Amines are compounds in which one or more of the hydrogens of ammonia \((\text{NH}_3)\) have been replaced by an alkyl group. Amines are among some of the most abundant compounds in the biological world. We will appreciate their importance in Chapter 23, when we look at amino acids and proteins; in Chapter 24, when we study how enzymes catalyze chemical reactions; in Chapter 25, when we investigate the ways in which coenzymes—compounds derived from vitamins—help enzymes catalyze chemical reactions; in Chapter 27, when we study nucleic acids (DNA and RNA); and in Chapter 30, when we take a look at how drugs are discovered and designed.

Amines are also exceedingly important compounds to organic chemists, far too important to leave until the end of a course in organic chemistry. We have, therefore, already studied many aspects of amines and their chemistry. For example, we have seen that the nitrogen in amines is \(sp^3\) hybridized and the lone pair resides in an empty \(sp^3\) orbital (Section 2.8). We also have examined the physical properties of amines—their hydrogen bonding properties, boiling points, and solubilities (Section 2.9). In Section 2.7, we learned how amines are named. Most important, we have seen that the lone-pair electrons of the nitrogen atom cause amines to react as bases, sharing their lone pair with a proton, and as nucleophiles, sharing their lone pair with an atom other than a proton.

\[
\text{R—} \overset{\sim}{\text{NH}}_2 + \overset{\sim}{\text{H}} \text{Br} \rightarrow \overset{\sim}{\text{H—}} \overset{\sim}{\text{NH}}_3 + \overset{\sim}{\text{Br}}^-
\]

\[
\text{R—} \overset{\sim}{\text{NH}}_2 + \overset{\sim}{\text{CH}}_2 \text{—Br} \rightarrow \overset{\sim}{\text{R—}} \overset{\sim}{\text{NH}}_2 \overset{\sim}{\text{—CH}}_3 + \overset{\sim}{\text{Br}}^-
\]

In this chapter, we will revisit some of these topics and look at some aspects of amines and their chemistry that we have not discussed previously.
Some amines are **heterocyclic compounds** (or **heterocycles**)—cyclic compounds in which one or more of the atoms of the ring are heteroatoms. A **heteroatom** is an atom other than carbon. The name comes from the Greek word *heteros*, which means “different.” A variety of atoms, such as N, O, S, Se, P, Si, B, and As, can be incorporated into ring structures.

Heterocycles are an extraordinarily important class of compounds, making up more than half of all known organic compounds. Almost all the compounds we know as drugs, most vitamins, and many other natural products are heterocycles. In this chapter, we will consider the most prevalent heterocyclic compounds—the ones that contain the heteroatoms N, O, and S.

A **natural product** is a compound synthesized by a plant or an animal. **Alkaloids** are natural products that contain one or more nitrogen heteroatoms and are found in the leaves, bark, roots, or seeds of plants. Examples include caffeine (found in tea leaves, coffee beans, and cola nuts) and nicotine (found in tobacco leaves). Morphine is an alkaloid obtained from opium, the juice derived from a species of poppy. Morphine is 50 times stronger than aspirin as an analgesic, but it is addictive and suppresses respiration. Heroin is a synthetic compound that is made by acetylating morphine (Section 30.3).

Two other heterocycles are Valium®, a synthetic tranquilizer, and serotonin, a neurotransmitter. Serotonin is responsible for, among other things, the feeling of having had enough to eat. When food is ingested, brain neurons are signaled to release serotonin. A once widely used diet drug (actually a combination of two drugs, fenfluramine and phentermine), popularly known as fen/phen, works by causing brain neurons to release extra serotonin (Chapter 16, p. 622). After finding that many of those who took fenfluramine had abnormal echocardiograms due to heart valve problems, the Food and Drug Administration asked the manufacturer of these diet drugs to withdraw the products. There is some evidence that faulty metabolism of serotonin plays a role in bipolar affective disorder.

### 21.1 More About Nomenclature

In Section 2.7, we saw that amines are classified as primary, secondary, or tertiary, depending on whether one, two, or three hydrogens of ammonia, respectively, have been replaced by an alkyl group. We also saw that amines have both common and systematic names. Common names are obtained by citing the names of the alkyl substituents...
(in alphabetical order) that have replaced the hydrogens of ammonia. Systematic names employ “amine” as a functional group suffix.

A saturated cyclic amine—a cyclic amine without any double bonds—can be named as a cycloalkane, using the prefix “aza” to denote the nitrogen atom. There are, however, other acceptable names. Some of the more commonly used names are shown here. Notice that heterocyclic rings are numbered so that the heteroatom has the lowest possible number.

Heterocycles with oxygen and sulfur heteroatoms are named similarly. The prefix for oxygen is “oxa” and that for sulfur is “thia.”

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Prefix</th>
<th>Heteroatom</th>
</tr>
</thead>
<tbody>
<tr>
<td>azacyclopentane</td>
<td>oxacyclopentane</td>
<td>O</td>
</tr>
<tr>
<td>azetidine</td>
<td>oxacyclobutane</td>
<td>S</td>
</tr>
<tr>
<td>3-methylpyrrolidine</td>
<td>oxacyclopentane</td>
<td>N</td>
</tr>
<tr>
<td>2-methylpiperidine</td>
<td>oxacyclopentane</td>
<td>N</td>
</tr>
<tr>
<td>N-ethylazacyclopentane</td>
<td>oxacyclopentane</td>
<td>N</td>
</tr>
</tbody>
</table>

PROBLEM 1

Name the following compounds:

a. \[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\]

b. \[
\begin{array}{c}
\text{CH}_2\text{CH}_3 \\
\end{array}
\]

c. \[
\begin{array}{c}
\text{OH} \\
\end{array}
\]

d. \[
\begin{array}{c}
\text{SH} \\
\end{array}
\]

e. \[
\begin{array}{c}
\text{CH}_3 \\
\end{array}
\]

f. \[
\begin{array}{c}
\text{O} \\
\text{CH}_2\text{CH}_3 \\
\end{array}
\]

21.2 Amine Inversion

The lone-pair electrons on nitrogen allow an amine to turn “inside out” rapidly at room temperature. This is called **amine inversion**. One way to picture amine inversion is to compare it to an umbrella that turns inside out in a windstorm.
The lone pair is required for inversion: Quaternary ammonium ions—ions with four bonds to nitrogen and hence no lone pair—do not invert.

Notice that amine inversion takes place through a transition state in which the \( sp^3 \) nitrogen becomes an \( sp^2 \) nitrogen. The three groups bonded to the \( sp^2 \) nitrogen are coplanar in the transition state with bond angles of 120°, and the lone pair is in a \( p \) orbital. The “inverted” and “non-inverted” amine molecules are enantiomers, but they cannot be separated because amine inversion is rapid. The energy required for amine inversion is approximately 25 kcal/mol (or 6 kJ/mol), about twice the amount of energy required for rotation about a carbon–carbon single bond, but still low enough to allow the enantiomers to interconvert rapidly at room temperature.

### 21.3 More About the Acid–Base Properties of Amines

Amines are the most common organic bases. We have seen that ammonium ions have \( pK_a \) values of about 11 (Section 1.17) and that anilinium ions have \( pK_a \) values of about 5 (Sections 7.10 and 16.5). The greater acidity of anilinium ions compared with ammonium ions is due to the greater stability of their conjugate bases as a result of electron delocalization. Amines have very high \( pK_a \) values. For example, the \( pK_a \) of methylamine is 40.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+ & \quad pK_a = 10.8 \\
\text{CH}_3\text{NH}_2^+ & \quad pK_a = 10.9 \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_3^+ & \quad pK_a = 11.1 \\
\text{CH}_3\text{CH}_2\text{NH}_3^+ & \quad pK_a = 4.58 \\
\text{CH}_3\text{CH}_2\text{NH}_3^+ & \quad pK_a = 5.07 \\
\text{CH}_3\text{NH}_2 & \quad pK_a = 40
\end{align*}
\]

Saturated heterocycles containing five or more atoms have physical and chemical properties typical of acyclic compounds that contain the same heteroatom. For example, pyrrolidine, piperidine, and morpholine are typical secondary amines, and \( N \)-methylpyrrolidine and quinuclidine are typical tertiary amines. The conjugate acids of these amines have \( pK_a \) values expected for ammonium ions. We have seen that the basicity of amines allows them to be easily separated from other organic compounds (Chapter 1, Problems 70 and 71).

