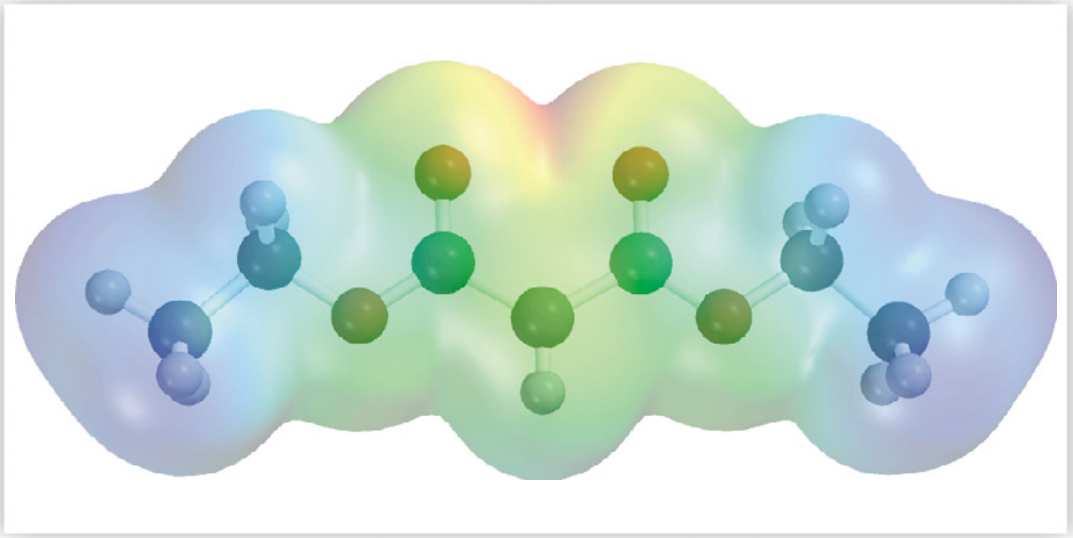
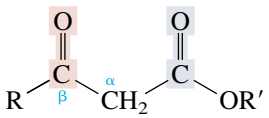


CHAPTER 21

ESTER ENOLATES

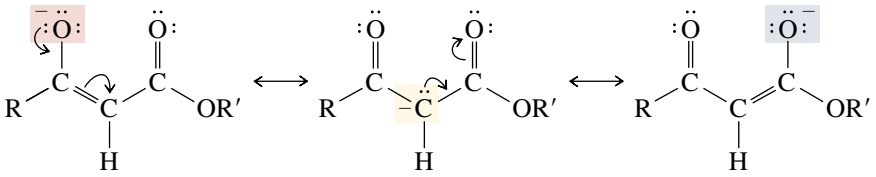
You have already had considerable experience with carbanionic compounds and their applications in synthetic organic chemistry. The first was acetylide ion in Chapter 9, followed in Chapter 14 by organometallic compounds—Grignard reagents, for example—that act as sources of negatively polarized carbon. In Chapter 18 you learned that enolate ions—reactive intermediates generated from aldehydes and ketones—are nucleophilic, and that this property can be used to advantage as a method for carbon–carbon bond formation.

The present chapter extends our study of carbanions to the enolate ions derived from esters. **Ester enolates** are important reagents in synthetic organic chemistry. The stabilized enolates derived from **β-keto esters** are particularly useful.



β-Keto ester: a ketone carbonyl is β to the carbonyl group of the ester.

A proton attached to the α-carbon atom of a β-keto ester is relatively acidic. Typical acid dissociation constants K_a for β-keto esters are $\approx 10^{-11}$ (pK_a 11). Because the α-carbon atom is flanked by two electron-withdrawing carbonyl groups, a carbanion formed at this site is highly stabilized. The electron delocalization in the anion of a β-keto ester is represented by the resonance structures



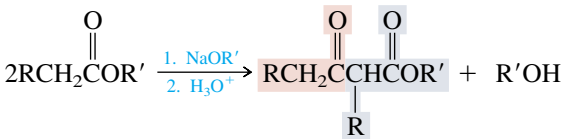
Principal resonance structures of the anion of a β-keto ester

We'll begin by describing the preparation and properties of β-keto esters, proceed to a discussion of their synthetic applications, continue to an examination of related species, and conclude by exploring some recent developments in the active field of synthetic carbanion chemistry.

21.1 THE CLAISEN CONDENSATION

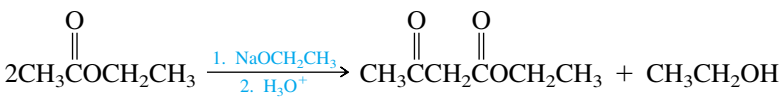
Before describing how β-keto esters are used as reagents for organic synthesis, we need to see how these compounds themselves are prepared. The main method for the preparation of β-keto esters is a reaction known as the **Claisen condensation:**

Ludwig Claisen was a German chemist who worked during the last two decades of the nineteenth century and the first two decades of the twentieth. His name is associated with three reactions. The *Claisen–Schmidt reaction* was presented in Section 18.10, the *Claisen condensation* is discussed in this section, and the *Claisen rearrangement* will be introduced in Section 24.13.



Ester β-Keto ester Alcohol

On treatment with alkoxide bases, esters undergo self-condensation to give a β-keto ester and an alcohol. Ethyl acetate, for example, undergoes a Claisen condensation on treatment with sodium ethoxide to give a β-keto ester known by its common name *ethyl acetoacetate* (also called *acetoacetic ester*):



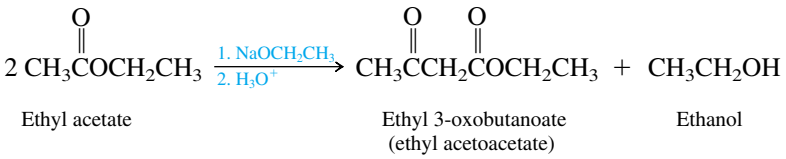
Ethyl acetate Ethyl acetoacetate (75%) (acetoacetic ester) Ethanol

The systematic IUPAC name of ethyl acetoacetate is *ethyl 3-oxobutanoate.* The presence of a ketone carbonyl group is indicated by the designation "*oxo*" along with the appropriate locant. Thus, there are four carbon atoms in the acyl group of ethyl 3-oxobutanoate, C-3 being the carbonyl carbon of the ketone function.

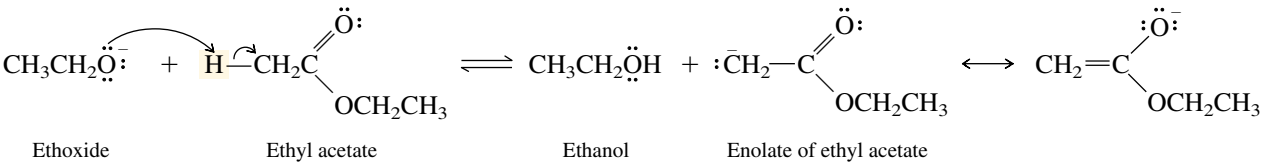
The mechanism of the Claisen condensation of ethyl acetate is presented in Figure 21.1. The first two steps of the mechanism are analogous to those of aldol addition (Section 18.9). An enolate ion is generated in step 1, which undergoes nucleophilic addition to the carbonyl group of a second ester molecule in step 2. The species formed in this step is a tetrahedral intermediate of the same type that we encountered in our discussion of nucleophilic acyl substitution of esters. It dissociates by expelling an ethoxide ion, as shown in step 3, which restores the carbonyl group to give the β-keto ester. Steps 1 to 3 show two different types of ester reactivity: one molecule of the ester gives rise to an enolate; the second molecule acts as an acylating agent.

Claisen condensations involve two distinct experimental operations. The first stage concludes in step 4 of Figure 21.1, where the base removes a proton from C-2 of the β-keto ester. Because this proton is relatively acidic, the position of equilibrium for step 4 lies far to the right.

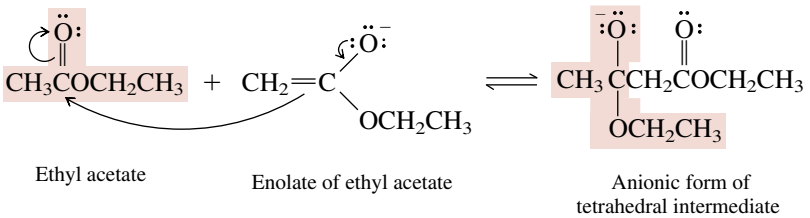
Overall reaction:



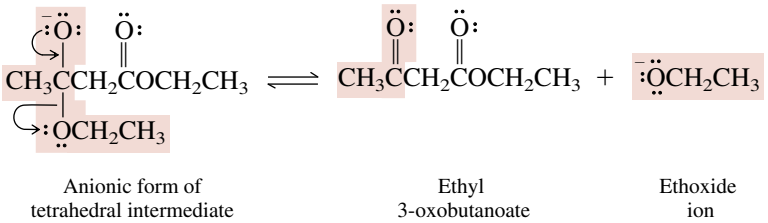
Step 1: Proton abstraction from the α carbon atom of ethyl acetate to give the corresponding enolate.



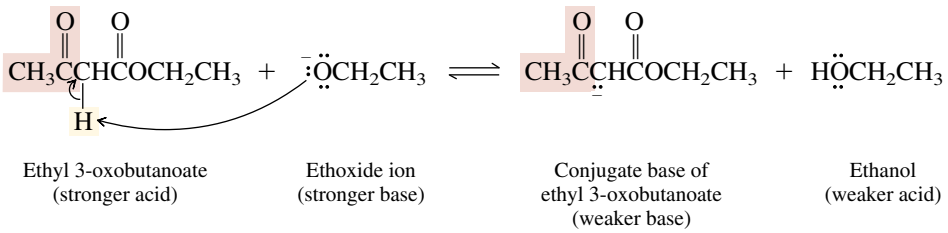
Step 2: Nucleophilic addition of the ester enolate to the carbonyl group of the neutral ester. The product is the anionic form of the tetrahedral intermediate.



Step 3: Dissociation of the tetrahedral intermediate.



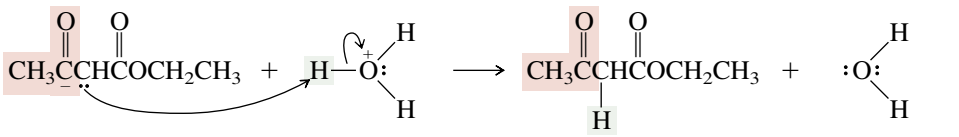
Step 4: Deprotonation of the β-keto ester product.



—Cont.

FIGURE 21.1 The mechanism of the Claisen condensation of ethyl acetate.

Step 5: Acidification of the reaction mixture. This is performed in a separate synthetic operation to give the product in its neutral form for eventual isolation.

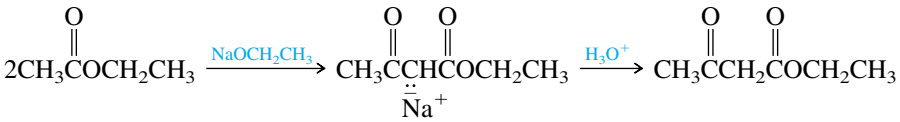


Conjugate base of ethyl 3-oxobutanoate (stronger base) | Hydronium ion (stronger acid) | Ethyl 3-oxobutanoate (weaker acid) | Water (weaker base)

FIGURE 21.1 (*Continued*)

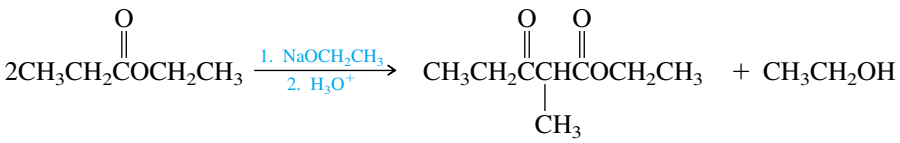
In general, the equilibrium represented by the sum of steps 1 to 3 is not favorable for condensation of two ester molecules to a β-keto ester. (Two ester carbonyl groups are more stable than one ester plus one ketone carbonyl.) However, because the β-keto ester is deprotonated under the reaction conditions, the equilibrium represented by the sum of steps 1 to 4 does lie to the side of products. On subsequent acidification (step 5), the anion of the β-keto ester is converted to its neutral form and isolated.

Organic chemists sometimes write equations for the Claisen condensation in a form that shows both stages explicitly:



Ethyl acetate | Sodium salt of ethyl acetoacetate | Ethyl acetoacetate

Like aldol condensations, Claisen condensations always involve bond formation between the α-carbon atom of one molecule and the carbonyl carbon of another:

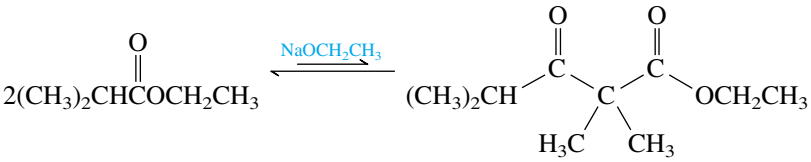


Ethyl propanoate | Ethyl 2-methyl-3-oxopentanoate (81%) | Ethanol

PROBLEM 21.1 One of the following esters cannot undergo the Claisen condensation. Which one? Write structural formulas for the Claisen condensation products of the other two.

$CH_3CH_2CH_2CH_2CO_2CH_2CH_3$	$C_6H_5CO_2CH_2CH_3$	$C_6H_5CH_2CO_2CH_2CH_3$
Ethyl pentanoate	Ethyl benzoate	Ethyl phenylacetate

Unless the β-keto ester can form a stable anion by deprotonation as in step 4 of Figure 21.1, the Claisen condensation product is present in only trace amounts at equilibrium. Ethyl 2-methylpropanoate, for example, does not give any of its condensation product under the customary conditions of the Claisen condensation.



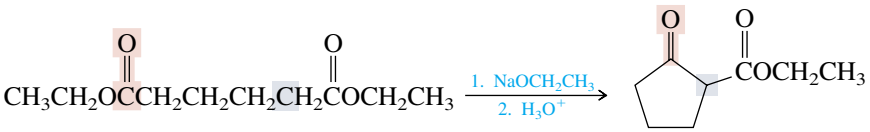
Ethyl 2-methylpropanoate

Ethyl 2,2,4-trimethyl-3-oxopentanoate
(cannot form a stable anion; formed in no more than trace amounts)

At least two protons must be present at the α carbon for the equilibrium to favor product formation. Claisen condensation is possible for esters of the type RCH_2CO_2R', but not for R_2CHCO_2R'.

21.2 INTRAMOLECULAR CLAISEN CONDENSATION: THE DIECKMANN REACTION

Esters of *dicarboxylic acids* undergo an intramolecular version of the Claisen condensation when a five- or six-membered ring can be formed.

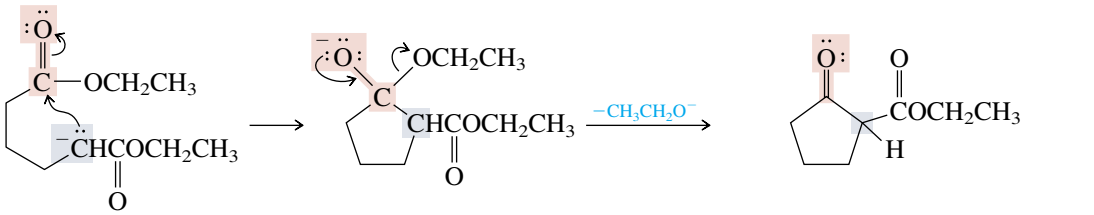


Diethyl hexanedioate

Ethyl (2-oxocyclopentane)-carboxylate (74–81%)

This reaction is an example of a **Dieckmann cyclization.** The anion formed by proton abstraction at the carbon α to one carbonyl group attacks the other carbonyl to form a five-membered ring.

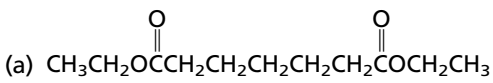
Walter Dieckmann was a German chemist and a contemporary of Claisen.

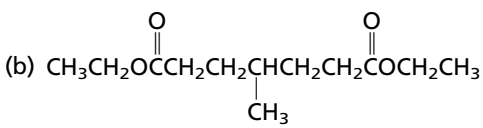


Enolate of diethyl hexanedioate

Ethyl (2-oxocyclopentane)carboxylate

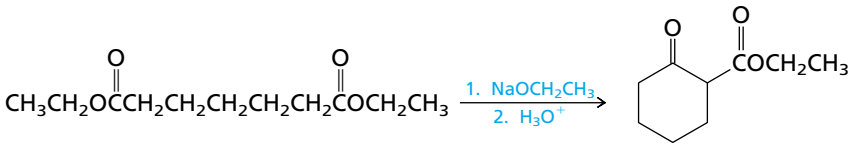
PROBLEM 21.2 Write the structure of the Dieckmann cyclization product formed on treatment of each of the following diesters with sodium ethoxide, followed by acidification.





(c) $CH_3CH_2OCCHCH_2CH_2CH_2COCH_2CH_3$ (with CH_3 on the α-carbon)

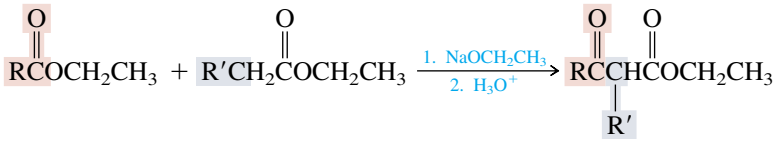
SAMPLE SOLUTION (a) Diethyl heptanedioate has one more methylene group in its chain than the diester cited in the example (diethyl hexanedioate). Its Dieckmann cyclization product contains a six-membered ring instead of the five-membered ring formed from diethyl hexanedioate.



Diethyl heptanedioate — Ethyl (2-oxocyclohexane)-carboxylate

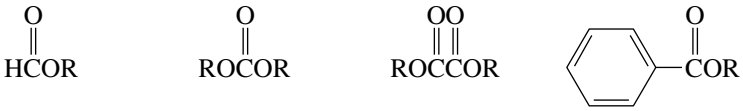
21.3 MIXED CLAISEN CONDENSATIONS

Analogous to mixed aldol condensations, mixed Claisen condensations involve carbon–carbon bond formation between the α-carbon atom of one ester and the carbonyl carbon of another.



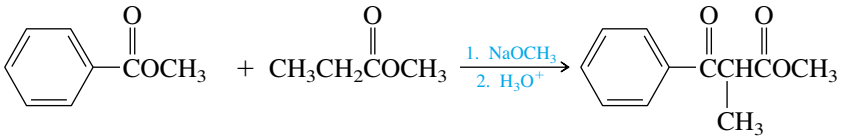
Ester — Another ester — β-Keto ester

The best results are obtained when one of the ester components is incapable of forming an enolate. Esters of this type include the following:



Formate esters — Carbonate esters — Oxalate esters — Benzoate esters

The following equation shows an example of a mixed Claisen condensation in which a benzoate ester is used as the nonenolizable component:

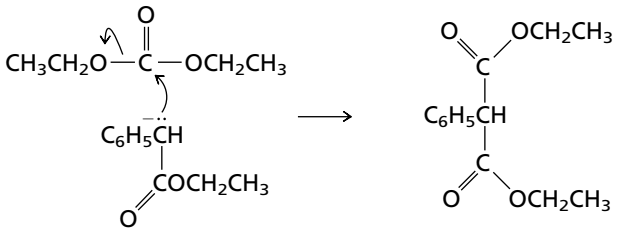


Methyl benzoate (cannot form an enolate) — Methyl propanoate — Methyl 2-methyl-3-oxo-3-phenylpropanoate (60%)

PROBLEM 21.3 Give the structure of the product obtained when ethyl phenylacetate ($C_6H_5CH_2CO_2CH_2CH_3$) is treated with each of the following esters under conditions of the mixed Claisen condensation:

(a) Diethyl carbonate
(b) Diethyl oxalate
(c) Ethyl formate

SAMPLE SOLUTION (a) Diethyl carbonate cannot form an enolate, but ethyl phenylacetate can. Nucleophilic acyl substitution on diethyl carbonate by the enolate of ethyl phenylacetate yields a *diester.*

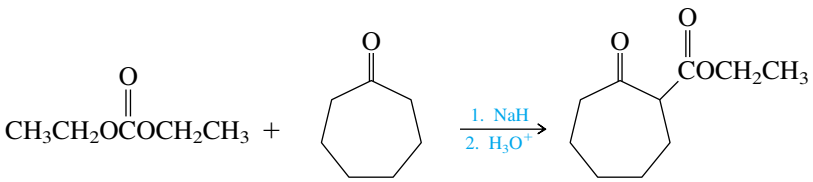


Diethyl 2-phenylpropanedioate
(diethyl phenylmalonate)

The reaction proceeds in good yield (86%), and the product is a useful one in further synthetic transformations of the type to be described in Section 21.7.

21.4 ACYLATION OF KETONES WITH ESTERS

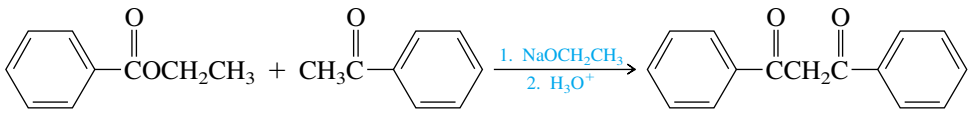
In a reaction related to the mixed Claisen condensation, nonenolizable esters are used as acylating agents for ketone enolates. Ketones (via their enolates) are converted to β-keto esters by reaction with diethyl carbonate.



Diethyl carbonate | Cycloheptanone | Ethyl (2-oxocycloheptane)-carboxylate (91–94%)

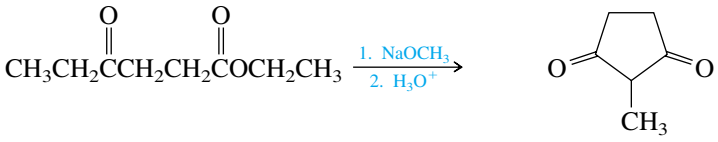
Sodium hydride was used as the base in this example. It is often used instead of sodium ethoxide in these reactions.

Esters of nonenolizable monocarboxylic acids such as ethyl benzoate give β-diketones on reaction with ketone enolates:



Ethyl benzoate | Acetophenone | 1,3-Diphenyl-1,3-propanedione (62–71%)

Intramolecular acylation of ketones yields cyclic β-diketones when the ring that is formed is five- or six-membered.



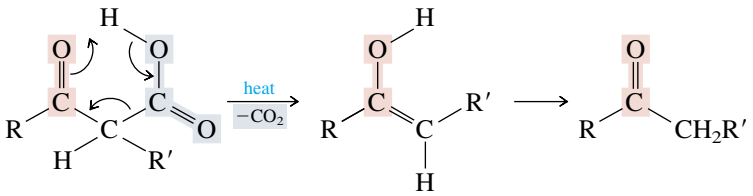
Ethyl 4-oxohexanoate | 2-Methyl-1,3-cyclopentanedione (70–71%)

PROBLEM 21.4 Write an equation for the carbon–carbon bond-forming step in the cyclization reaction just cited. Show clearly the structure of the enolate ion, and use curved arrows to represent its nucleophilic addition to the appropriate carbonyl group. Write a second equation showing dissociation of the tetrahedral intermediate formed in the carbon–carbon bond-forming step.

Even though ketones have the potential to react with themselves by aldol addition, recall that the position of equilibrium for such reactions lies to the side of the starting materials (Section 18.9). On the other hand, acylation of ketone enolates gives products (β-keto esters or β-diketones) that are converted to stabilized anions under the reaction conditions. Consequently, ketone acylation is observed to the exclusion of aldol addition when ketones are treated with base in the presence of esters.

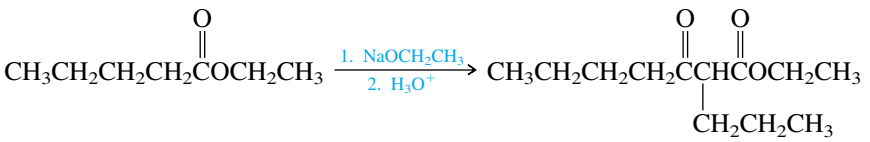
21.5 KETONE SYNTHESIS VIA β-KETO ESTERS

The carbon–carbon bond-forming potential inherent in the Claisen and Dieckmann reactions has been extensively exploited in organic synthesis. Subsequent transformations of the β-keto ester products permit the synthesis of other functional groups. One of these transformations converts β-keto esters to ketones; it is based on the fact that β-keto *acids* (not esters!) undergo decarboxylation readily (Section 19.17). Indeed, β-keto acids, and their corresponding carboxylate anions as well, lose carbon dioxide so easily that they tend to decarboxylate under the conditions of their formation.

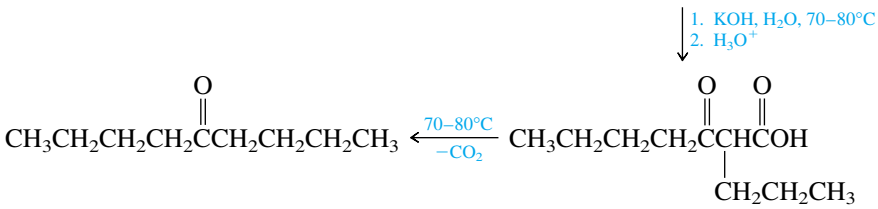


β-Keto acid | Enol form of ketone | Ketone

Thus, 5-nonanone has been prepared from ethyl pentanoate by the sequence



Ethyl pentanoate | Ethyl 3-oxo-2-propylheptanoate (80%)



5-Nonanone (81%) | 3-Oxo-2-propylheptanoic acid (not isolated; decarboxylates under conditions of its formation)

The sequence begins with a Claisen condensation of ethyl pentanoate to give a β-keto ester. The ester is hydrolyzed, and the resulting β-keto acid decarboxylates to yield the desired ketone.

PROBLEM 21.5 Write appropriate chemical equations showing how you could prepare cyclopentanone from diethyl hexanedioate.

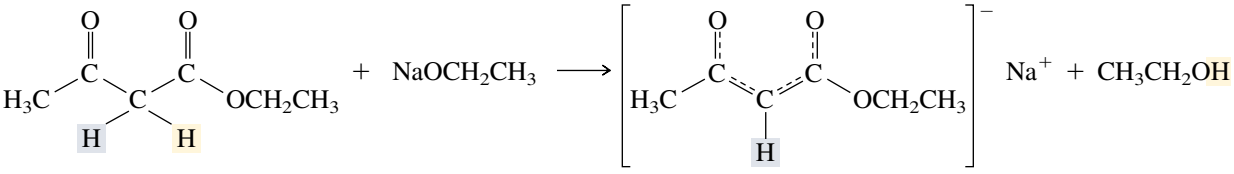
The major application of β-keto esters to organic synthesis employs a similar pattern of ester saponification and decarboxylation as its final stage, as described in the following section.

21.6 THE ACETOACETIC ESTER SYNTHESIS

Ethyl acetoacetate (acetoacetic ester), available by the Claisen condensation of ethyl acetate, has properties that make it a useful starting material for the preparation of ketones. These properties are

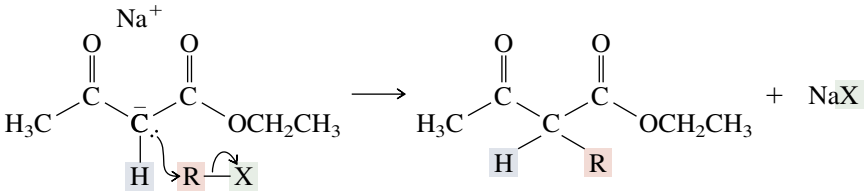
1. The acidity of the α proton
2. The ease with which acetoacetic acid undergoes thermal decarboxylation

Ethyl acetoacetate is a stronger acid than ethanol and is quantitatively converted to its anion on treatment with sodium ethoxide in ethanol.



Ethyl acetoacetate (stronger acid) K_a 10^{-11} (pK_a 11) | Sodium ethoxide (stronger base) | Sodium salt of ethyl acetoacetate (weaker base) | Ethanol (weaker acid) K_a 10^{-16} (pK_a 16)

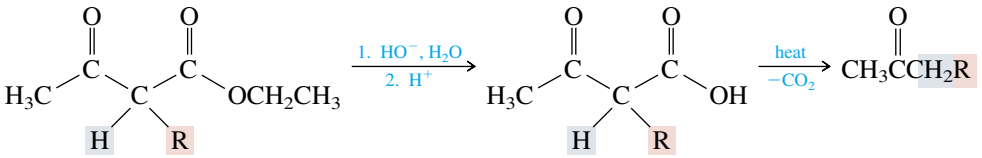
The anion produced by proton abstraction from ethyl acetoacetate is nucleophilic. Adding an alkyl halide to a solution of the sodium salt of ethyl acetoacetate leads to alkylation of the α carbon.



Sodium salt of ethyl acetoacetate; alkyl halide | 2-Alkyl derivative of ethyl acetoacetate | Sodium halide

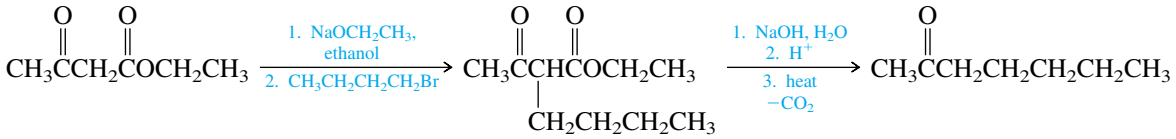
The new carbon–carbon bond is formed by an S_N2-type reaction. The alkyl halide must therefore be one that is not sterically hindered. Methyl and primary alkyl halides work best; secondary alkyl halides give lower yields. Tertiary alkyl halides react only by elimination, not substitution.

Saponification and decarboxylation of the alkylated derivative of ethyl acetoacetate yields a ketone.



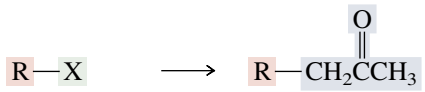
2-Alkyl derivative of ethyl acetoacetate | 2-Alkyl derivative of acetoacetic acid | Ketone

This reaction sequence is called the **acetoacetic ester synthesis.** It is a standard procedure for the preparation of ketones from alkyl halides, as the conversion of 1-bromobutane to 2-heptanone illustrates.



Ethyl acetoacetate | Ethyl 2-butyl-3-oxobutanoate (70%) | 2-Heptanone (60%)

The acetoacetic ester synthesis brings about the overall transformation of an alkyl halide to an alkyl derivative of acetone.



Primary or secondary alkyl halide | α-Alkylated derivative of acetone

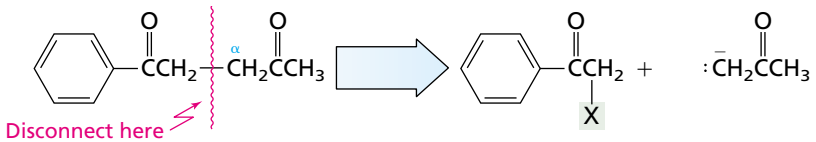
We call a structural unit in a molecule that is related to a synthetic operation a **synthon.** The three-carbon unit $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ is a synthon that alerts us to the possibility that a particular molecule may be accessible by the acetoacetic ester synthesis.

E. J. Corey (page 557) invented the word "synthon" in connection with his efforts to formalize synthetic planning.

PROBLEM 21.6 Show how you could prepare each of the following ketones from ethyl acetoacetate and any necessary organic or inorganic reagents:

(a) 1-Phenyl-1,4-pentanedione
(b) 4-Phenyl-2-butanone
(c) 5-Hexen-2-one

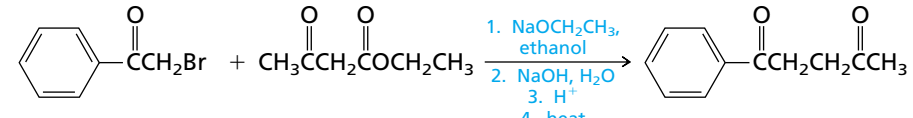
SAMPLE SOLUTION (a) Approach these syntheses in a retrosynthetic way. Identify the synthon $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ and mentally disconnect the bond to the α-carbon atom. The $-CH_2\overset{O}{\overset{\|}{C}}CH_3$ synthon is derived from ethyl acetoacetate; the remainder of the molecule originates in the alkyl halide.



1-Phenyl-1,4-pentanedione | Required alkyl halide | Derived from ethyl acetoacetate

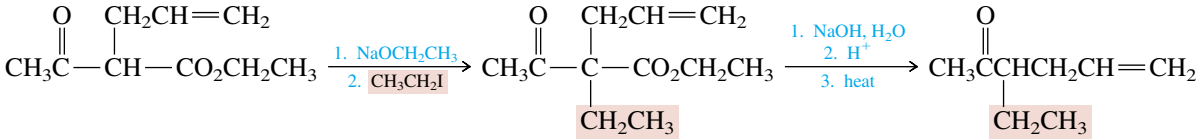
Analyzing the target molecule in this way reveals that the required alkyl halide is an α-halo ketone. Thus, a suitable starting material would be bromomethyl phenyl ketone.

Can you think of how bromomethyl phenyl ketone might be prepared?



Bromomethyl phenyl ketone | Ethyl acetoacetate | 1-Phenyl-1,4-pentanedione

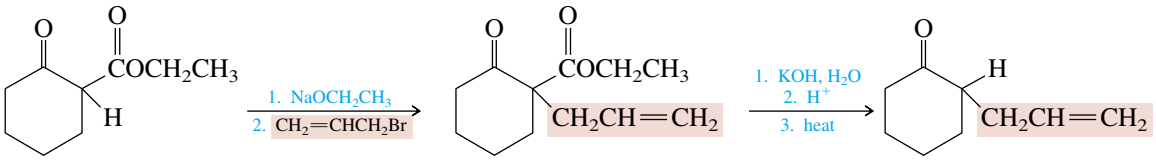
Dialkylation of ethyl acetoacetate can also be accomplished, opening the way to ketones with two alkyl substituents at the α carbon:



Ethyl 2-allylacetoacetate | Ethyl 2-allyl-2-ethylacetoacetate (75%) | 3-Ethyl-5-hexen-2-one (48%)

Recognize, too, that the reaction sequence is one that is characteristic of β-keto esters in general and not limited to just ethyl acetoacetate and its derivatives. Thus,

The starting material in the example is obtained by alkylation of ethyl acetoacetate with allyl bromide.



Ethyl 2-oxocyclohexanecarboxylate | Ethyl 1-allyl-2-oxocyclohexanecarboxylate (89%) | 2-Allylcyclohexanone (66%)

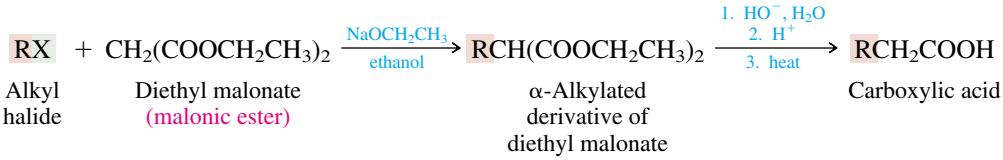
The starting material in this example is the Dieckmann cyclization product of diethyl heptanedioate (see Problem 21.2a).

It's reasonable to ask why one would prepare a ketone by way of a keto ester (ethyl acetoacetate, for example) rather than by direct alkylation of the enolate of a ketone. One reason is that the monoalkylation of ketones via their enolates is a difficult reaction to carry out in good yield. (Remember, however, that *acylation* of ketone enolates as described in Section 21.4 is achieved readily.) A second reason is that the delocalized enolates of β-keto esters, being far less basic than ketone enolates, give a higher substitution–elimination ratio when they react with alkyl halides. This can be quite important in those syntheses in which the alkyl halide is expensive or difficult to obtain.

Anions of β-keto esters are said to be *synthetically equivalent* to the enolates of ketones. The anion of ethyl acetoacetate is synthetically equivalent to the enolate of acetone, for example. The use of synthetically equivalent groups is a common tactic in synthetic organic chemistry. One of the skills that characterize the most creative practitioners of organic synthesis is an ability to recognize situations in which otherwise difficult transformations can be achieved through the use of synthetically equivalent reagents.

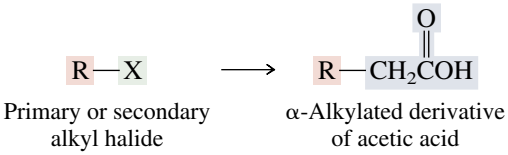
21.7 THE MALONIC ESTER SYNTHESIS

The **malonic ester synthesis** is a method for the preparation of carboxylic acids and is represented by the general equation



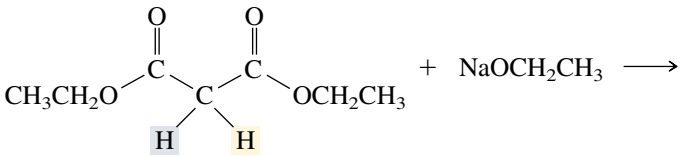
Among the methods for preparing carboxylic acids, carboxylation of a Grignard reagent and preparation and hydrolysis of a nitrile convert RBr to RCO_2H. The malonic ester synthesis converts RBr to RCH_2CO_2H.

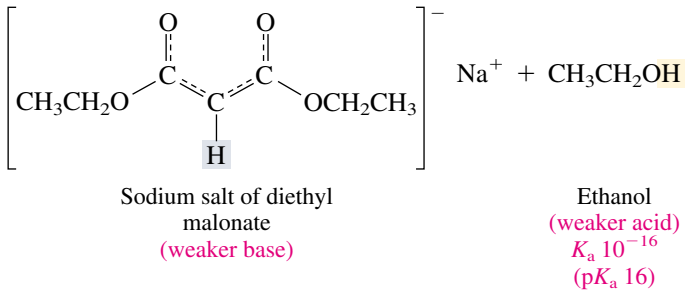
The malonic ester synthesis is conceptually analogous to the acetoacetic ester synthesis. The overall transformation is



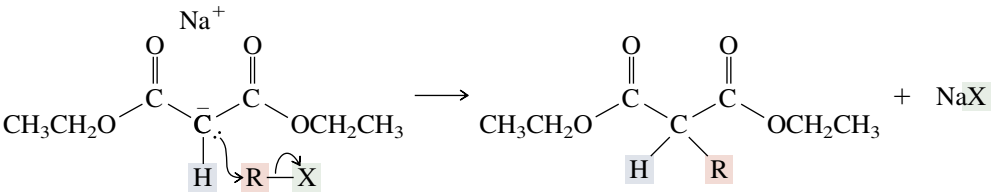
Diethyl malonate (also known as malonic ester) serves as a source of the synthon $-CH_2\overset{\overset{O}{\|}}{C}OH$ in the same way that the ethyl acetoacetate serves as a source of the synthon $-CH_2\overset{\overset{O}{\|}}{C}CH_3$.

The properties of diethyl malonate that make the malonic ester synthesis a useful procedure are the same as those responsible for the synthetic value of ethyl acetoacetate. The protons at C-2 of diethyl malonate are relatively acidic, and one is readily removed on treatment with sodium ethoxide.



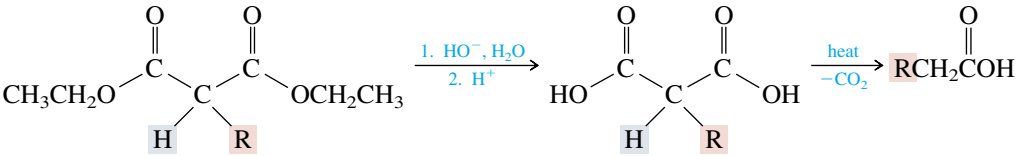


Treatment of the anion of diethyl malonate with alkyl halides leads to alkylation at C-2.



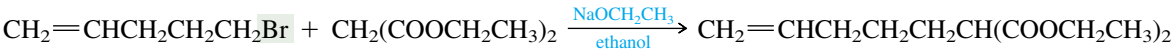
Sodium salt of diethyl malonate; alkyl halide — 2-Alkyl derivative of diethyl malonate — Sodium halide

Converting the C-2 alkylated derivative to the corresponding malonic acid derivative by ester hydrolysis gives a compound susceptible to thermal decarboxylation. Temperatures of approximately 180°C are normally required.

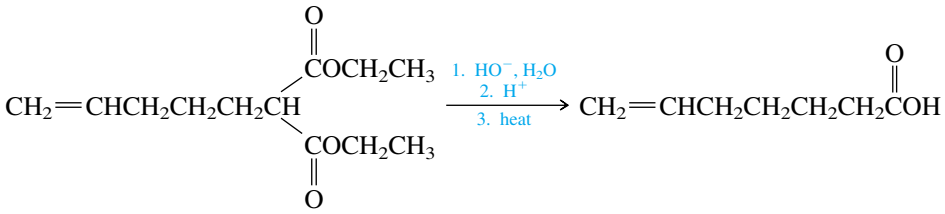


2-Alkyl derivative of diethyl malonate — 2-Alkyl derivative of malonic acid — Carboxylic acid

In a typical example of the malonic ester synthesis, 6-heptenoic acid has been prepared from 5-bromo-1-pentene:



5-Bromo-1-pentene — Diethyl malonate — Diethyl 2-(4-pentenyl)malonate (85%)

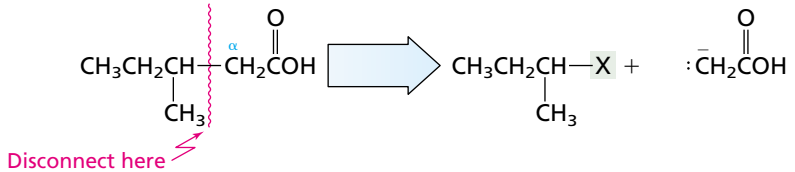


Diethyl 2-(4-pentenyl)malonate — 6-Heptenoic acid (75%)

PROBLEM 21.7 Show how you could prepare each of the following carboxylic acids from diethyl malonate and any necessary organic or inorganic reagents:

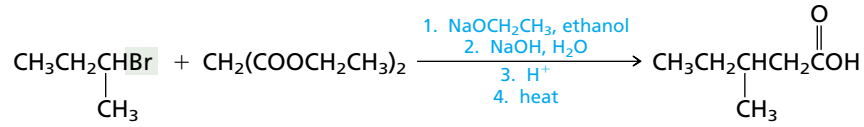
(a) 3-Methylpentanoic acid
(b) Nonanoic acid
(c) 4-Methylhexanoic acid
(d) 3-Phenylpropanoic acid

SAMPLE SOLUTION (a) Analyze the target molecule retrosynthetically by mentally disconnecting a bond to the α-carbon atom.



3-Methylpentanoic acid — Required alkyl halide — Derived from diethyl malonate

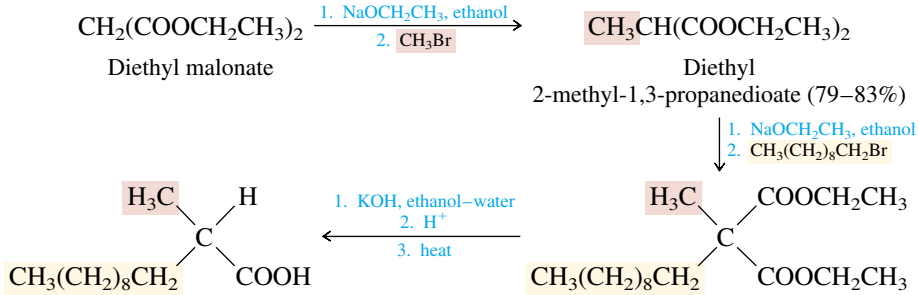
We see that a secondary alkyl halide is needed as the alkylating agent. The anion of diethyl malonate is a weaker base than ethoxide ion and reacts with secondary alkyl halides by substitution rather than elimination. Thus, the synthesis of 3-methylpentanoic acid begins with the alkylation of the anion of diethyl malonate by 2-bromobutane.



2-Bromobutane Diethyl malonate 3-Methylpentanoic acid

As actually carried out and reported in the chemical literature, diethyl malonate has been alkylated with 2-bromobutane in 83–84% yield and the product of that reaction converted to 3-methylpentanoic acid by saponification, acidification, and decarboxylation in 62–65% yield.

By performing two successive alkylation steps, the malonic ester synthesis can be applied to the synthesis of α,α-disubstituted derivatives of acetic acid:



Diethyl malonate

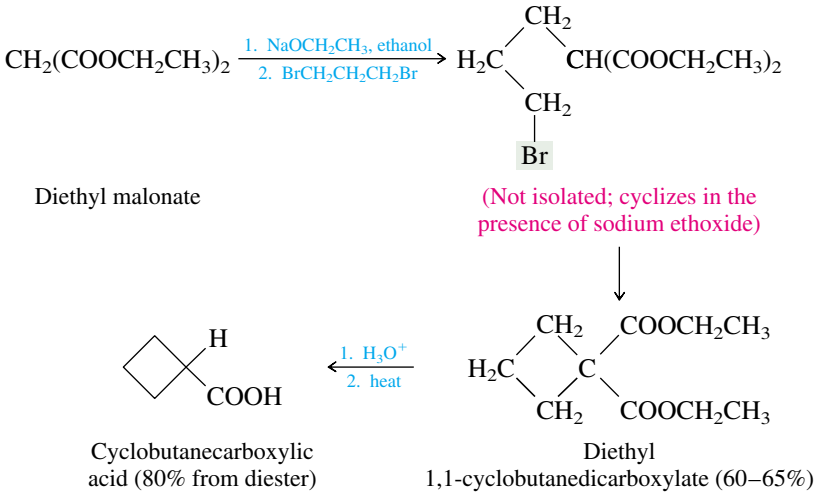
Diethyl 2-methyl-1,3-propanedioate (79–83%)

2-Methyldodecanoic acid (61–74%)

Diethyl 2-decyl-2-methyl-1,3-propanedioate

PROBLEM 21.8 Ethyl acetoacetate may also be subjected to double alkylation. Show how you could prepare 3-methyl-2-butanone by double alkylation of ethyl acetoacetate.

The malonic ester synthesis has been adapted to the preparation of cycloalkanecarboxylic acids from dihaloalkanes:



Diethyl malonate

(Not isolated; cyclizes in the presence of sodium ethoxide)

Cyclobutanecarboxylic acid (80% from diester)

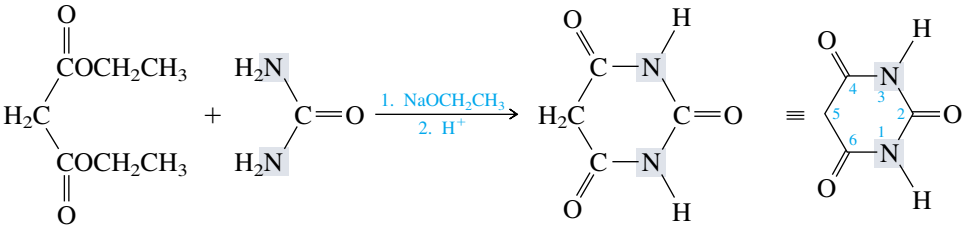
Diethyl 1,1-cyclobutanedicarboxylate (60–65%)

The cyclization step is limited to the formation of rings of seven carbons or fewer.

PROBLEM 21.9 Cyclopentyl methyl ketone has been prepared from 1,4-dibromobutane and ethyl acetoacetate. Outline the steps in this synthesis by writing a series of equations showing starting materials, reagents, and isolated intermediates.

21.8 BARBITURATES

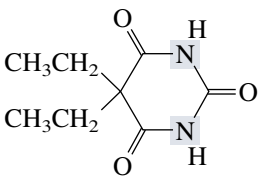
Diethyl malonate has uses other than in the synthesis of carboxylic acids. One particularly valuable application lies in the preparation of *barbituric acid* by nucleophilic acyl substitution with urea:



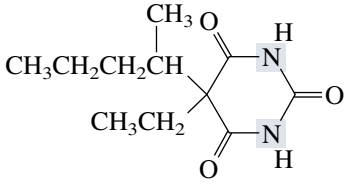
Diethyl malonate Urea Barbituric acid (72–78%)

Barbituric acid was first prepared in 1864 by Adolf von Baeyer (page 98). A historical account of his work and the later development of barbiturates as sedative–hypnotics appeared in the October 1951 issue of the *Journal of Chemical Education* (pp. 524–526).

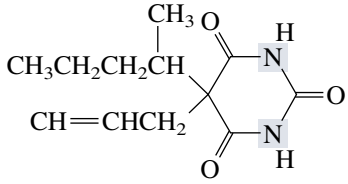
Barbituric acid is the parent of a group of compounds known as **barbiturates.** The barbiturates are classified as *sedative–hypnotic agents,* meaning that they decrease the responsiveness of the central nervous system and promote sleep. Thousands of derivatives of the parent ring system of barbituric acid have been tested for sedative–hypnotic activity; the most useful are the 5,5-disubstituted derivatives.



5,5-Diethylbarbituric acid (barbital; Veronal)

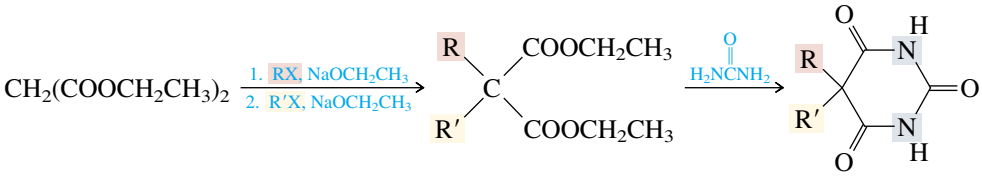


5-Ethyl-5-(1-methylbutyl)-barbituric acid (pentobarbital; Nembutal)



5-Allyl-5-(1-methylbutyl)-barbituric acid (secobarbital; Seconal)

These compounds are prepared in a manner analogous to that of barbituric acid itself. Diethyl malonate is alkylated twice, then treated with urea.



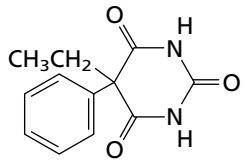
Diethyl malonate Dialkylated derivative of diethyl malonate 5,5-Disubstituted derivative of barbituric acid

PROBLEM 21.10 Show, by writing a suitable sequence of reactions, how you could prepare pentobarbital from diethyl malonate. (The structure of pentobarbital was shown in this section.)

Barbituric acids, as their name implies, are weakly acidic and are converted to their sodium salts (sodium barbiturates) in aqueous sodium hydroxide. Sometimes the drug is dispensed in its neutral form; sometimes the sodium salt is used. The salt is designated by appending the word "sodium" to the name of the barbituric acid—*pentobarbital sodium,* for example.

PROBLEM 21.11 Thiourea (H_2NCNH_2, with S double-bonded to C) reacts with diethyl malonate and its alkyl derivatives in the same way that urea does. Give the structure of the product obtained when thiourea is used instead of urea in the synthesis of pentobarbital. The anesthetic *thiopental* (*Pentothal*) *sodium* is the sodium salt of this product. What is the structure of this compound?

PROBLEM 21.12 Aryl halides react too slowly to undergo substitution by the S_N2 mechanism with the sodium salt of diethyl malonate, and so the phenyl substituent of *phenobarbital* cannot be introduced in the way that alkyl substituents can.



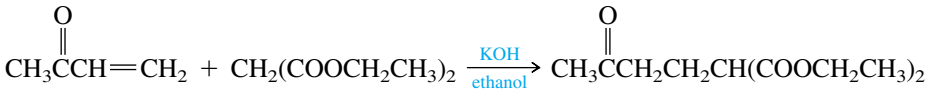
5-Ethyl-5-phenylbarbituric acid
(phenobarbital)

One synthesis of phenobarbital begins with ethyl phenylacetate and diethyl carbonate. Using these starting materials and any necessary organic or inorganic reagents, devise a synthesis of phenobarbital. (*Hint:* See the sample solution to Problem 21.3a.)

The various barbiturates differ in the time required for the onset of sleep and in the duration of their effects. All the barbiturates must be used only in strict accordance with instructions to avoid potentially lethal overdoses. Drug dependence in some individuals is also a problem.

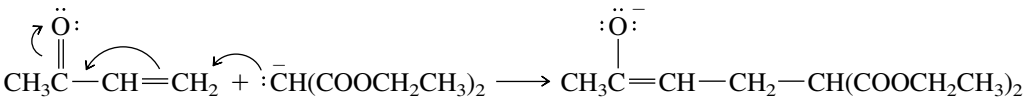
21.9 MICHAEL ADDITIONS OF STABILIZED ANIONS

Stabilized anions exhibit a pronounced tendency to undergo conjugate addition to α,β-unsaturated carbonyl compounds. This reaction, called the *Michael reaction,* has been described for anions derived from β-diketones in Section 18.13. The enolates of ethyl acetoacetate and diethyl malonate also undergo Michael addition to the β-carbon atom of α,β-unsaturated aldehydes, ketones, and esters. For example,

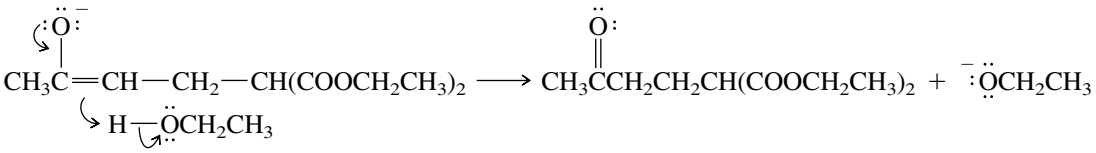


Methyl vinyl ketone | Diethyl malonate | Ethyl 2-carboethoxy-5-oxohexanoate (83%)

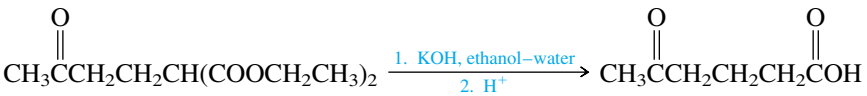
In this reaction the enolate of diethyl malonate adds to the β carbon of methyl vinyl ketone.



The intermediate formed in the nucleophilic addition step abstracts a proton from the solvent to give the observed product.



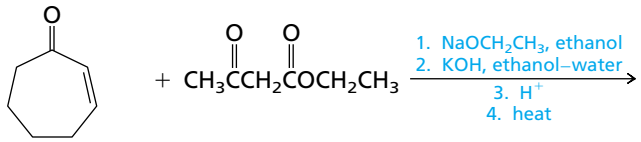
After isolation, the Michael adduct may be subjected to ester hydrolysis and decarboxylation. When α,β-unsaturated ketones are carried through this sequence, the final products are 5-keto acids (δ-keto acids).



Ethyl 2-carboethoxy-5-oxohexanoate (from diethyl malonate and methyl vinyl ketone)

5-Oxohexanoic acid (42%)

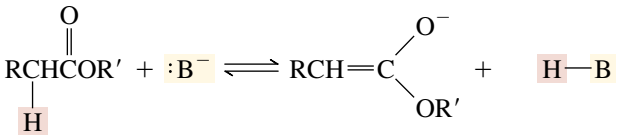
PROBLEM 21.13 Ethyl acetoacetate behaves similarly to diethyl malonate in its reactivity toward α,β-unsaturated carbonyl compounds. Give the structure of the product of the following reaction sequence:



2-Cycloheptenone Ethyl acetoacetate

21.10 α DEPROTONATION OF CARBONYL COMPOUNDS BY LITHIUM DIALKYLAMIDES

Most of the reactions of ester enolates described so far have centered on stabilized enolates derived from 1,3-dicarbonyl compounds such as diethyl malonate and ethyl acetoacetate. Although the synthetic value of these and related stabilized enolates is clear, chemists have long been interested in extending the usefulness of nonstabilized enolates derived from simple esters. Consider the deprotonation of an ester as represented by the acid–base reaction

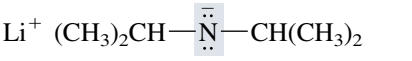


Ester Base Ester enolate Conjugate acid of base

We already know what happens when simple esters are treated with alkoxide bases—they undergo the Claisen condensation (Section 21.1). Simple esters have acid dissociation constants K_a of approximately 10^{-22} (pK_a 22) and are incompletely converted to their enolates with alkoxide bases. The small amount of enolate that is formed reacts by nucleophilic addition to the carbonyl group of the ester.

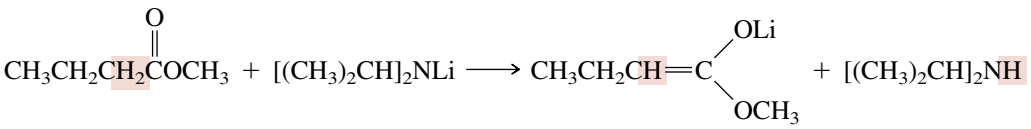
What happens if the base is much stronger than an alkoxide ion? *If the base is strong enough, it will convert the ester completely to its enolate.* Under these conditions the Claisen condensation is suppressed because there is no neutral ester present for the enolate to add to. A very strong base is one that is derived from a very weak acid. Referring to the table of acidities (Table 4.2, page 135), we see that ammonia is quite a weak acid; its K_a is 10^{-36} (pK_a 36). Therefore, amide ion ($H_2\ddot{N}:^-$) is a very strong base—more than strong enough to deprotonate an ester quantitatively. Amide ion, however, also tends to add to the carbonyl group of esters; to avoid this complication, highly hindered analogs of $H_2\ddot{N}:^-$ are used instead. The most frequently used base for ester enolate formation is *lithium diisopropylamide* (LDA):

Lithium diisopropylamide is commercially available. Alternatively, it may be prepared by the reaction of butyllithium with $[(CH_3)_2CH]_2NH$ (see Problem 14.4a for a related reaction).



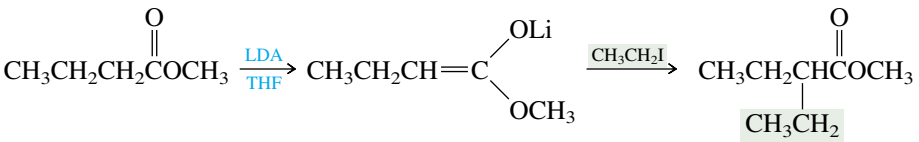
Lithium diisopropylamide

Lithium diisopropylamide is a strong enough base to abstract a proton from the α-carbon atom of an ester, but because it is so sterically hindered, it does not add readily to the carbonyl group. To illustrate,



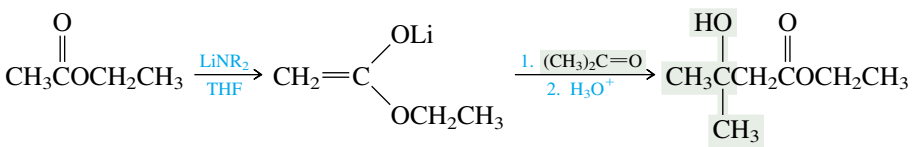
Methyl butanoate (stronger acid) K_a 10^{-22} (pK_a 22)	Lithium diisopropylamide (stronger base)	Lithium enolate of methyl butanoate (weaker base)	Diisopropylamine (weaker acid) K_a 10^{-36} (pK_a 36)

Direct alkylation of esters can be carried out by forming the enolate with LDA followed by addition of an alkyl halide. Tetrahydrofuran (THF) is the solvent most often used in these reactions.



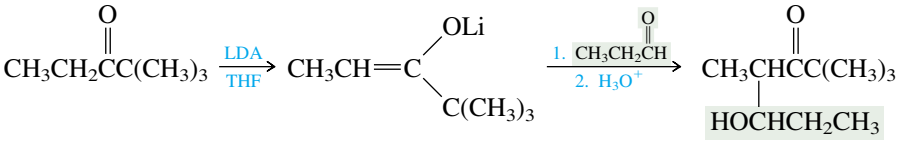
Methyl butanoate	Lithium enolate of methyl butanoate	Methyl 2-ethylbutanoate (92%)

Ester enolates generated by proton abstraction with dialkylamide bases add to aldehydes and ketones to give β-hydroxy esters.



Ethyl acetate	Lithium enolate of ethyl acetate	Ethyl 3-hydroxy-3-methylbutanoate (90%)

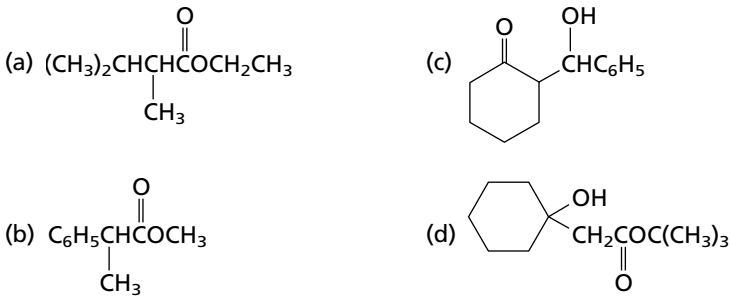
Lithium dialkylamides are excellent bases for making ketone enolates as well. Ketone enolates generated in this way can be alkylated with alkyl halides or, as illustrated in the following equation, treated with an aldehyde or a ketone.



