible]	0.0[illegible]
thyroxine	Thy			
proline	Pro		6.3	[illegible]
hydroxyproline	Hypro		[illegible]	[illegible]
tryptophan[b]	Try		[illegible]	1.1
histidine	His		7.[illegible]	[illegible]

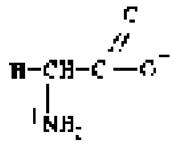
[a] Refers to the L isomer. The DL mixtures are usually less soluble.

[b] Must be included in diet for maintenance of normal nitrogen equilibrium in normal adult humans.

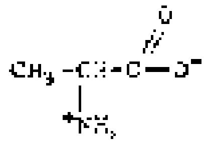
Solution: In order to determine the acidity and basicity of the various amino acids, we must draw out their structural formulas and analyze them. The structure of a neutral amino acid is best represented by the switterion (dipolar ion) form:



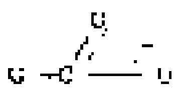
Therefore, in determining the acidity of the various amino acids, the zwitterion form will be used.

(a) glycine: 

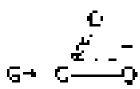
The hydrogen (R-H) has little effect on either ionic groups, therefore glycine is approximately neutral.

(b) alanine: 

The methyl group, like all alkyl groups, is electron-releasing, therefore it will stabilize the ammonium ion and destabilize the carboxylate anion:

(a) 

G (substituent) withdraws electrons: stabilizes anion, strengthens acid.

(b) 

G releases electrons: destabilizes anion, weakens acid.

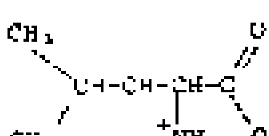
(c) $G \longleftarrow C-\overset{+}{N}H_3$

G withdraws electrons: destabilizes cation, weakens base.

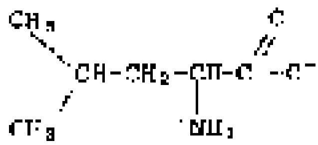
(d) $G \longrightarrow C-\overset{+}{N}H_3$

G releases electrons: stabilizes cation, strengthens base.

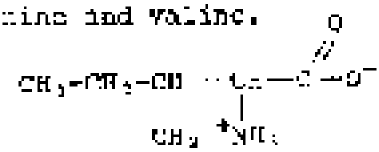
However, the inductive effect of alkyl groups is very slight and alanine is approximately neutral. Note that if the inductive effect of an electron-withdrawing substituent is very strong, it will stabilize the anion greatly and destabilize the cation greatly. This will result in the release of a proton by the carboxyl group much more readily than the acceptance of a proton by the amino group, causing the molecule, as a whole, to be acidic.

(c) valine: 

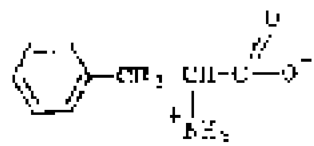
The inductive effect of the alkyl group is again very small, therefore valine is also approximately neutral.

(d) leucine: 

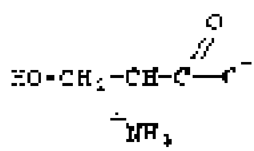
Same as alanine and valine.

(e) isoleucine: 

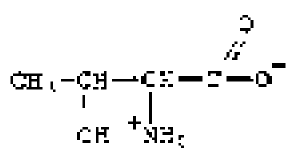
Same as alanine and valine.

(f) phenylalanine) 

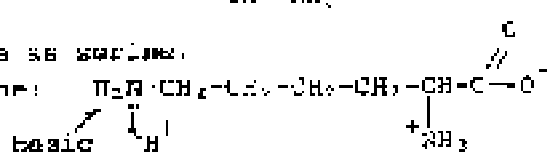
The benzyl group is slightly electron-withdrawing, but this effect is small and phenylalanine is approximately neutral.

(g) serine: 

The alcohol group is electron-withdrawing, but the effect on the ionic groups is small, therefore it is approximately neutral.

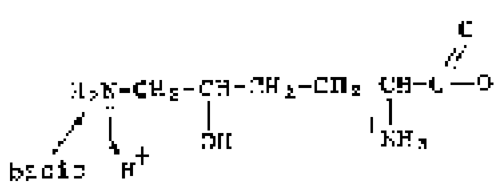
(h) threonine: 

Same as serine.

(i) lysine: 

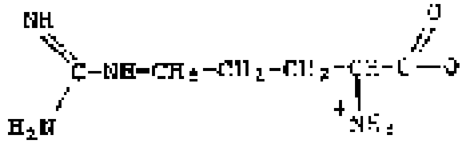
The amino group on the side-chain is basic, therefore lysine, as a whole, is basic.

(j) δ-hydroxylysine:

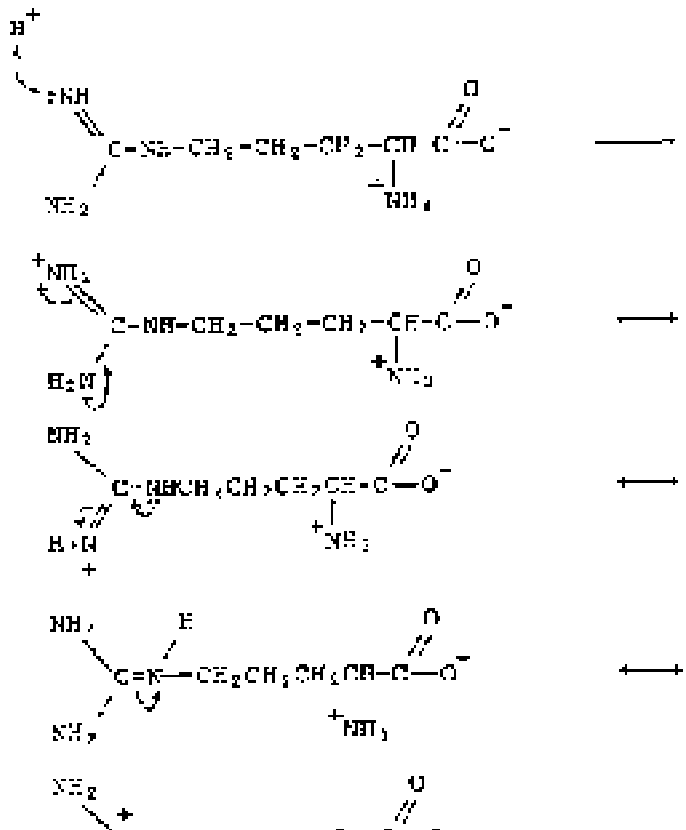


Same as lysine - basic.

(k) arginine:

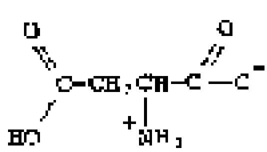


The imine group is basic; upon protonation, resonance stabilization of the cation renders arginine strongly basic:

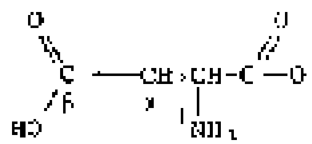


Delocalization of the positive charge causes the nitrogen on arginine to be the most basic, and hence its carboxylic group the least acidic of the amino acids in the table.

(l) aspartic acid:



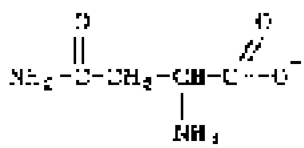
The carboxyl group $\left[-\overset{O}{\overset{\|}{C}}-OH\right]$ on the side chain is acidic, therefore it should dissociate in solution, making aspartic acid and acid. Of greater importance is the strong electron-withdrawing inductive effect of the β-$\overset{O}{\overset{\|}{C}}$—OH group:



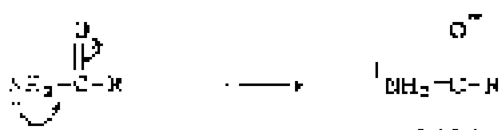
electron-withdrawing; stabilizes anion, destabilizes cation.

This renders the carboxylic group of aspartic acid the most acidic, and hence its amino group the least basic, of the amino acids in the table.

(m) asparagine:



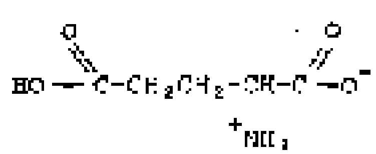
The amide group on the side-chain is slightly electron withdrawing, but this effect is small, therefore asparagine should be approximately neutral. Note that an amide group is not basic due to loss of resonance upon protonation:



resonance-stabilized amide

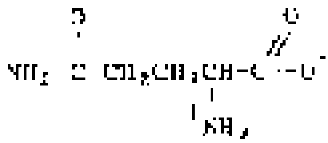
$^{+}NH_3-\overset{O}{\overset{\|}{C}}-R$: electrons on nitrogen can no longer participate in resonance.

(n) glutamic acid:



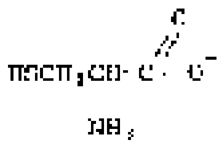
Same as aspartic acid, except the inductive effect of the $\overset{O}{\overset{/\!/}{C}}$—OH is now decreased due to the longer distance of the side chain. This will cause glutamic acid to be less acidic than aspartic acid.

(o) glutamine:



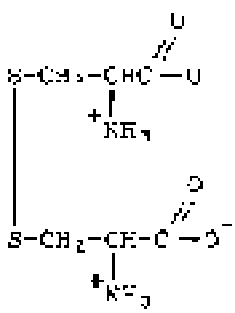
Same as asparagine.

(p) cysteine:



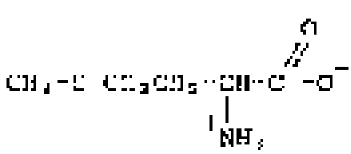
The thiol group (-SH) on the side chain has little effect on the acidity of this amino acid, therefore it should be approximately neutral.

(q) cystine:



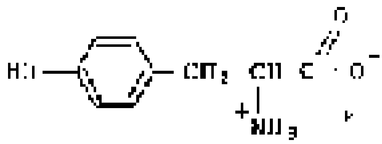
The disulfide group has little effect on the acidity of the amino acid, therefore cystine is approximately neutral.

(r) methionine:



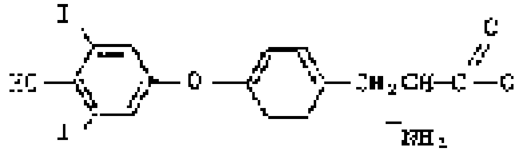
The sulfide group has little effect on the acidity of the amino acid, therefore methionine is approximately neutral.

(s) tyrosine:



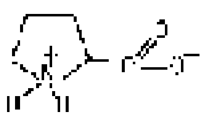
The side-chain is strongly electron-withdrawing, thereby stabilizing the anion and destabilizing the cation, causing tyrosine to be acidic.

(t) thyroxine:



Same as tyrosine -- acidic.

(u) proline:

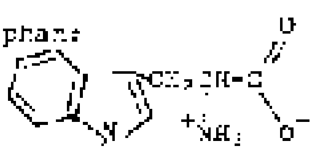


The alkyl ring has little effect on the acidity, therefore proline should be approximately neutral.

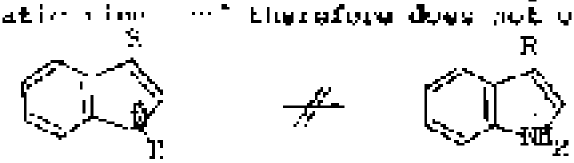
(v) hydroxyproline:

Same as proline.

(w) tryptophan:



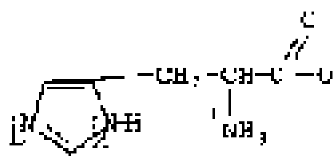
The side-chain has little effect on the acidity, therefore the amino acid is approximately neutral. Note that protonation of the side-chain nitrogen would disrupt the aromatic ring and therefore does not occur:

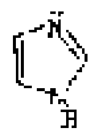


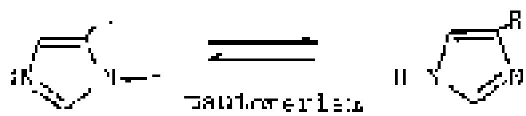
Aromatic — 10 π electrons (Hückel number) in two fused aromatic rings (the lone-pair electrons on nitrogen participate in the π cloud).

five-member ring is not aromatic, since the lone-pair electrons on nitrogen can no longer participate in a cyclic π cloud.

(x) histidine:



The side-chain has little effect on the acidity, therefore the amino acid is approximately neutral. Note that (N_2) is not basic for the same reason as the nitrogen in tryptophan. The azole nitrogen (N_1) is only slightly basic (pK_a of imidazole  is 7) for two reasons: (1) the lone-pair electrons on the azole nitrogen occupy sp^2 orbitals, therefore they are held more tightly than amine lone pair electrons in sp^3 orbitals, rendering them much less basic; (2) in solution, tautomers are in rapid equilibrium, rendering the two nitrogens equivalent:



This further lowers the basicity of the imidazole ring.

I- Summary:

Acidic amino acids: aspartic acid, glutamic acid, tyrosine, thyroxine.

Basic amino acids: lysine, δ-hydroxylysine, arginine, asparagine.

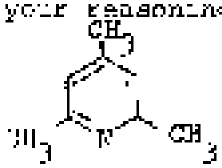
Most basic nitrogen: arginine.

Least basic amino nitrogen: aspartic acid.

Most acidic carboxyl group: aspartic acid.

Least acidic carboxyl group: arginine.

Arrange the following amino acids in order in which you would expect each to move in a paper chromatogram with the weak organic base, 2,4,6-collidine, as the organic phase; glycine, phenylalanine, arginine, and glutamic acid. Show your reasoning.

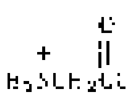


2,4,6-collidine

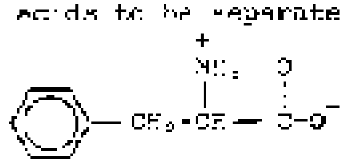
Solution: The movement of the amino acids on a paper chromatogram will depend upon their relative acidities. The acidities of the amino acids may be distinguished by using a weak organic base (in this case, 2,4,6-collidine). A strong acid will be strongly held by the base and will hence move at a relatively slow rate on the paper chromatogram. The weakest acid will move fastest on the paper chromatogram.

Amino acids in neutral solutions exist as zwitterions of the general form $H_3\overset{+}{N}CHRCOO^-$.

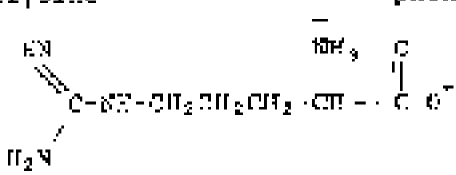
By comparing the amino acids' basicities, the relative rate at which they will move up a column, may be determined. The amino acids to be separated are:



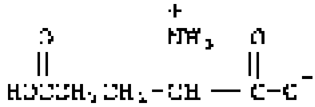
glycine



phenylalanine

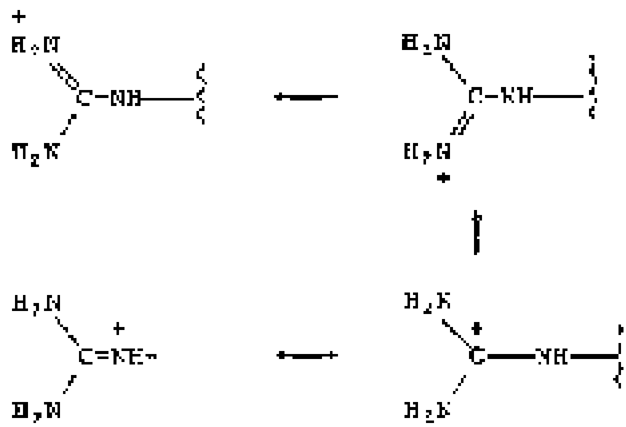


arginine



glutamic acid

The most easily protonated amino acid is arginine due to the resonance stabilized species that is formed. Protonation occurs at the imino nitrogen (HN=). The resonance stabilization of the resulting species is shown as:

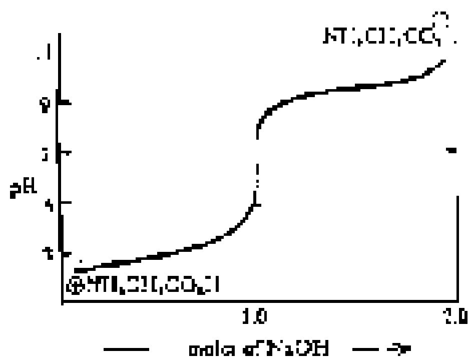


Hence arginine is the most basic (least acidic) of the amino acids being considered. The least easily protonated amino acid is glutamic acid. This is due to the electron withdrawing effect of the carboxylic acid group $\left[-\overset{\overset{\displaystyle O}{\|}}{C}-OH\right]$. In the zwitterion the $-\overset{+}{N}H_3$ is destabilized and the $-\overset{\overset{\displaystyle O}{\|}}{C}-O^-$ is stabilized. This means that it is easier to lose a proton from the carboxyl group than it is to gain a proton at the amino group; hence the compound is acidic. In fact, that the compound is the most acidic of the amino acids considered is clearly evident from the presence of a second carboxyl group, which, itself, has acidic properties. Thus glutamic acid, being the only dicarboxylic amino acid, is the most acidic one.

The relative acidities of glycine and phenylalanine are determined by analyzing the effects of their R groups upon the $-\overset{+}{N}H_3$ and $\overset{\overset{\displaystyle O}{|}}{C}\,O^-$ portions in their zwitterions. As compared with the hydrogen in glycine, the benzene ring of phenylalanine has a slight electron withdrawing effect, thus destabilizing the $-\overset{+}{N}H_3$ and stabilizing the $-\overset{\overset{\displaystyle O}{\|}}{C}-O^-$. Hence the ability to lose a proton is greater in phenylalanine than in glycine. As a result phenylalanine is more acidic than glycine. The relative acidity of the four amino acids is: glutamic acid > phenylalanine > glycine > arginine.

Since the relative rates of movement of amino acids in a paper chromatogram is the reverse of the relative acidities, the relative rates of the amino acids in a paper chromatogram is: arginine > glycine > phenylalanine > glutamic acid.

Suppose one were to titrate an equimolal mixture of ammonium chloride and acetic acid with two equivalents of sodium hydroxide. How would the neutralization of acetic acid and ammonium chloride be expected to differ from that of glycine hydrochloride shown in the figure below?



Titration curve of glycine, $NH_2CH_2CO_2H$.

Solution: The titration curve of glycine hydrochloride shows a sharp change in pH when one mole of NaOH has been added. This is due to the neutralization of glycine hydrochloride to neutral glycine, which undergoes an intramolecular acid-base reaction to form the zwitterion. The titration curve of an equimolal solution of ammonium chloride and acetic acid shows a gradual change in pH at one mole of NaOH. This difference is due to the fact that glycine hydrochloride is more acidic than both ammonium chloride and acetic acid. This greater acidity is due to electron withdrawing effect of the $-\overset{+}{N}H_3$ portion; it stabilizes the resulting carboxylate anion. Hence there is greater neutralization of glycine hydrochloride than of ammonium chloride and acetic acid by one mole of NaOH.

The neutralization of glycine hydrochloride is shown as:

$$\overset{-}{Cl}\ \ \overset{+}{H_3N}-CH_2\overset{\overset{O}{\|}}{C}OH \quad + \quad Na^+\ \overset{-}{O}H \quad \xrightarrow[-\ H_2O]{-\ NaCl}$$

glycine hydrochloride

$$H_2N-CH_2-\overset{\overset{O}{\|}}{C}OH \quad \rightleftharpoons \quad \overset{+}{H_3N}-CH_2-\overset{\overset{O}{\|}}{C}-O^-$$

neutral glycine $\qquad\qquad$ glycine zwitterion

$$\overset{+}{H_3N}-CH_2-\overset{\overset{O}{\|}}{C}-\overset{-}{O} \quad + \ Na\ \overset{-}{O}H \quad \xrightarrow[-\ H_2O]{}$$

$$H_2N-CH_2-\overset{O}{\overset{\|}{C}}-O^-\ Na^+$$

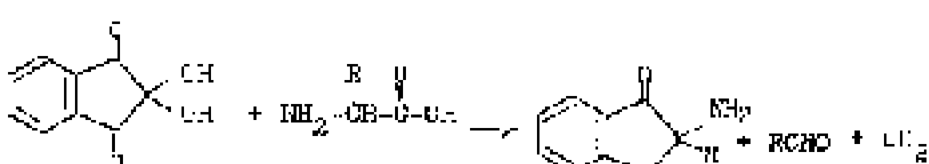
sodium salt of glycine

(conjugate base of glycine)

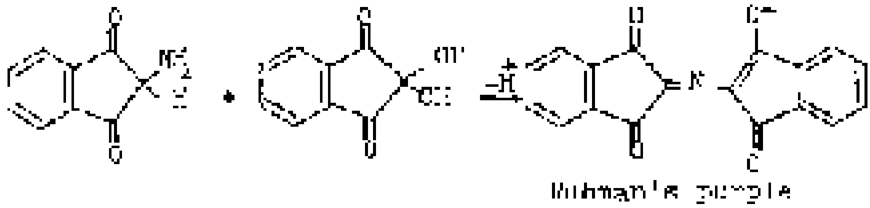
• PROBLEM 32-5

> Suggest a way to separate a mixture of amino acids into three fractions: monoamino monocarboxylic acids, monoamino dicarboxylic acids (the acidic amino acids), and diamino monocarboxylic acids (the basic amino acids).

Solution: The separation of a mixture of amino acids can be accomplished in quite a few ways. Perhaps the method most often used is ion exchange chromatography. This method uses a column of sulfonated polystyrene resin, a cation exchanger (other cation-exchange resins and anion exchange resins may also be used), into which the amino acid mixture is placed at pH 3. Under these conditions, the individual amino acids are positively charged, and will displace some of the sodium ions from the $-SO_3^-Na^+$ form of the column. Hence the amino acids are bound to the column material by electrostatic forces. Since the most basic amino acids have the most positive charges they will be bound most tightly, while the least basic amino acids are bound least tightly. The column is then developed by gradually increasing the pH and ionic strength of the buffers with which the column is washed. This causes a gradual neutralization of the positive charges on the amino acids, and thereby weakens the salt linkages of the amino acids to the column material. Therefore, as the column is developed, the acidic amino acids (e.g. aspartic acid – a mono amino dicarboxylic acid) are the first ones to be removed, followed by the neutral amino acids (e.g. glycine – a monoamino mono carboxylic acid), followed, finally, by the basic amino acids (e.g. lysine – a diamino monocarboxylic acid). As the amino acids are eluted from the column, they are collected individually in separate flasks. Once separated, the individual amino acids are quantitated by reaction with ninhydrin and measurement of the resultant color:



Ninhydrin amino acid



This absorption is nearly a linear function of the amount of amino acids originally present, therefore a quantitative colorimetric assay is possible. Automatic amino acid analyzers, some of which use this principle, are commercially available (see Fig. 1).

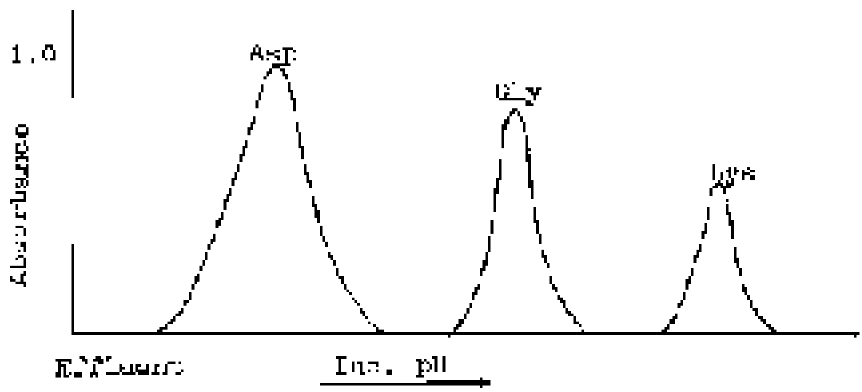


Fig. 1. Amino acid chromatogram by an automatic amino acid analyzer.

Other amino acid separation techniques include: (1) paper chromatography: amino acids are separated by their differences in partition coefficients between water and an organic solvent. The amino acid mixture is applied to an appropriate paper support, and then irrigated with a developing liquid composed of aqueous and organic components. The organic phase migrates up the paper by capillary action while the aqueous phase is stationary. Therefore, amino acids that are more soluble in the organic phase move more rapidly than those that are less soluble. In two-dimensional chromatography, the chromatogram is developed first in one direction with one solvent system, then rotated 90°, and developed a second time with a second solvent system. The individual amino acids are located by the use of ninhydrin (see Fig. 2).

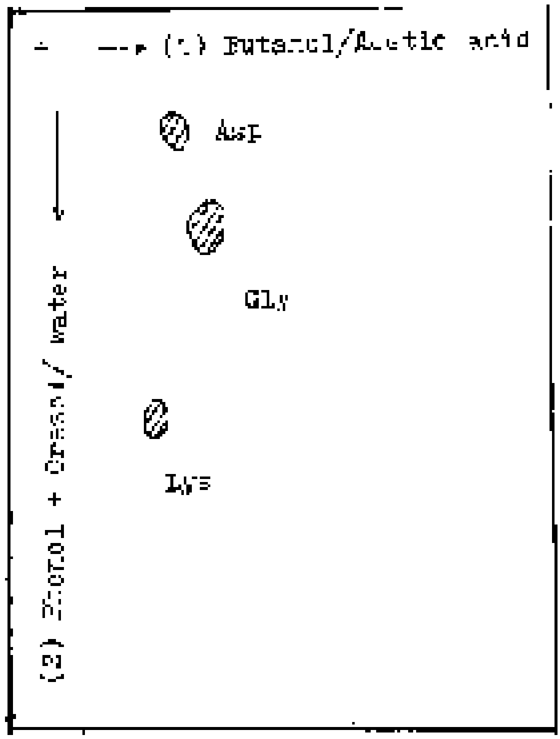


Fig. 2 - Two-dimensional chromatogram of an amino acid mixture.

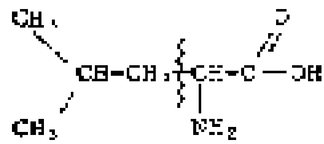
(2) Electrophoresis - an amino acid mixture on a suitable support is placed in an electric field. Due to the charge differences between the amino acids at appropriate values of pH, different amino acids will migrate differently in the electric field. For example, at neutral pH, acidic amino acids (e.g. aspartic acid - monoamino dicarboxylic acid) will migrate toward the anode, neutral amino acids (e.g. glycine - a monoamino monocarboxylic acid) will migrate to an area between the anode and the cathode, while the basic amino acids (e.g. lysine - a diamino monocarboxylic acid) will migrate toward the cathode.

• PROBLEM 32-8

Show how the following amino acids can be prepared from the indicated starting materials.

(a) leucine from isobutyl alcohol
(b) lysine from 1,4-dibromobutane
(c) proline from adipic acid
(d) glutamic acid from α-ketoglutaric acid

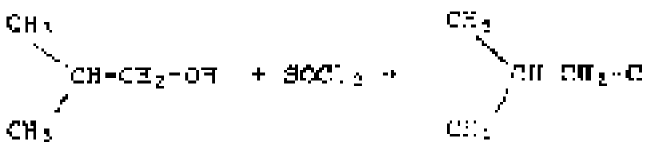
Solution: In order to synthesize an amino acid from the indicated starting material, we must analyze the product and see how it is derived from the starting material.

(a) 

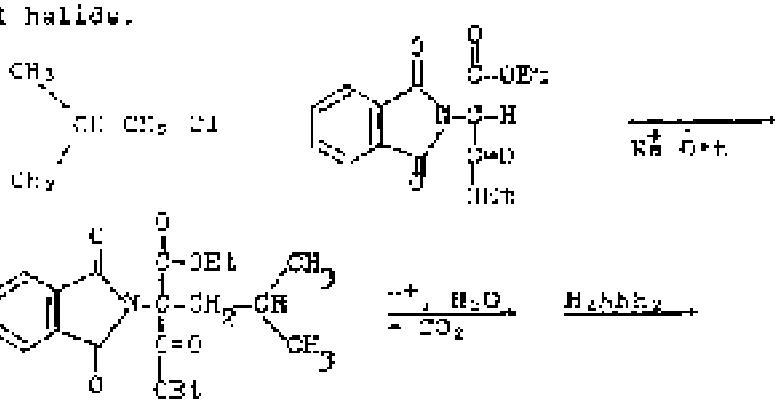
isobutyl

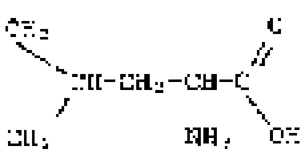
Leucine

Since the side-chain is an isobutyl group, we must attach an amino acid root to the isobutyl alcohol. This can be accomplished via the phthalimidomalonic ester synthesis:

(1) 

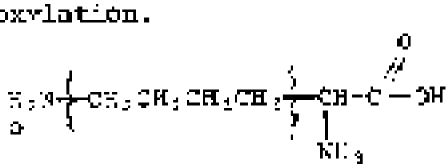
substitution reaction to form the corresponding alkyl halide.

(2) 



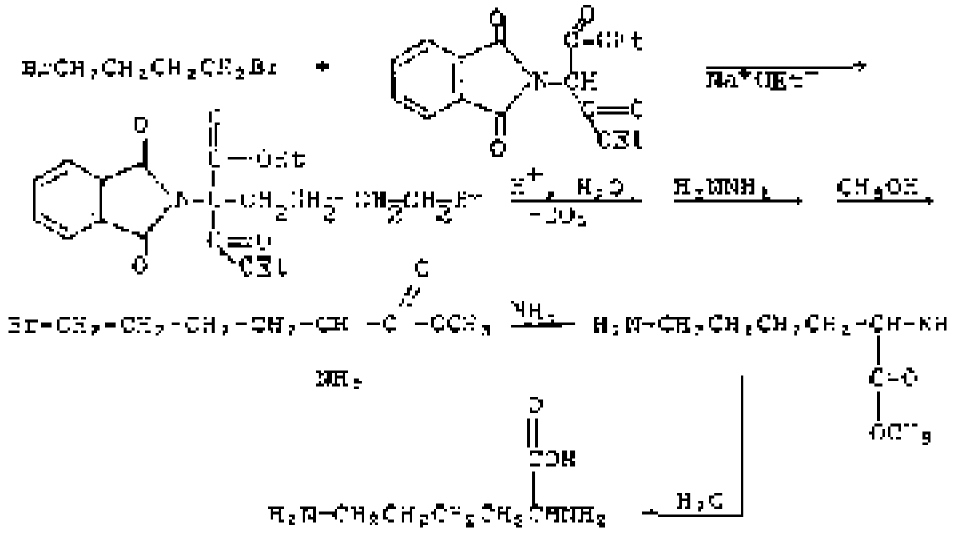
Leucine

This is a modified malonic ester synthesis made possible by (1) the high acidity of the α-hydrogens of malonic ester; (2) the extreme ease with which malonic acid and substituted malonic acids undergo de carboxylation.

(b) 

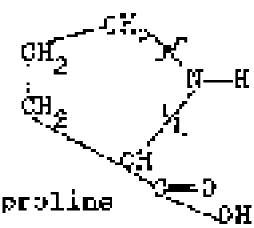
Lysine

Substituent a can be attached to the n-butyl group by phthalimidomalonic ester synthesis, while substituent b can be attached by a substitution reaction with ammonia with the carboxylic acid group protected. Therefore:



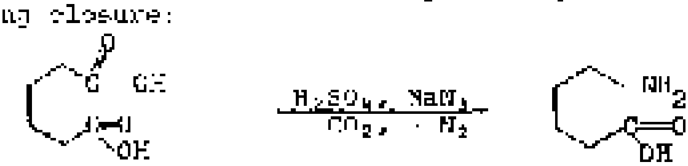
lysine

(c)



proline

Proline can be synthesized from adipic acid by (a) substituting an amino group for a carboxyl group; (b) ring closure at the α-carbon to the carboxyl group. Part a can be accomplished by the Schmidt reaction, while part b can be accomplished by a halogenation followed by ring closure:

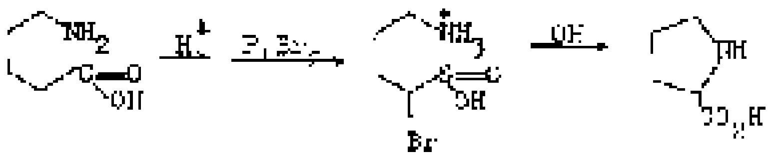


adipic acid

This is the Schmidt reaction of the general type:

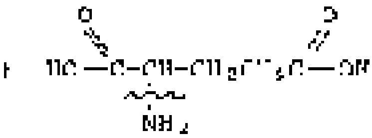
$$R-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[H_2SO_4]{NaN_3} RNH_2 + N_2 + CO_2$$

The next step is α-halogenation followed by ring closure:



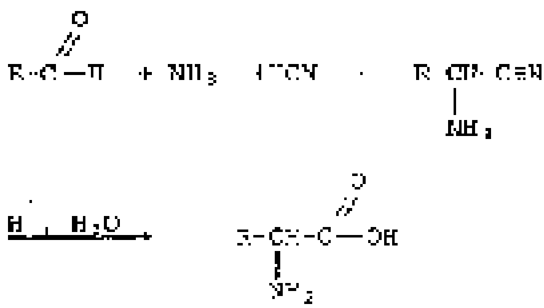
Proline

(d)

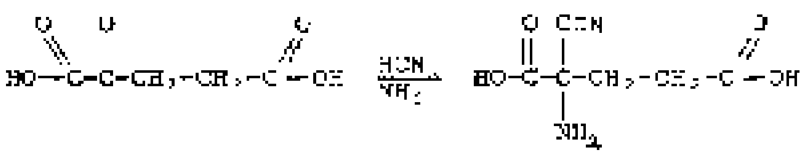


glutamic acid

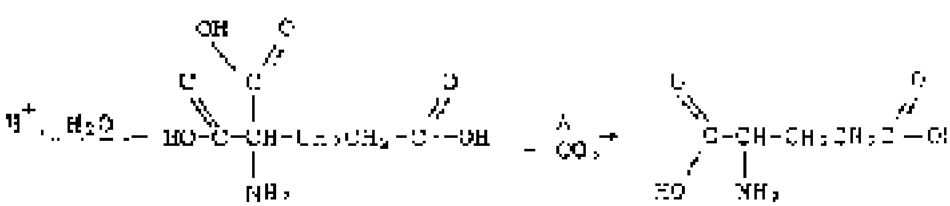
One method of synthesizing glutamic acid from α-ketoglutaric acid is via the Strecker synthesis of the general type:



This is followed by decarboxylation. Therefore:



α-Ketoglutaric acid



glutamic acid

• PROBLEM 32-7

It is thought that the first amino acids were synthesized from formaldehyde, hydrogen cyanide, ammonia and water in the primitive atmosphere. A possible synthesis involves a series of nucleophilic attacks and proton transfers. Propose a mechanism for the synthesis of glycine using the above mentioned compounds.

Solution: A possible synthesis might involve the following three steps:

(i) $H_2C=O \ + \ NH_3 \ \rightarrow \ H_2C=NH \ + \ H_2O$

(ii) $H_2C=NH \ + \ H-C\equiv N \ \rightarrow \ H_2N-CH_2-C\equiv N$

(iii) $H_2N-CH_2-C\equiv N \ + \ 2H_2O \ + \ H^+ \ \rightarrow \ H_2N-CH_2-\overset{O}{\overset{\|}{C}}-OH \ + \ NH_4^+$

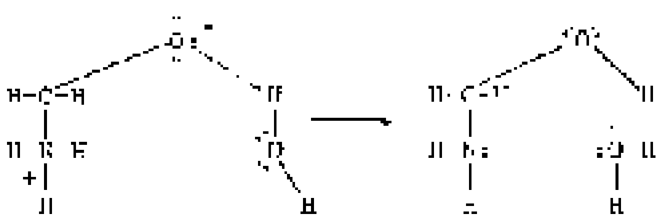
glycine

The first step involves a nucleophilic attack by ammonia on the carbonyl carbon of formaldehyde.

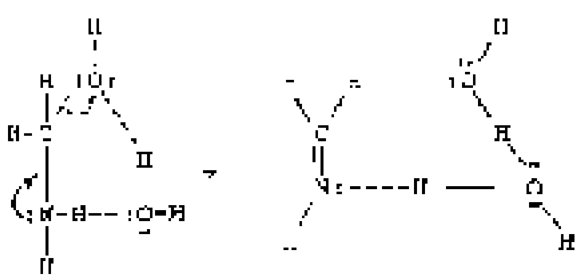
(iv) 

This occurs because the lone pair electrons on nitrogen (nitrogen is a good nucleophile) are attracted to the slightly positively charged carbon of the carbonyl group. The carbon has a slight positive charge because the oxygen atom is much more electronegative and a dipole is set up between them with the oxygen atom as the negative pole. In general, a reaction where electrons of one atom seek out the positively charged nucleus of another atom is termed a nucleophilic attack.

With the aid of a molecule of water a proton transfer neutralizes the charges.



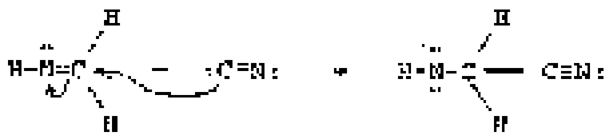
Proton transfer then assists in releasing the imine from the unstable hydrate.



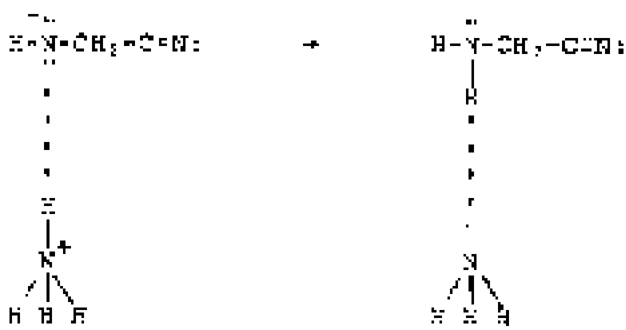
In the second step the hydrogen cyanide ionizes to form H+ and cyanide ion. The proton is transferred to ammonia.

$$H_3N: \;+\; H-C\equiv N \;\rightarrow\; H_4N^+ \;+\; {}^-C\equiv N:$$

The negative cyanide ion then joins the partially positive carbon atom of the imine in a nucleophilic attack

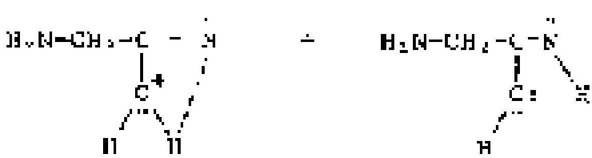


After this there is a proton transfer from the ammonium ion (NH_4^+) to the negatively charged nitrogen.

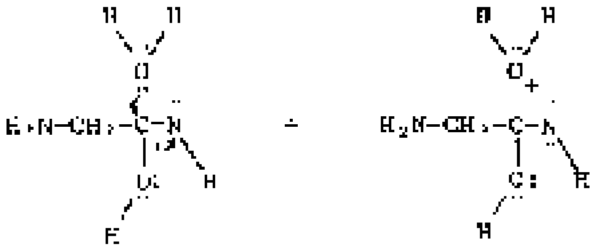


In the third step, the amino nitrile is hydrolyzed to form the amino acid. Water acts as nucleophile and attacks the cyanide carbon.

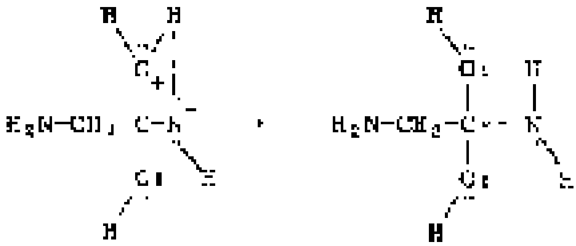
There is then a proton transfer from the water oxygen to the negative nitrogen.



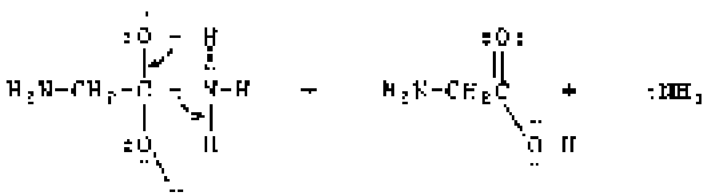
Because the carbon atom is still doubly bonded to the nitrogen it is still open to nucleophilic attack by another molecule of water.



Once again a proton transfer occurs.



This is still not glycine, though. This amino gem diol is quite unstable and may release either a molecule of water or a molecule of ammonia. When a molecule of ammonia is released glycine is formed.

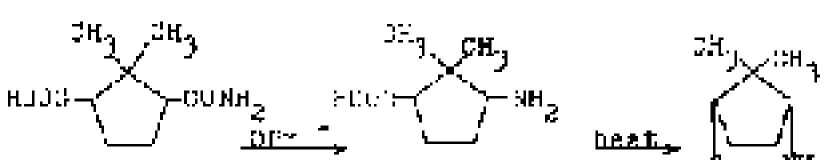


Remember, when writing mechanisms, that the arrows are drawn from the source of the electrons to the point to which they are being transferred.

LACTAMS

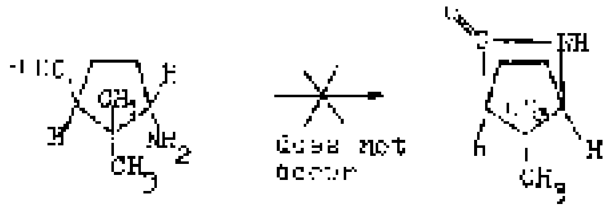
• PROBLEM 32-8

Many years before the Hofmann degradation of optically active α-phenylpropionamide was studied, the following observations were made: when the cyclopentane derivative I, in which the -COOH and $-CONH_2$ groups are cis to each other, was treated with hypobromite, compound II was obtained; compound II could be converted by heat into the amide III (called a lactam). What do these results show about the mechanism of the rearrangement? (Use models.)



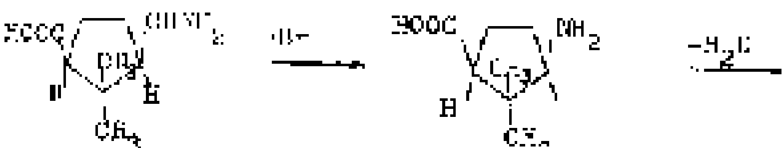
(I) (II) (III)

Solution: Lactam III can only be made from compound II if the amino and carboxyl groups are on the same face of the ring, that is if the groups are cis to each other. If compound II (a γ-amino acid) was in the trans configuration, lactam formation could not occur.



(II) (trans)

Since compound I and compound II are both in the cis orientation, the reaction of compound I with OBr^- resulted in decarbonylation of the amide with retention of configuration at the migrating group. The orientation of the compounds can be shown as:

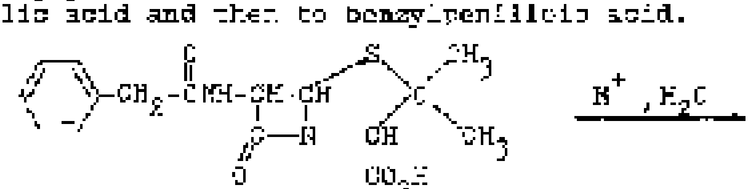


(I) (cis Amide) (II) (cis Amine)

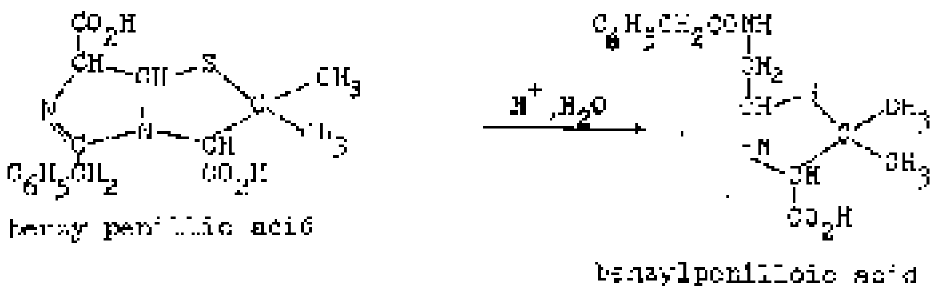
(III) (cis Lactam)

• PROBLEM 32-9

Some idea of the difficulties in determining the structure of the penicillins is illustrated by the conversion of benzylpenicillin in acid solution, first to benzylpenillic acid and then to benzylpenilloic acid.



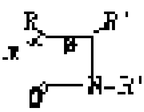
benzylpenicillin

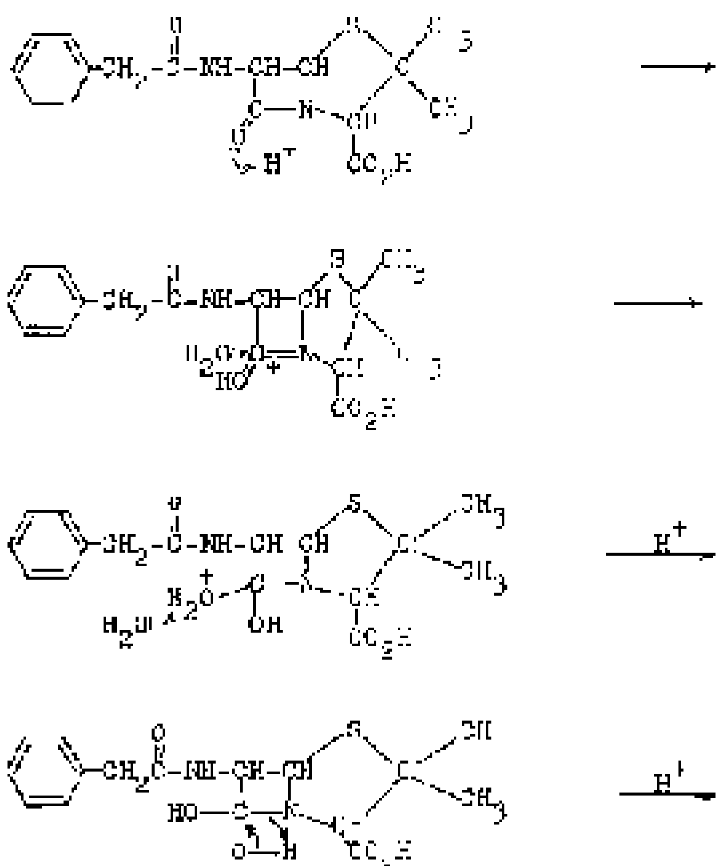


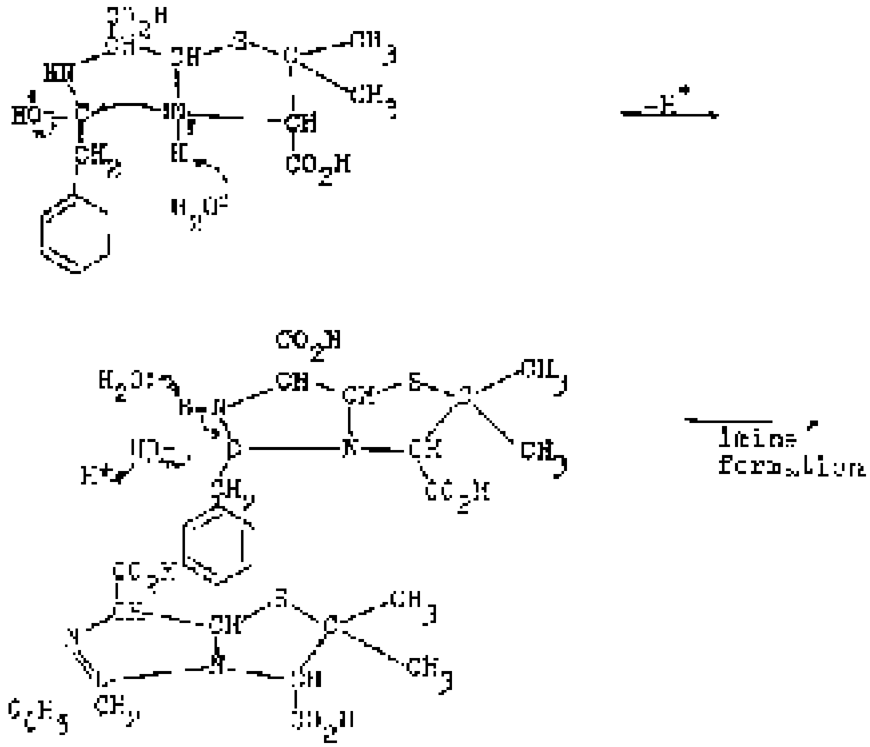
benzyl penillic acid

benzylpenilloic acid

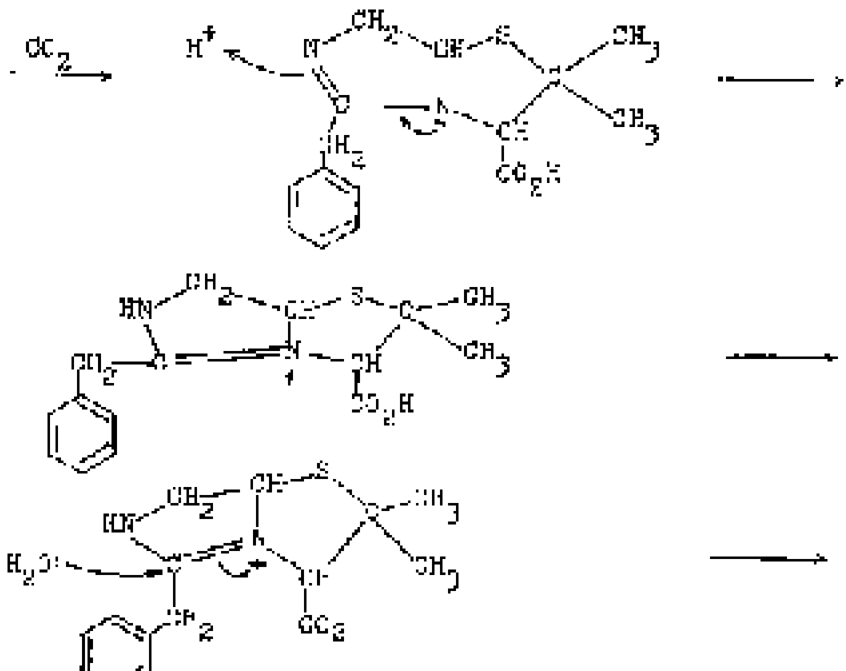
write mechanisms for these reactions which are consistent with the nature of the reactants and products.

Solution: Upon acid hydrolysis, the β-lactam  of penicillin should be hydrolyzed (hydrolysis would break the four-member ring, thereby relieving angle strain):

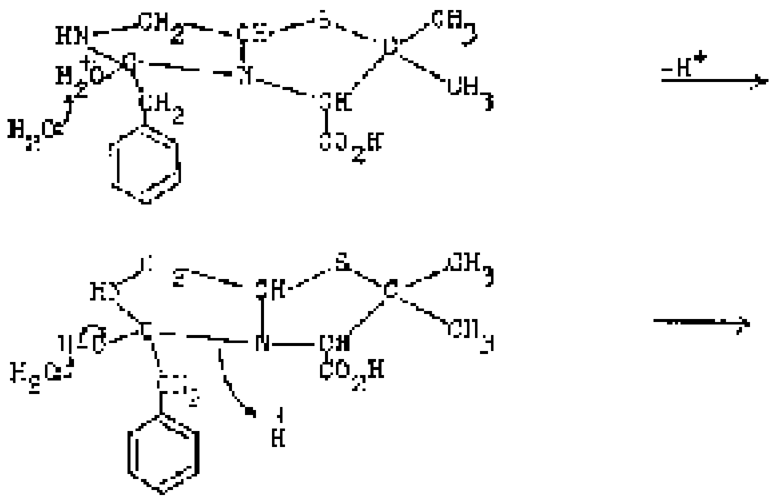


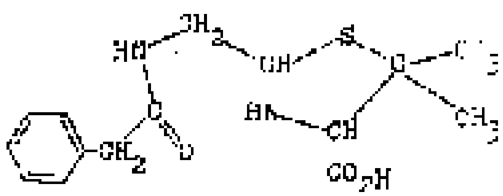


benzylpenicilloic acid-
an imine



hydrolysis of an imine



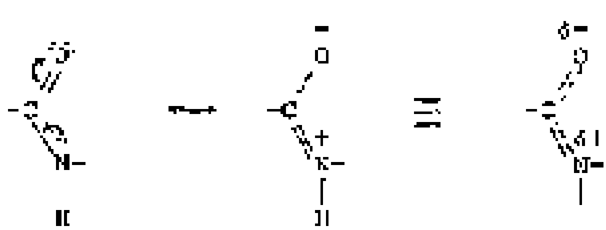


Benzylpenilloic acid

• PROBLEM 32-10

(a) What contributing structure(s) would account for the double-bond character of the carbon-nitrogen bond in amides? (b) What does this resonance mean in terms of orbitals?

Solution: (a) The lone-pair electrons on nitrogen can participate in the π-orbital of the carbonyl double-bond, giving the C-N bond partial double-bond character.



(b) Participation in the π-orbital of the carbonyl double bond would require the lone-pair electrons of nitrogen to be in p orbitals, thereby permitting overlap :

PEPTIDE SYNTHESIS AND DEGRADATION

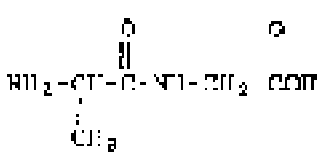
• PROBLEM 32-13

A pentapeptide on complete hydrolysis yields 3 moles of glycine, 1 mole of alanine, and 1 mole of phenylalanine. Among the products of partial hydrolysis are found H·Ala·Gly·OH and H·Gly·Ala·OH. What structures are possible for this substance on the basis of its giving no nitrogen in the Van Slyke determination?

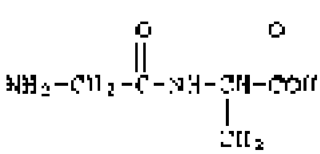
Solution: The structure of a peptide may be deduced by analyzing the complete and partial hydrolysis products. The products of complete hydrolysis of the peptide will give us the relative number of each amino acid in the peptide. Typically, complete hydrolysis is accomplished by exposing the amino acid to .03 N HCl at 110°C over a long period of time (24 - 28 hrs.). Partial hydrolysis, on the other hand, may be brought about by .03N HCl over shorter periods of time, or acid-specific enzyme peptide cleavers. Complete hydrolysis of the pentapeptide (a peptide consisting of five amino acid units) yielded three moles of glycine (NH_2CH_2COOH), one mole of alanine (NH_2CHCH_3COOH) and one mole of phenylalanine $\left(\begin{array}{l} NH_2CHCOOH \\ \quad | \\ \quad CH_2C_6H_5 \end{array}\right)$.

