23

ORGANONITROGEN COMPOUNDS I. AMINES

A wide variety of organic compounds contain nitrogen. In fact, the types of nitrogen compounds are so numerous and diverse that we shall be unable to consider them all. We shall give most attention to the chemistry of amines and amides in this and the following chapter, because these represent the two largest classes of nitrogen compounds.

23-1 AMINES COMPARED WITH ALCOHOLS

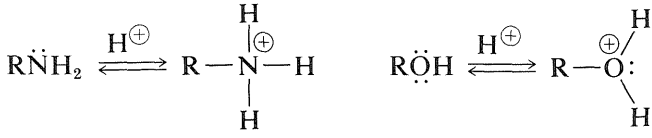
As you read the chapter you will recognize a similarity between the chemistry of amines and the chemistry of alcohols, which we discussed in Chapter 15. Primary amines (RNH_2) and secondary amines (R_2NH) are much weaker acids than alcohols (ROH) and form strongly basic anions:

Acids

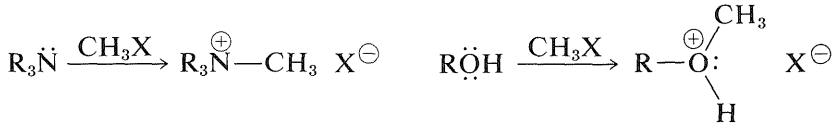
$$\ddot{R}\ddot{N}H_2 \overset{-H^{\oplus}}{\rightleftharpoons} R\ddot{\underset{\cdot\cdot}{N}}H^{\ominus} \qquad R\ddot{\underset{\cdot\cdot}{O}}H \overset{-H^{\oplus}}{\rightleftharpoons} R\ddot{\underset{\cdot\cdot}{O}}:^{\ominus}$$

Amines, like alcohols, have nonbonding electrons that impart basic and nucleophilic properties.

Bases



Nucleophiles



Also, amines and alcohols both can behave as carbon electrophiles under appropriate reaction conditions such that cleavage of C–N and C–O bonds occurs in the sense $\overset{\delta\oplus}{C}\,|\,\overset{\delta\ominus}{:N}$ and $\overset{\delta\oplus}{C}\,|\,\overset{\delta\ominus}{:O}$. However, because $-NH_2$ and $-OH$ both are poor leaving groups, each must be suitably activated to make this kind of reaction possible (see Section 8-7C). The OH group can be activated by addition of a proton or conversion to a sulfonate ester, RO_3SR', but these processes generally are ineffective for RNH_2. The most effective activation for RNH_2 is through conversion with nitrous acid, HONO, to $R-\overset{\oplus}{N}\equiv N$; then N_2 is the leaving group (this reaction is described in more detail in Section 23-10A):

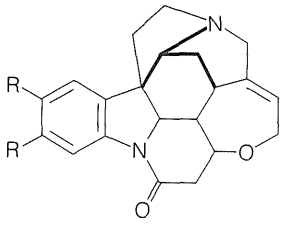
$$R-NH_2 \xrightarrow[H^{\oplus}]{HONO} [R-\overset{\oplus}{N}\equiv N] + 2H_2O \xrightarrow{-H^{\oplus}} R-OH + N_2 + H_2O$$

$$R-OH \xrightarrow{HBr} R-Br + H_2O$$

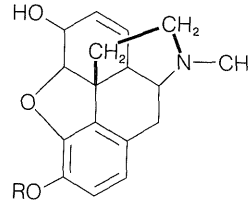
There is, though, a major difference in the way that amines and alcohols behave toward oxidizing agents. Amines generally show more complex behavior on oxidation because, as we shall see, nitrogen has a larger number of stable oxidation states than oxygen.

23-2 SOME NATURALLY OCCURRING AMINES. ALKALOIDS AND RELATED COMPOUNDS

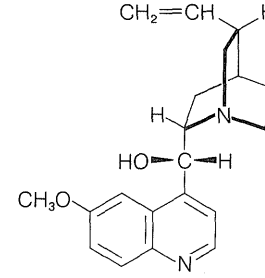
A large and widespread class of naturally occurring amines is known as **alkaloids.** These are basic organic nitrogen compounds, mostly of plant origin. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine (Figure 23-1) as basic, salt-forming, and ammonia-like. He used the term "organic alkali" from which is derived the name *alkaloid.*



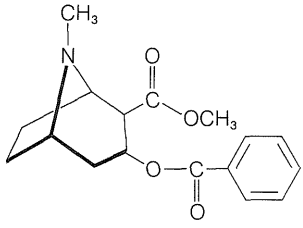
R = H, strychnine
R = OCH_3, brucine



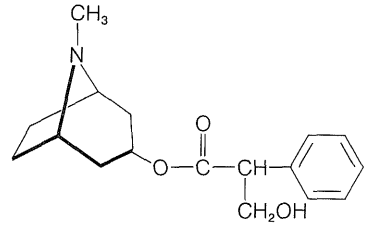
R = H, morphine
R = CH_3, codeine
(analgesic)



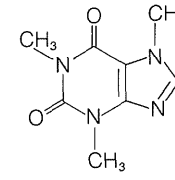
quinine
(antimicrobial)
(antimalarial)



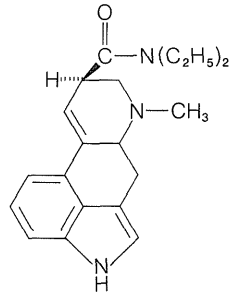
cocaine
(local anaesthetic)
(stimulant)



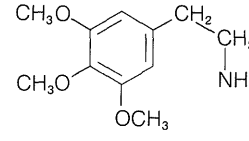
atropine
(stimulant)



caffeine
(stimulant)



lysergic acid diethylamide (LSD)
(hallucinogen)



mescaline
(hallucinogen)

Figure 23-1 Some naturally occurring basic nitrogen compounds (alkaloids)

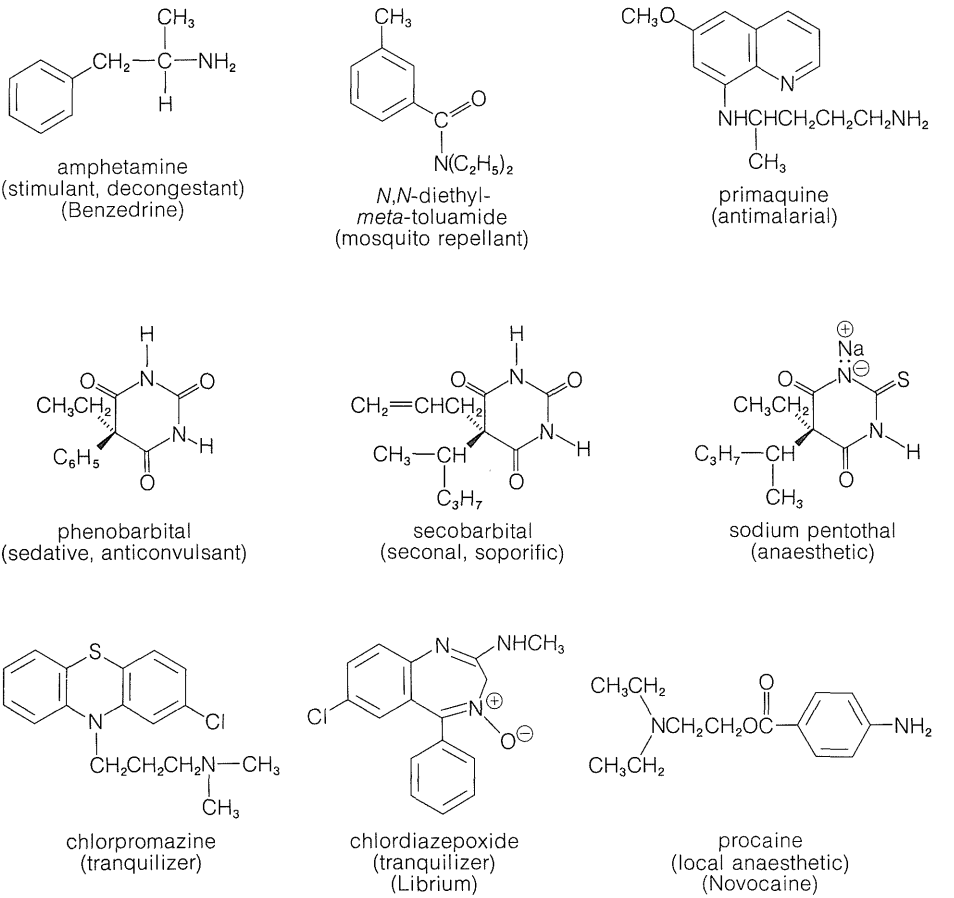


Figure 23-2 Synthetic drugs that are either basic or acidic nitrogen compounds

The structures of some of the better known plant alkaloids are shown in Figure 23-1. You will recognize some of them by name even if you have never seen their structures before. Many of the alkaloids are polycyclic structures and have other functional groups in addition to basic nitrogen. You will see that the nitrogens of alkaloids frequently are tertiary amine functions.

All of the alkaloids shown in Figure 23-1 are substances with very pronounced physiological action. Indeed, alkaloids in general have been used and abused for centuries as medicinals, drugs, and poisons. However, only in this century have their structures become known, and we are still a long way from understanding the chemistry that leads to their pronounced physiological effects. It is not even understood what function, if any, these compounds have in the host plant.

As you can see from Figure 23-1, alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), as stimulants (cocaine, atropine, caffeine),

as topical anaesthetics (cocaine). With the possible exception of caffeine, all may be described as potentially poisonous enough to warrant great care in their use. Although some of these compounds are used as natural medicinals, an entire industry has developed in an effort to produce synthetic analogs with similar, but safer, medicinal properties. Some of the better known of these synthetic drugs are shown in Figure 23-2. They include a group of narcotic substances known as barbiturates, which are used widely as sedatives, anticonvulsants, and sleep-inducing drugs. Several representative nitrogen-containing tranquilizing drugs, synthetic stimulants, and antibiotics also are shown.

Basic nitrogen compounds similar to the plant alkaloids also occur in animals, although the description *animal alkaloid* seldom is used. Certain amines and ammonium compounds play key roles in the function of the central nervous system (Figure 23-3) and the balance of amines in the brain is critical for normal brain functioning. Also, many essential vitamins and hormones are basic nitrogen compounds. Nitrogen bases also are vital constituents of nucleic acid polymers (DNA and RNA) and of proteins (Chapter 25).

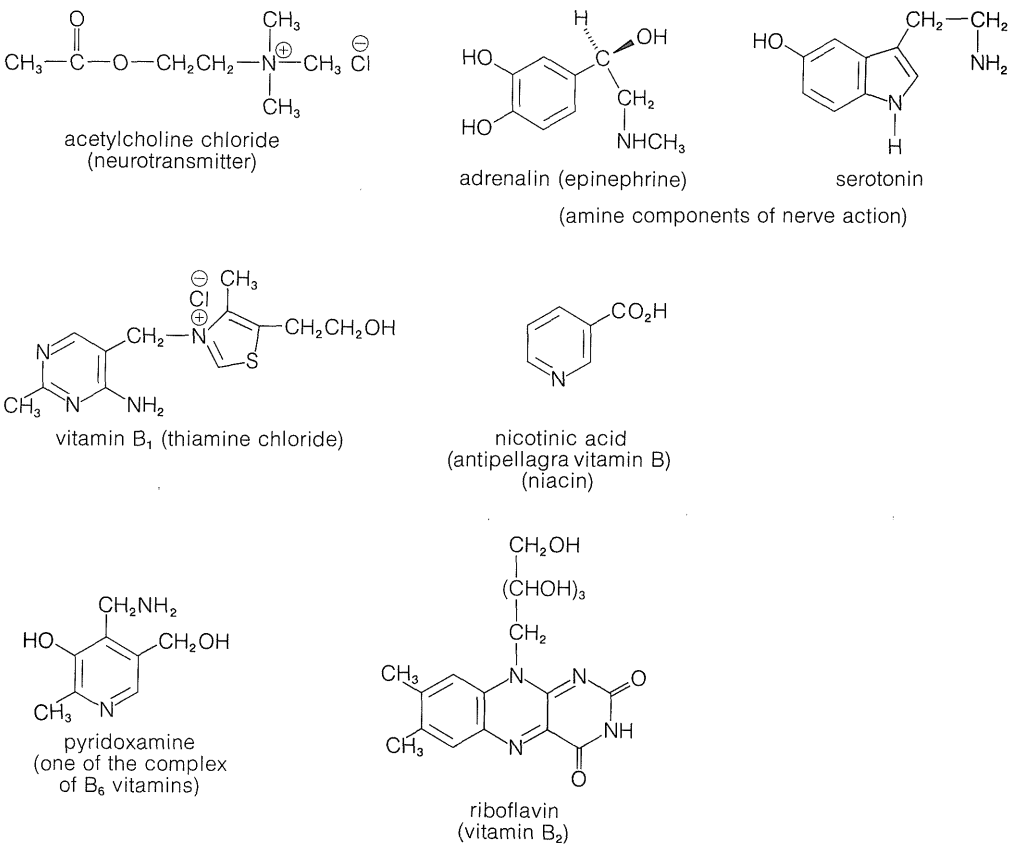
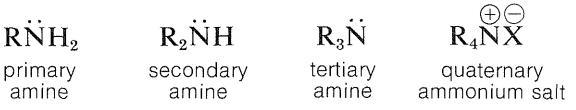


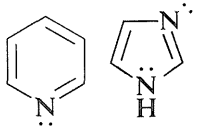
Figure 23-3 Some biologically important amines

23-3 TYPES AND NOMENCLATURE OF AMINES

Amine bases are classified according to the number of alkyl or aryl groups attached to nitrogen. This number is important in determining the chemical reactions that are possible at the nitrogen atom:



A further classification exists if the nitrogen is multiply bonded to carbon, as in imines and aromatic nitrogen compounds:

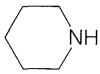
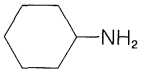
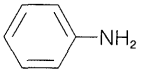


The nomenclature of amines was considered briefly in Section 7-8. We shall give only a short review here to focus on the main points. Amino compounds can be named either as derivatives of ammonia or as amino-substituted compounds:

$HOCH_2CH_2NH_2$ 2-hydroxyethan*amine* (2-hydroxyethyl*amine*) or 2-amino*ethanol* (preferred because —OH takes precedence over $—NH_2$; Section 7-1A)

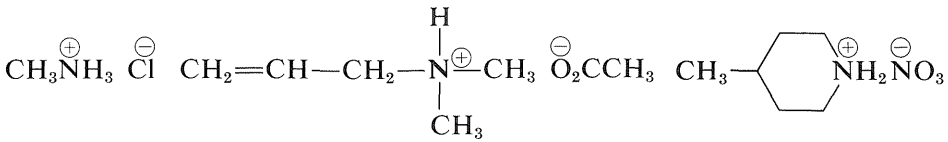
To be consistent and logical in naming amines as substituted ammonias, they strictly should be called *alkanamines* and *arenamines,* according to the nature of the hydrocarbon grouping. Unfortunately, the term *alkylamine* is used very commonly in place of alkanamine, while a host of trivial names are used for arenamines. We shall try to indicate both the trivial and the systematic names where possible. Some typical amines, their names, and their physical properties are listed in Table 23-1. The completely systematic names given in Table 23-1 illustrate in a poignant way the difficulty one gets into by using completely systematic names, and why simpler but less systematic names continue to be used for common compounds. A good example is *N,N*-dibutylbutanamine versus tributylamine. The special ways of naming heterocyclic amines were mentioned previously (Section 15-11A).

Table 23-1
Typical Amines and Their Properties

Amine	Name	Bp, °C	Mp, °C	Water solubility, g/100 ml	K_b in water[a]	pK_a[b]
NH_3	ammonia	−33	−77.7	90^0	1.8×10^{-5}	9.26
CH_3NH_2	methanamine (methylamine)	−6.5	−92.5	1156	4.4×10^{-4}	10.64
$CH_3CH_2NH_2$	ethanamine (ethylamine)	16.6	−80.6	∞	5.6×10^{-4}	10.75
$(CH_3)_3CNH_2$	1,1-dimethylethanamine (*tert*-butylamine)	46	−67.5	∞	2.8×10^{-4}	10.45
$(CH_3CH_2)_2NH$	*N*-ethylethanamine (diethylamine)	55.5	−50	v. sol.	9.6×10^{-4}	10.98
$(CH_3CH_2)_3N$	*N*,*N*-diethylethanamine (triethylamine)	89.5	−115	1.5^{20}	4.4×10^{-4}	10.64
$(CH_3CH_2CH_2CH_2)_3N$	*N*,*N*-dibutylbutanamine (tributylamine)	214		sl. sol.		
	azacyclohexane (piperidine)	106	−9	∞	1.6×10^{-3}	11.20
	azabenzene (pyridine)	115	−42	∞	1.7×10^{-9}	5.23
	cyclohexanamine	134	−18	sl. sol.	4.4×10^{-4}	10.64
	benzenamine (aniline)	184.4	−6.2	3.4^{20}	3.8×10^{-10}	4.58
$H_2NCH_2CH_2NH_2$	1,2-ethanediamine (ethylenediamine)	116	8.5	sol.	8.5×10^{-5}	9.93

[a]Usually at 20–25°. [b]The pK_a values refer to the dissociation of the conjugate acid $RNH_3^{\oplus}$ $+ H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + H_3O^{\oplus}$, where $pK_a = -\log K_a = 14 + \log K_b$ (see Sections 8-1 and 23-7).

Salts of amines with inorganic or organic acids are named as *substituted ammonium* salts, except when the nitrogen is part of a ring system. Examples are



methylammonium chloride

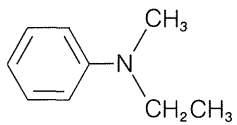
2-propenyldimethylammonium ethanoate

4-methylazoniacyclohexane nitrate[1]

Exercise 23-1 Name the following substances by an accepted system (Section 7-8):

a. $(CH_3)_2N—CH=CH_2$

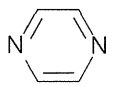
b.



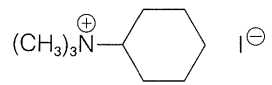
c. $H_2NCH_2CO_2H$

d. $H_2NCH_2CH_2CH_2CH_2NH_2$

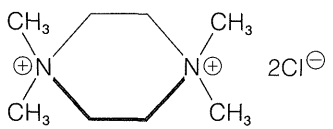
e.



f.



g.



23-4 PHYSICAL PROPERTIES OF AMINES

The physical properties of amines depend in an important way on the extent of substitution at nitrogen. Thus primary amines, RNH_2, and secondary amines, R_2NH, are less volatile than hydrocarbons of similar size, weight, and shape, as the following examples show:

$CH_3CH_2CH_2CH_2CH_2NH_2$
pentanamine
MW 87; bp 130°

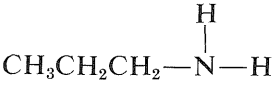
$CH_3CH_2CH_2CH_2CH_2CH_3$
hexane
MW 86; bp 69°

$CH_3CH_2NHCH_2CH_3$
N-ethylethanamine
MW 73; bp 55.5°

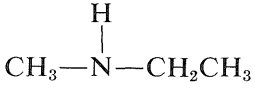
$CH_3CH_2CH_2CH_2CH_3$
pentane
MW 72; bp 36°

[1]Note the use of *azonia* to denote the cationic nitrogen in the ring, whereas *aza* is used for neutral nitrogen (see Section 15-11A).

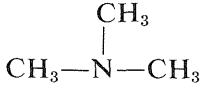
This is because the amines are associated through hydrogen bonding of the type N—H····:N. Generally, N—H····:N bonds are somewhat weaker than those of the corresponding types, O—H····:O and F—H····:F, because the electronegativity of nitrogen is *less* than that of oxygen or fluorine thereby making nitrogen a poorer hydrogen *donor*. Even so, association through hydrogen bonding is significant in amines of the type RNH_2 or R_2NH as the boiling-point comparison shows. With tertiary amines, where N—H····:N bonding is not possible, the boiling points are much lower and are similar to those of hydrocarbons of similar branching and molecular weights:



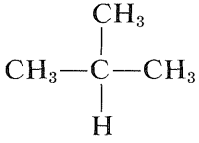
propanamine
MW 59; bp 49°



N-methylethanamine
MW 59; bp 35°

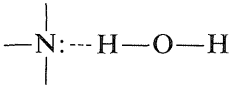


N,N-dimethylmethanamine
MW 59; bp 3.5°



2-methylpropane
MW 58; bp −0.5°

The water solubilities of the lower-molecular-weight amines are appreciable, as can be seen from the solubility data in Table 23-1. In fact, amines are more water-soluble than alcohols of similar molecular weights. This is the result of hydrogen bonding, with amine molecules as the hydrogen *acceptors* and water molecules as the hydrogen *donors:*



Hydrogen bonds of this type are stronger than  bonds.

Amines, especially those with significant volatility, have unpleasant odors. Some of them smell like ammonia, others smell fishy, while others are indescribably revolting. The alkanediamines of structure $H_2N(CH_2)_nNH_2$ are notably wretched and two are aptly called putrescine ($n = 4$) and cadaverine ($n = 5$). As you may guess from the names, these compounds are among the amines produced by bacterial decay of organic animal matter (putrefaction of protein) and are poisonous components (ptomaines) thereof.

23-5 SPECTROSCOPIC PROPERTIES OF AMINES

23-5A Infrared and Ultraviolet Spectra

A characteristic feature of the infrared spectra of primary and secondary amines is the moderately weak absorption at 3500 cm^{-1} to 3300 cm^{-1}, which corresponds to N—H stretching vibrations. Primary amines have two such bands in this region, whereas secondary amines generally show only one band. Absorption is shifted to lower frequencies by hydrogen bonding, but because NH----:N bonding is weaker than OH----:O bonding, the shift is not as great and the bands are not as intense as are the absorption bands of hydrogen-bonded O—H groups (see Table 9-2). Bands corresponding to N—H bending vibrations are observed around 1600 cm^{-1}. Absorptions corresponding to C—N vibrations are less easily identifiable, except in the case of arenamines, which absorb fairly strongly near 1300 cm^{-1}. Spectra that illustrate these effects are shown in Figure 23-4.

