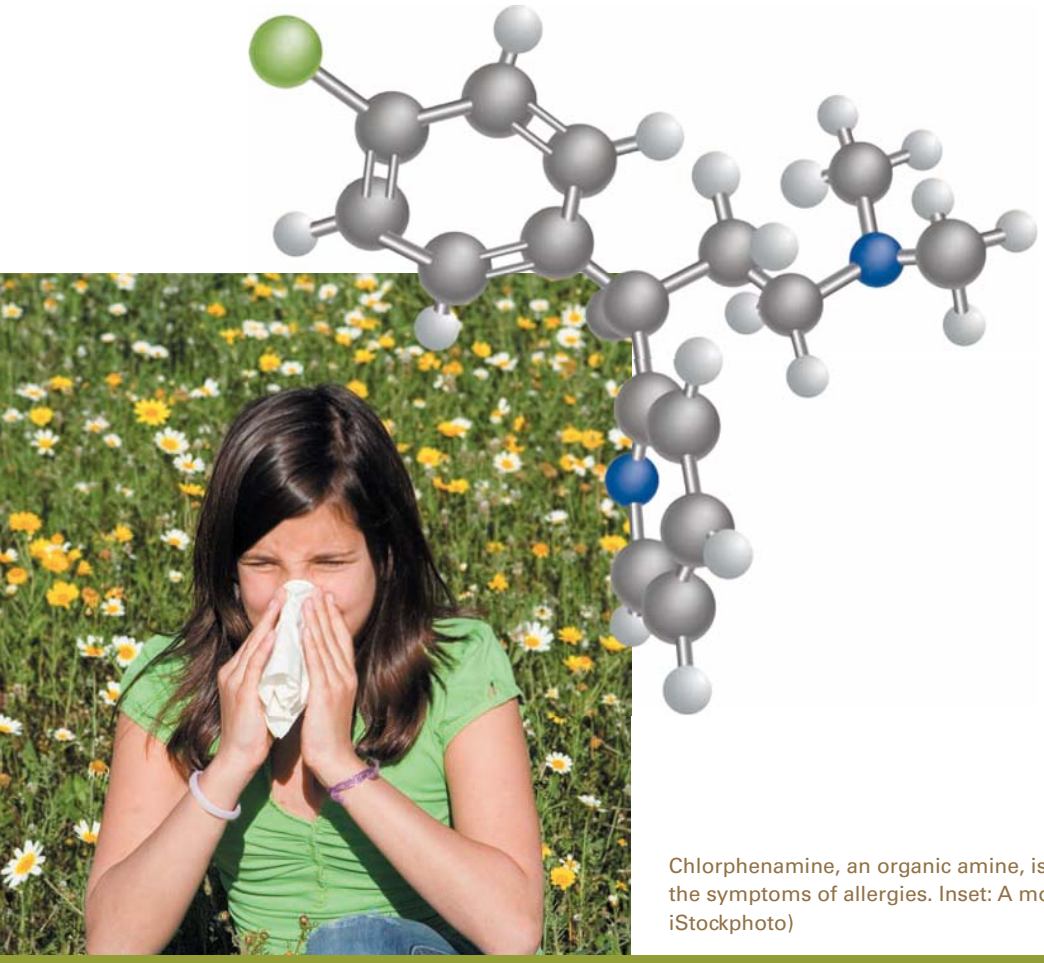
10

Amines



Chlorphenamine, an organic amine, is an antihistamine used to prevent some of the symptoms of allergies. Inset: A model of chlorphenamine. (© mandygodbehear/iStockphoto)

KEY QUESTIONS

HOW TO

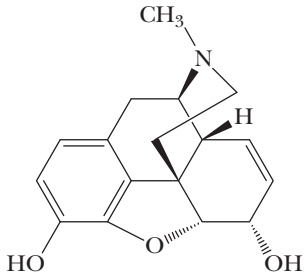
CHEMICAL CONNECTIONS

CARBON, HYDROGEN, and oxygen are the three most common elements in organic compounds. Because of the wide distribution of amines in the biological world, nitrogen is the fourth most common element in organic compounds. The most important chemical properties of amines are their basicity and their nucleophilicity.

Chemical Connections 10A

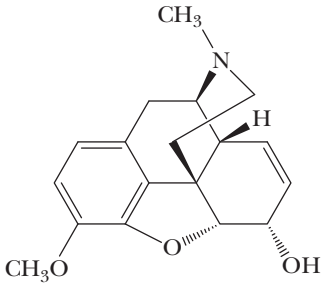
MORPHINE AS A CLUE IN THE DESIGN AND DISCOVERY OF DRUGS

The analgesic, soporific, and euphoriant properties of the dried juice obtained from unripe seed pods of the opium poppy *Papaver somniferum* have been known for centuries. By the beginning of the nineteenth century, the active principal, morphine, had been isolated and its structure determined:



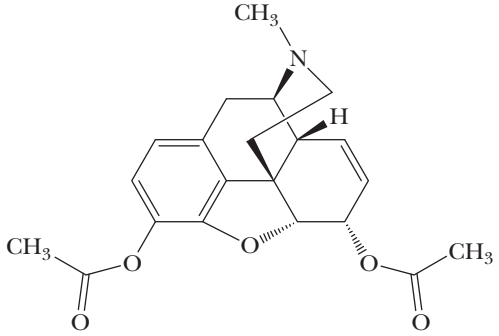
Morphine

Also occurring in the opium poppy is codeine, a monomethyl ether of morphine:



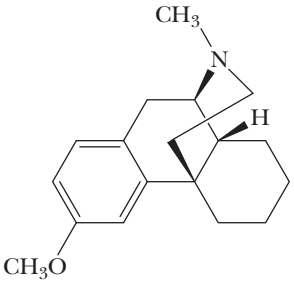
Codeine

Heroin is synthesized by treating morphine with two moles of acetic anhydride:

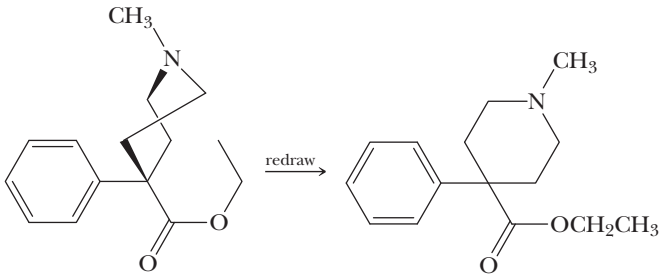


Heroin

Even though morphine is one of modern medicine's most effective painkillers, it has two serious side effects: It is addictive, and it depresses the respiratory control center of the central nervous system. Large doses of morphine (or heroin) can lead to death by respiratory failure. One strategy in the ongoing research to produce painkillers has been to synthesize compounds related in structure to morphine, in the hope that they would be equally effective analgesics, but with diminished side effects. Following are structural formulas for two such compounds that have proven to be clinically useful:



(–)-enantiomer = Levomethorphan
(+)-enantiomer = Dextromethorphan



Meperidine
(Demerol)

Levomethorphan is a potent analgesic. Interestingly, its dextrorotatory enantiomer, dextromethorphan, has no analgesic activity. It does, however, show approximately the same cough-suppressing activity as morphine and is used extensively in cough remedies.

It has been discovered that there can be even further simplification in the structure of morphine-like analgesics. One such simplification is represented by meperidine, the hydrochloride salt of which is the widely used analgesic Demerol®.

It was hoped that meperidine and related synthetic drugs would be free of many of the morphine-like undesirable side effects. It is now clear, however, that they are not. Meperidine, for example, is definitely addictive. In spite of much determined research, there are as yet no agents as effective as morphine for the relief of severe pain that are absolutely free of the risk of addiction.

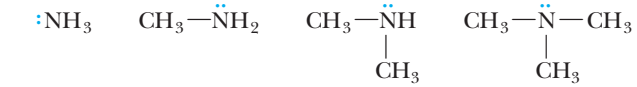
How and in what regions of the brain does morphine act? In 1979, scientists discovered that there are specific receptor sites for morphine and other opiates and that these sites are clustered in the brain's limbic system, the area involved in emotion and the perception of pain. Scientists then asked, "Why does the human brain have receptor sites specific for morphine?" Could it be that the brain produces its own opiates? In 1974, scientists discovered that opiate-like compounds are indeed present in the brain; in 1975, they isolated a brain opiate that was named *enkephalin*, meaning "in the brain." Unlike morphine and its derivatives, enkephalin possesses an entirely different structure consisting of a sequence of five amino acids (Section 18.4). Scientists have yet to understand the role of these natural brain opiates. Perhaps when we do understand their biochemistry, we may discover clues that will lead to the design and synthesis of more potent, but less addictive, analgesics.

Question

Identify the functional groups in morphine and meperidine. Classify the amino group in these opiates according to type (that is, primary, secondary, tertiary, heterocyclic, aliphatic, or aromatic).

10.1 What Are Amines?

Amines are derivatives of ammonia (NH_3) in which one or more hydrogens are replaced by alkyl or aryl groups. Amines are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of hydrogen atoms of ammonia that are replaced by alkyl or aryl groups (Section 1.7B). As we saw with ammonia, the three atoms or groups bonded to the nitrogen in amines assume a trigonal pyramidal geometry:

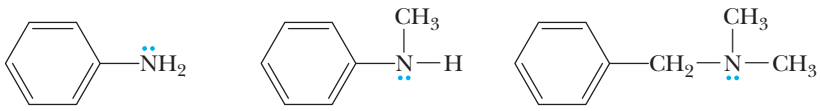


Ammonia | Methylamine (a 1° amine) | Dimethylamine (a 2° amine) | Trimethylamine (a 3° amine)

Amines are further divided into aliphatic amines and aromatic amines. In an **aliphatic amine**, all the carbons bonded directly to nitrogen are derived from alkyl groups; in an **aromatic amine**, one or more of the groups bonded directly to nitrogen are aryl groups:

Aliphatic amine An amine in which nitrogen is bonded only to alkyl groups.

Aromatic amine An amine in which nitrogen is bonded to one or more aryl groups.

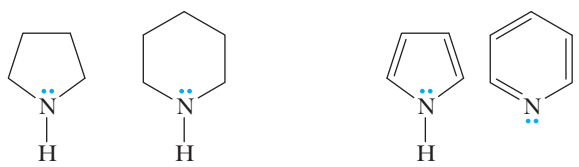


Aniline (a 1° aromatic amine) | *N*-Methylaniline (a 2° aromatic amine) | Benzyldimethylamine (a 3° aliphatic amine)

An amine in which the nitrogen atom is part of a ring is classified as a **heterocyclic amine**. When the nitrogen is part of an aromatic ring (Section 9.2), the amine is classified as a **heterocyclic aromatic amine**. Following are structural formulas for two heterocyclic aliphatic amines and two heterocyclic aromatic amines:

Heterocyclic amine An amine in which nitrogen is one of the atoms of a ring.

Heterocyclic aromatic amine An amine in which nitrogen is one of the atoms of an aromatic ring.

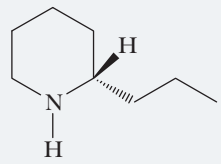


Pyrrolidine | Piperidine (heterocyclic aliphatic amines) | Pyrrole | Pyridine (heterocyclic aromatic amines)

EXAMPLE 10.1

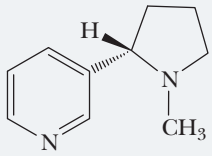
Alkaloids are basic nitrogen-containing compounds of plant origin, many of which have physiological activity when administered to humans. The ingestion of coniine, present in water hemlock, can cause weakness, labored respiration, paralysis, and, eventually, death. Coniine was the toxic substance in "poison hemlock" that caused the death of Socrates. In small doses, nicotine is an addictive stimulant. In larger doses, it causes depression, nausea, and vomiting. In still larger doses, it is a deadly poison. Solutions of nicotine in water are used as insecticides. Cocaine is a central nervous system stimulant obtained from the leaves of the coca plant. Classify each amino group in these alkaloids according to type (that is, primary, secondary, tertiary, heterocyclic, aliphatic, or aromatic):

(a)



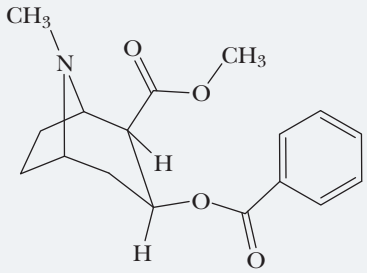
(*S*)-Coniine

(b)



(*S*)-Nicotine

(c)



Cocaine

STRATEGY

Locate each nitrogen in each compound. If a nitrogen is part of a ring, the amine is heterocyclic. If that ring is aromatic, it is classified as a heterocyclic aromatic amine (1°, 2°, or 3° does not apply). If the ring is not aromatic, it is a heterocyclic aliphatic amine that should also be classified as 1°, 2°, or 3°. *Note*: The presence of more than one nitrogen can result in multiple classifications for the molecule, depending on the part of the compound being referred to.

