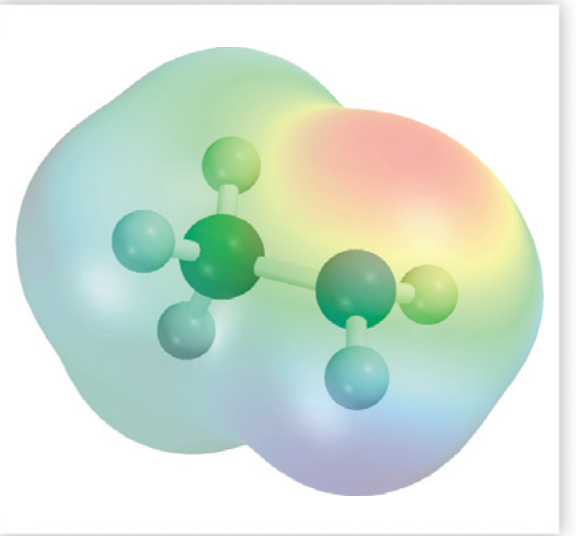
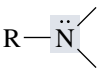


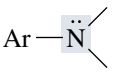
CHAPTER 22

AMINES

Nitrogen-containing compounds are essential to life. Their ultimate source is atmospheric nitrogen which, by a process known as *nitrogen fixation,* is reduced to ammonia, then converted to organic nitrogen compounds. This chapter describes the chemistry of **amines,** organic derivatives of ammonia. **Alkylamines** have their nitrogen attached to sp^3-hybridized carbon; **arylamines** have their nitrogen attached to an sp^2-hybridized carbon of a benzene or benzene-like ring.



R = alkyl group: alkylamine



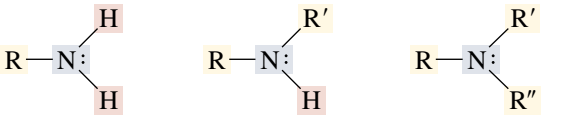
Ar = aryl group: arylamine

Amines, like ammonia, are weak bases. They are, however, the strongest uncharged bases found in significant quantities under physiological conditions. Amines are usually the bases involved in biological acid–base reactions; they are often the nucleophiles in biological nucleophilic substitutions.

Our word "vitamin" was coined in 1912 in the belief that the substances present in the diet that prevented scurvy, pellagra, beriberi, rickets, and other diseases were "vital amines." In many cases, that belief was confirmed; certain vitamins did prove to be amines. In many other cases, however, vitamins were not amines. Nevertheless, the name *vitamin* entered our language and stands as a reminder that early chemists recognized the crucial place occupied by amines in biological processes.

22.1 AMINE NOMENCLATURE

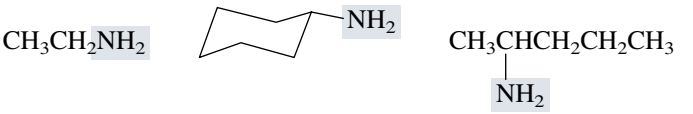
Unlike alcohols and alkyl halides, which are classified as primary, secondary, or tertiary according to the degree of substitution at the carbon that bears the functional group, amines are classified according to their *degree of substitution at nitrogen.* An amine with one carbon attached to nitrogen is a *primary amine,* an amine with two is a *secondary amine,* and an amine with three is a *tertiary amine.*



Primary amine Secondary amine Tertiary amine

The groups attached to nitrogen may be any combination of alkyl or aryl groups.

Amines are named in two main ways, in the IUPAC system: either as *alkylamines* or as *alkanamines.* When primary amines are named as alkylamines, the ending *-amine* is added to the name of the alkyl group that bears the nitrogen. When named as alkanamines, the alkyl group is named as an alkane and the *-e* ending replaced by *-amine.*



Ethylamine (ethanamine) Cyclohexylamine (cyclohexanamine) 1-Methylbutylamine (2-pentanamine)

PROBLEM 22.1 Give an acceptable alkylamine or alkanamine name for each of the following amines:

(a) $C_6H_5CH_2CH_2NH_2$

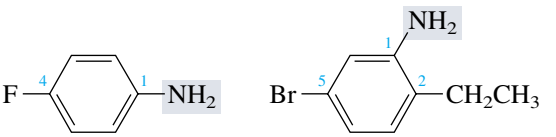
(b) $C_6H_5CHNH_2$ with CH_3 as a branch

(c) $CH_2{=}CHCH_2NH_2$

SAMPLE SOLUTION (a) The amino substituent is bonded to an ethyl group that bears a phenyl substituent at C-2. The compound $C_6H_5CH_2CH_2NH_2$ may be named as either 2-phenylethylamine or 2-phenylethanamine.

Aniline is the parent IUPAC name for amino-substituted derivatives of benzene. Substituted derivatives of aniline are numbered beginning at the carbon that bears the amino group. Substituents are listed in alphabetical order, and the direction of numbering is governed by the usual "first point of difference" rule.

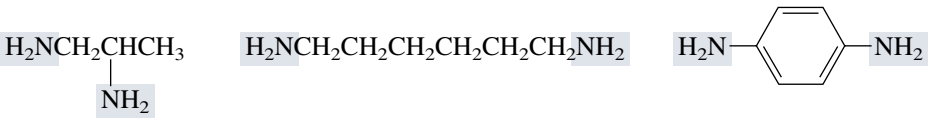
Aniline was first isolated in 1826 as a degradation product of indigo, a dark blue dye obtained from the West Indian plant *Indigofera anil,* from which the name *aniline* is derived.



p-Fluoroaniline 5-Bromo-2-ethylaniline

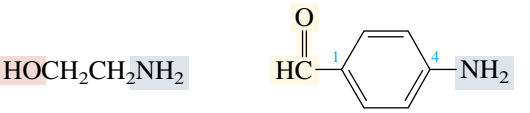
Arylamines may also be named as *arenamines.* Thus, *benzenamine* is an alternative, but rarely used, name for aniline.

Compounds with two amino groups are named by adding the suffix *-diamine* to the name of the corresponding alkane or arene. The final *-e* of the parent hydrocarbon is retained.



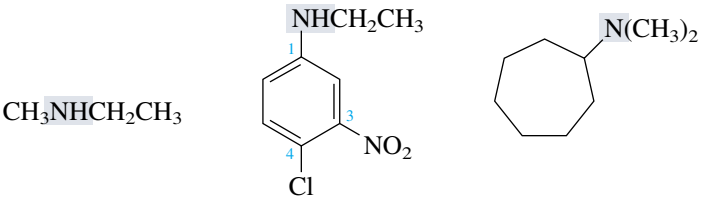
1,2-Propanediamine | 1,6-Hexanediamine | 1,4-Benzenediamine

Amino groups rank rather low in seniority when the parent compound is identified for naming purposes. Hydroxyl groups and carbonyl groups outrank amino groups. In these cases, the amino group is named as a substituent.



2-Aminoethanol | *p*-Aminobenzaldehyde (4-Aminobenzenecarbaldehyde)

Secondary and tertiary amines are named as *N*-substituted derivatives of primary amines. The parent primary amine is taken to be the one with the longest carbon chain. The prefix *N*- is added as a locant to identify substituents on the amino nitrogen as needed.

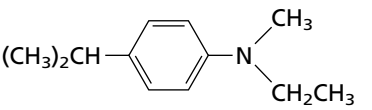


N-Methylethylamine (a secondary amine) | 4-Chloro-*N*-ethyl-3-nitroaniline (a secondary amine) | *N*,*N*-Dimethylcycloheptylamine (a tertiary amine)

PROBLEM 22.2 Assign alkanamine names to *N*-methylethylamine and to *N*,*N*-dimethylcycloheptylamine.

SAMPLE SOLUTION *N*-Methylethylamine (given as $CH_3NHCH_2CH_3$ in the preceding example) is an *N*-substituted derivative of ethanamine; it is *N*-methylethanamine.

PROBLEM 22.3 Classify the following amine as primary, secondary, or tertiary, and give it an acceptable IUPAC name.



A nitrogen that bears four substituents is positively charged and is named as an *ammonium* ion. The anion that is associated with it is also identified in the name.

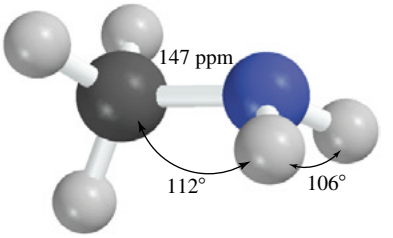
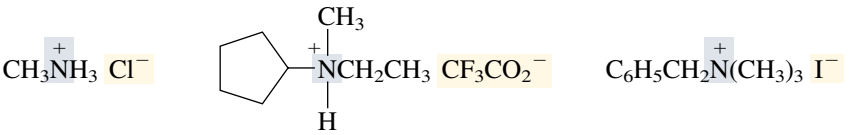


FIGURE 22.1 A ball-and-stick model of methylamine showing the trigonal pyramidal arrangement of bonds to nitrogen. The most stable conformation has the staggered arrangement of bonds shown. Other alkylamines have similar geometries.



Methylammonium chloride

N-Ethyl-*N*-methylcyclopentylammonium trifluoroacetate

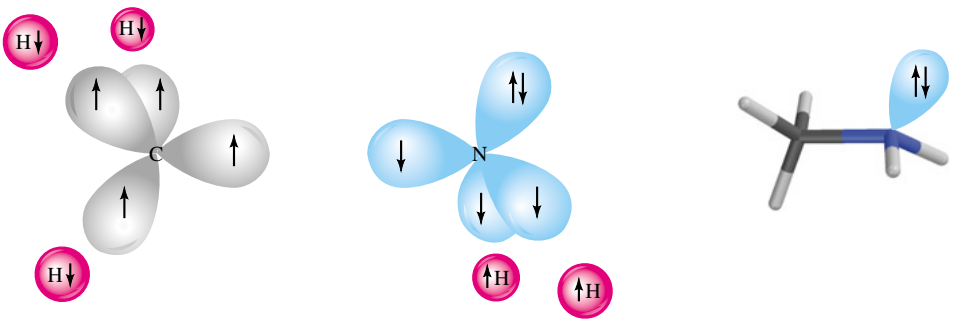
Benzyltrimethylammonium iodide (a quaternary ammonium salt)

Ammonium salts that have four alkyl groups bonded to nitrogen are called **quaternary ammonium salts.**

22.2 STRUCTURE AND BONDING

Alkylamines: As shown in Figure 22.1 methylamine, like ammonia, has a pyramidal arrangement of bonds to nitrogen. Its H—N—H angles (106°) are slightly smaller than the tetrahedral value of 109.5°, whereas the C—N—H angle (112°) is slightly larger. The C—N bond distance of 147 pm lies between typical C—C bond distances in alkanes (153 pm) and C—O bond distances in alcohols (143 pm).

An orbital hybridization description of bonding in methylamine is shown in Figure 22.2. Nitrogen and carbon are both sp^3-hybridized and are joined by a σ bond. The



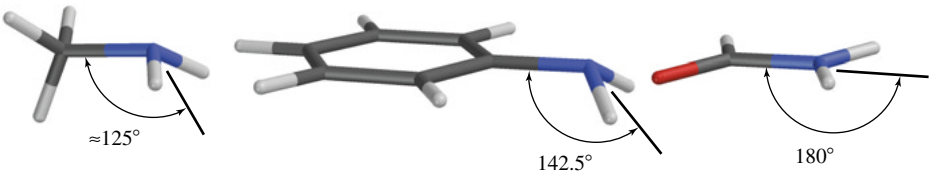
(*a*) (*b*)

FIGURE 22.2 Orbital hybridization description of bonding in methylamine. (*a*) Carbon has four valence electrons; each of four equivalent sp^3-hybridized orbitals contains one electron. Nitrogen has five valence electrons. Three of its sp^3 hybrid orbitals contain one electron each; the fourth sp^3 hybrid orbital contains two electrons. (*b*) Nitrogen and carbon are connected by a σ bond in methylamine. This σ bond is formed by overlap of an sp^3 hybrid orbital on each atom. The five hydrogen atoms of methylamine are joined to carbon and nitrogen by σ bonds. The two remaining electrons of nitrogen occupy an sp^3-hybridized orbital.

unshared electron pair on nitrogen occupies an sp^3-hybridized orbital. This lone pair is involved in reactions in which amines act as bases or nucleophiles. The graphic that opened this chapter is an electrostatic potential map that clearly shows the concentration of electron density at nitrogen in methylamine.

You can examine the structure of methylamine, including its electrostatic potential, in more detail on *Learning By Modeling.*

Arylamines: Aniline, like alkylamines, has a pyramidal arrangement of bonds around nitrogen, but its pyramid is somewhat shallower. One measure of the extent of this flattening is given by the angle between the carbon–nitrogen bond and the bisector of the H—N—H angle.

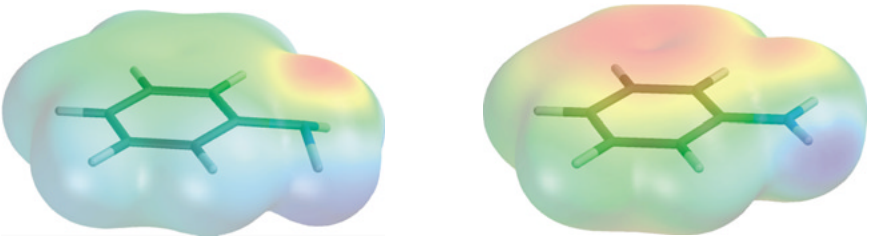


Methylamine (CH_3NH_2) Aniline ($C_6H_5NH_2$) Formamide ($O{=}CHNH_2$)

For sp^3-hybridized nitrogen, this angle (not the same as the C—N—H bond angle) is 125°, and the measured angles in simple alkylamines are close to that. The corresponding angle for sp^2 hybridization at nitrogen with a planar arrangement of bonds, as in amides, for example, is 180°. The measured value for this angle in aniline is 142.5°, suggesting a hybridization somewhat closer to sp^3 than to sp^2.

The geometry at nitrogen in amines is discussed in an article entitled "What Is the Geometry at Trigonal Nitrogen?" in the January 1998 issue of the *Journal of Chemical Education,* pp. 108–109.

The structure of aniline reflects a compromise between two modes of binding the nitrogen lone pair (Figure 22.3). The electrons are more strongly attracted to nitrogen when they are in an orbital with some *s* character—an sp^3-hybridized orbital, for example—than when they are in a *p* orbital. On the other hand, delocalization of these electrons into the aromatic π system is better achieved if they occupy a *p* orbital. A *p* orbital of nitrogen is better aligned for overlap with the *p* orbitals of the benzene ring to form

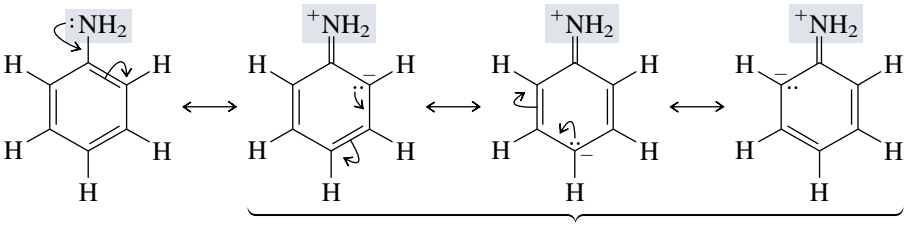


(*a*) (*b*)

FIGURE 22.3 Electrostatic potential maps of the aniline in which the geometry at nitrogen is (*a*) nonplanar and (*b*) planar. In the nonplanar geometry, the unshared pair occupies an sp^3 hybrid orbital of nitrogen. The region of highest electron density in (*a*) is associated with nitrogen. In the planar geometry, nitrogen is sp^2-hybridized and the electron pair is delocalized between a *p* orbital of nitrogen and the π system of the ring. The region of highest electron density in (*b*) encompasses both the ring and nitrogen. The actual structure combines features of both; nitrogen adopts a hybridization state between sp^3 and sp^2.

an extended π system than is an sp^3-hybridized orbital. As a result of these two opposing forces, nitrogen adopts an orbital hybridization that is between sp^3 and sp^2.

The corresponding resonance description shows the delocalization of the nitrogen lone-pair electrons in terms of contributions from dipolar structures.



Most stable Lewis structure for aniline

Dipolar resonance forms of aniline

The orbital and resonance models for bonding in arylamines are simply alternative ways of describing the same phenomenon. Delocalization of the nitrogen lone pair decreases the electron density at nitrogen while increasing it in the π system of the aromatic ring. We've already seen one chemical consequence of this in the high level of reactivity of aniline in electrophilic aromatic substitution reactions (Section 12.12). Other ways in which electron delocalization affects the properties of arylamines are described in later sections of this chapter.

PROBLEM 22.4 As the extent of electron delocalization into the ring increases, the geometry at nitrogen flattens. *p*-Nitroaniline, for example, is planar. Write a resonance form for *p*-nitroaniline that shows how the nitro group increases electron delocalization. Examine the electrostatic potential of the *p*-nitroaniline model on *Learning By Modeling*. Where is the greatest concentration of negative charge?

22.3 PHYSICAL PROPERTIES

We have often seen that the polar nature of a substance can affect physical properties such as boiling point. This is true for amines, which are more polar than alkanes but less polar than alcohols. For similarly constituted compounds, alkylamines have boiling points higher than those of alkanes but lower than those of alcohols.

A collection of physical properties of some representative amines is given in Appendix 1. Most commonly encountered alkylamines are liquids with unpleasant, "fishy" odors.

$CH_3CH_2CH_3$	$CH_3CH_2NH_2$	CH_3CH_2OH
Propane	Ethylamine	Ethanol
μ = 0 D	μ = 1.2 D	μ = 1.7 D
bp −42°C	bp 17°C	bp 78°C

Dipole–dipole interactions, especially hydrogen bonding, are present in amines but absent in alkanes. The less polar nature of amines as compared with alcohols, however, makes these intermolecular forces weaker in amines than in alcohols.

Among isomeric amines, primary amines have the highest boiling points, and tertiary amines the lowest.

$CH_3CH_2CH_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3N$
Propylamine	*N*-Methylethylamine	Trimethylamine
(a primary amine)	(a secondary amine)	(a tertiary amine)
bp 50°C	bp 34°C	bp 3°C

Primary and secondary amines can participate in intermolecular hydrogen bonding, but tertiary amines cannot.

Amines that have fewer than six or seven carbon atoms are soluble in water. All amines, even tertiary amines, can act as proton acceptors in hydrogen bonding to water molecules.

The simplest arylamine, aniline, is a liquid at room temperature and has a boiling point of 184°C. Almost all other arylamines have higher boiling points. Aniline is only slightly soluble in water (3 g/100 mL). Substituted derivatives of aniline tend to be even less water-soluble.

22.4 MEASURES OF AMINE BASICITY

Two conventions are used to measure the basicity of amines. One of them defines a **basicity constant K_b** for the amine acting as a proton acceptor from water:

$$R_3N: + H{-}\ddot{O}H \rightleftharpoons R_3\overset{+}{N}{-}H + \ddot{O}H^-$$

$$K_b = \frac{[R_3NH^+][HO^-]}{[R_3N]} \qquad \text{and} \qquad pK_b = -\log K_b$$

For ammonia, $K_b = 1.8 \times 10^{-5}$ ($pK_b = 4.7$). A typical amine such as methylamine (CH_3NH_2) is a stronger base than ammonia and has $K_b = 4.4 \times 10^{-4}$ ($pK_b = 3.3$).

The other convention relates the basicity of an amine (R_3N) to the *acid dissociation constant* K_a of its conjugate acid (R_3NH^+):

$$R_3\overset{+}{N}{-}H \rightleftharpoons H^+ + R_3N:$$

where K_a and pK_a have their usual meaning:

$$K_a = \frac{[H^+][R_3N]}{[R_3NH^+]} \qquad \text{and} \qquad pK_a = -\log K_a$$

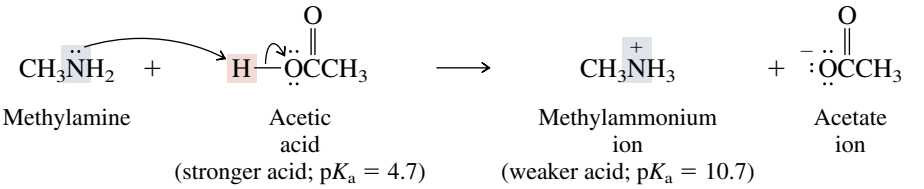
The conjugate acid of ammonia is ammonium ion (NH_4^+), which has $K_a = 5.6 \times 10^{-10}$ ($pK_a = 9.3$). The conjugate acid of methylamine is methylammonium ion ($CH_3NH_3^+$), which has $K_a = 2 \times 10^{-11}$ ($pK_a = 10.7$). *The more basic the amine, the weaker is its conjugate acid.* Methylamine is a stronger base than ammonia; methylammonium ion is a weaker acid than ammonium ion.

The relationship between the equilibrium constant K_b for an amine (R_3N) and K_a for its conjugate acid (R_3NH^+) is:

$$K_aK_b = 10^{-14} \qquad \text{and} \qquad pK_a + pK_b = 14$$

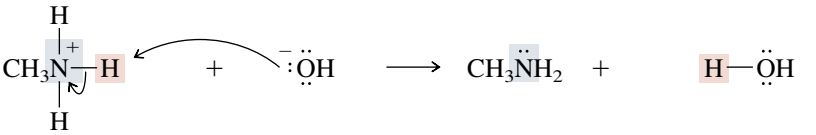
PROBLEM 22.5 A chemistry handbook lists K_b for *quinine* as 1×10^{-6}. What is pK_b for quinine? What are the values of K_a and pK_a for the conjugate acid of quinine?

Citing amine basicity according to the acidity of the conjugate acid permits acid–base reactions involving amines to be analyzed according to the usual Brønsted relationships. By comparing the acidity of an acid with the conjugate acid of an amine, for example, we see that amines are converted to ammonium ions by acids even as weak as acetic acid:



Recall from Section 4.6 that acid–base reactions are characterized by equilibrium constants greater than unity when the stronger acid is on the left side of the equation and the weaker acid on the right.

Conversely, adding sodium hydroxide to an ammonium salt converts it to the free amine:



PROBLEM 22.6 Apply the Henderson–Hasselbalch equation (see "Quantitative Relationships Involving Carboxylic Acids," the box accompanying Section 19.4) to calculate the $CH_3NH_3^+/CH_3NH_2$ ratio in water buffered at pH 7.