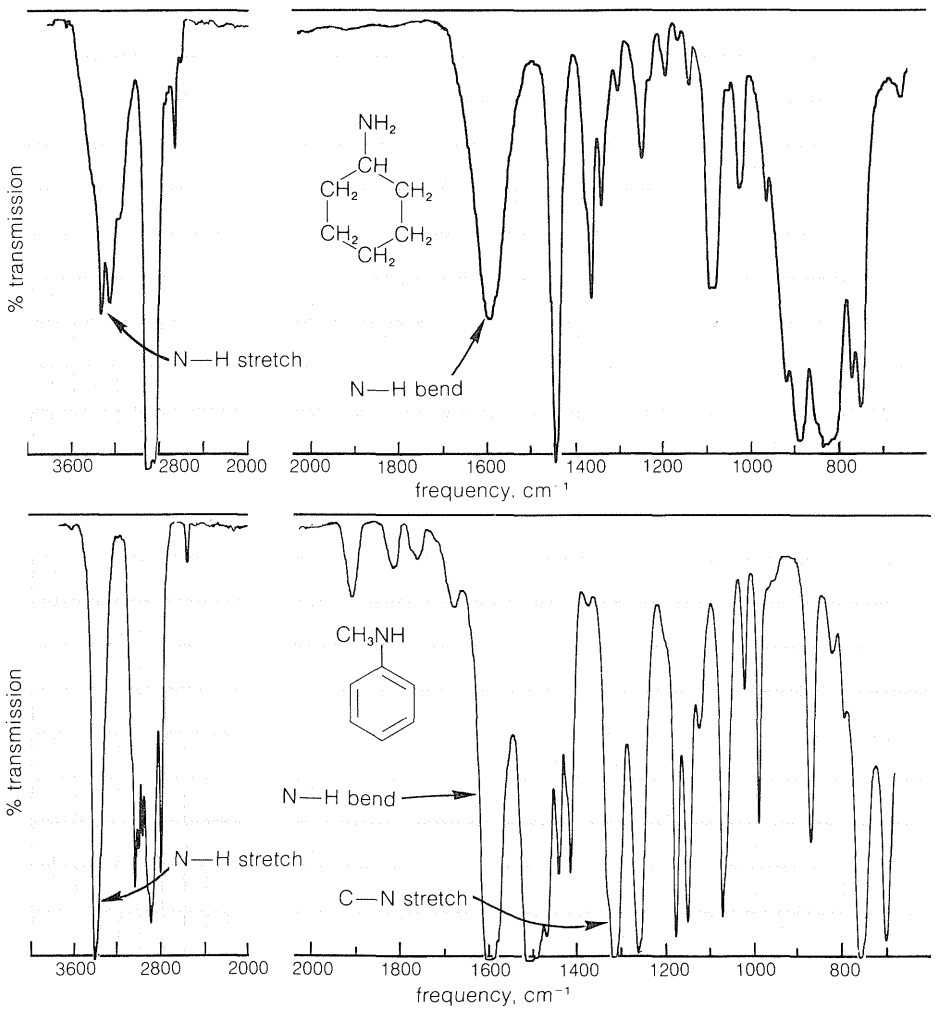


Figure 23-4 Infrared spectra of cyclohexanamine and *N*-methylbenzenamine (*N*-methylaniline)

The ultraviolet absorptions of simple saturated amines occur at rather short wavelengths (~220 nm) and are not particularly useful for identification. These are $n \longrightarrow \sigma^*$ transitions that correspond to excitation of an electron of the unshared pair on nitrogen to the antibonding σ orbital of a C—N bond.

23-5B NMR Spectra

The proton nmr spectra of amines show characteristic absorptions for H—C—N protons around 2.7 ppm. The positions of the resonances of N—H protons show considerable variability as the result of differences in degree of hydrogen bonding (Section 9-10E). Sometimes the N—H resonance has nearly the same chemical shift as the resonances of CH_3—C protons (as with *N*-ethylethanamine, Figure 23-5).

A further complication associated with N—H and H—C—N resonances is their variable chemical shift and line width in the presence of acidic substances because of a chemical exchange process of the type illustrated in Equation 23-1:

$$CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle \ddot{N}}{|}}-H + H'A \rightleftharpoons CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle H'}{\overset{\displaystyle \ddot{N}^{\oplus}}{|}}}-H + A^{\ominus} \rightleftharpoons CH_3-\underset{\displaystyle CH_3}{\overset{\displaystyle H'}{\overset{\displaystyle N:}{|}}} + HA \qquad (23\text{-}1)$$

Depending on the rate at which the proton transfers of Equation 23-1 occur and the concentrations of the reactants, the chemical shift of the N—H proton

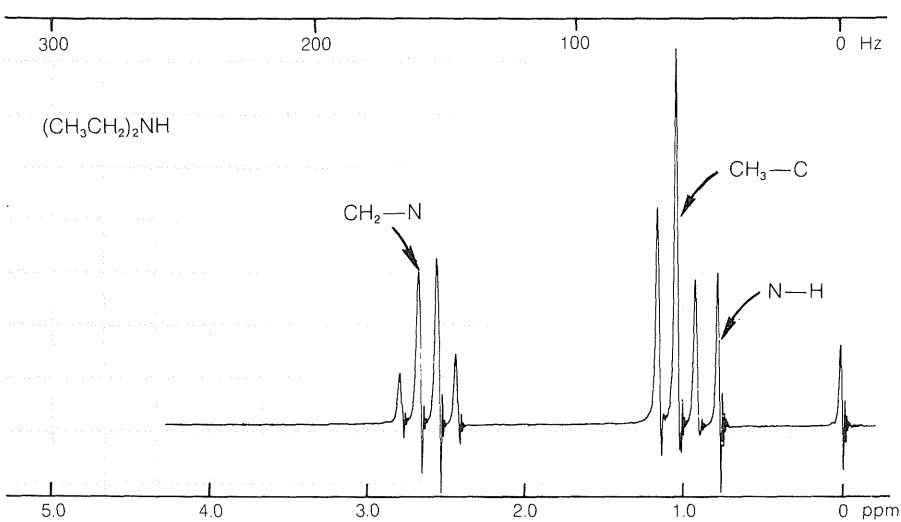


Figure 23-5 Nmr spectrum of *N*-ethylethanamine (diethylamine) at 60 MHz relative to TMS at 0 ppm. Rapid exchange of the N—H protons between different amine molecules causes the N—H resonance to be a single peak (Section 9-10I).

will come somewhere between that of pure $(CH_3)_2NH$ and pure HA. Except at high acid concentrations, this exchange eliminates any observable coupling between the N—H proton and the *N*-methyl protons (H—C—N—H); see Section 9-10I.

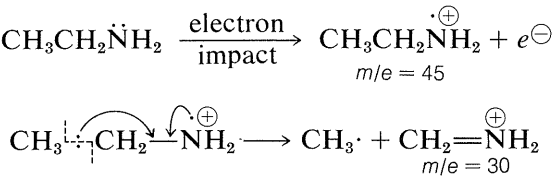
Exercise 23-2 How could one show with certainty that the peak at 47 Hz with reference to TMS in the nmr spectrum of *N*-ethylethanamine (Figure 23-5) is due to the N—H resonance?

Exercise 23-3 Show how structures can be deduced for the isomeric substances of molecular formula $C_8H_{11}N$, whose nmr and infrared spectra are shown in Figure 23-6.

In Section 9-10L, we discussed ^{13}C nmr and its many applications to structural problems. The nmr of ^{15}N nuclei has similar possibilities but, because ^{15}N is only 0.37% of natural nitrogen and has an even smaller nuclear magnetic moment than ^{13}C, it is very difficult to detect ^{15}N resonances at the natural-abundance level.[2] Indeed, natural ^{15}N has to be observed for about a 6×10^{10} longer time than protons to achieve the same signal-to-noise ratio! Despite this difficulty, natural-abundance ^{15}N spectra can be obtained for many compounds (even enzymes) and, in some cases, provide very useful chemical information (see Figure 24-4).

23-5C Mass Spectra of Amines

The most prominent cleavage of the parent molecular ion M^+ derived from amines occurs at the C_β–C_α bond to give an imminium ion which, for ethanamine, has $m/e = 30$:



(23-2)

It is helpful in identifying the molecular ion of an organonitrogen compound to remember that the m/e value of M^+ will be an uneven number if the

[2]The abundant nitrogen nucleus, ^{14}N, has a magnetic moment but generally gives very poor nmr spectra with very broad lines. The reason is that ^{14}N usually "relaxes" rapidly, which means that its nuclear magnetic states have short lifetimes (see Section 27-1).

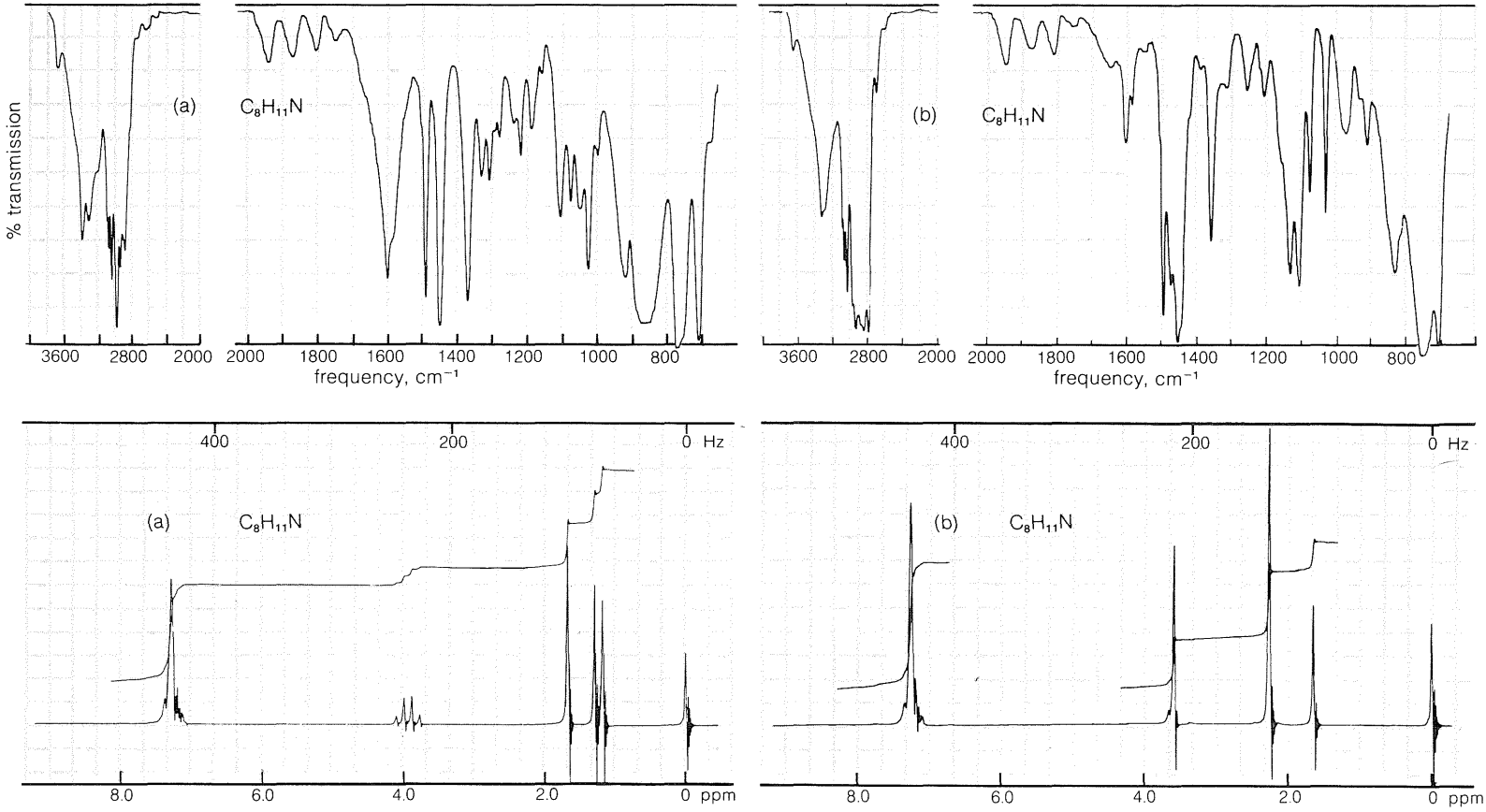


Figure 23-6 Infrared and nmr spectra of two isomeric compounds, (a) and (b), of formula $C_8H_{11}N$. The nmr spectra are at 60 MHz relative to TMS. See Exercise 23-3.

Table 23-2
m/e Values of Odd- and Even-Electron Ions from Organic Compounds

Composition	Odd-electron parent M^+ molecular ions, *m/e*	Even-electron ions, from fragmentation of M^+, *m/e*
C, H, O, even or zero N	even	odd
C, H, O, odd N	odd	even

ion contains one or another odd number of nitrogen atoms. Thus ethanamine, C_2H_7N, gives an M^+ of $m/e = 45$. For all other elemental compositions of C, H, O, or with an even number of nitrogens, the molecular ion will have an even *m/e* value.

The cleavage reaction of Equation 23-2 reveals other useful generalizations. Whatever its source, a parent molecular ion, M^+, has one unpaired electron and is properly described as an **odd-electron ion** (a radical cation). When a parent molecular ion fragments, it does so *homolytically,* as shown in Equation 23-2, and produces a radical and an ion in which the electrons are paired—an **even-electron ion.** The *m/e* value of an even-electron ion is an *even* number for any elemental composition of C, H, O in combination with an *odd* number of nitrogens. These generalizations are summarized in Table 23-2 and can be useful in the interpretation of mass spectra, as illustrated by Exercises 23-4 and 23-5.

Exercise 23-4 The highest mass peak in the mass spectrum of a certain compound is *m/e* 73. The most abundant peak has *m/e* 58. Suggest a structure for the compound and explain how it could form an ion of *m/e* 58.

Exercise 23-5 Prominent peaks in the mass spectrum of a basic nitrogen compound have *m/e* values of 87, 72, 57, and 30. The nmr spectrum shows only three proton resonances, having intensity ratios of 9:2:2 at 0.9, 1.3, and 2.3 ppm. Assign a structure to the compound and account for the fragment ions *m/e* 72, 57, and 30.

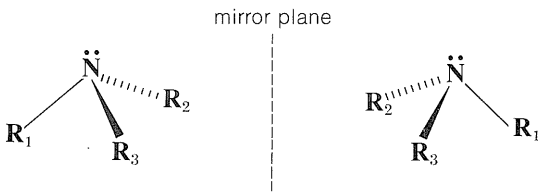
23-6 STEREOCHEMISTRY OF AMINES

In ammonia and amines, the bonds to nitrogen are pyramidal with bond angles closer to the tetrahedral value of 109.5° than to the 90° value expected for the

use of pure p orbitals of nitrogen in bond formation. We consider that the nitrogen in amines is formulated best with hybrid sp^3-type orbitals; three of these orbitals are used in σ-bond formation while the fourth contains the nonbonding electron pair:

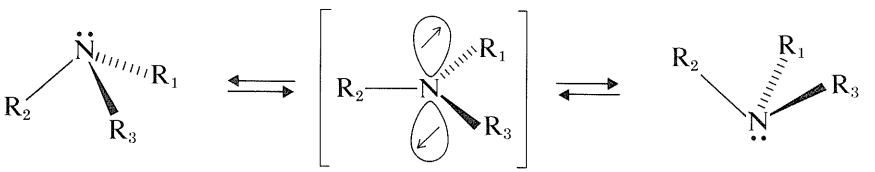
pyramidal configuration at nitrogen

A consequence of the pyramidal configuration at nitrogen is that, when the attached groups R_1, R_2 and R_3 are nonidentical, the nitrogen becomes a chiral atom. Under these circumstances, we would expect two enantiomeric configurations:



enantiomers of a chiral amine

The resolution of an acyclic chiral amine into its separate enantiomers has not been achieved yet, and it appears that the enantiomers are very rapidly interconverted by an inversion process involving a planar transition state:

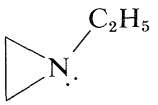


planar transition state

With ammonia, inversion of this type occurs about 4×10^{10} times per second at room temperature, which corresponds to the planar state being less stable than the pyramidal state by about 6 kcal mole^{-1}. With aliphatic tertiary amines, the inversion rate is more on the order of 10^3 to 10^5 times per second. Such rates of inversion are much too great to permit resolution of an amine into its enantiomers by presently available techniques.

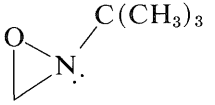
When the amine nitrogen is incorporated in a small ring, as in azacyclopropanes, **1**, the rate of inversion at nitrogen is markedly slower than in open-chain amines. In fact, with some oxazacyclopropanes, such as **2**, inversion

does not occur rapidly at ordinary temperatures, which means that the configuration at the nitrogen persists long enough for resolution into enantiomers to be possible:



1

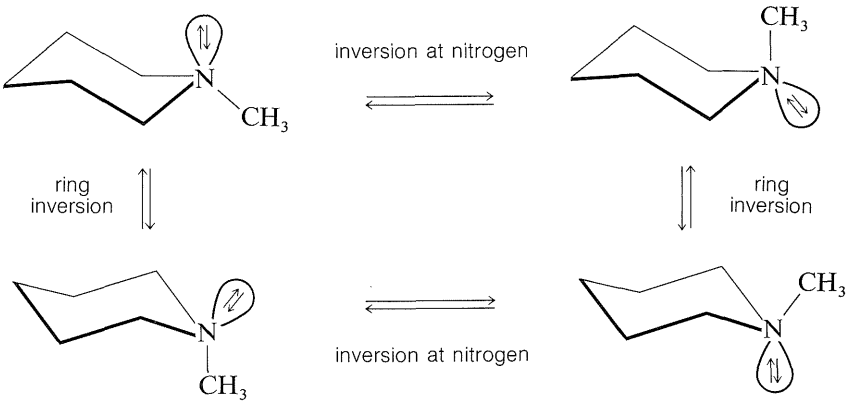
1-ethylazacyclopropane
$\Delta G^{\dagger}$ (inversion) = 19.4 kcal mole^{-1}



2

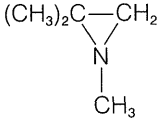
2-*tert*-butyloxazacyclopropane
$\Delta G^{\dagger}$ (inversion) = 33 kcal mole^{-1}

The stereochemistry of azacyclohexanes is complicated by the fact that there is a conformational change in the ring as well as inversion at the pyramidal nitrogen. Therefore it is difficult to say whether the axial-equatorial equilibrium of, for example, 1-methylazacyclohexane is achieved by ring inversion, or by nitrogen inversion, or both:



Exercise 23-6* Explain why the configuration of the nitrogen in 1-ethylazacyclopropane, **1**, is more stable than in triethylamine. Why is the configuration of oxazacyclopropanes, such as **2**, exceptionally stable? (Consider the π molecular orbitals of an ethene bond, Figure 21-3, as a model for orbitals of the *adjacent* O and N atoms in the planar transition state for inversion in **2**.)

Exercise 23-7 The proton nmr spectrum of 1,2,2-trimethylazacyclopropane, **3**, at room temperature is shown in Figure 23-7. When the material is heated to 110°, the two lines at 63 Hz and 70 Hz are found to have coalesced to a single line. At the same time, the lines at 50 Hz and 92 Hz coalesce to a single line.



3

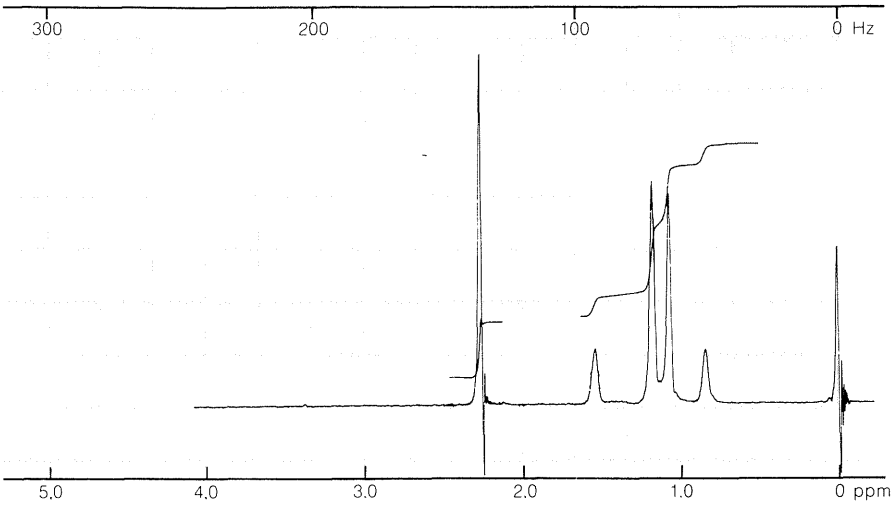


Figure 23-7 Proton nmr spectrum of 1,2,2-trimethylazacyclopropane at 60 MHz relative to TMS at 0.0 ppm. See Exercise 23-7.

When the sample is cooled the spectrum changes back to that of Figure 23-7. Account for all the nmr lines of **3** and explain the effect of temperature on the spectrum. Review Section 9-10C.[3]

Exercise 23-8* The ^{19}F spectrum of 4,4-difluoroazacyclohexane in acetone solution at 25° is a sharp, narrowly spaced 1:4:6:4:1 quintet; at −60° it is a broad quartet with a chemical-shift difference of 960 Hz and J of 235 Hz, and at −90° it is a pair of overlapping quartets with chemical-shift differences and relative intensities of 1050 Hz (75%) and 700 Hz (25%), both with J of 235 Hz. Account for these changes in the ^{19}F spectra with temperature. Review Section 9-10C.[3]

23-7 AMINES AS BASES

23-7A Standard Expressions of Base Strength

Perhaps the most characteristic property of amines is their ability to act as bases by accepting protons from a variety of acids:

$$R\ddot{N}H_2 + HA \rightleftharpoons R\overset{\oplus}{\ddot{N}}H_3 + :\overset{\ominus}{A}$$

[3]You also may wish to read ahead in Section 27-2.

When the reference acid, HA, is water, we can set up a scale of base strengths from the equilibrium constant, K_b, measured for the proton-transfer reaction shown in Equation 23-3:

$$R\ddot{N}H_2 + H_2O \overset{K_b}{\rightleftharpoons} R\overset{\oplus}{N}H_3 + :\overset{\ominus}{O}H \qquad (23\text{-}3)$$

In many reference works, it is customary to express the strengths of organic bases not as K_b values but as the acid-dissociation constants, K_a (or pK_a's) for the corresponding conjugate acids. These K_a values are then the *acid constants* of the corresponding ammonium ions in aqueous solution (Equation 23-4):

$$R\overset{\oplus}{N}H_3 + H_2O \overset{K_a}{\rightleftharpoons} RNH_2 + \overset{\oplus}{H_3}O \qquad (23\text{-}4)$$

With this convention, the *stronger* the base, RNH_2, the more the equilibrium in Equation 23-4 will lie to the left, and the *smaller* will be K_a. The relationship between K_a and K_b in water solution is

$$K_a \times K_b = 10^{-14}$$

and in terms of pK values, because by definition $pK = -\log K$,

$$pK_a + pK_b = 14$$

23-7B Base Strengths of Alkanamines and Cycloalkanamines

The base strengths of simple alkanamines usually are around $K_b = 10^{-4}$ ($K_a = 10^{-10}$) in water solution, and vary within perhaps a factor of 10 from ammonia to primary, secondary, and tertiary amines, as can be seen from the data in Table 23-1. Cyclohexanamine has about the same base strength as methanamine, whereas the effect on the basic nitrogen of being in a saturated ring, as in azacyclohexane, increases the base strength somewhat.

The trends that are evident, especially from basicities of amines measured in the gas phase, point to increasing basicity with the number and size of alkyl groups on the nitrogen atom.