From this data we can conclude that the pentapeptide is composed of three glycine units, one alanine unit and one phenylalanine unit.

The structure of the pentapeptide can be deduced by analyzing the peptide fragments that result from the partial hydrolysis of the pentapeptide. Two of the peptide fragments produced in the partial hydrolysis of the pentapeptide are H·Ala·Gly·OH and H·Gly·Ala·OH, where the N or amino terminal is symbolized by H· and the C or carboxyl terminal is symbolized by ·OH. Hence the two peptide fragments may be represented as:



H·Ala·Gly·OH



H·Gly·Ala·OH

Since there were two types of alanine-glycine peptide fragments, one with alanine as the N-terminal amino acid and the other with alanine as the C terminal amino acid, alanine must be bonded to two glycine portions in the pentapeptide. This means that we have accounted for a glycine-alanine-glycine portion which can be written as:

```
         O        O         O
         ||       ||        ||
-NH-CH2  C  NH CH  C  NH  CH2-C-
               |
              CH3
```

·Gly·Ala·Gly·

The pentapeptide is composed of three glycine, one alanine and one phenylalanine, which leaves us with one glycine unit and one phenylalanine unit to account for.

We are given additional information in this problem: the pentapeptide gave no nitrogen in the Van Slyke determination. The Van Slyke determination involves the treatment of an amino acid or a peptide with nitrous acid. Amino acids and peptides will react with nitrous acid as primary, secondary and/or tertiary amines. Primary aliphatic amines react with nitrous acid to produce nitrogen gas via the diazonium salt. Secondary amines react to produce the nitroso compound and do not give off nitrogen gas. Tertiary amines do not react with nitrous acid. All linear peptides have an N-terminal amino acid unit which rates as a primary amine. Hence all linear peptides will react with nitrous acid to release nitrogen gas. Since the pentapeptide does not react with nitrous acid to produce nitrogen, it cannot be a linear peptide, or more specifically it is a peptide that lacks a free amino group. We have already accounted for a glycine-alanine-glycine portion. The pentapeptide must be a cyclic peptide in order to be consistent with the data. The cyclic peptide will have only secondary amino portions and will therefore react with nitrous acid to produce the corresponding penta-nitroso compound and release no nitrogen. There are two possible cyclic pentapeptide compounds that differ with respect to the positions of the remaining glycine and phenylalanine units. The two structural possibilities for the pentapeptide are:

```
      Ala                    Ala
     /   \                  /   \
  Gly     Gly            Gly     Gly
    \     /                \     /
    Gly  Phe               Phe  Gly

      A                      B
```

Note that structures A and B are stereoisomers and differ only with respect to orientation.

• PROBLEM 32-16

The complete structure of Gramicidin S, a polypeptide with antibiotic properties, has been worked out as follows:

(a) Analysis of the hydrolysis products gave an empirical formula of Leu,Orn,Phe,Pro,Val. (Ornithine, Orn, is a rare amino acid of formula $^+H_3NCH_2CH_2CH_2CH(NH_2)COO^-$.) It is interesting that the phenylalanine has the unusual D-configuration.

Measurement of the molecular weight gave an approximate value of 1300. On this basis, what is the molecular formula of Gramicidin S?

(b) Analysis for the C-terminal residue was negative; analysis for the N-terminal residue using DNFB yielded only $DNP\text{-}NHCH_2CH_2CH_2CH(\overset{+}{N}H_3)COO^-$. What structural feature must the peptide chain possess?

(c) Partial hydrolysis of Gramicidin S gave the following di- and tripeptides:

Leu.Phe	Phe.Pro	Phe.Pro.Val	Val.Orn.Leu
Orn.Leu	Val.Orn	Pro.Val.Orn	

What is the structure of Gramicidin S?

Solution: (a) The molecular formula of any compound is an integral multiple of the compound's empirical formula. Hence the molecular weight of a compound is an integral multiple of the molecular weight corresponding to the empirical formula. In the problem we are given the empirical formula and the approximate molecular weight of Gramicidin S. By calculating the molecular weight of the empirical formula, the molecular formula of Gramicidin S can be determined. This is done as follows:

Empirical formula of Gramicidin S:

Leu Orn Phe Pro Val

Molecular weight (MW) of empirical formula =

MW Leu + MW Orn + MW Phe + MW Pro + MW Val

$$\text{MW Leucine } \left(NH_2\underset{}{\overset{COOH}{\overset{|}{C}}}H\text{-}C(CH_3)_2\right) = 131$$

$$\text{MW Ornithine } \left(NH_2(CH_2)_3\overset{COOH}{\overset{|}{C}}HNH_2\right) = 132$$

$$\text{MW Phenylalanine } \left(NH_2\overset{COOH}{\overset{|}{C}}H\text{-}CH_2C_6H_5\right) = 165$$

MW Proline  = 115

$$\text{MW valine}\left(\begin{array}{c}\text{COOH}\\ |\\ \text{NH}_2\text{CH-CH(CH}_3)_2\end{array}\right) = 117$$

MW of Gramicidin S empirical formula = 660

MW of Gramicidin S = 1300

$$\frac{\text{MW of Gramicidin S}}{\text{MW of Gramicidin S empirical formula}} \approx \frac{2}{1}$$

We find that the MW of Gramicidin S is approximately twice that of the empirical formula. Hence the molecular formula of Gramicidin S must be twice the empirical formula:

2 × empirical formula = molecular formula

Therefore Gramicidin S has a molecular formula of:

$Leu_2Orn_2Phe_2Pro_2Val_2$.

(b) The negative result of the analysis for the C-terminal residue indicates that there is no free carboxylic acid group in Gramicidin S.

DNFB (2,4-dinitrofluorobenzene or Sanger's reagent) reacted only with the ornithine portions of Gramicidin S. The product was the dinitrophenyl derivative of ornithine at the δ (not the α) amino group. This means that the α amino group of ornithine does not exist as an amino group in Gramicidin S. Hence there are no C-terminal amino acid units or N-terminal amino acid units in Gramicidin S. This suggests that Gramicidin S is not a linear decapeptide, but is a cyclic one.

(c) The structure of Gramicidin S may be deduced by analyzing the products of its partial hydrolysis. The peptide fragments must be arranged in a sequence that has identical amino acid units overlapping with each other. To have a continuous array of amino acid units we must start and finish the sequence with the same amino acid. The peptide fragments that resulted from the partial hydrolysis of Gramicidin S can be arranged in an overlapping manner as follows:

```
Leu · Phe
      Phe · Pro
      Phe · Pro · Val
                  Val · Orn · Leu
                        Orn · Leu
                  Val · Orn
            Pro · Val · Orn
```

The resulting sequence is:

Leu · Phe · Pro · Val · Orn · Leu

There is still one unit each of Phe, Pro, Val and Orn to be accounted for. The only sequence that is in accord with the partial hydrolysis products is Phe - Pro - Val - Orn. This is concluded from the following arrangement of peptide fragments:

```
Phe - Pro
Phe - Pro - Val
            Val - Orn
      Pro - Val - Orn
```

The two major peptide fragments must be joined in a manner that is consistent with all the data, that is the Leu - Phe - Pro - Val - Orn - Leu sequence must be continuous throughout the molecule. Hence the cyclic decapeptide, Gramicidin S, has the structure of

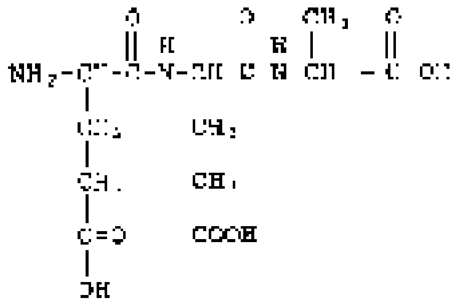
```
      Leu - Phe - Pro - Val
     /                     \
   Orn                     Orn
     \                     /
      Val   Pro   Phe   Leu
```

• PROBLEM 32-15

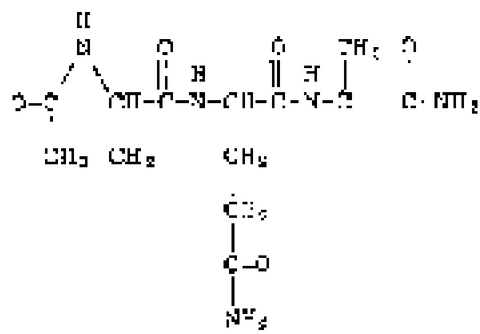
The tripeptide, eisenine, has only one free carboxyl group, does not react with dinitrofluorobenzene, and on complete hydrolysis yields 2 moles of L-glutamic acid, 1 mole of L-alanine, and 1 mole of ammonia. With anhydrous hydrazine, it forms L-alanine but no glutamic acid. Write a structure for eisenine that is in accord with the above facts.

<u>Solution</u>: The information given directly in the problem states that the tripeptide eisenine consists of two moles of glutamic acid and one mole of alanine. The fact that upon reaction with anhydrous hydrazine, the liberation of alanine ensues is indicative of alanine's position at the C terminus. Therefore the amino acid sequence must be Glu-Glu-Ala.

A problem arises here, however, in that eisenine has only one free carboxyl group. The fact that ammonia is released upon hydrolysis would indicate that the carboxyl is tied up in the form of an amide. Another factor in the determination of eisenine's structure is its inability to react with Sanger's reagent (2,4-dinitrofluorobenzene). This would be indicative of the amino terminus' being tied up in an amide form. Hence, a possible form for eisenine which would fit the data would be structure B.



Structure A: Glu -Gly -Ala

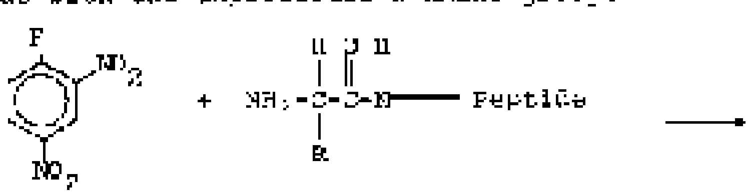


Structure B: Tisenine

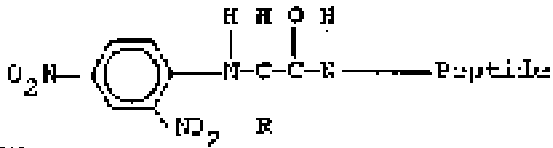
PROBLEM 32-16

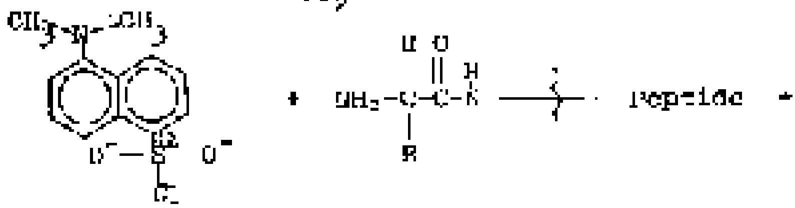
Edman has also devised the highly sensitive 'dansyl' method in which a peptide is treated with 5-dimethylaminonaphthalenesulfonyl chloride, followed by acidic hydrolysis. A derivative of the N-terminal residue is obtained which can be followed during its analysis by virtue of its characteristic fluorescence. What is the derivative? Why does it survive the acid treatment that cleaves the peptide bonds?

Solution: 5-dimethylaminonaphthalenesulfonyl chloride (dansyl chloride) reacts with an amino acid in the same manner as does 2,4 dinitrofluorobenzene (Sanger's reagent); it bonds with the unprotected α-amino group.

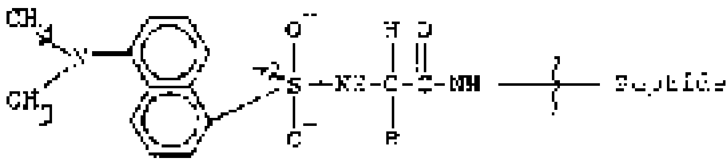


(Sanger's reagent)



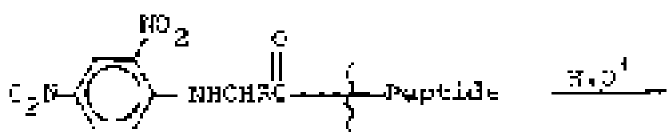


(dansyl chloride)

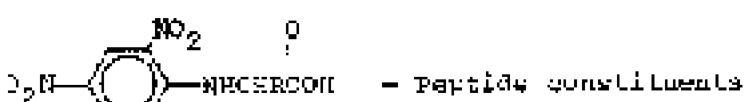


Upon acid hydrolysis, the Sanger and dansyl derivatives will react in a similar manner: they yield the amino acid constituents of the peptide plus the Sanger or dansyl derivative of the N-terminal amino acid. This is shown as:

(1) Hydrolysis of Sanger derivative

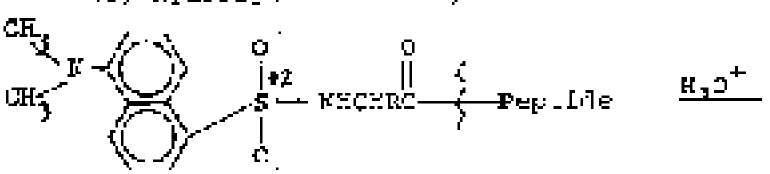


(Sanger derivative of peptide)

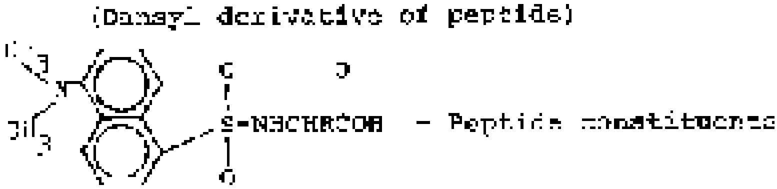


(Sanger derivative of N-terminal AA)

(2) Hydrolysis of Dansyl derivative:



(Dansyl derivative of peptide)

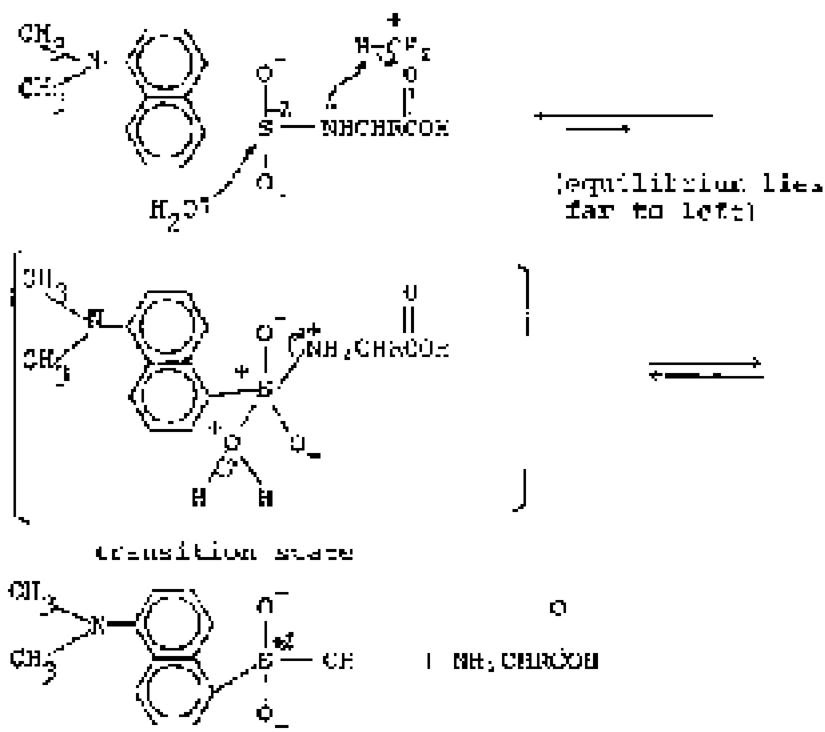


(Dansyl derivative of N-terminal AA)

The reason that hydrolysis of the dansyl derivative of the peptide does not result in cleavage of the N-terminal amino acid from the sulfonyl group involves steric and electronic factors. Sulfonamides in general are not as easily hydrolyzed as are the amides of carboxylic acids. Carboxylic amides have a trigonal arrangement whereas sulfonamides have a tetrahedral arrangement (due to sulfur having an extra substituent); nucleophilic attack upon sulfur is hence relatively hindered as compared to the attack upon carbon.

The nucleophilic attack upon the carbon in a carboxylic amide passes through a transition state that has a stable octet of electrons in a tetrahedral arrangement. The transition state of the nucleophilic attack upon a sulfonamide has a pentavalent sulfur, which is a relatively unstable species. This is because sulfur has a decet of electrons (remember that sulfur can accommodate more than eight valence electrons) which is less stable than an octet.

As a result of these unfavorable electronic and steric situations, hydrolysis of sulfonamides has its equilibrium leaning far to the left. The hydrolysis of the dansyl derivative of the peptide is shown below:



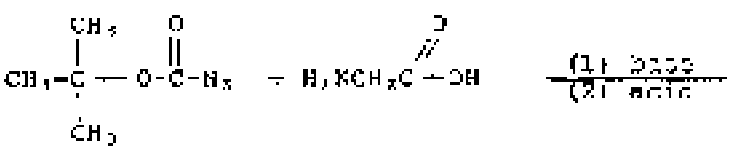
PROBLEM 32-17

Show how each of the following substances can be synthesized starting with the individual amino acids.

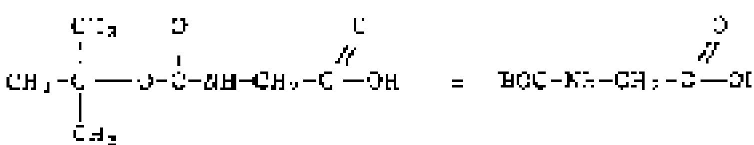
(a) glycylalanylcysteine
(b) $HO_2C(CH_2)_2CH(NH_2)CONHCH_2CO_2H$
(c) glutamine from glutamic acid

Solution: Peptide synthesis consists of three stages: (1) those amino and carboxyl groups (as well as other reactive groups) that are not involved in the reaction must be chemically blocked in order to prevent side reactions; (2) the free amino and carboxyl functionalities must be linked to form a peptide bond; (3) the blocking groups must be removed. In performing the chemical block, we must use a blocking agent that 1) reacts quantitatively and without racemization of the amino acid; 2) is stable, in the blocked amino acid form, to conditions of the condensation process; 3) is easily removed under conditions in which the peptide bond is stable and in which racemization of the peptide does not occur. Good blocking agents for amino groups include benzylchlorocarbonate, triphenylmethyl chloride, t-butylchlorocarbonate and trifluoroacetic anhydride. Carboxyl groups are generally blocked through formation of the corresponding methyl, ethyl, or benzyl esters; esterifications and subsequent hydrolysis are performed by classical means (e.g. Fischer esterifications). With this in mind, let us synthesize the tripeptide, glycylalanylcysteine.

The first step in this synthesis is to block the amino group of glycine. This can be achieved by using t-butoxycarbonylazide ($BOCN_3$), $(CH_3)_3C{-}O{-}\overset{O}{\overset{\|}{C}}{-}N_3$, which converts an amino group into its t-butoxylcarbonyl (BOC) derivative:

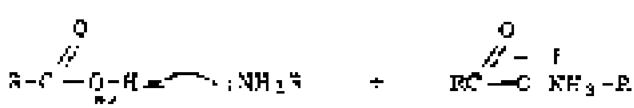


($BOCN_3$) glycine



N-protected glycine

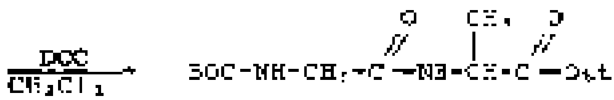
Mixing an aliphatic amine with a carboxylic acid at room temperature results in the formation of a salt:



acid base salt

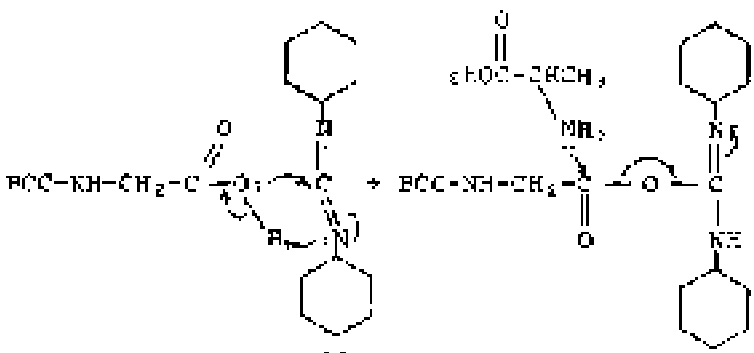
Conversion of this salt to an amide requires temperatures too high for the survival of the peptide, therefore we must convert the carboxyl group to a more reactive acyl derivative, that is, we must "activate" the carboxyl function. However, we do not have to activate the carboxyl group prior to amidation; instead we treat the N-protected amino acid with the ester of the second amino acid (remember we must use the ester form in order to block the carboxyl function) in the presence of dicyclohexylcarbodiimide (DCC), a potent non-acidic dehydrating agent:

N-protected glycine   C-protected alanine

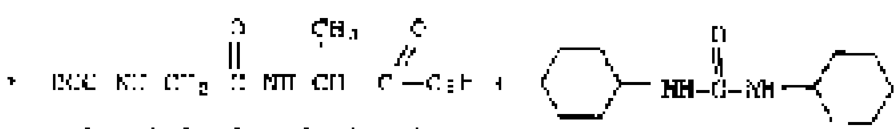


glycylalanine derivative

The mechanism for this remarkable reaction is:

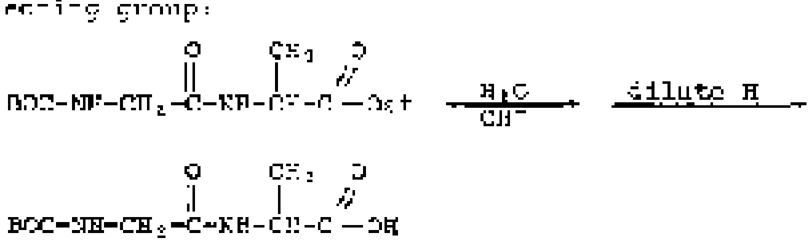


DCC



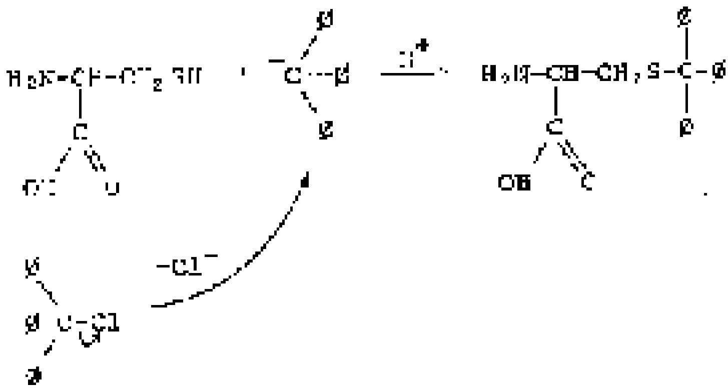
glycylalanine derivative   N,N'-Dicyclohexyl urea

The next step is removal of the ester carboxyl-protecting group:

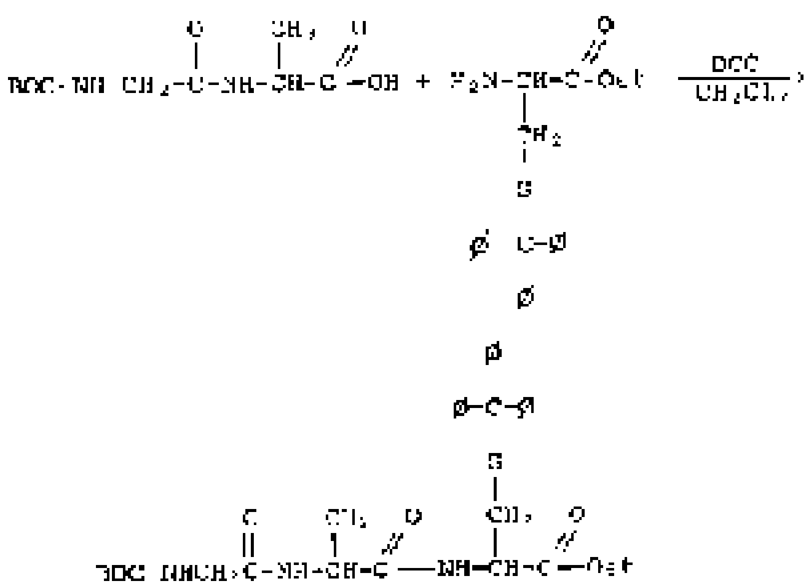


glycylalanine derivative

Before we can add the cysteine residue to the dipeptide, we must protect the carboxyl group and the thiol group. The blocking of the thiol function is achieved by reacting cysteine hydrochloride with triphenylmethyl chloride:

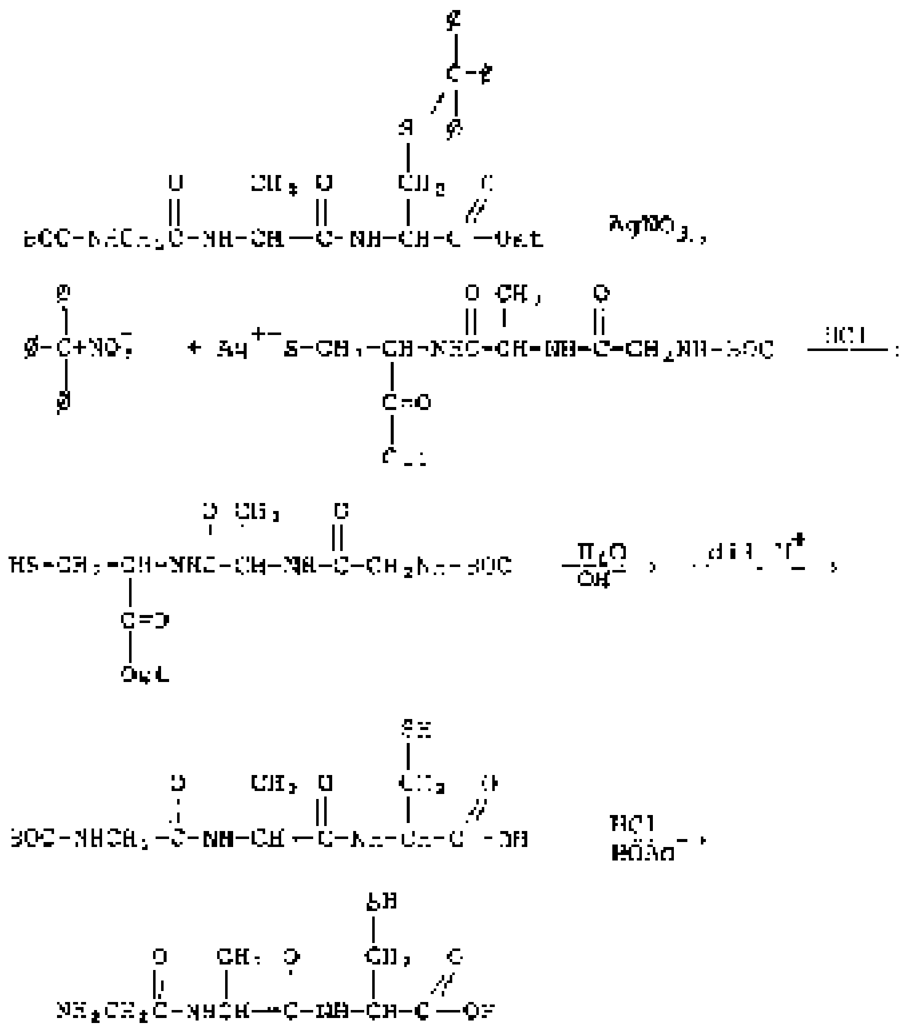


Note that the amino function is not blocked in this reaction because nitrogen is not as nucleophilic as sulfur. The carboxyl group is protected by esterification. The formation of a peptide bond between the cysteine derivative and the dipeptide can be achieved by using the method that we used before:



glycylalanylcysteine derivative

At this point we must remove all the blocking agents



glycylalanylcysteine

Recently, this classical approach has been augmented by a solid-phase-peptide synthesis (SPPS) technique. The basic idea is to synthesize the peptide in a stepwise fashion while the growing chain is attached to a solid support. The main advantage of this method is that purification of each product is avoided. Note that in the classical approach, for a sequence containing one hundred steps, each of which has a 90% yield, we will get an overall yield of $0.9^{100} \times 100\%$ or .003%. Since purification of each product in the synthesis is avoided in the solid-phase technique, the overall yield is much higher. The overall procedure for this technique consists of the following steps: 1) attachment of a suitable functional group to a solid particle (e.g. polystyrene resin); 2) a suitably blocked amino acid is added to the functional group of the particle; 3) blocking agent removed; 4) a second blocked amino acid is condensed with the first (see Fig. 1).

X - polymer

↓

protected amino acid$_1$ - polymer

↓

amino acid$_1$ - polymer

↓

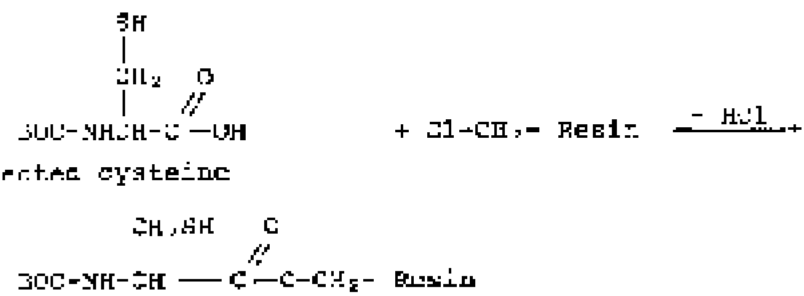
protected amino acid$_2$ amino acid$_1$ polymer

↓

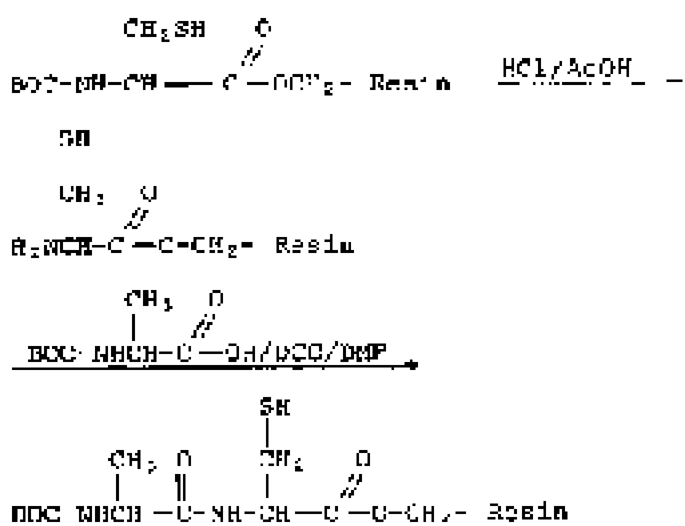
peptide

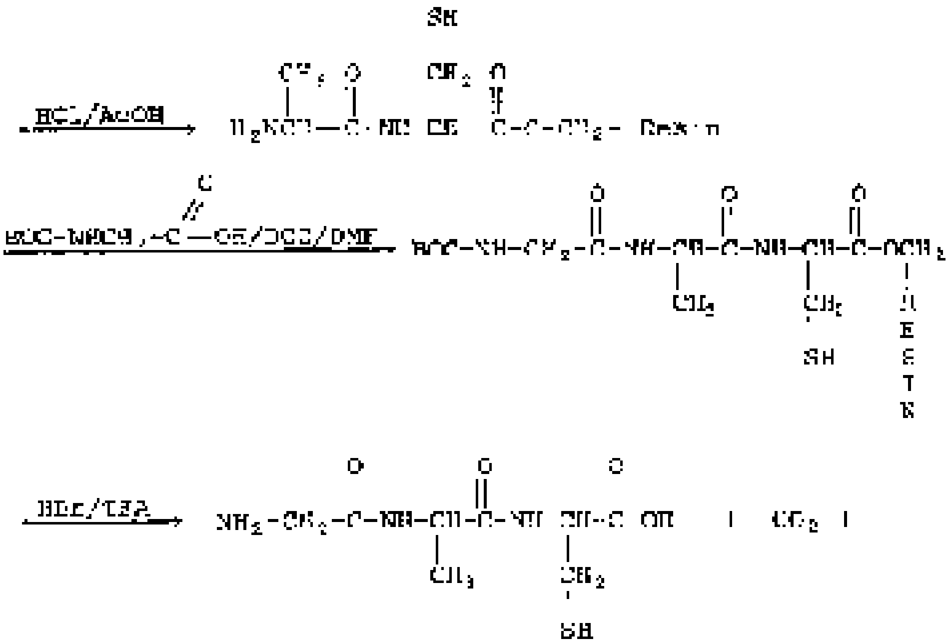
Fig. 1 - solid-phase peptide synthesis

Using this method, let us again synthesize glycyl-alanylcysteine.



The amino group is now deblocked and reacted with the suitable form of alanine, etc.



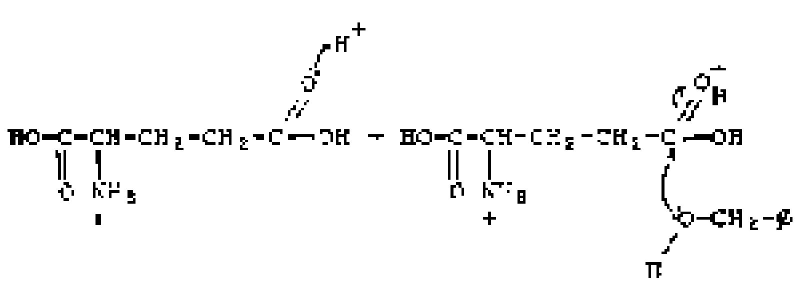


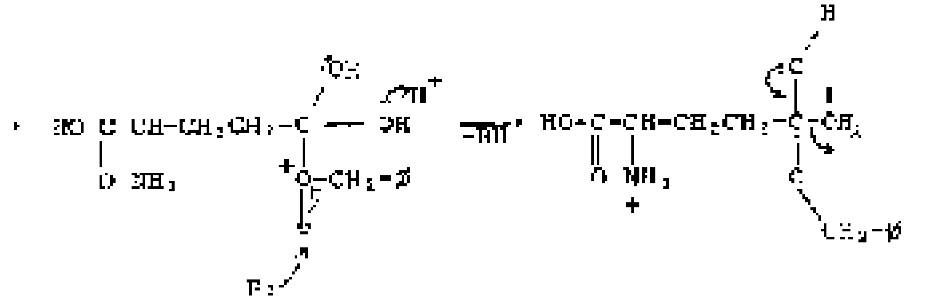
glycylalanylcysteine

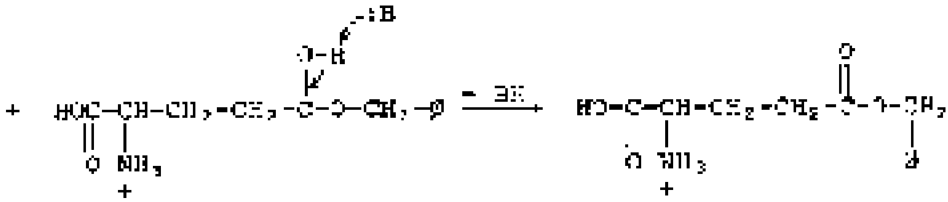
$(CH_3)_2C{=}CH_2$ + $BrCH_2$- Resin

The abbreviations used in this synthesis are: AcOH = acetic acid; DCC = dicyclohexylcarbodiimide; DMF = dimethylformamide; BOC = t butoxycarbonyl; TFA = trifluoroacetic acid. Note that in the last step of the synthesis, the mixture of hydrogen bromide and trifluoroacetic acid cleaves the polypeptide from the resin, as well as removing the protecting group from the N-terminal amino acid.

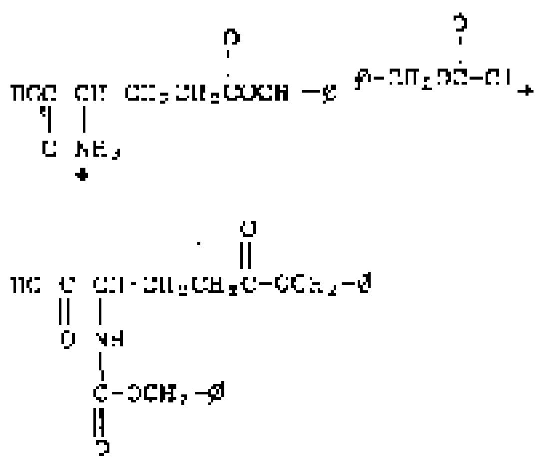
(b) Before we can synthesize this dipeptide of glutamic acid and glycine, we must block the side-chain carboxyl group and the amino group. Acid-catalyzed esterification of glutamic acid will yield only the side-chain ester if the esterification is not driven to completion. The side-chain carboxyl group is more reactive in acid-catalyzed esterification because it is farther from the positively charged α-amino group; the positive charge on this function hinders the protonation of the α-carboxyl oxygen:



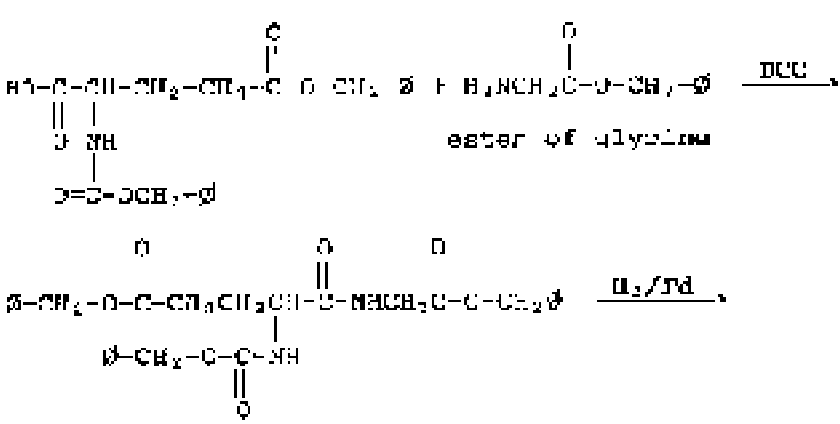


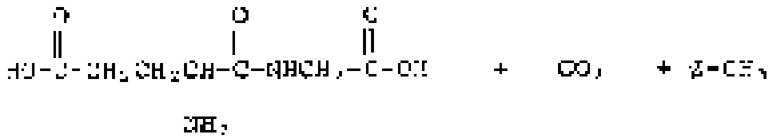


Now we can proceed with the rest of this dipeptide synthesis:

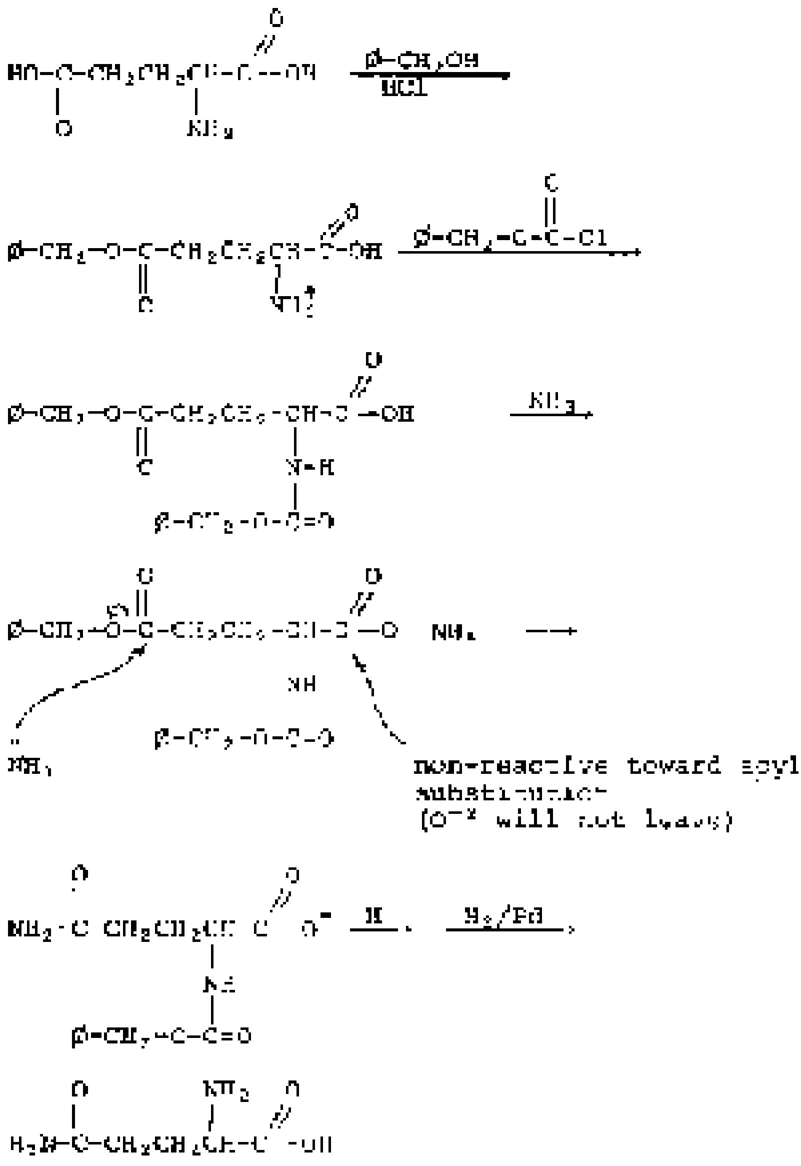


This last step blocked the amino function; the next step is the formation of the peptide bond:





(c) Preferential amidation of the γ-carboxyl group can be accomplished by using the γ-ester of glutamic acid.



glutamine

Give formulas for compounds A-G, and tell what is happening in each reaction.

$$\text{polystyrene} + CH_3OCH_2Cl \xrightarrow{SnCl_4} A + CH_3OH$$

$$A + C_6H_5CH_2OCONHCH_2COO^- \ {}^+NHEt_3 \rightarrow B + Et_3NHCl$$

$$B + \text{dil. } HBr \rightarrow C + C_6H_5CH_2Br + CO_2$$

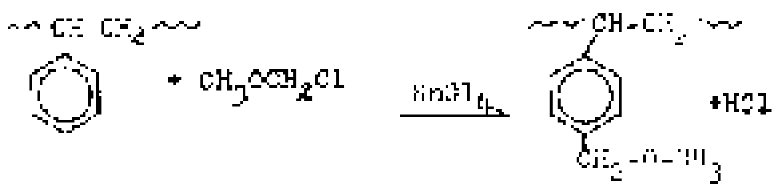
$$C + \text{carbobenzoxyalanylchloride} \rightarrow D$$

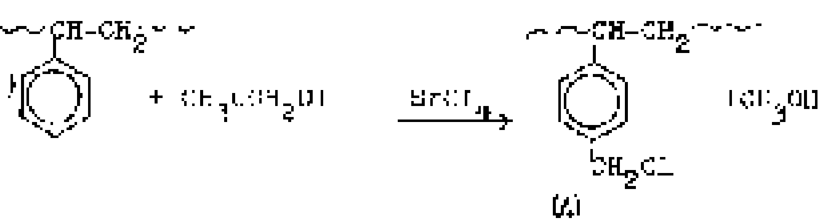
$$D + \text{dil.} HBr \rightarrow E + C_6H_5CH_2Br + CO_2$$

$$E + HBr \xrightarrow{CF_3COOH} F\ (C_5H_{10}O_3N_2) + G$$

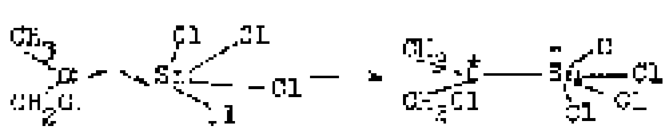
Solution: In order to answer this question, we must look at the nature of the reactants and products, and write a logical mechanism based on our knowledge of organic chemistry. By following the mechanism through, we should arrive at the products A-G.

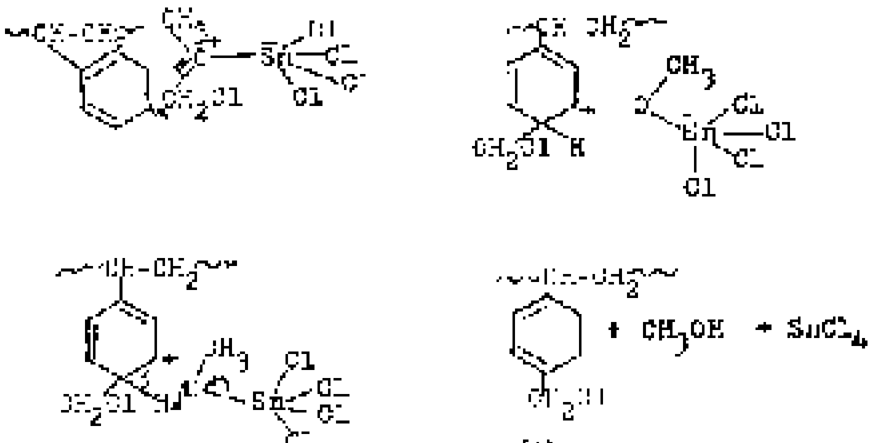
An alkyl benzene (polystyrene) reacting with an alkyl halide or ether in the presence of a Lewis acid ($SnCl_4$) is a Friedel-Crafts alkylation. However, there are two possible reactions:

(i)


(ii)


Since reaction (ii) gives us methanol as one of the products, this reaction must be the reaction, instead of (i). The mechanism is:

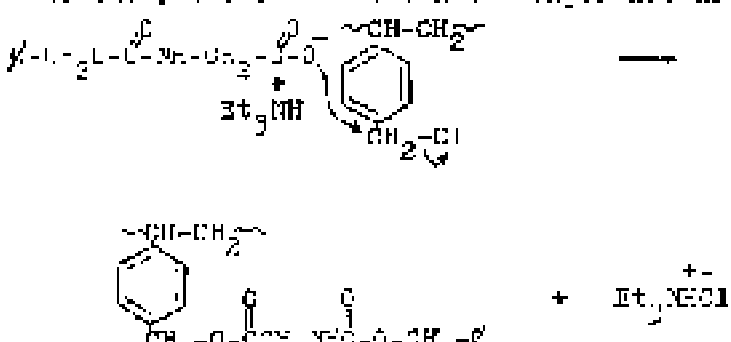




(A)

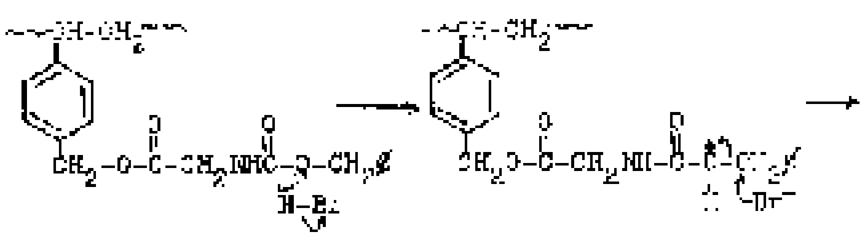
Note that alkyl benzenes are ortho, para directors. Since the para position is less hindered, the major product should be the para isomer.

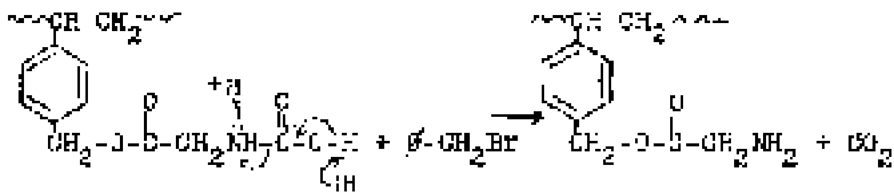
Since one of the side-chains on A is an alkyl halide, it is subject to nucleophilic substitution by the nucleophilic $-C(=O)O^-$ group. Note that the amino group of glycine is blocked, therefore it can no longer act as a nucleophile:



(B) a carbamate

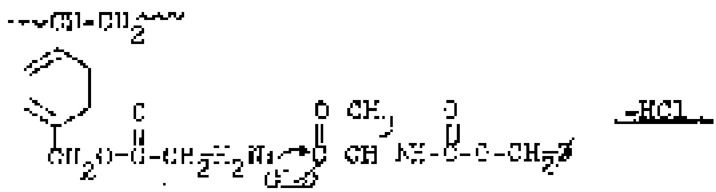
Carbamates are subject to acid hydrolysis, therefore:



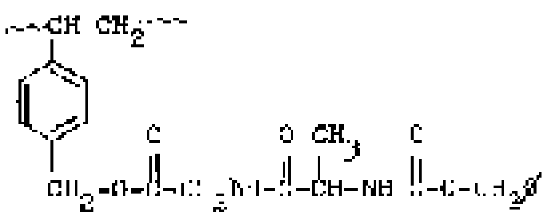


(C)

Acyl chlorides undergo acylation with amines, therefore:

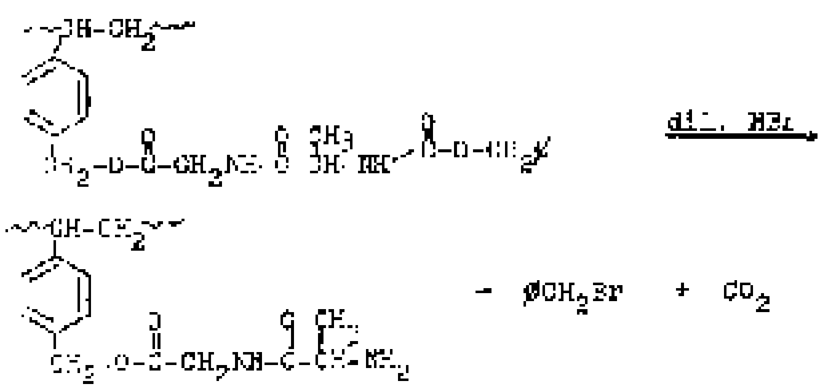


(C) carbobenzoxyalanyl chloride



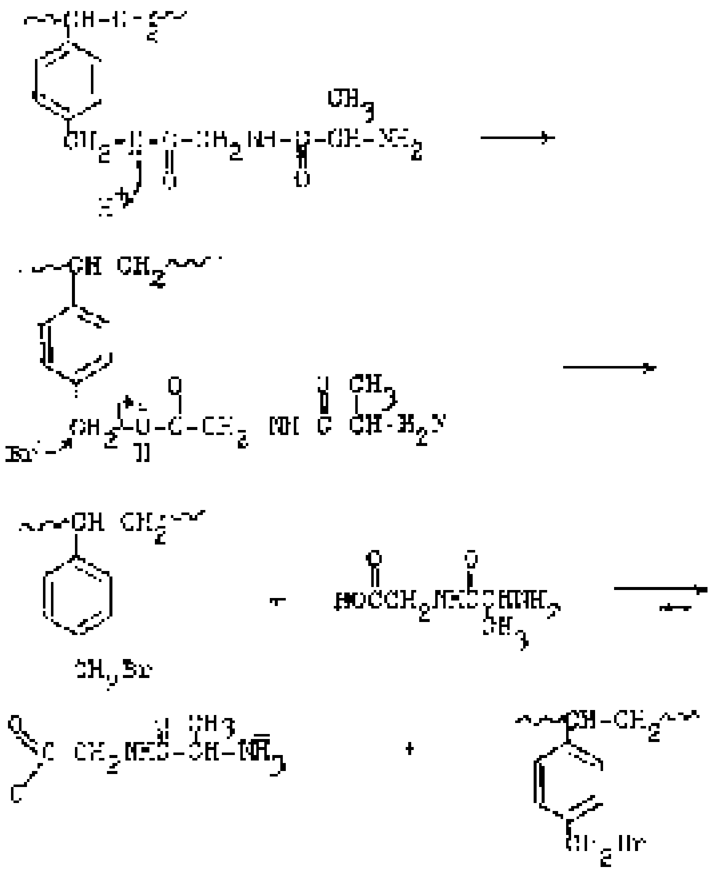
(D)

The next step is again hydrolysis of the carbamate (removal of N-protecting group):



(E)

The more acidic conditions of the last reaction will hydrolyze the ester via nucleophilic substitution:

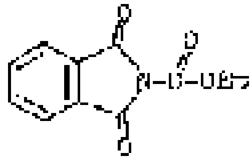


(F) alanyl glycine (G)

The molecular formula for our compound F is $C_5H_{10}O_3N_2$, which is the same as that given.