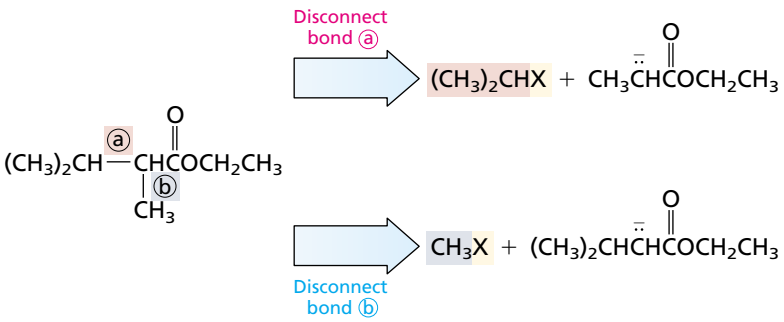
2,2-Dimethyl-3-pentanone | Lithium enolate of 2,2-dimethyl-3-pentanone | 5-Hydroxy-2,2,4-trimethyl-3-heptanone (81%)

Thus, mixed aldol additions can be achieved by the tactic of quantitative enolate formation using LDA followed by addition of a different aldehyde or ketone.

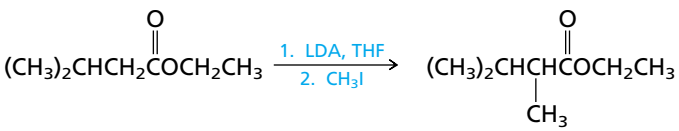
PROBLEM 21.14 Outline efficient syntheses of each of the following compounds from readily available aldehydes, ketones, esters, and alkyl halides according to the methods described in this section:



SAMPLE SOLUTION (a) The α-carbon atom of the ester has two different alkyl groups attached to it.



The critical carbon–carbon bond-forming step requires nucleophilic substitution on an alkyl halide by an ester enolate. Methyl halides are more reactive than isopropyl halides in S_N2 reactions and cannot undergo elimination as a competing process; therefore, choose the synthesis in which bond ⓑ is formed by alkylation.



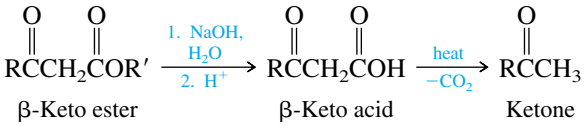
Ethyl 3-methylbutanoate | Ethyl 2,3-dimethylbutanoate

(This synthesis has been reported in the chemical literature and gives the desired product in 95% yield.)

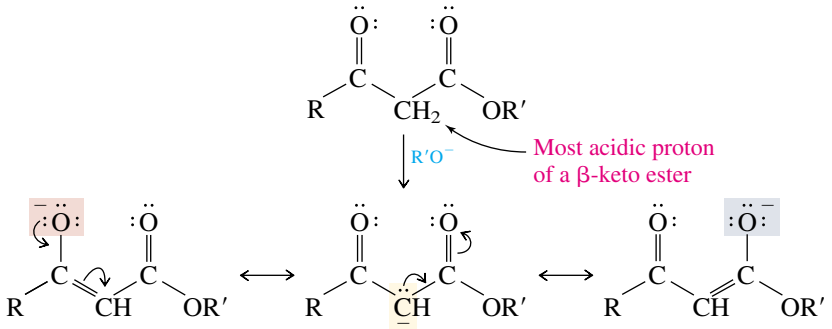
21.11 SUMMARY

Sections 21.1–21.4 β-Keto esters, which are useful reagents for a number of carbon–carbon bond-forming reactions, are prepared by the methods shown in Table 21.1.

Section 21.5 Hydrolysis of β-keto esters, such as those shown in Table 21.1, gives β-keto acids which undergo rapid decarboxylation, forming ketones.

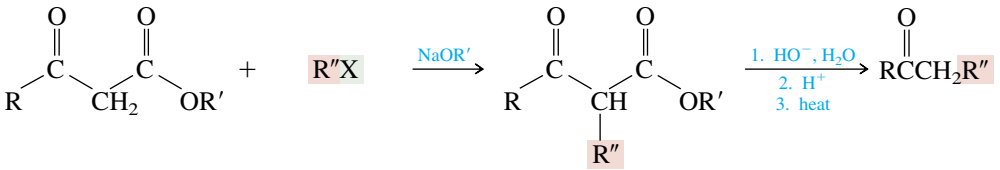


β-Keto esters are characterized by K_a's of about 10^{-11} (pK_a 11) and are quantitatively converted to their enolates on treatment with alkoxide bases.



Resonance forms illustrating charge delocalization in enolate of a β-keto ester

The anion of a β-keto ester may be alkylated at carbon with an alkyl halide and the product of this reaction subjected to ester hydrolysis and decarboxylation to give a ketone.



Section 21.6 The **acetoacetic ester synthesis** is a procedure in which ethyl acetoacetate is alkylated with an alkyl halide as the first step in the preparation of ketones of the type CH_3CCH_2R.

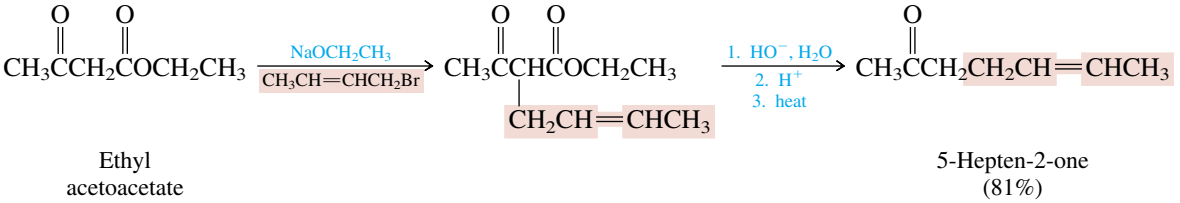
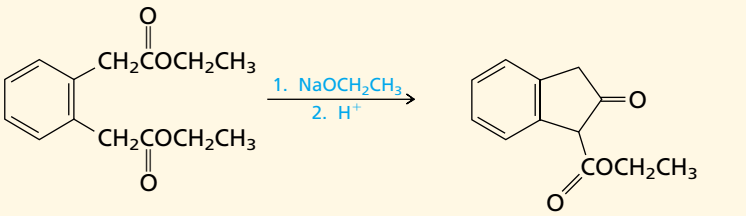


TABLE 21.1 Preparation of β-Keto Esters

Reaction (section) and comments	General equation and specific example
Claisen condensation (Section 21.1) Esters of the type RCH_2COR' are converted to β-keto esters on treatment with alkoxide bases. One molecule of an ester is converted to its enolate; a second molecule of ester acts as an acylating agent toward the enolate.	$2RCH_2COR' \xrightarrow[2.\ H^+]{1.\ NaOR'} RCH_2CCHCOR' + R'OH$ (R at the α-carbon) Ester → β-Keto ester + Alcohol $2CH_3CH_2CH_2COCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} CH_3CH_2CH_2CCHCOCH_2CH_3$ (CH_2CH_3 at the α-carbon) Ethyl butanoate → Ethyl 2-ethyl-3-oxohexanoate (76%)
Dieckmann cyclization (Section 21.2) An intramolecular analog of the Claisen condensation. Cyclic β-keto esters in which the ring is five- to seven-membered may be formed by using this reaction.	 Diethyl 1,2-benzenediacetate → Ethyl indan-2-one-1-carboxylate (70%)
Mixed Claisen condensations (Section 21.3) Diethyl carbonate, diethyl oxalate, ethyl formate, and benzoate esters cannot form ester enolates but can act as acylating agents toward other ester enolates.	$RCOCH_2CH_3 + R'CH_2COCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} RCCHCOCH_2CH_3$ (R′ at the α-carbon) Ester + Another ester → β-Keto ester $CH_3CH_2COCH_2CH_3 + CH_3CH_2OCCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} CH_3CHCOCH_2CH_3$ (C—$COCH_2CH_3$, O O) Ethyl propanoate + Diethyl oxalate → Diethyl 3-methyl-2-oxobutanedioate (60–70%)
Acylation of ketones (Section 21.4) Diethyl carbonate and diethyl oxalate can be used to acylate ketone enolates to give β-keto esters.	$RCH_2CR' + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} RCHCR'$ ($COCH_2CH_3$, O) Ketone + Diethyl carbonate → β-Keto ester $(CH_3)_3CCH_2CCH_3 + CH_3CH_2OCOCH_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3} (CH_3)_3CCH_2CCH_2COCH_2CH_3$ 4,4-Dimethyl-2-pentanone + Diethyl carbonate → Ethyl 5,5-dimethyl-3-oxohexanoate (66%)

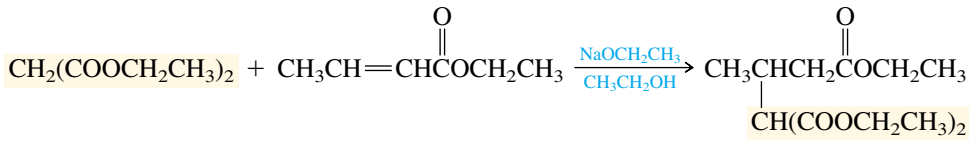
Section 21.7 The **malonic ester synthesis** is related to the acetoacetic ester synthesis. Alkyl halides (RX) are converted to carboxylic acids of the type RCH_2COOH by reaction with the enolate ion derived from diethyl malonate, followed by saponification and decarboxylation.

Diethyl malonate — (2-Cyclopentenyl)acetic acid (66%)

Section 21.8 Alkylation of diethyl malonate, followed by reaction with urea, gives derivatives of barbituric acid, called **barbiturates,** which are useful sleep-promoting drugs.

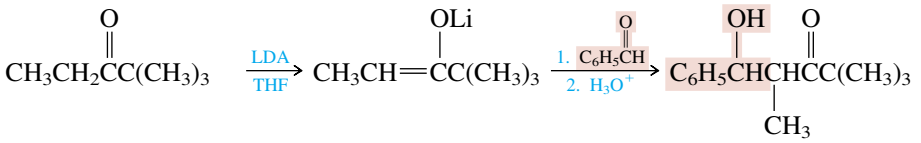
Diethyl malonate — Alkylated derivative of diethyl malonate — Alkylated derivative of barbituric acid

Section 21.9 **Michael addition** of the enolate ions derived from ethyl acetoacetate and diethyl malonate provides an alternative method for preparing their α-alkyl derivatives.



Diethyl malonate — Ethyl 2-butenoate — Triethyl 2-methylpropane-1,1,3-tricarboxylate (95%)

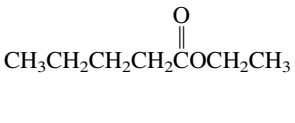
Section 21.10 It is possible to generate ester enolates by deprotonation provided that the base used is very strong. Lithium diisopropylamide (LDA) is often used for this purpose. It also converts ketones quantitatively to their enolates.



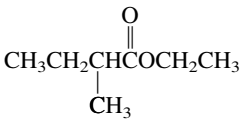
2,2-Dimethyl-3-pentanone — 1-Hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (78%)

PROBLEMS

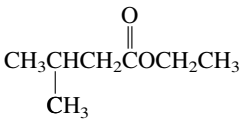
21.15 The following questions pertain to the esters shown and their behavior under conditions of the Claisen condensation.



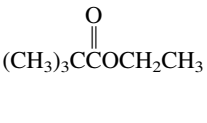
Ethyl pentanoate



Ethyl 2-methylbutanoate



Ethyl 3-methylbutanoate



Ethyl 2,2-dimethylpropanoate

(a) Two of these esters are converted to β-keto esters in good yield on treatment with sodium ethoxide and subsequent acidification of the reaction mixture. Which two are these? Write the structure of the Claisen condensation product of each one.

(b) One ester is capable of being converted to a β-keto ester on treatment with sodium ethoxide, but the amount of β-keto ester that can be isolated after acidification of the reaction mixture is quite small. Which ester is this?

(c) One ester is incapable of reaction under conditions of the Claisen condensation. Which one? Why?

21.16 (a) Give the structure of the Claisen condensation product of ethyl phenylacetate ($C_6H_5CH_2COOCH_2CH_3$).

(b) What ketone would you isolate after saponification and decarboxylation of this Claisen condensation product?

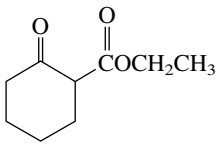
(c) What ketone would you isolate after treatment of the Claisen condensation product of ethyl phenylacetate with sodium ethoxide and allyl bromide, followed by saponification and decarboxylation?

(d) Give the structure of the mixed Claisen condensation product of ethyl phenylacetate and ethyl benzoate.

(e) What ketone would you isolate after saponification and decarboxylation of the product in part (d)?

(f) What ketone would you isolate after treatment of the product in part (d) with sodium ethoxide and allyl bromide, followed by saponification and decarboxylation?

21.17 All the following questions concern ethyl (2-oxocyclohexane)carboxylate.



Ethyl (2-oxocyclohexane)carboxylate

(a) Write a chemical equation showing how you could prepare ethyl (2-oxocyclohexane)carboxylate by a Dieckmann reaction.

(b) Write a chemical equation showing how you could prepare ethyl (2-oxocyclohexane)-carboxylate by acylation of a ketone.

(c) Write structural formulas for the two most stable enol forms of ethyl (2-oxocyclohexane)carboxylate.

(d) Write the three most stable resonance forms for the most stable enolate derived from ethyl (2-oxocyclohexane)carboxylate.

(e) Show how you could use ethyl (2-oxocyclohexane)carboxylate to prepare 2-methylcyclohexanone.

(f) Give the structure of the product formed on treatment of ethyl (2-oxocyclohexane)carboxylate with acrolein ($CH_2{=}CHC(=O)H$) in ethanol in the presence of sodium ethoxide.

21.18 Give the structure of the product formed on reaction of ethyl acetoacetate with each of the following:

(a) 1-Bromopentane and sodium ethoxide

(b) Saponification and decarboxylation of the product in part (a)

(c) Methyl iodide and the product in part (a) treated with sodium ethoxide

(d) Saponification and decarboxylation of the product in part (c)

(e) 1-Bromo-3-chloropropane and one equivalent of sodium ethoxide

(f) Product in part (e) treated with a second equivalent of sodium ethoxide

(g) Saponification and decarboxylation of the product in part (f)

(h) Phenyl vinyl ketone and sodium ethoxide

(i) Saponification and decarboxylation of the product in part (h)

21.19 Repeat the preceding problem for diethyl malonate.

21.20 (a) Only a small amount (less than 0.01%) of the enol form of diethyl malonate is present at equilibrium. Write a structural formula for this enol.

(b) Enol forms are present to the extent of about 8% in ethyl acetoacetate. There are three constitutionally isomeric enols possible. Write structural formulas for these three enols. Which one do you think is the most stable? The least stable? Why?

(c) Bromine reacts rapidly with both diethyl malonate and ethyl acetoacetate. The reaction is acid-catalyzed and liberates hydrogen bromide. What is the product formed in each reaction?

21.21 (a) On addition of one equivalent of methylmagnesium iodide to ethyl acetoacetate, the Grignard reagent is consumed, but the only organic product obtained after working up the reaction mixture is ethyl acetoacetate. Why? What happens to the Grignard reagent?

(b) On repeating the reaction but using D_2O and DCl to work up the reaction mixture, it is found that the recovered ethyl acetoacetate contains deuterium. Where is this deuterium located?

21.22 Give the structure of the principal organic product of each of the following reactions:

(a) Ethyl octanoate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(b) Product of part (a) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O,\ 2.\ H^+}$

(c) Ethyl acetoacetate + 1-bromobutane $\xrightarrow{NaOCH_2CH_3,\ \text{ethanol}}$

(d) Product of part (c) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O,\ 2.\ H^+}$

(e) Product of part (c) + 1-iodobutane $\xrightarrow{NaOCH_2CH_3,\ \text{ethanol}}$

(f) Product of part (e) $\xrightarrow[3.\ \text{heat}]{1.\ NaOH,\ H_2O,\ 2.\ H^+}$

(g) Acetophenone + diethyl carbonate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(h) Acetone + diethyl oxalate $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$

(i) Diethyl malonate + 1-bromo-2-methylbutane $\xrightarrow{NaOCH_2CH_3,\ ethanol}$

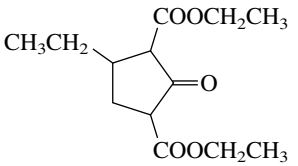
(j) Product of part (i) $\xrightarrow[3.\ heat]{1.\ NaOH,\ H_2O \\ 2.\ H^+}$

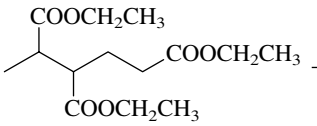
(k) Diethyl malonate + 6-methyl-2-cyclohexenone $\xrightarrow{NaOCH_2CH_3,\ ethanol}$

(l) Product of part (k) $\xrightarrow{H_2O,\ HCl,\ heat}$

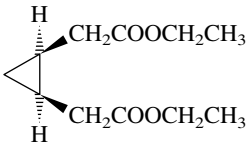
(m) *tert*-Butyl acetate $\xrightarrow[3.\ H^+]{1.\ [(CH_3)_2CH]_2NLi,\ THF \\ 2.\ benzaldehyde}$

21.23 Give the structure of the principal organic product of each of the following reactions:

(a)  $\xrightarrow[heat]{H_2O,\ H_2SO_4}$ $C_7H_{12}O$

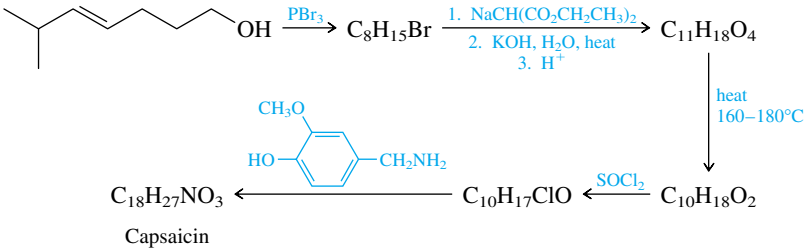
(b)  $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$ $C_{12}H_{18}O_5$

(c) Product of part (b) $\xrightarrow[heat]{H_2O,\ H^+}$ $C_7H_{10}O_3$

(d)  $\xrightarrow[2.\ H^+]{1.\ NaOCH_2CH_3}$ $C_9H_{12}O_3$

(e) Product of part (d) $\xrightarrow[3.\ heat]{1.\ HO^-,\ H_2O \\ 2.\ H^+}$ C_6H_8O

21.24 The spicy flavor of cayenne pepper is due mainly to a substance called *capsaicin.* The following sequence of steps was used in a 1955 synthesis of capsaicin. See if you can deduce the structure of capsaicin on the basis of this synthesis.



21.25 Show how you could prepare each of the following compounds. Use the starting material indicated along with ethyl acetoacetate or diethyl malonate and any necessary inorganic reagents. Assume also that the customary organic solvents are freely available.

(a) 4-Phenyl-2-butanone from benzyl alcohol

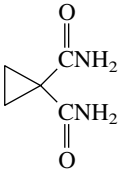
(b) 3-Phenylpropanoic acid from benzyl alcohol

(c) 2-Allyl-1,3-propanediol from propene

(d) 4-Penten-1-ol from propene

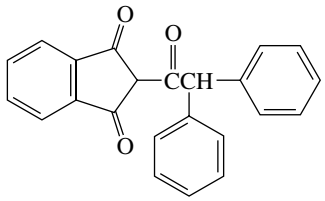
(e) 5-Hexen-2-ol from propene

(f) Cyclopropanecarboxylic acid from 1,2-dibromoethane

(g)  from 1,2-dibromoethane

(h) $HO_2C(CH_2)_{10}CO_2H$ from $HO_2C(CH_2)_6CO_2H$

21.26 *Diphenadione* inhibits the clotting of blood; that is, it is an *anticoagulant.* It is used to control vampire bat populations in South America by a "Trojan horse" strategy. A few bats are trapped, smeared with diphenadione, and then released back into their normal environment. Other bats, in the course of grooming these diphenadione-coated bats, ingest the anticoagulant and bleed to death, either internally or through accidental bites and scratches.



Diphenadione

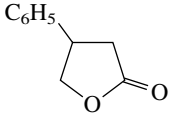
Suggest a synthesis of diphenadione from 1,1-diphenylacetone and dimethyl 1,2-benzenedicarboxylate.

21.27 *Phenylbutazone* is a frequently prescribed antiinflammatory drug. It is prepared by the reaction shown.

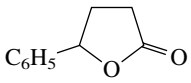
$$\underset{\text{Diethyl butylmalonate}}{CH_3CH_2CH_2CH_2CH(COOCH_2CH_3)_2} + \underset{\text{1,2-Diphenylhydrazine}}{C_6H_5NHNHC_6H_5} \longrightarrow \underset{\text{Phenylbutazone}}{C_{19}H_{20}N_2O_2}$$

What is the structure of phenylbutazone?

21.28 The use of epoxides as alkylating agents for diethyl malonate provides a useful route to γ-lactones. Write equations illustrating such a sequence for styrene oxide as the starting epoxide. Is the lactone formed by this reaction 3-phenylbutanolide, or is it 4-phenylbutanolide?

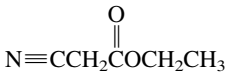


3-Phenylbutanolide



4-Phenylbutanolide

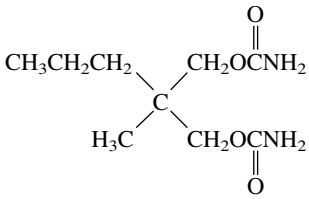
21.29 Diethyl malonate is prepared commercially by hydrolysis and esterification of ethyl cyanoacetate.



Ethyl cyanoacetate

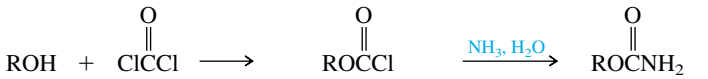
The preparation of ethyl cyanoacetate proceeds via ethyl chloroacetate and begins with acetic acid. Write a sequence of reactions describing this synthesis.

21.30 The tranquilizing drug *meprobamate* has the structure shown.



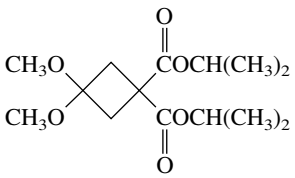
Meprobamate

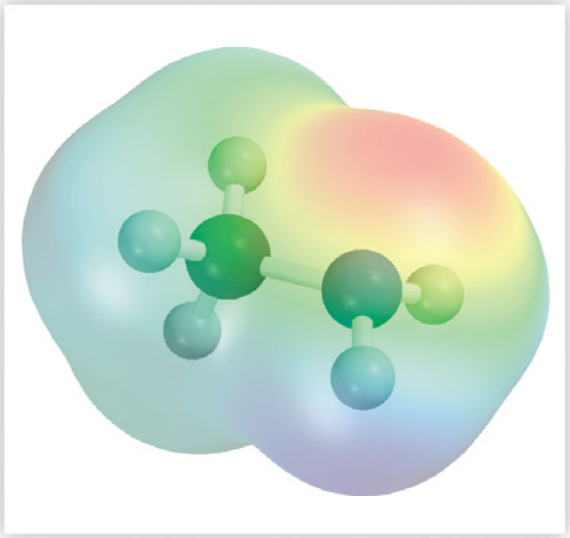
Devise a synthesis of meprobamate from diethyl malonate and any necessary organic or inorganic reagents. *Hint: Carbamate esters,* that is, compounds of the type $ROCNH_2$, are prepared from alcohols by the sequence of reactions



Alcohol Phosgene Chlorocarbonate ester Carbamate ester

21.31 When the compound shown was heated in refluxing hydrochloric acid for 60 hours, a product with the molecular formula $C_5H_6O_3$ was isolated in 97% yield. Identify this product. Along with this product, three other carbon-containing substances are formed. What are they?





CHAPTER 22

AMINES

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

R = alkyl group: alkylamine

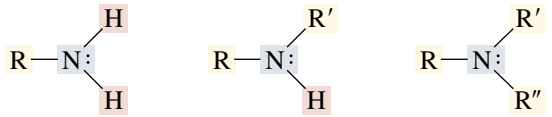
Ar = aryl group: arylamine

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

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

22.1 AMINE NOMENCLATURE

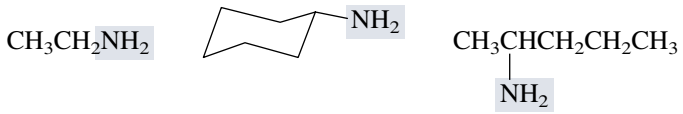
Unlike alcohols and alkyl halides, which are classified as primary, secondary, or tertiary according to the degree of substitution at the carbon that bears the functional group, amines are classified according to their *degree of substitution at nitrogen.* An amine with one carbon attached to nitrogen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



Primary amine Secondary amine Tertiary amine

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

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



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

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

(a) $C_6H_5CH_2CH_2NH_2$

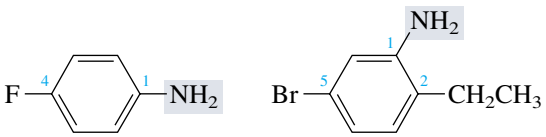
(b) $C_6H_5CHNH_2$ with CH_3 branch

(c) $CH_2{=}CHCH_2NH_2$

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

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

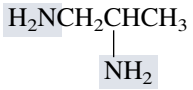
Aniline was first isolated in 1826 as a degradation product of indigo, a dark blue dye obtained from the West Indian plant *Indigofera anil,* from which the name *aniline* is derived.



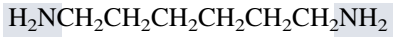
p-Fluoroaniline 5-Bromo-2-ethylaniline

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

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



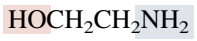
1,2-Propanediamine



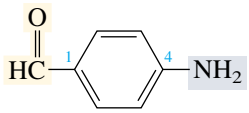
1,6-Hexanediamine

1,4-Benzenediamine

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



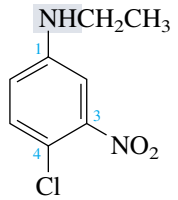
2-Aminoethanol



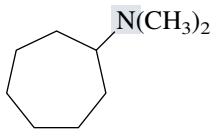
p-Aminobenzaldehyde
(4-Aminobenzenecarbaldehyde)

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

N-Methylethylamine
(a secondary amine)



4-Chloro-*N*-ethyl-3-nitroaniline
(a secondary amine)

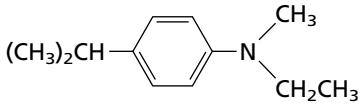


N,*N*-Dimethylcycloheptylamine
(a tertiary amine)

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

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

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



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

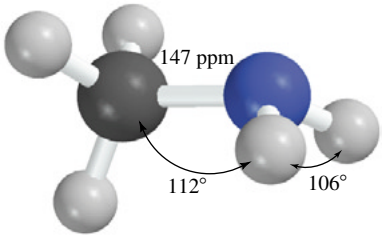
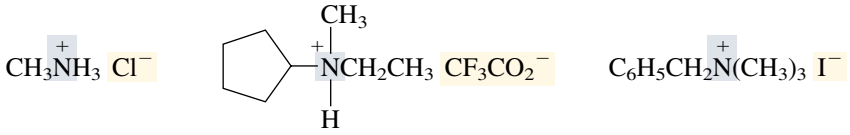


FIGURE 22.1 A ball-and-stick model of methylamine showing the trigonal pyramidal arrangement of bonds to nitrogen. The most stable conformation has the staggered arrangement of bonds shown. Other alkylamines have similar geometries.



Methylammonium chloride

N-Ethyl-*N*-methylcyclopentylammonium trifluoroacetate

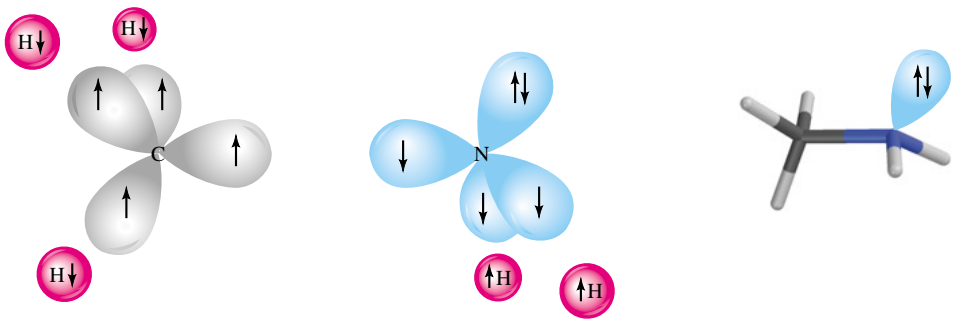
Benzyltrimethylammonium iodide (a quaternary ammonium salt)

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

22.2 STRUCTURE AND BONDING

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

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



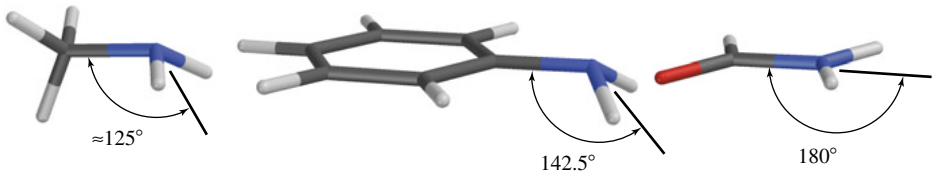
(*a*) (*b*)

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

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

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

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

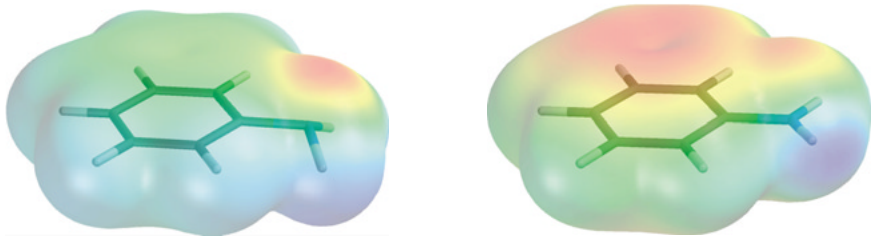


Methylamine (CH_3NH_2) Aniline ($C_6H_5NH_2$) Formamide ($O{=}CHNH_2$)

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

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

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

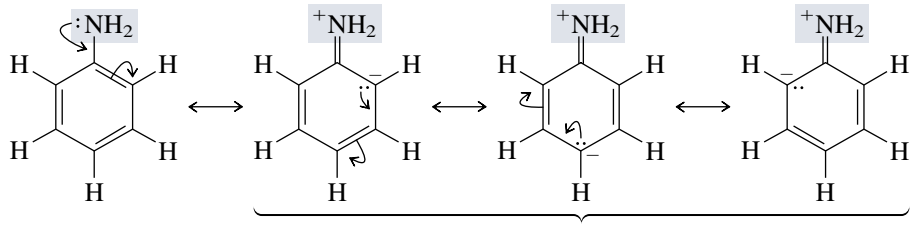


(*a*) (*b*)

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

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

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



Most stable Lewis structure for aniline

Dipolar resonance forms of aniline

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

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

22.3 PHYSICAL PROPERTIES

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

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

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

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

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

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

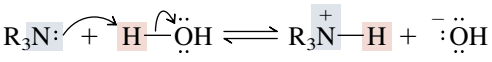
Primary and secondary amines can participate in intermolecular hydrogen bonding, but tertiary amines cannot.

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

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

22.4 MEASURES OF AMINE BASICITY

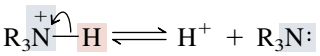
Two conventions are used to measure the basicity of amines. One of them defines a **basicity constant K_b** for the amine acting as a proton acceptor from water:



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

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

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



where K_a and pK_a have their usual meaning:

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

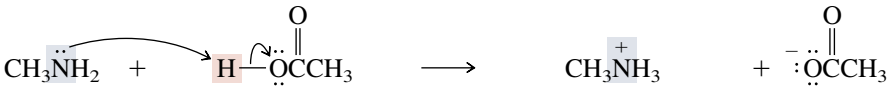
The conjugate acid of ammonia is ammonium ion (NH_4^+), which has $K_a = 5.6 \times 10^{-10}$ ($pK_a = 9.3$). The conjugate acid of methylamine is methylammonium ion ($CH_3NH_3^+$), which has $K_a = 2 \times 10^{-11}$ ($pK_a = 10.7$). *The more basic the amine, the weaker is its conjugate acid.* Methylamine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

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

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

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

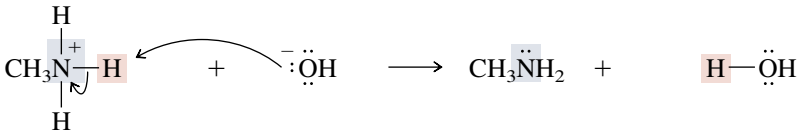
Citing amine basicity according to the acidity of the conjugate acid permits acid–base reactions involving amines to be analyzed according to the usual Brønsted relationships. By comparing the acidity of an acid with the conjugate acid of an amine, for example, we see that amines are converted to ammonium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



Methylamine | Acetic acid (stronger acid; $pK_a = 4.7$) | Methylammonium ion (weaker acid; $pK_a = 10.7$) | Acetate ion

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

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



Methylammonium ion (stronger acid; $pK_a = 10.7$) | Hydroxide ion | Methylamine | Water (weaker acid; $pK_a = 15.7$)

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

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

22.5 BASICITY OF AMINES

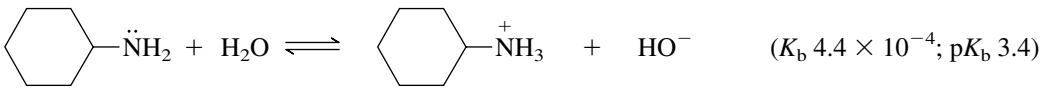
Amines are weak bases, but as a class, *amines are the strongest bases of all neutral molecules.* Table 22.1 lists basicity data for a number of amines. The most important relationships to be drawn from the data are

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

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

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

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



Cyclohexylamine | Water | Cyclohexylammonium ion | Hydroxide ion

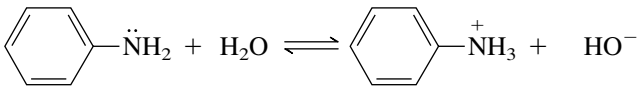
(K_b 4.4×10^{-4}; pK_b 3.4)

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

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

*In water at 25°C.

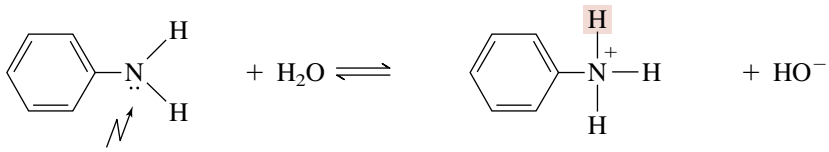
it is far less favorable for aniline.



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

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

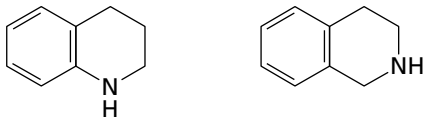
Aniline is a much weaker base because its delocalized lone pair is more strongly held than the nitrogen lone pair in cyclohexylamine. The more strongly held the electron pair, the less able it is to abstract a proton.



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

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

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

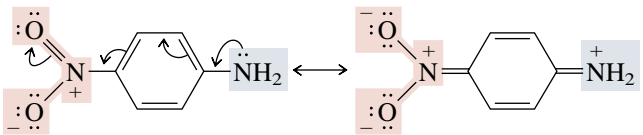


Tetrahydroquinoline Tetrahydroisoquinoline

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

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

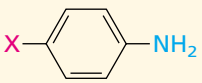
In general, electron-donating substituents on the aromatic ring increase the basicity of arylamines slightly. Thus, as shown in Table 22.2, an electron-donating methyl group in the para position *increases* the basicity of aniline by a factor of only 5–6 (less than 1 pK unit). Electron-withdrawing groups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



Electron delocalization in *p*-nitroaniline

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

TABLE 22.2 Effect of Substituents on the Basicity of Aniline



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

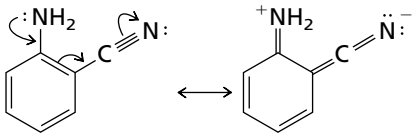
PROBLEM 22.8 Each of the following is a much weaker base than aniline. Present a resonance argument to explain the effect of the substituent in each case.

(a) *o*-Cyanoaniline

(c) *p*-Aminoacetophenone

(b) $C_6H_5NHCCH_3$ (O)

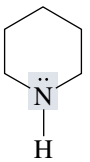
SAMPLE SOLUTION (a) A cyano substituent is strongly electron-withdrawing. When present at a position ortho to an amino group on an aromatic ring, a cyano substituent increases the delocalization of the amine lone-pair electrons by a direct resonance interaction.



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

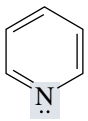
Multiple substitution by strongly electron-withdrawing groups diminishes the basicity of arylamines still more. As just noted, aniline is 3800 times as strong a base as *p*-nitroaniline; however, it is 10^9 times more basic than 2,4-dinitroaniline. A practical consequence of this is that arylamines that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

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



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

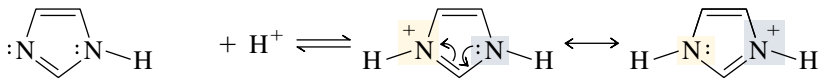
is more basic than



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

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

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



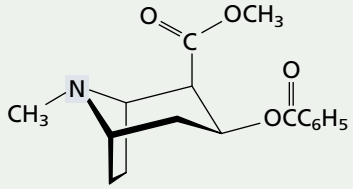
Imidazole
($K_b = 1 \times 10^{-7}$; $pK_b = 7$)

Imidazolium ion

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

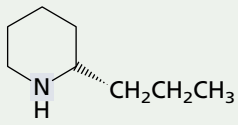
AMINES AS NATURAL PRODUCTS

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



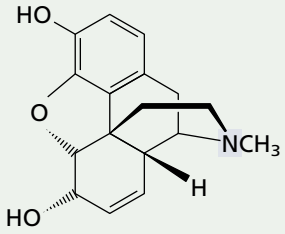
Cocaine

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



Coniine

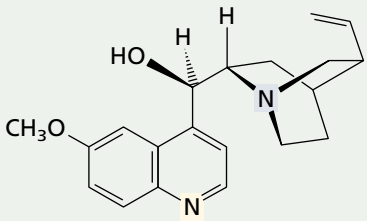
(Present along with other alkaloids in the hemlock extract used to poison Socrates.)



Morphine

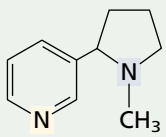
(An opium alkaloid. Although it is an excellent analgesic, its use is restricted because of the potential for addiction. Heroin is the diacetate ester of morphine.)

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



Quinine

(Alkaloid of cinchona bark used to treat malaria)



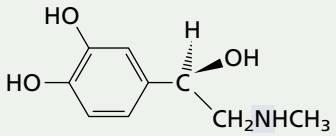
Nicotine

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

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

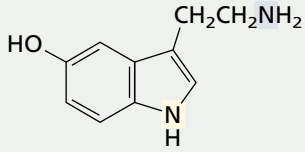
* The isolation of alkaloids from plants is reviewed in the August 1991 issue of the *Journal of Chemical Education*, pp. 700–703.

—Cont.



Epinephrine

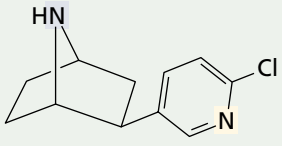
(Also called *adrenaline;* a hormone secreted by the adrenal gland that prepares the organism for "flight or fight.")



Serotonin

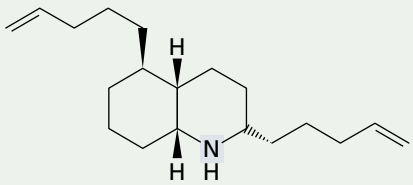
(A hormone synthesized in the pineal gland. Certain mental disorders are believed to be related to serotonin levels in the brain.)

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



Epibatidine

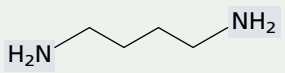
(Once used as an arrow poison, it is hundreds of times more powerful than morphine in relieving pain. It is too toxic to be used as a drug, however.)



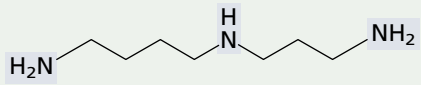
Dendrobine

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

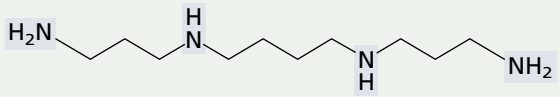
Among the more important amine derivatives found in the body are a group of compounds known as **polyamines,** which contain two to four nitrogen atoms separated by several methylene units:



Putrescine



Spermidine

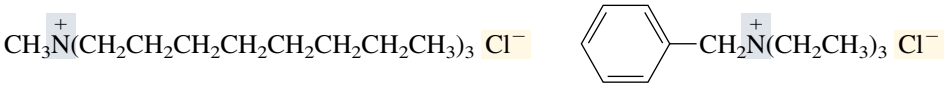


Spermine

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

22.6 TETRAALKYLAMMONIUM SALTS AS PHASE-TRANSFER CATALYSTS

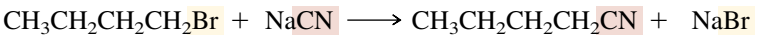
In spite of being ionic, many quaternary ammonium salts dissolve in nonpolar media. The four alkyl groups attached to nitrogen shield its positive charge and impart *lipophilic* character to the tetraalkylammonium ion. The following two quaternary ammonium salts, for example, are soluble in solvents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



Methyltrioctylammonium chloride

Benzyltriethylammonium chloride

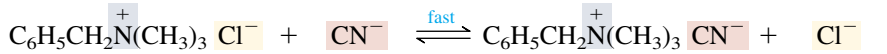
This property of quaternary ammonium salts is used to advantage in an experimental technique known as **phase-transfer catalysis.** Imagine that you wish to carry out the reaction



Butyl bromide — Sodium cyanide — Pentanenitrile — Sodium bromide

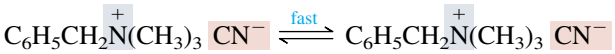
Sodium cyanide does not dissolve in butyl bromide. The two reactants contact each other only at the surface of the solid sodium cyanide, and the rate of reaction under these conditions is too slow to be of synthetic value. Dissolving the sodium cyanide in water is of little help, since butyl bromide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

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



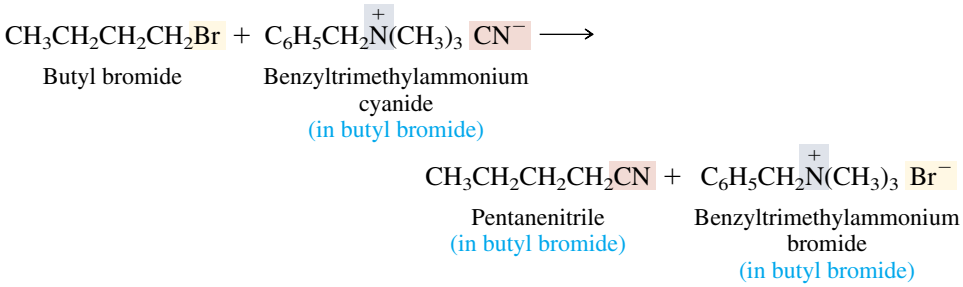
Benzyltrimethylammonium chloride (aqueous) — Cyanide ion (aqueous) — Benzyltrimethylammonium cyanide (aqueous) — Chloride ion (aqueous)

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



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

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



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

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

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

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

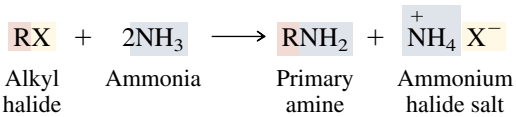
Methods for preparing amines address either or both of the following questions:

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

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

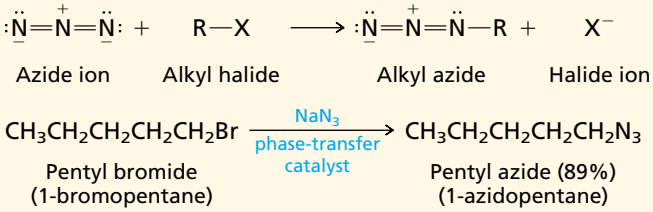
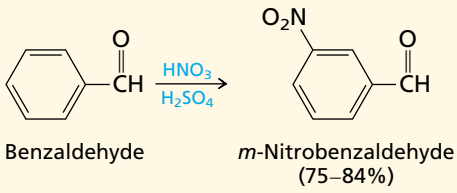
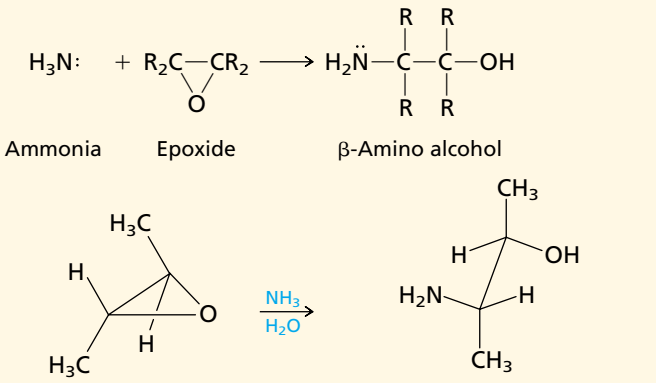
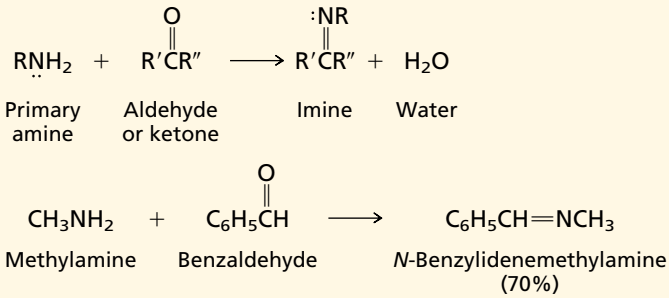
22.8 PREPARATION OF AMINES BY ALKYLATION OF AMMONIA

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



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

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

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

(Continued)

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

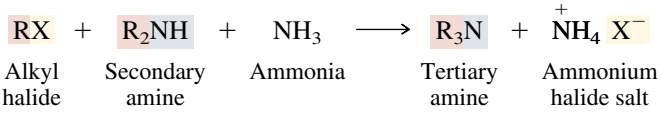
Reaction (section) and comments	General equation and specific example
Nucleophilic substitution by ammonia on α-halo acids (Section 19.16) The α-halo acids obtained by halogenation of carboxylic acids under conditions of the Hell–Volhard–Zelinsky reaction are reactive substrates in nucleophilic substitution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

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

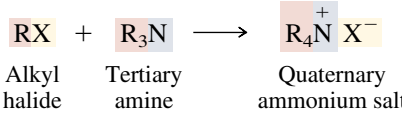
When 1-bromooctane, for example, is allowed to react with ammonia, both the primary amine and the secondary amine are isolated in comparable amounts.

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

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



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



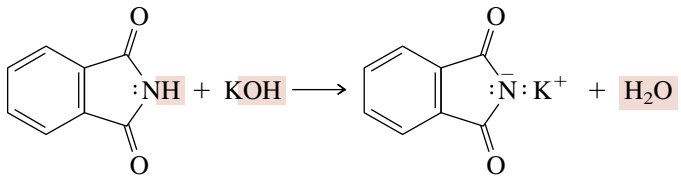
Because alkylation of ammonia can lead to a complex mixture of products, it is used to prepare primary amines only when the starting alkyl halide is not particularly expensive and the desired amine can be easily separated from the other components of the reaction mixture.

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

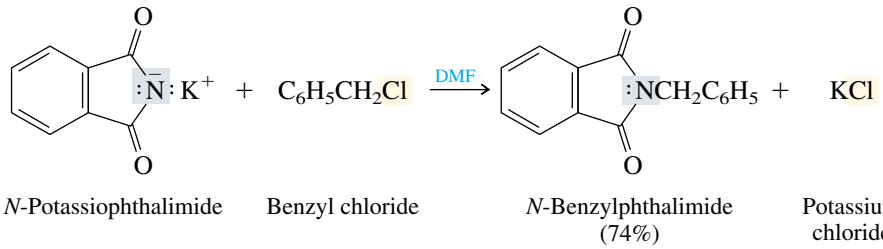
Aryl halides do not normally react with ammonia under these conditions. The few exceptions are special cases and will be described in Section 23.5.

22.9 THE GABRIEL SYNTHESIS OF PRIMARY ALKYLAMINES

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



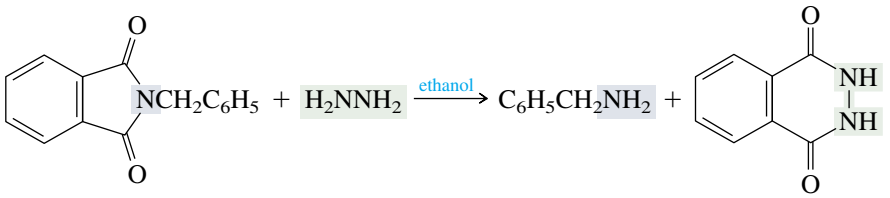
Phthalimide, with a K_a of 5×10^{-9} (pK_a 8.3), can be quantitatively converted to its potassium salt with potassium hydroxide. The potassium salt of phthalimide has a negatively charged nitrogen atom, which acts as a nucleophile toward primary alkyl halides in a bimolecular nucleophilic substitution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



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

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

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



N-Benzylphthalimide Hydrazine Benzylamine (97%) Phthalhydrazide

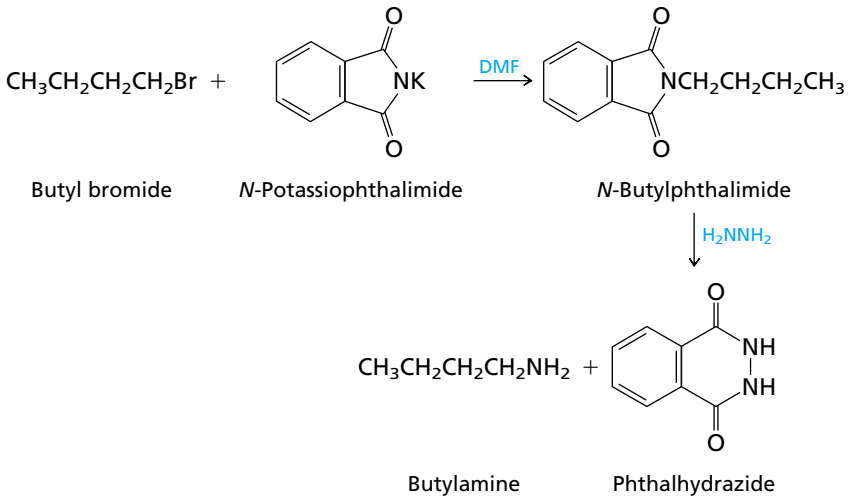
Aryl halides cannot be converted to arylamines by the Gabriel synthesis, because they do not undergo nucleophilic substitution with *N*-potassiophthalimide in the first step of the procedure.

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

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

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

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



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

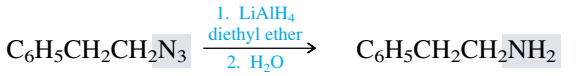
Butylamine Phthalhydrazide

22.10 PREPARATION OF AMINES BY REDUCTION

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

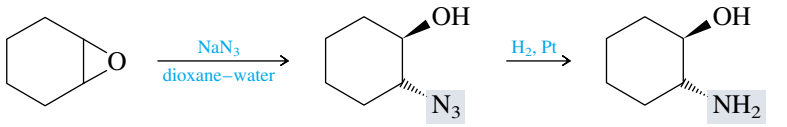
Alkyl *azides,* prepared by nucleophilic substitution of alkyl halides by sodium azide, as shown in the first entry of Table 22.3, are reduced to alkylamines by a variety of reagents, including lithium aluminum hydride.

Alkyl azide — Primary amine



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

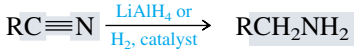
Catalytic hydrogenation is also effective:



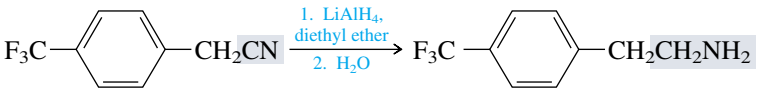
1,2-Epoxycyclohexane — *trans*-2-Azidocyclohexanol (61%) — *trans*-2-Aminocyclohexanol (81%)

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

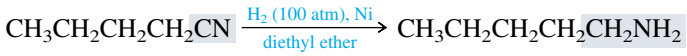
The same reduction methods may be applied to the conversion of *nitriles* to primary amines.



Nitrile — Primary amine



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



Pentanenitrile — 1-Pentanamine (56%)

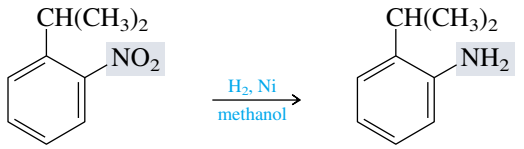
The preparation of pentanenitrile under phase-transfer conditions was described in Section 22.6.

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

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

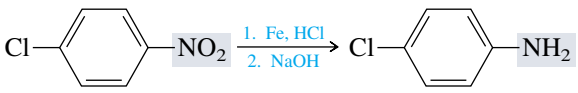
Nitro groups are readily reduced to primary amines by a variety of methods. Catalytic hydrogenation over platinum, palladium, or nickel is often used, as is reduction by iron or tin in hydrochloric acid. The ease with which nitro groups are reduced is

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

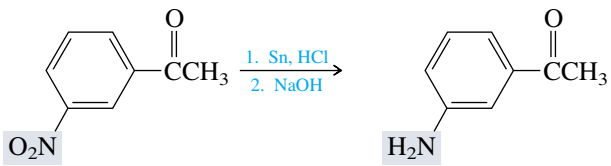


o-Isopropylnitrobenzene — *o*-Isopropylaniline (92%)

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



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

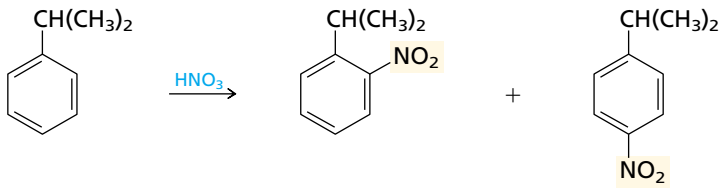


m-Nitroacetophenone — *m*-Aminoacetophenone (82%)

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

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

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

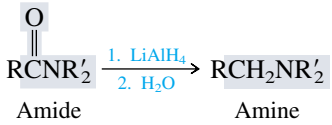


Isopropylbenzene — *o*-Isopropylnitrobenzene (bp 110°C) — *p*-Isopropylnitrobenzene (bp 131°C)

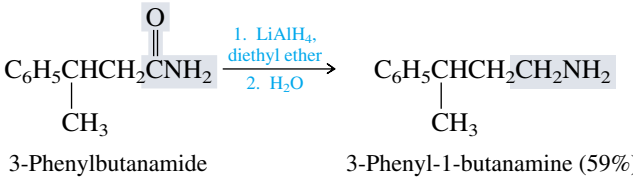
As actually performed, a 62% yield of a mixture of ortho and para nitration products has been obtained with an ortho–para ratio of about 1:3.

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

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

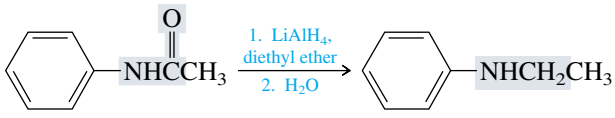


In this general equation, R and R′ may be either alkyl or aryl groups. When R′ = H, the product is a primary amine:

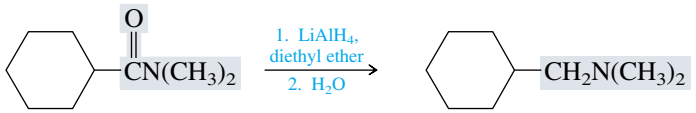


N-Substituted amides yield secondary amines:

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



N,N-Disubstituted amides yield tertiary amines:

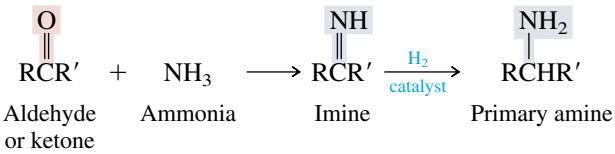


Because amides are so easy to prepare, this is a versatile method for the preparation of amines.

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

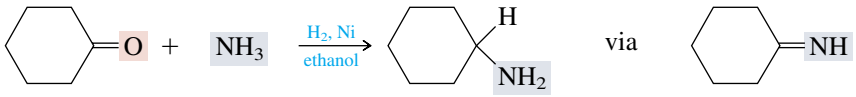
22.11 REDUCTIVE AMINATION

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



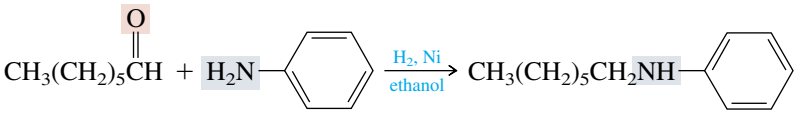
The overall reaction converts a carbonyl compound to an amine by carbon–nitrogen bond formation and reduction; it is commonly known as **reductive amination.** What makes it a particularly valuable synthetic procedure is that it can be carried out in a single operation by hydrogenation of a solution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

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

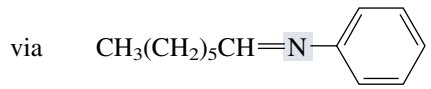


Cyclohexanone Ammonia Cyclohexylamine (80%)

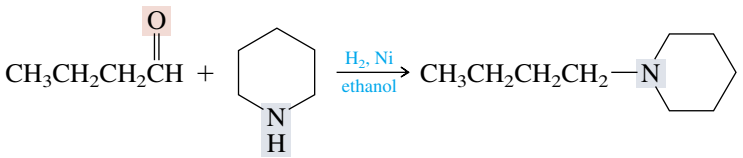
Secondary amines are prepared by hydrogenation of a carbonyl compound in the presence of a primary amine. An *N*-substituted imine, or *Schiff's base,* is an intermediate:



Heptanal Aniline *N*-Heptylaniline (65%)

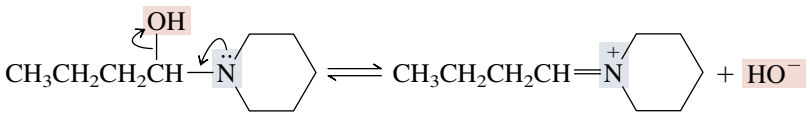


Reductive amination has been successfully applied to the preparation of tertiary amines from carbonyl compounds and secondary amines even though a neutral imine is not possible in this case.



