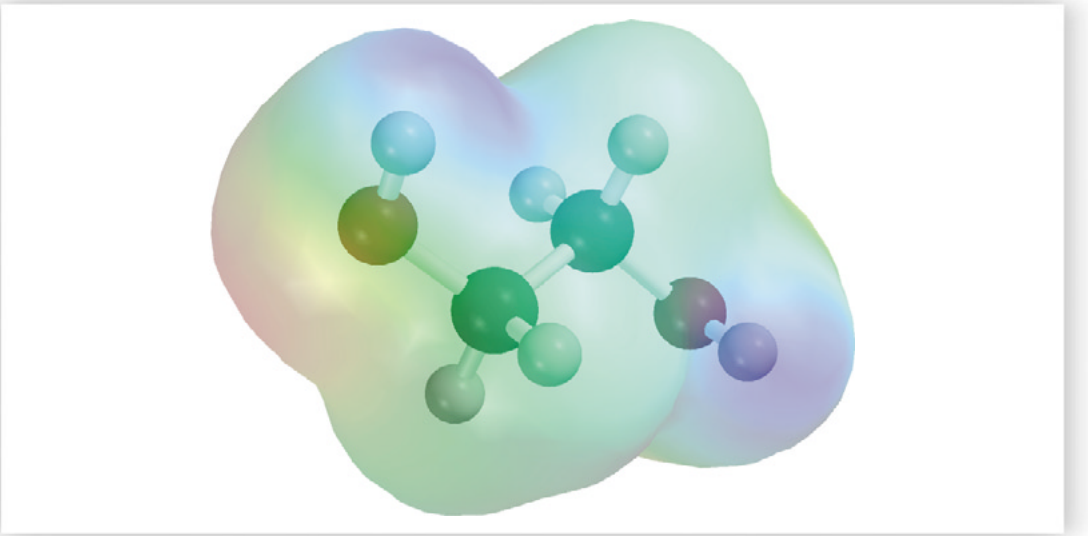


CHAPTER 15

ALCOHOLS, DIOLS, AND THIOLS

The next several chapters deal with the chemistry of various oxygen-containing functional groups. The interplay of these important classes of compounds—alcohols, ethers, aldehydes, ketones, carboxylic acids, and derivatives of carboxylic acids—is fundamental to organic chemistry and biochemistry.

ROH	ROR′	RCH (O)	RCR′ (O)	RCOH (O)
Alcohol	Ether	Aldehyde	Ketone	Carboxylic acid

We'll start by discussing in more detail a class of compounds already familiar to us, *alcohols.* Alcohols were introduced in Chapter 4 and have appeared regularly since then. With this chapter we extend our knowledge of alcohols, particularly with respect to their relationship to carbonyl-containing compounds. In the course of studying alcohols, we shall also look at some relatives. **Diols** are alcohols in which two hydroxyl groups (—OH) are present; **thiols** are compounds that contain an —SH group. **Phenols,** compounds of the type ArOH, share many properties in common with alcohols but are sufficiently different from them to warrant separate discussion in Chapter 24.

This chapter is a transitional one. It ties together much of the material encountered earlier and sets the stage for our study of other oxygen-containing functional groups in the chapters that follow.

15.1 SOURCES OF ALCOHOLS

Until the 1920s, the major source of *methanol* was as a byproduct in the production of charcoal from wood—hence, the name *wood alcohol.* Now, most of the more than 10

Carbon monoxide is obtained from coal, and hydrogen is one of the products formed when natural gas is converted to ethylene and propene (Section 5.1).

billion lb of methanol used annually in the United States is synthetic, prepared by reduction of carbon monoxide with hydrogen.

$$\underset{\text{Carbon monoxide}}{CO} + \underset{\text{Hydrogen}}{2H_2} \xrightarrow[400^\circ C]{ZnO/Cr_2O_3} \underset{\text{Methanol}}{CH_3OH}$$

Almost half of this methanol is converted to formaldehyde as a starting material for various resins and plastics. Methanol is also used as a solvent, as an antifreeze, and as a convenient clean-burning liquid fuel. This last property makes it a candidate as a fuel for automobiles—methanol is already used to power Indianapolis-class race cars—but extensive emissions tests remain to be done before it can be approved as a gasoline substitute. Methanol is a colorless liquid, boiling at 65°C, and is miscible with water in all proportions. It is poisonous; drinking as little as 30 mL has been fatal. Ingestion of sublethal amounts can lead to blindness.

When vegetable matter ferments, its carbohydrates are converted to *ethanol* and carbon dioxide by enzymes present in yeast. Fermentation of barley produces beer; grapes give wine. The maximum ethanol content is on the order of 15%, because higher concentrations inactivate the enzymes, halting fermentation. Since ethanol boils at 78°C

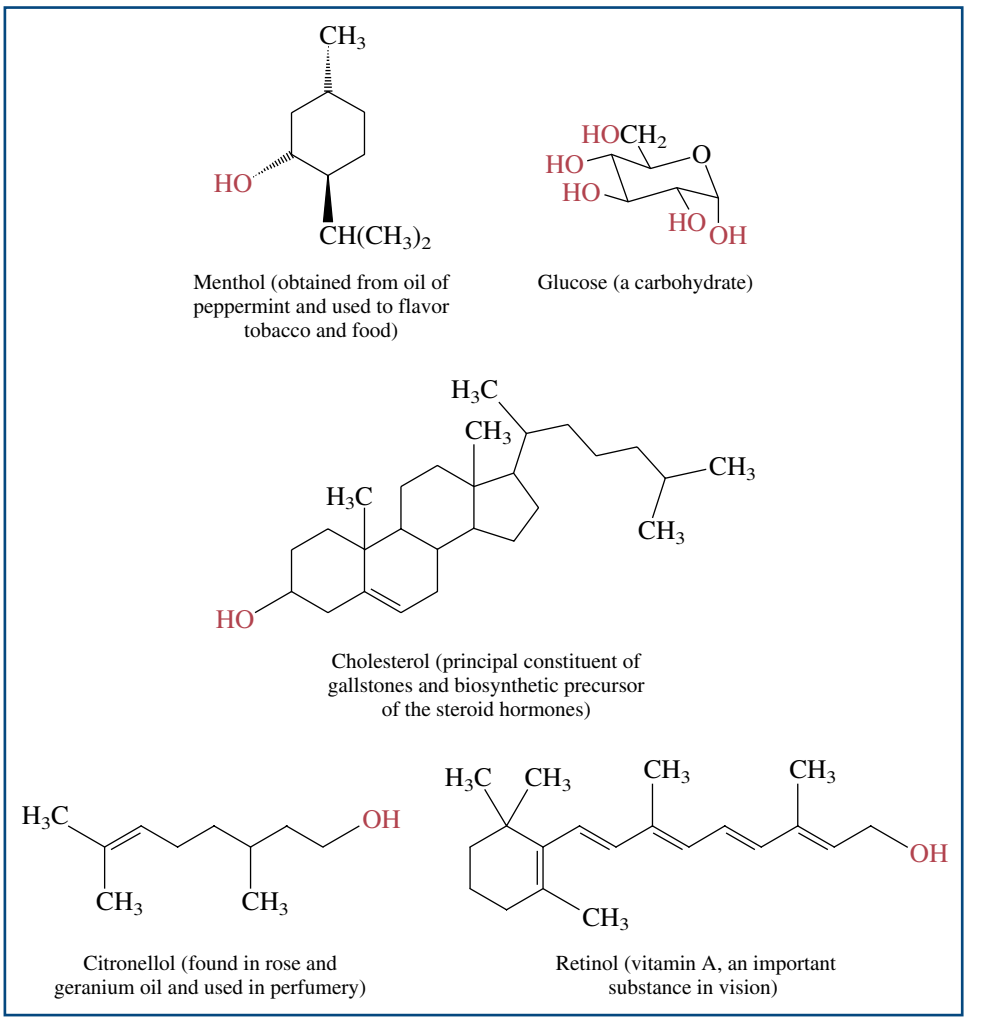


FIGURE 15.1 Some naturally occurring alcohols.

and water at 100°C, distillation of the fermentation broth can be used to give "distilled spirits" of increased ethanol content. Whiskey is the aged distillate of fermented grain and contains slightly less than 50% ethanol. Brandy and cognac are made by aging the distilled spirits from fermented grapes and other fruits. The characteristic flavors, odors, and colors of the various alcoholic beverages depend on both their origin and the way they are aged.

Synthetic ethanol is derived from petroleum by hydration of ethylene. In the United States, some 700 million lb of synthetic ethanol is produced annually. It is relatively inexpensive and useful for industrial applications. To make it unfit for drinking, it is *denatured* by adding any of a number of noxious materials, a process that exempts it from the high taxes most governments impose on ethanol used in beverages.

Some of the substances used to denature ethanol include methanol, benzene, pyridine, castor oil, and gasoline.

Our bodies are reasonably well equipped to metabolize ethanol, making it less dangerous than methanol. Alcohol abuse and alcoholism, however, have been and remain persistent problems.

Isopropyl alcohol is prepared from petroleum by hydration of propene. With a boiling point of 82°C, isopropyl alcohol evaporates quickly from the skin, producing a cooling effect. Often containing dissolved oils and fragrances, it is the major component of rubbing alcohol. Isopropyl alcohol possesses weak antibacterial properties and is used to maintain medical instruments in a sterile condition and to clean the skin before minor surgery.

Methanol, ethanol, and isopropyl alcohol are included among the readily available starting materials commonly found in laboratories where organic synthesis is carried out. So, too, are many other alcohols. All alcohols of four carbons or fewer, as well as most of the five- and six-carbon alcohols and many higher alcohols, are commercially available at low cost. Some occur naturally; others are the products of efficient syntheses. Figure 15.1 presents the structures of a few naturally occurring alcohols. Table 15.1 summarizes the reactions encountered in earlier chapters that give alcohols and illustrates a thread that runs through the fabric of organic chemistry: *a reaction that is characteristic of one functional group often serves as a synthetic method for preparing another.*

As Table 15.1 indicates, reactions leading to alcohols are not in short supply. Nevertheless, several more will be added to the list in the present chapter—testimony to the

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols

Reaction (section) and comments	General equation and specific example
Acid-catalyzed hydration of alkenes (Section 6.10) The elements of water add to the double bond in accordance with Markovnikov's rule.	$R_2C{=}CR_2 + H_2O \xrightarrow{H^+} R_2CHCR_2$ (OH) Alkene Water Alcohol $(CH_3)_2C{=}CHCH_3 \xrightarrow[H_2SO_4]{H_2O} CH_3CCH_2CH_3$ (CH₃ and OH) 2-Methyl-2-butene 2-Methyl-2-butanol (90%)

(Continued)

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols *(Continued)*

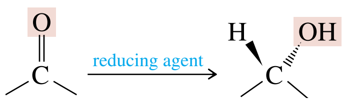
Reaction (section) and comments	General equation and specific example
Hydroboration–oxidation of alkenes (Section 6.11) The elements of water add to the double bond with regioselectivity opposite to that of Markovnikov's rule. This is a very good synthetic method; addition is syn, and no rearrangements are observed.	$R_2C{=}CR_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6} R_2CHCR_2$ (OH) Alkene — Alcohol $CH_3(CH_2)_7CH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6,\ \text{diglyme}} CH_3(CH_2)_7CH_2CH_2OH$ 1-Decene — 1-Decanol (93%)
Hydrolysis of alkyl halides (Section 8.1) A reaction useful only with substrates that do not undergo E2 elimination readily. It is rarely used for the synthesis of alcohols, since alkyl halides are normally prepared from alcohols.	$RX + HO^- \longrightarrow ROH + X^-$ Alkyl halide — Hydroxide ion — Alcohol — Halide ion 2,4,6-Trimethylbenzyl chloride $\xrightarrow[\text{heat}]{H_2O,\ Ca(OH)_2}$ 2,4,6-Trimethylbenzyl alcohol (78%)
Reaction of Grignard reagents with aldehydes and ketones (Section 14.6) A method that allows for alcohol preparation with formation of new carbon–carbon bonds. Primary, secondary, and tertiary alcohols can all be prepared.	$RMgX + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Grignard reagent — Aldehyde or ketone — Alcohol Cyclopentylmagnesium bromide + Formaldehyde $\xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ Cyclopentylmethanol (62–64%)
Reaction of organolithium reagents with aldehydes and ketones (Section 14.7) Organolithium reagents react with aldehydes and ketones in a manner similar to that of Grignard reagents to form alcohols.	$RLi + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Organolithium reagent — Aldehyde or ketone — Alcohol $CH_3CH_2CH_2CH_2Li$ + Acetophenone $\xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ 2-Phenyl-2-hexanol (67%)

(Continued)

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols *(Continued)*

Reaction (section) and comments	General equation and specific example
Reaction of Grignard reagents with esters (Section 14.10) Produces tertiary alcohols in which two of the substituents on the hydroxyl-bearing carbon are derived from the Grignard reagent.	$2RMgX + R'\overset{O}{\overset{\|}{C}}OR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RC(R')(R)OH + R''OH$ $\underset{\text{Pentylmagnesium bromide}}{2CH_3CH_2CH_2CH_2CH_2MgBr} + \underset{\text{Ethyl acetate}}{CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_3} \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ $CH_3C(OH)(CH_2CH_2CH_2CH_2CH_3)CH_2CH_2CH_2CH_2CH_3$ 6-Methyl-6-undecanol (75%)

importance of alcohols in synthetic organic chemistry. Some of these methods involve reduction of carbonyl groups:



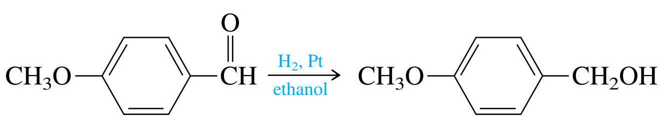
We will begin with the reduction of aldehydes and ketones.

Recall from Section 2.16 that reduction corresponds to a decrease in the number of bonds between carbon and oxygen or an increase in the number of bonds between carbon and hydrogen (or both).

15.2 PREPARATION OF ALCOHOLS BY REDUCTION OF ALDEHYDES AND KETONES

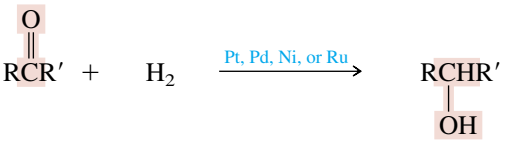
The most obvious way to reduce an aldehyde or a ketone to an alcohol is by hydrogenation of the carbon–oxygen double bond. Like the hydrogenation of alkenes, the reaction is exothermic but exceedingly slow in the absence of a catalyst. Finely divided metals such as platinum, palladium, nickel, and ruthenium are effective catalysts for the hydrogenation of aldehydes and ketones. Aldehydes yield primary alcohols:

$$\underset{\text{Aldehyde}}{R\overset{O}{\overset{\|}{C}}H} + \underset{\text{Hydrogen}}{H_2} \xrightarrow{\text{Pt, Pd, Ni, or Ru}} \underset{\text{Primary alcohol}}{RCH_2OH}$$

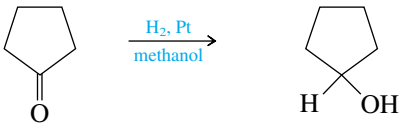


p-Methoxybenzaldehyde *p*-Methoxybenzyl alcohol (92%)

Ketones yield secondary alcohols:



Ketone Hydrogen Secondary alcohol



Cyclopentanone Cyclopentanol (93–95%)

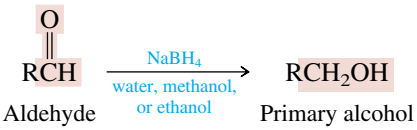
PROBLEM 15.1 Which of the isomeric $C_4H_{10}O$ alcohols can be prepared by hydrogenation of aldehydes? Which can be prepared by hydrogenation of ketones? Which cannot be prepared by hydrogenation of a carbonyl compound?

