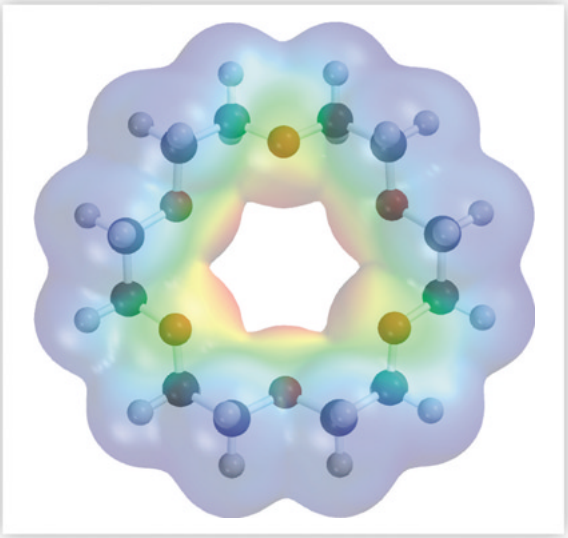


CHAPTER 16

ETHERS, EPOXIDES, AND SULFIDES

In contrast to alcohols with their rich chemical reactivity, **ethers** (compounds containing a C—O—C unit) undergo relatively few chemical reactions. As you saw when we discussed Grignard reagents in Chapter 14 and lithium aluminum hydride reductions in Chapter 15, this lack of reactivity of ethers makes them valuable as solvents in a number of synthetically important transformations. In the present chapter you will learn of the conditions in which an ether linkage acts as a functional group, as well as the methods by which ethers are prepared.

Unlike most ethers, **epoxides** (compounds in which the C—O—C unit forms a three-membered ring) are very reactive substances. The principles of nucleophilic substitution are important in understanding the preparation and properties of epoxides.

Sulfides (RSR′) are the sulfur analogs of ethers. Just as in the preceding chapter, where we saw that the properties of thiols (RSH) are different from those of alcohols, we will explore differences between sulfides and ethers in this chapter.

16.1 NOMENCLATURE OF ETHERS, EPOXIDES, AND SULFIDES

Ethers are named, in substitutive IUPAC nomenclature, as *alkoxy* derivatives of alkanes. Functional class IUPAC names of ethers are derived by listing the two alkyl groups in the general structure ROR′ in alphabetical order as separate words, and then adding the word "ether" at the end. When both alkyl groups are the same, the prefix *di-* precedes the name of the alkyl group.

	$CH_3CH_2OCH_2CH_3$	$CH_3CH_2OCH_3$	$CH_3CH_2OCH_2CH_2CH_2Cl$
Substitutive IUPAC name:	Ethoxyethane	Methoxyethane	1-Chloro-3-ethoxypropane
Functional class IUPAC name:	Diethyl ether	Ethyl methyl ether	3-Chloropropyl ethyl ether

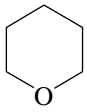
Ethers are described as **symmetrical** or **unsymmetrical** depending on whether the two groups bonded to oxygen are the same or different. Unsymmetrical ethers are also called **mixed ethers.** Diethyl ether is a symmetrical ether; ethyl methyl ether is an unsymmetrical ether.

Cyclic ethers have their oxygen as part of a ring—they are *heterocyclic compounds* (Section 3.15). Several have specific IUPAC names.

Oxirane
(Ethylene oxide)

Oxetane

Oxolane
(Tetrahydrofuran)



Oxane
(Tetrahydropyran)

Recall from Section 6.18 that epoxides may be named as *-epoxy* derivatives of alkanes in substitutive IUPAC nomenclature.

In each case the ring is numbered starting at the oxygen. The IUPAC rules also permit oxirane (without substituents) to be called *ethylene oxide. Tetrahydrofuran* and *tetrahydropyran* are acceptable synonyms for oxolane and oxane, respectively.

PROBLEM 16.1 Each of the following ethers has been shown to be or is suspected to be a *mutagen,* which means it can induce mutations in test cells. Write the structure of each of these ethers.

(a) Chloromethyl methyl ether

(b) 2-(Chloromethyl)oxirane (also known as epichlorohydrin)

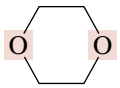
(c) 3,4-Epoxy-1-butene (2-vinyloxirane)

SAMPLE SOLUTION (a) Chloromethyl methyl ether has a chloromethyl group ($ClCH_2$—) and a methyl group (CH_3—) attached to oxygen. Its structure is $ClCH_2OCH_3$.

Many substances have more than one ether linkage. Two such compounds, often used as solvents, are the *diethers* 1,2-dimethoxyethane and 1,4-dioxane. Diglyme, also a commonly used solvent, is a *triether.*

$CH_3OCH_2CH_2OCH_3$

1,2-Dimethoxyethane



1,4-Dioxane

$CH_3OCH_2CH_2OCH_2CH_2OCH_3$

Diethylene glycol dimethyl ether
(diglyme)

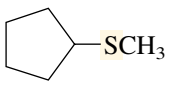
Molecules that contain several ether functions are referred to as *polyethers.* Polyethers have received much recent attention, and some examples of them will appear in Section 16.4.

Sulfides are sometimes informally referred to as *thioethers,* but this term is not part of systematic IUPAC nomenclature.

The sulfur analogs (RS—) of alkoxy groups are called *alkylthio* groups. The first two of the following examples illustrate the use of alkylthio prefixes in substitutive nomenclature of sulfides. Functional class IUPAC names of sulfides are derived in exactly the same way as those of ethers but end in the word "sulfide." Sulfur heterocycles have names analogous to their oxygen relatives, except that *ox-* is replaced by *thi-*. Thus the sulfur heterocycles containing three-, four-, five-, and six-membered rings are named *thiirane, thietane, thiolane,* and *thiane,* respectively.

$CH_3CH_2SCH_2CH_3$

Ethylthioethane
Diethyl sulfide

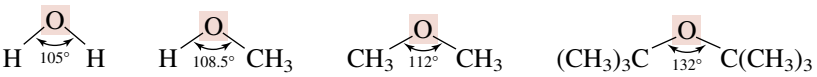


(Methylthio)cyclopentane
Cyclopentyl methyl sulfide

Thiirane

16.2 STRUCTURE AND BONDING IN ETHERS AND EPOXIDES

Bonding in ethers is readily understood by comparing ethers with water and alcohols. Van der Waals strain involving alkyl groups causes the bond angle at oxygen to be larger in ethers than alcohols, and larger in alcohols than in water. An extreme example is di-*tert*-butyl ether, where steric hindrance between the *tert*-butyl groups is responsible for a dramatic increase in the C—O—C bond angle.

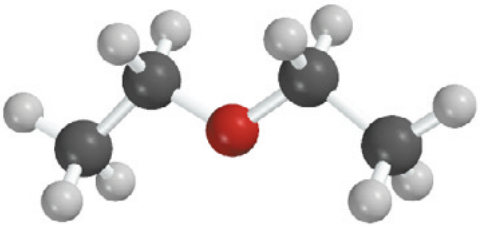


Water Methanol Dimethyl ether Di-*tert*-butyl ether

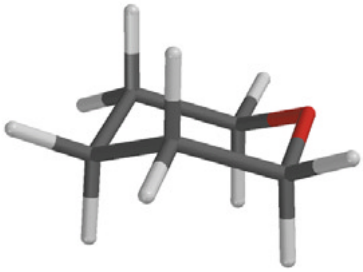
Use *Learning By Modeling* to make models of water, methanol, dimethyl ether, and di-*tert*-butyl ether. Minimize their geometries, and examine what happens to the C—O—C bond angle. Compare the C—O bond distances in dimethyl ether and di-*tert*-butyl ether.

Typical carbon–oxygen bond distances in ethers are similar to those of alcohols (≈142 pm) and are shorter than carbon–carbon bond distances in alkanes (≈153 pm).

An ether oxygen affects the conformation of a molecule in much the same way that a CH_2 unit does. The most stable conformation of diethyl ether is the all-staggered anti conformation. Tetrahydropyran is most stable in the chair conformation—a fact that has an important bearing on the structures of many carbohydrates.

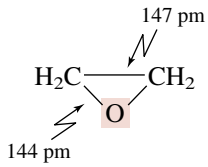


Anti conformation of diethyl ether



Chair conformation of tetrahydropyran

Incorporating an oxygen atom into a three-membered ring requires its bond angle to be seriously distorted from the normal tetrahedral value. In ethylene oxide, for example, the bond angle at oxygen is 61.5°.



C—O—C angle 61.5°

C—C—O angle 59.2°

Thus epoxides, like cyclopropanes, are strained. They tend to undergo reactions that open the three-membered ring by cleaving one of the carbon–oxygen bonds.

PROBLEM 16.2 The heats of combustion of 1,2-epoxybutane (2-ethyloxirane) and tetrahydrofuran have been measured: one is 2499 kJ/mol (597.8 kcal/mol); the other is 2546 kJ/mol (609.1 kcal/mol). Match the heats of combustion with the respective compounds.

Ethers, like water and alcohols, are polar. Diethyl ether, for example, has a dipole moment of 1.2 D. Cyclic ethers have larger dipole moments; ethylene oxide and tetrahydrofuran have dipole moments in the 1.7- to 1.8-D range—about the same as that of water.

16.3 PHYSICAL PROPERTIES OF ETHERS

It is instructive to compare the physical properties of ethers with alkanes and alcohols. With respect to boiling point, ethers resemble alkanes more than alcohols. With respect to solubility in water the reverse is true; ethers resemble alcohols more than alkanes. Why?

	$CH_3CH_2OCH_2CH_3$	$CH_3CH_2CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2OH$
	Diethyl ether	Pentane	1-Butanol
Boiling point:	35°C	36°C	117°C
Solubility in water:	7.5 g/100 mL	Insoluble	9 g/100 mL

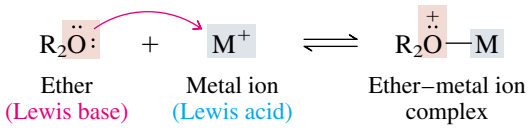
In general, the boiling points of alcohols are unusually high because of hydrogen bonding (Section 4.5). Attractive forces in the liquid phases of ethers and alkanes, which lack —OH groups and cannot form intermolecular hydrogen bonds, are much weaker, and their boiling points lower.

As shown in Figure 16.1, however, the presence of an oxygen atom permits ethers to participate in hydrogen bonds to water molecules. These attractive forces cause ethers to dissolve in water to approximately the same extent as comparably constituted alcohols. Alkanes cannot engage in hydrogen bonding to water.

PROBLEM 16.3 Ethers tend to dissolve in alcohols and vice versa. Represent the hydrogen-bonding interaction between an alcohol molecule and an ether molecule.

16.4 CROWN ETHERS

Their polar carbon–oxygen bonds and the presence of unshared electron pairs at oxygen contribute to the ability of ethers to form Lewis acid-Lewis base complexes with metal ions.



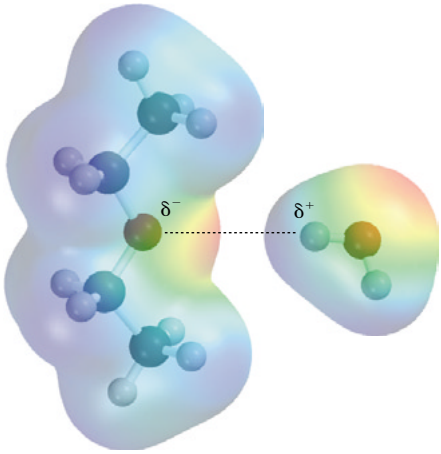
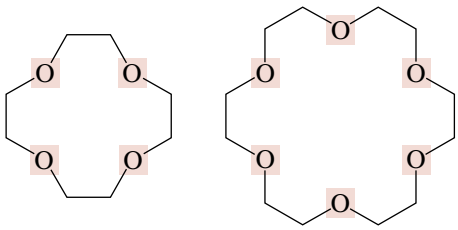


FIGURE 16.1 Hydrogen bonding between diethyl ether and water. The dashed line represents the attractive force between the negatively polarized oxygen of diethyl ether and one of the positively polarized hydrogens of water. The electrostatic potential surfaces illustrate the complementary interaction between the electron-rich (*red*) region of diethyl ether and the electron-poor (*blue*) region of water.

The strength of this bonding depends on the kind of ether. Simple ethers form relatively weak complexes with metal ions. A major advance in the area came in 1967 when Charles J. Pedersen of Du Pont described the preparation and properties of a class of *polyethers* that form much more stable complexes with metal ions than do simple ethers.

Pedersen was a corecipient of the 1987 Nobel Prize in chemistry.

Pedersen prepared a series of *macrocyclic polyethers,* cyclic compounds containing four or more oxygens in a ring of 12 or more atoms. He called these compounds **crown ethers,** because their molecular models resemble crowns. Systematic nomenclature of crown ethers is somewhat cumbersome, and so Pedersen devised a shorthand description whereby the word "crown" is preceded by the total number of atoms in the ring and is followed by the number of oxygen atoms.

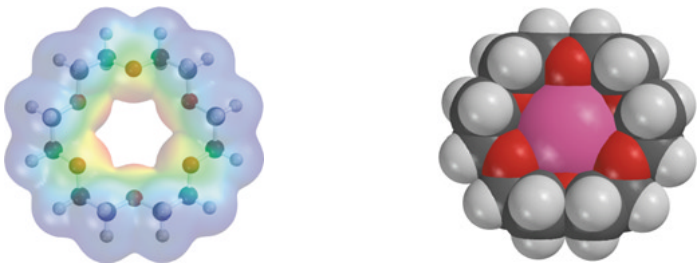


12-Crown-4 18-Crown-6

12-Crown-4 and 18-crown-6 are a cyclic tetramer and hexamer, respectively, of repeating $—OCH_2CH_2—$ units; they are polyethers based on ethylene glycol ($HOCH_2CH_2OH$) as the parent alcohol.

PROBLEM 16.4 What organic compound mentioned earlier in this chapter is a cyclic dimer of $—OCH_2CH_2—$ units?

The metal–ion complexing properties of crown ethers are clearly evident in their effects on the solubility and reactivity of ionic compounds in nonpolar media. Potassium fluoride (KF) is ionic and practically insoluble in benzene alone, but dissolves in it when 18-crown-6 is present. The reason for this has to do with the electron distribution of 18-crown-6 as shown in Figure 16.2*a.* The electrostatic potential surface consists of essentially two regions: an electron-rich interior associated with the oxygens and a hydrocarbon-like exterior associated with the CH_2 groups. When KF is added to a solution of 18-crown-6 in benzene, potassium ion (K^+) interacts with the oxygens of the crown ether to form a Lewis acid-Lewis base complex. As can be seen in the space-filling model of



(*a*) (*b*)

FIGURE 16.2 (*a*) An electrostatic potential map of 18-crown-6. The region of highest electron density (*red*) is associated with the negatively polarized oxygens and their lone pairs. The outer periphery of the crown ether (*blue*) is relatively nonpolar (hydrocarbon-like) and causes the molecule to be soluble in nonpolar solvents such as benzene. (*b*) A space-filling model of the complex formed between 18-crown-6 and potassium ion (K^+). K^+ fits into the cavity of the crown ether where it is bound by Lewis acid-Lewis base interaction with the oxygens.

POLYETHER ANTIBIOTICS

One way in which pharmaceutical companies search for new drugs is by growing colonies of microorganisms in nutrient broths and assaying the substances produced for their biological activity. This method has yielded thousands of antibiotic substances, of which hundreds have been developed into effective drugs. Antibiotics are, by definition, toxic (*anti* = "against"; *bios* = "life"), and the goal is to find substances that are more toxic to infectious organisms than to their human hosts.

Since 1950, a number of **polyether antibiotics** have been discovered using fermentation technology. They are characterized by the presence of several cyclic ether structural units, as illustrated for the case of *monensin* in Figure 16.3*a*. Monensin and other naturally occurring polyethers are similar to crown ethers in their ability to form stable complexes with metal ions. The structure of the monensin–sodium bromide complex is depicted in Figure 16.3*b*, where it can be seen that four ether oxygens and two hydroxyl groups surround a sodium ion. The alkyl groups are oriented toward the outside of the complex, and the polar oxygens and the metal ion are on the inside. The hydrocarbon-like surface of the complex permits it to carry its sodium ion through the hydrocarbon-like interior of a cell membrane. This disrupts the normal balance of sodium ions within the cell and interferes with important processes of cellular respiration. Small amounts of monensin are added to poultry feed in order to kill parasites that live in the intestines of chickens. Compounds such as monensin and the crown ethers that affect metal ion transport are referred to as **ionophores** ("ion carriers").

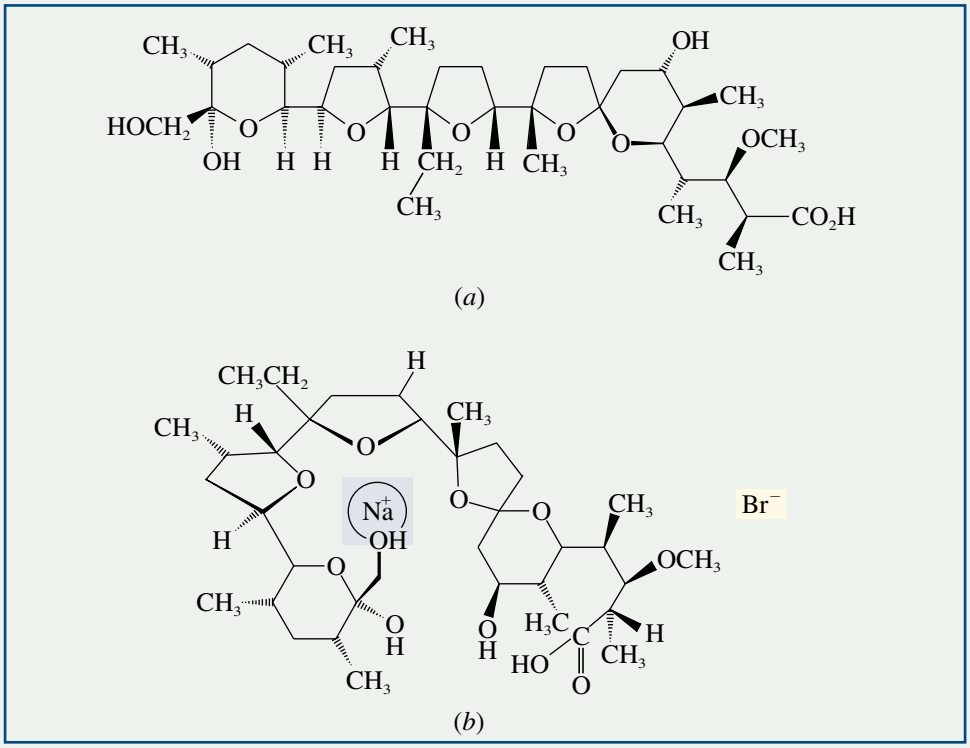
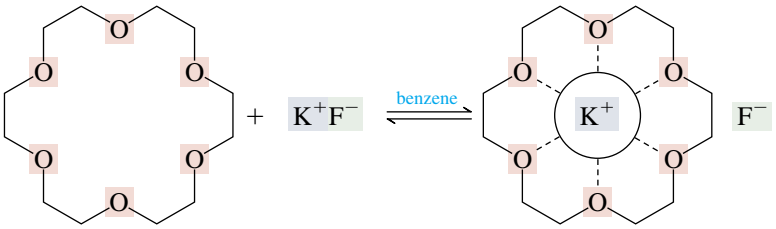


FIGURE 16.3 (*a*) The structure of monensin; (*b*) the structure of the monensin–sodium bromide complex showing coordination of sodium ion by oxygen atoms of monensin.

this complex (Figure 16.2*b*), K^+, with an ionic radius of 266 pm, fits comfortably within the 260–320 pm internal cavity of 18-crown-6. Nonpolar CH_2 groups dominate the outer surface of the complex, mask its polar interior, and permit the complex to dissolve in nonpolar solvents. Every K^+ that is carried into benzene brings a fluoride ion with it, resulting in a solution containing strongly complexed potassium ions and relatively unsolvated fluoride ions.



18-Crown-6 | Potassium fluoride (solid) | 18-Crown-6-potassium fluoride complex (in solution)

In media such as water and alcohols, fluoride ion is strongly solvated by hydrogen bonding and is neither very basic nor very nucleophilic. On the other hand, the poorly solvated, or "naked," fluoride ions that are present when potassium fluoride dissolves in benzene in the presence of a crown ether are better able to express their anionic reactivity. Thus, alkyl halides react with potassium fluoride in benzene containing 18-crown-6, thereby providing a method for the preparation of otherwise difficultly accessible alkyl fluorides.

$$\underset{\text{1-Bromooctane}}{CH_3(CH_2)_6CH_2Br} \xrightarrow[\text{18-crown-6}]{\text{KF, benzene, 90°C}} \underset{\text{1-Fluorooctane (92\%)}}{CH_3(CH_2)_6CH_2F}$$

The reaction proceeds in the direction indicated because a C—F bond is much stronger than a C—Br bond.

No reaction is observed when the process is carried out under comparable conditions but with the crown ether omitted.

Catalysis by crown ethers has been used to advantage to increase the rate of many organic reactions that involve anions as reactants. Just as important, though, is the increased understanding that studies of crown ether catalysis have brought to our knowledge of biological processes in which metal ions, including Na^+ and K^+, are transported through the nonpolar interiors of cell membranes.

16.5 PREPARATION OF ETHERS

Because they are widely used as solvents, many simple dialkyl ethers are commercially available. Diethyl ether and dibutyl ether, for example, are prepared by acid-catalyzed condensation of the corresponding alcohols, as described earlier in Section 15.7.

$$\underset{\text{1-Butanol}}{2CH_3CH_2CH_2CH_2OH} \xrightarrow[130°C]{H_2SO_4} \underset{\text{Dibutyl ether (60\%)}}{CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3} + \underset{\text{Water}}{H_2O}$$

In general, this method is limited to the preparation of symmetrical ethers in which both alkyl groups are primary. Isopropyl alcohol, however, is readily available at low cost and gives high enough yields of diisopropyl ether to justify making $(CH_3)_2CHOCH(CH_3)_2$ by this method on an industrial scale.

Approximately 4×10^9 lb of *tert*-butyl methyl ether is prepared in the United States each year by the acid-catalyzed addition of methanol to 2-methylpropene:

$$(CH_3)_2C{=}CH_2 + CH_3OH \xrightarrow{H^+} (CH_3)_3COCH_3$$

2-Methylpropene — Methanol — *tert*-Butyl methyl ether

tert-Butyl methyl ether is often referred to as MTBE, standing for the incorrect name "methyl *tert*-butyl ether." Remember, italicized prefixes are ignored when alphabetizing, and *tert*-butyl precedes methyl.

Small amounts of *tert*-butyl methyl ether are added to gasoline as an octane booster. The daily consumption of gasoline is so high that the demand for *tert*-butyl methyl ether exceeds our present capacity to produce it.

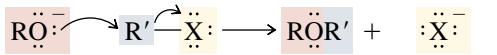
PROBLEM 16.5 Outline a reasonable mechanism for the formation of *tert*-butyl methyl ether according to the preceding equation.

The following section describes a versatile method for preparing either symmetrical or unsymmetrical ethers that is based on the principles of bimolecular nucleophilic substitution.

16.6 THE WILLIAMSON ETHER SYNTHESIS

The reaction is named for Alexander Williamson, a British chemist who used it to prepare diethyl ether in 1850.

A long-standing method for the preparation of ethers is the **Williamson ether synthesis.** Nucleophilic substitution of an alkyl halide by an alkoxide gives the carbon–oxygen bond of an ether:



Alkoxide ion — Alkyl halide — Ether — Halide ion

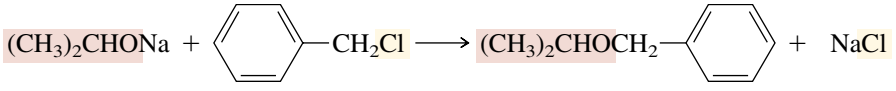
Preparation of ethers by the Williamson ether synthesis is most successful when the alkyl halide is one that is reactive toward S_N2 substitution. Methyl halides and primary alkyl halides are the best substrates.

$$CH_3CH_2CH_2CH_2ONa + CH_3CH_2I \longrightarrow CH_3CH_2CH_2CH_2OCH_2CH_3 + NaI$$

Sodium butoxide — Iodoethane — Butyl ethyl ether (71%) — Sodium iodide

PROBLEM 16.6 Write equations describing two different ways in which benzyl ethyl ether could be prepared by a Williamson ether synthesis.

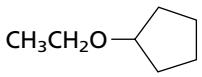
Secondary and tertiary alkyl halides are not suitable, because they tend to react with alkoxide bases by E2 elimination rather than by S_N2 substitution. Whether the alkoxide base is primary, secondary, or tertiary is much less important than the nature of the alkyl halide. Thus benzyl isopropyl ether is prepared in high yield from benzyl chloride, a primary chloride that is incapable of undergoing elimination, and sodium isopropoxide:



Sodium isopropoxide — Benzyl chloride — Benzyl isopropyl ether (84%) — Sodium chloride

The alternative synthetic route using the sodium salt of benzyl alcohol and an isopropyl halide would be much less effective, because of increased competition from elimination as the alkyl halide becomes more sterically hindered.