Their basicity provides a means by which amines may be separated from neutral organic compounds. A mixture containing an amine is dissolved in diethyl ether and shaken with dilute hydrochloric acid to convert the amine to an ammonium salt. The ammonium salt, being ionic, dissolves in the aqueous phase, which is separated from the ether layer. Adding sodium hydroxide to the aqueous layer converts the ammonium salt back to the free amine, which is then removed from the aqueous phase by extraction with a fresh portion of ether.

22.5 BASICITY OF AMINES

Amines are weak bases, but as a class, *amines are the strongest bases of all neutral molecules.* Table 22.1 lists basicity data for a number of amines. The most important relationships to be drawn from the data are

1. Alkylamines are slightly stronger bases than ammonia.
2. Alkylamines differ very little among themselves in basicity. Their basicities cover a range of less than 10 in equilibrium constant (1 pK unit).
3. Arylamines are much weaker bases than ammonia and alkylamines. Their basicity constants are on the order of 10^6 smaller than those of alkylamines (6 pK units).

The differences in basicity between ammonia, and primary, secondary, and tertiary alkylamines result from the interplay between steric and electronic effects on the molecules themselves and on the solvation of their conjugate acids. In total, the effects are small, and most alkylamines are very similar in basicity.

Arylamines are a different story, however; most are about a million times weaker as bases than ammonia and alkylamines.

As unfavorable as the equilibrium is for cyclohexylamine acting as a base in water,

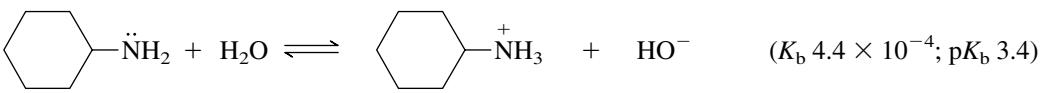
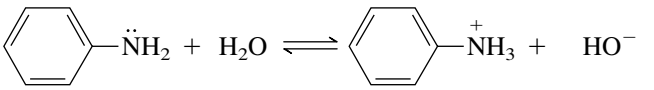


TABLE 22.1 Base Strength of Amines As Measured by Their Basicity Constants and the Dissociation Constants of Their Conjugate Acids*

Compound	Structure	Basicity K_b	Basicity pK_b	Acidity of conjugate acid K_a	Acidity of conjugate acid pK_a
Ammonia	NH_3	1.8×10^{-5}	4.7	5.5×10^{-10}	9.3
Primary amines					
Methylamine	CH_3NH_2	4.4×10^{-4}	3.4	2.3×10^{-11}	10.6
Ethylamine	$CH_3CH_2NH_2$	5.6×10^{-4}	3.2	1.8×10^{-11}	10.8
Isopropylamine	$(CH_3)_2CHNH_2$	4.3×10^{-4}	3.4	2.3×10^{-11}	10.6
tert-Butylamine	$(CH_3)_3CNH_2$	2.8×10^{-4}	3.6	3.6×10^{-11}	10.4
Aniline	$C_6H_5NH_2$	3.8×10^{-10}	9.4	2.6×10^{-5}	4.6
Secondary amines					
Dimethylamine	$(CH_3)_2NH$	5.1×10^{-4}	3.3	2.0×10^{-11}	10.7
Diethylamine	$(CH_3CH_2)_2NH$	1.3×10^{-3}	2.9	7.7×10^{-12}	11.1
N-Methylaniline	$C_6H_5NHCH_3$	6.1×10^{-10}	9.2	1.6×10^{-5}	4.8
Tertiary amines					
Trimethylamine	$(CH_3)_3N$	5.3×10^{-5}	4.3	1.9×10^{-10}	9.7
Triethylamine	$(CH_3CH_2)_3N$	5.6×10^{-4}	3.2	1.8×10^{-11}	10.8
N,*N*-Dimethylaniline	$C_6H_5N(CH_3)_2$	1.2×10^{-9}	8.9	8.3×10^{-6}	5.1

*In water at 25°C.

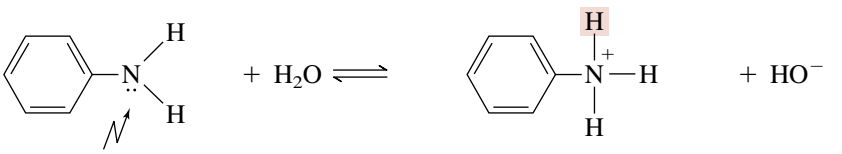
it is far less favorable for aniline.



Aniline + Water ⇌ Anilinium ion + Hydroxide ion (K_b 3.8×10^{-10}; pK_b 9.4)

Compare the calculated charge on nitrogen in cyclohexylamine and aniline on *Learning By Modeling.*

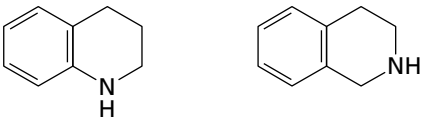
Aniline is a much weaker base because its delocalized lone pair is more strongly held than the nitrogen lone pair in cyclohexylamine. The more strongly held the electron pair, the less able it is to abstract a proton.



Aniline is stabilized by delocalization of lone pair into π system of ring, decreasing the electron density at nitrogen.

When the proton donor is a strong acid, arylamines can be completely protonated. Aniline is extracted from an ether solution into 1 M hydrochloric acid because it is converted to a water-soluble anilinium ion salt under these conditions.

PROBLEM 22.7 The two amines shown differ by a factor of 40,000 in their K_b values. Which is the stronger base? Why? View their structures on *Learning By Modeling.* What are the calculated charges on the two nitrogens?

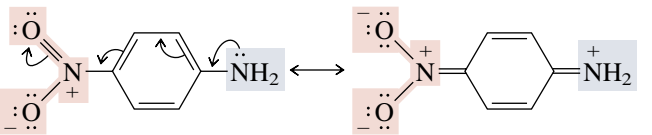


Tetrahydroquinoline Tetrahydroisoquinoline

Conjugation of the amino group of an arylamine with a second aromatic ring, then a third, reduces its basicity even further. Diphenylamine is 6300 times less basic than aniline, whereas triphenylamine is scarcely a base at all, being estimated as 10^8 times less basic than aniline and 10^{14} times less basic than ammonia.

$C_6H_5NH_2$	$(C_6H_5)_2NH$	$(C_6H_5)_3N$
Aniline (K_b 3.8×10^{-10}; pK_b 9.4)	Diphenylamine (K_b 6×10^{-14}; pK_b 13.2)	Triphenylamine ($K_b \approx 10^{-19}$; p$K_b \approx 19$)

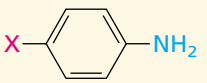
In general, electron-donating substituents on the aromatic ring increase the basicity of arylamines slightly. Thus, as shown in Table 22.2, an electron-donating methyl group in the para position *increases* the basicity of aniline by a factor of only 5–6 (less than 1 pK unit). Electron-withdrawing groups are base-weakening and exert larger effects. A *p*-trifluoromethyl group *decreases* the basicity of aniline by a factor of 200 and a *p*-nitro group by a factor of 3800. In the case of *p*-nitroaniline a resonance interaction of the type shown provides for extensive delocalization of the unshared electron pair of the amine group.



Electron delocalization in *p*-nitroaniline

Just as aniline is much less basic than alkylamines because the unshared electron pair of nitrogen is delocalized into the π system of the ring, *p*-nitroaniline is even less basic because the extent of this delocalization is greater and involves the oxygens of the nitro group.

TABLE 22.2 Effect of Substituents on the Basicity of Aniline



X	K_b	pK_b
H	4×10^{-10}	9.4
CH_3	2×10^{-9}	8.7
CF_3	2×10^{-12}	11.5
O_2N	1×10^{-13}	13.0

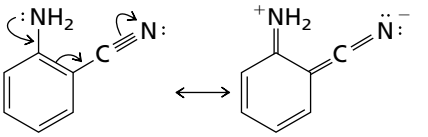
PROBLEM 22.8 Each of the following is a much weaker base than aniline. Present a resonance argument to explain the effect of the substituent in each case.

(a) *o*-Cyanoaniline

(c) *p*-Aminoacetophenone

(b) $C_6H_5NHCCH_3$ (O double-bonded to the carbonyl carbon)

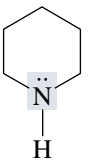
SAMPLE SOLUTION (a) A cyano substituent is strongly electron-withdrawing. When present at a position ortho to an amino group on an aromatic ring, a cyano substituent increases the delocalization of the amine lone-pair electrons by a direct resonance interaction.



This resonance stabilization is lost when the amine group becomes protonated, and *o*-cyanoaniline is therefore a weaker base than aniline.

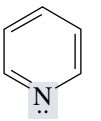
Multiple substitution by strongly electron-withdrawing groups diminishes the basicity of arylamines still more. As just noted, aniline is 3800 times as strong a base as *p*-nitroaniline; however, it is 10^9 times more basic than 2,4-dinitroaniline. A practical consequence of this is that arylamines that bear two or more strongly electron-withdrawing groups are often not capable of being extracted from ether solution into dilute aqueous acid.

Nonaromatic heterocyclic compounds, piperidine, for example, are similar in basicity to alkylamines. When nitrogen is part of an aromatic ring, however, its basicity decreases markedly. Pyridine, for example, resembles arylamines in being almost 1 million times less basic than piperidine.



Piperidine
($K_b = 1.6 \times 10^{-3}$; $pK_b = 2.8$)

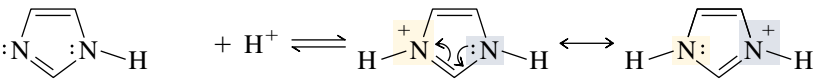
is more basic than



Pyridine
($K_b = 1.4 \times 10^{-9}$; $pK_b = 8.8$)

Pyridine and imidazole were two of the heterocyclic aromatic compounds described in Section 11.21.

Imidazole and its derivatives form an interesting and important class of heterocyclic aromatic amines. Imidazole is approximately 100 times more basic than pyridine. Protonation of imidazole yields an ion that is stabilized by the electron delocalization represented in the resonance structures shown:



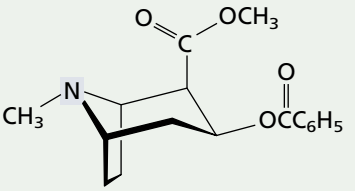
Imidazole
($K_b = 1 \times 10^{-7}$; $pK_b = 7$)

Imidazolium ion

An imidazole ring is a structural unit in the amino acid *histidine* (Section 27.1) and is involved in a large number of biological processes as a base and as a nucleophile.

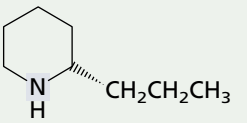
AMINES AS NATURAL PRODUCTS

The ease with which amines are extracted into aqueous acid, combined with their regeneration on treatment with base, makes it a simple matter to separate amines from other plant materials, and nitrogen-containing natural products were among the earliest organic compounds to be studied.* Their basic properties led amines obtained from plants to be called **alkaloids.** The number of known alkaloids exceeds 5000. They are of special interest because most are characterized by a high level of biological activity. Some examples include *cocaine, coniine,* and *morphine.*



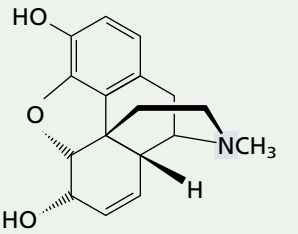
Cocaine

(A central nervous system stimulant obtained from the leaves of the coca plant.)



Coniine

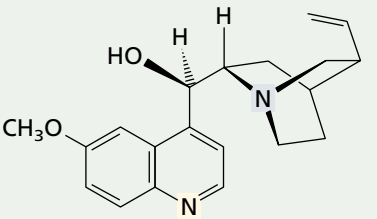
(Present along with other alkaloids in the hemlock extract used to poison Socrates.)



Morphine

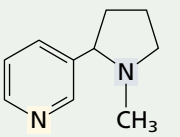
(An opium alkaloid. Although it is an excellent analgesic, its use is restricted because of the potential for addiction. Heroin is the diacetate ester of morphine.)

Many alkaloids, such as *nicotine* and *quinine,* contain two (or more) nitrogen atoms. The nitrogens highlighted in yellow in quinine and nicotine are part of a substituted quinoline and pyridine ring, respectively.



Quinine

(Alkaloid of cinchona bark used to treat malaria)



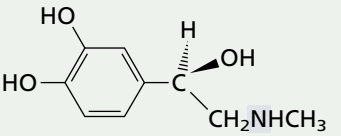
Nicotine

(An alkaloid present in tobacco; a very toxic compound sometimes used as an insecticide)

Several naturally occurring amines mediate the transmission of nerve impulses and are referred to as **neurotransmitters.** Two examples are *epinephrine* and *serotonin.* (Strictly speaking, these compounds are not classified as alkaloids, because they are not isolated from plants.)

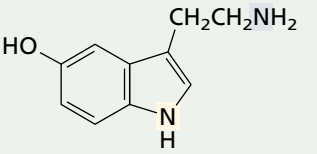
* The isolation of alkaloids from plants is reviewed in the August 1991 issue of the *Journal of Chemical Education*, pp. 700–703.

—Cont.



Epinephrine

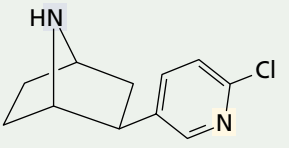
(Also called *adrenaline;* a hormone secreted by the adrenal gland that prepares the organism for "flight or fight.")



Serotonin

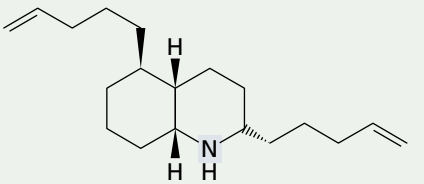
(A hormone synthesized in the pineal gland. Certain mental disorders are believed to be related to serotonin levels in the brain.)

Bioactive amines are also widespread in animals. A variety of structures and properties have been found in substances isolated from frogs, for example. One, called epibatidine, is a naturally occurring painkiller isolated from the skin of an Ecuadoran frog. Another family of frogs produces a toxic mixture of several stereoisomeric amines, called dendrobines, on their skin that protects them from attack.



Epibatidine

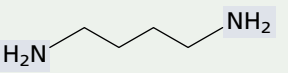
(Once used as an arrow poison, it is hundreds of times more powerful than morphine in relieving pain. It is too toxic to be used as a drug, however.)



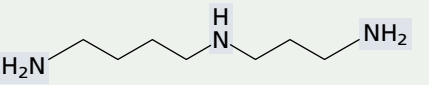
Dendrobine

(Isolated from frogs of the Dendrobatidae family. Related compounds have also been isolated from certain ants.)

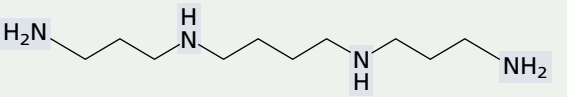
Among the more important amine derivatives found in the body are a group of compounds known as **polyamines,** which contain two to four nitrogen atoms separated by several methylene units:



Putrescine



Spermidine

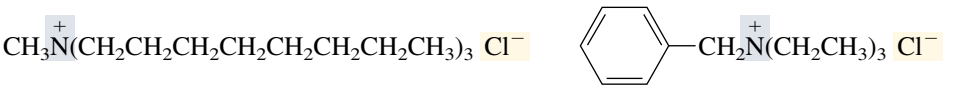


Spermine

These compounds are present in almost all mammalian cells, where they are believed to be involved in cell differentiation and proliferation. Because each nitrogen of a polyamine is protonated at physiological pH (7.4), putrescine, spermidine, and spermine exist as cations with a charge of + 2, + 3, and + 4, respectively, in body fluids. Structural studies suggest that these polyammonium ions affect the conformation of biological macromolecules by electrostatic binding to specific anionic sites—the negatively charged phosphate groups of DNA, for example.

22.6 TETRAALKYLAMMONIUM SALTS AS PHASE-TRANSFER CATALYSTS

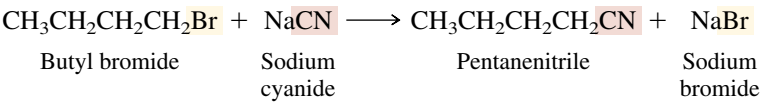
In spite of being ionic, many quaternary ammonium salts dissolve in nonpolar media. The four alkyl groups attached to nitrogen shield its positive charge and impart *lipophilic* character to the tetraalkylammonium ion. The following two quaternary ammonium salts, for example, are soluble in solvents of low polarity such as benzene, decane, and halogenated hydrocarbons:



Methyltrioctylammonium chloride

Benzyltriethylammonium chloride

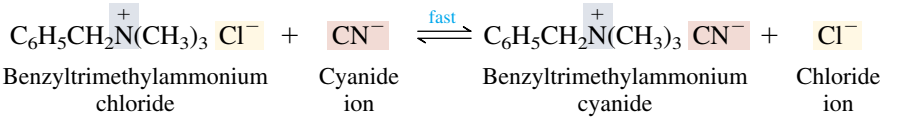
This property of quaternary ammonium salts is used to advantage in an experimental technique known as **phase-transfer catalysis.** Imagine that you wish to carry out the reaction



Butyl bromide — Sodium cyanide — Pentanenitrile — Sodium bromide

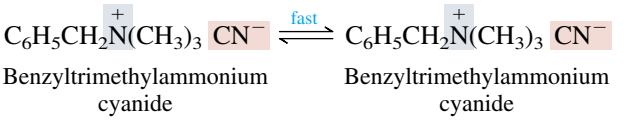
Sodium cyanide does not dissolve in butyl bromide. The two reactants contact each other only at the surface of the solid sodium cyanide, and the rate of reaction under these conditions is too slow to be of synthetic value. Dissolving the sodium cyanide in water is of little help, since butyl bromide is not soluble in water and reaction can occur only at the interface between the two phases. Adding a small amount of benzyltrimethylammonium chloride, however, causes pentanenitrile to form rapidly even at room temperature. The quaternary ammonium salt is acting as a *catalyst;* it increases the reaction rate. How?

Quaternary ammonium salts catalyze the reaction between an anion and an organic substrate by transferring the anion from the aqueous phase, where it cannot contact the substrate, to the organic phase. In the example just cited, the first step occurs in the aqueous phase and is an exchange of the anionic partner of the quaternary ammonium salt for cyanide ion:



Benzyltrimethylammonium chloride (aqueous) — Cyanide ion (aqueous) — Benzyltrimethylammonium cyanide (aqueous) — Chloride ion (aqueous)

The benzyltrimethylammonium ion migrates to the butyl bromide phase, carrying a cyanide ion along with it.



Benzyltrimethylammonium cyanide (aqueous) — Benzyltrimethylammonium cyanide (in butyl bromide)

Once in the organic phase, cyanide ion is only weakly solvated and is far more reactive than it is in water or ethanol, where it is strongly solvated by hydrogen bonding. Nucleophilic substitution takes place rapidly.

$$CH_3CH_2CH_2CH_2Br + C_6H_5CH_2\overset{+}{N}(CH_3)_3\ CN^- \longrightarrow$$

Butyl bromide — Benzyltrimethylammonium cyanide (in butyl bromide)

$$CH_3CH_2CH_2CH_2CN + C_6H_5CH_2\overset{+}{N}(CH_3)_3\ Br^-$$

Pentanenitrile (in butyl bromide) — Benzyltrimethylammonium bromide (in butyl bromide)

The benzyltrimethylammonium bromide formed in this step returns to the aqueous phase, where it can repeat the cycle.

Phase-transfer catalysis is the subject of an article in the April 1978 issue of the *Journal of Chemical Education* (pp. 235–238). This article includes examples of a variety of reactions carried out under phase-transfer conditions.

Phase-transfer catalysis succeeds for two reasons. First, it provides a mechanism for introducing an anion into the medium that contains the reactive substrate. More important, the anion is introduced in a weakly solvated, highly reactive state. You've already seen phase-transfer catalysis in another form in Section 16.4, where the metal-complexing properties of crown ethers were described. Crown ethers permit metal salts to dissolve in nonpolar solvents by surrounding the cation with a lipophilic cloak, leaving the anion free to react without the encumbrance of strong solvation forces.

22.7 REACTIONS THAT LEAD TO AMINES: A REVIEW AND A PREVIEW

Methods for preparing amines address either or both of the following questions:

1. How is the required carbon–nitrogen bond to be formed?
2. Given a nitrogen-containing organic compound such as an amide, a nitrile, or a nitro compound, how is the correct oxidation state of the desired amine to be achieved?

A number of reactions that lead to carbon–nitrogen bond formation were presented in earlier chapters and are summarized in Table 22.3. Among the reactions in the table, the nucleophilic ring opening of epoxides, reaction of α-halo acids with ammonia, and the Hofmann rearrangement give amines directly. The other reactions in Table 22.3 yield products that are converted to amines by some subsequent procedure. As these procedures are described in the following sections, you will see that they are largely applications of principles that you've already learned. You will encounter some new reagents and some new uses for familiar reagents, but very little in the way of new reaction types is involved.

22.8 PREPARATION OF AMINES BY ALKYLATION OF AMMONIA

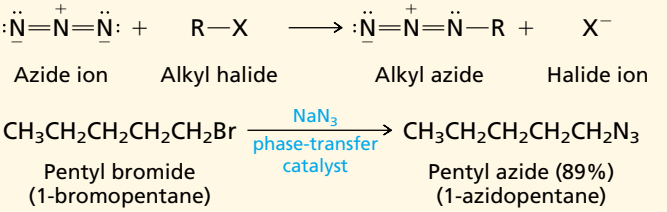
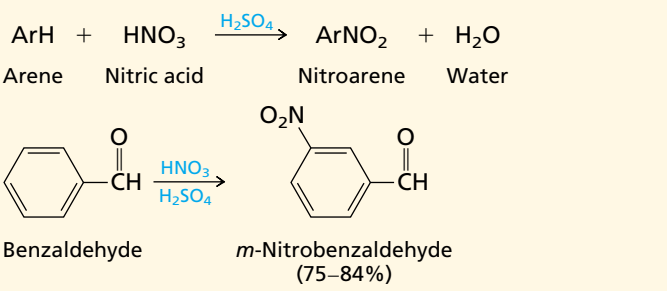
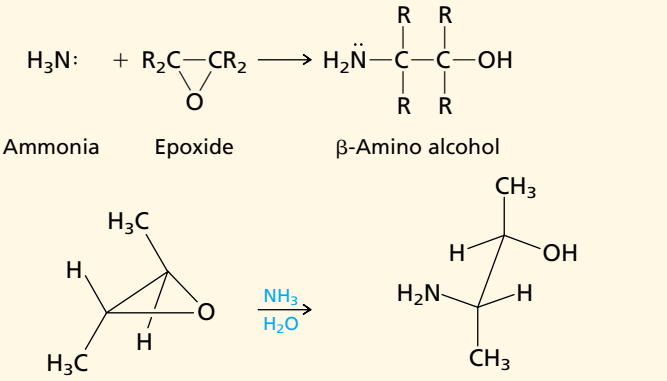
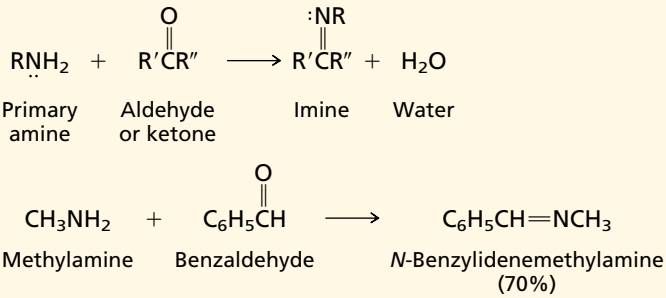
Alkylamines are, in principle, capable of being prepared by nucleophilic substitution reactions of alkyl halides with ammonia.

$$RX + 2NH_3 \longrightarrow RNH_2 + \overset{+}{N}H_4\ X^-$$

Alkyl halide — Ammonia — Primary amine — Ammonium halide salt

Although this reaction is useful for preparing α-amino acids (Table 22.3, fifth entry), it is not a general method for the synthesis of amines. Its major limitation is that the expected primary amine product is itself a nucleophile and competes with ammonia for the alkyl halide.