PROBLEM 32-15

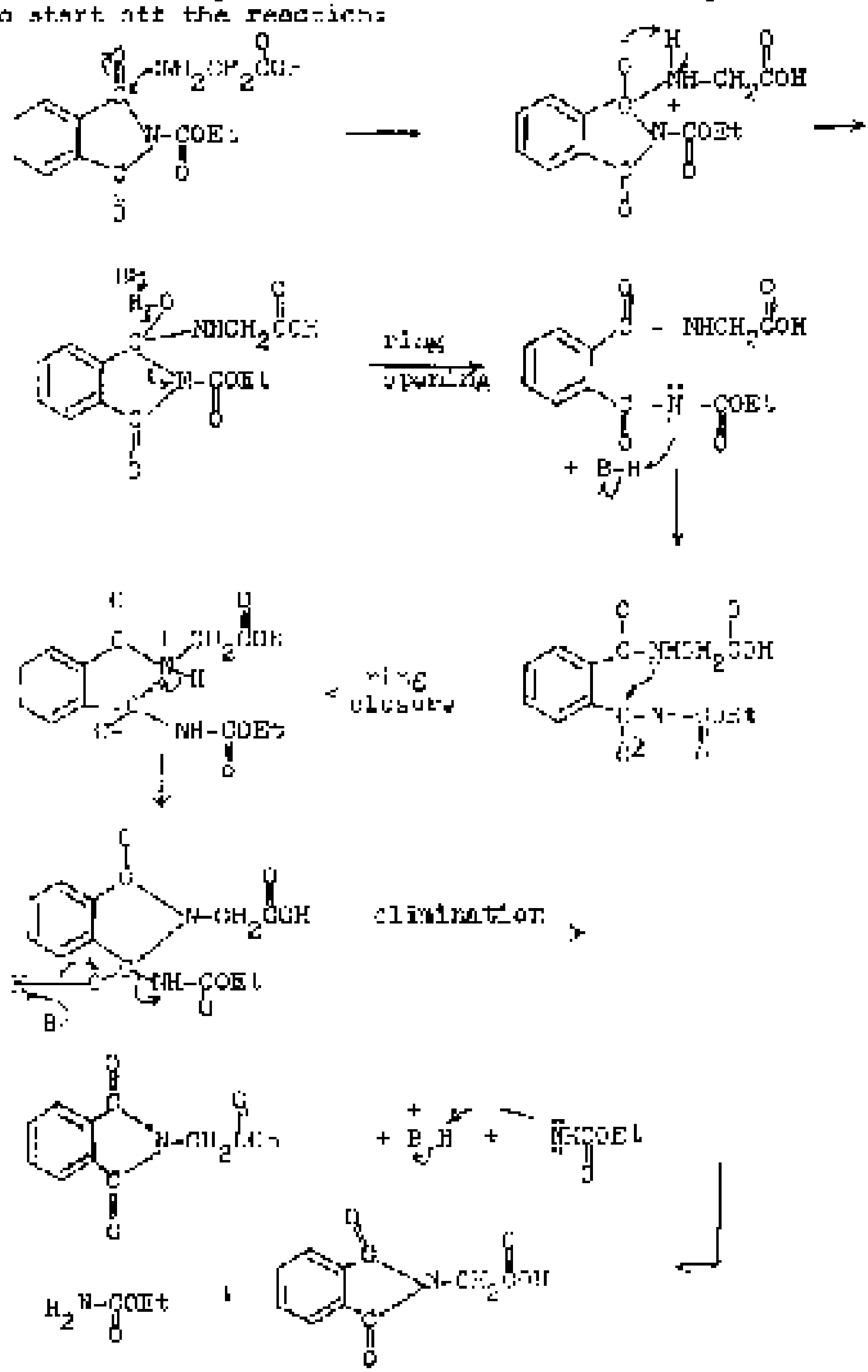
Write a mechanism for the reaction of glycine with N-carboethoxyphthalimide involving a sequence of carbonyl addition, ring opening, ring closure and elimination. Would you expect a similar reaction with L-phenylalanine to yield the L, the D, or the D,L-product?



N-carboethoxyphthalimide

Solution: In order to write the mechanism for a reaction, we must look at the nature of each reactant, and using our knowledge of organic chemistry, write out the logical course of the reaction:

The nucleophilic amine attacks the carbonyl carbon to start off the reaction:



Note that throughout this entire sequence, the α-carbon is not involved in the reaction. Since the chiral carbon in phenylalanine is the α-carbon, and if we start with L-phenylalanine, the reaction will yield the L-product.

• PROBLEM 32-20

For each enzyme catalyzed reaction shown in the following equations, tell what fundamental organic chemistry is involved.

(a) So that acetyl CoA can get through the membrane from the mitochondria where it is formed to the cytoplasm where fatty acids are made, it is converted into citric acid.

$$\underset{}{CH_3CO\text{-}S\text{-}CoA} + \underset{\text{Oxaloacetic acid}}{HOOCCOCH_2COOH} \rightleftarrows \underset{\text{Citric acid}}{HOOCCH_2\overset{\displaystyle OH}{\underset{\displaystyle COOH}{C}}CH_2COOH} + CoA\text{-}SH$$

(b) Cholesterol is made up of isoprene units derived from isopentenyl pyrophosphate, which is, in turn, formed from mevalonic acid.

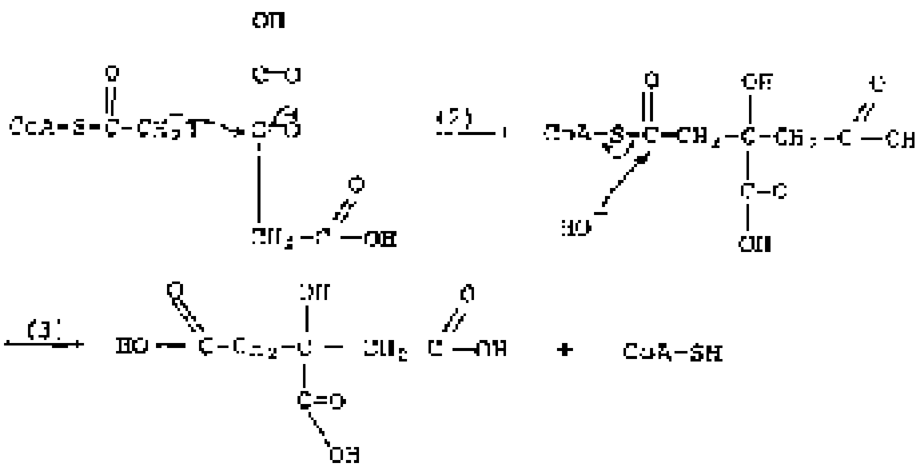
$$CH_3CO\text{-}S\text{-}CoA + CH_3COCH_2CO\text{-}S\text{-}CoA \rightleftarrows HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CO\text{-}S\text{-}CoA + CoA\text{-}SH$$

$$HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CO\text{-}S\text{-}CoA + 2NADPH + 2H^+ \rightleftarrows \underset{\text{Mevalonic acid}}{HOOCCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}CH_2CH_2OH} + 2NADP^+ + CoA\text{-}SH$$

Solution: In order to answer this question, we must look at the nature of the reactants and products, and write a logical mechanism based on our knowledge of organic chemistry. Note that the biological enzyme-catalyzed reaction might follow a different mechanism, but the fundamental principles which underlie these reactions can be deduced by this method.

(a) A plausible mechanism for this reaction would be

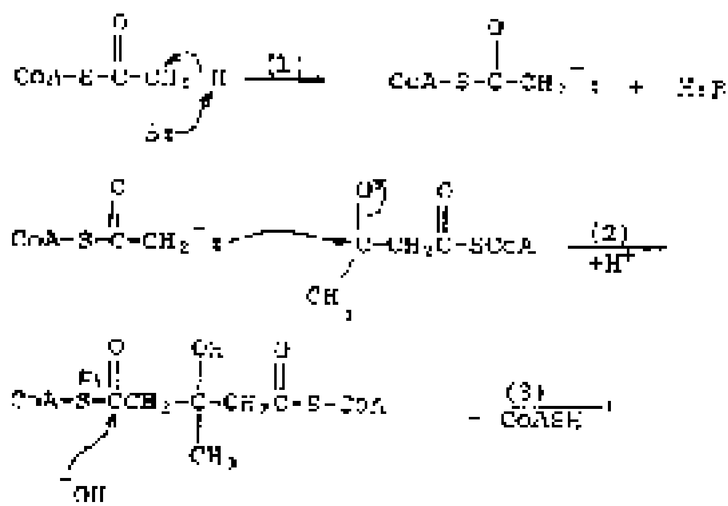
The carbanion is possible because oxygen, a very electronegative atom can help carry the negative charge. The next step is:

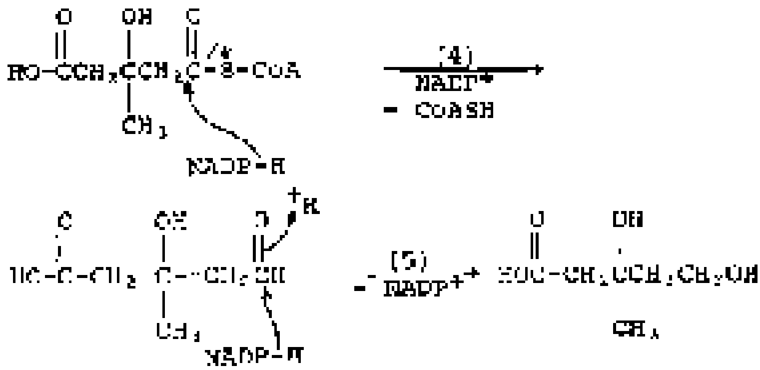


Citric acid

Steps (1) and (2) are the aldol condensation between the thioester (acetyl CoA) and the keto group of oxaloacetic acid. Step (3) is a reverse Fischer esterification reaction; the ester is hydrolysed to form the carboxylic acid and the thiol, CoA SH.

(b)





Mevalonic acid

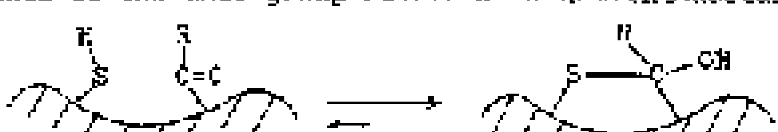
Steps (1) and (2) are the aldol condensation between acetyl CoA and the β-ketothioester. Step (3) is the hydrolysis of one of the thioester groups. Steps (4) and (5) involve the reduction of the thioester to a primary alcohol via hydride transfers from NADPH.

• PROBLEM 33-21

The proteolytic enzyme, papain, differs from α-chymotrypsin in having cysteine or a labile derivative thereof as part of its active site. The enzyme is deactivated by substances that form complexes with, or react with, -SH groups and the activity is restored by reactions expected to regenerate an -SH group. Work out a schematic mechanism for cleavage of a peptide chain with papain which is in agreement with the idea that, while papain may not normally contain a free SH group, it reacts readily with mercuric ion to give compounds of the type RSHgX.

One of the most interesting features of papain is that more than 120 of its total of 185 amino acid residues may be removed with the aid of an aminopeptidase to give a fragment with considerable enzymic activity.

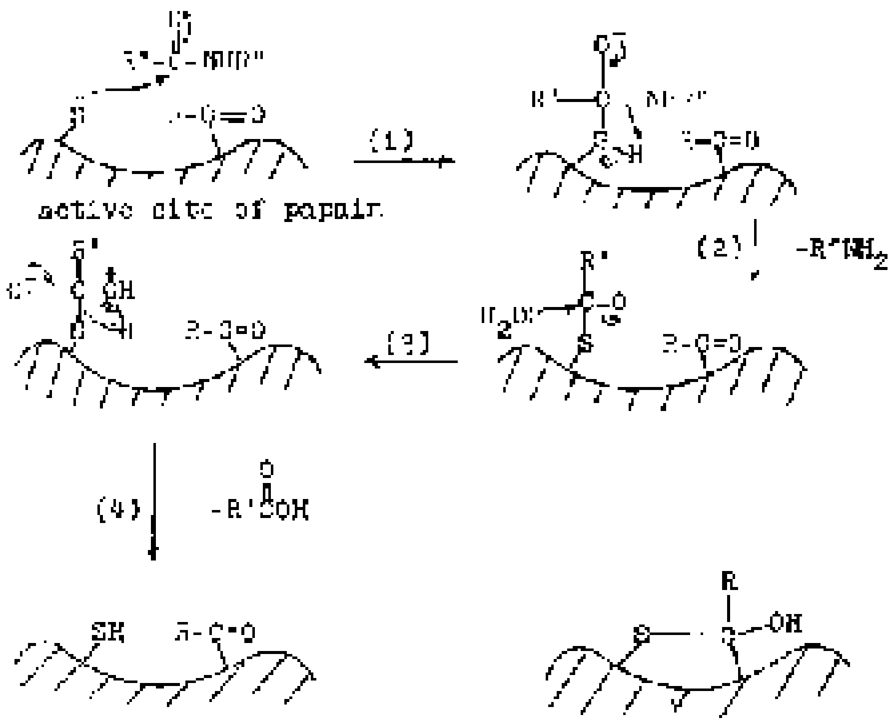
Solution: The experimental data that papain has a potential but not an actual thiol (-SH) group, can be explained if the thio group exists as a hemithioacetal:



thiol isomer hemithioacetal

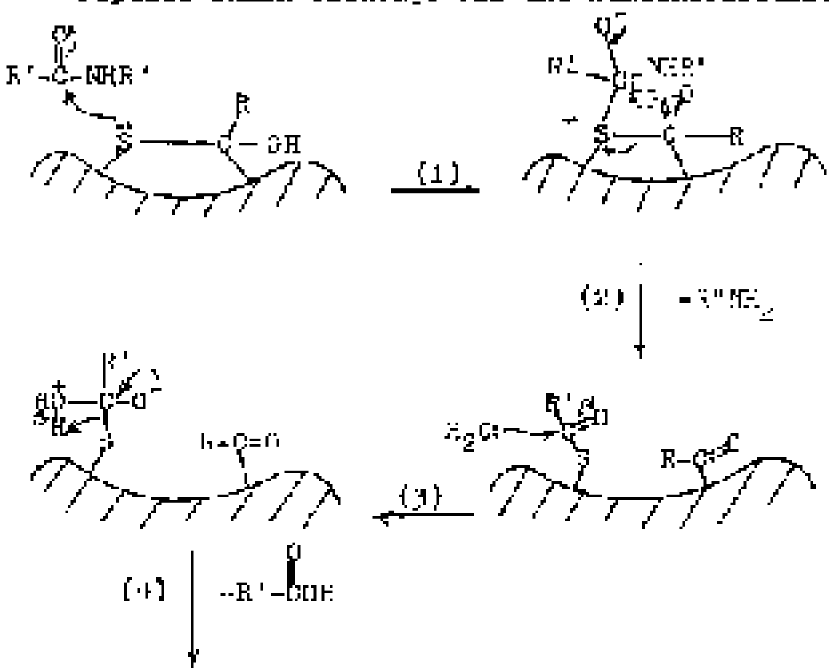
Cleavage of a peptide chain by papain can occur via the thiol isomer or the hemithioacetal. Thiols and sulfides (R-S-R') are nucleophilic, therefore we would expect a nucleophilic attack upon the peptide's carbonyl carbon by sulfur. Subsequent hydrolysis will regenerate the thiol.

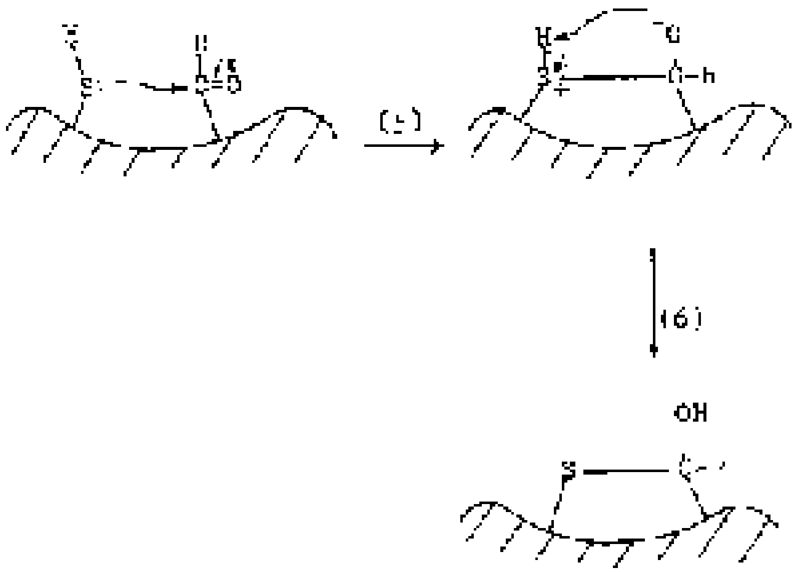
Peptide chain cleavage via the thiol:



Above: Steps (1) and (2) are peptide chain cleavage. Steps (3) and (4) are regeneration of the thiol by hydrolysis.

Peptide chain cleavage via the hemithioacetal:





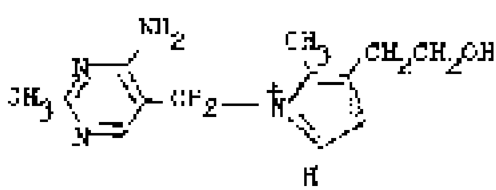
hemithioacetal

Above: Steps (1) and (2) are peptide chain cleavage. Steps (3) and (4) are thiol formation by hydrolysis. Steps (5) and (6) are hemithioacetal regeneration via cyclization of the thiol.

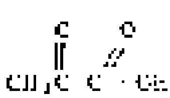
COENZYMES

• PROBLEM 32-22

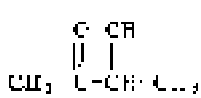
Explain how the conjugate base of thiamine might react with pyruvic acid to produce an intermediate which could easily decarboxylate. Complete the reaction sequence leading to the formation of acetoin.



thiamine

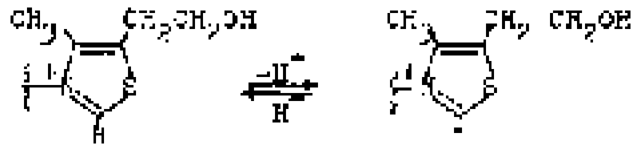


pyruvic acid



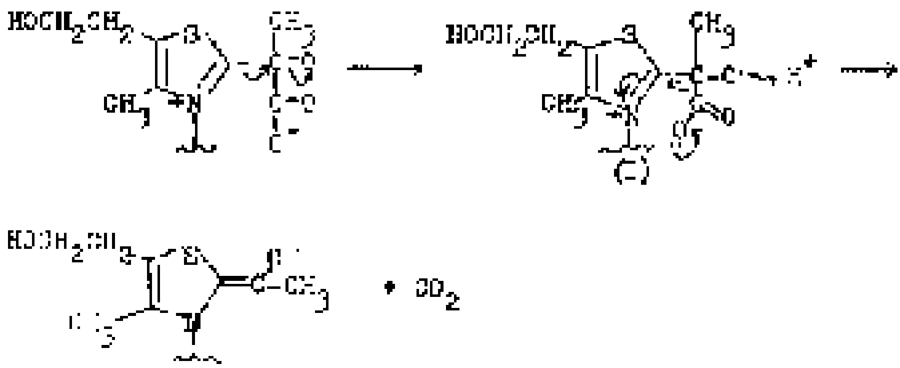
acetoin

Solution: Thiamine consists of a substituted pyrimidine linked by a methylene group to a substituted thiazole. The hydrogen at position 2 of the thiazole ring is acidic, and it is the conjugate base of this acid-base reaction that gives thiamine its enzymatic activity:



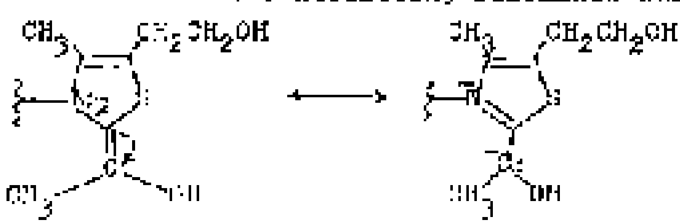
acid conjugate base

Like all carbanions, this conjugate base can undergo a nucleophilic attack on a carbonyl carbon, in this case, that of pyruvic acid:

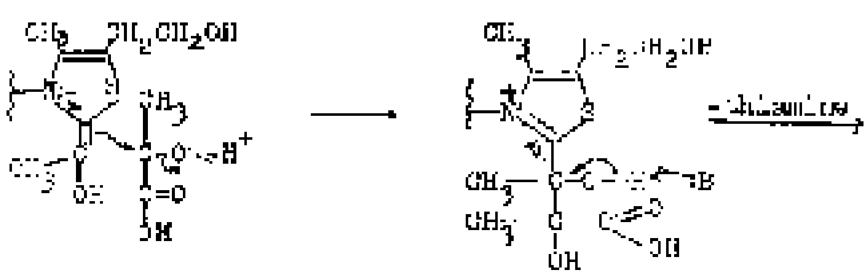


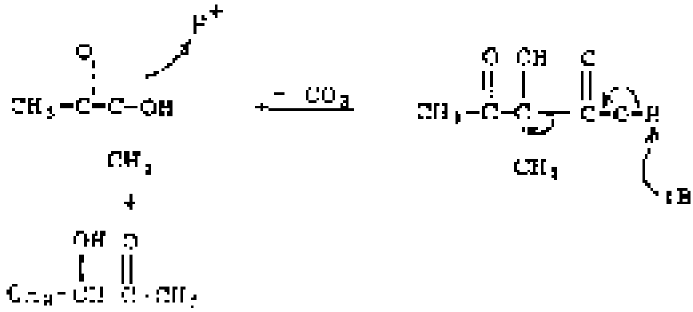
(II)

Note that decarboxylation of species I is greatly aided by the electrophilic nitrogen. The nucleophilic character of the hydroxy carbon in species II can be seen if we look at its contributing resonance structures:



This nucleophile can now attack another pyruvic acid, and subsequently form acetoin:





acetoin

CHAPTER 33

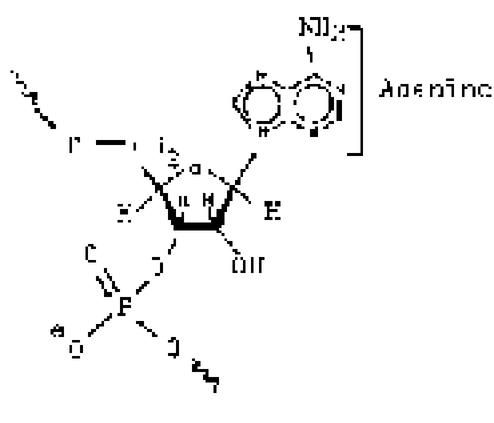
NUCLEIC ACIDS

DNA: ITS STRUCTURE AND PROPERTIES

• PROBLEM 33-1

(a) What is the difference between a nucleoside and a nucleotide? (b) What would you anticipate to be the difference between a riboside and a ribotide? (c) How would they be similar?

Solution: (a) A nucleoside is a base-sugar unit, while a nucleotide is a base-sugar-phosphoric acid unit. An example of a nucleotide would be:



Adenosine =
nucleoside -
Adenine (base) -
ribose (sugar)

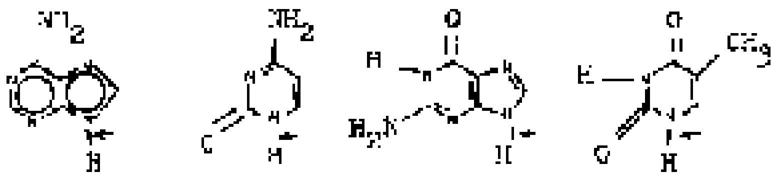
Fig. 1 A nucleotide = nucleoside + phosphate

From Fig. 1, we can see that a nucleotide is hydrolyzed to a nucleoside and phosphoric acid.

(b) Using the above convention, a ribotide would be a riboside bonded to a phosphate.

(c) Since they both have the prefix ribo-, their similarity would be ribose, a five-carbon sugar.

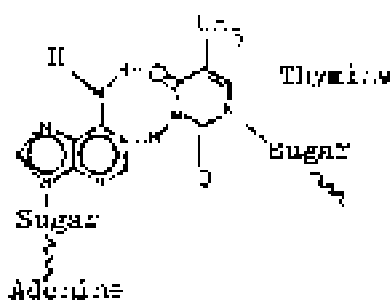
In DNA, the bases are bonded to deoxyribose at the following positions (that is a hydrogen in the figure below is replaced by C-1 of the sugar): adenine and guanine, NH in the five-membered ring; cytosine and thymine, the lower NH.



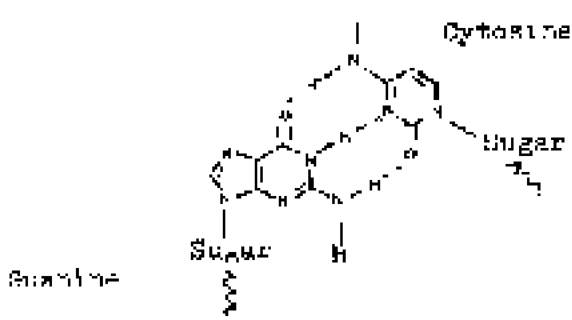
(a) Draw the structures to show likely hydrogen bonding between adenine and thymine; between guanine and cytosine. (b) Can you account for the fact that guanine and cytosine pairs hold the chains together more strongly than do adenine and thymine pairs?

Solution: Hydrogen bonding is not a "true" bond. It involves a hydrogen atom, serving as a bridge between two electronegative atoms; the hydrogen holds one electronegative atom by a covalent bond and the other by electrostatic attraction. For hydrogen bonding to be effective, both electronegative atoms must be either flourine, oxygen, or nitrogen. Hydrogen bonds have a strength of about 5 kcal mole^{-1}, as compared to that of covalent bonds — 50 - 100 kcal-mole^{-1}.

(a) For adenine and thymine, the only possible hydrogen bonds are:



For guanine and cytosine:



(b) There are three hydrogen bonds between guanine and cytosine, while there are only two hydrogen bonds between adenine and thymine; three hydrogen bonds between base pairs will hold the chain together more strongly than two hydrogen bonds between base pairs.

• PROBLEM 33-2

Escherichia coli bacteria grown in a medium containing ^{15}N-labeled ammonium chloride produce ^{15}N-containing DNA. This can be distinguished from ordinary ^{14}N-DNA by ultracentrifugation in concentrated cesium chloride solution – the heavier ^{15}N labeled DNA undergoing sedimentation more rapidly. When the bacteria grown in an ^{15}N medium are transferred to an ^{14}N medium, DNA replication continues but, after one generation, all the DNA present appears to be of one kind, containing equal amounts of ^{15}N and ^{14}N; after two generations, the DNA is now of two kinds present in equal amounts – all ^{14}N-DNA and ^{14}N, ^{15}N-DNA. What do these results tell about the replication of DNA and its stability in the cell?

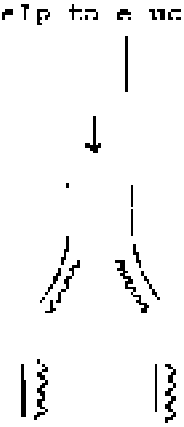
Solution: Deoxyribonucleic acid (DNA) is the basis for the transmission of genetic information, as well as the information that directs amino acid sequences in proteins. Double-stranded DNA consists of two polynucleotide chains, that is, each chain consists of many base-sugar-phosphoric acid units. In order to replicate, double stranded DNA must separate into single-stranded DNA, each strand serving as a template for the production of double-stranded DNA. From the first part of the experiment, we know that a "new" DNA molecule must contain one-half of the "old" DNA molecule: this is because after one generation all the DNA contains equal amounts of ^{15}N and ^{14}N. The second half of the experiment tells us that after two generations, the DNA is of two kinds, present in equal amounts -- all ^{14}N-DNA and ^{14}N, ^{15}N-DNA. This tells us that the "old" half of the "new" DNA molecule stays intact. That is, with regard to the stability of DNA in the cell, each strand of DNA retains its integrity throughout the replication process. A schematic diagram will help to elucidate the replication process:

(a) ^{15}N-original DNA

(b) separates to single strand, serving as template to 'new' strand

{ = ^{14}N DNA

(c) after first generation one kind of DNA – containing equal amounts of ^{15}N (-) and ^{14}N (~)



(d)  Replication

(e)  Second generation -- two kinds of DNA in equal amounts.

^{14}N, ^{15}N DNA $\quad$ ^{14}N DNA

This model, called the "semi-conservative" model for DNA replication, is the most widely accepted model for DNA replication; all data at this time seems to support this model.

• PROBLEM 33-4

The DNA of the bacterial virus designated as φX174 has several unusual properties. In the first place, it has the ratios, adenine:thymine: guanine: cytosine of 1:1.33:0.98:0.75. Second, while ordinary DNA undergoes a fairly sharp transition from a rather rigid rodlike structure to a collapsed random-coil structure when heated to just above 80°, the DNA of φX174 has the random-coil structure even at room temperature. Third, enzymes that are able to cleave DNA are much more reactive toward the DNA of φX174 than to ordinary DNA. Fourth, the rate of attack of formaldehyde on the organic bases of ordinary DNA to form Schiff's bases is much slower than the corresponding reactions with the DNA of φX174. Finally, when the protein coat is removed from φX174 and the DNA is centrifuged in an ultracentrifuge, the DNA is separated into two fractions; the faster moving fraction is able to infect specially treated cells, but the slower-moving fraction is not. Treatment of the faster fraction with an enzyme which cleaves DNA chains yields first the slower-moving inactive DNA and then fragments of different molecular weights. Show how the above facts can be accounted for by an appropriate structure for DNA of φX174.

Solution: Double-stranded DNA has equal amounts of adenine and thymine, and equal amounts of cytosine and guanine. This correspondence arises from the fact that adenine hydrogen bonds only to thymine, while guanine hydrogen bonds only to cytosine (rare exceptions to this are known as mutations). Therefore, for every adenine in a double-stranded DNA molecule, there must be a corresponding thymine, and vice versa. The same is also true for guanine and cytosine. The lack of a 1 : 1 ratio for adenine and thymine, as well as for guanine and cytosine in φX174 is indicative of single-stranded DNA. Because it is single-stranded, it will have a random-coil structure at room temperature. Its exceptional susceptibility to enzyme and formaldehyde attack also supports the single-stranded DNA model. This is especially true if the single stranded DNA has a cyclic structure. With such a structure, formation of double stranded DNA is inhibited and the chain will therefore be more susceptible to attack. The cyclic structure is further supported by the last experiment: the faster fraction, because it is infectious, must be the cyclic structure (infectious viral DNA is usually cyclic).

Enzymatic cleavage of the cyclic DNA would open the ring and result in the slower moving inactive DNA.

SYNTHESIS AND REACTIONS OF PURINES AND PYRIMIDINES

• PROBLEM 33-5

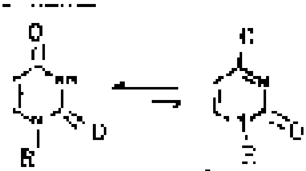
Devise a reaction sequence for converting the hydroxyl group in a uracil nucleotide residue of RNA to an amino group, thus achieving the conversion uracil → cytosine. Note that strongly acidic reagents should be avoided, to prevent breaking down the nucleotide groups.

Hint: The following steps have been used in the synthesis of 1-D-glucosylcytosine.

D glucose $\xrightarrow[(CH_3CO)_2O]{HBr}$ 1 bromoglucose tetraacetate

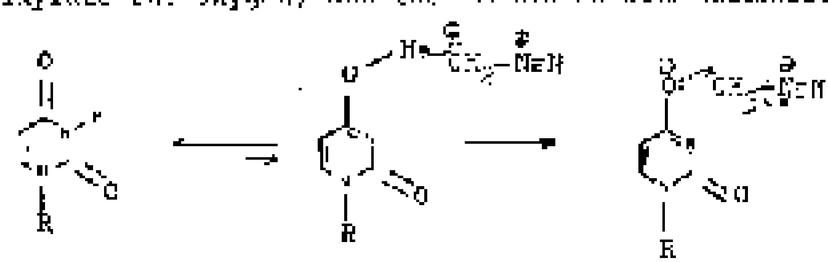
2,4-diethoxypyrimidine → 4-ethoxy-1-(tetraacetyl D-glycosyl)-pyrimid-2-one $\xrightarrow{NH_3 \text{ (excess)}}$ 1-D-glucosyl-cytosine.

Solution: Uracil exists in two tautomeric forms:

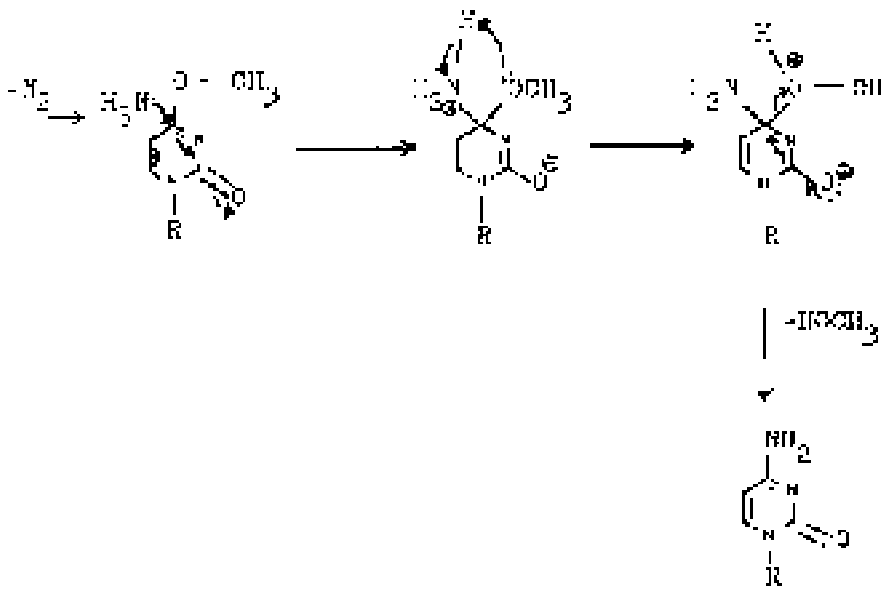


Uracil nucleotide

One way of converting the hydroxyl group of uracil to an amino group is by adding ammonia. But the hydrogen of the hydroxyl group is acidic and will protonate the ammonia, making it unreactive. Therefore, we must alkylate the oxygen before we add ammonia. A possible synthesis is to react the pyrimidine first with diazomethane (CH_2N_2) to alkylate the oxygen, and then react it with ammonia:



Uracil nucleotide

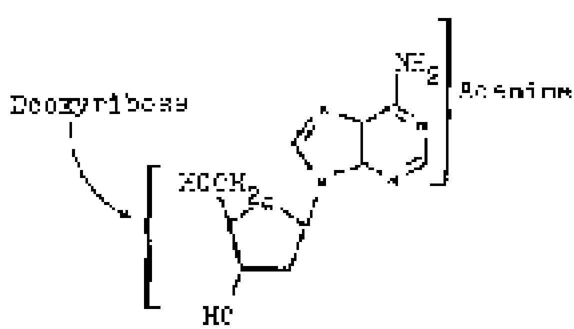


cytosine nucleotide

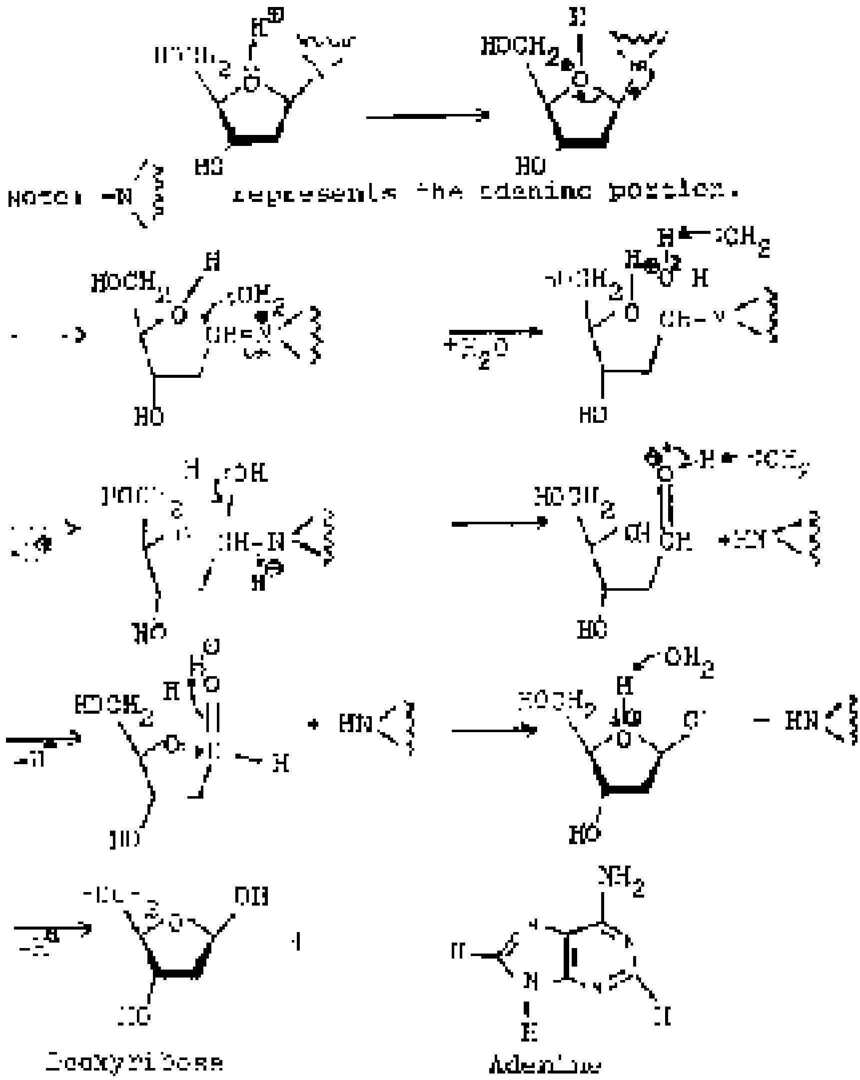
• **PROBLEM 33-8**

Write equations for the steps involved in hydrolysis of adenine deoxyribonucleoside to deoxyribose and adenine. Would you expect the reaction to occur more readily in acidic or basic solution?

<u>Solution</u>: The structure of adenine deoxyribonucleoside is:

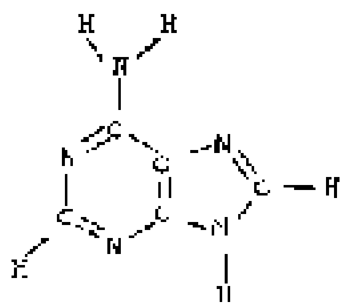


Since ethers and amines are stable toward base, hydrolysis should occur more readily in acidic conditions. The mechanism involved in hydrolysis of adenine deoxyribonucleoside is:



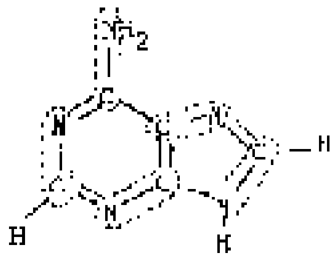
• **PROBLEM 33-7**

Outline a synthesis for adenine, one of the purines, from hydrogen cyanide and ammonia.



Adenine

Solution: It has been proposed that adenine can be synthesized from hydrogen cyanide and ammonia through a series of additions and "cyclizations". If we dissect adenine, we will see that it can be separated into five cyanide groups:



Adenine

Before we start the synthesis, we must review certain facts:

(1) Hydrogen cyanide is a weak acid

(2) The polarization of HCN is:

$$\overset{\delta+}{H} - \overset{\delta+}{C} \equiv \overset{\delta-}{N}:$$

(3) Ammonia is a weak base

(4) Imine-enamine tautomerism:

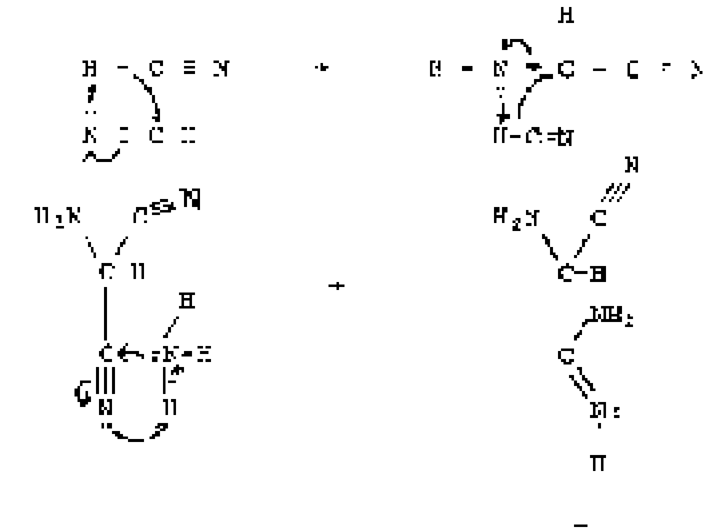
$$\underset{\text{Enamine}}{-C=C-\underset{H}{N}-R'} \rightleftarrows \underset{\text{Imine (more stable form)}}{-\underset{H}{\overset{|}{C}}-\overset{|}{C}=N-R'}$$

When synthesizing adenine, we will first form the five member ring, with reactive groups extending out; this way, we will be able to form the attached six-member ring:

Note: X and X' are the reactive groups.

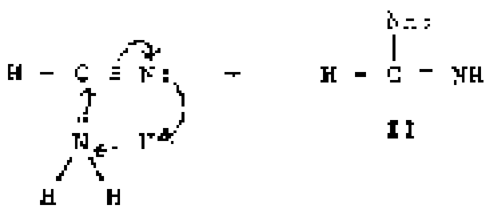
In synthesizing adenine, we must work systematically, keeping in mind our first goal, formation of the five-membered ring.

(i)

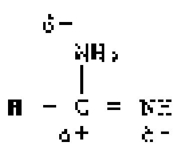


Note that this first step, and all subsequent steps are dependent on the polarity of HCN, the acidity of HCN, and the basic properties of the lone-pair electrons of nitrogen.

(ii) In the reaction vessel, we also have NH_3 reacting with HCN to form structure II:

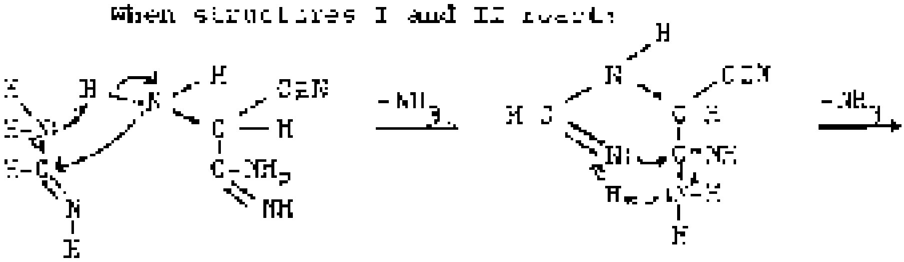


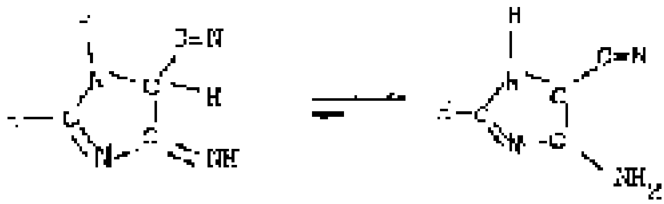
Note that the carbon in structure II is a good electrophile since it is singly bonded to one nitrogen and doubly bonded to another nitrogen:



II

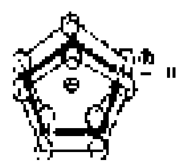
When structures I and II react:



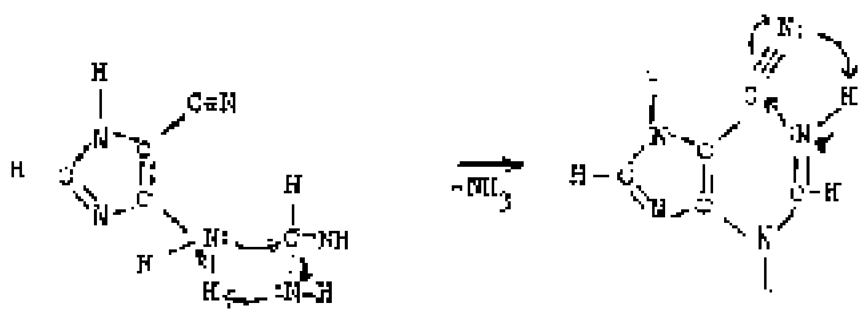


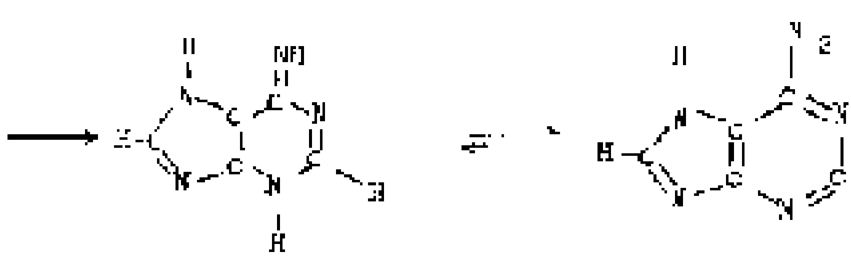
imine enamine (more stable form)

Note that the enamine is the more stable form in this case due to the stability of the aromatic five member ring: the lone-pair electrons of the top nitrogen in the above diagram is able to participate in the π cloud (compare with pyrrole):



The reactive groups extending out of the ring ("panhandles") are $-C\equiv N$ and $-NH_2$. When structure III reacts with another molecule of structure II.





Imine enamine (more stable)

Again the enamine is the more stable form due to the stabilization of the aromatic ring. Structure IV, we recognise, is adenine.

CHAPTER 34

NATURAL PRODUCTS

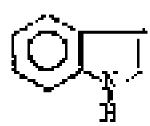
NOMENCLATURE AND STRUCTURE

• PROBLEM 34-1

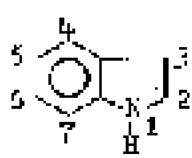
Give structural formulas for the following compounds:

(a) 3-Methylindole	(b) 3-Bromoquinoline
(c) Nicotinic acid	(d) 4-Methylisoquinoline
(e) Histidine	(f) 2-Methylimidazole

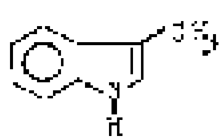
Solution: (a) The indole ring system has the following structure:



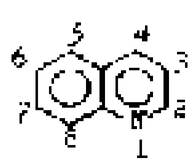
Following the IUPAC rules for nomenclature, the numbering of the ring begins with the hetero atom (atom other than carbon). Thus indole's numbering system is:



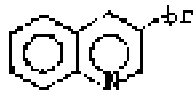
and 3-Methylindole has the structure:

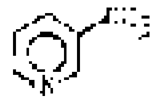
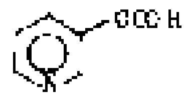


(b) Quinoline consists of a naphthalene ring containing nitrogen in place of one of the α carbons. Quinoline's numbering system is

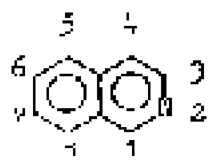


and the structure of 3-bromoquinoline is:

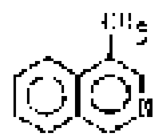


(c) Nicotinic acid (niacin) is a vitamin and is also known as 3 pyridine carboxylic acid. It can be derived from the oxidation of 3-picoline  . The structure of nicotinic acid is: 

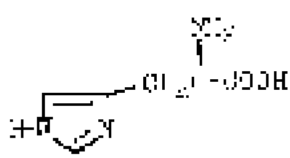
(d) Isoquinoline has a nitrogen in one of the B positions of the naphthalene ring. It is numbered as follows:



Therefore, the structure of 4-methylisoquinoline is:

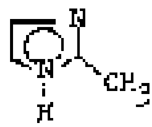


(e) The α-amino acid histidine contains an imidazole ring and its structure is:



(f) When heterocycle contains more than one hetero atom, the numbering starts with one atom and proceeds around the ring so as to give other hetero atoms the lowest possible numbered positions. Imidazole is thus numbered:

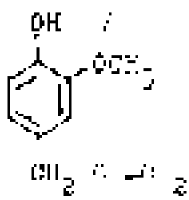
The structure of 2 methyl-imidazole is therefore:



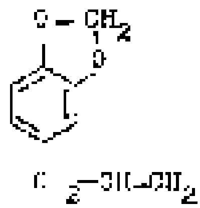
SYNTHESES AND REACTION MECHANISMS

• PROBLEM 34-2

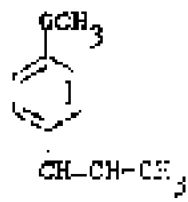
A number of phenols and phenolic derivatives cause the fragrances of many natural products. Some of them, and their sources, are presented below. Suggest syntheses for these, starting with any monosubstituted benzene derivative.



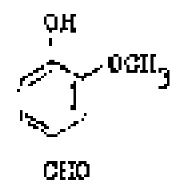
eugenol (oil of cloves)



safrole (oil of sassafras)



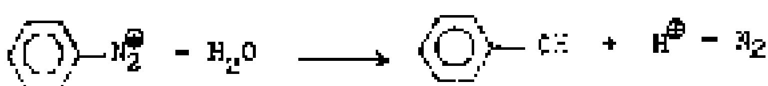
anethole (oil of anise)



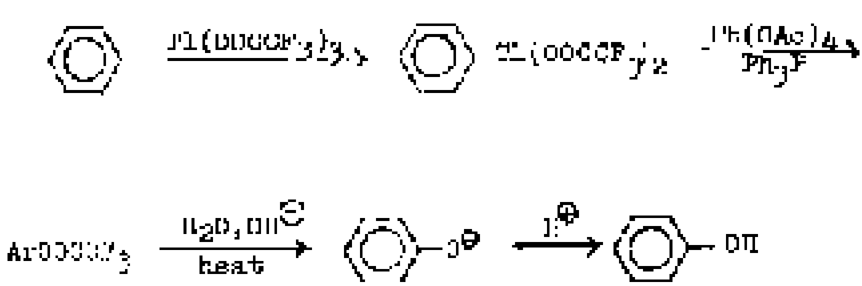
vanillin (oil of vanilla bean)

Solution: Some phenol compounds are responsible for the essential oils or essence of plants. There are generally three methods by which these natural products are made:

1. Diazonium Salt Hydrolysis:

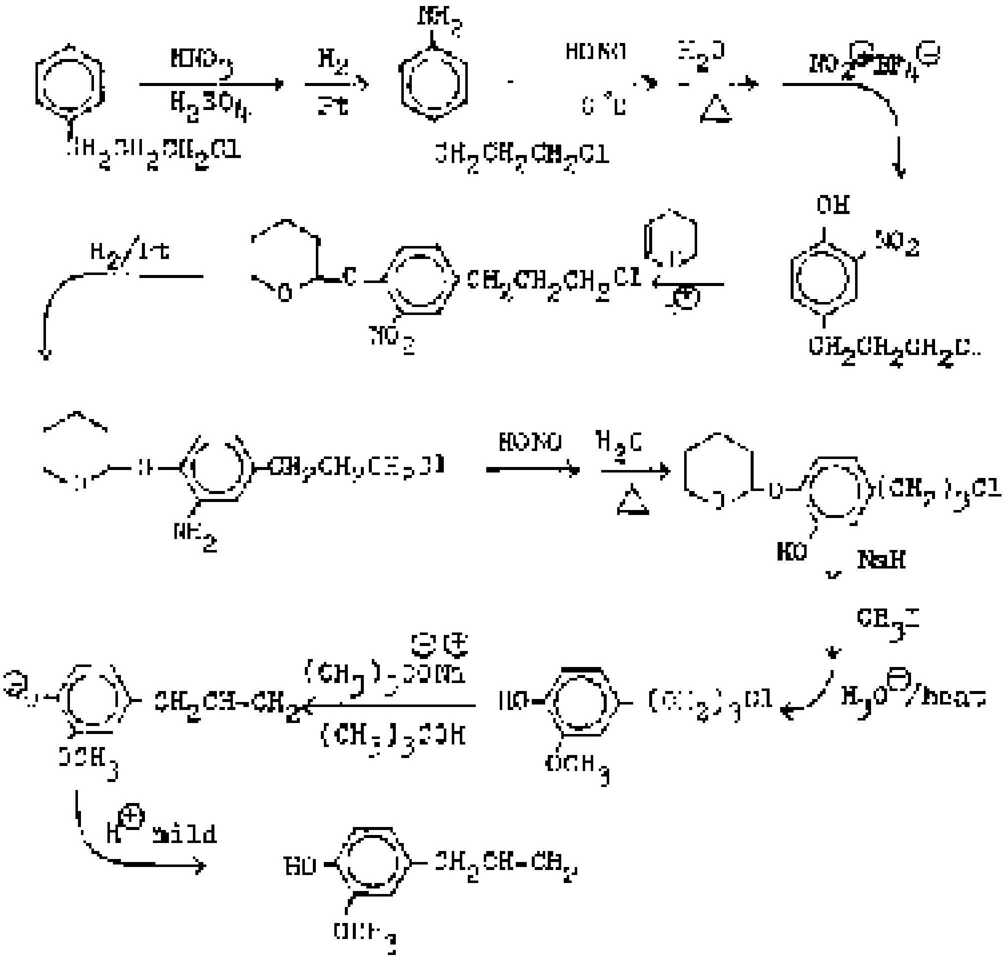


2. Arylthallium Oxidation:



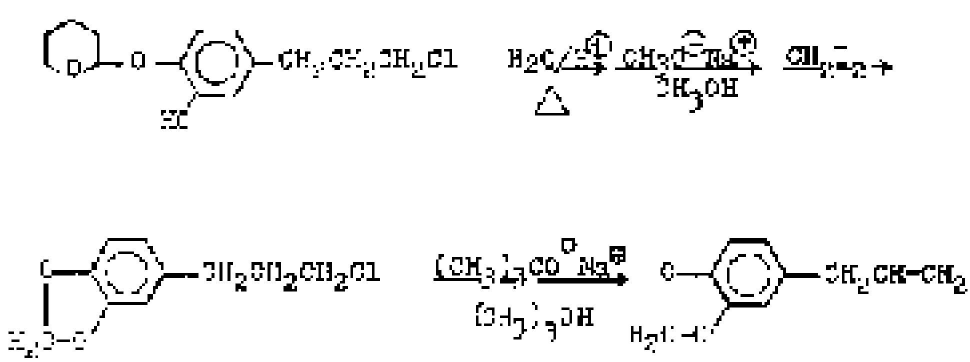
3. Sulfonate Alkali Fusion: See (a) below.

(a) Eugenol can be synthesized as follows:



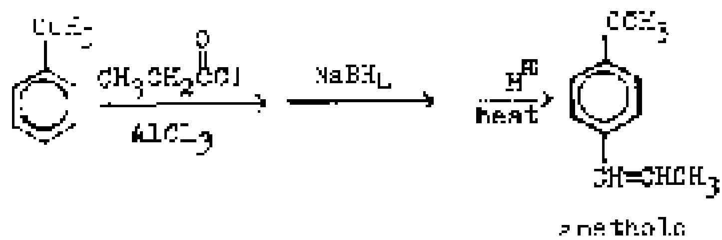
eugenol

(b) To make safrole we begin with a compound which was made in the synthesis of eugenol.