SOLUTION

(a) A secondary (2°) heterocyclic aliphatic amine.
(b) One tertiary (3°) heterocyclic aliphatic amine and one heterocyclic aromatic amine.
(c) A tertiary (3°) heterocyclic aliphatic amine.

See problems 10.13–10.16

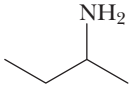
PROBLEM 10.1

Identify all carbon stereocenters in coniine, nicotine, and cocaine.

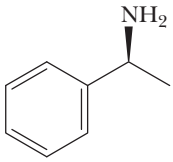
10.2 How Are Amines Named?

A. Systematic Names

Systematic names for aliphatic amines are derived just as they are for alcohols. The suffix *-e* of the parent alkane is dropped and is replaced by *-amine*; that is, they are named alkanamines:



2-Butanamine

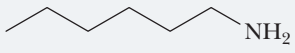


(*S*)-1-Phenylethanamine

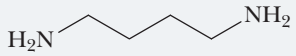
1,6-Hexanediamine

EXAMPLE 10.2

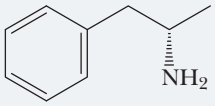
Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) 2-Methyl-1-propanamine

(c) 

(d) *trans*-4-Methylcyclohexanamine

(e) 

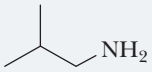
STRATEGY

When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. Then identify and name the substituents, the atoms or groups of atoms that are not part of that chain of carbons.

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the chain.

SOLUTION

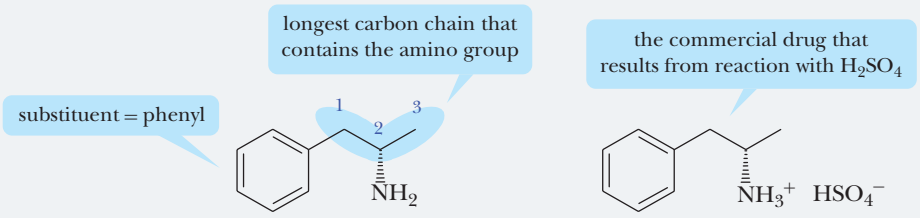
(a) 1-Hexanamine

(b) 

(c) 1,4-Butanediamine

(d) 

(e) The systematic name of this compound is (*S*)-1-phenyl-2-propanamine. Its common name is amphetamine. The dextrorotatory isomer of amphetamine (shown here) is a central nervous system stimulant and is manufactured and sold under several trade names. The salt with sulfuric acid is marketed as Dexedrine sulfate.



(*S*)-1-Phenyl-2-propanamine

Dexedrine sulfate

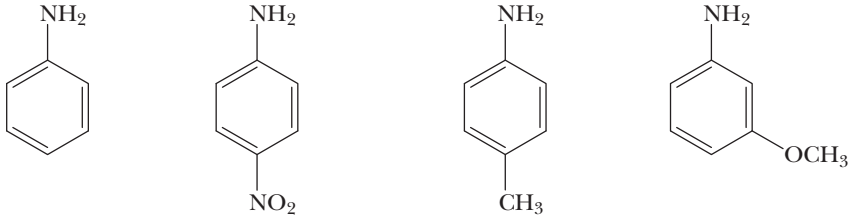
See problems 10.11, 10.12, 10.16

PROBLEM 10.2

Write a structural formula for each amine:

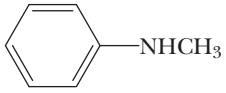
(a) 2-Methyl-1-propanamine **(b)** Cyclohexanamine **(c)** (*R*)-2-Butanamine

IUPAC nomenclature retains the common name **aniline** for $C_6H_5NH_2$, the simplest aromatic amine. Its simple derivatives are named with the prefixes *o*-, *m*-, and *p*-, or numbers to locate substituents. Several derivatives of aniline have common names that are still widely used. Among these are **toluidine**, for a methyl-substituted aniline, and **anisidine**, for a methoxy-substituted aniline:

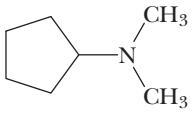


Aniline | 4-Nitroaniline (*p*-Nitroaniline) | 4-Methylaniline (*p*-Toluidine) | 3-Methoxyaniline (*m*-Anisidine)

Secondary and tertiary amines are commonly named as *N*-substituted primary amines. For unsymmetrical amines, the largest group is taken as the parent amine; then the smaller group or groups bonded to nitrogen are named, and their location is indicated by the prefix *N* (indicating that they are bonded to nitrogen):

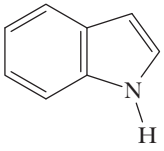


N-Methylaniline

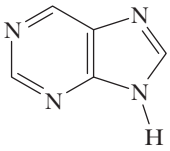


N,N-Dimethyl-cyclopentanamine

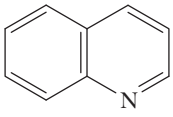
Following are names and structural formulas for four heterocyclic aromatic amines, the common names of which have been retained by the IUPAC:



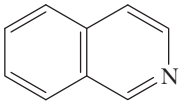
Indole



Purine

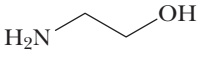


Quinoline

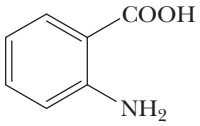


Isoquinoline

Among the various functional groups discussed in this text, the $-NH_2$ group has one of the lowest priorities. The following compounds each contain a functional group of higher precedence than the amino group, and, accordingly, the amino group is indicated by the prefix *amino-*:



2-Aminoethanol (Ethanolamine)

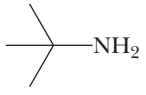


2-Aminobenzoic acid (Anthranilic acid)

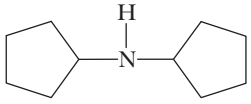
B. Common Names

Common names for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in alphabetical order in one word ending in the suffix *-amine*; that is, they are named as **alkylamines**:

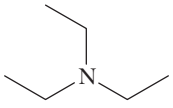
Methylamine



tert-Butylamine



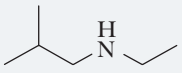
Dicyclopentylamine



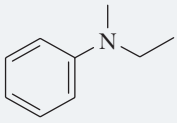
Triethylamine

EXAMPLE 10.3

Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) Cyclohexylmethylamine

(c) 

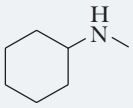
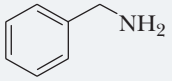
(d) Benzylamine

STRATEGY

When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. If the longest chain of carbons is a benzene ring, the amine may be named as an aniline derivative. When identifying the substituents, remember that substitutents bonded to a nitrogen are preceded by "*N*-."

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the molecule.

SOLUTION

(a) *N*-ethyl-2-methyl-1-propanamine **(b)**  **(c)** *N*-ethyl-*N*-methylaniline **(d)** 

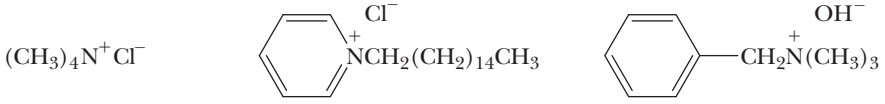
See problems 10.11, 10.12, 10.16

PROBLEM 10.3

Write a structural formula for each amine:

(a) Isobutylamine **(b)** Triphenylamine **(c)** Diisopropylamine

When four atoms or groups of atoms are bonded to a nitrogen atom, we name the compound as a salt of the corresponding amine. We replace the ending *-amine* (or aniline, pyridine, or the like) by *-ammonium* (or *anilinium*, *pyridinium*, or the like) and add the name of the anion (chloride, acetate, and so on). Compounds containing such ions have properties characteristic of salts, such as increased water solubility, high melting points, and high boiling points. Following are three examples (cetylpyridinium chloride is used as a topical antiseptic and disinfectant):



Tetramethylammonium chloride | Hexadecylpyridinium chloride (Cetylpyridinium chloride) | Benzyltrimethylammonium hydroxide

Charles D. Winters

Several over-the-counter mouthwashes contain *N*-alkylatedpyridinium chlorides as an antibacterial agent.

10.3 What Are the Characteristic Physical Properties of Amines?

Amines are polar compounds, and both primary and secondary amines form intermolecular hydrogen bonds (Figure 10.1).

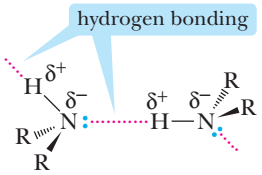


FIGURE 10.1
Intermolecular association of 1° and 2° amines by hydrogen bonding. Nitrogen is approximately tetrahedral in shape, with the axis of the hydrogen bond along the fourth position of the tetrahedron.

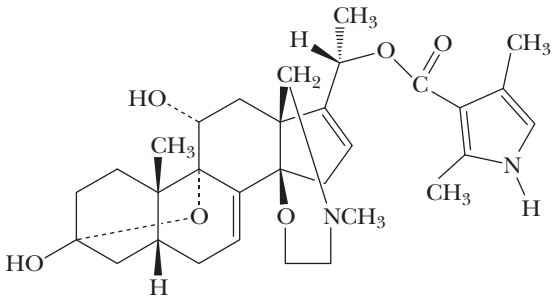
Chemical Connections 10B

THE POISON DART FROGS OF SOUTH AMERICA: LETHAL AMINES

The Noanamá and Embrá peoples of the jungles of western Colombia have used poison blow darts for centuries, perhaps millennia. The poisons are obtained from the skin secretions of several highly colored frogs of the genus *Phyllobates* (*neará* and *kokoi* in the language of the native peoples). A single frog contains enough poison for up to 20 darts. For the most poisonous species (*Phyllobates terribilis*), just rubbing a dart over the frog's back suffices to charge the dart with poison.

Scientists at the National Institutes of Health became interested in studying these poisons when it was discovered that they act on cellular ion channels, which would make them useful tools in basic research on mechanisms of ion transport. A field station was established in western Colombia to collect the relatively common poison dart frogs. From 5,000 frogs, 11 mg of batrachotoxin and batrachotoxinin A were isolated. These names are derived from *batrachos*, the Greek word for frog.

Batrachotoxin and batrachotoxinin A are among the most lethal poisons ever discovered:



Batrachotoxin

It is estimated that as little as 200 μg of batrachotoxin is sufficient to induce irreversible cardiac arrest in a human being. It has been determined that they act by causing voltage-gated Na^+ channels in nerve and muscle cells to be blocked in the open position, which leads to a huge influx of Na^+ ions into the affected cell.

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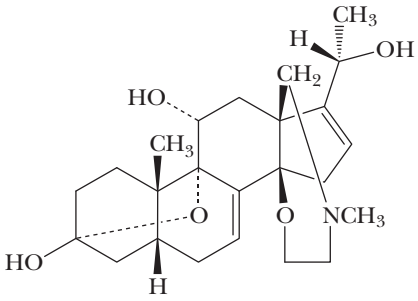
Poison dart frog, *Phyllobates terribilis.*

The batrachotoxin story illustrates several common themes in the discovery of new drugs. First, information about the kinds of biologically active compounds and their sources are often obtained from the native peoples of a region. Second, tropical rain forests are a rich source of structurally complex, biologically active substances. Third, an entire ecosystem, not only the plants, is a potential source of fascinating organic molecules.



Batrachotoxinin A

Questions

Would you expect batrachotoxin or batrachotoxinin A to be more soluble in water? Why?

Predict the product formed from the reaction of batrachotoxin with one equivalent of a weak acid such as acetic acid, CH_3COOH.