For most laboratory-scale reductions of aldehydes and ketones, catalytic hydrogenation has been replaced by methods based on metal hydride reducing agents. The two most common reagents are sodium borohydride and lithium aluminum hydride.

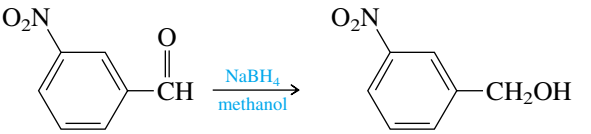
Compare the electrostatic potential maps of CH_4, BH_4^-, and AlH_4^- on *Learning By Modeling*. Notice how different the electrostatic potentials associated with hydrogen are.

Sodium borohydride ($NaBH_4$) Lithium aluminum hydride ($LiAlH_4$)

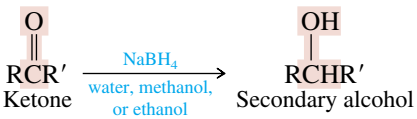
Sodium borohydride is especially easy to use, needing only to be added to an aqueous or alcoholic solution of an aldehyde or a ketone:

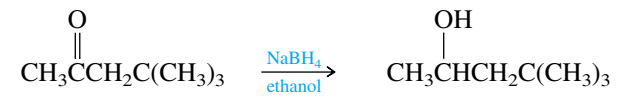


Aldehyde Primary alcohol



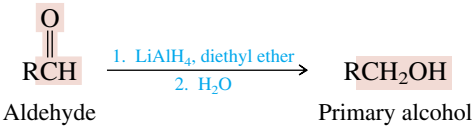
m-Nitrobenzaldehyde *m*-Nitrobenzyl alcohol (82%)



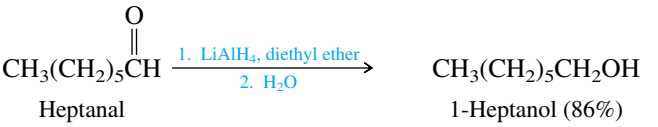


4,4-Dimethyl-2-pentanone 4,4-Dimethyl-2-pentanol (85%)

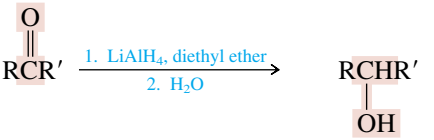
Lithium aluminum hydride reacts violently with water and alcohols, so it must be used in solvents such as anhydrous diethyl ether or tetrahydrofuran. Following reduction, a separate hydrolysis step is required to liberate the alcohol product:



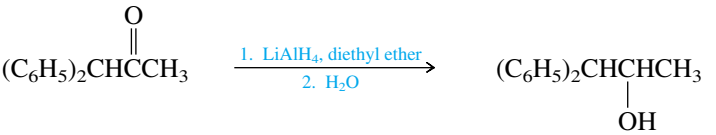
Aldehyde — Primary alcohol



Heptanal — 1-Heptanol (86%)

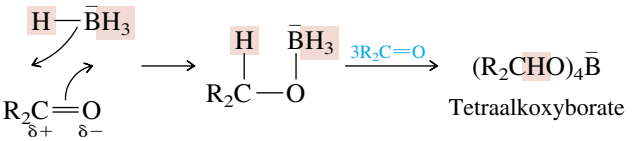


Ketone — Secondary alcohol



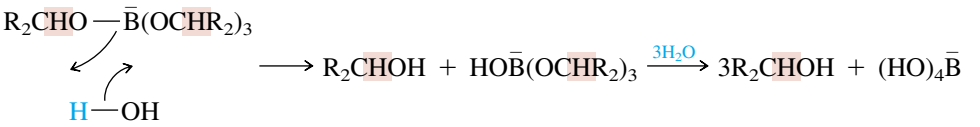
1,1-Diphenyl-2-propanone — 1,1-Diphenyl-2-propanol (84%)

Sodium borohydride and lithium aluminum hydride react with carbonyl compounds in much the same way that Grignard reagents do, except that they function as *hydride donors* rather than as carbanion sources. Borohydride transfers a hydrogen with its pair of bonding electrons to the positively polarized carbon of a carbonyl group. The negatively polarized oxygen attacks boron. Ultimately, all four of the hydrogens of borohydride are transferred and a tetraalkoxyborate is formed.

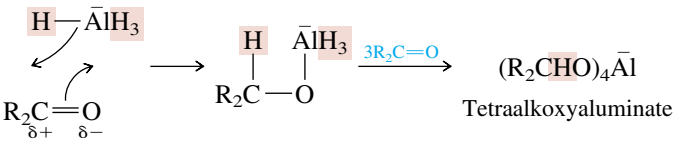


Tetraalkoxyborate

Hydrolysis or alcoholysis converts the tetraalkoxyborate intermediate to the corresponding alcohol. The following equation illustrates the process for reactions carried out in water. An analogous process occurs in methanol or ethanol and yields the alcohol and $(CH_3O)_4B^-$ or $(CH_3CH_2O)_4B^-$.



A similar series of hydride transfers occurs when aldehydes and ketones are treated with lithium aluminum hydride.



Addition of water converts the tetraalkoxyaluminate to the desired alcohol.

$$\underset{\text{Tetraalkoxyaluminate}}{(R_2CHO)_4\bar{A}l} + 4H_2O \longrightarrow \underset{\text{Alcohol}}{4R_2CHOH} + \bar{A}l(OH)_4$$

An undergraduate laboratory experiment related to Problem 15.2 appears in the March 1996 issue of the *Journal of Chemical Education*, pp. 264–266.

PROBLEM 15.2 Sodium borodeuteride ($NaBD_4$) and lithium aluminum deuteride ($LiAlD_4$) are convenient reagents for introducing deuterium, the mass 2 isotope of hydrogen, into organic compounds. Write the structure of the organic product of the following reactions, clearly showing the position of all the deuterium atoms in each:

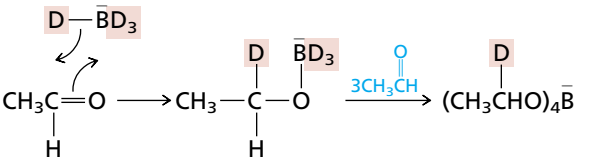
(a) Reduction of CH_3CH (acetaldehyde) with $NaBD_4$ in H_2O

(b) Reduction of CH_3CCH_3 (acetone) with $NaBD_4$ in CH_3OD

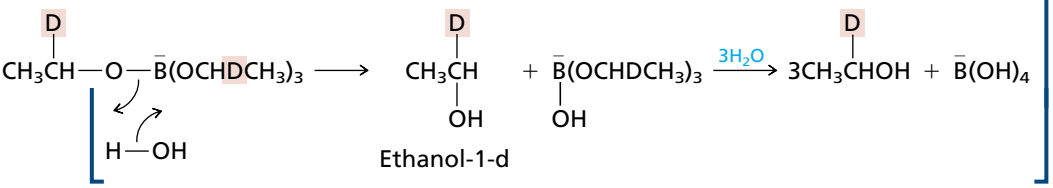
(c) Reduction of C_6H_5CH (benzaldehyde) with $NaBD_4$ in CD_3OH

(d) Reduction of HCH (formaldehyde) with $LiAlD_4$ in diethyl ether, followed by addition of D_2O

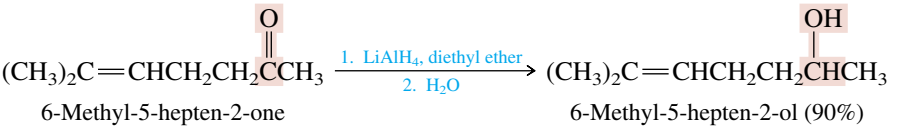
SAMPLE SOLUTION (a) Sodium borodeuteride transfers deuterium to the carbonyl group of acetaldehyde, forming a C—D bond.



Hydrolysis of $(CH_3CHDO)_4\bar{B}$ in H_2O leads to the formation of ethanol, retaining the C—D bond formed in the preceding step while forming an O—H bond.



Neither sodium borohydride nor lithium aluminum hydride reduces isolated carbon–carbon double bonds. This makes possible the selective reduction of a carbonyl group in a molecule that contains both carbon–carbon and carbon–oxygen double bonds.

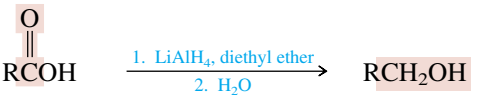


6-Methyl-5-hepten-2-one — 6-Methyl-5-hepten-2-ol (90%)

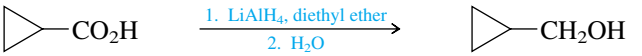
Catalytic hydrogenation would not be suitable for this transformation, because H_2 adds to carbon–carbon double bonds faster than it reduces carbonyl groups.

15.3 PREPARATION OF ALCOHOLS BY REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids are exceedingly difficult to reduce. Acetic acid, for example, is often used as a solvent in catalytic hydrogenations because it is inert under the reaction conditions. A very powerful reducing agent is required to convert a carboxylic acid to a primary alcohol. Lithium aluminum hydride is that reducing agent.



Carboxylic acid — Primary alcohol



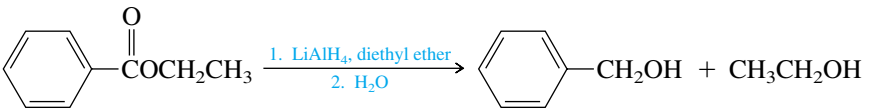
Cyclopropanecarboxylic acid — Cyclopropylmethanol (78%)

Sodium borohydride is not nearly as potent a hydride donor as lithium aluminum hydride and does not reduce carboxylic acids.

Esters are more easily reduced than carboxylic acids. Two alcohols are formed from each ester molecule. The acyl group of the ester is cleaved, giving a primary alcohol.

Ester — Primary alcohol — Alcohol

Lithium aluminum hydride is the reagent of choice for reducing esters to alcohols.



Ethyl benzoate — Benzyl alcohol (90%) — Ethanol

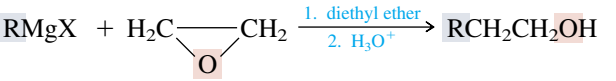
PROBLEM 15.3 Give the structure of an ester that will yield a mixture containing equimolar amounts of 1-propanol and 2-propanol on reduction with lithium aluminum hydride.

Sodium borohydride reduces esters, but the reaction is too slow to be useful. Hydrogenation of esters requires a special catalyst and extremely high pressures and temperatures; it is used in industrial settings but rarely in the laboratory.

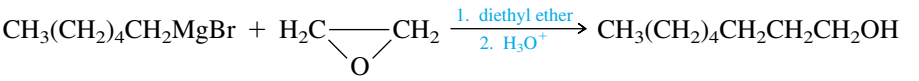
15.4 PREPARATION OF ALCOHOLS FROM EPOXIDES

Although the chemical reactions of epoxides will not be covered in detail until the following chapter, we shall introduce their use in the synthesis of alcohols here.

Grignard reagents react with ethylene oxide to yield primary alcohols containing two more carbon atoms than the alkyl halide from which the organometallic compound was prepared.



Grignard reagent | Ethylene oxide | Primary alcohol

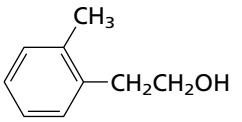


Hexylmagnesium bromide | Ethylene oxide | 1-Octanol (71%)

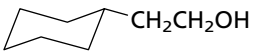
Organolithium reagents react with epoxides in a similar manner.

PROBLEM 15.4 Each of the following alcohols has been prepared by reaction of a Grignard reagent with ethylene oxide. Select the appropriate Grignard reagent in each case.

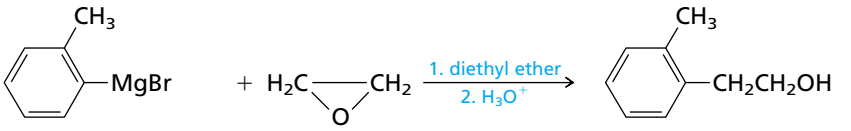
(a)



(b)

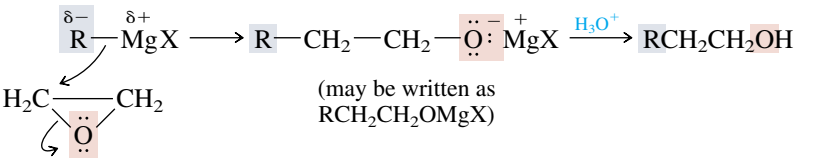


SAMPLE SOLUTION (a) Reaction with ethylene oxide results in the addition of a $-CH_2CH_2OH$ unit to the Grignard reagent. The Grignard reagent derived from *o*-bromotoluene (or *o*-chlorotoluene or *o*-iodotoluene) is appropriate here.



o-Methylphenylmagnesium bromide | Ethylene oxide | 2-(*o*-Methylphenyl)ethanol (66%)

Epoxide rings are readily opened with cleavage of the carbon–oxygen bond when attacked by nucleophiles. Grignard reagents and organolithium reagents react with ethylene oxide by serving as sources of nucleophilic carbon.

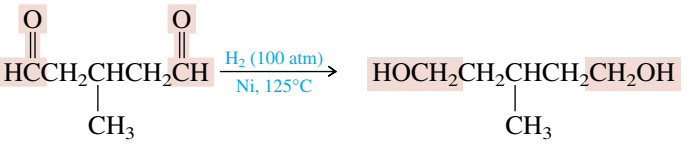


(may be written as RCH_2CH_2OMgX)

This kind of chemical reactivity of epoxides is rather general. Nucleophiles other than Grignard reagents react with epoxides, and epoxides more elaborate than ethylene oxide may be used. All these features of epoxide chemistry will be discussed in Sections 16.11 and 16.12.

15.5 PREPARATION OF DIOLS

Much of the chemistry of diols—compounds that bear two hydroxyl groups—is analogous to that of alcohols. Diols may be prepared, for example, from compounds that contain two carbonyl groups, using the same reducing agents employed in the preparation of alcohols. The following example shows the conversion of a dialdehyde to a diol by catalytic hydrogenation. Alternatively, the same transformation can be achieved by reduction with sodium borohydride or lithium aluminum hydride.