TABLE 22.3 Methods for Carbon–Nitrogen Bond Formation Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Nucleophilic substitution by azide ion on an alkyl halide (Sections 8.1, 8.13) Azide ion is a very good nucleophile and reacts with primary and secondary alkyl halides to give alkyl azides. Phase-transfer catalysts accelerate the rate of reaction.	
Nitration of arenes (Section 12.3) The standard method for introducing a nitrogen atom as a substituent on an aromatic ring is nitration with a mixture of nitric acid and sulfuric acid. The reaction proceeds by electrophilic aromatic substitution.	
Nucleophilic ring opening of epoxides by ammonia (Section 16.12) The strained ring of an epoxide is opened on nucleophilic attack by ammonia and amines to give β-amino alcohols. Azide ion also reacts with epoxides; the products are β-azido alcohols.	
Nucleophilic addition of amines to aldehydes and ketones (Sections 17.10, 17.11) Primary amines undergo nucleophilic addition to the carbonyl group of aldehydes and ketones to form carbinolamines. These carbinolamines dehydrate under the conditions of their formation to give *N*-substituted imines. Secondary amines yield enamines.	

(Continued)

TABLE 22.3 Methods for Carbon–Nitrogen Bond Formation Discussed in Earlier Chapters *(Continued)*

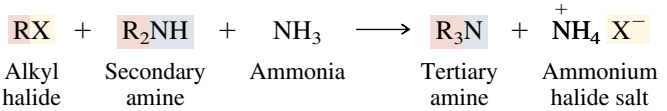
Reaction (section) and comments	General equation and specific example
Nucleophilic substitution by ammonia on α-halo acids (Section 19.16) The α-halo acids obtained by halogenation of carboxylic acids under conditions of the Hell–Volhard–Zelinsky reaction are reactive substrates in nucleophilic substitution processes. A standard method for the preparation of α-amino acids is displacement of halide from α-halo acids by nucleophilic substitution using excess aqueous ammonia.	$H_3N:$ + $RCHCO_2H$ (X) → $RCHCO_2^-$ ($^+NH_3$) + NH_4X Ammonia (excess); α-Halo carboxylic acid; α-Amino acid; Ammonium halide $(CH_3)_2CHCHCO_2H$ (Br) $\xrightarrow[H_2O]{NH_3}$ $(CH_3)_2CHCHCO_2^-$ ($^+NH_3$) 2-Bromo-3-methylbutanoic acid; 2-Amino-3-methylbutanoic acid (47–48%)
Nucleophilic acyl substitution (Sections 20.3, 20.5, and 20.11) Acylation of ammonia and amines by an acyl chloride, acid anhydride, or ester is an exceptionally effective method for the formation of carbon–nitrogen bonds.	R_2NH + $R'C(=O)X$ → R_2NCR' (=O) + HX Primary or secondary amine, or ammonia; Acyl chloride, acid anhydride, or ester; Amide; Water 2 Pyrrolidine + CH_3CCl (=O) → *N*-Acetylpyrrolidine (=O) (79%) + Pyrrolidine hydrochloride (Cl^-) Pyrrolidine; Acetyl chloride; *N*-Acetylpyrrolidine (79%); Pyrrolidine hydrochloride
The Hofmann rearrangement (Section 20.17) Amides are converted to amines by reaction with bromine in basic media. An *N*-bromo amide is an intermediate; it rearranges to an isocyanate. Hydrolysis of the isocyanate yields an amine.	$RCNH_2$ (=O) $\xrightarrow[H_2O]{Br_2,\ HO^-}$ RNH_2 Amide; Amine $(CH_3)_3CCNH_2$ (=O) $\xrightarrow[H_2O]{Br_2,\ HO^-}$ $(CH_3)_3CNH_2$ 2,2-Dimethylpropanamide; *tert*-Butylamine (64%)

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Primary amine}}{RNH_2} + \underset{\text{Ammonia}}{NH_3} \longrightarrow \underset{\text{Secondary amine}}{RNHR} + \underset{\text{Ammonium halide salt}}{\overset{+}{N}H_4\ X^-}$$

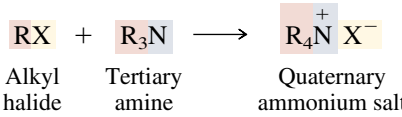
When 1-bromooctane, for example, is allowed to react with ammonia, both the primary amine and the secondary amine are isolated in comparable amounts.

$$\underset{\substack{\text{1-Bromooctane}\\(1\text{ mol})}}{CH_3(CH_2)_6CH_2Br} \xrightarrow{NH_3\ (2\text{ mol})} \underset{\substack{\text{Octylamine}\\(45\%)}}{CH_3(CH_2)_6CH_2NH_2} + \underset{\substack{\textit{N},\textit{N}\text{-Dioctylamine}\\(43\%)}}{[CH_3(CH_2)_6CH_2]_2NH}$$

In a similar manner, competitive alkylation may continue, resulting in formation of a trialkylamine.



Even the tertiary amine competes with ammonia for the alkylating agent. The product is a quaternary ammonium salt.



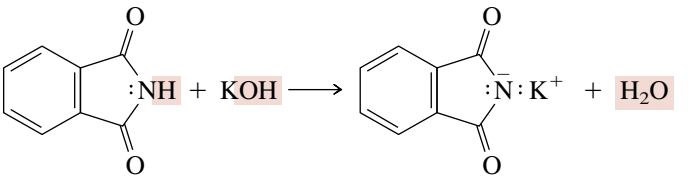
Because alkylation of ammonia can lead to a complex mixture of products, it is used to prepare primary amines only when the starting alkyl halide is not particularly expensive and the desired amine can be easily separated from the other components of the reaction mixture.

PROBLEM 22.9 Alkylation of ammonia is sometimes employed in industrial processes; the resulting mixture of amines is separated by distillation. The ultimate starting materials for the industrial preparation of allylamine are propene, chlorine, and ammonia. Write a series of equations showing the industrial preparation of allylamine from these starting materials. (Allylamine has a number of uses, including the preparation of the diuretic drugs *meralluride* and *mercaptomerin*.)

Aryl halides do not normally react with ammonia under these conditions. The few exceptions are special cases and will be described in Section 23.5.

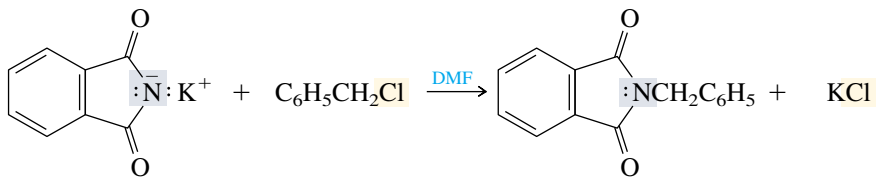
22.9 THE GABRIEL SYNTHESIS OF PRIMARY ALKYLAMINES

A method that achieves the same end result as that desired by alkylation of ammonia but which avoids the formation of secondary and tertiary amines as byproducts is the **Gabriel synthesis.** Alkyl halides are converted to primary alkylamines without contamination by secondary or tertiary amines. The key reagent is the potassium salt of phthalimide, prepared by the reaction



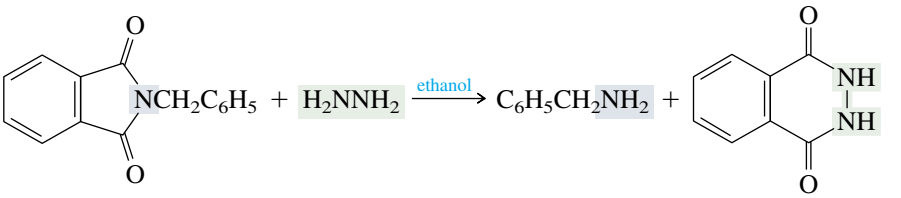
The Gabriel synthesis is based on work carried out by Siegmund Gabriel at the University of Berlin in the 1880s. A detailed discussion of each step in the Gabriel synthesis of benzylamine can be found in the October 1975 *Journal of Chemical Education* (pp. 670–671).

Phthalimide, with a K_a of 5×10^{-9} (pK_a 8.3), can be quantitatively converted to its potassium salt with potassium hydroxide. The potassium salt of phthalimide has a negatively charged nitrogen atom, which acts as a nucleophile toward primary alkyl halides in a bimolecular nucleophilic substitution (S_N2) process.



DMF is an abbreviation for *N,N*-dimethylformamide, $HCN(CH_3)_2$. DMF is a polar aprotic solvent (Section 8.12) and an excellent medium for S_N2 reactions.

The product of this reaction is an imide (Section 20.15), a diacyl derivative of an amine. Either aqueous acid or aqueous base can be used to hydrolyze its two amide bonds and liberate the desired primary amine. A more effective method of cleaving the two amide bonds is by acyl transfer to hydrazine:



N-Benzylphthalimide Hydrazine Benzylamine (97%) Phthalhydrazide

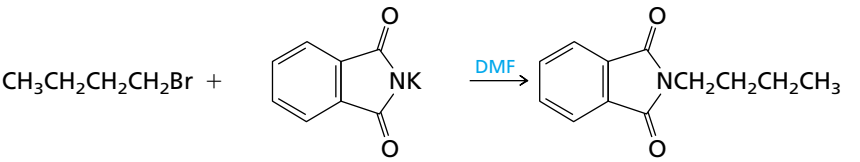
Aryl halides cannot be converted to arylamines by the Gabriel synthesis, because they do not undergo nucleophilic substitution with *N*-potassiophthalimide in the first step of the procedure.

Among compounds other than simple alkyl halides, α-halo ketones and α-halo esters have been employed as substrates in the Gabriel synthesis. Alkyl *p*-toluenesulfonate esters have also been used. Because phthalimide can undergo only a single alkylation, the formation of secondary and tertiary amines does not occur, and the Gabriel synthesis is a valuable procedure for the laboratory preparation of primary amines.

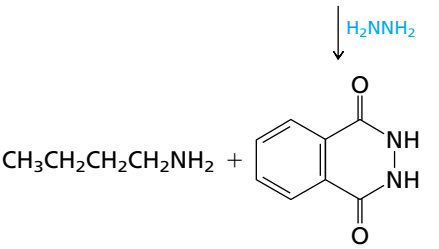
PROBLEM 22.10 Which of the following amines can be prepared by the Gabriel synthesis? Which ones cannot? Write equations showing the successful applications of this method.

(a) Butylamine
(b) Isobutylamine
(c) *tert*-Butylamine
(d) 2-Phenylethylamine
(e) *N*-Methylbenzylamine
(f) Aniline

SAMPLE SOLUTION (a) The Gabriel synthesis is limited to preparation of amines of the type RCH_2NH_2, that is, primary alkylamines in which the amino group is bonded to a primary carbon. Butylamine may be prepared from butyl bromide by this method.



Butyl bromide *N*-Potassiophthalimide *N*-Butylphthalimide



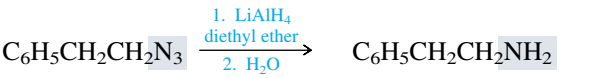
Butylamine Phthalhydrazide

22.10 PREPARATION OF AMINES BY REDUCTION

Almost any nitrogen-containing organic compound can be reduced to an amine. The synthesis of amines then becomes a question of the availability of suitable precursors and the choice of an appropriate reducing agent.

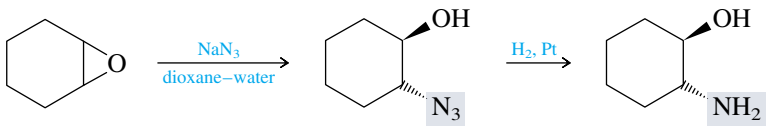
Alkyl *azides,* prepared by nucleophilic substitution of alkyl halides by sodium azide, as shown in the first entry of Table 22.3, are reduced to alkylamines by a variety of reagents, including lithium aluminum hydride.

Alkyl azide — Primary amine



2-Phenylethyl azide — 2-Phenylethylamine (89%)

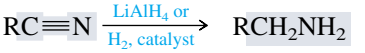
Catalytic hydrogenation is also effective:



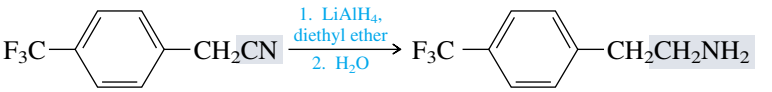
1,2-Epoxycyclohexane — *trans*-2-Azidocyclohexanol (61%) — *trans*-2-Aminocyclohexanol (81%)

In its overall design, this procedure is similar to the Gabriel synthesis; a nitrogen nucleophile is used in a carbon–nitrogen bond-forming operation and then converted to an amino group in a subsequent transformation.

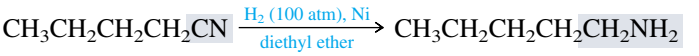
The same reduction methods may be applied to the conversion of *nitriles* to primary amines.



Nitrile — Primary amine



p-(Trifluoromethyl)benzyl cyanide — 2-(*p*-Trifluoromethyl)phenylethylamine (53%)



Pentanenitrile — 1-Pentanamine (56%)

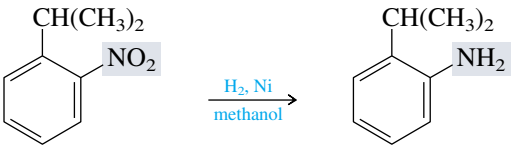
The preparation of pentanenitrile under phase-transfer conditions was described in Section 22.6.

Since nitriles can be prepared from alkyl halides by nucleophilic substitution with cyanide ion, the overall process RX → RC≡N → RCH_2NH_2 leads to primary amines that have one more carbon atom than the starting alkyl halide.

Cyano groups in *cyanohydrins* (Section 17.7) are reduced under the same reaction conditions.

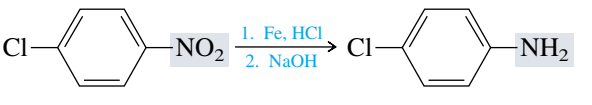
Nitro groups are readily reduced to primary amines by a variety of methods. Catalytic hydrogenation over platinum, palladium, or nickel is often used, as is reduction by iron or tin in hydrochloric acid. The ease with which nitro groups are reduced is

especially useful in the preparation of arylamines, where the sequence ArH → $ArNO_2$ → $ArNH_2$ is the standard route to these compounds.

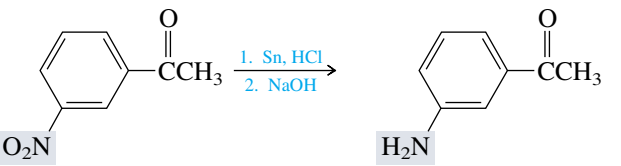


o-Isopropylnitrobenzene — *o*-Isopropylaniline (92%)

For reductions carried out in acidic media, a pH adjustment with sodium hydroxide is required in the last step in order to convert $ArNH_3^+$ to $ArNH_2$.



p-Chloronitrobenzene — *p*-Chloroaniline (95%)

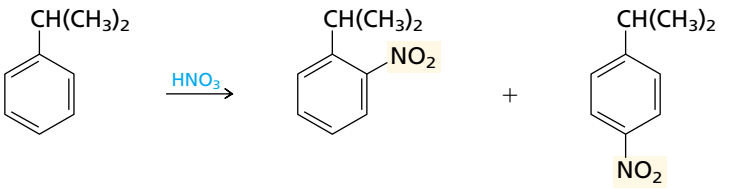


m-Nitroacetophenone — *m*-Aminoacetophenone (82%)

PROBLEM 22.11 Outline syntheses of each of the following arylamines from benzene:

(a) *o*-Isopropylaniline
(b) *p*-Isopropylaniline
(c) 4-Isopropyl-1,3-benzenediamine
(d) *p*-Chloroaniline
(e) *m*-Aminoacetophenone

SAMPLE SOLUTION (a) The last step in the synthesis of *o*-isopropylaniline, the reduction of the corresponding nitro compound by catalytic hydrogenation, is given as one of the three preceding examples. The necessary nitroarene is obtained by fractional distillation of the ortho–para mixture formed during nitration of isopropylbenzene.

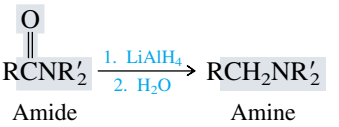


Isopropylbenzene — *o*-Isopropylnitrobenzene (bp 110°C) — *p*-Isopropylnitrobenzene (bp 131°C)

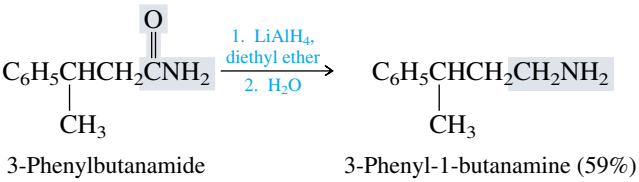
As actually performed, a 62% yield of a mixture of ortho and para nitration products has been obtained with an ortho–para ratio of about 1:3.

Isopropylbenzene is prepared by the Friedel–Crafts alkylation of benzene using isopropyl chloride and aluminum chloride (Section 12.6).

Reduction of an azide, a nitrile, or a nitro compound furnishes a primary amine. A method that provides access to primary, secondary, or tertiary amines is reduction of the carbonyl group of an amide by lithium aluminum hydride.

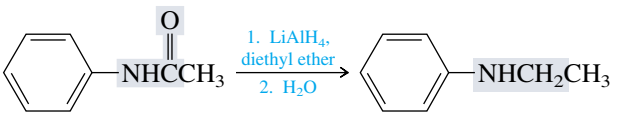


In this general equation, R and R′ may be either alkyl or aryl groups. When R′ = H, the product is a primary amine:

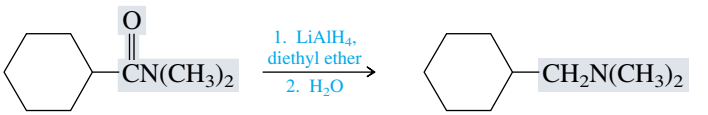


N-Substituted amides yield secondary amines:

Acetanilide is an acceptable IUPAC synonym for *N*-phenylethanamide.



N,N-Disubstituted amides yield tertiary amines:

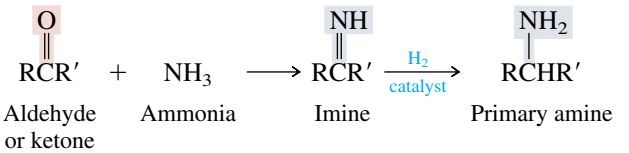


Because amides are so easy to prepare, this is a versatile method for the preparation of amines.

The preparation of amines by the methods described in this section involves the prior synthesis and isolation of some reducible material that has a carbon–nitrogen bond: an azide, a nitrile, a nitro-substituted arene, or an amide. The following section describes a method that combines the two steps of carbon–nitrogen bond formation and reduction into a single operation. Like the reduction of amides, it offers the possibility of preparing primary, secondary, or tertiary amines by proper choice of starting materials.

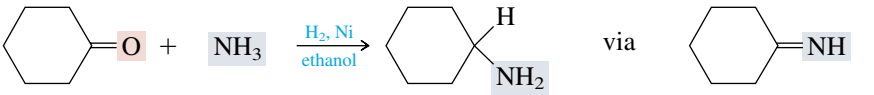
22.11 REDUCTIVE AMINATION

A class of nitrogen-containing compounds that was omitted from the section just discussed includes *imines* and their derivatives. Imines are formed by the reaction of aldehydes and ketones with ammonia. Imines can be reduced to primary amines by catalytic hydrogenation.



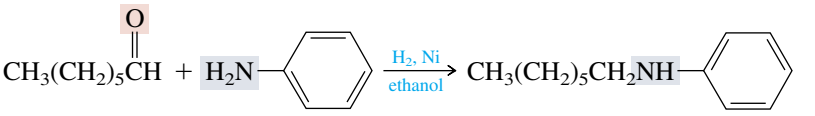
The overall reaction converts a carbonyl compound to an amine by carbon–nitrogen bond formation and reduction; it is commonly known as **reductive amination.** What makes it a particularly valuable synthetic procedure is that it can be carried out in a single operation by hydrogenation of a solution containing both ammonia and the carbonyl compound along with a hydrogenation catalyst. The intermediate imine is not isolated but undergoes reduction under the conditions of its formation. Also, the reaction is broader in scope than implied by the preceding equation. All classes of amines—primary, secondary, and tertiary—may be prepared by reductive amination.