An N—H----N hydrogen bond is weaker than an O—H----O hydrogen bond, because the difference in electronegativity between nitrogen and hydrogen (3.0 − 2.1 = 0.9) is less than that between oxygen and hydrogen (3.5 − 2.1 = 1.4). We can illustrate the effect of intermolecular hydrogen bonding by comparing the boiling points of methylamine and methanol:

	CH_3NH_2	CH_3OH
molecular weight (g/mol)	31.1	32.0
boiling point (°C)	−6.3	65.0

TABLE 10.1 Physical Properties of Selected Amines

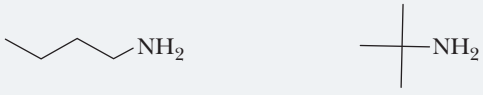
Name	Structural Formula	Melting Point (°C)	Boiling Point (°C)	Solubility in Water
Ammonia	NH_3	−78	−33	very soluble
Primary Amines				
methylamine	CH_3NH_2	−95	−6	very soluble
ethylamine	$CH_3CH_2NH_2$	−81	17	very soluble
propylamine	$CH_3CH_2CH_2NH_2$	−83	48	very soluble
butylamine	$CH_3(CH_2)_3NH_2$	−49	78	very soluble
benzylamine	$C_6H_5CH_2NH_2$	10	185	very soluble
cyclohexylamine	$C_6H_{11}NH_2$	−17	135	slightly soluble
Secondary Amines				
dimethylamine	$(CH_3)_2NH$	−93	7	very soluble
diethylamine	$(CH_3CH_2)_2NH$	−48	56	very soluble
Tertiary Amines				
trimethylamine	$(CH_3)_3N$	−117	3	very soluble
triethylamine	$(CH_3CH_2)_3N$	−114	89	slightly soluble
Aromatic Amines				
aniline	$C_6H_5NH_2$	−6	184	slightly soluble
Heterocyclic Aromatic Amines				
pyridine	C_5H_5N	−42	116	very soluble

Both compounds have polar molecules and interact in the pure liquid by hydrogen bonding. Methanol has the higher boiling point because hydrogen bonding between its molecules is stronger than that between molecules of methylamine.

All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight. Most low-molecular-weight amines are completely soluble in water (Table 10.1). Higher-molecular-weight amines are only moderately soluble or insoluble.

EXAMPLE 10.4

Account for the fact that butylamine has a higher boiling point than *t*-butylamine.



Butylamine
bp 78 °C

t-Butylamine
bp 46 °C

STRATEGY

Identify structural differences that might affect the intermolecular attractions between the molecules of each compound.

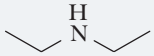
SOLUTION

Both molecules can participate in hydrogen bonding. However, the *t*-butyl group is larger and bulkier, making it more difficult for the molecules of *t*-butylamine to hydrogen bond to each other.

See problems 10.18–10.20

PROBLEM 10.4

Account for the fact that diethylamine has a higher boiling point than diethyl ether.

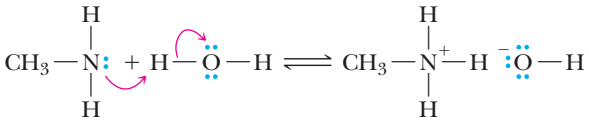


Diethylamine
bp 55 °C

Diethyl ether
bp 34.6 °C

10.4 What Are the Acid–Base Properties of Amines?

Like ammonia, all amines are weak bases, and aqueous solutions of amines are basic. The following acid–base reaction between an amine and water is written using curved arrows to emphasize that, in this proton-transfer reaction, the unshared pair of electrons on nitrogen forms a new covalent bond with hydrogen and displaces hydroxide ion:



Methylamine

Methylammonium hydroxide

The equilibrium constant for the reaction of an amine with water, K_{eq}, has the following form, illustrated for the reaction of methylamine with water to give methylammonium hydroxide:

$$K_{eq} = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2][H_2O]}$$

Because the concentration of water in dilute solutions of methylamine in water is essentially a constant ($[H_2O] = 55.5$ mol/L), it is combined with K_{eq} in a new constant called a *base ionization constant*, K_b. The value of K_b for methylamine is 4.37×10^{-4} ($pK_b = 3.36$):

$$K_b = K_{eq}[H_2O] = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]} = 4.37 \times 10^{-4} \quad pK_b = 3.36$$

It is also common to discuss the basicity of amines by referring to the acid ionization constant of the corresponding conjugate acid, as illustrated for the ionization of the methylammonium ion:

$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$$

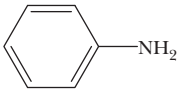
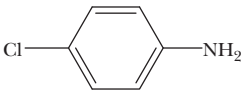
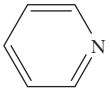
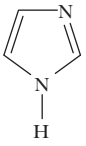
$$K_a = \frac{[CH_3NH_2][H_3O^+]}{[CH_3NH_3^+]} = 2.29 \times 10^{-11} \quad pK_a = 10.64$$

Values of pK_a and pK_b for any acid–conjugate base pair are related by the equation

$$pK_a + pK_b = 14.00$$

Values of pK_a and pK_b for selected amines are given in Table 10.2.

TABLE 10.2 Base Strengths (pK_b) of Selected Amines and Acid Strengths (pK_a) of Their Conjugate Acids*

Amine	Structure	pK_b	pK_a
Ammonia	NH_3	4.74	9.26
Primary Amines			
methylamine	CH_3NH_2	3.36	10.64
ethylamine	$CH_3CH_2NH_2$	3.19	10.81
cyclohexylamine	$C_6H_{11}NH_2$	3.34	10.66
Secondary Amines			
dimethylamine	$(CH_3)_2NH$	3.27	10.73
diethylamine	$(CH_3CH_2)_2NH$	3.02	10.98
Tertiary Amines			
trimethylamine	$(CH_3)_3N$	4.19	9.81
triethylamine	$(CH_3CH_2)_3N$	3.25	10.75
Aromatic Amines			
aniline		9.37	4.63
4-methylaniline (*p*-toluidine)		8.92	5.08
4-chloroaniline		9.85	4.15
4-nitroaniline		13.0	1.0
Heterocyclic Aromatic Amines			
pyridine		8.75	5.25
imidazole		7.05	6.95

*For each amine, $pK_a + pK_b = 14.00$.

EXAMPLE 10.5

Predict the position of equilibrium for this acid–base reaction:

$$CH_3NH_2 + CH_3COOH \rightleftharpoons CH_3NH_3^+ + CH_3COO^-$$

STRATEGY

Use the approach we developed in Section 2.4 to predict the position of equilibrium in acid–base reactions. Equilibrium favors reaction of the stronger acid and stronger base to form the weaker acid and the weaker base. It is helpful to remember that even though ammonium ions are positively charged, they are much weaker acids than carboxylic acids.

SOLUTION

In this reaction, equilibrium favors the formation of methylammonium ion and acetate ion, which are the weaker acid and base, respectively:

$$CH_3NH_2 + CH_3COOH \rightleftharpoons CH_3NH_3^+ + CH_3COO^-$$

$pK_a = 4.76$ $\quad$ $pK_a = 10.64$

Stronger base — Stronger acid — Weaker acid — Weaker base

See problem 10.25

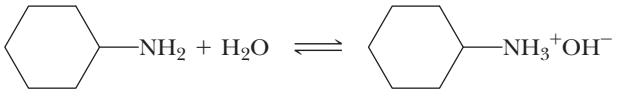
PROBLEM 10.5

Predict the position of equilibrium for this acid–base reaction:

$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$$

Given information such as that in Table 10.2, we can make the following generalizations about the acid–base properties of the various classes of amines:

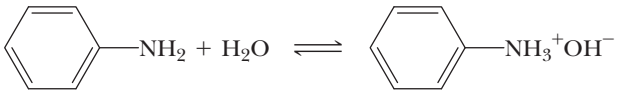
1. All aliphatic amines have about the same base strength, pK_b 3.0–4.0, and are slightly stronger bases than ammonia.
2. Aromatic amines and heterocyclic aromatic amines are considerably weaker bases than are aliphatic amines. Compare, for example, values of pK_b for aniline and cyclohexylamine:



Cyclohexylamine — Cyclohexylammonium hydroxide

pK_b = 3.34
$K_b = 4.5 \times 10^{-4}$

the lower the value of pK_b, the stronger the base

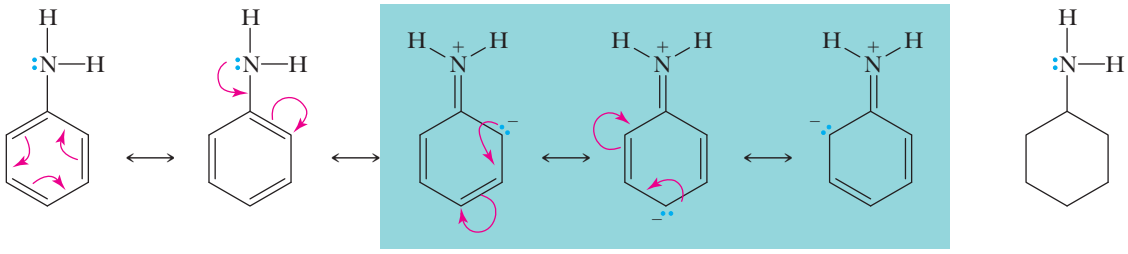


Aniline — Anilinium hydroxide

pK_b = 9.37
$K_b = 4.3 \times 10^{-10}$

The base ionization constant for aniline is smaller (the larger the value of pK_b, the weaker is the base) than that for cyclohexylamine by a factor of 10^6.

Aromatic amines are weaker bases than are aliphatic amines because of the resonance interaction of the unshared pair on nitrogen with the pi system of the aromatic ring. Because no such resonance interaction is possible for an alkylamine, the electron pair on its nitrogen is more available for reaction with an acid:

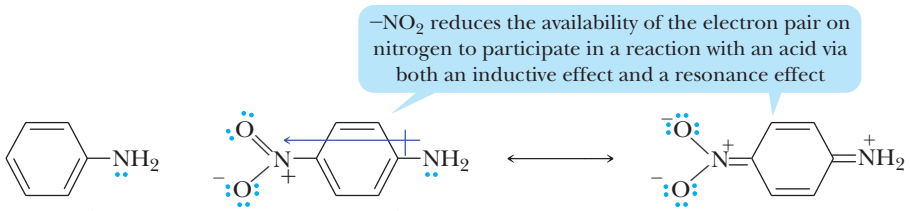


Two Kekulé structures

Interaction of the electron pair on nitrogen with the pi system of the aromatic ring reduces the availability of the electron pair to participate in a reaction with an acid

No resonance is possible with alkylamines

3. Electron-withdrawing groups such as halogen, nitro, and carbonyl decrease the basicity of substituted aromatic amines by decreasing the availability of the electron pair on nitrogen:



Aniline
pK_b 9.37

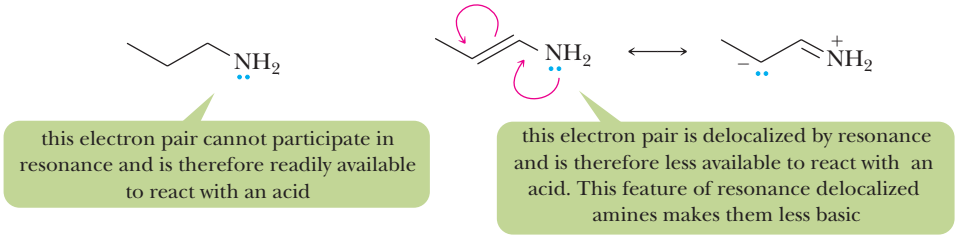
4-Nitroaniline
pK_b 13.0

Recall from Section 9.8B that these same substituents increase the acidity of phenols.

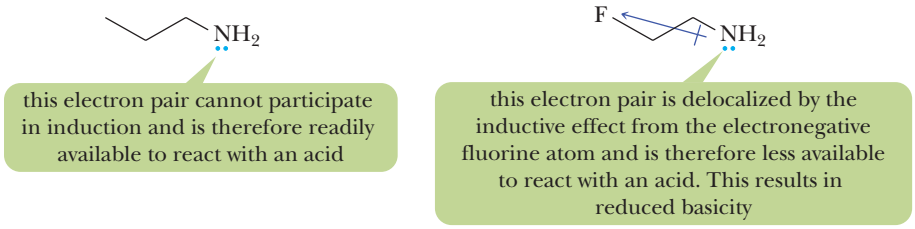
HOW TO 10.1 Predict the Relative Basicity of Amines

The basicity of an amine depends on the ability of its nitrogen atom to donate its lone pair of electrons in an acid–base reaction. When assessing an electron pair's availability, look for the following possibilities:

(a) Resonance contribution



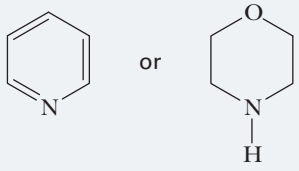
(b) Induction



EXAMPLE 10.6

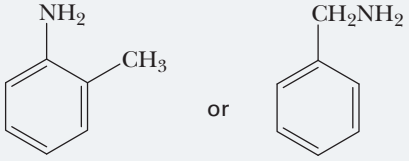
Select the stronger base in each pair of amines:

(a)



(A) (B)

(b)



(C) (D)

See problems 10.21–10.25, 10.29–10.31

STRATEGY

Use Table 10.2 to compare values of pK_b. Alternatively, look for resonance, inductive, or steric effects that might enhance or diminish the availability of a lone pair on the nitrogen of each molecule.