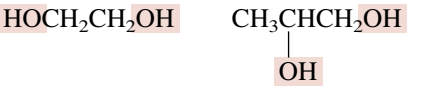


3-Methylpentanedial — 3-Methyl-1,5-pentanediol (81–83%)

Diols are almost always given substitutive IUPAC names. As the name of the product in the example indicates, the substitutive nomenclature of diols is similar to that of alcohols. The suffix *-diol* replaces *-ol,* and two locants, one for each hydroxyl group, are required. Note that the final *-e* of the alkane basis name is retained when the suffix begins with a consonant *(-diol),* but dropped when the suffix begins with a vowel *(-ol).*

PROBLEM 15.5 Write equations showing how 3-methyl-1,5-pentanediol could be prepared from a dicarboxylic acid or a diester.

Vicinal diols are diols that have their hydroxyl groups on adjacent carbons. Two commonly encountered vicinal diols are 1,2-ethanediol and 1,2-propanediol.

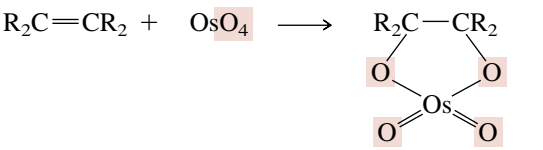


1,2-Ethanediol (ethylene glycol) — 1,2-Propanediol (propylene glycol)

Ethylene glycol and propylene glycol are prepared industrially from the corresponding alkenes by way of their epoxides. Some applications were given in the box in Section 6.21.

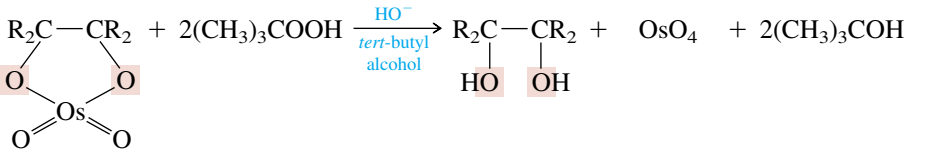
Ethylene glycol and *propylene glycol* are common names for these two diols and are acceptable IUPAC names. Aside from these two compounds, the IUPAC system does not use the word "glycol" for naming diols.

In the laboratory, vicinal diols are normally prepared from alkenes using the reagent *osmium tetraoxide* (OsO_4). Osmium tetraoxide reacts rapidly with alkenes to give cyclic osmate esters.



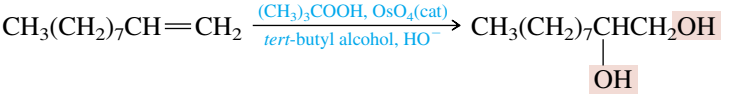
Alkene — Osmium tetraoxide — Cyclic osmate ester

Osmate esters are fairly stable but are readily cleaved in the presence of an oxidizing agent such as *tert*-butyl hydroperoxide.



tert-Butyl hydroperoxide | Vicinal diol | Osmium tetraoxide | *tert*-Butyl alcohol

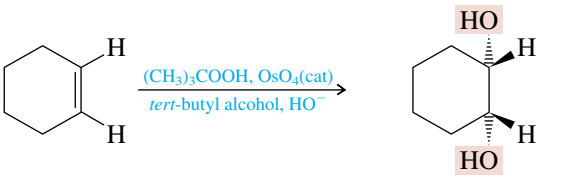
Since osmium tetraoxide is regenerated in this step, alkenes can be converted to vicinal diols using only catalytic amounts of osmium tetraoxide, which is both toxic and expensive. The entire process is performed in a single operation by simply allowing a solution of the alkene and *tert*-butyl hydroperoxide in *tert*-butyl alcohol containing a small amount of osmium tetraoxide and base to stand for several hours.



1-Decene | 1,2-Decanediol (73%)

Overall, the reaction leads to addition of two hydroxyl groups to the double bond and is referred to as **hydroxylation.** Both oxygens of the diol come from osmium tetraoxide via the cyclic osmate ester. The reaction of OsO_4 with the alkene is a syn addition, and the conversion of the cyclic osmate to the diol involves cleavage of the bonds between oxygen and osmium. Thus, both hydroxyl groups of the diol become attached to the same face of the double bond; *syn hydroxylation of the alkene is observed.*

Construct a molecular model of *cis*-1,2-cyclohexanediol. What is the orientation of the OH groups, axial or equatorial?



Cyclohexene | *cis*-1,2-Cyclohexanediol (62%)

PROBLEM 15.6 Give the structures, including stereochemistry, for the diols obtained by hydroxylation of *cis*-2-butene and *trans*-2-butene.

A complementary method, one that gives anti hydroxylation of alkenes by way of the hydrolysis of epoxides, will be described in Section 16.13.

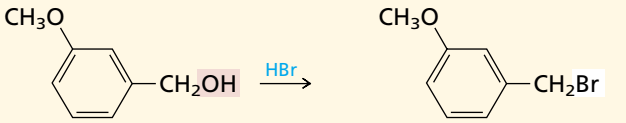
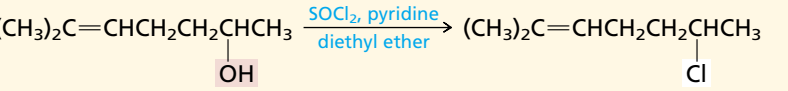
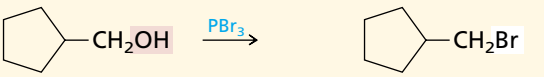
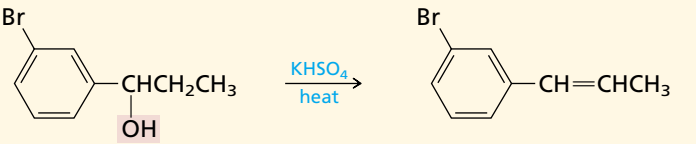
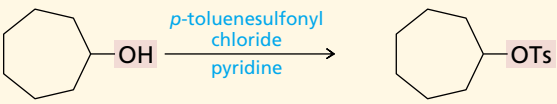
15.6 REACTIONS OF ALCOHOLS: A REVIEW AND A PREVIEW

Alcohols are versatile starting materials for the preparation of a variety of organic functional groups. Several reactions of alcohols have already been seen in earlier chapters and are summarized in Table 15.2. The remaining sections of this chapter add to the list.

15.7 CONVERSION OF ALCOHOLS TO ETHERS

Primary alcohols are converted to ethers on heating in the presence of an acid catalyst, usually sulfuric acid.

TABLE 15.2 Summary of Reactions of Alcohols Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Reaction with hydrogen halides (Section 4.8) The order of alcohol reactivity parallels the order of carbocation stability: $R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3^+$. Benzylic alcohols react readily.	$ROH + HX \longrightarrow RX + H_2O$ Alcohol — Hydrogen halide — Alkyl halide — Water  *m*-Methoxybenzyl alcohol — *m*-Methoxybenzyl bromide (98%)
Reaction with thionyl chloride (Section 4.14) Thionyl chloride converts alcohols to alkyl chlorides.	$ROH + SOCl_2 \longrightarrow RCl + SO_2 + HCl$ Alcohol — Thionyl chloride — Alkyl chloride — Sulfur dioxide — Hydrogen chloride  6-Methyl-5-hepten-2-ol — 6-Chloro-2-methyl-2-heptene (67%)
Reaction with phosphorus trihalides (Section 4.14) Phosphorus trichloride and phosphorus tribromide convert alcohols to alkyl halides.	$3ROH + PX_3 \longrightarrow 3RX + H_3PO_3$ Alcohol — Phosphorus trihalide — Alkyl halide — Phosphorous acid  Cyclopentylmethanol — (Bromomethyl)cyclopentane (50%)
Acid-catalyzed dehydration (Section 5.9) This is a frequently used procedure for the preparation of alkenes. The order of alcohol reactivity parallels the order of carbocation stability: $R_3C^+ > R_2CH^+ > RCH_2^+$. Benzylic alcohols react readily. Rearrangements are sometimes observed.	$R_2CCHR_2 \xrightarrow[\text{heat}]{H^+} R_2C{=}CR_2 + H_2O$ OH Alcohol — Alkene — Water  1-(*m*-Bromophenyl)-1-propanol — 1-(*m*-Bromophenyl)propene (71%)
Conversion to *p*-toluenesulfonate esters (Section 8.14) Alcohols react with *p*-toluenesulfonyl chloride to give *p*-toluenesulfonate esters. Sulfonate esters are reactive substrates for nucleophilic substitution and elimination reactions. The *p*-toluenesulfonate group is often abbreviated —OTs.	$ROH + H_3C\text{-}C_6H_4\text{-}SO_2Cl \longrightarrow ROS(=O)_2\text{-}C_6H_4\text{-}CH_3 + HCl$ Alcohol — *p*-Toluenesulfonyl chloride — Alkyl *p*-toluenesulfonate — Hydrogen chloride  Cycloheptanol — Cycloheptyl *p*-toluenesulfonate (83%)

$$2RCH_2OH \xrightarrow{H^+,\ heat} RCH_2OCH_2R + H_2O$$

Primary alcohol — Dialkyl ether — Water

This kind of reaction is called a **condensation.** A condensation is a reaction in which two molecules combine to form a larger one while liberating a small molecule. In this case two alcohol molecules combine to give an ether and water.

$$2CH_3CH_2CH_2CH_2OH \xrightarrow[130°C]{H_2SO_4} CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3 + H_2O$$

1-Butanol — Dibutyl ether (60%) — Water

When applied to the synthesis of ethers, the reaction is effective only with primary alcohols. Elimination to form alkenes predominates with secondary and tertiary alcohols.

Diethyl ether is prepared on an industrial scale by heating ethanol with sulfuric acid at 140°C. At higher temperatures elimination predominates, and ethylene is the major product. A mechanism for the formation of diethyl ether is outlined in Figure 15.2.

Overall Reaction:

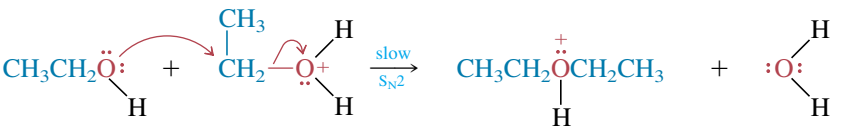
$$2CH_3CH_2OH \xrightarrow[140°C]{H_2SO_4} CH_3CH_2OCH_2CH_3 + H_2O$$

Ethanol — Diethyl ether — Water

Step 1: Proton transfer from the acid catalyst to the oxygen of the alcohol to produce an alkyloxonium ion

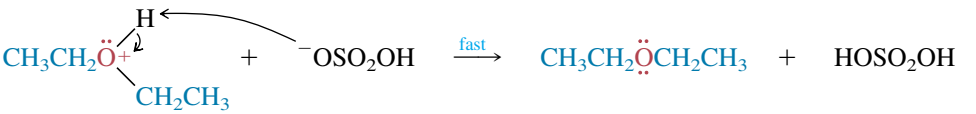
Ethyl alcohol — Sulfuric acid — Ethyloxonium ion — Hydrogen sulfate ion

Step 2: Nucleophilic attack by a molecule of alcohol on the alkyloxonium ion formed in step 1



Ethyl alcohol — Ethyloxonium ion — Diethyloxonium ion — Water

Step 3: The product of step 2 is the conjugate acid of the dialkyl ether. It is deprotonated in the final step of the process to give the ether.

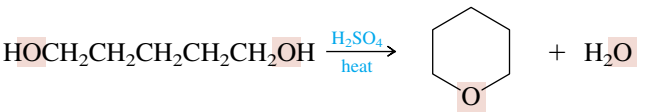


Diethyloxonium ion — Hydrogen sulfate ion — Diethyl ether — Sulfuric acid

FIGURE 15.2 The mechanism of acid-catalyzed formation of diethyl ether from ethyl alcohol. As an alternative in the third step, the Brønsted base that abstracts the proton could be a molecule of the starting alcohol.

The individual steps of this mechanism are analogous to those seen earlier. Nucleophilic attack on a protonated alcohol was encountered in the reaction of primary alcohols with hydrogen halides (Section 4.13), and the nucleophilic properties of alcohols were discussed in the context of solvolysis reactions (Section 8.7). Both the first and the last steps are proton-transfer reactions between oxygens.

Diols react intramolecularly to form cyclic ethers when a five-membered or six-membered ring can result.



1,5-Pentanediol — Oxane (76%) — Water

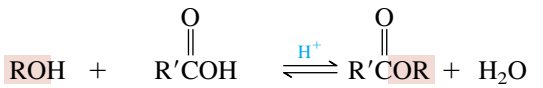
Oxane is also called tetrahydropyran.

In these intramolecular ether-forming reactions, the alcohol may be primary, secondary, or tertiary.

PROBLEM 15.7 On the basis of the mechanism for the acid-catalyzed formation of diethyl ether from ethanol in Figure 15.2, write a stepwise mechanism for the formation of oxane from 1,5-pentanediol (see the equation in the preceding paragraph).

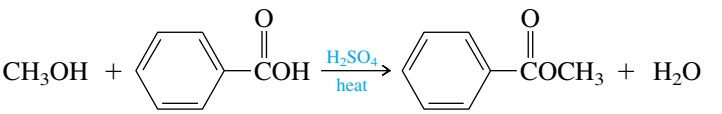
15.8 ESTERIFICATION

Acid-catalyzed condensation of an alcohol and a carboxylic acid yields an ester and water and is known as the **Fischer esterification.**



Alcohol — Carboxylic acid — Ester — Water

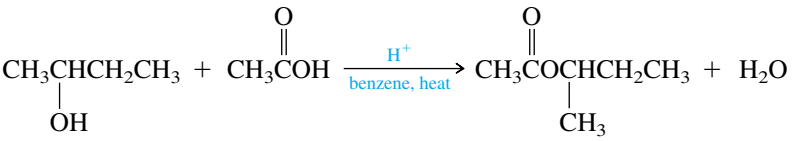
Fischer esterification is reversible, and the position of equilibrium lies slightly to the side of products when the reactants are simple alcohols and carboxylic acids. When the Fischer esterification is used for preparative purposes, the position of equilibrium can be made more favorable by using either the alcohol or the carboxylic acid in excess. In the following example, in which an excess of the alcohol was employed, the yield indicated is based on the carboxylic acid as the limiting reactant.



Methanol (0.6 mol) — Benzoic acid (0.1 mol) — Methyl benzoate (isolated in 70% yield based on benzoic acid) — Water

An *azeotropic mixture* contains two or more substances that distill together at a constant boiling point. The benzene–water azeotrope contains 9% water and boils at 69°C.

Another way to shift the position of equilibrium to favor the formation of ester is by removing water from the reaction mixture. This can be accomplished by adding benzene as a cosolvent and distilling the azeotropic mixture of benzene and water.



sec-Butyl alcohol (0.20 mol) | Acetic acid (0.25 mol) | *sec*-Butyl acetate (isolated in 71% yield based on *sec*-butyl alcohol) | Water (codistills with benzene)

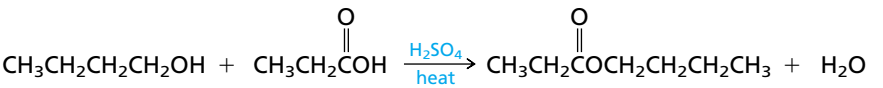
For steric reasons, the order of alcohol reactivity in the Fischer esterification is CH_3OH > primary > secondary > tertiary.