Order of basicity (gas phase): $(CH_3)_3\ddot{N} > (CH_3)_2\ddot{N}H > CH_3\ddot{N}H_2 > \ddot{N}H_3$

This is reasonable because the conjugate acids, $R_3\overset{\oplus}{N}H$, are likely to be stabilized by electron-donating and polarizable alkyl groups, thereby making R_3N a stronger base. That the same trend is not evident in aqueous solution again shows the influence of the solvent on thermochemical properties (see Section 11-8A).

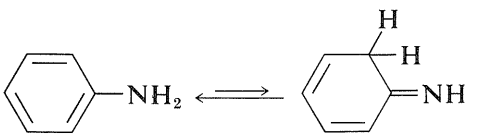
Generally, substituents located on saturated groups attached to nitrogen influence base strengths through their inductive effects in the same way that these substituents influence the strengths of carboxylic acids (see Section 18-2).

Exercise 23-9 Account for the following observations:
a. The proton nmr spectrum of trimethylamine in nitromethane-d_3 (CD_3NO_2) shows a single resonance near 2.7 ppm. On adding an equivalent of fluoroboric acid, HBF_4, the singlet at 2 7 ppm is replaced by a doublet at 3.5 ppm.
b. On adding trace amounts of trimethylamine to the solution described in Part a, the doublet at 3.5 ppm collapses to a singlet centered at 3.5 ppm. As more trimethylamine is added, the singlet resonance moves progressively upfield.

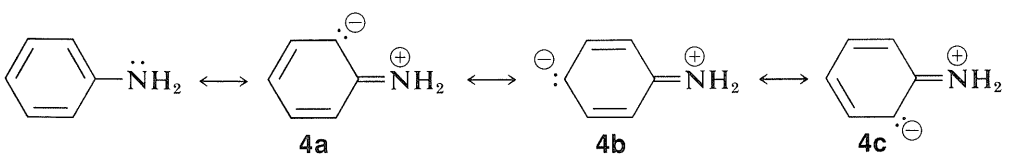
Exercise 23-10 Decide which member in each of the following pairs of compounds is the stronger base. Give your reasoning.
a. $CH_3CH_2NH_2$ or $(CH_3CH_2)_3N$
b. $(CH_2)_5NH$ or $(CH_2)_2NH$
c. $CF_3CH_2CH_2NH_2$ or $CH_3CH_2CH_2NH_2$
d. $(CH_3)_3\overset{\oplus}{N}CH_2CH_2NH_2$ or $O_2C\overset{\ominus}{C}H_2CH_2NH_2$

23-7C Base Strengths of Arenamines

Alkenamines, or enamines, $R—CH{=}CHNH_2$, usually are not stable and rearrange readily to imines (Section 16-4C). An important exception is benzenamine (aniline), $C_6H_5NH_2$, which has an amino group attached to a benzene ring. The imine structure is less favorable by virtue of the considerable stabilization energy of the aromatic ring:



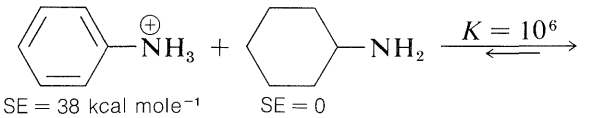
From the heat of combustion of benzenamine we know that it has a 3 kcal $mole^{-1}$ larger stabilization energy than benzene (Table 21-1). This difference in stabilization energies can be ascribed in either valence-bond or molecular-orbital theory to delocalization of the unshared pair of electrons on nitrogen over the benzene ring. The valence-bond structures are



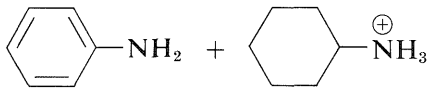
4a **4b** **4c**

The extra 3-kcal mole^{-1} stabilization energy of benzeneamine can be accounted for in terms of the structures **4a** to **4c**.

Benzenamine is only 1/1,000,000 as strong a base as cyclohexanamine. Most, if not all, of the difference can be accounted for by the decrease in stabilization when the unshared electron pair of nitrogen is localized in forming an N–H bond. Hence, benzenamine is stabilized *more* in the un-ionized state by electron delocalization, relative to cyclohexanamine, than in the ionized state, as expressed by the following equilibrium which lies far to the right:

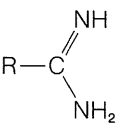


SE = 38 kcal mole^{-1} SE = 0



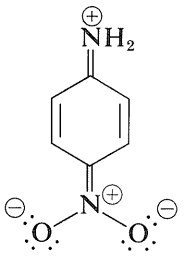
SE = 41 kcal mole^{-1} SE = 0

Exercise 23-11 Draw atomic-orbital models for benzenamine and its conjugate acid and describe the features of these models that account for the low base strength of benzenamine relative to saturated amines.

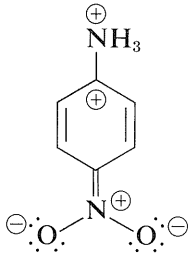
Exercise 23-12 Amidines,  , are stronger bases than saturated amines. Explain why this should be so, paying special attention to which nitrogen the proton adds to.

According to the valence-bond structures, **4a**, **4b**, and **4c**, benzenamine has some degree of double-bond character between the nitrogen and the ring, and some degree of negative charge at the ortho and para positions. Accordingly, the ability of the amine nitrogen to add a proton should be particularly sensitive to the electrical effects produced by the presence of substituent groups on the aromatic ring. For example, carbonyl, nitro, cyano, and ethoxycarbonyl substituents, which can delocalize an electron pair on an adjacent carbon (see Sections 17-1A, 17-3E, and 18-8B), are expected to *reduce* the base strength of the amine nitrogen when substituted in the ortho or para positions. The reason is that stabilization by the substituent, as shown by

structure **5** for 4-nitrobenzenamine, is important for the free base and *not* for the conjugate acid, **6**:



5



6
(unfavorable VB structure)

It is simpler and common practice to discuss substituent effects on base strength in terms of the dissociation equilibria of the conjugate acids, $ArNH_3^{\oplus} + H_2O \rightleftharpoons ArNH_2 + H_3O^{\oplus}$. Substituents that can stabilize the free base by electron delocalization or induction, as in **5**, will tend to *increase* the acid dissociation of $ArNH_3^{\oplus}$ (decrease base strength of $ArNH_2$). We see this in the data of Table 23-3 for electron-withdrawing groups (NO_2, CN, CF_3, CH_3CO—), which *increase acid strengths,* and for *electron-donating groups* (CH_3, NH_2), which *decrease acid strengths.* The effect is most pronounced when the groups are at the ortho or para (2 or 4) positions.

Table 23-3
Strengths of Conjugate Acids of Monosubstituted Benzenamines in Aqueous Solution at 25°

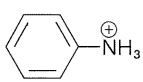
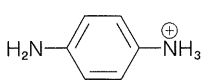
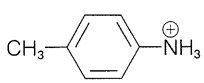
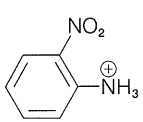
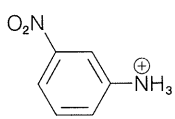
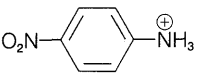
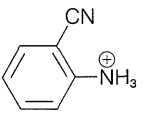
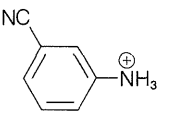
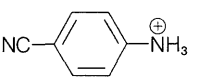
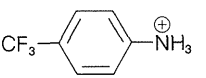
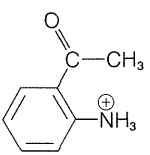
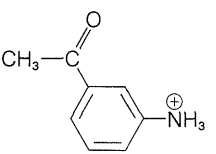
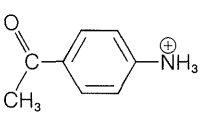
Substituent	Formula	pK_a
H		4.60
4-amino		6.16
4-methyl		5.10
2-nitro		−0.26
3-nitro		2.47

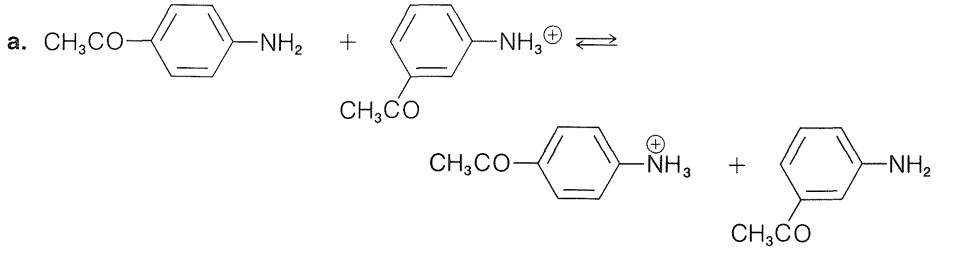
Table 23-3 (continued)
Strengths of Conjugate Acids of Monosubstituted Benzenamines in Aqueous Solution at 25°

Substituent	Formula	pK_a
4-nitro		1.11
2-cyano		0.95
3-cyano		2.76
4-cyano		1.74
4-trifluoromethyl		2.45
2-ethanoyl		2.22
3-ethanoyl		3.59
4-ethanoyl		2.19

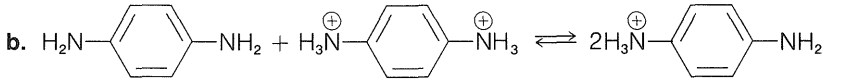
Exercise 23-13 3-Nitrobenzenamine is less than 1/100 as strong a base as benzenamine, but is 23 times stronger than 4-nitrobenzenamine. Remembering that the inductive effect falls off rapidly with the number of intervening bonds, why should 3-nitrobenzenamine be a much weaker base than benzenamine itself, but substantially stronger than 4-nitrobenzenamine?

Exercise 23-14 Indicate whether the following equilibria would have K greater, or less, than unity. This is equivalent to asking which amine is the stronger base. Give a reason for your answer.

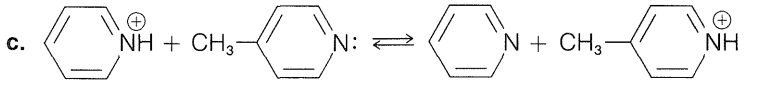
a.



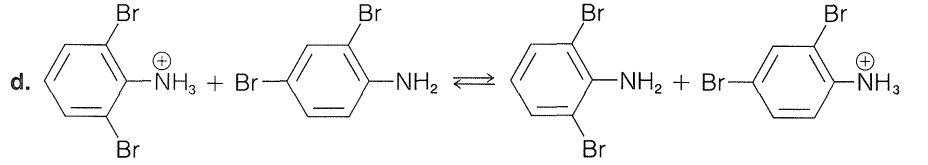
b.



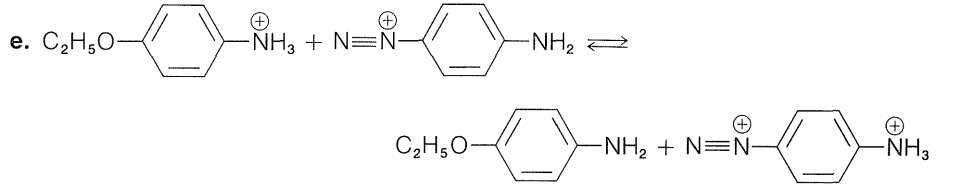
c.



d.

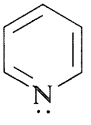


e.



23-7D Unsaturated Amines. Azarenes

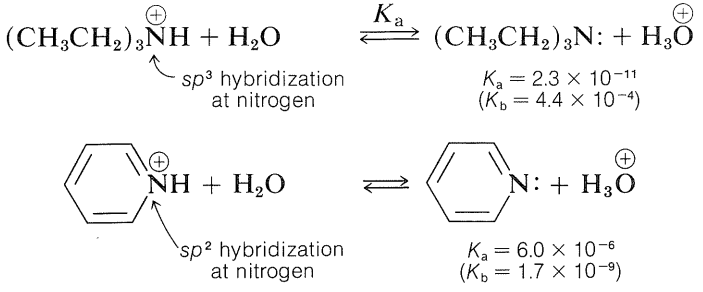
Substantial differences in base strength are found between alkanamines and unsaturated amines that have the group $\backslash C{=}\ddot{N}- /$. An example is azabenzene (pyridine, C_5H_5N), which is a nitrogen analog of benzene:



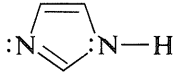
azabenzene
(pyridine)

Azabenzene is quite a weak base—in fact, it is 1/100,000 as strong a base as typical alkanamines. This low basicity can be ascribed to the hybridiza-

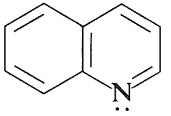
tion of the nitrogen orbitals (sp^2) in azabenzene. As we indicated in Section 11-8B in connection with C—H acidity, the more *s* character in the C—H bonding orbital, the higher the acidity. The same arguments hold for N–H bonds in the conjugate acids, $\diagdown\!\!\diagup C{=}\overset{\oplus}{N}H-$, as the following data show:



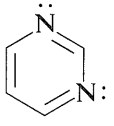
Other examples include:



1,3-diaza-2,4-cyclopentadiene (imidazole)
$K_b = 1.2 \times 10^{-7}$

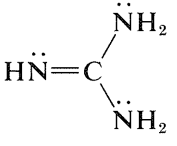


1-azanaphthalene (quinoline)
$K_b = 6.3 \times 10^{-10}$



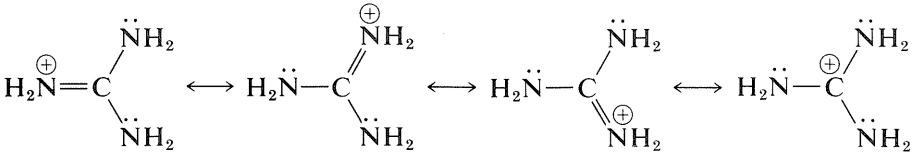
1,3-diazabenzene (pyrimidine)
$K_b = 2 \times 10^{-13}$

It is incorrect to assume that the bascity of unsaturated nitrogen in a C=N— group is always low. Consider, for example, the base strength of 2,2-diaminoazaethene (guanidine):

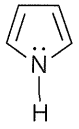


$K_b = 0.4$

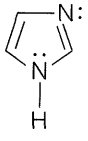
This substance is the strongest electrically neutral organonitrogen base known. The basic nitrogen is the imino (sp^2) nitrogen, which on protonation forms a particularly stable conjugate acid in which the three NH_2 groups become identical because of electron delocalization:

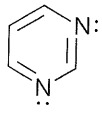


Exercise 23-15 Offer plausible explanations of the following facts:
a. Aza-2,4-cyclopentadiene (pyrrole) is unstable in acid solution and polymerizes. (Consider the effect of adding a proton to this molecule at the nitrogen and at carbon.)


pyrrole

b. 1,3-Diaza-2,4-cyclopentadiene (imidazole) is a much stronger base than 1,3-diazabenzene (pyrimidine).


imidazole


pyrimidine

c. The triaminomethyl cation, $(NH_2)_3\overset{\oplus}{C}$, is an exceptionally weak acid.

Exercise 23-16 The pK_a of the conjugate acid of caffeine (Figure 23-1) is 10.61. Calculate the K_b of caffeine. Write structures for the possible conjugate acids of caffeine in which the added proton is attached to one or the other of the nitrogens of the five-membered ring. Use the resonance method to determine which of these two nitrogens will be the preferred protonation site of caffeine. Give your reasoning.

Exercise 23-17* 2-Amino-1,3-diazabenzene (2-aminopyrimidine) undergoes *N*-methylation with methyl iodide to give two isomeric products, *A* and *B*, of formula $C_5H_7N_3$ (Section 23-9D). At high pH, the major methylation product is *A*, which is a weakly basic compound with $pK_a = 3.82$. *N*-Methylation in neutral conditions produces the more strongly basic compound *B* with $pK_a = 10.75$. Draw structures for the two isomers, *A* and *B*, and explain why *A* is a weak base and *B* is a much stronger base. Why is *A* the predominant product under basic conditions? Give your reasoning.

Exercise 23-18* The conjugate acid of *N,N*-dimethylbenzenamine has $pK_a = 5.06$, whereas the conjugate acid of diphenyldiazene (azobenzene, $C_6H_5N{=}NC_6H_5$) has $pK_a = -2.5$. Yet for many years there was considerable controversy about where a proton adds to 4-$(CH_3)_2N{-}C_6H_4N{=}NC_6H_5$. Why is it not an open-and-shut case that a proton would add most favorably to the $(CH_3)_2N{-}$ nitrogen? Which of the two $-N{=}N-$ nitrogens would you expect to be the more basic? Give your reasoning. (Consider the effect of the $-N{=}N-$ group on the basicity of the $(CH_3)_2N{-}$ nitrogen and also the effect of the $(CH_3)_2N{-}$ group on the basicity of each of the $-N{=}N-$ nitrogens.)

23-8 AMINES AS ACIDS

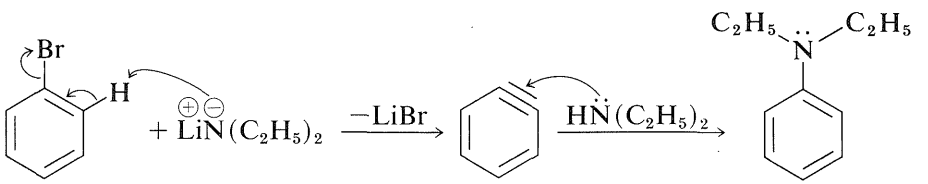
Primary and secondary amines are very weak acids. The lithium salts of such amines can be prepared in ether solution by treatment of the amine with phenyllithium:

$$HN(C_2H_5)_2 + C_6H_5Li \xrightarrow{\text{ether}} Li^{\oplus}\,:N^{\ominus}(C_2H_5)_2 + C_6H_6$$

lithium diethylamide

The lithium salt of *N*-ethylethanamine (diethylamine) is called lithium diethylamide,[4] but this nomenclature can lead to confusion with compounds of the type RCO_2NH_2, which are derived from carboxylic acids and also are called amides. We choose to avoid using the name "alkali amide" for $RNH^{\ominus}\,Li^{\oplus}$ and accordingly will refer to them as metal salts of the parent amine.

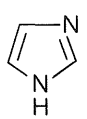
Alkanamines have acid strengths corresponding to K_a values of about 10^{-33}, which means that their conjugate bases are powerfully basic reagents. Therefore they are very effective in causing elimination reactions by the E2 mechanism (Section 8-8) and aromatic substitution by the aryne mechanism (Section 14-6C). The following example illustrates this property in a useful synthesis of a benzenamine from bromobenzene:



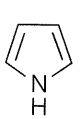
N,*N*-diethylbenzenamine
(*N*,*N*-diethylaniline)

Salts of alkanamines also are useful for generating enolate salts of carbonyl compounds (Sections 17-4A and 18-8C).

Exercise 23-19 a. Explain why 1,3-diazacyclopentadiene (imidazole) is a much stronger *acid* than azacyclopentadiene (pyrrole).



imidazole



pyrrole

b. Would you expect benzenamine to be a stronger or weaker *acid* than cyclohexanamine? Give your reasoning.

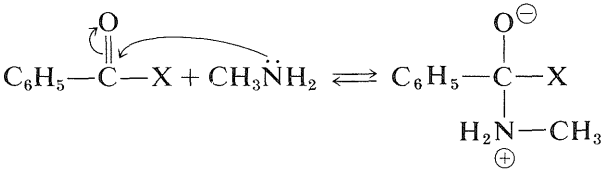
---

[4]The system used here names these salts as substitution products of $NH_2^{\ominus}$. Clearly, to give $LiN(C_2H_5)_2$ the name "lithium *N*-ethylethanamide" would be totally incorrect because *N*-ethylethanamide is $CH_3CONHC_2H_5$. Perhaps a better name would be lithium diethylazanide or *N*,*N*-diethylaminolithium.

23-9 AMINES AS NUCLEOPHILES

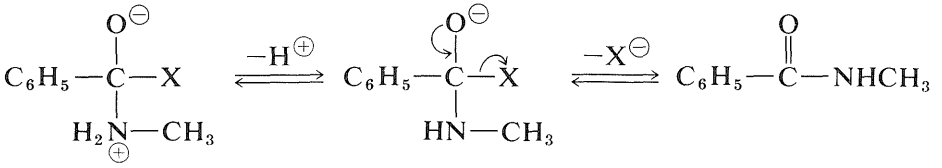
23-9A Acylation of Amines. Synthesis of Amides

The unshared electrons on nitrogen play a key role in the reactions of amines. In fact, almost all reactions of amines at the nitrogen atom have, as a first step, the formation of a bond involving the unshared electron pair on nitrogen. A typical example is **acylation,** which is amide formation through the reaction of an acyl chloride, an anhydride, or an ester with an amine. The initial step in these reactions with benzenecarbonyl derivatives and methanamine as illustrative reactants is as follows:

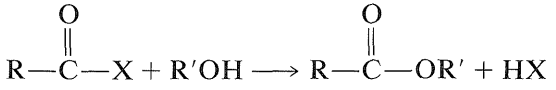


X = halogen, —O—C(=O)—C_6H_5, or —OR

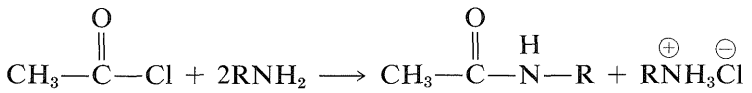
The reaction is completed by loss of a proton and elimination of $X^{\ominus}$:



The reaction is called acylation because an acyl group, R—C(=O)—, is transferred to the amine nitrogen. It will be seen that these reactions are very similar to the formation of esters by acylating agents, whereby the acyl group is transferred to the oxygen of an alcohol (Section 15-4D):



A serious disadvantage to the preparation of amides through the reaction of an amine with an acyl chloride (or anhydride) is the formation of one mole of amine salt for each mole of amide:



This is especially serious if the amine is the expensive ingredient in the reaction. In such circumstances, the reaction usually is carried on in a two-phase system with the acyl chloride and amine in the nonaqueous phase and sodium hydroxide in the aqueous phase. As the amine salt is formed and dissolves in the water, it is converted back to amine by the sodium hydroxide and extracted back into the nonaqueous phase:

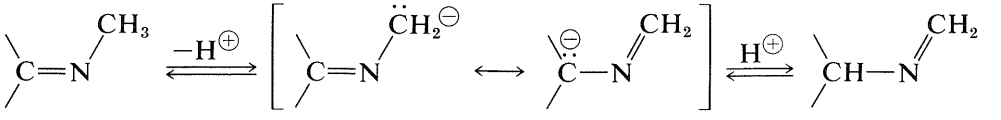
$$\overset{\oplus}{\text{RNH}_3}\overset{\ominus}{\text{Cl}} + \overset{\oplus}{\text{Na}}\overset{\ominus}{\text{OH}} \longrightarrow \text{RNH}_2 + \overset{\oplus}{\text{Na}}\overset{\ominus}{\text{Cl}} + \text{H}_2\text{O}$$

This procedure requires an excess of acid chloride because some of it is wasted by hydrolysis.

23-9B Imine and Enamine Formation

Amines also add to the carbonyl carbon of aldehydes and ketones, but the reactions take a different course from acylation and, with ammonia or a primary amine, yield *imines*, $\backslash\!\!/\text{C=N—R}$, as previously discussed in Section 16-4C.