SOLUTION

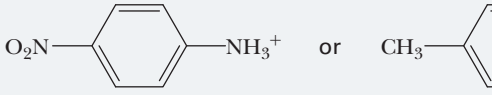
(a) Morpholine (B) is the stronger base (pK_b 5.79). It has a basicity comparable to that of secondary aliphatic amines. Pyridine (A), a heterocyclic aromatic amine (pK_b 8.75), is considerably less basic than aliphatic amines.

(b) Benzylamine (D), a primary aliphatic amine, is the stronger base (pK_b 3–4). *o*-Toluidine (C), an aromatic amine, is the weaker base (pK_b 9–10). In the absence of Table 10.2, one can see that the electron pair on nitrogen in *o*-toluidine can participate in resonance with the benzene ring, while there are no resonance possibilities in benzylamine. This results in *o*-toluidine's electron pair being less available for reaction with an acid.

PROBLEM 10.6

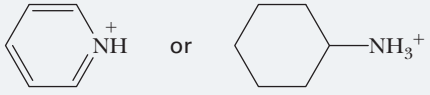
Select the stronger acid from each pair of ions:

(a)



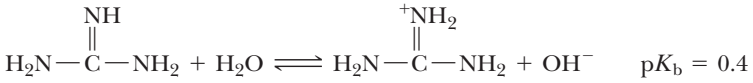
(A) (B)

(b)



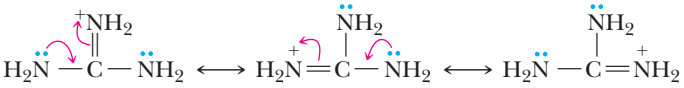
(C) (D)

Guanidine (pK_b 0.4) is the strongest base among neutral compounds:



Guanidine — Guanidinium ion

The remarkable basicity of guanidine is attributed to the fact that the positive charge on the guanidinium ion is delocalized equally over the three nitrogen atoms, as shown by these three equivalent contributing structures:

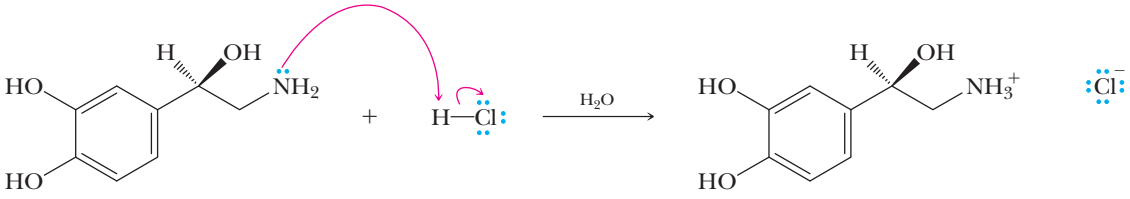


Three equivalent contributing structures

Hence, the guanidinium ion is a highly stable cation. The presence of a guanidine group on the side chain of the amino acid arginine accounts for the basicity of its side chain (Section 18.2A).

10.5 What Are the Reactions of Amines with Acids?

Amines, whether soluble or insoluble in water, react quantitatively with strong acids to form water-soluble salts, as illustrated by the reaction of (*R*)-norepinephrine (noradrenaline) with aqueous HCl to form a hydrochloride salt:



(*R*)-Norepinephrine
(only slightly soluble in water)

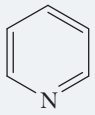
(*R*)-Norepinephrine hydrochloride
(a water-soluble salt)

Norepinephrine, secreted by the medulla of the adrenal gland, is a neurotransmitter. It has been suggested that it is a neurotransmitter in those areas of the brain that mediate emotional behavior.

EXAMPLE 10.7

Complete each acid–base reaction, and name the salt formed:

(a) $(CH_3CH_2)_2NH + HCl \longrightarrow$

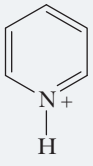
(b)  $+ CH_3COOH \longrightarrow$

STRATEGY

Identify the acidic proton in the acid. The amine nitrogen will abstract this proton to form the ammonium salt. In naming an ammonium salt, replace the ending *-amine* (or aniline, pyridine, or the like) by *-ammonium* (or *anilinium*, *pyridinium*, or the like) and add the name of the anion (chloride, acetate, and so on).

SOLUTION

(a) $(CH_3CH_2)_2NH_2^+Cl^-$
Diethylammonium chloride

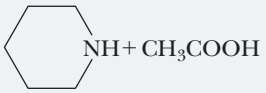
(b)  CH_3COO^-
Pyridinium acetate

See problems 10.25, 10.29, 10.31, 10.32, 10.35

PROBLEM 10.7

Complete each acid–base reaction and name the salt formed:

(a) $(CH_3CH_2)_3N + HCl \longrightarrow$

(b)  $+ CH_3COOH \longrightarrow$

The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds. Shown in Figure 10.2 is a flowchart for the separation of aniline from anisole. Note that aniline is recovered from its salt by treatment with NaOH.

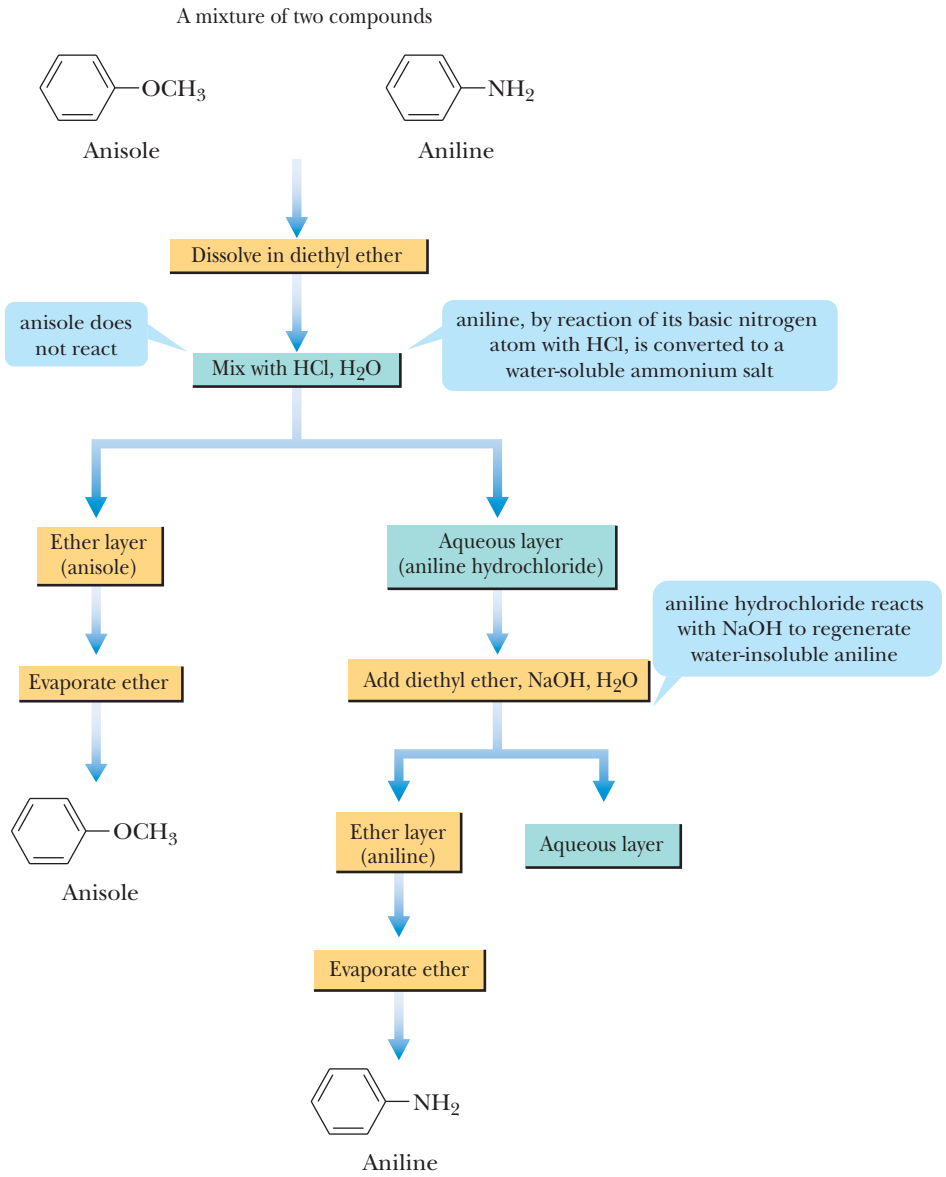
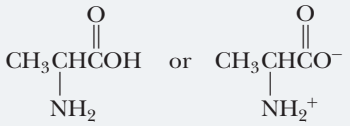


FIGURE 10.2
Separation and purification of an amine and a neutral compound.

EXAMPLE 10.8

Following are two structural formulas for alanine (2-aminopropanoic acid), one of the building blocks of proteins (Chapter 18):



(A) (B)

Is alanine better represented by structural formula (A) or structural formula (B)?

STRATEGY

Begin by considering the acidity and basicity of the functional groups within alanine. How might they react if they were part of separate molecules?

SOLUTION

Structural formula (A) contains both an amino group (a base) and a carboxyl group (an acid). Proton transfer from the stronger acid (—COOH) to the stronger base ($—NH_2$) gives an internal salt; therefore, (B) is the better representation for alanine. Within the field of amino acid chemistry, the internal salt represented by (B) is called a **zwitterion** (Chapter 18).

PROBLEM 10.8

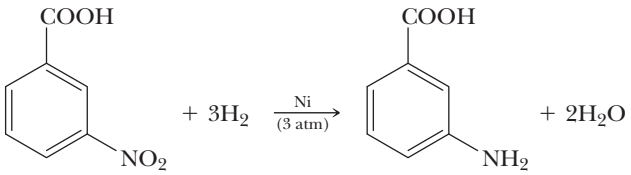
As shown in Example 10.8, alanine is better represented as an internal salt. Suppose that the internal salt is dissolved in water.

(a) In what way would you expect the structure of alanine in aqueous solution to change if concentrated HCl were added to adjust the pH of the solution to 2.0?

(b) In what way would you expect the structure of alanine in aqueous solution to change if concentrated NaOH were added to bring the pH of the solution to 12.0?

10.6 How Are Arylamines Synthesized?

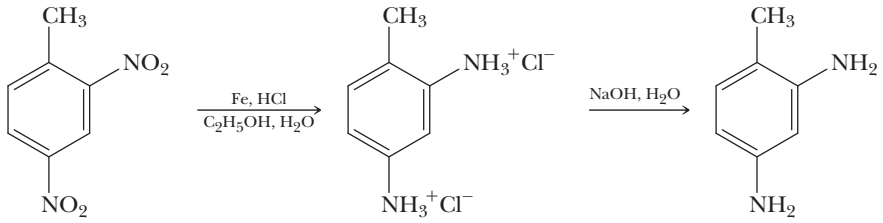
As we have already seen (Section 9.6B), the nitration of an aromatic ring introduces a NO_2 group. A particular value of nitration is the fact that the resulting nitro group can be reduced to a primary amino group, $—NH_2$, by hydrogenation in the presence of a transition metal catalyst such as nickel, palladium, or platinum:



3-Nitrobenzoic acid 3-Aminobenzoic acid

This method has the potential disadvantage that other susceptible groups, such as a carbon–carbon double bond, and the carbonyl group of an aldehyde or ketone, may also be reduced. Note that neither the —COOH nor the aromatic ring is reduced under these conditions.

Alternatively, a nitro group can be reduced to a primary amino group by a metal in acid:

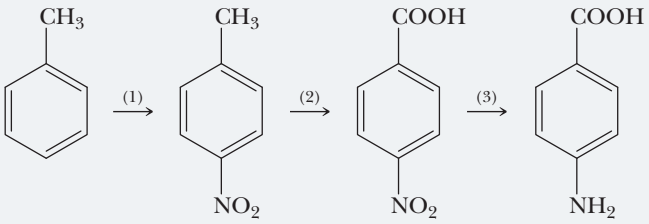


2,4-Dinitrotoluene 2,4-Diaminotoluene

The most commonly used metal-reducing agents are iron, zinc, and tin in dilute HCl. When reduced by this method, the amine is obtained as a salt, which is then treated with a strong base to liberate the free amine.

EXAMPLE 10.9

Show the reagents that will bring about each step in this conversion of toluene to 4-aminobenzoic acid:



Toluene

4-Amino-benzoic acid

STRATEGY

Use a combination of reactions from this chapter and previous chapters. Remember to consider the regioselectivity of reactions.

SOLUTION

STEP 1: Nitration of toluene, using nitric acid/sulfuric acid (Section 9.6B), followed by separation of the ortho and para isomers.

STEP 2: Oxidation of the benzylic carbon, using chromic acid (Section 9.4).

STEP 3: Reduction of the nitro group, either using H_2 in the presence of a transition metal catalyst or using Fe, Sn, or Zn in the presence of aqueous HCl (Section 10.6).