Butanal Piperidine *N*-Butylpiperidine (93%)

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

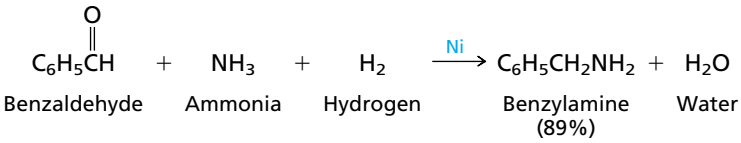


Carbinolamine Iminium ion

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

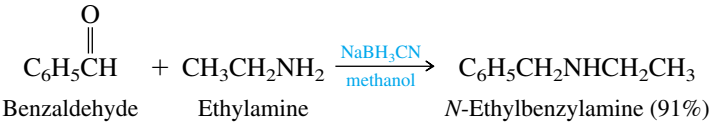
(a) Benzylamine
(b) Dibenzylamine
(c) *N,N*-Dimethylbenzylamine
(d) *N*-Benzylpiperidine

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



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

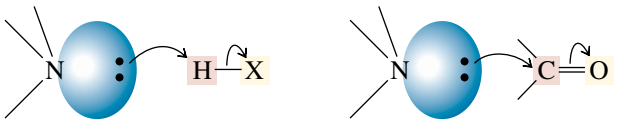
A variation of the classical reductive amination procedure uses sodium cyanoborohydride ($NaBH_3CN$) instead of hydrogen as the reducing agent and is better suited to amine syntheses in which only a few grams of material are needed. All that is required is to add sodium cyanoborohydride to an alcohol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



22.12 REACTIONS OF AMINES: A REVIEW AND A PREVIEW

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

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



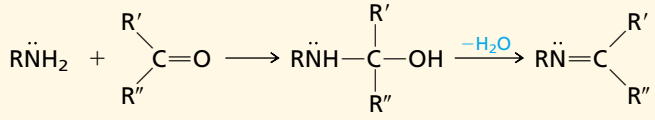
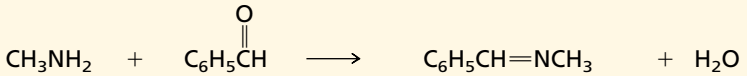
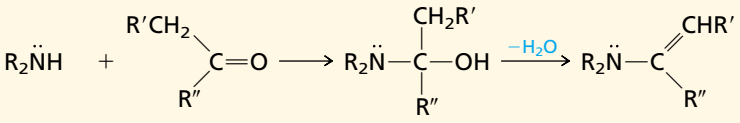
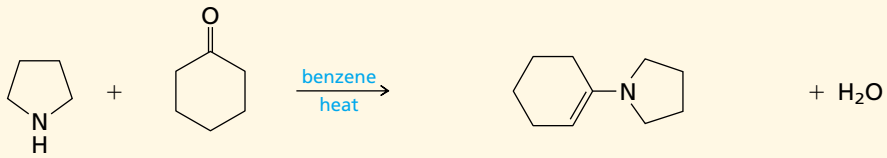
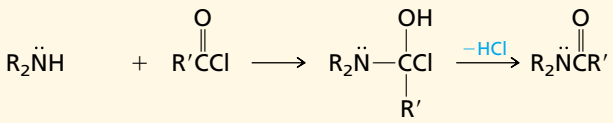
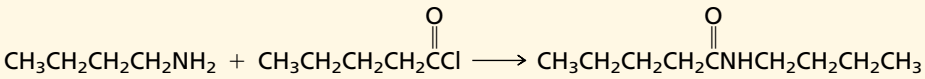
Amine acting as a base Amine acting as a nucleophile

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

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

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

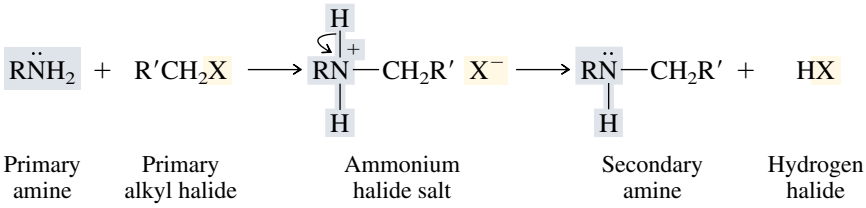
TABLE 22.4 Reactions of Amines Discussed in Previous Chapters*

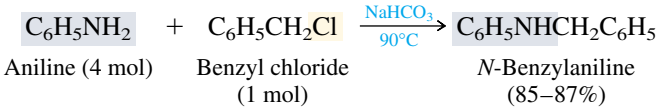
Reaction (section) and comments	General equation and specific example
Reaction of primary amines with aldehydes and ketones (Section 17.10) Imines are formed by nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or a ketone. The key step is formation of a carbinolamine intermediate,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

*Both alkylamines and arylamines undergo these reactions.

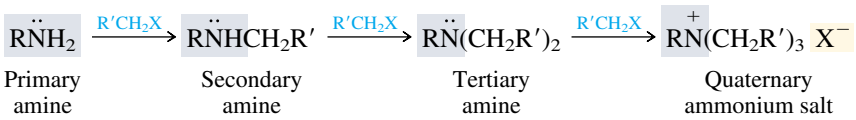
22.13 REACTION OF AMINES WITH ALKYL HALIDES

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

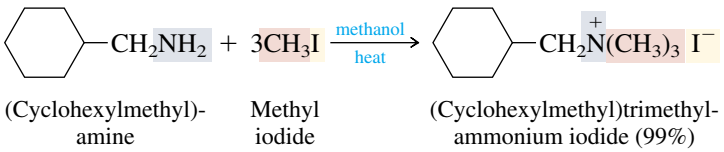




A second alkylation may follow, converting the secondary amine to a tertiary amine. Alkylation need not stop there; the tertiary amine may itself be alkylated, giving a quaternary ammonium salt.



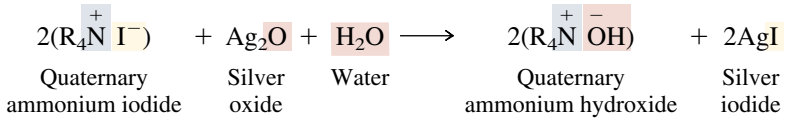
Because of its high reactivity toward nucleophilic substitution, methyl iodide is the alkyl halide most often used to prepare quaternary ammonium salts.

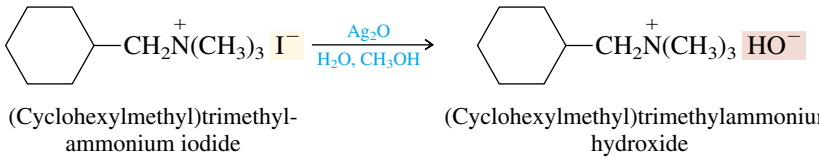


Quaternary ammonium salts, as we have seen, are useful in synthetic organic chemistry as phase-transfer catalysts. In another, more direct application, quaternary ammonium *hydroxides* are used as substrates in an elimination reaction to form alkenes.

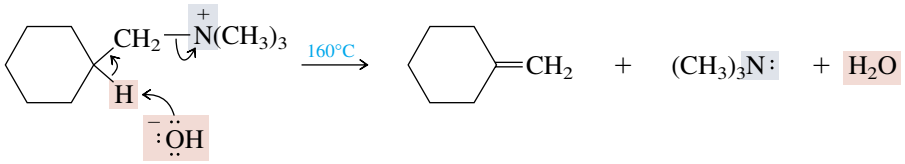
22.14 THE HOFMANN ELIMINATION

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





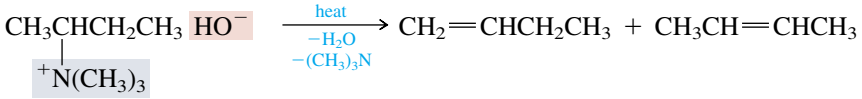
When quaternary ammonium hydroxides are heated, they undergo β-elimination to form an alkene and an amine.



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

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

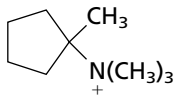
A novel aspect of the Hofmann elimination is its regioselectivity. Elimination in alkyltrimethylammonium hydroxides proceeds in the direction that gives the *less* substituted alkene.

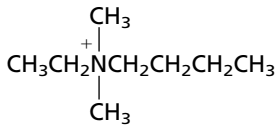


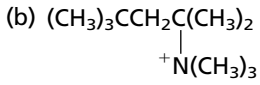
sec-Butyltrimethylammonium hydroxide — 1-Butene (95%) — 2-Butene (5%) (cis and trans)

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

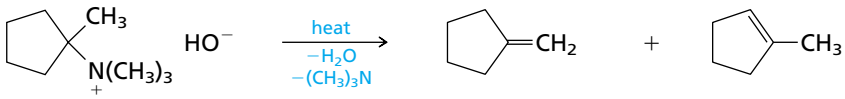
PROBLEM 22.13 Give the structure of the major alkene formed when the hydroxide of each of the following quaternary ammonium ions is heated.

(a) 

(c) 

(b) 

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



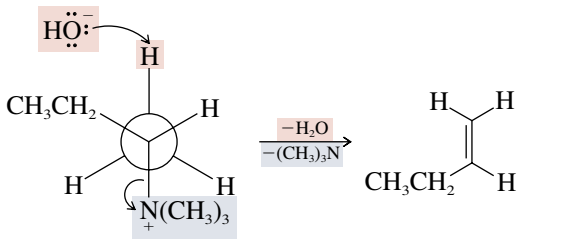
(1-Methylcyclopentyl)trimethylammonium hydroxide — Methylenecyclopentane — 1-Methylcyclopentene

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

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

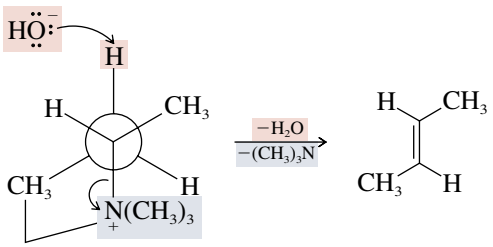
With a regioselectivity opposite to that of the Zaitsev rule, the Hofmann elimination is sometimes used in synthesis to prepare alkenes not accessible by dehydrohalogenation of alkyl halides. This application has decreased in importance since the Wittig reaction (Section 17.12) became established as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

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



1-Butene
(major product)

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



These two groups
crowd each other

trans-2-Butene
(minor product)

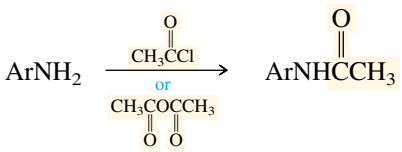
FIGURE 22.4 Newman projections showing the conformations leading to (*a*) 1-butene and (*b*) *trans*-2-butene by Hofmann elimination of *sec*-butyltrimethylammonium hydroxide. The major product is 1-butene.

22.15 ELECTROPHILIC AROMATIC SUBSTITUTION IN ARYLAMINES

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

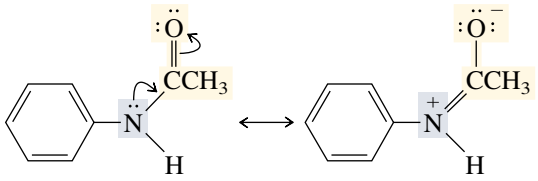
The reactivity of arylamines was noted in Section 12.12, where it was pointed out that $-\ddot{N}H_2$, $-\ddot{N}HR$, and $-\ddot{N}R_2$ are ortho, para-directing and exceedingly powerful activating groups. These substituents are such powerful activators that electrophilic aromatic substitution is only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

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



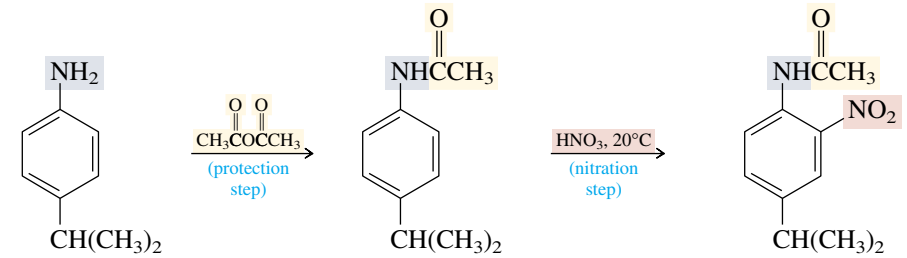
Arylamine *N*-Acetylarylamine

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



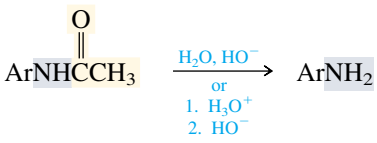
Amide resonance in acetanilide

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

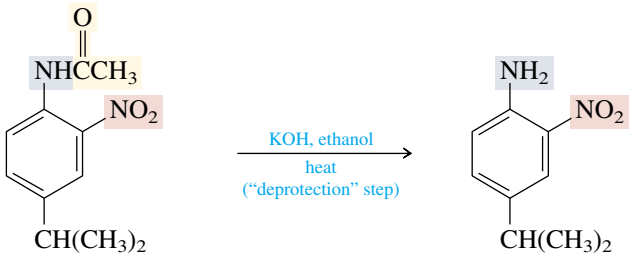


p-Isopropylaniline *p*-Isopropylacetanilide (98%) 4-Isopropyl-2-nitroacetanilide (94%)

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



N-Acetylarylamine Arylamine



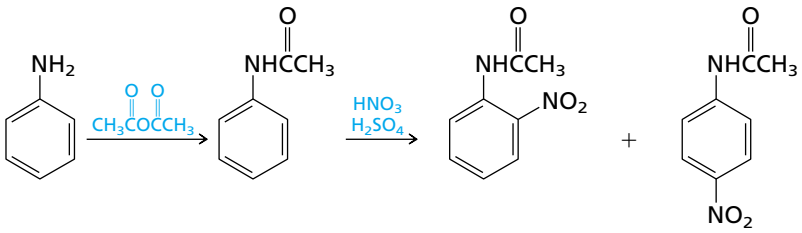
4-Isopropyl-2-nitroacetanilide 4-Isopropyl-2-nitroaniline (100%)

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

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

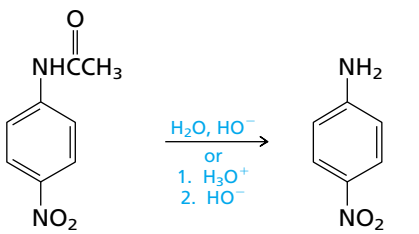
(a) *p*-Nitroaniline
(b) 2,4-Dinitroaniline
(c) *p*-Aminoacetanilide

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



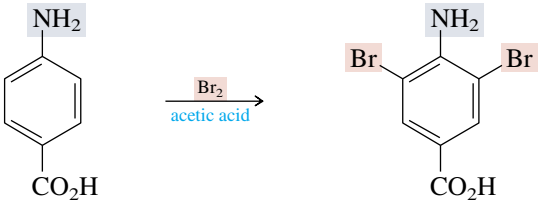
Aniline Acetanilide *o*-Nitroacetanilide *p*-Nitroacetanilide

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



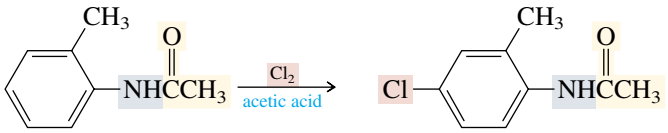
p-Nitroacetanilide *p*-Nitroaniline

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



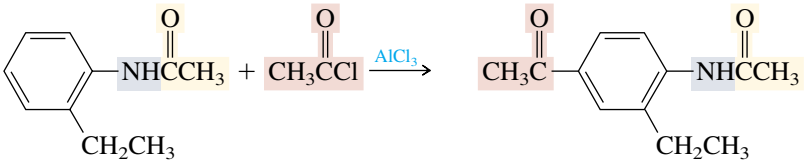
p-Aminobenzoic acid — 4-Amino-3,5-dibromobenzoic acid (82%)

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



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

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



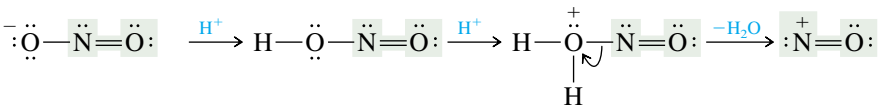
2-Ethylacetanilide — 4-Acetamido-3-ethylacetophenone (57%)

22.16 NITROSATION OF ALKYLAMINES

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

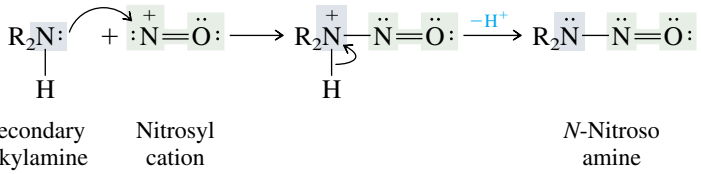
Nitrosyl cation is also called *nitrosonium* ion. It can be represented by the two resonance structures

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



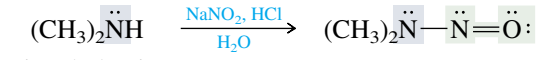
Nitrite ion (from sodium nitrite) — Nitrous acid — Nitrosyl cation

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



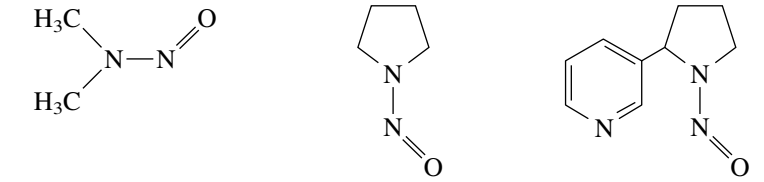
Refer to the molecular model of nitrosyl cation on *Learning By Modeling* to verify that the region of positive electrostatic potential is concentrated at nitrogen.

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



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

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



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

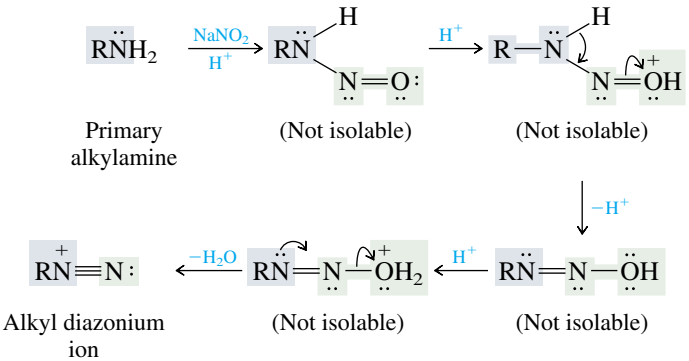
N-Nitrosopyrrolidine (formed when bacon that has been cured with sodium nitrite is fried)

N-Nitrosonornicotine (present in tobacco smoke)

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

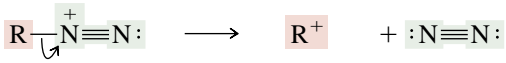
The July 1977 issue of the *Journal of Chemical Education* contains an article entitled "Formation of Nitrosamines in Food and in the Digestive System."

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



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

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



Alkyl diazonium ion Carbocation Nitrogen

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

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

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

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

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

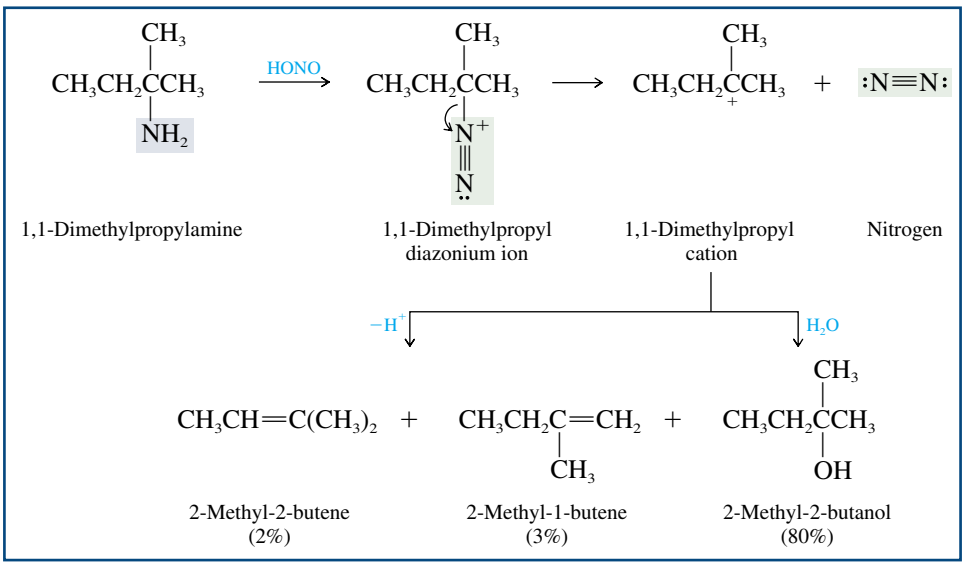
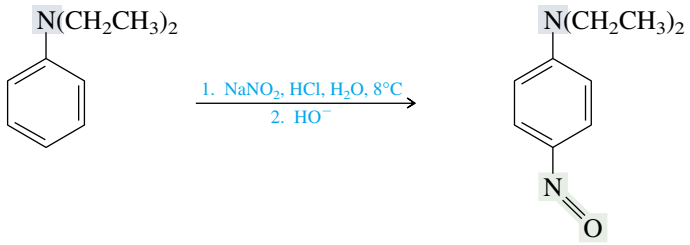


FIGURE 22.5 The diazonium ion generated by treatment of a primary alkylamine with nitrous acid loses nitrogen to give a carbocation. The isolated products are derived from the carbocation and include, in this example, alkenes (by loss of a proton) and an alcohol (nucleophilic capture by water).

22.17 NITROSATION OF ARYLAMINES

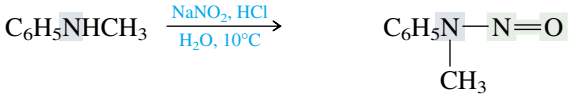
We learned in the preceding section that different reactions are observed when the various classes of alkylamines—primary, secondary, and tertiary—react with nitrosating agents. Although no useful chemistry attends the nitrosation of tertiary alkylamines, electrophilic aromatic substitution by nitrosyl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



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

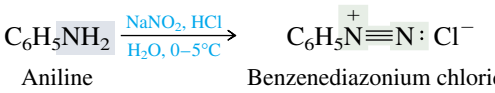
Nitrosyl cation is a relatively weak electrophile and attacks only very strongly activated aromatic rings.

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

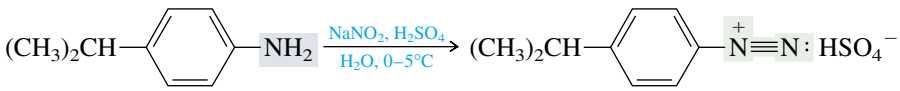


N-Methylaniline — *N*-Methyl-*N*-nitrosoaniline (87–93%)

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



Aniline — Benzenediazonium chloride



p-Isopropylaniline — *p*-Isopropylbenzenediazonium hydrogen sulfate

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

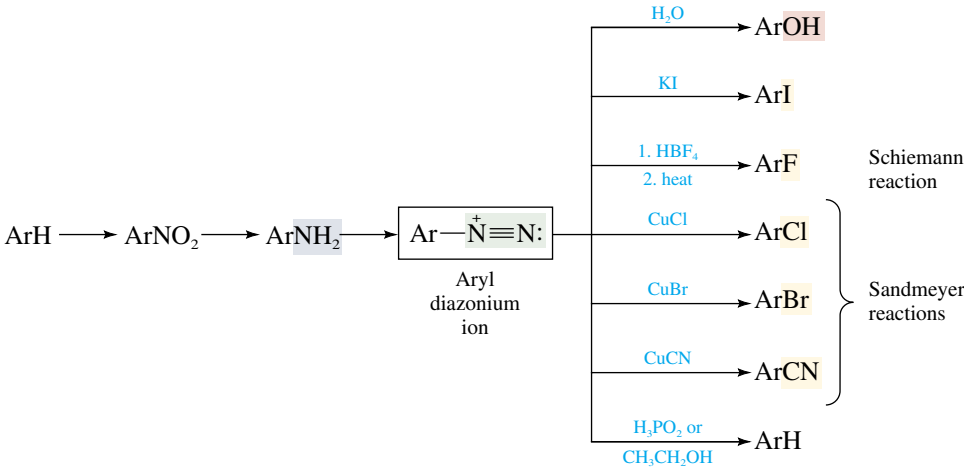
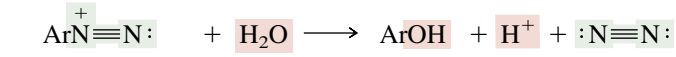


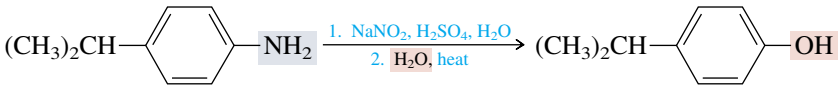
FIGURE 22.6 Flowchart showing the synthetic origin of aryl diazonium ions and their most useful transformations.

22.18 SYNTHETIC TRANSFORMATIONS OF ARYL DIAZONIUM SALTS

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



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

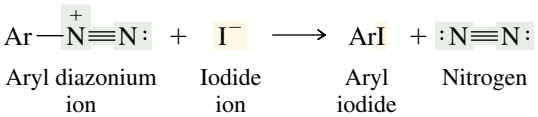


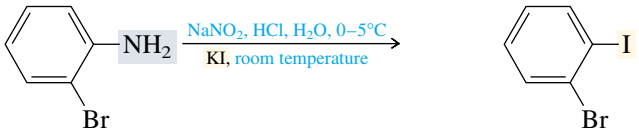
p-Isopropylaniline — *p*-Isopropylphenol (73%)

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

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

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





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

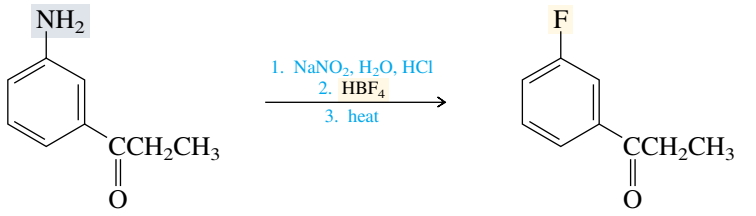
PROBLEM 22.18 Show by a series of equations how you could prepare *m*-bromoiodobenzene from benzene.

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

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

Aryl diazonium fluoroborate — Aryl fluoride — Boron trifluoride — Nitrogen

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



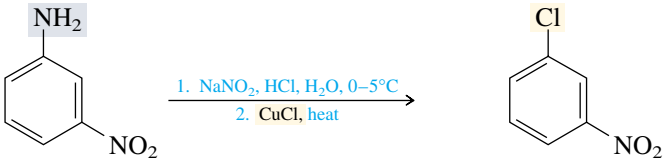
m-Aminophenyl ethyl ketone — Ethyl *m*-fluorophenyl ketone (68%)

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

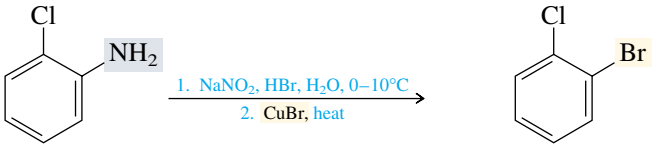
Although it is possible to prepare *aryl chlorides* and *aryl bromides* by electrophilic aromatic substitution, it is often necessary to prepare these compounds from an aromatic amine. The amine is converted to the corresponding diazonium salt and then treated with copper(I) chloride or copper(I) bromide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

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

Aryl diazonium ion — Aryl chloride or bromide — Nitrogen

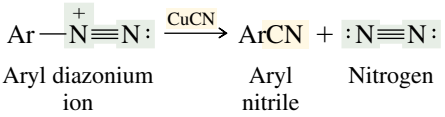


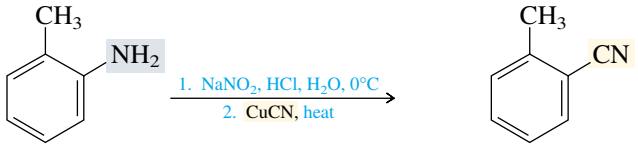
m-Nitroaniline — *m*-Chloronitrobenzene (68–71%)



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

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



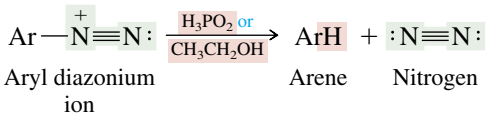


o-Toluidine *o*-Methylbenzonitrile (64–70%)

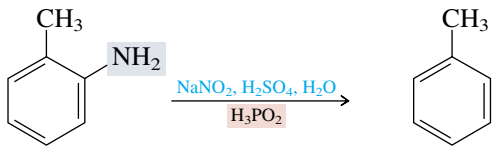
Since cyano groups may be hydrolyzed to carboxylic acids (Section 20.19), the Sandmeyer preparation of aryl nitriles is a key step in the conversion of arylamines to substituted benzoic acids. In the example just cited, the *o*-methylbenzonitrile that was formed was subsequently subjected to acid-catalyzed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

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

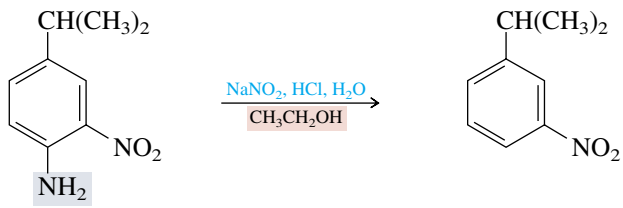
It is possible to replace amino substituents on an aromatic nucleus by hydrogen by reducing a diazonium salt with hypophosphorous acid (H_3PO_2) or with ethanol. These reductions are free-radical reactions in which ethanol or hypophosphorous acid acts as a hydrogen atom donor:



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



o-Toluidine Toluene (70–75%)



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

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

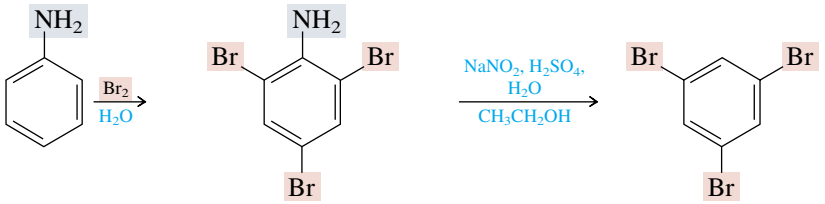
PROBLEM 22.20 Cumene (isopropylbenzene) is a relatively inexpensive commercially available starting material. Show how you could prepare *m*-isopropylnitrobenzene from cumene.

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

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

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

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



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

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

22.19 AZO COUPLING

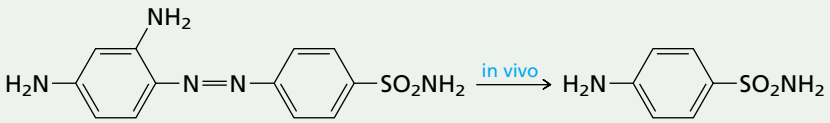
A reaction of aryl diazonium salts that does not involve loss of nitrogen takes place when they react with phenols and arylamines. Aryl diazonium ions are relatively weak

FROM DYES TO SULFA DRUGS

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

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

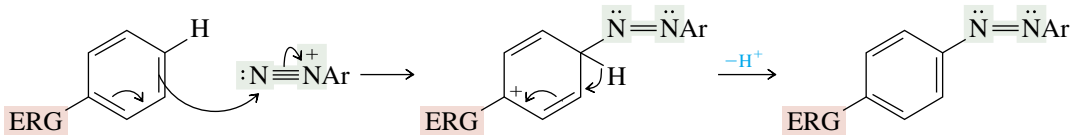
In spite of the rationale on which the testing of dyestuffs as antibiotics rested, subsequent research revealed that the antibacterial properties of Prontosil had nothing at all to do with its being a dye! In the body, Prontosil undergoes a reductive cleavage of its azo linkage to form *sulfanilamide,*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



Prontosil Sulfanilamide

—Cont.

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



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

Aryl diazonium ion

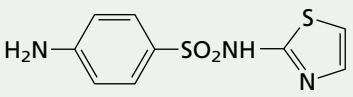
Intermediate in electrophilic aromatic substitution

Azo compound

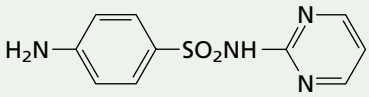
Azo compounds are often highly colored, and many of them are used as dyes.

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

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

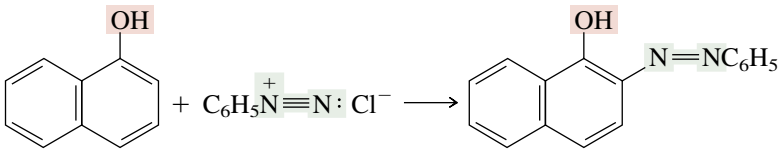


Sulfathiazole



Sulfadiazine

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



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

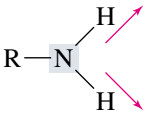
The colors of azo compounds vary with the nature of the aryl group, with its substituents, and with pH. Substituents also affect the water-solubility of azo dyes and how well they bind to a particular fabric. Countless combinations of diazonium salts and aromatic substrates have been examined with a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

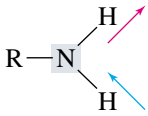
A number of pH indicators—methyl red, for example—are azo compounds.

22.20 SPECTROSCOPIC ANALYSIS OF AMINES

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

Symmetric N—H stretching of a primary amine





Antisymmetric N—H stretching of a primary amine

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

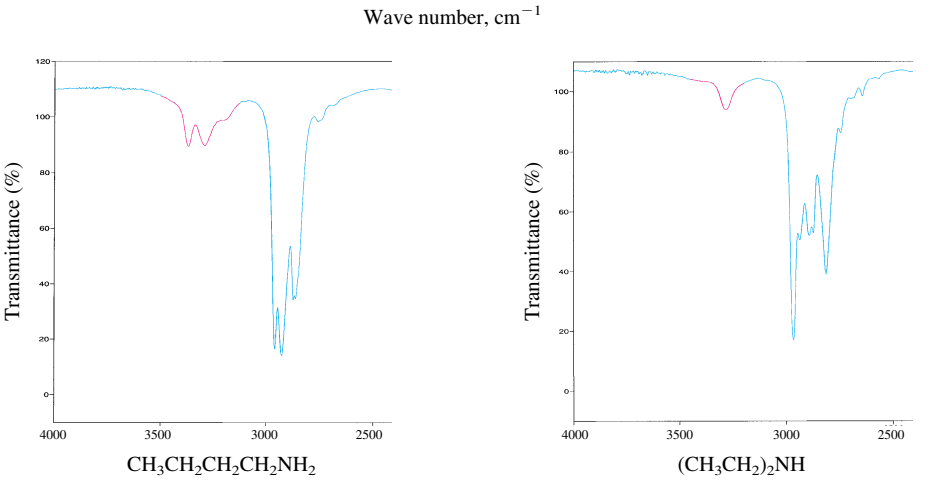


FIGURE 22.7 Portions of the infrared spectrum of (*a*) butylamine and (*b*) diethylamine. Primary amines exhibit two peaks due to N—H stretching, whereas secondary amines show only one.

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

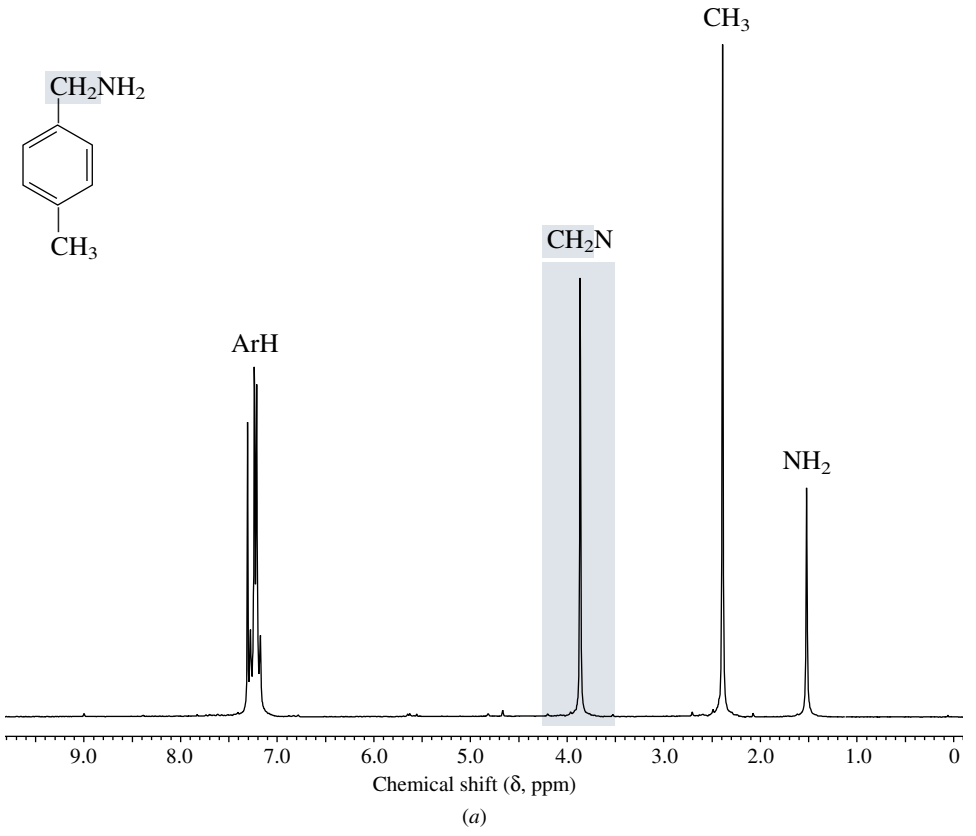


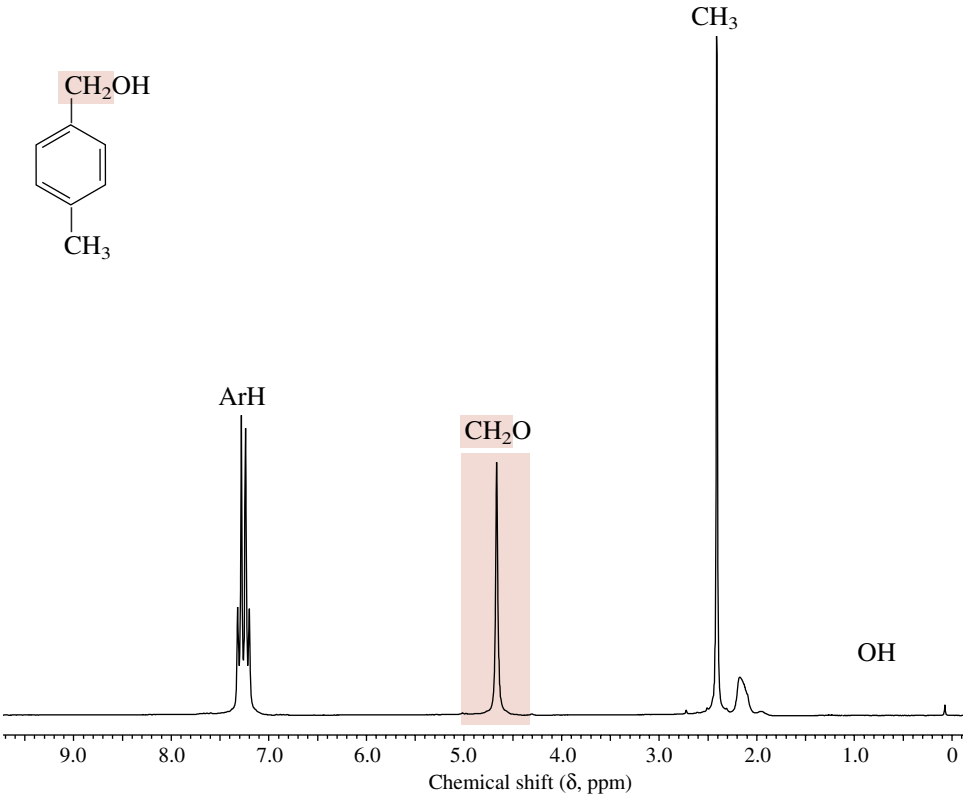
FIGURE 22.8 The 200-MHz ^{1}H NMR spectra of (*a*) 4-methylbenzylamine and of (*b*) 4-methylbenzyl alcohol. The singlet corresponding to CH_2N in (*a*) is more shielded than that of CH_2O in (*b*).

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

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

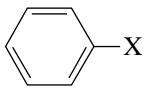
26.9 ppm	CH_3NH_2	48.0 ppm	CH_3OH
	Methylamine		Methanol

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



(Figure 22.8*b*)

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

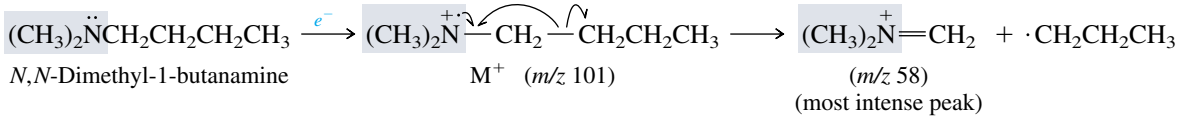


	X	λ_{max}, *nm*
Benzene	H	204, 256
Aniline	NH_2	230, 280
Anilinium ion	NH_3^+	203, 254

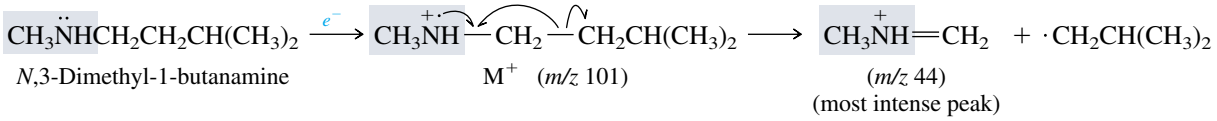
Mass Spectrometry: A number of features make amines easily identifiable by mass spectrometry.

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

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



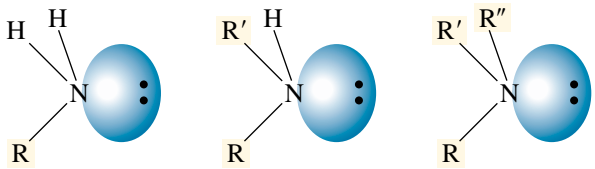
N,*N*-Dimethyl-1-butanamine — M^+ (*m/z* 101) — (*m/z* 58) (most intense peak)



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

22.21 SUMMARY

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



Primary amine — Secondary amine — Tertiary amine

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

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

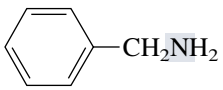
resides in an sp^3-hybridized orbital. The geometry at nitrogen in arylamines is somewhat flatter than in alkylamines, and the unshared electron pair is delocalized into the π system of the ring. Delocalization binds the electron pair more strongly in arylamines than in alkylamines. Arylamines are less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

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

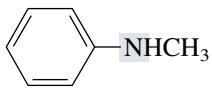
Section 22.4 Basicity of amines is expressed either as a basicity constant K_b (pK_b) of the amine or as a dissociation constant K_a (pK_a) of its conjugate acid.

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

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



Benzylamine
(alkylamine: $pK_b = 4.7$)



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

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

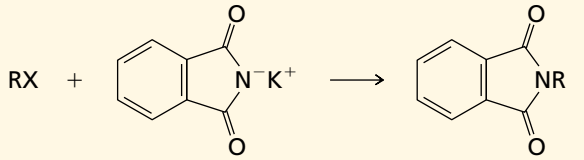
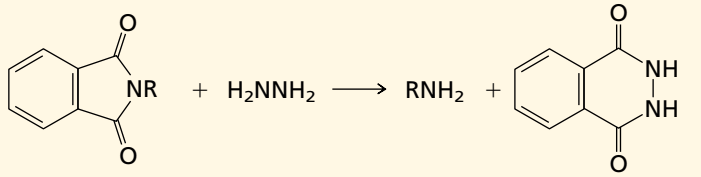
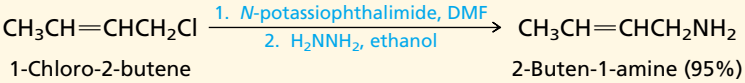
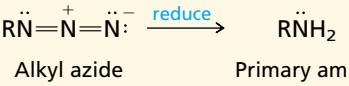
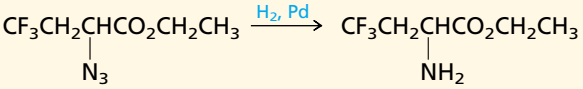
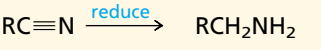
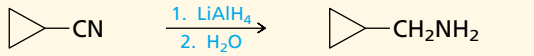
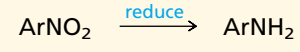
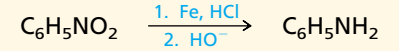
Sections 22.7–22.11 Methods for the preparation of amines are summarized in Table 22.5.

TABLE 22.5 Preparation of Amines

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

(Continued)

TABLE 22.5 Preparation of Amines *(Continued)*

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

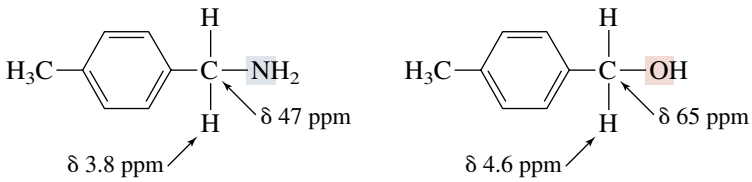
(Continued)

TABLE 22.5 Preparation of Amines *(Continued)*

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

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

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



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

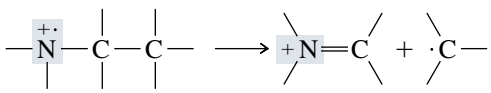
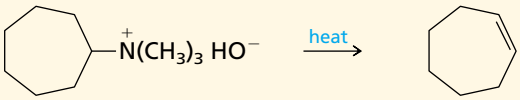
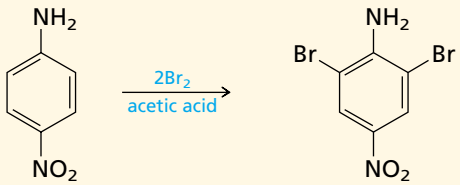
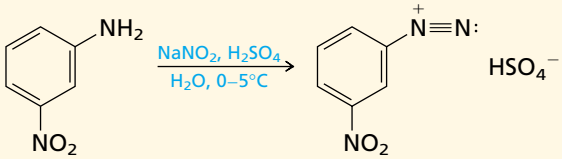


TABLE 22.6 Reactions of Amines Discussed in This Chapter

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

(Continued)

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

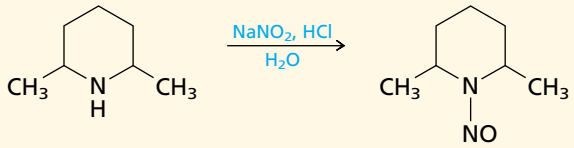
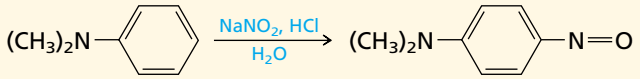
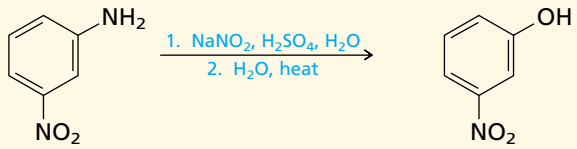
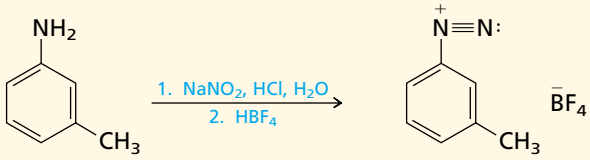
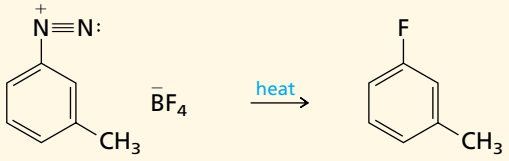
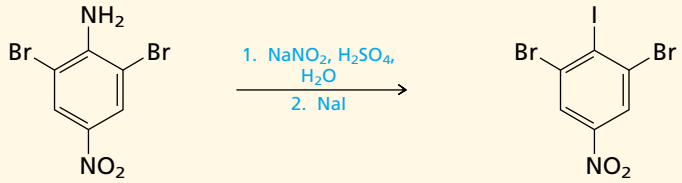
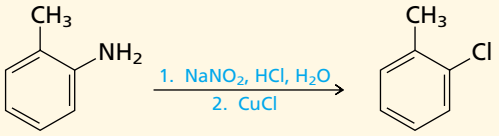
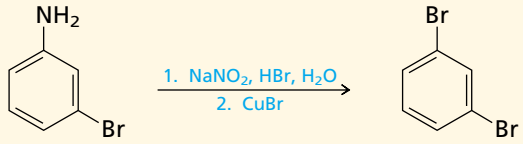
Reaction (section) and comments	General equation and specific example
Secondary alkylamines and *secondary arylamines* yield *N*-nitroso amines.	$R_2NH \xrightarrow[H_2O]{NaNO_2,\ H^+} R_2N{-}N{=}O$ Secondary amine → *N*-Nitroso amine  2,6-Dimethylpiperidine → 2,6-Dimethyl-*N*-nitrosopiperidine (72%)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

TABLE 22.7 Synthetically Useful Transformations Involving Aryl Diazonium Ions

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

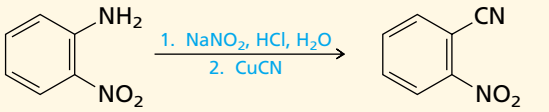
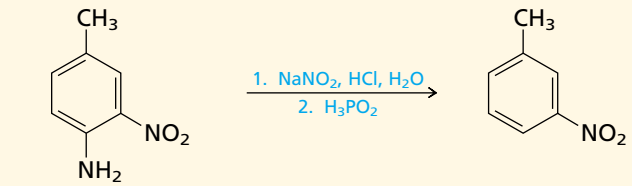
(Continued)

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

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

(Continued)

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

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

PROBLEMS

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

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

(a) 2-Ethyl-1-butanamine

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

(c) Dibenzylamine

(d) Tribenzylamine

(e) Tetraethylammonium hydroxide

(f) *N*-Allylcyclohexylamine

(g) *N*-Allylpiperidine

(h) Benzyl 2-aminopropanoate

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

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

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

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

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

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

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

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

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

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

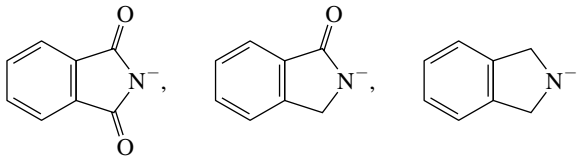
(d) Which, if any, of these isomers undergo nitrosation of their benzene ring on treatment with sodium nitrite and hydrochloric acid?

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

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

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

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

(d) 

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

(a) Ammonia, aniline, methylamine

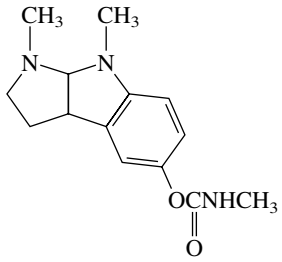
(b) Acetanilide, aniline, *N*-methylaniline

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

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

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

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



Physostigmine

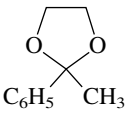
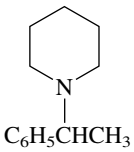
22.28 Describe procedures for preparing each of the following compounds, using ethanol as the source of all their carbon atoms. Once you prepare a compound, you need not repeat its synthesis in a subsequent part of this problem.

(a) Ethylamine

(b) *N*-Ethylacetamide

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

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

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

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

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

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

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

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

(a) Hydrogen bromide
(b) Excess methyl iodide

(c) Acetaldehyde

(d) Acetaldehyde and hydrogen (nickel catalyst)

(e) Acetic anhydride

(f) Benzoyl chloride

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

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

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

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

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

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

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

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

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

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

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

(a) Lithium aluminum hydride

(b) Nitric acid and sulfuric acid

(c) Sulfur trioxide and sulfuric acid

(d) Bromine in acetic acid

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

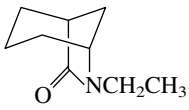
(f) Acetyl chloride, aluminum chloride

(g) 6 M hydrochloric acid, reflux

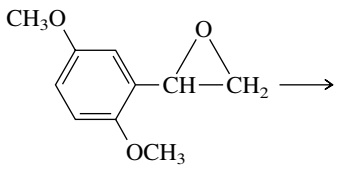
(h) Aqueous sodium hydroxide, reflux

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

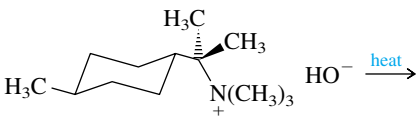
(a) Cyclohexanone + cyclohexylamine $\xrightarrow{H_2,\ Ni}$

(b) 

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

(d) $(CH_3)_2CHNH_2$ + 

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

(f) 

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

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

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

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

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

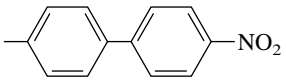
(d) Product of part (c) + $(CH_3CH_2)_2NH$ $\longrightarrow$

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

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

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

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

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

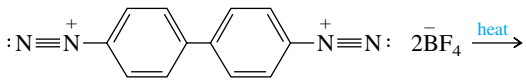
(j) Product of part (i) $\xrightarrow[2.\ H_2O,\ heat]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

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

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

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

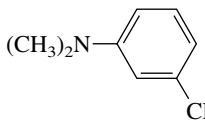
(n) 2,6-Diiodo-4-nitroaniline $\xrightarrow[2.\ KI]{1.\ NaNO_2,\ H_2SO_4,\ H_2O}$

(o)  $\xrightarrow{heat}$

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

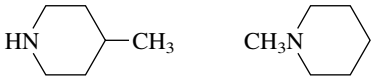
(q) 2-Amino-5-iodobenzoic acid $\xrightarrow[2.\ CH_3CH_2OH]{1.\ NaNO_2,\ HCl,\ H_2O}$

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

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

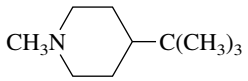
22.36 Provide a reasonable explanation for each of the following observations:

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



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

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

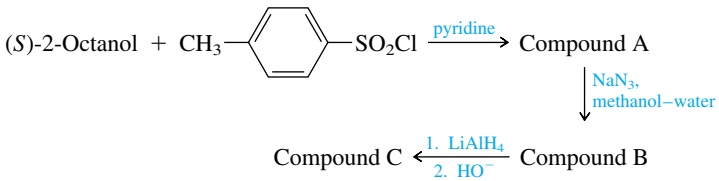


4-*tert*-Butyl-*N*-methylpiperidine

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

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

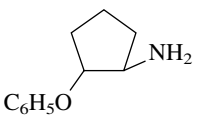
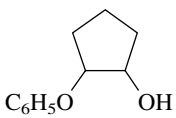
22.37 Give the structures, including stereochemistry, of compounds A through C.



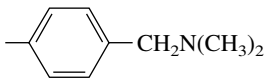
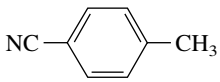
22.38 Devise efficient syntheses of each of the following compounds from the designated starting materials. You may also use any necessary organic or inorganic reagents.

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

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

(c)  from 

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

(e)  from 

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

(a) *p*-Nitrobenzonitrile

(b) 3,4,5-Trichloroaniline

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

(d) 3,5-Dibromoaniline

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

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

(a) *o*-Bromoanisole

(b) *o*-Fluoroanisole

(c) 3-Fluoro-4-methoxyacetophenone

(d) 3-Fluoro-4-methoxybenzonitrile

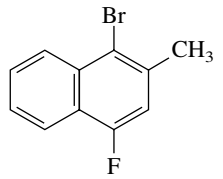
(e) 3-Fluoro-4-methoxyphenol

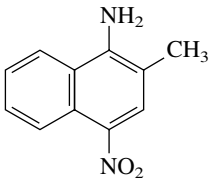
22.41 Design syntheses of each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents:

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

(b) $p\text{-}FC_6H_4\overset{\overset{O}{\|}}{C}CH_2CH_3$ from benzene

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

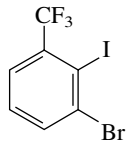
(d) 

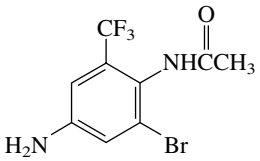
from


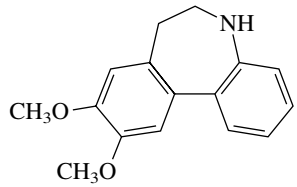
(e) $o\text{-}BrC_6H_4C(CH_3)_3$ from $p\text{-}O_2NC_6H_4C(CH_3)_3$

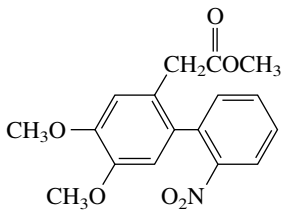
(f) $m\text{-}ClC_6H_4C(CH_3)_3$ from $p\text{-}O_2NC_6H_4C(CH_3)_3$

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

(h) 

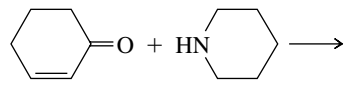
from


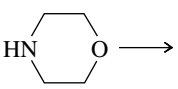
(i) 

from


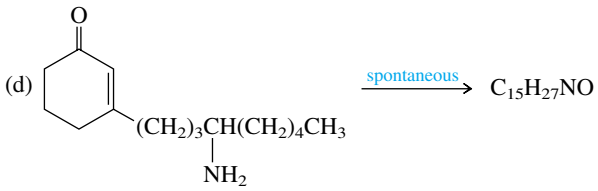
22.42 Ammonia and amines undergo conjugate addition to α,β-unsaturated carbonyl compounds (Section 18.12). On the basis of this information, predict the principal organic product of each of the following reactions:

(a) $(CH_3)_2C{=}CH\overset{\overset{O}{\|}}{C}CH_3 + NH_3 \longrightarrow$

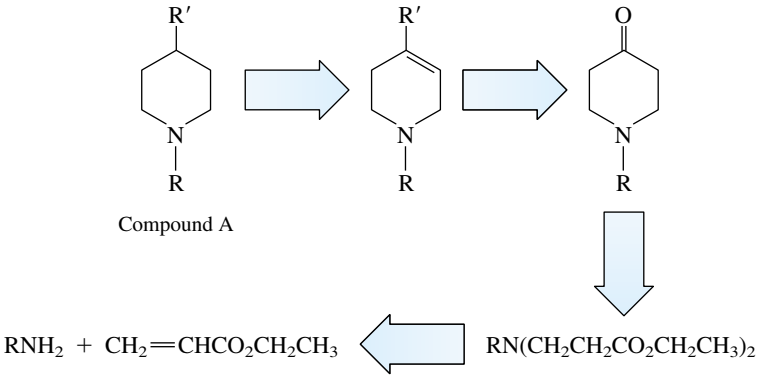
(b) 

(c) $C_6H_5\overset{\overset{O}{\|}}{C}CH{=}CHC_6H_5 +$ 

$\longrightarrow$



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

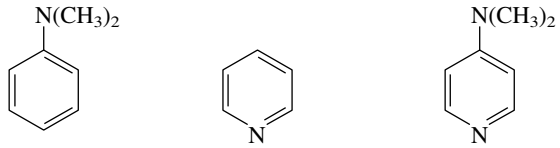


On the basis of this retrosynthetic analysis, design a synthesis of *N*-methyl-4-phenylpiperidine (compound A, where R = CH_3, R′ = C_6H_5). Present your answer as a series of equations, showing all necessary reagents and isolated intermediates.

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

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

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



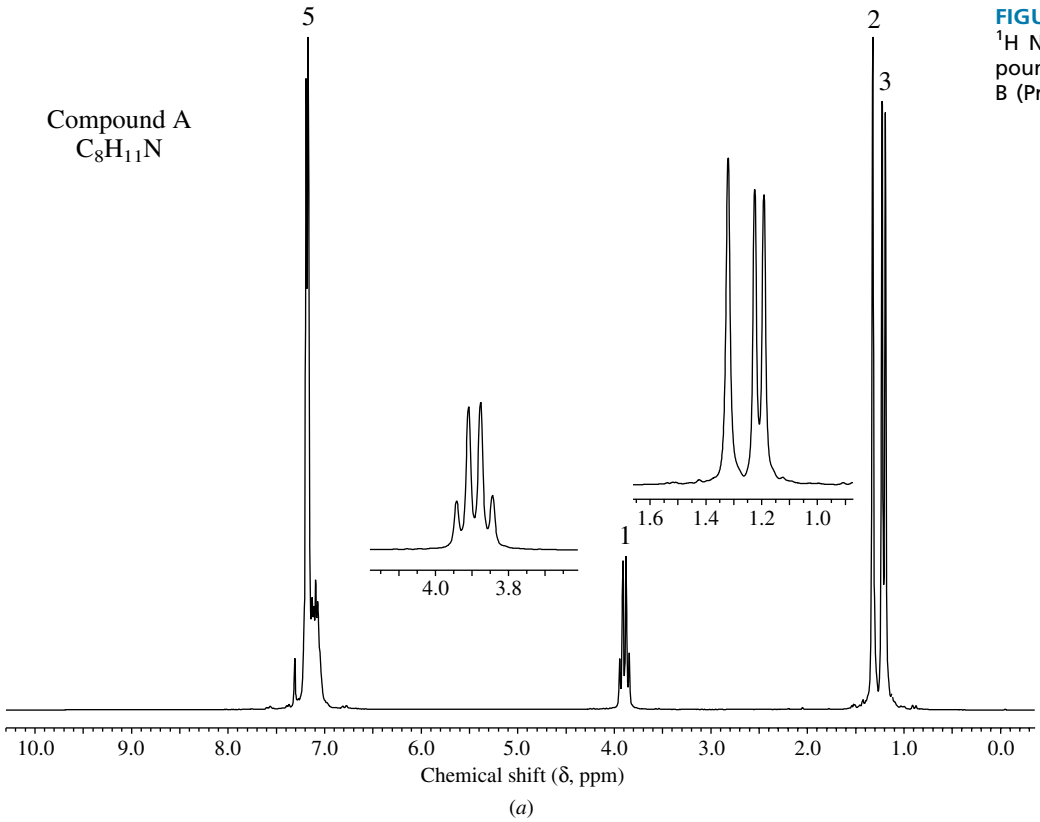
N,N-Dimethylaniline
K_b 1.3×10^{-9}
pK_b 8.9

Pyridine
K_b 2×10^{-9}
pK_b 8.7

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

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

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



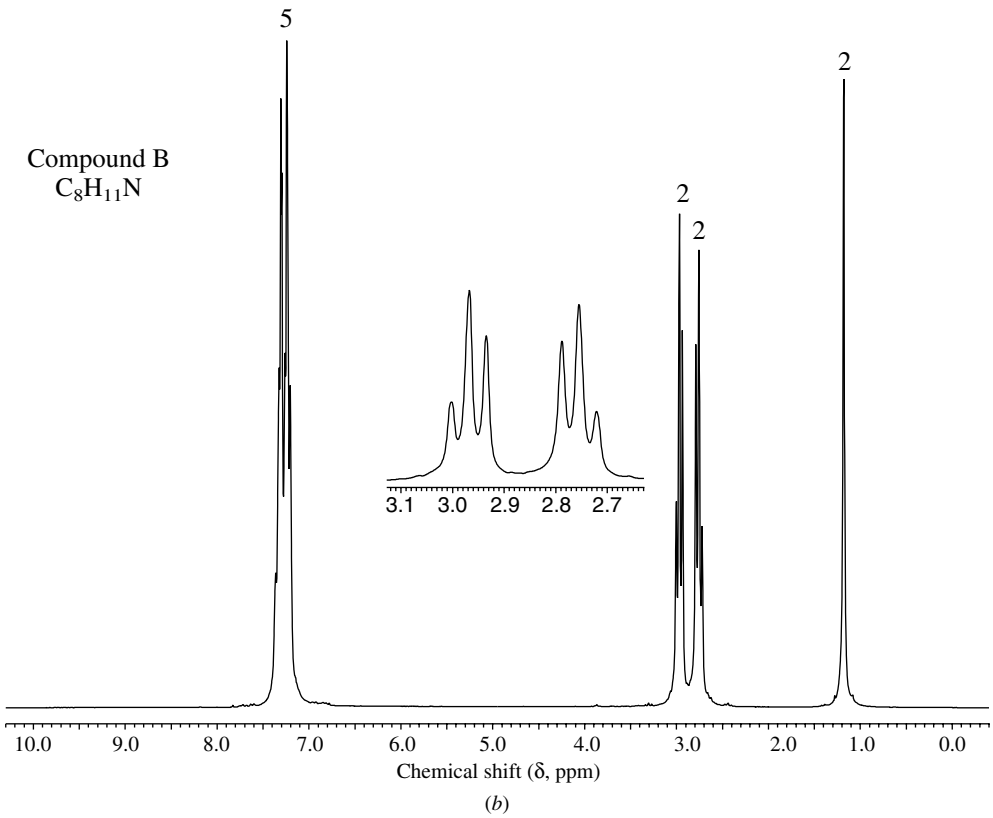
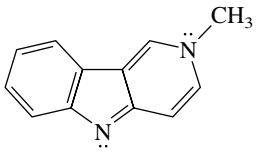


FIGURE 22.9 The 200-MHz ^{1}H NMR spectra of (*a*) compound A and (*b*) compound B (Problem 22.47).