Imines formed from ammonia and aldehydes (RCH=NH) are very unstable and readily polymerize (Section 16-4C). However, substitution of an alkyl or aryl group on the nitrogen increases the stability, and *N*-substituted imines, $\backslash\!\!/\text{C=N—R}$, are familiarly known as *Schiff bases*. They are key intermediates in a number of synthetic and biological reactions (see, for example, Section 17-3F) and are capable of rearrangement by reversible proton transfer that, in some respects, resembles the rearrangement of ketones to enols:

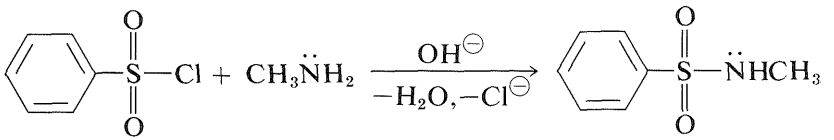


Secondary amines cannot form imines with aldehydes and ketones but may react instead to form *enamines*, $\backslash\!\!/\text{C=C—NR}_2$. The formation and synthetic uses of these compounds were discussed previously (Sections 16-4C, 17-4B, and 18-9D).

23-9C Sulfonamide Formation from Amines

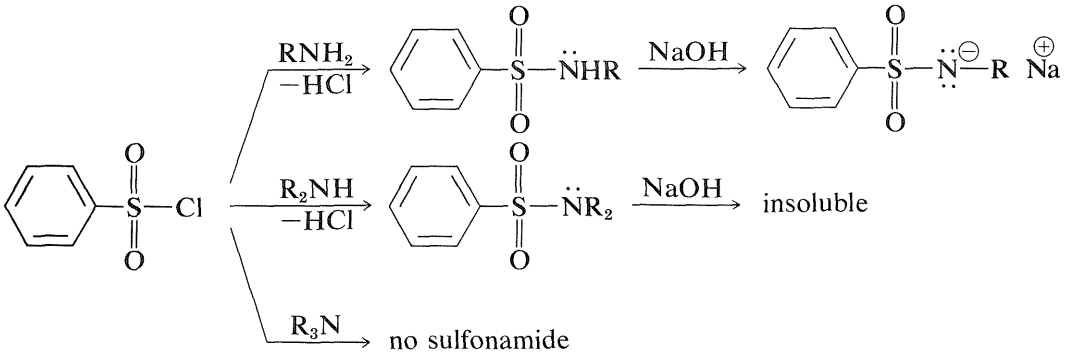
We have seen that amines react with acyl chlorides to give amides. A very similar reaction occurs with sulfonyl chlorides to give *sulfonamides*. An

example is benzenesulfonyl chloride reacting with methanamine to give *N*-methylbenzenesulfonamide:

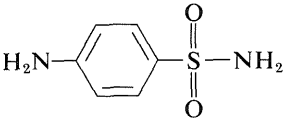


N-methylbenzenesulfonamide

Sulfonylation of amines can be a useful way of differentiating (chemically) between primary, secondary, and tertiary amines by what is known as the **Hinsberg test.** Primary and secondary amines both react with a sulfonyl chloride, but only the sulfonamide from the primary amines has an N—H hydrogen. The sulfonyl group makes this hydrogen relatively acidic and the sulfonamide therefore dissolves readily in sodium hydroxide solutions. The secondary amine does not give a base-soluble amide, whereas the tertiary amine gives no sulfonamide:



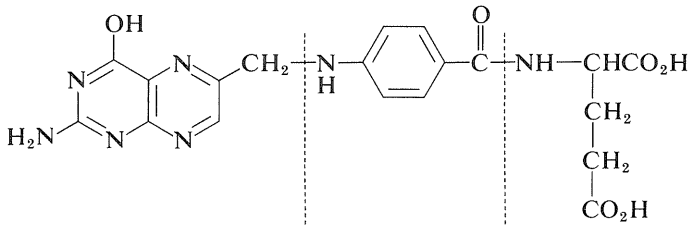
Sulfonamides have medicinal value as antibacterial agents. In fact, 4-aminobenzenesulfonamide was the first synthetic antibacterial drug in clinical use, and is effective against a large number of bacterial infections:



4-aminobenzenesulfonamide (sulfanilamide)

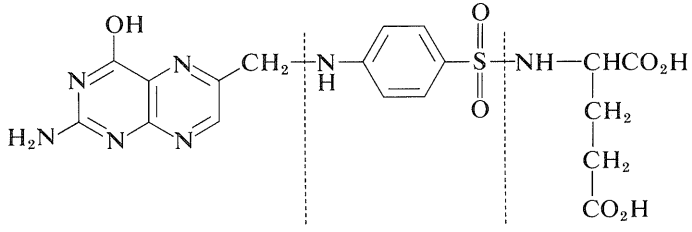
This substance inhibits the growth of bacteria by interfering with the synthesis of folic acid, **7**, which is an essential substance for bacteria and animals alike. However, animals acquire folic acid from a normal diet, whereas bacteria have to synthesize it. Biosynthesis of folic acid is blocked by 4-aminobenzenesulfonamide, probably because of the structural similarity of the sulfonamide to 4-aminobenzoic acid, which is a normal ingredient in the biosynthesis of folic acid. The enzyme system involved apparently substitutes the sulfonamide for

the aminobenzoic acid and creates a sulfonamide-type folic acid instead of the carboxamide derivative (compare structures **7** and **8**):



folic acid
7

derived from 4-aminobenzoic acid

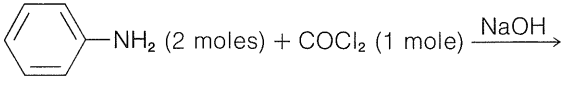


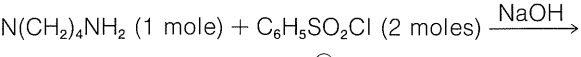
sulfonamide analog of folic acid
8

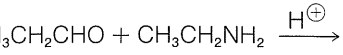
derived from 4-aminobenzene-sulfonic acid

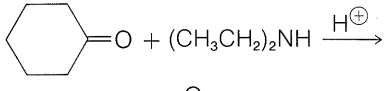
Some 10,000 structurally different sulfonamides have been synthesized as a result of the discovery of the antibacterial properties of sulfanilamide. The practice of synthesizing numerous structurally related compounds in an effort to find some that are more efficient or have fewer side effects than those already available is very important to the pharmaceutical industry. However, as is usually the case, of the many known sulfonamides only about thirty have the proper balance of qualities to be clinically useful.

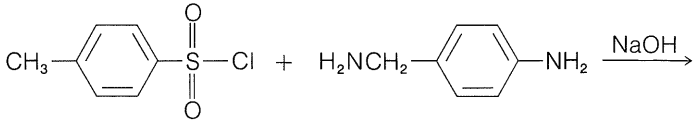
Exercise 23-20 Show the products you would expect to be obtained in each of the following reactions:

a. 

b. 

c. 

d. 

e. 

Exercise 23-21 2,4-Pentanedione reacts with methanamine to give a product of composition $C_6H_{11}NO$ that is an equilibrium mixture of three isomers. The nmr spectrum of the mixture indicates that all three isomers have strong hydrogen bonding. Draw the structures of the three isomers and indicate the nature of the hydrogen bonding.

Exercise 23-22 Write a structural formula (one for each part) that fits the following descriptions. (These descriptions can apply to more than one structural formula.) Write equations for the reactions involved.

a. A liquid basic nitrogen compound of formula C_3H_7N with $C_6H_5SO_2Cl$ and excess NaOH solution gives a clear solution. This solution when acidified gives a solid product of formula $C_9H_{11}O_2NS$.

b. A liquid diamine of formula $C_5H_{14}N_2$ with $C_6H_5SO_2Cl$ and NaOH gives an insoluble solid. This solid dissolves when the mixture is acidified with dilute hydrochloric acid.

23-9D Alkylation. Synthesis of Alkanamines

Ammonia and amines can function as nucleophiles in S_N2 displacement reactions of alkyl halides (Section 8-7E). Such processes provide syntheses of alkanamines only with those halides that are reactive in S_N2 but not E2 reactions. For example,

$$\ddot{N}H_3 + CH_3\!-\!\ddot{I} \xrightarrow{S_N2} CH_3\!-\!NH_3^{\oplus}\,I^{\ominus} \qquad (23\text{-}5)$$

The product formed according to Equation 23-5 is an ammonium salt from which the parent amine can be recovered by neutralization with a strong base, such as sodium hydroxide:

$$CH_3NH_3^{\oplus}\,I^{\ominus} + Na^{\oplus}\,{}^{\ominus}OH \rightleftharpoons CH_3NH_2 + \overset{\oplus}{N}a\,\overset{\ominus}{I} + H_2O \qquad (23\text{-}6)$$

Acid-base equilibria similar to Equation 23-6 also occur between an ammonium salt and a neutral amine (Equation 23-7). This can have serious consequences in amine alkylations because it can lead to mixtures of products, whereby more than one alkyl group is bonded to nitrogen:

$$\begin{aligned} &CH_3NH_3^{\oplus}\,I^{\ominus} + NH_3 \rightleftharpoons CH_3NH_2 + NH_4^{\oplus}\,I^{\ominus} \\ &CH_3\ddot{N}H_2 + CH_3\!-\!\ddot{I} \longrightarrow (CH_3)_2NH_2^{\oplus}\,I^{\ominus} \end{aligned} \qquad (23\text{-}7)$$

Therefore we may expect the reaction of ammonia with methyl iodide to give four possible alkylation products, mono-, di-, and trimethylamines, as well as tetramethylammonium iodide:

$$\ddot{N}H_3 \xrightarrow[-HI]{CH_3I} CH_3\ddot{N}H_2 \xrightarrow[-HI]{CH_3I} (CH_3)_2\ddot{N}H \xrightarrow[-HI]{CH_3I} (CH_3)_3\ddot{N} \xrightarrow{CH_3I} (CH_3)_4N^{\oplus}\,I^{\ominus}$$

Despite the fact that alkylation reactions of amines generally give mixtures of products, they are of practical value on an industrial scale. The commercial synthesis of methanamines uses methanol as the methylating agent and alumi-

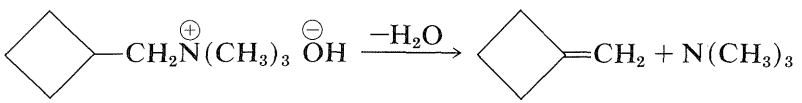
num oxide as an acidic catalyst; all three amines are formed, and are separated by distillation and extraction (see Exercise 23-24). The function of the catalyst is to make OH a better leaving group (Section 8-7D):

$$CH_3OH + NH_3 \xrightarrow[450°,\ 200\ psi]{Al_2O_3} CH_3NH_2 + (CH_3)_2NH + (CH_3)_3N + H_2O$$

The tetraalkylammonium halides formed by complete alkylation of amines are ionic compounds that resemble alkali-metal salts. When silver oxide is used to precipitate the halide ion, tetraalkylammonium halides are converted to tetraalkylammonium hydroxides, which are strongly basic substances similar to sodium or potassium hydroxide:

$$(CH_3)_4\overset{\oplus}{N}\ \overset{\ominus}{I} \xrightarrow[-AgI]{Ag_2O,\ H_2O} (CH_3)_4\overset{\oplus}{N}\ \overset{\ominus}{OH}$$

Higher-molecular-weight alkylammonium hydroxides decompose on heating to give alkenes. The reaction is a standard method for the preparation of alkenes and is known as the *Hofmann elimination* (see Section 8-8B):



Exercise 23-23 Show how the following compounds may be prepared from ammonia and the given starting materials:

a. 1,2-ethanediamine from ethene

b. 2-aminoethanol from ethene

c. benzenamine from chlorobenzene

Exercise 23-24 Show how a mixture of amines prepared from 1-bromobutane and an excess of butanamine may be resolved into its components by reaction with the anhydride of 1,4-butanedioic acid, $(CH_2)_2(CO)_2O$, separation of the products through advantage of their solubility properties in acid or base, and regeneration of the corresponding amines (Section 18-10C). Write equations for the reactions involved.

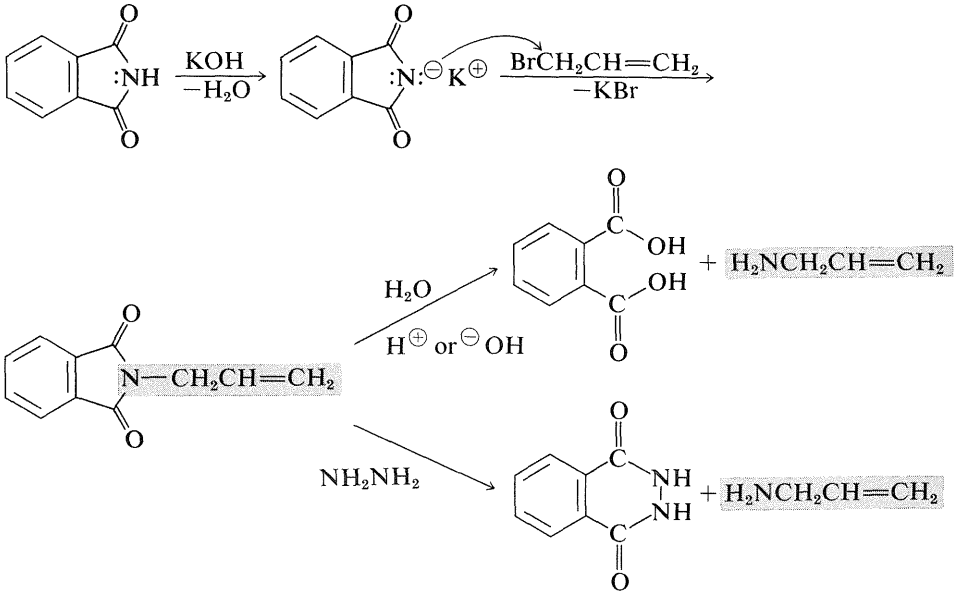
In principle, conversion of a primary or secondary amine into its conjugate base, $R\ddot{N}H^{\ominus}$ or $R_2\ddot{N}^{\ominus}$, should make the nitrogen powerfully nucleophilic toward alkylating agents:

$$R_2\ddot{N}H \xrightarrow{-H^{\oplus}} R_2\ddot{N}:^{\ominus} \xrightarrow{R-X} R_3\ddot{N} + X^{\ominus}$$

In practice, the same problems of polyalkylation and E2 elimination exist with the amine anion as with the neutral amine—and as far as E2 goes, much more so.

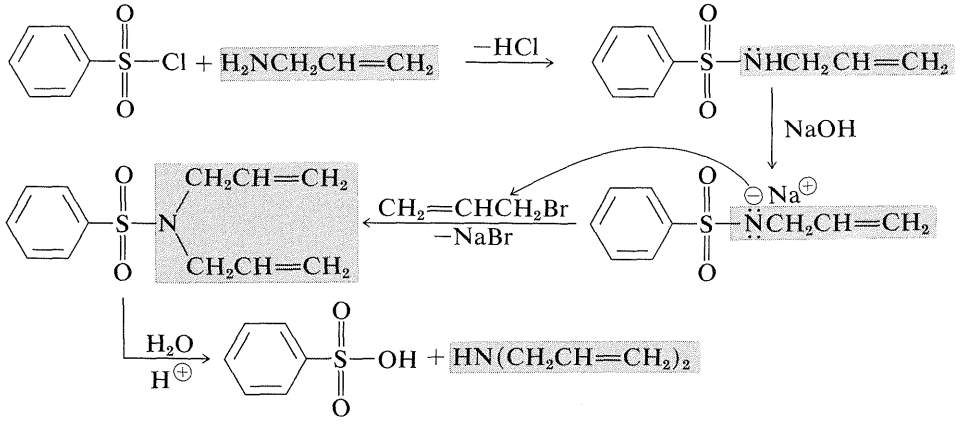
There are nitrogen anions that are useful in alkylation reactions, but they are derived from carboxamides and sulfonamides rather than amines. Two examples are given here to illustrate the synthesis of a primary and a secondary amine (also see Section 18-10C):

Gabriel synthesis of primary amines



The success of the Gabriel synthesis depends on N-alkylation being favored over O-alkylation and S_N2 being favored over E2. Polar, aprotic solvents such as methylsulfinylmethane, $(CH_3)_2SO$, are useful for the Gabriel synthesis. Hydrolysis of the alkylation product often is difficult and "amide interchange" (analogous to ester interchange, Section 18-7A) with hydrazine can be an effective way to free the amine from the imide.

Sulfonamide synthesis of secondary amines

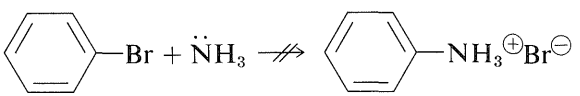


In this synthesis, the acidic properties of sulfonamides of the type $C_6H_5SO_2NHR$ are utilized to form anions capable of alkylation by the S_N2 mechanism.

Exercise 23-25* Assess the possibility of O-alkylation in the reaction of $CH_2{=}CH{-}CH_2Br$ with $C_6H_5SO_2NH^{\ominus}Na^{\oplus}$. Give your reasoning.

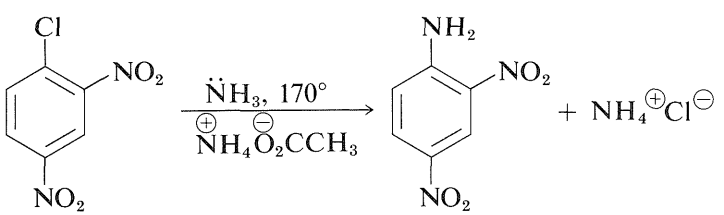
23-9E Arylation. Synthesis of Arenamines

In previous discussions (Section 14-6A) we stated that it is *not* possible to displace halogen from simple aryl halides such as bromobenzene by simple S_N2 reactions using amines or other weakly basic nucleophiles at ordinary temperatures:



However, arylation with such systems will occur with strong bases by the benzyne mechanism (Sections 14-6C and 23-8).

Arylation of amines by the direct displacement of aryl halides is possible when the halogen is activated by strong electron-withdrawing groups in the ortho and para positions. For example, 2,4-dinitrobenzenamine can be prepared by heating 2,4-dinitrochlorobenzene with ammonia:

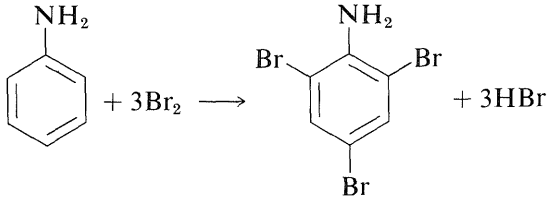


The reasons why this reaction proceeds are discussed in detail in Section 14-6B.

23-9F Arenamines as Nucleophiles. Electrophilic Aromatic Substitution

The nitrogen of arenamines is less basic and less nucleophilic than the nitrogen of alkanamines because of electron delocalization of the nitrogen lone pair, as shown for benzenamine in Section 23-7C. The polar valence-bond structures emphasize that the ring atoms, particularly the ortho and para positions, should be more nucleophilic than in benzene. Accordingly, the amino group strongly activates the ring toward attack by electrophiles. In fact, bromine reacts rapidly with benzenamine in aqueous solution to introduce three

bromine substituents and form 2,4,6-tribromobenzenamine; no catalyst is required:



2,4,6-tribromobenzenamine
(2,4,6-tribromoaniline)

Weakly electrophilic reagents that do not normally attack benzene will attack the ring carbons of arenamines. Some of those reactions are described later in the chapter (Sections 23-10C and 23-10D).

23-10 AMINES WITH NITROUS ACID

23-10A Alkanamines with Nitrous Acid

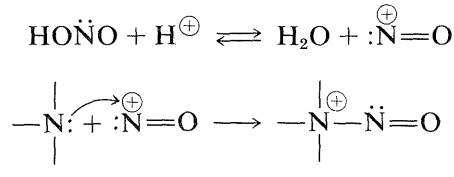
Some of the most important reactions of amines are brought about by nitrous acid (HONO). The character of the products depends very much on whether the amine is primary, secondary, or tertiary. In fact, nitrous acid is a useful reagent to determine whether a particular amine is primary, secondary, or tertiary. With primary amines nitrous acid results in evolution of nitrogen gas; with secondary amines insoluble yellow liquids or solid *N*-nitroso compounds, $R_2N—N{=}O$, separate; tertiary alkanamines dissolve in and react with nitrous acid solutions without evolution of nitrogen, usually to give complex products:

$RNH_2 + HONO \longrightarrow ROH + H_2O + N_2\uparrow$ (evolution of nitrogen)

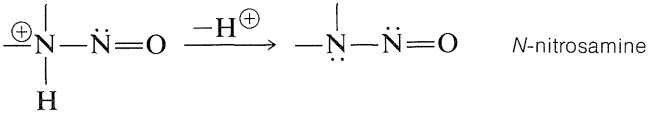
$R_2NH + HONO \longrightarrow R_2N—N{=}O + H_2O$ (separation of insoluble yellow *N*-nitroso compound)

$R_3N + HONO \longrightarrow$ (complex products, but no N_2 evolution)

Nitrous acid is unstable and always is prepared as needed, usually by mixing a solution of sodium nitrite, $NaNO_2$, with a strong acid at 0°. These conditions provide a source of $^{\oplus}NO$, which is transferred readily to the nucleophilic nitrogen of the amine:



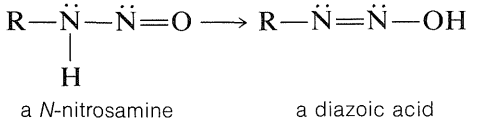
With this common key step, why do amines react differently with nitrous acid depending on their degree of substitution? The answer can be seen from the reactions that are most easily possible for the $-\overset{|}{\underset{|}{\overset{\oplus}{N}}}-NO$ intermediate. Clearly, if there is a hydrogen on the positive nitrogen, it can be lost as a proton and a *N*-nitrosamine formed:



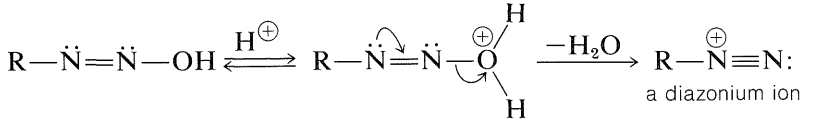
With a secondary amine, the reaction stops here, with formation of R_2N-NO, and because these substances are *very* weak bases, they are *insoluble* in dilute aqueous acids. They are characteristically yellow or orange-yellow solids or oils.

A tertiary amine·$\overset{\oplus}{N}O$ complex, $R_3\overset{\oplus}{N}-NO$, cannot lose a proton from nitrogen, but instead may lose a proton from carbon and go on to form complex products (see Exercise 23-26).