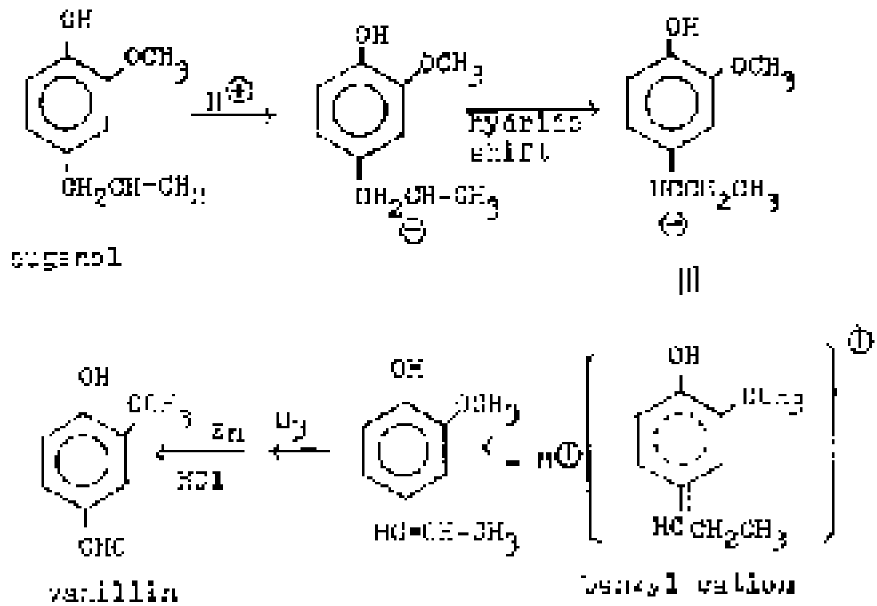


safrole

(c)



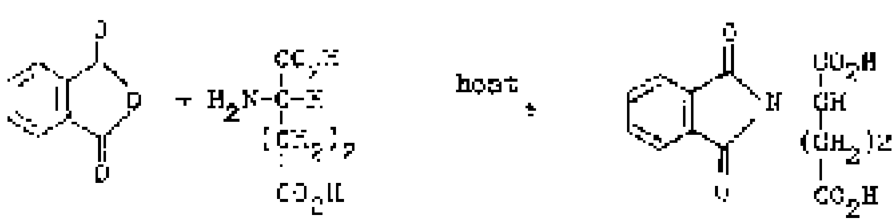
(d) To make vanillin we begin with eugenol which was previously synthesized in (a).



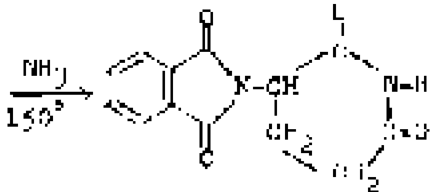
Note that the protonation of eugenol is favored for thermodynamic reasons - the protonated product can undergo a hydride shift to form a benzyl cation. Upon deprotonation, the resultant secondary alkene is more stable than eugenol due to the fact that it is more highly conjugated and substituted than before.

• PROBLEM 34-3

Thalidomide, the sedative and sleep-producer that led to many deformed babies in the 1960's, is synthesized as shown below. Suggest mechanisms for these reactions.

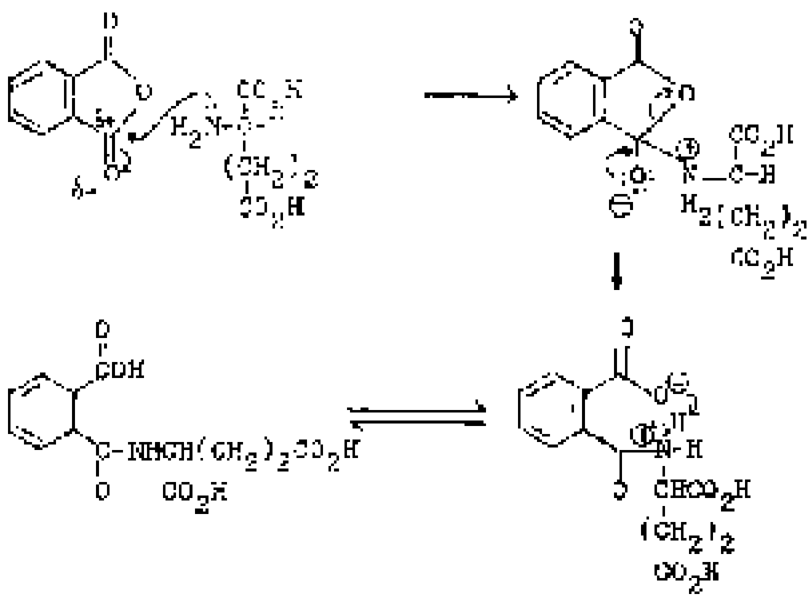


glutamic acid

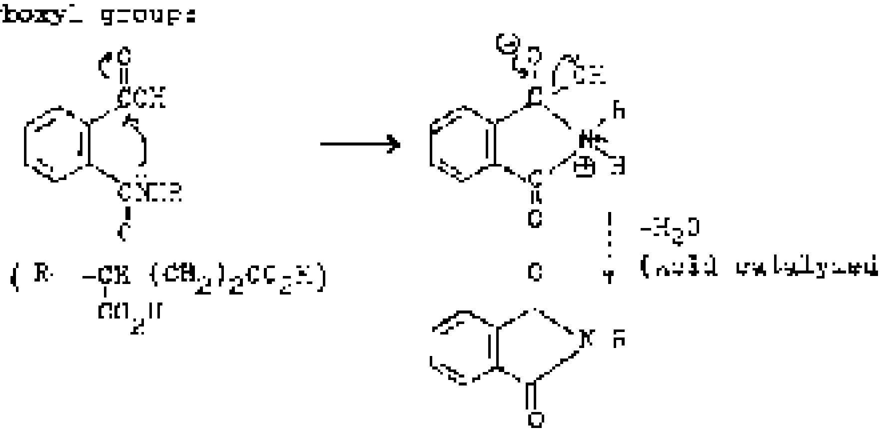


thalidomide

Solution: The synthesis of thalidomide is initiated by heat, which provides the activation energy. Looking at the structure of phthalic anhydride, we can see that the carbons of the carbonyl group are highly electropositive, due to the electron-withdrawing action of the two adjacent oxygens. The NH_2 group in glutamic acid is an electron-rich nucleophile, and will readily attack the electrophilic carbons of phthalic anhydride.

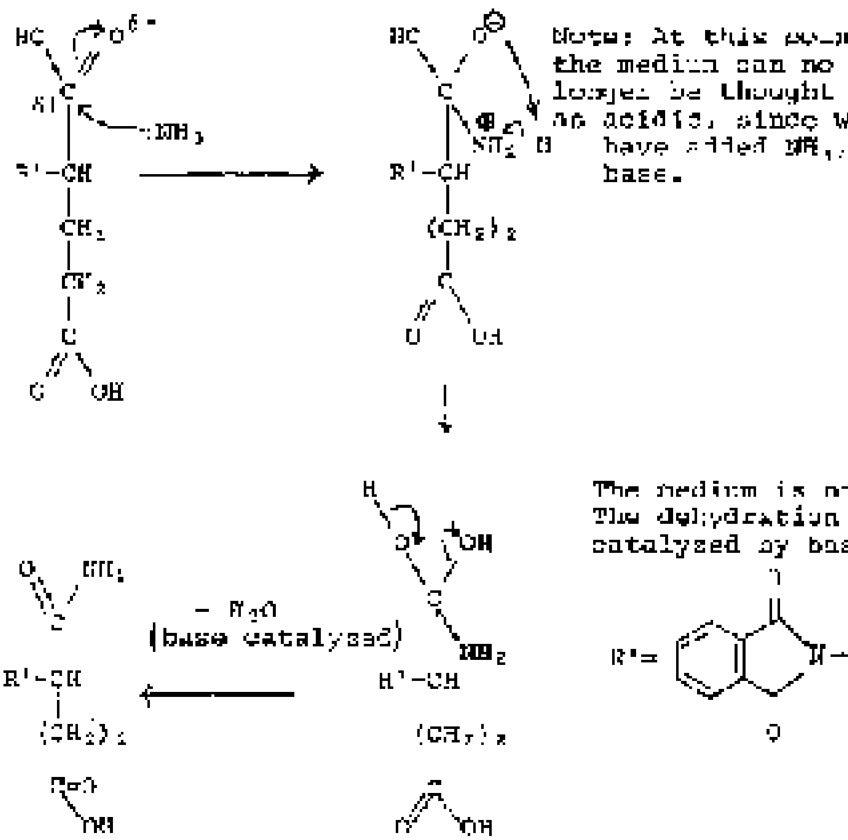


Again, the amide nitrogen can attack another electropositive center, here the carbon of the intramolecular carboxyl group:



Note: At this point, we have an acidic medium (H_3O^+), due to the use of glutamic acid as a reagent. Thus, OH is a good leaving group because it can become protonated and leave as water. The dehydration therefore is catalyzed by acid.

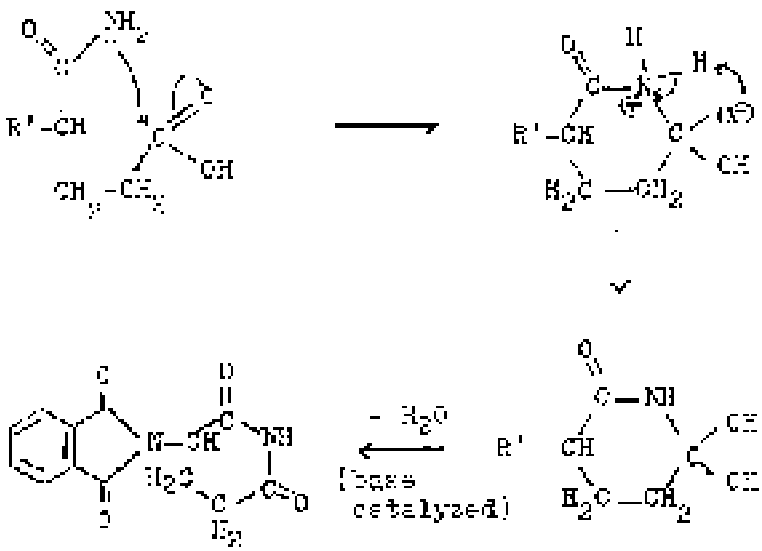
NH_3 is next introduced as a reagent. Again, the nitrogen is a strong nucleophile. Looking at probable points for its attack, we can see that the carboxyl carbons of glutamic acid are ideal due to their electropositive nature and the relative lack of steric hindrance (in comparison to the carbons in the ring). C_1, however, is more electropositive than C_5 because it is closer to the electron withdrawing nitrogenated ring. The reaction proceeds as follows:



Note: At this point, the medium can no longer be thought of as acidic, since we have added NH_3, a base.

The medium is now basic. The dehydration is thus catalyzed by base.

Again, the nitrogen of the amide can react with the other carboxyl carbon (C_5) via an intramolecular attack.



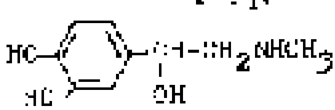
thalidomide

● **PROBLEM 34-4**

The following sequence can be used to synthesize adrenaline (epinephrine). Identify the intermediates A, B, and C.

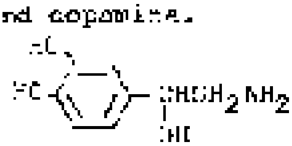
$$\text{o-nitrophenol} \xrightarrow[Pt]{H_2} \xrightarrow[HCl]{HONO} \xrightarrow[heat]{H_2O} A \xrightarrow[POCl_3]{ClCH_2COCl} B$$

$$\xrightarrow[(-HCl)]{CH_3NH_2} C \xrightarrow[Pt]{H_2} \text{adrenaline}$$

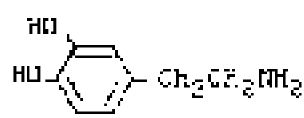


adrenaline (epinephrine)

Adrenaline, noradrenaline (also called norepinephrine), and dopamine are collectively called catecholamines. Suggest a reason for this name. Suggest syntheses of norepinephrine and dopamine.



norepinephrine

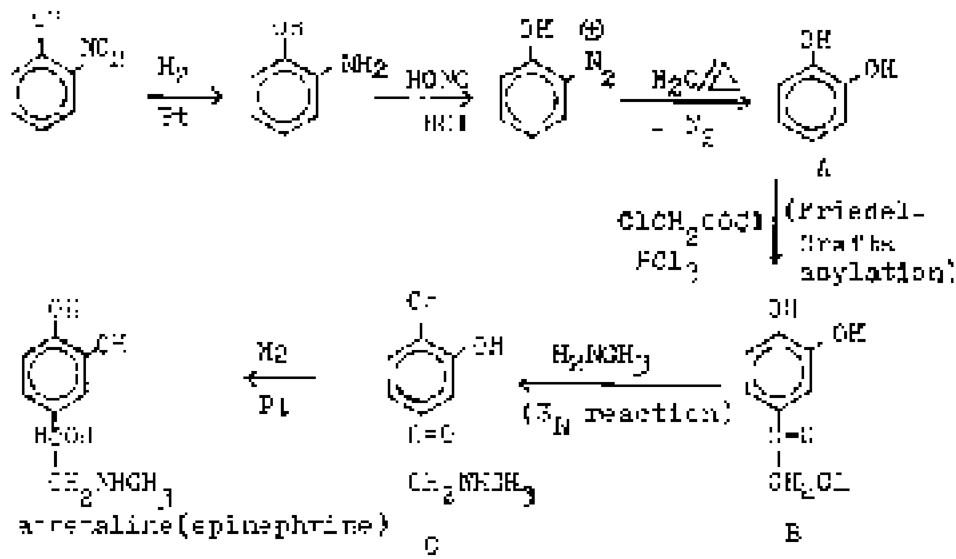


dopamine

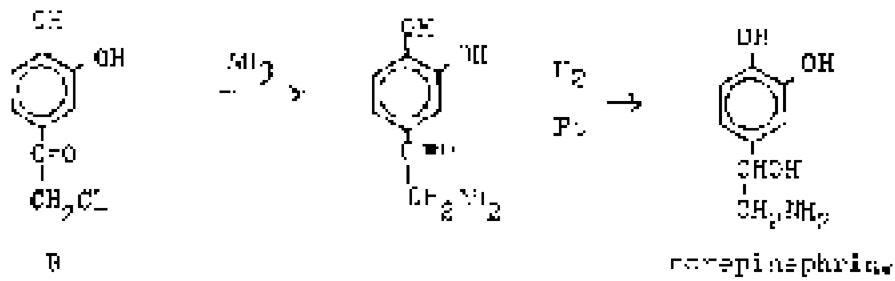
Solution: Catechol is a phenol with a substituted OH group at the ortho position:

A catecholamine is simply an amine with a catechol portion.

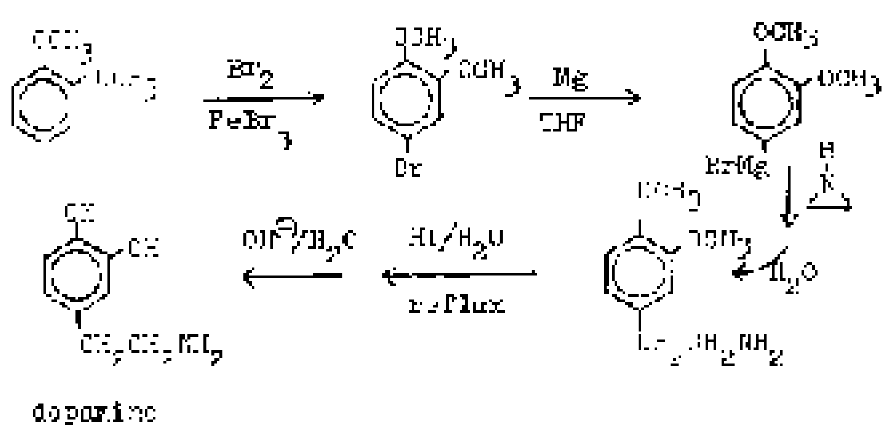
(a) Adrenaline (epinepherine) was the first hormone isolated and synthesized. It is, as the name implies, an adrenal hormone. Its synthesis is shown by the following reactions:



(b) Norepinephrine can be prepared in the same manner as epinephrine up until step "B". The following shows the subsequent steps:

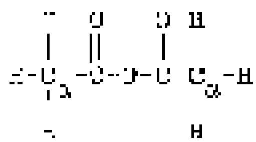


(c) Dopamine looks very much like norepinephrine and can be synthesized in the following manner:

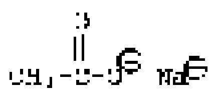


Show the probable mechanistic steps involved in the preparation of coumarin by the condensation of acetic anhydride with salicylaldehyde in the presence of sodium acetate as catalyst.

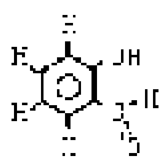
Solution: The key to determining the mechanism of the given reaction is in the structure of acetic anhydride:



Note the hydrogen atoms on the α carbons. These hydrogens are fairly acidic due to resonance stabilization of the carbanion formed upon proton loss. Notice also the fact that the catalyst, sodium acetate, contains the acetate anion:

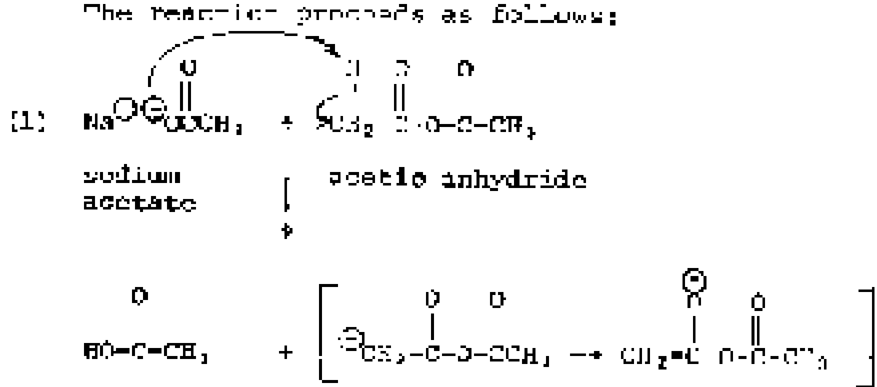


These facts strongly suggest Claisen type condensation by formation of the carbanion of acetic anhydride. The structure of salicylaldehyde (shown below) reveals no α hydrogens, and thus only a crossed Claisen condensation is feasible, since the salicylaldehyde will not form a carbanion or undergo self-condensation.



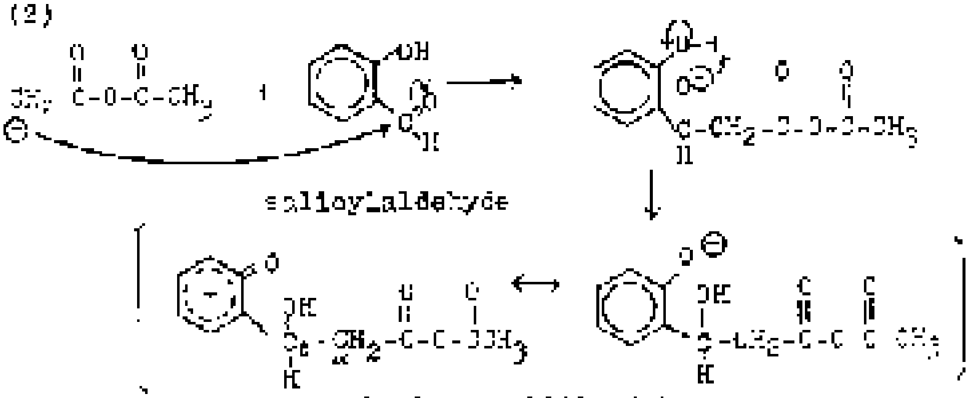
salicylaldehyde

The reaction proceeds as follows:



carbanion stabilized by resonance

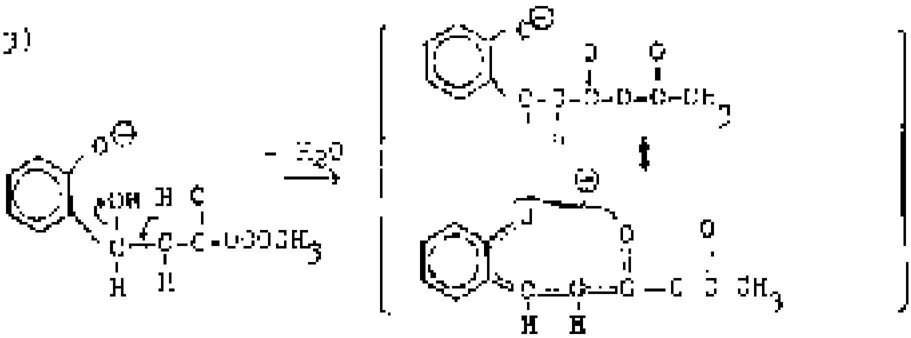
(2)



carbanion stabilized by resonance

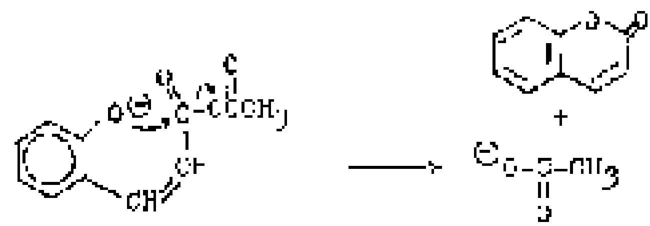
Note that the anion formed possesses a hydroxyl group on a beta (β) carbon. Such a compound is easily dehydrated, because dehydration would result in additional stability due to more extensive delocalization of the π electrons.

(3)



Greater stability due to increased conjugation

(4)

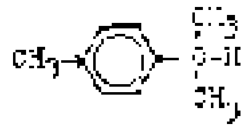


Notice that the catalyst, sodium acetate, is regenerated and not consumed in the reaction process.

• PROBLEM 34-6

The sulfonation of p-cymene (1-methyl-4-isopropylbenzene) gives the 2-sulfonic acid. Is this the expected orientation? Explain. Use this fact to synthesize carvacrol, 2-methyl-5-isopropylphenol, from p-cymene. Carvacrol is found in the essential oils from thyme, marjoram, and summer savory. It has a pleasant thymol-like odor.

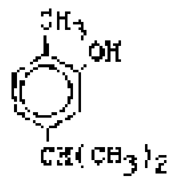
Solution:



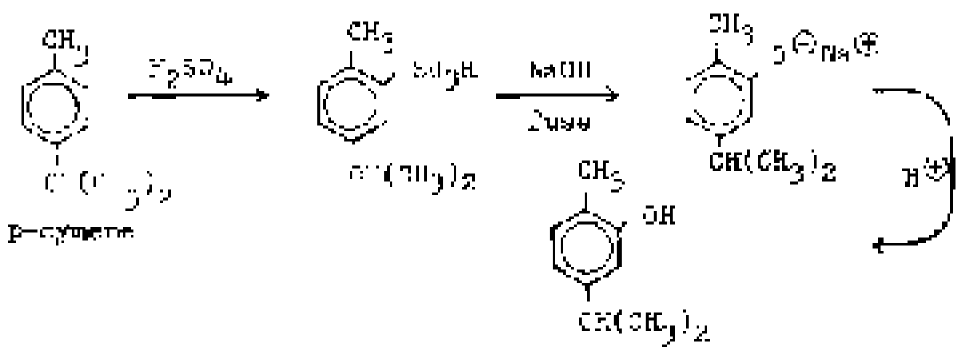
p-cymene

Both the methyl and the isopropyl groups are activating (electron releasing) substituents of the benzene ring, and thus direct ortho and para substitution. Since the isopropyl group is just slightly the more strongly activating substituent, one would expect sulfonation to occur mainly at its ortho position, namely C_3. (Both para positions are blocked.) However, SO_3 is a bulky group. The steric hindrance that would result is enough to make formation of the 3-sulfonated compound unfavorable, and to direct SO_3 ortho to the smaller CH_3 group rather than to the larger $(CH_3)_2CH$ group. This forms the 2-sulfonic acid.

Carvacrol has the following structure:

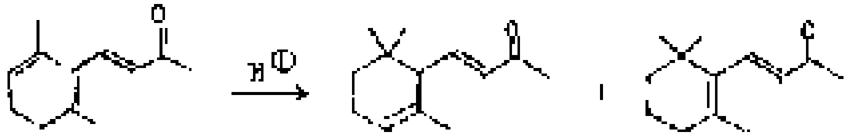


Aromatic sulfonic acids can be converted to phenols upon fusion with alkali. Thus carvacrol can be formed by first forming the 2-sulfonic acid of p-cymene, followed by fusion with NaOH.



• PROBLEM 34-7

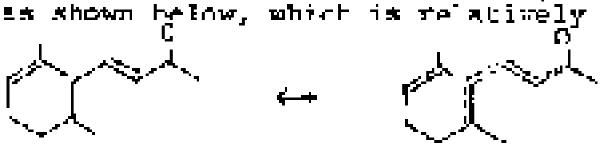
β-Ionone is an important chemical in the synthesis of vitamin A. It is prepared by the reaction of pseudo-ionone with sulfuric acid, α-ionone being produced in the same reaction. Suggest a mechanism for the acid-catalyzed conversion of pseudo-ionone to α- and β-ionone.



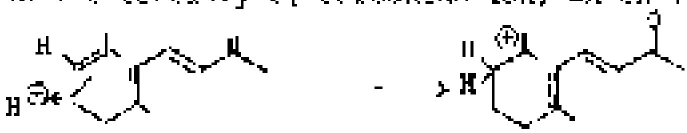
pseudo ionone α-ionone β ionone

Why might you anticipate that the cyclization produces more β- than α-ionone?

Solution: Looking at the structure of pseudo-ionone, one sees that the three double bonds present in the molecule provide a number of possible sites for initial proton attachment. However, the bonds between C_5-C_6, C_7-C_8, and C_9-O constitute an extensively conjugated system, as shown below, which is relatively stable and

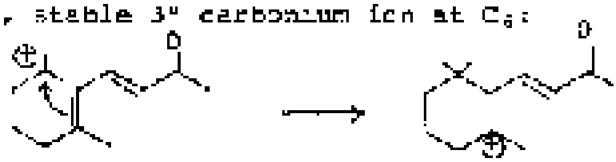


which makes the double bonds within the system less reactive. The proton would thus be more likely to attack at the C_1-C_2 double bond, and will result in formation of the tertiary C_1 carbonium ion, which is more stable

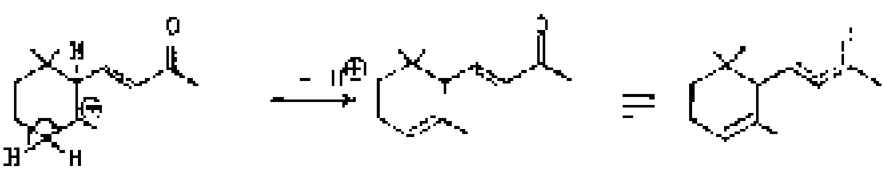


than would be the 2° C_2 cation.

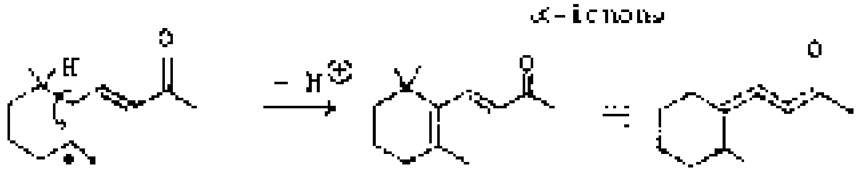
The carbonium ion can now pick up electrons from the C_5-C_6 double bond, effecting ring closure and forming another, stable 3° carbonium ion at C_5:



The compound can now lose a proton and reform a double bond. Loss of a proton from C_4 will lead to α-ionone, while loss of a C_6 proton leads to β-ionone.



α-ionone



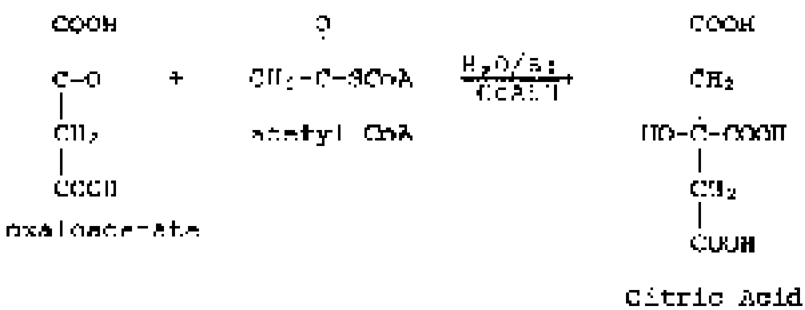
β -ionone

Note that β-ionone has a more extensive conjugated system than does α-ionone. It is therefore the more stable isomer and will be formed in larger quantities than the α-isomer.

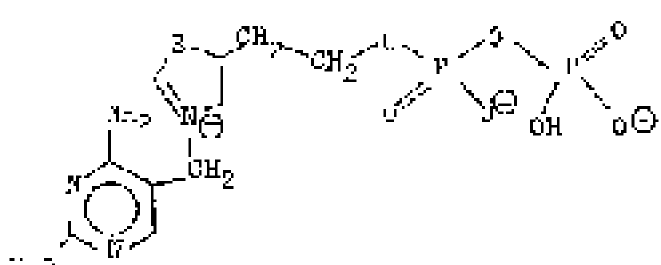
PROBLEM 34-8

If at this point the student is still unconvinced as to the importance of organic chemistry in daily life, let one consider glycolysis, the process whereby glucose is broken down into CO_2, ATP, and H_2O by the same nebulous mechanisms that the beginning organic student has been trying to master for two semesters.

(a) Consider the initial step of the Krebs Cycle: the reaction of oxaloacetate with acetyl CoA, in the presence of base and water to yield citric acid and CoASH. What would be the mechanism of this reaction if it occurs as written below:



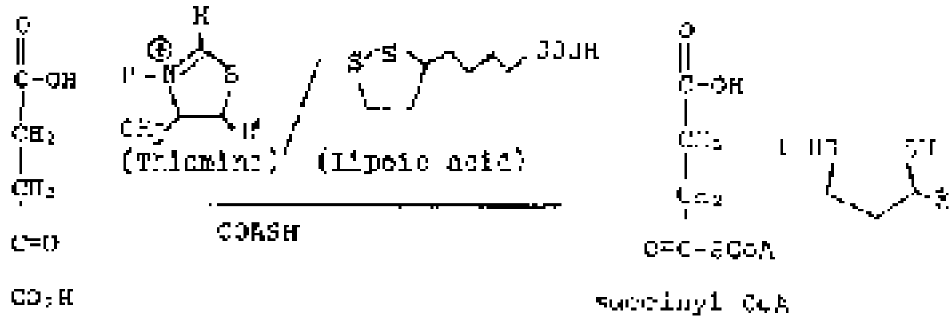
(b) Vitamin B_1 (Thiamine) also plays an important role in the Krebs cycle, catalyzing several important glycolysis reactions.



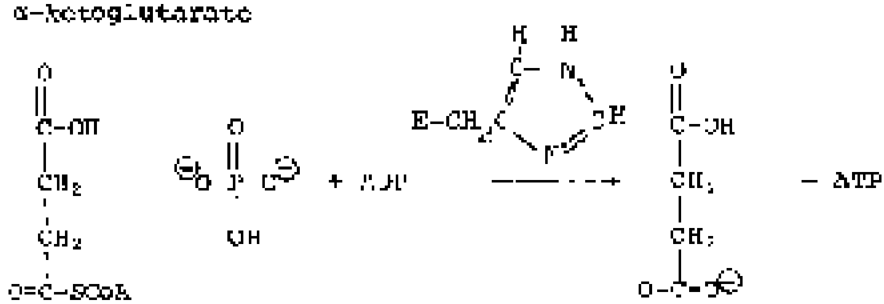
Thiamine pyrophosphate

One reaction it catalyzes in particular is the decarboxylation of α ketoglutaric acid to succinic acid.

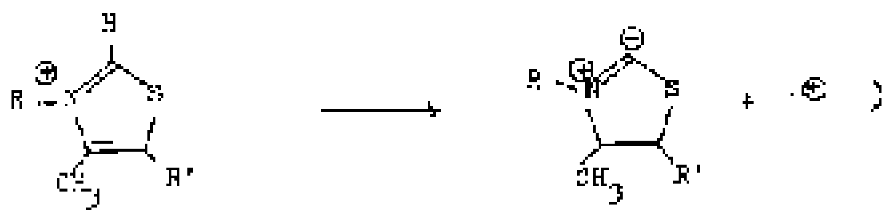
Given the following reactions, propose a mechanism for the decarboxylation of α ketoglutaric acid to succinic acid.



α-ketoglutarate

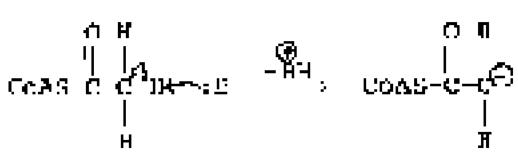


(Hint: Assume the carbonyl of thiamine to be in an ionized state.)

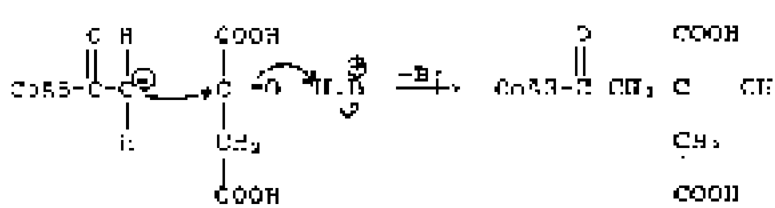


Solution: (a) The reaction of oxaloacetate with acetyl CoA to give citric acid is merely a cross-aldol condensation followed by the hydrolysis of the coenzyme group.

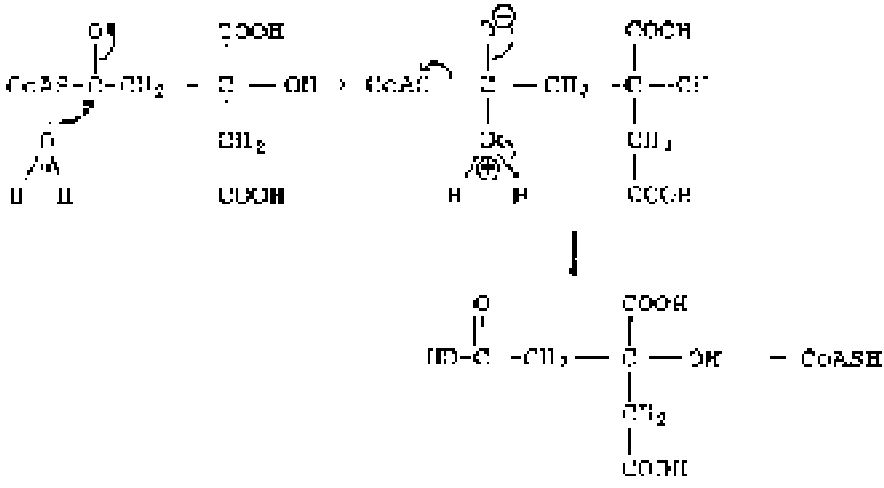
The first step of any aldol condensation involves the attack of a base on the α-carbon atom.



The carbanion will now attack the carbonyl of oxaloacetate.



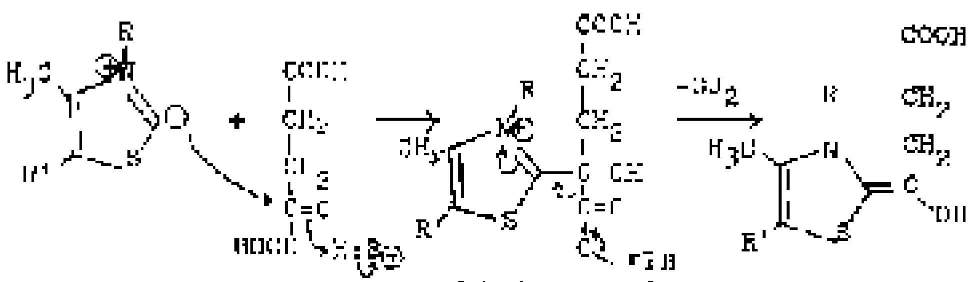
From this juncture, citric acid is obtained via the hydrolysis of the intermediate compound.



citric acid

(b) Like the reaction of oxaloacetate with acetyl CoA, the decarboxylation mechanism of α-ketoglutaric acid is similar to a familiar mechanism: the benzoin condensation.

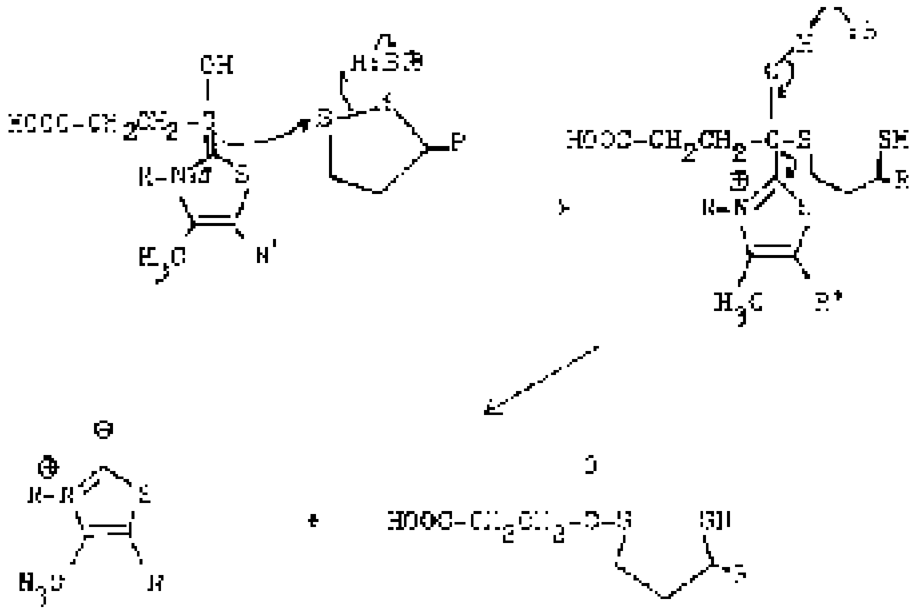
The first step involves the attack of the thiamine anion on α-ketoglutarate.



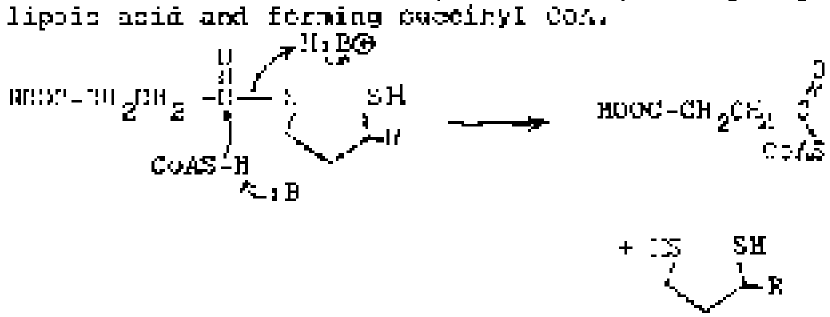
α hydroxy acid

It will be noted above that the thiamine attacks the carbonyl resulting in the formation of an α-hydroxy acid. The acid decarboxylates and CO_2 is liberated.

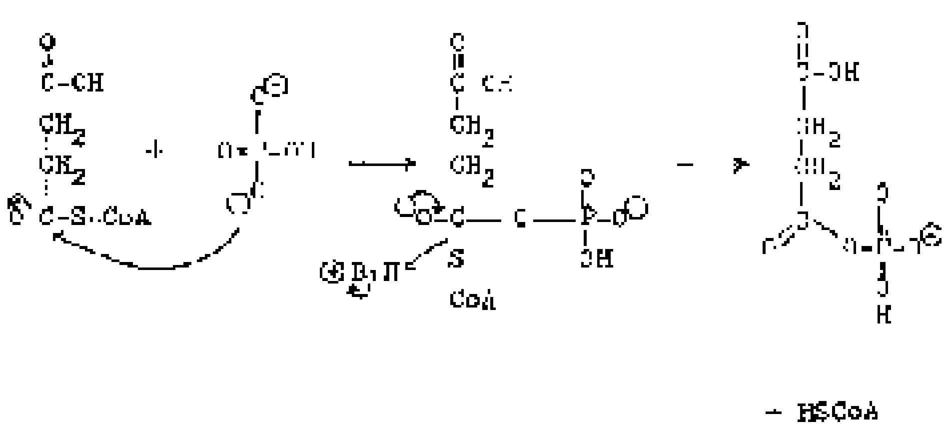
At this point, nature is confronted with the problem of reliberating thiamine. Nature, as always, has devised a route to liberate thiamine in a mechanism involving lipoic acid.

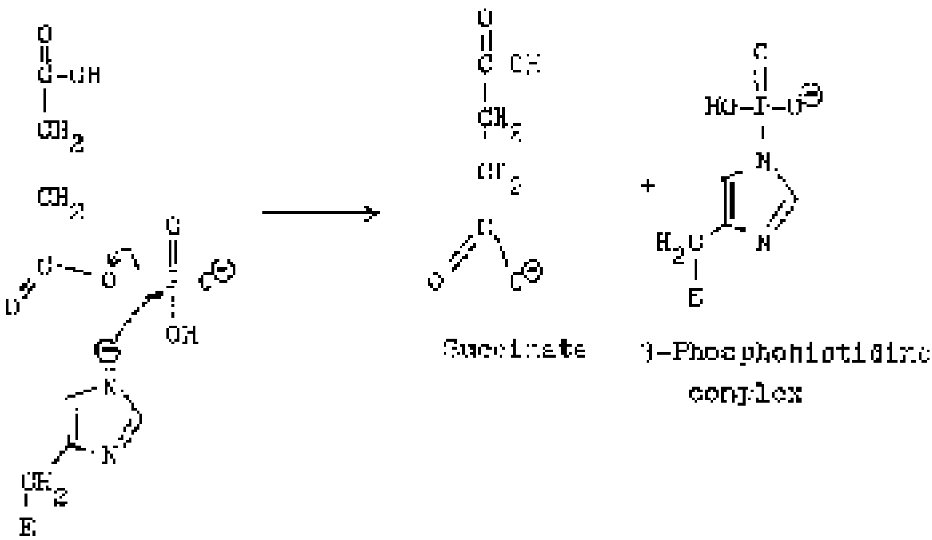


CoASH will now attack, liberating the hydrogenated lipoic acid and forming succinyl CoA.

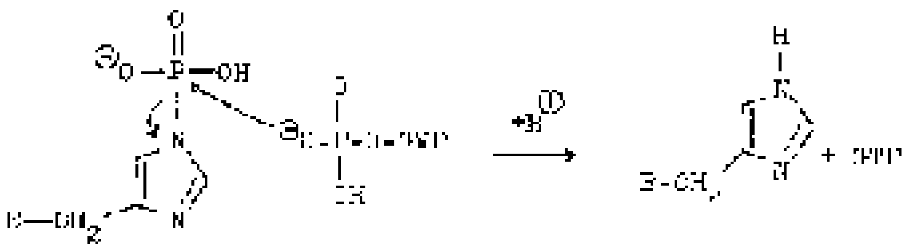


It is at this point of the Krebs cycle, the liberation of succinyl CoA to succinic acid in which ATP is produced.





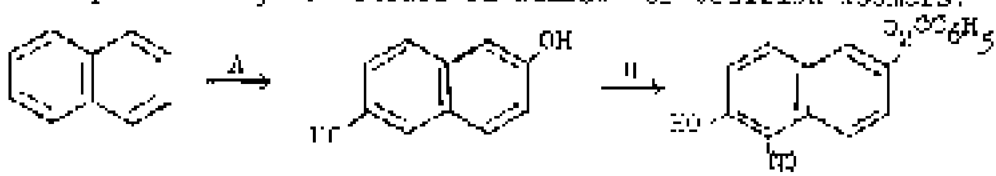
The 3-phosphohistidine complex now transfers its phosphate group to GDP, which subsequently transfers it to ADP:

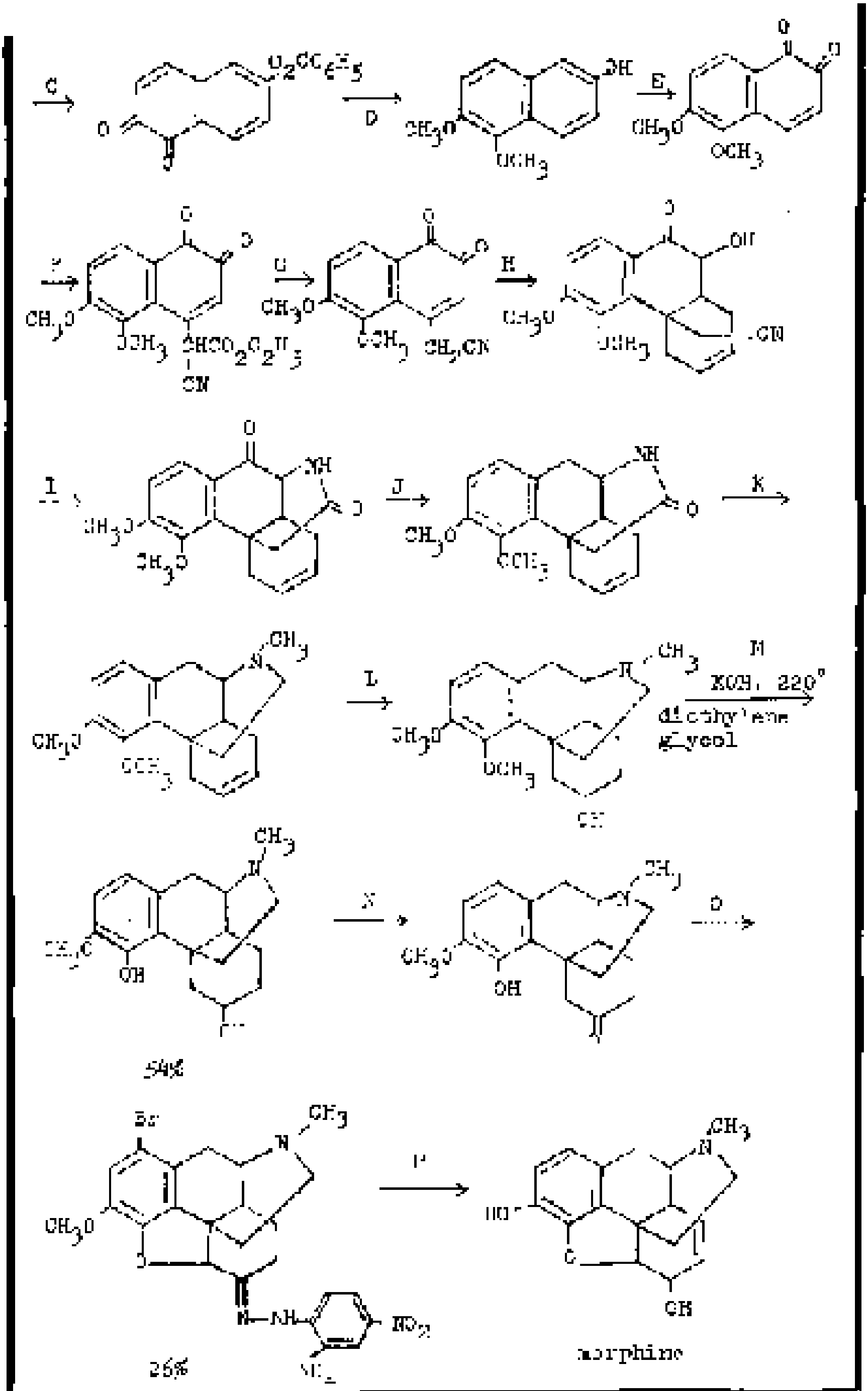


$$GTP + ADP \rightleftharpoons GDP + ATP$$

• PROBLEM 34-9

A synthesis of the alkaloid morphine was completed by Gates and Tschudi in 1952 by way of the following key intermediates starting from naphthalene. Show the reagents, conditions, and important reaction intermediates that you expect would be successful in achieving each of the indicated transformations, noting that more than one synthetic step may be required between each key compound and considering carefully the order in which the operations should be carried out. Indicate those reactions which might be expected to give mixture of stereo- or position-isomers.

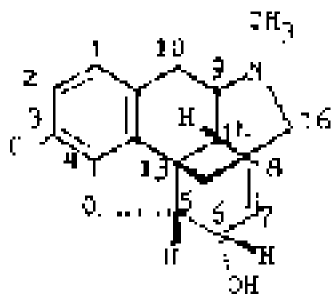



C
D
E
F
G
H
I
J
K
L
M
KOH, 220°
diethylene glycol
N
O
P
54%
26%
morphine

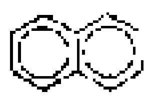
Solution: Morphine is the principle alkaloid of opium and the constituent primarily responsible for opium's physiological effects. Its analgesic and euphoric properties have been a source of study for over hundreds of years.

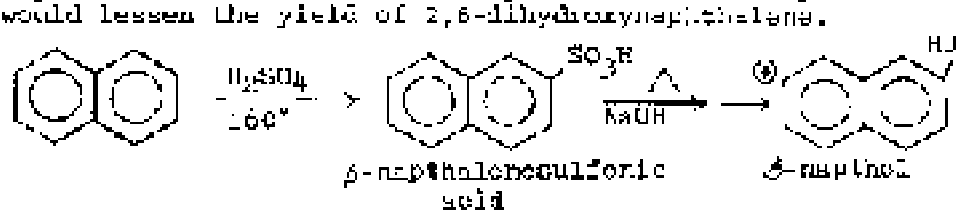
We should note that morphine's synthesis, as has often been the case with syntheses, served as the final and definitive proof of the structure of morphine. Some transformations used to synthesize morphine will be familiar while others will seem novel. It is often necessary to devise reactions unique to the particular reactants in order to achieve the required transformations. We will attempt to note the significance of each transformation used in the original undertaking of this synthesis. Details of slight modifications and the actual yields of the synthesis can be obtained from the original literature.

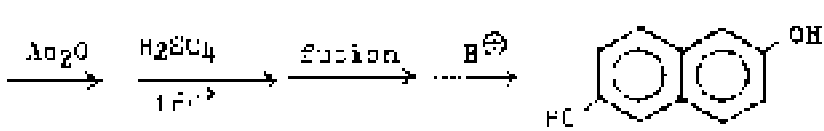
Morphine has the following structure and numbering system:



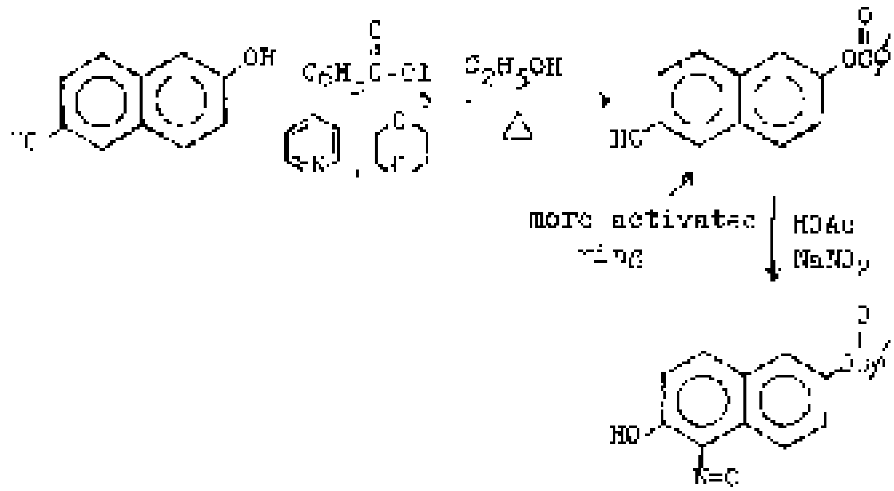
We can already see some of the difficulties in producing this molecule by examining the stereochemistry at its several chiral center bridgeheads. On the other hand, morphine may be seen as a combination of two phenylalanine units and its synthesis seemed quite possible.

(A) Naphthalene, , is a major constituent of coal tar. 2,6-dihydroxynapthalene can be obtained first by producing β-naphthol via fusion of β-naphthalenesulfonic acid which was made in turn from the high temperature sulfonation of naphthalene. β-naphthol (whose hydroxyl group will be protected) can be sulfonated at the 6-position and a second fusion performed. Minor products would lessen the yield of 2,6-dihydroxynaphthalene.

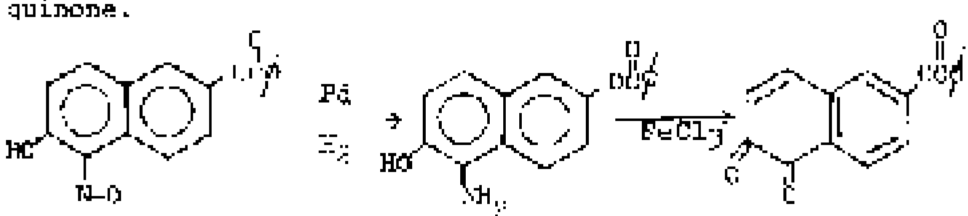




(b) The dihydroxynaphthalene is converted to the monobenzoate in high yield in the exclusion of the dibenzoate by making use of the latter's low solubility in boiling alcohol. The monobenzoate can be converted to 6-benzyloxy-1-nitroso-2-naphthol by nitrosating the reactant via the use of $NaNO_2$ in CH_3COOH. The attacking electrophile may be $[NO]^+$ itself or some more complicated species. We know that normally the electrophile attacks at the α-position of naphthalene due to the formation of a more stable carbocation than that which would have resulted from β-attack. This greater stability can be explained by the fact that the carbocation in the α attack has more resonance contributing structures in which the aromatic ring remains intact (2-α, 1-β).

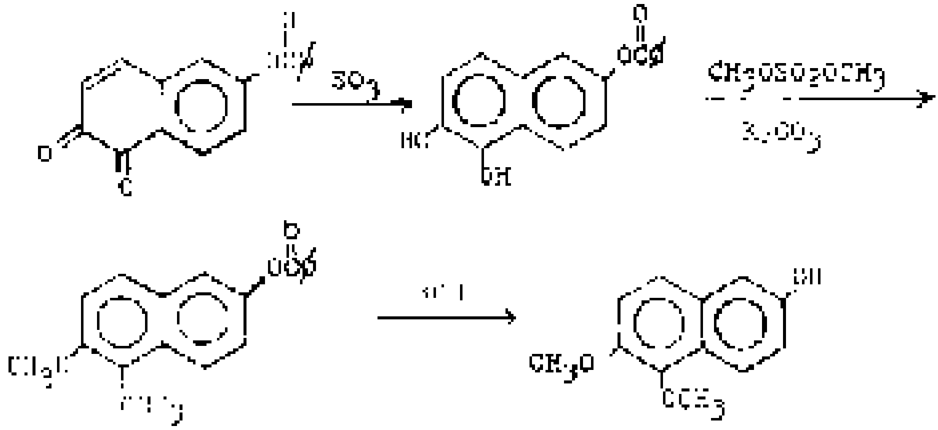


(c) The oxidation potential of the nitroso group is between that of a nitro group and an amino group and therefore it can be catalytically reduced to the latter. $FeCl_3$ is an oxidant that promotes a one-electron transfer which converts the o-aminonaphthol into 6-benzyloxy-1,2-naphthoquinone.