### PROBLEM 2◆

Why is the \( pK_a \) of the conjugate acid of morpholine significantly lower than the \( pK_a \) of the conjugate acid of piperidine?
Section 21.4 Reactions of Amines

The lone pair on the nitrogen of an amine causes it to be nucleophilic as well as basic. We have seen amines act as nucleophiles in a number of different kinds of reactions: in nucleophilic substitution reactions—reactions that alkylate the amine (Section 10.4)—such as

\[
\text{CH}_3\text{CH}_2\text{Br} + \text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{NH}_2\text{CH}_3 \xrightarrow{\text{Br}^-} \text{CH}_3\text{CH}_2\text{NHCH}_3 + \text{HBr}
\]

in nucleophilic acyl substitution reactions—reactions that acylate the amine (Sections 17.8, 17.9, and 17.10)—for example,

\[
\text{CH}_3\text{C} = \text{O} + 2\text{CH}_3\text{NH}_2 \rightarrow \text{CH}_3\text{C} = \text{O}\text{CH}_3 + \text{CH}_3\text{NH}_2\text{Cl}^-
\]

in nucleophilic addition–elimination reactions—the reactions of aldehydes and ketones with primary amines to form imines and with secondary amines to form enamines (Section 18.6)—such as

\[
\text{CH}_3\text{CH} = \text{CHCH}_3 + \text{H}_2\text{NCH}_2\text{H}_2\text{O} \xrightarrow{\text{catalytic}} \text{CH}_3\text{C} = \text{CHCH}_3 + \text{H}_2\text{O}
\]

\[
\text{CH}_3\text{CH} = \text{CHCH}_3 + \text{HNCH}_2\text{H}_2\text{O} \xrightarrow{\text{catalytic}} \text{CH}_3\text{C} = \text{CHCH}_3 + \text{H}_2\text{O}
\]

and in conjugate addition reactions (Section 18.13)—for instance,
We have seen that primary arylamines react with nitrous acid to form stable arenediazonium salts (Section 16.12). Arenediazonium salts are useful to synthetic chemists because the diazonium group can be replaced by a wide variety of nucleophiles. This reaction allows a wider variety of substituted benzenes to be prepared than can be prepared solely from electrophilic aromatic substitution reactions.

Amines are much less reactive than other compounds with electron-withdrawing groups bonded to \(sp^3\) hybridized carbons, such as alkyl halides, alcohols, and ethers. The relative reactivities of an alkyl fluoride (the least reactive of the alkyl halides), an alcohol, an ether, and an amine can be appreciated by comparing the \(pK_a\) values of the conjugate acids of their leaving groups, recalling that the stronger the base, the weaker is its conjugate acid and the poorer the base is as a leaving group. The leaving group of an amine (\(\text{NH}_2\)) is such a strong base that amines cannot undergo the substitution and elimination reactions that alkyl halides undergo.

**Problem 4**

Why is it that a halide ion such as \(\text{Br}^-\) can react with a protonated primary alcohol, but cannot react with a protonated primary amine?

**Problem 5**

Give the product of each of the following reactions:

a. \[
\begin{array}{c}
\text{O} \\
\text{CCH}_3 \\
\end{array}
\quad + \quad \begin{array}{c}
\text{CH}_3\text{CH}_2\text{NH}_2 \\
\end{array}
\quad \xrightarrow{\text{catalytic } \text{H}^+} \quad \begin{array}{c}
\text{CH}_3\text{CH}_2\text{NH}_3 \\
\end{array}
\]

\begin{array}{c}
\text{most reactive} \\
\text{strongest acid, weakest conjugate base} \\
\text{least reactive} \\
\text{weakest acid, strongest conjugate base} \\
\end{array}

\[
\begin{array}{cccc}
\text{RCH}_2\text{F} & > & \text{RCH}_2\text{OH} & \sim \quad \text{RCH}_2\text{OCH}_3 & > & \text{RCH}_2\text{NH}_2 \\
\text{HF} & \text{H}_2\text{O} & \text{RCH}_2\text{OH} & \text{NH}_3 & \text{least} \\
pK_a = 3.2 & pK_a = 15.7 & pK_a = 15.5 & pK_a = 36 & \text{reactive} \\
\end{array}
\]
21.5 Reactions of Quaternary Ammonium Hydroxides

The leaving group of a quaternary ammonium ion has about the same leaving tendency as a protonated amino group, but it does not have an acidic hydrogen that would protonate a basic reactant. A quaternary ammonium ion, therefore, can undergo a reaction with a strong base. The reaction of a quaternary ammonium ion with hydroxide ion is known as a Hofmann elimination reaction. The leaving group in a Hofmann elimination reaction is a tertiary amine. Because a tertiary amine is only a moderately good leaving group, the reaction requires heat.

A Hofmann elimination reaction is an E2 reaction. Recall that an E2 reaction is a concerted, one-step reaction—the proton and the tertiary amine are removed in the same step (Section 11.1). Very little substitution product is formed.

**mechanism of the Hofmann elimination**

![Mechanism of Hofmann Elimination](image)

**PROBLEM 6**

What is the difference between the reaction that occurs when isopropyltrimethylammonium hydroxide is heated and the reaction that occurs when 2-bromopropane is treated with hydroxide ion?

The carbon to which the tertiary amine is attached is designated as the $\alpha$-carbon, so the adjacent carbon, from which the proton is removed, is called the $\beta$-carbon. (Recall that E2 reactions are also called $\beta$-elimination reactions, since elimination is initiated by removing a proton from the $\beta$-carbon; Section 11.1.) If the quaternary ammonium ion has more than one $\beta$-carbon, the major alkene product is the one obtained by removing a proton from the $\beta$-carbon bonded to the greater number of hydrogens. In the following reaction, the major alkene product is obtained by removing a hydrogen from the $\beta$-carbon bonded to the most hydrogens.
the $\beta$-carbon bonded to three hydrogens, and the minor alkene product results from removing a hydrogen from the $\beta$-carbon bonded to two hydrogens.

In the next reaction, the major alkene product comes from removing a hydrogen from the $\beta$-carbon bonded to two hydrogens, because the other $\beta$-carbon is bonded to only one hydrogen.

**PROBLEM 7**

What are the minor products in the preceding Hofmann elimination reaction?

We saw that in an E2 reaction of an alkyl chloride, alkyl bromide, or alkyl iodide, a hydrogen is removed from the $\beta$-carbon bonded to the *fewest* hydrogens (Zaitsev’s rule; Section 11.2). Now we see that in an E2 reaction of a quaternary ammonium ion, the hydrogen is removed from the $\beta$-carbon bonded to the *most* hydrogens (anti-Zaitsev elimination).

Why do alkyl halides follow Zaitsev’s rule, while quaternary amines violate the rule? When hydroxide ion starts to remove a proton from the alkyl bromide, the bromide ion immediately begins to depart and a transition state with an alkene-like structure results. The proton is removed from the $\beta$-carbon bonded to the fewest hydrogens in order to achieve the most stable alkene-like transition state.

![Diagram of alkene-like and carbanion-like transition states](image)

When, however, hydroxide ion starts to remove a proton from a quaternary ammonium ion, the leaving group does not immediately begin to leave, because a tertiary amine is not as good a leaving group as Cl$^-$, Br$^-$, or I$^-$. As a result, a partial negative charge builds up on the carbon from which the proton is being removed. This gives the transition state a carbanion-like structure rather than an alkene-like structure. By removing a proton from the $\beta$-carbon bonded to the most hydrogens, the most stable carbanion-like transition state is achieved. (Recall from Section 11.2 that primary carbanions are more stable than secondary carbanions, which are more stable than tertiary carbanions.) Steric factors in the Hofmann reaction also favor anti-Zaitsev elimination.
Because the Hofmann elimination reaction occurs in an anti-Zaitsev manner, anti-Zaitsev elimination is also referred to as Hofmann elimination. We have previously seen anti-Zaitsev elimination in the E2 reactions of alkyl fluorides as a result of fluoride ion being a poorer leaving group than chloride, bromide, or iodide ions. As in a Hofmann elimination reaction, the poor leaving group results in a carbanion-like transition state rather than an alkene-like transition state (Section 11.2).