See problems 10.36–10.44

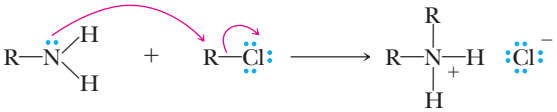
PROBLEM 10.9

Show how you can use the same set of steps in Example 10.9, but in a different order, to convert toluene to 3-aminobenzoic acid.

10.7 How Do Amines Act as Nucleophiles?

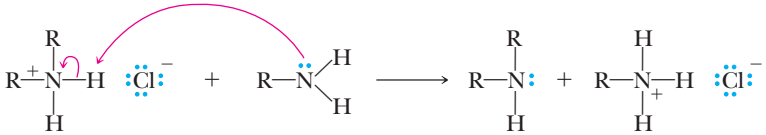
In Chapter 7, we learned that amines are moderate nucleophiles (Table 7.2) due to the presence of a lone pair of electrons on the nitrogen atom. Therefore, they should undergo nucleophilic substitution reactions with haloalkanes and other compounds containing a good leaving group (Section 7.5).

Step 1: **Reaction of an electrophile and a nucleophile to form a new covalent bond.** The nitrogen atom of an amine displaces chlorine in a haloalkane to yield an ammonium chloride ion.



(a nucleophile) (an electrophile)

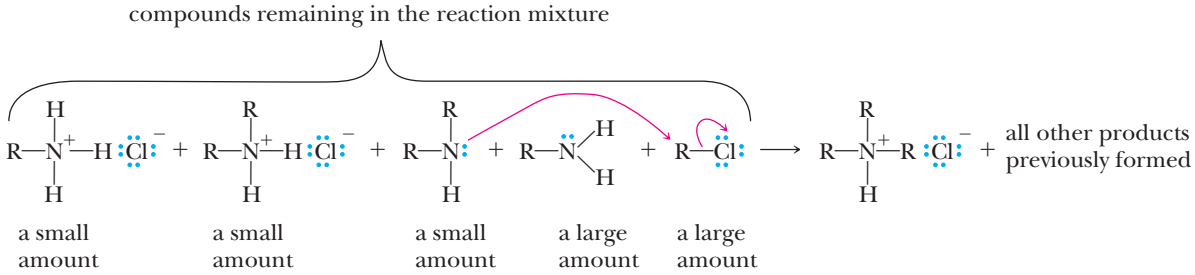
Step 2: **Take a proton away.** At the beginning of this reaction, when only a few product molecules are formed, plenty of amine starting material (a weak base) remains to react with the hydrogen of the ammonium salt to yield a secondary amine and another ammonium chloride ion.



unreacted starting material

Remaining in the reaction mixture are some initial product, $R_2NH_2^+ Cl^-$, some of the secondary amine, R_2NH, and lots of unreacted starting material and haloalkane.

Step 3: **Reaction of an electrophile and a nucleophile to form a new covalent bond.** The secondary amine is also a nucleophile, and because only a few of the initial R—Cl molecules have reacted at this early stage of the reaction, there are plenty left to react with either amine now in the reaction mixture.



The process can continue to give one other nitrogen-based product, the quaternary ammonium salt. The final composition of the reaction will consist of varying ratios of RNH_2, R_2NH, R_3N, and $R_4N^+Cl^-$. Because the ratio of products is difficult to control or predict, we avoid using an amine (or ammonia) as a nucleophile in nucleophilic aliphatic substitution reactions.

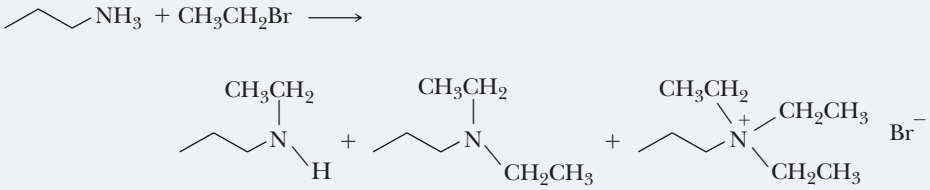
EXAMPLE 10.10

Determine all possible nitrogen-based products that can be formed in the following reaction:

STRATEGY

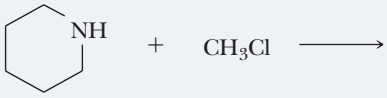
Keep in mind that the reaction of amines with haloalkanes often results in multiple nitrogen-based products with one or more alkyl groups from the haloalkane forming a bond with the nitrogen atom of the original amine.

SOLUTION



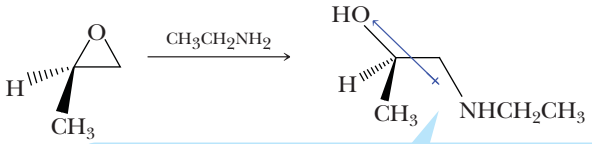
PROBLEM 10.10

Determine all possible nitrogen-based products that can be formed in the following reaction:



Although the use of amines in nucleophilic aliphatic substitution is problematic due to the mixtures of products that result, recall from Section 8.4C that amines are excellent nucleophiles for ring opening reactions of epoxides. This is because the inductive effect

of the hydroxyl oxygen atom diminishes the nucleophilicity of the nitrogen atom in the product:



the electron-withdrawing inductive effect of oxygen reduces the nucleophilicity of the nitrogen lone pair of electrons

SUMMARY OF KEY QUESTIONS

10.1 What Are Amines?

- Amines are derivatives of ammonia (NH_3) in which one or more hydrogens are replaced by alkyl or aryl groups.
- Amines are classified as **primary**, **secondary**, or **tertiary**, depending on the number of hydrogen atoms of ammonia replaced by alkyl or aryl groups.
- In an **aliphatic amine**, all carbon atoms bonded to nitrogen are derived from alkyl groups.
- In an **aromatic amine**, one or more of the groups bonded to nitrogen are aryl groups.
- A **heterocyclic amine** is an amine in which the nitrogen atom is part of a ring.
- A **heterocyclic aromatic amine** is an amine in which the nitrogen atom is part of an aromatic ring.

10.2 How Are Amines Named?

- In systematic nomenclature, aliphatic amines are named **alkanamines**.
- In the common system of nomenclature, aliphatic amines are named **alkylamines**; the alkyl groups are listed in alphabetical order in one word ending in the suffix *-amine*.
- An ion containing nitrogen bonded to four alkyl or aryl groups is named as a **quaternary ammonium ion**.

10.3 What Are the Characteristic Physical Properties of Amines?

- Amines are polar compounds, and primary and secondary amines associate by intermolecular hydrogen bonding.
- Because an N—H----N hydrogen bond is weaker than an O—H----O hydrogen bond, amines have lower boiling points than alcohols of comparable molecular weight and structure.
- All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight.

10.4 What Are the Acid–Base Properties of Amines?

- Amines are weak bases, and aqueous solutions of amines are basic. The **base ionization constant** for an amine in water is given the symbol K_b.
- It is also common to discuss the acid–base properties of amines by reference to the **acid ionization constant**, K_a, for the conjugate acid of the amine.
- Acid and base ionization constants for an amine in water are related by the equation $pK_a + pK_b = 14.0$.

10.5 What Are the Reactions of Amines with Acids?

- Amines react quantitatively with strong acids to form water-soluble salts.
- The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds.

10.6 How Are Arylamines Synthesized?

- Arylamines can be made by reducing the nitro group on a benzene ring.

10.7 How Do Amines Act as Nucleophiles?

- Amines are moderate nucleophiles and can participate in **nucleophilic aliphatic substitution** reactions.
- Reaction of ammonia or amines with haloalkanes often results in multiple products in varying ratios.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. An amine with an $-NH_2$ group bonded to a tertiary carbon is classified as a tertiary amine. (10.1)
2. The reaction of an amine with a haloalkane initially results in an ammonium halide salt. (10.7)
3. An efficient way to make diethylamine is to react ammonia with two equivalents of chloroethane. (10.7)
4. The IUPAC name of $CH_3CH_2CH_2CH_2NHCH_3$ is 2-pentanamine. (10.2)
5. An amino group can be directly added to a benzene ring via an electrophilic aromatic substitution reaction. (10.6)
6. A tertiary amine would be expected to be more water soluble than a secondary amine of the same molecular formula. (10.3)
7. The pK_b of an amine can be determined from the pK_a of its conjugate acid. (10.4)
8. The lower the value of pK_b, the stronger the base. (10.4)
9. The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds. (10.5)
10. Aromatic amines are more basic than aliphatic amines. (10.4)
11. A heterocyclic aromatic amine must contain one or more aryl groups directly bonded to nitrogen outside of the ring. (10.1)
12. Guanidine is a strong neutral base because its conjugate acid is resonance stabilized. (10.4)
13. Ammonia is a slightly weaker base than most aliphatic amines. (10.4)
14. An amino group forms stronger hydrogen bonds than a hydroxy group. (10.3)
15. A heterocyclic amine must contain a ring and a nitrogen atom as a member of the ring. (10.1)
16. An electron-withdrawing group in an amine decreases its basicity. (10.4)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) T (3) F (4) F (5) F (6) F (7) T (8) T (9) T (10) F (11) F (12) T (13) T (14) F (15) T (16) T

KEY REACTIONS

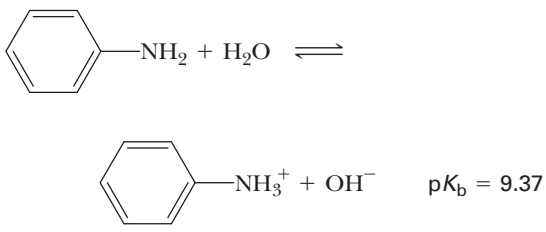
1. Basicity of Aliphatic Amines (Section 10.4)

Most aliphatic amines have comparable basicities (pK_b 3.0–4.0) and are slightly stronger bases than ammonia:

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + OH^- \qquad pK_b = 3.36$$

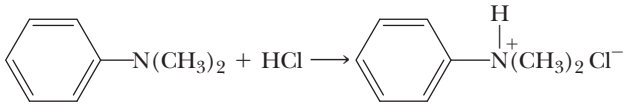
2. Basicity of Aromatic Amines (Section 10.4)

Aromatic amines (pK_b 9.0–10.0) are considerably weaker bases than are aliphatic amines. Resonance stabilization from interaction of the unshared electron pair on nitrogen with the pi system of the aromatic ring decreases the availability of that electron pair for reaction with an acid. Substitution on the ring by electron-withdrawing groups decreases the basicity of the $-NH_2$ group:



3. Reaction of Amines with Strong Acids (Section 10.5)

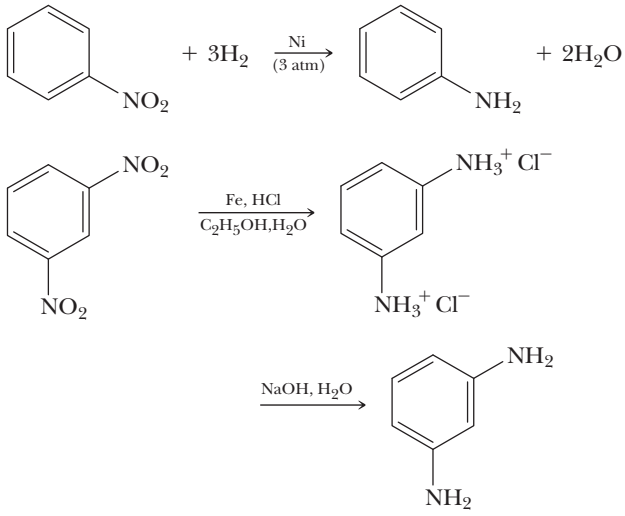
All amines react quantitatively with strong acids to form water-soluble salts:



Insoluble in water — A water-soluble salt

4. Reduction of an Aromatic NO_2 Group (Section 10.6)

An NO_2 group, for example on an aromatic ring, can be reduced to an amino group by catalytic hydrogenation or by treatment with a metal and hydrochloric acid, followed by a strong base to liberate the free amine:



PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

Structure and Nomenclature

10.11 Draw a structural formula for each amine: **(See Examples 10.2, 10.3)**

(a) (*R*)-2-Butanamine
(b) 1-Octanamine
(c) 2,2-Dimethyl-1-propanamine
(d) 1,5-Pentanediamine
(e) 2-Bromoaniline
(f) Tributylamine
(g) *N,N*-Dimethylaniline
(h) Benzylamine
(i) *tert*-Butylamine
(j) *N*-Ethylcyclohexanamine
(k) Diphenylamine
(l) Isobutylamine