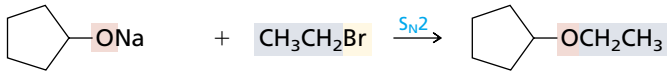
PROBLEM 16.7 Only one combination of alkyl halide and alkoxide is appropriate for the preparation of each of the following ethers by the Williamson ether synthesis. What is the correct combination in each case?

(a) 

(c) $(CH_3)_3COCH_2C_6H_5$

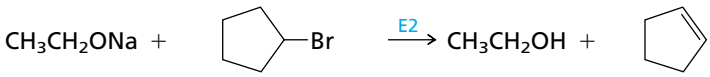
(b) $CH_2{=}CHCH_2OCH(CH_3)_2$

SAMPLE SOLUTION (a) The ether linkage of cyclopentyl ethyl ether involves a primary carbon and a secondary one. Choose the alkyl halide corresponding to the primary alkyl group, leaving the secondary alkyl group to arise from the alkoxide nucleophile.



Sodium cyclopentanolate — Ethyl bromide — Cyclopentyl ethyl ether

The alternative combination, cyclopentyl bromide and sodium ethoxide, is not appropriate, since elimination will be the major reaction:



Sodium ethoxide — Bromocyclopentane — Ethanol (major products) — Cyclopentene (major products)

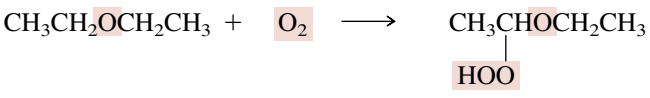
Both reactants in the Williamson ether synthesis usually originate in alcohol precursors. Sodium and potassium alkoxides are prepared by reaction of an alcohol with the appropriate metal, and alkyl halides are most commonly made from alcohols by reaction with a hydrogen halide (Section 4.8), thionyl chloride (Section 4.14), or phosphorus tribromide (Section 4.14). Alternatively, alkyl *p*-toluenesulfonates may be used in place of alkyl halides; alkyl *p*-toluenesulfonates are also prepared from alcohols as their immediate precursors (Section 8.14).

16.7 REACTIONS OF ETHERS: A REVIEW AND A PREVIEW

Up to this point, we haven't seen any reactions of dialkyl ethers. Indeed, ethers are one of the least reactive of the functional groups we shall study. It is this low level of reactivity, along with an ability to dissolve nonpolar substances, that makes ethers so often used as solvents when carrying out organic reactions. Nevertheless, most ethers are hazardous materials, and precautions must be taken when using them. Diethyl ether is extremely flammable and because of its high volatility can form explosive mixtures in air relatively quickly. Open flames must never be present in laboratories where diethyl ether is being used. Other low-molecular-weight ethers must also be treated as fire hazards.

PROBLEM 16.8 Combustion in air is, of course, a chemical property of ethers that is shared by many other organic compounds. Write a balanced chemical equation for the complete combustion (in air) of diethyl ether.

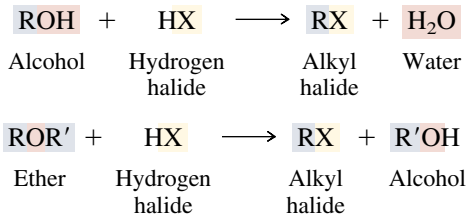
A second dangerous property of ethers is the ease with which they undergo oxidation in air to form explosive peroxides. Air oxidation of diethyl ether proceeds according to the equation



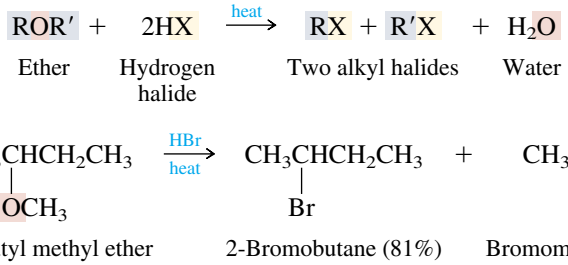
The reaction follows a free-radical mechanism and gives a hydroperoxide, a compound of the type ROOH. Hydroperoxides tend to be unstable and shock-sensitive. On standing, they form related peroxidic derivatives, which are also prone to violent decomposition. Air oxidation leads to peroxides within a few days if ethers are even briefly exposed to atmospheric oxygen. For this reason, one should never use old bottles of dialkyl ethers, and extreme care must be exercised in their disposal.

16.8 ACID-CATALYZED CLEAVAGE OF ETHERS

Just as the carbon–oxygen bond of alcohols is cleaved on reaction with hydrogen halides (Section 4.8), so too is an ether linkage broken:



The cleavage of ethers is normally carried out under conditions (excess hydrogen halide, heat) that convert the alcohol formed as one of the original products to an alkyl halide. Thus, the reaction typically leads to two alkyl halide molecules:



The order of hydrogen halide reactivity is HI > HBr >> HCl. Hydrogen fluoride is not effective.

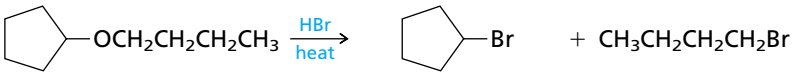
PROBLEM 16.9 A series of dialkyl ethers was allowed to react with excess hydrogen bromide, with the following results. Identify the ether in each case.

(a) One ether gave a mixture of bromocyclopentane and 1-bromobutane.

(b) Another ether gave only benzyl bromide.

(c) A third ether gave one mole of 1,5-dibromopentane per mole of ether.

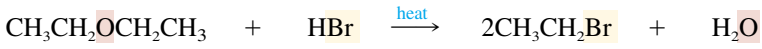
SAMPLE SOLUTION (a) In the reaction of dialkyl ethers with excess hydrogen bromide, each alkyl group of the ether function is cleaved and forms an alkyl bromide. Since bromocyclopentane and 1-bromobutane are the products, the starting ether must be butyl cyclopentyl ether.



Butyl cyclopentyl ether | Bromocyclopentane | 1-Bromobutane

A mechanism for the cleavage of diethyl ether by hydrogen bromide is outlined in Figure 16.4. The key step is an S_N2-like attack on a dialkyloxonium ion by bromide (step 2).

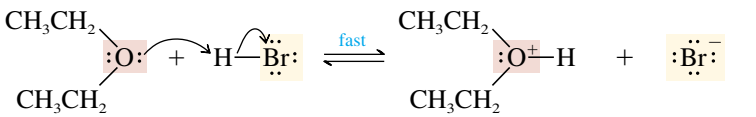
Overall Reaction:



Diethyl ether | Hydrogen bromide | Ethyl bromide | Water

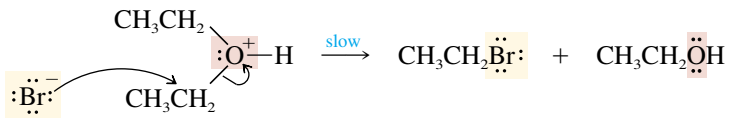
Mechanism:

Step 1: Proton transfer to the oxygen of the ether to give a dialkyloxonium ion.



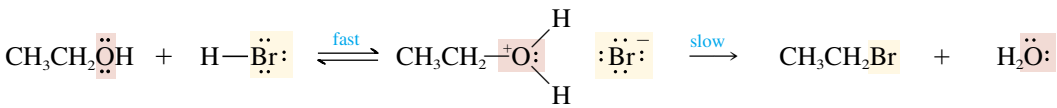
Diethyl ether | Hydrogen bromide | Diethyloxonium ion | Bromide ion

Step 2: Nucleophilic attack of the halide anion on carbon of the dialkyloxonium ion. This step gives one molecule of an alkyl halide and one molecule of an alcohol.



Bromide ion | Diethyloxonium ion | Ethyl bromide | Ethanol

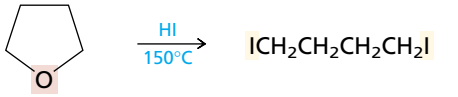
Step 3 and Step 4: These two steps do not involve an ether at all. They correspond to those in which an alcohol is converted to an alkyl halide (Sections 4.8–4.13).



Ethanol | Hydrogen bromide | Ethyl bromide | Water

FIGURE 16.4 The mechanism for the cleavage of ethers by hydrogen halides, using the reaction of diethyl ether with hydrogen bromide as an example.

PROBLEM 16.10 Adapt the mechanism shown in Figure 16.4 to the reaction:



Tetrahydrofuran 1,4-Diiodobutane (65%)

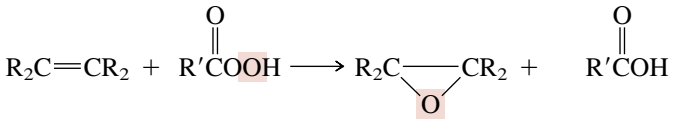
With mixed ethers of the type ROR′, the question of which carbon–oxygen bond is broken first arises. Although some studies have been carried out on this point of mechanistic detail, it is not one that we need examine at our level of study.

16.9 PREPARATION OF EPOXIDES: A REVIEW AND A PREVIEW

There are two main laboratory methods for the preparation of epoxides:

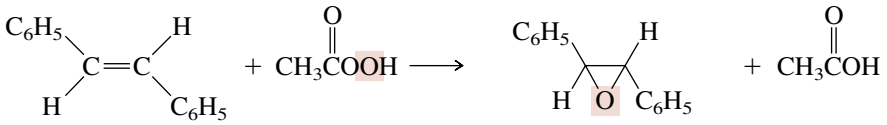
1. Epoxidation of alkenes by reaction with peroxy acids
2. Base-promoted ring closure of vicinal halohydrins

Epoxidation of alkenes was discussed in Section 6.18 and is represented by the general equation



Alkene Peroxy acid Epoxide Carboxylic acid

The reaction is easy to carry out, and yields are usually high. Epoxidation is a stereospecific syn addition.

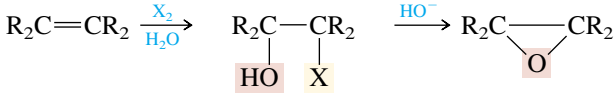


(*E*)-1,2-Diphenylethene Peroxyacetic acid *trans*-2,3-Diphenyloxirane (78–83%) Acetic acid

The following section describes the preparation of epoxides by the base-promoted ring closure of vicinal halohydrins. Since vicinal halohydrins are customarily prepared from alkenes (Section 6.17), both methods—epoxidation using peroxy acids and ring closure of halohydrins—are based on alkenes as the starting materials for preparing epoxides.

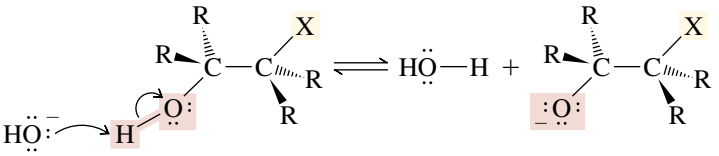
16.10 CONVERSION OF VICINAL HALOHYDRINS TO EPOXIDES

The formation of vicinal halohydrins from alkenes was described in Section 6.17. Halohydrins are readily converted to epoxides on treatment with base:



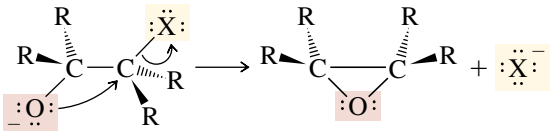
Alkene Vicinal halohydrin Epoxide

Reaction with base brings the alcohol function of the halohydrin into equilibrium with its corresponding alkoxide:

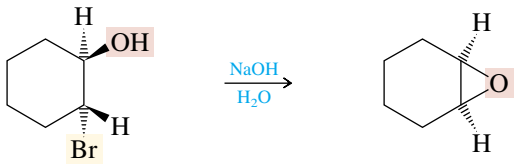


Vicinal halohydrin

Next, in what amounts to an *intramolecular* Williamson ether synthesis, the alkoxide oxygen attacks the carbon that bears the halide leaving group, giving an epoxide. As in other nucleophilic substitutions, the nucleophile approaches carbon from the side opposite the bond to the leaving group:

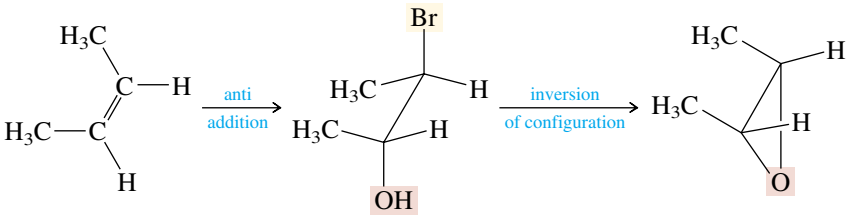


Epoxide



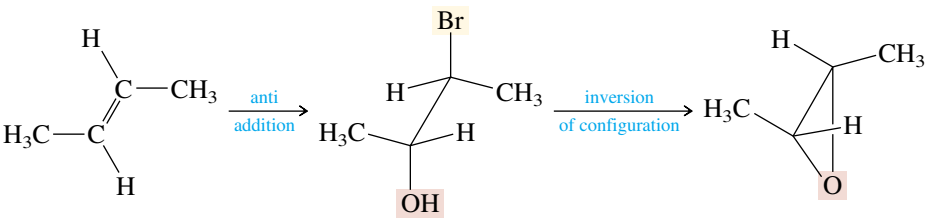
trans-2-Bromocyclohexanol 1,2-Epoxycyclohexane (81%)

Overall, the stereospecificity of this method is the same as that observed in peroxy acid oxidation of alkenes. Substituents that are cis to each other in the alkene remain cis in the epoxide. This is because formation of the bromohydrin involves anti addition, and the ensuing intramolecular nucleophilic substitution reaction takes place with inversion of configuration at the carbon that bears the halide leaving group.



(*Z*)-2-Butene
(*cis*-2-butene)

cis-2,3-Epoxybutane



(*E*)-2-Butene
(*trans*-2-butene)

trans-2,3-Epoxybutane

PROBLEM 16.11 Is either of the epoxides formed in the preceding reactions chiral? Is either epoxide optically active when prepared from the alkene by this method?

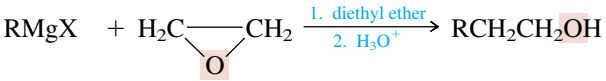
About 2×10^9 lb/year of 1,2-epoxypropane is produced in the United States as an intermediate in the preparation of various polymeric materials, including polyurethane plastics and foams and polyester resins. A large fraction of the 1,2-epoxypropane is made from propene by way of its chlorohydrin.

16.11 REACTIONS OF EPOXIDES: A REVIEW AND A PREVIEW

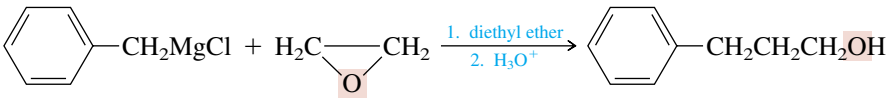
Angle strain is the main source of strain in epoxides, but torsional strain that results from the eclipsing of bonds on adjacent carbons is also present. Both kinds of strain are relieved when a ring-opening reaction occurs.

The most striking chemical property of epoxides is their far greater reactivity toward nucleophilic reagents compared with that of simple ethers. Epoxides react rapidly with nucleophiles under conditions in which other ethers are inert. This enhanced reactivity results from the ring strain of epoxides. Reactions that lead to ring opening relieve this strain.

We saw an example of nucleophilic ring opening of epoxides in Section 15.4, where the reaction of Grignard reagents with ethylene oxide was described as a synthetic route to primary alcohols:

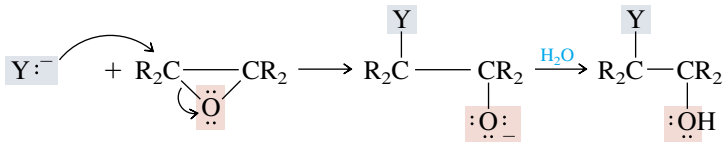


Grignard reagent — Ethylene oxide — Primary alcohol



Benzylmagnesium chloride — Ethylene oxide — 3-Phenyl-1-propanol (71%)

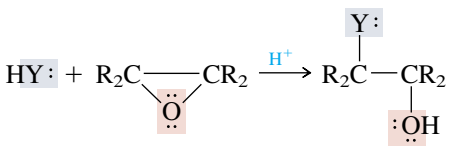
Nucleophiles other than Grignard reagents also open epoxide rings. There are two fundamental ways in which these reactions are carried out. The first (Section 16.12) involves anionic nucleophiles in neutral or basic solution.



Nucleophile — Epoxide — Alkoxide ion — Alcohol

These reactions are usually performed in water or alcohols as solvents, and the alkoxide ion intermediate is rapidly transformed to an alcohol by proton transfer.

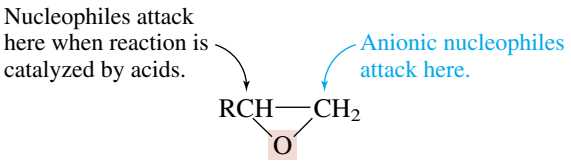
Nucleophilic ring-opening reactions of epoxides may also occur under conditions of acid catalysis. Here the nucleophile is not an anion but rather a solvent molecule.



Epoxide — Alcohol

Acid-catalyzed ring opening of epoxides is discussed in Section 16.13.

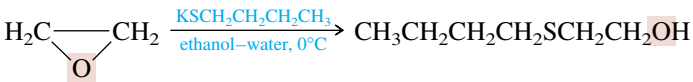
There is an important difference in the regiochemistry of ring-opening reactions of epoxides depending on the reaction conditions. Unsymmetrically substituted epoxides tend to react with anionic nucleophiles at the less hindered carbon of the ring. Under conditions of acid catalysis, however, the more highly substituted carbon is attacked.



The underlying reasons for this difference in regioselectivity will be explained in Section 16.13.

16.12 NUCLEOPHILIC RING-OPENING REACTIONS OF EPOXIDES

Ethylene oxide is a very reactive substance. It reacts rapidly and exothermically with anionic nucleophiles to yield 2-substituted derivatives of ethanol by cleaving the carbon–oxygen bond of the ring:

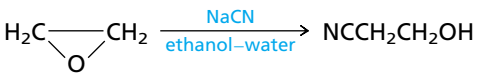


Ethylene oxide (oxirane) — 2-(Butylthio)ethanol (99%)

PROBLEM 16.12 What is the principal organic product formed in the reaction of ethylene oxide with each of the following?

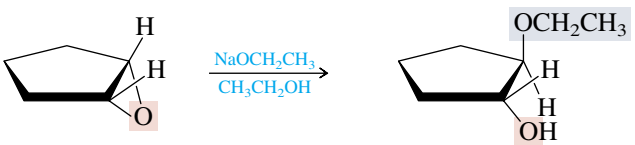
(a) Sodium cyanide (NaCN) in aqueous ethanol
(b) Sodium azide (NaN_3) in aqueous ethanol
(c) Sodium hydroxide (NaOH) in water
(d) Phenyllithium (C_6H_5Li) in ether, followed by addition of dilute sulfuric acid
(e) 1-Butynylsodium ($CH_3CH_2C{\equiv}CNa$) in liquid ammonia

SAMPLE SOLUTION (a) Sodium cyanide is a source of the nucleophilic cyanide anion. Cyanide ion attacks ethylene oxide, opening the ring and forming 2-cyanoethanol:

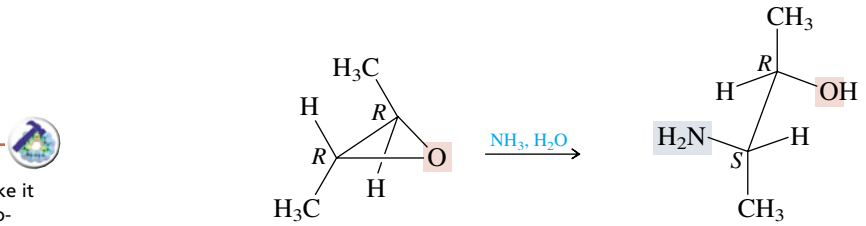


Ethylene oxide — 2-Cyanoethanol

Nucleophilic ring opening of epoxides has many of the features of an S_N2 reaction. Inversion of configuration is observed at the carbon at which substitution occurs.



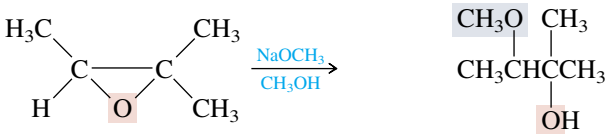
1,2-Epoxycyclopentane — *trans*-2-Ethoxycyclopentanol (67%)



(2*R*,3*R*)-2,3-Epoxybutane (2*R*,3*S*)-3-Amino-2-butanol (70%)

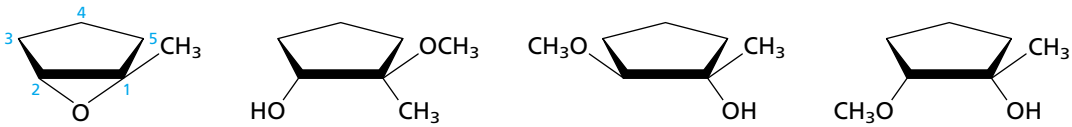
Manipulating models of these compounds can make it easier to follow the stereochemistry.

Unsymmetrical epoxides are attacked at the less substituted, less sterically hindered carbon of the ring:



2,2,3-Trimethyloxirane 3-Methoxy-2-methyl-2-butanol (53%)

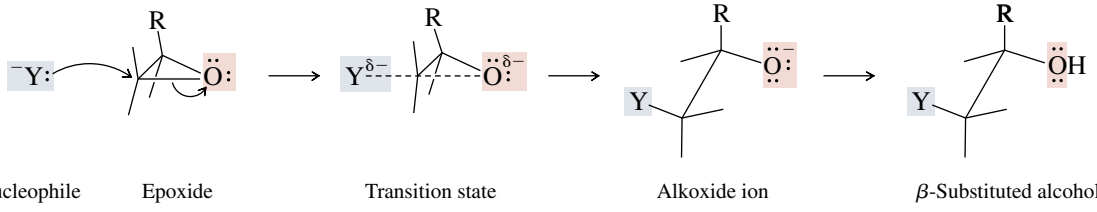
PROBLEM 16.13 Given the starting material 1-methyl-1,2-epoxycyclopentane, of absolute configuration as shown, decide which one of the compounds A through C correctly represents the product of its reaction with sodium methoxide in methanol.



1-Methyl-1,2-epoxycyclopentane Compound A Compound B Compound C

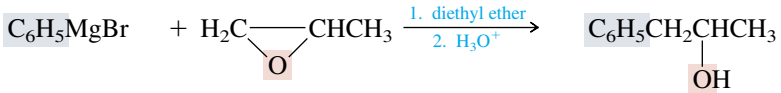
The experimental observations combine with the principles of nucleophilic substitution to give the picture of epoxide ring opening shown in Figure 16.5. The nucleophile attacks the less crowded carbon from the side opposite the carbon–oxygen bond. Bond formation with the nucleophile accompanies carbon–oxygen bond breaking, and a substantial portion of the strain in the three-membered ring is relieved as it begins to open in the transition state. The initial product of nucleophilic substitution is an alkoxide anion, which rapidly abstracts a proton from the solvent to give a β-substituted alcohol as the isolated product.

The reaction of Grignard reagents with epoxides is regioselective in the same sense. Attack occurs at the less substituted carbon of the ring.



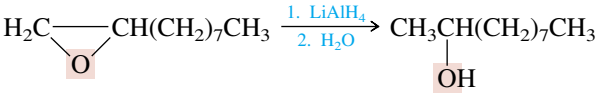
Nucleophile Epoxide Transition state Alkoxide ion β-Substituted alcohol

FIGURE 16.5 Nucleophilic ring opening of an epoxide.



Phenylmagnesium bromide | 1,2-Epoxypropane | 1-Phenyl-2-propanol (60%)

Epoxides are reduced to alcohols on treatment with lithium aluminum hydride. Hydride is transferred to the less crowded carbon.

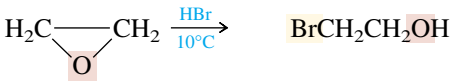


1,2-Epoxydecane | 2-Decanol (90%)

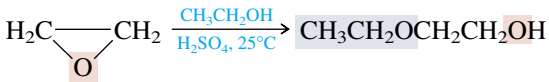
Epoxidation of an alkene, followed by lithium aluminum hydride reduction of the resulting epoxide, gives the same alcohol that would be obtained by acid-catalyzed hydration (Section 6.10) of the alkene.

16.13 ACID-CATALYZED RING-OPENING REACTIONS OF EPOXIDES

As we've just seen, nucleophilic ring opening of ethylene oxide yields 2-substituted derivatives of ethanol. Those reactions involved nucleophilic attack on the carbon of the ring under neutral or basic conditions. Other nucleophilic ring-openings of epoxides likewise give 2-substituted derivatives of ethanol but either involve an acid as a reactant or occur under conditions of acid catalysis:



Ethylene oxide | 2-Bromoethanol (87–92%)



Ethylene oxide | 2-Ethoxyethanol (85%)

A third example is the industrial preparation of ethylene glycol ($HOCH_2CH_2OH$) by hydrolysis of ethylene oxide in dilute sulfuric acid. This reaction and its mechanism (Figure 16.6) illustrate the difference between the ring openings of epoxides discussed in the preceding section and the acid-catalyzed ones described here. Under conditions of acid catalysis, the species that is attacked by the nucleophile is not the epoxide itself, but rather its conjugate acid. The transition state for ring opening has a fair measure of carbocation character. Breaking of the ring carbon–oxygen bond is more advanced than formation of the bond to the nucleophile.