When primary amines are desired, the reaction is carried out as just described:

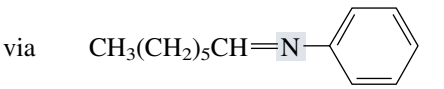


Cyclohexanone Ammonia Cyclohexylamine (80%)

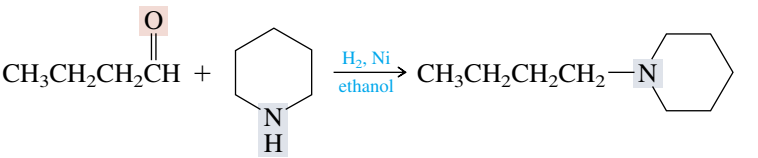
Secondary amines are prepared by hydrogenation of a carbonyl compound in the presence of a primary amine. An *N*-substituted imine, or *Schiff's base,* is an intermediate:



Heptanal Aniline *N*-Heptylaniline (65%)

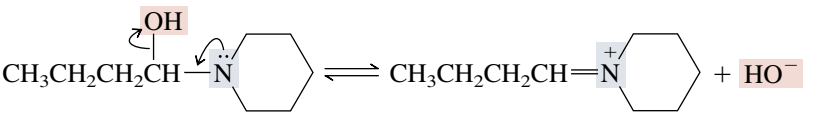


Reductive amination has been successfully applied to the preparation of tertiary amines from carbonyl compounds and secondary amines even though a neutral imine is not possible in this case.



Butanal Piperidine *N*-Butylpiperidine (93%)

Presumably, the species that undergoes reduction here is a carbinolamine or an iminium ion derived from it.

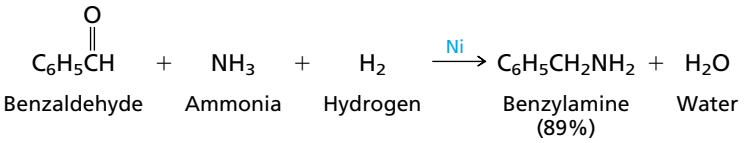


Carbinolamine Iminium ion

PROBLEM 22.12 Show how you could prepare each of the following amines from benzaldehyde by reductive amination:

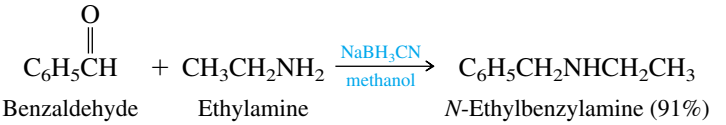
(a) Benzylamine
(b) Dibenzylamine
(c) *N,N*-Dimethylbenzylamine
(d) *N*-Benzylpiperidine

SAMPLE SOLUTION (a) Since benzylamine is a primary amine, it is derived from ammonia and benzaldehyde.



The reaction proceeds by initial formation of the imine $C_6H_5CH{=}NH$, followed by its hydrogenation.

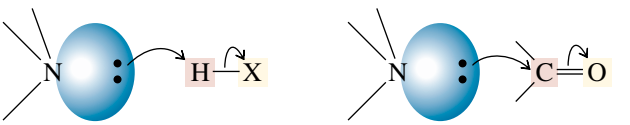
A variation of the classical reductive amination procedure uses sodium cyanoborohydride ($NaBH_3CN$) instead of hydrogen as the reducing agent and is better suited to amine syntheses in which only a few grams of material are needed. All that is required is to add sodium cyanoborohydride to an alcohol solution of the carbonyl compound and an amine.



22.12 REACTIONS OF AMINES: A REVIEW AND A PREVIEW

The noteworthy properties of amines are their *basicity* and their *nucleophilicity.* The basicity of amines has been discussed in Section 22.5. Several reactions in which amines act as nucleophiles have already been encountered in earlier chapters. These are summarized in Table 22.4.

Both the basicity and the nucleophilicity of amines originate in the unshared electron pair of nitrogen. When an amine acts as a base, this electron pair abstracts a proton from a Brønsted acid. When an amine undergoes the reactions summarized in Table 22.4, the first step in each case is the attack of the unshared electron pair on the positively polarized carbon of a carbonyl group.



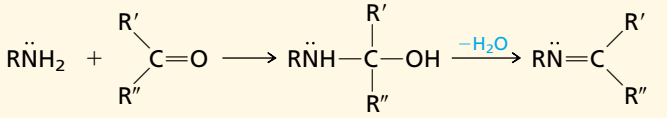
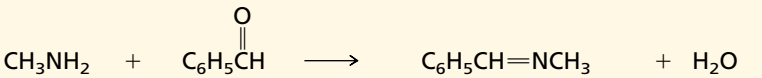
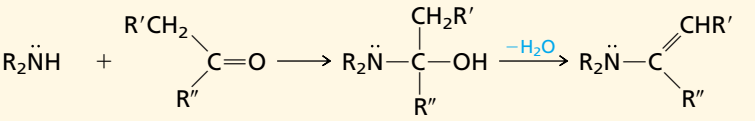
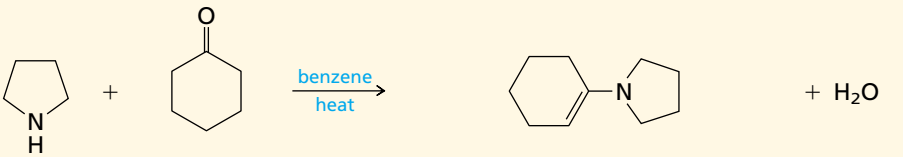
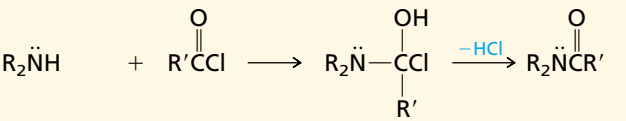
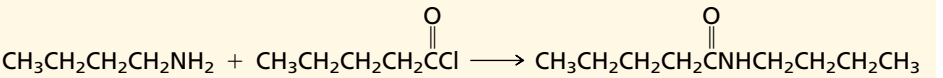
Amine acting as a base Amine acting as a nucleophile

In addition to being more basic than arylamines, alkylamines are also more nucleophilic. All the reactions in Table 22.4 take place faster with alkylamines than with arylamines.

The sections that follow introduce some additional reactions of amines. In all cases our understanding of how these reactions take place starts with a consideration of the role of the unshared electron pair of nitrogen.

We will begin with an examination of the reactivity of amines as nucleophiles in S_N2 reactions.

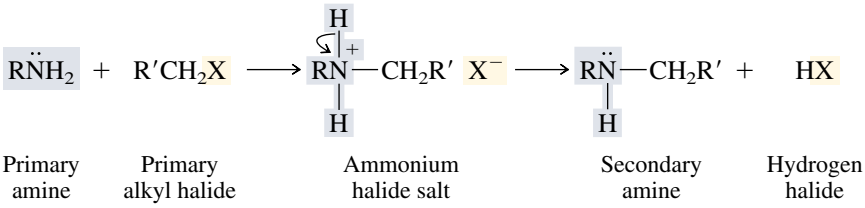
TABLE 22.4 Reactions of Amines Discussed in Previous Chapters*

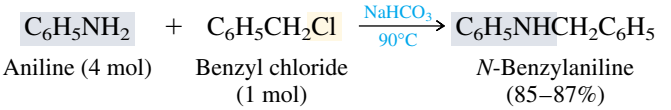
Reaction (section) and comments	General equation and specific example
Reaction of primary amines with aldehydes and ketones (Section 17.10) Imines are formed by nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or a ketone. The key step is formation of a carbinolamine intermediate, which then dehydrates to the imine.	 Primary amine · Aldehyde or ketone · Carbinolamine · Imine  Methylamine · Benzaldehyde · *N*-Benzylidenemethylamine (70%) · Water
Reaction of secondary amines with aldehydes and ketones (Section 17.11) Enamines are formed in the corresponding reaction of secondary amines with aldehydes and ketones.	 Secondary amine · Aldehyde or ketone · Carbinolamine · Enamine  Pyrrolidine · Cyclohexanone · *N*-(1-Cyclohexenyl)pyrrolidine (85–90%)
Reaction of amines with acyl chlorides (Section 20.3) Amines are converted to amides on reaction with acyl chlorides. Other acylating agents, such as carboxylic acid anhydrides and esters, may also be used but are less reactive.	 Primary or secondary amine · Acyl chloride · Tetrahedral intermediate · Amide  Butylamine · Pentanoyl chloride · *N*-Butylpentanamide (81%)

*Both alkylamines and arylamines undergo these reactions.

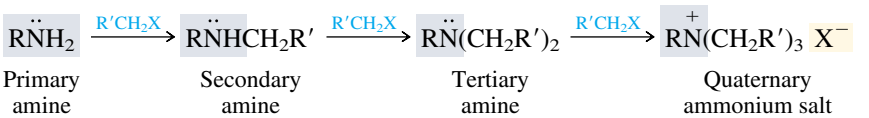
22.13 REACTION OF AMINES WITH ALKYL HALIDES

Nucleophilic substitution results when primary alkyl halides are treated with amines.

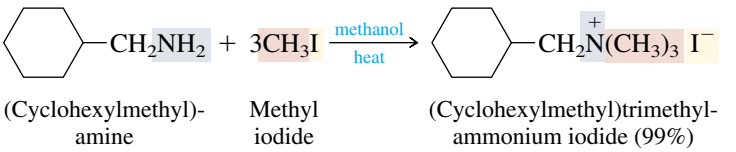




A second alkylation may follow, converting the secondary amine to a tertiary amine. Alkylation need not stop there; the tertiary amine may itself be alkylated, giving a quaternary ammonium salt.



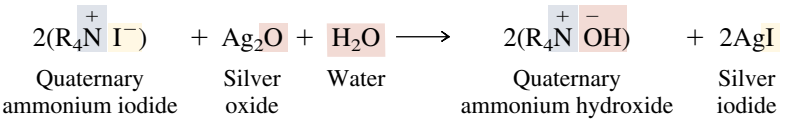
Because of its high reactivity toward nucleophilic substitution, methyl iodide is the alkyl halide most often used to prepare quaternary ammonium salts.

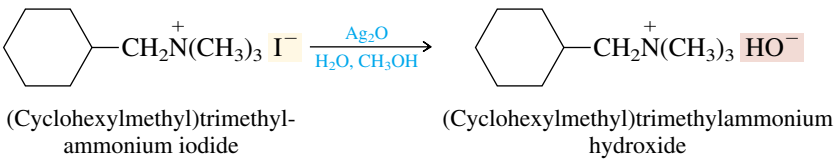


Quaternary ammonium salts, as we have seen, are useful in synthetic organic chemistry as phase-transfer catalysts. In another, more direct application, quaternary ammonium *hydroxides* are used as substrates in an elimination reaction to form alkenes.

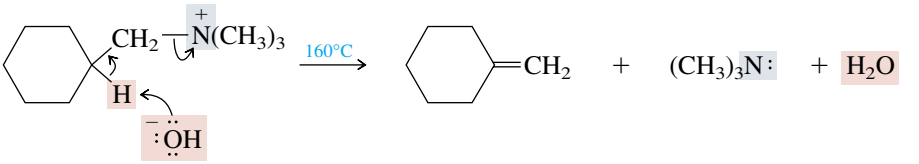
22.14 THE HOFMANN ELIMINATION

The halide anion of quaternary ammonium iodides may be replaced by hydroxide by treatment with an aqueous slurry of silver oxide. Silver iodide precipitates, and a solution of the quaternary ammonium hydroxide is formed.





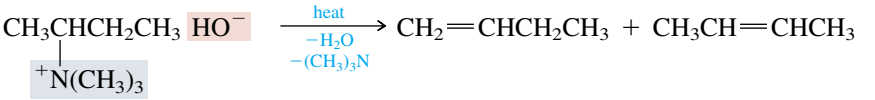
When quaternary ammonium hydroxides are heated, they undergo β-elimination to form an alkene and an amine.



(Cyclohexylmethyl)trimethylammonium hydroxide — Methylenecyclohexane (69%) — Trimethylamine — Water

This reaction is known as the **Hofmann elimination;** it was developed by August W. Hofmann in the middle of the nineteenth century and is both a synthetic method to prepare alkenes and an analytical tool for structure determination.

A novel aspect of the Hofmann elimination is its regioselectivity. Elimination in alkyltrimethylammonium hydroxides proceeds in the direction that gives the *less* substituted alkene.

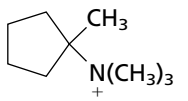


sec-Butyltrimethylammonium hydroxide — 1-Butene (95%) — 2-Butene (5%) (cis and trans)

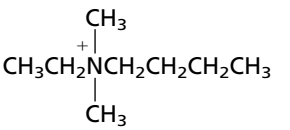
The least sterically hindered β hydrogen is removed by the base in Hofmann elimination reactions. Methyl groups are deprotonated in preference to methylene groups, and methylene groups are deprotonated in preference to methines. The regioselectivity of Hofmann elimination is opposite to that predicted by the Zaitsev rule (Section 5.10). Elimination reactions of alkyltrimethylammonium hydroxides are said to obey the **Hofmann rule;** they yield the less substituted alkene.

PROBLEM 22.13 Give the structure of the major alkene formed when the hydroxide of each of the following quaternary ammonium ions is heated.

(a)

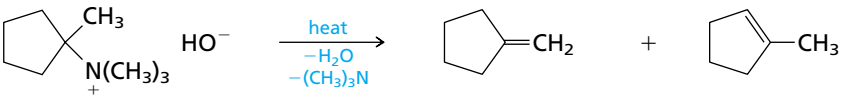


(c)



(b) $(CH_3)_3CCH_2C(CH_3)_2$
$^{+}N(CH_3)_3$

SAMPLE SOLUTION (a) Two alkenes are capable of being formed by β-elimination, methylenecyclopentane and 1-methylcyclopentene.



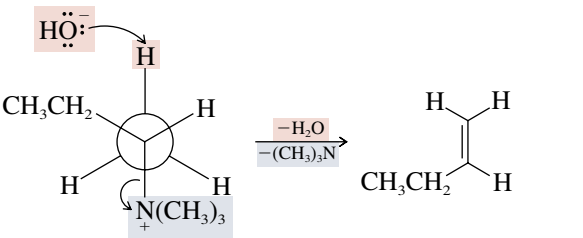
(1-Methylcyclopentyl)trimethylammonium hydroxide — Methylenecyclopentane — 1-Methylcyclopentene

Methylenecyclopentane has the less substituted double bond and is the major product. The reported isomer distribution is 91% methylenecyclopentane and 9% 1-methylcyclopentene.

We can understand the regioselectivity of the Hofmann elimination by comparing steric effects in the E2 transition states for formation of 1-butene and *trans*-2-butene from *sec*-butyltrimethylammonium hydroxide. In terms of its size, $(CH_3)_3\overset{+}{N}$— (trimethylammonio) is comparable to $(CH_3)_3C$— (*tert*-butyl). As Figure 22.4 illustrates, the E2 transition state requires an anti relationship between the proton that is removed and the trimethylammonio group. No serious van der Waals repulsions are evident in the transition state geometry for formation of 1-butene. The conformation leading to *trans*-2-butene, however, is destabilized by van der Waals strain between the trimethylammonio group and a methyl group gauche to it. Thus, the activation energy for formation of *trans*-2-butene exceeds that of 1-butene, which becomes the major product because it is formed faster.

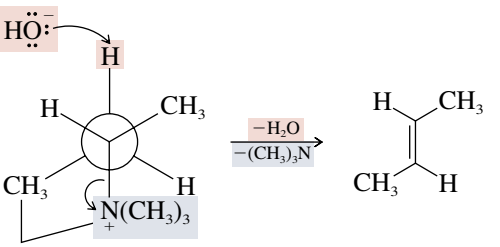
With a regioselectivity opposite to that of the Zaitsev rule, the Hofmann elimination is sometimes used in synthesis to prepare alkenes not accessible by dehydrohalogenation of alkyl halides. This application has decreased in importance since the Wittig reaction (Section 17.12) became established as a synthetic method beginning in the 1950s. Similarly, most of the analytical applications of Hofmann elimination have been replaced by spectroscopic methods.

(*a*) *Less crowded:* Conformation leading to 1-butene by anti elimination:



1-Butene
(major product)

(*b*) *More crowded:* Conformation leading to *trans*-2-butene by anti elimination:



These two groups
crowd each other

trans-2-Butene
(minor product)

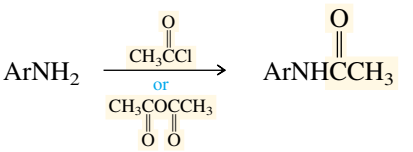
FIGURE 22.4 Newman projections showing the conformations leading to (*a*) 1-butene and (*b*) *trans*-2-butene by Hofmann elimination of *sec*-butyltrimethylammonium hydroxide. The major product is 1-butene.

22.15 ELECTROPHILIC AROMATIC SUBSTITUTION IN ARYLAMINES

Arylamines contain two functional groups, the amine group and the aromatic ring; they are **difunctional compounds.** The reactivity of the amine group is affected by its aryl substituent, and the reactivity of the ring is affected by its amine substituent. The same electron delocalization that reduces the basicity and the nucleophilicity of an arylamine nitrogen increases the electron density in the aromatic ring and makes arylamines extremely reactive toward electrophilic aromatic substitution.

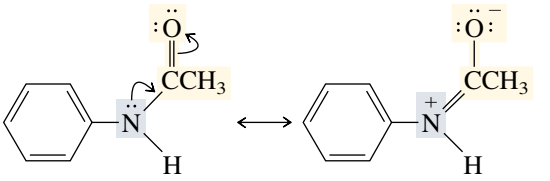
The reactivity of arylamines was noted in Section 12.12, where it was pointed out that $-\ddot{N}H_2$, $-\ddot{N}HR$, and $-\ddot{N}R_2$ are ortho, para-directing and exceedingly powerful activating groups. These substituents are such powerful activators that electrophilic aromatic substitution is only rarely performed directly on arylamines.

Direct nitration of aniline and other arylamines, for example, is difficult to carry out and is accompanied by oxidation that leads to the formation of dark-colored "tars." As a solution to this problem it is standard practice to first protect the amino group by acylation with either acetyl chloride or acetic anhydride.



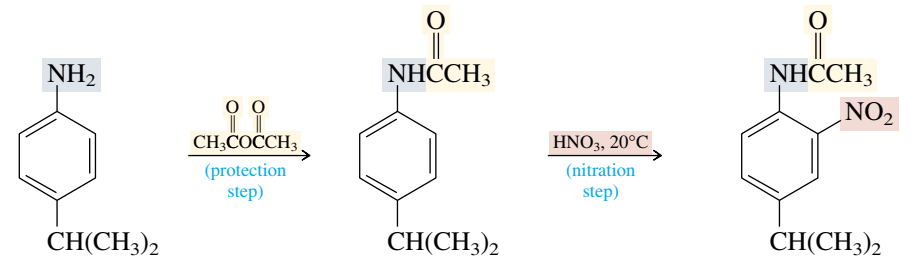
Arylamine *N*-Acetylarylamine

Amide resonance within the *N*-acetyl group competes with delocalization of the nitrogen lone pair into the ring.



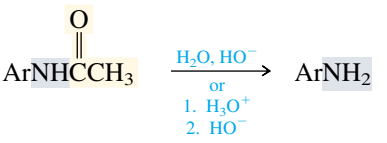
Amide resonance in acetanilide

Protecting the amino group of an arylamine in this way moderates its reactivity and permits nitration of the ring to be achieved. The acetamido group is activating toward electrophilic aromatic substitution and is ortho, para-directing.

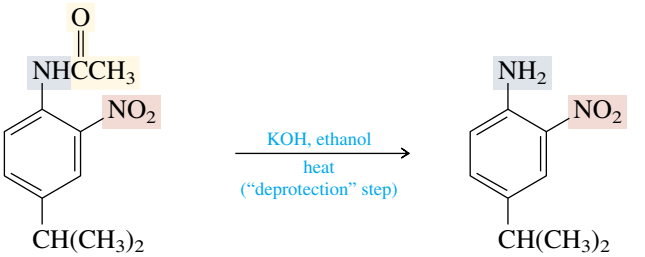


p-Isopropylaniline *p*-Isopropylacetanilide (98%) 4-Isopropyl-2-nitroacetanilide (94%)

After the *N*-acetyl-protecting group has served its purpose, it may be removed by hydrolysis, liberating the amino group:



N-Acetylarylamine Arylamine



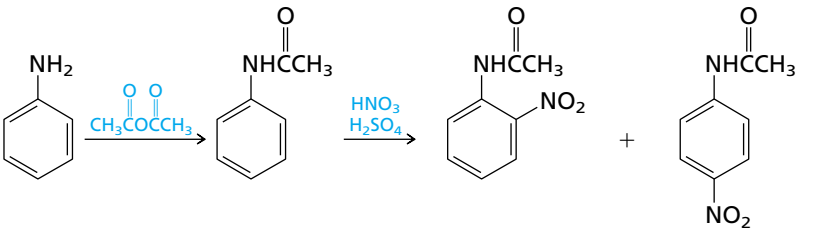
4-Isopropyl-2-nitroacetanilide 4-Isopropyl-2-nitroaniline (100%)

The net effect of the sequence *protect–nitrate–deprotect* is the same as if the substrate had been nitrated directly. Because direct nitration is impossible, however, the indirect route is the only practical method.

PROBLEM 22.14 Outline syntheses of each of the following from aniline and any necessary organic or inorganic reagents:

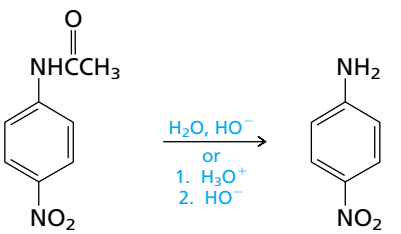
(a) *p*-Nitroaniline
(b) 2,4-Dinitroaniline
(c) *p*-Aminoacetanilide

SAMPLE SOLUTION (a) It has already been stated that direct nitration of aniline is not a practical reaction. The amino group must first be protected as its *N*-acetyl derivative.



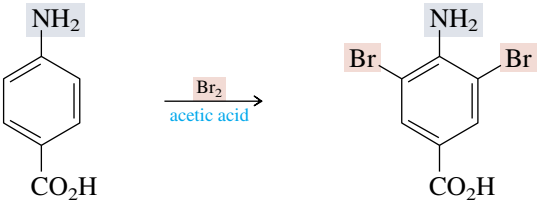
Aniline Acetanilide *o*-Nitroacetanilide *p*-Nitroacetanilide

Nitration of acetanilide yields a mixture of ortho and para substitution products. The para isomer is separated, then subjected to hydrolysis to give *p*-nitroaniline.



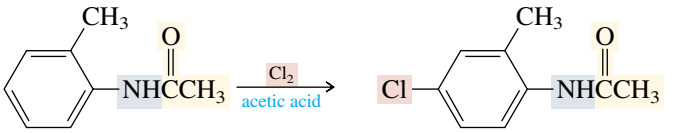
p-Nitroacetanilide *p*-Nitroaniline

Unprotected arylamines are so reactive toward halogenation that it is difficult to limit the reaction to monosubstitution. Generally, halogenation proceeds rapidly to replace all the available hydrogens that are ortho or para to the amino group.