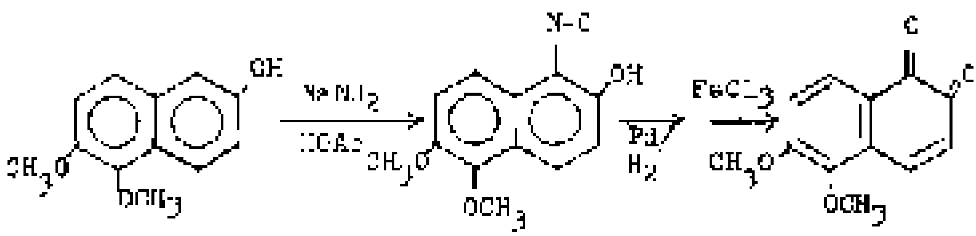


In practice the aminonaphthol was not actually isolated.

(d) The diquinone is reduced by sulfur trioxide and the resultant hydroquinone is protected in the standard way by treatment with dimethylsulfate in the presence of base (a weak base is used to prevent hydrolysis). The ester linkage (at the 6 position) is subsequently hydrolyzed by alkali.

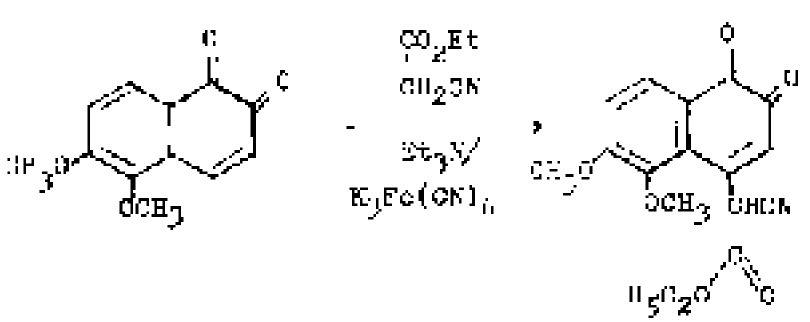


(E) The more activated ring of the dimethoxynaphthol is nitrosated using the same method as before. The nitroso group is catalytically reduced and the subsequent α-aminonaphthol is oxidized by $FeCl_3$ to the diquinone.

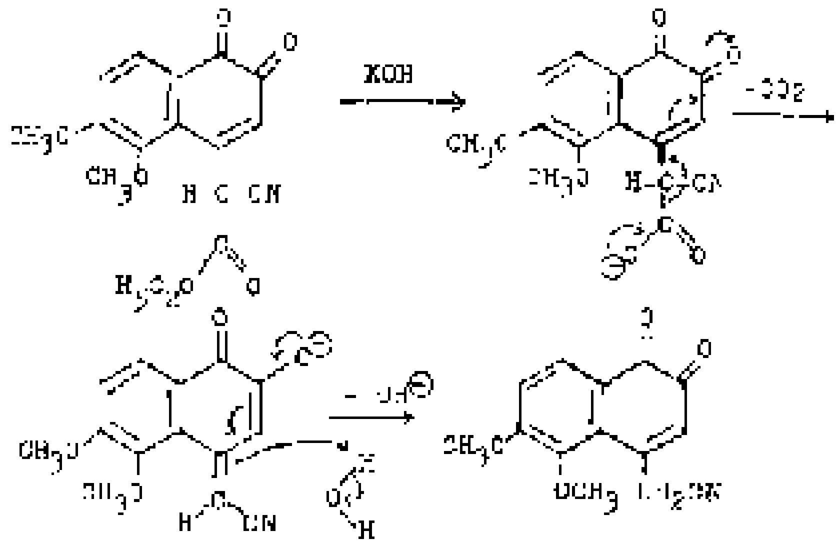


(F) The diquinone has an α,β unsaturated system which provides an excellent substrate for a Michael reaction. The nucleophile employed here is the carbanion of cyanoacetic ester which is generated by the combination of the ester and triethylamine, a tertiary amine and therefore a poor nucleophile.

The hydroquinone thus formed is immediately oxidized by ferricyanide incorporated in the reaction mixture.

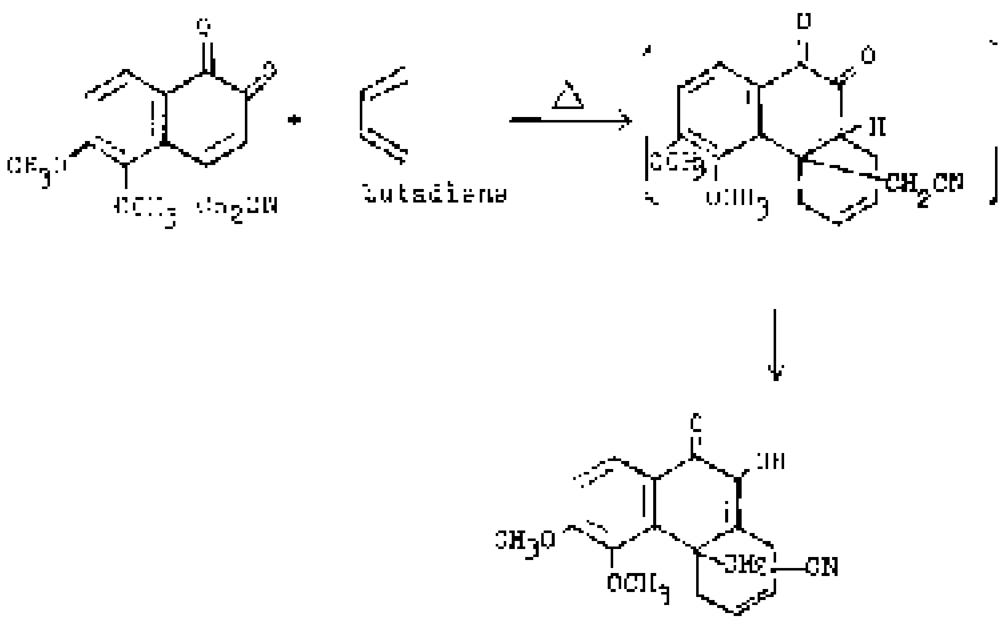


(G) Under the influence of alkali, the ester will be hydrolyzed to a carboxylate salt. This in turn can be easily decarboxylated due to the fact that it is both an α-cyanoester and a vinylogous β-ketoester. (The carbonyl group has its influence extended by the double bond.) Water then donates a proton to neutralize the negative charge.

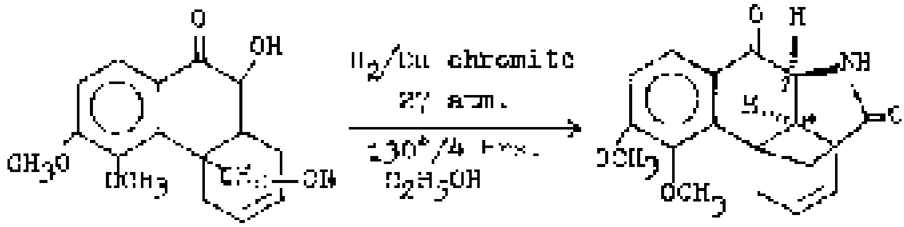


(H) The double bond of the non-aromatic ring may act as a dienophile in a Diels Alder reaction in which it reacts with butadiene.

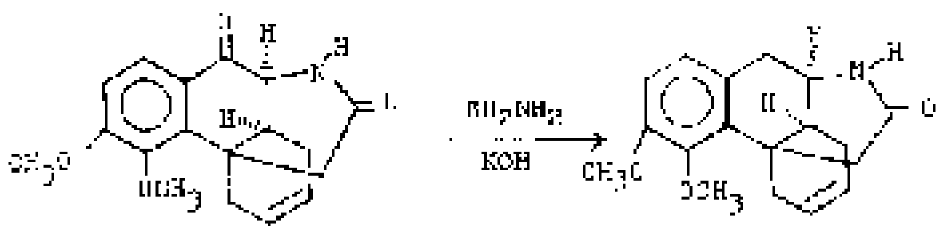
Note the usefulness of this reaction in formation of the six-carbon ring. It is also a stereospecific process, but its stereospecificity is not evident in the product, since the proton adjacent to the carbonyl group is lost in the subsequent tautomerization of the 1,2-diketone to form the α-hydroxy-α, β-unsaturated ketone.



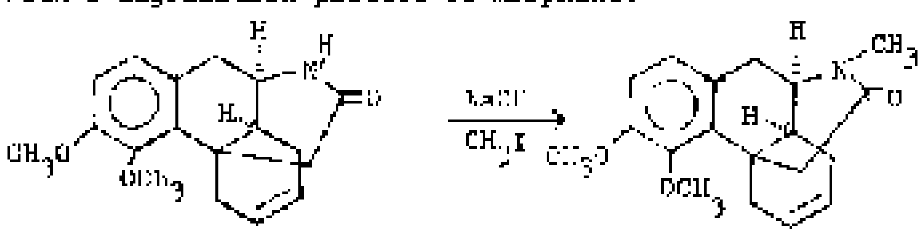
(I) The next step of the synthesis is such a surprising one that its actual mechanism was originally never considered. However, its product was finally verified using infrared spectroscopy. The reaction can be best termed a reductive cyclization. A possible mechanism involves the formation of an amide from the reduction of the nitrile. The amine portion of the amide then condenses with the carbonyl tautomer of the diosphenol. Although the lactam thus formed has three chiral centers, only one pair of enantiomers is obtained. This is due to the fact that the hydrogens are delivered to the less hindered side of the bridged compound (opposite the cyanomethyl group), giving C_{14} only one possible configuration in which the new ring could be formed.

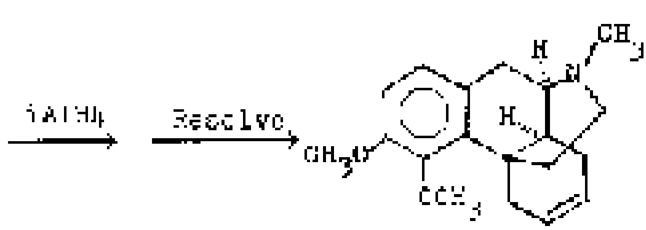


(D) The ketone functionality of the intermediate is removed by Wolff-Kishner reduction. There is no enolization or change in the stereochemistry of C_{14} because of the nature of the ring system.



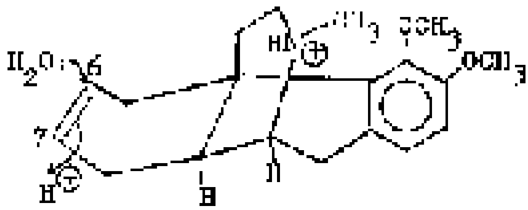
(E) In the presence of a potent base, we may alkylate the lactam and then produce the tertiary amine by reduction with $LiAlH_4$. The amine may now be resolved by employing optically active dibenzoyltartaric acid. After separation and regeneration, one of the enantiomeric amines coincides with a degradation product of morphine.

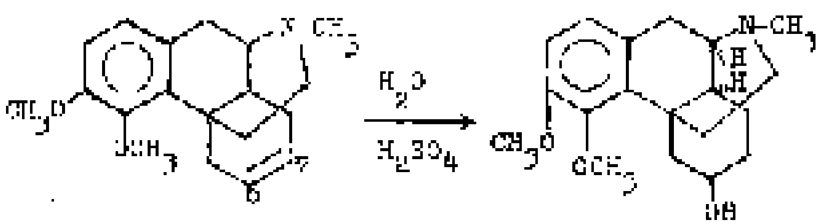




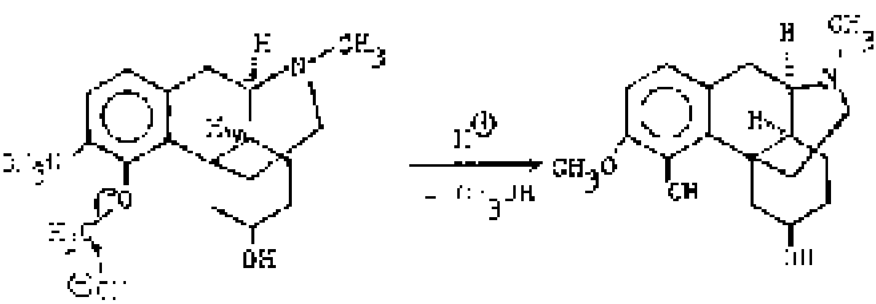
(optically active)

(L) The optically active amine can be hydrated at the isolated double bond, but it is difficult to determine whether the hydroxyl group will be situated at C_6 or C_7. Its placement at C_6 may be rationalized by the fact that the incoming nucleophile would be attracted to the protonated ethylamine bridge. This is a weak argument, however, and there are probably other products formed.



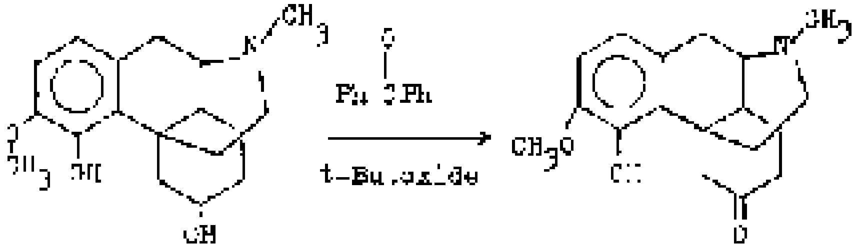


(M) The ether linkage at C_4 may be removed in a somewhat unusual fashion under alkaline conditions. This can be accounted for by noting that the methyl moiety is an excellent substrate for nucleophilic attack (since its electropositive nature is strengthened by the electron withdrawing powers of the ring) and the leaving group is a stable phenoxide anion.



Note, however, that base-catalyzed ether cleavage is still not a facile occurrence and thus vigorous conditions are necessary.

(N) The hydroxyl group is selectively oxidized to the ketone by a variation of the Oppenauer oxidation, namely a disproportionation process similar to the Cannizzaro reaction. The alcohol is oxidized to ketone while an alcohol is formed from the reduction of another ketone. The reaction is reversible depending on the concentration of the reactants.

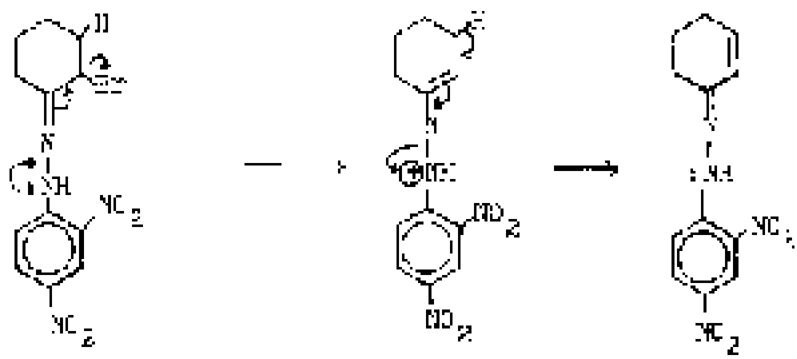


(D) At this junction in the synthesis, we must deduce a means to alter the stereochemistry at C_{14} because it is the inverse of that of morphine. This is done by introducing bromine into the molecule at C_7.

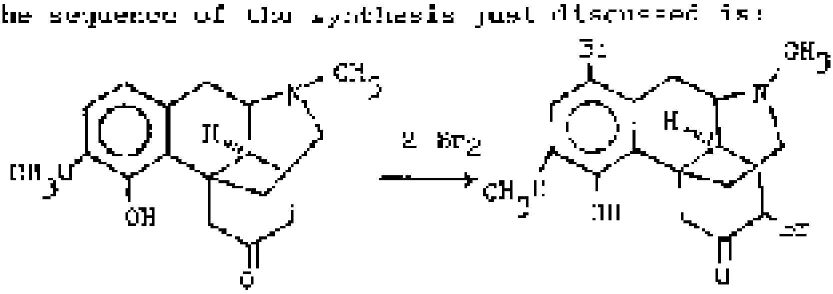
The yield was diminished because the bromide did not go exclusively to C_7, but also to C_5.

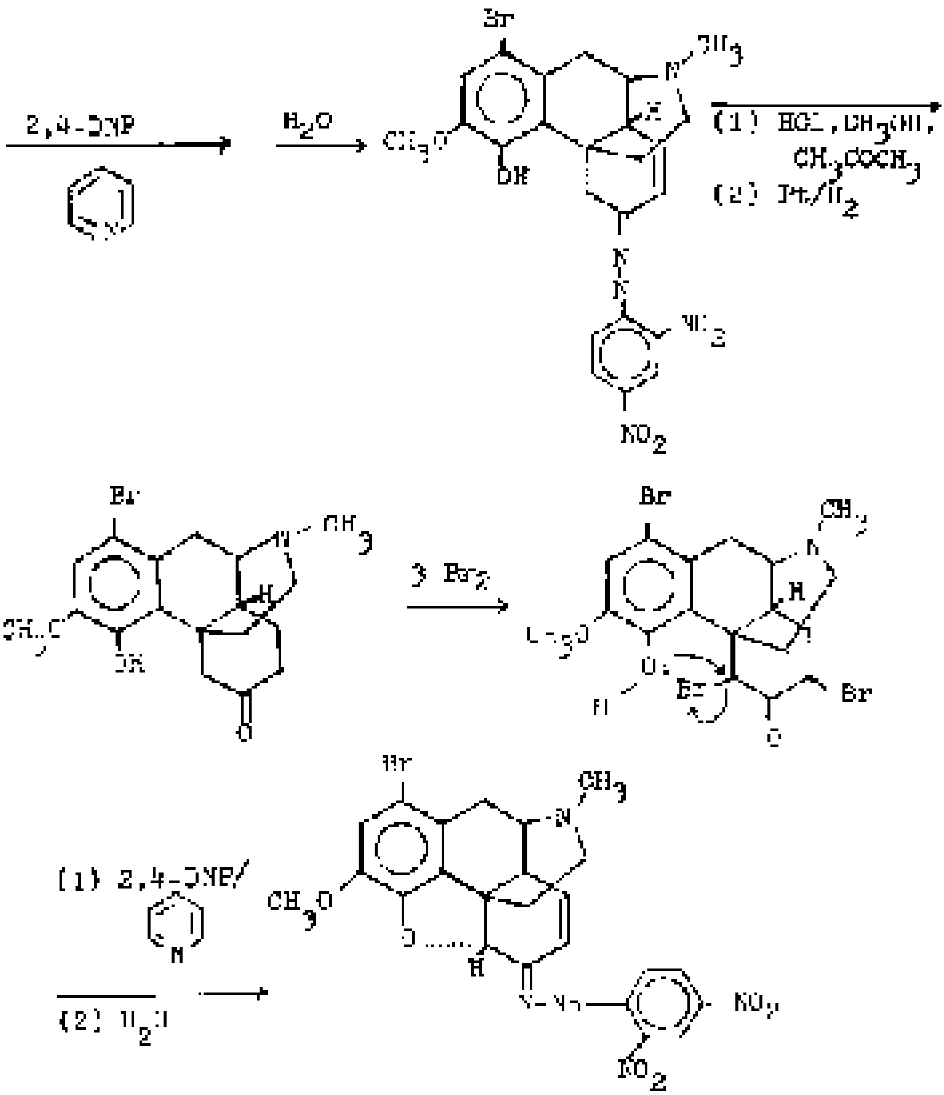
α-Bromo ketones are known to produce α,β-unsaturated ketones after treatment with 2,4-dinitrophenylhydrazine, followed by hydrolysis. Such formation of a conjugated double bond (between C_7 and C_8) allows the chiral center at C_{14} to invert its configuration through a sequence of enolization and reprotonation. The hydrazone was found to contain the opposite configuration at C_{14} than before and this was known to be the more stable of the two.

After the necessary stereochemical transformation is performed, the newly formed double bond is reduced and the ketone converted to a tribromo derivative. The bromine at C_5 will be displaced by the adjacent hydroxyl group in a nucleophilic reaction, forming a stable five-membered ring. The double bond between C_7 and C_8 was formed in the same way as before. A possible mechanism for this transformation is as follows:

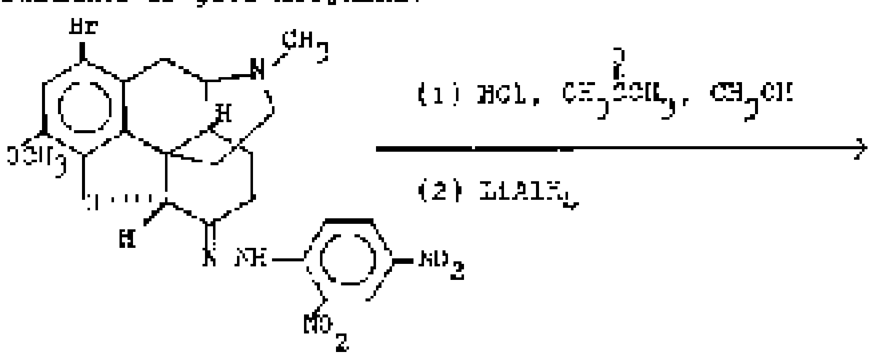


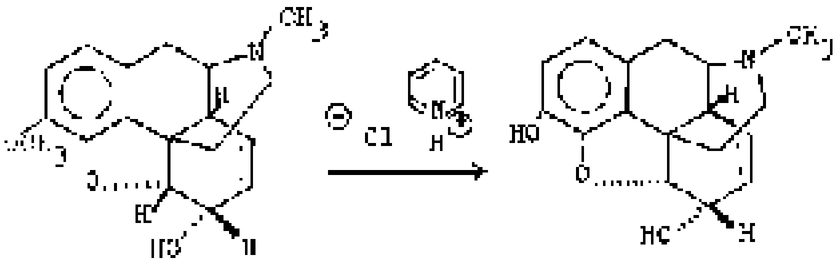
The sequence of the synthesis just discussed is:





(f) The hydrazone can now be hydrolyzed. The carbonyl group thus formed at C_6 may now be reduced, and the bromine removed from C_1, both by treatment with $LiAlH_4$. This reagent gives the correct stereochemistry in the reduction. The remaining methyl ether linkage is removed by acid treatment to give morphine.





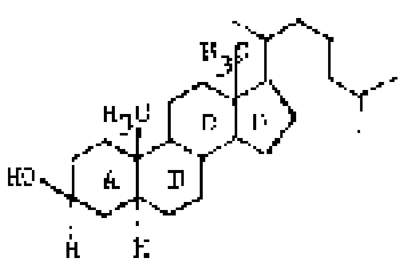
codeine morphine

STEROIDS

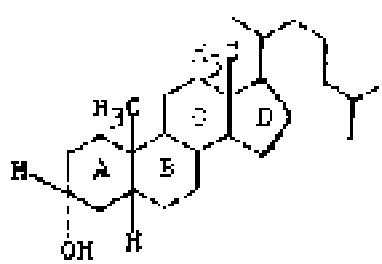
• PROBLEM 31-10

Cholesterol can be reduced either to cholestanol or coprostanol. Equilibration of cholestanol with a trace of cholestanone and base gives 90 per cent cholestanol and 10 per cent of a stereoisomer known as epicholestanol. Similar equilibration of coprostanol (in the presence of coprostanone) gives 10 per cent coprostanol and 90 per cent epicoprostanol. Write the configurations of each of these compounds and explain the orders of stabilities that are observed.

Solution: Proof that cholesterol and the bile acids have the same general ring system was achieved by the reduction of cholesterol to two different hydrocarbons, cholestane and coprostane. These two compounds differ only in the stereochemistry of the junctions between rings A and B (see below). In this problem the hydroxylated form of coprostane, coprostanol, and the hydroxylated form of cholestane, cholestanol, are considered. Their structures are shown below:



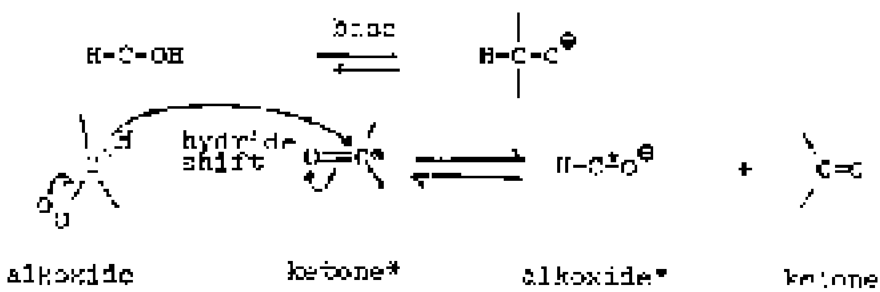
cholestanol
(equatorial OH)



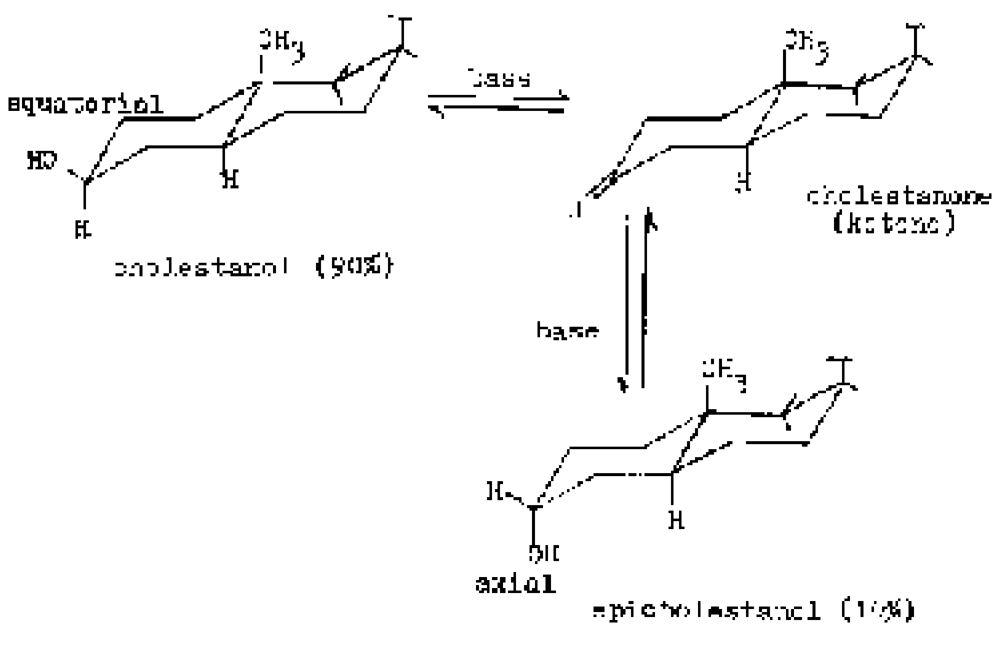
coprostanol
(axial OH)

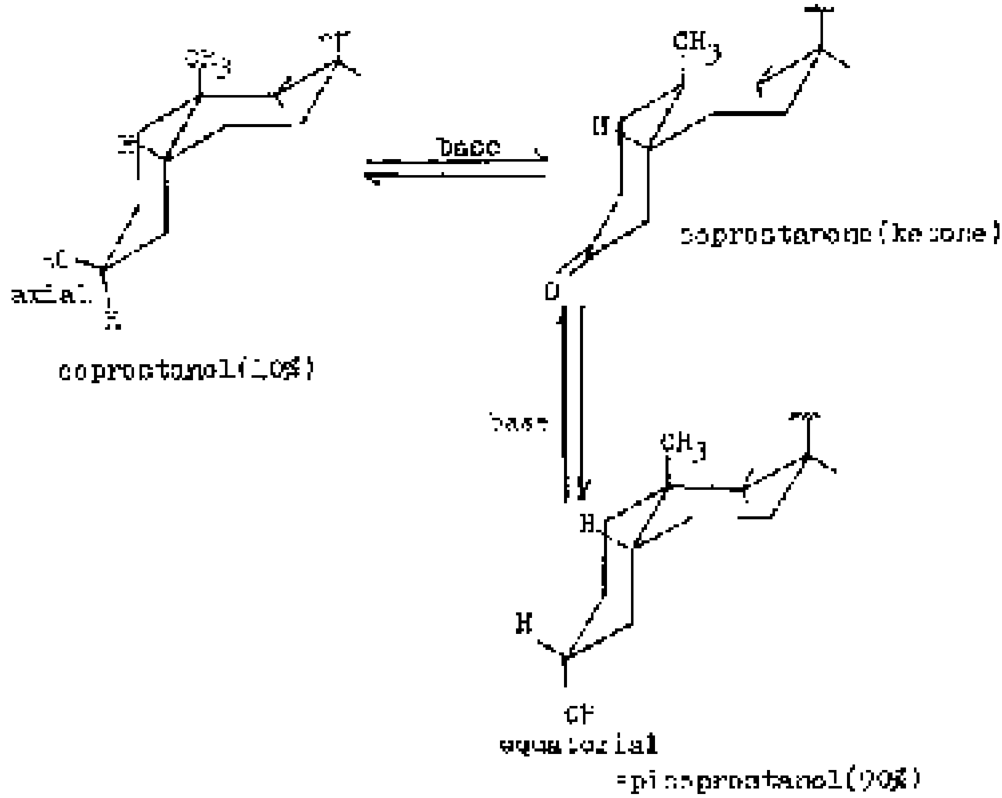
In previous chapters we have discussed the relative stabilities of cyclohexanes with axial and equatorial bulky substituents. We mentioned that instability is caused by nonbonded interactions between the axial substituents on the same side of the molecule. Because equatorial groups are pointing away from the ring, they will present significantly less steric hindrance. This explains why cholestanol, with the relatively bulky OH group in an equatorial position, is expected to be more stable than coprostanol, with an axial OH substituent.

Applying the same principles, we can readily ascertain the proportion of cholestanol and epicholestanol, and of coprostanol and epicoprostanol in equilibrium. In the presence of base and a trace of cholestanone, we are told that an equilibrium mixture containing 9 parts cholestanol and 1 part epicholestanol exists. Likewise, coprostanol exists in equilibrium with epicoprostanol in a 1 : 9 ratio. These two reactions involve the same mechanism, a generalized scheme of which is presented below:



Note that this is a reversible process, since the products are another alkoxide and another carbonyl compound. In equilibrium, therefore, we expect to find the following:



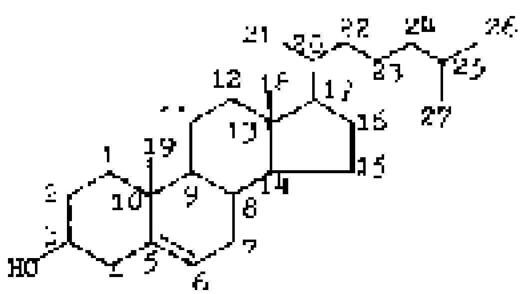


We can readily infer from their structures that epicholestanol, with an axial OH, will be less stable than its isomer, cholestanol, which has an equatorial OH. This explains why cholestanol is observed to predominate in the equilibrium mixture (90%). For the same reason, epicoprostanol will be more stable than coprostanol, and hence will be the favored isomer.

• PROBLEM 34-11

The conversion of cholesterol into 7-dehydrocholesterol is a process of importance in the manufacture of vitamin D_3. Suggest one reaction sequence for this conversion.

<u>Solution:</u> Cholesterol has the following structure:

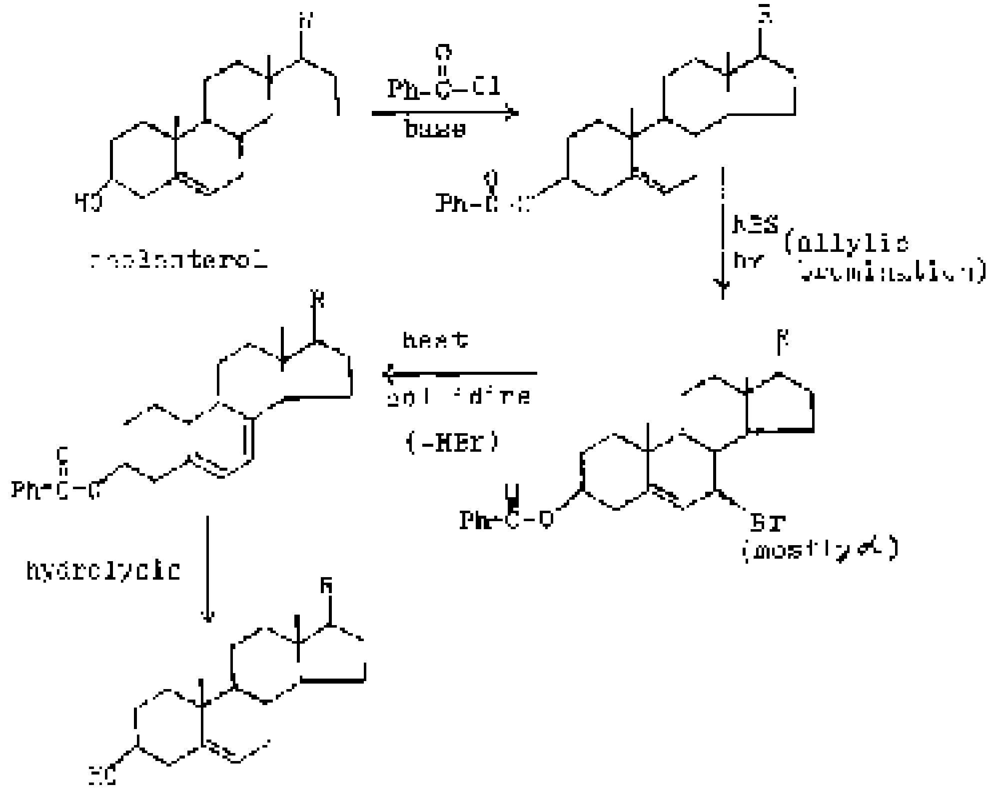


cholesterol

A substituent which is above the plane (as in C_{18} or C_{19}) is called β-oriented, while a substituent below the plane is α-oriented. β-oriented carbons are represented by a dark line, and α-oriented carbons by a dashed line.

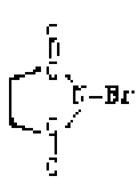
This reaction involves the conversion of cholesterol into 7-dehydrocholesterol with this then being converted into vitamin D_3.

The reaction proceeds as follows:

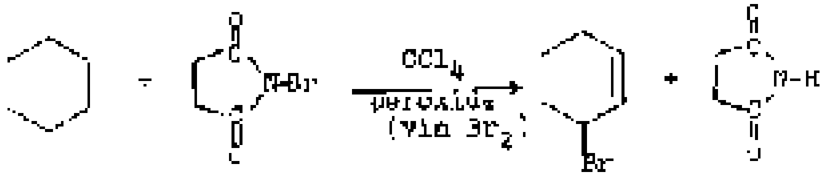


7-dehydrocholesterol

NBS stands for N-bromo succinimide. This is a brominating reagent having the structure:

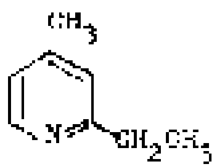


A replacement reaction occurs at the position α to the double bond of the molecule which is being acted upon.

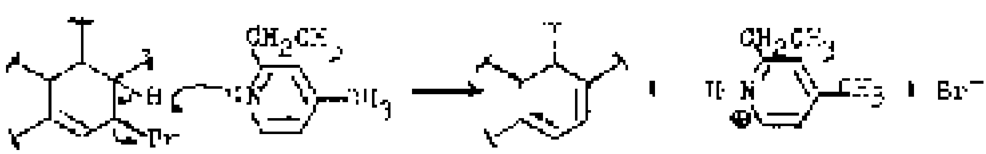


Note that were we to react unsubstituted cholesterol with NBS, bromination could occur at either C_4 or C_7, resulting in a mixture of 4- and 7-dehydrocholesterol as final products. Therefore, PhCOO- is first substituted for the hydroxy group on C_3, making the 4-bromination unfavorable due to steric and electronic considerations.

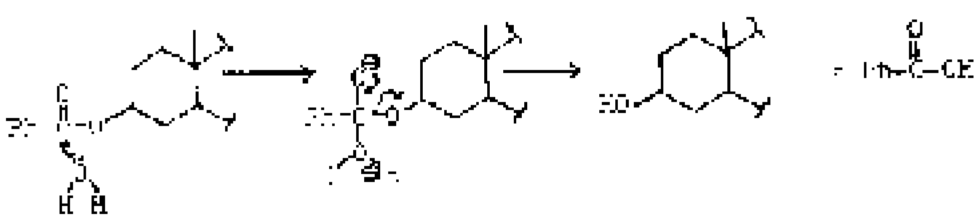
Collidine is a amine compound which pulls off the bromine. It acts as a nucleophile and not a base in the γ-collidine form. The structure of γ collidine is:



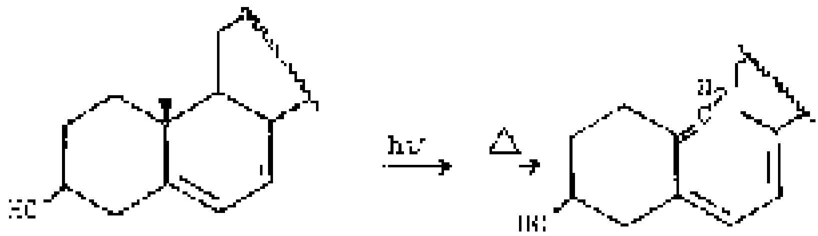
Collidine debrominates the compound via an E_2 elimination:



After the new double bond has been formed, the ester linkage at C_3 can be hydrolyzed, giving 7-dehydrocholesterol.



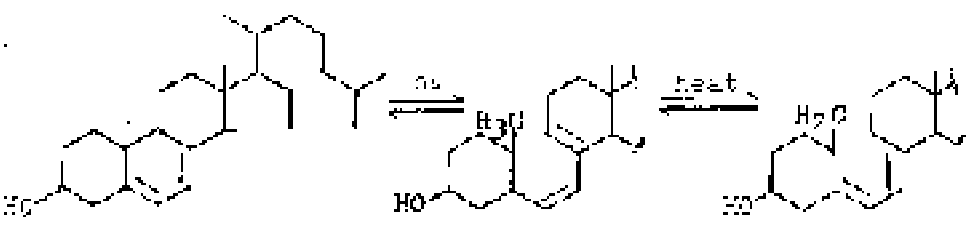
7-Dehydrocholesterol is present in high concentration in human skin. It undergoes a complex series of photochemical reactions upon exposure to sunlight.



7 Dehydrocholesterol | Cholecalciferol (Vitamin D_3)

• **PROBLEM 34-1[illegible]**

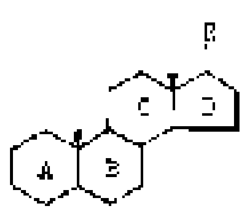
7 Dehydrocholesterol is converted (by the action of sunlight) to vitamin D_3, which, by regulating calcium metabolism, prevents the bone disease termed rickets. A laboratory analysis of the sequence indicates that an intermediate, pre-vitamin D_3, is the compound actually formed by the action of light. (a) Provide a mechanism for its formation.



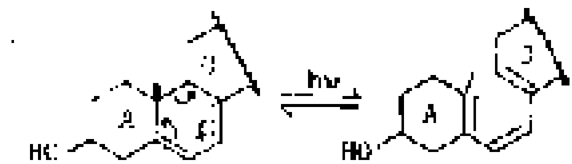
7-dehydrocholesterol | pre-vitamin D_3 | vitamin D_3

The conversion of pre-vitamin D_3 to vitamin D_3 can be "explained" with the aid of a "no mechanism" mechanism. (b) Suggest a "mechanism" for this interconversion that lacks any of the classical intermediates of organic chemistry.

<u>Solution</u>: (a) 7-Dehydrocholesterol belongs to the class of compounds called steroids. These compounds are of the general formula:



Because of the rigid cyclic system of steroids, conformational effects are marked, and often completely control the course of the reaction. With this in mind, let us look at the photochemical reaction of 7-dehydrocholesterol. As we can see, the first step involves the opening of ring B by an electrocyclic reaction. This ring opening involves three π bonds, or six π electrons. According to the Woodward Hoffman rules for electrocyclic reactions, a six-π-electron (4n+2 for n=1) photochemical reaction should occur with conrotatory ring opening. Therefore:



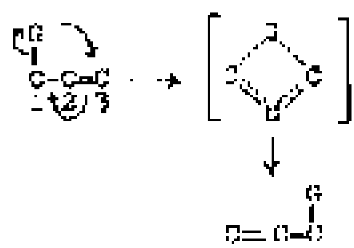
7-dehydrocholesterol   pre-vitamin D_3
(pre-cholecalciferol)

(b) The second step is a thermal [1,7] hydride shift, specifically a [1,7] sigmatropic reaction. A sigmatropic reaction is a concerted reaction of the type:

$$\underset{\text{C}}{\overset{\text{G}}{|}}\,(\text{C=C})_n \longrightarrow (\text{C=C})_n\!-\!\underset{\text{C}}{\overset{\text{G}}{|}}$$

This reaction involves the migration of a group, with its σ bond, within a π framework. This migration is accompanied by a shift in π bonds; for example:

[1,3] Sigmatropic reaction



In the designation [1,3], the "1" indicates that in both reactant and product, bonding is to the same atom in the migrating group. The "3" refers to the number of the carbon atom to which group G is migrating.

The stereochemistry of a sigmatropic hydride shift depends on the highest occupied molecular orbital (HOMO) of the π framework. In the transition state, a three centered bond is required, which involves overlap between the s orbital of the hydrogen and lobes of p orbitals of the two terminal carbons. From the HOMO configuration of a seven-carbon allylic radical in the ground state, we see that the symmetry-allowed shift is in an antarafacial manner (see Figure 1).

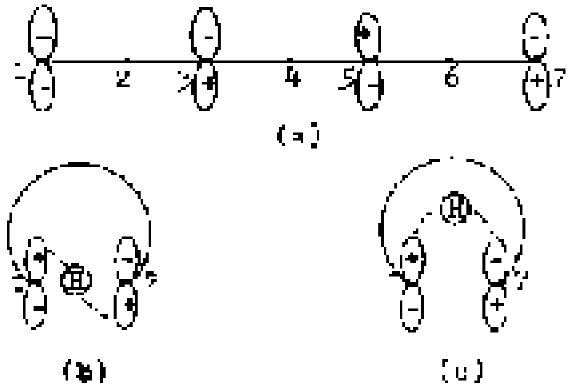
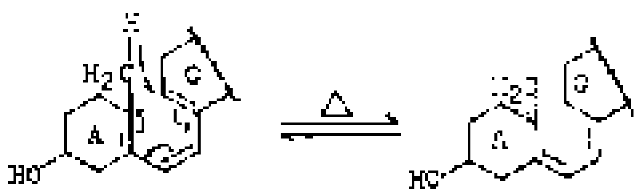


Figure 1. (a) HOMO of seven-carbon allyl radical in the ground state; (b) symmetry-allowed antarafacial migration; (c) symmetry-forbidden suprafacial migration.

Note that a [1,3] or [1,5] antarafacial hydride shift is very difficult due to geometric complications that would be encountered.

Since the hydride shift in this problem is a [1,7] H-shift, it must be in an antarafacial manner:

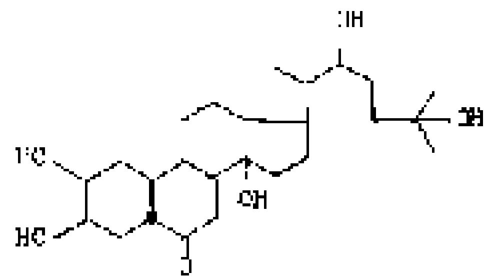


pro-vitamin D_3 (pre-cholecalciferol) — vitamin D_3 (cholecalciferol)

Note that this mechanism lacks the classical intermediates of organic chemistry. It is a concerted sigmatropic reaction that involves shifts in the π framework.

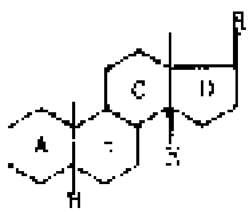
• PROBLEM 34-13

Ecdysone is the molting hormone (not a pheromone) that encourages the maturation of a larval stage of the silkworm into the pupal stage. It can kill insects by causing premature molting. (a) What general class of compounds is represented by ecdysone? (b) Identify the chiral centers and assign their absolute configurations where possible. (c) How many products would be produced if ecdysone were reduced by catalytic hydrogenation under conditions that resulted in the uptake of two equivalents of hydrogen? (d) What, if anything, would be the relationship among these compounds?



ecdysone

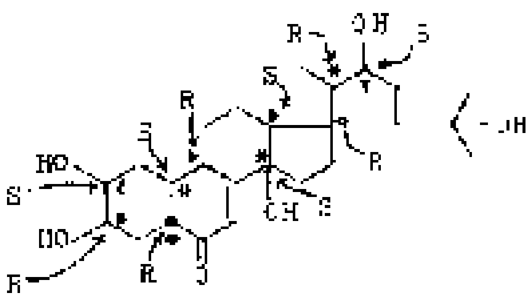
Solution: (a) Ecdysone represents the general class of compounds known as steroids. Steroids constitute a large and very important class of compounds which share the tetracyclic ring system indicated:



R = alkyl group

general steroid ring system

(b)

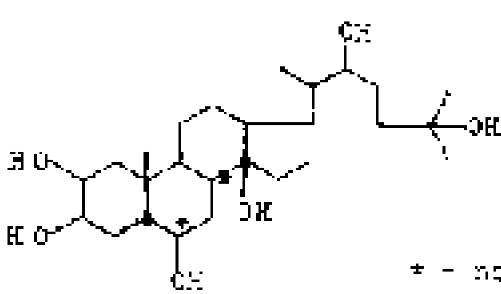


ecdysone

* = chiral center

R, S = absolute configurations

(c) Reduction of ecdysone with 2 equivalents of hydrogen would result in the creation of two new chiral centers and



* = new chiral center

four diastereomeric products.

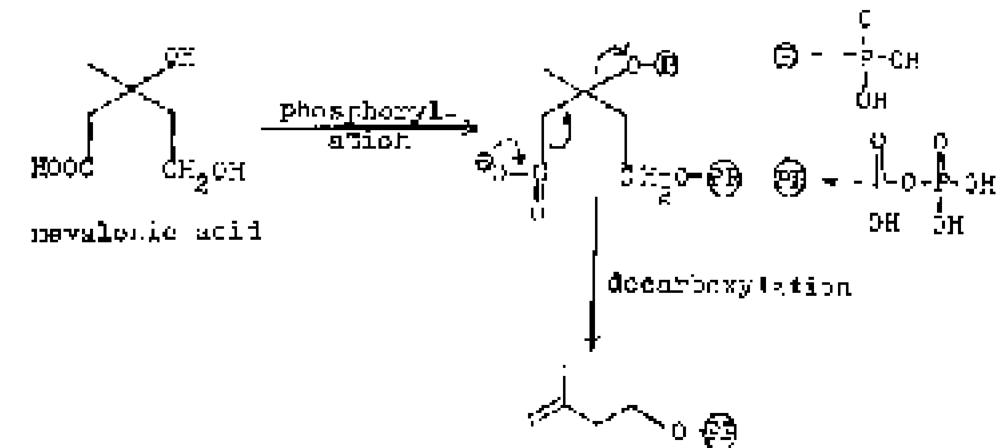
(d) The products are all stereoisomers.

TERPENES

• PROBLEM 34-14

Mevalonic acid is the precursor of the terpenes. Write its structure. After phosphorylation, it undergoes a decarboxylative elimination to yield 3-isopentenyl pyrophosphate. Outline the mechanism of this reaction. Where does the driving force for the reaction come from?

Solution:



3-isopentenylpyrophosphate (3-IPP)

Whereas an acidic proton is required for the decarboxylation of β,γ-unsaturated acids,

β,γ-unsaturated acid alkene

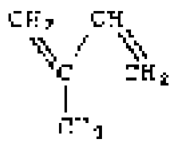
the carboxylate ion is required for decarboxylative elimination. In addition to the carboxylate ion, a good leaving group in the β position is needed. It should be noted that nature employs phosphate and pyrophosphate as good leaving groups. This good leaving ability of the phosphate provides the driving force required for decarboxylation.

• PROBLEM 34-15

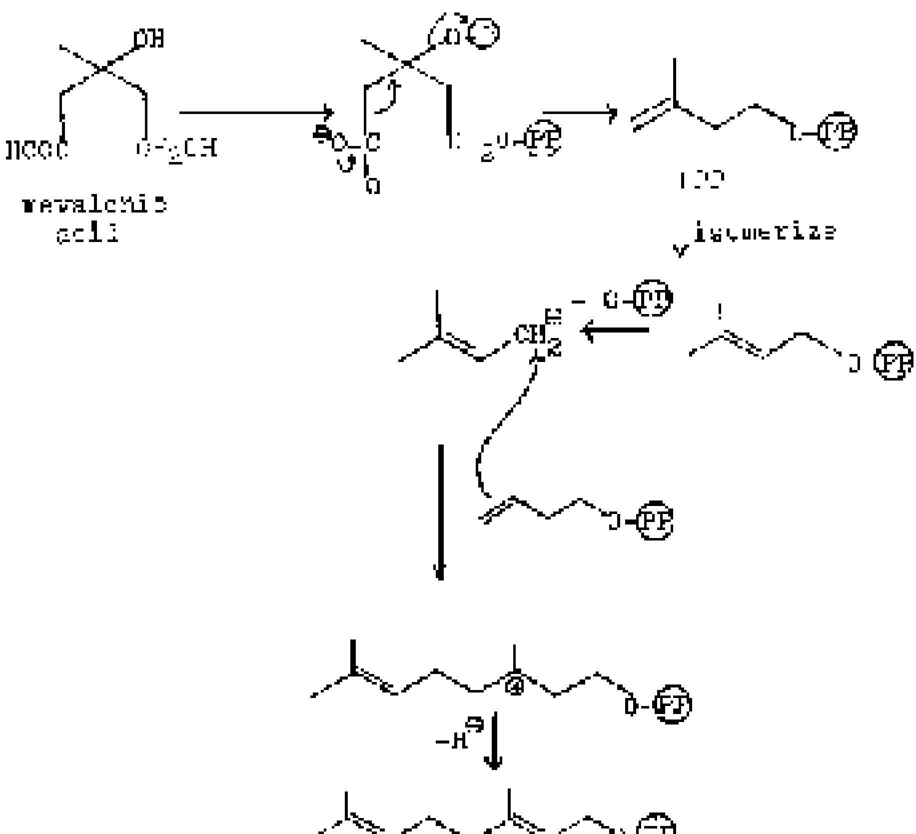
(a) Write out all of the possible carbon skeletons for acyclic terpene and sesquiterpene hydrocarbons that follow the isoprene rule. Do not consider double-bond position isomers.

(b) Do the same for monocyclic terpenes with a six-membered ring.

Solution: The isoprene rule states that all terpenes (polyisoprenes) should be formally divisible into isoprene units. Isoprene is a 5-carbon compound of the following structure:

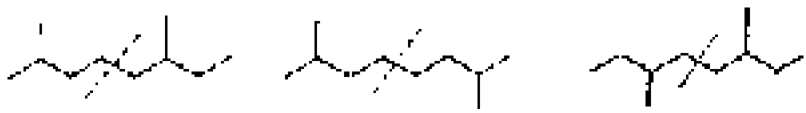


Terpenes are formed by the head to tail joining of isoprene units. In nature, this is accomplished via the formation of isopentenyl pyrophosphate (IPP) from mevalonic acid, followed by the polymerization of the isopentenyl-pyrophosphate.



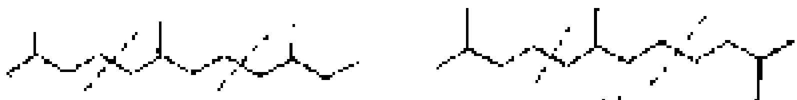
Polymerization can either stop at this point, resulting in a monoterpene (10 carbons) or continue to form the sesquiterpene (15 carbons), the diterpene (20-carbons) etc.

(a) Acyclic terpene is an aliphatic monoterpene. It can be divided into two isoprene units. Depending on the orientation of the two units with respect to each other, three different isomers are possible:



I II III

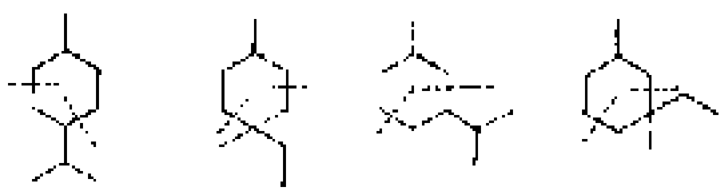
Sesquiterpene is composed of three isoprene units. It has four different possible isomers:



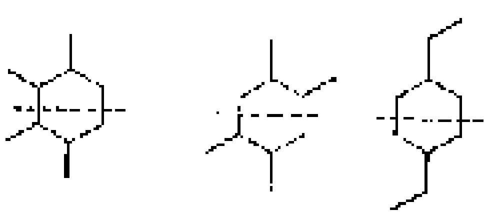
I II

III IV

(b) Isoprene units can also be joined to form ring structures. The isoprene rule can be applied to these cyclic terpenes as well. Six-membered monocyclic terpenes have seven isomeric possibilities:



I II III IV

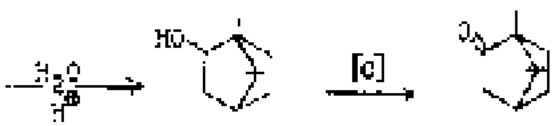


V VI VII

• PROBLEM 34-16

Camphor can be made on an industrial scale from α-pinene (turpentine) by the following reactions, some of which involve carbonium-ion rearrangements of a type particularly prevalent in the bicyclic terpenes and the scourge of the earlier workers in the field trying to determine terpene structures.

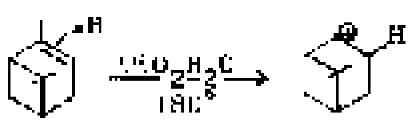
α-pinene camphene isobornyl acetate



isoborneol camphor

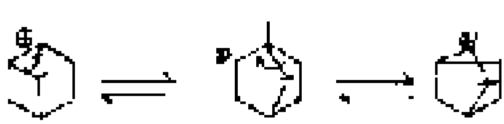
Write mechanisms for the rearrangement reactions noting that hydrated titanium oxide is an acidic catalyst.

Solution: α-pinene can be converted to camphene through addition of hydrogen to the double bond, followed by carbonium ion rearrangement. The proton will attach initially so as to form the more stable tertiary carbonium ion at C_1.



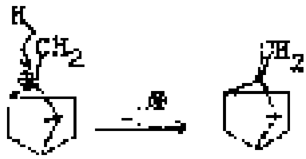
α-pinene

Rearrangement can now occur, via two subsequent 1,2-shifts. It should be noted that the rearrangement to form the less stable secondary carbonium ion (at C_1) is usually less favorable. However, the fact that the reaction conditions involve such high temperatures as 180°, plus the relief of angle strain in the four-membered ring, makes it feasible. In addition, the final carbonium ion formed is tertiary and should be just as stable as the first.