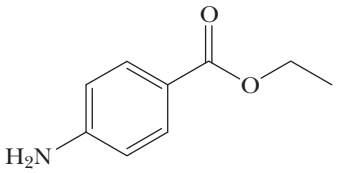
10.12 Draw a structural formula for each amine: **(See Examples 10.2, 10.3)**

(a) 4-Aminobutanoic acid
(b) 2-Aminoethanol (ethanolamine)
(c) 2-Aminobenzoic acid
(d) (*S*)-2-Aminopropanoic acid (alanine)
(e) 4-Aminobutanal
(f) 4-Amino-2-butanone

10.13 Draw examples of 1°, 2°, and 3° amines that contain at least four sp^3 hybridized carbon atoms. Using the same criterion, provide examples of 1°, 2°, and 3° alcohols. How does the classification system differ between the two functional groups? **(See Example 10.1)**

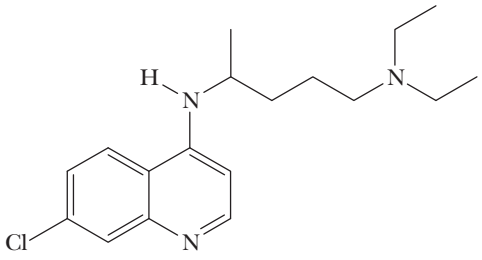
***10.14** Classify each amino group as primary, secondary, or tertiary and as aliphatic or aromatic: **(See Example 10.1)**

(a)



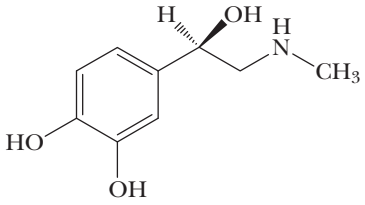
Benzocaine
(a topical anesthetic)

(b)

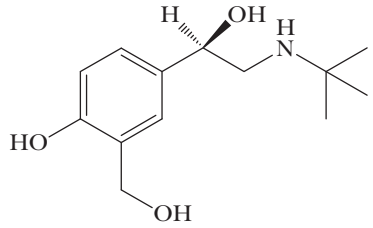


Chloroquine
(a drug for the treatment of malaria)

***10.15** Epinephrine is a hormone secreted by the adrenal medulla. Among epinephrine's actions, it is a bronchodilator. Albuterol, sold under several trade names, including Proventil® and Salbumol®, is one of the most effective and widely prescribed antiasthma drugs. The R enantiomer of albuterol is 68 times more effective in the treatment of asthma than the S enantiomer. **(See Example 10.1)**



(*R*)-Epinephrine
(Adrenaline)



(*R*)-Albuterol

(a) Classify each amino group as primary, secondary, or tertiary.
(b) List the similarities and differences between the structural formulas of these compounds.

10.16 There are eight constitutional isomers with the molecular formula $C_4H_{11}N$. Name and draw structural formulas for each. Classify each amine as primary, secondary, or tertiary. **(See Examples 10.1–10.3)**

10.17 Draw a structural formula for each compound with the given molecular formula: **(See Example 10.3)**

(a) A 2° arylamine, C_7H_9N
(b) A 3° arylamine, $C_8H_{11}N$
(c) A 1° aliphatic amine, C_7H_9N
(d) A chiral 1° amine, $C_4H_{11}N$
(e) A 3° heterocyclic amine, $C_5H_{11}N$
(f) A trisubstituted 1° arylamine, $C_9H_{13}N$
(g) A chiral quaternary ammonium salt, $C_9H_{22}NCl$

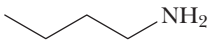
Physical Properties

10.18 Propylamine, ethylmethylamine, and trimethylamine are constitutional isomers with the molecular formula C_3H_9N: **(See Example 10.4)**

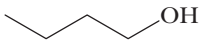
$CH_3CH_2CH_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3N$
bp 48 °C	bp 37 °C	bp 3 °C
Propylamine	Ethylmethylamine	Trimethylamine

Account for the fact that trimethylamine has the lowest boiling point of the three, and propylamine has the highest.

10.19 Account for the fact that 1-butanamine has a lower boiling point than 1-butanol: **(See Example 10.4)**

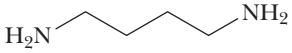


bp 78 °C
1-Butanamine



bp 117 °C
1-Butanol

***10.20** Account for the fact that putrescine, a foul-smelling compound produced by rotting flesh, ceases to smell upon treatment with two equivalents of HCl: **(See Example 10.4)**

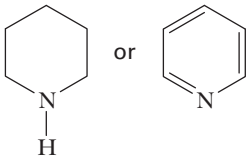


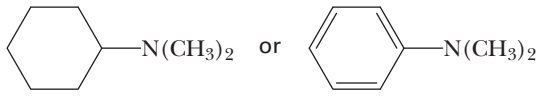
1,4-Butanediamine
(Putrescine)

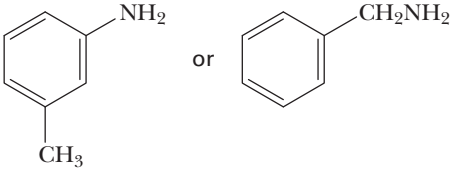
Basicity of Amines

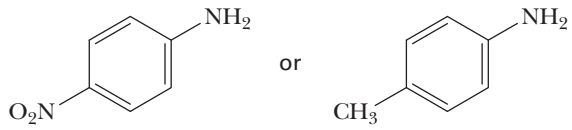
10.21 Account for the fact that amines are more basic than alcohols. **(See Example 10.6)**

10.22 From each pair of compounds, select the stronger base: **(See Example 10.6)**

(a) 

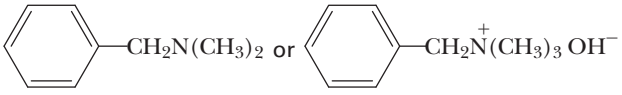
(b) 

(c) 

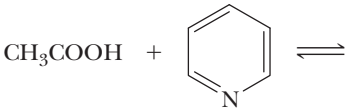
(d) 

10.23 Account for the fact that substitution of a nitro group makes an aromatic amine a weaker base, but makes a phenol a stronger acid. For example, 4-nitroaniline is a weaker base than aniline, but 4-nitrophenol is a stronger acid than phenol. **(See Example 10.6)**

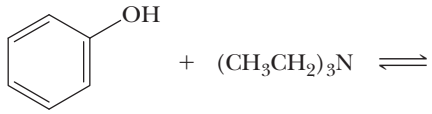
10.24 Select the stronger base in this pair of compounds: **(See Example 10.6)**



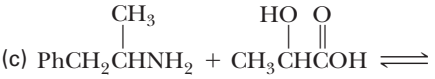
10.25 Complete the following acid–base reactions and predict the position of equilibrium for each. Justify your prediction by citing values of pK_a for the stronger and weaker acid in each equilibrium. For values of acid ionization constants, consult Table 2.2 (pK_a's of some inorganic and organic acids), Table 8.2 (pK_a's of alcohols), Section 9.8B (acidity of phenols), and Table 10.2 (base strengths of amines). Where no ionization constants are given, make the best estimate from aforementioned tables and section. **(See Examples 10.5–10.7)**

(a) 

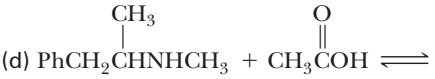
Acetic acid Pyridine

(b) 

Phenol Triethylamine

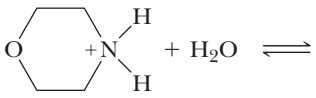
(c) 

1-Phenyl-2-propanamine (Amphetamine) 2-Hydroxypropanoic acid (Lactic acid)

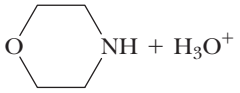
(d) 

Methamphetamine Acetic acid

10.26 The pK_a of the morpholinium ion is 8.33:



Morpholinium ion



pK_a=8.33

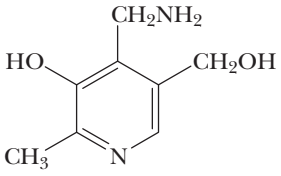
Morpholine

(a) Calculate the ratio of morpholine to morpholinium ion in aqueous solution at p*H* 7.0.
(b) At what p*H* are the concentrations of morpholine and morpholinium ion equal?

***10.27** The pK_b of amphetamine (Example 10.2e) is approximately 3.2. Calculate the ratio of amphetamine to its conjugate acid at p*H* 7.4, the p*H* of blood plasma.

10.28 Calculate the ratio of amphetamine to its conjugate acid at p*H* 1.0, such as might be present in stomach acid.

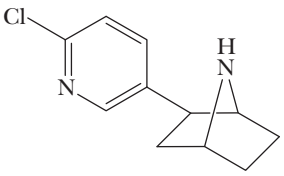
***10.29** Following is a structural formula of pyridoxamine, one form of vitamin B_6: **(See Examples 10.6, 10.7)**



Pyridoxamine
(Vitamin B_6)

(a) Which nitrogen atom of pyridoxamine is the stronger base?
(b) Draw the structural formula of the hydrochloride salt formed when pyridoxamine is treated with one mole of HCl.

***10.30** Epibatidine, a colorless oil isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*, has several times the analgesic potency of morphine. It is the first chlorine-containing, nonopioid (nonmorphine-like in structure) analgesic ever isolated from a natural source: **(See Example 10.6)**



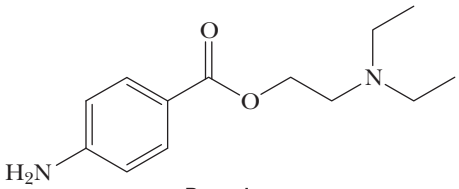
Epibatidine

Stephen J. Krasemann/Photo Researchers

Poison arrow frog.

(a) Which of the two nitrogen atoms of epibatidine is the more basic?
(b) Mark all stereocenters in this molecule.

***10.31** Procaine was one of the first local anesthetics for infiltration and regional anesthesia: **(See Examples 10.6, 10.7)**

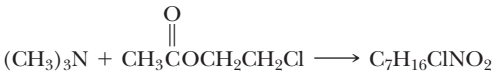


Procaine

The hydrochloride salt of procaine is marketed as Novocaine®.

(a) Which nitrogen atom of procaine is the stronger base?
(b) Draw the formula of the salt formed by treating procaine with one mole of HCl.
(c) Is procaine chiral? Would a solution of Novocaine in water be optically active or optically inactive?

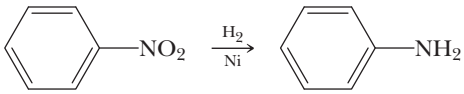
***10.32** Treatment of trimethylamine with 2-chloroethyl acetate gives the neurotransmitter acetylcholine as its chloride salt: **(See Example 10.7)**



Acetylcholine chloride

Propose a structural formula for this quaternary ammonium salt and a mechanism for its formation.

10.33 Aniline is prepared by the catalytic reduction of nitrobenzene:

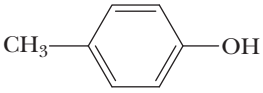


Devise a chemical procedure based on the basicity of aniline to separate it from any unreacted nitrobenzene.

10.34 Suppose that you have a mixture of the following three compounds:

4-Nitrotoluene
(*p*-Nitrotoluene)

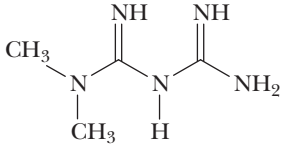
4-Methylaniline
(*p*-Toluidine)



4-Methylphenol
(*p*-Cresol)

Devise a chemical procedure based on their relative acidity or basicity to separate and isolate each in pure form.

***10.35** Following is a structural formula for metformin, the hydrochloride salt of which is marketed as the antidiabetic Glucophage®: **(See Example 10.7)**



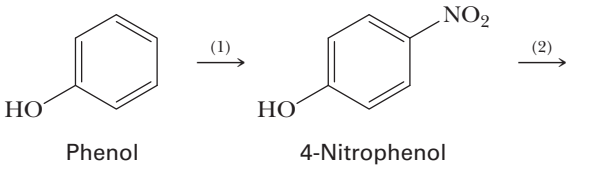
Metformin

Metformin was introduced into clinical medicine in the United States in 1995 for the treatment of type 2 diabetes. More than 25 million prescriptions for this drug were written in 2000, making it the most commonly prescribed brand-name diabetes medication in the nation.

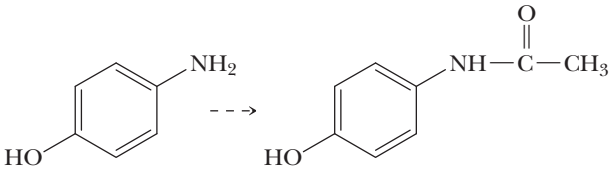
(a) Draw the structural formula for Glucophage®.
(b) Would you predict Glucophage® to be soluble or insoluble in water? Soluble or insoluble in blood plasma? Would you predict it to be soluble or insoluble in diethyl ether? In dichloromethane? Explain your reasoning.