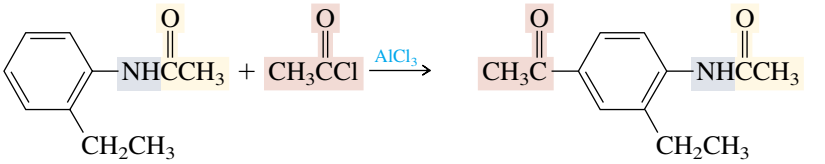
p-Aminobenzoic acid — 4-Amino-3,5-dibromobenzoic acid (82%)

Decreasing the electron-donating ability of an amino group by acylation makes it possible to limit halogenation to monosubstitution.



2-Methylacetanilide — 4-Chloro-2-methylacetanilide (74%)

Friedel–Crafts reactions are normally not successful when attempted on an arylamine, but can be carried out readily once the amino group is protected.



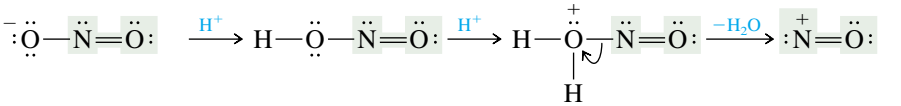
2-Ethylacetanilide — 4-Acetamido-3-ethylacetophenone (57%)

22.16 NITROSATION OF ALKYLAMINES

When solutions of sodium nitrite ($NaNO_2$) are acidified, a number of species are formed that act as **nitrosating agents.** That is, they react as sources of nitrosyl cation, $:\overset{+}{N}{=}\ddot{O}:$. In order to simplify discussion, organic chemists group all these species together and speak of the chemistry of one of them, *nitrous acid,* as a generalized precursor to nitrosyl cation.

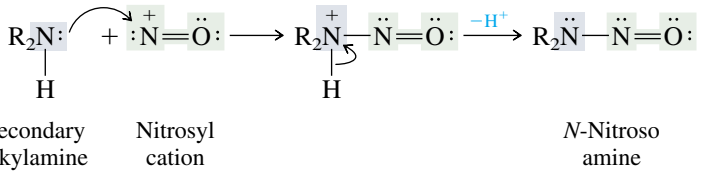
Nitrosyl cation is also called *nitrosonium* ion. It can be represented by the two resonance structures

$$:\overset{+}{N}{=}\ddot{O}: \longleftrightarrow :N{\equiv}\overset{+}{O}:$$



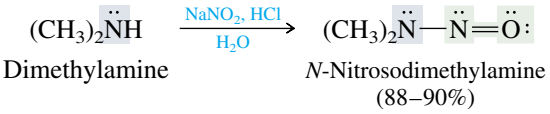
Nitrite ion (from sodium nitrite) — Nitrous acid — Nitrosyl cation

Nitrosation of amines is best illustrated by examining what happens when a secondary amine "reacts with nitrous acid." The amine acts as a nucleophile, attacking the nitrogen of nitrosyl cation.



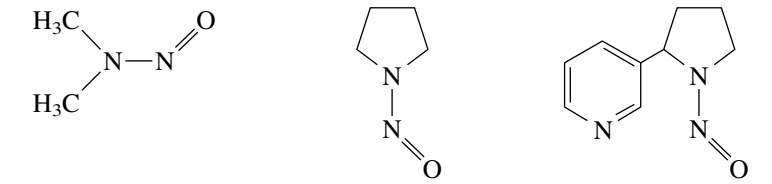
Refer to the molecular model of nitrosyl cation on *Learning By Modeling* to verify that the region of positive electrostatic potential is concentrated at nitrogen.

The intermediate that is formed in the first step loses a proton to give an *N*-nitroso amine as the isolated product.



PROBLEM 22.15 *N*-Nitroso amines are stabilized by electron delocalization. Write the two most stable resonance forms of *N*-nitrosodimethylamine, $(CH_3)_2NNO$.

N-Nitroso amines are more often called *nitrosamines,* and because many of them are potent carcinogens, they have been the object of much recent investigation. We encounter nitrosamines in the environment on a daily basis. A few of these, all of which are known carcinogens, are:



N-Nitrosodimethylamine (formed during tanning of leather; also found in beer and herbicides)

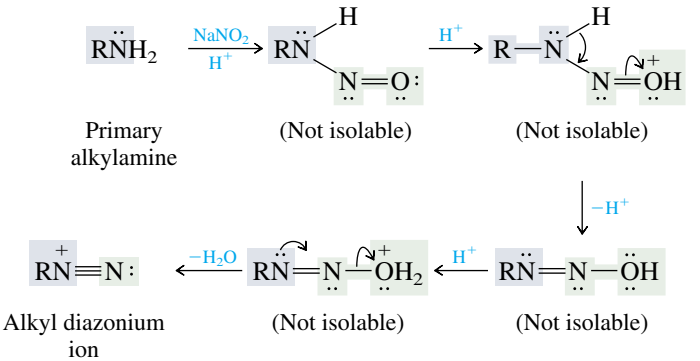
N-Nitrosopyrrolidine (formed when bacon that has been cured with sodium nitrite is fried)

N-Nitrosonornicotine (present in tobacco smoke)

Nitrosamines are formed whenever nitrosating agents come in contact with secondary amines. Indeed, more nitrosamines are probably synthesized within our body than enter it by environmental contamination. Enzyme-catalyzed reduction of nitrate (NO_3^-) produces nitrite (NO_2^-), which combines with amines present in the body to form *N*-nitroso amines.

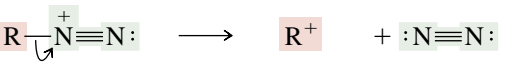
The July 1977 issue of the *Journal of Chemical Education* contains an article entitled "Formation of Nitrosamines in Food and in the Digestive System."

When primary amines are nitrosated, their *N*-nitroso compounds can't be isolated because they react further.



Recall from Section 8.14 that decreasing basicity is associated with increasing leaving-group ability. Molecular nitrogen is an exceedingly weak base and an excellent leaving group.

The product of this series of steps is an alkyl **diazonium ion,** and the amine is said to have been **diazotized.** Alkyl diazonium ions are not very stable, decomposing rapidly under the conditions of their formation. Molecular nitrogen is a leaving group par excellence, and the reaction products arise by solvolysis of the diazonium ion. Usually, a carbocation intermediate is involved.



Alkyl diazonium ion Carbocation Nitrogen

Figure 22.5 shows what happens when a typical primary alkylamine reacts with nitrous acid.

Since nitrogen-free products result from the formation and decomposition of diazonium ions, these reactions are often referred to as **deamination reactions.** Alkyl diazonium ions are rarely used in synthetic work but have been studied extensively to probe the behavior of carbocations generated under conditions in which the leaving group is lost rapidly and irreversibly.

PROBLEM 22.16 Nitrous acid deamination of 2,2-dimethylpropylamine, $(CH_3)_3CCH_2NH_2$, gives the same products as were indicated as being formed from 1,1-dimethylpropylamine in Figure 22.5. Suggest a mechanism for the formation of these compounds from 2,2-dimethylpropylamine.

Aryl diazonium ions, prepared by nitrous acid diazotization of primary arylamines, are substantially more stable than alkyl diazonium ions and are of enormous synthetic value. Their use in the synthesis of substituted aromatic compounds is described in the following two sections.

The nitrosation of tertiary alkylamines is rather complicated, and no generally useful chemistry is associated with reactions of this type.

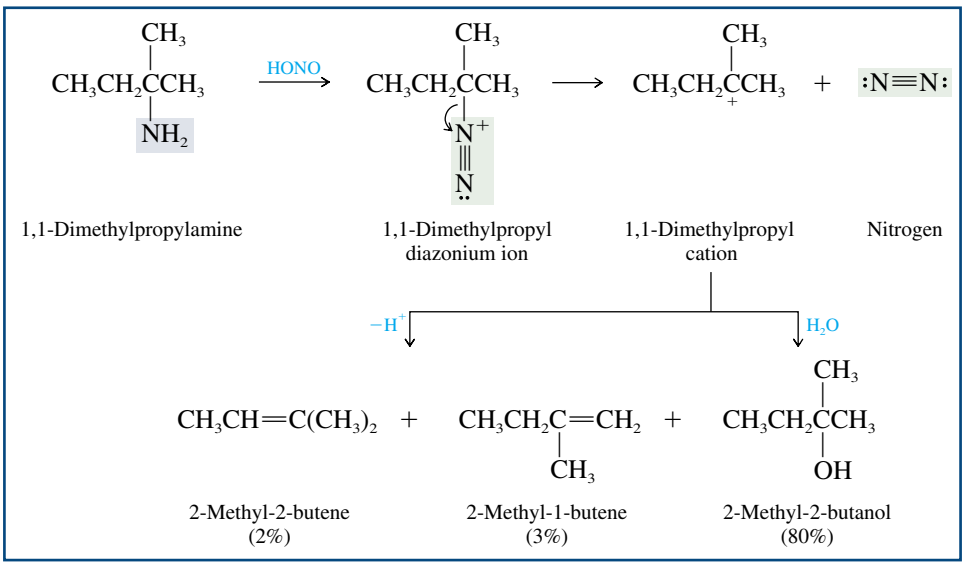
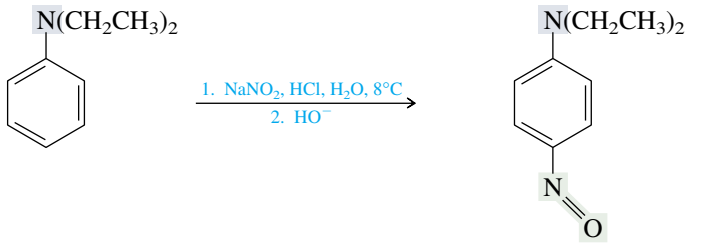


FIGURE 22.5 The diazonium ion generated by treatment of a primary alkylamine with nitrous acid loses nitrogen to give a carbocation. The isolated products are derived from the carbocation and include, in this example, alkenes (by loss of a proton) and an alcohol (nucleophilic capture by water).

22.17 NITROSATION OF ARYLAMINES

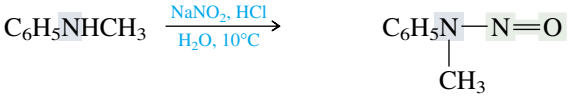
We learned in the preceding section that different reactions are observed when the various classes of alkylamines—primary, secondary, and tertiary—react with nitrosating agents. Although no useful chemistry attends the nitrosation of tertiary alkylamines, electrophilic aromatic substitution by nitrosyl cation ($:N\equiv\overset{+}{O}:$) takes place with *N,N*-dialkylarylamines.



N,N-Diethylaniline — *N,N*-Diethyl-*p*-nitrosoaniline (95%)

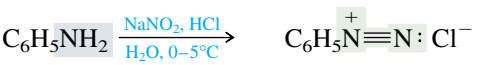
Nitrosyl cation is a relatively weak electrophile and attacks only very strongly activated aromatic rings.

N-Alkylarylamines resemble secondary alkylamines in that they form *N*-nitroso compounds on reaction with nitrous acid.

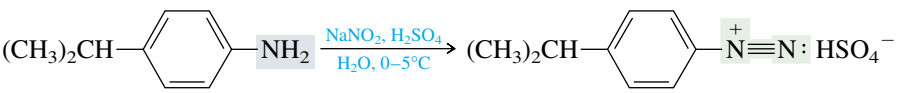


N-Methylaniline — *N*-Methyl-*N*-nitrosoaniline (87–93%)

Primary arylamines, like primary alkylamines, form diazonium ion salts on nitrosation. Aryl diazonium ions are considerably more stable than their alkyl counterparts. Whereas alkyl diazonium ions decompose under the conditions of their formation, aryl diazonium salts are stable enough to be stored in aqueous solution at 0–5°C for reasonable periods of time. Loss of nitrogen from an aryl diazonium ion generates an unstable aryl cation and is much slower than loss of nitrogen from an alkyl diazonium ion.



Aniline — Benzenediazonium chloride



p-Isopropylaniline — *p*-Isopropylbenzenediazonium hydrogen sulfate

Aryl diazonium ions undergo a variety of reactions that make them versatile intermediates for the preparation of a host of ring-substituted aromatic compounds. In these reactions, summarized in Figure 22.6 and discussed individually in the following section, molecular nitrogen acts as a leaving group and is replaced by another atom or group. All the reactions are regiospecific; the entering group becomes bonded to precisely the ring position from which nitrogen departs.

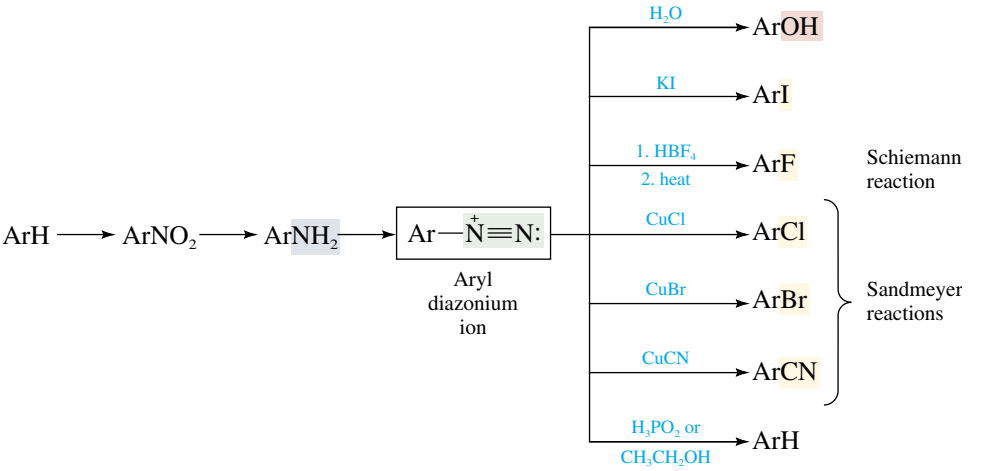


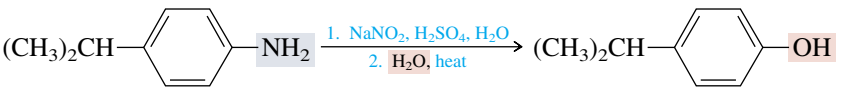
FIGURE 22.6 Flowchart showing the synthetic origin of aryl diazonium ions and their most useful transformations.

22.18 SYNTHETIC TRANSFORMATIONS OF ARYL DIAZONIUM SALTS

An important reaction of aryl diazonium ions is their conversion to *phenols* by hydrolysis:

$$\underset{\text{Aryl diazonium ion}}{ArN\equiv N:} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\text{A phenol}}{ArOH} + \underset{}{H^+} + \underset{\text{Nitrogen}}{:N\equiv N:}$$

This is the most general method for preparing phenols. It is easily performed; the aqueous acidic solution in which the diazonium salt is prepared is heated and gives the phenol directly. An aryl cation is probably generated, which is then captured by water acting as a nucleophile.



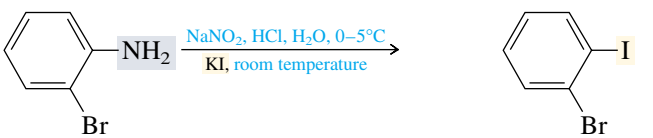
p-Isopropylaniline — *p*-Isopropylphenol (73%)

Sulfuric acid is normally used instead of hydrochloric acid in the diazotization step so as to minimize the competition with water for capture of the cationic intermediate. Hydrogen sulfate anion (HSO_4^-) is less nucleophilic than chloride.

PROBLEM 22.17 Design a synthesis of *m*-bromophenol from benzene.

The reaction of an aryl diazonium salt with potassium iodide is the standard method for the preparation of *aryl iodides*. The diazonium salt is prepared from a primary aromatic amine in the usual way, a solution of potassium iodide is then added, and the reaction mixture is brought to room temperature or heated to accelerate the reaction.

$$\underset{\text{Aryl diazonium ion}}{Ar—N\equiv N:} + \underset{\text{Iodide ion}}{I^-} \longrightarrow \underset{\text{Aryl iodide}}{ArI} + \underset{\text{Nitrogen}}{:N\equiv N:}$$



o-Bromoaniline — *o*-Bromoiodobenzene (72–83%)

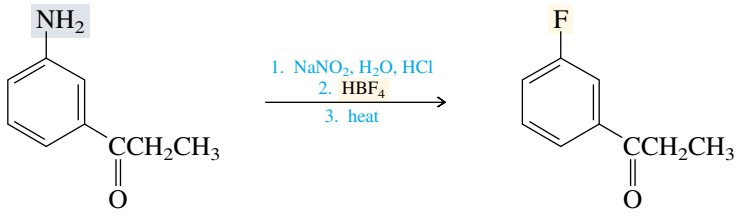
PROBLEM 22.18 Show by a series of equations how you could prepare *m*-bromoiodobenzene from benzene.

Diazonium salt chemistry provides the principal synthetic method for the preparation of *aryl fluorides* through a process known as the **Schiemann reaction.** In this procedure the aryl diazonium ion is isolated as its fluoroborate salt, which then yields the desired aryl fluoride on being heated.

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N:\ \overset{-}{B}F_4} \xrightarrow{\text{heat}} \mathrm{ArF} + \mathrm{BF_3} + \mathrm{:N{\equiv}N:}$$

Aryl diazonium fluoroborate — Aryl fluoride — Boron trifluoride — Nitrogen

A standard way to form the aryl diazonium fluoroborate salt is to add fluoroboric acid (HBF_4) or a fluoroborate salt to the diazotization medium.



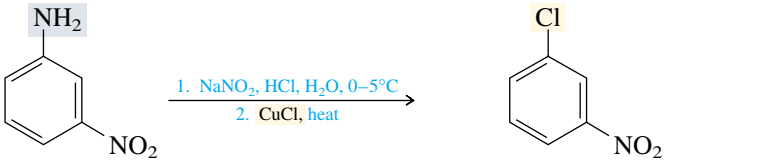
m-Aminophenyl ethyl ketone — Ethyl *m*-fluorophenyl ketone (68%)

PROBLEM 22.19 Show the proper sequence of synthetic transformations in the conversion of benzene to ethyl *m*-fluorophenyl ketone.

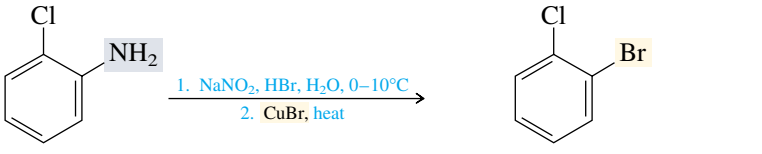
Although it is possible to prepare *aryl chlorides* and *aryl bromides* by electrophilic aromatic substitution, it is often necessary to prepare these compounds from an aromatic amine. The amine is converted to the corresponding diazonium salt and then treated with copper(I) chloride or copper(I) bromide as appropriate.

$$\mathrm{Ar{-}\overset{+}{N}{\equiv}N:} \xrightarrow{\mathrm{CuX}} \mathrm{ArX} + \mathrm{:N{\equiv}N:}$$

Aryl diazonium ion — Aryl chloride or bromide — Nitrogen

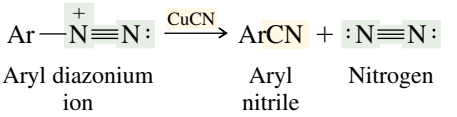


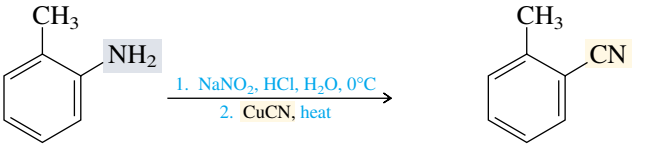
m-Nitroaniline — *m*-Chloronitrobenzene (68–71%)



o-Chloroaniline — *o*-Bromochlorobenzene (89–95%)

Reactions that employ copper(I) salts as reagents for replacement of nitrogen in diazonium salts are called **Sandmeyer reactions.** The Sandmeyer reaction using copper(I) cyanide is a good method for the preparation of aromatic *nitriles:*



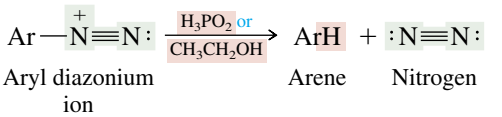


o-Toluidine *o*-Methylbenzonitrile (64–70%)

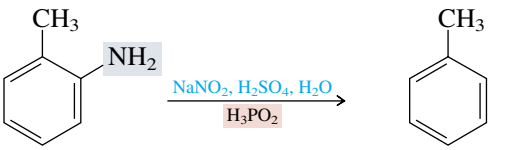
Since cyano groups may be hydrolyzed to carboxylic acids (Section 20.19), the Sandmeyer preparation of aryl nitriles is a key step in the conversion of arylamines to substituted benzoic acids. In the example just cited, the *o*-methylbenzonitrile that was formed was subsequently subjected to acid-catalyzed hydrolysis and gave *o*-methylbenzoic acid in 80–89 percent yield.

The preparation of aryl chlorides, bromides, and cyanides by the Sandmeyer reaction is mechanistically complicated and may involve arylcopper intermediates.

It is possible to replace amino substituents on an aromatic nucleus by hydrogen by reducing a diazonium salt with hypophosphorous acid (H_3PO_2) or with ethanol. These reductions are free-radical reactions in which ethanol or hypophosphorous acid acts as a hydrogen atom donor:



Reactions of this type are called **reductive deaminations.**



o-Toluidine Toluene (70–75%)

4-Isopropyl-2-nitroaniline *m*-Isopropylnitrobenzene (59%)

Sodium borohydride has also been used to reduce aryl diazonium salts in reductive deamination reactions.

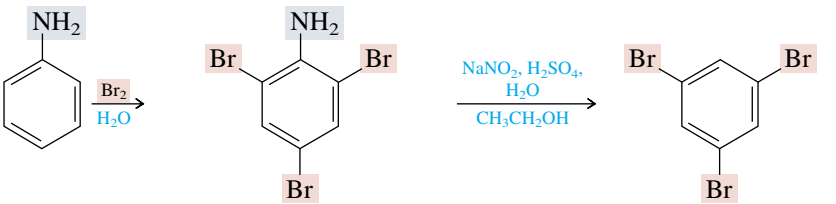
PROBLEM 22.20 Cumene (isopropylbenzene) is a relatively inexpensive commercially available starting material. Show how you could prepare *m*-isopropylnitrobenzene from cumene.