Transition state for attack by water on conjugate acid of ethylene oxide

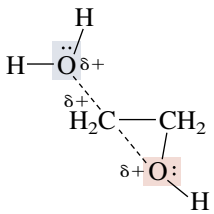
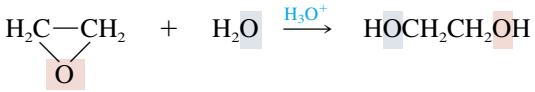


FIGURE 16.6 The mechanism for the acid-catalyzed nucleophilic ring opening of ethylene oxide by water.

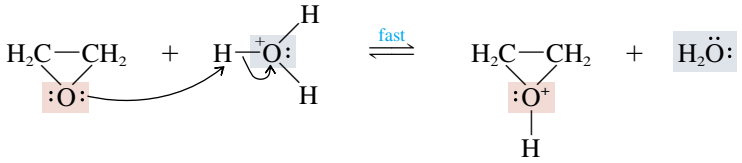
Overall Reaction:



Ethylene oxide Water 1,2-Ethanediol (ethylene glycol)

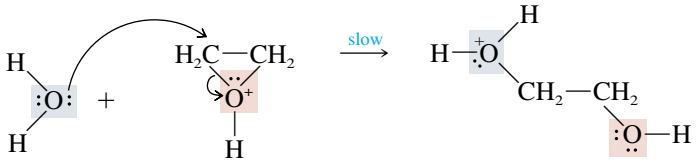
Mechanism:

Step 1: Proton transfer to the oxygen of the epoxide to give an oxonium ion.



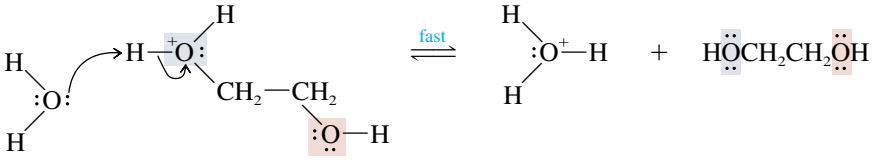
Ethylene oxide Hydronium ion Ethyleneoxonium ion Water

Step 2: Nucleophilic attack by water on carbon of the oxonium ion. The carbon–oxygen bond of the ring is broken in this step and the ring opens.



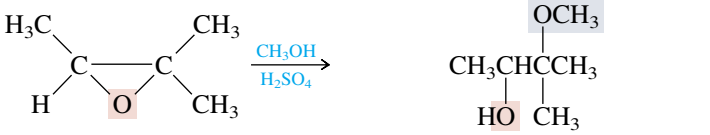
Water Ethyleneoxonium ion 2-Hydroxyethyloxonium ion

Step 3: Proton transfer to water completes the reaction and regenerates the acid catalyst.



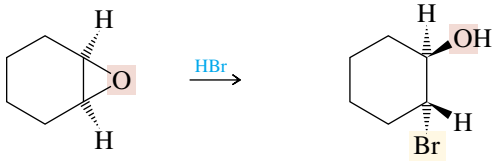
Water 2-Hydroxyethyloxonium ion Hydronium ion 1,2-Ethanediol

Because *carbocation* character develops at the transition state, substitution is favored at the carbon that can better support a developing positive charge. Thus, in contrast to the reaction of epoxides with relatively basic nucleophiles, in which S_N2-like attack is faster at the less crowded carbon of the three-membered ring, acid catalysis promotes substitution at the position that bears the greater number of alkyl groups:

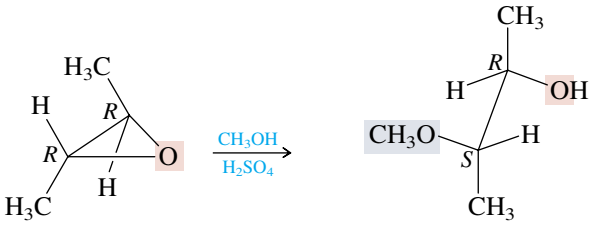


2,2,3-Trimethyloxirane 3-Methoxy-3-methyl-2-butanol (76%)

Although nucleophilic participation at the transition state is slight, it is enough to ensure that substitution proceeds with inversion of configuration.

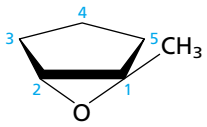


1,2-Epoxycyclohexane *trans*-2-Bromocyclohexanol (73%)

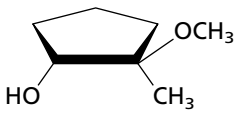


(2*R*,3*R*)-2,3-Epoxybutane (2*R*,3*S*)-3-Methoxy-2-butanol (57%)

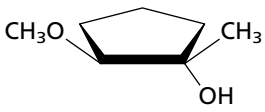
PROBLEM 16.14 Which product, compound A, B, or C, would you expect to be formed when 1-methyl-1,2-epoxycyclopentane of the absolute configuration shown is allowed to stand in methanol containing a few drops of sulfuric acid? Compare your answer with that given for Problem 16.13.



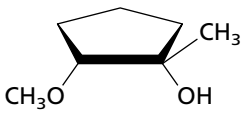
1-Methyl-1,2-epoxycyclopentane



Compound A

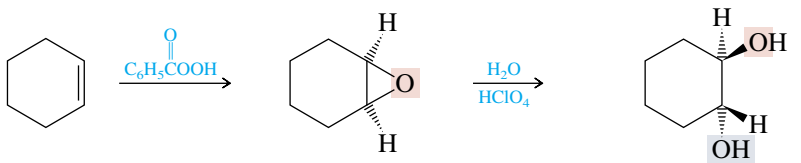


Compound B



Compound C

A method for achieving net anti hydroxylation of alkenes combines two stereospecific processes: epoxidation of the double bond and hydrolysis of the derived epoxide.



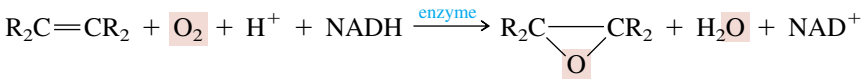
Cyclohexene 1,2-Epoxycyclohexane *trans*-1,2-Cyclohexanediol (80%)

PROBLEM 16.15 Which alkene, *cis*-2-butene or *trans*-2-butene, would you choose in order to prepare *meso*-2,3-butanediol by epoxidation followed by acid-catalyzed hydrolysis? Which alkene would yield *meso*-2,3,-butanediol by osmium tetraoxide hydroxylation?

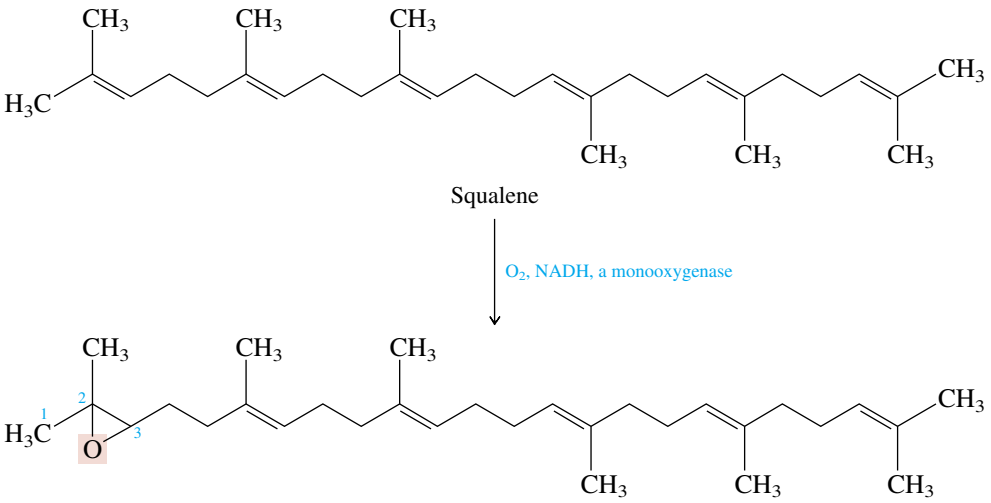
16.14 EPOXIDES IN BIOLOGICAL PROCESSES

Many naturally occurring substances are epoxides. You have seen two examples of such compounds already in disparlure, the sex attractant of the gypsy moth (Section 6.18), and in the carcinogenic epoxydiol formed from benzo[a]pyrene (Section 11.8). In most cases, epoxides are biosynthesized by the enzyme-catalyzed transfer of one of the oxygen atoms of an O_2 molecule to an alkene. Since only one of the atoms of O_2 is

transferred to the substrate, the enzymes that catalyze such transfers are classified as *monooxygenases.* A biological reducing agent, usually the coenzyme NADH (Section 15.11), is required as well.



A prominent example of such a reaction is the biological epoxidation of the polyene squalene.

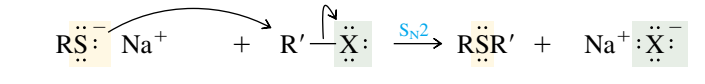


Squalene 2,3-epoxide

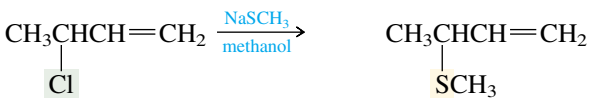
The reactivity of epoxides toward nucleophilic ring opening is responsible for one of the biological roles they play. Squalene 2,3-epoxide, for example, is the biological precursor to cholesterol and the steroid hormones, including testosterone, progesterone, estrone, and cortisone. The pathway from squalene 2,3-epoxide to these compounds is triggered by epoxide ring opening and will be described in Chapter 26.

16.15 PREPARATION OF SULFIDES

Sulfides, compounds of the type RSR′, are prepared by nucleophilic substitution reactions. Treatment of a primary or secondary alkyl halide with an alkanethiolate ion (RS^-) gives a sulfide:



Sodium alkanethiolate Alkyl halide Sulfide Sodium halide



3-Chloro-1-butene Methyl 1-methylallyl sulfide (62%)

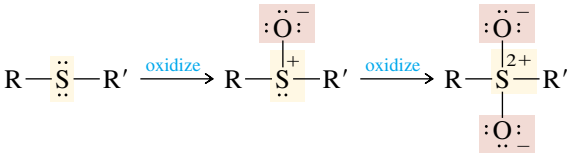
K_a for CH_3SH is 1.8×10^{-11} ($pK_a = 10.7$).

It is not necessary to prepare and isolate the sodium alkanethiolate in a separate operation. Because thiols are more acidic than water, they are quantitatively converted to their alkanethiolate anions by sodium hydroxide. Thus, all that is normally done is to add a thiol to sodium hydroxide in a suitable solvent (water or an alcohol) followed by the alkyl halide.

PROBLEM 16.16 The *p*-toluenesulfonate derived from (*R*)-2-octanol and *p*-toluenesulfonyl chloride was allowed to react with sodium benzenethiolate (C_6H_5SNa). Give the structure, including stereochemistry and the appropriate *R* or *S* descriptor, of the product.

16.16 OXIDATION OF SULFIDES: SULFOXIDES AND SULFONES

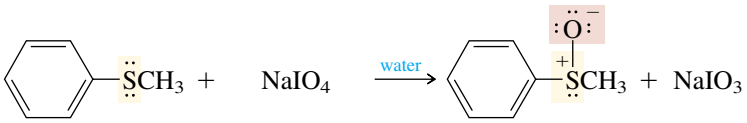
We saw in Section 15.14 that thiols differ from alcohols in respect to their behavior toward oxidation. Similarly, sulfides differ from ethers in their behavior toward oxidizing agents. Whereas ethers tend to undergo oxidation at carbon to give hydroperoxides (Section 16.7), sulfides are oxidized at sulfur to give **sulfoxides.** If the oxidizing agent is strong enough and present in excess, oxidation can proceed further to give **sulfones.**



Sulfide Sulfoxide Sulfone

Third-row elements such as sulfur can expand their valence shell beyond eight electrons, and so sulfur–oxygen bonds in sulfoxides and sulfones are sometimes represented as double bonds.

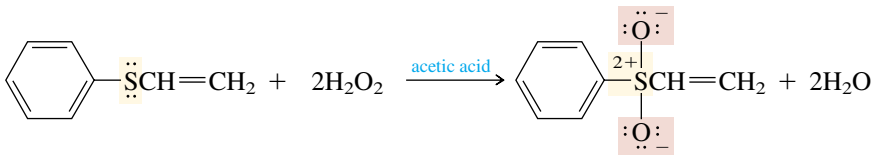
When the desired product is a sulfoxide, sodium metaperiodate ($NaIO_4$) is an ideal reagent. It oxidizes sulfides to sulfoxides in high yield but shows no tendency to oxidize sulfoxides to sulfones.



Methyl phenyl sulfide | Sodium metaperiodate | Methyl phenyl sulfoxide (91%) | Sodium iodate

Peroxy acids, usually in dichloromethane as the solvent, are also reliable reagents for converting sulfides to sulfoxides.

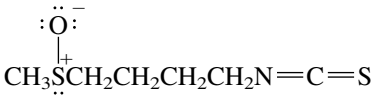
One equivalent of a peroxy acid or of hydrogen peroxide converts sulfides to sulfoxides; two equivalents gives the corresponding sulfone.



Phenyl vinyl sulfide | Hydrogen peroxide | Phenyl vinyl sulfone (74–78%) | Water

PROBLEM 16.17 Verify, by making molecular models, that the bonds to sulfur are arranged in a trigonal pyramidal geometry in sulfoxides and in a tetrahedral geometry in sulfones. Is phenyl vinyl sulfoxide chiral? What about phenyl vinyl sulfone?

Oxidation of sulfides occurs in living systems as well. Among naturally occurring sulfoxides, one that has received recent attention is *sulforaphane,* which is present in broccoli and other vegetables. Sulforaphane holds promise as a potential anticancer agent because, unlike most anticancer drugs, which act by killing rapidly dividing tumor cells faster than they kill normal cells, sulforaphane is nontoxic and may simply inhibit the formation of tumors.

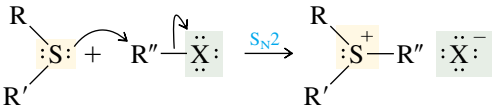


Sulforaphane

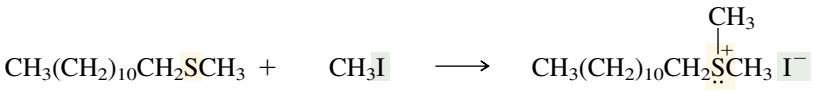
16.17 ALKYLATION OF SULFIDES: SULFONIUM SALTS

Sulfur is more nucleophilic than oxygen (Section 8.7), and sulfides react with alkyl halides much faster than do ethers. The products of these reactions, called **sulfonium salts,** are also more stable than the corresponding oxygen analogs.

Use *Learning By Modeling* to view the geometry of sulfur in trimethylsulfonium ion.



Sulfide Alkyl halide Sulfonium salt



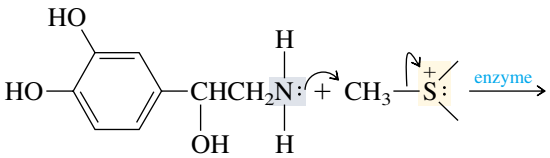
Dodecyl methyl sulfide Methyl iodide Dodecyldimethylsulfonium iodide

PROBLEM 16.18 What other combination of alkyl halide and sulfide will yield the same sulfonium salt shown in the preceding example? Predict which combination will yield the sulfonium salt at the faster rate.

The *S* in *S*-adenosylmethionine indicates that the adenosyl group is bonded to sulfur. It does not stand for the Cahn–Ingold–Prelog stereochemical descriptor.

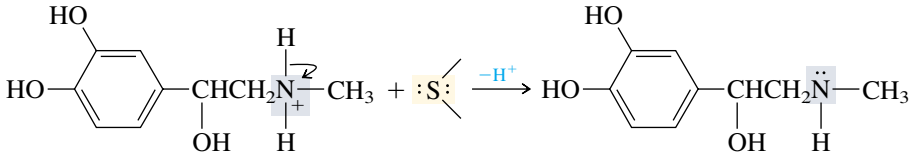
A naturally occurring sulfonium salt, *S-adenosylmethionine (SAM),* is a key substance in certain biological processes. It is formed by a nucleophilic substitution in which the sulfur atom of methionine attacks the primary carbon of adenosine triphosphate, displacing the triphosphate leaving group as shown in Figure 16.7.

S-Adenosylmethionine acts as a biological methyl-transfer agent. Nucleophiles, particularly nitrogen atoms of amines, attack the methyl carbon of SAM, breaking the carbon–sulfur bond. The following equation represents the biological formation of *epinephrine* by methylation of *norepinephrine.* Only the methyl group and the sulfur of SAM are shown explicitly in the equation in order to draw attention to the similarity of this reaction, which occurs in living systems, to the more familiar S_N2 reactions we have studied.



Norepinephrine SAM

Epinephrine is also known as *adrenaline* and is a hormone with profound physiological effects designed to prepare the body for "fight or flight."



Epinephrine

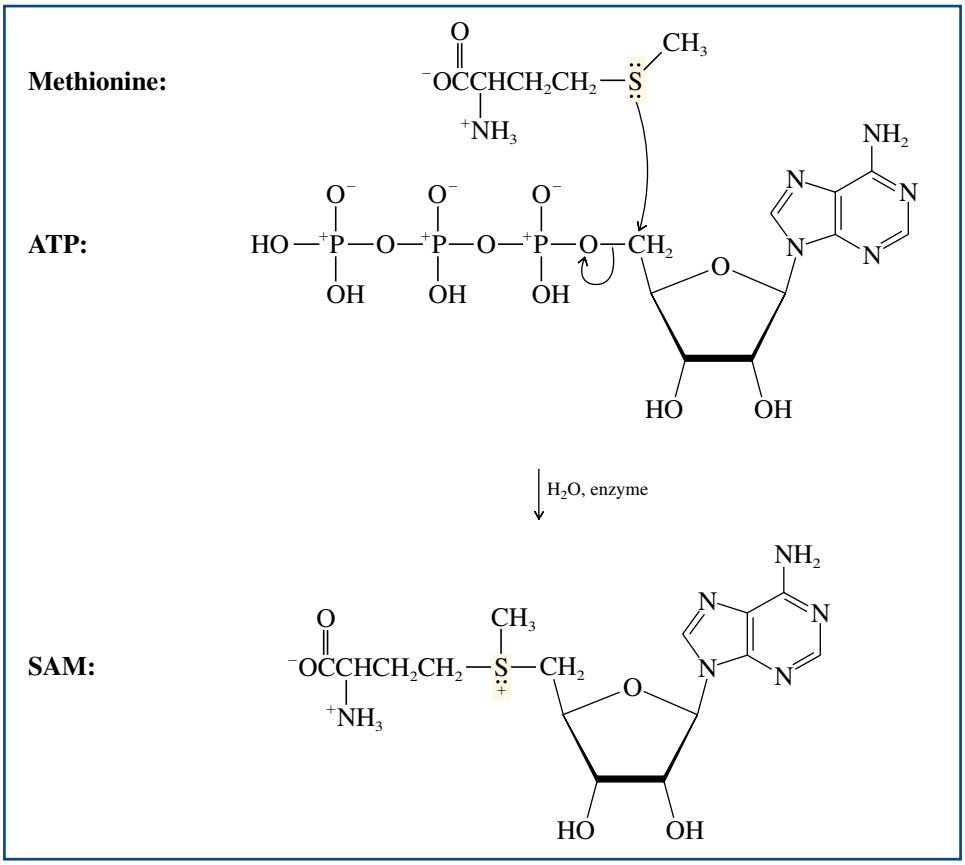
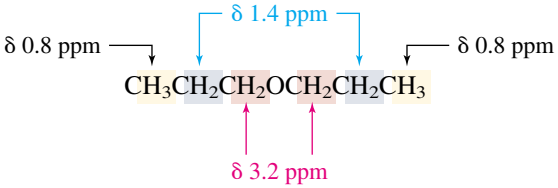


FIGURE 16.7 Nucleophilic substitution at the primary carbon of adenosine triphosphate (ATP) by the sulfur atom of methionine yields *S*-adenosylmethionine (SAM). The reaction is catalyzed by an enzyme.

16.18 SPECTROSCOPIC ANALYSIS OF ETHERS

Infrared: The infrared spectra of ethers are characterized by a strong, rather broad band due to C—O—C stretching between 1070 and 1150 cm^{-1}. Dialkyl ethers exhibit this band at near 1100 cm^{-1}, as the infrared spectrum of dipropyl ether shows (Figure 16.8).

^{1}H NMR: The chemical shift of the proton in the **H**—C—O—C unit of an ether is very similar to that of the proton in the **H**—C—OH unit of an alcohol. A range δ 3.3–4.0 ppm is typical. In the ^{1}H NMR spectrum of dipropyl ether, shown in Figure 16.9, the assignment of signals to the various protons in the molecule is



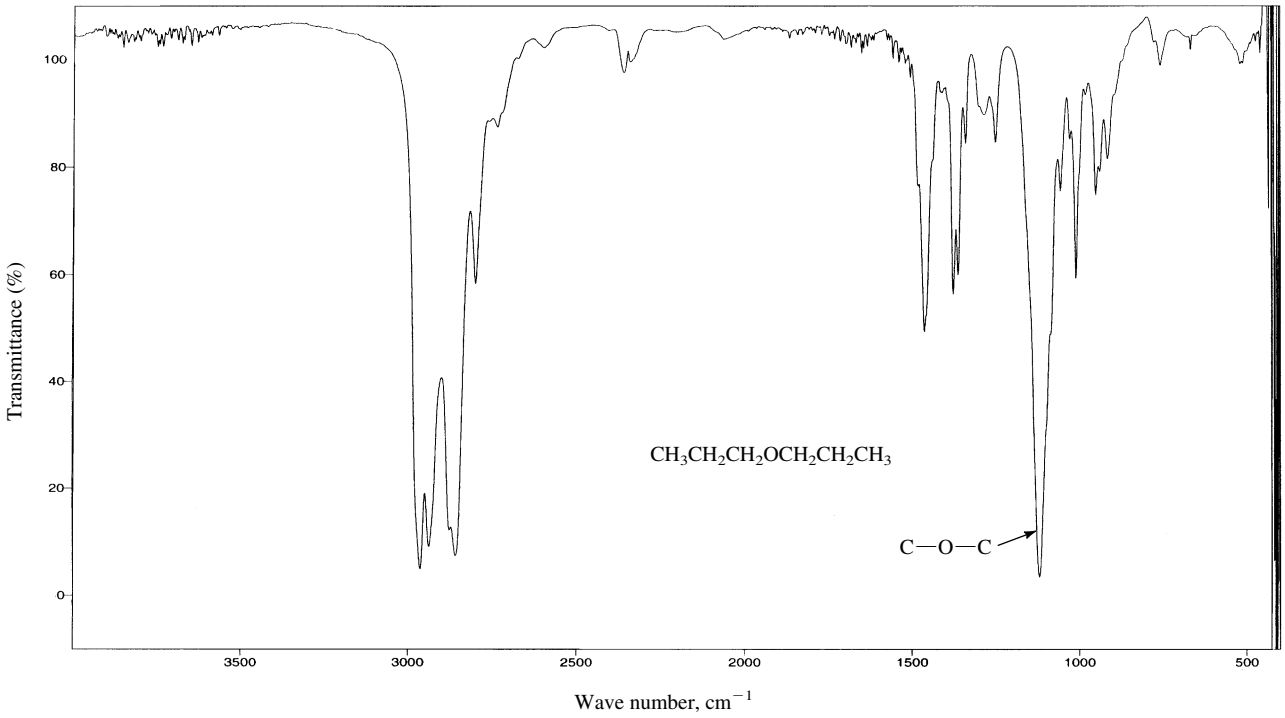


FIGURE 16.8 The infrared spectrum of dipropyl ether ($CH_3CH_2CH_2OCH_2CH_2CH_3$). The strong peak near 1100 cm^{-1} is due to C—O—C stretching.