PROBLEM 15.8 Write the structure of the ester formed in each of the following reactions:

(a) $CH_3CH_2CH_2CH_2OH + CH_3CH_2COH \xrightarrow[\text{heat}]{H_2SO_4}$

(b) $2CH_3OH + HOC(=O)C_6H_4C(=O)OH \xrightarrow[\text{heat}]{H_2SO_4} (C_{10}H_{10}O_4)$

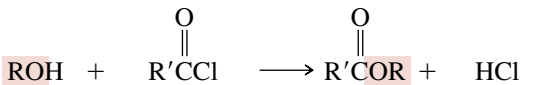
SAMPLE SOLUTION (a) By analogy to the general equation and to the examples cited in this section, we can write the equation



1-Butanol | Propanoic acid | Butyl propanoate | Water

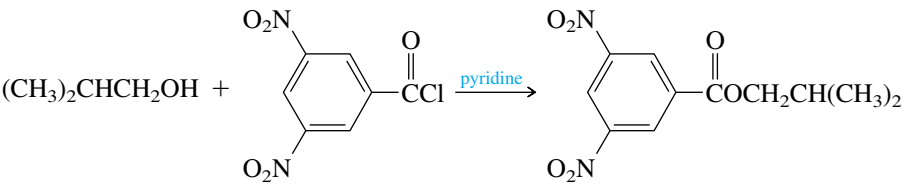
As actually carried out in the laboratory, 3 mol of propanoic acid was used per mole of 1-butanol, and the desired ester was obtained in 78% yield.

Esters are also formed by the reaction of alcohols with acyl chlorides:



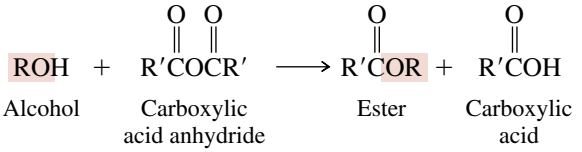
Alcohol | Acyl chloride | Ester | Hydrogen chloride

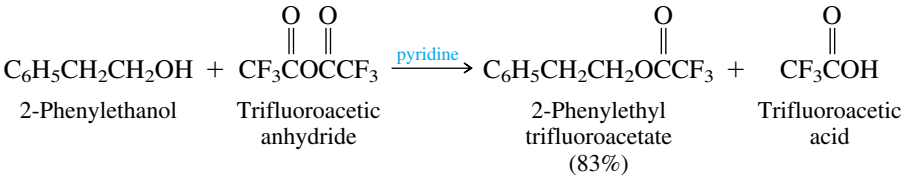
This reaction is normally carried out in the presence of a weak base such as pyridine, which reacts with the hydrogen chloride that is formed.



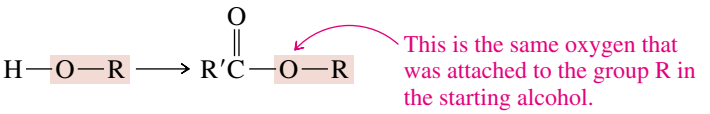
Isobutyl alcohol | 3,5-Dinitrobenzoyl chloride | Isobutyl 3,5-dinitrobenzoate (86%)

Carboxylic acid anhydrides react similarly to acyl chlorides.

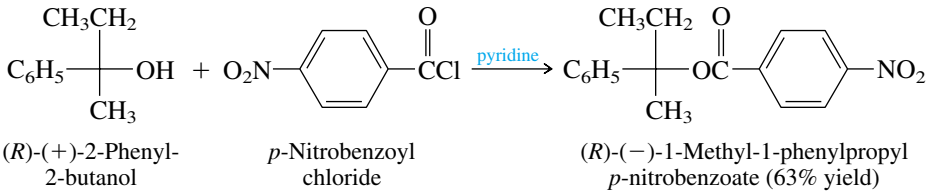




The mechanisms of the Fischer esterification and the reactions of alcohols with acyl chlorides and acid anhydrides will be discussed in detail in Chapters 19 and 20 after some fundamental principles of carbonyl group reactivity have been developed. For the present, it is sufficient to point out that most of the reactions that convert alcohols to esters leave the C—O bond of the alcohol intact.



The acyl group of the carboxylic acid, acyl chloride, or acid anhydride is transferred to the oxygen of the alcohol. This fact is most clearly evident in the esterification of chiral alcohols, where, since none of the bonds to the stereogenic center is broken in the process, *retention of configuration is observed.*



Make a molecular model corresponding to the stereochemistry of the Fischer projection of 2-phenyl-2-butanol shown in the equation and verify that it has the *R* configuration.

PROBLEM 15.9 A similar conclusion may be drawn by considering the reactions of the cis and trans isomers of 4-*tert*-butylcyclohexanol with acetic anhydride. On the basis of the information just presented, predict the product formed from each stereoisomer.

The reaction of alcohols with acyl chlorides is analogous to their reaction with *p*-toluenesulfonyl chloride described earlier (Section 8.14 and Table 15.2). In those reactions, a *p*-toluenesulfonate ester was formed by displacement of chloride from the sulfonyl group by the oxygen of the alcohol. Carboxylic esters arise by displacement of chloride from a carbonyl group by the alcohol oxygen.

15.9 ESTERS OF INORGANIC ACIDS

Although the term "ester," used without a modifier, is normally taken to mean an ester of a carboxylic acid, alcohols can react with inorganic acids in a process similar to the

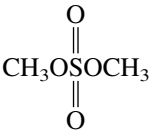
Fischer esterification. The products are esters of inorganic acids. For example, *alkyl nitrates* are esters formed by the reaction of alcohols with *nitric acid.*

$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Nitric acid}}{HONO_2} \xrightarrow{H^+} \underset{\text{Alkyl nitrate}}{RONO_2} + \underset{\text{Water}}{H_2O}$$

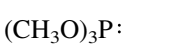
$$\underset{\text{Methanol}}{CH_3OH} + \underset{\text{Nitric acid}}{HONO_2} \xrightarrow{H_2SO_4} \underset{\text{Methyl nitrate (66–80\%)}}{CH_3ONO_2} + \underset{\text{Water}}{H_2O}$$

PROBLEM 15.10 Alfred Nobel's fortune was based on his 1866 discovery that nitroglycerin, which is far too shock-sensitive to be transported or used safely, can be stabilized by adsorption onto a substance called *kieselguhr* to give what is familiar to us as *dynamite.* Nitroglycerin is the trinitrate of glycerol (1,2,3-propanetriol). Write a structural formula or construct a molecular model of nitroglycerin.

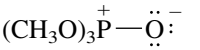
Dialkyl sulfates are esters of *sulfuric acid,* **trialkyl phosphites** are esters of *phosphorous acid* (H_3PO_3), and **trialkyl phosphates** are esters of *phosphoric acid* (H_3PO_4).



Dimethyl sulfate



Trimethyl phosphite



Trimethyl phosphate

Some esters of inorganic acids, such as dimethyl sulfate, are used as reagents in synthetic organic chemistry. Certain naturally occurring alkyl phosphates play an important role in biological processes.

15.10 OXIDATION OF ALCOHOLS

Oxidation of an alcohol yields a carbonyl compound. Whether the resulting carbonyl compound is an aldehyde, a ketone, or a carboxylic acid depends on the alcohol and on the oxidizing agent.

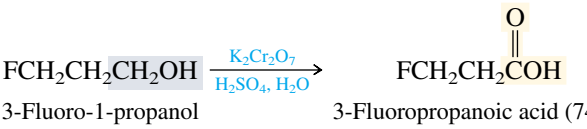
Primary alcohols may be oxidized either to an aldehyde or to a carboxylic acid:

$$\underset{\text{Primary alcohol}}{RCH_2OH} \xrightarrow{\text{oxidize}} \underset{\text{Aldehyde}}{RCH{=}O} \xrightarrow{\text{oxidize}} \underset{\text{Carboxylic acid}}{RCOH{=}O}$$

Vigorous oxidation leads to the formation of a carboxylic acid, but there are a number of methods that permit us to stop the oxidation at the intermediate aldehyde stage. The reagents that are most commonly used for oxidizing alcohols are based on high-oxidation-state transition metals, particularly chromium(VI).

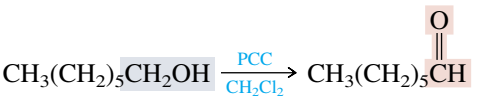
Chromic acid (H_2CrO_4) is a good oxidizing agent and is formed when solutions containing chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) are acidified. Sometimes it is possible to obtain aldehydes in satisfactory yield before they are further oxidized, but in most cases carboxylic acids are the major products isolated on treatment of primary alcohols with chromic acid.

Potassium permanganate ($KMnO_4$) will also oxidize primary alcohols to carboxylic acids. What is the oxidation state of manganese in $KMnO_4$?

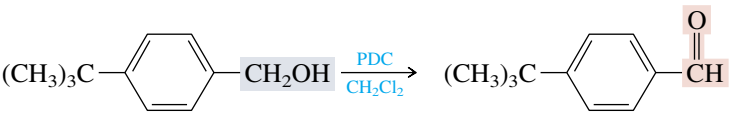


3-Fluoro-1-propanol 3-Fluoropropanoic acid (74%)

Conditions that do permit the easy isolation of aldehydes in good yield by oxidation of primary alcohols employ various Cr(VI) species as the oxidant in *anhydrous* media. Two such reagents are **pyridinium chlorochromate (PCC),** $C_5H_5NH^+\ ClCrO_3^-$, and **pyridinium dichromate (PDC),** $(C_5H_5NH)_2^{2+}\ Cr_2O_7^{2-}$; both are used in dichloromethane.



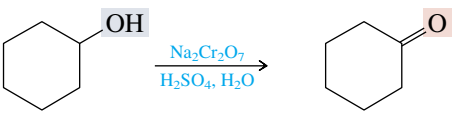
1-Heptanol Heptanal (78%)



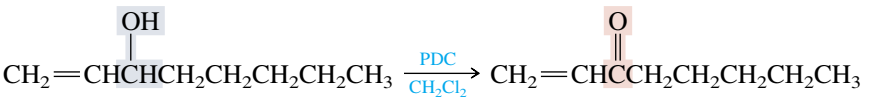
p-tert-Butylbenzyl alcohol *p-tert*-Butylbenzaldehyde (94%)

Secondary alcohols are oxidized to ketones by the same reagents that oxidize primary alcohols:

Secondary alcohol Ketone

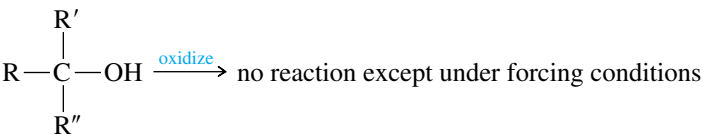


Cyclohexanol Cyclohexanone (85%)



1-Octen-3-ol 1-Octen-3-one (80%)

Tertiary alcohols have no hydrogen on their hydroxyl-bearing carbon and do not undergo oxidation readily:

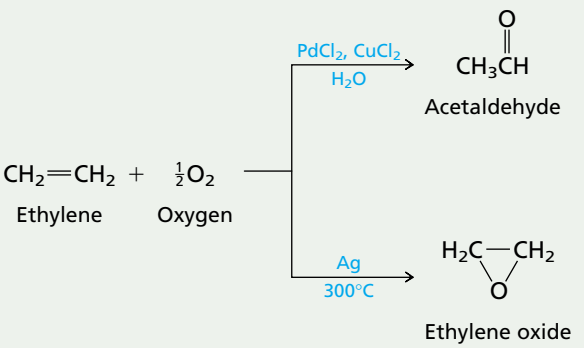


In the presence of strong oxidizing agents at elevated temperatures, oxidation of tertiary alcohols leads to cleavage of the various carbon–carbon bonds at the hydroxyl-bearing carbon atom, and a complex mixture of products results.

ECONOMIC AND ENVIRONMENTAL FACTORS IN ORGANIC SYNTHESIS

Beyond the obvious difference in scale that is evident when one compares preparing tons of a compound versus preparing just a few grams of it, there are sharp distinctions between "industrial" and "laboratory" syntheses. On a laboratory scale, a chemist is normally concerned only with obtaining a modest amount of a substance. Sometimes making the compound is an end in itself, but on other occasions the compound is needed for some further study of its physical, chemical, or biological properties. Considerations such as the cost of reagents and solvents tend to play only a minor role when planning most laboratory syntheses. Faced with a choice between two synthetic routes to a particular compound, one based on the cost of chemicals and the other on the efficient use of a chemist's time, the decision is almost always made in favor of the latter.

Not so for synthesis in the chemical industry, where not only must a compound be prepared on a large scale, but it must be prepared at low cost. There is a pronounced bias toward reactants and reagents that are both abundant and inexpensive. The oxidizing agent of choice, for example, in the chemical industry is O_2, and extensive research has been devoted to developing catalysts for preparing various compounds by air oxidation of readily available starting materials. To illustrate, air and ethylene are the reactants for the industrial preparation of both acetaldehyde and ethylene oxide. Which of the two products is obtained depends on the catalyst employed.



Dating approximately from the creation of the U.S. Environmental Protection Agency (EPA) in 1970, dealing with the byproducts of synthetic procedures has become an increasingly important consideration in designing a chemical synthesis. In terms of changing the strategy of synthetic planning, the chemical industry actually had a shorter road to travel than the pharmaceutical industry, academic laboratories, and research institutes. Simple business principles had long dictated that waste chemicals represented wasted opportunities. It made better sense for a chemical company to recover the solvent from a reaction and use it again than to throw it away and buy more. Similarly, it was far better to find a "value-added" use for a byproduct from a reaction than to throw it away. By raising the cost of generating chemical waste, environmental regulations increased the economic incentive to design processes that produced less of it.

The term "environmentally benign" synthesis has been coined to refer to procedures explicitly designed to minimize the formation of byproducts that present disposal problems. Both the National Science Foundation and the Environmental Protection Agency have allocated a portion of their grant budgets to encourage efforts in this vein.

The application of environmentally benign principles to laboratory-scale synthesis can be illustrated by revisiting the oxidation of alcohols. As noted in Section 15.10, the most widely used methods involve Cr(VI)-based oxidizing agents. Cr(VI) compounds are carcinogenic, however, and appear on the EPA list of compounds requiring special disposal methods. The best way to replace Cr(VI)-based oxidants would be to develop catalytic methods analogous to those used in industry. Another approach would be to use oxidizing agents that are less hazardous, such as sodium hypochlorite. Aqueous solutions of sodium hypochlorite are available as "swimming-pool chlorine," and procedures for their use in oxidizing secondary alcohols to ketones have been developed. One is described on page 71 of the January 1991 edition of the *Journal of Chemical Education.*

—Cont.

$$(CH_3)_2CHCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2CH_3 \xrightarrow[\text{acetic acid–water}]{NaOCl} (CH_3)_2CHCH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_3$$

2-Methyl-4-heptanol — 2-Methyl-4-heptanone (77%)

There is a curious irony in the nomination of hypochlorite as an environmentally benign oxidizing agent. It comes at a time of increasing pressure to eliminate chlorine and chlorine-containing compounds from the environment to as great a degree as possible. Any all-inclusive assault on chlorine needs to be carefully scrutinized, especially when one remembers that chlorination of the water supply has probably done more to extend human life than any other public health measure ever undertaken. (The role of chlorine in the formation of chlorinated hydrocarbons in water is discussed in Section 18.7.)