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



5-Methyl-γ-carboline (pK_b = 3.5)

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

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

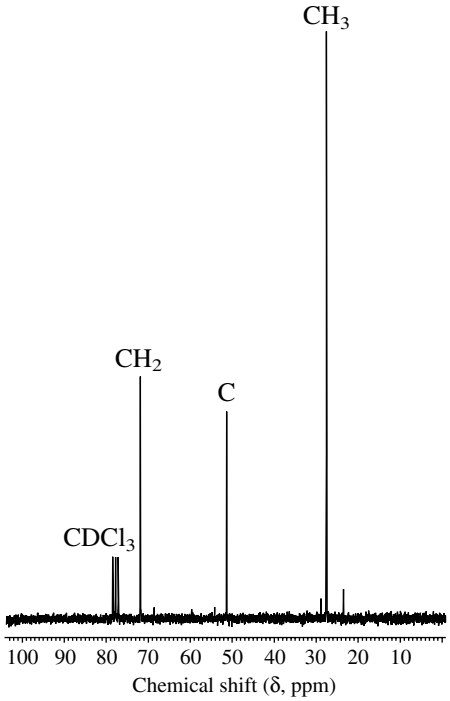
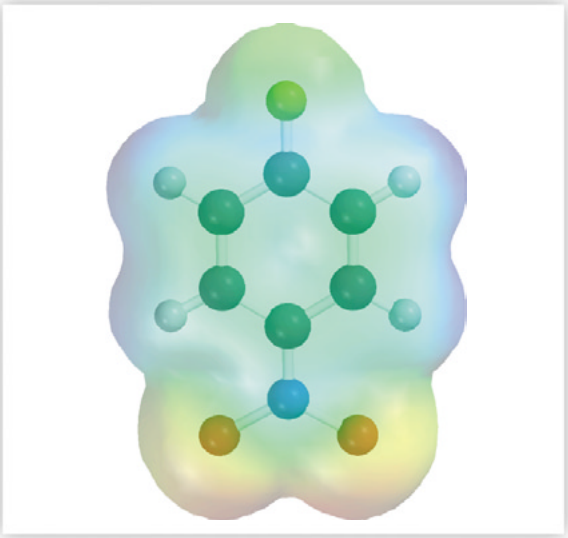


FIGURE 22.10 The ^{13}C NMR spectrum of the compound described in Problem 22.49.



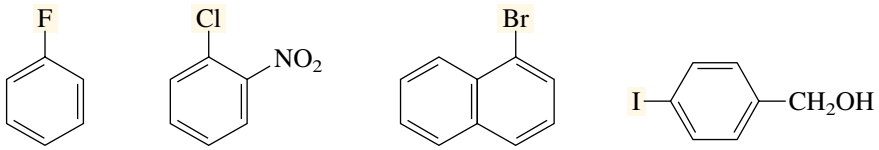
CHAPTER 23

ARYL HALIDES

The value of *alkyl halides* as starting materials for the preparation of a variety of organic functional groups has been stressed many times. In our earlier discussions, we noted that *aryl halides* are normally much less reactive than alkyl halides in reactions that involve carbon–halogen bond cleavage. In the present chapter you will see that aryl halides can exhibit their own patterns of chemical reactivity, and that these reactions are novel, useful, and mechanistically interesting.

23.1 BONDING IN ARYL HALIDES

Aryl halides are compounds in which a halogen substituent is attached directly to an aromatic ring. Representative aryl halides include

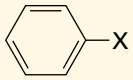


Fluorobenzene | 1-Chloro-2-nitrobenzene | 1-Bromonaphthalene | *p*-Iodobenzyl alcohol

Halogen-containing organic compounds in which the halogen substituent is not directly bonded to an aromatic ring, even though an aromatic ring may be present, are not aryl halides. Benzyl chloride ($C_6H_5CH_2Cl$), for example, is not an aryl halide.

The carbon–halogen bonds of aryl halides are both shorter and stronger than the carbon–halogen bonds of alkyl halides, and in this respect as well as in their chemical behavior, they resemble vinyl halides more than alkyl halides. A hybridization effect

TABLE 23.1 Carbon–Hydrogen and Carbon–Chlorine Bond Dissociation Energies of Selected Compounds

Compound	Hybridization of carbon to which X is attached	Bond energy, kJ/mol (kcal/mol)	
		X = H	X = Cl
CH_3CH_2X	sp^3	410 (98)	339 (81)
$CH_2{=}CHX$	sp^2	452 (108)	368 (88)
	sp^2	469 (112)	406 (97)

seems to be responsible because, as the data in Table 23.1 indicate, similar patterns are seen for both carbon–hydrogen bonds and carbon–halogen bonds. An increase in *s* character from 25% (sp^3 hybridization) to 33.3% *s* character (sp^2 hybridization) increases the tendency of carbon to attract electrons and strengthens the bond.

PROBLEM 23.1 Consider all the isomers of C_7H_7Cl containing a benzene ring and write the structure of the one that has the weakest carbon–chlorine bond as measured by its bond dissociation energy.

The strength of their carbon–halogen bonds causes aryl halides to react very slowly in reactions in which carbon–halogen bond cleavage is rate-determining, as in nucleophilic substitution, for example. Later in this chapter we will see examples of such reactions that do take place at reasonable rates but proceed by mechanisms distinctly different from the classical S_N1 and S_N2 pathways.

23.2 SOURCES OF ARYL HALIDES

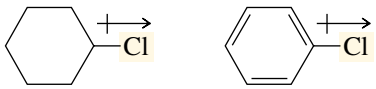
The two main methods for the preparation of aryl halides—halogenation of arenes by electrophilic aromatic substitution and preparation by way of aryl diazonium salts—were described earlier and are reviewed in Table 23.2. A number of aryl halides occur naturally, some of which are shown in Figure 23.1 on page 920.

23.3 PHYSICAL PROPERTIES OF ARYL HALIDES

Melting points and boiling points for some representative aryl halides are listed in Appendix 1.

Aryl halides resemble alkyl halides in many of their physical properties. All are practically insoluble in water and most are denser than water.

Aryl halides are polar molecules but are less polar than alkyl halides.



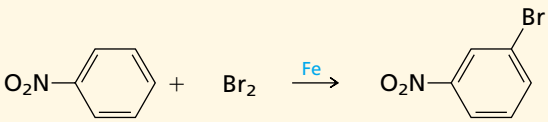
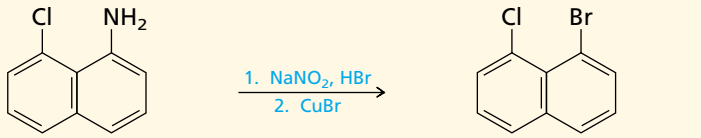
Chlorocyclohexane μ 2.2 D

Chlorobenzene μ 1.7 D

Compare the electronic charges at chlorine in chlorocyclohexane and chlorobenzene on *Learning By Modeling* to verify that the C—Cl bond is more polar in chlorocyclohexane.

Since carbon is sp^2-hybridized in chlorobenzene, it is more electronegative than the sp^3-hybridized carbon of chlorocyclohexane. Consequently, the withdrawal of electron density away from carbon by chlorine is less pronounced in aryl halides than in alkyl halides, and the molecular dipole moment is smaller.

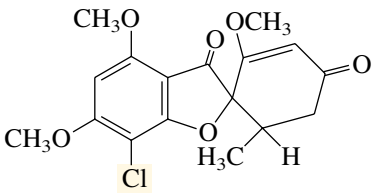
TABLE 23.2 Summary of Reactions Discussed in Earlier Chapters That Yield Aryl Halides

Reaction (section) and comments	General equation and specific example
Halogenation of arenes (Section 12.5) Aryl chlorides and bromides are conveniently prepared by electrophilic aromatic substitution. The reaction is limited to chlorination and bromination. Fluorination is difficult to control; iodination is too slow to be useful.	$ArH + X_2 \xrightarrow[\text{or } FeX_3]{Fe} ArX + HX$ Arene — Halogen — Aryl halide — Hydrogen halide  Nitrobenzene — Bromine — *m*-Bromonitrobenzene (85%)
The Sandmeyer reaction (Section 22.18) Diazotization of a primary arylamine followed by treatment of the diazonium salt with copper(I) bromide or copper(I) chloride yields the corresponding aryl bromide or aryl chloride.	$ArNH_2 \xrightarrow[2.\ CuX]{1.\ NaNO_2,\ H_3O^+} ArX$ Primary arylamine — Aryl halide  1-Amino-8-chloronaphthalene — 1-Bromo-8-chloronaphthalene (62%)
The Schiemann reaction (Section 22.18) Diazotization of an arylamine followed by treatment with fluoroboric acid gives an aryl diazonium fluoroborate salt. Heating this salt converts it to an aryl fluoride.	$ArNH_2 \xrightarrow[2.\ HBF_4]{1.\ NaNO_2,\ H_3O^+} ArN{\equiv}N{:}\ \bar{B}F_4 \xrightarrow{heat} ArF$ Primary arylamine — Aryl diazonium fluoroborate — Aryl fluoride $C_6H_5NH_2 \xrightarrow[2.\ HBF_4\ 3.\ heat]{1.\ NaNO_2,\ H_2O,\ HCl} C_6H_5F$ Aniline — Fluorobenzene (51–57%)
Reaction of aryl diazonium salts with iodide ion (Section 22.18) Adding potassium iodide to a solution of an aryl diazonium ion leads to the formation of an aryl iodide.	$ArNH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ H_3O^+} ArI$ Primary arylamine — Aryl iodide $C_6H_5NH_2 \xrightarrow[2.\ KI]{1.\ NaNO_2,\ HCl,\ H_2O} C_6H_5I$ Aniline — Iodobenzene (74–76%)

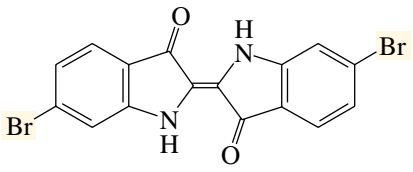
23.4 REACTIONS OF ARYL HALIDES: A REVIEW AND A PREVIEW

Table 23.3 summarizes the reactions of aryl halides that we have encountered to this point.

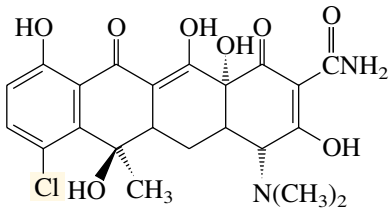
Noticeably absent from Table 23.3 are nucleophilic substitutions. We have, to this point, seen no nucleophilic substitution reactions of aryl halides in this text. Chlorobenzene, for example, is essentially inert to aqueous sodium hydroxide at room temperature. Reaction temperatures over 300°C are required for nucleophilic substitution to proceed at a reasonable rate.



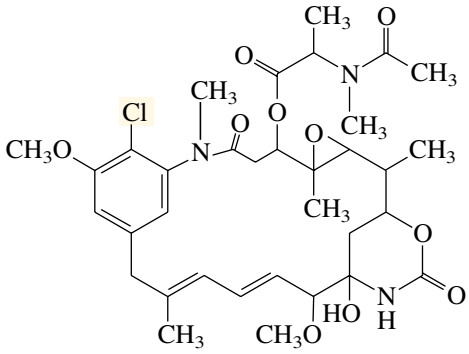
Griseofulvin: biosynthetic product of a particular microorganism, used as an orally administered antifungal agent.



Dibromoindigo: principal constituent of a dye known as Tyrian purple, which is isolated from a species of Mediterranean sea snail and was much prized by the ancients for its vivid color.



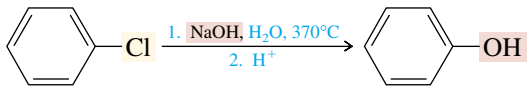
Chlortetracycline: an antibiotic.



Maytansine: a potent antitumor agent isolated from a bush native to Kenya; 10 tons of plant yielded 6 g of maytansine.

FIGURE 23.1 Some naturally occurring aryl halides.

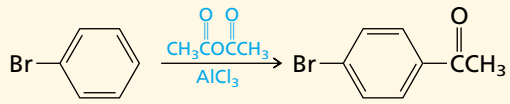
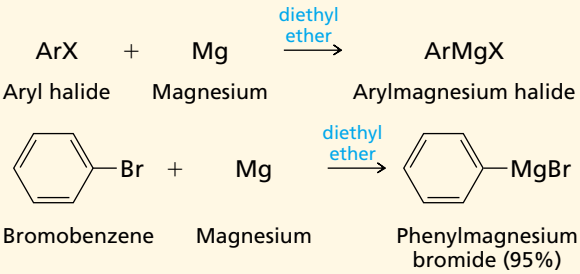
The mechanism of this reaction is discussed in Section 23.8.



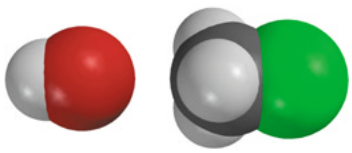
Chlorobenzene Phenol (97%)

Aryl halides are much less reactive than alkyl halides in nucleophilic substitution reactions. The carbon–halogen bonds of aryl halides are too strong, and aryl cations are too high in energy, to permit aryl halides to ionize readily in S_N1-type processes. Furthermore, as Figure 23.2 depicts, the optimal transition-state geometry required for S_N2 processes cannot be achieved. Nucleophilic attack from the side opposite the carbon–halogen bond is blocked by the aromatic ring.

TABLE 23.3 Summary of Reactions of Aryl Halides Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Electrophilic aromatic substitution (Section 12.14) Halogen substituents are slightly deactivating and ortho, para-directing.	 Bromobenzene — *p*-Bromoacetophenone (69–79%)
Formation of aryl Grignard reagents (Section 14.4) Aryl halides react with magnesium to form the corresponding arylmagnesium halide. Aryl iodides are the most reactive, aryl fluorides the least. A similar reaction occurs with lithium to give aryllithium reagents (Section 14.3).	 Aryl halide — Magnesium — Arylmagnesium halide Bromobenzene — Magnesium — Phenylmagnesium bromide (95%)

(*a*) Hydroxide ion + chloromethane



(*b*) Hydroxide ion + chlorobenzene

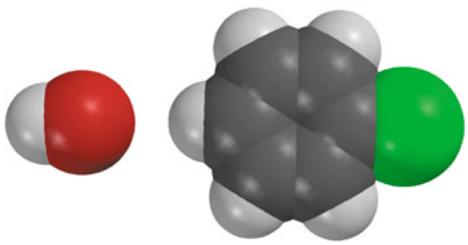
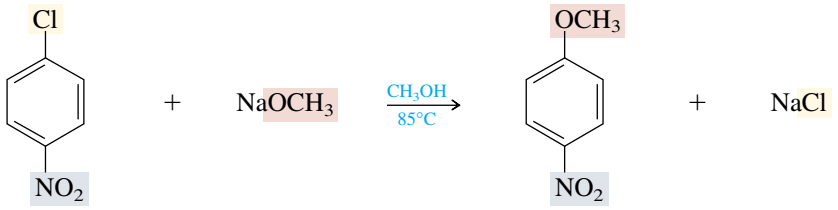


FIGURE 23.2 Nucleophilic substitution, with inversion of configuration, is blocked by the benzene ring of an aryl halide. (*a*) *Alkyl halide:* The new bond is formed by attack of the nucleophile at carbon from the side opposite the bond to the leaving group. Inversion of configuration is observed. (*b*) *Aryl halide:* The aromatic ring blocks the approach of the nucleophile to carbon at the side opposite the bond to the leaving group. Inversion of configuration is impossible.

23.5 NUCLEOPHILIC SUBSTITUTION IN NITRO-SUBSTITUTED ARYL HALIDES

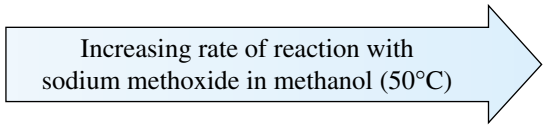
One group of aryl halides that do undergo nucleophilic substitution readily consists of those that bear a nitro group ortho or para to the halogen.

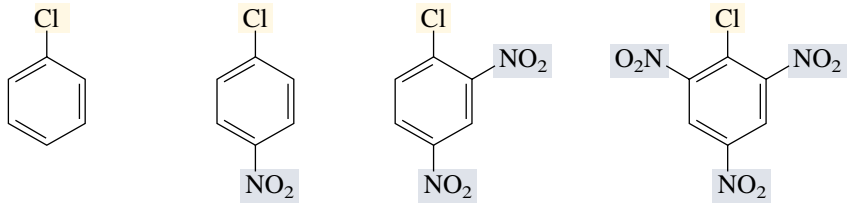


p-Chloronitrobenzene | Sodium methoxide | *p*-Nitroanisole (92%) | Sodium chloride

An *ortho*-nitro group exerts a comparable rate-enhancing effect. *m*-Chloronitrobenzene, although much more reactive than chlorobenzene itself, is thousands of times less reactive than either *o*- or *p*-chloronitrobenzene.

The effect of *o*- and *p*-nitro substituents is cumulative, as the following rate data demonstrate:



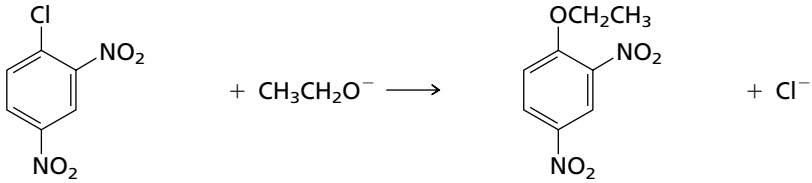


Chlorobenzene	1-Chloro-4-nitrobenzene	1-Chloro-2,4-dinitrobenzene	2-Chloro-1,3,5-trinitrobenzene
Relative rate: 1.0	7×10^{10}	2.4×10^{15}	(too fast to measure)

PROBLEM 23.2 Write the structure of the expected product from the reaction of 1-chloro-2,4-dinitrobenzene with each of the following reagents:

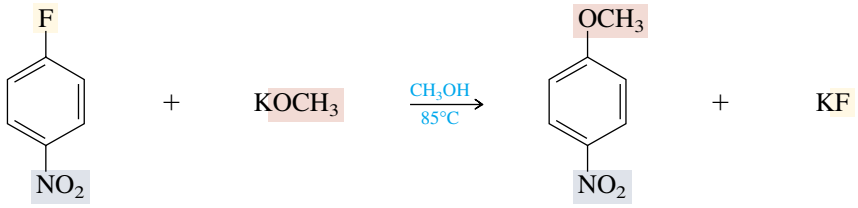
(a) CH_3CH_2ONa
(b) $C_6H_5CH_2SNa$
(c) NH_3
(d) CH_3NH_2

SAMPLE SOLUTION (a) Sodium ethoxide is a source of the nucleophile $CH_3CH_2O^-$, which displaces chloride from 1-chloro-2,4-dinitrobenzene.



1-Chloro-2,4-dinitrobenzene | Ethoxide anion | 1-Ethoxy-2,4-dinitrobenzene

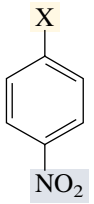
In contrast to nucleophilic substitution in alkyl halides, where *alkyl fluorides* are exceedingly unreactive, *aryl fluorides* undergo nucleophilic substitution readily when the ring bears an *o*- or a *p*-nitro group.



p-Fluoronitrobenzene Potassium methoxide *p*-Nitroanisole (93%) Potassium fluoride

The compound 1-fluoro-2,4-dinitrobenzene is exceedingly reactive toward nucleophilic aromatic substitution and was used in an imaginative way by Frederick Sanger (Section 27.10) in his determination of the structure of insulin.

Indeed, the order of leaving-group reactivity in nucleophilic aromatic substitution is the opposite of that seen in aliphatic substitution. *Fluoride is the most reactive leaving group in nucleophilic aromatic substitution, iodide the least reactive.*



Relative reactivity toward sodium methoxide in methanol (50°C):

X = F	312
X = Cl	1.0
X = Br	0.8
X = I	0.4

Kinetic studies of these reactions reveal that they follow a second-order rate law:

$$\text{Rate} = k[\text{Aryl halide}]\,[\text{Nucleophile}]$$

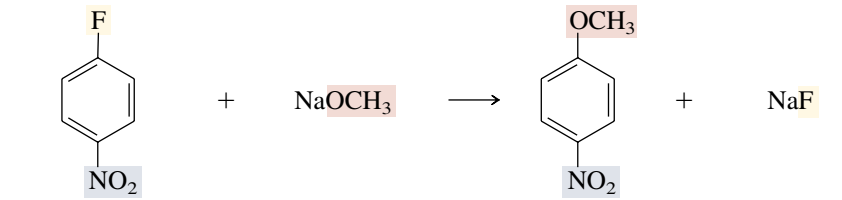
Second-order kinetics is usually interpreted in terms of a bimolecular rate-determining step. In this case, then, we look for a mechanism in which both the aryl halide and the nucleophile are involved in the slowest step. Such a mechanism is described in the following section.

23.6 THE ADDITION–ELIMINATION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION

The generally accepted mechanism for nucleophilic aromatic substitution in nitro-substituted aryl halides, illustrated for the reaction of *p*-fluoronitrobenzene with sodium methoxide, is outlined in Figure 23.3. It is a two-step **addition–elimination mechanism,** in which addition of the nucleophile to the aryl halide is followed by elimination of the halide leaving group. Figure 23.4 shows the structure of the key intermediate. The mechanism is consistent with the following experimental observations:

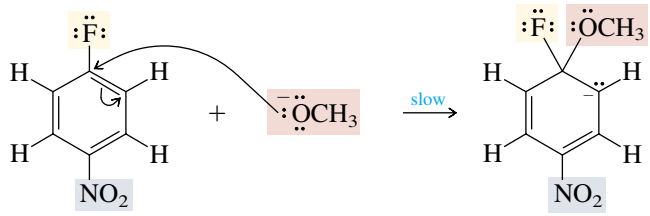
1. *Kinetics:* As the observation of second-order kinetics requires, the rate-determining step (step 1) involves both the aryl halide and the nucleophile.
2. *Rate-enhancing effect of the nitro group:* The nucleophilic addition step is rate-determining because the aromatic character of the ring must be sacrificed to form the cyclohexadienyl anion intermediate. Only when the anionic intermediate is stabilized by the presence of a strong electron-withdrawing substituent ortho or para to the leaving group will the activation energy for its formation be low enough to provide a reasonable reaction rate. We can illustrate the stabilization that a *p*-nitro group provides by examining the resonance structures for the cyclohexadienyl anion formed from methoxide and *p*-fluoronitrobenzene:

Overall reaction:



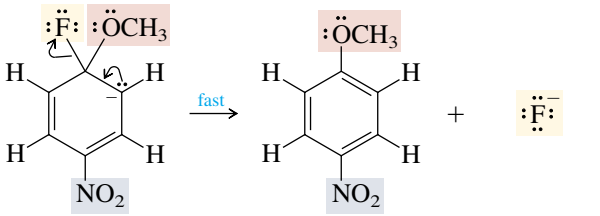
p-Fluoronitrobenzene | Sodium methoxide | *p*-Nitroanisole | Sodium fluoride

Step 1: Addition stage. The nucleophile, in this case methoxide ion, adds to the carbon atom that bears the leaving group to give a cyclohexadienyl anion intermediate.



p-Fluoronitrobenzene | Methoxide ion | Cyclohexadienyl anion intermediate

Step 2: Elimination stage. Loss of halide from the cyclohexadienyl intermediate restores the aromaticity of the ring and gives the product of nucleophilic aromatic substitution.



Cyclohexadienyl anion intermediate | *p*-Nitroanisole | Fluoride ion

FIGURE 23.3 The addition–elimination mechanism of nucleophilic aromatic substitution.

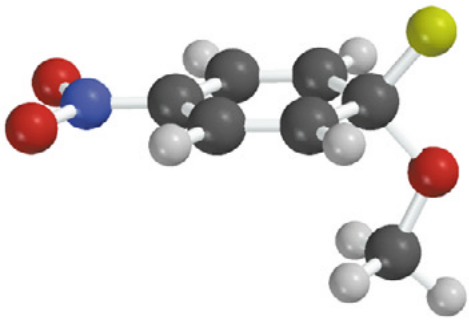
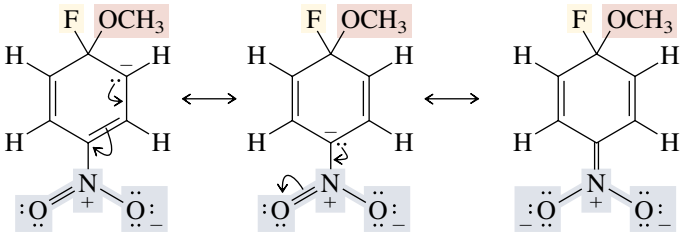


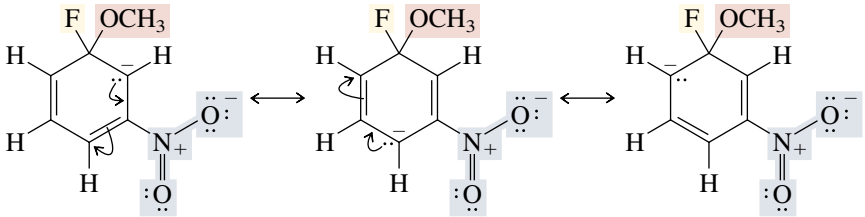
FIGURE 23.4 Structure of the rate-determining intermediate in the reaction of 1-fluoro-4-nitrobenzene with methoxide ion.



Most stable resonance structure; negative charge is on oxygen

PROBLEM 23.3 Write the most stable resonance structure for the cyclohexadienyl anion formed by reaction of methoxide ion with *o*-fluoronitrobenzene.

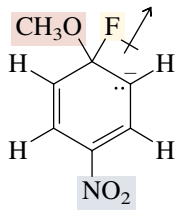
m-Fluoronitrobenzene reacts with sodium methoxide 10^5 times more slowly than its ortho and para isomers. According to the resonance description, direct conjugation of the negatively charged carbon with the nitro group is not possible in the cyclohexadienyl anion intermediate from *m*-fluoronitrobenzene, and the decreased reaction rate reflects the decreased stabilization afforded this intermediate.



(Negative charge is restricted to carbon in all resonance forms)

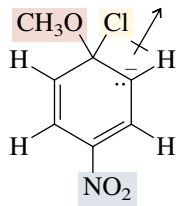
PROBLEM 23.4 Reaction of 1,2,3-tribromo-5-nitrobenzene with sodium ethoxide in ethanol gave a single product, $C_8H_7Br_2NO_3$, in quantitative yield. Suggest a reasonable structure for this compound.

3. *Leaving-group effects:* Since aryl fluorides have the strongest carbon–halogen bond and react fastest, the rate-determining step cannot involve carbon–halogen bond cleavage. According to the mechanism in Figure 23.3 the carbon–halogen bond breaks in the rapid elimination step that follows the rate-determining addition step. The unusually high reactivity of aryl fluorides arises because fluorine is the most electronegative of the halogens, and its greater ability to attract electrons increases the rate of formation of the cyclohexadienyl anion intermediate in the first step of the mechanism.



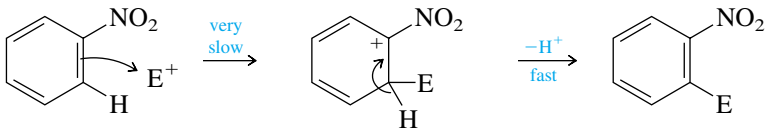
Fluorine stabilizes cyclohexadienyl anion by withdrawing electrons.

is more stable than



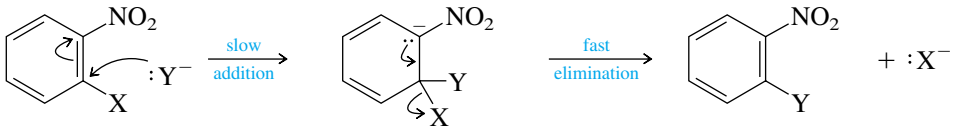
Chlorine is less electronegative than fluorine and does not stabilize cyclohexadienyl anion to as great an extent.

Before leaving this mechanistic discussion, we should mention that the addition–elimination mechanism for nucleophilic aromatic substitution illustrates a principle worth remembering. The words "activating" and "deactivating" as applied to substituent effects in organic chemistry are without meaning when they stand alone. When we say that a group is activating or deactivating, we need to specify the reaction type that is being considered. A nitro group is a strongly *deactivating* substituent in *electrophilic* aromatic substitution, where it markedly destabilizes the key cyclohexadienyl cation intermediate:



Nitrobenzene and an electrophile | Cyclohexadienyl cation intermediate; nitro group is destabilizing | Product of electrophilic aromatic substitution

A nitro group is a strongly *activating* substituent in *nucleophilic* aromatic substitution, where it stabilizes the key cyclohexadienyl anion intermediate:

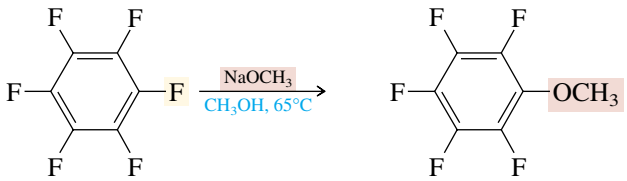


o-Halonitrobenzene (X = F, Cl, Br, or I) and a nucleophile | Cyclohexadienyl anion intermediate; nitro group is stabilizing | Product of nucleophilic aromatic substitution

A nitro group behaves the same way in both reactions: it attracts electrons. Reaction is retarded when electrons flow from the aromatic ring to the attacking species (electrophilic aromatic substitution). Reaction is facilitated when electrons flow from the attacking species to the aromatic ring (nucleophilic aromatic substitution). By being aware of the connection between reactivity and substituent effects, you will sharpen your appreciation of how chemical reactions occur.

23.7 RELATED NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

The most common types of aryl halides in nucleophilic aromatic substitutions are those that bear *o*- or *p*-nitro substituents. Among other classes of reactive aryl halides, a few merit special consideration. One class includes highly fluorinated aromatic compounds such as hexafluorobenzene, which undergoes substitution of one of its fluorines on reaction with nucleophiles such as sodium methoxide.

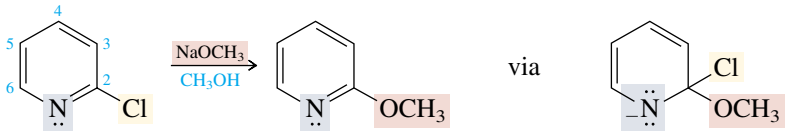


Hexafluorobenzene | 2,3,4,5,6-Pentafluoroanisole (72%)

Here it is the combined electron-attracting effects of the six fluorine substituents that stabilize the cyclohexadienyl anion intermediate and permit the reaction to proceed so readily.

PROBLEM 23.5 Write equations describing the addition–elimination mechanism for the reaction of hexafluorobenzene with sodium methoxide, clearly showing the structure of the rate-determining intermediate.

Halides derived from certain heterocyclic aromatic compounds are often quite reactive toward nucleophiles. 2-Chloropyridine, for example, reacts with sodium methoxide some 230 million times faster than chlorobenzene at 50°C.



2-Chloropyridine 2-Methoxypyridine Anionic intermediate

Again, rapid reaction is attributed to the stability of the intermediate formed in the addition step. In contrast to chlorobenzene, where the negative charge of the intermediate must be borne by carbon, the anionic intermediate in the case of 2-chloropyridine has its negative charge on nitrogen. Since nitrogen is more electronegative than carbon, the intermediate is more stable and is formed faster than the one from chlorobenzene.

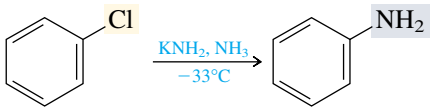
PROBLEM 23.6 Offer an explanation for the observation that 4-chloropyridine is more reactive toward nucleophiles than 3-chloropyridine.

Another type of nucleophilic aromatic substitution occurs under quite different reaction conditions from those discussed to this point and proceeds by a different and rather surprising mechanism. It is described in the following section.

23.8 THE ELIMINATION–ADDITION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION: BENZYNE

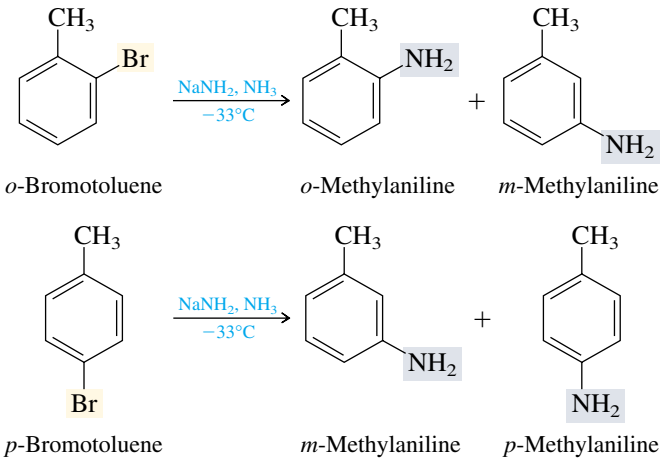
Very strong bases such as sodium or potassium amide react readily with aryl halides, even those without electron-withdrawing substituents, to give products corresponding to nucleophilic substitution of halide by the base.

Comparing the pK_a of ammonia (36) and water (16) tells us that NH_2^- is 10^{20} times more basic than OH^-.

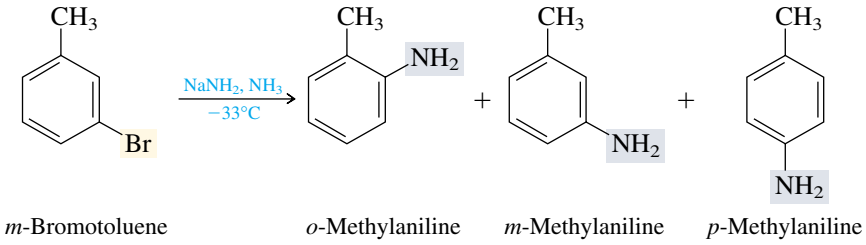


Chlorobenzene Aniline (52%)

For a long time, observations concerning the regiochemistry of these reactions presented organic chemists with a puzzle. Substitution did not occur exclusively at the carbon from which the halide leaving group departed. Rather, a mixture of regioisomers was obtained in which the amine group was either on the carbon that originally bore the leaving group or on one of the carbons adjacent to it. Thus *o*-bromotoluene gave a mixture of *o*-methylaniline and *m*-methylaniline; *p*-bromotoluene gave *m*-methylaniline and *p*-methylaniline.



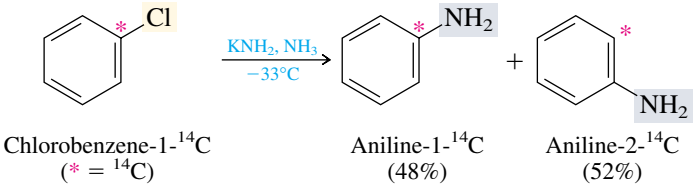
Three regioisomers (*o*-, *m*-, and *p*-methylaniline) were formed from *m*-bromotoluene.



These results rule out substitution by addition–elimination since that mechanism requires the nucleophile to attach itself to the carbon from which the leaving group departs.

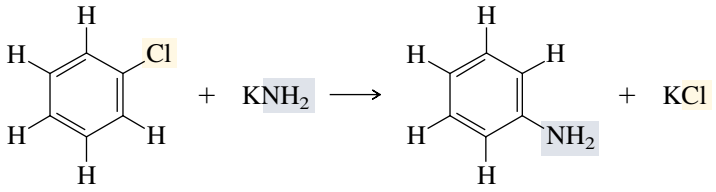
A solution to the question of the mechanism of these reactions was provided by John D. Roberts in 1953 on the basis of an imaginative experiment. Roberts prepared a sample of chlorobenzene in which one of the carbons, the one bearing the chlorine, was the radioactive mass-14 isotope of carbon. Reaction with potassium amide in liquid ammonia yielded aniline containing almost exactly half of its ^{14}C label at C-1 and half at C-2:

This work was done while Roberts was at MIT. He later moved to the California Institute of Technology, where he became a leader in applying NMR spectroscopy to nuclei other than protons, especially ^{13}C and ^{15}N.



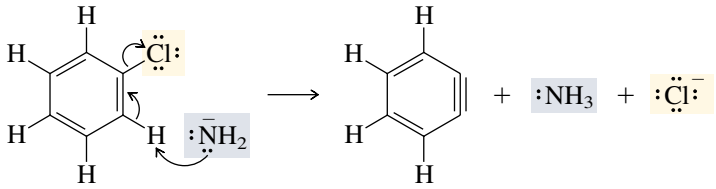
The mechanism most consistent with the observations of this isotopic labeling experiment is the **elimination–addition mechanism** outlined in Figure 23.5. The first stage in this mechanism is a base-promoted dehydrohalogenation of chlorobenzene. The intermediate formed in this step contains a triple bond in an aromatic ring and is called **benzyne.** Aromatic compounds related to benzyne are known as **arynes.** The triple bond in benzyne is somewhat different from the usual triple bond of an alkyne, however. In benzyne one of the π components of the triple bond is part of the delocalized π system of the aromatic ring. The second π component results from overlapping sp^2-hybridized orbitals (*not p-p* overlap), lies in the plane of the ring, and does not interact with the

Overall reaction:



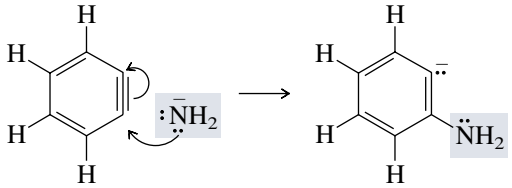
Chlorobenzene Aniline

Step 1: Elimination stage. Amide ion is a very strong base and brings about the dehydrohalogenation of chlorobenzene by abstracting a proton from the carbon adjacent to the one that bears the leaving group. The product of this step is an unstable intermediate called *benzyne*.



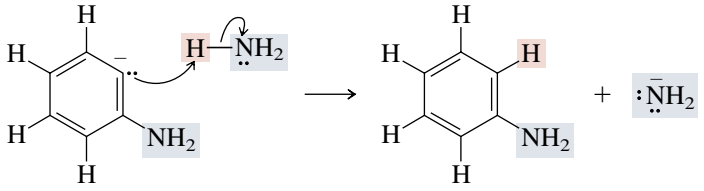
Chlorobenzene Benzyne

Step 2: Beginning of addition phase. Amide ion acts as a nucleophile and adds to one of the carbons of the triple bond. The product of this step is a carbanion.



Benzyne Aryl anion

Step 3: Completion of addition phase. The aryl anion abstracts a proton from the ammonia used as the solvent in the reaction.



Aryl anion Aniline

FIGURE 23.5 The elimination–addition mechanism of nucleophilic aromatic substitution.

aromatic π system. This π bond is relatively weak, since, as illustrated in Figure 23.6, its contributing sp^2 orbitals are not oriented properly for effective overlap.

Because the ring prevents linearity of the C—C≡C—C unit and π bonding in that unit is weak, benzyne is strained and highly reactive. This enhanced reactivity is evident in the second stage of the elimination–addition mechanism as shown in steps 2

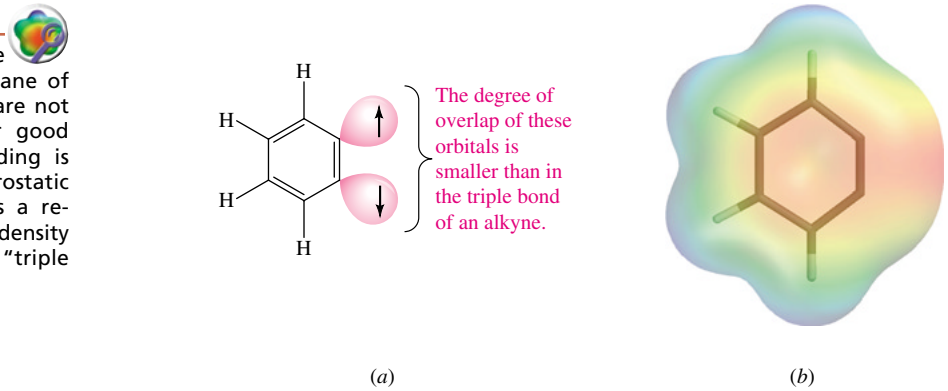


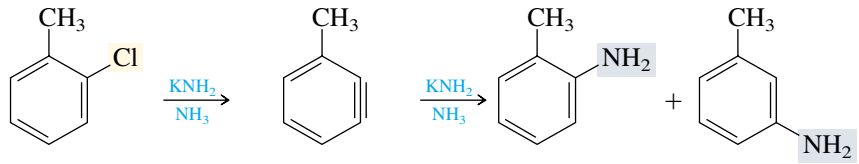
FIGURE 23.6 (*a*) The sp^2 orbitals in the plane of the ring in benzyne are not properly aligned for good overlap, and π bonding is weak. (*b*) The electrostatic potential map shows a region of high electron density associated with the "triple bond."

and 3 of Figure 23.5. In this stage the base acts as a nucleophile and adds to the strained bond of benzyne to form a carbanion. The carbanion, an *aryl anion,* then abstracts a proton from ammonia to yield the observed product.

The carbon that bears the leaving group and a carbon ortho to it become equivalent in the benzyne intermediate. Thus when chlorobenzene-1-^{14}C is the substrate, the amino group may be introduced with equal likelihood at either position.

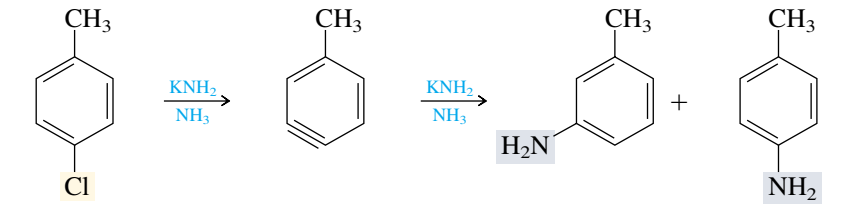
PROBLEM 23.7 2-Bromo-1,3-dimethylbenzene is inert to nucleophilic aromatic substitution on treatment with sodium amide in liquid ammonia. It is recovered unchanged even after extended contact with the reagent. Suggest an explanation for this lack of reactivity.

Once the intermediacy of an aryne intermediate was established, the reason for the observed regioselectivity of substitution in *o*-, *m*-, and *p*-chlorotoluene became evident. Only a single aryne intermediate may be formed from *o*-chlorotoluene, but this aryne yields a mixture containing comparable amounts of *o*- and *m*-methylaniline.



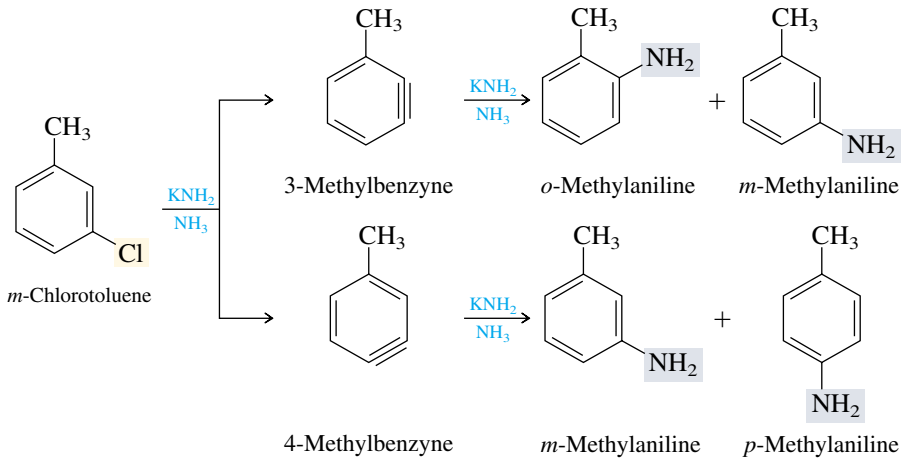
o-Chlorotoluene 3-Methylbenzyne *o*-Methylaniline *m*-Methylaniline

Similarly, *p*-chlorotoluene gives a single aryne, and this aryne gives a mixture of *m*- and *p*-methylaniline.

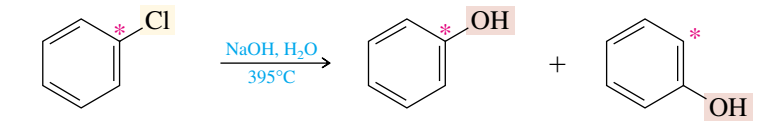


p-Chlorotoluene 4-Methylbenzyne *m*-Methylaniline *p*-Methylaniline

Two isomeric arynes give the three isomeric substitution products formed from *m*-chlorotoluene:



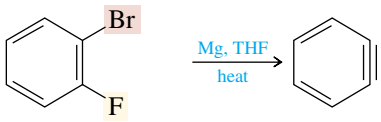
Although nucleophilic aromatic substitution by the elimination–addition mechanism is most commonly seen with very strong amide bases, it also occurs with bases such as hydroxide ion at high temperatures. A ^{14}C-labeling study revealed that hydrolysis of chlorobenzene proceeds by way of a benzyne intermediate.



PROBLEM 23.8 Two isomeric phenols are obtained in comparable amounts on hydrolysis of *p*-iodotoluene with 1 M sodium hydroxide at 300°C. Suggest reasonable structures for these two products.

23.9 DIELS–ALDER REACTIONS OF BENZYNE

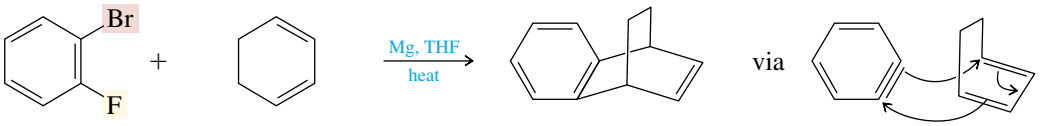
Alternative methods for its generation have made it possible to use benzyne as an intermediate in a number of synthetic applications. One such method involves treating *o*-bromofluorobenzene with magnesium, usually in tetrahydrofuran as the solvent.



The reaction proceeds by formation of the Grignard reagent from *o*-bromofluorobenzene. Since the order of reactivity of magnesium with aryl halides is ArI > ArBr > ArCl > ArF, the Grignard reagent has the structure shown and forms benzyne by loss of the salt FMgBr:

o-Fluorophenylmagnesium bromide Benzyne

Its strained triple bond makes benzyne a relatively good dienophile, and when benzyne is generated in the presence of a conjugated diene, Diels–Alder cycloaddition occurs.



o-Bromofluorobenzene 1,3-Cyclohexadiene 5,6-Benzobicyclo[2.2.2]-octa-2,5-diene (46%)

PROBLEM 23.9 Give the structure of the cycloaddition product formed when benzyne is generated in the presence of furan. (See Section 11.21, if necessary, to remind yourself of the structure of furan.)

Benzyne may also be generated by treating *o*-bromofluorobenzene with lithium. In this case, *o*-fluorophenyllithium is formed, which then loses lithium fluoride to form benzyne.

23.10 SUMMARY

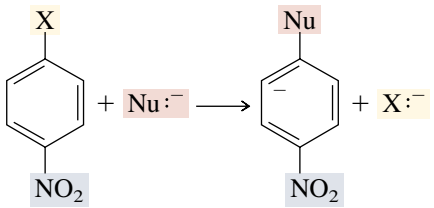
Section 23.1 Aryl halides are compounds of the type Ar—X where X = F, Cl, Br, or I. The carbon–halogen bond is stronger in ArX than in an alkyl halide (RX).

Section 23.2 Some aryl halides occur naturally, but most are the products of organic synthesis. The methods by which aryl halides are prepared were recalled in Table 23.2

Section 23.3 Aryl halides are less polar than alkyl halides.

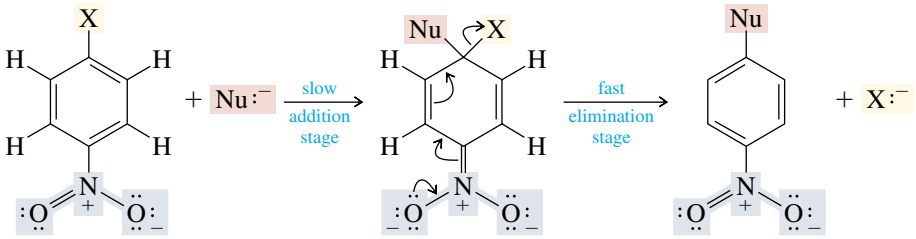
Section 23.4 Aryl halides are less reactive than alkyl halides in reactions in which C—X bond breaking is rate-determining, especially in nucleophilic substitution reactions.

Section 23.5 Nucleophilic substitution in ArX is facilitated by the presence of a strong electron-withdrawing group, such as NO_2, ortho or para to the halogen.



In reactions of this type, fluoride is the best leaving group of the halogens and iodide the poorest.

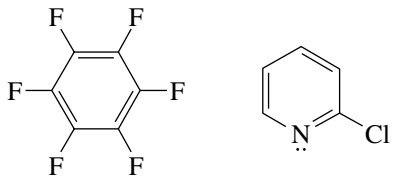
Section 23.6 Nucleophilic aromatic substitutions of the type just shown follow an **addition–elimination mechanism.**



Nitro-substituted aryl halide | Cyclohexadienyl anion intermediate | Product of nucleophilic aromatic substitution

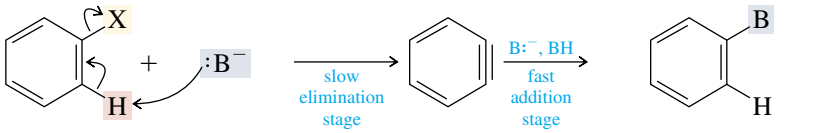
The rate-determining intermediate is a cyclohexadienyl anion and is stabilized by electron-withdrawing substituents.

Section 23.7 Other aryl halides that give stabilized anions can undergo nucleophilic aromatic substitution by the addition–elimination mechanism. Two examples are hexafluorobenzene and 2-chloropyridine.



Hexafluorobenzene | 2-Chloropyridine

Section 23.8 Nucleophilic aromatic substitution can also occur by an **elimination–addition mechanism.** This pathway is followed when the nucleophile is an exceptionally strong base such as amide ion in the form of sodium amide ($NaNH_2$) or potassium amide (KNH_2). **Benzyne** and related **arynes** are intermediates in nucleophilic aromatic substitutions that proceed by the elimination–addition mechanism.



Aryl halide | Strong base | Benzyne | Product of nucleophilic aromatic substitution

Nucleophilic aromatic substitution by the elimination–addition mechanism can lead to substitution on the same carbon that bore the leaving group or on an adjacent carbon.

Section 23.9 Benzyne is a reactive dienophile and gives Diels–Alder products when generated in the presence of dienes. In these cases it is convenient to form benzyne by dissociation of the Grignard reagent of *o*-bromofluorobenzene.

PROBLEMS

23.10 Write a structural formula for each of the following:

(a) *m*-Chlorotoluene
(b) 2,6-Dibromoanisole
(c) *p*-Fluorostyrene
(d) 4,4′-Diiodobiphenyl
(e) 2-Bromo-1-chloro-4-nitrobenzene
(f) 1-Chloro-1-phenylethane
(g) *p*-Bromobenzyl chloride
(h) 2-Chloronaphthalene
(i) 1,8-Dichloronaphthalene
(j) 9-Fluorophenanthrene

23.11 Identify the major organic product of each of the following reactions. If two regioisomers are formed in appreciable amounts, show them both.

(a) Chlorobenzene + acetyl chloride $\xrightarrow{AlCl_3}$

(b) Bromobenzene + magnesium $\xrightarrow{\text{diethyl ether}}$

(c) Product of part (b) + dilute hydrochloric acid $\longrightarrow$

(d) Iodobenzene + lithium $\xrightarrow{\text{diethyl ether}}$

(e) Bromobenzene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$

(f) *p*-Bromotoluene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$

(g) 1-Bromo-4-nitrobenzene + ammonia $\longrightarrow$

(h) *p*-Bromobenzyl bromide + sodium cyanide $\longrightarrow$

(i) *p*-Chlorobenzenediazonium chloride + *N,N*-dimethylaniline $\longrightarrow$

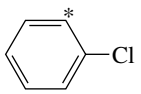
(j) Hexafluorobenzene + sodium hydrogen sulfide $\longrightarrow$

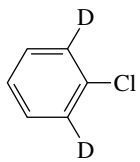
23.12 Potassium *tert*-butoxide reacts with halobenzenes on heating in dimethyl sulfoxide to give *tert*-butyl phenyl ether.

(a) *o*-Fluorotoluene yields *tert*-butyl *o*-methylphenyl ether almost exclusively under these conditions. By which mechanism (addition–elimination or elimination–addition) do aryl fluorides react with potassium *tert*-butoxide in dimethyl sulfoxide?

(b) At 100°C, bromobenzene reacts over 20 times faster than fluorobenzene. By which mechanism do aryl bromides react?

23.13 Predict the products formed when each of the following isotopically substituted derivatives of chlorobenzene is treated with sodium amide in liquid ammonia. Estimate as quantitatively as possible the composition of the product mixture. The asterisk (*) in part (a) designates ^{14}C, and D in part (b) is ^{2}H.

(a) 

(b) 

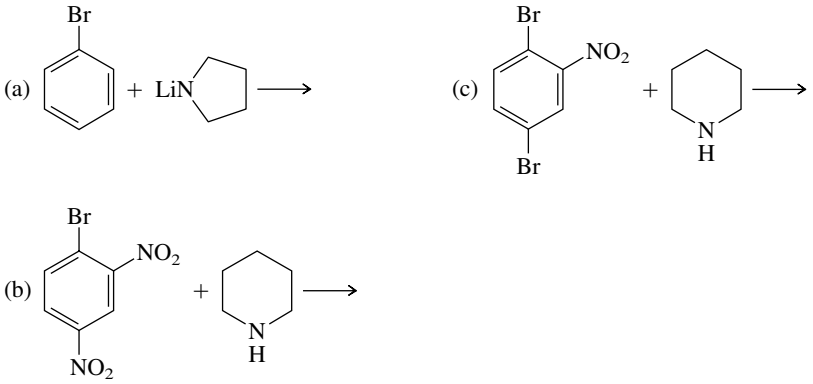
23.14 Choose the compound in each of the following pairs that reacts faster with sodium methoxide in methanol at 50°C:

(a) Chlorobenzene or *o*-chloronitrobenzene
(b) *o*-Chloronitrobenzene or *m*-chloronitrobenzene
(c) 4-Chloro-3-nitroacetophenone or 4-chloro-3-nitrotoluene

(d) 2-Fluoro-1,3-dinitrobenzene or 1-fluoro-3,5-dinitrobenzene

(e) 1,4-Dibromo-2-nitrobenzene or 1-bromo-2,4-dinitrobenzene

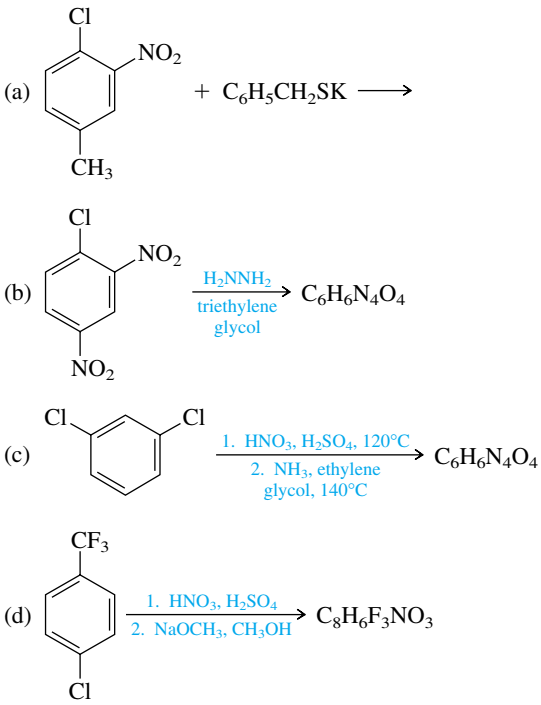
23.15 In each of the following reactions, an amine or a lithium amide derivative reacts with an aryl halide. Give the structure of the expected product, and specify the mechanism by which it is formed.

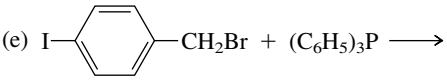


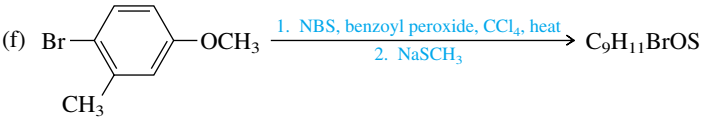
23.16 Piperidine, the amine reactant in parts (b) and (c) of the preceding problem, reacts with 1-bromonaphthalene on heating at 230°C to give a single product, compound A ($C_{15}H_{17}N$), as a noncrystallizable liquid. The same reaction using 2-bromonaphthalene yielded an isomeric product, compound B, a solid melting at 50–53°C. Mixtures of A and B were formed when either 1- or 2-bromonaphthalene was allowed to react with sodium piperidide in piperidine. Suggest reasonable structures for compounds A and B and offer an explanation for their formation under each set of reaction conditions.

23.17 1,2,3,4,5-Pentafluoro-6-nitrobenzene reacts readily with sodium methoxide in methanol at room temperature to yield two major products, each having the molecular formula $C_7H_3F_4NO_3$. Suggest reasonable structures for these two compounds.

23.18 Predict the major organic product in each of the following reactions:

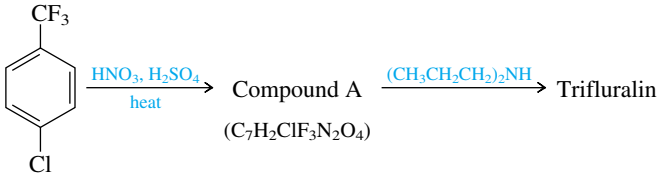


(e) 

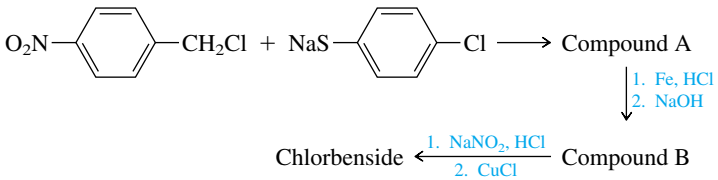
(f) 

23.19 The hydrolysis of *p*-bromotoluene with aqueous sodium hydroxide at 300°C yields *m*-methylphenol and *p*-methylphenol in a 5:4 ratio. What is the meta–para ratio for the same reaction carried out on *p*-chlorotoluene?

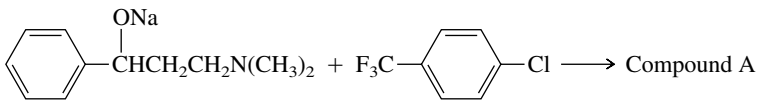
23.20 The herbicide *trifluralin* is prepared by the following sequence of reactions. Identify compound A and deduce the structure of trifluralin.