The value of diazonium salts in synthetic organic chemistry rests on two main points. Through the use of diazonium salt chemistry:

1. Substituents that are otherwise accessible only with difficulty, such as fluoro, iodo, cyano, and hydroxyl, may be introduced onto a benzene ring.
2. Compounds that have substitution patterns not directly available by electrophilic aromatic substitution can be prepared.

The first of these two features is readily apparent and is illustrated by Problems 22.17 to 22.19. If you have not done these problems yet, you are strongly encouraged to attempt them now.

The second point is somewhat less obvious but is readily illustrated by the synthesis of 1,3,5-tribromobenzene. This particular substitution pattern cannot be obtained by direct bromination of benzene, because bromine is an ortho, para director. Instead, advantage is taken of the powerful activating and ortho, para-directing effects of the amino group in aniline. Bromination of aniline yields 2,4,6-tribromoaniline in quantitative yield. Diazotization of the resulting 2,4,6-tribromoaniline and reduction of the diazonium salt gives the desired 1,3,5-tribromobenzene.



Aniline — 2,4,6-Tribromoaniline (100%) — 1,3,5-Tribromobenzene (74–77%)

To exploit the synthetic versatility of aryl diazonium salts, be prepared to reason backward. When you see a fluorine substituent in a synthetic target, for example, realize that it probably will have to be introduced by a Schiemann reaction of an arylamine; realize that the required arylamine is derived from a nitroarene, and that the nitro group is introduced by nitration. Be aware that an unsubstituted position of an aromatic ring need not have always been that way. It might once have borne an amino group that was used to control the orientation of electrophilic aromatic substitution reactions before being removed by reductive deamination. The strategy of synthesis is intellectually demanding, and a considerable sharpening of your reasoning power can be gained by attacking the synthesis problems at the end of each chapter. Remember, plan your sequence of accessible intermediates by reasoning backward from the target; then fill in the details on how each transformation is to be carried out.

22.19 AZO COUPLING

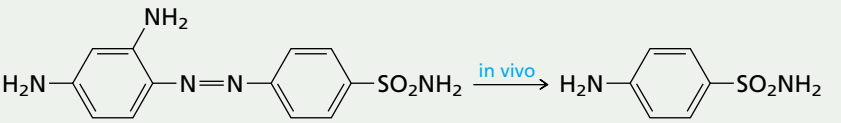
A reaction of aryl diazonium salts that does not involve loss of nitrogen takes place when they react with phenols and arylamines. Aryl diazonium ions are relatively weak

FROM DYES TO SULFA DRUGS

The medicine cabinet was virtually bare of antibacterial agents until **sulfa drugs** burst on the scene in the 1930s. Before sulfa drugs became available, bacterial infection might transform a small cut or puncture wound to a life-threatening event. The story of how sulfa drugs were developed is an interesting example of being right for the wrong reasons. It was known that many bacteria absorbed dyes, and staining was a standard method for making bacteria more visible under the microscope. Might there not be some dye that is both absorbed by bacteria and toxic to them? Acting on this hypothesis, scientists at the German dyestuff manufacturer I. G. Farbenindustrie undertook a program to test the thousands of compounds in their collection for their antibacterial properties.

In general, *in vitro* testing of drugs precedes *in vivo* testing. The two terms mean, respectively, "in glass" and "in life." In vitro testing of antibiotics is carried out using bacterial cultures in test tubes or Petri dishes. Drugs that are found to be active in vitro progress to the stage of in vivo testing. In vivo testing is carried out in living organisms: laboratory animals or human volunteers. The I. G. Farben scientists found that some dyes did possess antibacterial properties, both in vitro and in vivo. Others were active in vitro but were converted to inactive substances in vivo and therefore of no use as drugs. Unexpectedly, an azo dye called *Prontosil* was inactive in vitro but active in vivo. In 1932, a member of the I. G. Farben research group, Gerhard Domagk used Prontosil to treat a young child suffering from a serious, potentially fatal staphylococcal infection. According to many accounts, the child was Domagk's own daughter; her infection was cured and her recovery was rapid and complete. Systematic testing followed and Domagk was awarded the 1939 Nobel Prize in medicine or physiology.

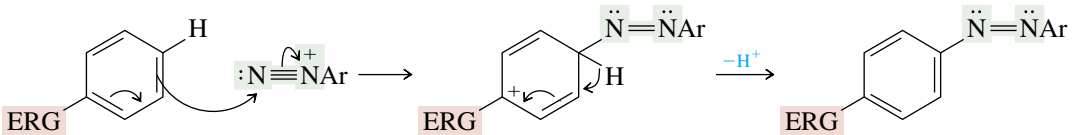
In spite of the rationale on which the testing of dyestuffs as antibiotics rested, subsequent research revealed that the antibacterial properties of Prontosil had nothing at all to do with its being a dye! In the body, Prontosil undergoes a reductive cleavage of its azo linkage to form *sulfanilamide,* which is the substance actually responsible for the observed biological activity. This is why Prontosil is active in vivo, but not in vitro.



Prontosil Sulfanilamide

—Cont.

electrophiles but have sufficient reactivity to attack strongly activated aromatic rings. The reaction is known as *azo coupling;* two aryl groups are joined together by an azo (—N=N—) function.



(ERG is a powerful electron-releasing group such as —OH or —NR_2)

Aryl diazonium ion

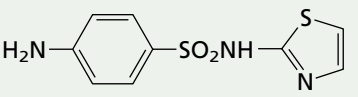
Intermediate in electrophilic aromatic substitution

Azo compound

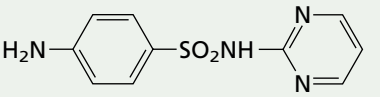
Azo compounds are often highly colored, and many of them are used as dyes.

Bacteria require *p*-aminobenzoic acid in order to biosynthesize *folic acid,* a growth factor. Structurally, sulfanilamide resembles *p*-aminobenzoic acid and is mistaken for it by the bacteria. Folic acid biosynthesis is inhibited and bacterial growth is slowed sufficiently to allow the body's natural defenses to effect a cure. Since animals do not biosynthesize folic acid but obtain it in their food, sulfanilamide halts the growth of bacteria without harm to the host.

Identification of the mechanism by which Prontosil combats bacterial infections was an early triumph of **pharmacology,** a branch of science at the interface of physiology and biochemistry that studies the mechanism of drug action. By recognizing that sulfanilamide was the active agent, the task of preparing structurally modified analogs with potentially superior properties was considerably simplified. Instead of preparing Prontosil analogs, chemists synthesized sulfanilamide analogs. They did this with a vengeance; over 5000 compounds related to sulfanilamide were prepared during the period 1935–1946. Two of the most widely used sulfa drugs are *sulfathiazole* and *sulfadiazine.*

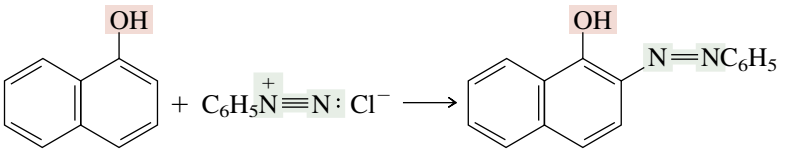


Sulfathiazole



Sulfadiazine

We tend to take the efficacy of modern drugs for granted. One comparison with the not-too-distant past might put this view into better perspective. Once sulfa drugs were introduced in the United States, the number of pneumonia deaths alone decreased by an estimated 25,000 per year. The sulfa drugs are used less now than they were in the mid-twentieth century. Not only are more-effective, less-toxic antibiotics available, such as the penicillins and tetracyclines, but many bacteria that were once susceptible to sulfa drugs have become resistant.



1-Naphthol | Benzenediazonium chloride | 2-(Phenylazo)-1-naphthol

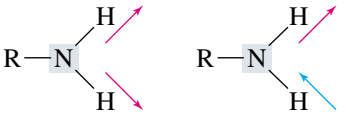
The colors of azo compounds vary with the nature of the aryl group, with its substituents, and with pH. Substituents also affect the water-solubility of azo dyes and how well they bind to a particular fabric. Countless combinations of diazonium salts and aromatic substrates have been examined with a view toward obtaining azo dyes suitable for a particular application.

A number of pH indicators—methyl red, for example—are azo compounds.

22.20 SPECTROSCOPIC ANALYSIS OF AMINES

Infrared: The absorptions of interest in the infrared spectra of amines are those associated with N—H vibrations. Primary alkyl- and arylamines exhibit two peaks in the range 3000–3500 cm^{-1}, which are due to symmetric and antisymmetric N—H stretching modes.

Symmetric N—H stretching of a primary amine



Antisymmetric N—H stretching of a primary amine

The symmetric and antisymmetric stretching vibrations of methylamine can be viewed on *Learning By Modeling.*

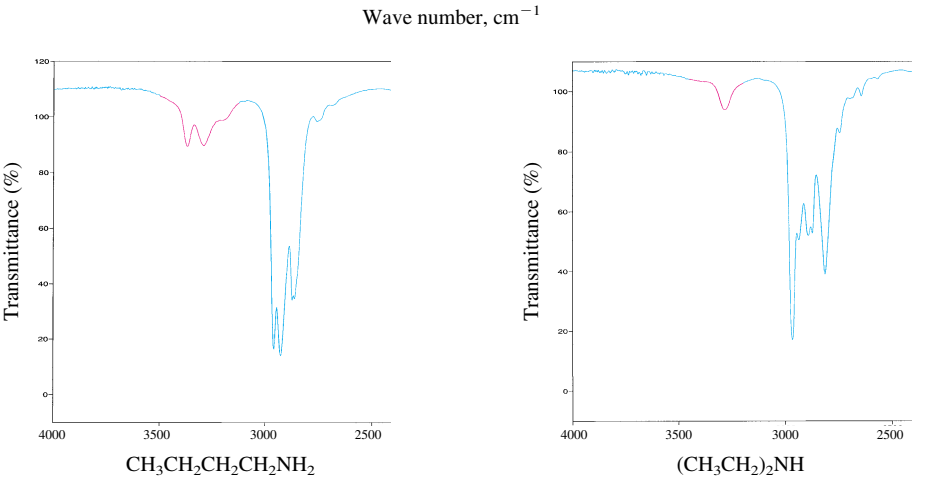


FIGURE 22.7 Portions of the infrared spectrum of (*a*) butylamine and (*b*) diethylamine. Primary amines exhibit two peaks due to N—H stretching, whereas secondary amines show only one.

These two vibrations are clearly visible at 3270 and 3380 cm^{-1} in the infrared spectrum of butylamine, shown in Figure 22.7*a*. Secondary amines such as diethylamine, shown in Figure 22.7*b*, exhibit only one peak, which is due to N—H stretching, at 3280 cm^{-1}. Tertiary amines, of course, are transparent in this region, since they have no N—H bonds.

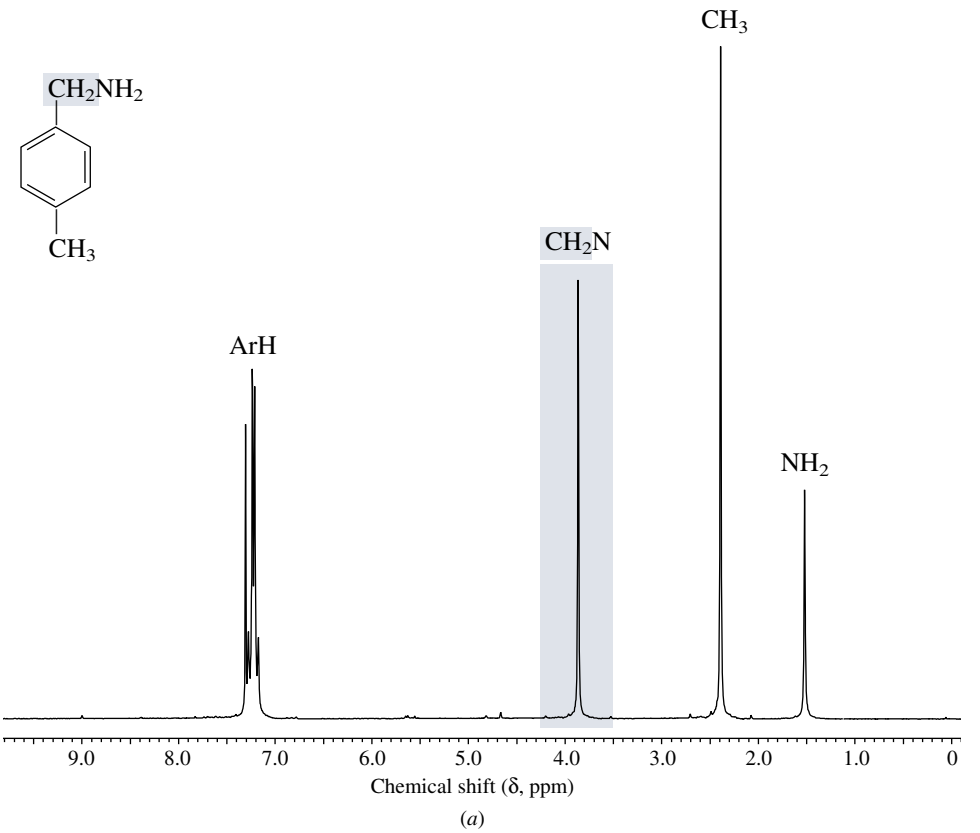
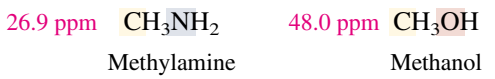


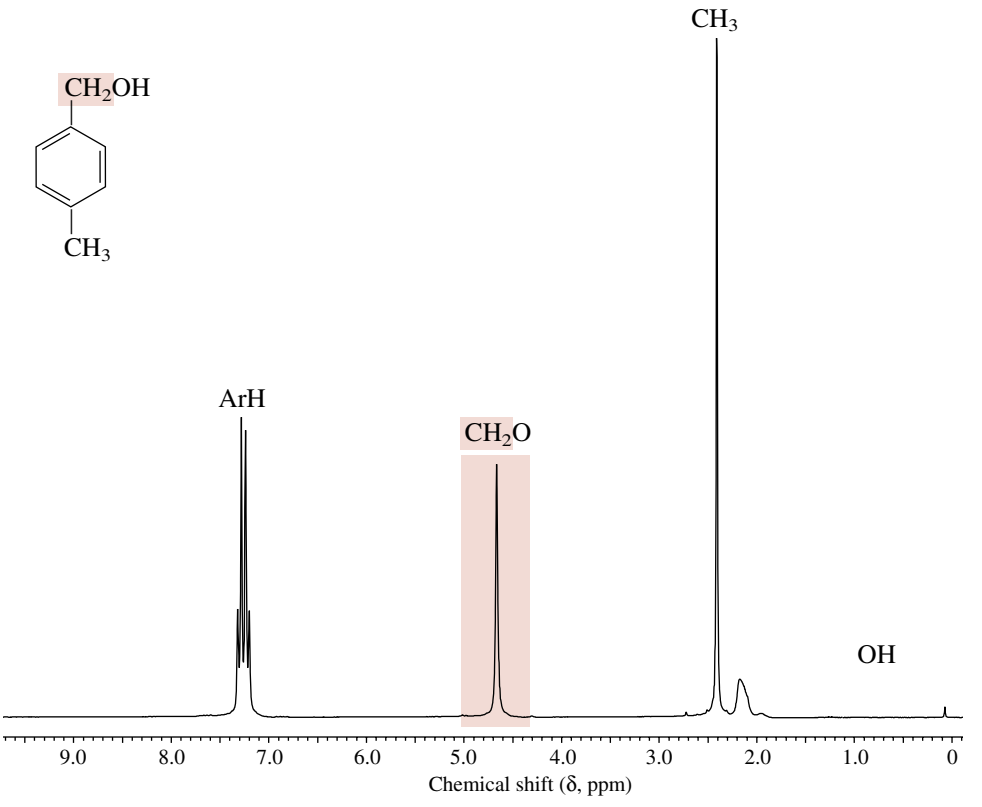
FIGURE 22.8 The 200-MHz ^{1}H NMR spectra of (*a*) 4-methylbenzylamine and of (*b*) 4-methylbenzyl alcohol. The singlet corresponding to CH_2N in (*a*) is more shielded than that of CH_2O in (*b*).

^{1}H NMR: Characteristics of the nuclear magnetic resonance spectra of amines may be illustrated by comparing 4-methylbenzylamine (Figure 22.8*a*) with 4-methylbenzyl alcohol (Figure 22.8*b*). Nitrogen is less electronegative than oxygen and so shields neighboring nuclei to a greater extent. The benzylic methylene group attached to nitrogen in 4-methylbenzylamine appears at higher field (δ 3.8 ppm) than the benzylic methylene of 4-methylbenzyl alcohol (δ 4.6 ppm). The N—H protons are somewhat more shielded than the O—H protons of an alcohol. In 4-methylbenzylamine the protons of the amino group correspond to the signal at δ 1.5 ppm, whereas the hydroxyl proton signal of 4-methylbenzyl alcohol is found at δ 2.1 ppm. The chemical shifts of amino group protons, like those of hydroxyl protons, are variable and are sensitive to solvent, concentration, and temperature.

^{13}C NMR: Similarly, carbons that are bonded to nitrogen are more shielded than those bonded to oxygen, as revealed by comparing the ^{13}C chemical shifts of methylamine and methanol.

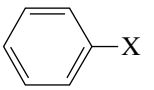


UV-VIS: In the absence of any other chromophore, the UV-Vis spectrum of an alkylamine is not very informative. The longest wavelength absorption involves promoting one of the unshared electrons of nitrogen to an antibonding σ orbital ($n \rightarrow \sigma^*$) with a λ_{max} in the relatively inaccessible region near 200 nm. Arylamines are a different story.



(Figure 22.8*b*)

There the interaction of the nitrogen lone pair with the π-electron system of the ring shifts the ring's absorptions to longer wavelength. Tying up the lone pair by protonation causes the UV-Vis spectrum of anilinium ion to resemble benzene.

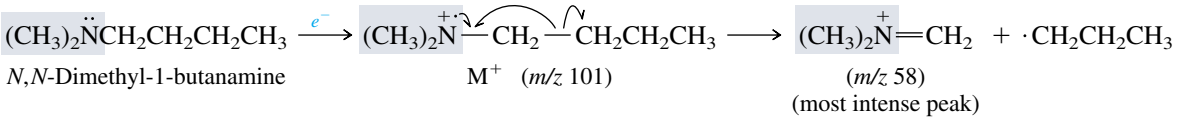


	X	λ_{max}, *nm*
Benzene	H	204, 256
Aniline	NH_2	230, 280
Anilinium ion	NH_3^+	203, 254

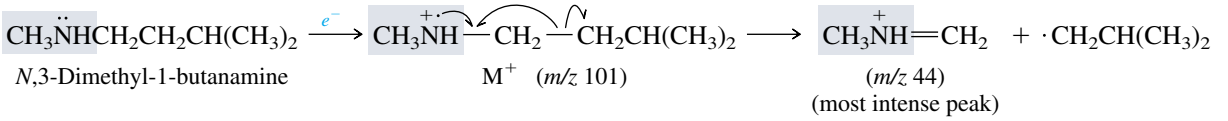
Mass Spectrometry: A number of features make amines easily identifiable by mass spectrometry.

First, the peak for the molecular ion M^+ for all compounds that contain only carbon, hydrogen, and oxygen has an *m/z* value that is an even number. The presence of a nitrogen atom in the molecule requires that the *m/z* value for the molecular ion be odd. An odd number of nitrogens corresponds to an odd value of the molecular weight; an even number of nitrogens corresponds to an even molecular weight.

Second, nitrogen is exceptionally good at stabilizing adjacent carbocation sites. The fragmentation pattern seen in the mass spectra of amines is dominated by cleavage of groups from the carbon atom attached to the nitrogen, as the data for the following pair of constitutionally isomeric amines illustrate:



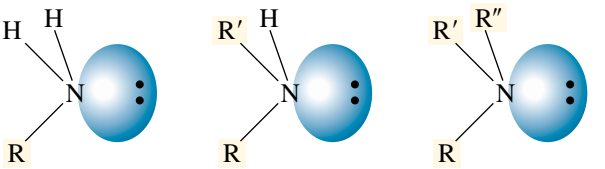
N,*N*-Dimethyl-1-butanamine — M^+ (*m/z* 101) — (*m/z* 58) (most intense peak)



N,3-Dimethyl-1-butanamine — M^+ (*m/z* 101) — (*m/z* 44) (most intense peak)

22.21 SUMMARY

Section 22.1 Alkylamines are compounds of the type shown, where R, R′, and R″ are alkyl groups. One or more of these groups is an aryl group in arylamines.



Primary amine — Secondary amine — Tertiary amine

Alkylamines are named in two ways. One method adds the ending *-amine* to the name of the alkyl group. The other applies the principles of substitutive nomenclature by replacing the *-e* ending of an alkane name by *-amine* and uses appropriate locants to identify the position of the amino group. Arylamines are named as derivatives of aniline.

Section 22.2 Nitrogen's unshared electron pair is of major importance in understanding the structure and properties of amines. Alkylamines have a pyramidal arrangement of bonds to nitrogen, and the unshared electron pair

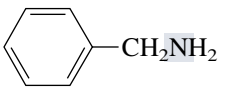
resides in an sp^3-hybridized orbital. The geometry at nitrogen in arylamines is somewhat flatter than in alkylamines, and the unshared electron pair is delocalized into the π system of the ring. Delocalization binds the electron pair more strongly in arylamines than in alkylamines. Arylamines are less basic and less nucleophilic than alkylamines.

Section 22.3 Amines are less polar than alcohols. Hydrogen bonding in amines is weaker than in alcohols because nitrogen is less electronegative than oxygen. Amines have lower boiling points than alcohols, but higher boiling points than alkanes. Primary amines have higher boiling points than isomeric secondary amines; tertiary amines, which cannot form intermolecular hydrogen bonds, have the lowest boiling points. Amines resemble alcohols in their solubility in water.

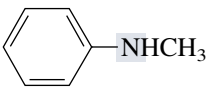
Section 22.4 Basicity of amines is expressed either as a basicity constant K_b (pK_b) of the amine or as a dissociation constant K_a (pK_a) of its conjugate acid.

$$R_3N: + H_2O \rightleftharpoons R_3\overset{+}{N}H + HO^- \qquad K_b = \frac{[R_3\overset{+}{N}H][HO^-]}{[R_3N]}$$

Section 22.5 The basicity constants of alkylamines lie in the range 10^{-3}–10^{-5}. Arylamines are much weaker bases, with K_b values in the 10^{-9}–10^{-11} range.