PROBLEM 15.11 Predict the principal organic product of each of the following reactions:

(a) $ClCH_2CH_2CH_2CH_2OH \xrightarrow[H_2SO_4,\ H_2O]{K_2Cr_2O_7}$

(b) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2CH_2CH_2CH_2CH_3 \xrightarrow[H_2SO_4,\ H_2O]{Na_2Cr_2O_7}$

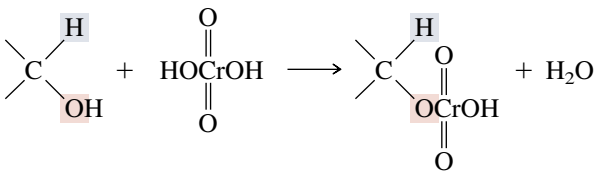
(c) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH \xrightarrow[CH_2Cl_2]{PCC}$

SAMPLE SOLUTION (a) The reactant is a primary alcohol and so can be oxidized either to an aldehyde or to a carboxylic acid. Aldehydes are the major products only when the oxidation is carried out in anhydrous media. Carboxylic acids are formed when water is present. The reaction shown produced 4-chlorobutanoic acid in 56% yield.

$$ClCH_2CH_2CH_2CH_2OH \xrightarrow[H_2SO_4,\ H_2O]{K_2Cr_2O_7} ClCH_2CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}OH$$

4-Chloro-1-butanol — 4-Chlorobutanoic acid

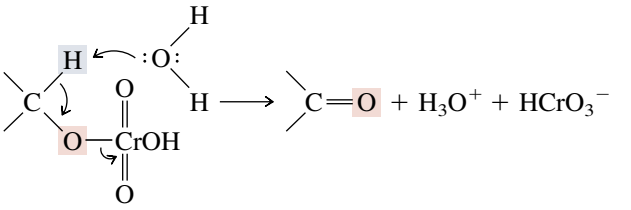
The mechanisms by which transition-metal oxidizing agents convert alcohols to aldehydes and ketones are rather complicated and will not be dealt with in detail here. In broad outline, chromic acid oxidation involves initial formation of an alkyl chromate:



Alcohol — Chromic acid — Alkyl chromate

An alkyl chromate is an example of an ester of an inorganic acid (Section 15.9).

This alkyl chromate then undergoes an elimination reaction to form the carbon–oxygen double bond.

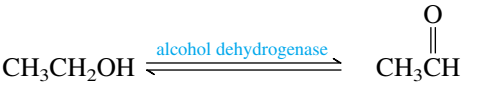


Alkyl chromate Aldehyde or ketone

In the elimination step, chromium is reduced from Cr(VI) to Cr(IV). Since the eventual product is Cr(III), further electron-transfer steps are also involved.

15.11 BIOLOGICAL OXIDATION OF ALCOHOLS

Many biological processes involve oxidation of alcohols to carbonyl compounds or the reverse process, reduction of carbonyl compounds to alcohols. Ethanol, for example, is metabolized in the liver to acetaldehyde. Such processes are catalyzed by enzymes; the enzyme that catalyzes the oxidation of ethanol is called *alcohol dehydrogenase.*



Ethanol Acetaldehyde

In addition to enzymes, biological oxidations require substances known as *coenzymes.* Coenzymes are organic molecules that, in concert with an enzyme, act on a substrate to bring about chemical change. Most of the substances that we call vitamins are coenzymes. The coenzyme contains a functional group that is complementary to a functional group of the substrate; the enzyme catalyzes the interaction of these mutually complementary functional groups. If ethanol is oxidized, some other substance must be reduced. This other substance is the oxidized form of the coenzyme *nicotinamide adenine dinucleotide* (NAD). Chemists and biochemists abbreviate the oxidized form of this

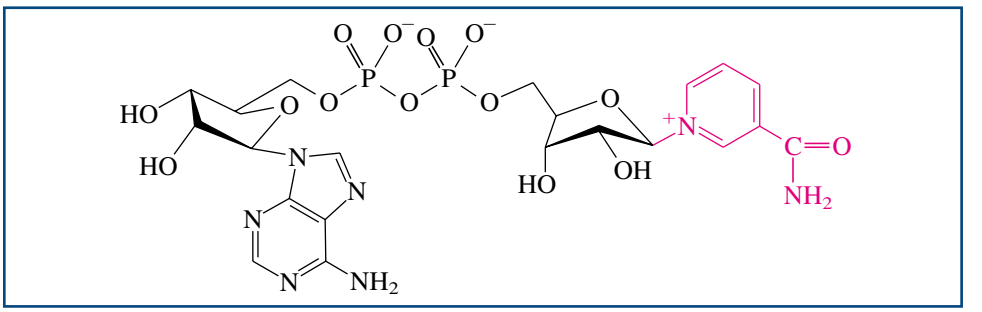
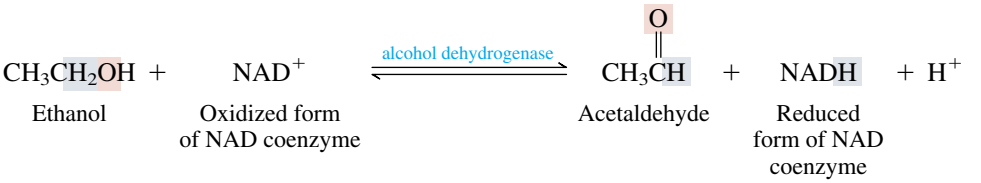
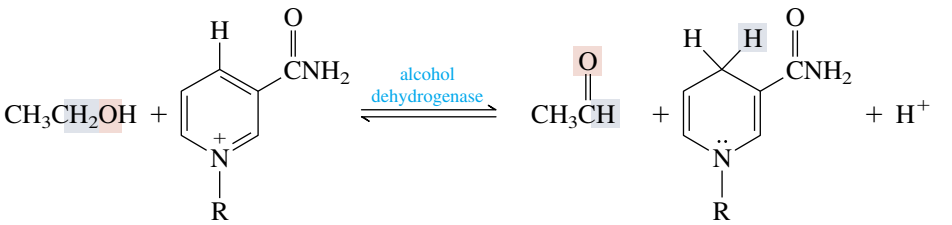


FIGURE 15.3 Structure of NAD^+, the oxidized form of the coenzyme nicotinamide adenine dinucleotide.

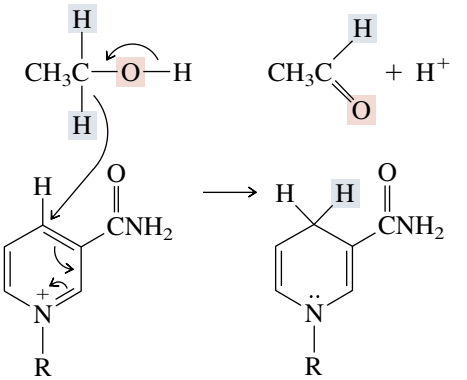
coenzyme as NAD^+ and its reduced form as NADH. More completely, the chemical equation for the biological oxidation of ethanol may be written:



The structure of the oxidized form of nicotinamide adenine dinucleotide is shown in Figure 15.3. The only portion of the coenzyme that undergoes chemical change in the reaction is the substituted pyridine ring of the nicotinamide unit (shown in red in Figure 15.3). If the remainder of the coenzyme molecule is represented by R, its role as an oxidizing agent is shown in the equation



According to one mechanistic interpretation, a hydrogen with a pair of electrons is transferred from ethanol to NAD^+, forming acetaldehyde and converting the positively charged pyridinium ring to a dihydropyridine:

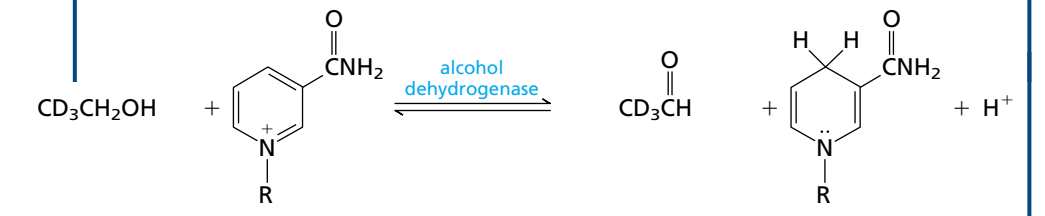


The pyridinium ring of NAD^+ serves as an acceptor of hydride (a proton plus two electrons) in this picture of its role in biological oxidation.

PROBLEM 15.12 The mechanism of enzymatic oxidation has been studied by isotopic labeling with the aid of deuterated derivatives of ethanol. Specify the number of deuterium atoms that you would expect to find attached to the dihydropyridine ring of the reduced form of the nicotinamide adenine dinucleotide coenzyme following enzymatic oxidation of each of the alcohols given:

(a) CD_3CH_2OH (b) CH_3CD_2OH (c) CH_3CH_2OD

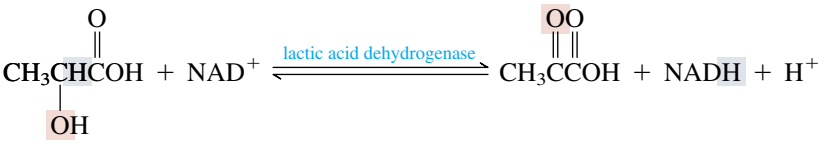
SAMPLE SOLUTION According to the proposed mechanism for biological oxidation of ethanol, the hydrogen that is transferred to the coenzyme comes from C-1 of ethanol. Therefore, the dihydropyridine ring will bear no deuterium atoms when CD_3CH_2OH is oxidized, because all the deuterium atoms of the alcohol are attached to C-2.



2,2,2-Trideuterioethanol — NAD^+ — 2,2,2-Trideuterioethanal — NADH

The reverse reaction also occurs in living systems; NADH reduces acetaldehyde to ethanol in the presence of alcohol dehydrogenase. In this process, NADH serves as a hydride donor and is oxidized to NAD^+ while acetaldehyde is reduced.

The NAD^+–NADH coenzyme system is involved in a large number of biological oxidation–reductions. Another reaction similar to the ethanol–acetaldehyde conversion is the oxidation of lactic acid to pyruvic acid by NAD^+ and the enzyme *lactic acid dehydrogenase:*



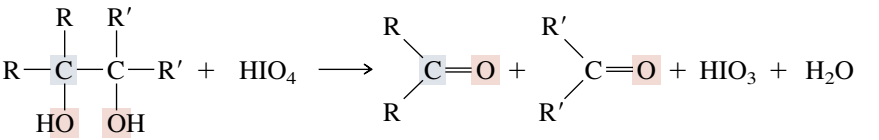
Lactic acid — Pyruvic acid

We shall encounter other biological processes in which the $NAD^+ \rightleftharpoons$ NADH interconversion plays a prominent role in biological oxidation–reduction.

15.12 OXIDATIVE CLEAVAGE OF VICINAL DIOLS

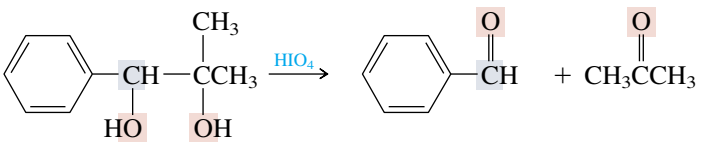
A reaction characteristic of vicinal diols is their oxidative cleavage on treatment with periodic acid (HIO_4). The carbon–carbon bond of the vicinal diol unit is broken and two carbonyl groups result. Periodic acid is reduced to iodic acid (HIO_3).

What is the oxidation state of iodine in HIO_4? In HIO_3?



Vicinal diol — Periodic acid — Aldehyde or ketone — Aldehyde or ketone — Iodic acid — Water

Can you remember what reaction of an alkene would give the same products as the periodic acid cleavage shown here?



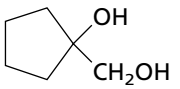
2-Methyl-1-phenyl-1,2-propanediol — Benzaldehyde (83%) — Acetone

This reaction occurs only when the hydroxyl groups are on adjacent carbons.

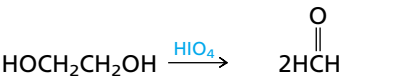
PROBLEM 15.13 Predict the products formed on oxidation of each of the following with periodic acid:

(a) $HOCH_2CH_2OH$

(b) $(CH_3)_2CHCH_2\underset{\displaystyle HO}{\underset{|}{CH}}\underset{\displaystyle OH}{\underset{|}{CH}}CH_2C_6H_5$

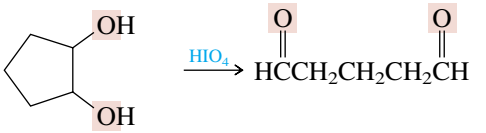
(c) 

SAMPLE SOLUTION (a) The carbon–carbon bond of 1,2-ethanediol is cleaved by periodic acid to give two molecules of formaldehyde:



1,2-Ethanediol Formaldehyde

Cyclic diols give dicarbonyl compounds. The reactions are faster when the hydroxyl groups are cis than when they are trans, but both stereoisomers are oxidized by periodic acid.



1,2-Cyclopentanediol (either stereoisomer) Pentanedial

Periodic acid cleavage of vicinal diols is often used for analytical purposes as an aid in structure determination. By identifying the carbonyl compounds produced, the constitution of the starting diol may be deduced. This technique finds its widest application with carbohydrates and will be discussed more fully in Chapter 25.

15.13 PREPARATION OF THIOLS

Sulfur lies just below oxygen in the periodic table, and many oxygen-containing organic compounds have sulfur analogs. The sulfur analogs of alcohols (ROH) are **thiols (RSH).** Thiols are given substitutive IUPAC names by appending the suffix *-thiol* to the name of the corresponding alkane, numbering the chain in the direction that gives the lower locant to the carbon that bears the —SH group. As with diols (Section 15.5), the final *-e* of the alkane name is retained. When the —SH group is named as a substituent, it is called a *mercapto* group. It is also often referred to as a *sulfhydryl* group, but this is a generic term, not used in systematic nomenclature.