23.21 *Chlorbenside* is a pesticide used to control red spider mites. It is prepared by the sequence shown. Identify compounds A and B in this sequence. What is the structure of chlorbenside?

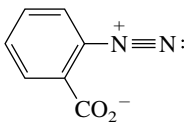


23.22 An article in the October 1998 issue of the *Journal of Chemical Education* (p. 1266) describes the following reaction.



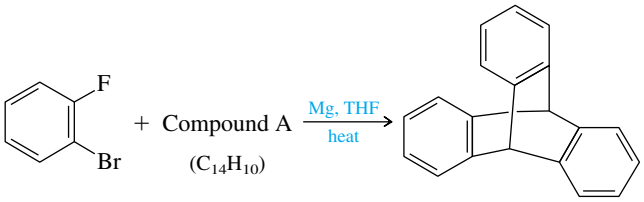
Fluoxetine hydrochloride (Prozac) is a widely prescribed antidepressant drug introduced by Eli Lilly & Co. in 1986. It differs from Compound A in having an —$NHCH_3$ group in place of —$N(CH_3)_2$. What is the structure of Prozac?

23.23 A method for the generation of benzyne involves heating the diazonium salt from *o*-aminobenzoic acid (benzenediazonium-2-carboxylate). Using curved arrows, show how this substance forms benzyne. What two inorganic compounds are formed in this reaction?



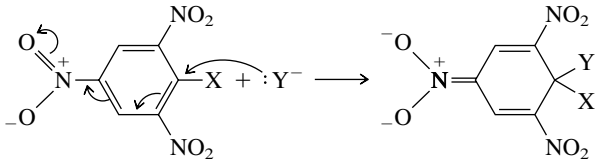
Benzenediazonium-2-carboxylate

23.24 The compound *triptycene* may be prepared as shown. What is compound A?



Triptycene

23.25 Nitro-substituted aromatic compounds that do not bear halide leaving groups react with nucleophiles according to the equation



The product of this reaction, as its sodium salt, is called a *Meisenheimer complex* after the German chemist Jacob Meisenheimer, who reported on their formation and reactions in 1902. A Meisenheimer complex corresponds to the product of the nucleophilic addition stage in the addition–elimination mechanism for nucleophilic aromatic substitution.

(a) Give the structure of the Meisenheimer complex formed by addition of sodium ethoxide to 2,4,6-trinitroanisole.

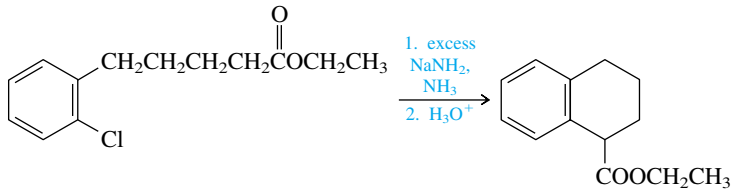
(b) What other combination of reactants yields the same Meisenheimer complex as that of part (a)?

23.26 A careful study of the reaction of 2,4,6-trinitroanisole with sodium methoxide revealed that two different Meisenheimer complexes were present. Suggest reasonable structures for these two complexes.

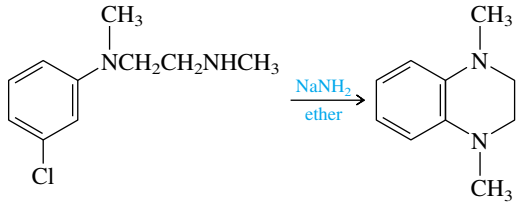
23.27 Suggest a reasonable mechanism for each of the following reactions:

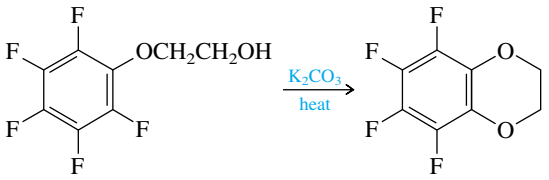
(a) $C_6H_5Br + CH_2(COOCH_2CH_3)_2 \xrightarrow[2.\ H_3O^+]{1.\ \text{excess } NaNH_2,\ NH_3} C_6H_5CH(COOCH_2CH_3)_2$

(b)



(c)



(d) 

23.28 Mixtures of chlorinated derivatives of biphenyl, called *polychlorinated biphenyls,* or *PCBs,* were once prepared industrially on a large scale as insulating materials in electrical equipment. As equipment containing PCBs was discarded, the PCBs entered the environment at a rate that reached an estimated 25,000 lb/year. PCBs are very stable and accumulate in the fatty tissue of fish, birds, and mammals. They have been shown to be *teratogenic,* meaning that they induce mutations in the offspring of affected individuals. Some countries have banned the use of PCBs. A large number of chlorinated biphenyls are possible, and the commercially produced material is a mixture of many compounds.

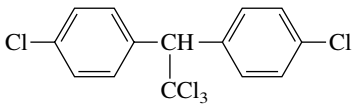
(a) How many monochloro derivatives of biphenyl are possible?

(b) How many dichloro derivatives are possible?

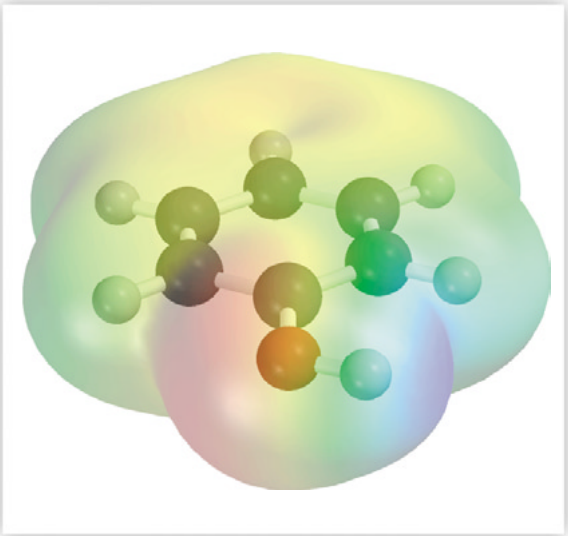
(c) How many octachloro derivatives are possible?

(d) How many nonachloro derivatives are possible?

23.29 DDT-resistant insects have the ability to convert DDT to a less toxic substance called DDE. The mass spectrum of DDE shows a cluster of peaks for the molecular ion at *m/z* 316, 318, 320, 322, and 324. Suggest a reasonable structure for DDE.



DDT (*d*ichloro*d*iphenyl*t*richloroethane)



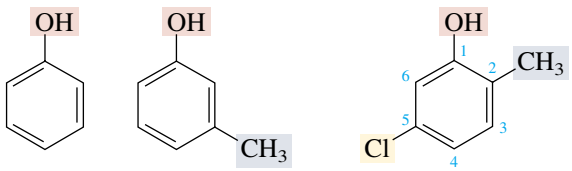
CHAPTER 24

PHENOLS

Phenols are compounds that have a hydroxyl group bonded directly to a benzene or benzenoid ring. The parent compound of this group, C_6H_5OH, called simply *phenol,* is an important industrial chemical. Many of the properties of phenols are analogous to those of alcohols, but this similarity is something of an oversimplification. Like arylamines, phenols are difunctional compounds; the hydroxyl group and the aromatic ring interact strongly, affecting each other's reactivity. This interaction leads to some novel and useful properties of phenols. A key step in the synthesis of aspirin, for example, is without parallel in the reactions of either alcohols or arenes. With periodic reminders of the ways in which phenols resemble alcohols and arenes, this chapter emphasizes the ways in which phenols are unique.

24.1 NOMENCLATURE

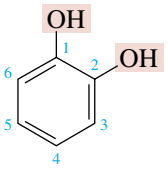
An old name for benzene was *phene,* and its hydroxyl derivative came to be called *phenol.** This, like many other entrenched common names, is an acceptable IUPAC name. Likewise, *o-, m-,* and *p*-cresol are acceptable names for the various ring-substituted hydroxyl derivatives of toluene. More highly substituted compounds are named as derivatives of phenol. Numbering of the ring begins at the hydroxyl-substituted carbon and proceeds in the direction that gives the lower number to the next substituted carbon. Substituents are cited in alphabetical order.



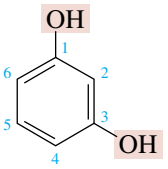
Phenol *m*-Cresol 5-Chloro-2-methylphenol

*The systematic name for phenol is *benzenol.*

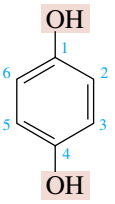
The three dihydroxy derivatives of benzene may be named as 1,2-, 1,3-, and 1,4-benzenediol, respectively, but each is more familiarly known by the common name indicated in parentheses below the structures shown here. These common names are permissible IUPAC names.



1,2-Benzenediol (pyrocatechol)



1,3-Benzenediol (resorcinol)



1,4-Benzenediol (hydroquinone)

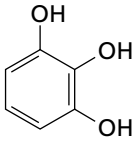
Pyrocatechol is often called *catechol.*

The common names for the two hydroxy derivatives of naphthalene are 1-naphthol and 2-naphthol. These are also acceptable IUPAC names.

PROBLEM 24.1 Write structural formulas for each of the following compounds:

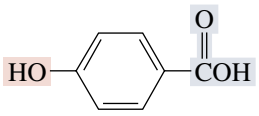
(a) Pyrogallol (1,2,3-benzenetriol)
(b) *o*-Benzylphenol
(c) 3-Nitro-1-naphthol
(d) 4-Chlororesorcinol

SAMPLE SOLUTION (a) Like the dihydroxybenzenes, the isomeric trihydroxybenzenes have unique names. Pyrogallol, used as a developer of photographic film, is 1,2,3-benzenetriol. The three hydroxyl groups occupy adjacent positions on a benzene ring.

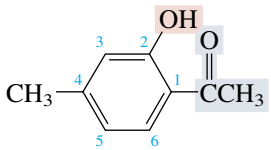


Pyrogallol (1,2,3-benzenetriol)

Carboxyl and acyl groups take precedence over the phenolic hydroxyl in determining the base name. The hydroxyl is treated as a substituent in these cases.



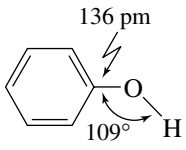
p-Hydroxybenzoic acid



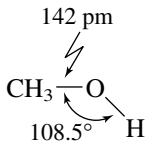
2-Hydroxy-4-methylacetophenone

24.2 STRUCTURE AND BONDING

Phenol is planar, with a C—O—H angle of 109°, almost the same as the tetrahedral angle and not much different from the 108.5° C—O—H angle of methanol:



Phenol

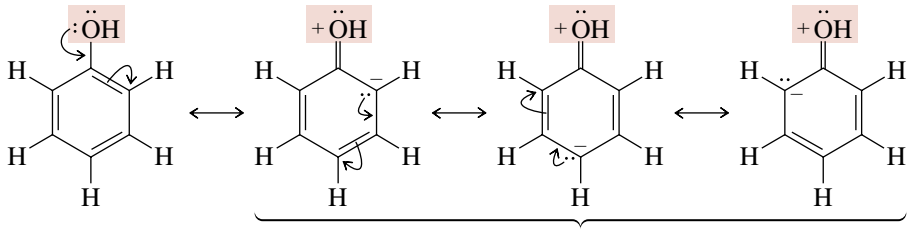


Methanol

The graphic that opened this chapter is a molecular model of phenol that shows its planar structure and electrostatic potential.

As we've seen on a number of occasions, bonds to sp^2-hybridized carbon are shorter than those to sp^3-hybridized carbon, and the case of phenols is no exception. The carbon–oxygen bond distance in phenol is slightly less than that in methanol.

In resonance terms, the shorter carbon–oxygen bond distance in phenol is attributed to the partial double-bond character that results from conjugation of the unshared electron pair of oxygen with the aromatic ring.



Most stable Lewis structure for phenol

Dipolar resonance forms of phenol

Many of the properties of phenols reflect the polarization implied by the resonance description. The hydroxyl oxygen is less basic, and the hydroxyl proton more acidic, in phenols than in alcohols. Electrophiles attack the aromatic ring of phenols much faster than they attack benzene, indicating that the ring, especially at the positions ortho and para to the hydroxyl group, is relatively "electron-rich."

24.3 PHYSICAL PROPERTIES

The physical properties of phenols are strongly influenced by the hydroxyl group, which permits phenols to form hydrogen bonds with other phenol molecules (Figure 24.1*a*) and with water (Figure 24.1*b*). Thus, phenols have higher melting points and boiling points and are more soluble in water than arenes and aryl halides of comparable molecular weight. Table 24.1 compares phenol, toluene, and fluorobenzene with regard to these physical properties.

The physical properties of some representative phenols are collected in Appendix 1.

Some ortho-substituted phenols, such as *o*-nitrophenol, have significantly lower boiling points than those of the meta and para isomers. This is because the *intramolecular* hydrogen bond that forms between the hydroxyl group and the substituent partially compensates for the energy required to go from the liquid state to the vapor.

TABLE 24.1 Comparison of Physical Properties of an Arene, a Phenol, and an Aryl Halide

	Compound		
Physical property	**Toluene, $C_6H_5CH_3$**	**Phenol, C_6H_5OH**	**Fluorobenzene, C_6H_5F**
Molecular weight	92	94	96
Melting point	−95°C	43°C	−41°C
Boiling point (1 atm)	111°C	132°C	85°C
Solubility in water (25°C)	0.05 g/100 mL	8.2 g/100 mL	0.2 g/100 mL

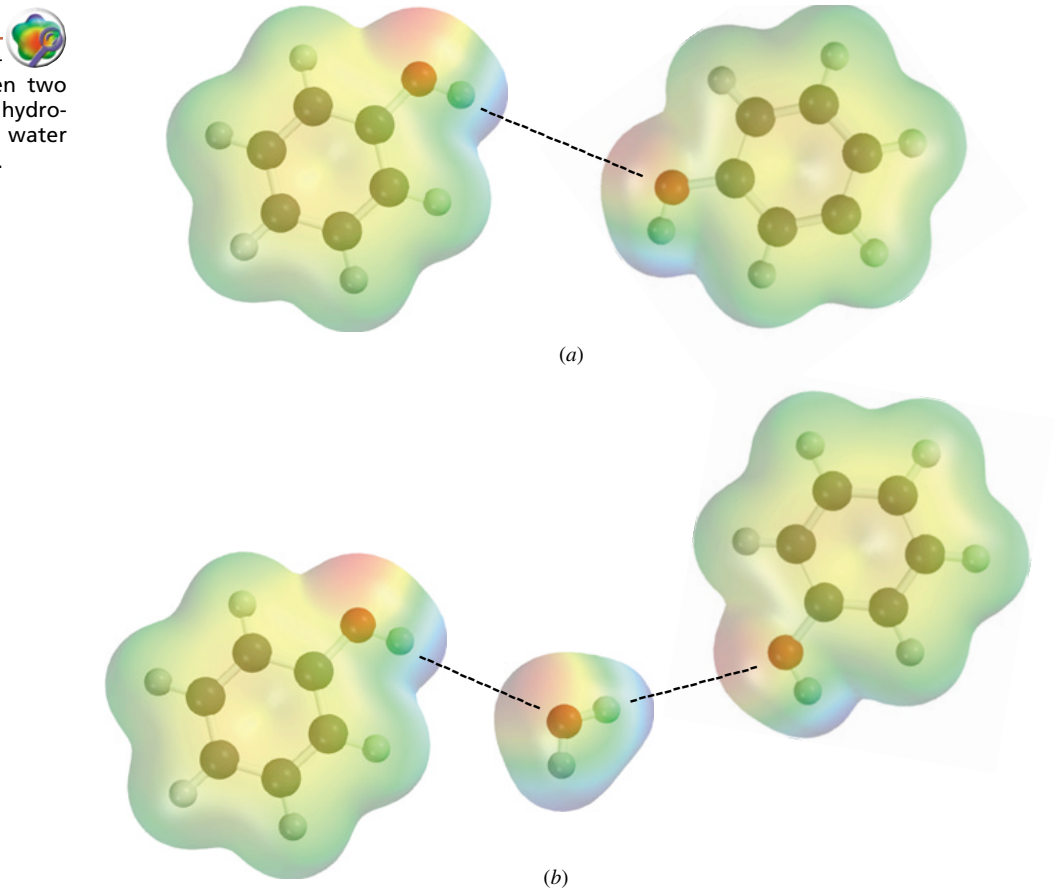
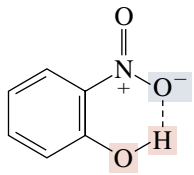


FIGURE 24.1 (*a*) A hydrogen bond between two phenol molecules; (*b*) hydrogen bonds between water and phenol molecules.



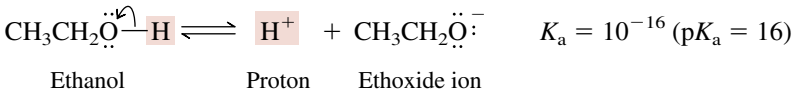
Intramolecular hydrogen bond in *o*-nitrophenol

PROBLEM 24.2 One of the hydroxybenzoic acids is known by the common name *salicylic acid.* Its methyl ester, methyl salicylate, occurs in oil of wintergreen. Methyl salicylate boils over 50°C lower than either of the other two methyl hydroxybenzoates. What is the structure of methyl salicylate? Why is its boiling point so much lower than that of either of its regioisomers?

24.4 ACIDITY OF PHENOLS

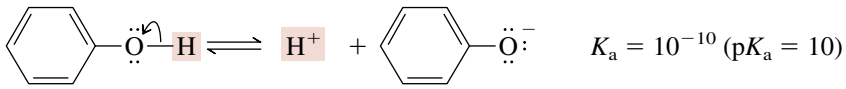
The most characteristic property of phenols is their acidity. Phenols are more acidic than alcohols but less acidic than carboxylic acids. Recall that carboxylic acids have ionization constants K_a of approximately 10^{-5} (pK_a 5), whereas the K_a's of alcohols are in the 10^{-16} to 10^{-20} range (pK_a 16–20). The K_a for most phenols is about 10^{-10} (pK_a 10).

To help us understand why phenols are more acidic than alcohols, let's compare the ionization equilibria for phenol and ethanol. In particular, consider the differences in charge delocalization in ethoxide ion and in phenoxide ion. The negative charge in ethoxide ion is localized on oxygen and is stabilized only by solvation forces.

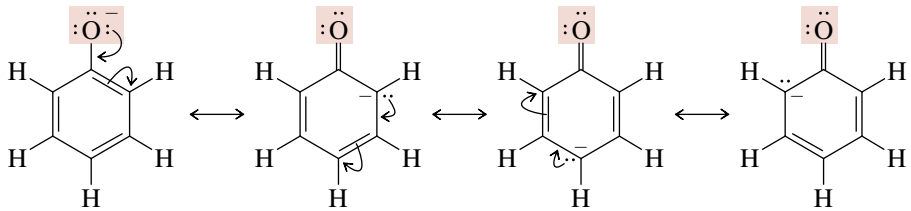


Because of its acidity, phenol was known as *carbolic acid* when Joseph Lister introduced it as an antiseptic in 1865 to prevent postoperative bacterial infections that were then a life-threatening hazard in even minor surgical procedures.

The negative charge in phenoxide ion is stabilized both by solvation and by electron delocalization into the ring.



Electron delocalization in phenoxide is represented by resonance among the structures:



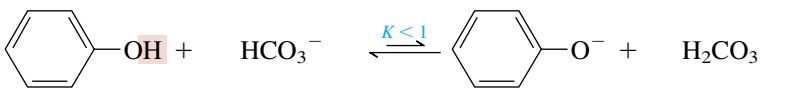

The electrostatic potential map of phenoxide ion on *Learning By Modeling* displays the delocalization of electrons into the ring.

The negative charge in phenoxide ion is shared by the oxygen and the carbons that are ortho and para to it. Delocalization of its negative charge strongly stabilizes phenoxide ion.

To place the acidity of phenol in perspective, note that although phenol is more than a million times more acidic than ethanol, it is over a hundred thousand times weaker than acetic acid. Thus, phenols can be separated from alcohols because they are more acidic, and from carboxylic acids because they are less acidic. On shaking an ether solution containing both an alcohol and a phenol with dilute sodium hydroxide, the phenol is converted quantitatively to its sodium salt, which is extracted into the aqueous phase. The alcohol remains in the ether phase.

How do we know that water is a weaker acid than phenol? What are their respective pK_a values?

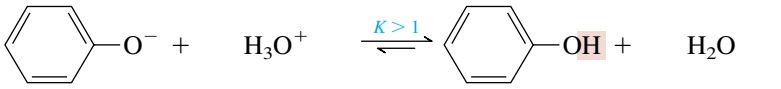
On shaking an ether solution of a phenol and a carboxylic acid with dilute sodium bicarbonate, the carboxylic acid is converted quantitatively to its sodium salt and extracted into the aqueous phase. The phenol remains in the ether phase.



How do we know that carbonic acid is a stronger acid than phenol? What are their respective pK_a values?

It is necessary to keep the acidity of phenols in mind when we discuss preparation and reactions. Reactions that produce phenols, when carried out in basic solution, require an acidification step in order to convert the phenoxide ion to the neutral form of the phenol.

How do we know that hydronium ion is a stronger acid than phenol? What are their respective pK_a values?



Phenoxide ion (stronger base) | Hydronium ion (stronger acid) | Phenol (weaker acid) | Water (weaker base)

Many synthetic reactions involving phenols as nucleophiles are carried out in the presence of sodium or potassium hydroxide. Under these conditions the phenol is converted to the corresponding phenoxide ion, which is a far better nucleophile.

24.5 SUBSTITUENT EFFECTS ON THE ACIDITY OF PHENOLS

As Table 24.2 shows, most phenols have ionization constants similar to that of phenol itself. Substituent effects, in general, are small.

Alkyl substitution produces negligible changes in acidities, as do weakly electronegative groups attached to the ring.

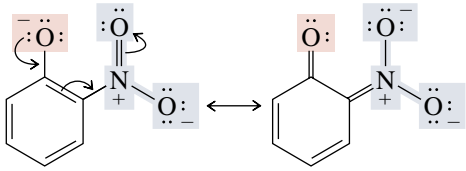
Recall from Section 24.1 that cresols are methyl-substituted derivatives of phenol.

TABLE 24.2 Acidities of Some Phenols

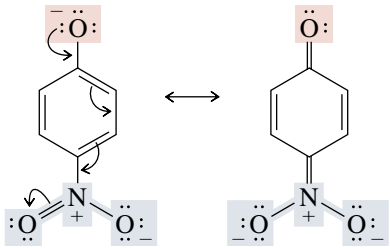
Compound name	Ionization constant K_a	pK_a
Monosubstituted phenols		
Phenol	1.0×10^{-10}	10.0
o-Cresol	4.7×10^{-11}	10.3
m-Cresol	8.0×10^{-11}	10.1
p-Cresol	5.2×10^{-11}	10.3
o-Chlorophenol	2.7×10^{-9}	8.6
m-Chlorophenol	7.6×10^{-9}	9.1
p-Chlorophenol	3.9×10^{-9}	9.4
o-Methoxyphenol	1.0×10^{-10}	10.0
m-Methoxyphenol	2.2×10^{-10}	9.6
p-Methoxyphenol	6.3×10^{-11}	10.2
o-Nitrophenol	5.9×10^{-8}	7.2
m-Nitrophenol	4.4×10^{-9}	8.4
p-Nitrophenol	6.9×10^{-8}	7.2
Di- and trinitrophenols		
2,4-Dinitrophenol	1.1×10^{-4}	4.0
3,5-Dinitrophenol	2.0×10^{-7}	6.7
2,4,6-Trinitrophenol	4.2×10^{-1}	0.4
Naphthols		
1-Naphthol	5.9×10^{-10}	9.2
2-Naphthol	3.5×10^{-10}	9.5

Only when the substituent is strongly electron-withdrawing, as is a nitro group, is a substantial change in acidity noted. The ionization constants of *o*- and *p*-nitrophenol are several hundred times greater than that of phenol. An ortho- or para-nitro group greatly stabilizes the phenoxide ion by permitting a portion of the negative charge to be carried by its own oxygens.

Electron delocalization in* o-*nitrophenoxide ion



Electron delocalization in* p-*nitrophenoxide ion



A meta-nitro group is not directly conjugated to the phenoxide oxygen and thus stabilizes a phenoxide ion to a smaller extent. *m*-Nitrophenol is more acidic than phenol but less acidic than either *o*- or *p*-nitrophenol.

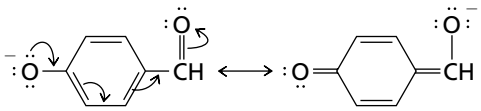
PROBLEM 24.3 Which is the stronger acid in each of the following pairs? Explain your reasoning.

(a) Phenol or *p*-hydroxybenzaldehyde

(b) *m*-Cyanophenol or *p*-cyanophenol

(c) *o*-Fluorophenol or *p*-fluorophenol

SAMPLE SOLUTION (a) The best approach when comparing the acidities of different phenols is to assess opportunities for stabilization of negative charge in their anions. Electron delocalization in the anion of *p*-hydroxybenzaldehyde is very effective because of conjugation with the formyl group.



A formyl substituent, like a nitro group, is strongly electron-withdrawing and acid-strengthening, especially when ortho or para to the hydroxyl group. *p*-Hydroxybenzaldehyde, with a K_a of 2.4×10^{-8}, is a stronger acid than phenol.

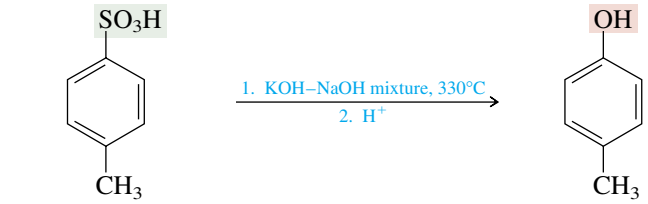
Multiple substitution by strongly electron-withdrawing groups greatly increases the acidity of phenols, as the K_a values for 2,4-dinitrophenol (K_a 1.1×10^{-4}) and 2,4,6-trinitrophenol (K_a 4.2×10^{-1}) in Table 24.2 attest.

24.6 SOURCES OF PHENOLS

Phenol was first isolated in the early nineteenth century from coal tar, and a small portion of the more than 4 billion lb of phenol produced in the United States each year comes from this source. Although significant quantities of phenol are used to prepare aspirin and dyes, most of it is converted to phenolic resins used in adhesives and plastics. Almost all the phenol produced commercially is synthetic, with several different processes in current use. These are summarized in Table 24.3.

The reaction of benzenesulfonic acid with sodium hydroxide (first entry in Table 24.3) proceeds by the addition–elimination mechanism of nucleophilic aromatic substitution (Section 23.6). Hydroxide replaces sulfite ion (SO_3^{2-}) at the carbon atom that bears the leaving group. Thus, *p*-toluenesulfonic acid is converted exclusively to *p*-cresol by an analogous reaction:

Can you recall how to prepare *p*-toluenesulfonic acid?



p-Toluenesulfonic acid — *p*-Cresol (63–72%)

PROBLEM 24.4 Write a stepwise mechanism for the conversion of *p*-toluenesulfonic acid to *p*-cresol under the conditions shown in the preceding equation.

On the other hand, ^{14}C-labeling studies have shown that the base-promoted hydrolysis of chlorobenzene (second entry in Table 24.3) proceeds by the elimination–addition mechanism and involves benzyne as an intermediate.

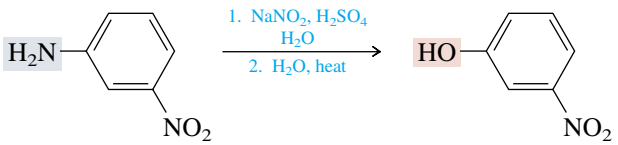
Can you recall how to prepare chlorobenzene?

PROBLEM 24.5 Write a stepwise mechanism for the hydrolysis of chlorobenzene under the conditions shown in Table 24.3.

The most widely used industrial synthesis of phenol is based on isopropylbenzene (cumene) as the starting material and is shown in the third entry of Table 24.3. The economically attractive features of this process are its use of cheap reagents (oxygen and sulfuric acid) and the fact that it yields two high-volume industrial chemicals: phenol and acetone. The mechanism of this novel synthesis forms the basis of Problem 24.29 at the end of this chapter.

Can you recall how to prepare isopropylbenzene?

The most important synthesis of phenols in the laboratory is from amines by hydrolysis of their corresponding diazonium salts, as described in Section 22.18:

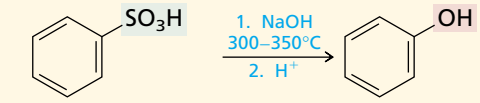
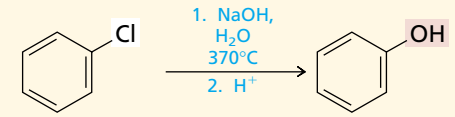
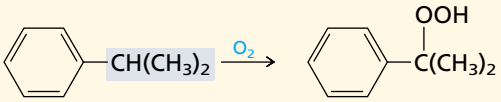
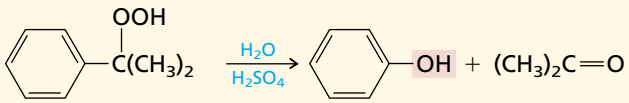


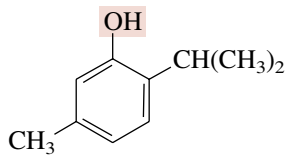
m-Nitroaniline — *m*-Nitrophenol (81–86%)

24.7 NATURALLY OCCURRING PHENOLS

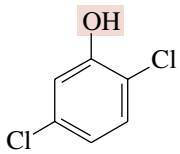
Phenolic compounds are commonplace natural products. Figure 24.2 presents a sampling of some naturally occurring phenols. Phenolic natural products can arise by a number of different biosynthetic pathways. In mammals, aromatic rings are hydroxylated by way

TABLE 24.3 Industrial Syntheses of Phenol

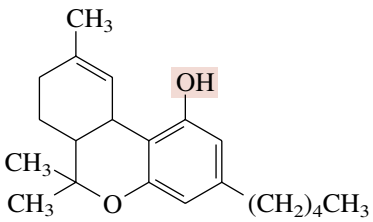
Reaction and comments	Chemical equation
Reaction of benzenesulfonic acid with sodium hydroxide This is the oldest method for the preparation of phenol. Benzene is sulfonated and the benzenesulfonic acid heated with molten sodium hydroxide. Acidification of the reaction mixture gives phenol.	 Benzenesulfonic acid — Phenol
Hydrolysis of chlorobenzene Heating chlorobenzene with aqueous sodium hydroxide at high pressure gives phenol after acidification.	 Chlorobenzene — Phenol
From cumene Almost all the phenol produced in the United States is prepared by this method. Oxidation of cumene takes place at the benzylic position to give a hydroperoxide. On treatment with dilute sulfuric acid, this hydroperoxide is converted to phenol and acetone.	 Isopropylbenzene (cumene) — 1-Methyl-1-phenylethyl hydroperoxide
	 1-Methyl-1-phenylethyl hydroperoxide — Phenol — Acetone



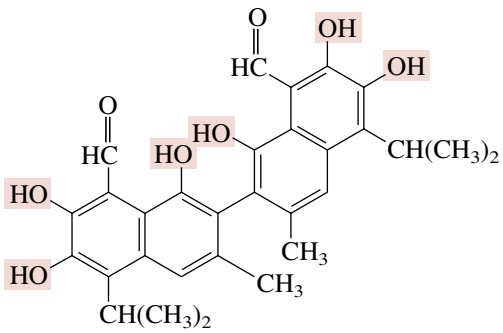
Thymol
(major constituent of oil of thyme)



2,5-Dichlorophenol
(isolated from defensive secretion of a species of grasshopper)



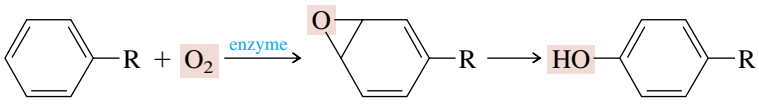
Δ^9-Tetrahydrocannabinol
(active component of marijuana)



Gossypol
(About 10^9 lb of this material is obtained each year in the United States as a byproduct of cotton-oil production.)

FIGURE 24.2 Some naturally occurring phenols.

of arene oxide intermediates formed by the enzyme-catalyzed reaction between an aromatic ring and molecular oxygen:



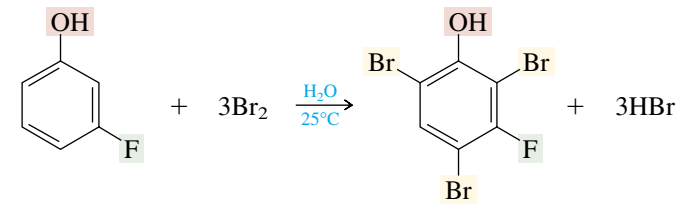
Arene Arene oxide Phenol

In plants, phenol biosynthesis proceeds by building the aromatic ring from carbohydrate precursors that already contain the required hydroxyl group.

24.8 REACTIONS OF PHENOLS: ELECTROPHILIC AROMATIC SUBSTITUTION

In most of their reactions phenols behave as nucleophiles, and the reagents that act on them are electrophiles. Either the hydroxyl oxygen or the aromatic ring may be the site of nucleophilic reactivity in a phenol. Reactions that take place on the ring lead to electrophilic aromatic substitution; Table 24.4 (p. 950) summarizes the behavior of phenols in reactions of this type.

A hydroxyl group is a very powerful activating substituent, and electrophilic aromatic substitution in phenols occurs far faster, and under milder conditions, than in benzene. The first entry in Table 24.4, for example, shows the monobromination of phenol in high yield at low temperature and in the absence of any catalyst. In this case, the reaction was carried out in the nonpolar solvent 1,2-dichloroethane. In polar solvents such as water it is difficult to limit the bromination of phenols to monosubstitution. In the following example, all three positions that are ortho or para to the hydroxyl undergo rapid substitution:



m-Fluorophenol Bromine 2,4,6-Tribromo-3-fluorophenol (95%) Hydrogen bromide

Other typical electrophilic aromatic substitution reactions—nitration (second entry), sulfonation (fourth entry), and Friedel–Crafts alkylation and acylation (fifth and sixth entries)—take place readily and are synthetically useful. Phenols also undergo electrophilic substitution reactions that are limited to only the most active aromatic compounds; these include nitrosation (third entry) and coupling with diazonium salts (seventh entry).

PROBLEM 24.6 Each of the following reactions has been reported in the chemical literature and gives a single organic product in high yield. Identify the product in each case.

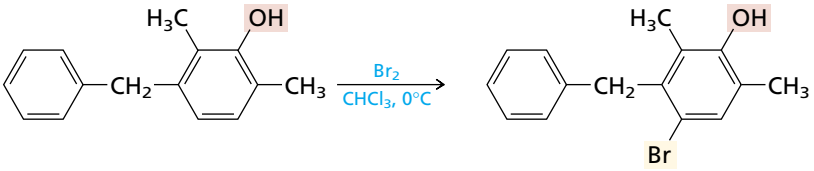
(a) 3-Benzyl-2,6-dimethylphenol treated with bromine in chloroform

(b) 4-Bromo-2-methylphenol treated with 2-methylpropene and sulfuric acid

(c) 2-Isopropyl-5-methylphenol (thymol) treated with sodium nitrite and dilute hydrochloric acid

(d) *p*-Cresol treated with propanoyl chloride and aluminum chloride

SAMPLE SOLUTION (a) The ring that bears the hydroxyl group is much more reactive than the other ring. In electrophilic aromatic substitution reactions of rings that bear several substituents, it is the most activating substituent that controls the orientation. Bromination occurs para to the hydroxyl group.



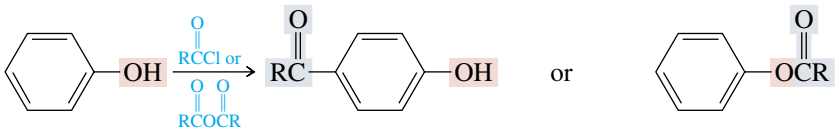
3-Benzyl-2,6-dimethylphenol

3-Benzyl-4-bromo-2,6-dimethylphenol (isolated in 100% yield)

The aromatic ring of a phenol, like that of an arylamine, is seen as an electron-rich functional unit and is capable of a variety of reactions. In some cases, however, it is the hydroxyl oxygen that reacts instead. An example of this kind of chemical reactivity is described in the following section.

24.9 ACYLATION OF PHENOLS

Acylating agents, such as acyl chlorides and carboxylic acid anhydrides, can react with phenols either at the aromatic ring (C-acylation) or at the hydroxyl oxygen (O-acylation):

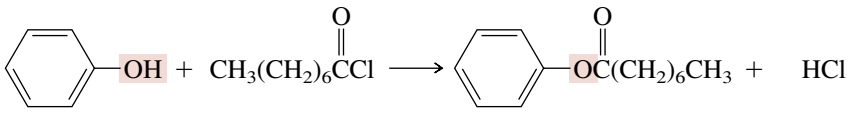


Phenol

Aryl ketone (product of C-acylation)

Aryl ester (product of O-acylation)

As shown in the sixth entry of Table 24.4, C-acylation of phenols is observed under the customary conditions of the Friedel–Crafts reaction (treatment with an acyl chloride or acid anhydride in the presence of aluminum chloride). In the absence of aluminum chloride, however, O-acylation occurs instead.



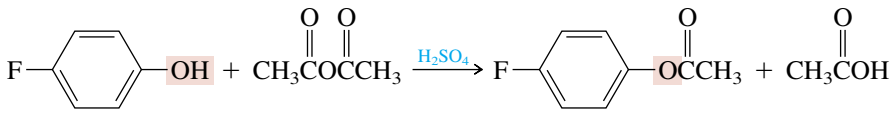
Phenol

Octanoyl chloride

Phenyl octanoate (95%)

Hydrogen chloride

The O-acylation of phenols with carboxylic acid anhydrides can be conveniently catalyzed in either of two ways. One method involves converting the acid anhydride to a more powerful acylating agent by protonation of one of its carbonyl oxygens. Addition of a few drops of sulfuric acid is usually sufficient.



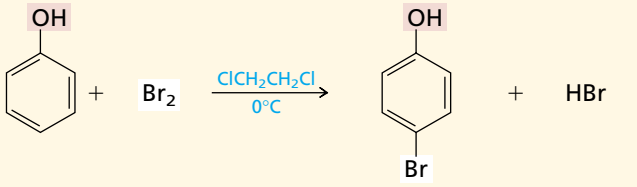
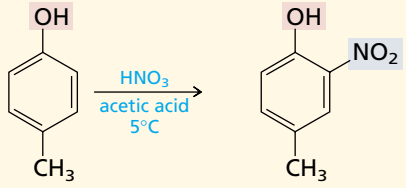
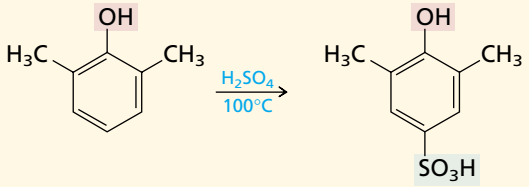
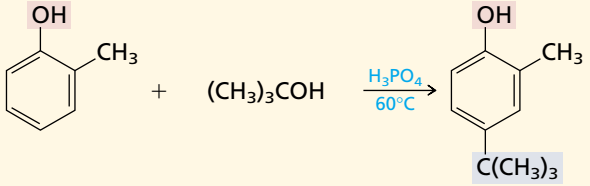
p-Fluorophenol

Acetic anhydride

p-Fluorophenyl acetate (81%)

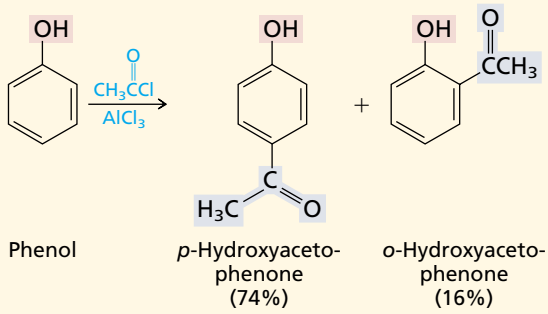
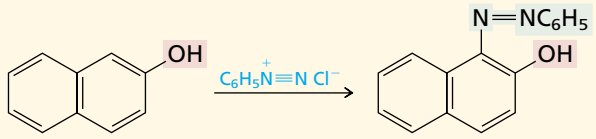
Acetic acid

TABLE 24.4 Electrophilic Aromatic Substitution Reactions of Phenols

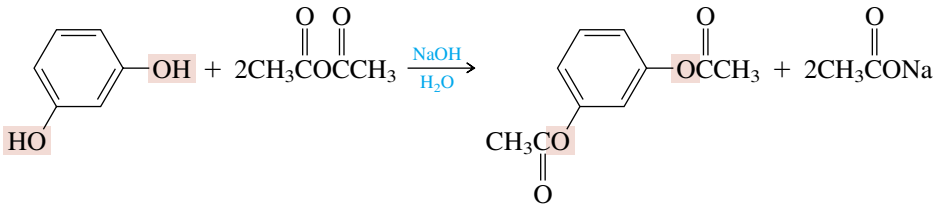
Reaction and comments	Specific example
Halogenation Bromination and chlorination of phenols occur readily even in the absence of a catalyst. Substitution occurs primarily at the position para to the hydroxyl group. When the para position is blocked, ortho substitution is observed.	 Phenol Bromine *p*-Bromophenol (93%) Hydrogen bromide
Nitration Phenols are nitrated on treatment with a dilute solution of nitric acid in either water or acetic acid. It is not necessary to use mixtures of nitric and sulfuric acids, because of the high reactivity of phenols.	 *p*-Cresol 4-Methyl-2-nitrophenol (73–77%)
Nitrosation On acidification of aqueous solutions of sodium nitrite, the nitrosonium ion (:N≡O:$^+$) is formed, which is a weak electrophile and attacks the strongly activated ring of a phenol. The product is a nitroso phenol.	 2-Naphthol 1-Nitroso-2-naphthol (99%)
Sulfonation Heating a phenol with concentrated sulfuric acid causes sulfonation of the ring.	 2,6-Dimethylphenol 4-Hydroxy-3,5-dimethylbenzenesulfonic acid (69%)
Friedel–Crafts alkylation Alcohols in combination with acids serve as sources of carbocations. Attack of a carbocation on the electron-rich ring of a phenol brings about its alkylation.	 *o*-Cresol *tert*-Butyl alcohol 4-*tert*-Butyl-2-methylphenol (63%)

(Continued)

TABLE 24.4 Electrophilic Aromatic Substitution Reactions of Phenols *(Continued)*

Reaction and comments	Specific example
Friedel–Crafts acylation In the presence of aluminum chloride, acyl chlorides and carboxylic acid anhydrides acylate the aromatic ring of phenols.	 Phenol; *p*-Hydroxyacetophenone (74%); *o*-Hydroxyacetophenone (16%)
Reaction with arenediazonium salts Adding a phenol to a solution of a diazonium salt formed from a primary aromatic amine leads to formation of an azo compound. The reaction is carried out at a pH such that a significant portion of the phenol is present as its phenoxide ion. The diazonium ion acts as an electrophile toward the strongly activated ring of the phenoxide ion.	 2-Naphthol; 1-Phenylazo-2-naphthol (48%)

An alternative approach is to increase the nucleophilicity of the phenol by converting it to its phenoxide anion in basic solution:



Resorcinol; Acetic anhydride; 1,3-Diacetoxybenzene (93%); Sodium acetate

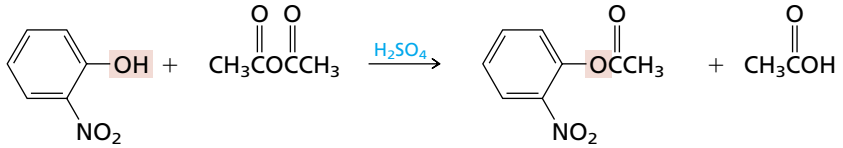
PROBLEM 24.7 Write chemical equations expressing each of the following:

(a) Preparation of *o*-nitrophenyl acetate by sulfuric acid catalysis of the reaction between a phenol and a carboxylic acid anhydride.

(b) Esterification of 2-naphthol with acetic anhydride in aqueous sodium hydroxide

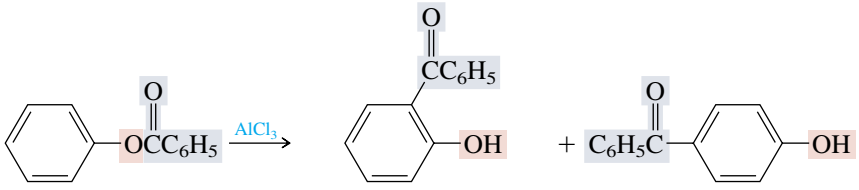
(c) Reaction of phenol with benzoyl chloride

SAMPLE SOLUTION (a) The problem specifies that an acid anhydride be used; therefore, use acetic anhydride to prepare the acetate ester of *o*-nitrophenol:



o-Nitrophenol; Acetic anhydride; *o*-Nitrophenyl acetate (isolated in 93% yield by this method); Acetic acid

The preference for O-acylation of phenols arises because these reactions are *kinetically controlled.* O-acylation is faster than C-acylation. The C-acyl isomers are more stable, however, and it is known that aluminum chloride is a very effective catalyst for the conversion of aryl esters to aryl ketones. (This isomerization is called the **Fries rearrangement.**)



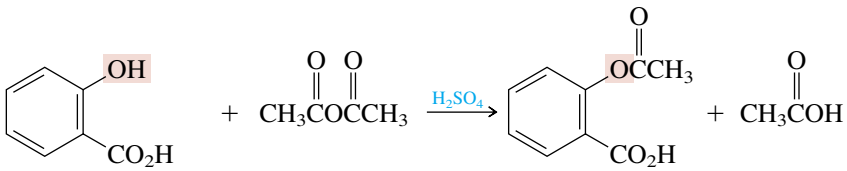
Phenyl benzoate — *o*-Hydroxybenzophenone (9%) — *p*-Hydroxybenzophenone (64%)

Thus, ring acylation of phenols is observed under Friedel–Crafts conditions because the presence of aluminum chloride causes that reaction to be subject to *thermodynamic* (*equilibrium*) *control.*

Fischer esterification, in which a phenol and a carboxylic acid condense in the presence of an acid catalyst, is not used to prepare aryl esters.

24.10 CARBOXYLATION OF PHENOLS: ASPIRIN AND THE KOLBE–SCHMITT REACTION

The best known aryl ester is *O*-acetylsalicylic acid, better known as *aspirin.* It is prepared by acetylation of the phenolic hydroxyl group of salicylic acid:

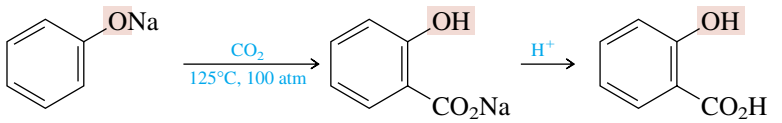


Salicylic acid (*o*-hydroxybenzoic acid) — Acetic anhydride — *O*-Acetylsalicylic acid (aspirin) — Acetic acid

An entertaining account of the history of aspirin can be found in the 1991 book *The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition,* by Charles C. Mann.

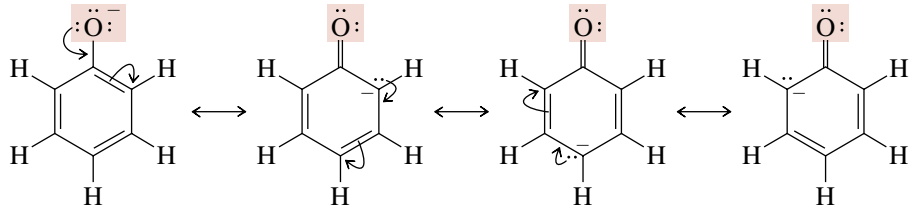
Aspirin possesses a number of properties that make it an often-recommended drug. It is an analgesic, effective in relieving headache pain. It is also an antiinflammatory agent, providing some relief from the swelling associated with arthritis and minor injuries. Aspirin is an antipyretic compound; that is, it reduces fever. Each year, more than 40 million lb of aspirin is produced in the United States, a rate equal to 300 tablets per year for every man, woman, and child.

The key compound in the synthesis of aspirin, salicylic acid, is prepared from phenol by a process discovered in the nineteenth century by the German chemist Hermann Kolbe. In the Kolbe synthesis, also known as the **Kolbe–Schmitt reaction,** sodium phenoxide is heated with carbon dioxide under pressure, and the reaction mixture is subsequently acidified to yield salicylic acid:



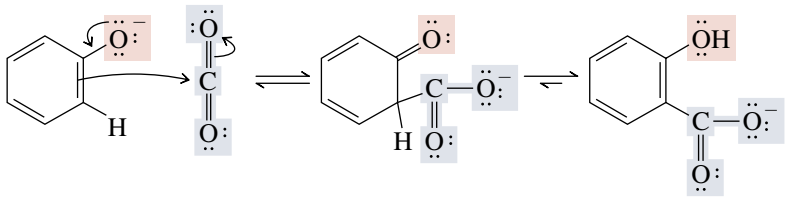
Sodium phenoxide — Sodium salicylate — Salicylic acid (79%)

Although a hydroxyl group strongly activates an aromatic ring toward electrophilic attack, an oxyanion substituent is an even more powerful activator. Electron delocalization in phenoxide anion leads to increased electron density at the positions ortho and para to oxygen.



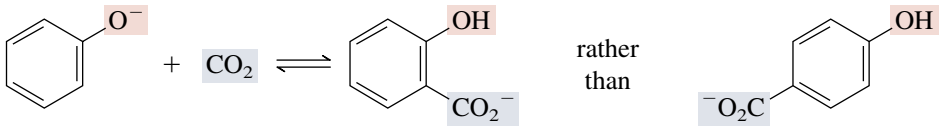
This is the same resonance description shown in Section 24.4.

The increased nucleophilicity of the ring permits it to react with carbon dioxide. An intermediate is formed that is simply the keto form of salicylate anion:



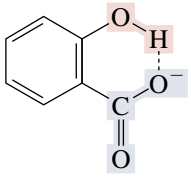
Phenoxide anion (stronger base) | Carbon dioxide | Cyclohexadienone intermediate | Salicylate anion (weaker base)

The Kolbe–Schmitt reaction is an equilibrium process governed by thermodynamic control. The position of equilibrium favors formation of the weaker base (salicylate ion) at the expense of the stronger one (phenoxide ion). Thermodynamic control is also responsible for the pronounced bias toward ortho over para substitution. Salicylate anion is a weaker base than *p*-hydroxybenzoate and so is the predominant species at equilibrium.



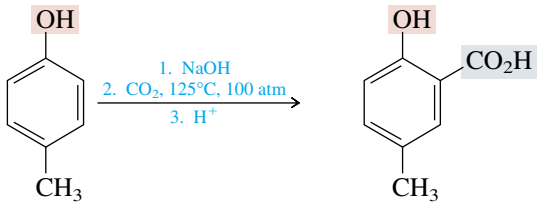
Phenoxide ion (strongest base; K_a of conjugate acid, 10^{-10}) | Carbon dioxide | Salicylate anion (weakest base; K_a of conjugate acid, 1.06×10^{-3}) | rather than | *p*-Hydroxybenzoate anion (K_a of conjugate acid, 3.3×10^{-5})

Salicylate anion is a weaker base than *p*-hydroxybenzoate because it is stabilized by intramolecular hydrogen bonding.



Intramolecular hydrogen bonding in salicylate anion

The Kolbe–Schmitt reaction has been applied to the preparation of other *o*-hydroxybenzoic acids. Alkyl derivatives of phenol behave very much like phenol itself.



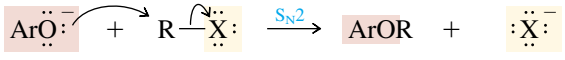
p-Cresol

2-Hydroxy-5-methylbenzoic acid (78%)

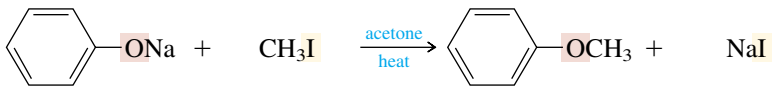
Phenols that bear strongly electron-withdrawing substituents usually give low yields of carboxylated products; their derived phenoxide anions are less basic, and the equilibrium constants for their carboxylation are smaller.

24.11 PREPARATION OF ARYL ETHERS

Aryl ethers are best prepared by the Williamson method (Section 16.6). Alkylation of the hydroxyl oxygen of a phenol takes place readily when a phenoxide anion reacts with an alkyl halide.



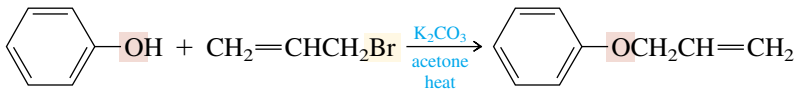
Phenoxide anion | Alkyl halide | Alkyl aryl ether | Halide anion



Sodium phenoxide | Iodomethane | Anisole (95%) | Sodium iodide

As the synthesis is normally performed, a solution of the phenol and alkyl halide is simply heated in the presence of a suitable base such as potassium carbonate:

This is an example of an S_N2 reaction in a polar aprotic solvent.



Phenol | Allyl bromide | Allyl phenyl ether (86%)

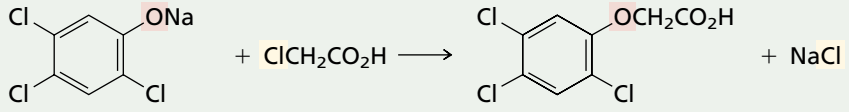
The alkyl halide must be one that reacts readily in an S_N2 process. Thus, methyl and primary alkyl halides are the most effective alkylating agents. Elimination becomes competitive with substitution when secondary alkyl halides are used and is the only reaction observed with tertiary alkyl halides.

PROBLEM 24.8 Reaction of phenol with 1,2-epoxypropane in aqueous sodium hydroxide at 150°C gives a single product, $C_9H_{12}O_2$, in 90% yield. Suggest a reasonable structure for this compound.

The reaction between an alkoxide ion and an aryl halide can be used to prepare alkyl aryl ethers only when the aryl halide is one that reacts rapidly by the addition–elimination mechanism of nucleophilic aromatic substitution (Section 23.6).

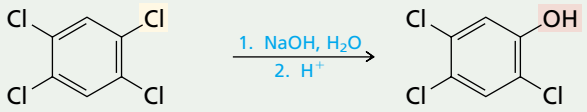
AGENT ORANGE AND DIOXIN

The once widely used herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) is prepared by reaction of the sodium salt of 2,4,5-trichlorophenol with chloroacetic acid:



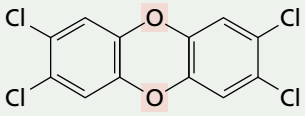
Sodium 2,4,5-trichlorophenolate | Chloroacetic acid | 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)

The starting material for this process, 2,4,5-trichlorophenol, is made by treating 1,2,4,5-tetrachlorobenzene with aqueous base. Nucleophilic aromatic substitution of one of the chlorines by an addition–elimination mechanism yields 2,4,5-trichlorophenol:



1,2,4,5-Tetrachlorobenzene | 2,4,5-Trichlorophenol

In the course of making 2,4,5-trichlorophenol, it almost always becomes contaminated with small amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, better known as *dioxin.*



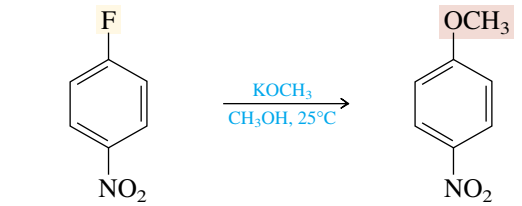
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin)

Dioxin is carried along when 2,4,5-trichlorophenol is converted to 2,4,5-T, and enters the environment when 2,4,5-T is sprayed on vegetation. Typically, the amount of dioxin present in 2,4,5-T is very small. *Agent Orange,* a 2,4,5-T–based defoliant used on a large scale in the Vietnam War, contained about 2 ppm of dioxin.

Tests with animals have revealed that dioxin is one of the most toxic substances known. Toward mice it is about 2000 times more toxic than strychnine and about 150,000 times more toxic than sodium cyanide. Fortunately, however, available evidence indicates that humans are far more resistant to dioxin than are test animals, and so far there have been no human fatalities directly attributable to dioxin. The most prominent short-term symptom seen so far has been a severe skin disorder known as *chloracne.* Yet to be determined is the answer to the question of long-term effects. A 1991 study of the health records of over 5000 workers who were exposed to dioxin-contaminated chemicals indicated a 15% increase in incidences of cancer compared with those of a control group. Workers who were exposed to higher dioxin levels for prolonged periods exhibited a 50% increase in their risk of dying from cancer, especially soft-tissue sarcomas, compared with the control group.*

Since 1979, the use of 2,4,5-T has been regulated in the United States.

* The biological properties of dioxin include an ability to bind to a protein known as the AH (aromatic hydrocarbon) receptor. Dioxin is not a hydrocarbon, but it shares a certain structural property with aromatic hydrocarbons. Try constructing molecular models of dioxin and anthracene to see these similarities.



p-Fluoronitrobenzene *p*-Nitroanisole (93%)

PROBLEM 24.9 Which of the following two combinations of reactants is more appropriate for the preparation of *p*-nitrophenyl phenyl ether?

(a) Fluorobenzene and *p*-nitrophenol

(b) *p*-Fluoronitrobenzene and phenol

24.12 CLEAVAGE OF ARYL ETHERS BY HYDROGEN HALIDES

The cleavage of *dialkyl ethers* by hydrogen halides was discussed in Section 16.8, where it was noted that the same pair of alkyl halides results, irrespective of the order in which the carbon–oxygen bonds of the ether are broken.

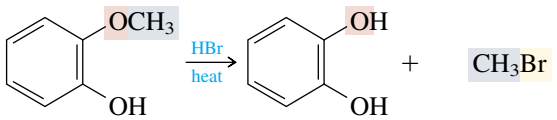
$$\underset{\text{Dialkyl ether}}{ROR'} + \underset{\text{Hydrogen halide}}{2HX} \longrightarrow \underset{\text{Two alkyl halides}}{RX + R'X} + \underset{\text{Water}}{H_2O}$$

Cleavage of *alkyl aryl ethers* by hydrogen halides always proceeds so that the alkyl–oxygen bond is broken and yields an alkyl halide and a phenol as the *final* products.

$$\underset{\text{Alkyl aryl ether}}{ArOR} + \underset{\text{Hydrogen halide}}{HX} \longrightarrow \underset{\text{Phenol}}{ArOH} + \underset{\text{Alkyl halide}}{RX}$$

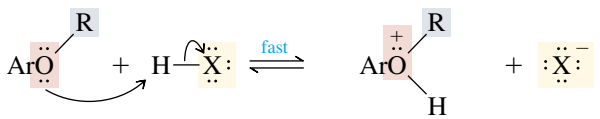
Since phenols are not converted to aryl halides by reaction with hydrogen halides, reaction proceeds no further than shown in the preceding general equation. For example,

Guaiacol is obtained by chemical treatment of *lignum vitae,* the wood from a species of tree that grows in warm climates. It is sometimes used as an expectorant to help relieve bronchial congestion.



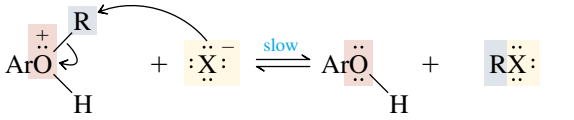
Guaiacol Pyrocatechol (85–87%) Methyl bromide (57–72%)

The first step in the reaction of an alkyl aryl ether with a hydrogen halide is protonation of oxygen to form an alkylaryloxonium ion:



Alkyl aryl ether Hydrogen halide Alkylaryloxonium ion Halide ion

This is followed by a nucleophilic substitution step:

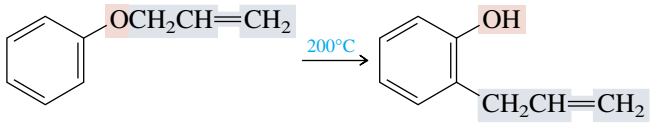


Alkylaryloxonium ion | Halide ion | Phenol | Alkyl halide

Attack by the halide nucleophile at the sp^3-hybridized carbon of the alkyl group is analogous to what takes place in the cleavage of dialkyl ethers. Attack at the sp^2-hybridized carbon of the aromatic ring is much slower. Indeed, nucleophilic aromatic substitution does not occur at all under these conditions.