Benzylamine
(alkylamine: $pK_b = 4.7$)



N-Methylaniline
(arylamine: $pK_b = 11.8$)

Section 22.6 Quaternary ammonium salts, compounds of the type $R_4N^+ X^-$, find application in a technique called **phase-transfer catalysis.** A small amount of a quaternary ammonium salt promotes the transfer of an anion from aqueous solution, where it is highly solvated, to an organic solvent, where it is much less solvated and much more reactive.

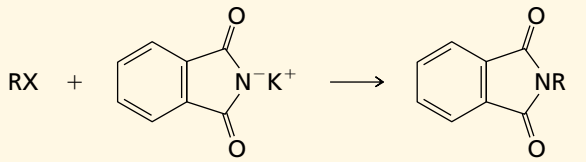
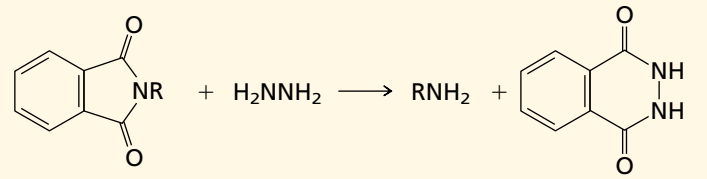
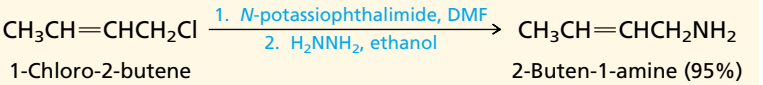
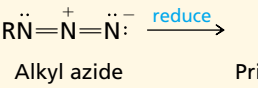
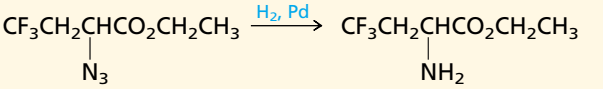
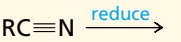
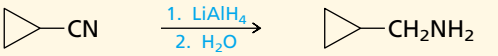
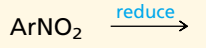
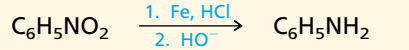
Sections 22.7–22.11 Methods for the preparation of amines are summarized in Table 22.5.

TABLE 22.5 Preparation of Amines

Reaction (section) and comments	General equation and specific example
Alkylation methods	
Alkylation of ammonia (Section 22.8) Ammonia can act as a nucleophile toward primary and some secondary alkyl halides to give primary alkylamines. Yields tend to be modest because the primary amine is itself a nucleophile and undergoes alkylation. Alkylation of ammonia can lead to a mixture containing a primary amine, a secondary amine, a tertiary amine, and a quaternary ammonium salt.	$RX + 2NH_3 \longrightarrow RNH_2 + NH_4X$ Alkyl halide; Ammonia; Alkylamine; Ammonium halide $C_6H_5CH_2Cl \xrightarrow{NH_3\ (8\ mol)} C_6H_5CH_2NH_2 + (C_6H_5CH_2)_2NH$ Benzyl chloride (1 mol); Benzylamine (53%); Dibenzylamine (39%)

(Continued)

TABLE 22.5 Preparation of Amines *(Continued)*

Reaction (section) and comments	General equation and specific example
Alkylation of phthalimide. The Gabriel synthesis (Section 22.9) The potassium salt of phthalimide reacts with alkyl halides to give *N*-alkylphthalimide derivatives. Hydrolysis or hydrazinolysis of this derivative yields a primary alkylamine.	 Alkyl halide — *N*-Potassiophthalimide — *N*-Alkylphthalimide  *N*-Alkylphthalimide — Hydrazine — Primary amine — Phthalhydrazide  1-Chloro-2-butene — 2-Buten-1-amine (95%)
Reduction methods	
Reduction of alkyl azides (Section 22.10) Alkyl azides, prepared by nucleophilic substitution by azide ion in primary or secondary alkyl halides, are reduced to primary alkylamines by lithium aluminum hydride or by catalytic hydrogenation.	 Alkyl azide — Primary amine  Ethyl 2-azido-4,4,4-trifluorobutanoate — Ethyl 2-amino-4,4,4-trifluorobutanoate (96%)
Reduction of nitriles (Section 22.10) Nitriles are reduced to primary amines by lithium aluminum hydride or by catalytic hydrogenation.	 Nitrile — Primary amine  Cyclopropyl cyanide — Cyclopropylmethanamine (75%)
Reduction of aryl nitro compounds (Section 22.10) The standard method for the preparation of an arylamine is by nitration of an aromatic ring, followed by reduction of the nitro group. Typical reducing agents include iron or tin in hydrochloric acid or catalytic hydrogenation.	 Nitroarene — Arylamine  Nitrobenzene — Aniline (97%)

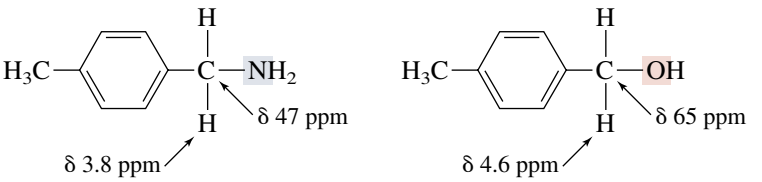
(Continued)

TABLE 22.5 Preparation of Amines *(Continued)*

Reaction (section) and comments	General equation and specific example
Reduction of amides (Section 22.10) Lithium aluminum hydride reduces the carbonyl group of an amide to a methylene group. Primary, secondary, or tertiary amines may be prepared by proper choice of the starting amide. R and R′ may be either alkyl or aryl.	$\underset{\text{Amide}}{RCNR'_2} \xrightarrow{\text{reduce}} \underset{\text{Amine}}{RCH_2NR'_2}$ $CH_3CNHC(CH_3)_3 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4} CH_3CH_2NHC(CH_3)_3$ *N-tert*-Butylacetamide → *N*-Ethyl-*tert*-butylamine (60%)
Reductive amination (Section 22.11) Reaction of ammonia or an amine with an aldehyde or a ketone in the presence of a reducing agent is an effective method for the preparation of primary, secondary, or tertiary amines. The reducing agent may be either hydrogen in the presence of a metal catalyst or sodium cyanoborohydride. R, R′, and R″ may be either alkyl or aryl.	$RCR' + R''_2NH \xrightarrow{\text{reducing agent}} RCR'(NR''_2)H$ Aldehyde or ketone + Ammonia or an amine → Amine $CH_3CCH_3 + C_6H_5NH_2 \xrightarrow{H_2,\ Pt} C_6H_5NHCH(CH_3)_2$ Acetone + Cyclohexylamine → *N*-Isopropylcyclohexylamine (79%)

Sections 22.12–22.19 The reactions of amines are summarized in Tables 22.6 and 22.7.

Section 22.20 The N—H stretching frequency of primary and secondary amines appears in the infrared in the 3000–3500 cm^{-1} region. In the NMR spectra of amines, protons and carbons of the type H—C—N are more shielded than H—C—O.



Amines have odd-numbered molecular weights, which helps identify them by mass spectrometry. Fragmentation tends to be controlled by the formation of a nitrogen-stabilized cation.

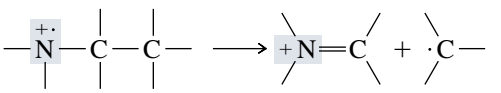
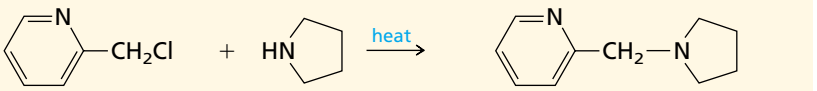
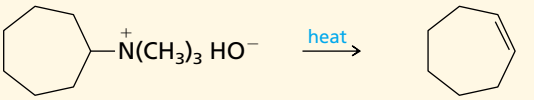
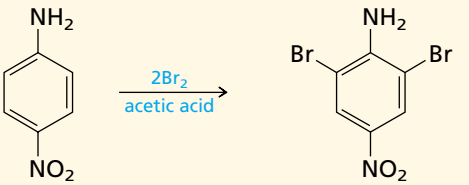
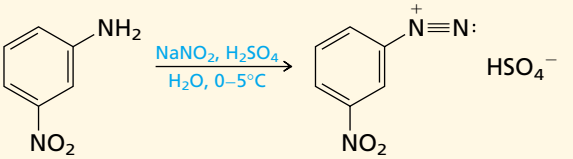


TABLE 22.6 Reactions of Amines Discussed in This Chapter

Reaction (section) and comments	General equation and specific example
Alkylation (Section 22.13) Amines act as nucleophiles toward alkyl halides. Primary amines yield secondary amines, secondary amines yield tertiary amines, and tertiary amines yield quaternary ammonium salts.	$RNH_2 \xrightarrow{R'CH_2X} RNHCH_2R' \xrightarrow{R'CH_2X} RN(CH_2R')_2 \xrightarrow{R'CH_2X} RN^+(CH_2R')_3\,X^-$ Primary amine → Secondary amine → Tertiary amine → Quaternary ammonium salt  2-Chloromethylpyridine + Pyrrolidine → 2-(Pyrrolidinylmethyl)pyridine (93%)
Hofmann elimination (Section 22.14) Quaternary ammonium hydroxides undergo elimination on being heated. It is an anti elimination of the E2 type. The regioselectivity of the Hofmann elimination is opposite to that of the Zaitsev rule and leads to the less highly substituted alkene.	$RCH_2CHR'\,HO^-$ (with $^+N(CH_3)_3$) $\xrightarrow{heat} RCH{=}CHR' + :N(CH_3)_3 + H_2O$ Alkyltrimethylammonium hydroxide → Alkene + Trimethylamine + Water  Cycloheptyltrimethylammonium hydroxide → Cycloheptene (87%)
Electrophilic aromatic substitution (Section 22.15) Arylamines are very reactive toward electrophilic aromatic substitution. It is customary to protect arylamines as their *N*-acyl derivatives before carrying out ring nitration, chlorination, bromination, sulfonation, or Friedel–Crafts reactions.	$ArH + E^+ \longrightarrow ArE + H^+$ Arylamine + Electrophile → Product of electrophilic aromatic substitution + Proton  *p*-Nitroaniline → 2,6-Dibromo-4-nitroaniline (95%)
Nitrosation (Section 22.16) Nitrosation of amines occurs when sodium nitrite is added to a solution containing an amine and an acid. *Primary amines* yield alkyl diazonium salts. Alkyl diazonium salts are very unstable and yield carbocation-derived products. Aryl diazonium salts are exceedingly useful synthetic intermediates. Their reactions are described in Table 22.7.	$RNH_2 \xrightarrow[H^+,\,H_2O]{NaNO_2} RN^+{\equiv}N:$ Primary amine → Diazonium ion  *m*-Nitroaniline → *m*-Nitrobenzenediazonium hydrogen sulfate

(Continued)

TABLE 22.6 Reactions of Amines Discussed in This Chapter *(Continued)*

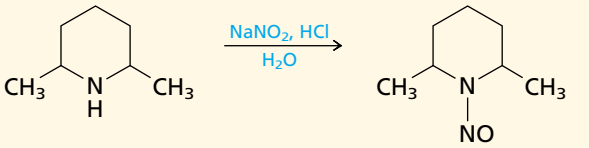
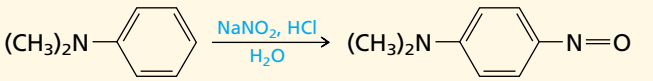
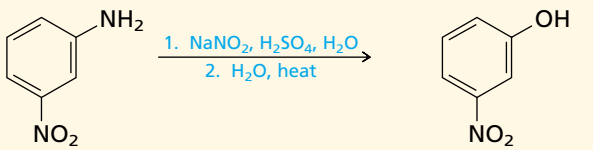
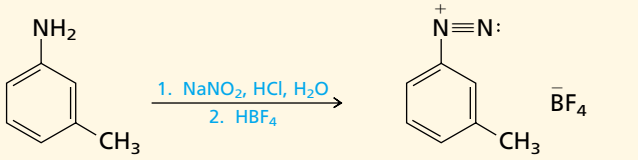
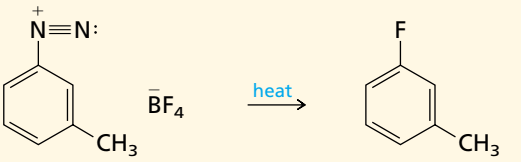
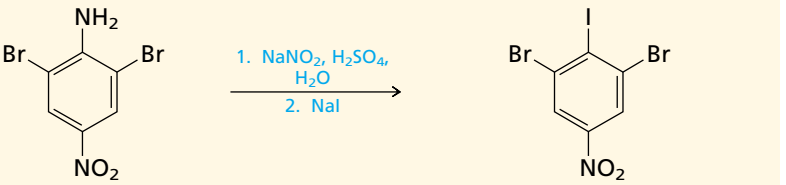
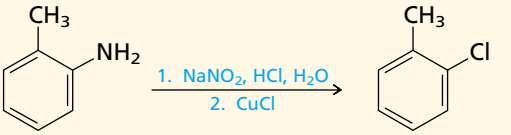
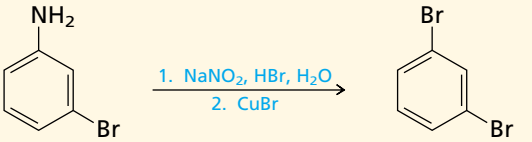
Reaction (section) and comments	General equation and specific example
Secondary alkylamines and *secondary arylamines* yield *N*-nitroso amines.	$R_2NH \xrightarrow[H_2O]{NaNO_2,\ H^+} R_2N{-}N{=}O$ Secondary amine → *N*-Nitroso amine  2,6-Dimethylpiperidine → 2,6-Dimethyl-*N*-nitrosopiperidine (72%)
Tertiary alkylamines illustrate no useful chemistry on nitrosation. *Tertiary arylamines* undergo nitrosation of the ring by electrophilic aromatic substitution.	 *N*,*N*-Dimethylaniline → *N*,*N*-Dimethyl-4-nitrosoaniline (80–89%)

TABLE 22.7 Synthetically Useful Transformations Involving Aryl Diazonium Ions

Reaction and comments	General equation and specific example
Preparation of phenols Heating its aqueous acidic solution converts a diazonium salt to a phenol. This is the most general method for the synthesis of phenols.	$ArNH_2 \xrightarrow[2.\ H_2O,\ heat]{1.\ NaNO_2,\ H_2SO_4,\ H_2O} ArOH$ Primary arylamine → Phenol  *m*-Nitroaniline → *m*-Nitrophenol (81–86%)
Preparation of aryl fluorides Addition of fluoroboric acid to a solution of a diazonium salt causes the precipitation of an aryl diazonium fluoroborate. When the dry aryl diazonium fluoroborate is heated, an aryl fluoride results. This is the Schiemann reaction; it is the most general method for the preparation of aryl fluorides.	$ArNH_2 \xrightarrow[2.\ HBF_4]{1.\ NaNO_2,\ H^+,\ H_2O} ArN{\equiv}N{:}\ \bar{B}F_4 \xrightarrow{heat} ArF$ Primary arylamine → Aryl diazonium fluoroborate → Aryl fluoride  *m*-Toluidine → *m*-Methylbenzenediazonium fluoroborate (76–84%)

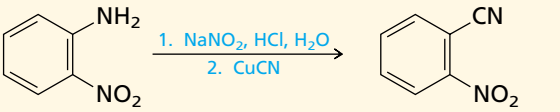
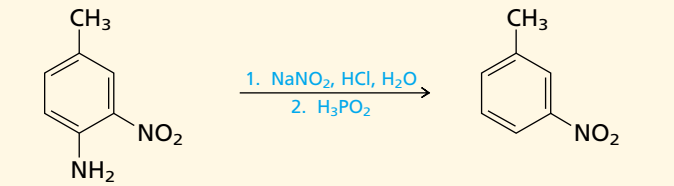
(Continued)

TABLE 22.7 Synthetically Useful Transformations Involving Aryl Diazonium Ions ***(Continued)***

Reaction and comments	General equation and specific example
	 *m*-Methylbenzenediazonium fluoroborate → *m*-Fluorotoluene (89%)
Preparation of aryl iodides Aryl diazonium salts react with sodium or potassium iodide to form aryl iodides. This is the most general method for the synthesis of aryl iodides.	$ArNH_2$ → (1. $NaNO_2$, H^+, H_2O; 2. NaI or KI) → ArI Primary arylamine → Aryl iodide
	 2,6-Dibromo-4-nitroaniline → 1,3-Dibromo-2-iodo-5-nitrobenzene (84–88%)
Preparation of aryl chlorides In the Sandmeyer reaction a solution containing an aryl diazonium salt is treated with copper(I) chloride to give an aryl chloride.	$ArNH_2$ → (1. $NaNO_2$, HCl, H_2O; 2. CuCl) → ArCl Primary arylamine → Aryl chloride
	 *o*-Toluidine → *o*-Chlorotoluene (74–79%)
Preparation of aryl bromides The Sandmeyer reaction using copper(I) bromide is applicable to the conversion of primary arylamines to aryl bromides.	$ArNH_2$ → (1. $NaNO_2$, HBr, H_2O; 2. CuBr) → ArBr Primary arylamine → Aryl bromide
	 *m*-Bromoaniline → *m*-Dibromobenzene (80–87%)

(Continued)

TABLE 22.7 Synthetically Useful Transformations Involving Aryl Diazonium Ions ***(Continued)***

Reaction and comments	General equation and specific example
Preparation of aryl nitriles Copper(I) cyanide converts aryl diazonium salts to aryl nitriles.	$ArNH_2 \xrightarrow[2.\ CuCN]{1.\ NaNO_2,\ H_2O} ArCN$ Primary arylamine → Aryl nitrile  *o*-Nitroaniline → *o*-Nitrobenzonitrile (87%)
Reductive deamination of primary arylamines The amino substituent of an arylamine can be replaced by hydrogen by treatment of its derived diazonium salt with ethanol or with hypophosphorous acid.	$ArNH_2 \xrightarrow[2.\ CH_3CH_2OH \text{ or } H_3PO_2]{1.\ NaNO_2,\ H^+,\ H_2O} ArH$ Primary arylamine → Arene  4-Methyl-2-nitroaniline → *m*-Nitrotoluene (80%)

PROBLEMS

22.21 Write structural formulas or build molecular models for all the amines of molecular formula $C_4H_{11}N$. Give an acceptable name for each one, and classify it as a primary, secondary, or tertiary amine.

22.22 Provide a structural formula for each of the following compounds:

(a) 2-Ethyl-1-butanamine

(b) *N*-Ethyl-1-butanamine

(c) Dibenzylamine

(d) Tribenzylamine

(e) Tetraethylammonium hydroxide

(f) *N*-Allylcyclohexylamine

(g) *N*-Allylpiperidine

(h) Benzyl 2-aminopropanoate

(i) 4-(*N,N*-Dimethylamino)cyclohexanone

(j) 2,2-Dimethyl-1,3-propanediamine

22.23 Many naturally occurring nitrogen compounds and many nitrogen-containing drugs are better known by common names than by their systematic names. A few of these follow. Write a structural formula for each one.

(a) *trans*-2-Phenylcyclopropylamine, better known as *tranylcypromine:* an antidepressant drug

(b) *N*-Benzyl-*N*-methyl-2-propynylamine, better known as *pargyline:* a drug used to treat high blood pressure

(c) 1-Phenyl-2-propanamine, better known as *amphetamine:* a stimulant

(d) 1-(*m*-Hydroxyphenyl)-2-(methylamino)ethanol: better known as *phenylephrine:* a nasal decongestant

22.24 (a) Give the structures or build molecular models and provide an acceptable name for all the isomers of molecular formula C_7H_9N that contain a benzene ring.

(b) Which one of these isomers is the strongest base?

(c) Which, if any, of these isomers yield an *N*-nitroso amine on treatment with sodium nitrite and hydrochloric acid?

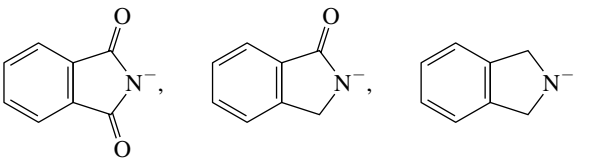
(d) Which, if any, of these isomers undergo nitrosation of their benzene ring on treatment with sodium nitrite and hydrochloric acid?

22.25 Arrange the following compounds or anions in each group in order of decreasing basicity:

(a) H_3C^-, H_2N^-, HO^-, F^-

(b) H_2O, NH_3, HO^-, H_2N^-

(c) HO^-, H_2N^-, $:\bar{C}{\equiv}N:$, NO_3^-

(d) 

22.26 Arrange the members of each group in order of decreasing basicity:

(a) Ammonia, aniline, methylamine

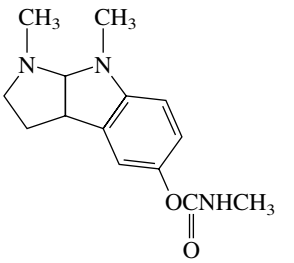
(b) Acetanilide, aniline, *N*-methylaniline

(c) 2,4-Dichloroaniline, 2,4-dimethylaniline, 2,4-dinitroaniline

(d) 3,4-Dichloroaniline, 4-chloro-2-nitroaniline, 4-chloro-3-nitroaniline

(e) Dimethylamine, diphenylamine, *N*-methylaniline

22.27 *Physostigmine,* an alkaloid obtained from a West African plant, is used in the treatment of glaucoma. Treatment of physostigmine with methyl iodide gives a quaternary ammonium salt. What is the structure of this salt?



Physostigmine

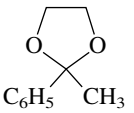
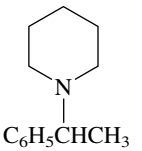
22.28 Describe procedures for preparing each of the following compounds, using ethanol as the source of all their carbon atoms. Once you prepare a compound, you need not repeat its synthesis in a subsequent part of this problem.

(a) Ethylamine

(b) *N*-Ethylacetamide

(c) Diethylamine
(d) *N,N*-Diethylacetamide
(e) Triethylamine
(f) Tetraethylammonium bromide

22.29 Show by writing the appropriate sequence of equations how you could carry out each of the following transformations:

(a) 1-Butanol to 1-pentanamine
(b) *tert*-Butyl chloride to 2,2-dimethyl-1-propanamine
(c) Cyclohexanol to *N*-methylcyclohexylamine
(d) Isopropyl alcohol to 1-amino-2-methyl-2-propanol
(e) Isopropyl alcohol to 1-amino-2-propanol
(f) Isopropyl alcohol to 1-(*N,N*-dimethylamino)-2-propanol
(g)  to 

22.30 Each of the following dihaloalkanes gives an *N*-(haloalkyl)phthalimide on reaction with one equivalent of the potassium salt of phthalimide. Write the structure of the phthalimide derivative formed in each case and explain the basis for your answer.