Synthesis

***10.36** 4-Aminophenol is a building block in the synthesis of the analgesic acetaminophen. Show how this building block can be synthesized in two steps from phenol (in Chapter 15, we will see how to complete the synthesis of acetaminophen): **(See Example 10.9)**

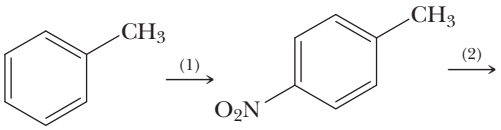


Phenol 4-Nitrophenol

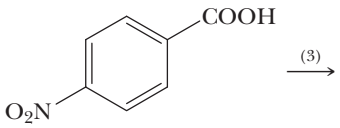


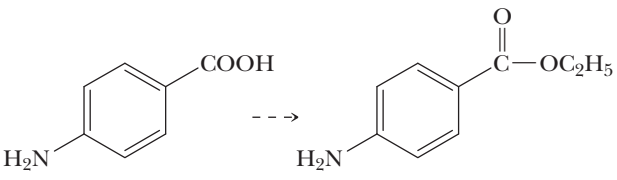
4-Aminophenol Acetaminophen

***10.37** 4-Aminobenzoic acid is a building block in the synthesis of the topical anesthetic benzocaine. Show how this building block can be synthesized in three steps from toluene (in Chapter 14, we will see how to complete the synthesis of benzocaine): **(See Example 10.9)**



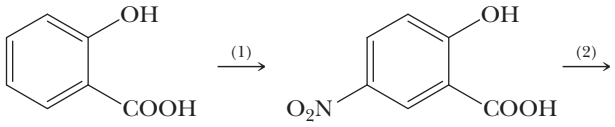
Toluene



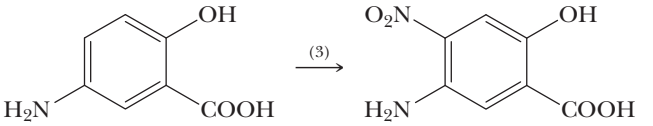


4-Aminobenzoic acid Ethyl 4-aminobenzoate (Benzocaine)

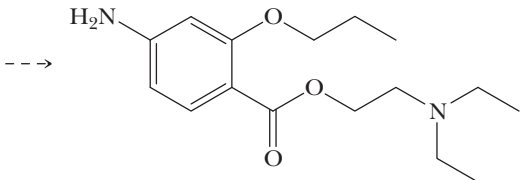
***10.38** The compound 4-amino-5-nitrosalicylic acid is one of the building blocks needed for the synthesis of propoxycaine, one of the family of "caine" anesthetics. Some other members of this family of local anesthetics are procaine (Novocaine®), lidocaine (Xylocaine®), and mepivicaine (Carbocaine®). 4-Amino-5-nitrosalicylic acid is synthesized from salicylic acid in three steps: **(See Example 10.9)**



Salicylic acid



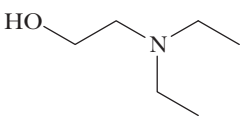
4-Amino-5-nitrosalicylic acid



Propoxycaine

Show reagents that will bring about the synthesis of 4-amino-5-nitrosalicylic acid.

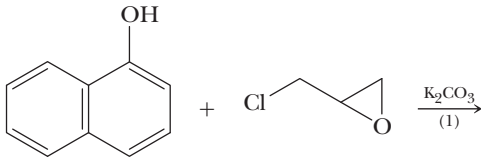
***10.39** A second building block for the synthesis of propoxycaine is 2-diethylaminoethanol: **(See Example 10.10)**



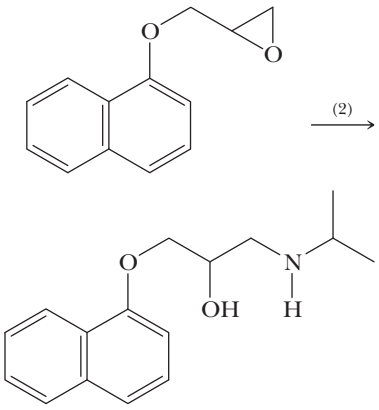
2-Diethylaminoethanol

Show how this compound can be prepared from ethylene oxide and diethylamine.

***10.40** Following is a two-step synthesis of the antihypertensive drug propranolol, a so-called beta blocker with vasodilating action: **(See Example 10.10)**



1-Naphthol Epichlorohydrin



Propranolol
(Cardinol)

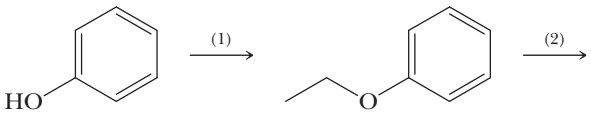
Propranolol and other beta blockers have received enormous clinical attention because of their effectiveness in treating hypertension (high blood pressure), migraine headaches, glaucoma, ischemic heart disease, and certain cardiac arrhythmias. The hydrochloride salt of propranolol has been marketed under at least 30 brand names, one of which is Cardinol®. (Note the "card-" part of the name, after *cardiac*.)

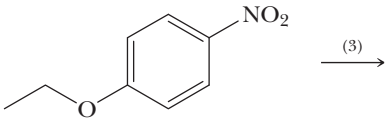
(a) What is the function of potassium carbonate, K_2CO_3, in Step 1? Propose a mechanism for the formation of the new oxygen–carbon bond in this step.

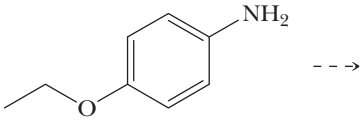
(b) Name the amine used to bring about Step 2, and propose a mechanism for this step.

(c) Is propranolol chiral? If so, how many stereoisomers are possible for it?

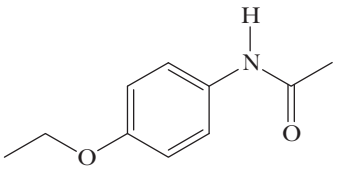
***10.41** The compound 4-ethoxyaniline, a building block of the over-the-counter analgesic phenacetin, is synthesized in three steps from phenol: **(See Example 10.9)**







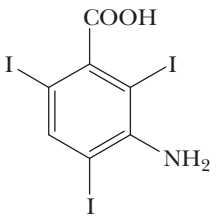
4-Ethoxyaniline



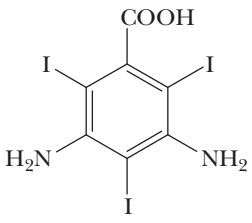
Phenacetin

Show reagents for each step of the synthesis of 4-ethoxyaniline. (In Chapter 14, we will see how to complete this synthesis.)

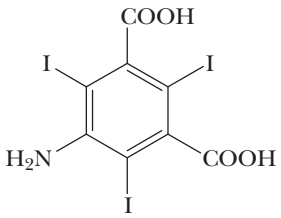
***10.42** Radiopaque imaging agents are substances administered either orally or intravenously that absorb X rays more strongly than body material does. One of the best known of these agents is barium sulfate, the key ingredient in the "barium cocktail" used for imaging of the gastrointestinal tract. Among other X-ray imaging agents are the so-called triiodoaromatics. You can get some idea of the kinds of imaging for which they are used from the following selection of trade names: Angiografin®, Gastrografin, Cardiografin, Cholografin, Renografin, and Urografin®. The most common of the triiodoaromatics are derivatives of these three triiodobenzenecarboxylic acids: **(See Example 10.9)**



3-Amino-2,4,6-triiodobenzoic acid

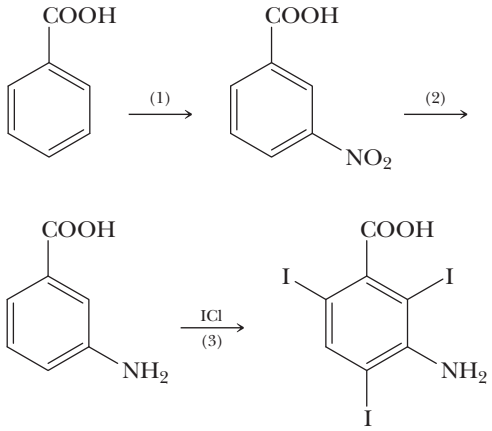


3,5-Diamino-2,4,6-triiodobenzoic acid



5-Amino-2,4,6-triiodoisophthalic acid

3-Amino-2,4,6-triiodobenzoic acid is synthesized from benzoic acid in three steps:

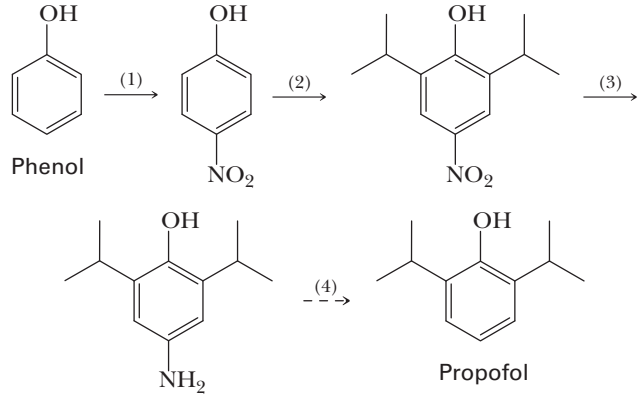


3-Amino-benzoic acid

3-Amino-2,4,6-triiodobenzoic acid

(a) Show reagents for Steps (1) and (2).
(b) Iodine monochloride, ICl, a black crystalline solid with a melting point of 27.2°C and a boiling point of 97°C, is prepared by mixing equimolar amounts of I_2 and Cl_2. Propose a mechanism for the iodination of 3-aminobenzoic acid by this reagent.
(c) Show how to prepare 3,5-diamino-2,4,6-triiodobenzoic acid from benzoic acid.
(d) Show how to prepare 5-amino-2,4,6-triiodoisophthalic acid from isophthalic acid (1,3-benzenedicarboxylic acid).

***10.43** The intravenous anesthetic propofol is synthesized in four steps from phenol: **(See Example 10.9)**



Phenol

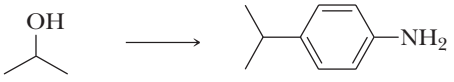
4-Amino-2,6-diisopropylphenol

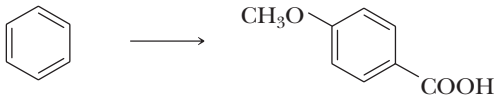
Propofol

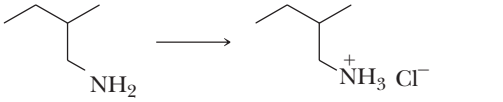
Show reagents to bring about steps 1–3.

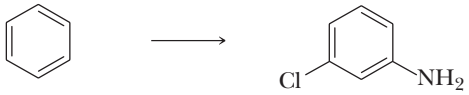
CHEMICAL TRANSFORMATIONS

10.44 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.* **(See Example 10.9)**

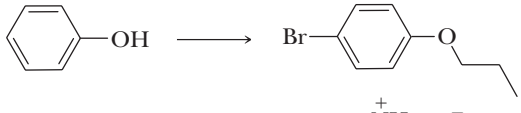
(a) 

(b) 

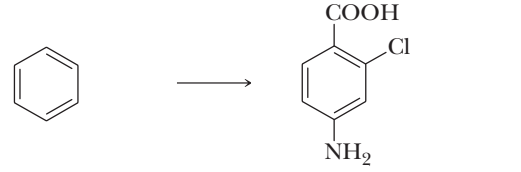
(c) 

(d) 

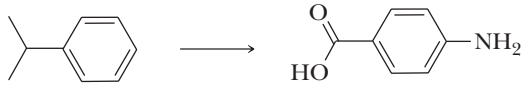
(e) 

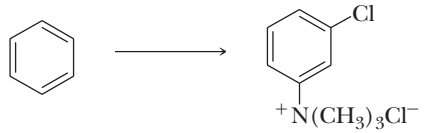
(f) 

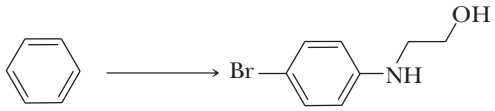
(g) 

(h) 

(i) 

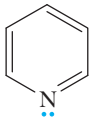
(j) 

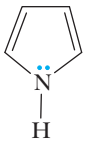
(k) 

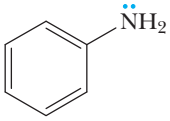
(l) 

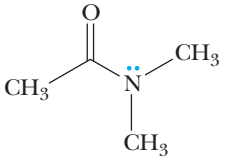
LOOKING AHEAD

10.45 State the hybridization of the nitrogen atom in each of the following compounds:

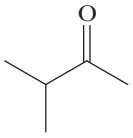
(a) 

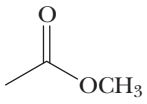
(b) 

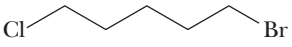
(c) 

(d) 

10.46 Amines can act as nucleophiles. For each of the following molecules, circle the most likely atom that would be attacked by the nitrogen of an amine:

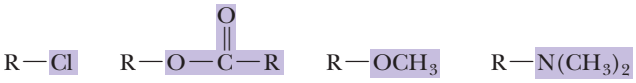
(a) 

(b) 

(c) 

10.47 Draw a Lewis structure for a molecule with the formula C_3H_7N that does not contain a ring or an alkene (a carbon–carbon double bond).