24.13 CLAISEN REARRANGEMENT OF ALLYL ARYL ETHERS

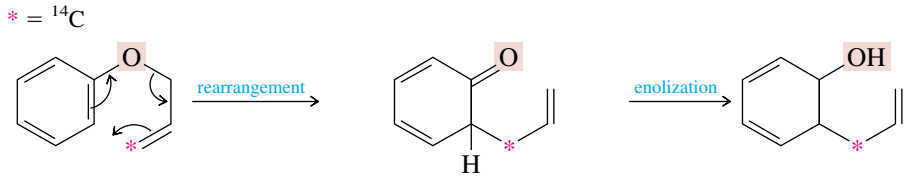
Allyl aryl ethers undergo an interesting reaction, called the **Claisen rearrangement,** on being heated. The allyl group migrates from oxygen to the ring carbon ortho to it.



Allyl phenyl ether | *o*-Allylphenol (73%)

Allyl phenyl ether is prepared by the reaction of phenol with allyl bromide, as described in Section 24.11

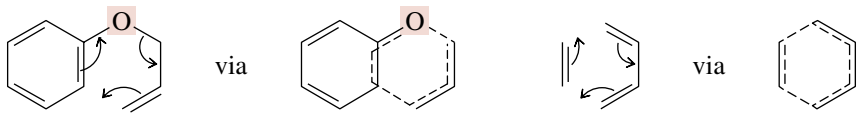
Carbon-14 labeling of the allyl group revealed that the terminal carbon of the allyl group is the one that becomes bonded to the ring and suggests a mechanism involving a concerted electron reorganization in the first step. This step is followed by enolization of the resulting cyclohexadienone to regenerate the aromatic ring.



Allyl phenyl ether | 6-Allyl-2,4-cyclohexadienone | *o*-Allylphenol

PROBLEM 24.10 The mechanism of the Claisen rearrangement of other allylic ethers of phenol is analogous to that of allyl phenyl ether. What is the product of the Claisen rearrangement of $C_6H_5OCH_2CH{=}CHCH_3$?

The transition state for the first step of the Claisen rearrangement bears much in common with the transition state for the Diels–Alder cycloaddition. Both involve a concerted six-electron reorganization.

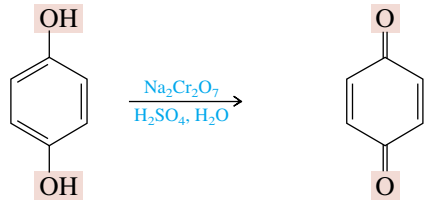


Claisen rearrangement | Diels–Alder cycloaddition

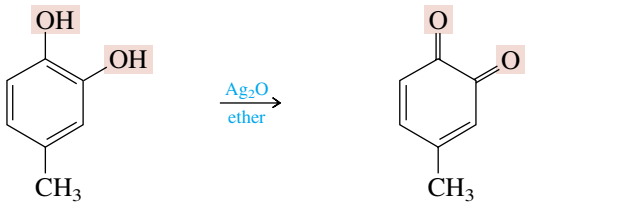
The Claisen rearrangement is an example of a **sigmatropic rearrangement.** A sigmatropic rearrangement is characterized by a transition state in which a σ bond migrates from one end of a conjugated π electron system to the other. In this case the σ bond to oxygen at one end of an allyl unit is broken and replaced by a σ bond to the ring carbon at the other end.

24.14 OXIDATION OF PHENOLS: QUINONES

Phenols are more easily oxidized than alcohols, and a large number of inorganic oxidizing agents have been used for this purpose. The phenol oxidations that are of the most use to the organic chemist are those involving derivatives of 1,2-benzenediol (pyrocatechol) and 1,4-benzenediol (hydroquinone). Oxidation of compounds of this type with silver oxide or with chromic acid yields conjugated dicarbonyl compounds called **quinones.**



Hydroquinone *p*-Benzoquinone (76–81%)

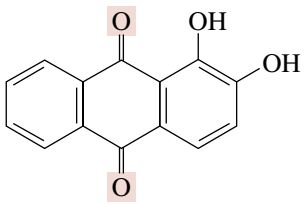


4-Methylpyrocatechol (4-methyl-1,2-benzenediol) 4-Methyl-1,2-benzoquinone (68%)

Silver oxide is a weak oxidizing agent.

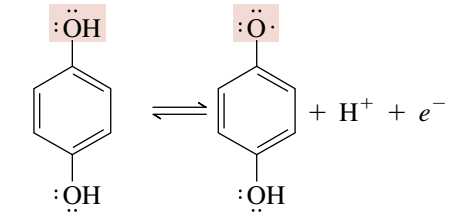
Quinones are colored; *p*-benzoquinone, for example, is yellow. Many occur naturally and have been used as dyes. *Alizarin* is a red pigment extracted from the roots of the madder plant. Its preparation from anthracene, a coal tar derivative, in 1868 was a significant step in the development of the synthetic dyestuff industry.

Quinones that are based on the anthracene ring system are called *anthraquinones.* Alizarin is one example of an *anthraquinone dye.*

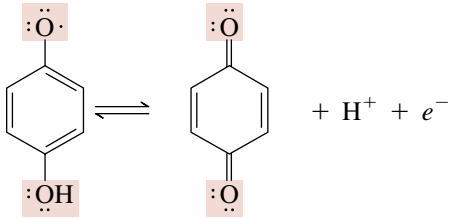


Alizarin

The oxidation–reduction process that connects hydroquinone and benzoquinone involves two 1-electron transfers:

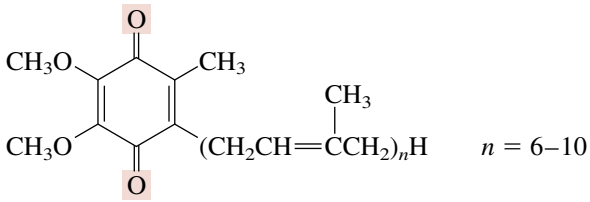


Hydroquinone



Benzoquinone

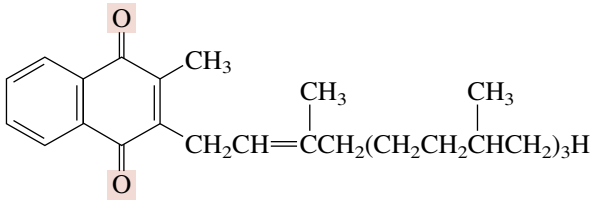
The ready reversibility of this reaction is essential to the role that quinones play in cellular respiration, the process by which an organism uses molecular oxygen to convert its food to carbon dioxide, water, and energy. Electrons are not transferred directly from the substrate molecule to oxygen but instead are transferred by way of an *electron transport chain* involving a succession of oxidation–reduction reactions. A key component of this electron transport chain is the substance known as *ubiquinone,* or coenzyme Q:



Ubiquinone (coenzyme Q)

The name *ubiquinone* is a shortened form of *ubiquitous quinone,* a term coined to describe the observation that this substance can be found in all cells. The length of its side chain varies among different organisms; the most common form in vertebrates has $n = 10$, and ubiquinones in which $n = 6$ to 9 are found in yeasts and plants.

Another physiologically important quinone is vitamin K. Here "K" stands for *koagulation* (Danish), since this substance was first identified as essential for the normal clotting of blood.



Vitamin K

Some vitamin K is provided in the normal diet, but a large proportion of that required by humans is produced by their intestinal flora.

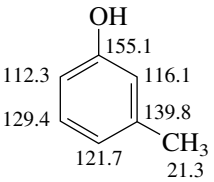
"Intestinal flora" is a general term for the bacteria, yeast, and fungi that live in the large intestine.

24.15 SPECTROSCOPIC ANALYSIS OF PHENOLS

Infrared: The infrared spectra of phenols combine features of those of alcohols and aromatic compounds. Hydroxyl absorbances resulting from O—H stretching are found in the 3600-cm^{-1} region, and the peak due to C—O stretching appears around 1200–1250 cm^{-1}. These features can be seen in the infrared spectrum of *p*-cresol, shown in Figure 24.3.

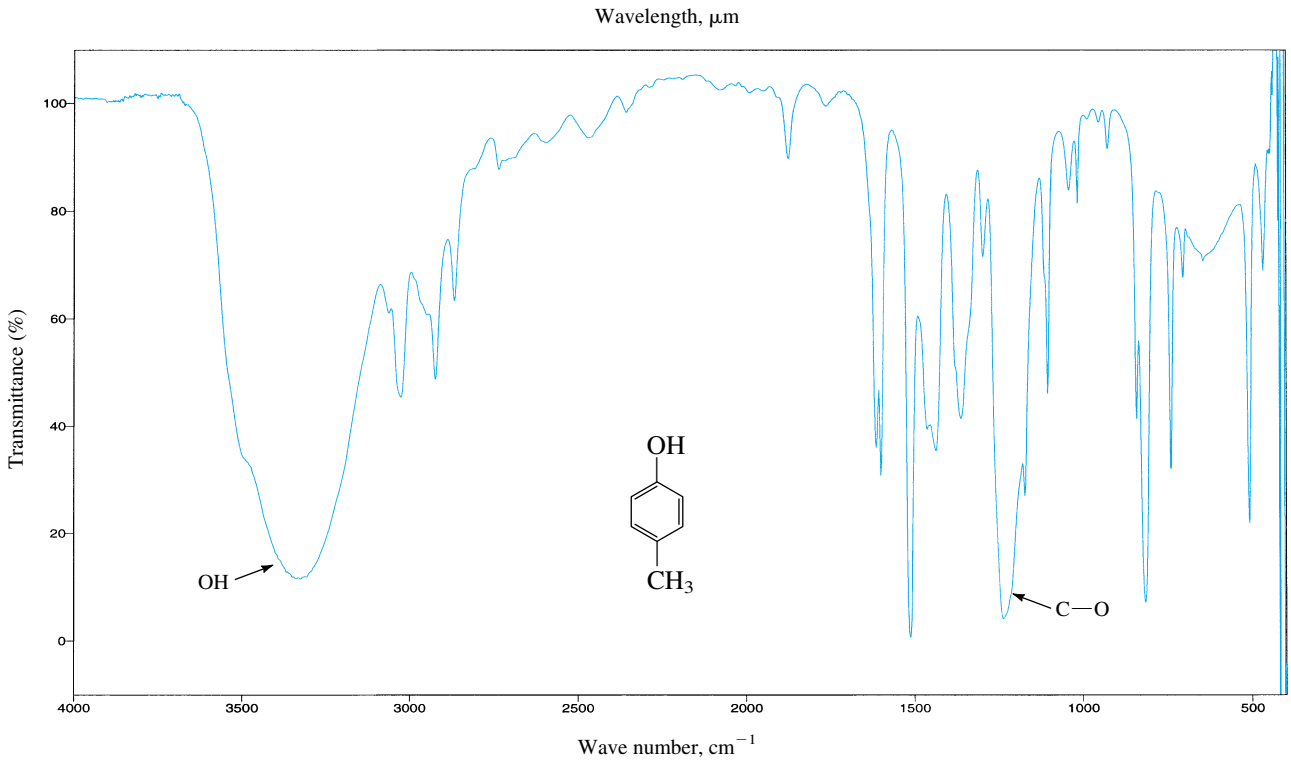
^{1}H NMR: The ^{1}H NMR signals for the hydroxyl protons of phenols are often broad, and their chemical shift, like their acidity, lies between alcohols and carboxylic acids. The range is δ 4–12 ppm, with the exact chemical shift depending on the concentration, the solvent, and the temperature. The phenolic proton in the ^{1}H NMR spectrum shown for *p*-cresol, for example, appears at δ 5.1 ppm (Figure 24.4).

^{13}C NMR: Compared with C—H, the carbon of C—O in a phenol is deshielded by about 25 ppm. In the case of *m*-cresol, for example, the C—O carbon gives the signal at lowest field.



^{13}C chemical shifts δ in *m*-cresol (ppm)

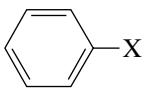
FIGURE 24.3 The infrared spectrum of *p*-cresol.



Notice, too, that the most shielded carbons of the aromatic ring are the ones that are ortho and para to the hydroxyl group in keeping with our experience that the OH group donates electrons preferentially to these positions.

The ^{13}C NMR spectrum of *m*-cresol appeared in Chapter 13 (Figure 13.21).

UV-VIS: Just as with arylamines (Section 22.20), it is informative to look at the UV-VIS behavior of phenols in terms of how the OH group affects the benzene chromophore.



	X	λ_{max}, ***nm***
Benzene	H	204, 256
Aniline	NH_2	230, 280
Anilinium ion	NH_3^+	203, 254
Phenol	OH	210, 270
Phenoxide ion	O^-	235, 287

An OH group affects the UV-VIS spectrum of benzene in a way similar to that of an NH_2 group, but to a smaller extent. In basic solution, in which OH is converted to O^-, however, the shift to longer wavelengths exceeds that of an NH_2 group.

Mass Spectrometry: A peak for the molecular ion is usually quite prominent in the mass spectra of phenols. It is, for example, the most intense peak in phenol.

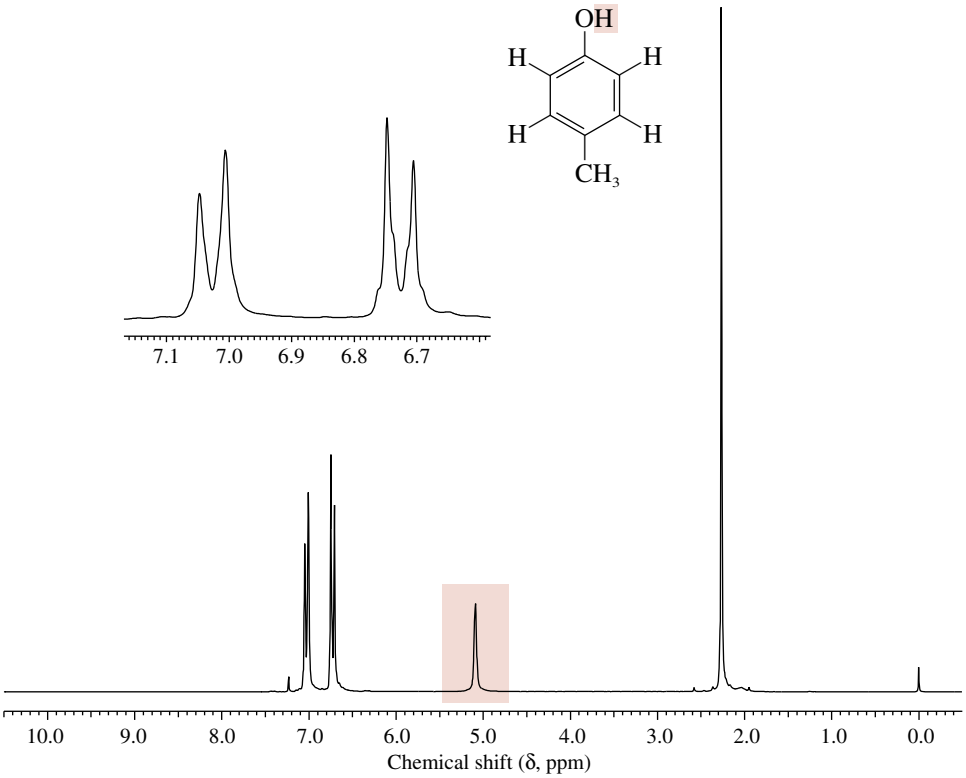


FIGURE 24.4 The 200-MHz ^1H NMR spectrum of *p*-cresol.

24.16 SUMMARY

Section 24.1 Phenol is both an important industrial chemical and the parent of a large class of compounds widely distributed as natural products. Although *benzenol* is the systematic name for C_6H_5OH, the IUPAC rules permit *phenol* to be used instead. Substituted derivatives are named on the basis of phenol as the parent compound.

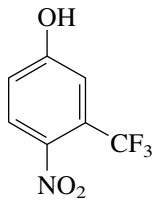
Section 24.2 Phenols are polar compounds, but less polar than alcohols. They resemble arylamines in having an electron-rich aromatic ring.

Section 24.3 The —OH group of phenols makes it possible for them to participate in hydrogen bonding. This contributes to the higher boiling points and greater water-solubility of phenolic compounds compared with arenes and aryl halides.

Section 24.4 With K_a's of approximately 10^{-10} ($pK_a = 10$), phenols are stronger acids than alcohols, but weaker than carboxylic acids. They are converted quantitatively to phenoxide anions on treatment with aqueous sodium hydroxide.

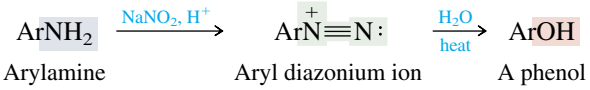
$$ArOH + NaOH \longrightarrow ArONa + H_2O$$

Section 24.5 Electron-releasing substituents attached to the ring have a negligible effect on the acidity of phenols. Strongly electron-withdrawing groups increase the acidity. The compound 4-nitro-3-(trifluoromethyl)phenol, for example, is 10,000 times more acidic than phenol.

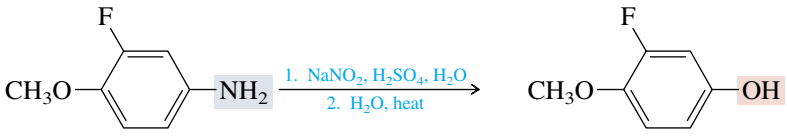


4-Nitro-3-(trifluoromethyl)phenol:
$pK_a = 6.0$

Section 24.6 Table 24.3 listed the main industrial methods for the preparation of phenol. Laboratory syntheses of phenols is usually carried out by hydrolysis of aryl diazonium salts.

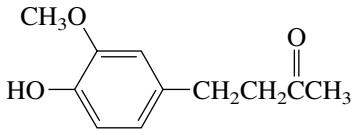


Arylamine — Aryl diazonium ion — A phenol



3-Fluoro-4-methoxyaniline — 3-Fluoro-4-methoxyphenol (70%)

Section 24.7 Many phenols occur naturally.

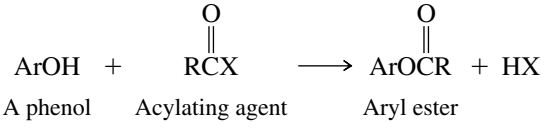


Zingerone
(responsible for spicy taste of ginger)

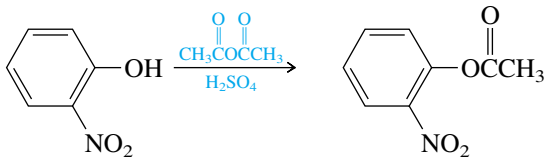
Phenol biosynthesis in plants proceeds from carbohydrate precursors, whereas the pathway in animals involves oxidation of aromatic rings.

Section 24.8 The hydroxyl group of a phenol is a strongly activating substituent, and electrophilic aromatic substitution occurs readily in phenol and its derivatives. Typical examples were presented in Table 24.4.

Section 24.9 On reaction with acyl chlorides and acid anhydrides, phenols may undergo either acylation of the hydroxyl group (O-acylation) or acylation of the ring (C-acylation). The product of C-acylation is more stable and predominates under conditions of thermodynamic control when aluminum chloride is present (see entry 6 in Table 24.4, Section 24.8). O-acylation is faster than C-acylation, and aryl esters are formed under conditions of kinetic control.

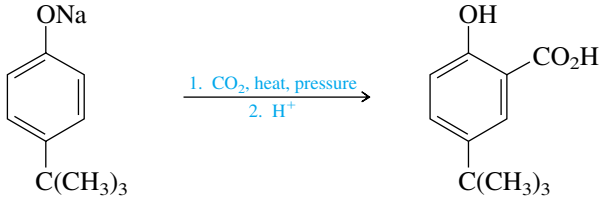


A phenol Acylating agent Aryl ester



o-Nitrophenol *o*-Nitrophenyl acetate (93%)

Section 24.10 The **Kolbe–Schmitt synthesis** of salicylic acid is a vital step in the preparation of aspirin. Phenols, as their sodium salts, undergo highly regioselective ortho carboxylation on treatment with carbon dioxide at elevated temperature and pressure.

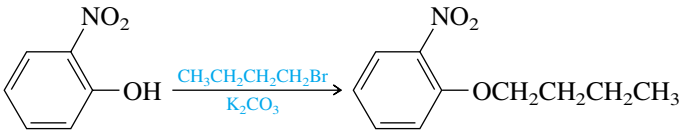


Sodium
p-*tert*-butylphenoxide

5-*tert*-Butyl-2-
hydroxybenzoic acid (74%)

Section 24.11 Phenoxide anions are nucleophilic toward alkyl halides, and the preparation of alkyl aryl ethers is easily achieved under S_N2 conditions.

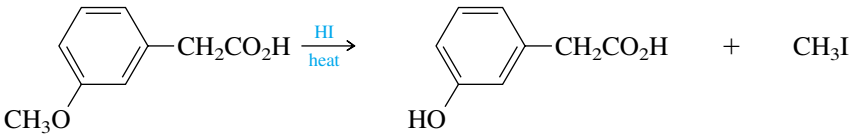
$$\underset{\text{Phenoxide anion}}{ArO^-} + \underset{\text{Alkyl halide}}{RX} \longrightarrow \underset{\text{Alkyl aryl ether}}{ArOR} + \underset{\text{Halide anion}}{X^-}$$



o-Nitrophenol — Butyl *o*-nitrophenyl ether (75/80%)

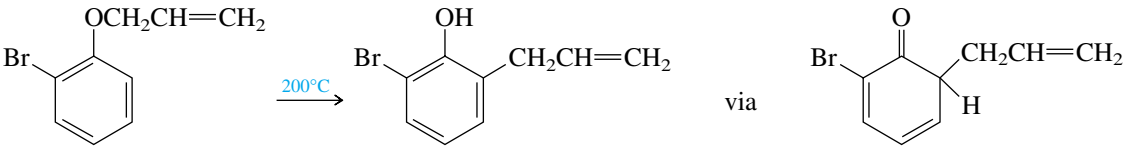
Section 24.12 The cleavage of alkyl aryl ethers by hydrogen halides yields a phenol and an alkyl halide.

$$\underset{\text{Alkyl aryl ether}}{ArOR} + \underset{\text{Hydrogen halide}}{HX} \xrightarrow{\text{heat}} \underset{\text{A phenol}}{ArOH} + \underset{\text{Alkyl halide}}{RX}$$



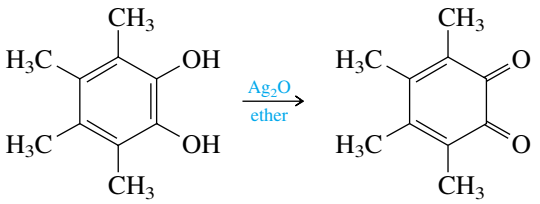
m-Methoxyphenylacetic acid — *m*-Hydroxyphenylacetic acid (72%) — Methyl iodide

Section 24.13 On being heated, allyl aryl ethers undergo a **Claisen rearrangement** to form *o*-allylphenols. A cyclohexadienone, formed by a concerted six-π-electron reorganization, is an intermediate.



Allyl *o*-bromophenyl ether — 2-Allyl-6-bromophenol (82%) — 6-Allyl-2-bromo-2,4-cyclohexadienone

Section 24.14 Oxidation of 1,2- and 1,4-benzenediols gives colored compounds known as **quinones.**



3,4,5,6-Tetramethyl-1,2-benzenediol — 3,4,5,6-Tetramethyl-1,2-benzoquinone (81%)

Section 24.15 The infrared and ^1H NMR spectra of phenols are similar to those for alcohols, except that the OH proton is somewhat less shielded in a phenol than in an alcohol. In ^{13}C NMR, an OH group deshields the carbon of

an aromatic ring to which it is attached. An OH group causes a shift in the UV-VIS spectrum of benzene to longer wavelengths. The effect is quite large in basic solution because of conversion of OH to O^-.

PROBLEMS

24.11 The IUPAC rules permit the use of common names for a number of familiar phenols and aryl ethers. These common names are listed here along with their systematic names. Write the structure of each compound.

(a) *Vanillin* (4-hydroxy-3-methoxybenzaldehyde): a component of vanilla bean oil, which contributes to its characteristic flavor

(b) *Thymol* (2-isopropyl-5-methylphenol): obtained from oil of thyme

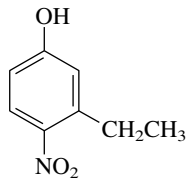
(c) *Carvacrol* (5-isopropyl-2-methylphenol): present in oil of thyme and marjoram

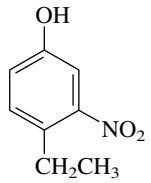
(d) *Eugenol* (4-allyl-2-methoxyphenol): obtained from oil of cloves

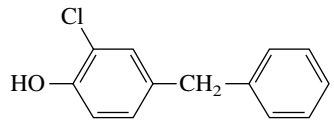
(e) *Gallic acid* (3,4,5-trihydroxybenzoic acid): prepared by hydrolysis of tannins derived from plants

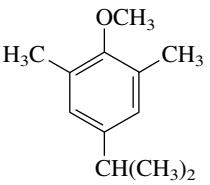
(f) *Salicyl alcohol* (o-hydroxybenzyl alcohol): obtained from bark of poplar and willow trees

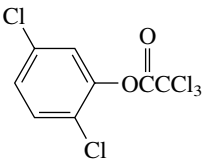
24.12 Name each of the following compounds:

(a) 

(b) 

(c) 

(d) 

(e) 

24.13 Write a balanced chemical equation for each of the following reactions:

(a) Phenol + sodium hydroxide

(b) Product of part (a) + ethyl bromide

(c) Product of part (a) + butyl *p*-toluenesulfonate

(d) Product of part (a) + acetic anhydride

(e) *o*-Cresol + benzoyl chloride

(f) *m*-Cresol + ethylene oxide

(g) 2,6-Dichlorophenol + bromine

(h) *p*-Cresol + excess aqueous bromine

(i) Isopropyl phenyl ether + excess hydrogen bromide + heat

24.14 Which phenol in each of the following pairs is more acidic? Justify your choice.

(a) 2,4,6-Trimethylphenol or 2,4,6-trinitrophenol

(b) 2,6-Dichlorophenol or 3,5-dichlorophenol

(c) 3-Nitrophenol or 4-nitrophenol

(d) Phenol or 4-cyanophenol

(e) 2,5-Dinitrophenol or 2,6-dinitrophenol

24.15 Choose the reaction in each of the following pairs that proceeds at the faster rate. Explain your reasoning.

(a) Basic hydrolysis of phenyl acetate or *m*-nitrophenyl acetate

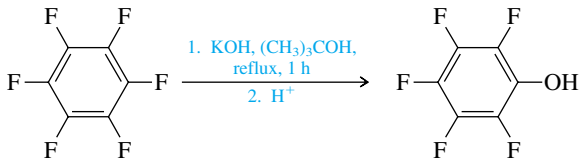
(b) Basic hydrolysis of *m*-nitrophenyl acetate or *p*-nitrophenyl acetate

(c) Reaction of ethyl bromide with phenol or with the sodium salt of phenol

(d) Reaction of ethylene oxide with the sodium salt of phenol or with the sodium salt of *p*-nitrophenol

(e) Bromination of phenol or phenyl acetate

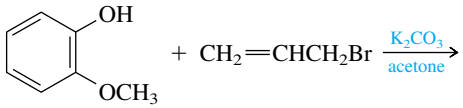
24.16 Pentafluorophenol is readily prepared by heating hexafluorobenzene with potassium hydroxide in *tert*-butyl alcohol:

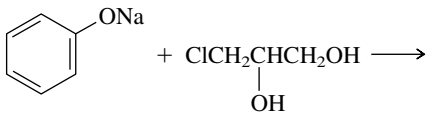


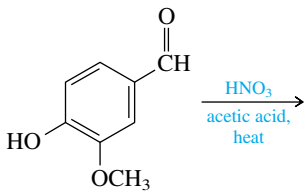
Hexafluorobenzene Pentafluorophenol (71%)

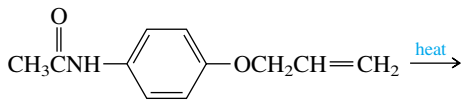
What is the most reasonable mechanism for this reaction? Comment on the comparative ease with which this conversion occurs.

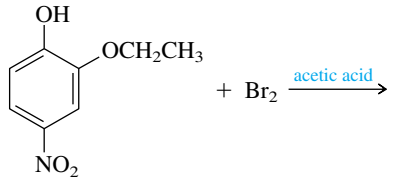
24.17 Each of the following reactions has been reported in the chemical literature and proceeds cleanly in good yield. Identify the principal organic product in each case.

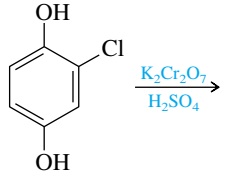
(a) 

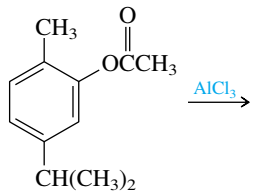
(b) 

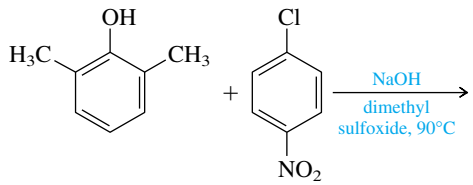
(c) 

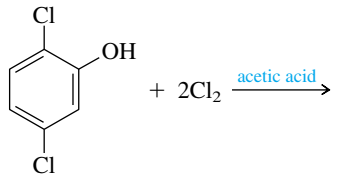
(d) 

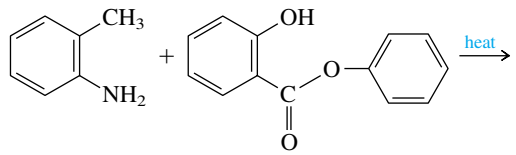
(e) 

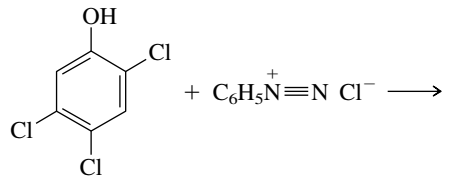
(f) 

(g) 

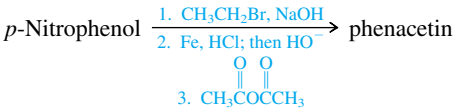
(h) 

(i) 

(j) 

(k) 

24.18 A synthesis of the analgesic substance *phenacetin* is outlined in the following equation. What is the structure of phenacetin?



24.19 Identify compounds A through C in the synthetic sequence represented by equations (a) through (c).

(a) Phenol + H_2SO_4 $\xrightarrow{\text{heat}}$ Compound A ($C_6H_6O_7S_2$)

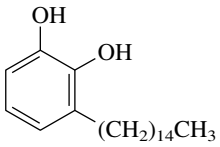
(b) Compound A + Br_2 $\xrightarrow[\text{2. } H^+]{\text{1. } HO^-}$ Compound B ($C_6H_5BrO_7S_2$)

(c) Compound B + H_2O $\xrightarrow[\text{heat}]{H^+}$ Compound C (C_6H_5BrO)

24.20 Treatment of 3,5-dimethylphenol with dilute nitric acid, followed by steam distillation of the reaction mixture, gave a compound A ($C_8H_9NO_3$, mp 66°C) in 36% yield. The nonvolatile residue from the steam distillation gave a compound B ($C_8H_9NO_3$, mp 108°C) in 25% yield on extraction with chloroform. Identify compounds A and B.

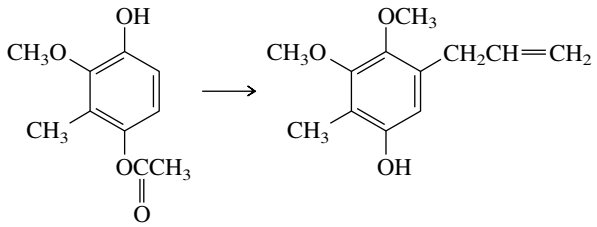
24.21 Outline a reasonable synthesis of 4-nitrophenyl phenyl ether from chlorobenzene and phenol.

24.22 As an allergen for testing purposes, synthetic 3-pentadecylcatechol is more useful than natural poison ivy extracts (of which it is one component). A stable crystalline solid, it is efficiently prepared in pure form from readily available starting materials. Outline a reasonable synthesis of this compound from 2,3-dimethoxybenzaldehyde and any necessary organic or inorganic reagents.

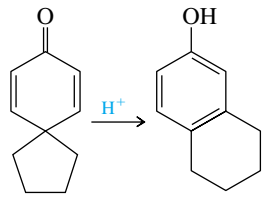


3-Pentadecylcatechol

24.23 Describe a scheme for carrying out the following synthesis. (In the synthesis reported in the literature, four separate operations were required.)



24.24 In a general reaction known as the *cyclohexadienone-phenol rearrangement,* cyclohexadienones are converted to phenols under conditions of acid catalysis. An example is



(100%)

Write a reasonable mechanism for this reaction.

24.25 Treatment of *p*-hydroxybenzoic acid with aqueous bromine leads to the evolution of carbon dioxide and the formation of 2,4,6-tribromophenol. Explain.

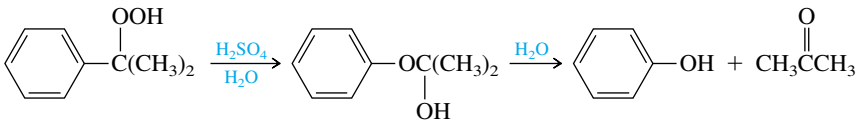
24.26 Treatment of phenol with excess aqueous bromine is actually more complicated than expected. A white precipitate forms rapidly, which on closer examination is not 2,4,6-tribromophenol but is instead 2,4,4,6-tetrabromocyclohexadienone. Explain the formation of this product.

24.27 Treatment of 2,4,6-tri-*tert*-butylphenol with bromine in cold acetic acid gives the compound $C_{18}H_{29}BrO$ in quantitative yield. The infrared spectrum of this compound contains absorptions at 1630 and 1655 cm^{-1}. Its ^1H NMR spectrum shows only three peaks (all singlets), at δ 1.2, 1.3, and 6.9 ppm, in the ratio 9:18:2. What is a reasonable structure for the compound?

24.28 Compound A undergoes hydrolysis of its acetal function in dilute sulfuric acid to yield 1,2-ethanediol and compound B ($C_6H_6O_2$), mp 54°C. Compound B exhibits a carbonyl stretching band in the infrared at 1690 cm^{-1} and has two singlets in its ^1H NMR spectrum, at δ 2.9 and 6.7 ppm, in the ratio 2:1. On standing in water or ethanol, compound B is converted cleanly to an isomeric substance, compound C, mp 172–173°C. Compound C has no peaks attributable to carbonyl groups in its infrared spectrum. Identify compounds B and C.

Compound A

24.29 One of the industrial processes for the preparation of phenol, discussed in Section 24.6, includes an acid-catalyzed rearrangement of cumene hydroperoxide as a key step. This reaction proceeds by way of an intermediate hemiacetal:



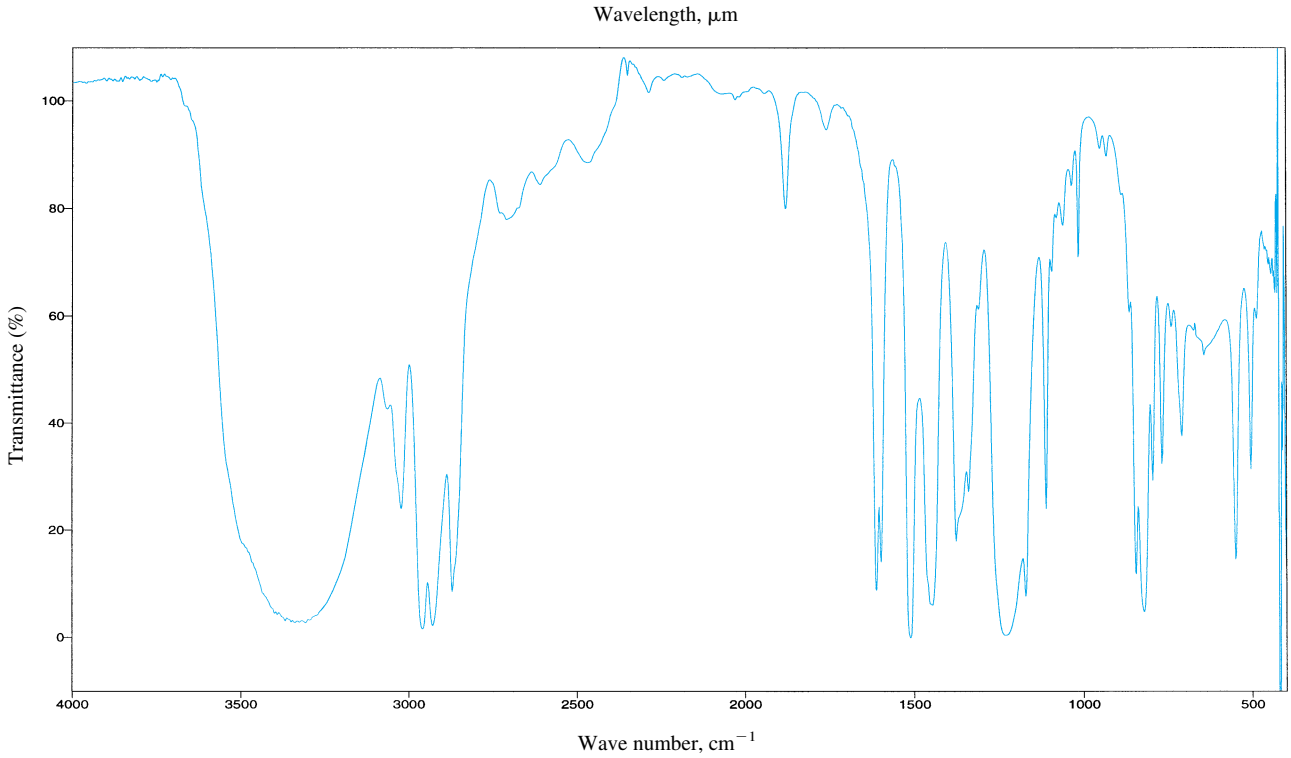
Cumene hydroperoxide Hemiacetal Phenol Acetone

You learned in Section 17.8 of the relationship among hemiacetals, ketones, and alcohols; the formation of phenol and acetone is simply an example of hemiacetal hydrolysis. The formation of the hemiacetal intermediate is a key step in the synthetic procedure; it is the step in which the aryl–oxygen bond is generated. Can you suggest a reasonable mechanism for this step?

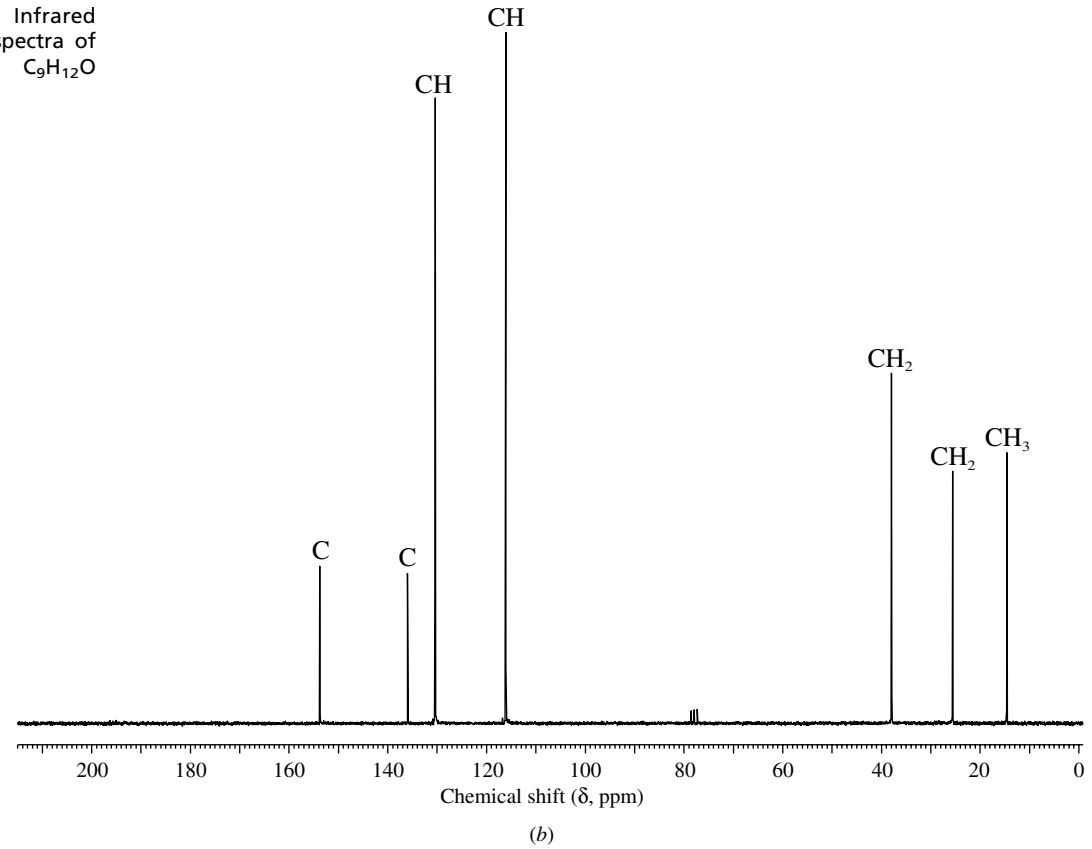
24.30 Identify the following compounds on the basis of the information provided:

(a) $C_9H_{12}O$: Its infrared and ^1H NMR spectra are shown in Figure 24.5.

(b) $C_9H_{11}BrO$: Its infrared and ^1H NMR spectra are shown in Figure 24.6.

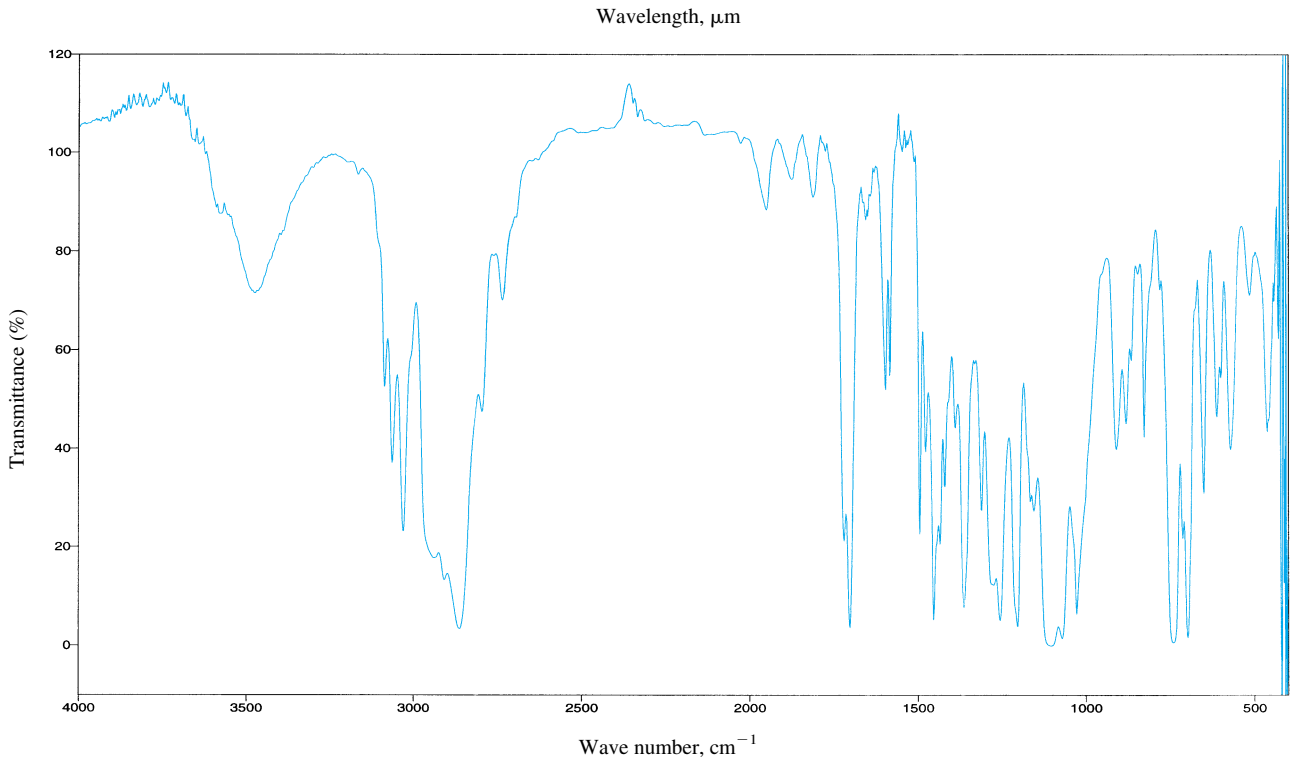


(*a*)

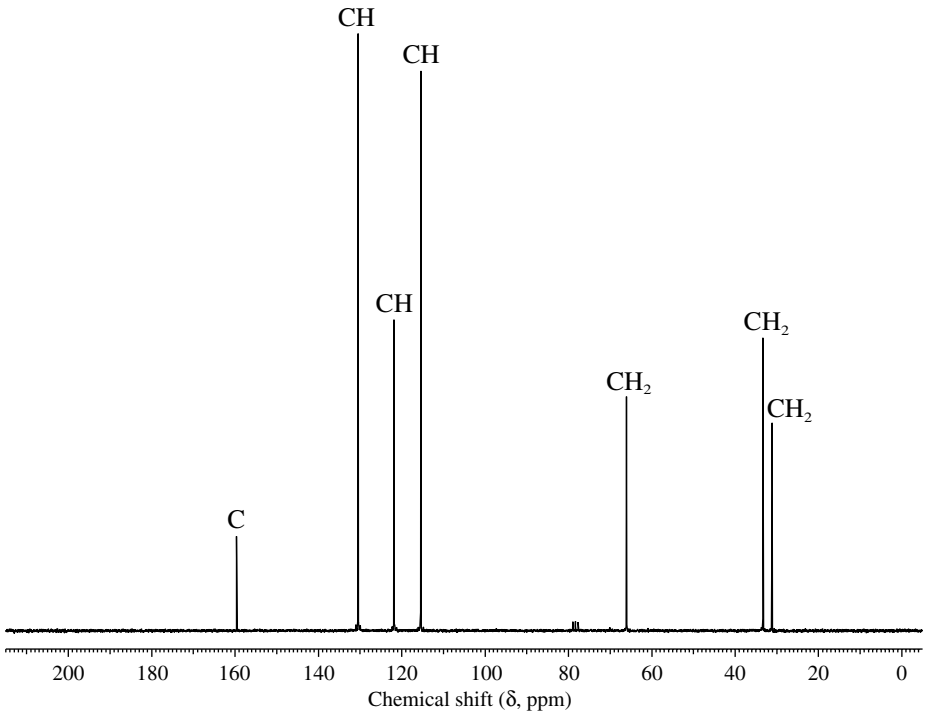


(*b*)

FIGURE 24.5 (*a*) Infrared and (*b*) ^{13}C NMR spectra of the compound $C_9H_{12}O$ (Problem 24.30a).

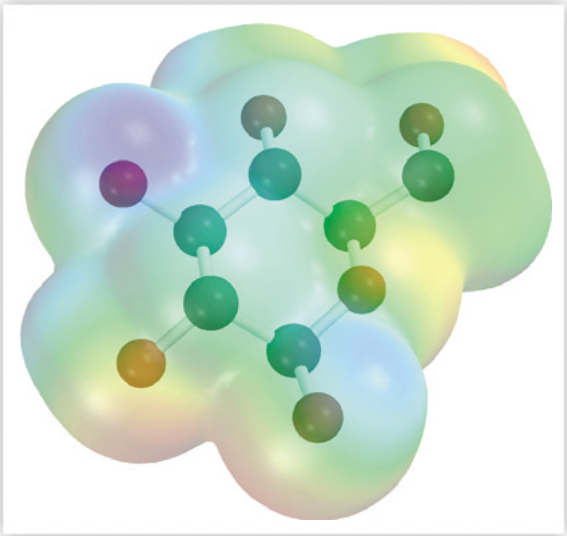


(*a*)



(*b*)

FIGURE 24.6 (*a*) Infrared and (*b*) ^{13}C NMR spectra of the compound $C_9H_{11}BrO$ (Problem 24.30b).



CHAPTER 25

CARBOHYDRATES

The major classes of organic compounds common to living systems are *lipids, proteins, nucleic acids,* and *carbohydrates.* Carbohydrates are very familiar to us—we call many of them "sugars." They make up a substantial portion of the food we eat and provide most of the energy that keeps the human engine running. Carbohydrates are structural components of the walls of plant cells and the wood of trees. Genetic information is stored and transferred by way of nucleic acids, specialized derivatives of carbohydrates, which we'll examine in more detail in Chapter 27.

Historically, carbohydrates were once considered to be "hydrates of carbon" because their molecular formulas in many (but not all) cases correspond to $C_n(H_2O)_m$. It is more realistic to define a carbohydrate as a *polyhydroxy aldehyde* or *polyhydroxy ketone,* a point of view closer to structural reality and more suggestive of chemical reactivity.

This chapter is divided into two parts. The first, and major, portion is devoted to carbohydrate structure. You will see how the principles of stereochemistry and conformational analysis combine to aid our understanding of this complex subject. The remainder of the chapter describes chemical reactions of carbohydrates. Most of these reactions are simply extensions of what you have already learned concerning alcohols, aldehydes, ketones, and acetals.

25.1 CLASSIFICATION OF CARBOHYDRATES

The Latin word for "sugar"* is *saccharum,* and the derived term "saccharide" is the basis of a system of carbohydrate classification. A **monosaccharide** is a simple carbohydrate, one that on attempted hydrolysis is not cleaved to smaller carbohydrates. *Glucose*

*"Sugar" is a combination of the Sanskrit words *su* (sweet) and *gar* (sand). Thus, its literal meaning is "sweet sand."

($C_6H_{12}O_6$), for example, is a monosaccharide. A **disaccharide** on hydrolysis is cleaved to two monosaccharides, which may be the same or different. *Sucrose*—common table sugar—is a disaccharide that yields one molecule of glucose and one of fructose on hydrolysis.

$$\text{Sucrose } (C_{12}H_{22}O_{11}) + H_2O \longrightarrow \text{glucose } (C_6H_{12}O_6) + \text{fructose } (C_6H_{12}O_6)$$

An **oligosaccharide** (*oligos* is a Greek word that in its plural form means "few") yields 3–10 monosaccharide units on hydrolysis. **Polysaccharides** are hydrolyzed to more than 10 monosaccharide units. *Cellulose* is a polysaccharide molecule that gives thousands of glucose molecules when completely hydrolyzed.

Over 200 different monosaccharides are known. They can be grouped according to the number of carbon atoms they contain and whether they are polyhydroxy aldehydes or polyhydroxy ketones. Monosaccharides that are polyhydroxy aldehydes are called **aldoses;** those that are polyhydroxy ketones are **ketoses.** Aldoses and ketoses are further classified according to the number of carbon atoms in the main chain. Table 25.1 lists the terms applied to monosaccharides having four to eight carbon atoms.

25.2 FISCHER PROJECTIONS AND D–L NOTATION

Stereochemistry is the key to understanding carbohydrate structure, a fact that was clearly appreciated by the German chemist Emil Fischer. The projection formulas used by Fischer to represent stereochemistry in chiral molecules are particularly well-suited to studying carbohydrates. Figure 25.1 illustrates their application to the enantiomers of *glyceraldehyde* (2,3-dihydroxypropanal), a fundamental molecule in carbohydrate stereochemistry. When the Fischer projection is oriented as shown in the figure, with the carbon chain vertical and the aldehyde carbon at the top, the C-2 hydroxyl group points to the right in (+)-glyceraldehyde and to the left in (−)-glyceraldehyde.

Fischer determined the structure of glucose in 1900 and won the Nobel Prize in chemistry in 1902.

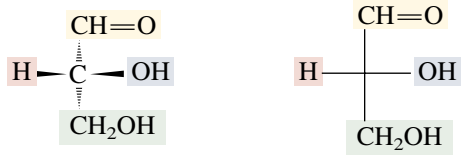
Techniques for determining the absolute configuration of chiral molecules were not developed until the 1950s, and so it was not possible for Fischer and his contemporaries to relate the sign of rotation of any substance to its absolute configuration. A system evolved based on the arbitrary assumption, later shown to be correct, that the enantiomers of glyceraldehyde have the signs of rotation and absolute configurations shown in Figure 25.1. Two stereochemical descriptors were defined: D and L. The absolute configuration of (+)-glyceraldehyde, as depicted in the figure, was said to be D and that of its enantiomer, (−)-glyceraldehyde, L. Compounds that had a spatial arrangement of substituents analogous to D-(+)- and L-(−)-glyceraldehyde were said to have the D and L configurations, respectively.

Adopting the enantiomers of glyceraldehyde as stereochemical reference compounds originated with proposals made in 1906 by M. A. Rosanoff, a chemist at New York University.

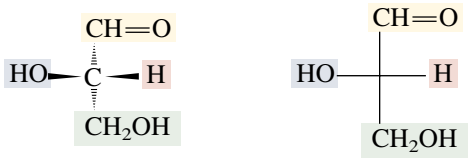
TABLE 25.1 Some Classes of Monosaccharides

Number of carbon atoms	Aldose	Ketose
Four	Aldotetrose	Ketotetrose
Five	Aldopentose	Ketopentose
Six	Aldohexose	Ketohexose
Seven	Aldoheptose	Ketoheptose
Eight	Aldooctose	Ketooctose

FIGURE 25.1 Three-dimensional representations and Fischer projections of the enantiomers of glyceraldehyde.

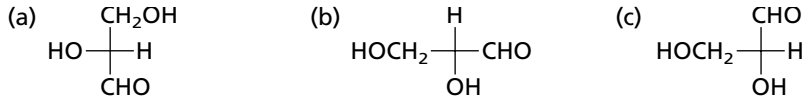


R-(+)-Glyceraldehyde

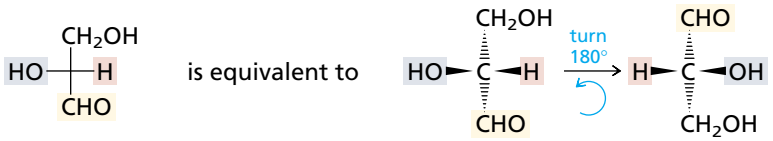


S-(–)-Glyceraldehyde

PROBLEM 25.1 Identify each of the following as either D- or L-glyceraldehyde:



SAMPLE SOLUTION (a) Redraw the Fischer projection so as to more clearly show the true spatial orientation of the groups. Next, reorient the molecule so that its relationship to the glyceraldehyde enantiomers in Figure 25.1 is apparent.



The structure is the same as that of (+)-glyceraldehyde in the figure. It is D-glyceraldehyde.

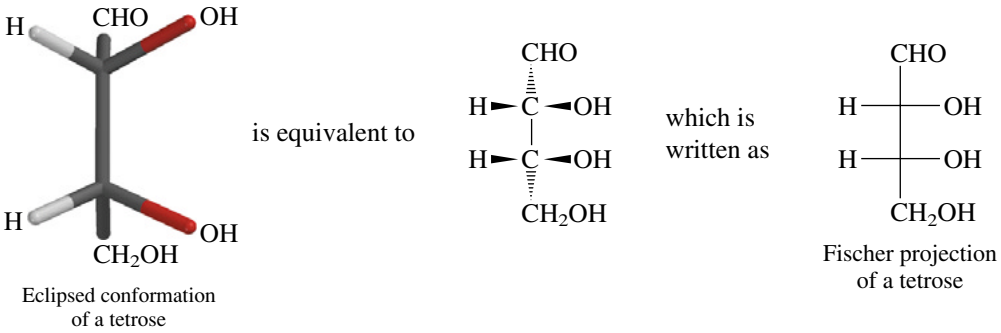
Fischer projections and D–L notation have proved to be so helpful in representing carbohydrate stereochemistry that the chemical and biochemical literature is replete with their use. To read that literature you need to be acquainted with these devices, as well as the more modern Cahn–Ingold–Prelog system.

25.3 THE ALDOTETROSES

Glyceraldehyde can be considered to be the simplest chiral carbohydrate. It is an **aldotriose** and, since it contains one stereogenic center, exists in two stereoisomeric forms: the D and L enantiomers. Moving up the scale in complexity, next come the **aldotetroses.** Examination of their structures illustrates the application of the Fischer system to compounds that contain more than one stereogenic center.

Molecular models of the four stereoisomeric aldotetroses may be viewed on the CD that accompanies this text.

The aldotetroses are the four stereoisomers of 2,3,4-trihydroxybutanal. Fischer projections are constructed by orienting the molecule in an eclipsed conformation with the aldehyde group at what will be the top. The four carbon atoms define the main chain of the Fischer projection and are arranged vertically. Horizontal bonds are directed outward, vertical bonds back.

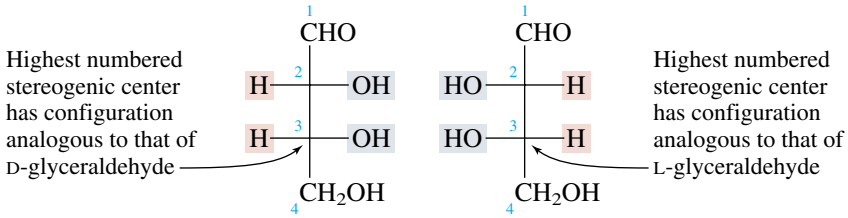


Eclipsed conformation of a tetrose

Fischer projection of a tetrose

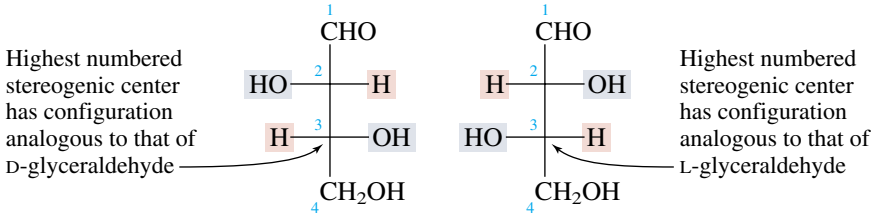
The particular aldotetrose just shown is called D-*erythrose*. The prefix D tells us that the configuration at the *highest numbered stereogenic center* is analogous to that of D-(+)-glyceraldehyde. Its mirror image is L-erythrose.

For a first-person account of the development of systematic carbohydrate nomenclature see C. D. Hurd's article in the December 1989 issue of the *Journal of Chemical Education*, pp. 984–988.



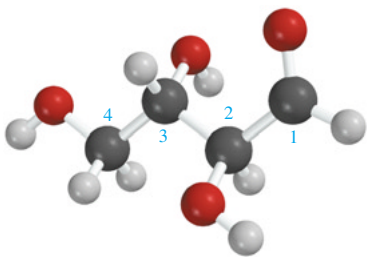
D-Erythrose L-Erythrose

Relative to each other, both hydroxyl groups are on the same side in Fischer projections of the erythrose enantiomers. The remaining two stereoisomers have hydroxyl groups on opposite sides in their Fischer projection. They are diastereomers of D- and L-erythrose and are called D- and L-*threose*. The D and L prefixes again specify the configuration of the highest numbered stereogenic center. D-Threose and L-threose are enantiomers of each other:



D-Threose L-Threose

PROBLEM 25.2 Which aldotetrose is the structure shown? Is it D-erythrose, D-threose, L-erythrose, or L-threose? (Be careful! The conformation given is not the same as that used to generate a Fischer projection.)



As shown for the aldotetroses, an aldose belongs to the D or the L series according to the configuration of the stereogenic center farthest removed from the aldehyde function. Individual names, such as erythrose and threose, specify the particular arrangement of stereogenic centers within the molecule relative to each other. Optical activities cannot be determined directly from the D and L prefixes. As it turns out, both D-erythrose and D-threose are levorotatory, but D-glyceraldehyde is dextrorotatory.

25.4 ALDOPENTOSES AND ALDOHEXOSES

Aldopentoses have three stereogenic centers. The eight stereoisomers are divided into a set of four D-aldopentoses and an enantiomeric set of four L-aldopentoses. The aldopentoses are named *ribose, arabinose, xylose,* and *lyxose.* Fischer projections of the D stereoisomers of the aldopentoses are given in Figure 25.2. Notice that all these diastereomers have the same configuration at C-4 and that this configuration is analogous to that of D-(+)-glyceraldehyde.

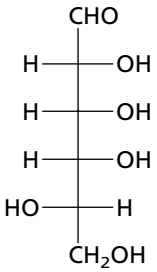
PROBLEM 25.3 L-(+)-Arabinose is a naturally occurring L sugar. It is obtained by acid hydrolysis of the polysaccharide present in mesquite gum. Write a Fischer projection for L-(+)-arabinose.

Among the aldopentoses, D-ribose is a component of many biologically important substances, most notably the ribonucleic acids, and D-xylose is very abundant and is isolated by hydrolysis of the polysaccharides present in corncobs and the wood of trees.

Cellulose is more abundant than glucose, but each cellulose molecule is a polysaccharide composed of thousands of glucose units (Section 25.15). Methane may also be more abundant, but most of the methane comes from glucose.