With a *primary* amine, the initially formed *N*-nitrosamine can undergo a proton shift by a sequence analogous to interconversion of a ketone to an enol. The product is called a **diazoic acid**:

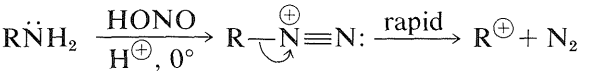


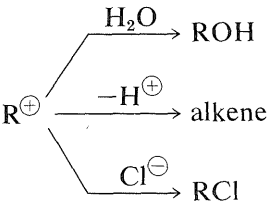
Some diazoic acids form salts that are quite stable, but the acids themselves usually decompose rapidly to diazonium ions:



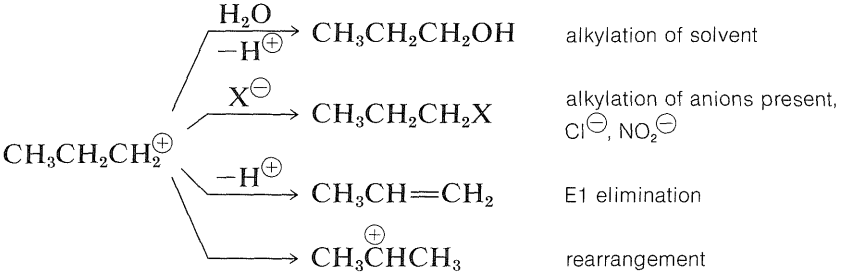
Diazonium salts can be regarded as combinations of carbocations $R^{\oplus}$ with N_2 and, because of the considerable stability of nitrogen in the form of N_2, we would expect diazonium salts to decompose readily with evolution of nitrogen and formation of carbocations. This expectation is realized, and diazonium salts normally decompose in this manner in water solution. The aliphatic diazonium ions decompose so rapidly that their presence can only be inferred

from the fact that the products are typically those of reactions of carbocations:



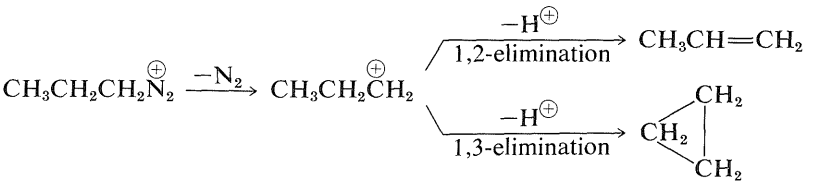


With propanamine, loss of nitrogen from the diazonium ion gives the very poorly stabilized propyl cation, which then undergoes a variety of reactions that are consistent with the carbocation reactions discussed previously (see Sections 8-9B and 15-5E):



The isopropyl cation formed by rearrangement undergoes substitution and elimination like the propyl cation. About half of the products arise from isopropyl cations.

There is one exceptional reaction of the propyl cation that involves *1,3-elimination* and formation of about 10% of cyclopropane:



Clearly, the plethora of products to be expected, particularly those resulting from rearrangement (see Exercise 23-31), prevents the reaction of the simple primary amines with nitrous acid from having any substantial synthetic utility.

Exercise 23-26 The tertiary amine, $C_6H_5CH_2N(CH_3)_2$, reacts with nitrous acid to give benzenecarbaldehyde and *N*-nitroso-*N*-methylmethanamine (*N*-nitrosodimethylamine):

$$2C_6H_5CH_2N(CH_3)_2 + 4HONO \longrightarrow 2C_6H_5CHO + 2(CH_3)_2N{-}NO + 3H_2O + N_2O$$

A possible reaction sequence that explains the formation of benzenecarbaldehyde involves nitrosation, E2 elimination, hydrolysis, and finally nitrosation. Write each of the steps involved in this sequence. Formation of N_2O appears to take place by dimerization of the hypothetical substance HNO ($2HNO \longrightarrow N_2O + H_2O$).

Exercise 23-27 a. Write two valence-bond structures for *N*-nitroso-*N*-methylmethanamine and show how these structures explain the fact that the *N*-nitrosamine is a much weaker base than *N*-methylmethanamine.

b. *N*-Nitroso-*N*-methylmethanamine shows two separate methyl resonances in its proton nmr spectrum. These collapse to a single resonance when the material is heated to 190° and reappear on cooling. Studies of the changes in the line shapes with temperature show that the process involved has an energy barrier of about 23 kcal $mole^{-1}$. Explain why there should be separate methyl peaks in the nmr and why they should coalesce on heating. (Review Section 9-10C. You also may wish to read Section 27-2.)

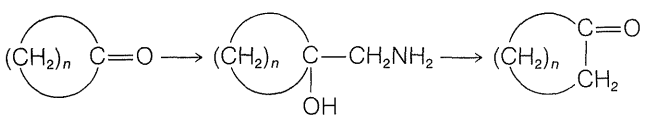
Exercise 23-28 a. When ethyl aminoethanoate ($H_2NCH_2CO_2C_2H_5$) is treated with nitrous acid in the presence of a layer of diethyl ether, a yellow compound known as ethyl diazoethanoate ($N_2CHCO_2C_2H_5$) is extracted into the ether layer. What is the probable structure of this compound and what is the mechanism by which it is formed?

b. Would you expect the same type of reaction sequence to occur with ethyl 3-aminopropanoate? Explain.

Exercise 23-29 Predict the products expected from the reactions of the following amines with nitrous acid (prepared from $NaNO_2 + HCl$ in aqueous solution):

a. 2-methylpropanamine
b. azacyclopentane
c. 2-butenamine
d. 3-amino-2,3-dimethyl-2-butanol

Exercise 23-30 The following sequence is very useful for expanding the ring size of a cyclic ketone:



List reagents, conditions, and the important intermediates for the sequence, noting that several individual synthetic steps may be required. (Refer to Table 23-6 for amine synthesis.)

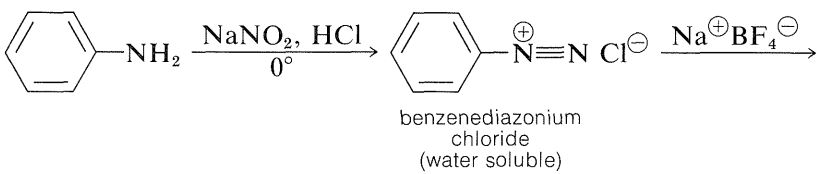
Exercise 23-31* The reaction of nitrous acid with 3-butenamine, $CH_2{=}CHCH_2CH_2NH_2$, has been found to give the following mixture of alcohols: 3-buten-1-ol (45%), 3-buten-

2-ol (21%), 2-buten-1-ol (7%) cyclobutanol (12%), and cyclopropylmethanol (15%). Show how each of these products may be formed from the 3-butenyl cation.

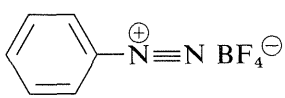
Exercise 23-32* How could one determine experimentally how much of the propene formed in the reaction of propanamine with nitrous acid arises from the propyl cation and how much from the isopropyl cation?

23-10B Arenamines with Nitrous Acid. Arenediazonium Salts

Unlike primary alkylamines, primary arenamines react with nitrous acid at 0° to give diazonium ions that, in most cases, are stable enough to be isolated as crystalline $BF_4^{\ominus}$ salts. Other salts can be isolated, but some of these, such as benzenediazonium chloride, in the solid state may decompose with explosive violence:

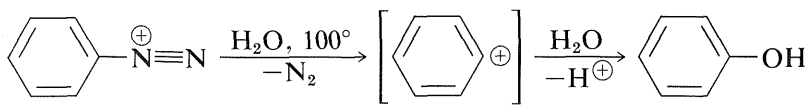


benzenediazonium chloride (water soluble)



benzenediazonium fluoroborate (water insoluble)

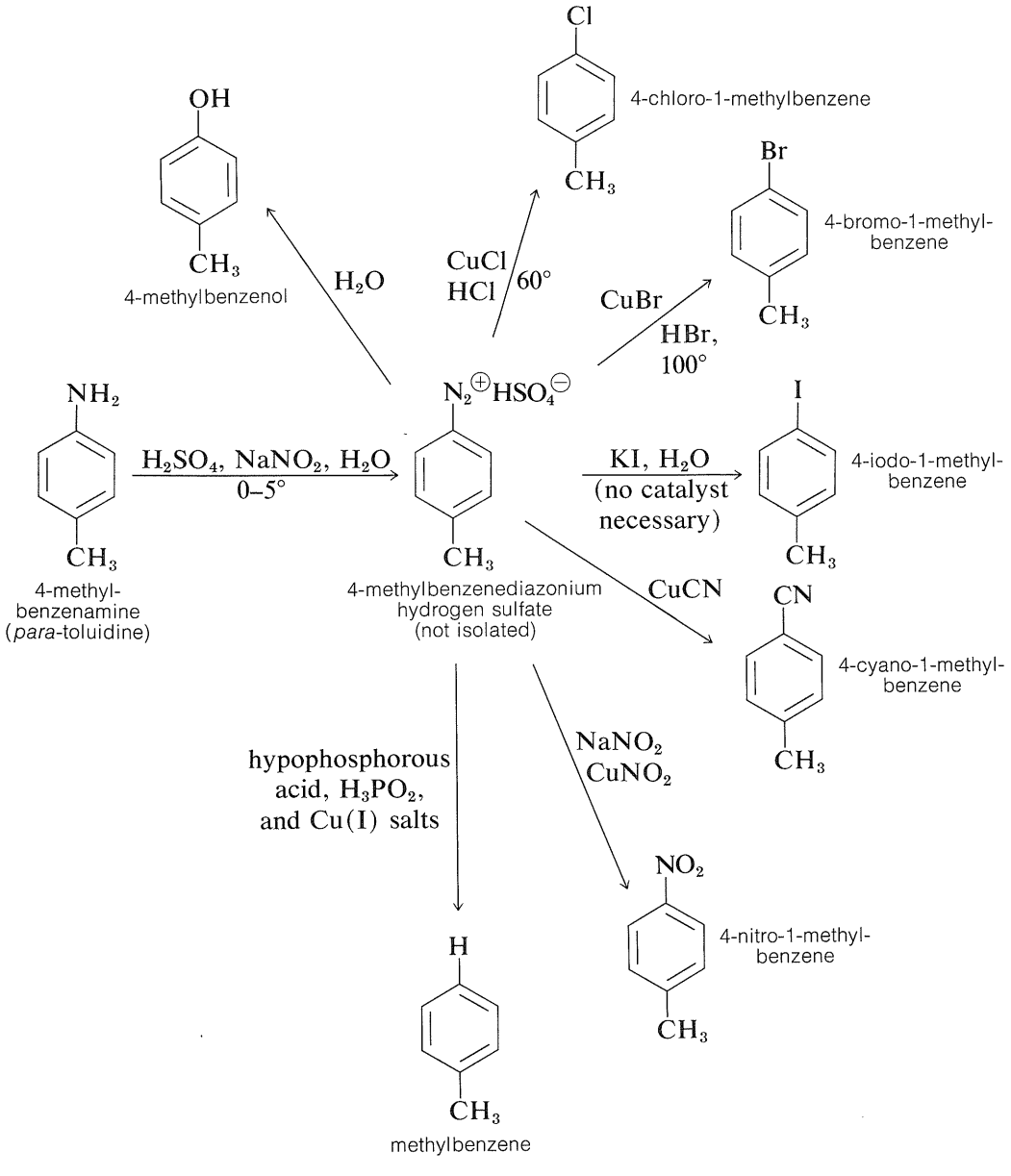
The reason for the greater stability of arenediazonium salts compared with alkanediazonium salts appears to be related to the difficulty of forming aryl carbocations (Section 14-6A). Even the gain in energy associated with having nitrogen as the leaving group is not sufficient to make aryl cations form readily, although the solvolysis of arenediazonium ions in water does proceed by an S_N1 mechanism (see Exercise 23-33):



This reaction has general utility for replacement of aromatic amino groups by hydroxyl groups. In contrast to the behavior of alkylamines, no rearrangements occur.

Generally, diazonium salts from arenamines are much more useful intermediates than diazonium salts from alkanamines. In fact, arenediazonium salts provide the only substances that undergo nucleophilic substitution

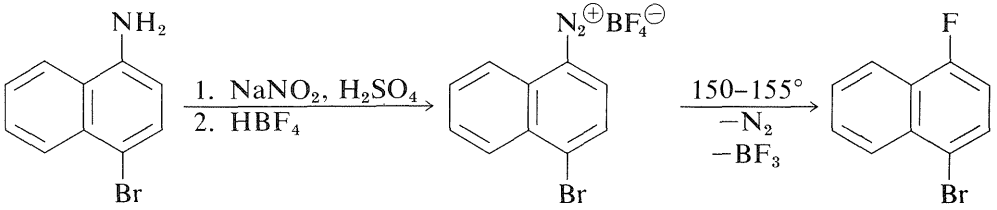
reactions on the aromatic ring under mild conditions, without the necessity of having activating groups, such as nitro or cyano, in the ortho or para position. The most important reactions of this type include the replacement of the diazonium group by nucleophiles such as $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $CN^{\ominus}$, $NO_2^{\ominus}$, and these reactions lead to the formation of aryl halogen, cyano, and nitro compounds. Most of these reactions require cuprous ions, Cu(I), as catalysts. The method is known as the **Sandmeyer reaction.** The following examples illustrate how a primary arenamine can be converted to a variety of different groups by way of its diazonium salt:



Aryl fluorides also may be prepared from arenamines by way of diazonium salts if the procedure is slightly modified. The amine is diazotized with nitrous acid in the usual way; then fluoroboric acid or a fluoroborate salt is added, which usually causes precipitation of a sparingly soluble diazonium fluoroborate. The salt is collected and thoroughly dried, then carefully heated to the decomposition point—the products being an aryl fluoride, nitrogen, and boron trifluoride:

$$C_6H_5\overset{\oplus}{N}_2\ \overset{\ominus}{BF_4} \xrightarrow{\text{heat}} C_6H_5F + N_2 + BF_3$$

This reaction is known as the **Schiemann reaction.** An example (which gives a better than usual yield) follows:



4-bromo-1-naphthalenamine

4-bromo-1-napthalene-diazonium fluoroborate

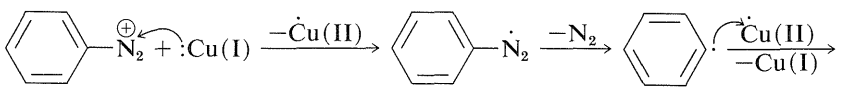
1-bromo-4-fluoro naphthalene (97%)

The utility of all these transformations may become clearer if you work Exercise 23-34. It will give you practice in seeing how various benzene derivatives can be prepared from primary benzenamines. Later in the chapter we shall see that amines can be prepared by the reduction of nitro compounds, which permits the following sequence of reactions:

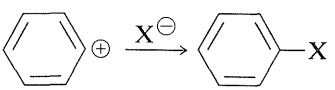
$$ArH \xrightarrow{HNO_3} ArNO_2 \xrightarrow{[H]} ArNH_2 \xrightarrow{HONO} ArN_2^{\oplus} \xrightarrow[-N_2]{CuX} ArX$$

This sequence is especially useful to introduce groups or produce orientations of substituents that may not be possible by direct substitution.

The Sandmeyer group of reactions is an example of the production of *nucleophilic substitution by way of radical intermediates* (see Section 14-10A):



phenyl radical



phenyl cation

This mechanism is supported by the fact that Cu(II) is important in the formation of C_6H_5X. If the concentration of Cu(II) is kept very low so as to slow

down conversion of $C_6H_5\cdot$ to $C_6H_5^{\oplus}$, and a compound with a reactive double bond is present, then products are formed by attack of $C_6H_5\cdot$ on the double bond. This is called the **Meerwein reaction:**

$$C_6H_5\overset{\oplus}{N}_2\ \overset{\ominus}{X} + CH_2{=}CHCN \xrightarrow{Cu(I)} C_6H_5CH_2{-}CHXCN + N_2$$

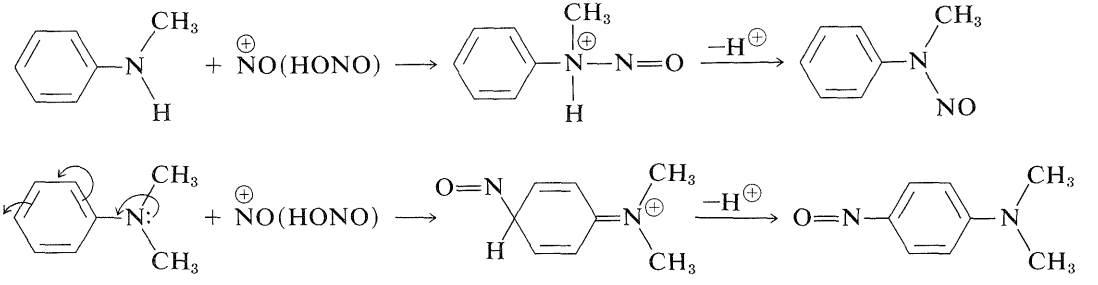
Iodide ion appears to be a good enough reducing agent to form $C_6H_5\cdot$ without the intervention of Cu(I); considerable I_2 usually is formed in the reaction:

$$C_6H_5\overset{\oplus}{N}_2\ + \overset{\ominus}{I} \longrightarrow C_6H_5\cdot + N_2 + I\cdot$$

$$C_6H_5\cdot + I\cdot \longrightarrow C_6H_5I$$

$$2I\cdot \longrightarrow I_2$$

Secondary arenamines react with nitrous acid to form *N*-nitroso compounds while tertiary arenamines undergo electrophilic substitution with $NO^{\oplus}$ if they have an unsubstituted *para* position:



Exercise 23-33 Benzenediazonium chloride solvolyzes in water to give a mixture of benzenol and chlorobenzene. Some of the facts known about this and related reactions are

1. The ratio C_6H_5Cl/C_6H_5OH increases markedly with $Cl^{\ominus}$ concentration but the rate hardly changes at all.

2. There is no rearrangement observed with 4-substituted benzenediazonium ions, and when the solvolysis is carried out in D_2O, instead of H_2O, no C–D bonds are formed to the benzene ring.

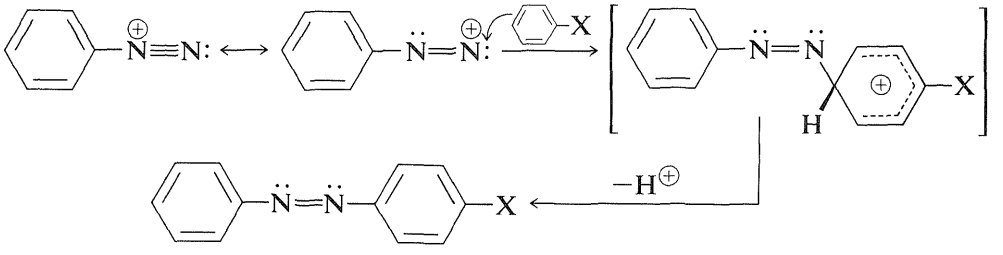
3. 4-Methoxybenzenediazonium chloride solvolyzes about 30 times faster than 4-nitrobenzenediazonium chloride.

4. Benzenediazonium salts solvolyze in 98% H_2SO_4 at almost the same rate as in 80% H_2SO_4 and, in these solutions, the effective H_2O concentration differs by a factor of 1000.

Show how these observations support an S_N1 reaction of benzenediazonium chloride, and can be used to argue against a benzyne-type elimination-addition with water acting as the E2 base (Section 14-6C) or an S_N2 reaction with water as the nucleophile (Section 8-4, Mechanism B, and Section 14-6).

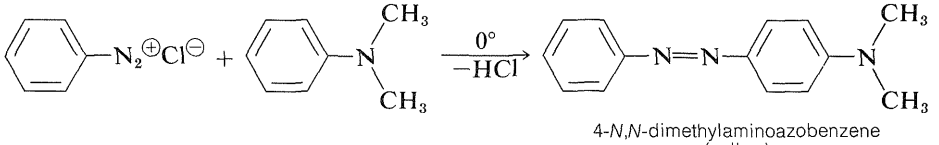
23-10C Diazo Coupling Reactions

Not all reactions of diazonium ions involve cleavage of the C–N bond. An important group of reactions of arenediazonium ions involves aromatic substitution by the diazonium ion acting as an *electrophilic* agent to yield azo compounds, Ar—N=N—Ar:



This reaction is highly sensitive to the nature of the substituent X, and coupling to benzene derivatives normally occurs only when X is a strongly electron-donating group such as $-O^{\ominus}$, $-N(CH_3)_2$, and —OH. However, coupling with X = $-OCH_3$ may take place with particularly active diazonium ions.

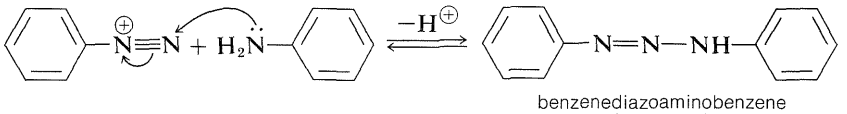
Diazo coupling has considerable technical value, because the azo compounds that are produced are highly colored. Many are used as fabric dyes and for other coloring purposes. A typical example of diazo coupling is formation of 4-*N*,*N*-dimethylaminoazobenzene from benzenediazonium chloride and *N*,*N*-dimethylbenzenamine:



4-*N*,*N*-dimethylaminoazobenzene
(yellow)

The product once was used to color edible fats and therefore was known as "Butter Yellow," but its use to color food is prohibited because it is reported to be a potent liver carcinogen for rats.

The pH used for diazo coupling of amines is very important in determining the nature of the products. Under near-neutral conditions the diazonium ion may attack the *nitrogen* of the arenamine rather than a ring carbon. In this event a diazoamino compound, a triazene, —N=N—N—, is formed:



benzenediazoaminobenzene
(a triazene)

The reaction is readily reversed if the pH is lowered sufficiently (see Exercise 23-35).

As you see from this brief discussion of arenediazonium salts, their chemistry is complex. It is inappropriate to discuss all of their many reactions here, but a summary of the most important types of reactions is given in Table 23-4.