**PROBLEM 8**

Give the major products of each of the following reactions:

a. \( \text{CH}_3\text{CH}_2\text{CH}_2\text{NCH}_3 \xrightarrow{\Delta} \text{CH}_3\text{HO}^- \)

b. \( \text{HO}^- \xrightarrow{\Delta} \)

c. \( \text{HO}^- \xrightarrow{\Delta} \)

d. \( \text{HO}^- \xrightarrow{\Delta} \)

For a quaternary ammonium ion to undergo an elimination reaction, the counterion must be hydroxide ion because a strong base is needed to start the reaction by removing a proton from a \( \beta \)-carbon. Since halide ions are weak bases, quaternary ammonium halides cannot undergo a Hofmann elimination reaction. However, a quaternary ammonium halide can be converted into a quaternary ammonium hydroxide by treating it with silver oxide and water. The silver halide precipitates, and the halide ion is replaced by hydroxide ion. The compound can now undergo an elimination reaction.

\[
2 \text{R}^+\text{N}^-\text{R} + \text{Ag}_2\text{O} + \text{H}_2\text{O} \rightarrow 2 \text{R}^+\text{N}^-\text{R} + 2 \text{AgI} \downarrow
\]

The reaction of an amine with sufficient methyl iodide to convert the amine into a quaternary ammonium iodide is called **exhaustive methylation**. (See Chapter 10, Problem 8.) The reaction is carried out in a basic solution of potassium carbonate, so the amines will be predominantly in their basic forms.

**exhaustive methylation**

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 + \text{CH}_3\text{I} \xrightarrow{\text{excess} \text{K}_2\text{CO}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{NCH}_3\text{I}^-\]

The Hofmann elimination reaction was used by early organic chemists as the last step of a process known as a Hofmann degradation—a method used to identify amines. In a **Hofmann degradation**, an amine is exhaustively methylated with methyl iodide, treated with silver oxide to convert the quaternary ammonium iodide to a quaternary ammonium hydroxide, and then heated to allow it to undergo a Hofmann elimination. Once the alkene is identified, working backwards gives the structure of the amine.
A USEFUL BAD-TASTING COMPOUND

Several practical uses have been found for Bitrex®, a quaternary ammonium salt, because it is one of the most bitter-tasting substances known and is nontoxic. Bitrex® is put on bait to encourage deer to look elsewhere for their food, it is put on the backs of animals to keep them from biting one another, it is put on children’s’ fingers to persuade them to stop sucking their thumbs or biting their fingernails, and it is added to toxic substances to keep them from being ingested accidentally.

PROBLEM 9

Identify the amine in each case.

a. 4-Methyl-2-pentene is obtained from the Hofmann degradation of a primary amine.

b. 2-Methyl-1,3-butadiene is obtained from two successive Hofmann degradations of a secondary amine.

PROBLEM 10 SOLVED

Describe a synthesis for each of the following compounds, using the given starting material and any necessary reagents:

a. \[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \rightarrow \text{CH}_3\text{CH}_2\text{CH}==\text{CH}_2 \]

b. \[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3\text{CH}==\text{CH}_2 \]

SOLUTION TO 10a

Although an amine cannot undergo an elimination reaction, a quaternary ammonium hydroxide can. The amine, therefore, must first be converted into a quaternary ammonium hydroxide. Reaction with excess methyl iodide converts the amine into a quaternary ammonium iodide, and treatment with aqueous silver oxide forms the quaternary ammonium hydroxide. Heat is required for the elimination reaction.

21.6 Phase Transfer Catalysis

A problem organic chemists face in the laboratory is finding a solvent that will dissolve all the reactants needed for a given reaction. For example, if we want cyanide ion to react with 1-bromohexane, we encounter a problem: Sodium cyanide is an ionic compound that is soluble only in water, whereas the alkyl halide is insoluble in water. Therefore, if we mix an aqueous solution of sodium cyanide with a solution of 1-bromohexane in a nonpolar solvent, there will be two distinct phases—an aqueous phase and an organic phase—because the solutions are immiscible. How, then, can sodium cyanide react with the alkyl halide?
Section 21.6 Phase Transfer Catalysis

The two compounds will be able to react with each other if a catalytic amount of a **phase transfer catalyst** is added to the reaction mixture.

The reaction can be represented as:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{C≡N} \overset{?}{\longrightarrow} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C≡N} + \text{Br}^- \]

Quaternary ammonium salts are the most common phase transfer catalysts. However, we saw in Section 12.9 that crown ethers can also be used as phase transfer catalysts.

**phase transfer catalysts**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetrabutylammonium hydrogen sulfate</td>
<td>[\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3]</td>
</tr>
<tr>
<td>hexadecyltrimethylammonium hydrogen sulfate</td>
<td>[\text{CH}_3\text{(CH}<em>2\text{)}</em>{14}\text{CH}_2\text{NCH}_3]</td>
</tr>
<tr>
<td>benzyltriethylammonium hydrogen sulfate</td>
<td>[\text{CH}_2\text{NCH}_2\text{CH}_3]</td>
</tr>
</tbody>
</table>

How does the addition of a phase transfer catalyst allow the reaction of cyanide ion with 1-bromohexane to take place? Because of its nonpolar alkyl groups, the quaternary ammonium salt is soluble in nonpolar solvents, but because of its charge, it is also soluble in water. This means that the quaternary ammonium salt can act as a mediator between the two immiscible phases. When a phase transfer catalyst such as tetrabutylammonium hydrogen sulfate passes into the nonpolar, organic phase, it must carry a counterion with it to balance its positive charge. The counterion can be either its original counterion (hydrogen sulfate) or another ion that is present in the solution (in the reaction under discussion, it will be cyanide ion). Because there is more cyanide ion than hydrogen sulfate ion in the aqueous phase, cyanide ion will more often be the accompanying ion. Once in the organic phase, cyanide ion can react with the alkyl halide. (When hydrogen sulfate is transported into the organic phase, it is unreactive because it is both a weak base and a poor nucleophile.) The quaternary ammonium ion will pass back into the aqueous phase carrying with it either hydrogen sulfate or bromide ion as a counterion. The reaction continues with the phase transfer catalyst shuttling back and forth between the two phases. **Phase transfer catalysis** has been successfully used in a wide variety of organic reactions.
21.7 Oxidation of Amines; The Cope Elimination Reaction

Amines are easily oxidized, sometimes just by being exposed to air. Amines, therefore, are stored as salts (e.g., as amine hydrochlorides), and drugs that contain amino groups are often sold as salts.

Primary amines are oxidized to hydroxylamines, which in turn are oxidized to nitroso compounds, which are oxidized to nitro compounds. Hydrogen peroxide, peroxyacids, and other common oxidizing agents are used to oxidize amines. The oxidation reactions generally take place by mechanisms that involve radicals, so they are not well characterized.

Secondary amines are oxidized to secondary hydroxylamines, and tertiary amines are oxidized to amine oxides.

Amine oxides undergo a reaction similar to the Hofmann elimination reaction, called the Cope elimination reaction. In a Cope elimination reaction, a tertiary amine oxide rather than a quaternary ammonium ion undergoes elimination. The Cope elimination reaction occurs under milder conditions than does a Hofmann elimination reaction.

A strong base is not needed for a Cope elimination because the amine oxide acts as its own base. The Cope elimination, therefore, is an intramolecular E2 reaction and involves syn elimination.

Arthur C. Cope (1909–1966) was born in Indiana. He received a Ph.D. from the University of Wisconsin and was a professor of chemistry at Bryn Mawr College, Columbia University, and MIT.
The major product of the Cope elimination, like that of the Hofmann elimination, is the one obtained by removing a hydrogen from the \( \beta \)-carbon bonded to the greater number of hydrogens.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{NCH}_2\text{CH}_2\text{CH}_3 & \xrightarrow{\Delta} \text{CH}_2=\text{CH}_2 + \text{NCH}_2\text{CH}_2\text{CH}_3 \\
\end{align*}
\]

**PROBLEM 11**

Does the Cope elimination have an alkene-like transition state or a carbanion-like transition state?