The aldohexoses include some of the most familiar of the monosaccharides, as well as one of the most abundant organic compounds on earth, D-(+)-glucose. With four stereogenic centers, 16 stereoisomeric aldohexoses are possible; 8 belong to the D series and 8 to the L series. All are known, either as naturally occurring substances or as the products of synthesis. The eight D-aldohexoses are given in Figure 25.2; it is the spatial arrangement at C-5, hydrogen to the left in a Fischer projection and hydroxyl to the right, that identifies them as carbohydrates of the D series.

PROBLEM 25.4 Name the following sugar:



Of all the monosaccharides, D-(+)-*glucose* is the best known, most important, and most abundant. Its formation from carbon dioxide, water, and sunlight is the central theme of photosynthesis. Carbohydrate formation by photosynthesis is estimated to be on the order of 10^{11} tons per year, a source of stored energy utilized, directly or indirectly, by all higher forms of life on the planet. Glucose was isolated from raisins in 1747 and by hydrolysis of starch in 1811. Its structure was determined, in work culminating in 1900, by Emil Fischer.

D-(+)-*Galactose* is a constituent of numerous polysaccharides. It is best obtained by acid hydrolysis of lactose (milk sugar), a disaccharide of D-glucose and D-galactose.

FIGURE 25.2 Configurations of the D series of aldoses containing three through six carbon atoms.

L(−)-Galactose also occurs naturally and can be prepared by hydrolysis of flaxseed gum and agar. The principal source of D-(+)-*mannose* is hydrolysis of the polysaccharide of the ivory nut, a large, nut-like seed obtained from a South American palm.

25.5 A MNEMONIC FOR CARBOHYDRATE CONFIGURATIONS

See, for example, the November 1955 issue of the *Journal of Chemical Education* (p. 584). An article giving references to a variety of chemistry mnemonics appears in the July 1960 issue of the *Journal of Chemical Education* (p. 366).

The task of relating carbohydrate configurations to names requires either a world-class memory or an easily recalled mnemonic. A mnemonic that serves us well here was popularized by the husband–wife team of Louis F. Fieser and Mary Fieser of Harvard University in their 1956 textbook, *Organic Chemistry.* As with many mnemonics, it's not clear who actually invented it, and references to this particular one appeared in the chemical education literature before publication of the Fiesers' text. The mnemonic has two features: (1) a system for setting down all the stereoisomeric D-aldohexoses in a logical order; and (2) a way to assign the correct name to each one.

A systematic way to set down all the D-hexoses (as in Fig. 25.2) is to draw skeletons of the necessary eight Fischer projections, placing the hydroxyl group at C-5 to the right in each so as to guarantee that they all belong to the D series. Working up the carbon chain, place the hydroxyl group at C-4 to the right in the first four structures, and to the left in the next four. In each of these two sets of four, place the C-3 hydroxyl group to the right in the first two and to the left in the next two; in each of the resulting four sets of two, place the C-2 hydroxyl group to the right in the first one and to the left in the second.

Once the eight Fischer projections have been written, they are named in order with the aid of the sentence: All altruists gladly make gum in gallon tanks. The words of the sentence stand for *allose, altrose, glucose, mannose, gulose, idose, galactose, talose.*

An analogous pattern of configurations can be seen in the aldopentoses when they are arranged in the order *ribose, arabinose, xylose, lyxose.* (RAXL is an easily remembered nonsense word that gives the correct sequence.) This pattern is discernible even in the aldotetroses erythrose and threose.

25.6 CYCLIC FORMS OF CARBOHYDRATES: FURANOSE FORMS

Aldoses incorporate two functional groups, C═O and OH, which are capable of reacting with each other. We saw in Section 17.8 that nucleophilic addition of an alcohol function to a carbonyl group gives a hemiacetal. When the hydroxyl and carbonyl groups are part of the same molecule, a *cyclic hemiacetal* results, as illustrated in Figure 25.3.

Cyclic hemiacetal formation is most common when the ring that results is five- or six-membered. Five-membered cyclic hemiacetals of carbohydrates are called **furanose** forms; six-membered ones are called **pyranose** forms. The ring carbon that is derived from the carbonyl group, the one that bears two oxygen substituents, is called the **anomeric** carbon.

Aldoses exist almost exclusively as their cyclic hemiacetals; very little of the open-chain form is present at equilibrium. To understand their structures and chemical reactions, we need to be able to translate Fischer projections of carbohydrates into their cyclic hemiacetal forms. Consider first cyclic hemiacetal formation in D-erythrose. So as to visualize furanose ring formation more clearly, redraw the Fischer projection in a form more suited to cyclization, being careful to maintain the stereochemistry at each stereogenic center.

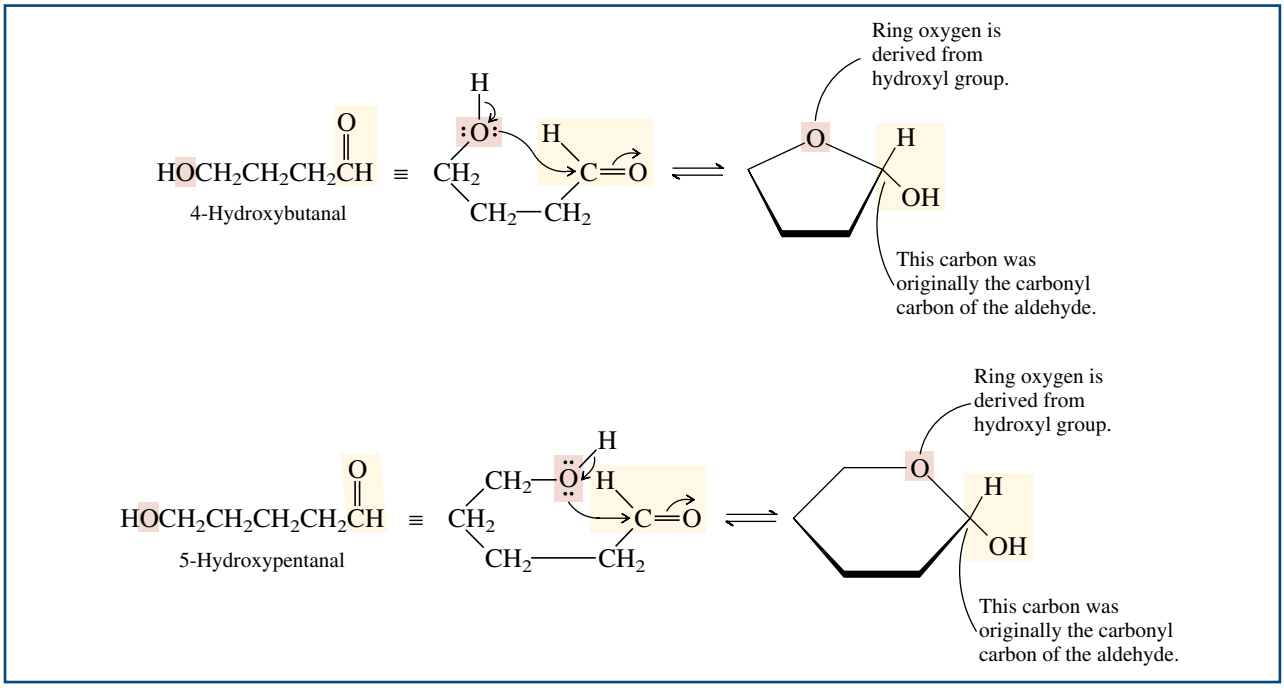
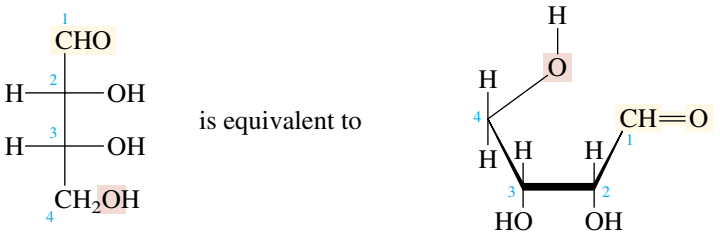


FIGURE 25.3 Cyclic hemiacetal formation in 4-hydroxybutanal and 5-hydroxypentanal.

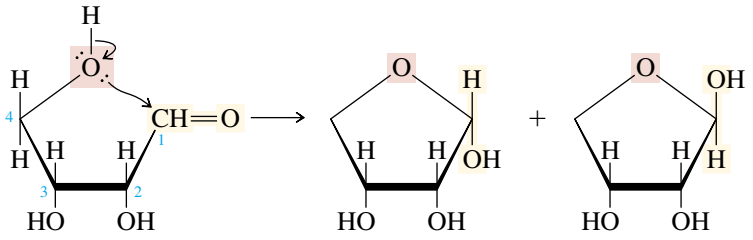
A molecular model can help you to visualize this relationship.



D-Erythrose

Reoriented eclipsed conformation of D-erythrose showing C-4 hydroxyl group in position to add to carbonyl group

Hemiacetal formation between the carbonyl group and the terminal hydroxyl yields the five-membered furanose ring form. The anomeric carbon becomes a new stereogenic center; its hydroxyl group can be either cis or trans to the other hydroxyl groups of the molecule.



D-Erythrose

α-D-Erythrofuranose (hydroxyl group at anomeric carbon is down)

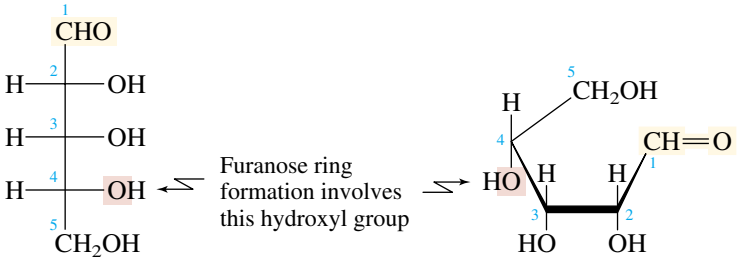
β-D-Erythrofuranose (hydroxyl group at anomeric carbon is up)

Structural drawings of carbohydrates of this type are called **Haworth formulas,** after the British carbohydrate chemist Sir Walter Norman Haworth (St. Andrew's University and the University of Birmingham). Early in his career Haworth contributed to the discovery that sugars exist as cyclic hemiacetals rather than in open-chain forms. Later he collaborated on an efficient synthesis of vitamin C from carbohydrate precursors. This was the first chemical synthesis of a vitamin and provided an inexpensive route to its preparation on a commercial scale. Haworth was a corecipient of the Nobel Prize for chemistry in 1937.

The two stereoisomeric furanose forms of D-erythrose are named α-D-erythrofuranose and β-D-erythrofuranose. The prefixes α and β describe *relative configuration.* The configuration of the anomeric carbon is α when its hydroxyl group is on the same side of a Fischer projection as the hydroxyl group at the highest numbered stereogenic center. When the hydroxyl groups at the anomeric carbon and the highest numbered stereogenic center are on opposite sides of a Fischer projection, the configuration at the anomeric carbon is β.

Substituents that are to the right in a Fischer projection are "down" in the corresponding Haworth formula.

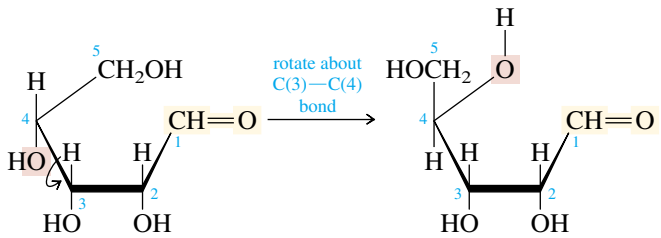
Generating Haworth formulas to show stereochemistry in furanose forms of higher aldoses is slightly more complicated and requires an additional operation. Furanose forms of D-ribose are frequently encountered building blocks in biologically important organic molecules. They result from hemiacetal formation between the aldehyde group and the hydroxyl at C-4:



D-Ribose — Eclipsed conformation of D-ribose

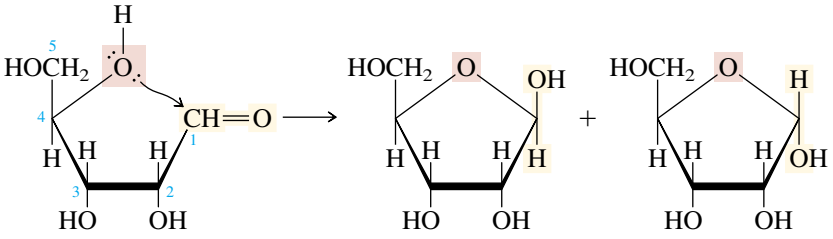
Notice that the eclipsed conformation of D-ribose derived directly from the Fischer projection does not have its C-4 hydroxyl group properly oriented for furanose ring formation. We must redraw it in a conformation that permits the five-membered cyclic hemiacetal to form. This is accomplished by rotation about the C(3)—C(4) bond, taking care that the configuration at C-4 is not changed.

Try using a molecular model to help see this.



Conformation of D-ribose suitable for furanose ring formation

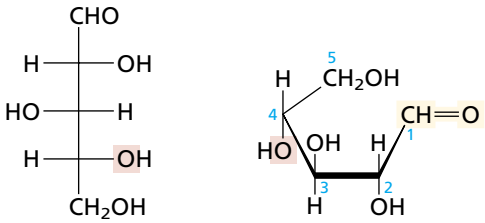
As viewed in the drawing, a 120° anticlockwise rotation of C-4 places its hydroxyl group in the proper position. At the same time, this rotation moves the CH_2OH group to a position such that it will become a substituent that is "up" on the five-membered ring. The hydrogen at C-4 then will be "down" in the furanose form.



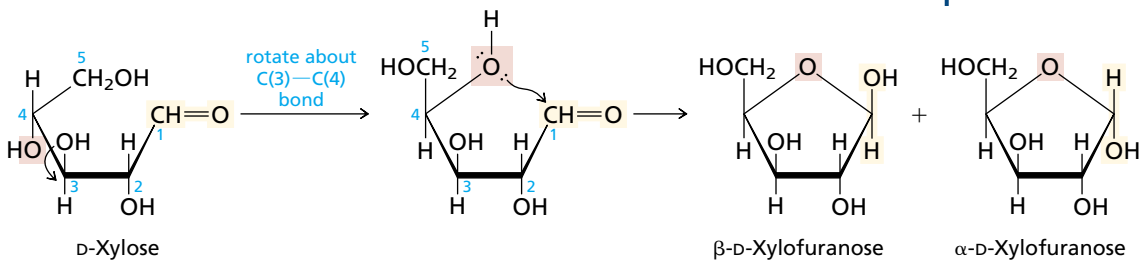
PROBLEM 25.5 Write Haworth formulas corresponding to the furanose forms of each of the following carbohydrates:

(a) D-Xylose
(b) D-Arabinose
(c) L-Arabinose
(d) D-Threose

SAMPLE SOLUTION (a) The Fischer projection of D-xylose is given in Figure 25.2.

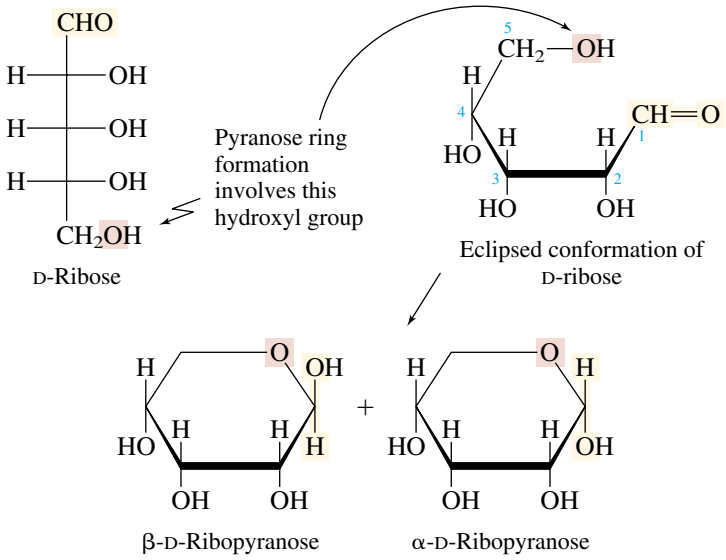


Carbon-4 of D-xylose must be rotated in an anticlockwise sense in order to bring its hydroxyl group into the proper orientation for furanose ring formation.



25.7 CYCLIC FORMS OF CARBOHYDRATES: PYRANOSE FORMS

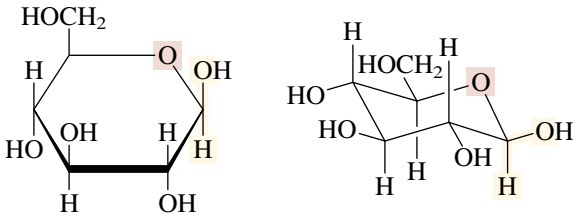
During the discussion of hemiacetal formation in D-ribose in the preceding section, you may have noticed that aldopentoses have the potential of forming a six-membered cyclic hemiacetal via addition of the C-5 hydroxyl to the carbonyl group. This mode of ring closure leads to α- and β-*pyranose* forms:

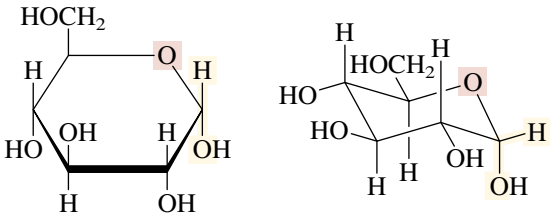


Like aldopentoses, aldohexoses such as D-glucose are capable of forming two furanose forms (α and β) and two pyranose forms (α and β). The Haworth representations of the pyranose forms of D-glucose are constructed as shown in Figure 25.4; each has a CH_2OH group as a substituent on the six-membered ring.

Haworth formulas are satisfactory for representing *configurational* relationships in pyranose forms but are uninformative as to carbohydrate *conformations.* X-ray crystallographic studies of a large number of carbohydrates reveal that the six-membered pyranose ring of D-glucose adopts a chair conformation:

Make a molecular model of the chair conformation of β-D-glucopyranose.





All the ring substituents other than hydrogen in β-D-glucopyranose are equatorial in the most stable chair conformation. Only the anomeric hydroxyl group is axial in the α isomer; all the other substituents are equatorial.

Other aldohexoses behave similarly in adopting chair conformations that permit the CH_2OH substituent to occupy an equatorial orientation. Normally the CH_2OH group is the bulkiest, most conformationally demanding substituent in the pyranose form of a hexose.

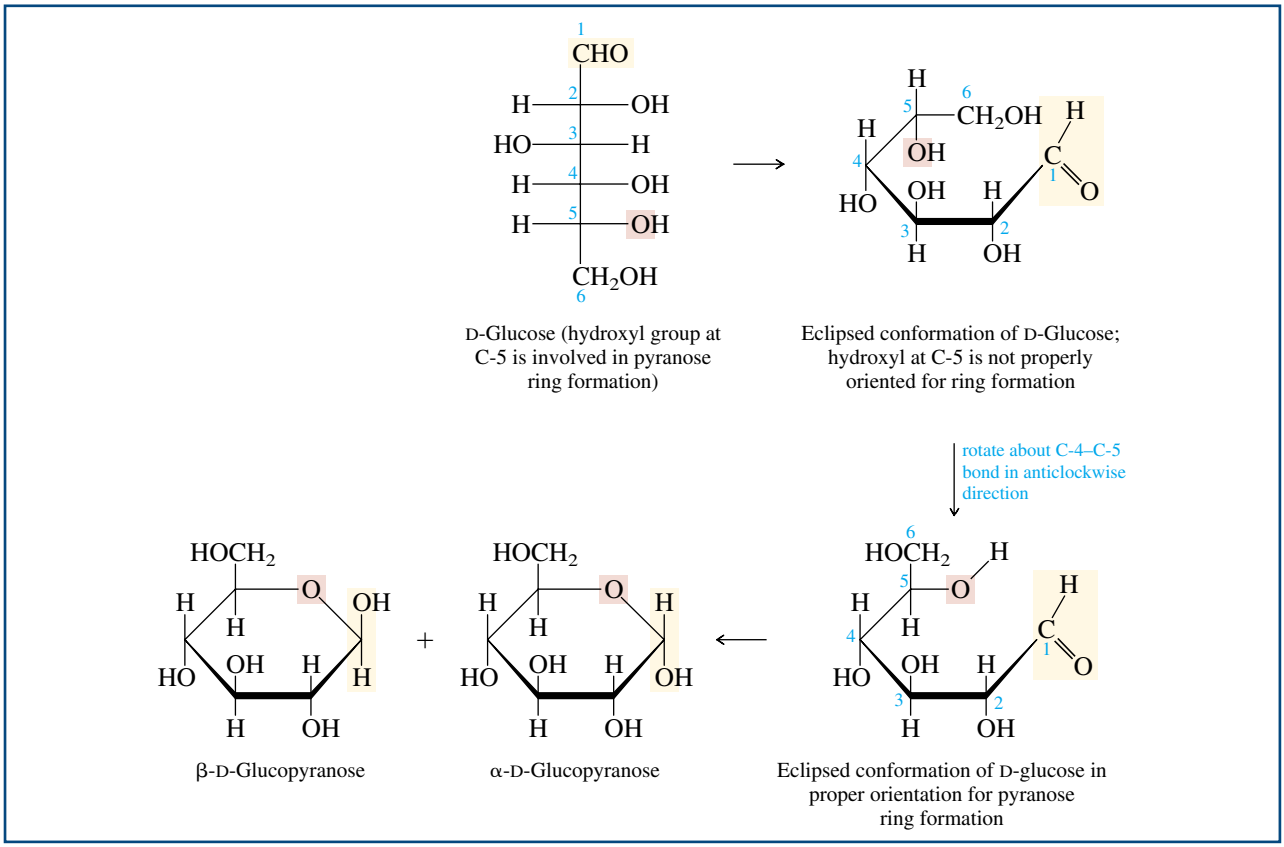
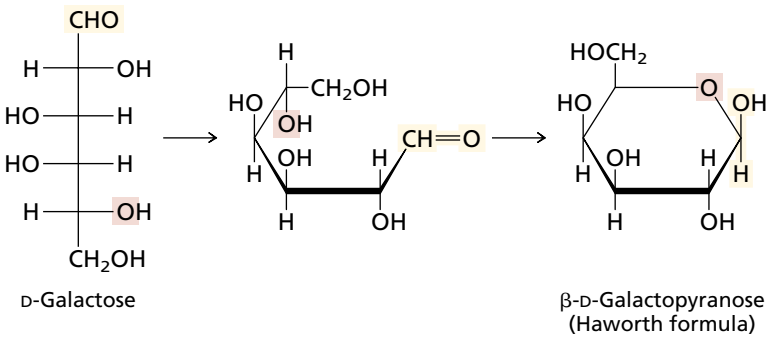


FIGURE 25.4 Haworth formulas for α- and β-pyranose forms of D-glucose.

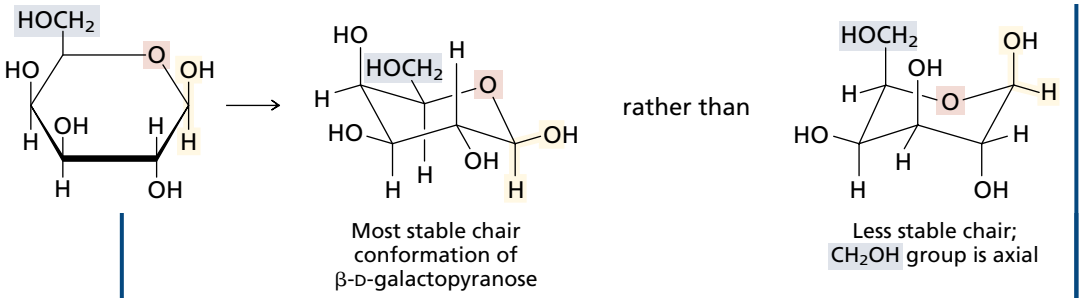
PROBLEM 25.6 Clearly represent the most stable conformation of the β-pyranose form of each of the following sugars:

(a) D-Galactose
(b) D-Mannose
(c) L-Mannose
(d) L-Ribose

SAMPLE SOLUTION (a) By analogy with the procedure outlined for D-glucose in Figure 25.4, first generate a Haworth formula for β-D-galactopyranose:



Next, redraw the planar Haworth formula more realistically as a chair conformation, choosing the one that has the CH_2OH group equatorial.



Galactose differs from glucose in configuration at C-4. The C-4 hydroxyl is axial in β-D-galactopyranose, but it is equatorial in β-D-glucopyranose.

Since six-membered rings are normally less strained than five-membered ones, pyranose forms are usually present in greater amounts than furanose forms at equilibrium, and the concentration of the open-chain form is quite small. The distribution of carbohydrates among their various hemiacetal forms has been examined by using ^{1}H and ^{13}C NMR spectroscopy. In aqueous solution, for example, D-ribose is found to contain the various α and β-furanose and pyranose forms in the amounts shown in Figure 25.5. The concentration of the open-chain form at equilibrium is too small to measure directly. Nevertheless, it occupies a central position, in that interconversions of α and β anomers and furanose and pyranose forms take place by way of the open-chain form as an intermediate. As will be seen later, certain chemical reactions also proceed by way of the open-chain form.

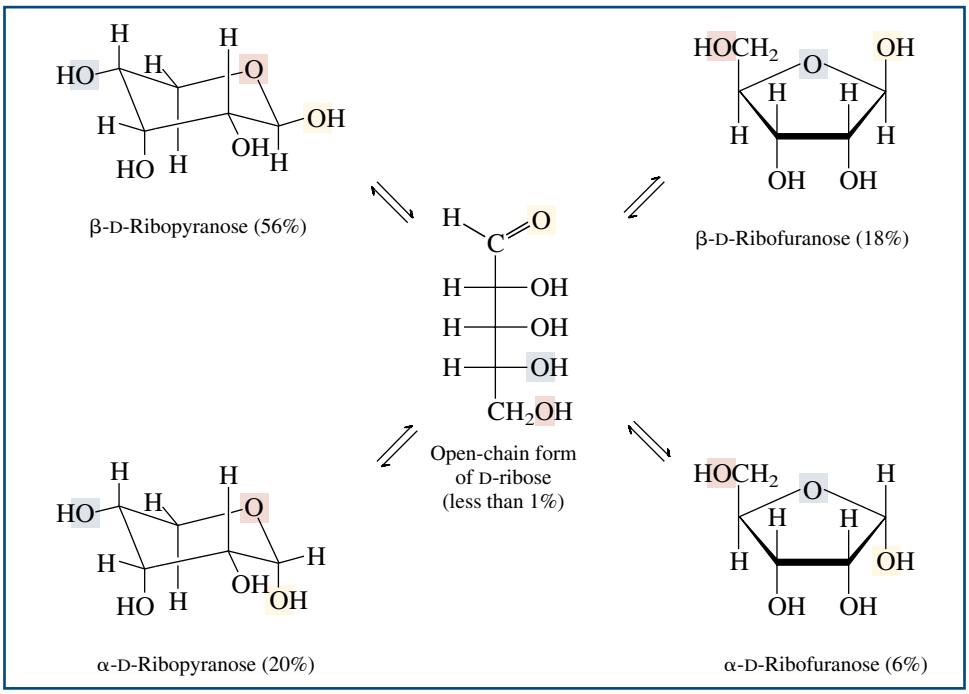
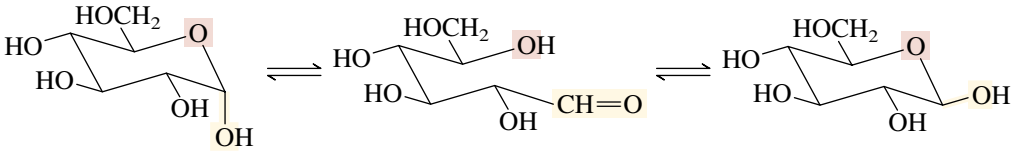


FIGURE 25.5 Distribution of furanose, pyranose, and open-chain forms of D-ribose in aqueous solution as measured by ^{1}H and ^{13}C NMR spectroscopy.

25.8 MUTAROTATION

In spite of their easy interconversion in solution, α and β forms of carbohydrates are capable of independent existence, and many have been isolated in pure form as crystalline solids. When crystallized from ethanol, D-glucose yields α-D-glucopyranose, mp 146°C, $[\alpha]_D$ +112.2°. Crystallization from a water–ethanol mixture produces β-D-glucopyranose, mp 148–155°C, $[\alpha]_D$ +18.7°. In the solid state the two forms do not interconvert and are stable indefinitely. Their structures have been unambiguously confirmed by X-ray crystallography.

The optical rotations just cited for each isomer are those measured immediately after each one is dissolved in water. On standing, the rotation of the solution containing the α isomer decreases from +112.2° to +52.5°; the rotation of the solution of the β isomer increases from +18.7° to the same value of +52.5°. This phenomenon is called **mutarotation.** What is happening is that each solution, initially containing only one anomeric form, undergoes equilibration to the same mixture of α- and β-pyranose forms. The open-chain form is an intermediate in the process.



α-D-Glucopyranose (mp 146°C; $[\alpha]_D$ +112.2°)

Open-chain form of D-glucose

β-D-Glucopyranose (mp 148–155°C; $[\alpha]_D$ +18.7°)

The distribution between the α and β anomeric forms at equilibrium is readily calculated from the optical rotations of the pure isomers and the final optical rotation of the solution, and is determined to be 36% α to 64% β. Independent measurements have established that only the pyranose forms of D-glucose are present in significant quantities at equilibrium.

A ^{13}C NMR study of D-glucose in water detected five species: the α-pyranose (38.8%), β-pyranose (60.9%), α-furanose (0.14%), and β-furanose (0.15%) forms, and the hydrate of the open-chain form (0.0045%).

PROBLEM 25.7 The specific optical rotations of pure α- and β-D-mannopyranose are +29.3° and −17.0°, respectively. When either form is dissolved in water, mutarotation occurs, and the observed rotation of the solution changes until a final rotation of +14.2° is observed. Assuming that only α- and β-pyranose forms are present, calculate the percent of each isomer at equilibrium.

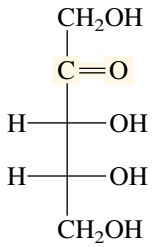
It's not possible to tell by inspection whether the α- or β-pyranose form of a particular carbohydrate predominates at equilibrium. As just described, the β-pyranose form is the major species present in an aqueous solution of D-glucose, whereas the α-pyranose form predominates in a solution of D-mannose (Problem 25.7). The relative abundance of α-and β-pyranose forms in solution is a complicated issue and depends on several factors. One is solvation of the anomeric hydroxyl group. An equatorial OH is less crowded and better solvated by water than an axial one. This effect stabilizes the β-pyranose form in aqueous solution. A second factor, called the **anomeric effect,** involves an electronic interaction between the ring oxygen and the anomeric substituent and preferentially stabilizes the axial OH of the α-pyranose form. Because the two effects

The anomeric effect is best explained by a molecular orbital analysis that is beyond the scope of this text.

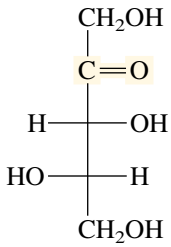
operate in different directions but are comparable in magnitude in aqueous solution, the α-pyranose form is more abundant for some carbohydrates and the β-pyranose form for others.

25.9 KETOSES

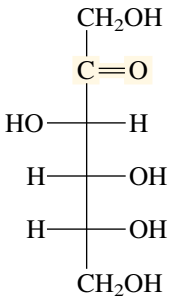
Up to this point all our attention has been directed toward aldoses, carbohydrates having an aldehyde function in their open-chain form. Aldoses are more common than ketoses, and their role in biological processes has been more thoroughly studied. Nevertheless, a large number of ketoses are known, and several of them are pivotal intermediates in carbohydrate biosynthesis and metabolism. Examples of some ketoses include D-*ribulose,* L-*xylulose,* and D-*fructose:*



D-Ribulose
(a 2-ketopentose that is a key compound in photosynthesis)



L-Xylulose
(a 2-ketopentose excreted in excessive amounts in the urine of persons afflicted with the mild genetic disorder pentosuria)

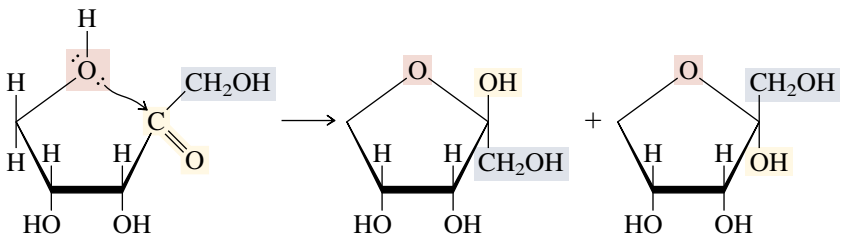


D-Fructose
(a 2-ketohexose also known as *levulose;* it is found in honey and is signficantly sweeter than table sugar)

In these three examples the carbonyl group is located at C-2, which is the most common location for the carbonyl function in naturally occurring ketoses.

PROBLEM 25.8 How many ketotetroses are possible? Write Fischer projections for each.

Ketoses, like aldoses, exist mainly as cyclic hemiacetals. In the case of D-ribulose, furanose forms result from addition of the C-5 hydroxyl to the carbonyl group.



Eclipsed conformation of D-ribulose

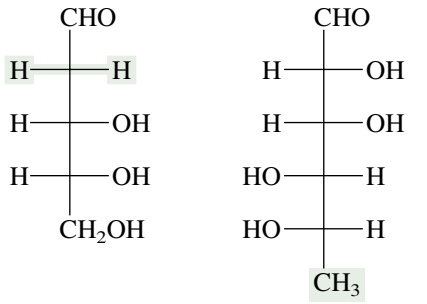
β-D-Ribulofuranose

α-D-Ribulofuranose

The anomeric carbon of a furanose or pyranose form of a ketose bears both a hydroxyl group and a carbon substituent. In the case of 2-ketoses, this substituent is a CH_2OH group. As with aldoses, the anomeric carbon of a cyclic hemiacetal is readily identifiable because it is bonded to two oxygens.

25.10 DEOXY SUGARS

A commonplace variation on the general pattern seen in carbohydrate structure is the replacement of one or more of the hydroxyl substituents by some other atom or group. In **deoxy sugars** the hydroxyl group is replaced by hydrogen. Two examples of deoxy sugars are 2-deoxy-D-ribose and L-rhamnose:



2-Deoxy-D-ribose L-Rhamnose (6-deoxy-L-mannose)

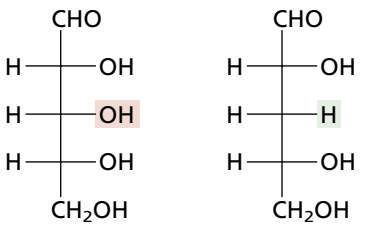
The hydroxyl at C-2 in D-ribose is absent in 2-deoxy-D-ribose. In Chapter 27 we shall see how derivatives of 2-deoxy-D-ribose, called *deoxyribonucleotides,* are the fundamental building blocks of deoxyribonucleic acid (DNA), the material responsible for storing genetic information. L-Rhamnose is a compound isolated from a number of plants. Its carbon chain terminates in a methyl rather than a CH_2OH group.

PROBLEM 25.9 Write Fischer projections of

(a) *Cordycepose* (3-deoxy-D-ribose): a deoxy sugar isolated by hydrolysis of the antibiotic substance *cordycepin*

(b) L-*Fucose* (6-deoxy-L-galactose): obtained from seaweed

SAMPLE SOLUTION (a) The hydroxyl group at C-3 in D-ribose is replaced by hydrogen in 3-deoxy-D-ribose.

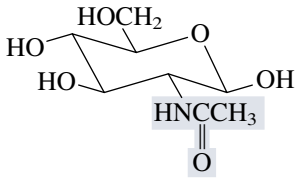


D-Ribose (from Figure 25.2) 3-Deoxy-D-ribose (cordycepose)

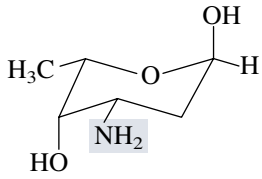
25.11 AMINO SUGARS

For a review of the isolation of chitin from natural sources and some of its uses, see the November 1990 issue of the *Journal of Chemical Education* (pp. 938–942).

Another structural variation is the replacement of a hydroxyl group in a carbohydrate by an amino group to give an **amino sugar.** The most abundant amino sugar is one of the oldest and most abundant organic compounds on earth. *N*-Acetyl-D-glucosamine is the main component of the polysaccharide in *chitin,* the substance that makes up the tough outer skeleton of arthropods and insects. Chitin has been isolated from a 25-million-year-old beetle fossil, and more than 10^{11} tons of chitin is produced in the biosphere each year. Lobster shells, for example, are mainly chitin. More than 60 amino sugars are known, many of them having been isolated and identified only recently as components of antibiotics. The anticancer drug doxorubicin hydrochloride (Adriamycin), for example, contains the amino sugar L-daunosamine as one of its structural units.



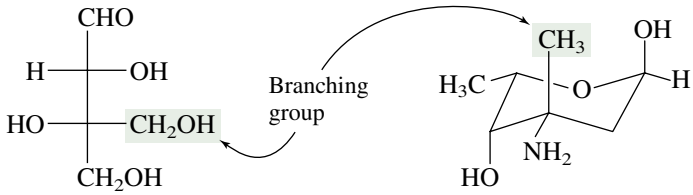
N-Acetyl-D-glucosamine



L-Daunosamine

25.12 BRANCHED-CHAIN CARBOHYDRATES

Carbohydrates that have a carbon substituent attached to the main chain are said to have a **branched chain.** D-Apiose and L-vancosamine are representative branched-chain carbohydrates:

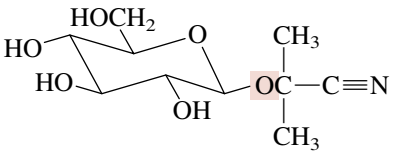


D-Apiose L-Vancosamine

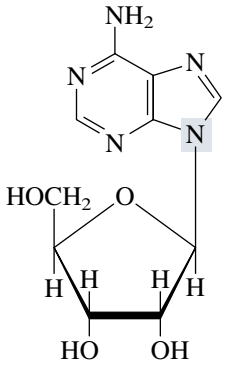
D-Apiose can be isolated from parsley and is a component of the cell wall polysaccharide of various marine plants. Among its novel structural features is the presence of only a single stereogenic center. L-Vancosamine is but one portion of vancomycin, a powerful antibiotic that is reserved for treating only the most stubborn infections. L-Vancosamine is not only a branched-chain carbohydrate, it is a deoxy sugar and an amino sugar as well.

25.13 GLYCOSIDES

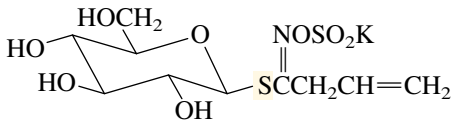
Glycosides are a large and very important class of carbohydrate derivatives characterized by the replacement of the anomeric hydroxyl group by some other substituent. Glycosides are termed *O*-glycosides, *N*-glycosides, *S*-glycosides, and so on, according to the atom attached to the anomeric carbon.



Linamarin
(an *O*-glycoside: obtained from manioc, a type of yam widely distributed in southeast Asia)



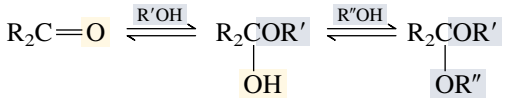
Adenosine
(an *N*-glycoside: also known as a nucleoside; adenosine is one of the fundamental molecules of biochemistry)



Sinigrin
(an *S*-glycoside: contributes to the characteristic flavor of mustard and horseradish)

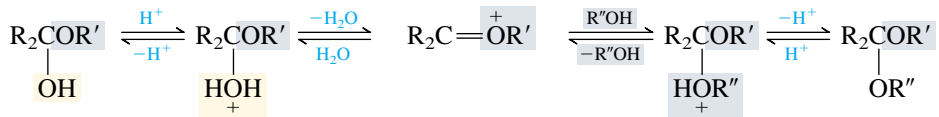
Usually, the term "glycoside" without a prefix is taken to mean an *O*-glycoside and will be used that way in this chapter. Glycosides are classified as α or β in the customary way, according to the configuration at the anomeric carbon. All three of the glycosides just shown are β-glycosides. Linamarin and sinigrin are glycosides of D-glucose; adenosine is a glycoside of D-ribose.

Structurally, *O*-glycosides are mixed acetals that involve the anomeric position of furanose and pyranose forms of carbohydrates. Recall the sequence of intermediates in acetal formation (Section 17.8):



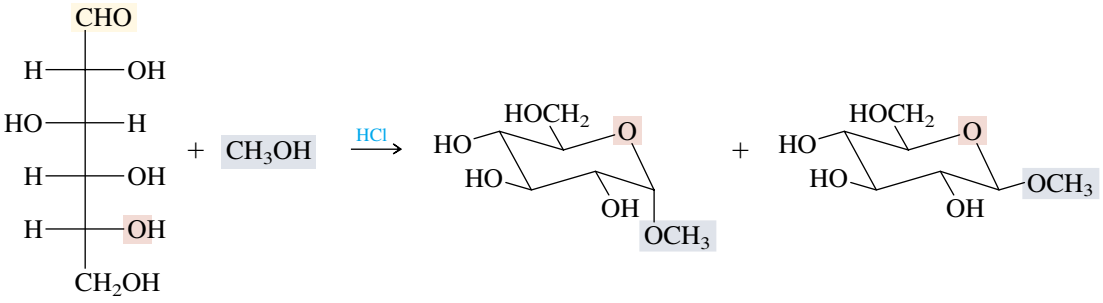
Aldehyde or ketone — Hemiacetal — Acetal

When this sequence is applied to carbohydrates, the first step takes place *intramolecularly* and spontaneously to yield a cyclic hemiacetal. The second step is *intermolecular,* requires an alcohol R″OH as a reactant, and proceeds readily only in the presence of an acid catalyst. An oxygen-stabilized carbocation is an intermediate.



Hemiacetal — Oxygen-stabilized carbocation — Mixed acetal

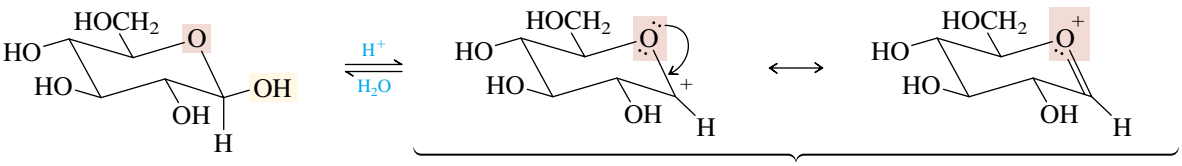
The preparation of glycosides in the laboratory is carried out by simply allowing a carbohydrate to react with an alcohol in the presence of an acid catalyst:



D-Glucose | Methanol | Methyl α-D-glucopyranoside (major product; isolated in 49% yield) | Methyl β-D-glucopyranoside (minor product)

PROBLEM 25.10 Write structural formulas for the α- and β-methyl pyranosides formed by reaction of D-galactose with methanol in the presence of hydrogen chloride.

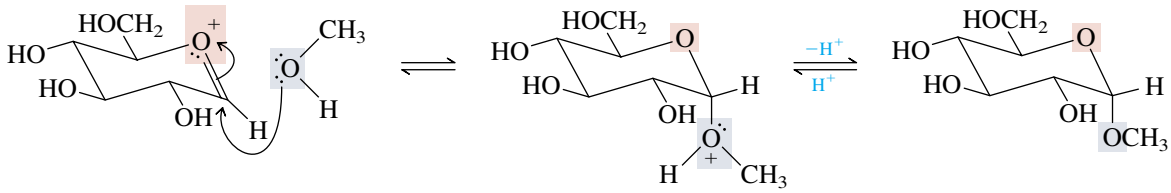
A point to be emphasized about glycoside formation is that, despite the presence of a number of other hydroxyl groups in the carbohydrate, *only the anomeric hydroxyl group is replaced.* This is because a carbocation at the anomeric position is stabilized by the ring oxygen and is the only one capable of being formed under the reaction conditions.



D-Glucose (shown in β-pyranose form) | Electron pair on ring oxygen can stabilize carbocation at anomeric position only.

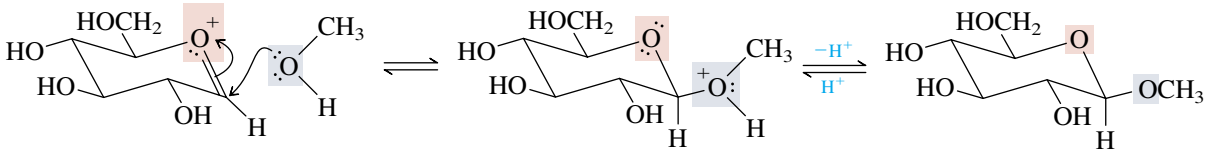
Once the carbocation is formed, it is captured by the alcohol acting as a nucleophile. Attack can occur at either the α or β face of the carbocation.

Attack at the α face gives methyl α-D-glucopyranoside:



Carbocation intermediate + Methanol | Methyl α-D-glucopyranoside

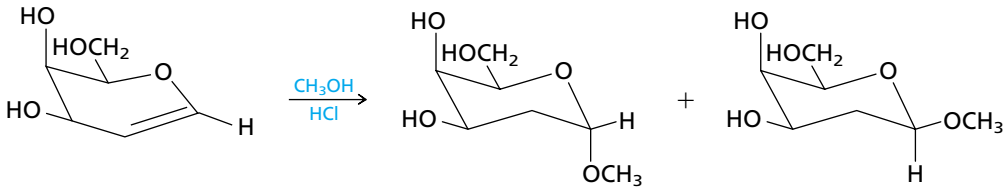
Attack at the β face gives methyl β-D-glucopyranoside:



Carbocation intermediate + Methanol | Methyl β-D-glucopyranoside

All of the reactions, from D-glucose to the methyl glycosides via the carbocation, are reversible. The overall reaction is *thermodynamically controlled* and gives the same mixture of glycosides irrespective of which stereoisomeric pyranose form of D-glucose we start with. Nor does it matter whether we start with a pyranose form or a furanose form of D-glucose. Glucopyranosides are more stable than glucofuranosides and predominate at equilibrium.

PROBLEM 25.11 Methyl glycosides of 2-deoxy sugars have been prepared by the acid-catalyzed addition of methanol to unsaturated sugars known as *glycals.*



Galactal

Methyl 2-deoxy-α-D-lyxohexopyranoside (38%)

Methyl 2-deoxy-β-D-lyxohexopyranoside (36%)

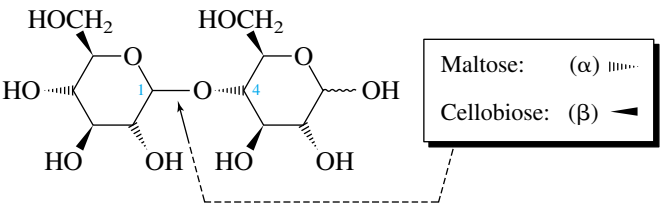
Suggest a reasonable mechanism for this reaction.

Under neutral or basic conditions glycosides are configurationally stable; unlike the free sugars from which they are derived, glycosides do not exhibit mutarotation. Converting the anomeric hydroxyl group to an ether function (hemiacetal → acetal) prevents its reversion to the open-chain form in neutral or basic media. In aqueous acid, acetal formation can be reversed and the glycoside hydrolyzed to an alcohol and the free sugar.

25.14 DISACCHARIDES

Disaccharides are carbohydrates that yield two monosaccharide molecules on hydrolysis. Structurally, disaccharides are *glycosides* in which the alkoxy group attached to the anomeric carbon is derived from a second sugar molecule.

Maltose, obtained by the hydrolysis of starch, and *cellobiose,* by the hydrolysis of cellulose, are isomeric disaccharides. In both maltose and cellobiose two D-glucopyranose units are joined by a glycosidic bond between C-1 of one unit and C-4 of the other. The two are diastereomers, differing only in the stereochemistry at the anomeric carbon of the glycoside bond; maltose is an α-glycoside, cellobiose is a β-glycoside.



You can view molecular models of maltose and cellobiose on *Learning By Modeling.*

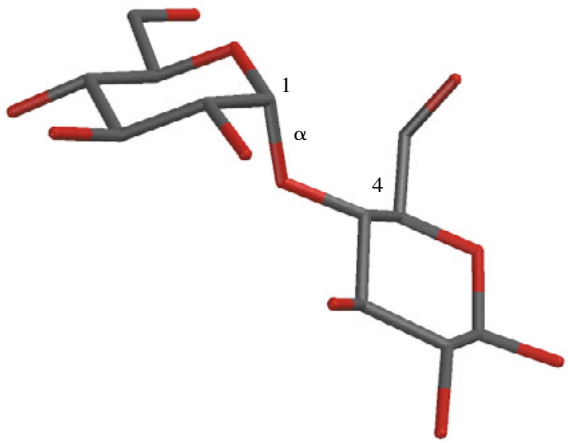
The stereochemistry and points of connection of glycosidic bonds are commonly designated by symbols such as α(1,4) for maltose and β(1,4) for cellobiose; α and β designate the stereochemistry at the anomeric position; the numerals specify the ring carbons involved.

The free anomeric hydroxyl group is the one shown at the far right of the preceding structural formula. The symbol ∿∿∿ is used to represent a bond of variable stereochemistry.

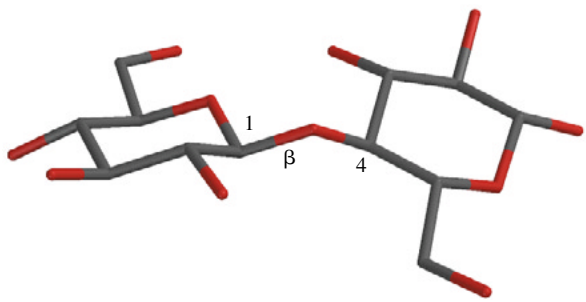
Both maltose and cellobiose have a free anomeric hydroxyl group that is not involved in a glycoside bond. The configuration at the free anomeric center is variable and may be either α or β. Indeed, two stereoisomeric forms of maltose have been isolated: one has its anomeric hydroxyl group in an equatorial orientation; the other has an axial anomeric hydroxyl.

PROBLEM 25.12 The two stereoisomeric forms of maltose just mentioned undergo mutarotation when dissolved in water. What is the structure of the key intermediate in this process?

The single difference in their structures, the stereochemistry of the glycosidic bond, causes maltose and cellobiose to differ significantly in their three-dimensional shape, as the molecular models of Figure 25.6 illustrate. This difference in shape affects the way in which maltose and cellobiose interact with other chiral molecules such as proteins, and they behave much differently toward enzyme-catalyzed hydrolysis. An enzyme known as *maltase* catalyzes the hydrolytic cleavage of the α-glycosidic bond of maltose but is without effect in promoting the hydrolysis of the β-glycosidic bond of cellobiose. A different enzyme, *emulsin,* produces the opposite result: emulsin catalyzes the hydrolysis of cellobiose but not of maltose. The behavior of each enzyme is general for glucosides (glycosides of glucose). Maltase catalyzes the hydrolysis of α-glucosides and is



Maltose



Cellobiose

FIGURE 25.6 Molecular models of the disaccharides maltose and cellobiose. Two D-glucopyranose units are connected by a glycoside linkage between C-1 and C-4. The glycosidic bond has the α orientation in maltose and is β in cellobiose. Maltose and cellobiose are diastereomers.

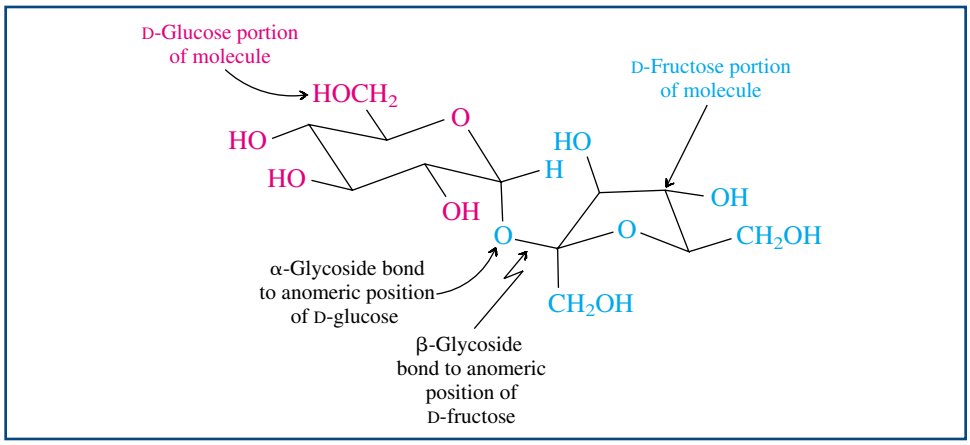
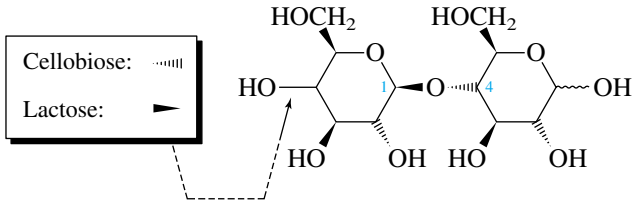


FIGURE 25.7 The structure of sucrose.

also known as α-*glucosidase,* whereas emulsin catalyzes the hydrolysis of β-glucosides and is known as β-*glucosidase.* The specificity of these enzymes offers a useful tool for structure determination because it allows the stereochemistry of glycosidic linkages to be assigned.

Lactose is a disaccharide constituting 2–6% of milk and is known as *milk sugar.* It differs from maltose and cellobiose in that only one of its monosaccharide units is D-glucose. The other monosaccharide unit, the one that contributes its anomeric carbon to the glycoside bond, is D-galactose. Like cellobiose, lactose is a β-glycoside.



You can view molecular models of cellobiose and lactose on *Learning By Modeling.*

Digestion of lactose is facilitated by the β-glycosidase *lactase.* A deficiency of this enzyme makes it difficult to digest lactose and causes abdominal discomfort. Lactose intolerance is a genetic trait; it is treatable through over-the-counter formulations of lactase and by limiting the amount of milk in the diet.

The most familiar of all the carbohydrates is *sucrose*—common table sugar. Sucrose is a disaccharide in which D-glucose and D-fructose are joined at their anomeric carbons by a glycosidic bond (Figure 25.7). Its chemical composition is the same irrespective of its source; sucrose from cane and sucrose from sugar beets are chemically identical. Since sucrose does not have a free anomeric hydroxyl group, it does not undergo mutarotation.

25.15 POLYSACCHARIDES

Cellulose is the principal structural component of vegetable matter. Wood is 30–40% cellulose, cotton over 90%. Photosynthesis in plants is responsible for the formation of 10^9 tons per year of cellulose. Structurally, cellulose is a polysaccharide composed of several thousand D-glucose units joined by β(1,4)-glycosidic linkages (Figure 25.8). Complete hydrolysis of all the glycosidic bonds of cellulose yields D-glucose. The disaccharide fraction that results from partial hydrolysis is cellobiose.

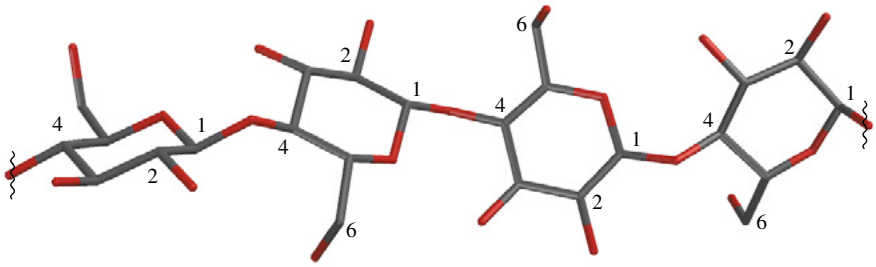


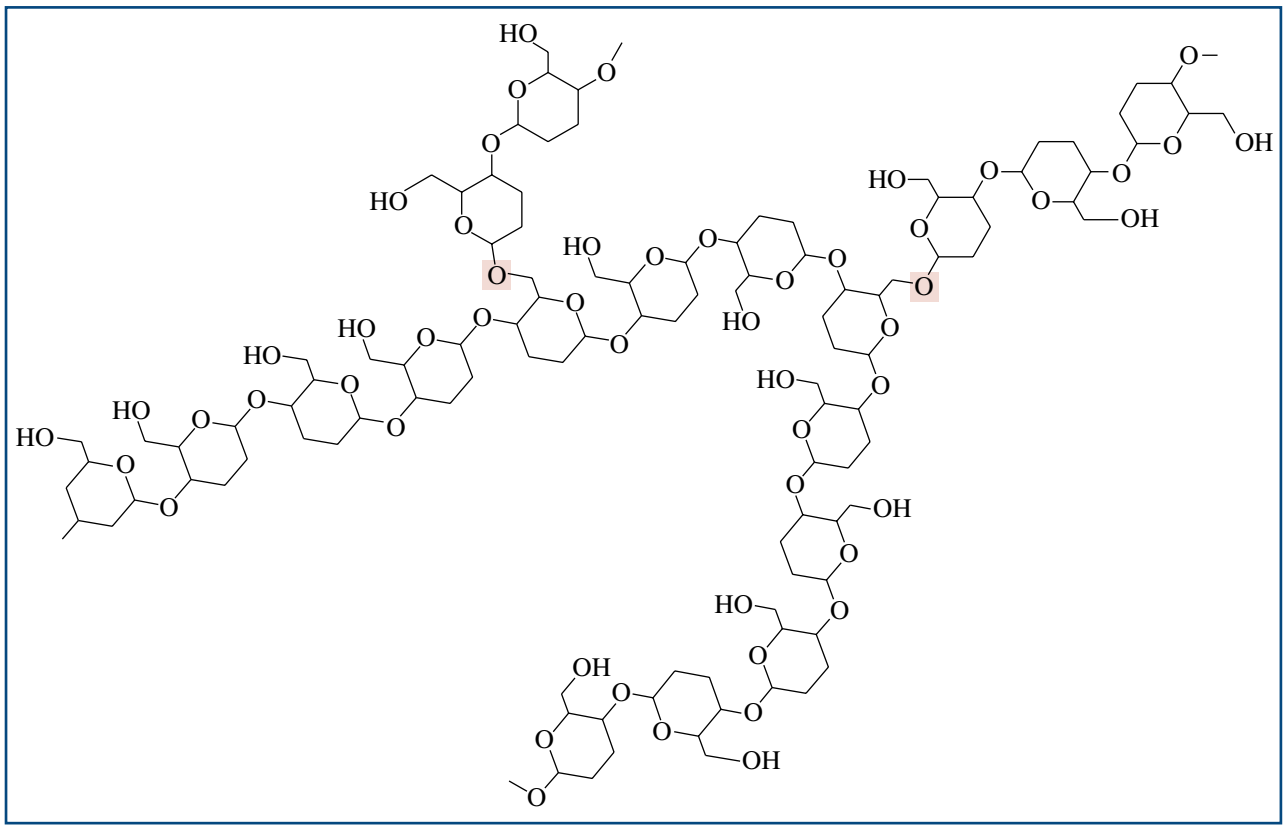
FIGURE 25.8 Cellulose is a polysaccharide in which D-glucose units are connected by β(1,4)-glycoside linkages analogous to cellobiose. Hydrogen bonding, especially between the C-2 and C-6 hydroxyl groups, causes adjacent glucose units to be turned at an angle of 180° with each other.

Animals lack the enzymes necessary to catalyze the hydrolysis of cellulose and so can't digest it. Cattle and other ruminants use cellulose as a food source in an indirect way. Colonies of microorganisms that live in their digestive tract consume cellulose and in the process convert it to other substances that the animal can digest.

A more direct source of energy for animals is provided by the starches found in many foods. Starch is a mixture of a water-dispersible fraction called *amylose* and a second component, *amylopectin.* Amylose is a polysaccharide made up of about 100 to several thousand D-glucose units joined by α(1,4)-glycosidic bonds (Figure 25.9).

Like amylose, amylopectin is a polysaccharide of α(1,4)-linked D-glucose units. Instead of being a continuous length of α(1,4) units, however, amylopectin is branched. Attached to C-6 at various points on the main chain are short polysaccharide branches of 24–30 glucose units joined by α(1,4)-glycosidic bonds.

FIGURE 25.9 Amylose is a polysaccharide in which D-glucose units are connected by α(1,4)-glycoside linkages analogous to maltose.



Starch is a plant's way of storing glucose to meet its energy needs. Animals can tap that source by eating starchy foods and, with the aid of their α-glycosidase enzymes, hydrolyze the starch to glucose. When more glucose is available than is needed as fuel, animals store it as glycogen. *Glycogen* is similar to amylopectin in that it is a branched polysaccharide of α(1,4)-linked D-glucose units with subunits connected to C-6 of the main chain.