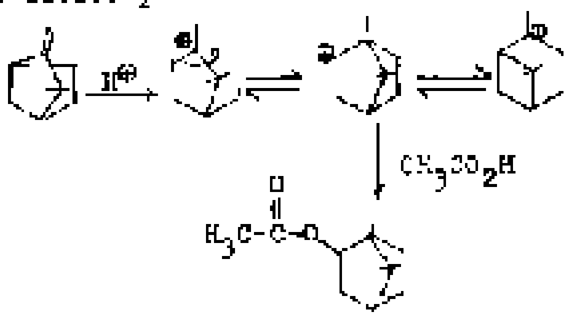
3° ion 2° ion 3° ion

At this point, a proton can be lost, and a double bond formed.



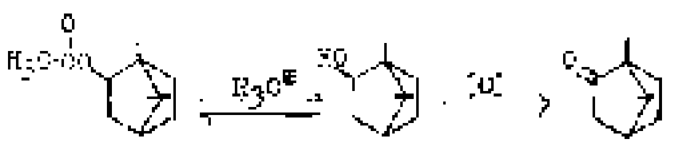
camphene

Acid catalysis can again lead to carbonium ion formation and a rearrangement similar to the first one. Now, however, acetate ion is present and can act as a nucleophile, adding to the secondary carbonium ion to form isobornyl acetate.



Isobornyl acetate

Isoborneol can be formed via simple acid hydrolysis of the ester linkage. Oxidation of the alcohol forms the ketone (camphor):

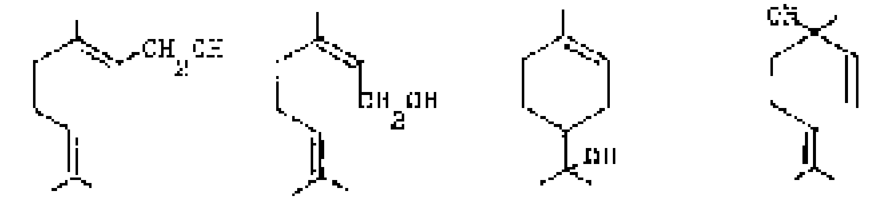


isoborneol camphor

• PROBLEM 34-17

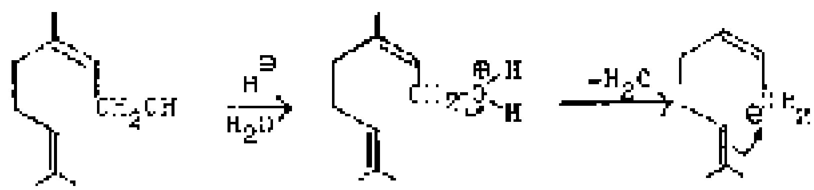
(a) Nerol and geraniol cyclize under the influence of acid to yield α-terpineol. How could the relative ease of cyclization of these alcohols, coupled with other reactions, be used to establish the configurations of the double bond of geraniol and nerol? What is the mechanism of this reaction?

(b) The cyclization of optically active linalool produces optically active α-terpineol. Explain.

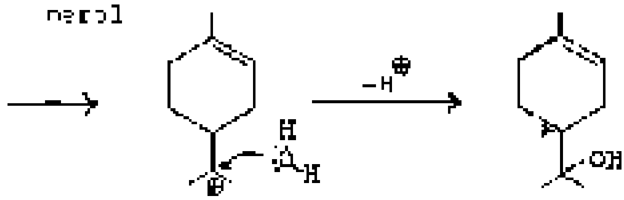


geraniol nerol α terpineol linalool

Solution: The conversion of nerol to α-terpineol should proceed by the following mechanism:

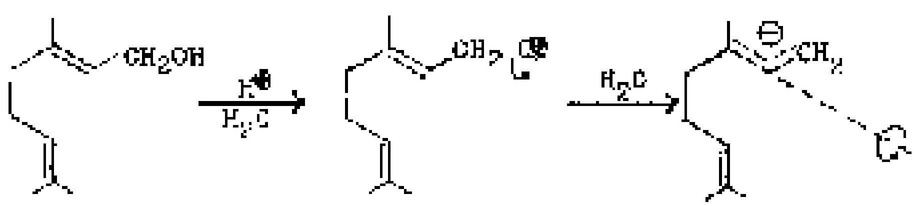


nerol



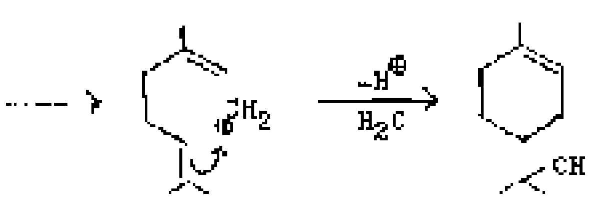
α-terpineol
(optically active at *)

Geraniol would not be expected to convert as fast as nerol into α-terpineol in that the conversion of geraniol would involve inversion of configuration about the double bond due to geraniol's trans configuration.



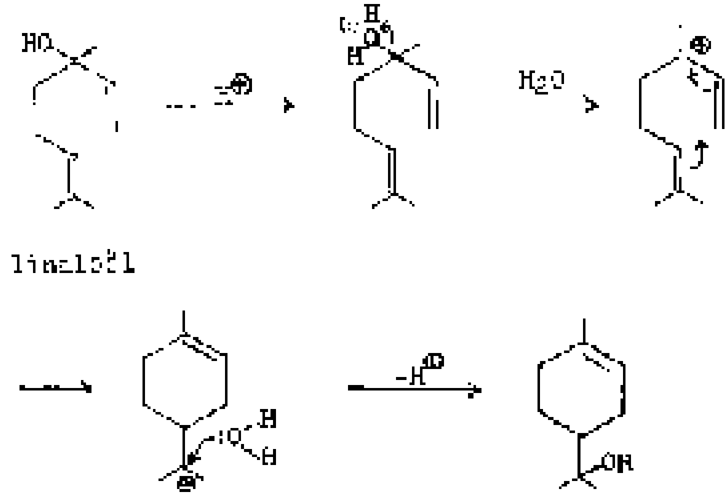
geraniol

rotation about C-C
allyl bond (unfavorable)



α-terpineol

(b) Linaloöl will convert via a mechanism similar to that involved in the conversion of nerol to α-terpineol. The only difference is that the linaloöl reaction is stereospecific, and will only occur if the process is reasonably concerted.



linaloöl

α-terpineol
(optically active)

• PROBLEM 34-18

Citral, $C_{10}H_{16}O$, is a terpene that is the major constituent of lemongrass oil. It reacts with hydroxylamine to yield a compound of formula $C_{10}H_{16}NOH$, and with Tollens' reagent to give a silver mirror and a compound of formula $C_{10}H_{16}O_2$. Upon vigorous oxidation citral yields acetone, oxalic acid (HOOC-COOH), and levulinic acid ($CH_3COCH_2CH_2COOH$).

(a) Propose a structure for citral that is consistent with these facts and with the isoprene rule.

(b) Citral has two isomers, geranial and neral, which yield the same oxidation products. What is the most likely structural difference between these two isomers?

(c) Geranial is obtained by mild oxidation of geraniol; neral is obtained in a similar way from nerol. On this basis assign structures to geranial and neral.

Solution: (a) Monoterpenes are compounds which have the general formula of $C_{10}H_{16}$. They can be found in essential oils, resins, and many other natural substances. They are usually made up of isoprene units (2-methyl-1,3-butadiene), joined in a head-to-tail manner. This information tells one that citral has at least one olefinic bond.

When citral reacts with hydroxylamine, it yields $C_{10}H_{17}ON$, an addition of NH. Since hydroxylamine can react with a carbonyl group to form an oxime by adding an NH, one can suggest that citral contains a carbonyl group.

Tollens' test is a standard test to detect aldehydes. Tollens' reagent, $Ag(NH_3)_2^+$, oxidizes an aldehyde in an alkaline solution to give a carboxylic acid and a silver mirror. The reaction is illustrated below, using acetaldehyde as an example.

$$\underset{}{CH_3CHO} + \underset{\text{Tollen's reagent}}{2Ag(NH_3)_2^{\oplus}} + 3OH^{\ominus} \rightarrow \underset{\text{silver mirror}}{2Ag} + CH_3COO^{\ominus} + 4NH_3 + 2H_2O$$

Thus, we can conclude that citral is an aldehyde.

Vigorous oxidation cleaves citral into three separate compounds. This indicates that there are two double bonds in citral. To put these three compounds back together according to the isoprene rule, one ends up with the following skeletal structure for citral:

```
      C              C     H
                     |     |
C-C=C-C-C-C=C-C=O
   (1)   (2)       (3)
```

where upon vigorous oxidation, (1) gives acetone, (2) gives levulinic acid, and (3) gives oxalic acid.

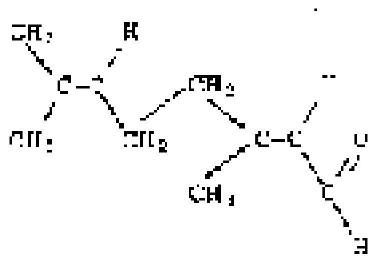
Therefore, the structure of citral with chemical formula of $C_{10}H_{16}O$ is:

```
      CH3                 CH3      O
      |                   |
H3C-C=CH-CH2-CH2-C  =  CH-C-H
```

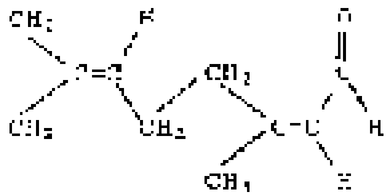
citral

(b) Since geranial and neral yield the same oxidation products, they have the same basic skeletal structure. Also, since citral is an unsaturated aldehyde, the isomers are likely to be cis-trans isomers.

(c) Geraniol and nerol are cis-trans isomers at the unsaturated carbons C2 and C3. (Notice, carbons in the backbone are numbered starting from the main functional group. In geraniol and nerol, the alcohol carbon is numbered carbon one.) Geraniol has the H and CH_3 trans at C2 and C3; nerol has the H and CH_3 cis. Since geranial is obtained by mild oxidation of geraniol, and neral from nerol, one can conclude that geranial is the trans-isomer and neral is the cis-isomer.



Geranial (E-conformation)

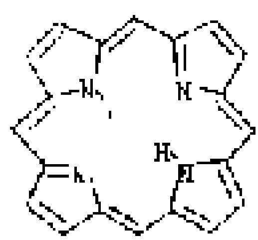


Neral (Z-conformation)

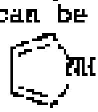
AROMATIC NATURAL PRODUCTS

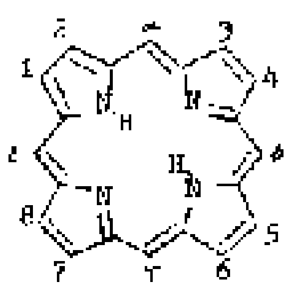
• PROBLEM 34-19

Would you anticipate porphyrin to possess aromatic character? Explain.



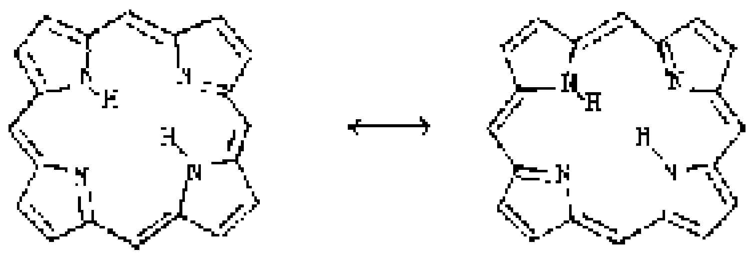
Solution: Porphyrin, whose structure is shown below, can be thought of as being composed of four pyrrole

() fragments.



Important natural products such as hemoglobin and chlorophyll contain the porphyrin ring system.

In considering its aromaticity, if one excludes the double bonds between C_1 and C_2 and C_3 and C_4, one may envision a closed, cyclic, planar, conjugated system which contains 18 π electrons. This agrees with Hückel's Rule for the determination of aromaticity. Electron delocalization over the porphyrin ring system can be depicted by the following resonance structures:

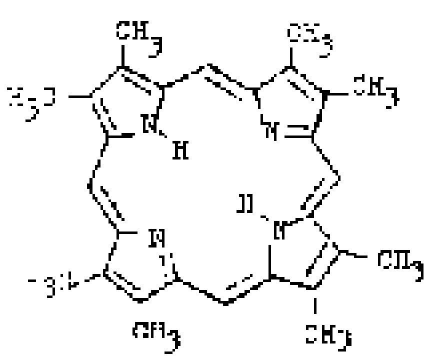


The aromaticity of porphyrin is also indicated by its n.m.r. spectrum which shows separate signals for the outer deshielded hydrogens (δ=8) and the inner shielded hydrogens. In addition, the compound tends to yield substitution rather than addition products, giving evidence that it is highly stable in its unsaturated form. The stability can be most correctly interpreted as a result of electron delocalization due to its aromatic character.

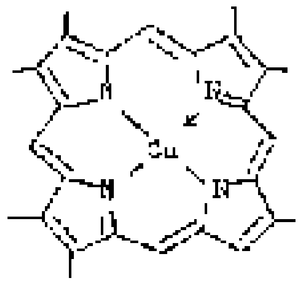
• PROBLEM 34-20

The blood of lobsters contains a blue copper porphyrin complex. As a model for the lobster blood pigment, draw the structure of the Cu^{2+} pigment of octamethylporphin. What charge, if any, does this complex have?

Solution: In octamethyl porphyrin, 8 ring hydrogens are substituted by methyl groups.



This compound can form a chelate in which a metal ion is held tightly between the four nitrogen atoms of the planar system. In lobster blood pigment, this metal ion is Cu^{+2}.



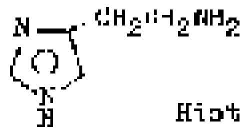
The coordination of this structure is that the entire complex is uncharged.

There are only two formal bonds between the Cu^{+2} ion and the nitrogens, and these two bonds neutralize the positive charges on the Cu^{+2} ion. Two other bonds are present; these are analogous to hydrogen bonds in that they result from the electrostatic attraction of the electropositive Cu and the electronegative nitrogens.

• PROBLEM 34-21

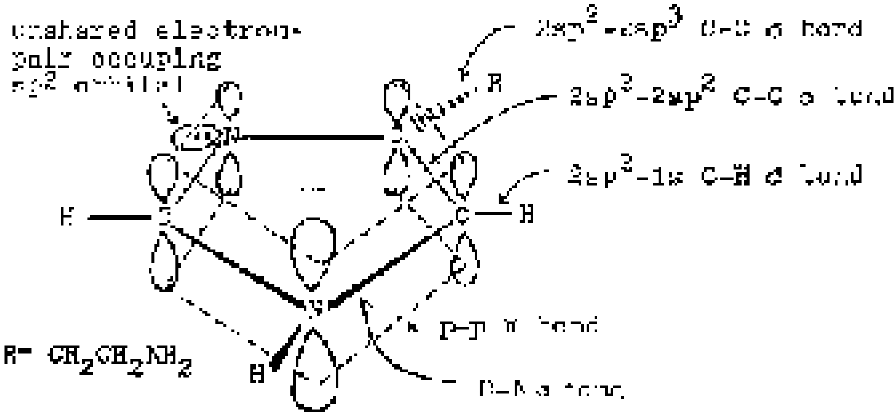
(a) Account for the aromatic properties of the imidazole ring.

(b) Arrange the nitrogen atoms of histamine (the substance responsible for many allergenic reactions) in order of their expected basicity, and account for your answer.



Histamine

Solution: (a) The aromatic properties of the imidazole ring can best be accounted for by looking at its orbital structure.



Every atom of the ring is sp^2 hybridized and has three bonding orbitals. These orbitals lie in a common plane and are 120° apart. Each carbon atom contributes one electron to each of its sp^2 orbitals, thereby forming σ bonds with three other atoms, and has one electron left over, which occupies a 2p orbital.

The "pyridine" nitrogen contributes one electron to each of its two σ bonds with carbon, and its unshared (lone) pair of electrons occupies the third sp^2 orbital. It has one electron left over, then, which occupies a 2p orbital.

The "pyrrole" nitrogen differs from the "pyridine" nitrogen in that it is bonded not only to two carbons but also to a hydrogen atom. While contributing an electron to each of its three σ bonds, it still has an unshared pair of electrons left. These electrons will occupy a 2p orbital. This p orbital and the other p orbitals of the ring are situated close enough to overlap, giving rise to two π clouds, one above and one below the plane of the ring. The six electrons are delocalized in these clouds around the ring and stabilize the system.

Note that the imidazole ring satisfies Hückel's rule for aromaticity, which states that in order for a molecule to satisfy the closed-shell stability of the π system, the number of π electrons must be $4n + 2$ (where n equals 0, 1, 2, 3, ...). For the imidazole ring, there are 6 π electrons, or $(4n + 2)$ π electrons where $n = 1$.

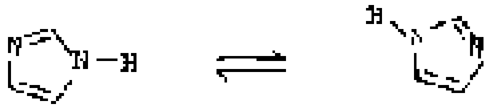
(b) The basicity of a nitrogen atom is a direct result of its ability to accept a proton or share its free electron-pair with an acid.

The aliphatic nitrogen is tetrahedral and its lone electron-pair occupies an sp^3 orbital. This is in contrast to the "pyridine" nitrogen, which occupies an sp^2 orbital. Since an sp^2 orbital has more s character than an sp^3 orbital, the lone-pair electrons in the sp^2 orbital will be held more tightly; therefore they are less available for sharing, resulting in the "pyridine" nitrogen being less basic than the aliphatic. A "pyrrole" nitrogen atom is still less basic than a "pyridine" one, since its lone electron pair is involved in the formation of the π cloud, and is thus not able to be shared with an acid.

Whereas in general the following order of basicity holds:

aliphatic $-NH_2$ > "pyridine" N > "pyrrole" -N,

the "pyridine" nitrogen in the imidazole ring in histamine is actually indistinguishable from the "pyrrole" nitrogen. This is because of the presence of tautomeric shifts:

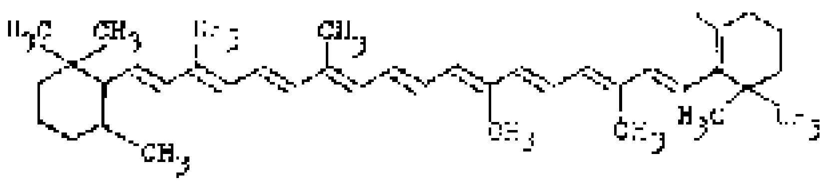


Therefore, the two nitrogen atoms in the ring will display the same degree of basicity.

REACTIONS

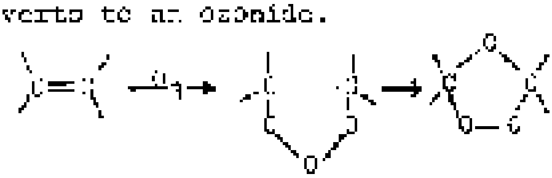
• PROBLEM 34-[illegible]

What are the products, and their relative ratios, resulting from the ozonolysis of β-carotene? (Assume reductive work-up.)



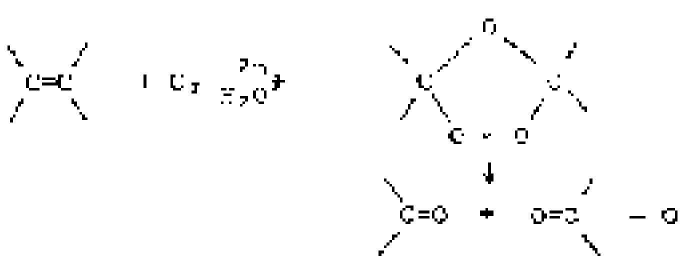
β-carotene

Solution: Treatment of an olefin with ozone will result in the initial formation of a molozonide which rapidly interconverts to an ozonide.

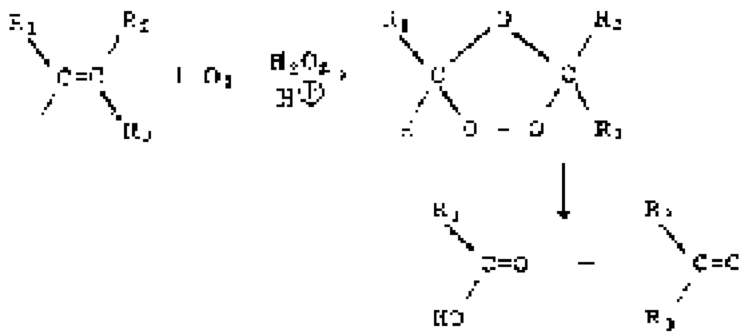


molozonide ozonide

From here, one can either proceed with reductive work-up (addition of zinc dust and water to yield an aldehyde or ketone), or oxidative work-up (the addition of H_2O_2 in an acidic media to yield the carboxylic acid and/or ketone



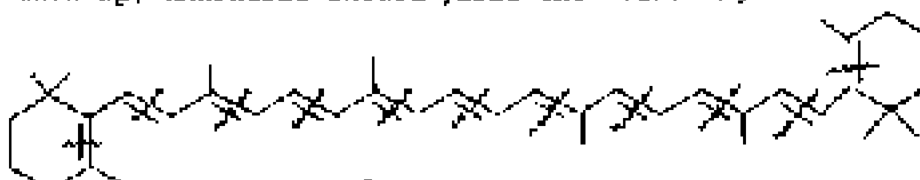
Above: Reductive work-up



Above: Oxidative work-up.

It should be noted that the oxidative work-up will not oxidize a keto portion of an ozonide, only the aldo part.

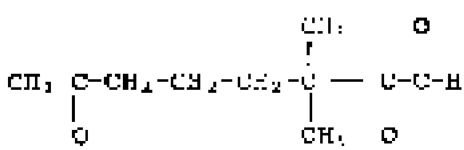
The ozonolysis of β-carotene followed by reductive work-up, therefore should yield the following:



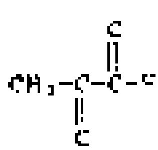
β carotene

$\downarrow O_3$

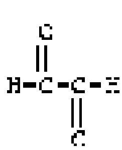
$\downarrow Zn, H_2O$



(two moles)



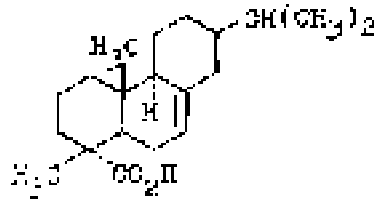
(four moles)



(four moles)

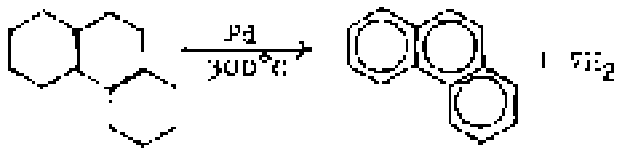
■ PROBLEM 34-23

Vigorous dehydrogenation of abietic acid yields the hydrocarbon retene ($C_{18}H_{18}$). Suggest a structure for retene. Abietic acid ($C_{20}H_{30}O_2$) has the following structure:

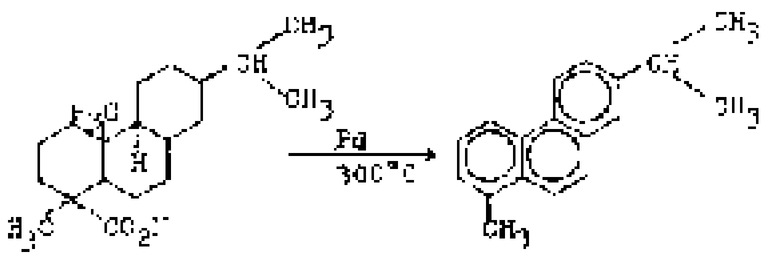


Solution:

Cycloalkanes and cycloalkenes containing one or more six-membered rings can usually be dehydrogenated to the corresponding benzoid derivatives by heating to a high temperature with a platinum or palladium catalyst.



Abietic acid can undergo a similar dehydrogenation to form retene. Note that the angular methyl group and the carboxylic acid group will be lost in the reaction.



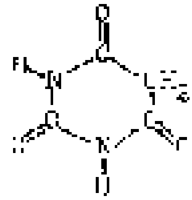
abietic acid

retene ($C_{18}H_{18}$)

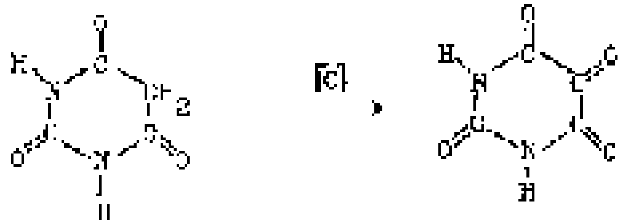
● PROBLEM 34-24

Uric acid, a purine derivative found mainly in the excrement of snakes and birds, has the molecular formula $C_5H_4N_4O_3$. On nitric acid oxidation it breaks down to urea and a hydrated compound called alloxan of formula $C_4H_2N_2O_4 \cdot H_2O$. Alloxan is readily obtained by oxidation of barbituric acid. What is the probable structure of alloxan and uric acid? Why is alloxan hydrated?

Solution: Barbituric acid ($C_4H_4N_2O_3$) has the following structure:

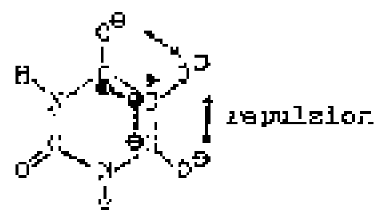


We are told that oxidation of barbituric acid yields alloxan, which is the hydrated form of the tetraketone, $C_4H_2N_2O_4$. By comparing the molecular formulas of barbituric acid and the tetraketone, we see that two hydrogens have been lost, and one oxygen added. Oxidation must therefore have occurred at the methylene carbon, forming the ketone, as shown below:



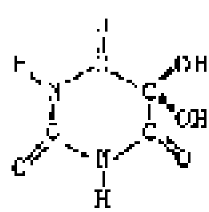
We could also have predicted this oxidation by noting that the CH_2 group is the most highly reduced member of the ring, and thus most likely to undergo oxidation.

We are told furthermore that alloxan is a hydrated molecule. Looking at the structure of the tetraketone, we note three adjacent carbonyl groups, which is a highly unstable situation. Resonance structures can be drawn showing a great deal of charge separation, in addition to electrostatic repulsion and steric interaction (due to the large and highly electronegative oxygen atoms).



highly unstable
resonance structure

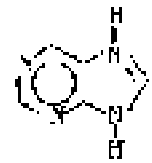
If the middle carbonyl group (*) were hydrated, charge separation and repulsion would be reduced. This is because a hydroxyl group has a smaller electron-withdrawing effect than an oxygen atom. In addition, steric interaction is diminished by the fact that the OH substituents are situated out of the plane of the ring.



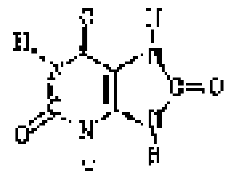
alloxan($C_4H_2N_2O_4$)$\cdot H_2O$

Alloxan is also formed (along with urea) as a product of the oxidation of uric acid. Since uric acid is a purine derivative, its structure should have the following

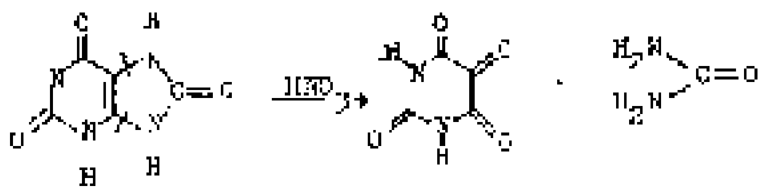
Skeleton:



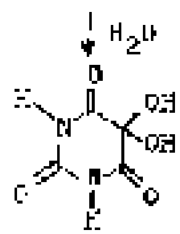
Here, we can recognize the structure of alloxan in the 6-membered ring, and urea in the 5-membered ring. Uric acid would then have the structure:



Oxidation could then proceed so as to split urea out of the purine system, forming the tetraketone, which is then hydrated.



uric acid tetraketone urea



alloxan

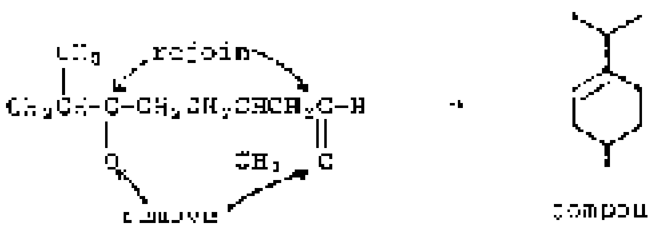
• PROBLEM 34-25

Professor Rufus T. Firefly of Fredonia State University wanted to stump his ace chemistry student, Sea Water ($C-H_2O$, alias formaldehyde). The professor asked Sea Water to deduce the structure of menthol, the principal flavoring constituent of peppermint, on the basis of the following data: the molecular formula of menthol is $C_{10}H_{20}O$; when heated in the presence of sulfuric acid, a dehydration reaction ensues to form compound A; ozonolysis of compound A followed by a reductive workup yields 3,7-dimethyl-6-oxo-octanal; menthol also reacts with nitric acid and vanadium oxide, when heated, to form 2-isopropyl-5-methyl-hexanedioic acid.

Solution: It is always clearer to work one's way backwards in an analytical problem of this type. It should be recalled that ozonolysis of compound A followed by reductive workup will yield 3,7-dimethyl-6-oxo-octanal:

$$A \xrightarrow{O_3,\ Zn/H^{\oplus}} CH_3-\overset{CH_3}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}-CH_2CH_2\overset{CH_3}{\overset{|}{C}H}CH_2\overset{O}{\overset{\|}{C}}H$$

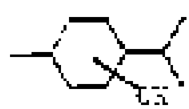
In an ozonolysis reaction with reductive workup, carbon-carbon double bonds are cleaved to form carbonyl groups. Hence the structure of A is deduced by rejoining the two carbonyl carbons in 3,7 dimethyl 6 oxo octanal:



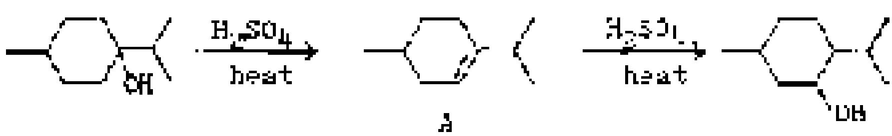
compound A

Since compound A was formed by the dehydration of menthol in sulfuric acid, and the molecular formula of A ($C_{10}H_{18}$) differs from that of menthol by one H_2O molecule,

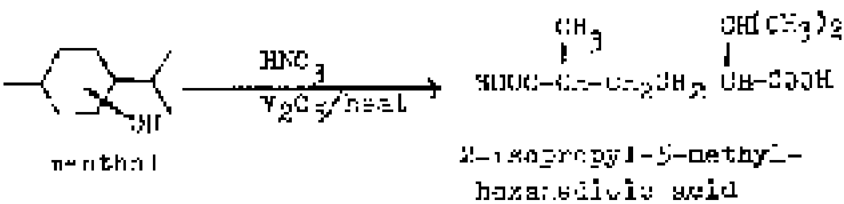
the structure of menthol may be written as:



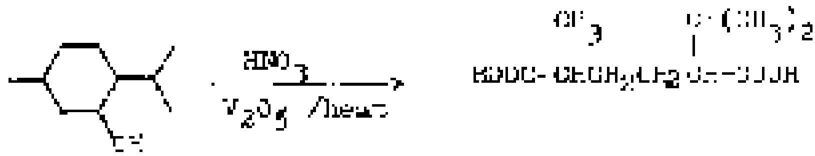
where the -OH group may be bonded to the secondary or tertiary carbon on the ring. Indeed, dehydration of either compound will produce compound A:



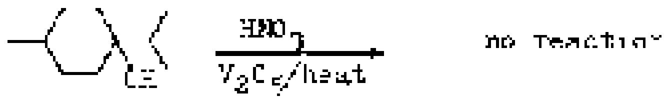
Reaction of menthol with HNO_3 and vanadium oxide, with heat, produces 2-isopropyl-5-methyl-hexanedioic acid:



The vigorous oxidation reaction depicted above will occur with primary and secondary alcohols, but not with tertiary alcohols. This means that the hydroxyl group in menthol must be on the secondary and not the tertiary carbon on the ring:

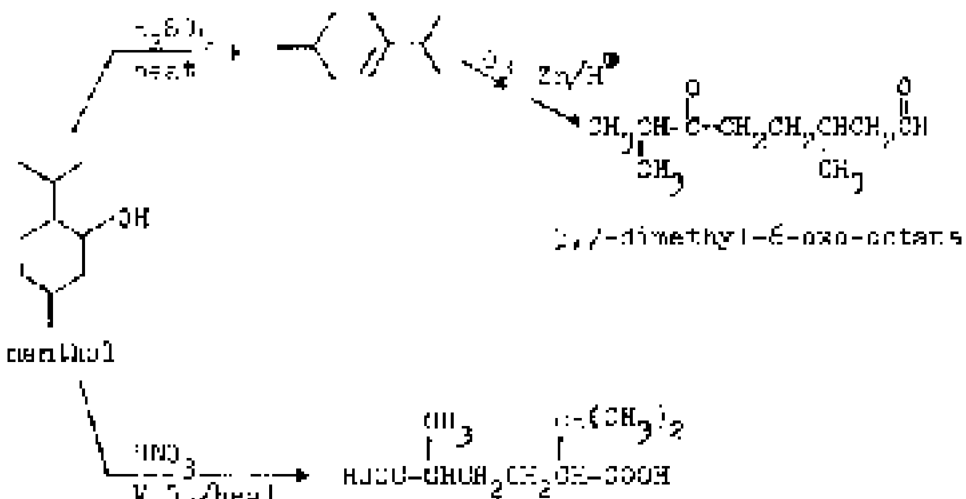


menthol
(2° alcohol)



(3° alcohol)

Hence the structure and reactions of menthol can be written as:



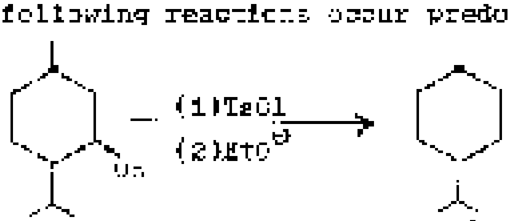
3,7-dimethyl-6-oxo-octanoic

menthol

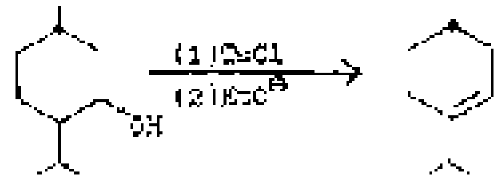
2-isopropyl-5-methyl-hexanedioic acid

• PROBLEM 34-26

Menthol and neomenthol have the structures I and II, respectively, and differ only in the configuration of the hydroxyl. When they are converted to their tosylates and the latter are treated with sodium ethoxide in ethanol, the following reactions occur predominantly.



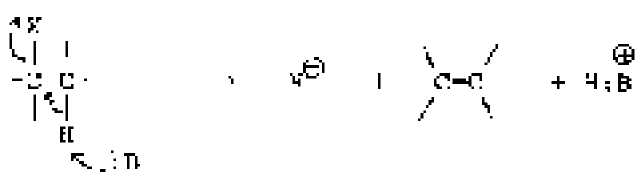
I I'



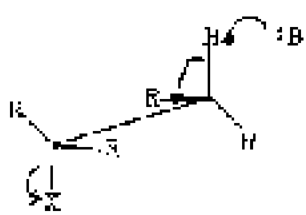
II II'

What can you conclude about the stereochemistry of the hydroxyl? Which of the tosylates (from I or II) do you predict reacts the faster under these conditions? Explain.

Solution: In this problem we are asked to determine the stereochemistry of the hydroxyl group in menthol and neomenthol, which are stereoisomers of each other. We know that the substituent of a chair cyclohexane can have either an axial or equatorial position. We also know that elimination reactions, in the presence of ethoxide ions ($^-OC_2H_5$), take place predominately via the E2 mechanism. This mechanism involves a single step: base ($^-OC_2H_5$) pulls a proton away from carbon, and simultaneously a good electron-accommodating group (such as a halide ion or a hydroxide) leaves, resulting in the formation of a double bond.

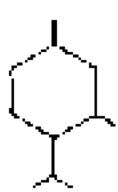


For dehydrohalogenation (in this case, with tosylate), the mechanism is usually anti elimination. That is, the hydrogen and the leaving group are in an anti-conformation:



This preference for anti elimination can be very strong and can often guide the course of a reaction.

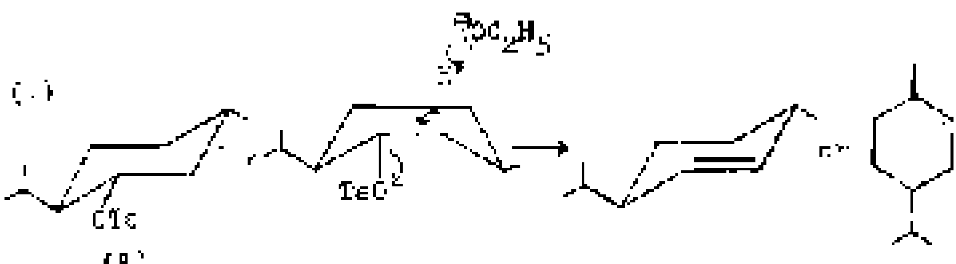
With the above information in mind, we can proceed to deduce the stereochemistry of menthol and neomenthol.

The compound  OH can be tosylated via reaction with tosyl chloride. Depending on the stereochemistry of the hydroxyl group in the compound, two different stereoisomeric products are possible: one with the tosyl group occupying an axial position and the other an equatorial

A (equatorial TsO-) B (axial TsO)

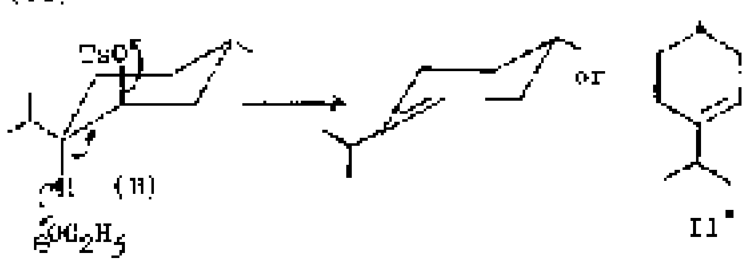
position. Due to this stereochemical difference, the tosylates will eliminate via the E2-anti mechanism to generate two different alkenes.

(I)



I'

(II)



II'

In reaction II, structure II' is the preferred product because it has the most substituted double bond. (The more substituted the alkene, the more stable the transition state.) In addition, the axial position of the tosyl group puts it in the correct orientation for elimination with the proton on C1. In reaction I, the tosylate must first convert to the boat conformation in order for the tosyl group and the hydrogen to be in an anti-conformation; and the double bond in the product (I') will have a 2,3 rather than 3,4 position.

Since we are told that menthol gives rise to structure I', its tosylate must have structure A. Menthol must therefore have an equatorial hydroxyl. By the same principle neomenthol must have an axial hydroxyl.

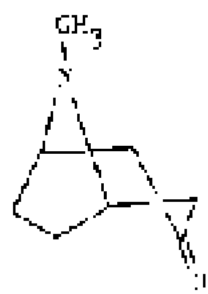
Since the tosylate of menthol must be in a boat conformation in order for anti-elimination to occur, its rate of product formation must be slower than that of neomenthol. This is due to the fact that the boat conformation is at an energy maximum, approximately 7.1 kcal/mole less stable than the chair conformation. Because the boat conformation is at an energy maximum, it is really not a conformer at all; instead, it can be considered as a transition state between two conformers. As such, its probability of existence at a given time is very low, and it probably occurs at a ratio of 1 to 10,000 when compared to the more stable chair conformation at room temperature.

● PROBLEM 34-27

Tropinic acid, $C_8H_{13}O_4N$, is a degradation product of atropine, an alkaloid of the deadly nightshade, *Atropa belladonna*. It has a neutralization equivalent of 94 ± 1. It does not react with benzenesulfonyl chloride, cold dilute $KMnO_4$, or Br_2/CCl_4. Exhaustive methylation gives the following results:

tropinic acid + CH_3I → EEE ($C_9H_{16}O_4NI$)
EEE + Ag_2O, then strong heat → FFF ($C_9H_{15}O_4N$) + H_2O + AgI
FFF + CH_3I → GGG ($C_{10}H_{18}O_4NI$)
GGG + Ag_2O, then strong heat → HHH ($C_7H_8O_4$) + $(CH_3)_3N$
+ H_2O + AgI
HHH + H_2, Ni → heptanedioic acid (pimelic acid)

(a) What structures are likely for tropinic acid?
(b) Tropinic acid is formed by oxidation with CrO_3 of tropinone, whose structure has been shown by synthesis to be



Tropinone

Now what is the most likely structure for tropinic acid?

Solution: Tropinic acid has a molecular weight of 187 g (calculated from its molecular formula, $C_8H_{13}O_4N$). But its equivalent weight is found to be 94 ± 1 g, or half of its molecular weight. It must therefore be a diacid. A negative reaction with cold $KMnO_4$, a strong oxidizing agent, indicates that the compound contains no easily oxidizable functions. Therefore we might expect tropinic acid to have two carboxyl groups, which cannot be further oxidized but are reducible. Reaction with Br_2/CCl_4 is a test for saturation. If double bonds are present, halogen addition will occur. A negative reaction with benzenesulfonyl chloride is the usual test for distinguishing amongst 1°, 2° and 3° amines. Only 1° and 2° amines react visibly with benzenesulfonyl chloride. Tropinic acid, if it is an amine, is therefore 3°. We know it must be an amine since it contains only 4 oxygens which must necessarily be bonded into its two carboxyl groups, leaving only carbons and hydrogens available to bond with nitrogen.

With these in mind, we can proceed to perform the following calculations:

	$C_6H_{15}N$	saturated open chain, 3° amine
+	$C_2H_2O_4$	two CO_2H groups
−	2H	hydrogens lost due to bonding with CO_2H groups
	$C_8H_{15}O_4N$	

This molecular formula, $C_8H_{15}O_4N$, represents an open chain compound. It deviates from that of tropinic acid, $C_8H_{13}O_4N$, by having two more hydrogens. Since we know that tropinic acid is saturated, this discrepancy can be explained only by a ring structure, in the formation of which two hydrogens are liberated as the ends of the aliphatic chain fuse. Thus, we know now that tropinic acid is dicarboxylic, saturated, cyclic, reducible, and is a 3° amine.

In exhaustive methylation, an amine will react with CH_3I to form the quaternary ammonium salt ($RN(CH_3)_3^+I^-$), with 1°, 2° and 3° amines incorporating three, two and one methyl groups respectively. Looking at the data:

	$C_9H_{16}O_4NI$	???
−	$C_8H_{13}O_4N$	tropinic acid
	CH_3I	

we can see that only one methyl group is incorporated, confirming that tropinic acid is indeed, as we have expected, a 3° amine.

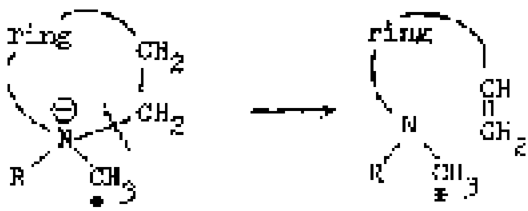
The reaction forming FFF is the formation of the quaternary ammonium hydroxide, followed by the Hofmann elimination, typical of ammonium hydroxides. A generalized Hofmann reaction is given below:

$$CH_3CH_2\overset{R}{\underset{R'}{\overset{|}{N^{\oplus}}}}CH_3\ I^{\ominus} \xrightarrow{Ag_2O} CH_2{:}CH_2 + \overset{R}{\underset{R'}{N}}CH_3 + AgI$$

(aqueous)

$$OH^{\ominus}\ CH_3-CH_2-\overset{\oplus}{\underset{R'}{\overset{H}{N}}}-CH_3 \xrightarrow{heat} CH_2=CH_2 + H_2O + H\underset{R'}{\overset{H}{N}}-CH_3$$

Note that in this reaction involving an aliphatic amine, the amine group is eliminated and an alkene is formed. However, in the product FFF, the amino substituent remains attached. Therefore, it must be part of the ring.



(*CH$_3$- comes from the methylating agent.)

Note that FFF ($C_9H_{15}O_3N$), the elimination product, has one hydrogen less than EEE ($C_9H_{16}O_3NI$), the reactant.

Methylation now proceeds further to form GGG, another quaternary ammonium salt. GGG in turn reacts with Ag_2O to form a quaternary ammonium hydroxide, which undergoes the Hofmann elimination. The amino group is finally lost from GGG. The tertiary amine that leaves has the formula $(\overset{*}{C}H_3)_2CH_3N$. Since we know that two of the methyl groups are the result of methylation, tropinic acid must have a $\underset{|}{N}-CH_3$ unit.

Catalyzed by Ni, the unsaturated diacid, HHH, next undergoes hydrogenation at the two double bonds formed previously in the Hofmann eliminations and gives rise to heptanedioic acid, which is an unbranched, open-chained diacid with the structure $HOOC-CH_2-CH_2-CH_2-CH_2-CH_2-COOH$.

Therefore, HHH has one of several possible structures:

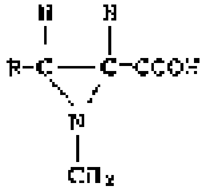
$^1HOOC-CH=CH-CH_2-CH=CH-COOH$

$^2HOOC-CH=CH-CH=CH-CH_2-COOH$

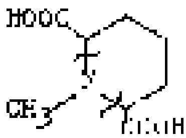
$^3HOOC-CH=C=CH-CH_2-CH_2-COOH$

$^4HOOC-CH_2-CH=C=CH-CH_2-COOH$

The allenic isomers are unlikely products of the Hofmann eliminations, because they are not favored by kinetic control. (Recall that Hofmann elimination is kinetically controlled and tends to yield the least substituted olefin.) Also, we are discounting the possibility of an acetylenic structure, which could have arisen only from a highly unstable aziridine-type ring.

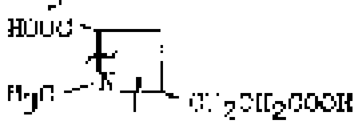


(a) Depending, then, on the structure of EEE and the position of the double bonds, tropinic acid can have one of four possible structures (⌐ indicates possible bond breakage in the Hofmann process):

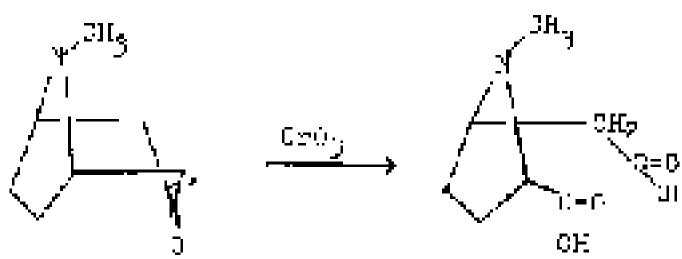
(A)  (Hofmann elimination would yield 1.)

(B)  (Hofmann elimination would yield 1 or 2.)

(C)  (Hofmann elimination would yield 1 or 2.)

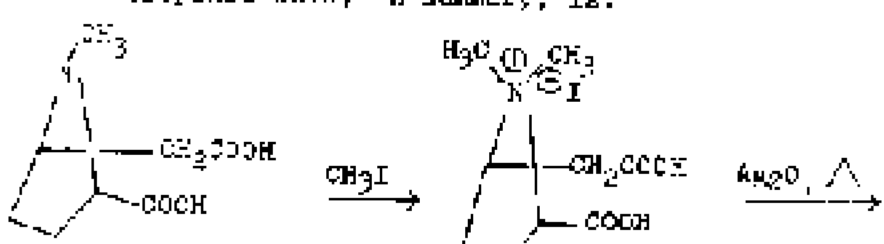
(D)  (Hofmann elimination would yield mainly 2.)

(b) Oxidation of Tropinone proceeds so as to break the ring, forming the diacid as shown below.

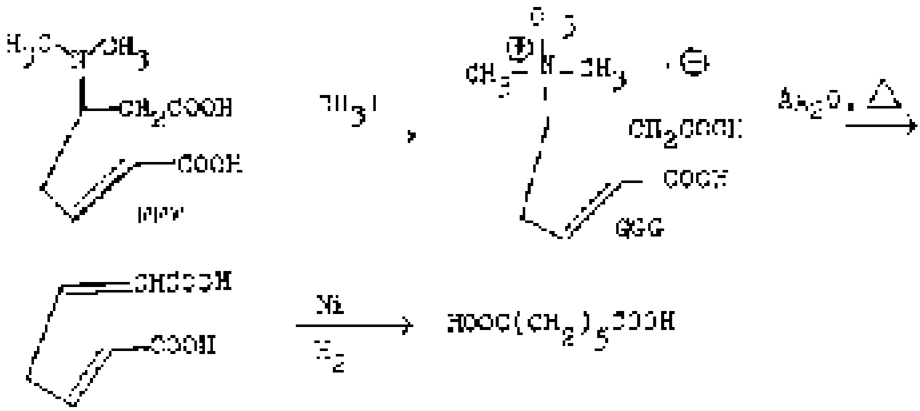


This leads us to conclude that B is the correct structure for tropinic acid.

The entire mechanism for the formation of pimelic acid from tropinic acid, in summary, is:



Tropinic acid EEE



FFF GGG HHH

Heptanedioic acid

Note that the Hofmann elimination follows a mechanism typical of an E2 elimination and products such as α,β unsaturated acids are favored.

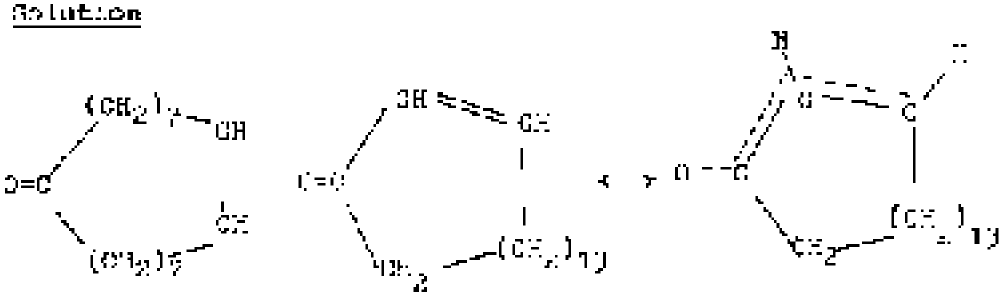
SPECTROSCOPY

• PROBLEM 34-28

Explain how use of ultraviolet, infrared, or n.m.r. spectroscopy could be used to distinguish between the following possible structures for civetone.

(a) 9-cycloheptadecenone and 2-cycloheptadecenone
(b) cis 9-cycloheptadecenone and trans 9-cycloheptadecenone
(c) 8-methyl-8-cyclohexadecenone and 9-cycloheptadecenone
(d) 8-cycloheptadecenone and 9-cycloheptadecenone

Solution

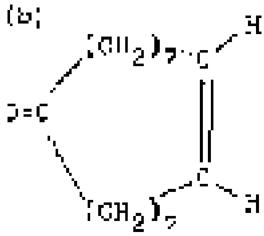


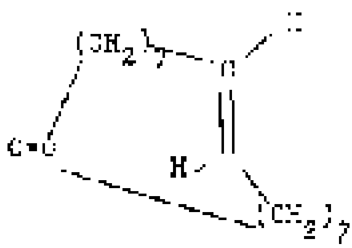
9-cycloheptadecenone   2-cycloheptadecenone

We can see that 2-cycloheptadecenone is an α,β-unsaturated ketone. This conjugation allows for significant delocalization of the electrons of the double bonds. Such resonance stabilizes the molecule, but this stabilization is even greater in the excited state. This causes an increase in the wavelength of the absorption (recall that $E = \frac{hc}{\lambda}$; E = energy; h = Planck's constant, c = speed of light, and λ = wavelength). Thus 2-cycloheptadecenone will absorb at longer wavelengths in the IR and UV spectra than 9-cycloheptadecenone, which contains only an isolated double bond and carbonyl group and hence lacks resonance stabilization.

The two isomers will also exhibit differences in their n.m.r. spectra. The most obvious of these is that the absorption band of the vinyl (double bond) protons of 2-cycloheptadecenone will be further downfield than that of the vinyl protons of 9-cycloheptadecenone, due to the electron withdrawing (deshielding) effect of the nearby carbonyl group. In addition, 9-cycloheptadecenone will show only 7 different peaks (corresponding to 4 protons each) for the 28 CH_2 protons, since each CH_2 group on one side of the carbonyl group and the double bond has an equivalent CH_2 partner on the other side. 2-Cycloheptadecenone has no such equivalent CH_2 groups, and will show separate signals for each proton pair (though some of these may be so close as to be indistinguishable).

(b)



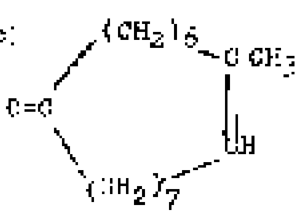


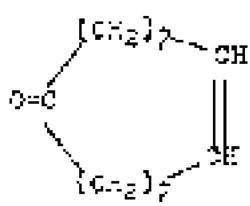
cis-9-cycloheptadecenone   trans-9-cycloheptadecenone

The cis isomer of 9-cycloheptadecenone will show a more intense double-bond absorption in the IR spectrum, due to the greater change of its dipole moment with vibration. The trans isomer has no net dipole moment, and will show comparatively little absorption intensity. Also, the trans isomer will show a characteristic band at 965-975 cm^{-1}.

In the n.m.r., one can theorize that the protons of the trans-isomer would have a greater coupling constant than those of the cis-isomer, due to the greater physical distance separating them. However, in the absence of delicate techniques, the coupling is not observable, and the spectrum shows only a single unsplit peak for protons of both the cis and trans isomers.

(c)



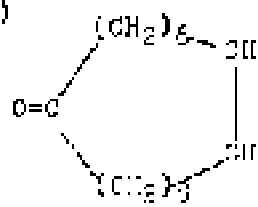


8-methyl-8-cyclohexadecenone   9-cycloheptadecenone

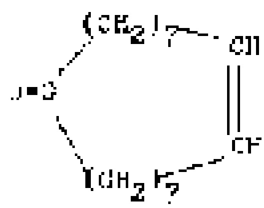
The n.m.r. spectra of these two compounds would be clearly different. The hexadecenone lacks the symmetry of the heptadecenone with respect to the double bond, and will not show equivalent CH_2 pairs. In addition, the heptadecenone has two vinyl protons, while the hexadecenone has but one.