**PROBLEM 12**

Give the products that would be obtained by treating the following tertiary amines with hydrogen peroxide followed by heat:

- (a) \( \text{CH}_3\text{NCH}_2\text{CH}_2\text{CH}_3 \)
- (b) \( \text{CH}_3\text{NCH}_2\text{CH}_2\text{CH}_3 \)
- (c) \( \text{CH}_3\text{CH}_2\text{NCH}_2\text{CHCH}_3 \)
- (d) \( \text{NCH}_2\text{CH}_2\text{CH}_3 \)

---

21.8 **Synthesis of Amines**

Because ammonia and amines are good nucleophiles, they readily undergo ionic reactions with alkyl halides. (\( X \) denotes a halogen.)

\[
\begin{align*}
\text{NH}_3 + \text{RCH}_2\text{X} & \rightarrow \text{RCH}_2\text{N}^+\text{X}^- + \text{HX} \\
\text{SN}_2 & \\
\end{align*}
\]

Although these ionic reactions can be used to synthesize amines, the yields are poor because it is difficult to stop the reaction after a single alkylation since ammonia and primary, secondary, and tertiary amines have similar reactivities.

A much better way to prepare a primary amine is by means of a Gabriel synthesis (Section 17.17). This reaction involves alkylating phthalimide and then hydrolyzing the \( N \)-substituted phthalimide.
Primary amines also can be prepared in good yields if azide ion (\(\text{N}_3\)) is used as the nucleophile in anSn2 reaction. The product of the reaction is an alkyl azide, which can be reduced to a primary amine. (See Chapter 10, Problem 9.)

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \text{N}_3 \quad \xrightarrow{\text{NaC}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}═\text{N}═\text{N} \quad \xrightarrow{\text{H}_2} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2
\]

Other reduction reactions also result in the formation of primary amines. For example, the catalytic reduction of a nitrile forms a primary amine. (Recall that a nitrile can be obtained from the reaction of cyanide ion with an alkyl halide.)

Amines are obtained from the reduction of amides with LiAlH4 (Sections 18.5 and 20.1). This method can be used to synthesize primary, secondary, and tertiary amines. The class of amine obtained depends on the number of substituents on the nitrogen atom of the amide.

A primary amine can be obtained from the reaction of an aldehyde or a ketone with excess ammonia in the presence of \(\text{H}_2\) and Raney nickel. Because the imine does not have a substituent other than a hydrogen bonded to the nitrogen, it is relatively unstable, so the amine is obtained by adding \(\text{H}_2\) to the \(\text{C}═\text{N}\) bond as it is formed. This is called reductive amination.

Secondary and tertiary amines can be prepared from imines and enamines by reducing the imine or enamine. Sodium triacetoxyborohydride is a commonly used reducing agent for this reaction.
A primary amine is obtained from the reduction of a nitroalkane, and an arylamine is obtained from the reduction of nitrobenzene.

\[
\text{CH}_2\text{CH}_2\text{NO}_2 + \text{H}_2 \xrightarrow{\text{Pd/C}} \text{CH}_2\text{CH}_2\text{NH}_2
\]

nitroethane

\[
\text{nitrobenzene} + \text{H}_2 \xrightarrow{\text{Pd/C}} \text{aniline}
\]

Excess ammonia must be used when a primary amine is synthesized by reductive amination. What product will be obtained if the reaction is carried out with an excess of the carbonyl compound instead?

**PROBLEM 13**

**21.9 Aromatic Five-Membered-Ring Heterocycles**

**Pyrrole, Furan, and Thiophene**

Pyrrole, furan, and thiophene are five-membered-ring heterocycles. Each has three pairs of delocalized π electrons: Two of the pairs are shown as π bonds, and one pair is shown as a lone pair on the heteroatom. Furan and thiophene have a second lone pair that is not part of the π cloud. These electrons are in an \( sp^2 \) orbital perpendicular to the \( p \) orbitals. Pyrrole, furan, and thiophene are aromatic because they are cyclic and planar, every carbon in the ring has a \( p \) orbital, and the π cloud contains three pairs of π electrons (Sections 15.1 and 15.3).
Pyrrole is an extremely weak base because the electrons shown as a lone pair are part of the π cloud. Therefore, when pyrrole is protonated, its aromaticity is destroyed. Consequently, the conjugate acid of pyrrole is a very strong acid (pK_a = −3.8); that is, it has a strong tendency to lose a proton.

The resonance contributors of pyrrole show that nitrogen donates the electrons depicted as a lone pair into the five-membered ring.

Pyrrolidine—a saturated five-membered-ring heterocyclic amine—has a dipole moment of 1.57 D because the nitrogen atom is electron withdrawing. Pyrrole—an unsaturated five-membered-ring heterocyclic amine—has a slightly larger dipole moment (1.80 D), but as we see from the electrostatic potential maps, the two dipole moments are in opposite directions. (The red areas are on opposite sides of the two molecules.) Apparently, the ability of pyrrole’s nitrogen to donate electrons into the ring by resonance more than makes up for its inductive electron withdrawal (Section 16.3).

In Section 7.6, we saw that the more stable and more nearly equivalent the resonance contributors, the greater is the resonance energy. The resonance energies of pyrrole, furan, and thiophene are not as great as the resonance energies of benzene and the cyclopentadienyl anion, compounds for which the resonance contributors are all equivalent. Thiophene, with the least electronegative heteroatom, has the greatest resonance energy of these five-membered heterocycles; and furan, with the most electronegative heteroatom, has the smallest resonance energy.

**relative resonance energies of some aromatic compounds**

Because pyrrole, furan, and thiophene are aromatic, they undergo electrophilic aromatic substitution preferentially at C-2.
Substitution occurs preferentially at C-2 because the intermediate obtained by attaching a substituent at this position is more stable than the intermediate obtained by attaching a substituent at C-3 (Figure 21.1). Both intermediates have a relatively stable resonance contributor in which all the atoms (except H) have complete octets. The intermediate resulting from C-2 substitution of pyrrole has two additional resonance contributors, each with a positive charge on a secondary allylic carbon. The intermediate resulting from C-3 substitution, however, has only one additional resonance contributor, which has a positive charge on a secondary carbon. This resonance contributor is further destabilized by being adjacent to an electron-withdrawing nitrogen atom, so its predicted stability is less than that of a resonance contributor with a positive charge on a secondary allylic carbon. If both positions adjacent to the heteroatom are occupied, electrophilic substitution will take place at C-3.

Pyrrole, furan, and thiophene are all more reactive than benzene toward electrophilic substitution because they are better able to stabilize the positive charge on the carbocation intermediate, since the lone pair on the heteroatom can donate electrons into the ring by resonance (Figure 21.1).

Relative reactivity toward electrophilic aromatic substitution

\[
\begin{array}{c}
\text{pyrrole} > \text{furan} > \text{thiophene} > \text{benzene}
\end{array}
\]

Furan is not as reactive as pyrrole in electrophilic aromatic substitution reactions. The oxygen of furan is more electronegative than the nitrogen of pyrrole, so the oxygen is not as effective as nitrogen in stabilizing the carbocation. Thiophene is less reactive than furan toward electrophilic substitution because sulfur’s \( \pi \) electrons are in a \( 3p \) orbital, which overlaps less effectively than the \( 2p \) orbital of nitrogen or oxygen with the \( 2p \) orbital of carbon. The electrostatic potential maps illustrate the different electron densities of the three rings.

![Figure 21.1](image-url) Structures of the intermediates that can be formed from the reaction of an electrophile with pyrrole at C-2 and C-3.
The relative reactivities of the five-membered-ring heterocycles are reflected in the Lewis acid required to catalyze a Friedel–Crafts acylation reaction (Section 15.13). Benzene requires AlCl₃, a relatively strong Lewis acid. Thiophene is more reactive than benzene, so it can undergo a Friedel–Crafts reaction using SnCl₄, a weaker Lewis acid. An even weaker Lewis acid, BF₃, can be used when the substrate is furan. Pyrrole is so reactive that an anhydride is used instead of a more reactive acyl chloride, and no catalyst is necessary.