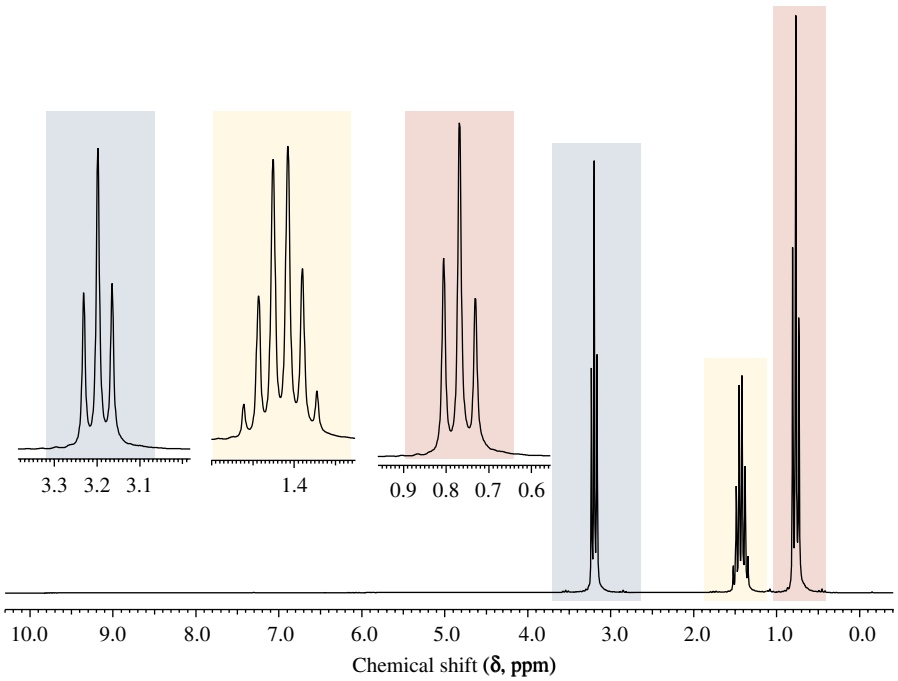
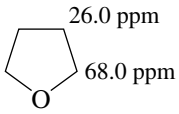


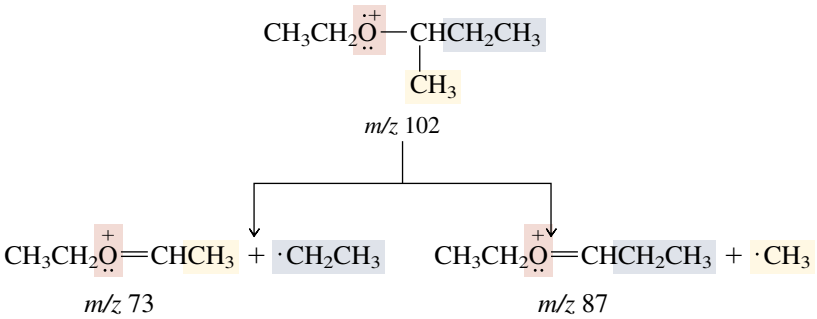
FIGURE 16.9 The 200-MHz ^{1}H NMR spectrum of dipropyl ether ($CH_3CH_2CH_2OCH_2CH_2CH_3$).

^{13}C NMR: The carbons of an ether function (C—O—C) are about 10 ppm less shielded than those of an alcohol and appear in the range δ 57–87 ppm. The chemical shifts in tetrahydrofuran offer a comparison of C—O—C and C—C—C units.



UV-VIS: Simple ethers have their absorption maximum at about 185 nm and are transparent to ultraviolet radiation above about 220 nm.

Mass Spectrometry: Ethers, like alcohols, lose an alkyl radical from their molecular ion to give an oxygen-stabilized cation. Thus, *m/z* 73 and *m/z* 87 are both more abundant than the molecular ion in the mass spectrum of *sec*-butyl ethyl ether.



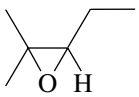
PROBLEM 16.19 There is another oxygen-stabilized cation of *m/z* 87 capable of being formed by fragmentation of the molecular ion in the mass spectrum of *sec*-butyl ethyl ether. Suggest a reasonable structure for this ion.

16.19 SUMMARY

Section 16.1 **Ethers** are compounds that contain a C—O—C linkage. In substitutive IUPAC nomenclature, they are named as *alkoxy* derivatives of alkanes. In functional class IUPAC nomenclature, we name each alkyl group as a separate word (in alphabetical order) followed by the word "ether."

$CH_3OCH_2CH_2CH_2CH_2CH_2CH_3$ **Substitutive IUPAC name:** 1-Methoxyhexane
Functional class name: Hexyl methyl ether

Epoxides are normally named as *epoxy* derivatives of alkanes or as substituted *oxiranes.*

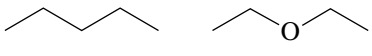


2-Methyl-2,3-epoxypentane
3-Ethyl-2,2-dimethyloxirane

Sulfides are sulfur analogs of ethers: they contain the C—S—C functional group. They are named as *alkylthio* derivatives of alkanes in substitutive IUPAC nomenclature. The functional class IUPAC names of sulfides are derived in the same manner as those of ethers, but the concluding word is "sulfide."

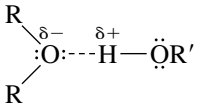
$CH_3SCH_2CH_2CH_2CH_2CH_2CH_3$ **Substitutive IUPAC name:** 1-(Methylthio)hexane
Functional class name: Hexyl methyl sulfide

Section 16.2 The oxygen atom in an ether or epoxide affects the shape of the molecule in much the same way as an sp^3-hybridized carbon of an alkane or cycloalkane.



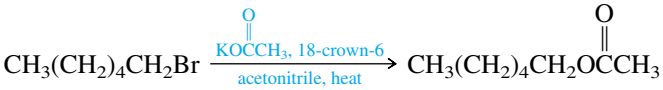
Pentane Diethyl ether

Section 16.3 The carbon–oxygen bond of ethers is polar, and ethers can act as proton *acceptors* in hydrogen bonds with water and alcohols.



But ethers lack OH groups and cannot act as proton *donors* in forming hydrogen bonds.

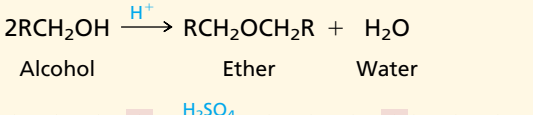
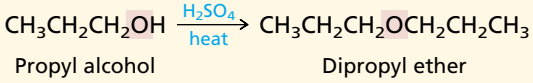
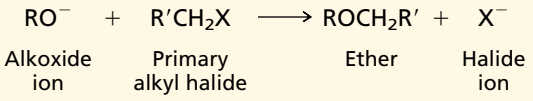
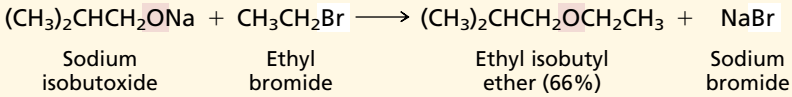
Section 16.4 Ethers form Lewis acid-Lewis base complexes with metal ions. Certain cyclic polyethers, called **crown ethers,** are particularly effective in coordinating with Na^+ and K^+, and salts of these cations can be dissolved in nonpolar solvents when crown ethers are present. Under these conditions the rates of many reactions that involve anions are accelerated.



1-Bromohexane Hexyl acetate (96%)

Sections 16.5 and 16.6 The two major methods for preparing ethers are summarized in Table 16.1.

TABLE 16.1 Preparation of Ethers

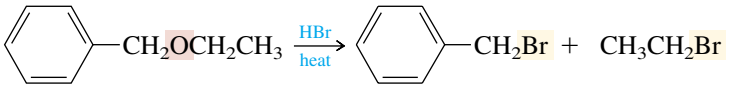
Reaction (section) and comments	General equation and specific example
Acid-catalyzed condensation of alcohols (Sections 15.7 and 16.5) Two molecules of an alcohol condense in the presence of an acid catalyst to yield a dialkyl ether and water. The reaction is limited to the synthesis of symmetrical ethers from primary alcohols.	 Alcohol Ether Water  Propyl alcohol Dipropyl ether
The Williamson ether synthesis (Section 16.6) An alkoxide ion displaces a halide or similar leaving group in an S_N2 reaction. The alkyl halide cannot be one that is prone to elimination, and so this reaction is limited to methyl and primary alkyl halides. There is no limitation on the alkoxide ion that can be used.	 Alkoxide ion Primary alkyl halide Ether Halide ion  Sodium isobutoxide Ethyl bromide Ethyl isobutyl ether (66%) Sodium bromide

Section 16.7 Dialkyl ethers are useful solvents for organic reactions, but dangerous ones due to their tendency to form explosive hydroperoxides by air oxidation in opened bottles.

Section 16.8 The only important reaction of ethers is their cleavage by hydrogen halides.

$$\underset{\text{Ether}}{ROR'} + \underset{\substack{\text{Hydrogen}\\\text{halide}}}{2HX} \longrightarrow \underset{\substack{\text{Alkyl}\\\text{halide}}}{RX} + \underset{\substack{\text{Alkyl}\\\text{halide}}}{R'X} + \underset{\text{Water}}{H_2O}$$

The order of hydrogen halide reactivity is HI > HBr > HCl.

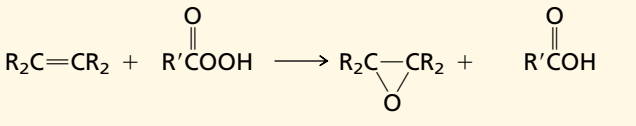
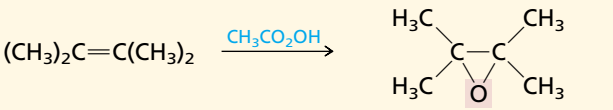
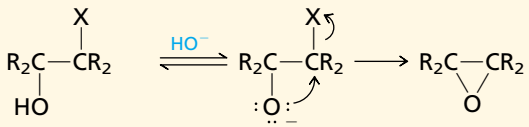
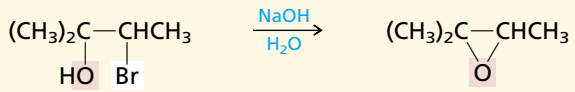


Benzyl ethyl ether — Benzyl bromide — Ethyl bromide

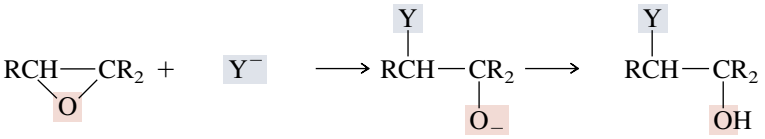
Sections 16.9 and 16.10 Epoxides are prepared by the methods listed in Table 16.2.

Section 16.11 Epoxides are much more reactive than ethers, especially in reactions that lead to cleavage of their three-membered ring.

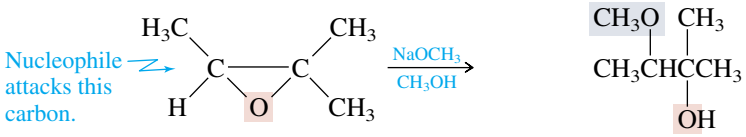
TABLE 16.2 Preparation of Epoxides

Reaction (section) and comments	General equation and specific example
Peroxy acid oxidation of alkenes (Sections 6.18 and 16.9) Peroxy acids transfer oxygen to alkenes to yield epoxides. Stereospecific syn addition is observed.	 Alkene — Peroxy acid — Epoxide — Carboxylic acid  2,3-Dimethyl-2-butene — 2,2,3,3-Tetramethyloxirane (70–80%)
Base-promoted cyclization of vicinal halohydrins (Section 16.10) This reaction is an intramolecular version of the Williamson ether synthesis. The alcohol function of a vicinal halohydrin is converted to its conjugate base, which then displaces halide from the adjacent carbon to give an epoxide.	 Vicinal halohydrin — Epoxide  3-Bromo-2-methyl-2-butanol — 2,2,3-Trimethyloxirane (78%)

Section 16.12 Anionic nucleophiles usually attack the less substituted carbon of the epoxide in an S_N2-like fashion.

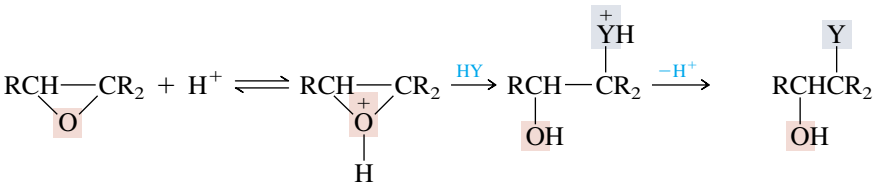


Epoxide Nucleophile β-substituted alcohol

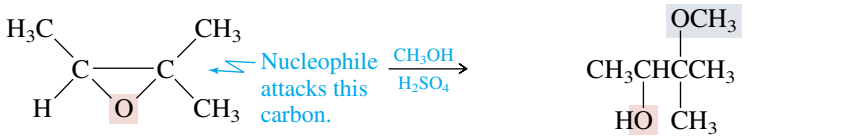


2,2,3-Trimethyloxirane 3-Methoxy-2-methyl-2-butanol (53%)

Section 16.13 Under conditions of acid catalysis, nucleophiles attack the carbon that can better support a positive charge. Carbocation character is developed in the transition state



Epoxide β-substituted alcohol

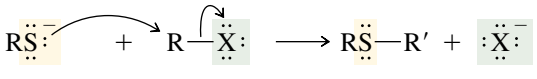


2,2,3-Trimethyloxirane 3-Methoxy-3-methyl-2-butanol (76%)

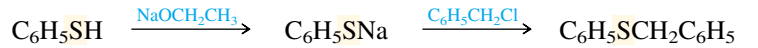
Inversion of configuration is observed at the carbon that is attacked by the nucleophile, irrespective of whether the reaction takes place in acidic or basic solution.

Section 16.14 Epoxide functions are present in a great many natural products, and epoxide ring opening is sometimes a key step in the biosynthesis of other substances.

Section 16.15 Sulfides are prepared by nucleophilic substitution (S_N2) in which an alkanethiolate ion attacks an alkyl halide.



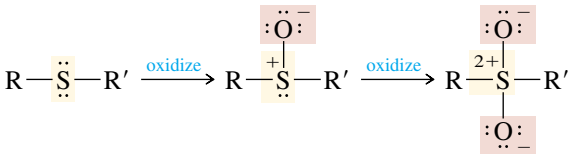
Alkanethiolate Alkyl halide Sulfide Halide



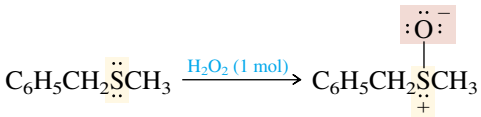
Benzenethiol Sodium benzenethiolate Benzyl phenyl sulfide (60%)

Section 16.16 Oxidation of sulfides yields sulfoxides, then sulfones. Sodium metaperiodate is specific for the oxidation of sulfides to sulfoxides, and no further.

Hydrogen peroxide or peroxy acids can yield sulfoxides (1 mol of oxidant per mole of sulfide) or sulfone (2 mol of oxidant) per mole of sulfide.

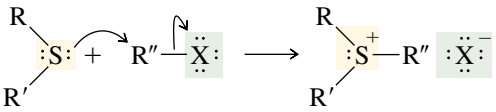


Sulfide Sulfoxide Sulfone

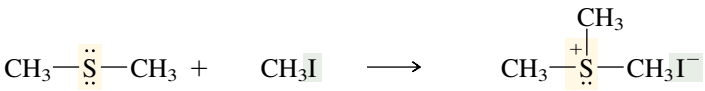


Benzyl methyl sulfide Benzyl methyl sulfoxide (94%)

Section 16.17 Sulfides react with alkyl halides to give sulfonium salts.



Sulfide Alkyl halide Sulfonium salt



Dimethyl sulfide Methyl iodide Trimethylsulfonium iodide (100%)

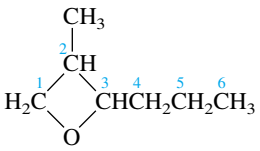
Section 16.18 An H—C—O—C structural unit in an ether resembles an H—C—O—H unit of an alcohol with respect to the C—O stretching frequency in its infrared spectrum and the H—C chemical shift in its ^{1}H NMR spectrum.

PROBLEMS

16.20 Write the structures of all the constitutionally isomeric ethers of molecular formula $C_5H_{12}O$, and give an acceptable name for each.

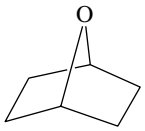
16.21 Many ethers, including diethyl ether, are effective as general anesthetics. Because simple ethers are quite flammable, their place in medical practice has been taken by highly halogenated nonflammable ethers. Two such general anesthetic agents are *isoflurane* and *enflurane*. These compounds are isomeric; isoflurane is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether; enflurane is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether. Write the structural formulas of isoflurane and enflurane.

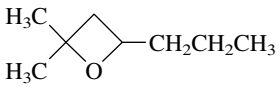
16.22 Although epoxides are always considered to have their oxygen atom as part of a three-membered ring, the prefix *epoxy* in the IUPAC system of nomenclature can be used to denote a cyclic ether of various sizes. Thus



may be named 2-methyl-1,3-epoxyhexane. Using the epoxy prefix in this way, name each of the following compounds:

(a) 

(c) 

(b) 

(d) 

16.23 The name of the parent six-membered sulfur-containing heterocycle is *thiane*. It is numbered beginning at sulfur. Multiple incorporation of sulfur in the ring is indicated by the prefixes *di-, tri-,* and so on.

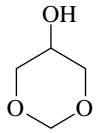
(a) How many methyl-substituted thianes are there? Which ones are chiral?

(b) Write structural formulas for 1,4-dithiane and 1,3,5-trithiane.

(c) Which dithiane isomer is a disulfide?

(d) Draw the two most stable conformations of the sulfoxide derived from thiane.

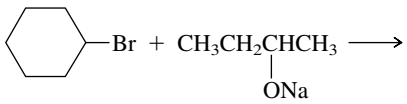
16.24 The most stable conformation of 1,3-dioxan-5-ol is the chair form that has its hydroxyl group in an axial orientation. Suggest a reasonable explanation for this fact. Building a molecular model is helpful.

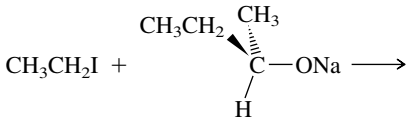


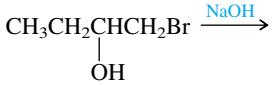
1,3-Dioxan-5-ol

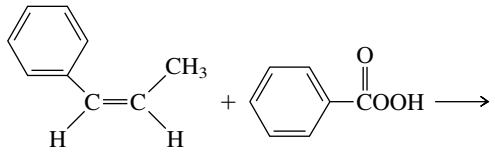
16.25 Outline the steps in the preparation of each of the constitutionally isomeric ethers of molecular formula $C_4H_{10}O$, starting with the appropriate alcohols. Use the Williamson ether synthesis as your key reaction.

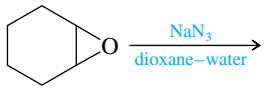
16.26 Predict the principal organic product of each of the following reactions. Specify stereochemistry where appropriate.

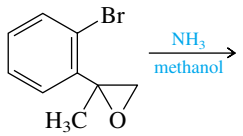
(a) 

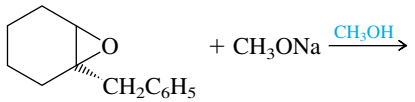
(b) 

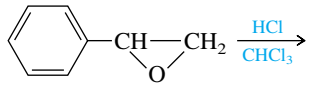
(c) 

(d) 

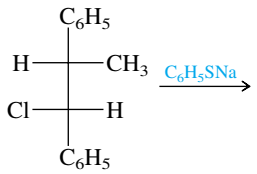
(e) 

(f) 

(g) 

(h) 

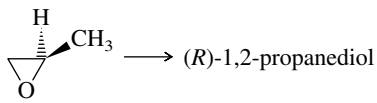
(i) $CH_3(CH_2)_{16}CH_2OTs + CH_3CH_2CH_2CH_2SNa \longrightarrow$

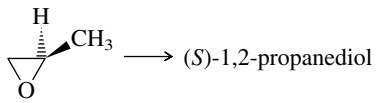
(j) 

16.27 Oxidation of 4-*tert*-butylthiane (see Problem 16.23 for the structure of thiane) with sodium metaperiodate gives a mixture of two compounds of molecular formula $C_9H_{18}OS$. Both products give the same sulfone on further oxidation with hydrogen peroxide. What is the relationship between the two compounds?

16.28 When (*R*)-(+)-2-phenyl-2-butanol is allowed to stand in methanol containing a few drops of sulfuric acid, racemic 2-methoxy-2-phenylbutane is formed. Suggest a reasonable mechanism for this reaction.

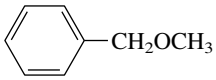
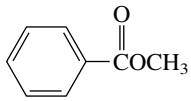
16.29 Select reaction conditions that would allow you to carry out each of the following stereospecific transformations:

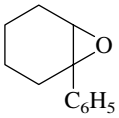
(a)  (*R*)-1,2-propanediol

(b)  (*S*)-1,2-propanediol

16.30 The last step in the synthesis of divinyl ether (used as an anesthetic under the name *Vinethene*) involves heating $ClCH_2CH_2OCH_2CH_2Cl$ with potassium hydroxide. Show how you could prepare the necessary starting material $ClCH_2CH_2OCH_2CH_2Cl$ from ethylene.

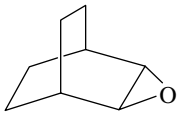
16.31 Suggest short, efficient reaction sequences suitable for preparing each of the following compounds from the given starting materials and any necessary organic or inorganic reagents:

(a)  from 

(b)  from bromobenzene and cyclohexanol

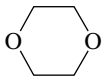
(c) $C_6H_5CH_2CHCH_3$ (OH) from bromobenzene and isopropyl alcohol

(d) $C_6H_5CH_2CH_2CH_2OCH_2CH_3$ from benzyl alcohol and ethanol

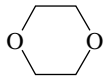
(e)  from 1,3-cyclohexadiene and ethanol

(f) $C_6H_5CHCH_2SCH_2CH_3$ (OH) from styrene and ethanol

16.32 Among the ways in which 1,4-dioxane may be prepared are the methods expressed in the equations shown:

(a) $2HOCH_2CH_2OH \xrightarrow[\text{heat}]{H_2SO_4}$  $+ 2H_2O$

Ethylene glycol — 1,4-Dioxane — Water

(b) $ClCH_2CH_2OCH_2CH_2Cl \xrightarrow{NaOH}$ 

Bis(2-chloroethyl) ether — 1,4-Dioxane

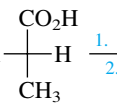
Suggest reasonable mechanisms for each of these reactions.

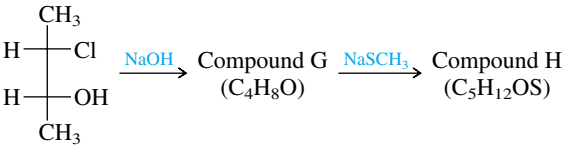
16.33 Deduce the identity of the missing compounds in the following reaction sequences. Show stereochemistry in parts (b) through (d).

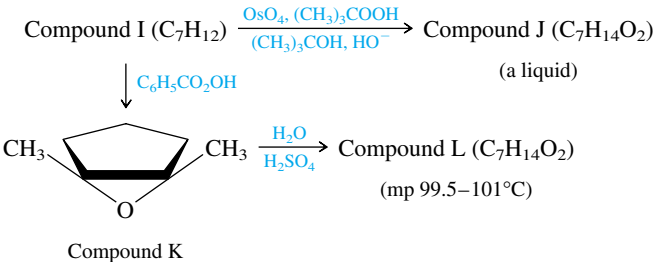
(a) $CH_2{=}CHCH_2Br \xrightarrow[2.\ CH_2{=}O\ \ 3.\ H_3O^+]{1.\ Mg}$ Compound A $(C_4H_8O) \xrightarrow{Br_2}$ Compound B $(C_4H_8Br_2O)$

Compound B $\xrightarrow{KOH,\ 25°C}$ Compound C $(C_4H_7BrO) \xrightarrow[\text{heat}]{KOH}$ 

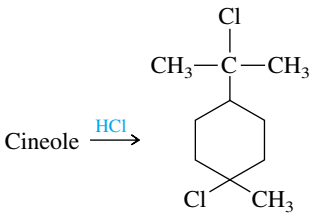
Compound D

(b)  $\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$ Compound E $(C_3H_7ClO) \xrightarrow{KOH,\ H_2O}$ Compound F (C_3H_6O)

(c) 

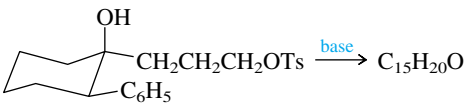
(d) 

16.34 Cineole is the chief component of eucalyptus oil; it has the molecular formula $C_{10}H_{18}O$ and contains no double or triple bonds. It reacts with hydrochloric acid to give the dichloride shown:



Deduce the structure of cineole.

16.35 The *p*-toluenesulfonate shown undergoes an intramolecular Williamson reaction on treatment with base to give a spirocyclic ether. Demonstrate your understanding of the terminology used in the preceding sentence by writing the structure, including stereochemistry, of the product.



16.36 All the following questions pertain to ^{1}H NMR spectra of isomeric ethers having the molecular formula $C_5H_{12}O$.

(a) Which one has only singlets in its ^{1}H NMR spectrum?

(b) Along with other signals, this ether has a coupled doublet–septet pattern. None of the protons responsible for this pattern are coupled to protons anywhere else in the molecule. Identify this ether.

(c) In addition to other signals in its ^{1}H NMR spectrum, this ether exhibits two signals at relatively low field. One is a singlet; the other is a doublet. What is the structure of this ether?

(d) In addition to other signals in its ^{1}H NMR spectrum, this ether exhibits two signals at relatively low field. One is a triplet; the other is a quartet. Which ether is this?