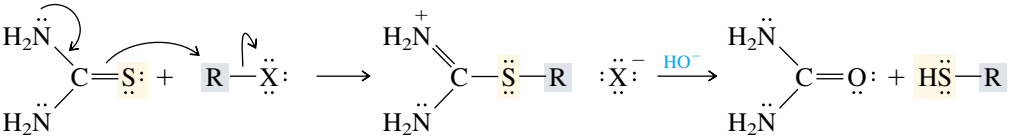
$(CH_3)_2CHCH_2CH_2SH$	$HSCH_2CH_2OH$	$HSCH_2CH_2CH_2SH$
3-Methyl-1-butanethiol	2-Mercaptoethanol	1,3-Propanedithiol

At one time thiols were named *mercaptans.* Thus, CH_3CH_2SH was called "ethyl mercaptan" according to this system. This nomenclature was abandoned beginning with

Thiols have a marked tendency to bond to mercury, and the word *mercaptan* comes from the Latin *mercurium captans,* which means "seizing mercury." The drug *dimercaprol* is used to treat mercury and lead poisoning; it is 2,3-dimercapto-1-propanol.

the 1965 revision of the IUPAC rules but is still sometimes encountered, especially in the older literature.

The preparation of thiols involves nucleophilic substitution of the S_N2 type on alkyl halides and uses the reagent *thiourea* as the source of sulfur. Reaction of the alkyl halide with thiourea gives a compound known as an *isothiouronium salt* in the first step. Hydrolysis of the isothiouronium salt in base gives the desired thiol (along with urea):



Both steps can be carried out sequentially without isolating the isothiouronium salt.

$$CH_3(CH_2)_4CH_2Br \xrightarrow[2.\ NaOH]{1.\ (H_2N)_2C{=}S} CH_3(CH_2)_4CH_2SH$$

1-Bromohexane — 1-Hexanethiol (84%)

PROBLEM 15.14 Outline a synthesis of 1-hexanethiol from 1-hexanol.

15.14 PROPERTIES OF THIOLS

A historical account of the analysis of skunk scent and a modern determination of its composition appear in the March 1978 issue of the *Journal of Chemical Education.*

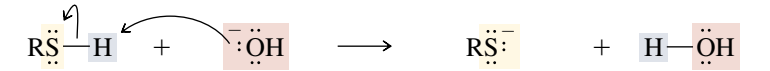
When one encounters a thiol for the first time, especially a low-molecular-weight thiol, its most obvious property is its foul odor. Ethanethiol is added to natural gas so that leaks can be detected without special equipment—your nose is so sensitive that it can detect less than one part of ethanethiol in 10,000,000,000 parts of air! The odor of thiols weakens with the number of carbons, because both the volatility and the sulfur content decrease. 1-Dodecanethiol, for example, has only a faint odor.

PROBLEM 15.15 The main components of a skunk's scent fluid are 3-methyl-1-butanethiol and *cis*- and *trans*-2-butene-1-thiol. Write structural formulas for each of these compounds.

Compare the boiling points of H_2S (−60°C) and H_2O (100°C).

The S—H bond is less polar than the O—H bond, and hydrogen bonding in thiols is much weaker than that of alcohols. Thus, methanethiol (CH_3SH) is a gas at room temperature (bp 6°C), and methanol (CH_3OH) is a liquid (bp 65°C).

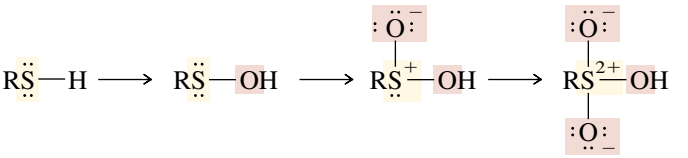
Thiols are weak acids, but are far more acidic than alcohols. We have seen that most alcohols have K_a values in the range 10^{-16} to 10^{-19} (pK_a = 16 to 19). The corresponding values for thiols are about $K_a = 10^{-10}$ (pK_a = 10). The significance of this difference is that a thiol can be quantitatively converted to its conjugate base (RS^-), called an **alkanethiolate** anion, by hydroxide:



Thiols, therefore, dissolve in aqueous media when the pH is greater than 10.

Another difference between thiols and alcohols concerns their oxidation. We have seen earlier in this chapter that oxidation of alcohols gives compounds having carbonyl

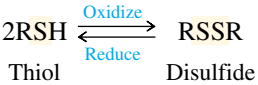
groups. Analogous oxidation of thiols to compounds with C═S functions does *not* occur. Only sulfur is oxidized, not carbon, and compounds containing sulfur in various oxidation states are possible. These include a series of acids classified as *sulfenic, sulfinic,* and *sulfonic* according to the number of oxygens attached to sulfur.



Thiol Sulfenic acid Sulfinic acid Sulfonic acid

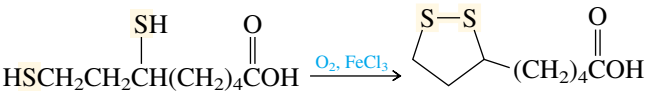
Of these the most important are the sulfonic acids. In general, however, sulfonic acids are not prepared by oxidation of thiols. Arenesulfonic acids ($ArSO_3H$), for example, are prepared by sulfonation of arenes (Section 12.4).

One of the most important oxidative processes, especially from a biochemical perspective, is the oxidation of thiols to **disulfides.**



Thiol Disulfide

Although a variety of oxidizing agents are available for this transformation, it occurs so readily that thiols are slowly converted to disulfides by the oxygen in the air. Dithiols give cyclic disulfides by intramolecular sulfur–sulfur bond formation. An example of a cyclic disulfide is the coenzyme α-*lipoic acid.* The last step in the laboratory synthesis of α-lipoic acid is an iron(III)-catalyzed oxidation of the dithiol shown:



6,8-Dimercaptooctanoic acid α-Lipoic acid (78%)

Rapid and reversible making and breaking of the sulfur–sulfur bond is essential to the biological function of α-lipoic acid.

15.15 SPECTROSCOPIC ANALYSIS OF ALCOHOLS

Infrared: We discussed the most characteristic features of the infrared spectra of alcohols earlier (Section 13.19). The O—H stretching vibration is especially easy to identify, appearing in the 3200–3650 cm^{-1} region. As the infrared spectrum of cyclohexanol, presented in Figure 15.4, demonstrates, this peak is seen as a broad absorption of moderate intensity. The C—O bond stretching of alcohols gives rise to a moderate to strong absorbance between 1025 and 1200 cm^{-1}. It appears at 1070 cm^{-1} in cyclohexanol, a typical secondary alcohol, but is shifted to slightly higher energy in tertiary alcohols and slightly lower energy in primary alcohols.

^{1}H NMR: The most helpful signals in the NMR spectrum of alcohols result from the hydroxyl proton and the proton in the H—C—O unit of primary and secondary alcohols.

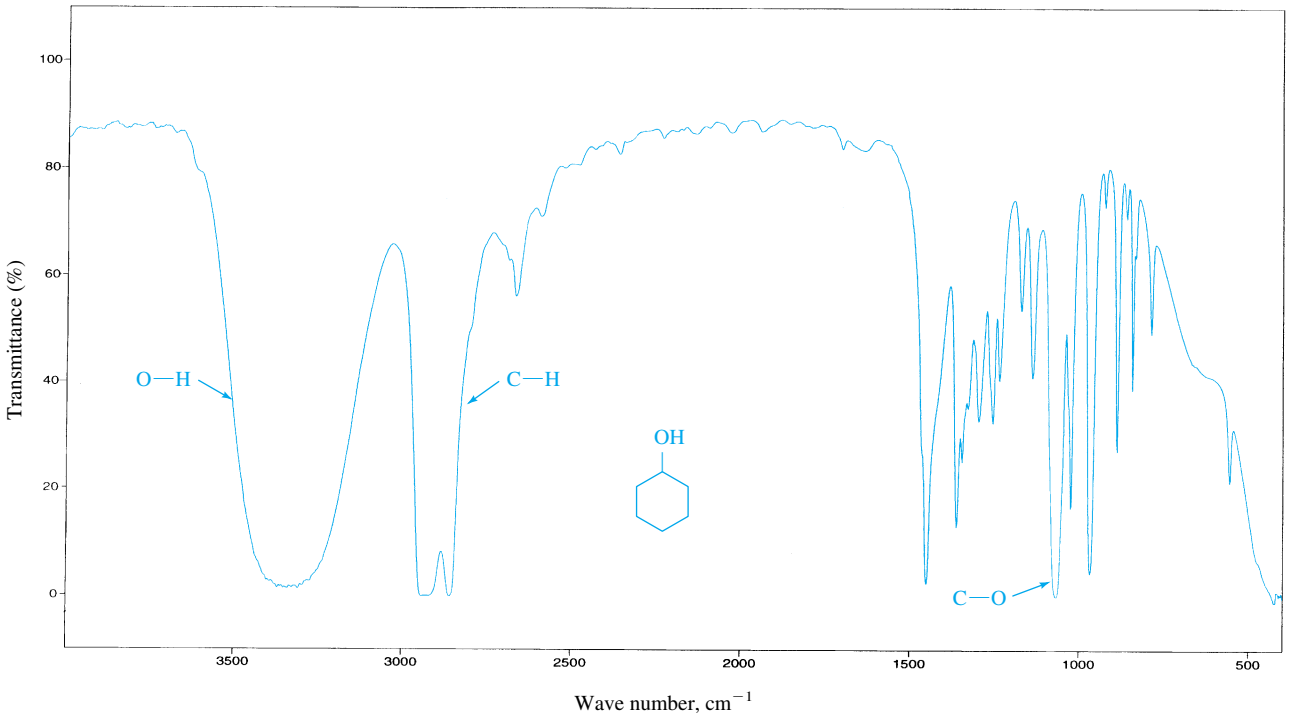
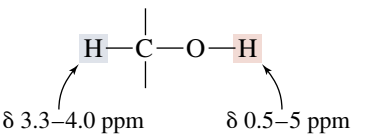
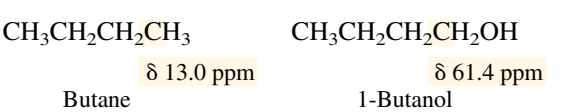


FIGURE 15.4 The infrared spectrum of cyclohexanol.



The chemical shift of the hydroxyl proton signal is variable, depending on solvent, temperature, and concentration. Its precise position is not particularly significant in structure determination. Because the signals due to hydroxyl protons are not usually split by other protons in the molecule and are often rather broad, they are often fairly easy to identify. To illustrate, Figure 15.5 shows the ^{1}H NMR spectrum of 2-phenylethanol, in which the hydroxyl proton signal appears as a singlet at δ 4.5 ppm. Of the two triplets in this spectrum, the one at lower field strength (δ 4.0 ppm) corresponds to the protons of the CH_2O unit. The higher-field strength triplet at δ 3.1 ppm arises from the benzylic CH_2 group. The assignment of a particular signal to the hydroxyl proton can be confirmed by adding D_2O. The hydroxyl proton is replaced by deuterium, and its ^{1}H NMR signal disappears.

^{13}C NMR: The electronegative oxygen of an alcohol decreases the shielding of the carbon to which it is attached. The chemical shift for the carbon of the C—OH unit is 60–75 ppm for most alcohols. Compared with an attached H, an attached OH causes a downfield shift of 35–50 ppm in the carbon signal.



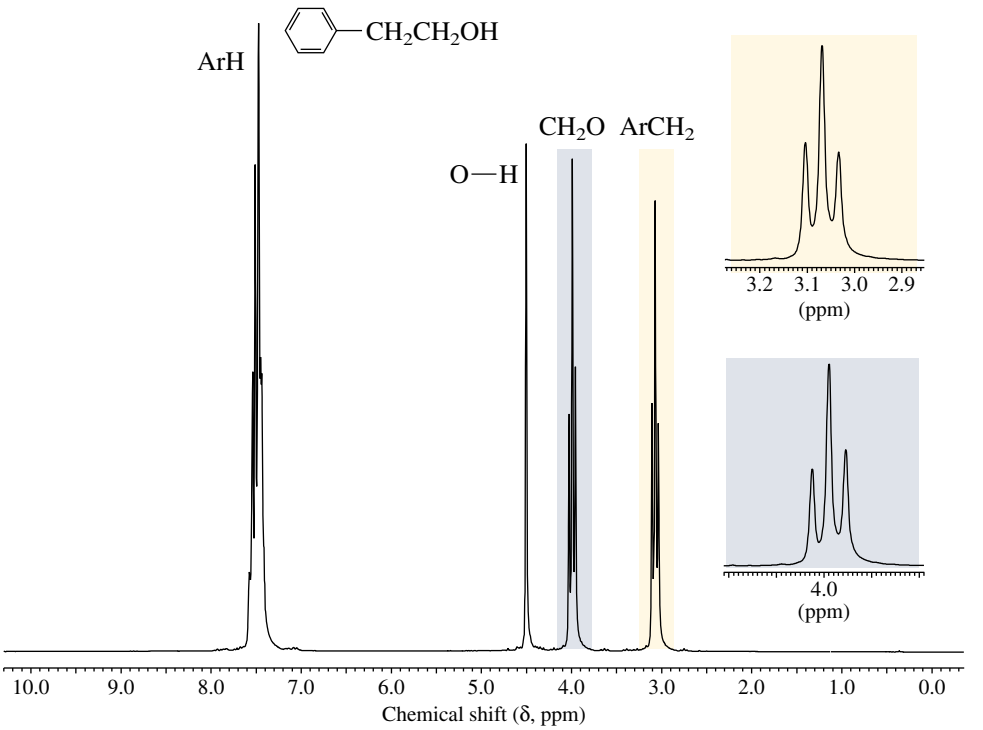
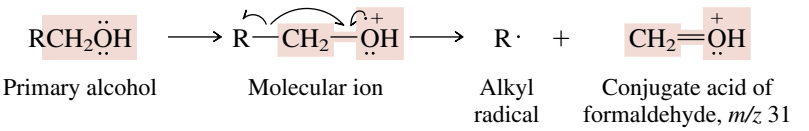


FIGURE 15.5 The 200-MHz ^{1}H NMR spectrum of 2-phenylethanol ($C_6H_5CH_2CH_2OH$).

UV-VIS: Unless there are other chromophores in the molecule, alcohols are transparent above about 200 nm; λ_{max} for methanol, for example, is 177 nm.

Mass Spectrometry: The molecular ion peak is usually quite small in the mass spectrum of an alcohol. A peak corresponding to loss of water is often evident. Alcohols also fragment readily by a pathway in which the molecular ion loses an alkyl group from the hydroxyl-bearing carbon to form a stable cation. Thus, the mass spectra of most primary alcohols exhibit a prominent peak at *m/z* 31.



PROBLEM 15.16 Three of the most intense peaks in the mass spectrum of 2-methyl-2-butanol appear at *m/z* 59, 70, and 73. Explain the origin of these peaks.

15.17 SUMMARY

Section 15.1 Functional group interconversions involving alcohols either as reactants or as products are the focus of this chapter. Alcohols are commonplace natural products. Table 15.1 summarizes reactions discussed in earlier sections that can be used to prepare alcohols.

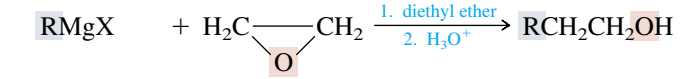
Section 15.2 Alcohols can be prepared from carbonyl compounds by reduction of aldehydes and ketones. See Table 15.3.