The resonance hybrid of pyrrole indicates that there is a partial positive charge on the nitrogen. Therefore, pyrrole is protonated on C-2 rather than on nitrogen. Remember, a proton is an electrophile and, like other electrophiles, attaches to the C-2 position of pyrrole.

\[
\begin{align*}
\text{phenylethanone} & : \text{CCH}_3 + \text{HCl} \\
\text{2-acetyltiophene} & : \text{CCH}_3 + \text{HCl} \\
\text{2-acetylfuran} & : \text{CCH}_3 + \text{HCl} \\
\text{2-acetylpyrrole} & : \text{CCH}_3 + \text{CH}_3\text{COH}
\end{align*}
\]

Pyrrole is unstable in strongly acidic solutions because once protonated, it can readily polymerize.

Pyrrole is more acidic (\(pK_a \approx 17\)) than the analogous saturated amine (\(pK_a \approx 36\)), because the nitrogen in pyrrole is \(sp^2\) hybridized and is, therefore, more electronegative than the \(sp^3\) nitrogen of a saturated amine (Table 21.1). Pyrrole’s acidity also is increased as a result of its conjugate base being stabilized by electron
Section 21.9  Aromatic Five-Membered-Ring Heterocycles

Delocalization. (Recall that the more stable the base, the stronger is its conjugate acid; Section 1.17).

\[
\begin{align*}
\text{N} & \quad \text{N} \\
pK_a = -17 & \quad pK_a = -36
\end{align*}
\]

**PROBLEM 14**

When pyrrole is added to a dilute solution of D₂SO₄ in D₂O, 2-deuteriopyrrole is formed. Propose a mechanism to account for the formation of this compound.

**PROBLEM 15**

Use resonance contributors to explain why pyrrole is protonated on C-2 rather than on nitrogen.

**PROBLEM 16**

Explain why pyrrole \((pK_a \approx 17)\) is less acidic than cyclopentadiene \((pK_a = 15)\), even though nitrogen is considerably more electronegative than carbon.

**Indole, Benzofuran, and Benzothiophene**

Indole, benzofuran, and benzothiophene contain a five-membered aromatic ring fused to a benzene ring. The rings are numbered in a way that gives the heteroatom the lowest possible number. Indole, benzofuran, and benzothiophene are aromatic because they are cyclic and planar, every carbon in the ring has a \(p\) orbital, and the \(\pi\) cloud of each compound contains five pairs of \(\pi\) electrons (Section 15.1). Notice that the electrons shown as a lone pair on the indole nitrogen are part of the \(\pi\) cloud; therefore, the conjugate acid of indole, like the conjugate acid of pyrrole, is a strong acid \((pK_a = -2.4)\). In other words, indole is an extremely weak base.
21.10 Aromatic Six-Membered-Ring Heterocycles

Pyridine
When one of the carbons of a benzene ring is replaced by a nitrogen, the resulting compound is called pyridine.

The pyridinium ion is a stronger acid than a typical ammonium ion because the acidic hydrogen of a pyridinium ion is attached to an sp² hybridized nitrogen, which is more electronegative than an sp³ hybridized nitrogen (Section 6.9).

Pyridine is a tertiary amine, so it undergoes reactions characteristic of tertiary amines. For example, pyridine undergoes SN2 reactions with alkyl halides (Section 10.4), and it reacts with hydrogen peroxide to form an N-oxide (Section 21.7).

PROBLEM 17 SOLVED
Will an amide be formed from the reaction of an acyl chloride with an aqueous solution of pyridine? Explain your answer.
SOLUTION An amide will not be formed because the positively charged nitrogen causes pyridine to be an excellent leaving group. Therefore, the final product of the reaction will be a carboxylic acid. (If the final pH of the solution is greater than the $pK_a$ of the carboxylic acid, the carboxylic acid will be predominantly in its basic form.)

$$
\begin{align*}
\text{O} & \quad \text{RCCl} + \quad \text{O} \\
& \quad \text{RC}^{-}+ \quad \text{H}_2\text{O} \quad \text{RCO}^- \\
& \quad \text{N} \\
\end{align*}
$$

Pyridine is aromatic. Like benzene, it has two uncharged resonance contributors. Because of the electron-withdrawing nitrogen, it also has three charged resonance contributors that benzene does not have.

The dipole moment of pyridine is 1.57 D. As the resonance contributors and the electrostatic potential map indicate, the electron-withdrawing nitrogen is the negative end of the dipole.

Because it is aromatic, pyridine (like benzene) undergoes electrophilic aromatic substitution reactions ($\ddot{\text{B}}$ is any base in the solution).

**mechanism for electrophilic aromatic substitution**

Electrophilic aromatic substitution of pyridine takes place at C-3 because the most stable intermediate is obtained by placing an electrophilic substituent at that position (Figure 21.2). When the substituent is placed at C-2 or C-4, one of the resulting resonance contributors is particularly unstable because its nitrogen atom has an incomplete octet and a positive charge. The electron-withdrawing nitrogen atom makes the intermediate obtained from electrophilic aromatic substitution of pyridine less stable than the carbocation intermediate obtained from electrophilic aromatic substitution of benzene. Pyridine, therefore, is less reactive than benzene. Indeed, it is even less reactive than nitrobenzene. (Recall from Section 16.3 that an electron-withdrawing nitro group strongly deactivates a benzene ring toward electrophilic aromatic substitution.)

**relative reactivity toward electrophilic aromatic substitution**

$$
\begin{align*}
\text{NO}_2 & > \quad \text{NO}_2 \\
\text{NO}_2 & > \quad \text{NO}_2
\end{align*}
$$
Pyridine, therefore, undergoes electrophilic aromatic substitution reactions only under vigorous conditions, and the yields of these reactions are often quite low. If the nitrogen becomes protonated under the reaction conditions, the reactivity is further decreased because a positively charged nitrogen is more electron withdrawing than a neutral nitrogen.

We have seen that highly deactivated benzene rings do not undergo Friedel–Crafts alkylation or acylation reactions. Therefore, pyridine, whose reactivity is similar to that of a highly deactivated benzene, does not undergo these reactions either.

Since pyridine is less reactive than benzene toward electrophilic aromatic substitution, it is not surprising that pyridine is more reactive than benzene toward nucleophilic aromatic substitution. The electron-withdrawing nitrogen atom that destabilizes the intermediate in electrophilic aromatic substitution stabilizes it in nucleophilic aromatic substitution.
Nucleophilic aromatic substitution of pyridine takes place at C-2 and C-4, because attack at these positions leads to the most stable intermediate. Only when nucleophilic attack occurs at these positions is a resonance contributor obtained that has the greatest electron density on nitrogen, the most electronegative of the ring atoms (Figure 21.3).

If the leaving groups at C-2 and C-4 are different, the incoming nucleophile will preferentially substitute for the weaker base (the better leaving group).

PROBLEM 19

Compare the mechanisms of the following reactions:

PROBLEM 20

a. Propose a mechanism for the following reaction:

b. What other product is formed?
Substituted pyridines undergo many of the side-chain reactions that substituted benzenes undergo, such as bromination and oxidation.

When 2- or 4-aminopyridine is diazotized, α-pyridone or γ-pyridone is formed. Apparently, the diazonium salt reacts immediately with water to form a hydroxypyridine (Section 16.10). The product of the reaction is a pyridone because the keto form of a hydroxypyridine is more stable than the enol form. (The mechanism for the conversion of a primary amino group into a diazonium group is shown in Section 16.12).

The electron-withdrawing nitrogen causes the α-hydrogens of alkyl groups attached to the 2- and 4-positions of the pyridine ring to have about the same acidity as the α-hydrogens of ketones (Section 19.1).

Consequently, the α-hydrogens of alkyl substituents can be removed by base, and the resulting carbanions can react as nucleophiles.
**PROBLEM 21**

Rank the following compounds in order of decreasing ease of removing a proton from a methyl group:

![Chemical structures of Quinoline and Isoquinoline](image.png)

**Quinoline and Isoquinoline**

Quinoline and isoquinoline are known as *benzopyridines* because they have both a benzene ring and a pyridine ring. Like benzene and pyridine, they are aromatic compounds. The $pK_a$ values of their conjugate acids are similar to the $pK_a$ of the conjugate acid of pyridine. (In order for the carbons in quinoline and isoquinoline to have the same numbers, the nitrogen in isoquinoline is assigned the 2-position, not the lowest possible number.)