Thus the vinyl hydrogen peak of 8-methyl-8-hexadecenone (at about 5.3 δ) will have half the area of the one of 9-cycloheptadecenone, whose methyl protons will give an additional peak at about 1.8 δ.

(d)



8-cycloheptadecenone



9-cycloheptadecenone

Although theoretically these two compounds should exhibit differences in their IR, UV, and n.m.r. spectra, they will not in reality be significant enough to be noticeable. For example, the vinyl hydrogens of 8-cycloheptadecenone are non-equivalent, but the difference of only one CH_2 group out of 7 on either side of the double bond is not great enough to significantly affect the chemical shifts.

CHAPTER 35

PHOTOCHEMISTRY AND COLOR

LIGHT ABSORPTION, FLUORESCENCE AND PHOSPHORESCENCE

• PROBLEM 35-1

> The fluorescence of many substances can be "quenched" (diminished or even prevented) by a variety of means. Explain how concentration, temperature, and presence of dissolved oxygen and impurities might affect the degree of fluorescence observed for solutions of a fluorescent material. Would you expect similar effects on phosphorescence? Explain.

Solution: Before we can answer this question, we must define certain terms that are used extensively in photochemistry. A given number of atomic orbitals always combine to form the same number of molecular orbitals. For example, if two s orbitals overlap, they form two molecular orbitals; one is a bonding orbital, σ, and the other is an antibonding orbital, σ^*. Electronic excitation of a molecule occurs when an electron from one molecular orbital is promoted to another of higher energy. Such transitions are written as:

$$\sigma \rightarrow \sigma^*, \quad \pi \rightarrow \pi^*, \quad n \rightarrow \pi^*, \text{ etc. (n refers to a}$$

non-bonding electron). These transitions can result in two possible electron arrangements: (1) Singlet state, S_1: electron spins paired (the two electrons have different spin quantum numbers), (2) Triplet state, T_1: electron spins parallel (the two electrons have the same spin quantum numbers). The subscript 1 after S and T indicates the first excited state. The ground state with paired electrons is indicated by S_0. Fluorescence and phosphorescence are radiative deactivating transitions. Fluorescence is the emission of radiation accompanying the deactivation of an excited species to a lower state of the same multiplicity (e.g. $S_1 \rightarrow S_0$, $T_2 \rightarrow T_1$). Phosphorescence is the emission of radiation accompanying the deactivation of an excited species to a lower state of different multiplicity (e.g. $T_1 \rightarrow S_0$). Multiplicity is the spin state of the molecule, that is, triplet or singlet. Sensitization is defined as the excitation of a ground state molecule by energy transfer from another excited species; quenching is the deactivation of the excited species. In these energy transfers, electron spin is conserved (see Fig.1)

$$D_{S_1}(\uparrow\downarrow) + A_{S_0}(\uparrow\downarrow) \rightarrow D_{S_0}(\uparrow\downarrow) + A_{S_1}(\uparrow\downarrow)$$

$$D_{T_1}(\uparrow\uparrow) + A_{S_0}(\uparrow\downarrow) \rightarrow D_{S_0}(\uparrow\downarrow) + A_{T_1}(\uparrow\uparrow)$$

$$D_{T_1}(\uparrow\uparrow) + A_{T_1}(\uparrow\uparrow) \rightarrow D_{S_0}(\uparrow\downarrow) + A_{T_1}(\uparrow\uparrow)$$

Fig. 1 - Examples of conservation of spin angular momentum. D = donor molecule or sensitizer; A = acceptor molecule or quencher.

Molecules in electronic excited states are highly reactive. The presence of any dissolved oxygen or impurities makes it possible for the excited species to react with oxygen or the impurities, or to dimerize; this decreases the probability of electronic transitions to the ground state. Note that fluorescence and phosphorescence are both radiative decay processes, therefore they are both subject to the same influences; the differences that would exist would be the differences in reactions and reactivity of singlet vs. triplet states.

An increase in temperature will increase the collision rate, and hence the self quenching and reaction rates. This will decrease the number of electronic transitions to the ground state (the number of radiative decays). This happens because radiative decay is in competition with non-radiative transitions, and if the number of non-radiative transitions (e.g. chemical reactions) is increased, there will be fewer molecules undergoing radiative decay.

An increase in concentration would increase the reaction rate of the excited molecules, thereby quenching radiative deactivation.

Note that radiative deactivation is at all times in competition with:

(1) Radiationless transition. -

(a) Internal conversion (IC) - a radiationless process where a molecule goes from one electronic state to another electronic state of the same multiplicity. For example, an $S_1 \rightarrow S_0$ transition without loss of energy (see Fig.2).

(b) Intersystem crossing (ISC) - a transfer involving electronic states of different multiplicity, for example, $S_1 \rightarrow T_1$. (see Fig. 3).

(2) Intermolecular deactivation of excited states

(a) Quenching by chemical reaction

(b) deactivation of excited state by collision with substrate molecule.

(c) self-quenching of excited molecule by bimolecular collisions.

(d) deactivation of excited state by donation of electronic energy to an acceptor molecule.

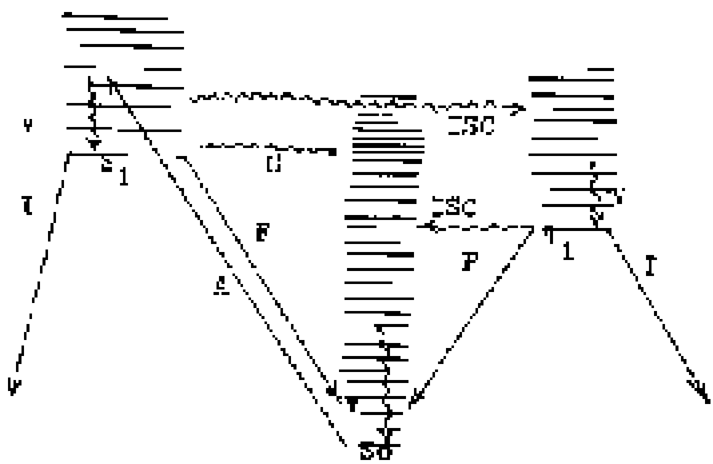


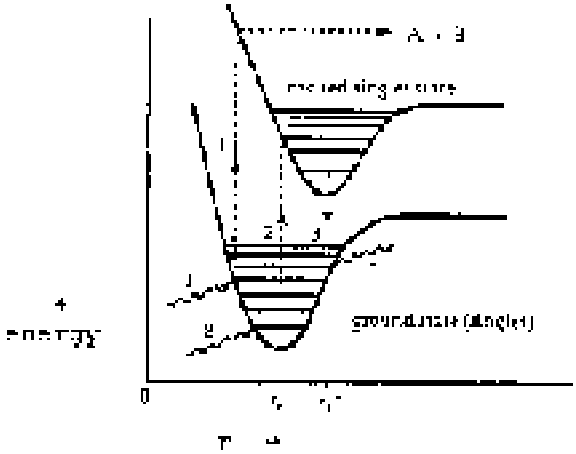
Fig. 2. - A Jablonski diagram showing excitation and deactivation routes.

A = absorption
F = fluorescence
P = phosphorescence
V = vibrational cascade (energy lost by collisional transfer)
I = intermolecular deactivation (e.g. chemical reaction)
IC = internal conversion
ISC = intersystem crossing

Any factor which will increase the rate of pathways other than radiative transitions will quench fluorescence and phosphorescence.

• PROBLEM 35-2

Explain qualitatively how temperature could have an effect on the appearance of the absorption spectrum of a system such as that shown, knowing that most molecules are usually in their lowest vibrational state at room temperature.



Schematic potential energy diagram for ground and excited electronic singlet states of a diatomic molecule, A-B and A-B*, respectively. The horizontal lines represent vibrational energy levels. The wavy lines represent the arrival or departure of light quanta. It is important to recognize that the curves shown here are schematic and, for actual systems, the positions and shapes of the curves may be quite different from those shown.

Solution: The above figure is an example of a potential-energy curve for an anharmonic oscillator, or a Morse curve (see Fig. 1).

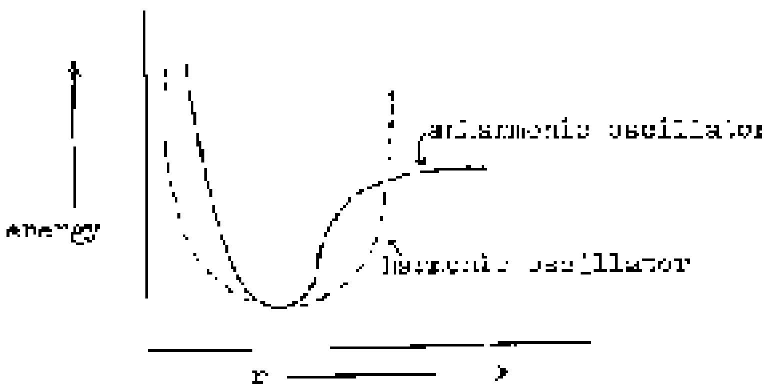


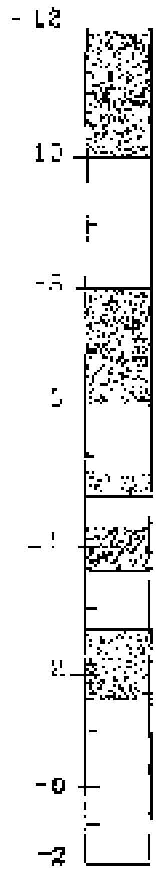
Fig. 1 - Comparison of a harmonic oscillator curve with an anharmonic oscillator curve.

This system approximates the potential energy for ground state diatomic molecules. In the diagram given in the question, the potential energy curve for ground and excited electronic singlet states of a diatomic molecule, A-B and A-B* are shown. The horizontal lines represent vibrational energy levels. The appearance of an absorption spectrum is dependent on the number and kinds of transitions from a vibrational energy level in the excited state to a vibrational energy level in the ground state. It is because of these various possible transitions that an absorption band is broad, instead of being narrow or linear. At room temperature, because of the vibrational cascade effect (where energy is rapidly lost by collisional transfer), most molecules are usually in their lowest vibrational state. If we were to increase the temperature, more molecules would go into the higher vibrational states; this would change the energies of the possible transitions, thereby changing the appearance of the absorption spectrum. The magnitude and direction of this effect will depend on the specific properties of the system. An approximation of this perturbation would require quantum mechanical methods.

• PROBLEM 35-8

What color would you expect to perceive if white light were passed through a solution containing a substance that absorbed very strongly but only within the band 4800 ± 0.5 Å? Refer to the tables below.

λ, log cm



	Wavelength range, cm
cosmic rays	10^{-13} to 10^{-11}
gamma rays	10^{-10} to 10^{-8}
x-rays	10^{-8} to 10^{-6}
far ultraviolet	10^{-6} to 2×10^{-5}
ultraviolet	2×10^{-5} to 3.8×10^{-5}
visible	3.8×10^{-5} to 7.8×10^{-5}
near infrared	7.8×10^{-5} to 3×10^{-4}
middle infrared	3×10^{-4} to 3×10^{-3}
far infrared	3×10^{-3} to 3×10^{-2}
microwave	3×10^{-2} to 10^{2}

The electromagnetic spectrum.

Color and Wavelength

Wavelength, Å	Observed color	Complementary (subtraction) color
4000	violet	green-yellow
4800	blue	yellow
5300	green	purple (magenta)
5800	yellow	blue
6100	orange	green-blue
6600	red	blue-green (cyan)
7200	purple-red	green

Solution: To answer this problem a thorough knowledge of the electromagnetic spectrum is required, of which visible light is but a small fraction. All the different forms of radiation (e.g. x-rays, radiowaves, etc.) collectively known as electromagnetic radiation, travel at a constant velocity (the speed of light, $c = 2.998 \times 10^{10}$ cm/sec) in the form of waves. However, the wavelengths of the different radiations differ and their various properties depend on their wavelength or frequency where, $\nu = \frac{c}{\lambda}$ (ν = frequency, c = speed of light, λ = wavelength).

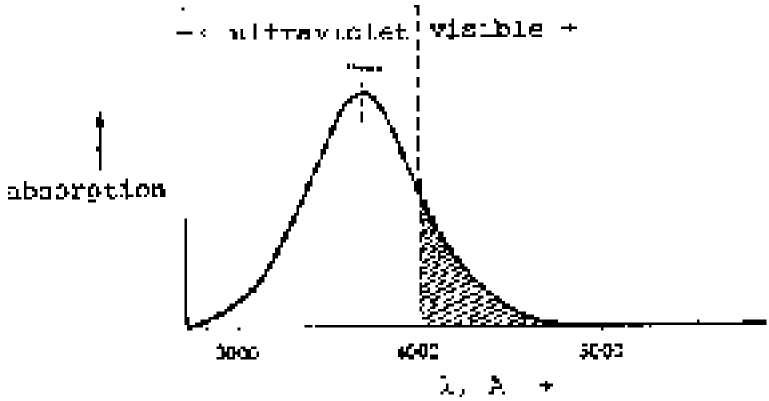
Visible light is the only part of the electromagnetic spectrum which is sensed by the human eye. As depicted by the table above, visible light extends between the wavelengths of 3.8×10^{-5} and 7.8×10^{-5} cm. By refracting a beam of white light through a prism to several beams containing narrow ranges of wavelength, we find that white light is comprised of 7 distinct monochromatic bands. White light could also be produced by the superposition of two bands of monochromatic light with the proper relative intensities; these two colors are called complementary colors.

In order to fully illustrate the nature of complementary colors, consider the following. If white light is passed through a medium which absorbs all the blue light (wavelength of blue light: 4800 ± 300 Å), the emergent beam would appear to be yellow.

In this problem we are told that the substance absorbs within the band -- 4800 ± 125 Å. Therefore part of the blue light would be deleted from the emerging band. However, only when the whole range of blue light (i.e. wavelengths of 4800 ± 300 Å) is absorbed will the emergent beam appear yellow. In this case, the absorption will have almost no effect.

• PROBLEM 35-4

What visible color would you expect the substance to have whose spectrum is shown in the figure below.



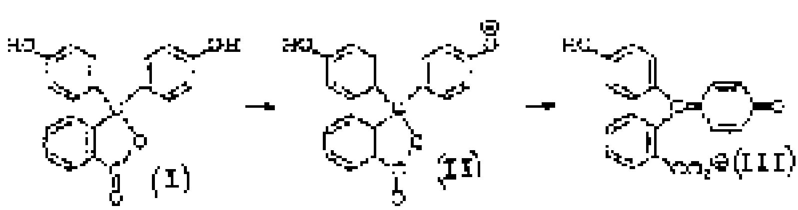
Absorption in the visible region by a substance that has λ_{max} in the ultraviolet.

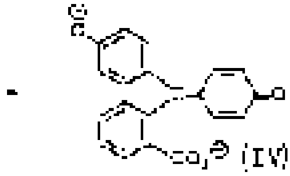
Solution: This substance has λ_{max} at ≈ 3700 Å, which is in the ultraviolet region. However, this substance absorbs into the visible region, corresponding to the region which we perceive as violet. Since this substance absorbs violet light, it will only transmit or reflect that portion of the visible spectrum that is not in the violet region. The transmitted light will be perceived by us as green-yellow. Note that green-yellow and violet are complementary colors; that is, the equal combination of green-yellow light with violet light gives white light. Correspondingly, the deletion of violet light from the visible spectrum gives green-yellow light.

STRUCTURAL EFFECTS

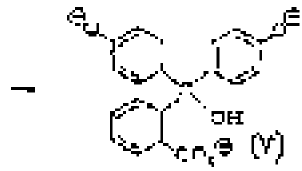
• PROBLEM 35-5

The well-known indicator and laxative, phenolphthalein, undergoes the following changes as a neutral solution is made successively basic:





(IV)



(V)

Some of these forms are colorless, some intensely colored. Which would you expect to absorb at sufficiently long wavelengths to be visibly colored? Give your reasoning.

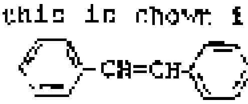
Solution: In order for a compound to be visibly colored, it must absorb radiation in the visible region (4000 - 8000 Å). Absorption of electromagnetic radiation will result in a corresponding change in the electronic state of the molecule. Alkenes and compounds with isolated double bonds absorb in the ultraviolet region (e.g. ethylene absorbs at 1800 Å); conjugated systems absorb at higher wavelengths, with some extending into the visible region. Since $E = \frac{hc}{\lambda}$, absorption at higher wavelengths by conjugated systems means that the difference in energy between the normal and excited states of conjugated systems must be less than that of compounds containing isolated double bonds. This can be explained qualitatively by looking at the resonance structures for butadiene:

$$CH_2{=}CH{-}CH{=}CH_2 \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH{-}\overset{\ominus}{C}H_2 \longleftrightarrow \overset{\ominus}{C}H_2{-}CH{=}CH{-}\overset{\oplus}{C}H_2, \quad \text{etc.}$$

(I) (II) (III)

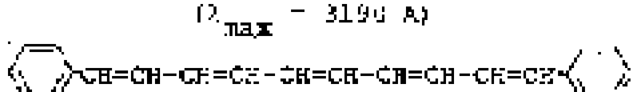
In the ground state, only structure I has a low enough energy to be important; therefore the other resonance structures are relatively insignificant. However, when the molecule is in the excited state, its energy is closer to the energies of II and III than it is to I; therefore these high energy structures are now significant resonance structures.

Conjugation lowers the energy of the excited state more than the ground state. In general, the more extended a planar system of conjugated bonds is, the smaller is the energy difference between the ground and excited state. An example of this is shown in Fig. 1.



colorless

(λ_{max} = 3190 Å)



orange

(λ_{max} = 4240 Å)

Fig. 1

There is an especially high degree of electron delocalization when an electron withdrawing group is at one end, and an electron-donating group is at the other end of a conjugated system (see Fig. 2).

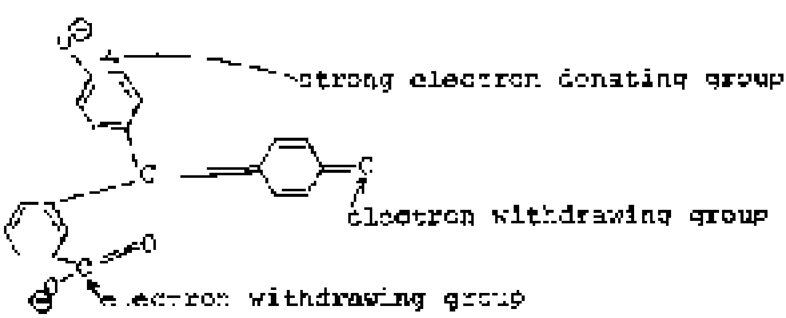
2340 Å | 2350 Å (electron donating) | 2700 Å (electron withdrawing)

2660 Å (2 electron withdrawing) | 4000 Å (1 electron withdrawing at one end, 1 electron donating at the other end)

Fig. 2

To answer this question, we must look for the structure that has (1) an electron-donating group at one end of the conjugated system, and an electron-withdrawing group at the other end; (2) the most highly conjugated system. The structure that best fits these criteria is:

(IV)

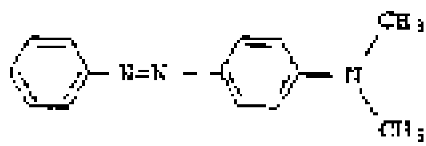


This structure has a total of eleven conjugated double bonds and is red in color.

The other structures have: I - three conjugated systems of 3,3, and 4 double bonds; II - same as I, with $-O^{\ominus}$, a better electron-donating group, replacing OH; III - conjugated system of eleven double bonds, but this structure is not as good as IV because the $-O^{\ominus}$ in IV is a better electron-donating group than -OH; V - three conjugated systems of 3,3, and 4 double bonds.

(a) p-Nitrodimethylaniline gives a yellow solution in water which fades to colorless when made acidic. Explain.
(b) p-Dimethylaminoazobenzene is bright yellow in aqueous solution (λ_{max} 4200 Å) but turns intense red (λ_{max} 5300 Å) if dilute acid is added. If the solution is then made very strongly acidic, the red color changes to a different yellow (λ_{max} 4300 Å) than the starting solution.

Show how one proton could be added to p-dimethylaminoazobenzene to cause the absorption to shift to longer wavelengths and how addition of a second proton could shift the absorption back to shorter wavelengths.



p-dimethylaminoazobenzene

(yellow)

Solution: a) The structure for p nitrodimethylaniline is:

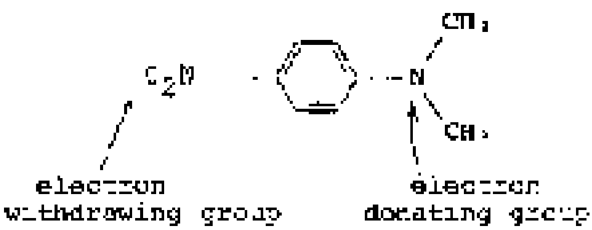
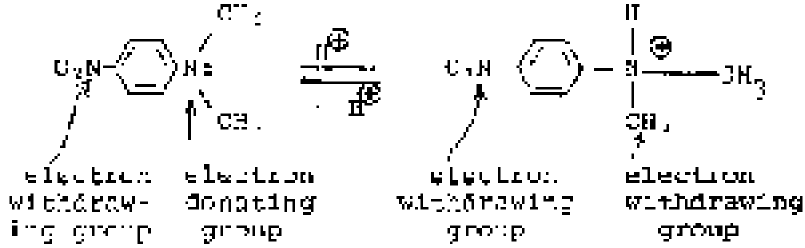
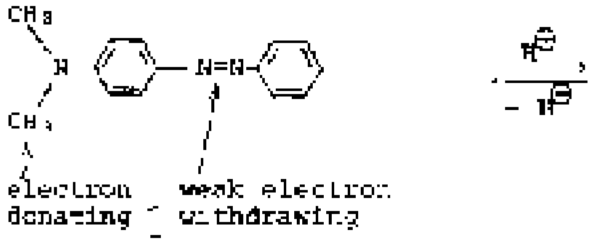


Fig. 1

This compound absorbs at high wavelengths due to an electron withdrawing group at one end, and an electron donating group at the other end of the conjugated system. In acidic solution, the amine group gets protonated, thereby becoming an electron-withdrawing group. This increases the energy difference between the excited state and the ground state, resulting in the absorption of radiation at shorter wavelengths (higher energy). The absorbed radiation is beyond the visible region, therefore the solution appears colorless.



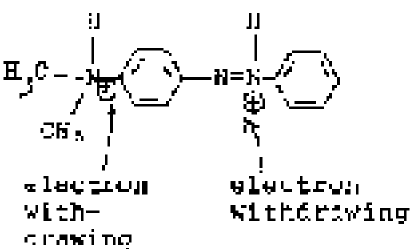
(b) Let us look at the structure of this molecule in acidic solution:



yellow

II

red



III

yellow

As we can see from the above reaction, the color changes are due to protonation of nitrogen. In slightly acidic medium, the azo group gets protonated, transforming a weak, electron-withdrawing group to a strong electron withdrawing group. This decreases the energy difference between the excited state and the ground state, resulting in the absorption of radiation at longer wavelengths (λ_{max} = 4200 Å → λ_{max} = 5300 Å). When the solution is made more acidic, the amine group gets protonated, transforming an electron donating group into an electron withdrawing group:

electron donating

positive charge on nitrogen → electron withdrawing

This increases the energy difference between the excited state and the ground state, resulting in the absorption of radiation at shorter wavelengths (λ_{max} = 5300 Å → λ_{max} = 4300 Å). The result is a solution that goes from yellow to red, and back to yellow as the solution gets more acidic.

MOLECULAR ORBITAL THEORY

• PROBLEM 35-7

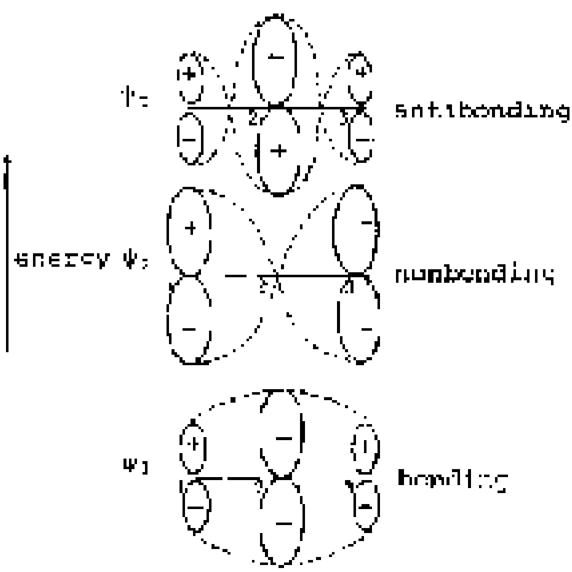
The LCAO π molecular orbitals of the allyl system $CH_2-CH=CH_2$ are shown below.

(a) Show the π-electron configurations of the ground states of the allyl cation, free radical, and anion. Do the same for the first excited singlet state of each.

(b) Arguing qualitatively from the appearance of the molecular orbitals in the figure below, show how one could deduce which carbons carry most of the positive charge in the ground state of the allyl cation; most of the negative charge in the ground state of the allyl anion. At which carbon(s) would an electron donating group have the most effect in stabilizing the allyl cation?

(c) Suppose the allyl system were bent to a linear configuration so that its orbitals had a center of symmetry. Show the changes in electronic configuration for two different π → π* transitions, one allowed by symmetry and one forbidden by symmetry, for the cation, radical, and anion.

(d) Show at which carbon atom of the allyl cation a substituent group would have the most influence on the energy of transition of an electron from orbital 1 to 2.



Schematic representation of the LCAO π molecular orbitals of the allyl system. The "nonbonding" orbital is really antibonding but only very slightly so, because atoms 1 and 3 are rather widely separated in space.

(e) Consider the lowest excited state of the allyl cation. Would you expect this state to be more stable in a planar or a nonplanar configuration? Explain.

Solution: From the figure shown in the problem, we know that there are three LCAO (linear combination of atomic orbitals) π molecular orbitals in the allyl system, one of which is a non-bonding orbital (ψ_2). Before we start this problem, let us review molecular orbital theory. Molecular orbitals are orbitals that are not centered about individual nuclei, they are centered about all the nuclei in the molecule. Our approach to molecular orbitals will be the method of linear combination of atomic orbitals (LCAO). This method uses a linear combination (that is, a combination through addition or subtraction) of atomic orbitals (AO) to calculate an approximate molecular orbital (MO):

$$\psi = \phi_A + \phi_B$$

where ψ is the molecular orbital

ϕ_A is atomic orbital A

ϕ_B is atomic orbital B

The linear combination of two atomic orbitals gives two molecular orbitals. One is a bonding orbital, which is more stable than the component atomic orbitals, while the other is an antibonding orbital, which is less stable than the component atomic orbitals:

$$\psi_+ = \phi_A + \phi_B$$

e.g. (A) + (B) → (A B)

ϕ_A = s orbital $\quad$ ϕ_B = s orbital $\quad$ ψ = σ bond bonding

$$\psi_- = \phi_A - \phi_B$$

e.g. (A) − (B) → (A)(B)

ϕ_A = s $\quad$ ϕ_B = s $\quad$ ψ = σ* bond antibonding

There is a third kind of orbital called a non-bonding orbital. Electrons in these orbitals neither strengthen nor weaken the bonding between atoms. The π-electron configurations for the ground states, and first excited states of the allyl cation, free radical, and anion are:

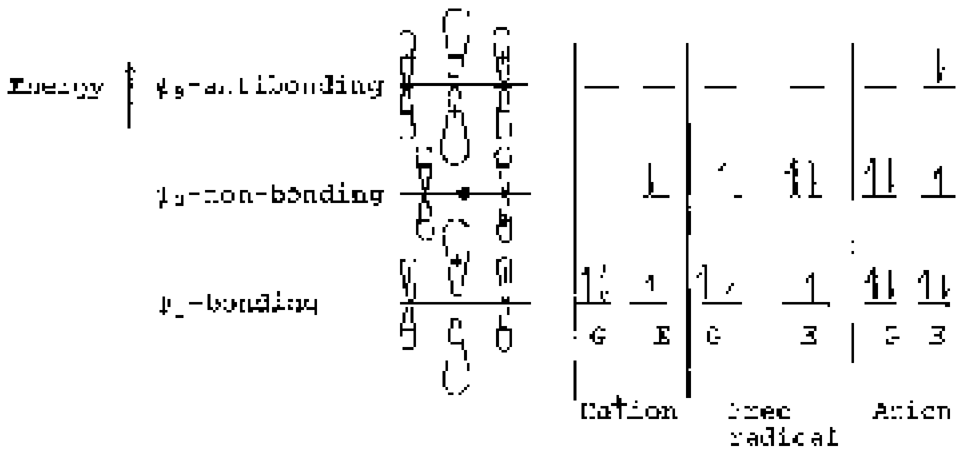
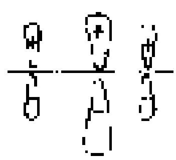


Fig. 1 - π-electron configuration of allyl system (G=ground state; E=first excited state).

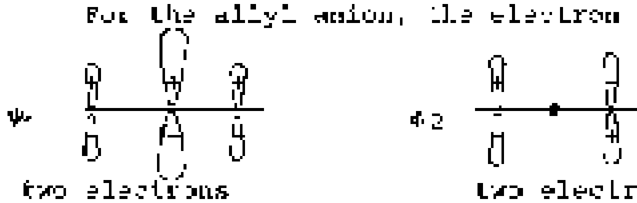
Note that the rules for the filling of ground state electrons in the molecular orbitals are the same as that for the atomic orbitals.

(b) Looking at figure 1, we see that the electron distribution in the ψ_1 molecular orbital is:



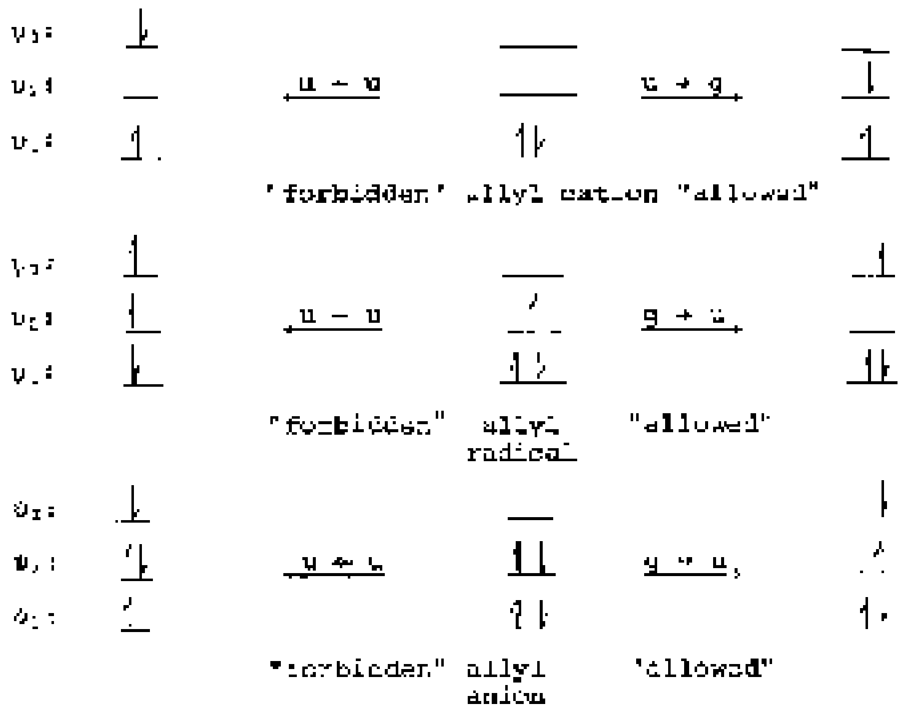
Therefore, the electrons spend more time around C_2 than around C_1 or C_3. This means that C_1 and C_3 carry most of the positive charge. An electron-donating substituent would have the most effect if it is situated at C_1 or C_3 since these are the more electron deficient centers.

For the allyl anion, the electron distribution is:



The allyl radical (in the ground state) has two electrons in ψ_1 and one electron in ψ_2. Since an allyl radical is neutral at all positions, one electron in ψ_2 and two electrons in ψ_1 will give us an even electron density at all carbons. Since C_2 has zero electron density in ψ_2, if we add another electron into this orbital it will be distributed equally at C_1 and C_3; therefore most of the negative charge will be at C_1 and C_3.

(c) Before we can answer this question, we must understand the concept of parity. When the wave function of a molecule changes sign on reflection through a center of symmetry, it is called ungerade (u); if it does not change sign, it is called gerade (g). Looking at ψ_1, ψ_2, and ψ_3 of the allyl system, we see that ψ_1 is ungerade, ψ_2 is gerade, and ψ_3 is ungerade. According to the parity selection rule, electronic transitions from g → u and u → g are allowed, but those from g → g or u → u are forbidden. The changes in electronic configuration for two different $\pi \rightarrow \pi^*$ transitions, one allowed by symmetry and one forbidden by symmetry, for the cation, radical, and anion are:



(d) In order for a substituent group to exert the most influence on the energy of transition, it must have opposite effects on the system before and after the transition:

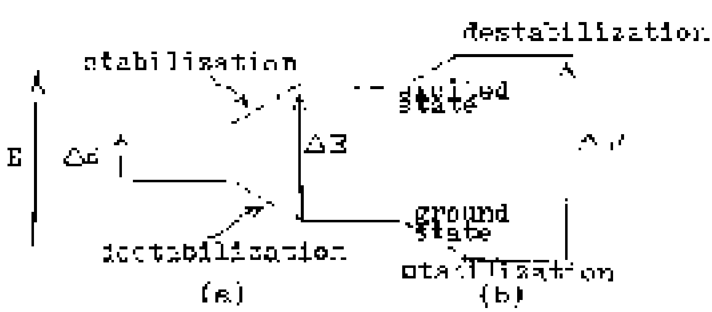
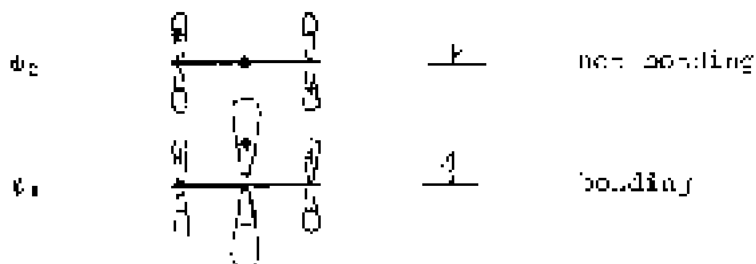


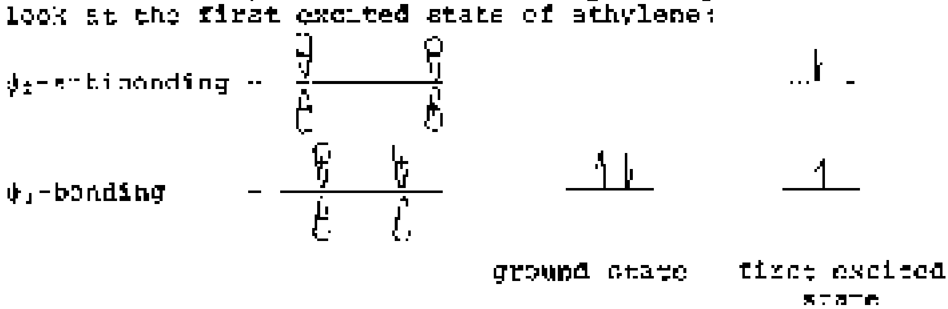
Fig. 2

A substituent group at C_1 or C_3 will have this effect. In ψ_1, most of the positive charge of the allyl cation is at C_1 and C_3. In ψ_2, the excited electron is distributed equally between C_1 and C_3, with no electron density at C_2. Therefore, if an electron-withdrawing substituent is at C_1, this would destabilize the ground state and stabilize the excited state. This is the case shown in Fig. 2a. An electron-releasing substituent would have the opposite effect (Fig. 2b). Since there is no electron density at C_2 in ψ_2, a substituent group at C_2 would have a substantial effect only on the ground state, therefore the larger net effect should come at C_1 (or C_3).

(e) The lowest excited state of the allyl cation has the following electron configuration:



There is one electron in a bonding orbital, and one electron in a non-bonding orbital. A non-bonding electron neither weakens nor strengthens the bonding, therefore a planar geometry would be more stable since this would result in a net bonding (ψ_1 requires a planar geometry in the molecule). In order to clarify this point, let us look at the first excited state of ethylene:

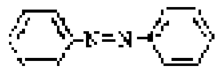


The bonding effect of one electron in the bonding orbital is just cancelled by one electron in the anti-bonding orbital, therefore there is no net bonding. In this case, the nonplanar geometry is more stable because the interelectronic repulsion is less (the electrons are farther apart in perpendicular p-orbitals on each carbon).

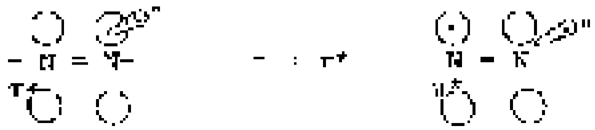
• PROBLEM 35-8

Suggest an explanation in terms of orbitals for the fact that azobenzene is a deep red-orange color, while hydrazobenzene is colorless.

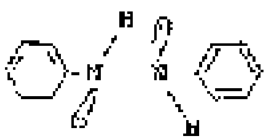
Solution: The structure of azobenzene is:



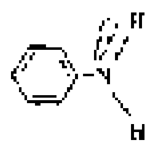
As we can see, the nitrogen-nitrogen double bond is conjugated with the two benzene rings. This decreases the energy difference between the excited state and the ground state. Therefore, the transition $n \rightarrow \pi^*$ occurs at a longer wavelength (lower energy):



This long-wavelength transition at 440 nm ($\varepsilon \sim 500$) gives rise to the deep red-orange color. There are $\pi \rightarrow \pi^*$ bands at 320 and 230 nm ($\varepsilon > 10^4$), which is in the ultraviolet region. Hydrazobenzene is not a continuously conjugated system, therefore it should absorb at a shorter wavelength. Its orbital system is similar to that of aniline, which has its longest wavelength absorption band at 280 nm; therefore hydrazobenzene should also absorb in that vicinity, which is in the ultraviolet region.



hydrazobenzene



aniline

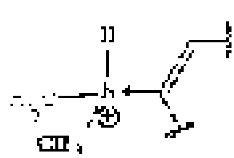
DYES

• PROBLEM 35-9

Aqueous solutions of Crystal Violet turn from violet to blue to green to yellow on addition of successive amounts of acid. The color changes are reversed by adding alkali. What kind of chemical changes could be taking place to give these color changes?

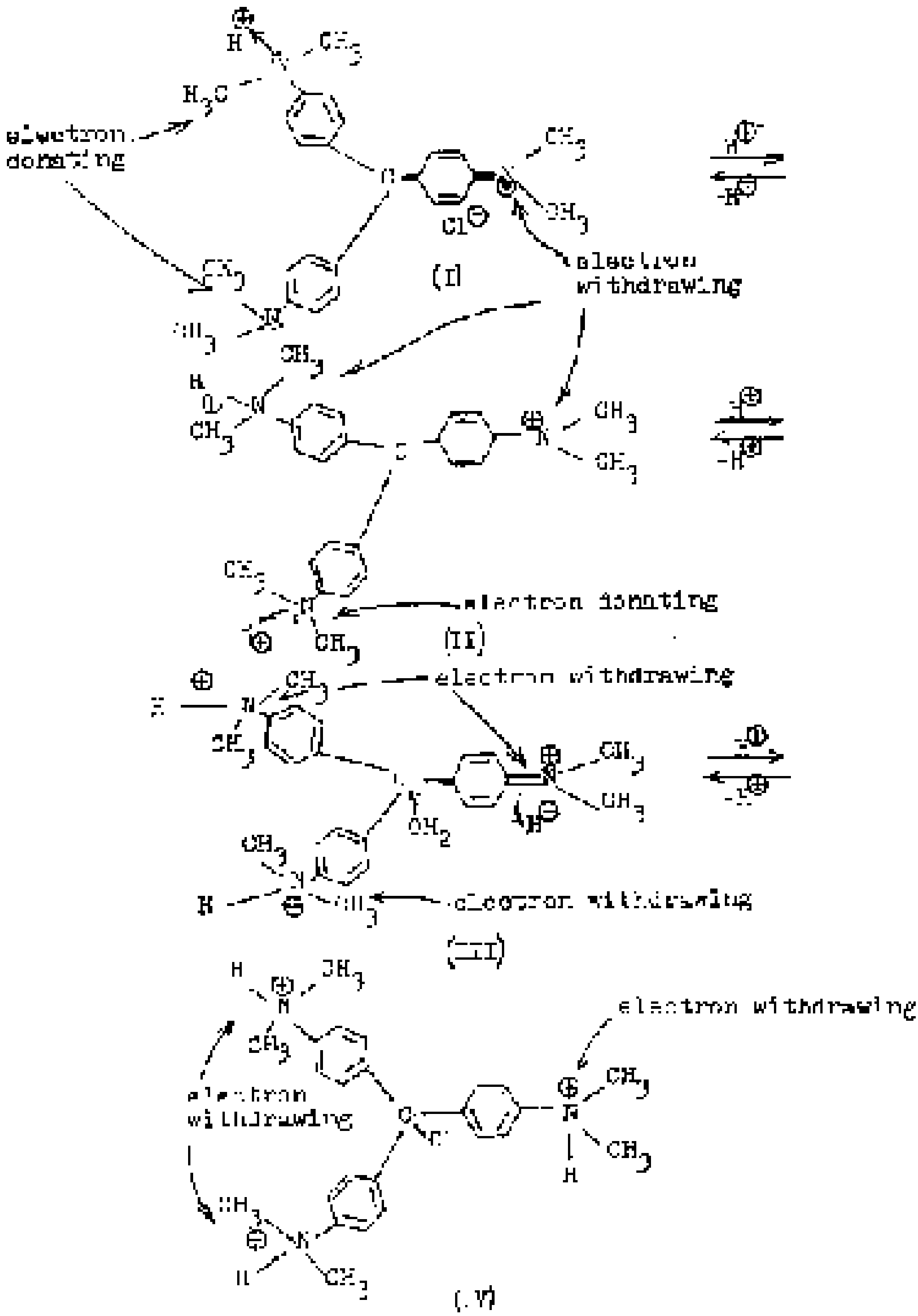
Solution: The reversal of these color changes by alkali indicates that this reaction is an acid-base reaction. Successive protonation of the $-N(CH_3)_2$ groups will change their effect on the conjugated system from electron-donating to electron-withdrawing.

electron-donating



positive charge on nitrogen → electron withdrawing

Therefore the reaction is:



Structure I absorbs at high wavelengths because of the highly conjugated system (ten conjugated double bonds), and the effect of an electron-withdrawing group at one end, and two electron-donating groups at the other end. Structure II appears blue (absorbs at lower wavelength than I), because there is an electron-withdrawing group at one end, while an electron-withdrawing group and an electron donating group are at the other end. Structure II can no longer resonate as well; therefore there is an increase in the energy difference between the excited state and the ground state (see Fig. 1).

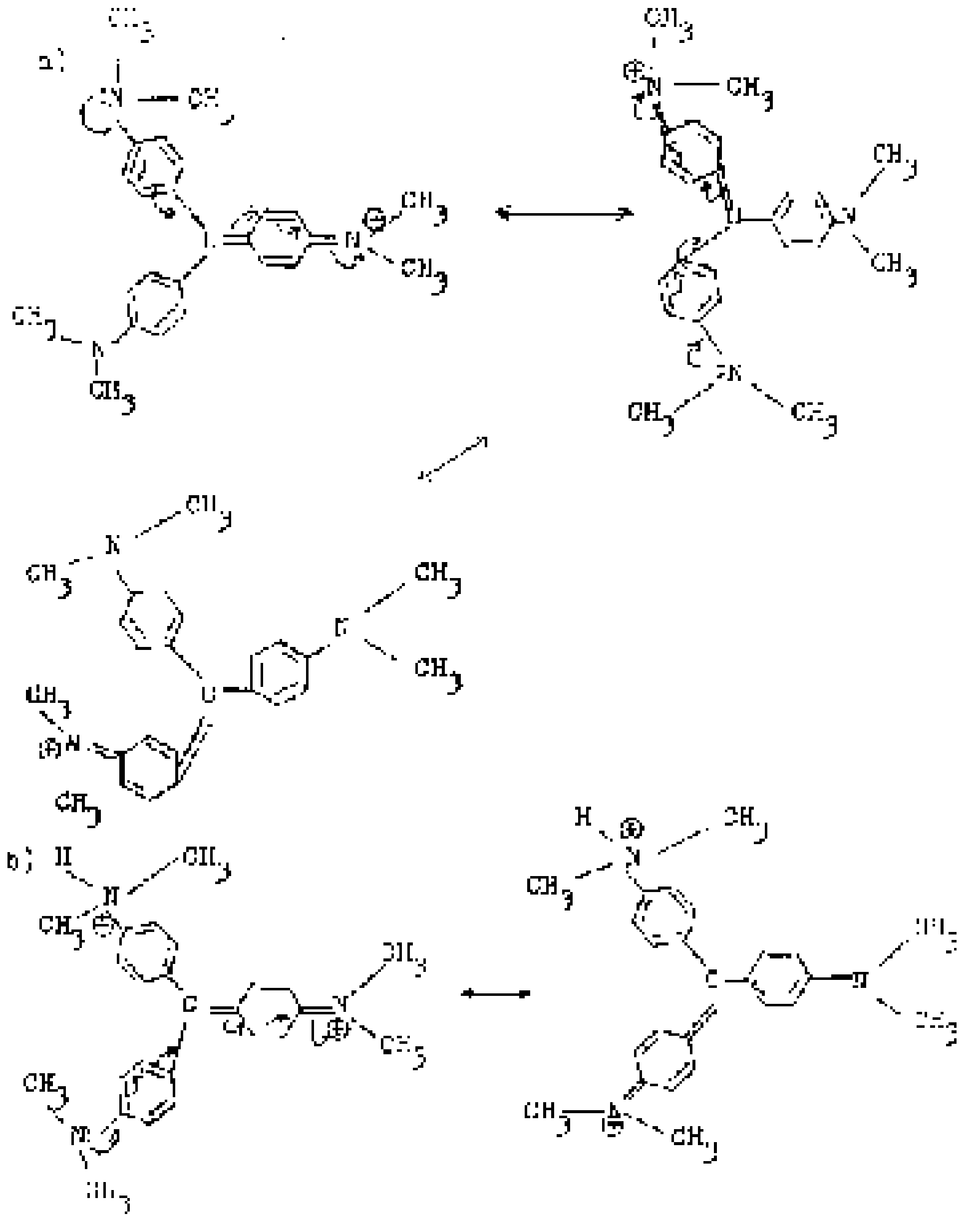


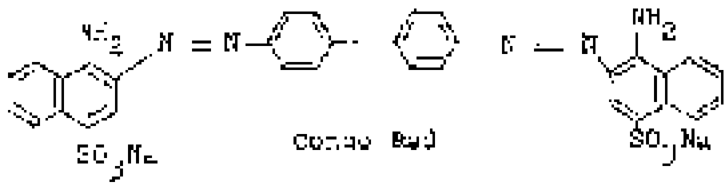
Fig. 1 - (a) resonance structures for crystal violet
(b) resonance structures for crystal violet in slightly acidic medium.

In Stucture III, there are three electron-withdrawing groups on the conjugated system and this increases the energy difference between the excited state and the ground state even more. This results in the absorption of radiation at shorter wavelengths (higher energy).

In structure IV, the conjugated system is separated into three conjugated systems of 3,3, and 3 double bonds. This results in the absorption of radiation at even shorter wavelengths.

• PROBLEM 35-10

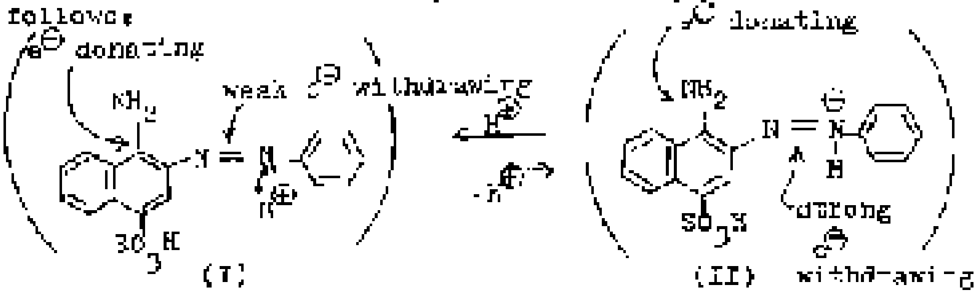
Congo Red in neutral water solution has a λ_{max} in the visible spectrum at 4970 Å. In acid solution it shows absorption maxima at 6470 and 5895 Å. (a) What colors are likely to be observed for neutral and acidic Congo Red solutions? (b) How could addition of acid to a neutral Congo Red solution cause the absorption maximum to shift to longer wavelengths? (c) What would you expect to happen to the color in very strong acid solution?



Congo Red

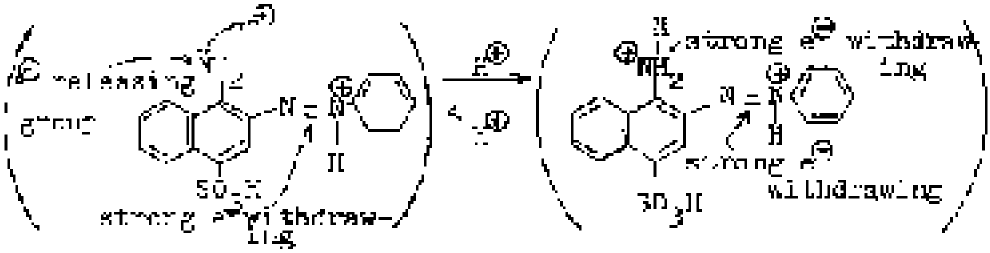
Solution: (a) We can answer this question by referring to the Table of Color and Wavelength. In neutral solution, Congo Red absorbs at 4970 Å, which is in the blue-green region. Therefore the color that we should observe is the complementary color of blue-green, which is red. In acid solution, Congo Red absorbs strongly at two wavelengths, 6470 and 5895 Å; the colors absorbed (deleted) from the spectrum are orange red (at 6470 Å),and yellow orange (at 5895 Å). The complementary color of orange-red is green-blue, while that of yellow-orange is also approximately green-blue, therefore the color that we will observe will be green-blue.

(b) In acid solution, Congo Red will be protonated as follows:



Structure I has an extensive conjugated system with a weak electron-withdrawing group and an electron releasing group attached to the conjugated system, therefore it absorbs at a long-wavelength (4970 Å). Structure II has a better electron-withdrawing group attached to the conjugated system, therefore it absorbs at a longer-wavelength (6470 Å and 5593 Å).

(d) Under very acidic conditions, the amino group will be protonated as well as the azo group:

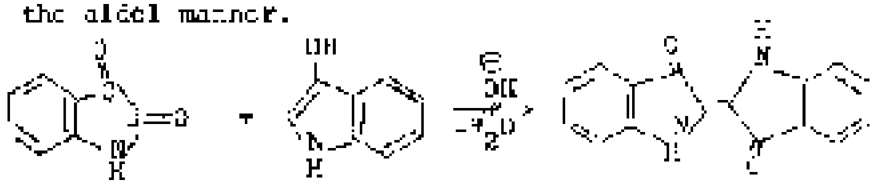


(II) (III)

The result is a structure that has two electron-withdrawing groups attached to the conjugated system. This decreases electron delocalization, as compared to structure II, therefore structure III should absorb at a shorter wavelength (~ 4300 Å), and have a yellow color.

• PROBLEM 35-11

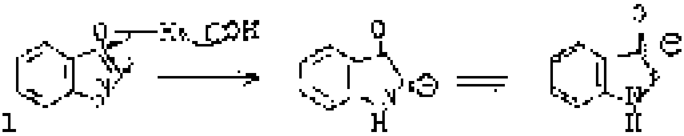
The formation of indigo by oxidation of indoxyl in alkaline solution might be formulated as involving formation of isatin and condensation of this substance with indoxyl in the aldol manner.



isatin

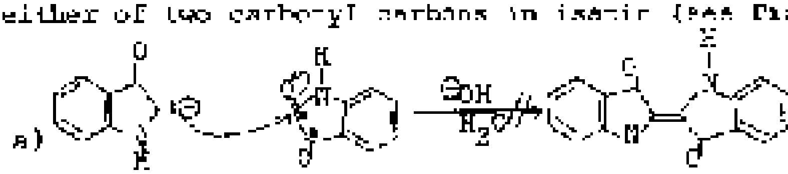
However, the reaction of isatin and indoxyl actually takes a different course and produces a colored isomer of indigo known as indigo red, which does not form leucoindigo when reduced with sodium dithionite. What is the structure of indigo red likely to be and why is it formed in preference to indigo in the condensation reaction?

Solution: The most acidic hydrogen in this system is the hydroxyl hydrogen. Abstraction of this hydrogen yields the corresponding carbanion:

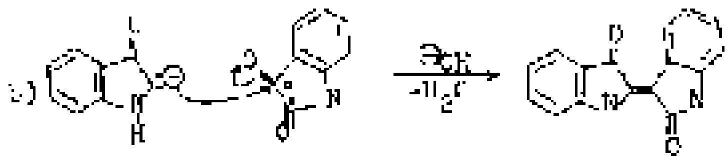


indoxyl

This carbanion would appear to be able to attack either of two carbonyl carbons in isatin (see Fig. 1).



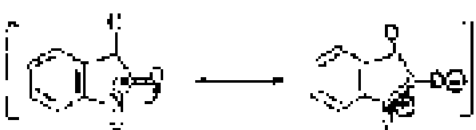
indigo



indigo red

Fig. 1

However, only indigo red is formed via an aldol-type condensation shown in Fig. 1b. Carbonyl carbon a (see Fig. 1) is not attacked by the carbanion because it is substantially deactivated by an amide resonance with the adjacent NH group:

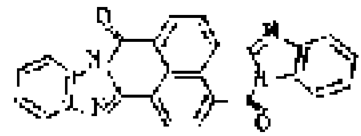


Isatin

Therefore attack by the carbanion takes place at carbonyl carbon b, which yields indigo red upon the loss of H_2O.