TABLE 15.3 Preparation of Alcohols by Reduction of Carbonyl Functional Groups

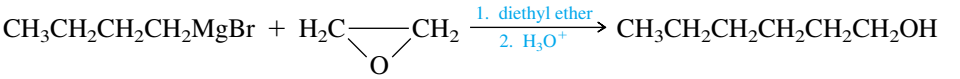
Carbonyl compound	Product of reduction of carbonyl compound by specified reducing agent: Lithium aluminum hydride ($LiAlH_4$)	Sodium borohydride ($NaBH_4$)	Hydrogen (in the presence of a catalyst)
Aldehyde RCH (O) (Section 15.2)	Primary alcohol RCH_2OH	Primary alcohol RCH_2OH	Primary alcohol RCH_2OH
Ketone RCR′ (O) (Section 15.2)	Secondary alcohol RCHR′ (OH)	Secondary alcohol RCHR′ (OH)	Secondary alcohol RCHR′ (OH)
Carboxylic acid RCOH (O) (Section 15.3)	Primary alcohol RCH_2OH	Not reduced	Not reduced
Carboxylic ester RCOR′ (O) (Section 15.3)	Primary alcohol RCH_2OH plus R′OH	Reduced too slowly to be of practical value	Requires special catalyst, high pressures and temperatures

Section 15.3 Alcohols can be prepared from carbonyl compounds by reduction of carboxylic acids and esters. See Table 15.3.

Section 15.4 Grignard and organolithium reagents react with ethylene oxide to give primary alcohols.

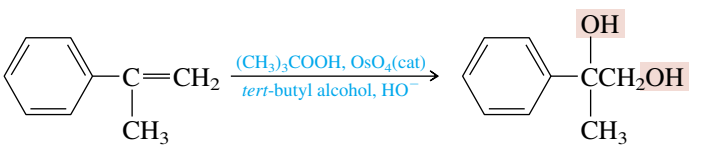


Grignard reagent — Ethylene oxide — Primary alcohol



Butylmagnesium bromide — Ethylene oxide — 1-Hexanol (60–62%)

Section 15.5 Osmium tetraoxide is a key reactant in the conversion of alkenes to vicinal diols.



2-Phenylpropene — 2-Phenyl-1,2-propanediol (71%)

The reaction is called **hydroxylation** and proceeds by syn addition to the double bond.

Section 15.6 Table 15.2 summarizes reactions of alcohols that were introduced in earlier chapters.

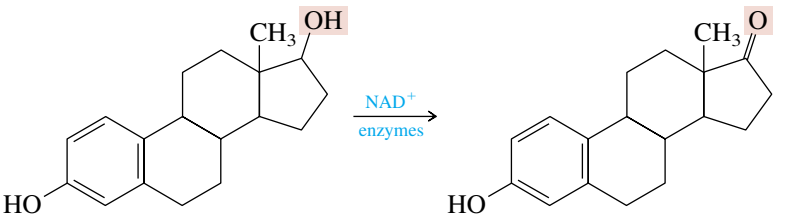
Section 15.7 See Table 15.4

Section 15.8 See Table 15.4

Section 15.9 See Table 15.4

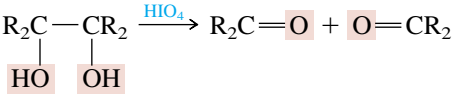
Section 15.10 See Table 15.5

Section 15.11 Oxidation of alcohols to aldehydes and ketones is a common biological reaction. Most require a coenzyme such as the oxidized form of nicotinamide adenine dinucleotide (NAD^+).

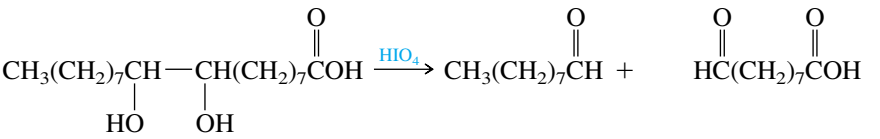


Estradiol Estrone

Section 15.12 Periodic acid cleaves vicinal diols; two aldehydes, two ketones, or an aldehyde and a ketone are formed.

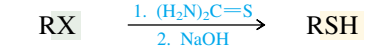


Diol Two carbonyl-containing compounds

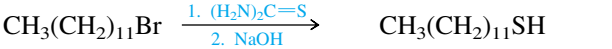


9,10-Dihydroxyoctadecanoic acid Nonanal (89%) 9-Oxononanoic acid (76%)

Section 15.13 **Thiols,** compounds of the type RSH, are prepared by the reaction of alkyl halides with thiourea. An intermediate isothiouronium salt is formed, which is then subjected to basic hydrolysis.



Alkyl halide Alkanethiol



1-Bromododecane 1-Dodecanethiol (79–83%)

Section 15.14 Thiols are more acidic than alcohols and are readily deprotonated by reaction with aqueous base. Thiols can be oxidized to disulfides (RSSR), sulfenic acids (RSOH), sulfinic acids (RSO_2H), and sulfonic acids (RSO_3H).

TABLE 15.4 Summary of Reactions of Alcohols Presented in This Chapter

Reaction (section) and comments	General equation and specific example
Conversion to dialkyl ethers (Section 15.7) On being heated in the presence of an acid catalyst, two molecules of a primary alcohol combine to form an ether and water. Diols can undergo an intramolecular condensation if a five-membered or six-membered cyclic ether results.	$2RCH_2OH \xrightarrow[\text{heat}]{H^+} RCH_2OCH_2R + H_2O$ Alcohol → Dialkyl ether + Water $2(CH_3)_2CHCH_2CH_2OH \xrightarrow[150^\circ C]{H_2SO_4} (CH_3)_2CHCH_2CH_2OCH_2CH_2CH(CH_3)_2$ 3-Methyl-1-butanol → Di-(3-methylbutyl) ether (27%)
Fischer esterification (Section 15.8) Alcohols and carboxylic acids yield an ester and water in the presence of an acid catalyst. The reaction is an equilibrium process that can be driven to completion by using either the alcohol or the acid in excess or by removing the water as it is formed.	$ROH + R'COH \xrightarrow{H^+} R'COR + H_2O$ Alcohol + Carboxylic acid → Ester + Water $CH_3CH_2CH_2CH_2CH_2OH + CH_3COH \xrightarrow{H^+} CH_3COCH_2CH_2CH_2CH_2CH_3$ 1-Pentanol + Acetic acid → Pentyl acetate (71%)
Esterification with acyl chlorides (Section 15.8) Acyl chlorides react with alcohols to give esters. The reaction is usually carried out in the presence of pyridine.	$ROH + R'CCl \longrightarrow R'COR + HCl$ Alcohol + Acyl chloride → Ester + Hydrogen chloride $(CH_3)_3COH + CH_3CCl \xrightarrow{\text{pyridine}} CH_3COC(CH_3)_3$ *tert*-Butyl alcohol + Acetyl chloride → *tert*-Butyl acetate (62%)
Esterification with carboxylic acid anhydrides (Section 15.8) Carboxylic acid anhydrides react with alcohols to form esters in the same way that acyl chlorides do.	$ROH + R'COCR' \longrightarrow R'COR + R'COH$ Alcohol + Carboxylic acid anhydride → Ester + Carboxylic acid *m*-Methoxybenzyl alcohol + Acetic anhydride → *m*-Methoxybenzyl acetate (99%)
Formation of esters of inorganic acids (Section 15.9) Alkyl nitrates, dialkyl sulfates, trialkyl phosphites, and trialkyl phosphates are examples of alkyl esters of inorganic acids. In some cases, these compounds are prepared by the direct reaction of an alcohol and the inorganic acid.	$ROH + HONO_2 \xrightarrow{H^+} RONO_2 + H_2O$ Alcohol + Nitric acid → Alkyl nitrate + Water Cyclopentanol → Cyclopentyl nitrate (69%)

TABLE 15.5 Oxidation of Alcohols

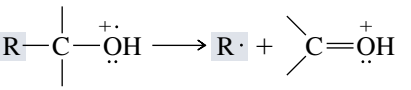
Class of alcohol	Desired product	Suitable oxidizing agent(s)
Primary, RCH_2OH	Aldehyde RCH (O)	PCC* PDC
Primary, RCH_2OH	Carboxylic acid $RCOH$ (O)	$Na_2Cr_2O_7$, H_2SO_4, H_2O H_2CrO_4
Secondary, $RCHR'$ (OH)	Ketone RCR' (O)	PCC PDC $Na_2Cr_2O_7$, H_2SO_4, H_2O H_2CrO_4

*PCC is pyridinium chlorochromate; PDC is pyridinium dichromate. Both are used in dichloromethane.

Section 15.15 The hydroxyl group of an alcohol has its O—H and C—O stretching vibrations at 3200–3650 and 1025–1200 cm^{-1}, respectively.

The chemical shift of the proton of an O—H group is variable (δ 1–5 ppm) and depends on concentration, temperature, and solvent. Oxygen deshields both the proton and the carbon of an H—C—O unit. Typical NMR chemical shifts are δ 3.3–4.0 ppm for ^1H and 60–75 ppm for ^{13}C of H—C—O.

The most intense peaks in the mass spectrum of an alcohol correspond to the ion formed according to carbon–carbon cleavage of the type shown:



PROBLEMS

15.17 Write chemical equations, showing all necessary reagents, for the preparation of 1-butanol by each of the following methods:

(a) Hydroboration–oxidation of an alkene

(b) Use of a Grignard reagent

(c) Use of a Grignard reagent in a way different from part (b)

(d) Reduction of a carboxylic acid

(e) Reduction of a methyl ester

(f) Reduction of a butyl ester

(g) Hydrogenation of an aldehyde

(h) Reduction with sodium borohydride

15.18 Write chemical equations, showing all necessary reagents, for the preparation of 2-butanol by each of the following methods:

(a) Hydroboration–oxidation of an alkene

(b) Use of a Grignard reagent

(c) Use of a Grignard reagent different from that used in part (b)

(d–f) Three different methods for reducing a ketone

15.19 Write chemical equations, showing all necessary reagents, for the preparation of *tert*-butyl alcohol by:

(a) Reaction of a Grignard reagent with a ketone

(b) Reaction of a Grignard reagent with an ester of the type $RCOCH_3$ (O above C)

15.20 Which of the isomeric $C_5H_{12}O$ alcohols can be prepared by lithium aluminum hydride reduction of:

(a) An aldehyde

(b) A ketone

(c) A carboxylic acid

(d) An ester of the type $RCOCH_3$ (O above C)

15.21 Evaluate the feasibility of the route

$$RH \xrightarrow[\text{light or heat}]{Br_2} RBr \xrightarrow{KOH} ROH$$

as a method for preparing

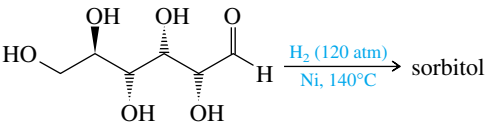
(a) 1-Butanol from butane

(b) 2-Methyl-2-propanol from 2-methylpropane

(c) Benzyl alcohol from toluene

(d) (*R*)-1-Phenylethanol from ethylbenzene

15.22 Sorbitol is a sweetener often substituted for cane sugar, since it is better tolerated by diabetics. It is also an intermediate in the commercial synthesis of vitamin C. Sorbitol is prepared by high-pressure hydrogenation of glucose over a nickel catalyst. What is the structure (including stereochemistry) of sorbitol?



Glucose

15.23 Write equations showing how 1-phenylethanol ($C_6H_5CHCH_3$, OH on CH) could be prepared from each of the following starting materials:

(a) Bromobenzene

(b) Benzaldehyde

(c) Benzyl alcohol

(d) Acetophenone

(e) Benzene

15.24 Write equations showing how 2-phenylethanol ($C_6H_5CH_2CH_2OH$) could be prepared from each of the following starting materials:

(a) Bromobenzene

(b) Styrene

(c) 2-Phenylethanal ($C_6H_5CH_2CHO$)

(d) Ethyl 2-phenylethanoate ($C_6H_5CH_2CO_2CH_2CH_3$)

(e) 2-Phenylethanoic acid ($C_6H_5CH_2CO_2H$)

15.25 Outline practical syntheses of each of the following compounds from alcohols containing no more than four carbon atoms and any necessary organic or inorganic reagents. In many cases the desired compound can be made from one prepared in an earlier part of the problem.

(a) 1-Butanethiol

(b) 1-Hexanol

(c) 2-Hexanol

(d) Hexanal, $CH_3CH_2CH_2CH_2CH_2CH{=}O$

(e) 2-Hexanone, $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2CH_3$

(f) Hexanoic acid, $CH_3(CH_2)_4CO_2H$

(g) Ethyl hexanoate, $CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}OCH_2CH_3$

(h) 2-Methyl-1,2-propanediol

(i) 2,2-Dimethylpropanal, $(CH_3)_3\overset{\overset{O}{\|}}{C}CH$

15.26 Outline practical syntheses of each of the following compounds from benzene, alcohols, and any necessary organic or inorganic reagents:

(a) 1-Chloro-2-phenylethane

(b) 2-Methyl-1-phenyl-1-propanone, $C_6H_5\overset{\overset{O}{\|}}{C}CH(CH_3)_2$

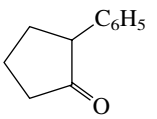
(c) Isobutylbenzene, $C_6H_5CH_2CH(CH_3)_2$

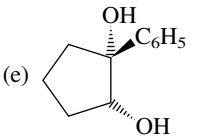
15.27 Show how each of the following compounds can be synthesized from cyclopentanol and any necessary organic or inorganic reagents. In many cases the desired compound can be made from one prepared in an earlier part of the problem.

(a) 1-Phenylcyclopentanol

(b) 1-Phenylcyclopentene

(c) *trans*-2-Phenylcyclopentanol

(d) 

(e) 

(f) $C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}H$

(g) 1-Phenyl-1,5-pentanediol

15.28 Write the structure of the principal organic product formed in the reaction of 1-propanol with each of the following reagents:

(a) Sulfuric acid (catalytic amount), heat at 140°C

(b) Sulfuric acid (catalytic amount), heat at 200°C

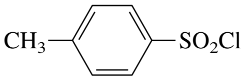
(c) Nitric acid (H_2SO_4 catalyst)

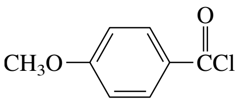
(d) Pyridinium chlorochromate (PCC) in dichloromethane

(e) Potassium dichromate ($K_2Cr_2O_7$) in aqueous sulfuric acid, heat

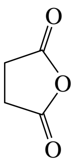
(f) Sodium amide ($NaNH_2$)

(g) Acetic acid ($CH_3\overset{O}{\overset{\|}{C}}OH$) in the presence of dissolved hydrogen chloride

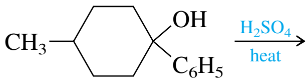
(h)  in the presence of pyridine

(i)  in the presence of pyridine

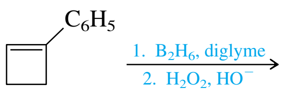
(j) $C_6H_5\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}C_6H_5$ in the presence of pyridine

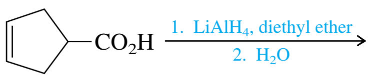
(k)  in the presence of pyridine

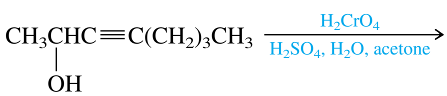
15.29 Each of the following reactions has been reported in the chemical literature. Predict the product in each case, showing stereochemistry where appropriate.