16.37 The ^{1}H NMR spectrum of compound A (C_8H_8O) consists of two singlets of equal area at δ 5.1 (sharp) and 7.2 ppm (broad). On treatment with excess hydrogen bromide, compound A is converted to a single dibromide ($C_8H_8Br_2$). The ^{1}H NMR spectrum of the dibromide is similar to that of A in that it exhibits two singlets of equal area at δ 4.7 (sharp) and 7.3 ppm (broad). Suggest reasonable structures for compound A and the dibromide derived from it.

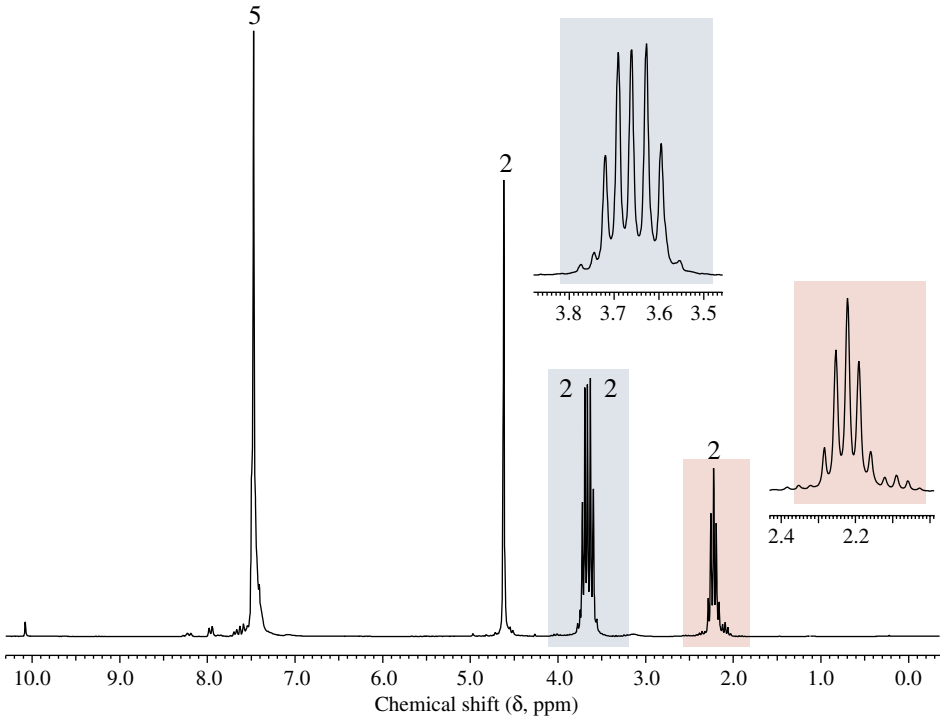


FIGURE 16.10 The 200-MHz ^{1}H NMR spectrum of a compound, $C_{10}H_{13}BrO$ (Problem 16.38). The integral ratios of the signals reading from left to right (low to high field) are 5:2:2:2:2. The signals centered at 3.6 and 3.7 ppm are two overlapping triplets.

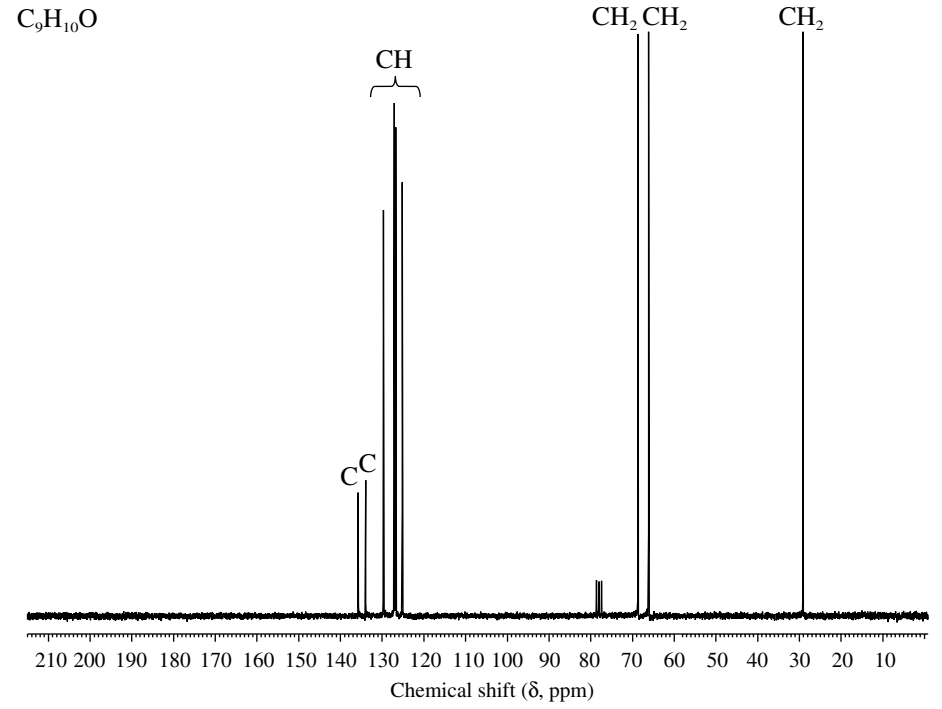


FIGURE 16.11 The ^{13}C NMR spectrum of a compound, $C_9H_{10}O$ (Problem 16.39).

16.38 The ^{1}H NMR spectrum of a compound ($C_{10}H_{13}BrO$) is shown in Figure 16.10. The compound gives benzyl bromide, along with a second compound $C_3H_6Br_2$, when heated with HBr. What is the first compound?

16.39 A compound is a cyclic ether of molecular formula $C_9H_{10}O$. Its ^{13}C NMR spectrum is shown in Figure 16.11. Oxidation of the compound with sodium dichromate and sulfuric acid gave 1,2-benzenedicarboxylic acid. What is the compound?

16.40 Make a molecular model of dimethyl sulfide. How does its bond angle at sulfur compare with the C—O—C bond angle in dimethyl ether?

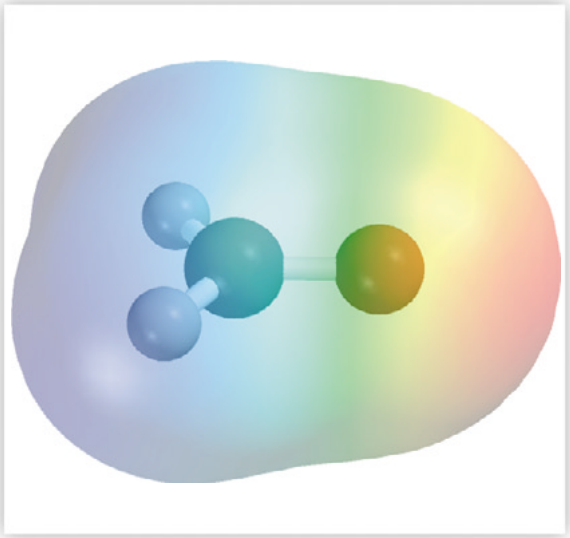
16.41 View molecular models of dimethyl ether and ethylene oxide on *Learning By Modeling.* Which one has the greater dipole moment? Do the calculated dipole moments bear any relationship to the observed boiling points (ethylene oxide: +10°C; dimethyl ether: −25°C)?

16.42 Find the molecular model of 18-crown-6 (Figure 16.2) on *Learning By Modeling,* and examine its electrostatic potential surface. View the surface in various modes (dots, contours, and as a transparent surface). Does 18-crown-6 have a dipole moment? Are vicinal oxygens anti or gauche to one another?

16.43 Find the model of dimethyl sulfoxide [$(CH_3)_2S{=}O$] on *Learning By Modeling,* and examine its electrostatic potential surface. To which atom (S or O) would you expect a proton to bond?

16.44 Construct a molecular model of *trans*-2-bromocyclohexanol in its most stable conformation. This conformation is ill-suited to undergo epoxide formation on treatment with base. Why? What must happen in order to produce 1,2-epoxycyclohexane from *trans*-2-bromocyclohexanol?

16.45 Construct a molecular model of *threo*-3-bromo-2-butanol. What is the stereochemistry (cis or trans) of the 2,3-epoxybutane formed on treatment of *threo*-3-bromo-2-butanol with base? Repeat the exercise for *erythro*-3-bromo-2-butanol.



CHAPTER 17

ALDEHYDES AND KETONES: NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

Aldehydes and ketones contain an acyl group $RC(=O)-$ bonded either to hydrogen or to another carbon.

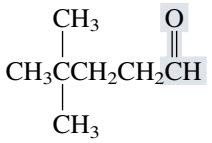
$HC(=O)H$	$RC(=O)H$	$RC(=O)R'$
Formaldehyde	Aldehyde	Ketone

Although the present chapter includes the usual collection of topics designed to acquaint us with a particular class of compounds, its central theme is a fundamental reaction type, *nucleophilic addition to carbonyl groups.* The principles of nucleophilic addition to aldehydes and ketones developed here will be seen to have broad applicability in later chapters when transformations of various derivatives of carboxylic acids are discussed.

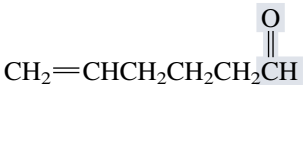
17.1 NOMENCLATURE

The longest continuous chain that contains the $-C(=O)H$ group provides the base name for aldehydes. The *-e* ending of the corresponding alkane name is replaced by *-al,* and substituents are specified in the usual way. It is not necessary to specify the location of the $-C(=O)H$ group in the name, since the chain must be numbered by starting with this group as C-1. The suffix *-dial* is added to the appropriate alkane name when the compound contains two aldehyde functions.*

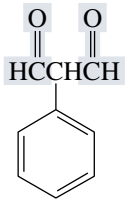
* The *-e* ending of an alkane name is dropped before a suffix beginning with a vowel *(-al)* and retained before one beginning with a consonant *(-dial).*



4,4-Dimethylpentanal

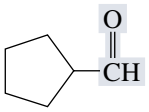


5-Hexenal

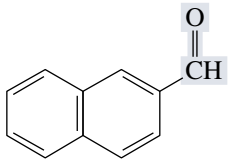


2-Phenylpropanedial

When a formyl group (—CH═O) is attached to a ring, the ring name is followed by the suffix *-carbaldehyde*.



Cyclopentanecarbaldehyde

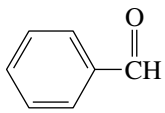


2-Naphthalenecarbaldehyde

Certain common names of familiar aldehydes are acceptable as IUPAC names. A few examples include

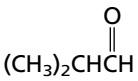
Formaldehyde
(methanal)

Acetaldehyde
(ethanal)

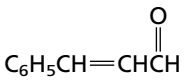


Benzaldehyde
(benzenecarbaldehyde)

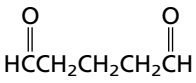
PROBLEM 17.1 The common names and structural formulas of a few aldehydes follow. Provide an IUPAC name.

(a) 

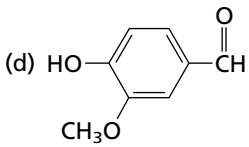
(isobutyraldehyde)

(c) 

(cinnamaldehyde)

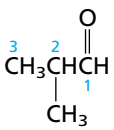
(b) 

(glutaraldehyde)

(d) 

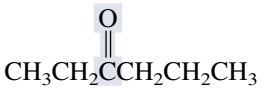
(vanillin)

SAMPLE SOLUTION (a) Don't be fooled by the fact that the common name is isobutyraldehyde. The longest continuous chain has three carbons, and so the base name is *propanal*. There is a methyl group at C-2; thus the compound is 2-methylpropanal.

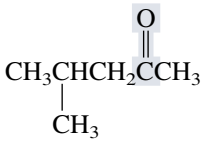


2-Methylpropanal
(isobutyraldehyde)

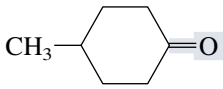
With ketones, the *-e* ending of an alkane is replaced by *-one* in the longest continuous chain containing the carbonyl group. The chain is numbered in the direction that provides the lower number for this group.



3-Hexanone

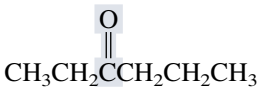


4-Methyl-2-pentanone

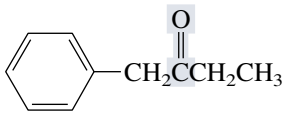


4-Methylcyclohexanone

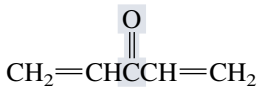
Although substitutive names of the type just described are preferred, the IUPAC rules also permit ketones to be named by functional class nomenclature. The groups attached to the carbonyl group are named as separate words followed by the word "ketone." The groups are listed alphabetically.



Ethyl propyl ketone



Benzyl ethyl ketone

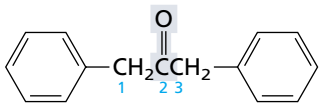


Divinyl ketone

PROBLEM 17.2 Convert each of the following functional class IUPAC names to a substitutive name.

(a) Dibenzyl ketone
(b) Ethyl isopropyl ketone
(c) Methyl 2,2-dimethylpropyl ketone
(d) Allyl methyl ketone

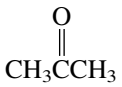
SAMPLE SOLUTION (a) First write the structure corresponding to the name. Dibenzyl ketone has two benzyl groups attached to a carbonyl.



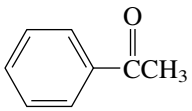
Dibenzyl ketone

The longest continuous chain contains three carbons, and C-2 is the carbon of the carbonyl group. The substitutive IUPAC name for this ketone is *1,3-diphenyl-2-propanone.*

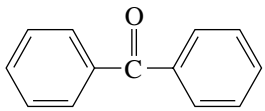
A few of the common names acceptable for ketones in the IUPAC system are



Acetone



Acetophenone

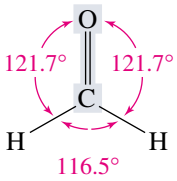


Benzophenone

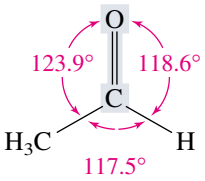
(The suffix *-phenone* indicates that the acyl group is attached to a benzene ring.)

17.2 STRUCTURE AND BONDING: THE CARBONYL GROUP

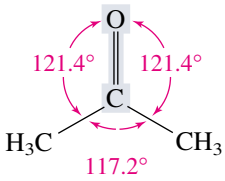
Two notable aspects of the carbonyl group are its geometry and its polarity. The carbonyl group and the atoms directly attached to it lie in the same plane. Formaldehyde, for example, is planar. The bond angles involving the carbonyl group of aldehydes and ketones are close to 120°.



Formaldehyde



Acetaldehyde



Acetone


Verify their geometries by making models of formaldehyde, acetaldehyde, and acetone. Make sure you execute the minimization routine.

At 122 pm, the carbon–oxygen double bond distance in aldehydes and ketones is significantly shorter than the typical carbon–oxygen single bond distance of 141 pm in alcohols and ethers.

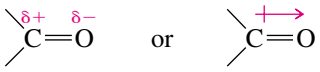
The carbonyl group makes aldehydes and ketones rather polar, with molecular dipole moments that are substantially larger than those of comparable compounds that contain carbon–carbon double bonds.

$CH_3CH_2CH{=}CH_2$	$CH_3CH_2CH{=}O$
1-Butene	Propanal
Dipole moment: 0.3 D	Dipole moment: 2.5 D


Compare the dipole moments and electrostatic potential maps of 1-butene and propanal on *Learning By Modeling.*

Bonding in formaldehyde can be described according to an sp^2 hybridization model analogous to that of ethylene, as shown in Figure 17.1.

Figure 17.2 compares the electrostatic potential surfaces of ethylene and formaldehyde and vividly demonstrates how oxygen affects the electron distribution in formaldehyde. The electron density in both the σ and π components of the carbon–oxygen double bond is displaced toward oxygen. The carbonyl group is polarized so that carbon is partially positive and oxygen is partially negative.



In resonance terms, electron delocalization in the carbonyl group is represented by contributions from two principal resonance structures:

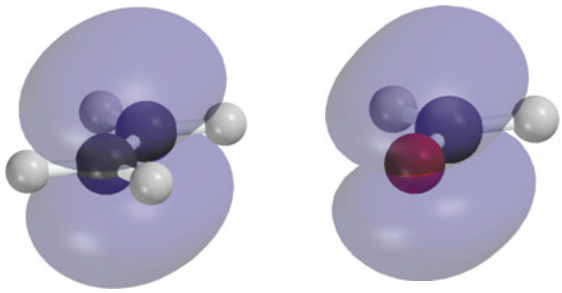

(*a*) Ethylene (*b*) Formaldehyde


FIGURE 17.1 Similarities between the orbital hybridization models of bonding in (*a*) ethylene and (*b*) formaldehyde. Both molecules have the same number of electrons, and carbon is sp^2-hybridized in both. In formaldehyde, one of the carbons is replaced by an sp^2-hybridized oxygen *(shown in red).* Oxygen has two unshared electron pairs; each pair occupies an sp^2-hybridized orbital. Like the carbon–carbon double bond of ethylene, the carbon–oxygen double bond of formaldehyde is composed of a two-electron σ component and a two-electron π component.

(*a*) Ethylene (*b*) Formaldehyde

FIGURE 17.2 Differences in the electron distribution of (*a*) ethylene and (*b*) formaldehyde. The region of highest electrostatic potential (*red*) in ethylene lies above and below the plane of the atoms and is associated with the π electrons. The region close to oxygen is the site of highest electrostatic potential in formaldehyde.

The chemistry of the carbonyl group is considerably simplified if you remember that carbon is partially positive (has carbocation character) and oxygen is partially negative (weakly basic).

A B

Of these two, A, having one more covalent bond and avoiding the separation of positive and negative charges that characterizes B, better approximates the bonding in a carbonyl group.

Alkyl substituents stabilize a carbonyl group in much the same way that they stabilize carbon–carbon double bonds and carbocations—by releasing electrons to sp^2-hybridized carbon. Thus, as their heats of combustion reveal, the ketone 2-butanone is more stable than its aldehyde isomer butanal.

	$CH_3CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}H$	$CH_3CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_3$
	Butanal	2-Butanone
Heat of combustion:	2475 kJ/mol (592 kcal/mol)	2442 kJ/mol (584 kcal/mol)

The carbonyl carbon of a ketone bears two electron-releasing alkyl groups; an aldehyde carbonyl group has only one. Just as a disubstituted double bond in an alkene is more stable than a monosubstituted double bond, a ketone carbonyl is more stable than an aldehyde carbonyl. We'll see later in this chapter that structural effects on the relative *stability* of carbonyl groups in aldehydes and ketones are an important factor in their relative *reactivity*.

17.3 PHYSICAL PROPERTIES

Physical constants such as melting point, boiling point, and solubility in water are collected for a variety of aldehydes and ketones in Appendix 1.

In general, aldehydes and ketones have higher boiling points than alkenes because they are more polar and the dipole–dipole attractive forces between molecules are stronger. But they have lower boiling points than alcohols because, unlike alcohols, two carbonyl groups can't form hydrogen bonds to each other.

	$CH_3CH_2CH{=}CH_2$	$CH_3CH_2CH{=}O$	$CH_3CH_2CH_2OH$
	1-Butene	Propanal	1-Propanol
bp (1 atm)	−6°C	49°C	97°C
Solubility in water (g/100 mL)	Negligible	20	Miscible in all proportions

Aldehydes and ketones can form hydrogen bonds with the protons of OH groups. This makes them more soluble in water than alkenes, but less soluble than alcohols.

17.4 SOURCES OF ALDEHYDES AND KETONES

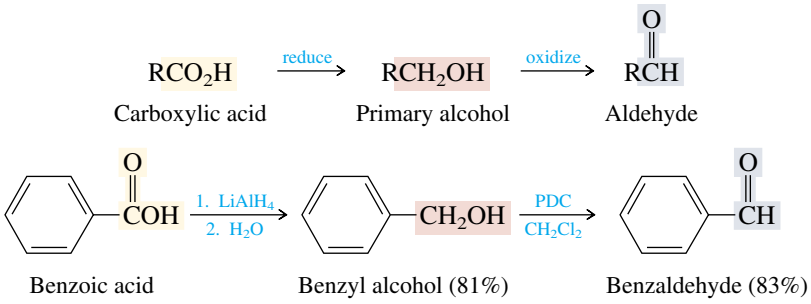
As we'll see later in this chapter and the next, aldehydes and ketones are involved in many of the most used reactions in synthetic organic chemistry. Where do aldehydes and ketones come from?

Many occur naturally. In terms of both variety and quantity, aldehydes and ketones rank among the most common and familiar natural products. Several are shown in Figure 17.3.

Many are made in the laboratory from alkenes, alkynes, arenes, and alcohols by reactions that you already know about and are summarized in Table 17.1.

To the synthetic chemist, the most important of the reactions in Table 17.1 are the last two: the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones. *Indeed, when combined with reactions that yield alcohols, the oxidation methods are so versatile that it will not be necessary to introduce any new methods for preparing aldehydes and ketones in this chapter.* A few examples will illustrate this point.

Let's first consider how to prepare an aldehyde from a carboxylic acid. There are no good methods for going from RCO_2H to RCHO directly. Instead, we do it indirectly by first reducing the carboxylic acid to the corresponding primary alcohol, then oxidizing the primary alcohol to the aldehyde.



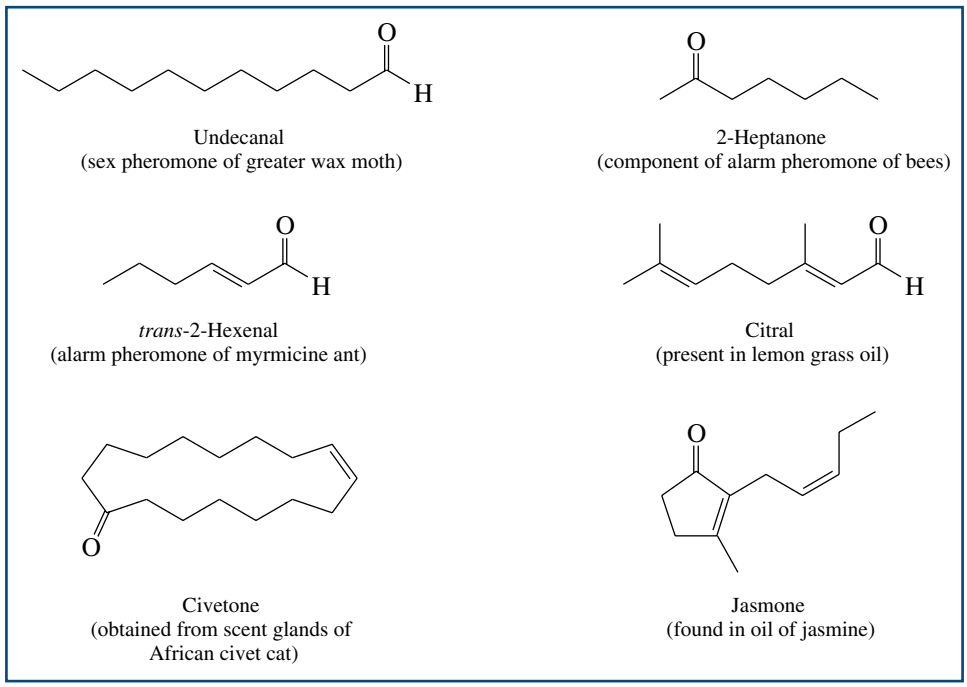
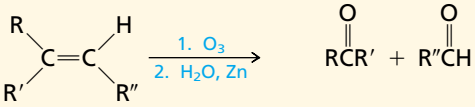
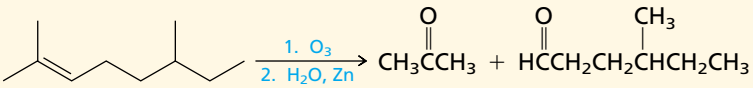
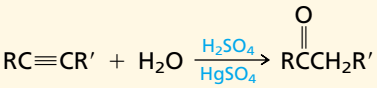
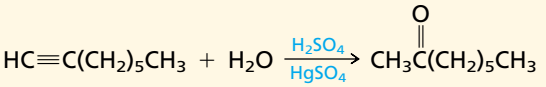
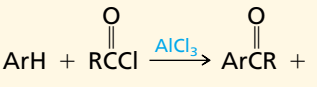
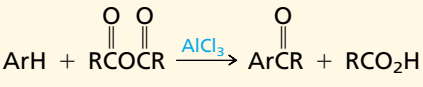
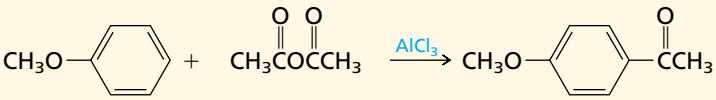
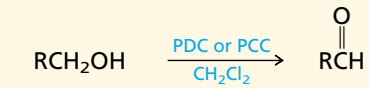
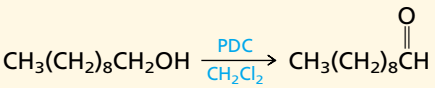
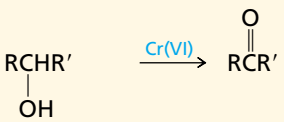
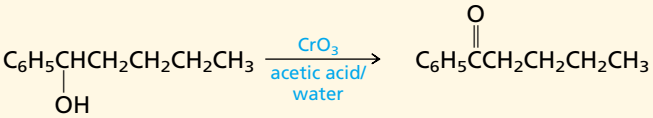


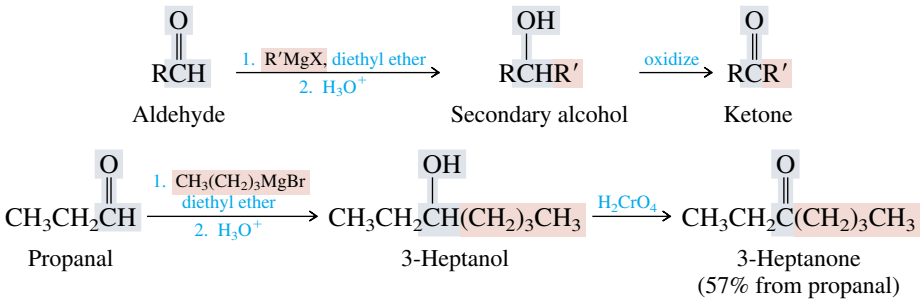
FIGURE 17.3 Some naturally occurring aldehydes and ketones.