25.16 CELL-SURFACE GLYCOPROTEINS

That carbohydrates play an informational role in biological interactions is a recent revelation of great importance. *Glycoproteins,* protein molecules covalently bound to carbohydrates, are often the principal species involved. When a cell is attacked by a virus or bacterium or when it interacts with another cell, the drama begins when the foreign particle attaches itself to the surface of the host cell. The invader recognizes the host by the glycoproteins on the cell surface. More specifically, it recognizes particular carbohydrate sequences at the end of the glycoprotein. For example, the receptor on the cell surface to which an influenza virus attaches itself has been identified as a glycoprotein terminating in a disaccharide of *N*-acetylgalactosamine and *N*-acetylneuraminic acid (Figure 25.10). Since attachment of the invader to the surface of the host cell is the first step in infection, one approach to disease prevention is to selectively inhibit this "host–guest" interaction. Identifying the precise nature of the interaction is the first step in the rational design of drugs that prevent it.

Human blood group substances offer another example of the informational role played by carbohydrates. The structure of the glycoproteins attached to the surface of blood cells determines whether blood is type A, B, AB, or O. Differences between the carbohydrate components of the various glycoproteins have been identified and are shown in Figure 25.11. Compatibility of blood types is dictated by *antigen–antibody* interactions. The cell-surface glycoproteins are *antigens. Antibodies* present in certain blood types can cause the blood cells of certain other types to clump together, and thus set practical limitations on transfusion procedures. The antibodies "recognize" the antigens they act on by their terminal saccharide units.

Antigen–antibody interactions are the fundamental basis by which the immune system functions. These interactions are chemical in nature and often involve associations between glycoproteins of an antigen and complementary glycoproteins of the antibody. The precise chemical nature of antigen–antibody association is an area of active investigation, with significant implications for chemistry, biochemistry, and physiology.

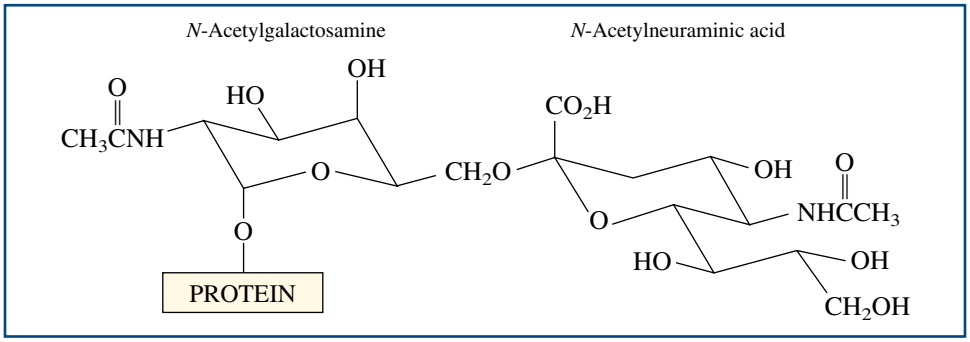


FIGURE 25.10 Diagram of a cell-surface glycoprotein, showing the disaccharide unit that is recognized by an invading influenza virus.

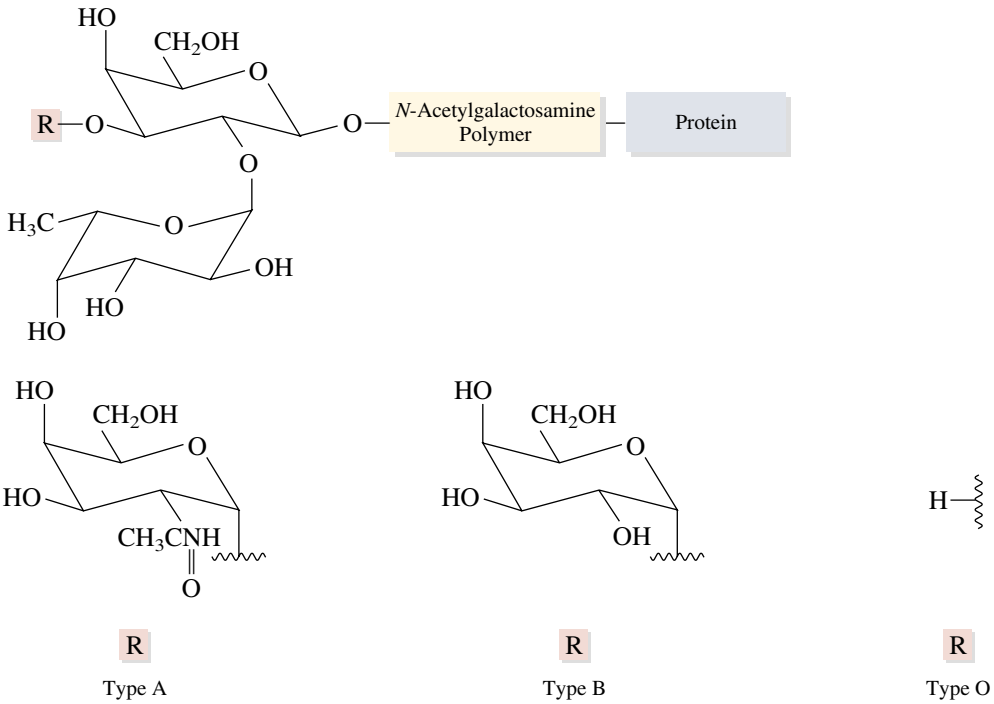


FIGURE 25.11 Terminal carbohydrate units of human blood-group glycoproteins. The structural difference between the type A, type B, and type O glycoproteins lies in the group designated R.

25.17 CARBOHYDRATE STRUCTURE DETERMINATION

Present-day techniques for structure determination in carbohydrate chemistry are substantially the same as those for any other type of compound. The full range of modern instrumental methods, including mass spectrometry and infrared and nuclear magnetic resonance spectroscopy, is brought to bear on the problem. If the unknown substance is crystalline, X-ray diffraction can provide precise structural information that in the best cases is equivalent to taking a three-dimensional photograph of the molecule.

The classical approach to structure determination in carbohydrate chemistry is best exemplified by Fischer's work with D-glucose. A detailed account of this study appears in the August 1941 issue of the *Journal of Chemical Education* (pp. 353–357).

Before the widespread availability of instrumental methods, the major approach to structure determination relied on a battery of chemical reactions and tests. The response of an unknown substance to various reagents and procedures provided a body of data from which the structure could be deduced. Some of these procedures are still used to supplement the information obtained by instrumental methods. To better understand the scope and limitations of these tests, a brief survey of the chemical reactions of carbohydrates is in order. In many cases these reactions are simply applications of chemistry you have already learned. Certain of the transformations, however, are unique to carbohydrates.

25.18 REDUCTION OF CARBOHYDRATES

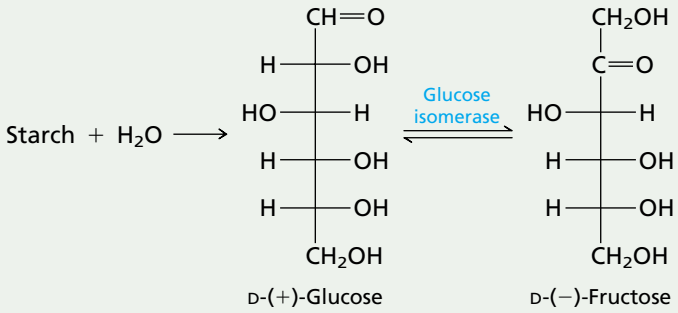
Although carbohydrates exist almost entirely as cyclic hemiacetals in aqueous solution, they are in rapid equilibrium with their open-chain forms, and most of the reagents that react with simple aldehydes and ketones react in an analogous way with the carbonyl functional groups of carbohydrates.

The carbonyl group of carbohydrates can be reduced to an alcohol function. Typical procedures include catalytic hydrogenation and sodium borohydride reduction. Lithium aluminum hydride is not suitable, because it is not compatible with the solvents (water,

HOW SWEET IT IS!

How sweet is it?

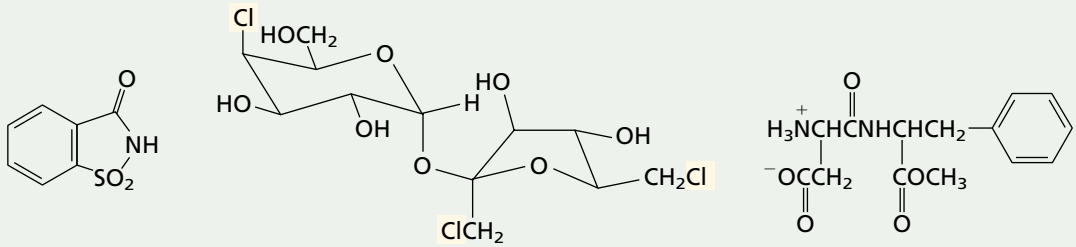
There is no shortage of compounds, natural or synthetic, that taste sweet. The most familiar are naturally occurring sugars, especially sucrose, glucose, and fructose. All occur naturally, with worldwide production of sucrose from cane and sugar beets exceeding 100 million tons per year. Glucose is prepared by the enzymatic hydrolysis of starch, and fructose is made by the isomerization of glucose.



Among sucrose, glucose, and fructose, fructose is the sweetest. Honey is sweeter than table sugar because it contains fructose formed by the isomerization of glucose as shown in the equation.

You may have noticed that most soft drinks contain "high-fructose corn syrup." Corn starch is hydrolyzed to glucose, which is then treated with glucose isomerase to produce a fructose-rich mixture. The enhanced sweetness permits less to be used, reducing the cost of production. Using less carbohydrate-based sweetener also reduces the number of calories.

Artificial sweeteners are a billion-dollar-per-year industry. The primary goal is, of course, to maximize sweetness and minimize calories. We'll look at the following three sweeteners to give us an overview of the field.



Saccharin Sucralose Aspartame

All three of these are hundreds of times sweeter than sucrose and variously described as "low-calorie" or "nonnutritive" sweeteners.

Saccharin was discovered at Johns Hopkins University in 1879 in the course of research on coal-tar derivatives and is the oldest artificial sweetener. In spite of its name, which comes from the Latin word for sugar, saccharin bears no structural relationship to any sugar. Nor is saccharin itself very soluble in water. The proton bonded to nitrogen, however, is fairly acidic and saccharin is normally marketed as its water-soluble sodium or calcium salt. Its earliest applications were not in weight control, but as a replacement for sugar in the diet of diabetics before insulin became widely available.

Sucralose has the structure most similar to sucrose. Galactose replaces the glucose unit of sucrose, and chlorines replace three of the hydroxyl groups. Sucralose is the newest artificial sweetener, having been approved by the U.S. Food and Drug Administration in 1998. The three chlorine substituents do not diminish sweetness, but do interfere with the ability of the body to metabolize sucralose. It, therefore, has no food value and is "noncaloric."

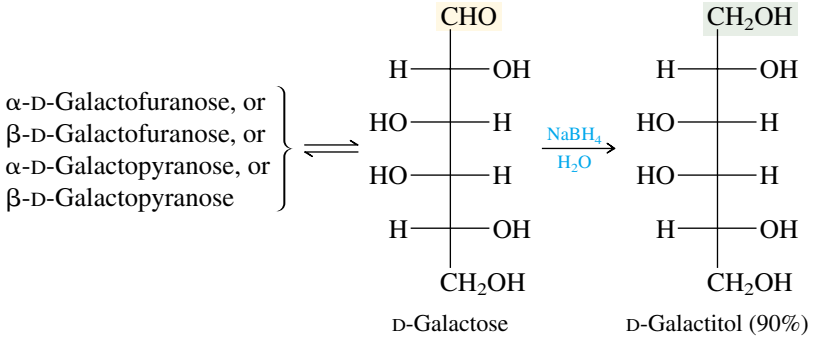
—Cont.

Aspartame is the market leader among artificial sweeteners. It is a methyl ester of a dipeptide, unrelated to any carbohydrate. It was discovered in the course of research directed toward developing drugs to relieve indigestion.

Saccharin, sucralose, and aspartame illustrate the diversity of structural types that taste sweet, and the vitality and continuing development of the industry of which they are a part.*

*For more information, including theories of structure–taste relationships, see the symposium "Sweeteners and Sweetness Theory" in the August, 1995 issue of the *Journal of Chemical Education,* pp. 671–683.

alcohols) that are required to dissolve carbohydrates. The products of carbohydrate reduction are called **alditols.** Since these alditols lack a carbonyl group, they are, of course, incapable of forming cyclic hemiacetals and exist exclusively in noncyclic forms.

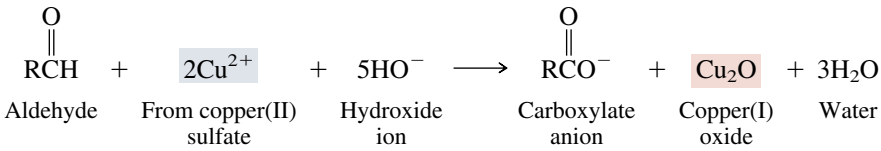


PROBLEM 25.13 Does sodium borohydride reduction of D-ribose yield an optically active product? Explain.

Another name for glucitol, obtained by reduction of D-glucose, is *sorbitol;* it is used as a sweetener, especially in special diets required to be low in sugar. Reduction of D-fructose yields a mixture of glucitol and mannitol, corresponding to the two possible configurations at the newly generated stereogenic center at C-2.

25.19 OXIDATION OF CARBOHYDRATES

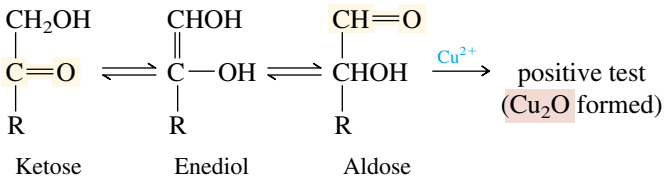
A characteristic property of an aldehyde function is its sensitivity to oxidation. A solution of copper(II) sulfate as its citrate complex **(Benedict's reagent)** is capable of oxidizing aliphatic aldehydes to the corresponding carboxylic acid.



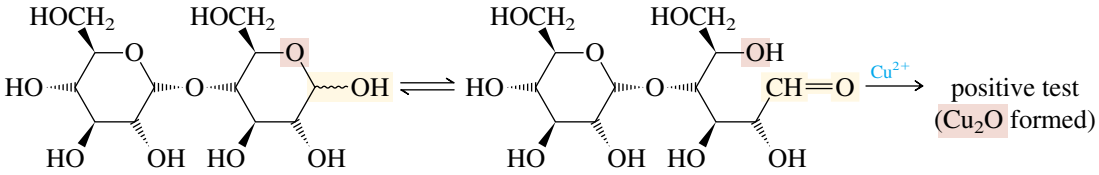
Benedict's reagent is the key material in a test kit available from drugstores that permits individuals to monitor the glucose levels in their urine.

The formation of a red precipitate of copper(I) oxide by reduction of Cu(II) is taken as a positive test for an aldehyde. Carbohydrates that give positive tests with Benedict's reagent are termed **reducing sugars.**

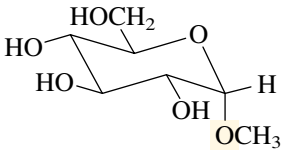
Aldoses are reducing sugars, since they possess an aldehyde function in their open-chain form. Ketoses are also reducing sugars. Under the conditions of the test, ketoses equilibrate with aldoses by way of *enediol intermediates,* and the aldoses are oxidized by the reagent.



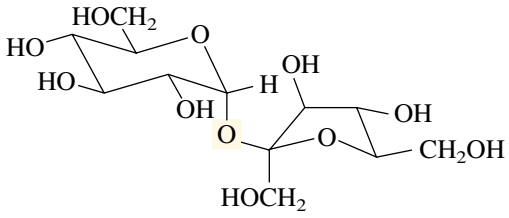
The same kind of equilibrium is available to α-hydroxy ketones generally; such compounds give a positive test with Benedict's reagent. Any carbohydrate that contains a free hemiacetal function is a reducing sugar. The free hemiacetal is in equilibrium with the open-chain form and through it is susceptible to oxidation. Maltose, for example, gives a positive test with Benedict's reagent.



Glycosides, in which the anomeric carbon is part of an acetal function, are not reducing sugars and do not give a positive test.



Methyl α-D-glucopyranoside: not a reducing sugar

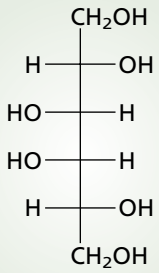


Sucrose: not a reducing sugar

PROBLEM 25.14 Which of the following would be expected to give a positive test with Benedict's reagent? Why?

(a) D-Galactitol (see structure in margin)
(b) L-Arabinose
(c) 1,3-Dihydroxyacetone
(d) D-Fructose
(e) Lactose
(f) Amylose

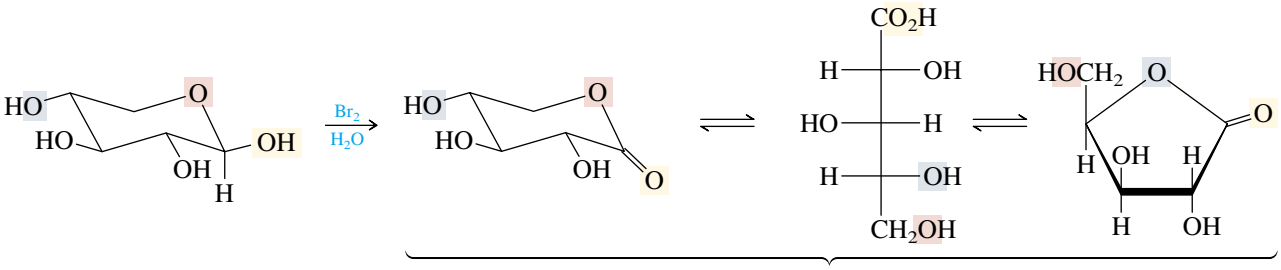
SAMPLE SOLUTION (a) D-Galactitol lacks an aldehyde, an α-hydroxy ketone, or a hemiacetal function, so cannot be oxidized by Cu^{2+} and will not give a positive test with Benedict's reagent.



D-Galactitol

Fehling's solution, a tartrate complex of copper(II) sulfate, has also been used as a test for reducing sugars.

Derivatives of aldoses in which the terminal aldehyde function is oxidized to a carboxylic acid are called **aldonic acids.** Aldonic acids are named by replacing the *-ose* ending of the aldose by *-onic acid.* Oxidation of aldoses with bromine is the most commonly used method for the preparation of aldonic acids and involves the furanose or pyranose form of the carbohydrate.

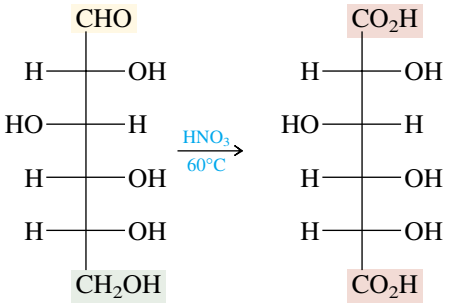


β-D-Xylopyranose

D-Xylonic acid (90%)

Aldonic acids exist in equilibrium with their five- or six-membered lactones. They can be isolated as carboxylate salts of their open-chain forms on treatment with base.

The reaction of aldoses with nitric acid leads to the formation of **aldaric acids** by oxidation of both the aldehyde and the terminal primary alcohol function to carboxylic acid groups. Aldaric acids are also known as *saccharic acids* and are named by substituting *-aric acid* for the *-ose* ending of the corresponding carbohydrate.



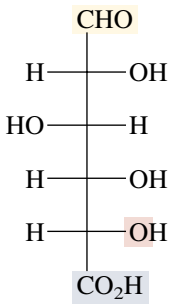
D-Glucose

D-Glucaric acid (41%)

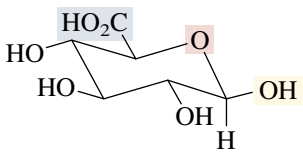
Like aldonic acids, aldaric acids exist mainly as lactones.

PROBLEM 25.15 Another hexose gives the same aldaric acid on oxidation as does D-glucose. Which one?

Uronic acids occupy an oxidation state between aldonic and aldaric acids. They have an aldehyde function at one end of their carbon chain and a carboxylic acid group at the other.



Fischer projection of D-glucuronic acid

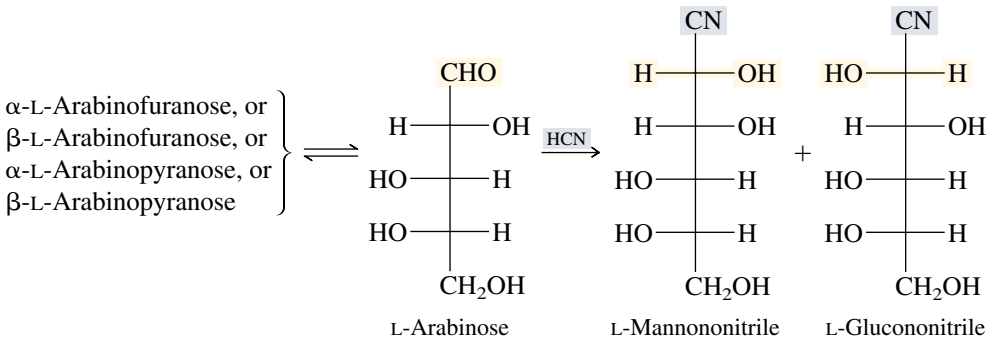


β-Pyranose form of D-glucuronic acid

Uronic acids are biosynthetic intermediates in various metabolic processes; ascorbic acid (vitamin C), for example, is biosynthesized by way of glucuronic acid. Many metabolic waste products are excreted in the urine as their glucuronate salts.

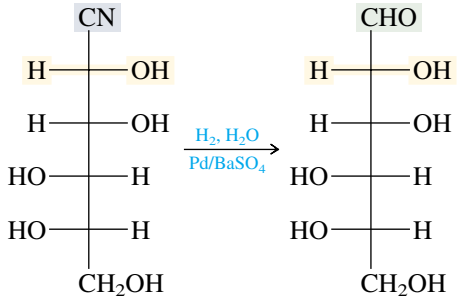
25.20 CYANOHYDRIN FORMATION AND CARBOHYDRATE CHAIN EXTENSION

The presence of an aldehyde function in their open-chain forms makes aldoses reactive toward nucleophilic addition of hydrogen cyanide. Addition yields a mixture of diastereomeric cyanohydrins.



L-Arabinose L-Mannononitrile L-Gluconononitrile

The reaction is used for the chain extension of aldoses in the synthesis of new or unusual sugars. In this case, the starting material, L-arabinose, is an abundant natural product and possesses the correct configurations at its three stereogenic centers for elaboration to the relatively rare L-enantiomers of glucose and mannose. After cyanohydrin formation, the cyano groups are converted to aldehyde functions by hydrogenation in aqueous solution. Under these conditions, —C≡N is reduced to —CH═NH and hydrolyzes rapidly to —CH═O. Use of a poisoned palladium-on-barium sulfate catalyst prevents further reduction to the alditols.



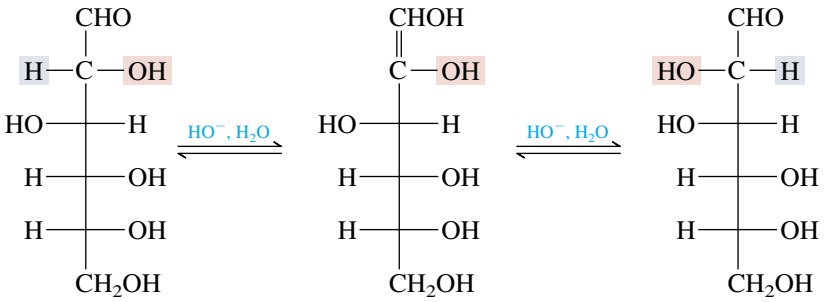
L-Mannononitrile L-Mannose (56% yield from L-arabinose)

(Similarly, L-gluconononitrile has been reduced to L-glucose; its yield was 26% from L-arabinose.)

An older version of this sequence is called the **Kiliani-Fischer synthesis.** It, too, proceeds through a cyanohydrin, but it uses a less efficient method for converting the cyano group to the required aldehyde.

25.21 EPIMERIZATION, ISOMERIZATION, AND RETRO-ALDOL CLEAVAGE REACTIONS OF CARBOHYDRATES

Carbohydrates undergo a number of isomerization and degradation reactions under both laboratory and physiological conditions. For example, a mixture of glucose, fructose, and mannose results when any one of them is treated with aqueous base. This reaction can be understood by examining the consequences of enolization of glucose:

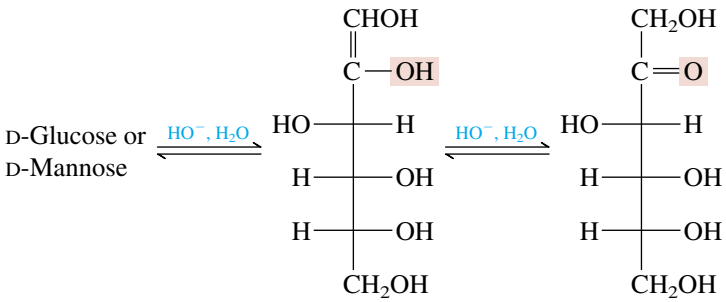


D-Glucose (*R* configuration at C-2) | Enediol (C-2 not a stereogenic center) | D-Mannose (*S* configuration at C-2)

Because the configuration at C-2 is lost on enolization, the enediol intermediate can revert either to D-glucose or to D-mannose. Two stereoisomers that have multiple stereogenic centers but differ in configuration at only one of them are referred to as **epimers.** Glucose and mannose are epimeric at C-2. Under these conditions epimerization occurs only at C-2 because it alone is α to the carbonyl group.

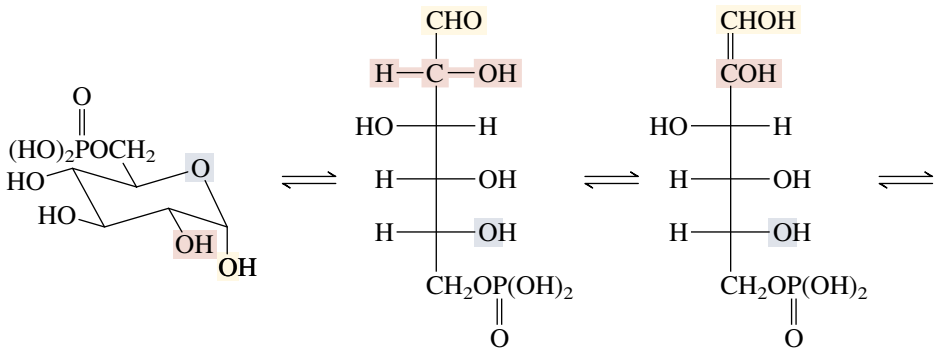
There is another reaction available to the enediol intermediate. Proton transfer from water to C-1 converts the enediol not to an aldose but to the ketose D-fructose:

See the boxed essay "How Sweet It Is!" for more on this process.



Enediol | D-Fructose

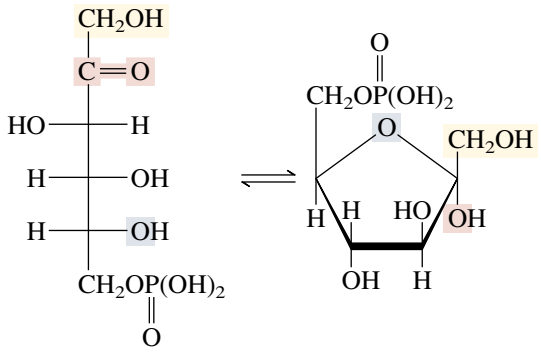
The isomerization of D-glucose to D-fructose by way of an enediol intermediate is an important step in **glycolysis,** a complex process (11 steps) by which an organism converts glucose to chemical energy. The substrate is not glucose itself but its 6-phosphate ester. The enzyme that catalyzes the isomerization is called *phosphoglucose isomerase.*



D-Glucose 6-phosphate

Open-chain form of D-glucose 6-phosphate

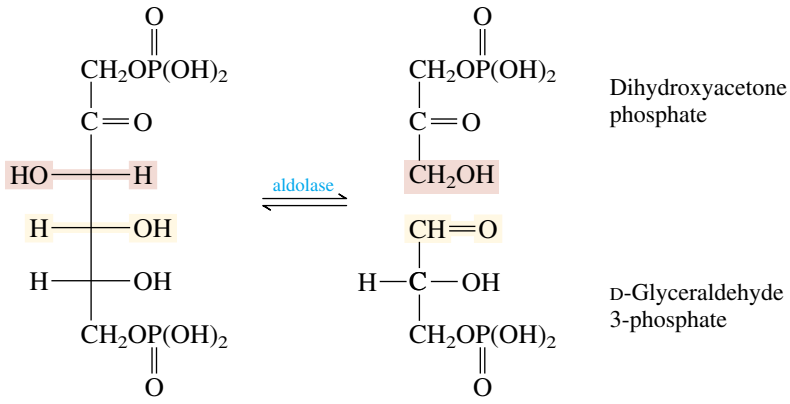
Enediol



Open-chain form of D-Fructose 6-phosphate

D-Fructose 6-phosphate

Following its formation, D-fructose 6-phosphate is converted to its corresponding 1,6-phosphate diester, which is then cleaved to two 3-carbon fragments under the influence of the enzyme *aldolase:*



D-Fructose 1,6-diphosphate

Dihydroxyacetone phosphate

D-Glyceraldehyde 3-phosphate

This cleavage is a *retro-aldol* reaction. It is the reverse of the process by which D-fructose 1,6-diphosphate would be formed by addition of the enolate of dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate. The enzyme aldolase catalyzes both the

aldol condensation of the two components and, in glycolysis, the retro-aldol cleavage of D-fructose 1,6-diphosphate.

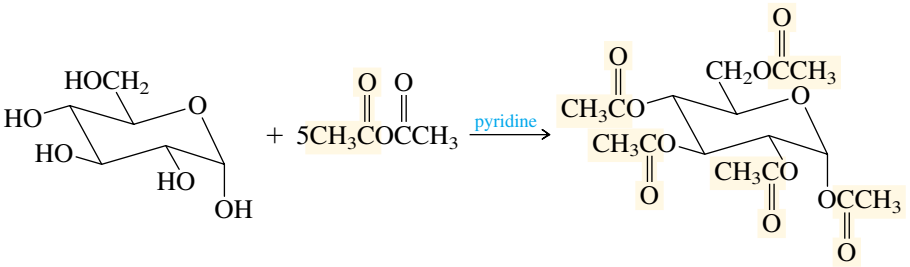
Further steps in glycolysis use the D-glyceraldehyde 3-phosphate formed in the aldolase-catalyzed cleavage reaction as a substrate. Its coproduct, dihydroxyacetone phosphate, is not wasted, however. The enzyme *triose phosphate isomerase* converts dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate, which enters the glycolysis pathway for further transformations.

PROBLEM 25.16 Suggest a reasonable structure for the intermediate in the conversion of dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate.

Cleavage reactions of carbohydrates also occur on treatment with aqueous base for prolonged periods as a consequence of base-catalyzed retro-aldol reactions. As pointed out in Section 18.9, aldol addition is a reversible process, and β-hydroxy carbonyl compounds can be cleaved to an enolate and either an aldehyde or a ketone.

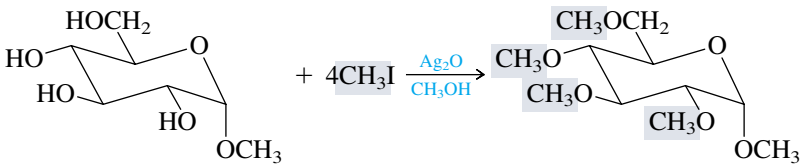
25.22 ACYLATION AND ALKYLATION OF HYDROXYL GROUPS IN CARBOHYDRATES

The alcohol groups of carbohydrates undergo chemical reactions typical of hydroxyl functions. They are converted to esters by reaction with acyl chlorides and carboxylic acid anhydrides.



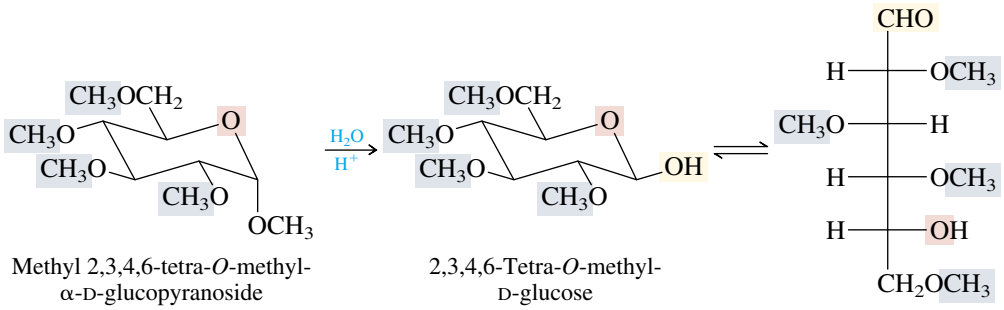
α-D-Glucopyranose | Acetic anhydride | 1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose (88%)

Ethers are formed under conditions of the Williamson ether synthesis. Methyl ethers of carbohydrates are efficiently prepared by alkylation with methyl iodide in the presence of silver oxide.



Methyl α-D-glucopyranoside | Methyl iodide | Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (97%)

This reaction has been used in an imaginative way to determine the ring size of glycosides. Once all the free hydroxyl groups of a glycoside have been methylated, the glycoside is subjected to acid-catalyzed hydrolysis. Only the anomeric methoxy group is hydrolyzed under these conditions—another example of the ease of carbocation formation at the anomeric position.



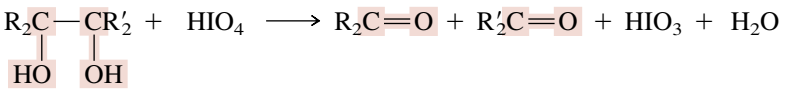
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside

2,3,4,6-Tetra-*O*-methyl-D-glucose

Notice that all the hydroxyl groups in the free sugar except C-5 are methylated. Carbon-5 is not methylated, because it was originally the site of the ring oxygen in the methyl glycoside. Once the position of the hydroxyl group in the free sugar has been determined, either by spectroscopy or by converting the sugar to a known compound, the ring size stands revealed.

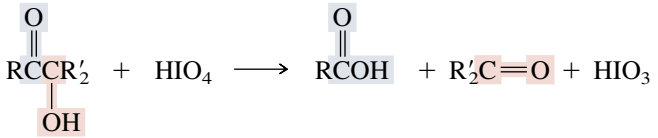
25.23 PERIODIC ACID OXIDATION OF CARBOHYDRATES

Periodic acid oxidation (Section 15.12) finds extensive use as an analytical method in carbohydrate chemistry. Structural information is obtained by measuring the number of equivalents of periodic acid that react with a given compound and by identifying the reaction products. A vicinal diol consumes one equivalent of periodate and is cleaved to two carbonyl compounds:



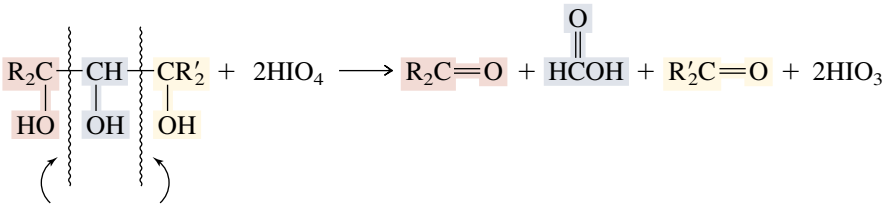
Vicinal diol | Periodic acid | Two carbonyl compounds | Iodic acid | Water

α-Hydroxy carbonyl compounds are cleaved to a carboxylic acid and a carbonyl compound:



α-Hydroxy carbonyl compound | Periodic acid | Carboxylic acid | Carbonyl compound | Iodic acid

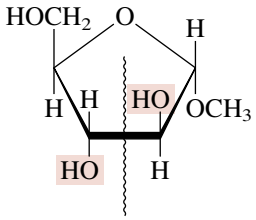
When three contiguous carbons bear hydroxyl groups, two moles of periodate are consumed per mole of carbohydrate and the central carbon is oxidized to a molecule of formic acid:



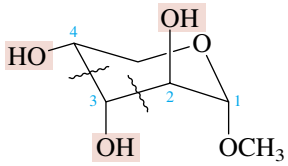
Points at which cleavage occurs | Periodic acid | Carbonyl compound | Formic acid | Carbonyl compound | Iodic acid

Ether and acetal functions are not affected by the reagent.

The use of periodic acid oxidation in structure determination can be illustrated by a case in which a previously unknown methyl glycoside was obtained by the reaction of D-arabinose with methanol and hydrogen chloride. The size of the ring was identified as five-membered because only one mole of periodic acid was consumed per mole of glycoside and no formic acid was produced. Were the ring six-membered, two moles of periodic acid would be required per mole of glycoside and one mole of formic acid would be produced.



Only one site for periodic acid cleavage in methyl α-D-arabinofuranoside

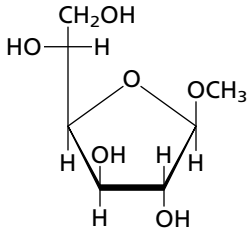


Two sites of periodic acid cleavage in methyl α-D-arabinopyranoside, C-3 lost as formic acid

PROBLEM 25.17 Give the products of periodic acid oxidation of each of the following. How many moles of reagent will be consumed per mole of substrate in each case?

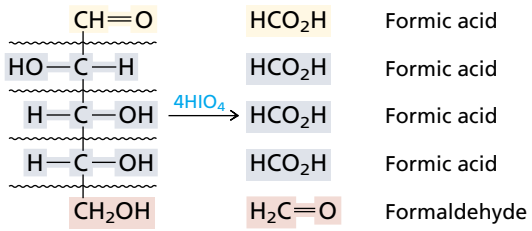
(a) D-Arabinose
(b) D-Ribose
(c) Methyl β-D-glucopyranoside

(d)



SAMPLE SOLUTION (a) The α-hydroxy aldehyde unit at the end of the sugar chain is cleaved, as well as all the vicinal diol functions. Four moles of periodic acid are required per mole of D-arabinose. Four moles of formic acid and one mole of formaldehyde are produced.

D-Arabinose, showing points of cleavage by periodic acid; each cleavage requires one equivalent of HIO_4.



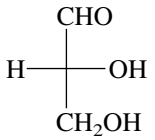
25.24 SUMMARY

Section 25.1 Carbohydrates are marvelous molecules! In most of them, every carbon bears a functional group, and the nature of the functional groups changes as the molecule interconverts between open-chain and cyclic hemiacetal

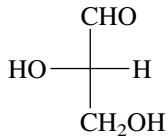
forms. Any approach to understanding carbohydrates must begin with structure.

Carbohydrates are polyhydroxy aldehydes and ketones. Those derived from aldehydes are classified as **aldoses;** those derived from ketones are **ketoses.**

Section 25.2 Fischer projections and D–L notation are commonly used to describe carbohydrate stereochemistry. The standards are the enantiomers of glyceraldehyde.



D-(+)-Glyceraldehyde



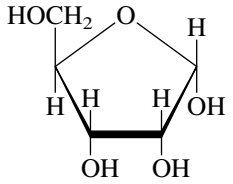
L-(−)-Glyceraldehyde

Section 25.3 Aldotetroses have two stereogenic centers, so four stereoisomers are possible. They are assigned to the D or the L series according to whether the configuration at their highest numbered stereogenic center is analogous to D- or L-glyceraldehyde, respectively. Both hydroxyl groups are on the same side of the Fischer projection in erythrose, but on opposite sides in threose. The Fischer projections of D-erythrose and D-threose are shown in Figure 25.2.

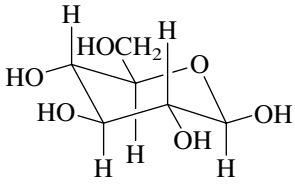
Section 25.4 Of the eight stereoisomeric aldopentoses, Figure 25.2 shows the Fischer projections of the D-enantiomers (D-ribose, D-arabinose, D-xylose, and D-lyxose). Likewise, Figure 25.2 gives the Fischer projections of the eight D-aldohexoses.

Section 25.5 The aldohexoses are allose, altrose, glucose, mannose, gulose, idose, galactose, and talose. The mnemonic "All altruists gladly make gum in gallon tanks" is helpful in writing the correct Fischer projection for each one.

Sections 25.6–25.7 Most carbohydrates exist as cyclic hemiacetals. Cyclic acetals with five-membered rings are called **furanose** forms; those with six-membered rings are called **pyranose** forms.



α-D-Ribofuranose



β-D-Glucopyranose

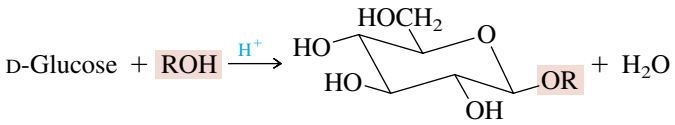
The **anomeric carbon** in a cyclic acetal is the one attached to *two* oxygens. It is the carbon that corresponds to the carbonyl carbon in the open-chain form. The symbols α and β refer to the configuration at the anomeric carbon.

Section 25.8 A particular carbohydrate can interconvert between furanose and pyranose forms and between the α and β configuration of each form. The change from one form to an equilibrium mixture of all the possible hemiacetals causes a change in optical rotation called **mutarotation.**

Section 25.9 Ketoses are characterized by the ending *-ulose* in their name. Most naturally occurring ketoses have their carbonyl group located at C-2. Like aldoses, ketoses cyclize to hemiacetals and exist as furanose or pyranose forms.

Sections 25.10–25.12 Structurally modified carbohydrates include **deoxy sugars, amino sugars,** and **branched-chain carbohydrates.**

Section 25.13 Glycosides are acetals, compounds in which the anomeric hydroxyl group has been replaced by an alkoxy group. Glycosides are easily prepared by allowing a carbohydrate and an alcohol to stand in the presence of an acid catalyst.



A glycoside

Sections 25.14–25.15 **Disaccharides** are carbohydrates in which two monosaccharides are joined by a glycoside bond. **Polysaccharides** have many monosaccharide units connected through glycosidic linkages. Complete hydrolysis of disaccharides and polysaccharides cleaves the glycoside bonds, yielding the free monosaccharide components.

Section 25.16 Carbohydrates and proteins that are connected by a chemical bond are called **glycoproteins** and often occur on the surfaces of cells. They play an important role in the recognition events connected with the immune response.

Sections 25.17–25.24 Carbohydrates undergo chemical reactions characteristic of aldehydes and ketones, alcohols, diols, and other classes of compounds, depending on their structure. A review of the reactions described in this chapter is presented in Table 25.2. Although some of the reactions have synthetic value, many of them are used in analysis and structure determination.

PROBLEMS

25.18 Refer to the Fischer projection of D-(+)-xylose in Figure 25.2 (Section 25.4) and give structural formulas for

(a) (−)-Xylose (Fischer projection)

(b) D-Xylitol

(c) β-D-Xylopyranose

(d) α-L-Xylofuranose

(e) Methyl α-L-xylofuranoside

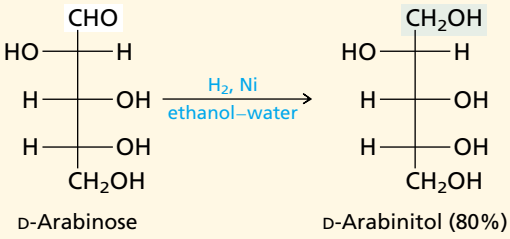
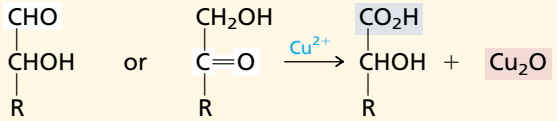
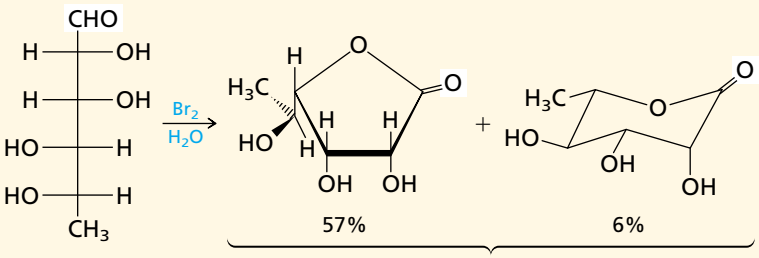
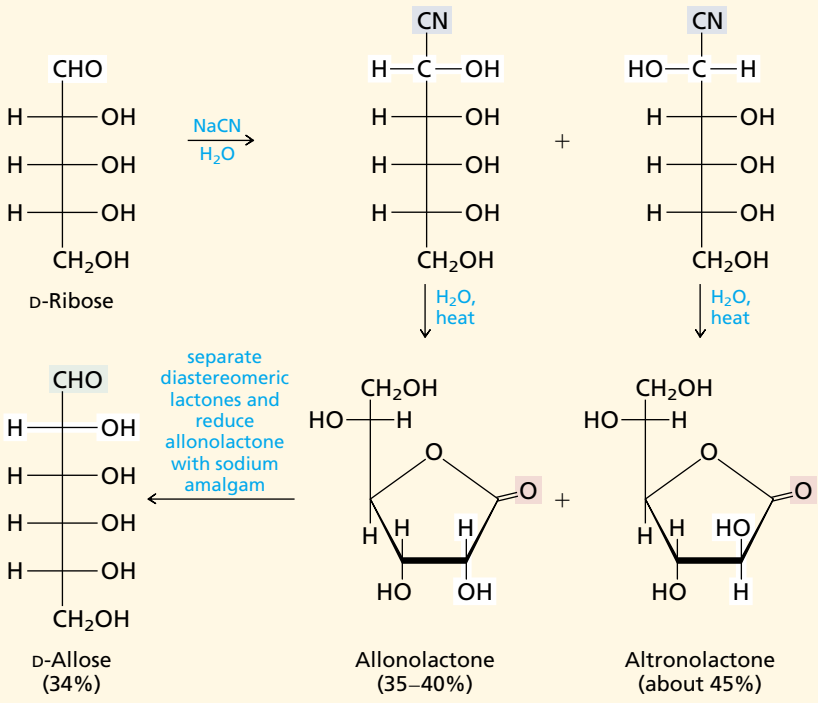
(f) D-Xylonic acid (open-chain Fischer projection)

(g) δ-Lactone of D-xylonic acid

(h) γ-Lactone of D-xylonic acid

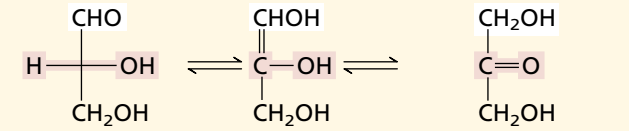
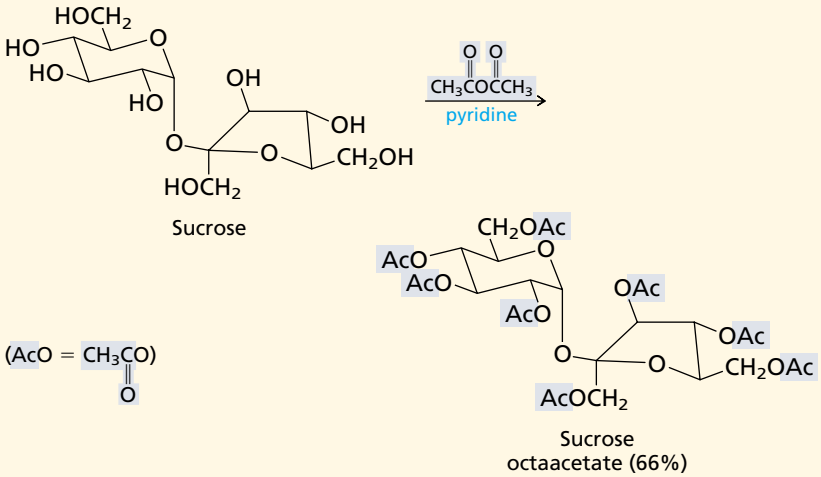
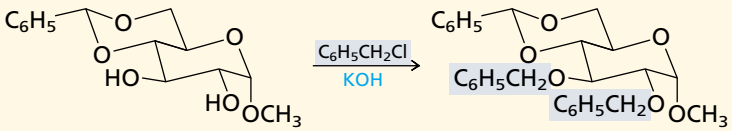
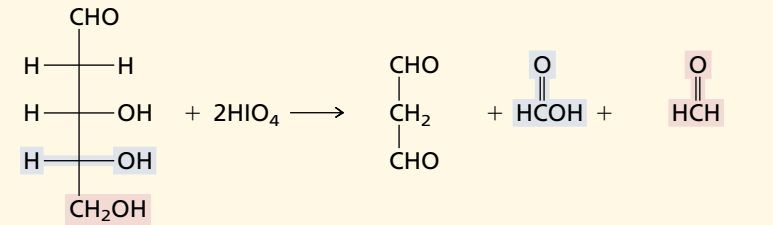
(i) D-Xylaric acid (open-chain Fischer projection)

TABLE 25.2 Summary of Reactions of Carbohydrates

Reaction (section) and comments	Example
Transformations of the carbonyl group	
Reduction (Section 25.18) The carbonyl group of aldoses and ketoses is reduced by sodium borohydride or by catalytic hydrogenation. The products are called *alditols*.	 D-Arabinose D-Arabinitol (80%)
Oxidation with Benedict's reagent (Section 25.19) Sugars that contain a free hemiacetal function are called reducing sugars. They react with copper(II) sulfate in a sodium citrate/sodium carbonate buffer (Benedict's reagent) to form a red precipitate of copper(I) oxide. Used as a qualitative test for reducing sugars.	 Aldose Ketose Aldonic acid Copper(I) oxide
Oxidation with bromine (Section 25.19) When a preparative method for an aldonic acid is required, bromine oxidation is used. The aldonic acid is formed as its lactone. More properly described as a reaction of the anomeric hydroxyl group than of a free aldehyde.	 L-Rhamnose L-Rhamnonolactone
Chain extension by way of cyanohydrin formation (Section 25.20) The Kiliani–Fischer synthesis proceeds by nucleophilic addition of HCN to an aldose, followed by conversion of the cyano group to an aldehyde. A mixture of stereoisomers results; the two aldoses are epimeric at C-2. Section 25.20 describes the modern version of the Kiliani–Fischer synthesis. The example at the right illustrates the classical version.	

(Continued)

TABLE 25.2 Summary of Reactions of Carbohydrates *(Continued)*

Reaction (section) and comments	Example
Enediol formation (Section 25.21) Enolization of an aldose or a ketose gives an enediol. Enediols can revert to aldoses or ketoses with loss of stereochemical integrity at the α-carbon atom.	 D-Glyceraldehyde ⇌ Enediol ⇌ 1,3-Dihydroxyacetone
Reactions of the hydroxyl group	
Acylation (Section 25.22) Esterification of the available hydroxyl groups occurs when carbohydrates are treated with acylating agents.	 Sucrose → Sucrose octaacetate (66%)
Alkylation (Section 25.22) Alkyl halides react with carbohydrates to form ethers at the available hydroxyl groups. An application of the Williamson ether synthesis to carbohydrates.	 Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside → Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (92%)
Periodic acid oxidation (Section 25.23) Vicinal diol and α-hydroxy carbonyl functions in carbohydrates are cleaved by periodic acid. Used analytically as a tool for structure determination.	 2-Deoxy-D-ribose → Propanedial + Formic acid + Formaldehyde

25.19 From among the carbohydrates shown in Figure 25.2, choose the D-aldohexoses that yield

(a) An optically inactive product on reduction with sodium borohydride

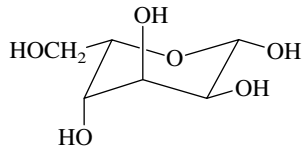
(b) An optically inactive product on oxidation with bromine

(c) An optically inactive product on oxidation with nitric acid

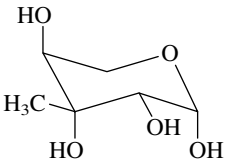
(d) The same enediol

25.20 Write the Fischer projection of the open-chain form of each of the following:

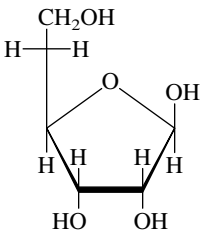
(a)



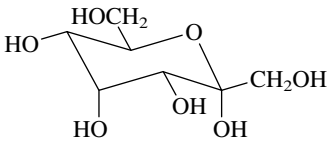
(c)



(b)



(d)



25.21 What are the *R,S* configurations of the three stereogenic centers in D-ribose? (A molecular model will be helpful here.)

25.22 From among the carbohydrates shown in Problem 25.20 choose the one(s) that

(a) Belong to the L series

(b) Are deoxy sugars

(c) Are branched-chain sugars

(d) Are ketoses

(e) Are furanose forms

(f) Have the α configuration at their anomeric carbon

25.23 How many pentuloses are possible? Write their Fischer projections.

25.24 The Fischer projection of the branched-chain carbohydrate D-apiose has been presented in Section 25.12.

(a) How many stereogenic centers are in the open-chain form of D-apiose?

(b) Does D-apiose form an optically active alditol on reduction?

(c) How many stereogenic centers are in the furanose forms of D-apiose?

(d) How many stereoisomeric furanose forms of D-apiose are possible? Write their Haworth formulas.

25.25 Treatment of D-mannose with methanol in the presence of an acid catalyst yields four isomeric products having the molecular formula $C_7H_{14}O_6$. What are these four products?

25.26 Maltose and cellobiose (Section 25.14) are examples of disaccharides derived from D-glucopyranosyl units.

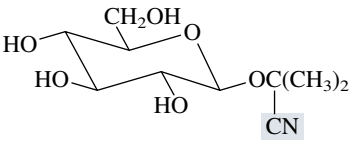
(a) How many other disaccharides are possible that meet this structural requirement?

(b) How many of these are reducing sugars?

25.27 Gentiobiose has the molecular formula $C_{12}H_{22}O_{11}$ and has been isolated from gentian root and by hydrolysis of amygdalin. Gentiobiose exists in two different forms, one melting at 86°C and the other at 190°C. The lower melting form is dextrorotatory ($[\alpha]_D^{22}$ +16°), the higher melting one is levorotatory ($[\alpha]_D^{22}$ −6°). The rotation of an aqueous solution of either form, however, gradually changes until a final value of $[\alpha]_D^{22}$ +9.6° is observed. Hydrolysis of gentiobiose is efficiently catalyzed by emulsin and produces two moles of D-glucose per mole of gentiobiose. Gentiobiose forms an octamethyl ether, which on hydrolysis in dilute acid yields 2,3,4,6-tetra-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-D-glucose. What is the structure of gentiobiose?

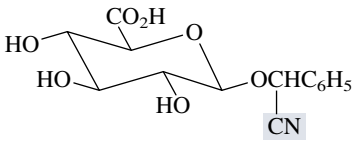
25.28 *Cyanogenic glycosides* are potentially toxic because they liberate hydrogen cyanide on enzyme-catalyzed or acidic hydrolysis. Give a mechanistic explanation for this behavior for the specific cases of

(a)



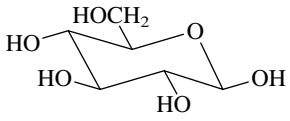
Linamarin

(b)

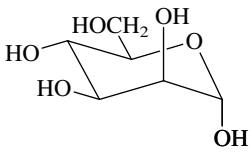


Laetrile

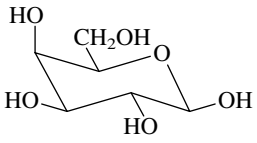
25.29 The following are the more stable anomers of the pyranose forms of D-glucose, D-mannose, and D-galactose:



β-D-Glucopyranose
(64% at equilibrium)



α-D-Mannopyranose
(68% at equilibrium)

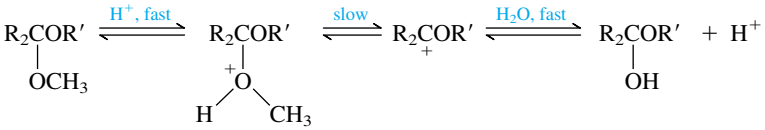


β-D-Galactopyranose
(64% at equilibrium)

On the basis of these empirical observations and your own knowledge of steric effects in six-membered rings, predict the preferred form (α- or β-pyranose) at equilibrium in aqueous solution for each of the following:

(a) D-Gulose
(b) D-Talose
(c) D-Xylose
(d) D-Lyxose

25.30 Basing your answers on the general mechanism for the first stage of acid-catalyzed acetal hydrolysis

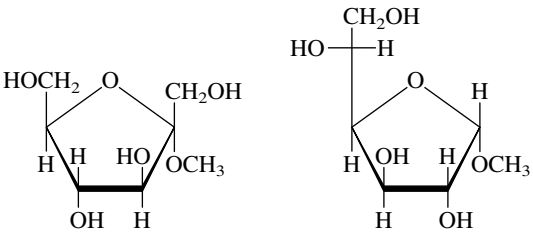


Acetal

Hemiacetal

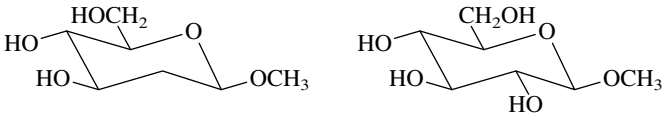
suggest reasonable explanations for the following observations:

(a) Methyl α-D-fructofuranoside (compound A) undergoes acid-catalyzed hydrolysis some 10^5 times faster than methyl α-D-glucofuranoside (compound B).



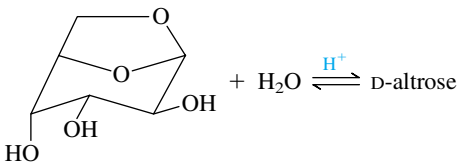
Compound A Compound B

(b) The β-methyl glucopyranoside of 2-deoxy-D-glucose (compound C) undergoes hydrolysis several thousand times faster than that of D-glucose (compound D).



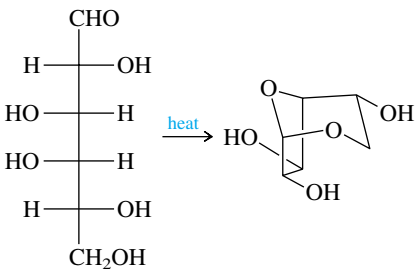
Compound C Compound D

25.31 D-Altrosan is converted to D-altrose by dilute aqueous acid. Suggest a reasonable mechanism for this reaction.



D-Altrosan

25.32 When D-galactose was heated at 165°C, a small amount of compound A was isolated:



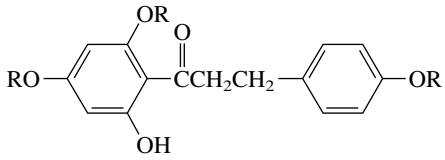
D-Galactose Compound A

The structure of compound A was established, in part, by converting it to known compounds. Treatment of A with excess methyl iodide in the presence of silver oxide, followed by hydrolysis with dilute hydrochloric acid, gave a trimethyl ether of D-galactose. Comparing this trimethyl ether with known trimethyl ethers of D-galactose allowed the structure of compound A to be deduced.

How many trimethyl ethers of D-galactose are there? Which one is the same as the product derived from compound A?

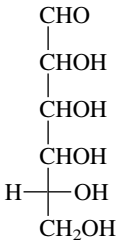
25.33 Phlorizin is obtained from the root bark of apple, pear, cherry, and plum trees. It has the molecular formula $C_{21}H_{24}O_{10}$ and yields a compound A and D-glucose on hydrolysis in the presence of emulsin. When phlorizin is treated with excess methyl iodide in the presence of potassium

carbonate and then subjected to acid-catalyzed hydrolysis, a compound B is obtained. Deduce the structure of phlorizin from this information.



Compound A: R = H
Compound B: R = CH_3

25.34 Emil Fischer's determination of the structure of glucose was carried out as the nineteenth century ended and the twentieth began. The structure of no other sugar was known at that time, and none of the spectroscopic techniques that aid organic analysis were then available. All Fischer had was information from chemical transformations, polarimetry, and his own intellect. Fischer realized that (+)-glucose could be represented by 16 possible stereostructures. By arbitrarily assigning a particular configuration to the stereogenic center at C-5, the configurations of C-2, C-3, and C-4 could be determined relative to it. This reduces the number of structural possibilities to eight. Thus, he started with a structural representation shown as follows, in which C-5 of (+)-glucose has what is now known as the D configuration.



Eventually, Fischer's arbitrary assumption proved to be correct, and the structure he proposed for (+)-glucose is correct in an absolute as well as a relative sense. The following exercise uses information available to Fischer and leads you through a reasoning process similar to that employed in his determination of the structure of (+)-glucose. See if you can work out the configuration of (+)-glucose from the information provided, assuming the configuration of C-5 as shown here.

1. Chain extension of the aldopentose (−)-arabinose by way of the derived cyanohydrin gave a mixture of (+)-glucose and (+)-mannose.
2. Oxidation of (−)-arabinose with warm nitric acid gave an optically active aldaric acid.
3. Both (+)-glucose and (+)-mannose were oxidized to optically active aldaric acids with nitric acid.
4. There is another sugar, (+)-gulose, that gives the same aldaric acid on oxidation as does (+)-glucose.