(a) 

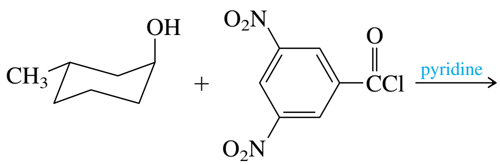
(b) $(CH_3)_2C{=}C(CH_3)_2 \xrightarrow[(CH_3)_3COH,\ HO^-]{(CH_3)_3COOH,\ OsO_4(cat)}$

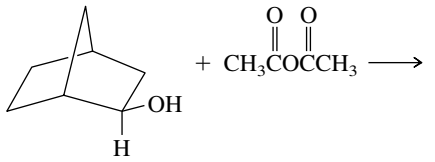
(c) 

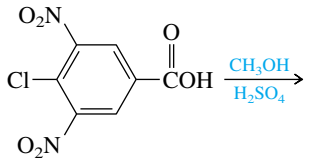
(d) 

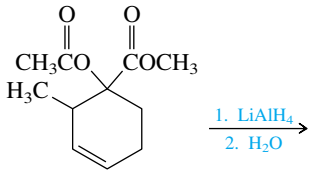
(e) 

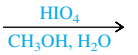
(f) $CH_3\overset{O}{\overset{\|}{C}}CH_2CH{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4,\ \text{diethyl ether}}$

(g) 

(h) 

(i) 

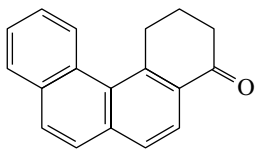
(j) 

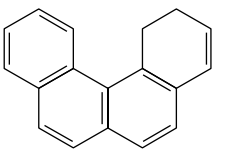
(k) Product of part (j) 

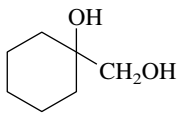
15.30 On heating 1,2,4-butanetriol in the presence of an acid catalyst, a cyclic ether of molecular formula $C_4H_8O_2$ was obtained in 81–88% yield. Suggest a reasonable structure for this product.

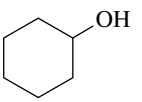
15.31 Give the Cahn–Ingold–Prelog *R* and *S* descriptors for the diol(s) formed from *cis*-2-pentene and *trans*-2-pentene on treatment with the osmium tetraoxide/*tert*-butyl hydroperoxide reagent.

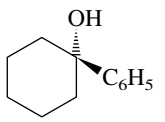
15.32 Suggest reaction sequences and reagents suitable for carrying out each of the following conversions. Two synthetic operations are required in each case.

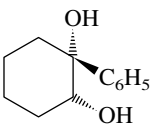
(a) 

to 

(b) 

to 

(c) 

to 

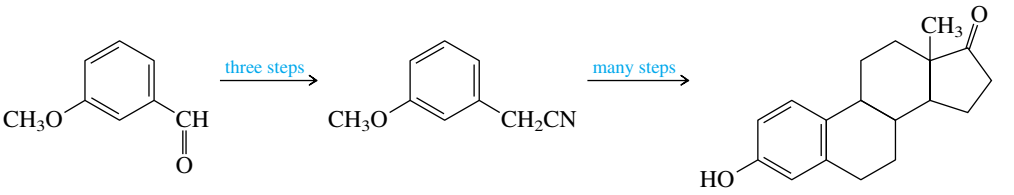
15.33 The fungus responsible for Dutch elm disease is spread by European bark beetles when they burrow into the tree. Other beetles congregate at the site, attracted by the scent of a mixture of chemicals, some emitted by other beetles and some coming from the tree. One of the compounds given off by female bark beetles is 4-methyl-3-heptanol. Suggest an efficient synthesis of this pheromone from alcohols of five carbon atoms or fewer.

15.34 Show by a series of equations how you could prepare 3-methylpentane from ethanol and any necessary inorganic reagents.

15.35 (a) The cis isomer of 3-hexen-1-ol ($CH_3CH_2CH{=}CHCH_2CH_2OH$) has the characteristic odor of green leaves and grass. Suggest a synthesis for this compound from acetylene and any necessary organic or inorganic reagents.

(b) One of the compounds responsible for the characteristic odor of ripe tomatoes is the cis isomer of $CH_3CH_2CH{=}CHCH_2CH{=}O$. How could you prepare this compound?

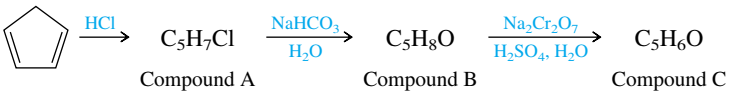
15.36 R. B. Woodward was one of the leading organic chemists of the middle part of the twentieth century. Known primarily for his achievements in the synthesis of complex natural products, he was awarded the Nobel Prize in chemistry in 1965. He entered Massachusetts Institute of Technology as a 16-year-old freshman in 1933 and four years later was awarded the Ph.D. While a student there he carried out a synthesis of *estrone,* a female sex hormone. The early stages of Woodward's estrone synthesis required the conversion of *m*-methoxybenzaldehyde to *m*-methoxybenzyl cyanide, which was accomplished in three steps:



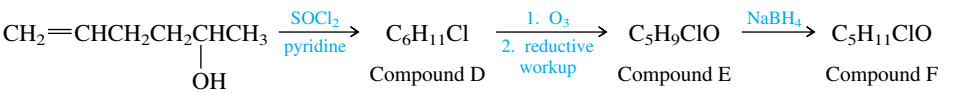
Estrone

Suggest a reasonable three-step sequence, showing all necessary reagents, for the preparation of *m*-methoxybenzyl cyanide from m-methoxybenzaldehyde.

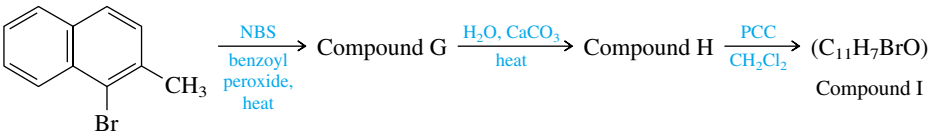
15.37 Complete the following series of equations by writing structural formulas for compounds A through I:

(a) 

Compound A Compound B Compound C

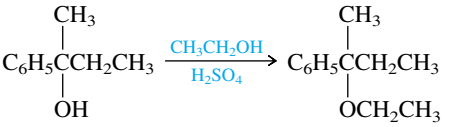
(b) 

Compound D Compound E Compound F

(c) 

Compound I

15.38 When 2-phenyl-2-butanol is allowed to stand in ethanol containing a few drops of sulfuric acid, the following ether is formed:



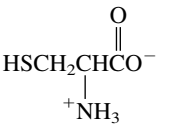
Suggest a reasonable mechanism for this reaction based on the observation that the ether produced from optically active alcohol is racemic, and that alkenes can be shown not to be intermediates in the reaction.

15.39 Suggest a chemical test that would permit you to distinguish between the two glycerol monobenzyl ethers shown.

1-*O*-Benzylglycerol 2-*O*-Benzylglycerol

15.40 Choose the correct enantiomer of 2-butanol that would permit you to prepare (*R*)-2-butanethiol by way of a *p*-toluenesulfonate ester.

15.41 The amino acid *cysteine* has the structure shown:



Cysteine

(a) A second sulfur-containing amino acid called *cystine* ($C_6H_{12}N_2O_4S_2$) is formed when cysteine undergoes biological oxidation. Suggest a reasonable structure for cystine.

(b) Another metabolic pathway converts cysteine to *cysteine sulfinic acid* ($C_3H_7NO_4S$), then to *cysteic acid* ($C_3H_7NO_5S$). What are the structures of these two compounds?

15.42 A diol ($C_8H_{18}O_2$) does not react with periodic acid. Its ^{1}H NMR spectrum contains three singlets at δ 1.2 (12 protons), 1.6 (4 protons), and 2.0 ppm (2 protons). What is the structure of this diol?

15.43 Identify compound A ($C_8H_{10}O$) on the basis of its ^{1}H NMR spectrum (Figure 15.6). The broad peak at δ 2.1 ppm disappears when D_2O is added.

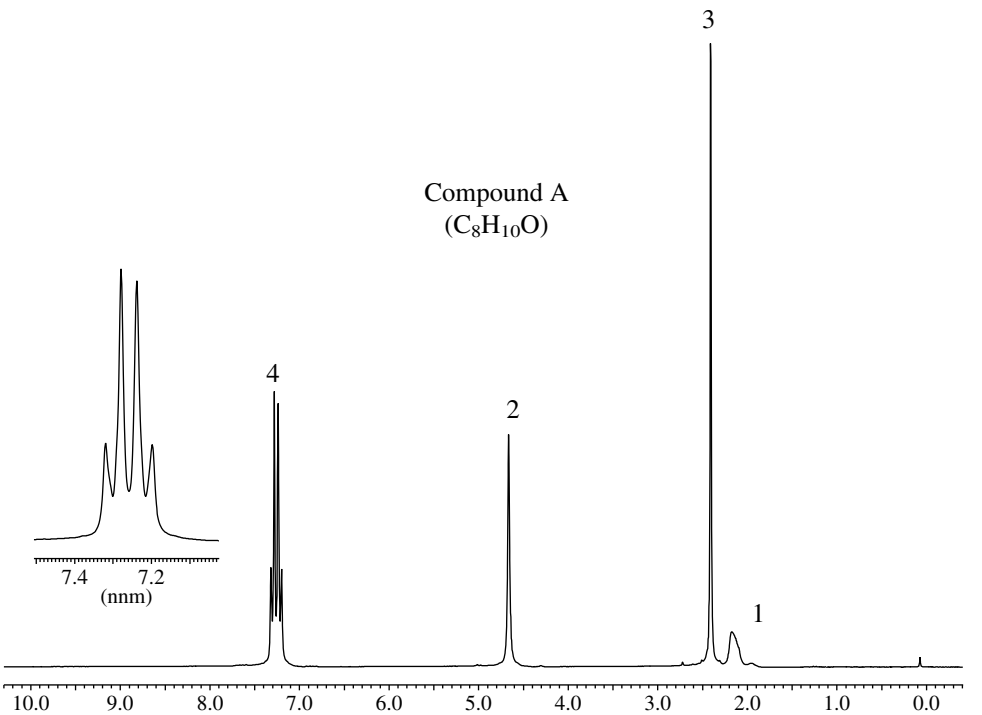


FIGURE 15.6 The 200-MHz ^{1}H NMR spectrum of compound A ($C_8H_{10}O$) (Problem 15.43).

15.44 Identify each of the following ($C_4H_{10}O$) isomers on the basis of their ^{13}C NMR spectra:

(a) δ 31.2 ppm: CH_3
δ 68.9 ppm: C

(b) δ 10.0 ppm: CH_3
δ 22.7 ppm: CH_3
δ 32.0 ppm: CH_2
δ 69.2 ppm: CH

(c) δ 18.9 ppm: CH_3, area 2
δ 30.8 ppm: CH, area 1
δ 69.4 ppm: CH_2, area 1

15.45 A compound $C_3H_7ClO_2$ exhibited three peaks in its ^{13}C NMR spectrum at δ 46.8 (CH_2), δ 63.5 (CH_2), and δ 72.0 ppm (CH). What is the structure of this compound?

15.46 A compound $C_6H_{14}O$ has the ^{13}C NMR spectrum shown in Figure 15.7. Its mass spectrum has a prominent peak at *m/z* 31. Suggest a reasonable structure for this compound.

15.47 Refer to *Learning By Modeling* and compare the properties calculated for CH_3CH_2OH and CH_3CH_2SH. Which has the greater dipole moment? Compare the charges at carbon and hydrogen in C—O—H versus C—S—H. Why does ethanol have a higher boiling point than ethanethiol?

15.48 Construct molecular models of the gauche and anti conformations of 1,2-ethanediol and explore the possibility of intramolecular hydrogen bond formation in each one.

15.49 Intramolecular hydrogen bonding is present in the chiral diastereomer of 2,2,5,5-tetramethylhexane-3,4-diol, but absent in the meso diastereomer. Construct molecular models of each, and suggest a reason for the difference between the two.

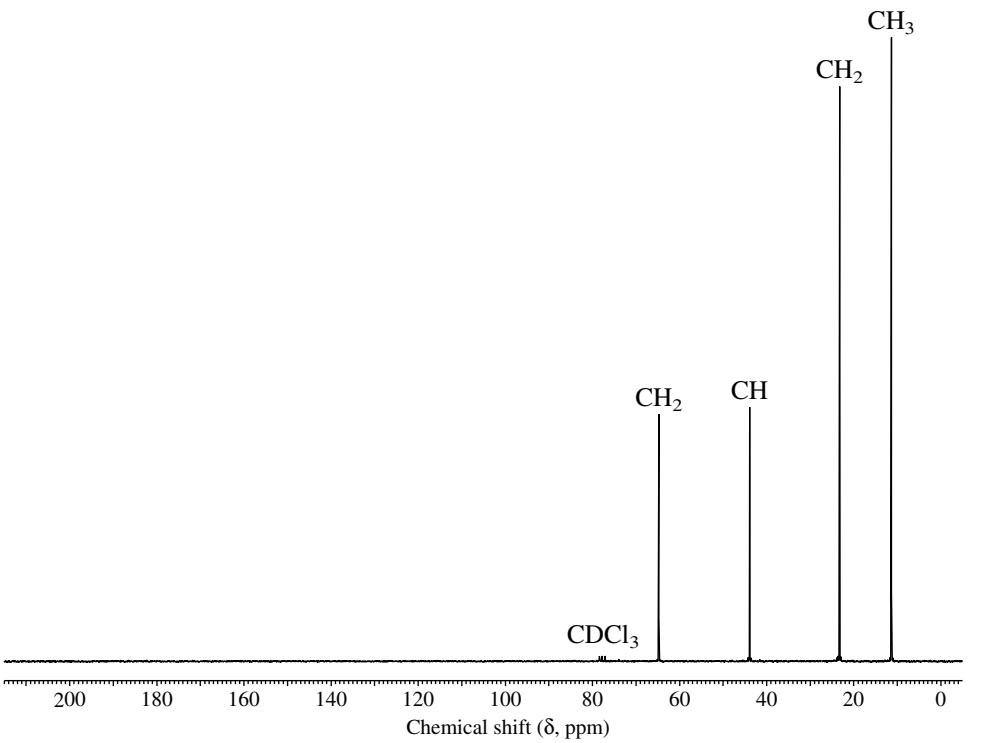


FIGURE 15.7 The ^{13}C NMR spectrum of the compound $C_6H_{14}O$ (Problem 15.46).