![Chemical structures of Quinoline and Isoquinoline](image.png)

**21.11 Biologically Important Heterocycles**

Proteins are naturally occurring polymers of $\alpha$-amino acids (Chapter 23). Three of the 20 most common naturally occurring amino acids contain heterocyclic rings: Proline contains a pyrrolidine ring, tryptophan contains an indole ring, and histidine contains an imidazole ring.

![Chemical structures of Proline, Tryptophan, and Histidine](image.png)

**Imidazole**

Imidazole, the heterocyclic ring of histidine, is the first heterocyclic compound we have encountered that has two heteroatoms. Imidazole is an aromatic compound because it is cyclic and planar; every carbon in the ring has a $p$ orbital, and the $\pi$ cloud contains *three* pairs of $\pi$ electrons (Section 15.1). The electrons drawn as lone-pair electrons on N-1 (see p. 896) are part of the $\pi$ cloud because they are in a $p$ orbital, whereas the lone-pair electrons on N-3 are not part of the $\pi$ cloud because they are in an $sp^2$ orbital, perpendicular to the $p$ orbitals.
The resonance energy of imidazole is significantly less than the resonance energy of benzene (or ).

Imidazole can be protonated because the lone-pair electrons in the orbital are not part of the cloud. Since the conjugate acid of imidazole has a of 6.8, imidazole exists in both the protonated and unprotonated forms at physiological pH (7.3). This is one of the reasons that histidine, the imidazole-containing amino acid, is an important catalytic component of many enzymes (Section 24.9).

Neutral imidazole is a stronger acid than neutral pyrrole because of the second ring nitrogen.

Notice that both protonated imidazole and the imidazole anion have two equivalent resonance contributors. This means that the two nitrogens become equivalent when imidazole is either protonated or deprotonated.

PROBLEM 22◆

Give the major product of the following reaction:

\[
\text{FeBr}_3 + \text{N} = \text{NCH}_3 + \text{Br}_2 \xrightarrow{\text{FeBr}_3} \]

PROBLEM 23◆

List imidazole, pyrrole, and benzene in order of decreasing reactivity toward electrophilic aromatic substitution.
**PROBLEM 24**

Imidazole boils at 257 °C, whereas N-methylimidazole boils at 199 °C. Explain this difference in boiling points.

**PROBLEM 25**

What percent of imidazole will be protonated at physiological pH (7.3)?

---

**Purine and Pyrimidine**

Nucleic acids (DNA and RNA) contain substituted purines and substituted pyrimidines (Section 27.1); DNA contains A, G, C, and T, and RNA contains A, G, C, and U. (Why DNA contains T instead of U is explained in Section 27.14.) Unsubstituted purine and pyrimidine are not found in nature. Notice that hydroxypurines and hydroxypyrimidines are more stable in the keto form. We will see that the preference for the keto form is crucial for proper base pairing in DNA (Section 27.7).

![Diagram of Purine and Pyrimidine](image)

**Porphyrin**

Substituted porphyrins are important naturally occurring heterocyclic compounds. A porphyrin ring system consists of four pyrrole rings joined by one-carbon bridges. Heme, which is found in hemoglobin and myoglobin, contains an iron ion (Fe²⁺) ligated by the four nitrogens of a porphyrin ring system. Ligation is the sharing of nonbonding electrons with a metal ion. The porphyrin ring system of heme is known as protoporphyrin IX; the ring system plus the iron atom is called iron protoporphyrin IX.

![Diagram of Heme](image)

Hemoglobin is responsible for transporting oxygen to cells and carbon dioxide away from cells, whereas myoglobin is responsible for storing oxygen in cells. Hemoglobin has four polypeptide chains and four heme groups; myoglobin has one polypeptide chain and one heme group. The iron atoms in hemoglobin and myoglobin, in addition to being ligated to the four nitrogens of the porphyrin ring, are also ligated to a histidine of the protein component (globin), and the sixth ligand is oxygen or carbon dioxide. Carbon monoxide is about the same size and shape as 

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**3-D Molecule:**

- Heme
more tightly than \( \text{O}_2 \) to \( \text{Fe}^{2+} \). Consequently, breathing carbon monoxide can be fatal because it prevents the transport of oxygen in the bloodstream.

The extensive conjugated system of porphyrin gives blood its characteristic red color. Its high molar absorptivity (about 160,000) allows concentrations as low as \( 1 \times 10^{-8} \text{ M} \) to be detected by UV spectroscopy (Section 8.10).

The biosynthesis of porphyrin involves the formation of porphobilinogen from two molecules of \( \delta \)-aminolevulinic acid. The precise mechanism for this biosynthesis is as yet unknown. A possible mechanism starts with the formation of an imine between the enzyme that catalyzes the reaction and one of the molecules of \( \delta \)-aminolevulinic acid. An aldol-type condensation occurs between the imine and a free molecule of \( \delta \)-aminolevulinic acid. Nucleophilic attack by the amino group on the imine closes the ring. The enzyme is then eliminated, and removal of a proton creates the aromatic ring.

**a mechanism for the biosynthesis of porphyrin**

\[
\text{E} - \text{NH}_2 \quad \text{enzyme} \quad \xrightarrow{\text{\delta-aminolevulinic acid}} \quad \text{E} - \text{N} = \text{C} \quad \xrightarrow{\text{base}} \quad \text{E} - \text{N} = \text{C} \quad \xrightarrow{\text{H}^+ - \text{H}^+} \quad \text{porphobilinogen}
\]

Four porphobilinogen molecules react to form porphyrin.

\[
\text{repeat three more times using an intramolecular reaction for the third repetition} \quad \xrightarrow{\text{subsequent oxidation increases the unsaturation}} \quad \text{porphyrin}
\]
The ring system in chlorophyll \( \text{a} \), the substance responsible for the green color of plants, is similar to porphyrin but contains a cyclopentanone ring, and one of its pyrrole rings is partially reduced. The metal atom in chlorophyll \( \text{a} \) is magnesium (\( \text{Mg}^{2+} \)).

Vitamin \( \text{B}_{12} \) also has a ring system similar to porphyrin, but one of the methine bridges is missing. The ring system of vitamin \( \text{B}_{12} \) is known as a corrin ring system. The metal atom in vitamin \( \text{B}_{12} \) is cobalt (\( \text{Co}^{3+} \)). The chemistry of vitamin \( \text{B}_{12} \) is discussed in Section 25.7.

**PROBLEM 26**

Is porphyrin aromatic?

**PROBLEM 27**

Show how the last two porphobilinogen molecules are incorporated into the porphyrin ring.
Amines are compounds in which one or more of the hydrogens of ammonia have been replaced by R groups. Amines are classified as primary, secondary, or tertiary, depending on whether one, two, or three hydrogens of ammonia have been replaced. Amines undergo amine inversion through a transition state in which the nitrogen becomes a nitrogen.

Some amines are heterocyclic compounds—cyclic compounds in which one or more of the atoms of the ring is an atom other than carbon. Heterocyclic rings are numbered so that the heteroatom has the lowest possible number. A natural product is a compound synthesized by a plant or an animal. Alkaloids are natural products containing one or more nitrogen heteroatoms and are found in the leaves, bark, roots, or seeds of plants.

Because of the lone pair on the nitrogen, amines are both bases and nucleophiles. Amines react as nucleophiles in nucleophilic substitution reactions, in nucleophilic acyl substitution reactions, in nucleophilic addition–elimination reactions, and in conjugate addition reactions.

Amines cannot undergo the substitution and elimination reactions that alkyl halides undergo, because the leaving groups of amines are too basic. Protonated amines also cannot undergo the reactions that protonated alcohols and protonated ethers undergo. Amines are easily oxidized. Saturated heterocycles containing five or more atoms have physical and chemical properties typical of acyclic compounds that contain the same heteroatom.

Quaternary ammonium hydroxides and amine oxides undergo E2 elimination reactions known as Hofmann elimination reactions and Cope elimination reactions, respectively. In both reactions, the proton from the β-carbon bonded to the greater number of hydrogens is removed.