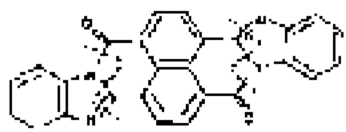
• PROBLEM 35-13

Indanthrene Brilliant Orange can be synthesized by heating naphthalene-1,4,5,8-tetracarboxylic acid with 2 moles of o-phenylenediamine. The product is a scarlet mixture (which itself is useful as a vat dye) of Indanthrene Brilliant Orange and an isomer called Indanthrene Bordeaux (red-purple). Formulate a reasonable mechanism for the formation of Indanthrene Brilliant Orange from the reaction of the tetracarboxylic acid and the diamine with attention to the possible formation of isomeric products.

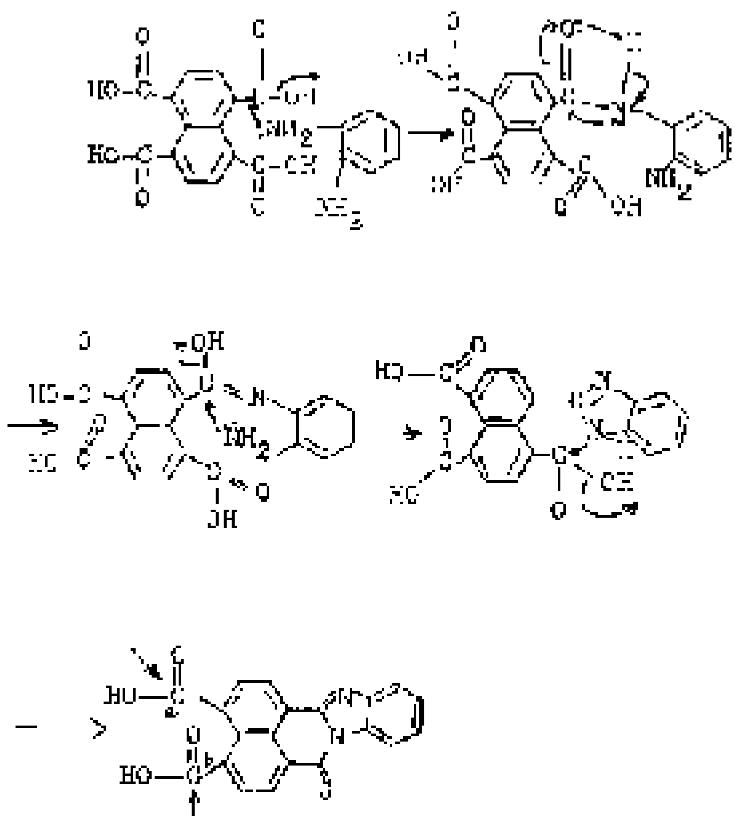


Indanthrene Brilliant Orange

Solution: From the structure of Indanthrene Brilliant Orange, we can see how it can be synthesized from naphthalene-1,4,5-8-tetracarboxylic acid and o-phenylenediamine:



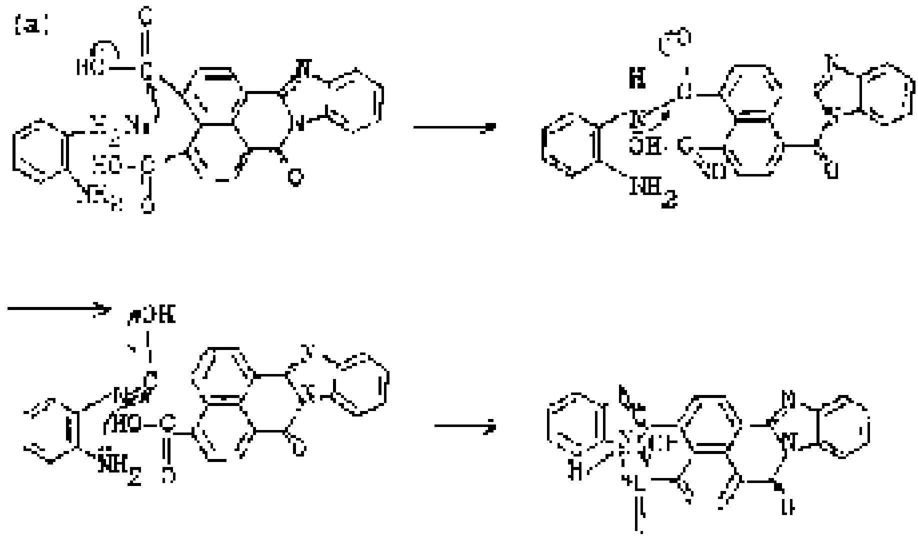
Therefore, the reaction mechanism should be:

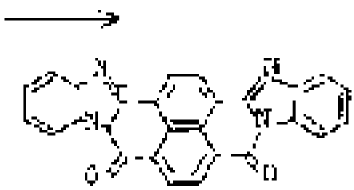


(I)

Note that all these steps are dependent on the nucleophilic attack of the carbonyl carbon by the nucleophilic amine. With the formation of structure I, two possible pathways can now occur: (a) - nucleophilic attack at carbonyl carbon a; (b) nucleophilic attack at carbonyl carbon b:

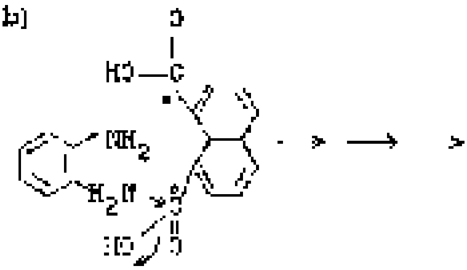
(a)

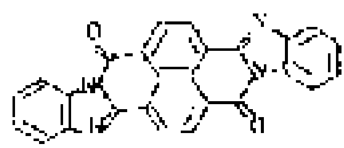




Indanthrene Bordeaux

(b)





Indanthrene
Brilliant Orange

PHOTODISSOCIATION

• PROBLEM 35-33

The quantum yield in photochemical chlorination of a hydrocarbon such as methane is quite sensitive to the experimental conditions. How would you expect it to vary with (a) the intensity of the incident light, (b) the wavelength of the incident light from 2500 to 4500 Å, (c) the presence of oxygen, and (d) the presence of alkenes? Explain.

Solution: The chlorination of hydrocarbons requires ultraviolet radiation to energize the reaction. The chlorine molecule (Cl_2) is homolytically cleaved by light and one of the resultant radicals abstracts a hydrogen atom from the methane. The energy of this ultraviolet light (available from sunlight or through artificial means) is equal to Plank's constant multiplied by the frequency of the wave. Written, mathematically, $E = h\nu$. We also know that the velocity of light is equal to the frequency multiplied by its wavelength (i.e. $c = \nu\lambda$, or $\nu = \frac{c}{\lambda}$), therefore $E = \frac{hc}{\lambda}$. The intensity of a given beam of light is directly proportional to the amount of energy held by it. This would also be the amount of energy that is directly transferable to the chlorine molecules, thus producing a greater number of chlorine radicals.

The photochemical reaction for the chlorination of methane can be expressed as:

1.	$Cl_2 + h\nu \rightarrow 2Cl\cdot$	Photo initiation
2.	$Cl\cdot + CH_4 \rightarrow HCl + CH_3\cdot$	Propagation
3.	$CH_3\cdot + Cl_2 \rightarrow CH_3Cl + Cl\cdot$	Propagation
4.	$2Cl\cdot \rightarrow Cl_2$	Termination.

Since the number of chlorine radicals available determine the rate and also the yield of the reaction (because that reaction is the initiator of the overall reaction), the higher the intensity of light, the greater will be the yield of this photochemical chlorination.

(b) The number of radicals produced is directly proportional to the number of quantums of light energy absorbed in the reaction. According to the Stark Einstein Law, the absorption of one quantum of radiation results in the formation of one photo-excited molecule, in this case, the chlorine radical. The quantum yield, Φ, for a photochemical process is given by:

$$\Phi = \frac{\text{number of molecules undergoing the process}}{\text{number of quanta absorbed}}$$

Note that Φ is related to the number of quanta absorbed. When we vary the wavelength, those quanta of light that are insufficient in energy will not be absorbed, and will not be of consequence in the equation. It is important to realize that the quantum yield, Φ, is constant for a particular reaction. This means that although the number of quanta absorbed will vary with the wavelength, the number of molecules undergoing the process will also vary, in a manner that will keep Φ constant.

(c) Oxygen will probably retard the rate of the reaction and therefore the yield because it could compete with the radicals produced from methane in the following manner:

$$CH_3\cdot \quad + \quad O_2 \quad \rightarrow \quad CH_3OO\cdot$$

$$CH_3OO\cdot \quad + \quad CH_3OO\cdot \quad \rightarrow \quad CH_3OOCH_3 \quad + \quad O_2$$

This would mean that less radicals of methane will be available for propagation reactions and sizably reduce the yield of the reaction.

(c) The presence of alkenes could also reduce the yield because allylic hydrogens are much easier to abstract than methyl hydrogens. Therefore, the presence of alkenes will successfully compete against methane in free-radical reactions, thereby lowering the quantum yield.

• PROBLEM 35-14

The vapor-phase photochemical decomposition of acetone proceeds in the presence of iodine vapor but the amount of carbon monoxide formed becomes very small. Explain how this result argues against the one step process. acetone $\xrightarrow{h\nu} 2CH_3\cdot + CO$. What do you expect the products to be in the presence of iodine?

Solution: The absorption of ultraviolet light ($\sim$ 3130 Å) by acetone results in an $n \rightarrow \pi^*$ transition. This excited molecule has one electron in a π^* orbital and one electron in one of the non-bonding (n) orbitals (see Fig. 1).

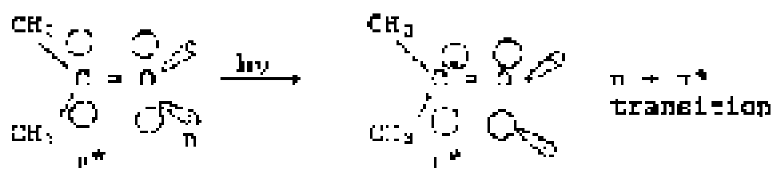
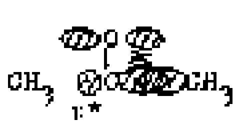


Fig. 1

The half-vacant nonbonding orbital of the excited state overlaps the σ bond orbital between the carbonyl group and the α-carbon, thereby facilitating the cleavage of the σ-bond:



$$\rightarrow \quad CH_3-\overset{O}{\overset{\|}{C}}\cdot \quad + \quad \cdot CH_3$$

This process is known as α-cleavage or Norrish type I cleavage:

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{h\nu} CH_3-\overset{O}{\overset{\|}{C}}\cdot \quad + \quad \cdot CH_3$$

Since carbon monoxide is formed in this reaction, the next step is decarbonylation of the acyl radical:

$$CH_3-\overset{\overset{O}{\|}}{C}\cdot \longrightarrow CH_3\cdot + :\bar{C}\equiv \overset{+}{O}:$$

Note that half headed arrows (⇀) indicate the movement of one electron, while full-headed arrows (→) indicate the movement of a pair of electrons.

The experiment conducted in this problem is consistent with this mechanism. If decarbonylation is a one step process, then the presence of I_2 should not influence the formation of carbon monoxide:

$$CH_3\overset{\overset{O}{\|}}{C}-CH_3 \xrightarrow{h\nu} 2CH_3\cdot + CO$$

$$CH_3\cdot + I_2 \rightarrow CH_3I + I\cdot$$

The fact that the presence of I_2 reduces carbon monoxide formation is indicative of intermediates that can react with I_2 to give different products. The Norrish type I cleavage mechanism is consistent with this:

$$CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{h\nu} CH_3-\overset{\overset{O}{\|}}{C}\cdot + CH_3\cdot$$

competing reaction: $CH_3\overset{\overset{O}{\|}}{C}\cdot + I_2 \rightarrow CH_3-\overset{\overset{O}{\|}}{C}-I + I\cdot$

$$CH_3-\overset{\overset{O}{\|}}{C}\cdot \rightarrow CH_3\cdot + CO$$

$$CH_3\cdot + I_2 \rightarrow CH_3I + I\cdot$$

$$CH_3\cdot + CH_3\cdot \rightarrow CH_3-CH_3$$

Therefore the products in the presence of iodine are:

$CH_3\overset{\overset{O}{\|}}{C}I$, CH_3I, CO, and CH_3-CH_3.

PHOTOCHEMICAL REDUCTION

• PROBLEM 35-15

Irradiation of benzophenone in isopropyl alcohol in the presence of oxygen gives no benzopinacol (the benzophenone is not consumed), acetone (with Φ equal to unity), and hydrogen peroxide (with Φ nearly unity). The reaction does not occur readily in the absence of benzophenone. Explain how benzophenone acts as a photosensitizer for the oxidation of isopropyl alcohol by oxygen.

Solution: A photosensitizer is an excited species which excites another ground state molecule by energy transfer. Since benzophenone is not consumed in this reaction, it is acting as a true photosensitizer. Photosensitized oxidations (since oxygen is present) usually proceed via the triplet state (T_1) of the sensitizer. The sensitizer in these reactions can act in one of two ways:

(a) Type I process - sensitizer abstracts hydrogen from a substrate molecule to form a radical which reacts with oxygen

(b) Type II process - sensitizer activates oxygen for a direct reaction between substrate and oxygen.

The principles behind these two mechanisms are very similar, and only the type I process will be discussed in this problem:

(1) $$\phi_2C = O \xrightarrow{h\nu} \phi_2C = O\ (S_1)$$

This step involves the excitation of benzophenone to the singlet state (S_1).

(2) $$\phi_2C = O\ (S_1) \rightarrow \phi_2C = O\ (T_1)$$

This step is an intersystem crossing (ISC) transition, that is, the excited species changes multiplicity ($S_1 \rightarrow T_1$). Reactions often occur via the triplet state because the lifetime of the triplet state ($\sim 10^{-3}$ sec) is greater than that of the singlet state ($\sim 10^{-8}$ sec).

(3) $$\phi_2C = O\ (T_1) + (CH_3)_2CHOH \rightarrow \underset{\text{fairly stable radical}}{\phi_2\dot{C}OH} + \underset{\text{less stable radical}}{(CH_3)_2\dot{C}OH}$$

This step involves abstraction of an isopropyl alcohol hydrogen by the excited triplet state of benzophenone. The hydrogen abstracted is the one that results in the more stable radical:

$$\phi_2C{=}O\ (T_1) + CH_3-\overset{\overset{\large H}{|}}{\underset{\underset{\large CH_3}{|}}{C}}-OH \not\rightarrow \phi_2\dot{C}OH + \underset{\text{primary radical (not stable)}}{\dot{C}H_2-\overset{OH}{CH}-CH_3}$$

$$\phi_2C = O(T_1) + CH_3-\underset{CH_3}{\overset{H}{C}}-OH \rightarrow \phi_2\dot{C}OH + CH_3-\underset{\cdot}{\overset{OH}{C}}-CH_3$$

The next step is reaction with oxygen:

(4) $(CH_3)_2\dot{C}OH + O_2 \rightarrow (CH_3)_2\underset{O-O\cdot}{C}-OH$

(5) $(CH_3)_2\underset{O-O\cdot}{C}-OH + \phi_2\dot{C}-OH \rightarrow (CH_3)_2\underset{O-O-H}{C}OH + \phi_2C=O$

Step five regenerates benzophenone.

(6) $(CH_3)_2\underset{O-O-H}{-C}-OH \rightarrow (CH_3)_2C=O + H_2O_2$

With this mechanism, the quantum yield (ϕ) is approximately equal to one for acetone and hydrogen peroxide; one excited benzophenone molecule results in the formation of one acetone molecule and one H_2O_2 molecule, and according to the Stark-Einstein principle, a molecule can only absorb one quantum of radiation. Therefore:

$$\Phi_{form} = \frac{\text{number of molecules of product formed}}{\text{number of quanta absorbed}}$$

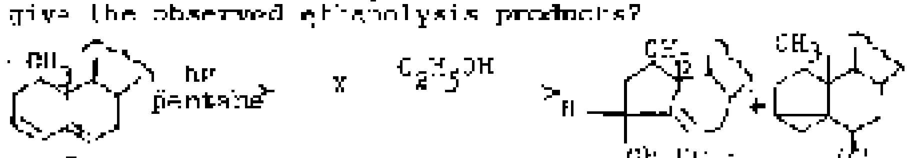
$$\cong 1 \text{ for acetone and } H_2O_2$$

where Φ_{form} = quantum yield for the formation of a product.

PHOTOCHEMICAL ISOMERIZATION

PROBLEM 25-16

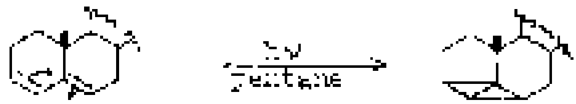
3,5-Cholestadiene (see partial structure below) on irradiation in pentane solution with ultraviolet light is converted to an unstable isomeric compound (X) which shows no vinyl hydrogens in its n.m.r. spectrum and reacts with ethanol in the dark to give the products shown. What is a likely structure for X and how might it give the observed ethanolysis products?



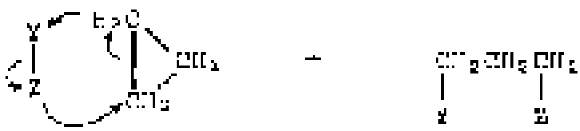
I II OCH_2CH_3 III OC_2H_5

3,5-cholestadiene

Solution: In order to solve this problem, we must look at the products and see how they can be formed from a common intermediate in a reaction with ethanol. Looking at structure III, we see that attack by ethanol occurs at C_4. Since there are no double bonds in the intermediate, we can assume that the reactive group is a highly strained bicyclic derivative, which is easily attacked to enable ring opening. The mechanism for this reaction is:

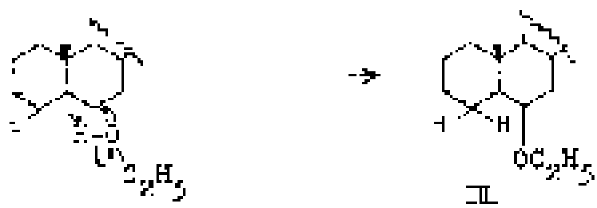


This step is a [2 + 2] photochemical electrocyclic reaction which yields a bicyclo (1.1.0) butane derivative. Cyclopropanes undergo addition reactions of the type:

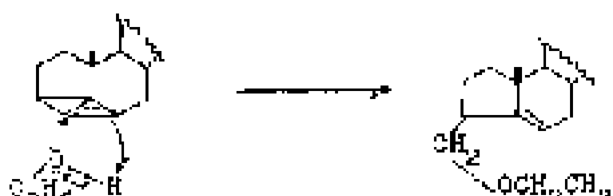


Therefore, this highly strained bicyclic compound should also undergo addition reactions:

(a)

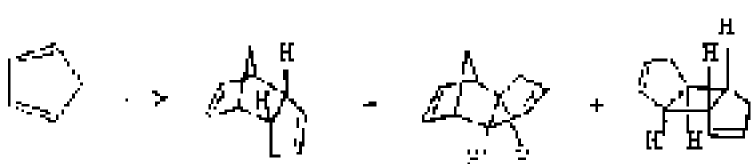


(b)



■ PROBLEM 35-17

1,3-Cyclopentadiene gives the following substances on irradiation in the presence of a ketone sensitizer:

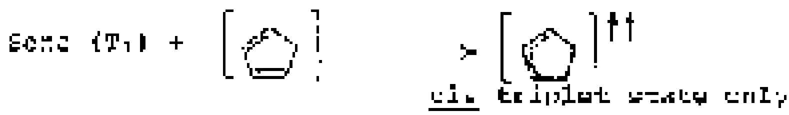


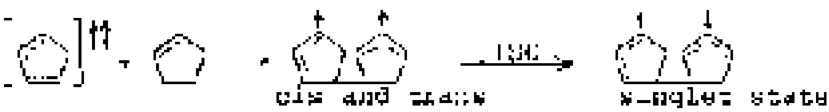
Write reasonable mechanisms for the formation of these substances. Would you expect the ratios of the products to depend on the nature of the ketone used as sensitizer? Why?

Solution: Dimerization usually requires a triplet state. In order to obtain a significant triplet population of olefins, a sensitizer must be used. A sensitizer is an excited molecule which excites another ground state molecule by energy transfer.

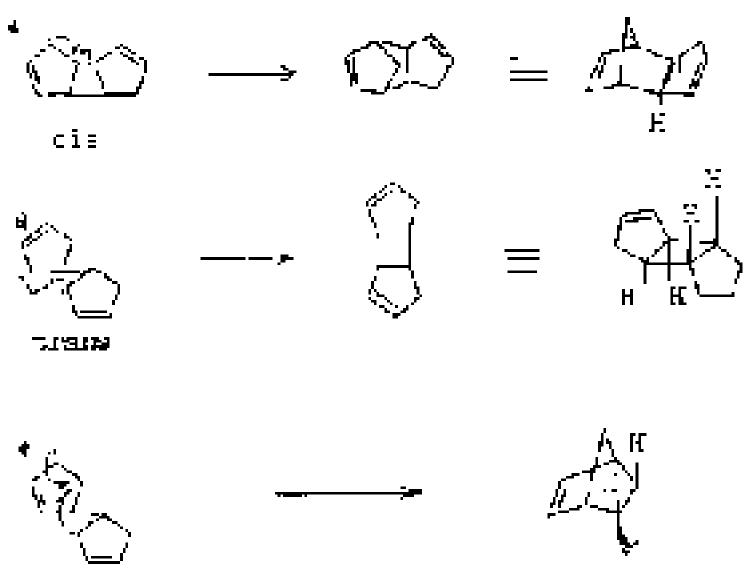
Since this reaction is not stereospecific, a concerted reaction is not the case. The mechanism for this reaction is (Sens = sensitizer):

$$\text{Sens } (S_0) \xrightarrow{h\nu} \text{Sens } (S_1) \xrightarrow{ISC} \text{Sens } (T_1)$$





Note that there is free rotation around the single bond connecting the two rings:

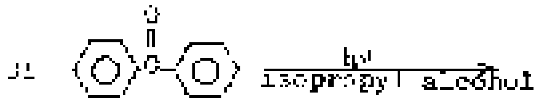


The proportions of the products are independent of sensitizer because only the cis-triplet is possible from cyclopentadiene. The proportion of cis and trans combinations between the cyclopentadiene triplet and cyclopentadiene is probably temperature sensitive, but it would not be sensitizer sensitive because the combination reaction (a - c) involves the same species independently of the sensitizer.

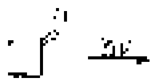
• PROBLEM 35-18

Predict the products of the following photochemical reactions of ketone:

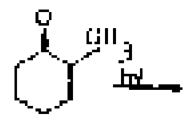
a)



b)



c)

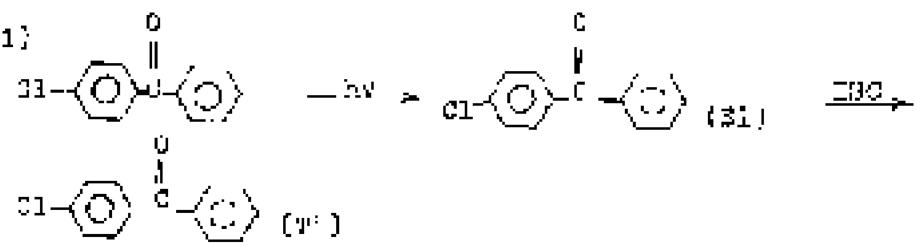


d)

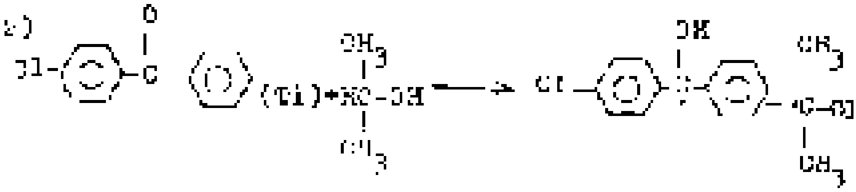
Solution: In order to predict the products of a reaction, we must look at the reactants under the reaction conditions and see what can happen. By formulating a mechanism and following it through, the products will appear spontaneously.

(a) Photoreduction of ketones is usually done in the presence of an alcohol because alcohols are excellent hydrogen donors. Therefore, the probable mechanism for this reaction is:

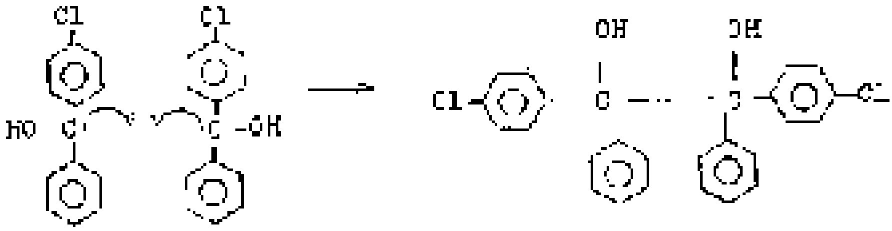
1)



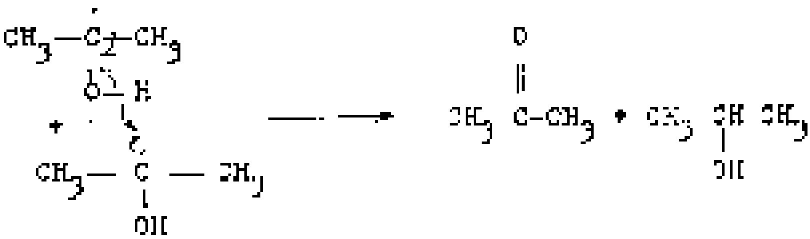
2)



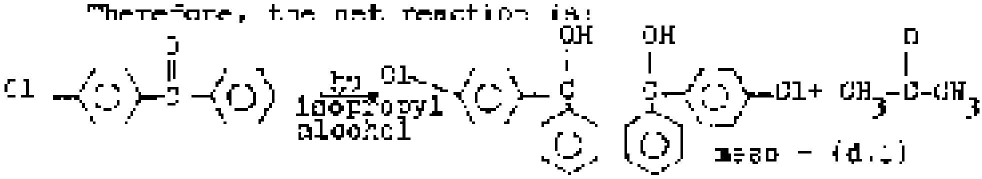
Note that abstraction of this hydrogen yields the most stable isopropanol radical.



meso + (d,l)



Therefore, the net reaction is:



(b) The photochemistry of saturated cyclic carbonyl compounds is dominated by the Norrish type I process, that is, initial cleavage of the α-bond to give an acyl and an alkyl radical, which can undergo stabilization by the following three routes:

(a) α-hydrogen abstraction by alkyl radical to form a ketene and an alkane:

$$R_2\overset{H}{\underset{|}{C}}-\overset{O}{\overset{||}{C}}\cdot + \cdot CR_3 \rightarrow R_2C=C=O + R_3CH$$

(b) Decarbonylation of the acyl radical to give carbon monoxide and an alkyl radical:

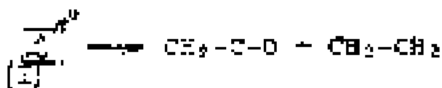
$$R_3C-\dot{C}=O \xrightarrow[\Delta H]{} R_3C\cdot + CO$$

(c) Intermolecular hydrogen abstraction by the acyl radical from the alkyl radical to give an aldehyde and an alkene:

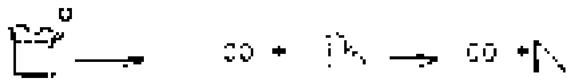
$$R_3C-\dot{C}=O + H-CH_2-\dot{C}R_2 \rightarrow R_3C-CHO + H_2C=CR_2$$

Although the above scheme for the Norrish type I process is written for acyclic compounds, they can be applied to cyclic compounds as well. In cyclic compounds, cleavage of the α-bond results in a diradical, instead of two separate radicals. We must remember that the above scheme is to be used only as a guideline. We have to analyze each individual system, and apply our organic chemical principles to that system, in order to see what can or cannot happen. Upon irradiation, the α-bond of cyclobutanone will be homolytically cleaved:

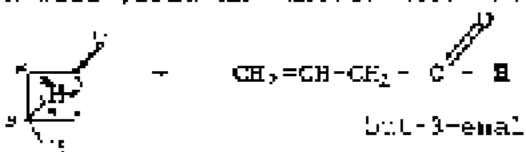
Since α-hydrogen abstraction is difficult in this short-chained compound, the α-β carbon-carbon bond will cleave instead of the α-carbon hydrogen bond:



Decarbonylation of structure I can also occur:



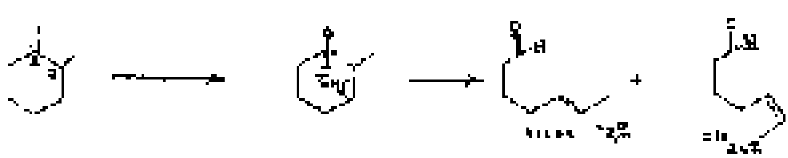
Intramolecular hydrogen abstraction by the carbonyl carbon will yield an unsaturated aldehyde:



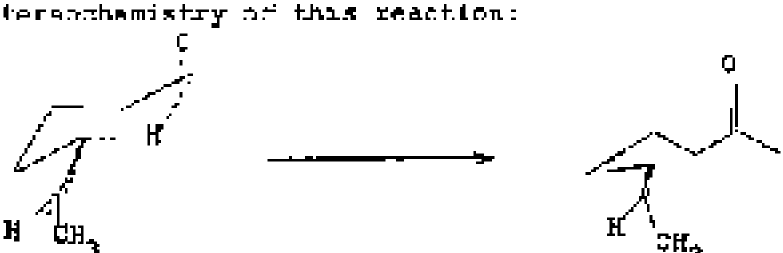
Since this reaction is abstraction of a β-hydrogen (stereochemically difficult), the yield for but-3-enal should be very low, and in fact is found only in negligible amounts.

The net reaction is therefore:

(c) The photolysis of 2-methylcyclohexanone yields hept-5-enal:



Cleavage of the $C_1 - C_2$ bond is overwhelmingly preferred due to the much greater stability of the secondary radical. In order to understand why this reaction is preferred over the other reactions, we must look at the stereochemistry of this reaction:

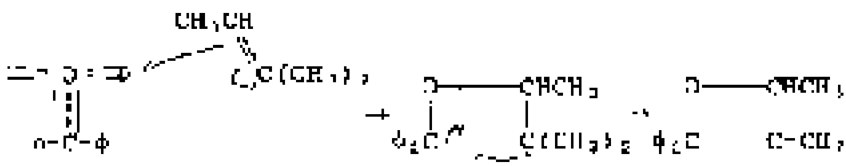


The conformation is a stable, six membered, hydrogen-bridged, cyclic transition state. Therefore, abstraction of this hydrogen occurs before the other reactions can occur. Under reduced pressure, decarbonylation occurs due to the lower collision rate; a lower collision rate means that the excitation energy is not as readily lost, and decarbonylation is greatly favored.

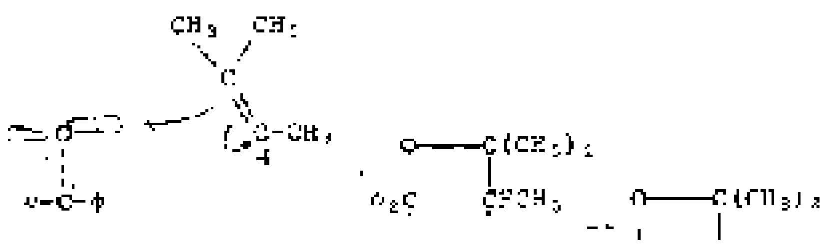
(c) At wavelength greater than 300 nm, the energy is low and only benzophenone will be photochemically excited to the triplet state. The low energy of this transition (E_T = 69 kcal/mole) causes benzophenone to add to the alkene, instead of transferring its energy. The resultant addition of an excited ketone to an alkene to form an oxetane is called the Paterno-Büchi reaction. The mechanism is:

$$\phi-\overset{O}{\overset{\|}{C}}-\phi \xrightarrow[>300\text{ nm}]{h\nu} {}^{1}[\phi_2C=O] \xrightarrow{ISC} {}^{3}[\phi_2C=O]$$

The subscripts indicate the multiplicity: 1 = singlet; 3 = triplet



triplet state | more stable biradical | major product

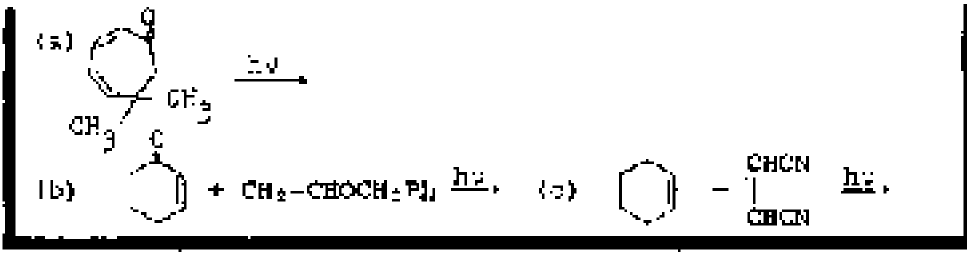


triplet state | less stable biradical | minor product

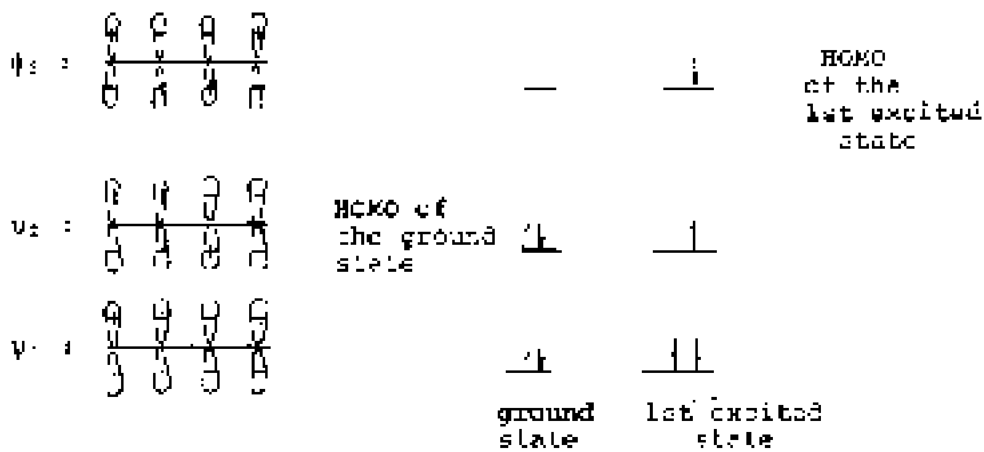
Note that formation of a tertiary radical is preferred over the formation of a secondary radical, because tertiary radicals are more stable.

• PROBLEM 35-19

Give the products of the following photocycloaddition reactions:



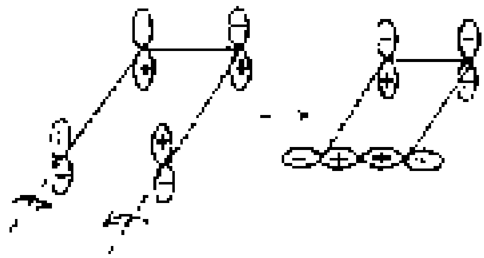
Solution: (a) This is a photochemical electrocyclic reaction. Electrocyclic reactions are concerted, therefore they are completely stereospecific. The exact stereochemistry of the product depends upon the number of double bonds in the polyene; molecular orbital theory allows us to predict this stereochemistry. Let us look at the electron configuration of butadiene, a four π electron system, in the ground state and in the first excited state (achieved by the absorption of radiation):



The electron that is the least tightly held, and therefore the one that is involved in the reaction is the electron in the highest occupied molecular orbital (HOMO) of the polyene. As we can see from the above diagram, the highest occupied molecular orbital of the conjugated diene in the first excited state is ψ_3. It is the electron in this orbital that will form the bond that closes the ring. Bond formation requires overlap of the lobes on C_1 and C_4 of the diene. Only a disrotatory motion, in which the bonds rotate in opposite directions, can bring together lobes of the same phase, resulting in the formation of a bond.

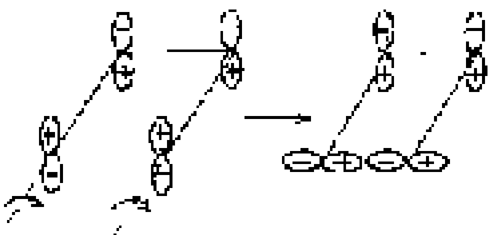
A conrotatory motion, in which the bonds rotate in the same direction, would bring together lobes of opposite phase, resulting in the formation of an antibond:

HOMO
ψ_3



Disrotatory: bonding

HOMO
ψ_3



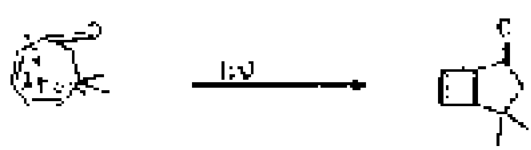
Conrotatory: antibonding

Therefore, photochemical electrocyclic reactions of four π electrons can only occur in a disrotatory manner. This is summarized by the Woodward-Hoffman rules for electrocyclic reactions:

Table 1: Woodward-Hoffman Rules for Electrocyclic Reactions

Number of π electrons	Reaction	Motion
4n (n=any integer)	thermal	conrotatory
4n	photochemical	disrotatory
4n + 2	thermal	disrotatory
4n + 2	photochemical	conrotatory

Since this problem is a photochemical electrocyclic reaction involving four π electrons, the motion must be disrotatory:



(b) Upon irradiation, two unsaturated molecules can undergo photocycloadditions. In cycloaddition, two new σ bonds are formed by the use of π electrons of the reactants. The concerted reaction results from overlap of orbitals of one molecule with orbitals of the other. In order for two unsaturated molecules to react in a concerted cycloaddition (e.g. photocycloaddition of two ethylenes Fig. 1), the highest occupied molecular orbital (HOMO)

cyclobutane

Fig. 1

of one reactant must overlap with the lowest unoccupied molecular orbital (LUMO - the most stable empty orbital) of the other reactant (See Figs. 4, 5 and 6). Stabilization of the transition state of a cycloaddition comes chiefly from this overlap between the HOMO of one reactant and the LUMO of the other. The Woodward-Hoffman rules for [i + j] cycloadditions tell us how cycloadditions occur with respect to the number of π electrons in each reactant.

Table 2 - Woodward - Hoffman Rules for [i + j] Cycloadditions

i + j	Thermal	Photochemical
4n	supra-antara	supra-supra
	antara-supra	antara-antara
4n+2	supra-supra	supra-antara
	antara-antara	antara-supra

The [i + j] refers to the number of π electrons in each reactant that are active in the reaction. A more comprehensive system denotes the nature of the orbitals undergoing change (π or σ), and the stereochemical mode of cycloaddition (suprafacial (S) or antarafacial (a) - see Fig. 2), as well as the number of electrons in each reactant that are participating in the cycloaddition.

suprafacial antarafacial

Fig. 2

For example, a [π2s + π2s] cycloaddition indicates a cycloaddition involving two π electrons of one reactant with two π electrons of another in a suprafacial-suprafacial manner (See Fig. 3).

Fig. 3 (a) a [$\pi 2s - \pi 2s$] cycloaddition: the preferred [2 − 2] cycloaddition (b) a [$\pi 2s + \pi 2s$] cycloaddition: very difficult since it requires high-energy steric interactions in the transition-state, and will be favored only when the ethylenes are twisted.

From the Woodward Hoffman rules, we see that a [$\pi 2s + \pi 2s$] photochemical cycloaddition is "allowed" ($i + j = 2 + 2 = 4$, which is a $4n$ reaction for $n = 1$). Let us look at the electron configuration of ethylene, a two π electron system, to see why this is true:

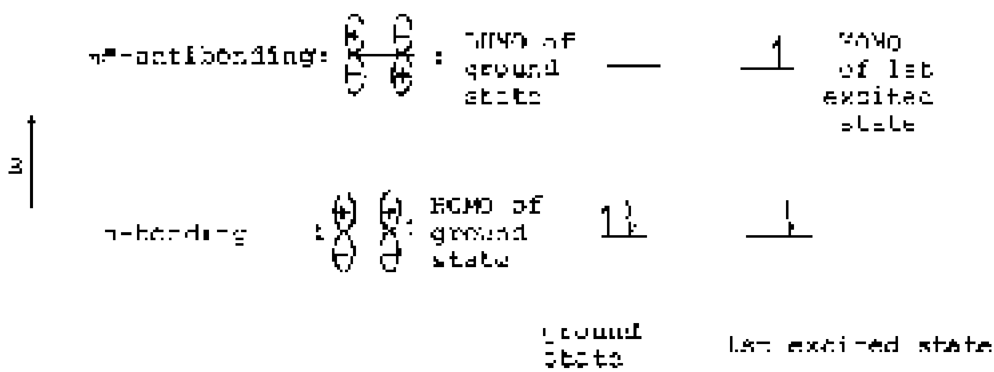


Fig. 4

Since we need the HOMO of one reactant to overlap with the LUMO of the other, a [$\pi 2s + \pi 2s$] thermal reaction would involve the overlap of opposite phase lobes, which is symmetry-forbidden:

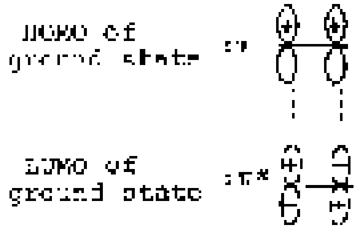


Fig. 5 - symmetry forbidden

However, a [$\pi 2s + \pi 2s$] photochemical cycloaddition would involve overlap of same-phase lobes, which is symmetry-allowed:

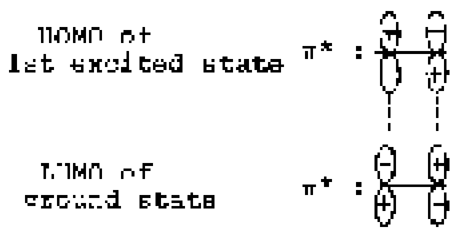
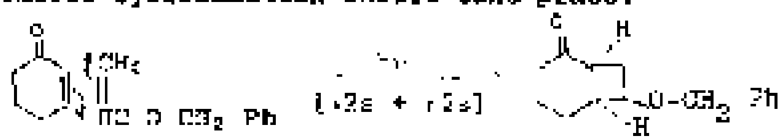


Fig. 6 - symmetry-allowed

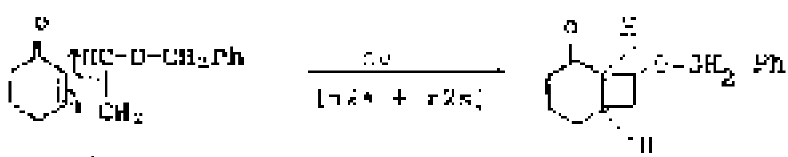
Note that only concerted cycloadditions require the conservation of orbital symmetry. Non-concerted cycloadditions can proceed by other routes which do not require orbital symmetry (e.g. diradical intermediates).

This problem involves two systems of two π electrons in a photochemical process, therefore a [π2s + π2s] photochemical cycloaddition should take place:



trans

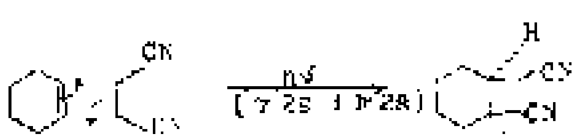
+



cis

Note that the vinylic hydrogens of the cyclohexenone are on the same side of the molecule in the products. This is the result of a supra supra attack.

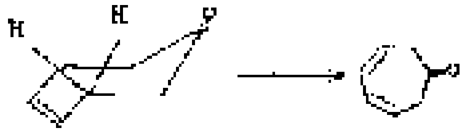
(c) This problem involves two systems of two π electrons in a photocycloaddition. Therefore in accordance with the Woodward-Hoffman rules, a [π2s + π2s] photocycloaddition should occur:



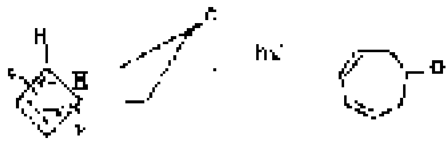
The vinylic hydrogens of the cyclohexene are cis in the product due to the supra supra attack.

• PROBLEM 35-20

Will the following reaction go more smoothly with activation by heat or by light?



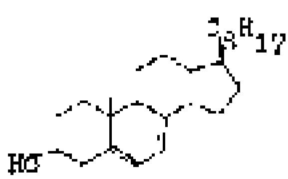
Solution: This is an electrocyclic reaction involving four π electrons moving in a disrotatory manner, that is, the bonds rotate in opposite directions:



According to the Woodward-Hoffman rules for electrocyclic reactions, a photochemical reaction is required for concertedness in a disrotatory manner when the number of π electrons is $4n$ (4 π electrons $= 4n$ for $n = 1$).

• PROBLEM 35-21

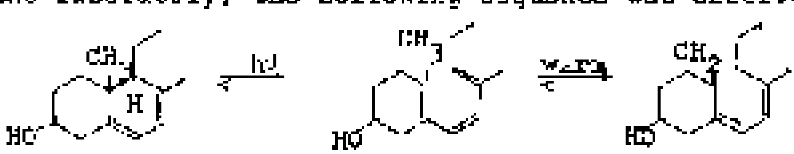
(a) In the skin of animals exposed to sunlight, 7-dehydrocholesterol is converted



$$C_8H_{17} = -\underset{|}{\overset{CH_3}{}}CHCH_2CH_2CH_2CH(CH_3)_2$$

7-Dehydrocholesterol

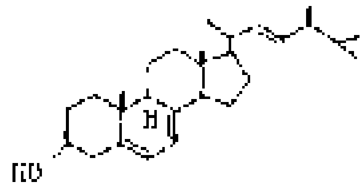
into the hormone cholecalciferol, the so-called 'vitamin' D_3 that plays a vital role in the development of bones. In the laboratory, the following sequence was observed:



7-Dehydrocholesterol (I) Pre-cholecalciferol (II) Cholecalciferol (III)

What processes are actually taking place in these two reactions? Show details.

(b) An exactly analogous reaction sequence is used to convert the plant steroid ergosterol into ergocalciferol, the "vitamin" D_2 that is added to milk:



ergosterol $\xrightarrow{h\nu}$ pre-ergocalciferol $\xrightarrow{\text{warm}}$ ergocalciferol

What is the structure of pre-ergocalciferol? Of ergocalciferol?

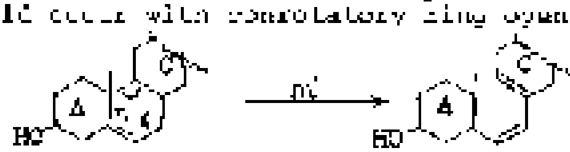
(c) On heating at 190°, pre-ergocalciferol is converted into IX and X, stereoisomers of ergosterol. What reaction is taking place, and what are the structures of IX and X?

(d) Still another stereoisomer of ergosterol, XI, can be converted by ultraviolet light into pre-ergocalciferol. What must XI be?

Solution: (a) 7-Dehydrocholesterol belongs to the class of compounds called steroids. These compounds are of the general formula:

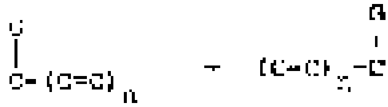
A steroid

Because of the rigid cyclic system of steroids, conformational effects are marked, and often completely control the course of reaction. With this in mind, let us look at the photochemical reaction of 7-dehydrocholesterol. As we can see, the first step involves the opening of ring B by electrocyclic reaction. This ring opening involves three double bonds, or six π electrons. According to the Woodward-Hoffman rules for electrocyclic reactions, a six π electron ($4n + 2$ for $n = 1$) photochemical reaction should occur with conrotatory ring opening, therefore:



Note that a thermal ring-opening cannot take place. The symmetry allowed disrotatory motion would generate a trans double bond in either ring A or C. This is geometrically impossible in a six-membered ring.

The second step is a thermal [1, 7] hydride shift, specifically a [1, 7] sigmatropic reaction. A sigmatropic reaction is a concerted reaction of the type:



This reaction involves the migration of a group, with its σ bond, within a π framework. This migration is accompanied by a shift in π bonds, for example:

[1,3] sigmatropic reaction

In the designation [1, 3], the "1" indicates that in both reactant and product, bonding is to the same atom in the migrating group. The "3" refers to the number of the carbon to which group G is migrating.

The stereochemistry of a sigmatropic hydride shift depends on the highest occupied molecular orbital (HOMO) of the π framework. In the transition state, a three-center bond is required, which involves overlap between the s orbital of the hydrogen and lobes of p orbitals of the two terminal carbons. From the HOMO configuration of a seven carbon allylic radical in the ground state, we see that the symmetry-allowed shift is in an antarafacial manner (see Fig. 1).

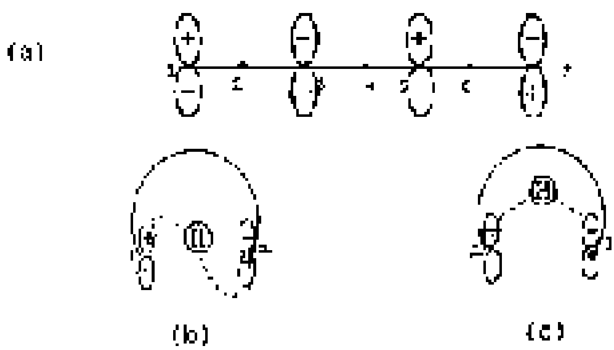


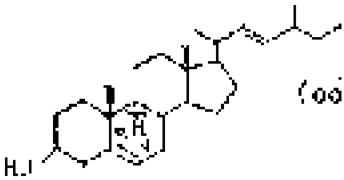
Fig. 1 - (a) HOMO of seven-carbon allyl radical in the ground state; (b) symmetry-allowed antarafacial migration; (c) symmetry-forbidden suprafacial migration.

Note that a [1, 3] or [1, 5] antarafacial hydride shift is very difficult due to geometric complications that would be encountered.

Since the hydride shift in this problem is a [1, 7] H shift, it must be in an antarafacial manner:

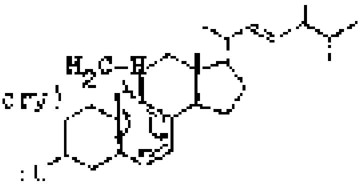
Pre-cholecalciferol cholecalciferol

(b) Since the reaction mechanism is the same as in part (a), the structures are:



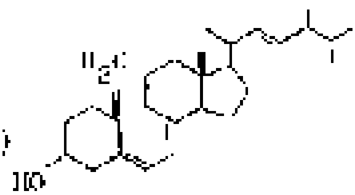
ergosterol

$\xrightarrow[\text{(conrotatory)}]{h\nu}$



pre-ergocalciferol

$\xrightarrow[\text{(antarafacial)}]{\Delta}$



ergocalciferol

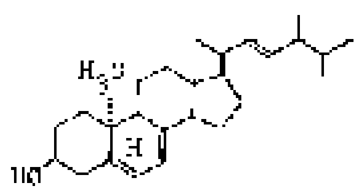
(c) Since compounds IX and X are stereoisomers of ergosterol, the reaction taking place must be a thermal electrocyclic closure of ring B. This ring-closure involves three double bonds, or six π electrons. According to the Woodward-Hoffman rules for electrocyclic reactions, a six π electron (4n + 2 for n = 1) thermal reaction should occur with disrotatory ring closure. There are, however, two disrotatory modes:

 and 

Each mode yields a different stereoisomer of ergosterol, IX and X.

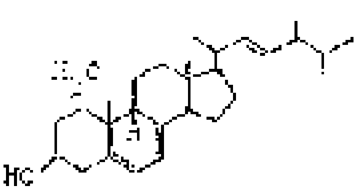
pre-ergocalciferol

$\xrightarrow{190°}$



IX

$\downarrow$ 190°



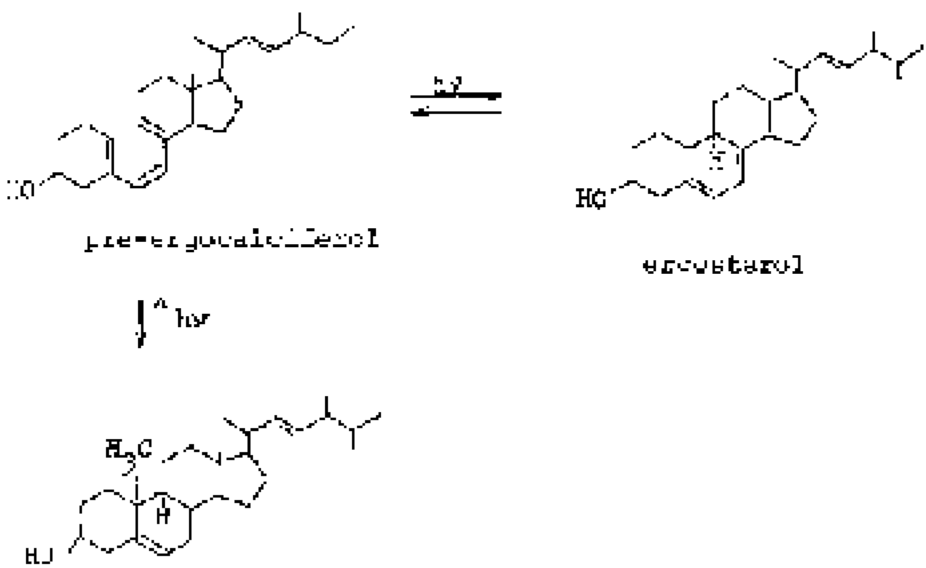
X

In ergosterol, the C_{10} methyl group is β (coming out of the plane of the paper -- solid lines), and the C_9 hydrogen is α (going behind the plane of the paper -- dotted lines). In stereoisomer IX, both the C_{10} methyl and the C_9 hydrogen are α, while in stereoisomer X, both are β.

(d) The reaction to form pre-ergocalciferol must be an electrocyclic opening of ring B. This ring opening involves three double bonds, or six π electrons. According to the Woodward-Hoffman rules for electrocyclic reactions, a six π electron (4n + 2 for n = 1) photochemical reaction should occur with conrotatory ring opening, as in the first step of part (b) of this problem. Let us consider the photochemical ring-closure of pre-ergocalciferol. There are two conrotatory modes:

 and 

These two motions yield two different stereoisomers:



pre-ergocalciferol

ergosterol

XI

As we can see, one of these stereoisomers is ergosterol, which has the C_{10} methyl β, and the C_9 hydrogen α. The other stereoisomer is XI, which has the C_{10} methyl α, and the C_9 hydrogen β.

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