10.48 Rank the following leaving groups in order from best to worst:



GROUP LEARNING ACTIVITIES

10.49 Discuss why $-NH_2$ is a stronger base than —OH. Are both bases strong enough to quantitatively (100%) abstract the hydrogen from a terminal alkyne? Why or why not?

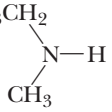
10.50 Take turns listing all of the factors that affect the basicity of an atom in an organic molecule. Then do the same for acidity, nucleophilicity, and leaving group ability. Which factors are common to all four properties? Take turns providing molecules that are good or strong examples of each (e.g., a strong base, a good nucleophile, etc.). Then do the same for weak examples of each.

PUTTING IT TOGETHER

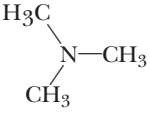
The following problems bring together concepts and material from Chapters 7–10. Although the focus may be on these chapters, the problems will also build on concepts discussed throughout the text thus far.

Choose the best answer for each of the following questions.

1. Arrange the following amines from lowest to highest boiling point.

A 

B 

C 

(a) **A, B, C** (b) **C, B, A** (c) **B, C, A**
(d) **B, A, C** (e) **C, A, B**

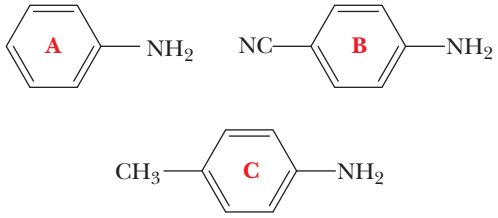
2. Which of the following statements is true regarding the following two molecules?

(a) Both **A** and **B** are aromatic.
(b) Both **A** and **B** are aliphatic amines.
(c) The nitrogen atoms in **A** and **B** are both sp^3 hybridized.
(d) **B** is more basic than **A**.
(e) Both **A** and **B** are planar molecules.

3. Which series of reagents can be used to achieve the following transformation?

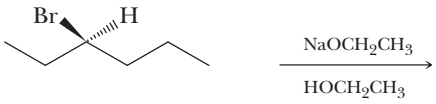
(a) 1. HBr 2. H_2SO_4
(b) 1. H_2SO_4, H_2O 2. PCC
(c) 1. HCl 2. $SOCl_2$
(d) 1. H_3PO_4, H_2O 2. H_2CrO_4
(e) More than one of these will achieve the transformation.

4. Arrange the following from strongest to weakest base.



(a) **A, B, C** (b) **B, C, A** (c) **C, A, B** (d) **A, C, B** (e) **B, A, C**

5. How many products are possible from the following elimination reaction?



(a) one (b) two (c) three (d) four (e) six

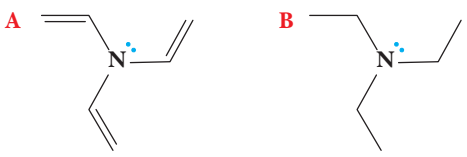
6. Which series of reagents can be used to achieve the following transformation?

(a) 1) HCl 2) RCO_3H
(b) 1) $SOCl_2$ 2) RCO_3H
(c) 1) Na 2) RCO_3H
(d) 1) H_3PO_4 2) RCO_3H
(e) 1) H_2CrO_4 2) RCO_3H

7. Consider the following situation: An ether solution containing phenol and a neutral compound is extracted with 30% sodium bicarbonate. Next the ether solution is extracted with 30% NaOH. Finally, the ether solution is extracted with distilled water. Which solution contains the phenol?

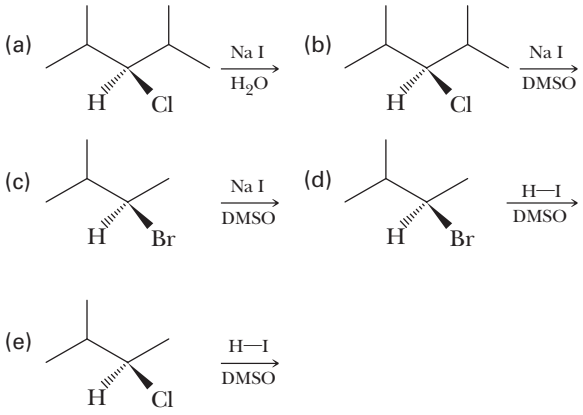
(a) The 30% sodium bicarbonate solution.
(b) The 30% NaOH solution.
(c) The ether.
(d) The distilled water.
(e) Not enough information to determine.

8. Which of the following statements is true concerning the following two molecules?

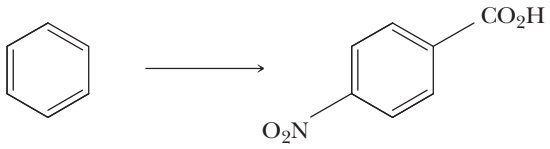


(a) Both are aromatic.
(b) Only one molecule is an amine.
(c) **B** is more polar than **A**.
(d) **A** is more basic than **B**.
(e) All of these statements are true.

9. Which combination of reagents would be most likely to undergo an S_N2 reaction?

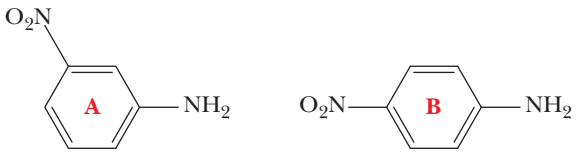


10. Which series of reagents can be used to achieve the following transformation?

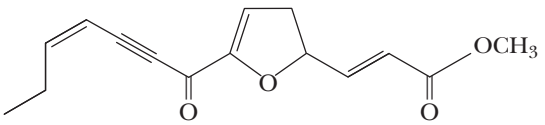


(a) 1) $CH_3Br/FeBr_3$
2) H_2SO_4/HNO_3
3) $H_2SO_4/K_2Cr_2O_4$
(b) 1) H_2SO_4/HNO_3
2) $H_2SO_4/K_2Cr_2O_4$
3) $CH_3Br/FeBr_3$
(c) 1) $H_2SO_4/K_2Cr_2O_4$
2) $CH_3Br/FeBr_3$
3) H_2SO_4/HNO_3
(d) 1) $CH_3Br/FeBr_3$
2) $H_2SO_4/K_2Cr_2O_4$
3) H_2SO_4/HNO_3
(e) 1) H_2SO_4/HNO_3
2) $CH_3Br/FeBr_3$
3) $H_2SO_4/K_2Cr_2O_4$

11. Determine which aryl amine (**A** or **B**) is more basic and provide a rationale for your determination.



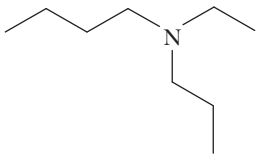
12. Answer the questions that follow regarding the compound Wyerone, which is obtained from fava beans (*Vicia faba*) and has been found to possess antifungal properties.

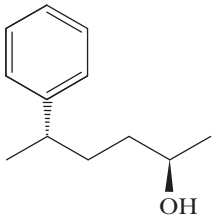


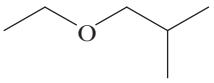
Wyerone

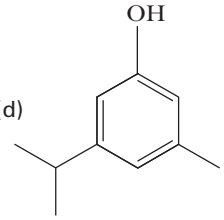
(a) Would you expect the compound to be soluble in water?
(b) How many stereoisomers exist for the compound shown?
(c) Is the molecule chiral?
(d) How many equivalents of Br_2 in CH_2Cl_2 would Wyerone be expected to react with?

13. Provide IUPAC names for the following compounds.

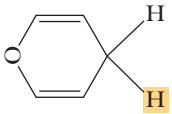
(a) 

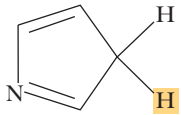
(b) 

(c) 

(d) 

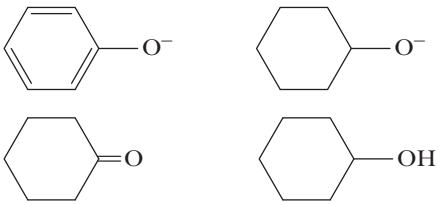
14. Determine whether highlighted proton **A** or **B** is more acidic and provide a rationale for your selection.

(a) 

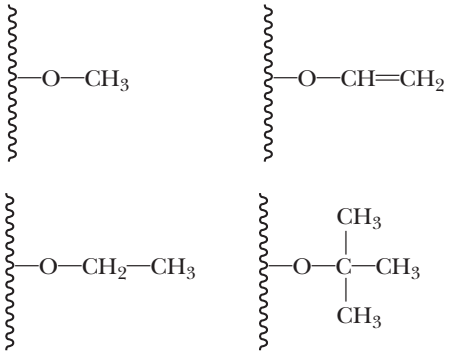
(b) 

15. Select the answer that best fits each description and provide an explanation for your decision.

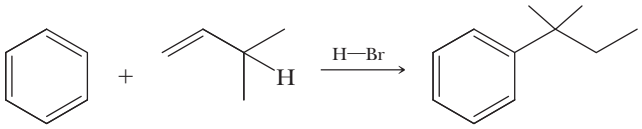
(a) The best nucleophile



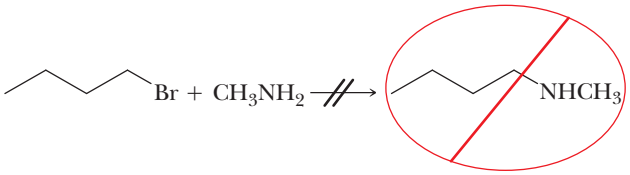
(b) The best leaving group



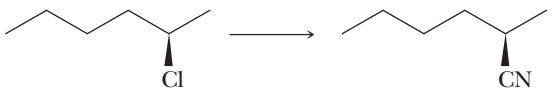
16. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.



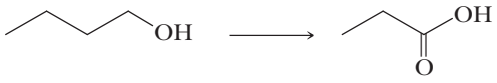
17. When the following nucleophilic substitution reaction was performed, the major product was found to possess the molecular formula $C_{13}H_{30}N$ rather than $C_5H_{13}N$, the formula of the desired product shown below. Provide the structure of the major product and explain why it is formed over the desired product.

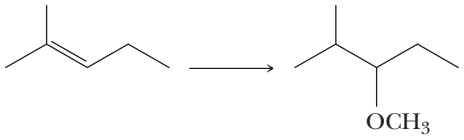


18. Complete the following chemical transformations.

(a) 

This enantiomer as the *only* product

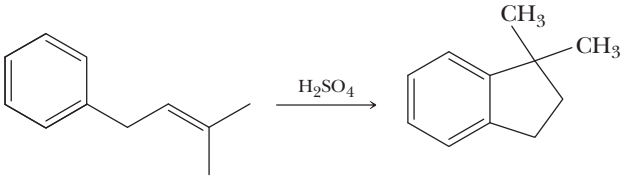
(b) 

(c) 

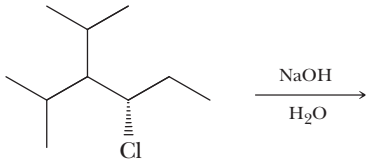
(racemic)

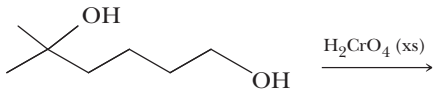
(d) 

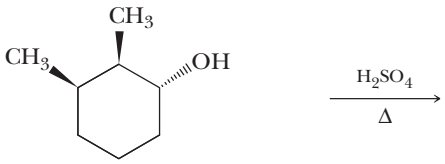
19. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.

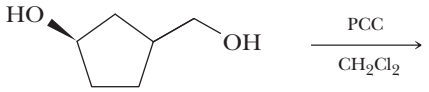


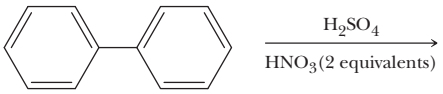
20. Predict the major product or products of each of the following reactions. Be sure to consider stereochemistry in your answers.

(a) 

(b) 

(c) 

(d) 

(e) 

21. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.