TABLE 17.1 Summary of Reactions Discussed in Earlier Chapters That Yield Aldehydes and Ketones

Reaction (section) and comments	General equation and specific example
Ozonolysis of alkenes (Section 6.19) This cleavage reaction is more often seen in structural analysis than in synthesis. The substitution pattern around a double bond is revealed by identifying the carbonyl-containing compounds that make up the product. Hydrolysis of the ozonide intermediate in the presence of zinc (reductive workup) permits aldehyde products to be isolated without further oxidation.	 Alkene — Two carbonyl compounds  2,6-Dimethyl-2-octene — Acetone — 4-Methylhexanal (91%)
Hydration of alkynes (Section 9.12) Reaction occurs by way of an enol intermediate formed by Markovnikov addition of water to the triple bond.	 Alkyne — Ketone  1-Octyne — 2-Octanone (91%)
Friedel–Crafts acylation of aromatic compounds (Section 12.7) Acyl chlorides and carboxylic acid anhydrides acylate aromatic rings in the presence of aluminum chloride. The reaction is electrophilic aromatic substitution in which acylium ions are generated and attack the ring.	 or   Anisole — Acetic anhydride — *p*-Methoxyacetophenone (90–94%)
Oxidation of primary alcohols to aldehydes (Section 15.10) Pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) in anhydrous media such as dichloromethane oxidizes primary alcohols to aldehydes while avoiding overoxidation to carboxylic acids.	 Primary alcohol — Aldehyde  1-Decanol — Decanal (98%)
Oxidation of secondary alcohols to ketones (Section 15.10) Many oxidizing agents are available for converting secondary alcohols to ketones. PDC or PCC may be used, as well as other Cr(VI)-based agents such as chromic acid or potassium dichromate and sulfuric acid.	 Secondary alcohol — Ketone  1-Phenyl-1-pentanol — 1-Phenyl-1-pentanone (93%)

PROBLEM 17.3 Can catalytic hydrogenation be used to reduce a carboxylic acid to a primary alcohol in the first step of this sequence?

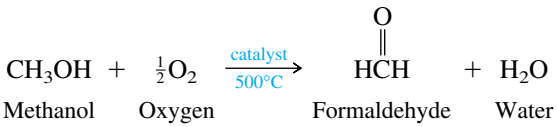
It is often necessary to prepare ketones by processes involving carbon–carbon bond formation. In such cases the standard method combines addition of a Grignard reagent to an aldehyde with oxidation of the resulting secondary alcohol:



PROBLEM 17.4 Show how 2-butanone could be prepared by a procedure in which all of the carbons originate in acetic acid (CH_3CO_2H).

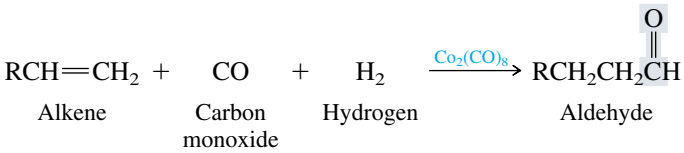
Many low-molecular-weight aldehydes and ketones are important industrial chemicals. Formaldehyde, a starting material for a number of plastics, is prepared by oxidation of methanol over a silver or iron oxide/molybdenum oxide catalyst at elevated temperature.

The name *aldehyde* was invented to stand for *al*cohol *dehyd*rogenatum, indicating that aldehydes are related to alcohols by loss of hydrogen.



Similar processes are used to convert ethanol to acetaldehyde and isopropyl alcohol to acetone.

The "linear α-olefins" described in Section 14.15 are starting materials for the preparation of a variety of aldehydes by reaction with carbon monoxide. The process is called **hydroformylation.**



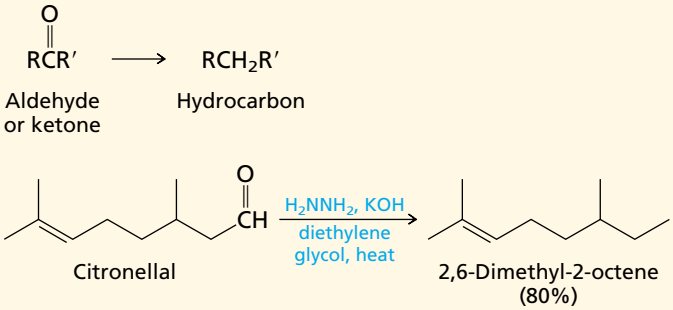
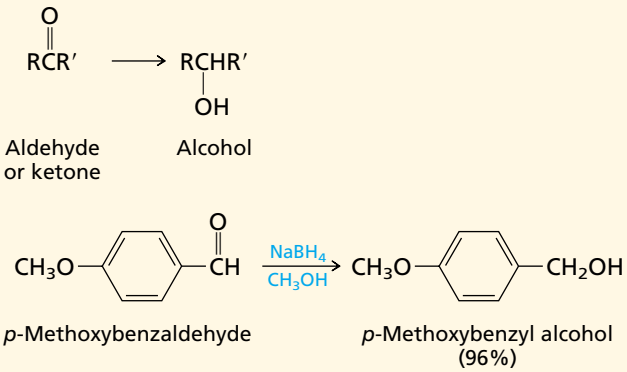
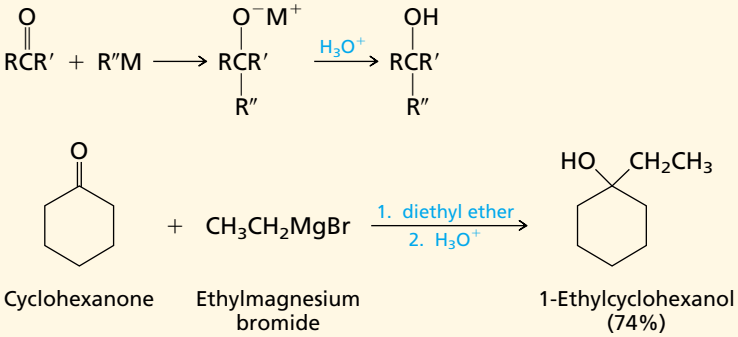
Excess hydrogen brings about the hydrogenation of the aldehyde and allows the process to be adapted to the preparation of primary alcohols. Over 2×10^9 lb/year of a variety of aldehydes and alcohols is prepared in the United States by hydroformylation.

A number of aldehydes and ketones are prepared both in industry and in the laboratory by a reaction known as the *aldol condensation,* which will be discussed in detail in Chapter 18.

17.5 REACTIONS OF ALDEHYDES AND KETONES: A REVIEW AND A PREVIEW

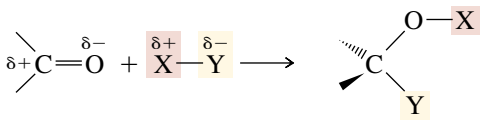
Table 17.2 summarizes the reactions of aldehydes and ketones that you've seen in earlier chapters. All are valuable tools to the synthetic chemist. Carbonyl groups provide access to hydrocarbons by Clemmensen of Wolff–Kishner reduction (Section 12.8), to

TABLE 17.2 Summary of Reactions of Aldehydes and Ketones Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Reduction to hydrocarbons (Section 12.8) Two methods for converting carbonyl groups to methylene units are the Clemmensen reduction (zinc amalgam and concentrated hydrochloric acid) and the Wolff–Kishner reduction (heat with hydrazine and potassium hydroxide in a high-boiling alcohol).	
Reduction to alcohols (Section 15.2) Aldehydes are reduced to primary alcohols, and ketones are reduced to secondary alcohols by a variety of reducing agents. Catalytic hydrogenation over a metal catalyst and reduction with sodium borohydride or lithium aluminum hydride are general methods.	
Addition of Grignard reagents and organolithium compounds (Sections 14.6–14.7) Aldehydes are converted to secondary alcohols and ketones to tertiary alcohols.	

alcohols by reduction (Section 15.2) or by reaction with Grignard or organolithium reagents (Sections 14.6 and 14.7).

The most important chemical property of the carbonyl group is its tendency to undergo *nucleophilic addition* reactions of the type represented in the general equation:

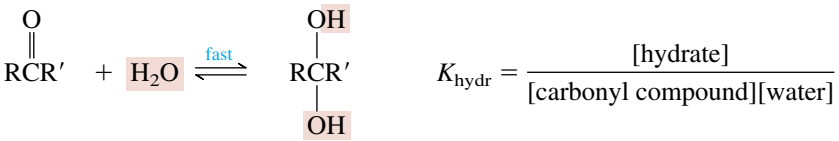


A negatively polarized atom or group attacks the positively polarized carbon of the carbonyl group in the rate-determining step of these reactions. Grignard reagents, organolithium reagents, lithium aluminum hydride, and sodium borohydride, for example, all react with carbonyl compounds by nucleophilic addition.

The next section explores the mechanism of nucleophilic addition to aldehydes and ketones. There we'll discuss their *hydration,* a reaction in which water adds to the C=O group. After we use this reaction to develop some general principles, we'll then survey a number of related reactions of synthetic, mechanistic, or biological interest.

17.6 PRINCIPLES OF NUCLEOPHILIC ADDITION: HYDRATION OF ALDEHYDES AND KETONES

Effects of Structure on Equilibrium: Aldehydes and ketones react with water in a rapid equilibrium:



$$K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$$

Overall, the reaction is classified as an *addition.* The elements of water add to the carbonyl group. Hydrogen becomes bonded to the negatively polarized carbonyl oxygen, hydroxyl to the positively polarized carbon.

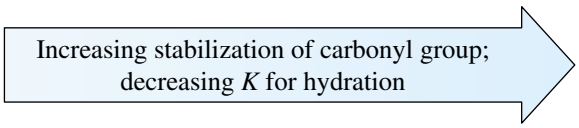
Table 17.3 compares the equilibrium constants K_{hydr} for hydration of some simple aldehydes and ketones. The position of equilibrium depends on what groups are attached to C=O and how they affect its *steric* and *electronic* environment. Both effects contribute, but the electronic effect controls K_{hydr} more than the steric effect.

TABLE 17.3 Equilibrium Constants (K_{hydr}) for Hydration of Some Aldehydes and Ketones

Carbonyl compound	Hydrate	K_{hydr}*	Percent conversion to hydrate†
HCH=O	$CH_2(OH)_2$	41	99.96
CH_3CH=O	$CH_3CH(OH)_2$	1.8×10^{-2}	50
$(CH_3)_3CCH$=O	$(CH_3)_3CCH(OH)_2$	4.1×10^{-3}	19
CH_3CCH_3=O	$(CH_3)_2C(OH)_2$	2.5×10^{-5}	0.14

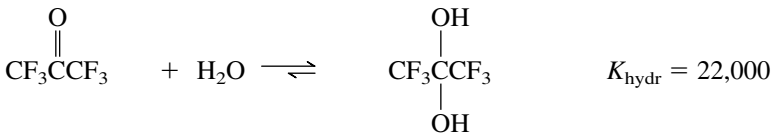
*$K_{hydr} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}][\text{water}]}$. Units of K_{hydr} are M^{-1}.
†Total concentration (hydrate plus carbonyl compound) assumed to be 1 M. Water concentration is 55.5 M.

Consider first the electronic effect of alkyl groups versus hydrogen atoms attached to C═O. Recall from Section 17.2 that alkyl substituents stabilize C═O, making a ketone carbonyl more stable than an aldehyde carbonyl. As with all equilibria, factors that stabilize the reactants decrease the equilibrium constant. Thus, the extent of hydration decreases as the number of alkyl groups on the carbonyl increase.



Formaldehyde	Acetaldehyde	Acetone
(almost completely hydrated in water)	(comparable amounts of aldehyde and hydrate present in water)	(hardly any hydrate present in water)

A striking example of an electronic effect on carbonyl group stability and its relation to the equilibrium constant for hydration is seen in the case of hexafluoroacetone. In contrast to the almost negligible hydration of acetone, hexafluoroacetone is completely hydrated.

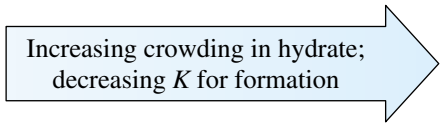


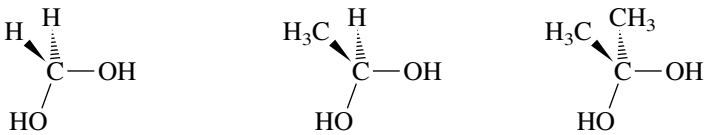
Hexafluoroacetone Water 1,1,1,3,3,3-Hexafluoro-2,2-propanediol

Instead of stabilizing the carbonyl group by electron donation as alkyl substituents do, trifluoromethyl groups destabilize it by withdrawing electrons. A less stabilized carbonyl group is associated with a greater equilibrium constant for addition.

PROBLEM 17.5 *Chloral* is one of the common names for trichloroethanal. A solution of chloral in water is called *chloral hydrate;* this material has featured prominently in countless detective stories as the notorious "Mickey Finn" knockout drops. Write a structural formula for chloral hydrate.

Now let's turn our attention to steric effects by looking at how the size of the groups that were attached to C═O affect K_{hydr}. The bond angles at carbon shrink from ≈120° to ≈109.5° as the hybridization changes from sp^2 in the reactant (aldehyde or ketone) to sp^3 in the product (hydrate). The increased crowding this produces in the hydrate is better tolerated, and K_{hydr} is greater when the groups are small (hydrogen) than when they are large (alkyl).





Hydrate of formaldehyde Hydrate of acetaldehyde Hydrate of acetone

Electronic and steric effects operate in the same direction. Both cause the equilibrium constants for hydration of aldehydes to be greater than those of ketones.

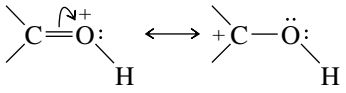
Mechanism of Hydration: Hydration of aldehydes and ketones is a rapid reaction, quickly reaching equilibrium, but faster in acid or base than in neutral solution. Thus instead of a single mechanism for hydration, we'll look at two mechanisms, one for basic and the other for acidic solution.

The base-catalyzed mechanism (Figure 17.4) is a two-step process in which the first step is rate-determining. In it, the nucleophile, a hydroxide ion, attacks the carbon of the carbonyl group and bonds to it. The product of this step is an alkoxide ion, which abstracts a proton from water in the second step, yielding the geminal diol. The second step, like all the other proton transfers between oxygens that we have seen, is fast.

The role of the basic catalyst (HO^-) is to increase the rate of the nucleophilic addition step. Hydroxide ion, the nucleophile in the base-catalyzed reaction, is much more reactive than a water molecule, the nucleophile in neutral media.

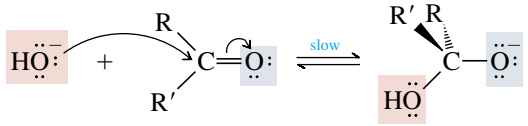
Aldehydes react faster than ketones for almost the same reasons that their equilibrium constants for hydration are more favorable. The $sp^2 \rightarrow sp^3$ hybridization change that the carbonyl carbon undergoes on hydration is partially developed in the transition state for the rate-determining nucleophilic addition step (Figure 17.5). Alkyl groups at the reaction site increase the activation energy by simultaneously lowering the energy of the starting state (ketones have a more stabilized carbonyl group than aldehydes) and raising the energy of the transition state (a steric crowding effect).

Three steps are involved in the acid-catalyzed hydration reaction, as shown in Figure 17.6. The first and last are rapid proton-transfer processes. The second is the nucleophilic addition step. The acid catalyst activates the carbonyl group toward attack by a weakly nucleophilic water molecule. Protonation of oxygen makes the carbonyl carbon of an aldehyde or a ketone much more electrophilic. Expressed in resonance terms, the protonated carbonyl has a greater degree of carbocation character than an unprotonated carbonyl.



Learning By Modeling includes models of formaldehyde ($H_2C{=}O$) and its protonated form ($H_2C{=}OH^+$). Compare the two with respect to their electrostatic potential maps and the degree of positive charge at carbon.

Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



Step 2: Proton transfer from water to the intermediate formed in the first step

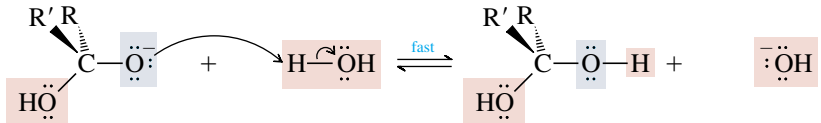


FIGURE 17.4 The mechanism of hydration of an aldehyde or ketone in basic solution. Hydroxide ion is a catalyst; it is consumed in the first step, and regenerated in the second.

FIGURE 17.5 Potential energy diagram for base-catalyzed hydration of an aldehyde or ketone.

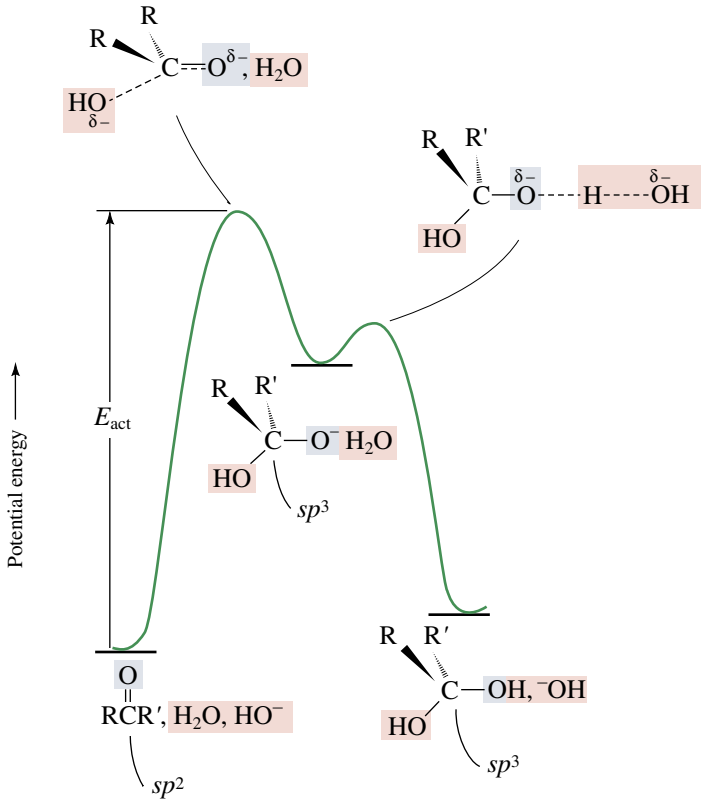
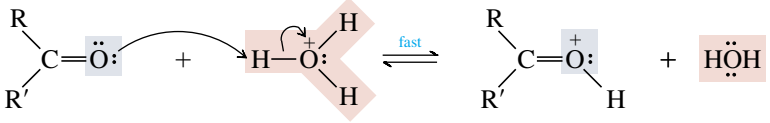


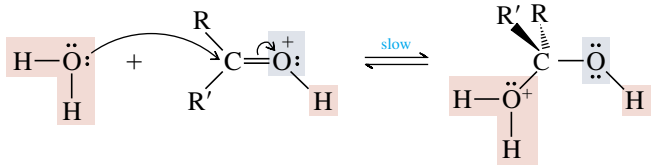
FIGURE 17.6 The mechanism of hydration of an aldehyde or ketone in acidic solution. Hydronium ion is a catalyst; it is consumed in the first step, and regenerated in the third.

Step 1: Protonation of the carbonyl oxgyen



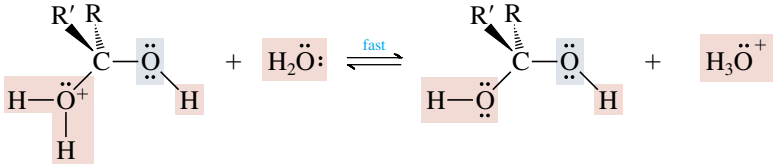
Aldehyde or ketone | Hydronium ion | Conjugate acid of carbonyl compound | Water

Step 2: Nucleophilic addition to the protonated aldehyde or ketone



Water | Conjugate acid of carbonyl compound | Conjugate acid of geminal diol

Step 3: Proton transfer from the conjugate acid of the geminal diol to a water molecule



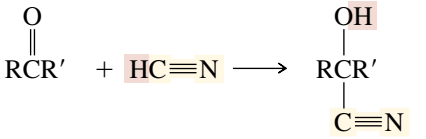
Conjugate acid of geminal diol | Water | Geminal diol | Hydronium ion

Steric and electronic effects influence the rate of nucleophilic addition to a protonated carbonyl group in much the same way as they do for the case of a neutral one, and protonated aldehydes react faster than protonated ketones.

With this as background, let us now examine how the principles of nucleophilic addition apply to the characteristic reactions of aldehydes and ketones. We'll begin with the addition of hydrogen cyanide.

17.7 CYANOHYDRIN FORMATION

The product of addition of hydrogen cyanide to an aldehyde or a ketone contains both a hydroxyl group and a cyano group bonded to the same carbon. Compounds of this type are called **cyanohydrins.**



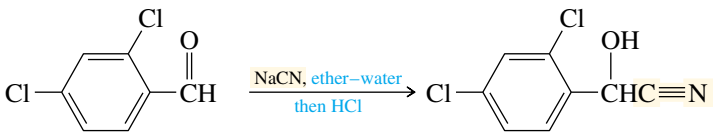
Aldehyde or ketone — Hydrogen cyanide — Cyanohydrin

The mechanism of this reaction is outlined in Figure 17.7. It is analogous to the mechanism of base-catalyzed hydration in that the nucleophile (cyanide ion) attacks the carbonyl carbon in the first step of the reaction, followed by proton transfer to the carbonyl oxygen in the second step.

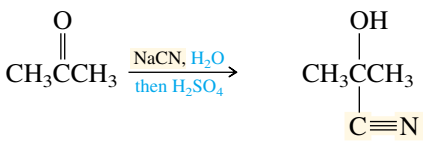
The addition of hydrogen cyanide is catalyzed by cyanide ion, but HCN is too weak an acid to provide enough $:\bar{C}\equiv N:$ for the reaction to proceed at a reasonable rate. Cyanohydrins are therefore normally prepared by adding an acid to a solution containing the carbonyl compound and sodium or potassium cyanide. This procedure ensures that free cyanide ion is always present in amounts sufficient to increase the rate of the reaction.

Cyanohydrin formation is reversible, and the position of equilibrium depends on the steric and electronic factors governing nucleophilic addition to carbonyl groups described in the preceding section. Aldehydes and unhindered ketones give good yields of cyanohydrins.

In substitutive IUPAC nomenclature, cyanohydrins are named as hydroxy derivatives of nitriles. Since nitrile nomenclature will not be discussed until Section 20.1, we will refer to cyanohydrins as derivatives of the parent aldehyde or ketone as shown in the examples. This conforms to the practice of most chemists.



2,4-Dichlorobenzaldehyde — 2,4-Dichlorobenzaldehyde cyanohydrin (100%)

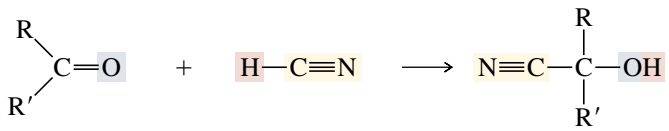


Acetone — Acetone cyanohydrin (77–78%)

Converting aldehydes and ketones to cyanohydrins is of synthetic value for two reasons: (1) a new carbon–carbon bond is formed, and (2) the cyano group in the product can be converted to a carboxylic acid function (CO_2H) by hydrolysis (to be discussed in Section 19.12) or to an amine of the type CH_2NH_2 by reduction (to be discussed in Section 22.10).

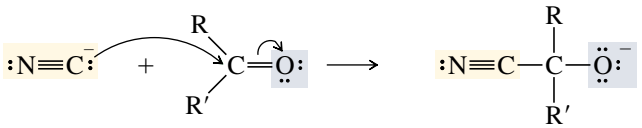
FIGURE 17.7 The mechanism of cyanohydrin formation from an aldehyde or a ketone. Cyanide ion is a catalyst; it is consumed in the first step, and regenerated in the second.