Quaternary ammonium salts are the most common phase transfer catalysts.

Primary amines can be synthesized by means of a Gabriel synthesis, by reduction of an alkyl azide or a nitrile, by reductive amination, and by reduction of an amide.

Pyrrole, furan, and thiophene are aromatic compounds that undergo electrophilic aromatic substitution reactions preferentially at C-2. These compounds are more reactive than benzene toward electrophiles. When pyrrole is protonated, its aromaticity is destroyed. Pyrrole polymerizes in strongly acidic solutions. Indole, benzofuran, and benzothiophene are aromatic compounds that contain a five-membered aromatic ring fused to a benzene ring.

Replacing one of benzene’s carbons with a nitrogen forms pyridine, an aromatic compound that undergoes electrophilic aromatic substitution reactions at C-3 and nucleophilic aromatic substitution reactions at C-2 and C-4. Pyridine is less reactive than benzene toward electrophilic aromatic substitution and more reactive toward nucleophilic aromatic substitution. Quinoline and isoquinoline are aromatic compounds with both a benzene ring and a pyridine ring.

Imidazole is the heterocyclic ring of the amino acid histidine. The conjugate acid of imidazole has a pKₐ of 6.8, allowing it to exist in both the protonated and unprotonated forms at physiological pH (pH = 7.3). Nucleic acids (DNA and RNA) contain substituted purines and substituted pyrimidines. Hydroxypurines and hydroxypyrimidines are more stable in the keto form. A porphyrin ring system consists of four pyrrole rings joined by one-carbon bridges; in hemoglobin and myoglobin, the four nitrogen atoms are ligated to Fe²⁺. The metal atom in chlorophyll a is Mg²⁺ and the metal atom in vitamin B₁₂ is Co³⁺.

Summary of Reactions

1. Reaction of amines as nucleophiles (Section 21.4).
   a. In alklylation reactions:

   \[
   \begin{align*}
   R'\text{-}NH_2 + R'\text{-}\text{Br} & \rightarrow R'\text{-}\text{NH}_2 \text{Br}^- \\
   R'\text{-}\text{NH}_2 + \text{Br}^- & \rightarrow R'\text{-}\text{NH}_2 \text{Br}^- \\
   R'\text{-}NH_2 + \text{HBr} & \rightarrow R'\text{-}\text{NH}_2 \text{Br}^- \\
   R'\text{-}\text{NH}_2 + \text{Br}^- & \rightarrow R'\text{-}\text{NH}_2 \text{Br}^- \\
   \end{align*}
   \]
b. In acylation reactions:

\[
\text{RC} = \text{OCl} + 2 \text{R'}\text{NH}_2 \rightarrow \text{RCO} - \text{NHR'} + \text{R'}\text{NH}_3^+ \text{Cl}^{-}
\]

c. In nucleophilic addition–elimination reactions:

i. Reaction of a primary amine with an aldehyde or ketone to form an imine:

\[
\text{R} - \text{NH}_2 + \text{R} - \text{CHO} \rightarrow \text{RCH(NH}_2)^- + \text{H}_2\text{O}
\]

ii. Reaction of a secondary amine with an aldehyde or ketone to form an enamine:

\[
\text{R} - \text{NHRL} + \text{R} - \text{CHO} \rightarrow \text{RCH(NHRL)}^- + \text{H}_2\text{O}
\]

d. In conjugate addition reactions:

\[
\text{RCH} = \text{CR} + \text{R'}\text{NH}_2 \rightarrow \text{RCH} - \text{CH}_2\text{CR} - \text{NHR'}
\]

2. Primary arylamines react with nitrous acid to form stable arenediazonium salts (Section 21.4).

\[
\text{PhNH}_2 + \text{HCl} + \text{NaNO}_2 \rightarrow \text{PhN}=\text{N}^+\text{Cl}^{-}
\]

3. Oxidation of amines: Primary amines are oxidized to nitro compounds, secondary amines to hydroxylamines, and tertiary amines to amine oxides (Section 21.7).

\[\text{R} - \text{NH}_2 \xrightarrow{\text{oxidation}} \text{R} - \text{NH} - \text{OH} \xrightarrow{\text{oxidation}} \text{R} - \text{N}=\text{O} \xrightarrow{\text{oxidation}} \text{R} - \text{N}^+\text{O}^-\]

\[\text{R} - \text{NH} \xrightarrow{\text{oxidation}} \text{R} - \text{N} - \text{OH} + \text{H}_2\text{O}\]

a secondary amine  a secondary hydroxylamine

\[\text{R} - \text{N} - \text{R} \xrightarrow{\text{oxidation}} \text{R} - \text{N}^+\text{R}^- + \text{H}_2\text{O}\]

a tertiary amine  a tertiary amine oxide

4. Elimination reactions of \textit{quaternary ammonium hydroxides} or \textit{tertiary amine oxides} (Sections 21.5 and 21.7).

\[
\begin{align*}
\text{RCH}_2\text{CH}_2\text{NCH}_3^- + \text{CH}_3\text{OH} \xrightarrow{\Delta \text{ Hofmann elimination}} & \text{RCH} = \text{CH}_2 + \text{CH}_3\text{NCH}_3 + \text{H}_2\text{O} \\
\text{RCH}_2\text{CH}_2\text{NCH}_3^- + \text{H}_2\text{O}_2 \xrightarrow{\Delta \text{ Cope elimination}} & \text{RCH}_2\text{CH}_2\text{NCH}_3^- + \text{CH}_3\text{OH} + \text{CH}_3\text{NCH}_3
\end{align*}
\]

in both eliminations, the proton is removed from the $\beta$-carbon bonded to the most hydrogens
5. Synthesis of amines (Section 21.8).

a. Gabriel synthesis of primary amines:

\[
\begin{align*}
\text{C}=\text{O} & \quad \text{H}_2 \text{O} \quad 1. \text{H}^+ \\
\text{R}-\text{Br} & \quad \xrightarrow{1.} \text{C}=\text{O} \quad \text{H}_2 \text{O}^+ \quad \xrightarrow{2.} \text{R} \quad \text{H}^+ \\
\text{C}=\text{N} & \quad \text{H}^+ \quad \text{H}_2 \text{O} \quad \xrightarrow{3.} \text{R} \quad \text{N}^+ \quad \text{N}^+ \\
\end{align*}
\]

b. Reduction of an alkyl azide or a nitrile:

\[
\begin{align*}
\text{R} \quad \text{Br} & \quad \xrightarrow{1.} \text{N}_3 \quad \text{R} \quad \text{N}^+ \quad \text{N}^+ \\
\text{R} \quad \text{C}=\text{N} & \quad \xrightarrow{2.} \text{H}_2 \quad \text{Pd/C} \quad \text{R} \quad \text{CH}_2\text{NH}_2 \\
\end{align*}
\]

c. Reduction of a nitroalkane or nitrobenzene:

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2 & \quad + \quad \text{H}_2 \quad \xrightarrow{\text{Pd/C}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2 \\
\text{NO}_2 & \quad + \quad \text{H}_2 \quad \xrightarrow{\text{Pd/C}} \quad \text{NH}_2 \\
\end{align*}
\]

d. Aldehydes and ketones react (1) with excess ammonia plus \( \text{H}_2 / \text{metal catalyst} \) to form primary amines, (2) with a primary amine followed by reduction with sodium triacetoxyborohydride to form secondary amines, and (3) with a secondary amine followed by reduction with sodium triacetoxyborohydride to form tertiary amines:

\[
\begin{align*}
\text{C}=\text{O} & \quad \text{excess NH}_3 \quad \xrightarrow{1.} \text{C}=\text{N} \quad \text{H}^+ \quad \text{H}_2 \text{O} \\
\text{R} \quad \text{C}=\text{O} & \quad \text{CH}_3\text{NH}_2 \quad \xrightarrow{2.} \text{R} \quad \text{C}=\text{N} \quad \text{H}^+ \quad \text{H}_2 \text{O} \\
\text{C}=\text{O} & \quad \text{CH}_3\text{NH} \quad \xrightarrow{3.} \text{R} \quad \text{N}^+ \quad \text{N}^+ \\
\end{align*}
\]

6. Electrophilic aromatic substitution reactions.

a. Pyrrole, furan, and thiophene (Section 21.9):

\[
\begin{align*}
\text{C} & \quad \text{HNO}_3 \quad \xrightarrow{1.} \text{C} \quad \text{HNO}_3 \quad \xrightarrow{2.} \text{H}_2 \text{O} \\
\text{C} & \quad \text{Br}_2 \quad \xrightarrow{1.} \text{C} \quad \text{Br} \quad \xrightarrow{2.} \text{HBr} \\
\text{C} & \quad \text{CH}_3\text{CCL} \quad \xrightarrow{1.} \text{SnCl}_4 \quad \text{C} \quad \text{HCl} \\
\end{align*}
\]
b. Pyridine (Section 21.10):

![Chemical reactions]

7. Nucleophilic aromatic substitution reactions of pyridine (Section 21.10).

![Chemical reactions]

**Key Terms**

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**Problems**

28. Name the following compounds:

- a. 
- b. 
- c. 
- d. 