(a) FCH_2CH_2Br
(b) $BrCH_2CH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$
(c) $BrCH_2\overset{\displaystyle CH_3}{\overset{|}{\underset{\displaystyle CH_3}{\underset{|}{C}}}}CH_2CH_2Br$

22.31 Give the structure of the expected product formed when benzylamine reacts with each of the following reagents:

(a) Hydrogen bromide
(b) Sulfuric acid
(c) Acetic acid
(d) Acetyl chloride
(e) Acetic anhydride
(f) Acetone
(g) Acetone and hydrogen (nickel catalyst)
(h) Ethylene oxide
(i) 1,2-Epoxypropane
(j) Excess methyl iodide
(k) Sodium nitrite in dilute hydrochloric acid

22.32 Write the structure of the product formed on reaction of aniline with each of the following:

(a) Hydrogen bromide
(b) Excess methyl iodide

(c) Acetaldehyde

(d) Acetaldehyde and hydrogen (nickel catalyst)

(e) Acetic anhydride

(f) Benzoyl chloride

(g) Sodium nitrite, aqueous sulfuric acid, 0–5°C

(h) Product of part (g), heated in aqueous acid

(i) Product of part (g), treated with copper(I) chloride

(j) Product of part (g), treated with copper(I) bromide

(k) Product of part (g), treated with copper(I) cyanide

(l) Product of part (g), treated with hypophosphorous acid

(m) Product of part (g), treated with potassium iodide

(n) Product of part (g), treated with fluoroboric acid, then heated

(o) Product of part (g), treated with phenol

(p) Product of part (g), treated with *N,N*-dimethylaniline

22.33 Write the structure of the product formed on reaction of acetanilide with each of the following:

(a) Lithium aluminum hydride

(b) Nitric acid and sulfuric acid

(c) Sulfur trioxide and sulfuric acid

(d) Bromine in acetic acid

(e) *tert*-Butyl chloride, aluminum chloride

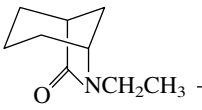
(f) Acetyl chloride, aluminum chloride

(g) 6 M hydrochloric acid, reflux

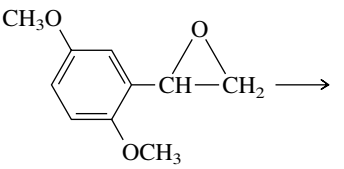
(h) Aqueous sodium hydroxide, reflux

22.34 Identify the principal organic products of each of the following reactions:

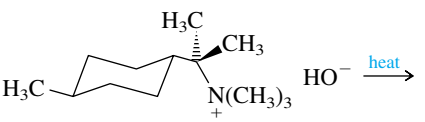
(a) Cyclohexanone + cyclohexylamine $\xrightarrow{H_2,\ Ni}$

(b) 

(c) $C_6H_5CH_2CH_2CH_2OH \xrightarrow[2.\ (CH_3)_2NH\ (excess)]{1.\ p\text{-toluenesulfonyl chloride, pyridine}}$

(d) $(CH_3)_2CHNH_2$ + 

(e) $(C_6H_5CH_2)_2NH + CH_3CCH_2Cl \xrightarrow[THF]{triethylamine}$

(f) 

(g) $(CH_3)_2CHNHCH(CH_3)_2 \xrightarrow[HCl,\ H_2O]{NaNO_2}$

22.35 Each of the following reactions has been reported in the chemical literature and proceeds in good yield. Identify the principal organic product of each reaction.

(a) 1,2-Diethyl-4-nitrobenzene $\xrightarrow[\text{ethanol}]{H_2,\ Pt}$

(b) 1,3-Dimethyl-2-nitrobenzene $\xrightarrow[2.\ HO^-]{1.\ SnCl_2,\ HCl}$

(c) Product of part (b) + $ClCH_2\overset{O}{\overset{\|}{C}}Cl$ $\longrightarrow$

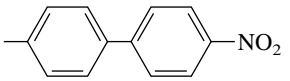
(d) Product of part (c) + $(CH_3CH_2)_2NH$ $\longrightarrow$

(e) Product of part (d) + HCl $\longrightarrow$

(f) $C_6H_5NH\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$ $\xrightarrow[2.\ HO^-]{1.\ LiAlH_4}$

(g) Aniline + heptanal $\xrightarrow{H_2,\ Ni}$

(h) Acetanilide + $ClCH_2\overset{O}{\overset{\|}{C}}Cl$ $\xrightarrow{AlCl_3}$

(i)  $\xrightarrow[2.\ HO^-]{1.\ Fe,\ HCl}$

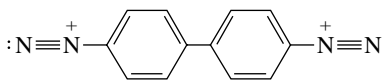
(j) Product of part (i) $\xrightarrow[2.\ H_2O,\ heat]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

(k) 2,6-Dinitroaniline $\xrightarrow[2.\ CuCl]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

(l) *m*-Bromoaniline $\xrightarrow[2.\ CuBr]{1.\ NaNO_2,\ HBr,\ H_2O}$

(m) *o*-Nitroaniline $\xrightarrow[2.\ CuCN]{1.\ NaNO_2,\ HCl,\ H_2O}$

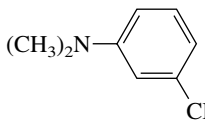
(n) 2,6-Diiodo-4-nitroaniline $\xrightarrow[2.\ KI]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

(o)  $\xrightarrow{heat}$

(p) 2,4,6-Trinitroaniline $\xrightarrow[H_2O,\ H_3PO_2]{NaNO_2,\ H_2SO_4}$

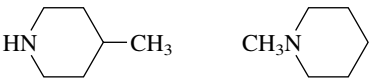
(q) 2-Amino-5-iodobenzoic acid $\xrightarrow[2.\ CH_3CH_2OH]{1.\ NaNO_2,\ HCl,\ H_2O}$

(r) Aniline $\xrightarrow[2.\ 2,3,6\text{-trimethylphenol}]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

(s)  $\xrightarrow[2.\ HO^-]{1.\ NaNO_2,\ HCl,\ H_2O}$

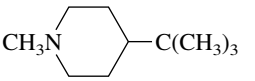
22.36 Provide a reasonable explanation for each of the following observations:

(a) 4-Methylpiperidine has a higher boiling point than *N*-methylpiperidine.



4-Methylpiperidine (bp 129°C) *N*-Methylpiperidine (bp 106°C)

(b) Two isomeric quaternary ammonium salts are formed in comparable amounts when 4-*tert*-butyl-*N*-methylpiperidine is treated with benzyl chloride. (*Hint:* Building a molecular model will help.)

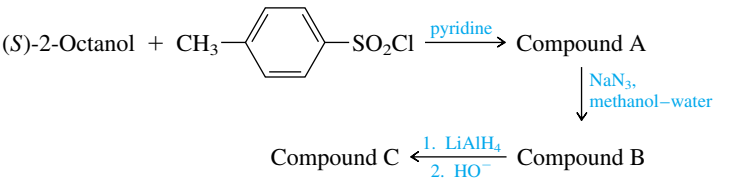


4-*tert*-Butyl-*N*-methylpiperidine

(c) When tetramethylammonium hydroxide is heated at 130°C, trimethylamine and methanol are formed.

(d) The major product formed on treatment of 1-propanamine with sodium nitrite in dilute hydrochloric acid is 2-propanol.

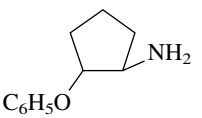
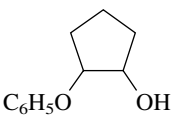
22.37 Give the structures, including stereochemistry, of compounds A through C.



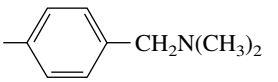
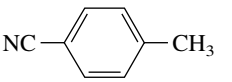
22.38 Devise efficient syntheses of each of the following compounds from the designated starting materials. You may also use any necessary organic or inorganic reagents.

(a) 3,3-Dimethyl-1-butanamine from 1-bromo-2,2-dimethylpropane

(b) $CH_2{=}CH(CH_2)_8CH_2$—N (pyrrolidine) from 10-undecenoic acid and pyrrolidine

(c)  from 

(d) $C_6H_5CH_2N(CH_3)CH_2CH_2CH_2CH_2NH_2$ from $C_6H_5CH_2NHCH_3$ and $BrCH_2CH_2CH_2CN$

(e)  from 

22.39 Each of the following compounds has been prepared from *p*-nitroaniline. Outline a reasonable series of steps leading to each one.

(a) *p*-Nitrobenzonitrile

(b) 3,4,5-Trichloroaniline

(c) 1,3-Dibromo-5-nitrobenzene

(d) 3,5-Dibromoaniline

(e) *p*-Acetamidophenol *(acetaminophen)*

22.40 Each of the following compounds has been prepared from *o*-anisidine (*o*-methoxyaniline). Outline a series of steps leading to each one.

(a) *o*-Bromoanisole

(b) *o*-Fluoroanisole

(c) 3-Fluoro-4-methoxyacetophenone

(d) 3-Fluoro-4-methoxybenzonitrile

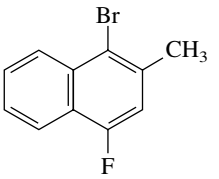
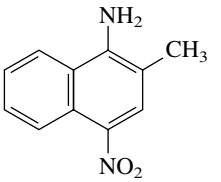
(e) 3-Fluoro-4-methoxyphenol

22.41 Design syntheses of each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents:

(a) *p*-Aminobenzoic acid from *p*-methylaniline

(b) $p\text{-FC}_6\text{H}_4\text{C}(=\text{O})\text{CH}_2\text{CH}_3$ from benzene

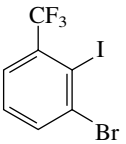
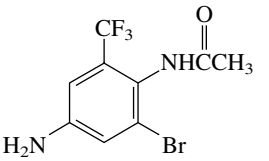
(c) 1-Bromo-2-fluoro-3,5-dimethylbenzene from *m*-xylene

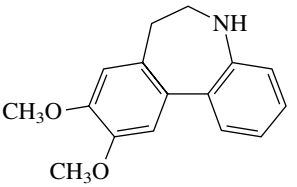
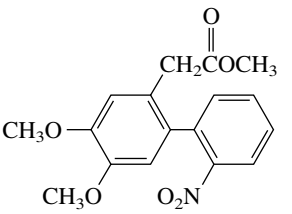
(d)  from 

(e) $o\text{-BrC}_6\text{H}_4\text{C(CH}_3)_3$ from $p\text{-O}_2\text{NC}_6\text{H}_4\text{C(CH}_3)_3$

(f) $m\text{-ClC}_6\text{H}_4\text{C(CH}_3)_3$ from $p\text{-O}_2\text{NC}_6\text{H}_4\text{C(CH}_3)_3$

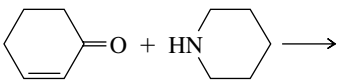
(g) 1-Bromo-3,5-diethylbenzene from *m*-diethylbenzene

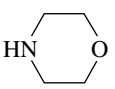
(h)  from 

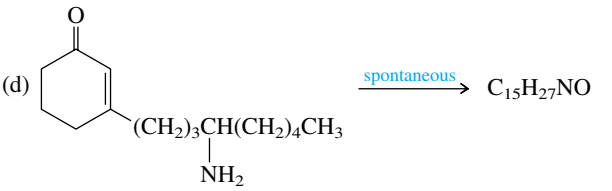
(i)  from 

22.42 Ammonia and amines undergo conjugate addition to α,β-unsaturated carbonyl compounds (Section 18.12). On the basis of this information, predict the principal organic product of each of the following reactions:

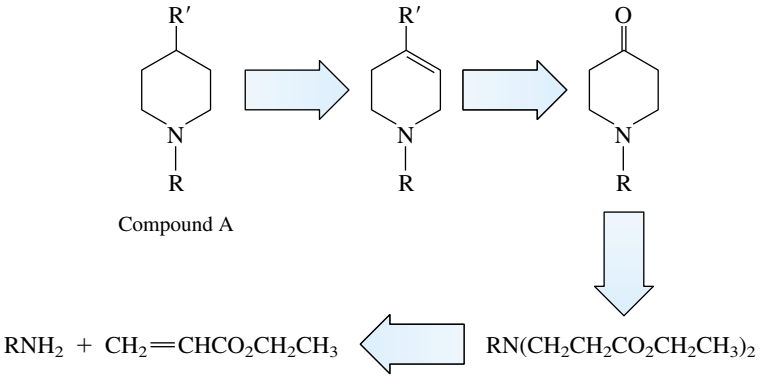
(a) $(\text{CH}_3)_2\text{C}{=}\text{CHC(}{=}\text{O)CH}_3 + \text{NH}_3 \longrightarrow$

(b) 

(c) $\text{C}_6\text{H}_5\text{C(}{=}\text{O)CH}{=}\text{CHC}_6\text{H}_5 + \text{HN}$  $\longrightarrow$



22.43 A number of compounds of the type represented by compound A were prepared for evaluation as potential analgesic drugs. Their preparation is described in a retrosynthetic format as shown.

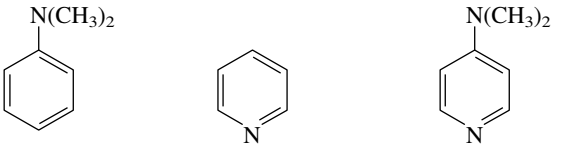


On the basis of this retrosynthetic analysis, design a synthesis of *N*-methyl-4-phenylpiperidine (compound A, where R = CH_3, R′ = C_6H_5). Present your answer as a series of equations, showing all necessary reagents and isolated intermediates.

22.44 *Mescaline,* a hallucinogenic amine obtained from the peyote cactus, has been synthesized in two steps from 3,4,5-trimethoxybenzyl bromide. The first step is nucleophilic substitution by sodium cyanide. The second step is a lithium aluminum hydride reduction. What is the structure of mescaline?

22.45 *Methamphetamine* is a notorious street drug. One synthesis involves reductive amination of benzyl methyl ketone with methylamine. What is the structure of methamphetamine?

22.46 The basicity constants of *N,N*-dimethylaniline and pyridine are almost the same, whereas 4-(*N,N*-dimethylamino)pyridine is considerably more basic than either.



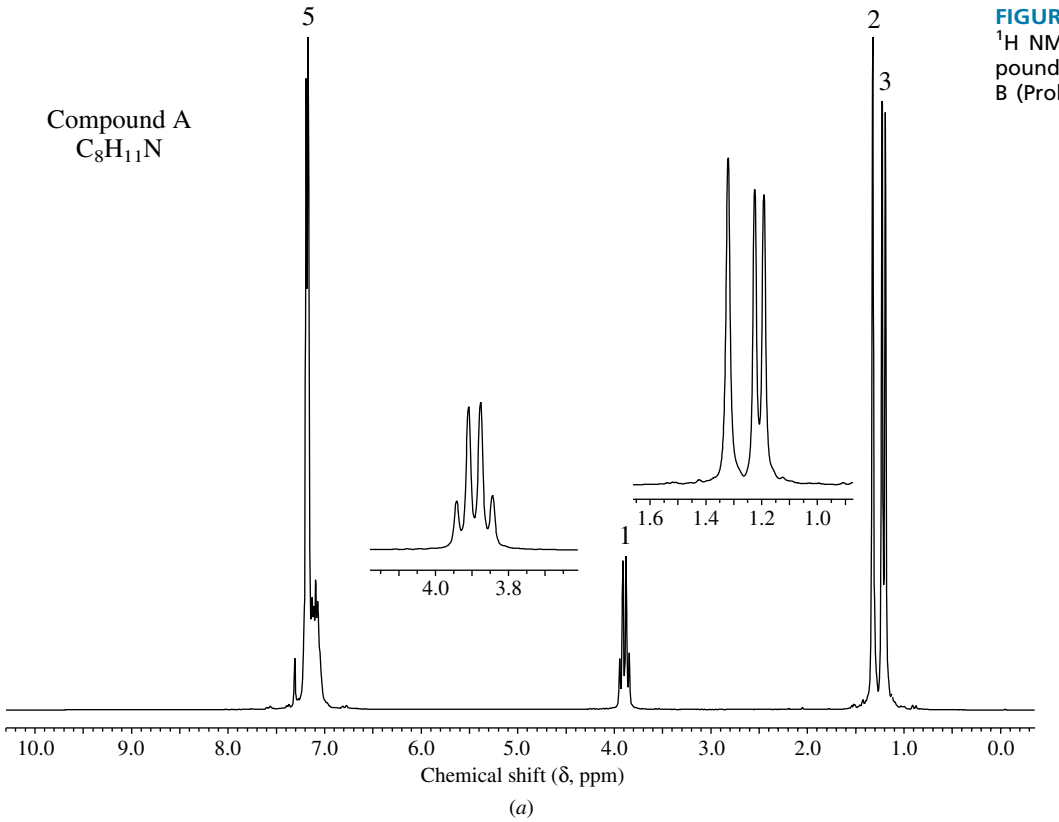
N,N-Dimethylaniline
K_b 1.3×10^{-9}
pK_b 8.9

Pyridine
K_b 2×10^{-9}
pK_b 8.7

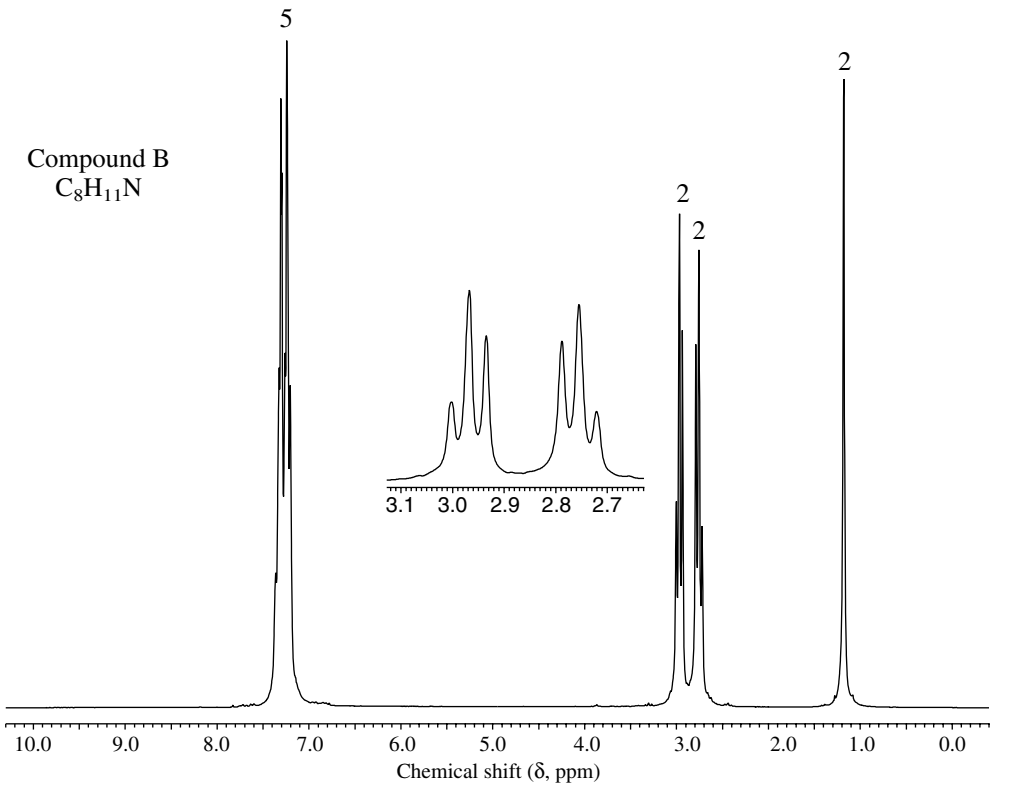
4-(*N,N*-Dimethylamino)pyridine
$K_b = 5 \times 10^{-5}$
pK_b 4.3

Identify the more basic of the two nitrogens of 4-(*N,N*-dimethylamino)pyridine, and suggest an explanation for its enhanced basicity as compared with pyridine and *N,N*-dimethylaniline. Refer to *Learning By Modeling* and compare your prediction to one based on the calculated charge and electrostatic potential of each nitrogen.

22.47 Compounds A and B are isomeric amines of molecular formula $C_8H_{11}N$. Identify each isomer on the basis of the ^1H NMR spectra given in Figure 22.9.



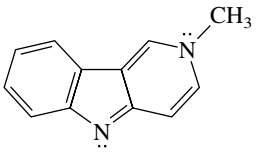
(*a*)



(*b*)

FIGURE 22.9 The 200-MHz ^{1}H NMR spectra of (*a*) compound A and (*b*) compound B (Problem 22.47).

22.48 The compound shown is a somewhat stronger base than ammonia. Which nitrogen do you think is protonated when it is treated with an acid? Write a structural formula for the species that results.



5-Methyl-γ-carboline (pK_b = 3.5)

Refer to *Learning By Modeling,* and compare your prediction to one based on the calculated charge and electrostatic potential of each nitrogen.

22.49 Does the ^{13}C NMR spectrum shown in Figure 22.10 correspond to that of 1-amino-2-methyl-2-propanol or to 2-amino-2-methyl-1-propanol? Could this compound be prepared by reaction of an epoxide with ammonia?

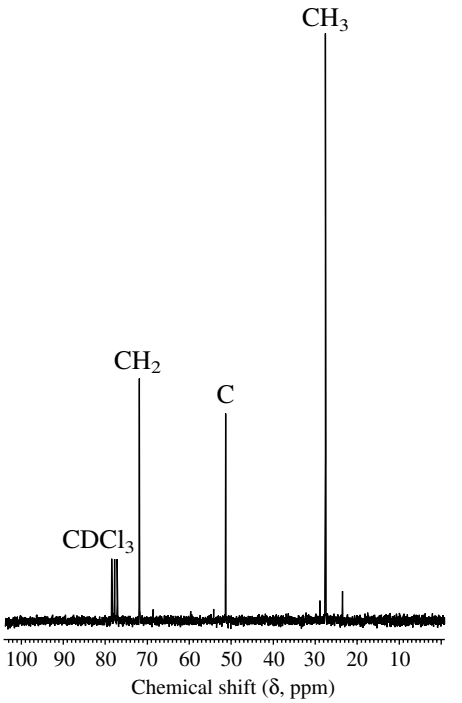


FIGURE 22.10 The ^{13}C NMR spectrum of the compound described in Problem 22.49.