The overall reaction:



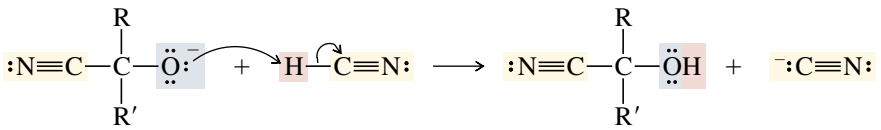
Aldehyde or ketone | Hydrogen cyanide | Cyanohydrin

Step 1: Nucleophilic attack by the negatively charged carbon of cyanide ion at the carbonyl carbon of the aldehyde or ketone. Hydrogen cyanide itself is not very nucleophilic and does not ionize to form cyanide ion to a significant extent. Thus, a source of cyanide ion such as NaCN or KCN is used.



Cyanide ion | Aldehyde or ketone | Conjugate base of cyanohydrin

Step 2: The alkoxide ion formed in the first step abstracts a proton from hydrogen cyanide. This step yields the cyanohydrin product and regenerates cyanide ion.



Conjugate base of cyanohydrin | Hydrogen cyanide | Cyanohydrin | Cyanide ion

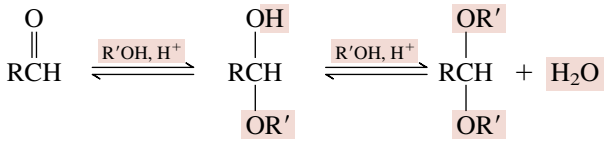
PROBLEM 17.6 The hydroxyl group of a cyanohydrin is also a potentially reactive site. *Methacrylonitrile* is an industrial chemical used in the production of plastics and fibers. One method for its preparation is the acid-catalyzed dehydration of acetone cyanohydrin. Deduce the structure of *methacrylonitrile.*

A few cyanohydrins and ethers of cyanohydrins occur naturally. One species of millipede stores benzaldehyde cyanohydrin, along with an enzyme that catalyzes its cleavage to benzaldehyde and hydrogen cyanide, in separate compartments above its legs. When attacked, the insect ejects a mixture of the cyanohydrin and the enzyme, repelling the invader by spraying it with hydrogen cyanide.

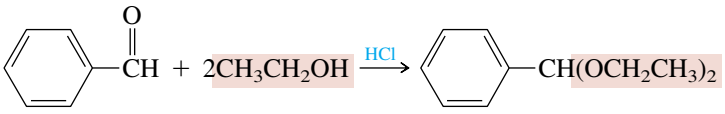
17.8 ACETAL FORMATION

Many of the most interesting and useful reactions of aldehydes and ketones involve transformation of the initial product of nucleophilic addition to some other substance under the reaction conditions. An example is the reaction of aldehydes with alcohols under con-

ditions of acid catalysis. The expected product of nucleophilic addition of the alcohol to the carbonyl group is called a **hemiacetal.** The product actually isolated, however, corresponds to reaction of one mole of the aldehyde with *two* moles of alcohol to give *geminal diethers* known as **acetals:**

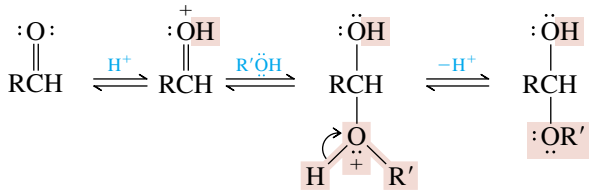


Aldehyde Hemiacetal Acetal Water



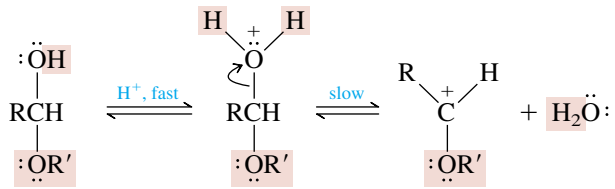
Benzaldehyde Ethanol Benzaldehyde diethyl acetal (66%)

The overall reaction proceeds in two stages. The hemiacetal is formed in the first stage by nucleophilic addition of the alcohol to the carbonyl group. The mechanism of hemiacetal formation is exactly analogous to that of acid-catalyzed hydration of aldehydes and ketones (Section 17.6):



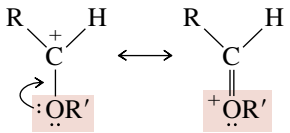
Aldehyde Hemiacetal

Under the acidic conditions of its formation, the hemiacetal is converted to an acetal by way of a carbocation intermediate:



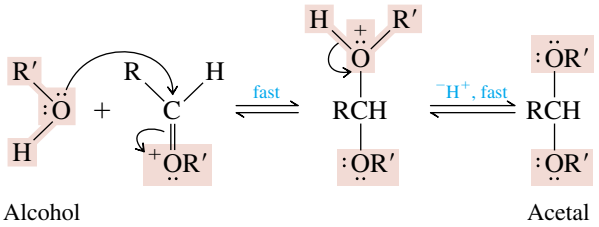
Hemiacetal Carbocation Water

This carbocation is stabilized by electron release from its oxygen substituent:



A particularly stable resonance form; both carbon and oxygen have octets of electrons.

Nucleophilic capture of the carbocation intermediate by an alcohol molecule leads to an acetal:



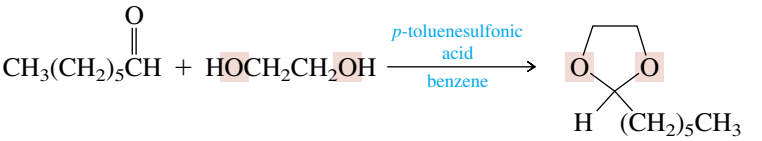
Alcohol Acetal

PROBLEM 17.7 Write a stepwise mechanism for the formation of benzaldehyde diethyl acetal from benzaldehyde and ethanol under conditions of acid catalysis.

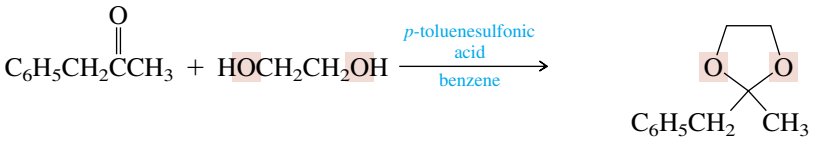
At one time it was customary to designate the products of addition of alcohols to ketones as *ketals*. This term has been dropped from the IUPAC system of nomenclature, and the term *acetal* is now applied to the adducts of both aldehydes and ketones.

Acetal formation is reversible in acid. An equilibrium is established between the reactants, that is, the carbonyl compound and the alcohol, and the acetal product. The position of equilibrium is favorable for acetal formation from most aldehydes, especially when excess alcohol is present as the reaction solvent. For most ketones the position of equilibrium is unfavorable, and other methods must be used for the preparation of acetals from ketones.

Diols that bear two hydroxyl groups in a 1,2 or 1,3 relationship to each other yield *cyclic acetals* on reaction with either aldehydes or ketones. The five-membered cyclic acetals derived from ethylene glycol are the most commonly encountered examples. Often the position of equilibrium is made more favorable by removing the water formed in the reaction by azeotropic distillation with benzene or toluene:



Heptanal Ethylene glycol (1,2-ethanediol) 2-Hexyl-1,3-dioxolane (81%)

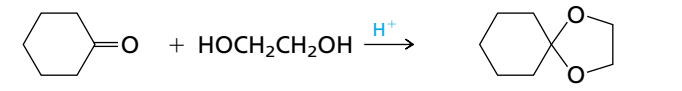


Benzyl methyl ketone Ethylene glycol (1,2-ethanediol) 2-Benzyl-2-methyl-1,3-dioxolane (78%)

PROBLEM 17.8 Write the structures of the cyclic acetals derived from each of the following.

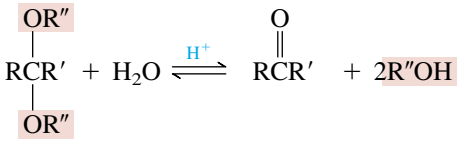
(a) Cyclohexanone and ethylene glycol
(b) Benzaldehyde and 1,3-propanediol
(c) Isobutyl methyl ketone and ethylene glycol
(d) Isobutyl methyl ketone and 2,2-dimethyl-1,3-propanediol

SAMPLE SOLUTION (a) The cyclic acetals derived from ethylene glycol contain a five-membered 1,3-dioxolane ring.



Cyclohexanone Ethylene glycol Acetal of cyclohexanone and ethylene glycol

Acetals are susceptible to hydrolysis in aqueous acid:



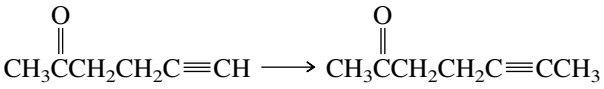
Acetal Aldehyde or ketone Alcohol

This reaction is simply the reverse of the reaction by which acetals are formed—acetal formation is favored by excess alcohol, acetal hydrolysis by excess water. Acetal formation and acetal hydrolysis share the same mechanistic pathway but travel along that pathway in opposite directions. In the following section you'll see a clever way in which acetal formation and hydrolysis have been applied to synthetic organic chemistry.

PROBLEM 17.9 Problem 17.7 asked you to write a mechanism describing formation of benzaldehyde diethyl acetal from benzaldehyde and ethanol. Write a stepwise mechanism for the acid hydrolysis of this acetal.

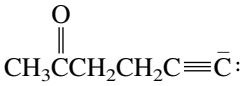
17.9 ACETALS AS PROTECTING GROUPS

In an organic synthesis, it sometimes happens that one of the reactants contains a functional group that is incompatible with the reaction conditions. Consider, for example, the conversion



5-Hexyn-2-one 5-Heptyn-2-one

It looks as though all that is needed is to prepare the acetylenic anion, then alkylate it with methyl iodide (Section 9.6). There is a complication, however. The carbonyl group in the starting alkyne will neither tolerate the strongly basic conditions required for anion formation nor survive in a solution containing carbanions. Acetylide ions add to carbonyl groups (Section 14.8). Thus, the necessary anion

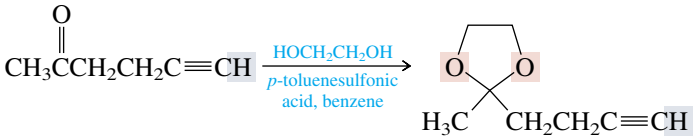


is inaccessible.

The strategy that is routinely followed is to *protect* the carbonyl group during the reactions with which it is incompatible and then to *remove* the protecting group in a subsequent step. Acetals, especially those derived from ethylene glycol, are among the most

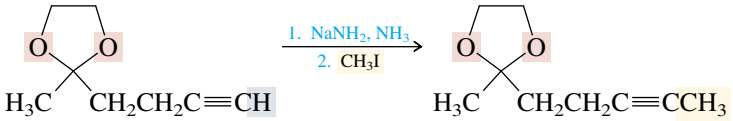
useful groups for carbonyl protection, because they can be introduced and removed readily. A key fact is that acetals resemble ethers in being inert to many of the reagents, such as hydride reducing agents and organometallic compounds, that react readily with carbonyl groups. The following sequence is the one that was actually used to bring about the desired transformation.

(a) Protection of carbonyl group



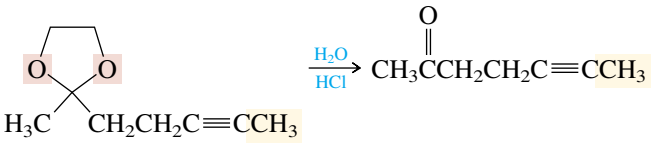
5-Hexyn-2-one Acetal of reactant

(b) Alkylation of alkyne



Acetal of product

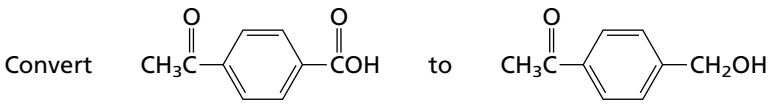
(c) Unmasking of the carbonyl group by hydrolysis



5-Heptyn-2-one (96%)

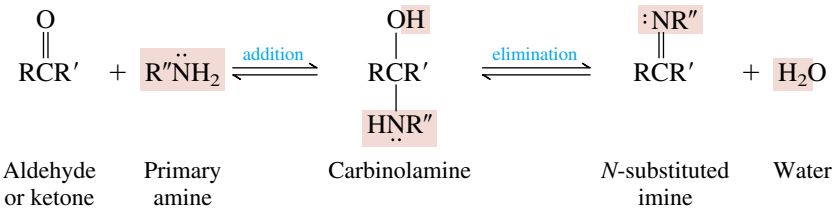
Although protecting and unmasking the carbonyl group add two steps to the synthetic procedure, both steps are essential to its success. The tactic of functional group protection is frequently encountered in preparative organic chemistry, and considerable attention has been paid to the design of effective protecting groups for a variety of functionalities.

PROBLEM 17.10 Acetal formation is a characteristic reaction of aldehydes and ketones, but not of carboxylic acids. Show how you could advantageously use a cyclic acetal protecting group in the following synthesis:

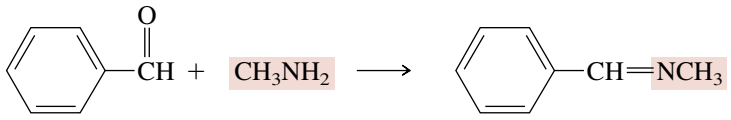


17.10 REACTION WITH PRIMARY AMINES: IMINES

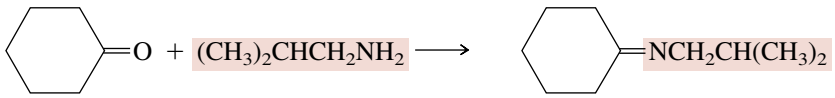
A second two-stage reaction that begins with nucleophilic addition to aldehydes and ketones is their reaction with primary amines, compounds of the type RNH_2 or $ArNH_2$. In the first stage of the reaction the amine adds to the carbonyl group to give a species known as a **carbinolamine.** Once formed, the carbinolamine undergoes dehydration to yield the product of the reaction, an *N*-alkyl- or *N*-aryl-substituted **imine:**



Aldehyde or ketone | Primary amine | Carbinolamine | *N*-substituted imine | Water



Benzaldehyde | Methylamine | *N*-Benzylidenemethylamine (70%)



Cyclohexanone | Isobutylamine | *N*-Cyclohexylideneisobutylamine (79%)

Both the addition and the elimination phase of the reaction are accelerated by acid catalysis. Careful control of pH is essential, since sufficient acid must be present to give a reasonable equilibrium concentration of the protonated form of the aldehyde or ketone. Too acidic a reaction medium, however, converts the amine to its protonated form, a form that is not nucleophilic, and retards reaction.

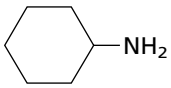
N-substituted imines are sometimes called **Schiff's bases,** after Hugo Schiff, a German chemist who described their formation in 1864.

PROBLEM 17.11 Write the structure of the carbinolamine intermediate and the imine product formed in the reaction of each of the following:

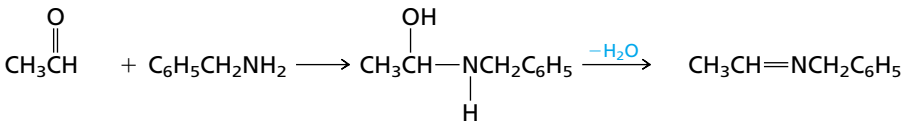
(a) Acetaldehyde and benzylamine, $C_6H_5CH_2NH_2$

(b) Benzaldehyde and butylamine, $CH_3CH_2CH_2CH_2NH_2$

(c) Cyclohexanone and *tert*-butylamine, $(CH_3)_3CNH_2$

(d) Acetophenone and cyclohexylamine, 

SAMPLE SOLUTION The carbinolamine is formed by nucleophilic addition of the amine to the carbonyl group. Its dehydration gives the imine product.



Acetaldehyde | Benzylamine | Carbinolamine intermediate | Imine product (*N*-ethylidenebenzylamine)

A number of compounds of the general type H_2NZ react with aldehydes and ketones in a manner analogous to that of primary amines. The carbonyl group (C=O) is converted to C=NZ, and a molecule of water is formed. Table 17.4 presents examples of some of these reactions. The mechanism by which each proceeds is similar to the nucleophilic addition–elimination mechanism described for the reaction of primary amines with aldehydes and ketones.

The reactions listed in Table 17.4 are reversible and have been extensively studied from a mechanistic perspective because of their relevance to biological processes.

TABLE 17.4 Reaction of Aldehydes and Ketones with Derivatives of Ammonia: $RCR' + H_2NZ \longrightarrow RCR' + H_2O$

Reagent (H_2NZ)	Name of reagent	Type of product	Example
H_2NOH	Hydroxylamine	Oxime	$CH_3(CH_2)_5CH \xrightarrow{H_2NOH} CH_3(CH_2)_5CH$ (NOH); Heptanal → Heptanal oxime (81–93%)
$H_2NNHC_6H_5$*	Phenylhydrazine	Phenylhydrazone	$C_6H_5CCH_3 \xrightarrow{H_2NNHC_6H_5} C_6H_5C(CH_3)$ ($NNHC_6H_5$); Acetophenone → Acetophenone phenylhydrazone (87–91%)
$H_2NNHCNH_2$	Semicarbazide	Semicarbazone	$CH_3C(CH_2)_9CH_3 \xrightarrow{H_2NNHCNH_2} CH_3C(CH_2)_9CH_3$ ($NNHCNH_2$); 2-Dodecanone → 2-Dodecanone semicarbazone (93%)

*Compounds related to phenylhydrazine react in an analogous way. *p*-Nitrophenylhydrazine yields *p*-nitrophenylhydrazones; 2,4-dinitrophenylhydrazine yields 2,4-dinitrophenylhydrazones.

Many biological reactions involve initial binding of a carbonyl compound to an enzyme or coenzyme via imine formation. The boxed essay "Imines in Biological Chemistry" gives some important examples.

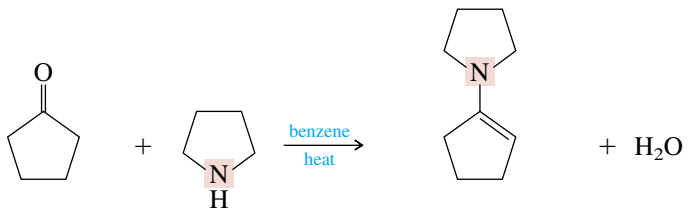
17.11 REACTION WITH SECONDARY AMINES: ENAMINES

Secondary amines are compounds of the type R_2NH. They add to aldehydes and ketones to form carbinolamines, but their carbinolamine intermediates can dehydrate to a stable product only in the direction that leads to a carbon–carbon double bond:

$$RCH_2CR' + R''_2\ddot{N}H \rightleftharpoons RCH_2C(OH)(NR''_2)R' \xrightleftharpoons{-H_2O} RCH{=}CR'(NR''_2)$$

Aldehyde or ketone | Secondary amine | Carbinolamine | Enamine

The product of this dehydration is an alkenyl-substituted amine, or **enamine.**



Cyclopentanone | Pyrrolidine | *N*-(1-Cyclopentenyl)-pyrrolidine (80–90%) | Water

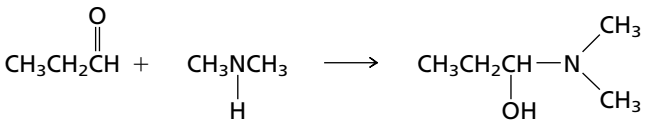
PROBLEM 17.12 Write the structure of the carbinolamine intermediate and the enamine product formed in the reaction of each of the following:

(a) Propanal and dimethylamine, CH_3NHCH_3

(b) 3-Pentanone and pyrrolidine

(c) Acetophenone and 

SAMPLE SOLUTION (a) Nucleophilic addition of dimethylamine to the carbonyl group of propanal produces a carbinolamine:



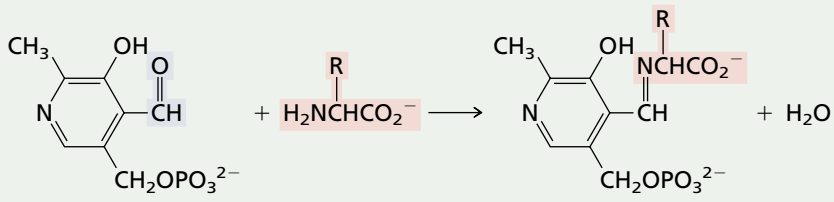
Propanal Dimethylamine Carbinolamine intermediate

IMINES IN BIOLOGICAL CHEMISTRY

Many biological processes involve an "association" between two species in a step prior to some subsequent transformation. This association can take many forms. It can be a weak association of the attractive van der Waals type, or a stronger interaction such as a hydrogen bond. It can be an electrostatic attraction between a positively charged atom of one molecule and a negatively charged atom of another. Covalent bond formation between two species of complementary chemical reactivity represents an extreme kind of "association." It often occurs in biological processes in which aldehydes or ketones react with amines via imine intermediates.

An example of a biologically important aldehyde is *pyridoxal phosphate.* Pyridoxal phosphate is the active form of *vitamin* B_6 and is a coenzyme for many of the reactions of α-amino acids. In these reactions the amino acid binds to the coenzyme by reacting with it to form an imine of the kind shown in the equation. Reactions then take place at the amino acid portion of the imine, modifying the amino acid. In the last step, enzyme-catalyzed hydrolysis cleaves the imine to pyridoxal and the modified amino acid.

A key step in the chemistry of vision is binding of an aldehyde to an enzyme via an imine. An outline of the steps involved is presented in Figure 17.8. It starts with *β-carotene,* a pigment that occurs naturally in several fruits and vegetables, including carrots. β-Carotene undergoes oxidative cleavage in the liver to give an alcohol known as *retinol* or *vitamin A.* Oxidation of vitamin A, followed by isomerization of one of its double bonds, gives the aldehyde 11-*cis*-retinal. In the eye, the aldehyde function of 11-*cis*-retinal combines with an amino group of the protein *opsin* to form an imine called *rhodopsin.* When rhodopsin absorbs a photon of visible light, the cis double bond of the retinal unit undergoes a photochemical cis-to-trans isomerization, which is attended by a dramatic change in its shape and a change in the conformation of rhodopsin. This conformational change is translated into a nerve impulse perceived by the brain as a visual image. Enzyme-promoted hydrolysis of the photochemically isomerized rhodopsin regenerates opsin and a molecule of all-*trans*-retinal. Once all-*trans*-retinal has been enzymatically converted to its 11-cis isomer, it and opsin reenter the cycle.



Pyridoxal phosphate α-Amino acid Imine

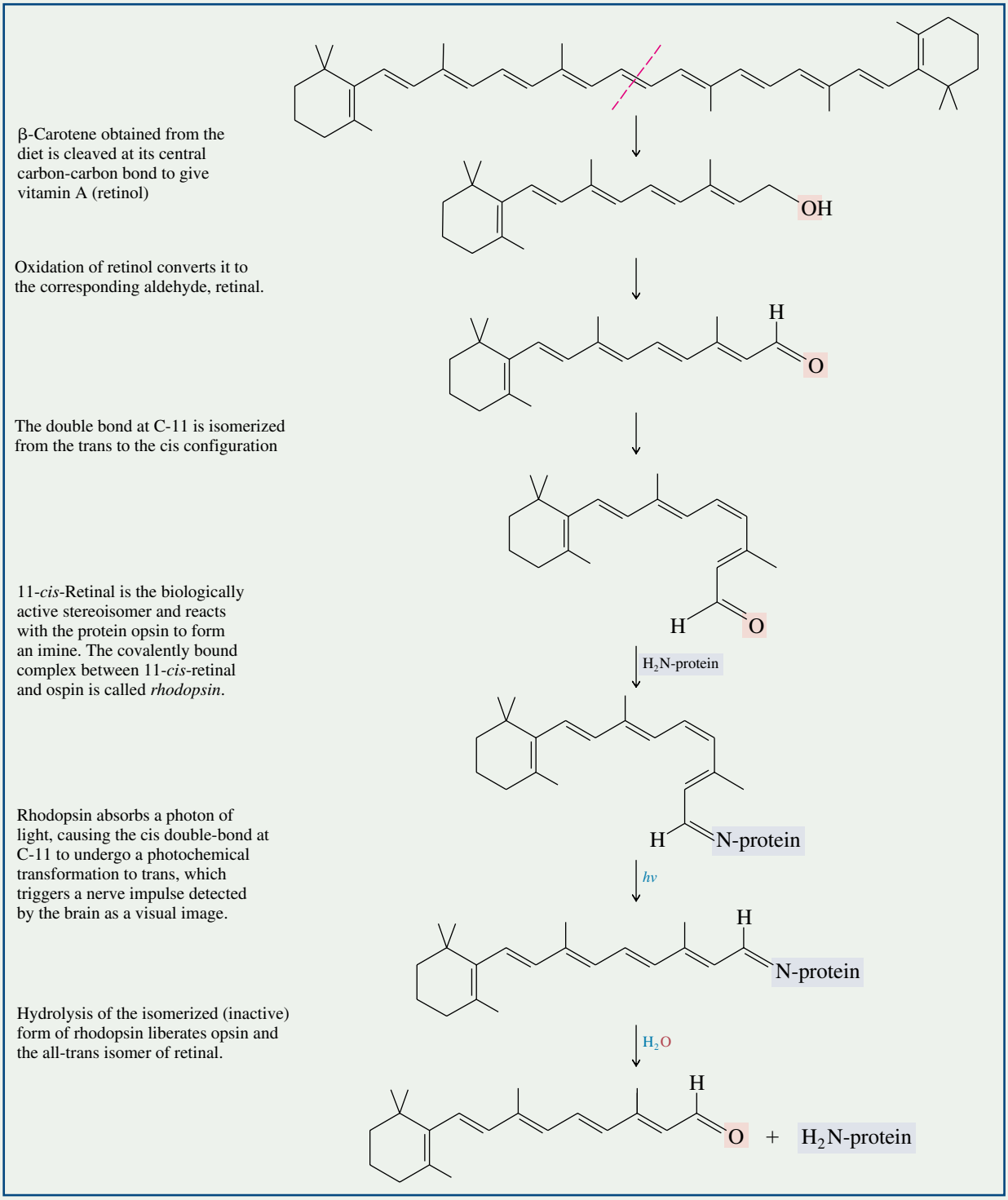
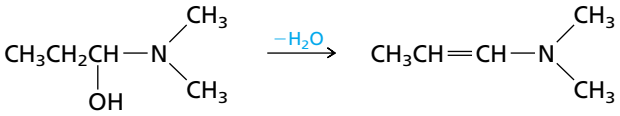


FIGURE 17.8 Imine formation between the aldehyde function of 11-*cis*-retinal and an amino group of a protein (opsin) is involved in the chemistry of vision. The numbering scheme used in retinal is based on one specifically developed for carotenes and compounds derived from them.