Table 23-4
Summary of Reactions of Arenediazonium Salts

Reaction	Comment
1. *Replacement reactions:* $ArN_2^{\oplus} + X^{\ominus} \longrightarrow ArX + N_2$	Cuprous-catalyzed replacement reactions are called **Sandmeyer reactions**; aryl chlorides, bromides, cyanides, and nitro compounds are prepared in this way; formation of aryl iodides requires no catalyst, fluorides are obtained by heating diazonium fluoroborates (i.e., **Schiemann reaction**); benzenols are obtained by warming aqueous diazonium salt solutions.
a. aryl halide formation	
$ArN_2^{\oplus} + Cl^{\ominus} \xrightarrow{Cu(I)} ArCl + N_2$	
$ArN_2^{\oplus}{}^{\ominus}BF_4 \xrightarrow{heat} ArF + N_2 + BF_3$	
b. arenecarbonitrile formation	
$ArN_2^{\oplus} + {}^{\ominus}CN \xrightarrow{Cu_2(CN)_2} ArCN + N_2$	
c. aryl nitro compound formation	
$ArN_2^{\oplus} + {}^{\ominus}NO_2 \xrightarrow{Cu(I)} ArNO_2 + N_2$	
d. benzenols by hydrolysis	
$ArN_2^{\oplus} + H_2O \xrightarrow{-H^{\oplus}} ArOH + N_2$	
e. aryl azide formation	
$ArN_2^{\oplus} + {}^{\ominus}N_3 \longrightarrow ArN_3 + N_2$	
2. *Addition to conjugated alkenes*	Cuprous-catalyzed addition of a diazonium salt to activated double bonds of alkenes and related compounds is known as the **Meerwein reaction**; *it competes with the* Sandmeyer reaction.
$ArN_2^{\oplus}Cl^{\ominus} + \diagdown C{=}C \diagup \xrightarrow[-N_2]{Cu(I)} Ar{-}\overset{|}{C}{-}\overset{|}{C}{-}Cl$	
3. *Biaryl formation*	Decomposition of diazonium salts in presence of Cu(I) and ammonia leads to biaryls.
a. $ArN_2^{\oplus} + Cu(I) \xrightarrow[-H^{\oplus}]{NH_3} Ar{-}Ar + Cu(II) + N_2$	
b. $ArN_2^{\oplus}{}^{\ominus}O_2CCH_3 \rightleftharpoons ArN{=}NO_2CCH_3$	Thermal decomposition of diazo ethanoates in an aromatic solvent leads to biaryl formation by attack of aryl radicals on solvent.
$ArN{=}NO_2CCH_3 \xrightarrow[-CH_3CO_2\cdot]{-N_2} Ar\cdot \xrightarrow{Ar'H} Ar{-}Ar'$	
4. *Reduction of diazonium salts*	Reductive replacement of $-N_2^{\oplus}$ by hydrogen is effected by hypophosphorous acid; reduction is initiated with Cu(I).
a. arene formation	
$ArN_2^{\oplus} + H_2O + H_3PO_2 \xrightarrow{Cu(I)} ArH + N_2 + H^{\oplus} + H_3PO_3$	
b. hydrazine formation	Sulfite reduction of diazonium salts leads to hydrazines.
$ArN_2^{\oplus} + 2SO_3{}^{2\ominus} + HO^{\ominus} + H_2O \longrightarrow ArNHNH_2 + 2SO_4{}^{2\ominus}$	
5. *Diazo-coupling reactions*	Electrophilic attack of $ArN_2^{\oplus}$ on Ar'X leads to azo compounds; the substituent X must be powerfully activating [e.g., $-O^{\ominus}$, $-N(CH_3)_2$].
a. formation of azo compounds	
$ArN_2^{\oplus} + Ar'X \xrightarrow[0°]{-H^{\oplus}} Ar{-}N{=}N{-}Ar'X$	

Table 23-4 (continued)
Summary of Reactions of Arenediazonium Salts

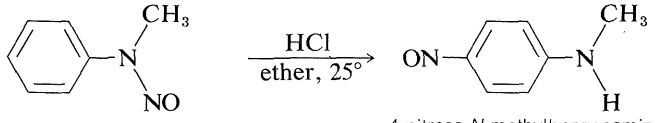
Reaction	Comment
b. formation of triazenes (diazoamino) compounds $ArN_2^{\oplus} + Ar'NH_2 \xrightarrow{pH \geq 7} Ar{-}N{=}N{-}NHAr' + H^{\oplus}$	Electrophilic attack of $ArN_2^{\oplus}$ on nitrogen of a *prim-* or *sec*-arylamine in neutral or alkaline solution.
6. *Diazotate formation* $ArN_2^{\oplus}{}^{\ominus}Cl + {}^{\ominus}OH \overset{0°}{\rightleftharpoons} Ar{-}N{=}N{-}OH + Cl^{\ominus}$ diazoic acid $ArN{=}N{-}OH + {}^{\ominus}OH \overset{0°}{\rightleftharpoons} ArN{=}N{-}O^{\ominus} + H_2O$ diazotate	Diazotate salts are formed reversibly from diazonium salts in basic solution.

Exercise 23-34 Indicate how you could prepare each of the following compounds, starting with benzene. One of the steps in each synthesis should involve formation of a diazonium salt. (Review Sections 22-4 and 22-5 if necessary.)

a. monodeuteriobenzene
b. 2-cyano-1-isopropylbenzene
c. 4-*tert*-butylbenzenol
d. 3-hydroxyphenylethanone
e. 3-chloronitrobenzene
f. 3-iodobenzenecarboxylic acid
g. 4-chlorophenyl azide
h. 4-methylphenylhydrazine
i. 2-amino-4′-methylazobenzene
j. 2-chloro-1-phenylpropane

23-10D Rearrangements of *N*-Substituted Arenamines

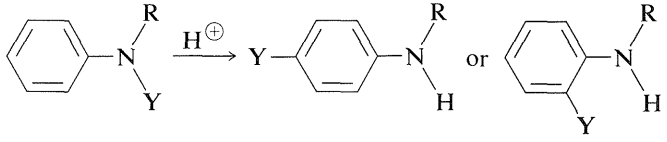
A secondary arenamine behaves like a secondary alkanamine in reacting with nitrous acid to give an *N*-nitrosamine. However, when treated with an acid the *N*-nitrosamine rearranges:



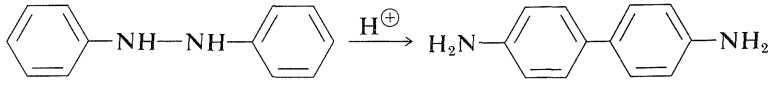
N-nitroso-*N*-methylbenzenamine — 4-nitroso-*N*-methylbenzenamine

This is one example of a group of formally related rearrangements in which a substituent, Y, attached to the nitrogen of a benzenamine derivative migrates

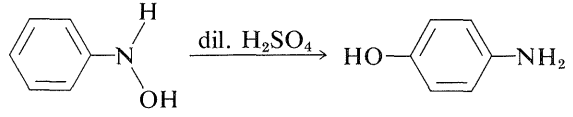
to the ortho or para position of the aromatic ring under the influence of acid:



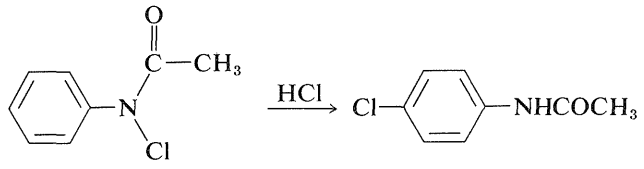
Rearrangement occurs most readily when Y is a strongly electron-attracting group and the N–Y bond that is broken is not as strong as the C–Y bond that is formed. A few of the many examples of this type of reaction follow:



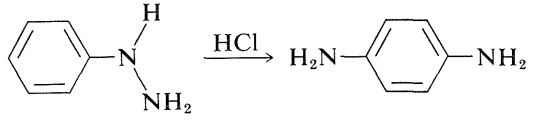
hydrazobenzene — 4,4′-diaminobiphenyl (benzidine)



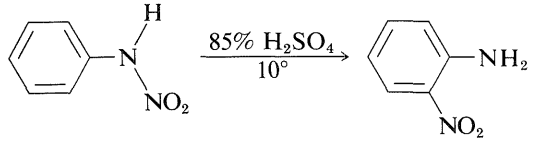
N-phenylazanol (*N*-phenylhydroxylamine) — 4-aminobenzenol (*para*-aminophenol)



N-chloro-*N*-phenylethanamide (*N*-chloroacetanilide) — *N*-(4-chlorophenyl)ethanamide (*para*-chloroacetanilide)



phenyldiazane (phenylhydrazine) — 1,4-benzenediamine (*para*-diaminobenzene)

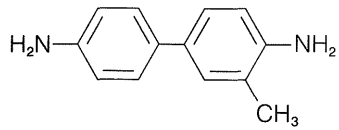


N-nitrobenzenamine — 2-nitrobenzenamine

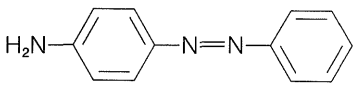
Exercise 23-35* Some of the rearrangements of arenamines, ArNHY, to Y—Ar—NH_2 shown above proceed by an intermolecular mechanism involving acid-catalyzed cleavage of the N–Y bond followed by a normal electrophilic substitution of the aromatic ring. Show the steps in this mechanism for Y = NO and Cl.

Exercise 23-36* Treatment of a mixture of 2,2′dimethylhydrazobenzene and hydrazobenzene with acid gives *only* 4,4′-diaminobiphenyl and 4,4′-diamino-2,2′-dimethylbiphenyl. What does this tell you about the mechanism of this type of rearrangement? Write a mechanism for the rearrangement of hydrazobenzene that is in accord with the acid catalysis (the rate depends on the *square* of the $H^{\oplus}$ concentration) and the lack of mixing of groups as described above.

Exercise 23-37* Show how the following substances could be prepared by a suitable ArNRY-type rearrangement.

a. 

b. 4-amino-3-methylbenzenol

c. 

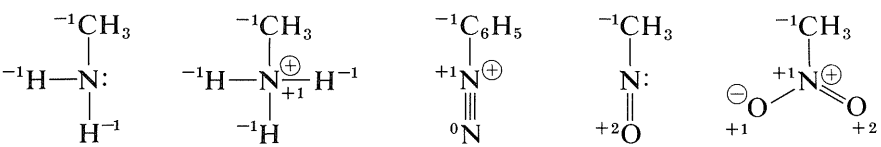
d. *N*-methyl-1,4-benzenediamine

23-11 OXIDATION OF AMINES

23-11A Oxidation States of Nitrogen in Organic Compounds

Nitrogen has a wide range of oxidation states in organic compounds. We can arrive at an arbitrary scale for the oxidation of nitrogen in much the same way as we did for carbon (Section 11-1). We simply define elementary nitrogen as the zero oxidation state, and every atom bonded to nitrogen contributes −1 to the oxidation state if it is more electropositive than nitrogen (e.g., H, C, Li, B, Mg) and +1 if it is more electronegative (e.g., O, F, Cl). Doubly bonded atoms are counted twice, and a formal positive charge associated with nitrogen counts as +1.

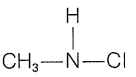
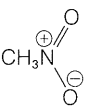
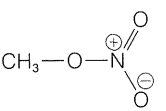
To illustrate, the oxidation states of several representative compounds are as follows:



Oxidation state: −3	−3	0 (for each N)	+1	+3

Several types of nitrogen compounds are listed in Table 23-5 to illustrate the range of oxidation states that are possible.

Table 23-5
Oxidation States of Nitrogen

Compound or class of compound	Example	Oxidation state
amine	CH_3NH_2	−3
imine	$CH_2{=}NH$ (unstable)	−3
nitrile	$CH_3C{\equiv}N$	−3
azanol (hydroxylamine)	CH_3NHOH	−1
N-chloroamine		−1
nitrogen	$:N{\equiv}N:$	0
nitroso	$CH_3N{=}O$	+1
nitric oxide	$\cdot N{=}O$	+2
nitro		+3
nitrite ester	$CH_3{-}O{-}N{=}O$	+3
nitrogen dioxide	$\cdot NO_2$	+4
nitrate ester		+5

Exercise 23-38 What is the oxidation state of each nitrogen in each of the following substances?

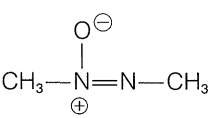
a. 

b. $F_2N{-}NF_2$

c. $(CH_3)_2C{=}NOH$

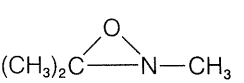
d. $CH_3N_2^{\oplus}Cl^{\ominus}$

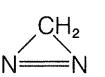
e. $CH_3N{=}C:$

f. 

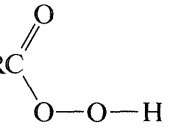
g. 

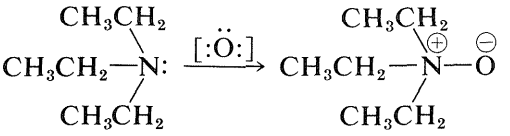
h. CH_3NCl_2

i. 

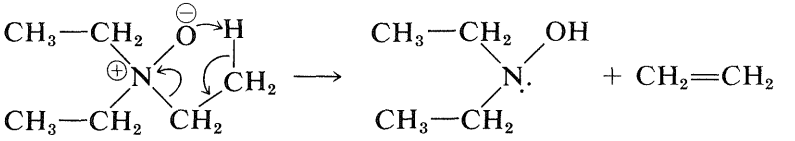
j. 

23-11B Oxidation of Tertiary Amines. Amine Oxides

For the oxidation of a tertiary amine by reagents such as hydrogen peroxide, H_2O_2, or peroxycarboxylic acids,  , which can supply an oxygen atom with six electrons, the expected product is an azane oxide (amine oxide). Thus *N,N*-diethylethanamine (triethylamine) can be oxidized to triethylazane oxide (triethylamine oxide):



Amine oxides are interesting for two reasons. First, amine oxides decompose when strongly heated, and this reaction provides a useful preparation of alkenes. With triethylazane oxide (triethylamine oxide), ethene is formed:



N,N-diethylazanol
(*N,N*-diethylhydroxylamine)

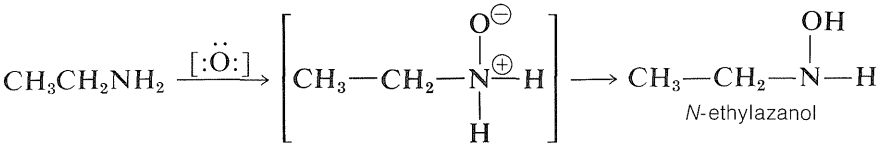
The second interesting point about amine oxides is that, unlike amines, they do not undergo rapid inversion at the nitrogen atom, and the oxides from amines with three different R groups are resolvable into optically active forms. This has been achieved for several amine oxides, including the one from *N*-ethyl-*N*-methyl-2-propenamine.

Exercise 23-39 Show how one could synthesize and resolve the oxide from *N*-ethyl-*N*-methyl-2-propenamine with the knowledge that amine oxides are somewhat basic substances having K_b values of about 10^{-11} ($K_a \sim 10^{-3}$).

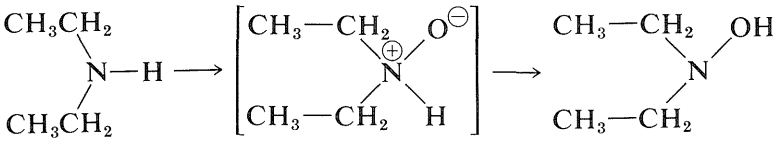
23-11C Oxidation of Primary and Secondary Alkanamines

Addition of an oxygen atom from hydrogen peroxide or a peroxyacid to a primary or secondary amine might be expected to yield an amine oxide-type

intermediate, which then could rearrange to an azanol (hydroxylamine):

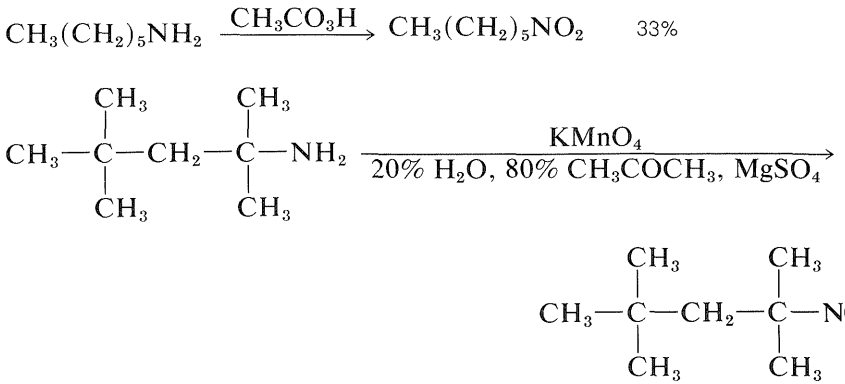


N-ethylazanol



N,N-diethylazanol

However, these oxidations usually take a more complicated course, because the azanols themselves are oxidized easily, and in the case of primary amines, oxidation occurs all the way to nitro compounds, in fair-to-good yields:

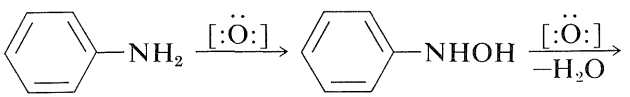


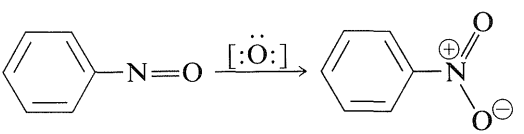
33%

77%

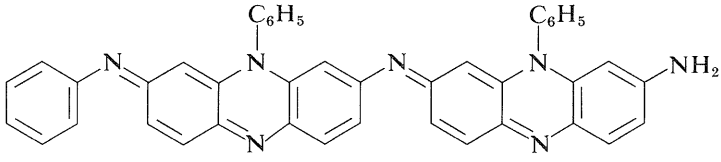
23-11D Oxidation of Aromatic Amines

We shall use benzenamine to illustrate some typical oxidation reactions of arenamines. The course of oxidation depends on the nature of the oxidizing agent and on the arenamine. With hydrogen peroxide or peroxycarboxylic acids, each of which functions *to donate oxygen to nitrogen,* oxidation to the azanol, the nitroso, or the nitro compound may occur, depending on the temperature, the pH, and the amount of oxidizing agent:

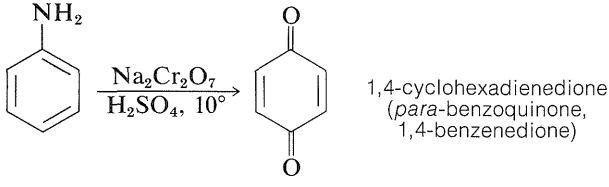




Oxidizing agents that *abstract a hydrogen atom or hydride ion* lead to more complex reactions, which often result in highly colored products. One of the best black dyes for fabric (Aniline Black) is produced by impregnating cloth with phenylammonium chloride solution and then oxidizing, first with sodium chlorate ($NaClO_3$) and finally with sodium dichromate ($Na_2Cr_2O_7$). Aniline Black probably is not a single substance, and its exact structure(s) is not known; but its formation certainly involves addition reactions in which carbon–nitrogen bonds are made. A possible structure is shown in which there are seven aniline units:



Oxidation of benzenamine with sodium dichromate in aqueous sulfuric acid solution produces 1,4-cyclohexadienedione (*para*-benzoquinone), which is the simplest member of an interesting class of conjugated cyclic diketones that will be discussed in more detail in Chapter 26:



1,4-cyclohexadienedione
(*para*-benzoquinone,
1,4-benzenedione)

23-12 SYNTHESIS OF AMINES

23-12A Main Types of Synthesis

There are seemingly many different ways in which amines can be prepared. However, a careful look at these methods reveals that they fall into three main groups of reactions. The first group starts with a simple amine, or with ammonia, and builds up the carbon framework by alkylation or arylation reactions on nitrogen, as discussed in Section 23-9D:

$$RX + NH_3 \longrightarrow RNH_2 + HX$$

The second group starts with compounds of the same carbon–nitrogen framework as in the desired amine but with nitrogen in a higher oxidation state. The amine then is obtained from these compounds by catalytic hydrogenation or metal-hydride reduction, as will be described in the next section:

$$RNO_2 + 3H_2 \xrightarrow{Pt} RNH_2 + 2H_2O$$

The third group of reactions relies on the fact that amides usually can be converted to amines, either by reduction, hydrolysis, or rearrangement, so that any viable synthesis of amides usually is also a synthesis of amines:

$$R'-\overset{\overset{O}{\|}}{C}-NHR \xrightarrow{H_2O} R'-\overset{\overset{O}{\|}}{C}-OH + RNH_2 \qquad \text{(Sections 23-12D and 24-4)}$$

$$R'-\overset{\overset{O}{\|}}{C}-NHR \xrightarrow[\text{or } LiAlH_4]{H_2,\ Pt} R'CH_2NHR \qquad \text{(Section 23-12B)}$$

$$R-\overset{\overset{O}{\|}}{C}-NH_2 \xrightarrow{Cl_2,\ OH^{\ominus}} RNH_2 + CO_2 \qquad \text{(Section 23-12E)}$$

These and related reactions are discussed in further detail in the following sections. For your convenience, a tabular summary of methods for the synthesis of amines appears in Tables 23-6 and 23-7.

23-12B Formation of Amines by Reduction

Excellent procedures are available for the preparation of primary, secondary, and tertiary amines by the reduction of a variety of nitrogen compounds. Primary amines can be obtained by hydrogenation or by lithium aluminum hydride reduction of nitro compounds, azides, oximes, imines, nitriles, or unsubstituted amides [all possible with H_2 over a metal catalyst (Pt or Ni) or with $LiAlH_4$]:

nitro $R-NO_2 \longrightarrow RNH_2$

azide $R-N=\overset{\oplus}{N}=\overset{\ominus}{N} \longrightarrow RNH_2$

oxime $R_2C=N-OH \longrightarrow R_2CHNH_2$

imine $R_2C=NH \longrightarrow R_2CHNH_2$

nitrile $RC\equiv N \longrightarrow RCH_2NH_2$

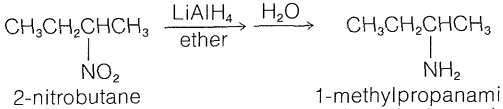
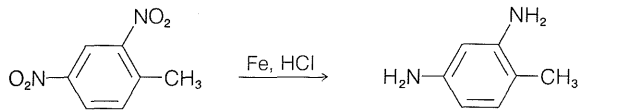
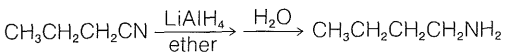
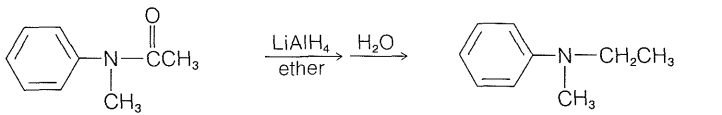
amide $R\underset{\underset{O}{\|}}{C}NH_2 \longrightarrow RCH_2NH_2$

Some care must be exercised in the reduction of nitro compounds because such reductions can be highly exothermic. For example, the reaction of 1 mole (61 g) of nitromethane with hydrogen to give methanamine liberates sufficient heat to increase the temperature of a 25-lb iron bomb 100°:

$$CH_3NO_2 + 3H_2 \longrightarrow CH_3NH_2 + 2H_2O \qquad \Delta H^0 = -85 \text{ kcal}$$

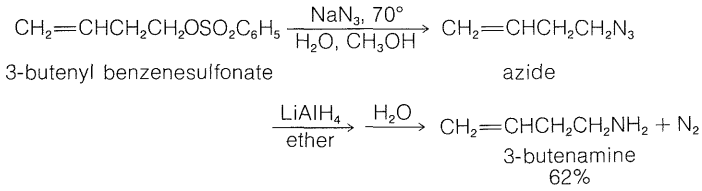
Secondary and tertiary amines, particularly those with different R groups, are prepared easily by lithium aluminum hydride reduction of substituted amides (Section 18-7C).

Table 23-6
Practical Examples of the Synthesis of Amines

Reaction	Comment
1. *Reduction of nitrogen compounds* a. nitro compounds  2-nitrobutane → 1-methylpropanamine (2-aminobutane) 85%  2,4-dinitromethylbenzene → 4-methyl-1,3-benzenediamine	Lithium aluminum hydride is a convenient reagent for reduction of nitro compounds, nitriles, amides, azides, and oximes to primary amines. Catalytic hydrogenation works also. Aromatic nitro compounds are reduced best by reaction of a metal and aqueous acid or with ammonium or sodium polysulfides (see Section 23-12B). Reduction of *N*-substituted amides leads to secondary amines.
b. nitriles  butanenitrile → butanamine 57%	See Section 23-12B.
c. amides  *N*-methyl-*N*-phenylethanamide (*N*-methylacetanilide) → *N*-ethyl-*N*-methylbenzenamine 91%	See Section 23-12B.