29. Give the product of each of the following reactions:

- a. 
- b. 
- c. 
- d. 
- e. 
- f. 

AU: These terms are bold in text. Add to list? Or make lightface in text?
30. List the following compounds in order of decreasing acidity:

31. Which of the following compounds is easier to decarboxylate?

32. Rank the following compounds in order of decreasing reactivity in an electrophilic aromatic substitution reaction:

33. One of the following compounds undergoes electrophilic aromatic substitution predominantly at C-3, and one undergoes electrophilic aromatic substitution predominantly at C-4. Which is which?

34. Benzene undergoes electrophilic aromatic substitution reactions with aziridines in the presence of a Lewis acid such as AlCl₃.
   a. What are the major and minor products of the following reaction?

   b. Would you expect epoxides to undergo similar reactions?

35. A Hofmann degradation of a primary amine forms an alkene that gives butanal and 2-methylpropanal upon ozonolysis and work-up under reducing conditions. Identify the amine.

36. The dipole moments of furan and tetrahydrofuran are in the same direction. One compound has a dipole moment of 0.70 D, and the other has a dipole moment of 1.73 D. Which is which?

37. Show how the vitamin niacin can be synthesized from nicotine.

38. The chemical shifts of the C-2 hydrogen in the ¹H NMR spectra of pyrrole, pyridine, and pyrrolidine are δ2.82, δ6.42, and δ8.50. Match each chemical shift with its heterocycle.

39. Explain why protonation of aniline has a dramatic effect on the compound’s UV spectrum, whereas protonation of pyridine has only a small effect on that compound’s UV spectrum.
40. Explain why pyrrole ($pK_a \sim 17$) is a much stronger acid than ammonia ($pK_a = 36$).

\[
\begin{align*}
\text{Pyrrole} & \quad \xrightarrow{+ \text{H}^+} \quad \text{NH}_3 \\
\text{pK}_a = -17 & \quad \text{vs.} \quad \text{pK}_a = 36
\end{align*}
\]

41. Propose a mechanism for the following reaction:

\[
\begin{align*}
2 \text{pyrrole} + \text{H}_2\text{C}=\text{O} & \quad \xrightarrow{\text{trace H}^+} \quad \text{pyrrole} \quad \text{CH}_2=\text{CH}_2 \\
\end{align*}
\]

42. Quinolines are commonly synthesized by a method known as the Skraup synthesis, which involves the reaction of aniline with glycerol under acidic conditions. Nitrobenzene is added to the reaction mixture to serve as an oxidizing agent. The first step in the synthesis is the dehydration of glycerol to propenal.

\[
\begin{align*}
\text{CH}_2=\text{CH}_2 & \quad \xrightarrow{\Delta \text{H}_2\text{SO}_4} \quad \text{CH}_2=\text{CH}=\text{O} + 2 \text{H}_2\text{O} \\
\text{glycerol} & \quad \text{propenal}
\end{align*}
\]

a. What product would be obtained if para-ethylaniline were used instead of aniline?
b. What product would be obtained if 3-hexen-2-one were used instead of glycerol?
c. What starting materials are needed for the synthesis of 2,7-diethyl-3-methylquinoline?

43. Propose a mechanism for each of the following reactions:

\[
\begin{align*}
a. & \quad \text{H}_2\text{C} & \text{O} & \text{CH}_3 & \quad \xrightarrow{\text{H}^+ / \text{H}_2\text{O} \Delta} & \quad \text{CH}_3\text{CCH}_2\text{CCH}_3 \\
b. & \quad \text{pyrrole} & + & \text{Br}_2 & \quad \xrightarrow{\text{CH}_3\text{OH}} & \quad \text{CH}_3\text{O} & \text{OCH}_3
\end{align*}
\]

44. Give the major product of each of the following reactions:

\[
\begin{align*}
a. & \quad \text{H}_2\text{C} & \text{O} & \xrightarrow{\text{HNO}_3} & \quad \text{CH}_3\text{NCH}_3 \\
b. & \quad \text{pyrrole} & \text{NO}_2 & \xrightarrow{\text{Br}_2} & \quad \text{CH}_3\text{I} \quad \xrightarrow{\text{PCl}_4} \\
c. & \quad \text{CH}_3\text{CH}_2\text{NCH}_3\text{CH}_3 & \xrightarrow{H\text{O}^- / \Delta} & \quad \text{H}_3\text{C} & \text{N} & \xrightarrow{\text{H}_2\text{O}_2 / \Delta} \\
d. & \quad \text{pyrrole} & \text{NO} & \xrightarrow{\text{H}_3\text{O}^+} & \quad \text{CH}_3\text{CH}_2\text{MgBr} \quad \xrightarrow{\text{H}_2\text{O} / \Delta}
\end{align*}
\]

45. When piperidine undergoes the indicated series of reactions, 1,4-pentadiene is obtained as the product. When the four different methyl-substituted piperidines undergo the same series of reactions, each forms a different diene: 1,5-hexadiene, 1,4-pentadiene, 2-methyl-1,4-pentadiene, and 3-methyl-1,4-pentadiene. Which methyl-substituted piperidine yields which diene?

\[
\begin{align*}
\text{Piperidine} & \quad \xrightarrow{1. \text{excess CH}_3\text{I}/\text{K}_2\text{CO}_3, 2. \text{Ag}_2\text{O}, \text{H}_2\text{O} / \Delta} \quad \text{CH}_3\text{NCH}_2\text{CH}_2\text{CH}==\text{CH}_2 \\
& \quad \xrightarrow{1. \text{excess CH}_3\text{I}/\text{K}_2\text{CO}_3, 2. \text{Ag}_2\text{O}, \text{H}_2\text{O} / \Delta} \quad \text{CH}_2==\text{CHCH}_2\text{CH}==\text{CH}_2
\end{align*}
\]
46. a. Draw resonance contributors to show why pyridine-N-oxide is more reactive than pyridine toward electrophilic aromatic substitution.
   b. At what position does pyridine-N-oxide undergo electrophilic aromatic substitution?

47. Propose a mechanism for the following reaction:

48. Explain why the aziridinium ion has a considerably lower $pK_a$ (8.0) than that of a typical secondary ammonium ion (10.0). (Hint: Recall that the larger the bond angle, the greater the $s$ character, and the greater the $s$ character, the more electronegative the atom.)

49. Pyrrole reacts with excess para-($N,N$-dimethylamino)benzaldehyde to form a highly colored compound. Draw the structure of the colored compound.

50. 2-Phenylindole is prepared from the reaction of acetophenone and phenylhydrazine, a method known as the Fischer indole synthesis. Propose a mechanism for this reaction. (Hint: The reactive species is the enamine tautomer of the phenylhydrazone.)

51. What starting materials are required for the synthesis of the following compounds, using the Fischer indole synthesis? (Hint: See Problem 50.)
   a.  
   b.  
   c.  

52. Organic chemists work with tetraphenylporphyrins rather than porphyrins because tetraphenylporphyrins are much more resistant to air oxidation. Tetraphenylporphyrin can be prepared by the reaction of benzaldehyde with pyrrole. Propose a mechanism for the formation of the ring system shown here:

53. Propose a mechanism different from the one shown in Section 21.11 for the biosynthesis of porphobilinogen.