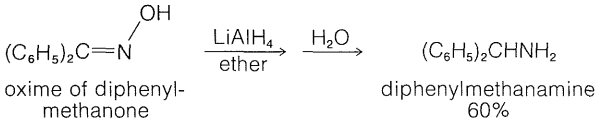
(Table continued on next page.)

d. azides



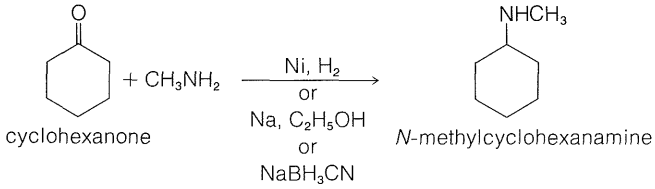
See Section 23-12B.

e. oximes



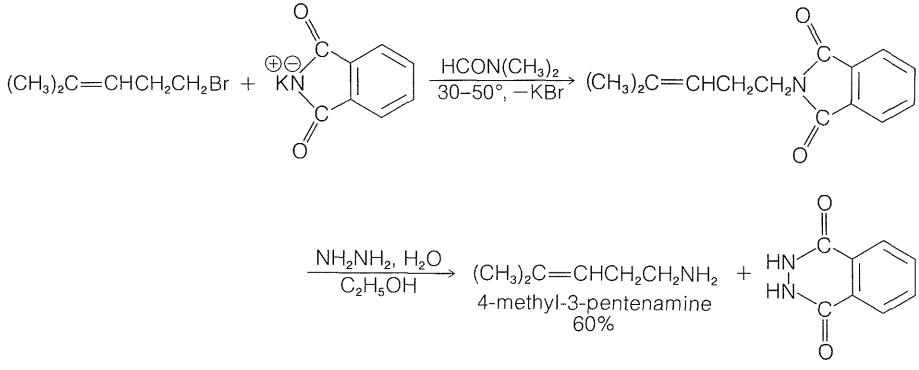
See Section 23-12B.

2. *Reductive alkylation of amines with carbonyl compounds*



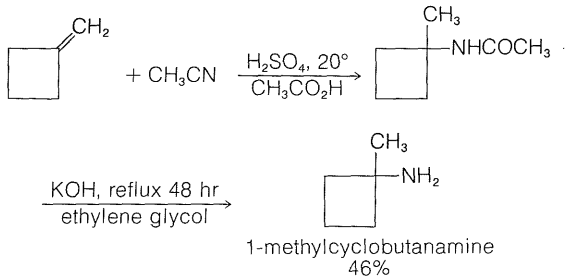
See Section 23-12C. A variety of reducing agents can be used, including hydrogen, sodium in alcohol, and sodium borohydrides.

3. *Gabriel synthesis using potassium phthalimide*



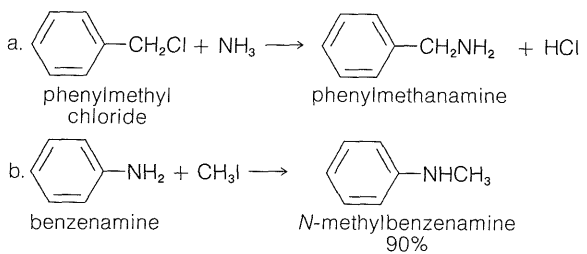
Affords primary amines. Satisfactory for primary and some secondary halides (see Section 23-9D).

4. *Ritter reaction*



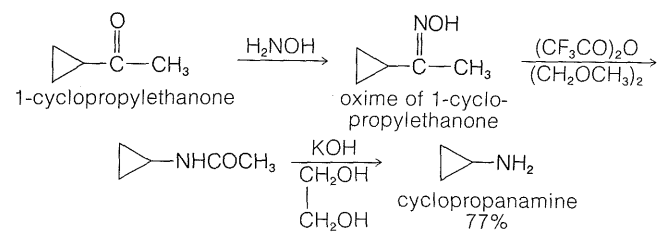
Yields primary amines with tertiary alkyl groups. Satisfactory for alkenes and alcohols that give a tertiary carbocation in strong acid (see Section 24-3B).

5. *Alkylation of ammonia and amines*



Primary amines are obtained from ammonia, and secondary amines from primary amines. Alkylating agent must have good S_N2 reactivity. Limitations are discussed in Section 23-9D.

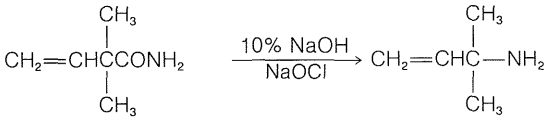
6. *Beckmann rearrangement of oximes*



See Section 24-3C.

(Table continued on next page.)

7. *Hofmann degradation of amides*

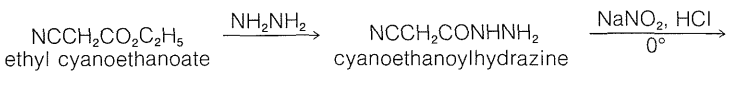


2,2-dimethyl-3-butenamide → 1,1-dimethyl-2-propenamine

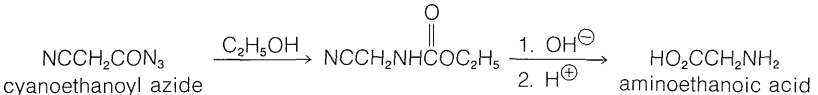
See Section 23-12E. Either NaOCl or NaOBr may be used.

8. *Curtius degradation of acyl azides*

a. acyl azide from hydrazide



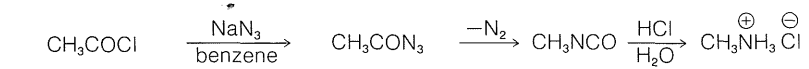
ethyl cyanoethanoate → cyanoethanoylhydrazine



cyanoethanoyl azide → aminoethanoic acid (glycine) 54%

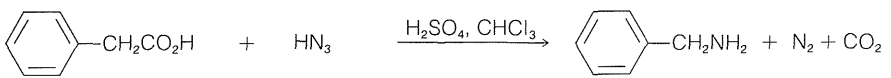
Hofmann, Curtius, and Schmidt reactions yield primary amines free of secondary or tertiary amines. The three reactions are closely related but differ in reaction conditions. They apply to alkyl, allyl, and aryl derivatives. See Section 23-12E.

b. acyl azide from acyl chloride



ethanoyl chloride → ethanoyl azide → 65%

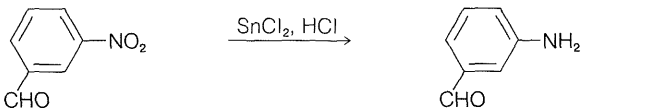
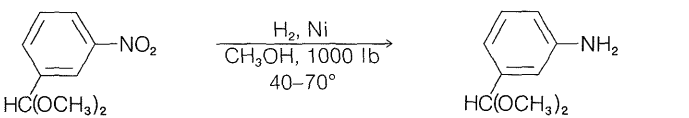
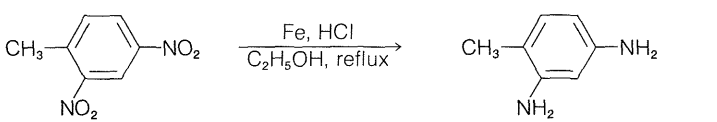
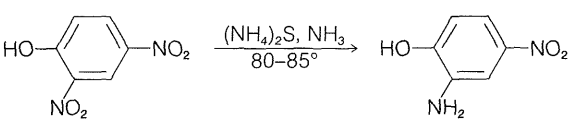
9. *Schmidt degradation of acyl azides* (obtained from carboxylic acids)



phenylethanoic acid + hydrazoic acid → phenylmethanamine 92%

See Section 23-12E.

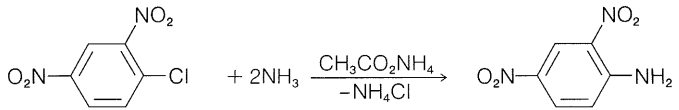
Table 23-7
Practical Examples of the Synthesis of Aromatic Amines

Reaction	Comment
1. *Reduction of nitro compounds*	Reducing agents commonly employed are iron, tin, or $SnCl_2$ in hydrochloric acid; and ammonium or alkali-metal sulfides; catalytic hydrogenation and electrolytic reduction also are employed (see Section 23-12B).
a.  3-nitrobenzenecarbaldehyde → 3-aminobenzenecarbaldehyde	
b.  (3-nitrophenyl)dimethoxymethane → (3-aminophenyl)dimethoxymethane, 67–78%	Notice, in the example given, that the acetal function is a protecting group for CHO.
c.  2,4-dinitromethylbenzene → 4-methyl-1,3-benzenediamine	
d.  2,4-dinitrobenzenol → 2-amino-4-nitrobenzenol, 64–67%	Notice that, with the right conditions and reducing agent, one nitro group can be selectively reduced in the presence of another.

(Table continued on next page.)

2. *Amination of aryl halides*

a. activated aryl halides

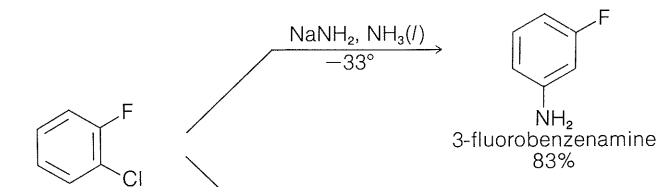


2,4-dinitrochlorobenzene

2,4-dinitrobenzenamine
68–76°

Nucleophilic replacement of halogen of aryl halides is discussed in Section 14-6B; ortho and para substituents that activate halogen include NO_2, $N_2^{\oplus}$, SO_3H, NO.

b. nonactivated aryl halides



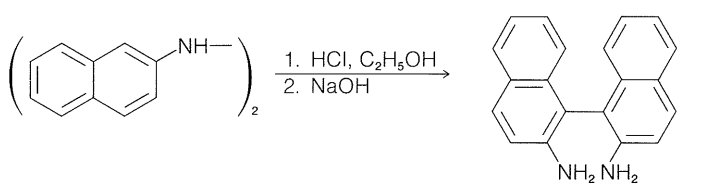
1-chloro-2-fluoro-benzene

3-fluorobenzenamine
83%

2-fluorobenzenamine
100%

Elimination-addition reactions of aryl halides with alkali-metal amides are discussed in Section 14-6C; high-temperature copper-catalyzed amination, also effective, usually does not lead to rearrangement.

3. *Benzidine rearrangement of hydrazo compounds*



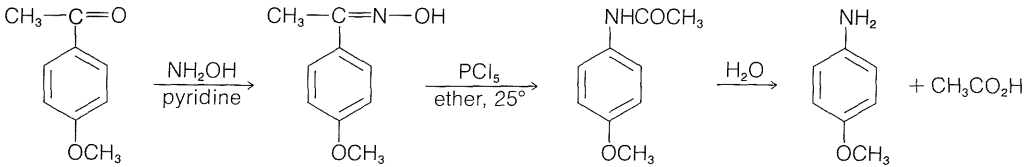
2,2′-hydrazonaphthalene

2,2′-diamino-1,1′-binaphthyl
92%

Acid-catalyzed rearrangement of aromatic hydrazo compounds leads to diaminobiaryl compounds (see Section 23-10D).

4. *Beckmann rearrangement of oximes*

Satisfactory with 1-phenylethanone (acetophenone) oxime and other diaryl ketoximes; acid catalysts include HCl, H_2SO_4, PCl_5, H_3PO_4 (Section 24-3C).

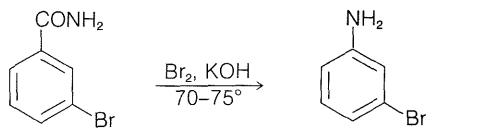


1-(4-methoxyphenyl)-ethanone

4-methoxybenzenamine
75–85%

5. *Hofmann degradation of amides*

See Section 23-12E.

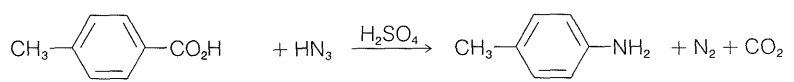


3-bromobenzene-carboxamide

3-bromobenzenamine
87%

6. *Schmidt degradation of acyl azides* (obtained from carboxylic acids)

See Section 23-12E.

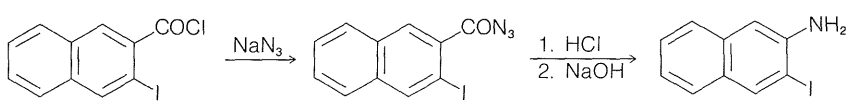


4-methylbenzenecarboxylic acid
(*para*-toluic acid)

4-methylbenzenamine
(*para*-toluidine)
70%

7. *Curtius degradation of acyl azides* (obtained from acid chlorides)

See Section 23-12E.



3-iodo-2-naphthalene-carbonyl chloride

3-iodo-2-naphthalen-amine

23-12C Amines by Reductive Alkylation of Aldehydes and Ketones

A useful synthesis of primary and secondary amines that is related to the reductions just described utilizes the reaction of an aldehyde or a ketone with ammonia or a primary amine in the presence of hydrogen and a metal catalyst:

$$RCHO + NH_3 + H_2 \xrightarrow{Pt} RCH_2NH_2 + H_2O$$

$$R_2C{=}O + CH_3NH_2 + H_2 \xrightarrow{Pd} R_2CHNHCH_3 + H_2O$$

It is reasonable to suppose that the carbonyl compound first forms the imine derivative by way of the aminoalcohol (see Section 16-4C), and this derivative is hydrogenated under the reaction conditions:

$$R{-}CH{=}O + NH_3 \rightleftharpoons R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}OH \xrightleftharpoons{-H_2O}$$

$$R{-}CH{=}NH \xrightarrow{H_2,\ Pt} R{-}CH_2NH_2$$

Other reducing agents may be used, and the borohydride salt $Na^{\oplus}{}^{\ominus}BH_3(CN)$ is convenient to use in place of H_2 and a metal catalyst.

In a formal sense, the carbonyl compound is reduced in this reaction while the amine is alkylated, hence the term **reductive alkylation** or **reductive amination.**

Exercise 23-40 Show how the following transformations may be achieved. List reagents and approximate reaction conditions.

a. 3-bromopropene to 3-butenamine
b. cyclohexanone to cyclohexanamine
c. benzenecarboxylic acid to phenylmethanamine (not *N*-phenylmethanamine)
d. benzenecarbaldehyde to *N*-methylphenylmethanamine ($C_6H_5CH_2NHCH_3$)

23-12D Amines from Amides by Hydrolysis or Reduction

There are a number of ways in which an amide can be transformed into an amine. Two of these ways have been mentioned already and involve hydrolysis or reduction:

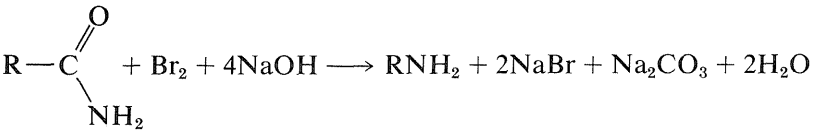
$$R'{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NHR \xrightarrow[H^{\oplus} \text{ or } {}^{\ominus}OH]{H_2O} R'{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH + H_2NR$$

$$R'{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NHR \xrightarrow[\text{or } LiAlH_4]{H_2,\ Ni} R'CH_2NHR$$

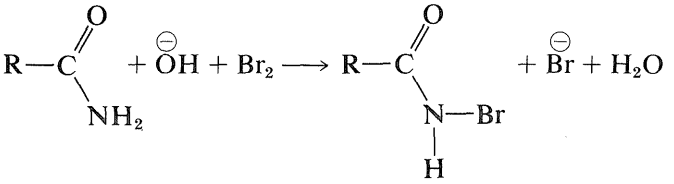
As a means of amine synthesis, both methods depend on the availability or the ease of synthesis of the corresponding amide.

23-12E Amines from Amides by the Hofmann Degradation

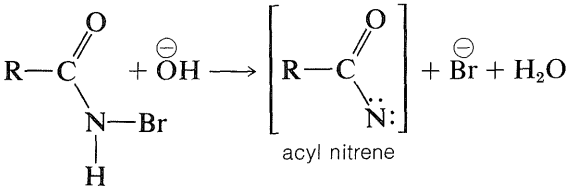
An interesting and general reaction for the preparation of primary amines is the **Hofmann degradation,** in which an unsubstituted amide is converted to an amine by bromine (or chlorine) in sodium hydroxide solution:



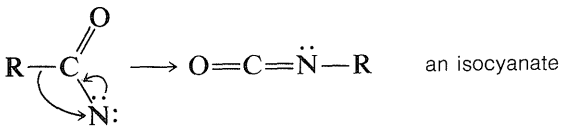
The mechanism of this unusual reaction first involves base-catalyzed bromination of the amide on nitrogen to give an *N*-bromoamide intermediate:



There follows a base-induced elimination of HBr from nitrogen to form a "nitrene" intermediate, which is analogous to the formation of a carbene (Section 14-7B):



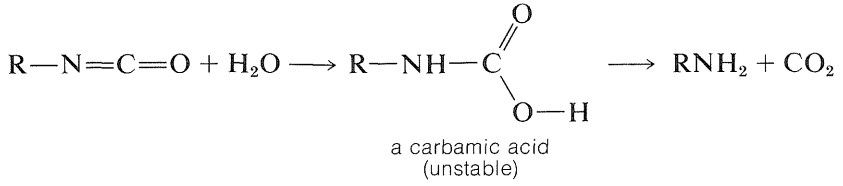
As you might expect from the structure of an acyl nitrene (only six electrons in the valence shell of nitrogen), it is highly unstable but can become stabilized by having the substituent group move as $R:^{\ominus}$ from carbon to nitrogen:[5]



The rearrangement is stereospecific and the configuration at the migrating carbon is *retained* (see Section 21-10F). The rearrangement product is called an **isocyanate** and is a nitrogen analog of a ketene ($R_2C{=}C{=}O$); like ketenes,

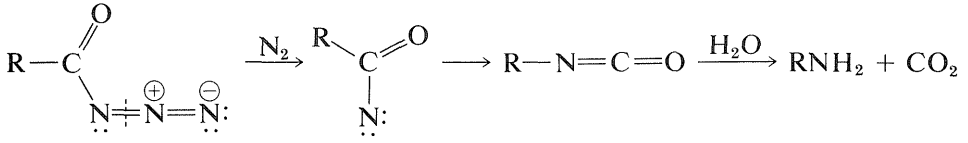
[5]There are several analogies for this kind of rearrangement that involve electron-deficient carbon (Sections 8-9B and 15-5E) and oxygen (Sections 16-9E).

isocyanates readily add water. The products are carbamic acids, which are not very stable, especially in basic solution, and readily lose carbon dioxide to give the amine:



a carbamic acid
(unstable)

A practical example of this reaction is given in Table 23-6 together with examples of related reactions known as the **Curtius** and **Schmidt** rearrangements. The latter two probably also involve rearrangement of an acyl nitrene, this time formed by decomposition of an acyl azide:

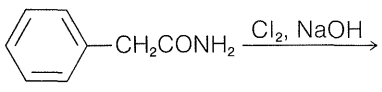


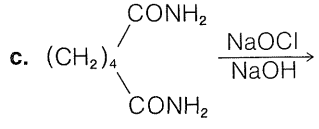
Exercise 23-41 The point of this exercise is to show that reactions of known stereospecificity can be used to establish configuration at chiral centers.

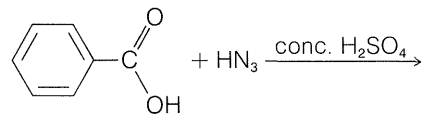
A carboxylic acid of (+) optical rotation was converted to an amide by way of the acyl chloride. The amide in turn was converted to a primary amine of one less carbon atom than the starting carboxylic acid. The primary amine was identified as 2-*S*-aminobutane. What was the structure and configuration of the (+)-carboxylic acid? *Indicate the reagents you would need to carry out each step in the overall sequence* $RCO_2H \longrightarrow RCOCl \longrightarrow RCONH_2 \longrightarrow RNH_2$.

Exercise 23-42 Draw the structures of the products expected to be formed in the following reactions:

a. $(CH_3)_2CHCH_2CONH_2 \xrightarrow{Br_2,\ NaOH}$

b. 

c. 

d. 

23-13 PROTECTION OF AMINO GROUPS IN SYNTHESIS

We have mentioned previously that it may be difficult to ensure selective chemical reaction at one functional group when other functional groups are present in the same molecule. Amino groups are particularly susceptible to reactions with a wide variety of reagents, especially oxidizing reagents, alkylating reagents, and many carbonyl compounds. Therefore, if we wish to prevent the amino group from undergoing undesired reactions while chemical change occurs elsewhere in the molecule, it must be suitably protected. There is more documented chemistry on methods of protecting amino groups than of any other functional group. This is because peptide synthesis has become very important and, as we shall see in Chapter 25, it is not possible to build a peptide of specific structure from its component amino acids unless the amino groups can be suitably protected. Therefore we now will consider the more useful protecting groups that are available—how they are introduced and how they are removed.

23-13A Protonation

It should be clear that the reactivity of amines normally involves some process in which a bond is made to the unshared electron pair on nitrogen. Therefore any reaction of an amine that reduces the reactivity of this electron pair should reduce the reactivity of the nitrogen atom. The simplest way to do this would be to convert the amine to an ammonium salt with an acid. Protonation amounts to protection of the amine function:

$$RNH_2 + HX \rightleftharpoons \overset{\oplus}{R}NH_3 \ \overset{\ominus}{X}$$

Examples are known in which amines indeed can be protected in this manner, but unless the acid concentration is very high, there will be a significant proportion of unprotected free base present. Also, many desirable reactions are not feasible in acid solution.

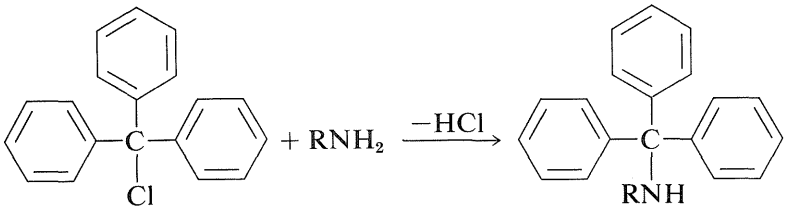
23-13B Alkylation

A related protection procedure is alkylation (Equations 23-8 and 23-9), which is suitable for primary and secondary amines:

$$R'\ddot{N}H_2 + RX \longrightarrow R'\ddot{N}HR + HX \qquad (23\text{-}8)$$

$$R_2'\ddot{N}H + RX \longrightarrow R_2'\ddot{N}R + HX \qquad (23\text{-}9)$$

At first glance, you may not consider that such reactions achieve protection because there is an electron pair on nitrogen in the products. However, if a suitably bulky alkylating agent, RX, is used the reactivity of the resulting alkylated amine can be reduced considerably by a steric effect. The most useful group of this type is the triphenylmethyl group $(C_6H_5)_3C—$, which can be introduced on the amine nitrogen by the reaction of triphenylmethyl chloride ("trityl" chloride) with the amine in the presence of a suitable base to remove the HCl that is formed:



The triphenylmethyl group can be removed from the amine nitrogen under very mild conditions, either by catalytic hydrogenation or by hydrolysis in the presence of a weak acid:

$$(C_6H_5)_3C—NHR \xrightarrow{H_2,\ Pt} (C_6H_5)_3CH + RNH_2$$

$$(C_6H_5)_3C—NHR \xrightarrow[H_2O,\ 30°]{CH_3CO_2H,\ 15\%} (C_6H_5)_3COH + RNH_2$$

Exercise 23-43 Cleavage of C–N bonds by catalytic hydrogenation is achieved much more readily with diphenylmethanamine or triphenylmethanamine than with alkanamines. Explain why this should be so on the basis that the cleavage is a *homolytic* reaction.

Exercise 23-44 Write the steps involved in (a) the formation of triphenylmethanamine from triphenylmethyl chloride in *aqueous* ammonia containing sodium hydroxide and (b) the hydrolysis of triphenylmethanamine in aqueous ethanoic acid. (This is an unusually facile heterolytic cleavage of a saturated C–N bond.)

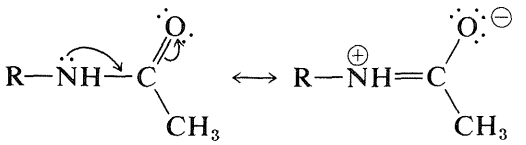
23-13C Acylation

One useful way of reducing the basicity and nucleophilicity of an amine nitrogen is to convert it to an amide by treatment with an acid chloride or acid anhydride (Section 18-7):

$$RNH_2 + CH_3COCl \longrightarrow RNHCOCH_3 + HCl$$

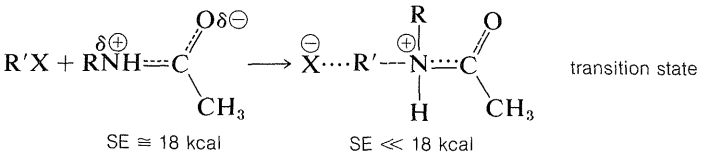
$$RNH_2 + (CH_3CO)_2O \longrightarrow RNHCOCH_3 + CH_3CO_2H$$

The reduced reactivity is associated with the stabilization produced by the attached carbonyl group because of its ability to accept electrons from the nitrogen atom. This can be seen clearly in valence-bond structures **9a** and **9b**, which show electron delocalization of the unshared pair of the amide function:



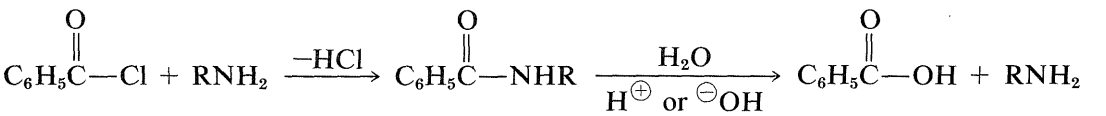
9a **9b**

The stabilization energy (SE) of a simple amide grouping is about 18 kcal $mole^{-1}$, and if a reaction occurs in which the amide nitrogen acts as an electron-pair donor, almost all of the electron delocalization of the amide group is lost in the transition state:

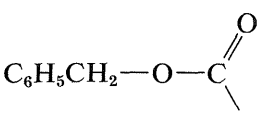


This loss in stabilization energy at the transition state makes an amide far less nucleophilic than an amine.

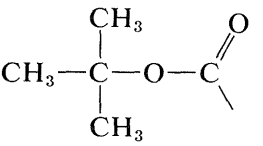
The most common acylating agents are the acyl chlorides and acid anhydrides of ethanoic acid and benzoic acid. The amine can be recovered from the amide by acid- or base-catalyzed hydrolysis:



Another useful protecting group for amines has the structure R—O—C(=O)—. It differs from the common acyl groups of the type R—C(=O)— in that it has the *alkoxy*carbonyl structure rather than an *alkyl*carbonyl structure. The most used examples are:



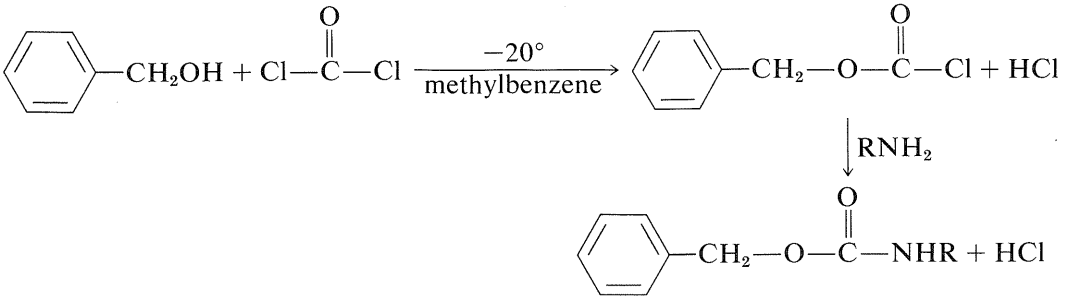
phenylmethoxycarbonyl
(benzyloxycarbonyl, abbreviation Z)[6]



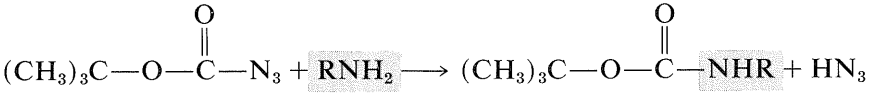
tert-butoxycarbonyl
(abbreviation BOC)[6]

[6]This abbreviation is approved by the IUPAC–IUB Commission on Biochemical Nomenclature and is typical of the kind of "alphabet soup" that is making biochemistry almost completely unintelligible without a glossary of approved (and unapproved) abbreviations at hand at all times. We shall make minimum use of such designations. You will remember we already use *Z* for something else (Section 19-7).

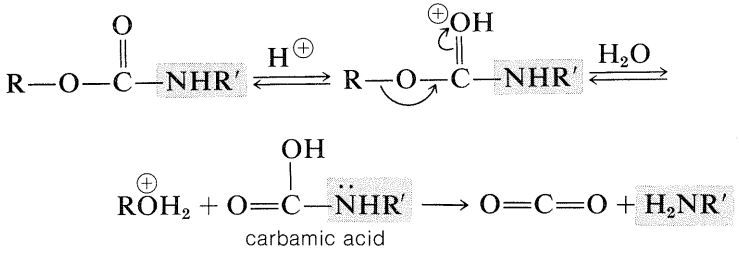
The phenylmethoxycarbonyl (benzyloxycarbonyl) group can be introduced by way of the corresponding acyl chloride, which is prepared from phenylmethanol (benzyl alcohol) and carbonyl dichloride:



The *tert*-butoxycarbonyl group cannot be introduced by way of the corresponding acyl chloride because $(CH_3)_3COCOCl$ is unstable. One of several alternative derivatives is the azide, $ROCON_3$:

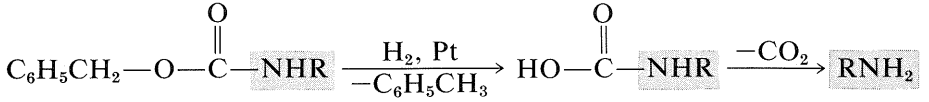


Although these protecting groups may seem bizarre, their value lies in the fact that they can be removed easily by acid-catalyzed hydrolysis under very mild conditions. The sequence of steps is shown in Equation 23-10 and involves proton transfer to the carbonyl oxygen and cleavage of the carbon–oxygen bond by an S_N1 process (R = *tert*-butyl) or S_N2 process (R = phenylmethyl). The product of this step is a carbamic acid. Acids of this type are unstable and readily eliminate carbon dioxide, leaving only the free amine (also see Section 23-12E):



(23-10)

The benzyloxycarbonyl group, but not the *tert*-butoxycarbonyl group, may be removed by catalytic hydrogenation. Again a carbamic acid is formed, which readily loses CO_2:

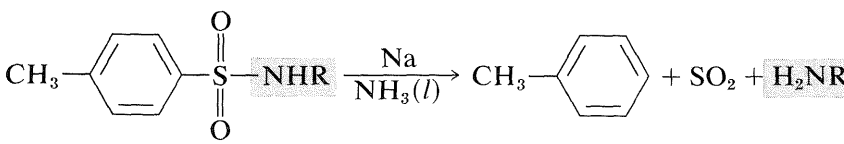


23-13D Sulfonylation

A sulfonyl group, $R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-$, like an acyl group, $R-\overset{\overset{O}{\|}}{C}-$ or $RO-\overset{\overset{O}{\|}}{C}-$, will deactivate an attached nitrogen. Therefore amines can be protected by transformation to sulfonamides with sulfonyl chlorides (Section 23-9C):

$$C_6H_5SO_2Cl + RNH_2 \longrightarrow C_6H_5SO_2NHR + HCl$$

However, sulfonamides are much more difficult to hydrolyze back to the amine than are carboxamides. In peptide synthesis (Section 25-7C) the commonly used sulfonyl protecting groups are 4-methylbenzenesulfonyl or 4-bromobenzenesulfonyl groups. These groups can be removed as necessary from the sulfonamide by reduction with sodium metal in liquid ammonia:



Exercise 23-45 Explain why the nitration of benzenamine to give 2- and 4-nitrobenzenamines is unsatisfactory with nitric acid–sulfuric acid mixtures. Show how this synthesis could be achieved by suitably modifying the amine function.

Exercise 23-46 Suggest protecting groups and reaction sequences whereby the following transformations could be achieved:

a. 3-amino-1-propanol to 3-aminopropanoic acid

b. 4-(2-aminoethyl)benzenamine to 2-(4-nitrophenyl)ethanamine

23-14 CARCINOGENIC NITROGEN COMPOUNDS

23-14A Amines

Everyone who works with organic chemicals should be aware that a number of arenamines are carcinogens. The most dangerous examples (see Figure 23-8) are known to induce human bladder cancer. These chemicals were used widely in the chemical industry (mostly in azo dye manufacture) long before they were

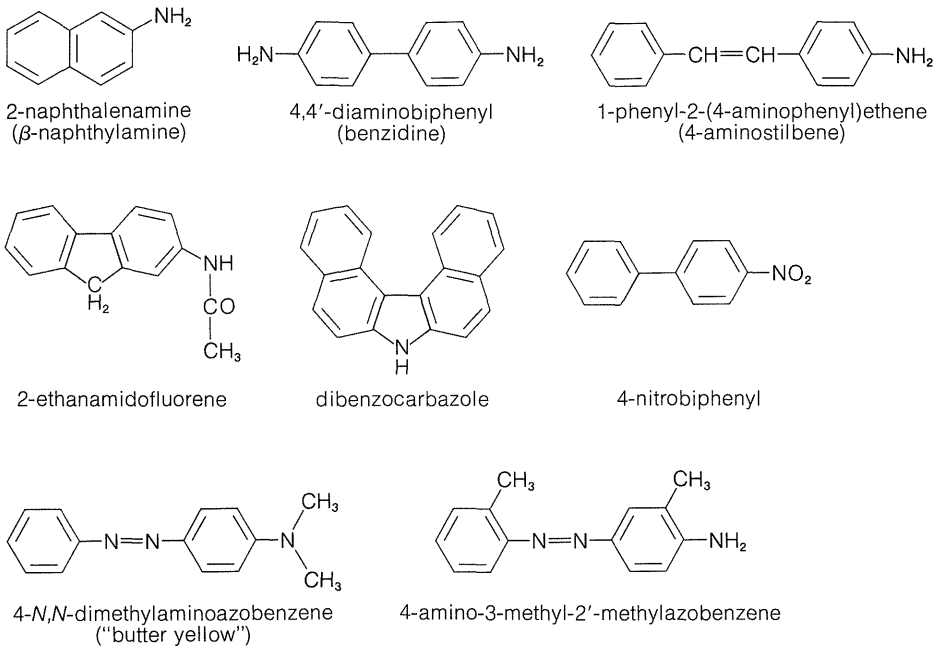


Figure 23-8 Some carcinogenic aromatic nitrogen compounds

recognized as hazardous carcinogens. Voluntary action and appropriate legislation now controls the industrial uses of these substances, and there also are some controls for uses in research and teaching. It is important to be aware of the potential hazards of known carcinogens and to recognize that *all* chemicals, both organic and inorganic, should be treated with great respect if their thermodynamic and physiological properties are not known. Carcinogenic character is just one of many possible hazards.

23-14B Azo Compounds

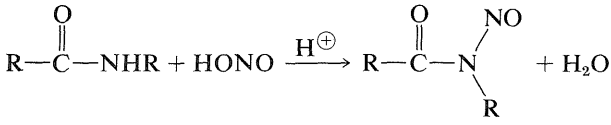
Other nitrogen compounds besides amines are known to be carcinogenic. For example, certain azo dyes (see Figure 23-8) have been found to produce tumors in animals. This fact has caused concern for human health because, as we indicated in Section 23-10C, azo dyes are coloring agents that are used in many products. They certainly are not all carcinogenic, but the structural requirements for a compound to show this property as yet are poorly understood. Seemingly minor structural changes may change completely the toxic properties of a chemical. For example, the *N,N*-diethylamino analog of "butter yellow" (Figure 23-8) is apparently harmless.

23-14C *N*-Nitroso Compounds

We have seen that *N*-nitroso compounds are formed from secondary amines and nitrous acid:

$$R_2NH + HONO \xrightarrow{H^{\oplus}} R_2N{-}NO + H_2O$$

N-nitroso compounds also can be formed from carboxamides and nitrous acid:



Some of these nitrosoamines and nitrosoamides are known to be potent carcinogens for some animals, which is reason to suspect they also may be carcinogenic for humans. However, it is clear that there may be very marked differences in carcinogenic properties of a given compound for different animal species.

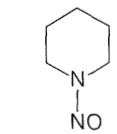
Why some of these substances have carcinogenic activity is a matter of chemical interest. Recall from Section 23-10 that nitrosation of amines usually leads to cleavage of a C–N bond in the sense C⁞:N. The carbon fragment ultimately is transferred to some nucleophilic atom. In effect, this means that nitrosamines can function as *alkylating agents* and, in a biological system, the functions that probably would be alkylated are the nucleophilic sites along the polymeric protein or nucleic acid chains. It is not difficult to appreciate that alkylation of these substances may well disrupt the pattern of normal cell growth.

There is an unresolved problem related to the carcinogenic properties of nitroso compounds. You probably are aware (if you read the labels on food packages) that sodium nitrite is added to many packaged meat products. Sodium nitrite prevents the growth of harmful bacteria, thereby retarding spoilage, and it also enhances the appearance by maintaining the red look of fresh meat. There is a possibility that nitrite may have adverse effects on human health by nitrosating the amino and amide functions of proteins in the presence of acids. This possibility has to be balanced against the alternate threat to human health if the use of nitrite were discontinued, that of increased food spoilage. In any case, it seems clear that the amount of sodium nitrite actually used in most processing is in excess of that needed to retard bacterial decay.

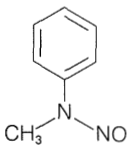
There are many other chemicals that are active alkylating agents besides nitrosamines, and some are unquestionably carcinogenic (see Figure 23-9), whereas others apparently are not. In fact, it is a paradox that some of the most useful synthetic drugs in treating certain forms of cancer are alkylating agents. Several of these are shown in Figure 23-10. They all have two or more active centers in the molecule that enable them to form cross-links between protein or nucleic acid molecules.

It should be recognized that not all of the carcinogenic substances loosed on mankind are the result of modern technology. The most potent carcinogens known, which are lethal in test animals at levels of a few parts per billion, are mold metabolites called **aflatoxins.** These substances are complex non-nitrogenous, heterocyclic oxygen compounds, which often are formed by molds growing on cereal grains, peanuts, and so on. (See Figure 23-9.)

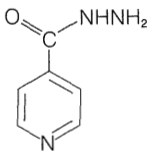
Carcinogenic nitroso compounds and amides



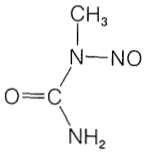
N-nitrosaza-cyclohexane



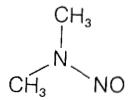
N-methyl-*N*-nitroso-benzenamine



isonicotinic acid hydrazide (isoniazid)



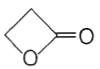
N-methyl-*N*-nitrosourea



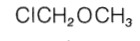
N,N-dimethyl-nitrosamine

Carcinogenic alkylating agents

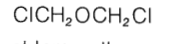
diazomethane



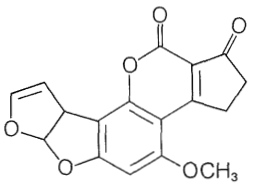
2-oxacyclo-butanone (propiolactone)



methoxy-chloromethane (methyl chloro-methyl ether)

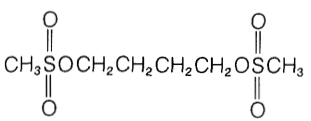


chloromethoxy-chloromethane (bis-chloromethyl ether)

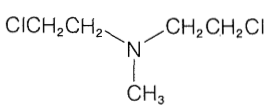


aflatoxin B_1

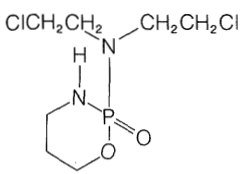
Figure 23-9 Chemical carcinogens (not all of these have been established as carcinogenic for humans)



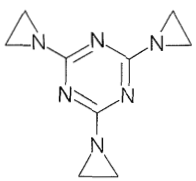
myleran



nitrogen mustard



cyclophosphoramide



trimethylenemelamine

Figure 23-10 Some illustrative antitumor agents (biological alkylating agents)

Additional Reading

H. Zollinger, "Reactivity and Stability of Arenediazonium Ions," *Accts. Chem. Res.* **6,** 335 (1973).

L. N. Ferguson, "Cancer and Chemicals," *Chemical Society (London) Reviews* **4,** 289 (1975).

I. T. Miller and H. D. Springall, *Sidgwick's Organic Chemistry of Nitrogen,* 3rd ed., The Clarendon Press, Oxford, 1966.

A. C. Cope and E. R. Trumbull, "Olefins from Amines. The Hofmann Elimination Reaction and Amine Oxide Pyrolysis," *Organic Reactions* **11,** 317 (1960).

Supplementary Exercises

23-47 Write equations for a practical laboratory synthesis of each of the following compounds from the indicated starting materials. Give reagents and conditions.

a. $(CH_3)_3CCH_2NH_2$ from $(CH_3)_3CCO_2H$ **b.** 1,6-hexanediamine from butadiene

23-48 Write a structure of at least one substance that fits each of the following descriptions. (Different structures may be written for each part.)

a. a water-insoluble, acid-soluble nitrogen compound that gives no nitrogen gas with nitrous acid

b. a compound that gives off water on heating to 200°

c. a chiral ester that hydrolyzes to give only achiral compounds

23-49 Compound *A* is chiral and is a liquid with the formula $C_5H_{11}O_2N$. *A* is insoluble in water and dilute acid but dissolves in sodium hydroxide solution. Acidification of a sodium hydroxide solution of chiral *A* gives *racemic A.* Reduction of chiral *A* with hydrogen over nickel produces chiral compound *B* of formula $C_5H_{13}N$. Treatment of chiral *B* with nitrous acid gives a mixture containing some chiral alcohol *C* and some 2-methyl-2-butanol. Write structures for compounds *A, B,* and *C* that agree with all the given facts. Write balanced equations for all the reactions involved. Show your reasoning.

In this type of problem, one should work backward from the structures of the final products, analyzing each reaction for the structural information it gives. The key questions to be inferred in the preceding problem are (a) What kind of chiral compound or compounds could give 2-methyl-2-butanol and a chiral alcohol with nitrous acid? (b) What kinds of compounds could give *B* on reduction? (c) What does the solubility behavior of *A* indicate about the type of compound that it is? (d) Why does chiral *A* racemize when dissolved in alkali?

23-50 Arrange the following pairs of substances in order of expected base strengths. Show your reasoning.

a. *N,N*-dimethylmethanamine and trifluoro-*N,N*-bis(trifluoromethyl)methanamine

b. phenylmethanamine and 4-methylbenzenamine

c. ethanenitrile and azabenzene

d. methamidine [$HC(=NH)NH_2$] and methanamide (review Exercise 23-12)
e. *N*-methylazacyclopropane and *N*-methylazacyclopentane (review Section 11-8B)

23-51 What reagents and conditions would you use to prepare 2-methylpropanamine by the following reactions:
a. Hofmann rearrangement
b. Schmidt rearrangement
c. Curtius rearrangement
d. Gabriel synthesis
e. lithium aluminum hydride reduction

23-52 Write structural formulas for substances (one for each part) that fit the following descriptions:
a. an aromatic amine that is a stronger base than benzenamine
b. a substituted phenol that would not be expected to couple with benzenediazonium chloride in acid, alkaline, or neutral solution
c. a substituted benzenediazonium chloride that would be a more active coupling agent than benzenediazonium chloride itself
d. methyl *Z*-benzenediazotate
e. the important resonance structures of the ammonium salt of *N*-nitroso-*N*-phenylhydroxylamine (Cupferron)

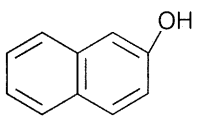
23-53 Diazotization of 4-chlorobenzenamine with sodium nitrite and hydrobromic acid yields a diazonium salt solution that couples with *N,N*-dimethylbenzenamine to give substantial amounts of 4-dimethylamino-4′-bromoazobenzene. Explain.

23-54* Hypophosphorous acid, H_3PO_2, in the presence of copper reduces aryldiazonium salts to arenes (Table 23-4) by a radical-chain mechanism with formation of H_3PO_3. Cupric copper, Cu(II), initiates the chain by reducing H_3PO_2 to $H_2\dot{P}O_2$. Write a chain mechanism for reduction of $ArN_2^{\oplus}$ to ArH that involves $H_2\dot{P}O_2$ in the chain-propagating steps.

23-55 Give the principal product(s) to be expected from the following reactions:

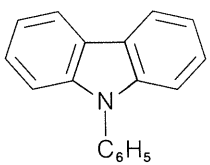
a. $C_6H_5N_2^{\oplus}Cl^{\ominus} + C_6H_5NHCH_3 \xrightarrow{\text{pH 7, 0°}}$

b. $p\text{-}CH_3C_6H_4NHNHC_6H_5 \xrightarrow{H_2SO_4}$

c.  $+ C_6H_5N_2^{\oplus} \xrightarrow[\text{pH 11}]{0°}$

d.  $+ C_6H_5N_2^{\oplus} \xrightarrow{0°}$

23-56 Explain why triphenylamine is a much weaker base than benzenamine and why its electronic absorption spectrum is shifted to longer wavelengths compared with the spectrum of benzenamine. Would you expect *N*-phenylcarbazole to be a stronger, or weaker, base than triphenylamine? Explain.



N-phenylcarbazole