Dehydration of this carbinolamine yields the enamine:



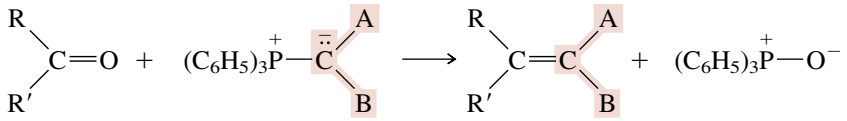
Carbinolamine intermediate — *N*-(1-Propenyl)dimethylamine

Enamines are used as reagents in synthetic organic chemistry and are involved in certain biochemical transformations.

17.12 THE WITTIG REACTION

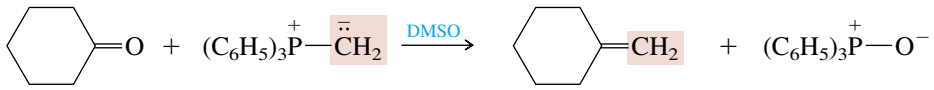
The **Wittig reaction** uses *phosphorus ylides* (called *Wittig reagents*) to convert aldehydes and ketones to alkenes.

The reaction is named after Georg Wittig, a German chemist who shared the 1979 Nobel Prize in chemistry for demonstrating its synthetic potential.



Aldehyde or ketone — Triphenylphosphonium ylide — Alkene — Triphenylphosphine oxide

Wittig reactions may be carried out in a number of different solvents; normally tetrahydrofuran (THF) or dimethyl sulfoxide (DMSO) is used.



Cyclohexanone — Methylenetriphenylphosphorane — Methylenecyclohexane (86%) — Triphenylphosphine oxide

The most attractive feature of the Wittig reaction is its regiospecificity. The location of the double bond is never in doubt. The double bond connects the carbon of the original C═O group of the aldehyde or ketone and the negatively charged carbon of the ylide.

PROBLEM 17.13 Identify the alkene product in each of the following Wittig reactions:

(a) Benzaldehyde + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}$(cyclopentyl)

(b) Butanal + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH=CH_2$

(c) Cyclohexyl methyl ketone + $(C_6H_5)_3\overset{+}{P}-\overset{-}{C}H_2$

SAMPLE SOLUTION (a) In a Wittig reaction the negatively charged substituent attached to phosphorus is transferred to the aldehyde or ketone, replacing the carbonyl oxygen. The reaction shown has been used to prepare the indicated alkene in 65% yield.

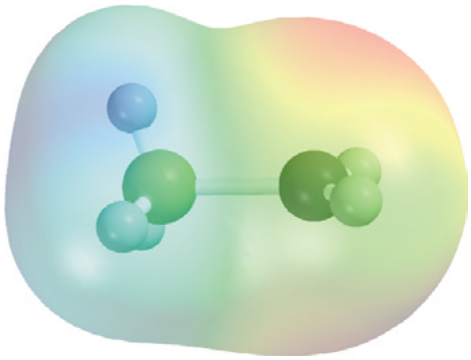
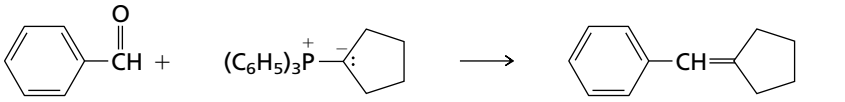


FIGURE 17.9 An electrostatic potential map of the ylide $H_3\overset{+}{P}—\overset{-}{\ddot{C}}H_2$. The region of greatest negative charge is concentrated at carbon.



Benzaldehyde | Cyclopentylidenetriphenylphosphorane | Benzylidenecyclopentane (65%)

In order to understand the mechanism of the Wittig reaction, we need to examine the structure and properties of ylides. **Ylides** are neutral molecules that have two oppositely charged atoms, each with an octet of electrons, directly bonded to each other. In an ylide such as $(C_6H_5)_3\overset{+}{P}—\overset{-}{\ddot{C}}H_2$, phosphorus has eight electrons and is positively charged; its attached carbon has eight electrons and is negatively charged.

PROBLEM 17.14 Can you write a resonance structure for $(C_6H_5)_3\overset{+}{P}—\overset{-}{\ddot{C}}H_2$ in which neither phosphorus nor carbon has a formal charge? (*Hint:* Remember phosphorus can have more than eight electrons in its valence shell.)

We can focus on the charge distribution in an ylide by replacing the phenyl groups in $(C_6H_5)_3\overset{+}{P}—\overset{-}{\ddot{C}}H_2$ by hydrogens. Figure 17.9 shows the electrostatic potential map of $H_3\overset{+}{P}—\overset{-}{\ddot{C}}H_2$, where it can be seen that the electron distribution is highly polarized in the direction that makes carbon electron-rich. The carbon has much of the character of a carbanion and can act as a nucleophile toward C═O.

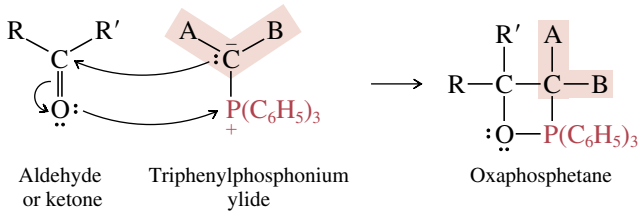
The Wittig reaction is one that is still undergoing mechanistic investigation. Another possibility is that the oxaphosphetane intermediate is formed by a two-step process, rather than the one-step process shown in Figure 17.10.

Figure 17.10 outlines a mechanism for the Wittig reaction. The first stage is a cycloaddition in which the ylide reacts with the carbonyl group to give an intermediate containing a four-membered ring called an **oxaphosphetane.** This oxaphosphetane then dissociates to give an alkene and triphenylphosphine oxide. Presumably the direction of dissociation of the oxaphosphetane is dictated by the strong phosphorus–oxygen bond that results. The P—O bond strength in triphenylphosphine oxide has been estimated to be greater than 540 kJ/mol (130 kcal/mol).

17.13 PLANNING AN ALKENE SYNTHESIS VIA THE WITTIG REACTION

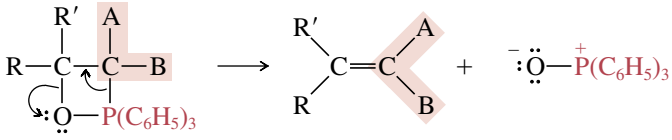
In order to identify the carbonyl compound and the ylide required to produce a given alkene, mentally disconnect the double bond so that one of its carbons is derived from a carbonyl group and the other is derived from an ylide. Taking styrene as a representative example, we see that two such disconnections are possible; either benzaldehyde or formaldehyde is an appropriate precursor.

Step 1: The ylide and the aldehyde or ketone combine to form an oxaphosphetane.



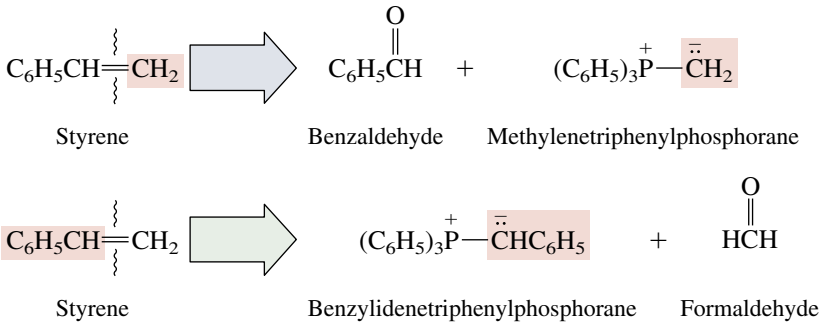
Aldehyde or ketone | Triphenylphosphonium ylide | Oxaphosphetane

Step 2: The oxaphosphetane dissociates to an alkene and triphenylphosphine oxide.



Oxaphosphetane | Alkene | Triphenylphosphine oxide

FIGURE 17.10 The mechanism of the Wittig reaction.

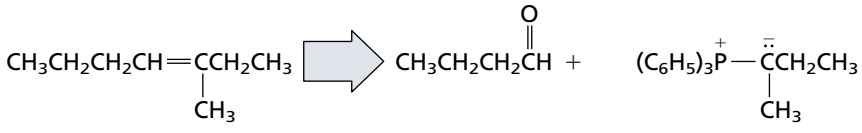


Either route is a feasible one, and indeed styrene has been prepared from both combinations of reactants. Typically there will be two Wittig routes to an alkene, and any choice between them is made on the basis of availability of the particular starting materials.

PROBLEM 17.15 What combinations of carbonyl compound and ylide could you use to prepare each of the following alkenes?

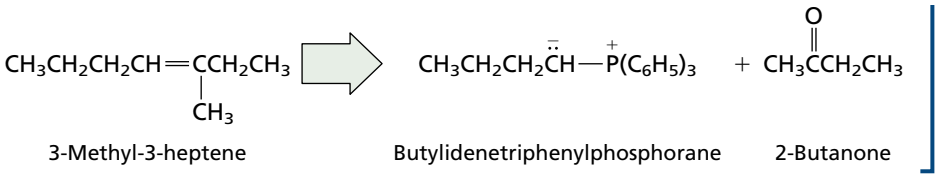
(a) $CH_3CH_2CH_2CH{=}C(CH_2CH_3)(CH_3)$ (b) $CH_3CH_2CH_2CH{=}CH_2$

SAMPLE SOLUTION (a) Two Wittig reaction routes lead to the target molecule.

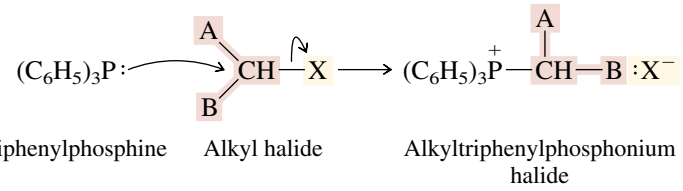


3-Methyl-3-heptene | Butanal | 1-Methylpropylidenetriphenylphosphorane

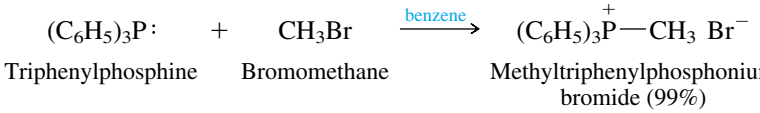
and



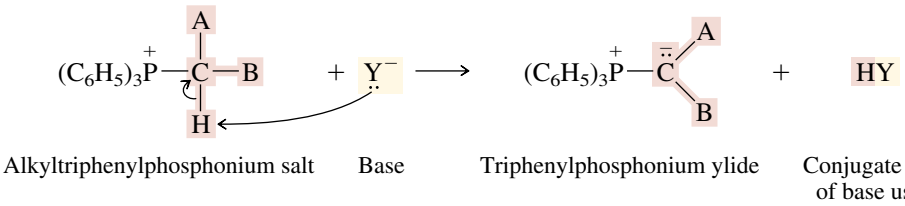
Phosphorus ylides are prepared from alkyl halides by a two-step sequence. The first step is a nucleophilic substitution of the S_N2 type by triphenylphosphine on an alkyl halide to give an alkyltriphenylphosphonium salt:



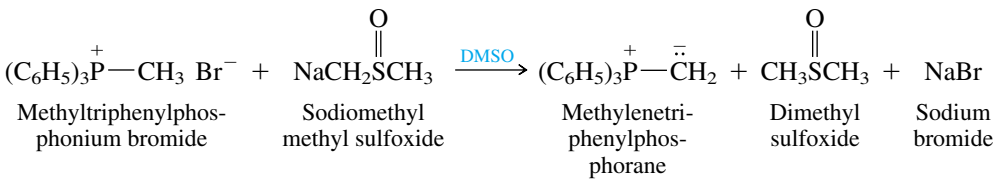
Triphenylphosphine is a very powerful nucleophile, yet is not strongly basic. Methyl, primary, and secondary alkyl halides are all suitable substrates.



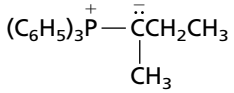
The alkyltriphenylphosphonium salt products are ionic and crystallize in high yield from the nonpolar solvents in which they are prepared. After isolation, the alkyltriphenylphosphonium halide is converted to the desired ylide by deprotonation with a strong base:



Suitable strong bases include the sodium salt of dimethyl sulfoxide (in dimethyl sulfoxide as the solvent) and organolithium reagents (in diethyl ether or tetrahydrofuran).



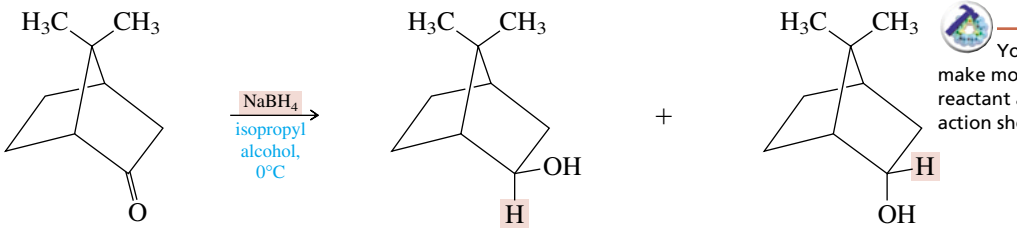
PROBLEM 17.16 The sample solution to Problem 17.15(a) showed the preparation of 3-methyl-3-heptene by a Wittig reaction involving the ylide shown. Write equations showing the formation of this ylide beginning with 2-bromobutane.



Normally the ylides are not isolated. Instead, the appropriate aldehyde or ketone is added directly to the solution in which the ylide was generated.

17.14 STEREOSELECTIVE ADDITION TO CARBONYL GROUPS

Nucleophilic addition to carbonyl groups sometimes leads to a mixture of stereoisomeric products. The direction of attack is often controlled by steric factors, with the nucleophile approaching the carbonyl group at its less hindered face. Sodium borohydride reduction of 7,7-dimethylbicyclo[2.2.1]heptan-2-one illustrates this point:



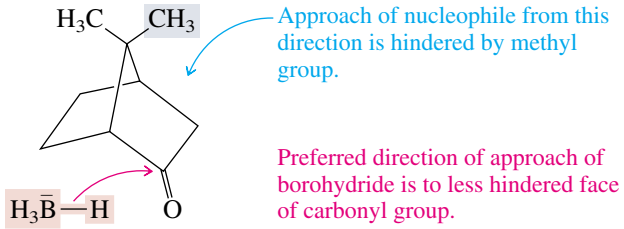
7,7-Dimethylbicyclo[2.2.1]-heptan-2-one

exo-7,7-Dimethylbicyclo[2.2.1]-heptan-2-ol (80%)

endo-7,7-Dimethylbicyclo[2.2.1]-heptan-2-ol (20%)

You may find it helpful to make molecular models of the reactant and products in the reaction shown.

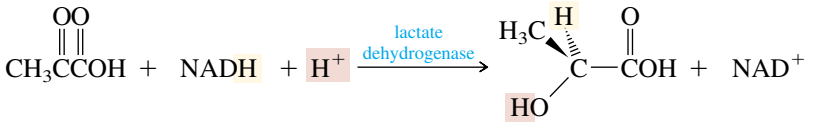
Approach of borohydride to the top face of the carbonyl group is sterically hindered by one of the methyl groups. The bottom face of the carbonyl group is less congested, and the major product is formed by hydride transfer from this direction.



The reduction is *stereoselective*. A single starting material can form two stereoisomers of the product but yields one of them preferentially.

It is possible to predict the preferred stereochemical path of nucleophilic addition if one face of a carbonyl group is significantly more hindered to the approach of the reagent than the other. When no clear distinction between the two faces is evident, other, more subtle effects, which are still incompletely understood, come into play.

Enzyme-catalyzed reductions of carbonyl groups are, more often than not, completely stereoselective. Pyruvic acid is converted exclusively to (*S*)-(+)-lactic acid by the lactate dehydrogenase-NADH system (Section 15.11). The enantiomer (*R*)-(−)-lactic acid is not formed.



Pyruvic acid

Reduced form of coenzyme

(*S*)-(+)-Lactic acid

Oxidized form of coenzyme

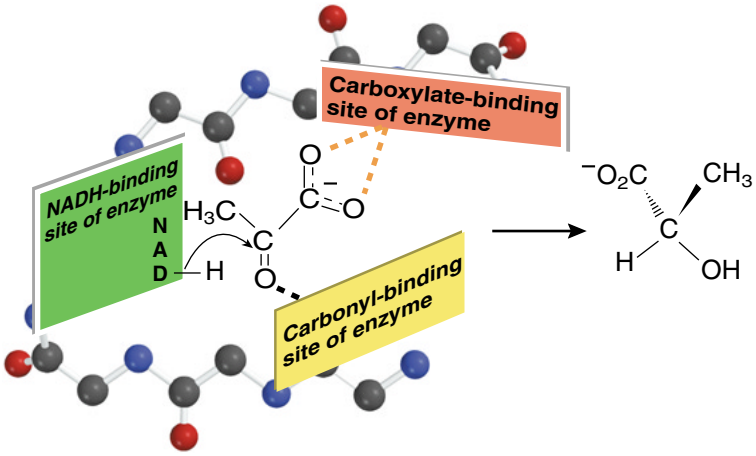


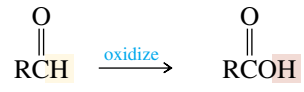
FIGURE 17.11 Enzyme-catalyzed reduction of pyruvate to (*S*)-(+)-lactate. A preferred orientation of binding of pyruvate to the enzyme, coupled with a prescribed location of the reducing agent, the coenzyme NADH, leads to hydrogen transfer exclusively to a single face of the carbonyl group.

Here the enzyme, a chiral molecule, binds the coenzyme and substrate in such a way that hydrogen is transferred exclusively to the face of the carbonyl group that leads to (*S*)-(+)-lactic acid (Figure 17.11).

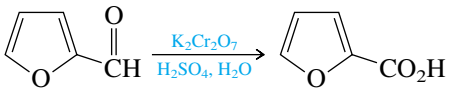
The stereochemical outcome of enzyme-mediated reactions depends heavily on the way the protein chain is folded. Aspects of protein conformation will be discussed in Chapter 27.

17.15 OXIDATION OF ALDEHYDES

Aldehydes are readily oxidized to carboxylic acids by a number of reagents, including those based on Cr(VI) in aqueous media.

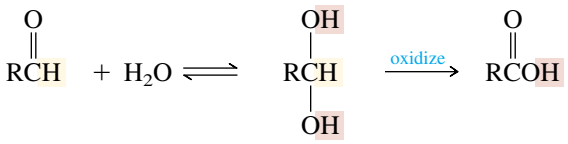


Aldehyde Carboxylic acid



Furfural Furoic acid (75%)

Mechanistically, these reactions probably proceed through the hydrate of the aldehyde and follow a course similar to that of alcohol oxidation.

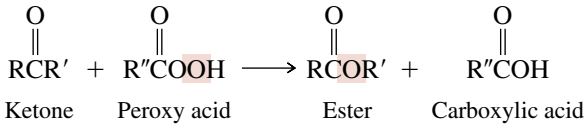


Aldehyde Geminal diol (hydrate) Carboxylic acid

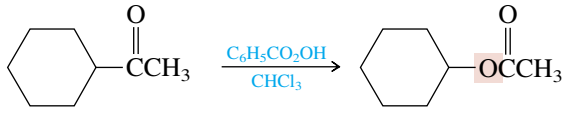
17.16 BAEYER–VILLIGER OXIDATION OF KETONES

The reaction of ketones with peroxy acids is both novel and synthetically useful. An oxygen from the peroxy acid is inserted between the carbonyl group and one of the attached carbons of the ketone to give an *ester*. Reactions of this type were first described by Adolf von Baeyer and Victor Villiger in 1899 and are known as **Baeyer–Villiger oxidations.**

Peroxy acids have been seen before as reagents for the epoxidation of alkenes (Section 6.18).

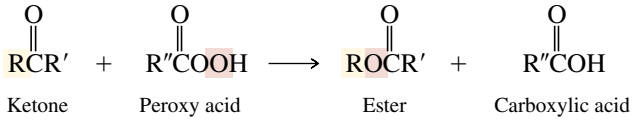


Methyl ketones give esters of acetic acid; that is, oxygen insertion occurs between the carbonyl carbon and the larger of the two groups attached to it.

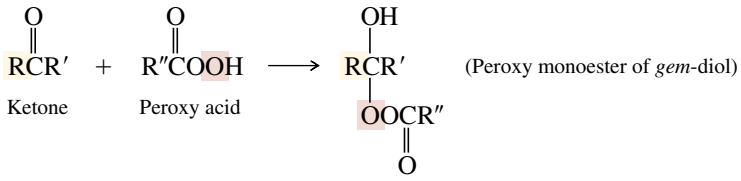


The mechanism of the Baeyer–Villiger oxidation is shown in Figure 17.12. It begins with nucleophilic addition of the peroxy acid to the carbonyl group of the ketone, which is followed by migration of an alkyl group from the carbonyl group to oxygen.

The overall reaction:



Step 1: The peroxy acid adds to the carbonyl group of the ketone. This step is a nucleophilic addition analogous to *gem*-diol and hemiacetal formation.



Step 2: The intermediate from step 1 undergoes rearrangement. Cleavage of the weak O—O bond of the peroxy ester is assisted by migration of one of the substituents from the carbonyl group to oxygen. The group R migrates with its pair of electrons in much the same way as alkyl groups migrate in carbocation rearrangements.

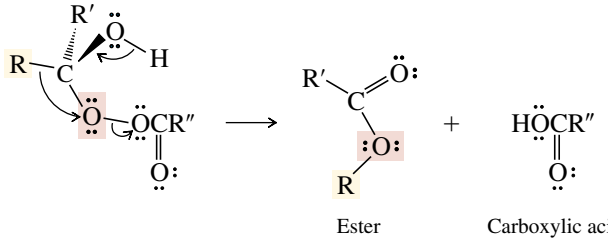


FIGURE 17.12 Mechanism of the Baeyer–Villiger oxidation of a ketone.

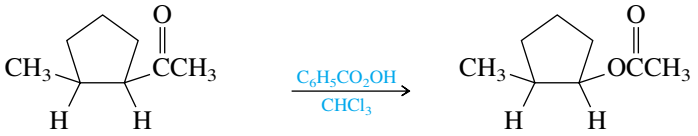
In general, it is the more substituted group that migrates. The *migratory aptitude* of the various alkyl groups is:

Tertiary alkyl > secondary alkyl > primary alkyl > methyl

PROBLEM 17.17 Using Figure 17.12 as a guide, write a mechanism for the Baeyer–Villiger oxidation of cyclohexyl methyl ketone by peroxybenzoic acid.

PROBLEM 17.18 Baeyer–Villiger oxidation of aldehydes yields carboxylic acids (e.g., *m*-nitrobenzaldehyde yields *m*-nitrobenzoic acid). What group migrates to oxygen?

The reaction is stereospecific; the alkyl group migrates with retention of configuration.

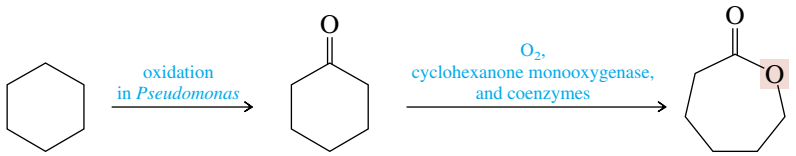


cis-1-Acetyl-2-methylcyclopentane

cis-2-Methylcyclopentyl acetate
(only product; 66% yield)

In the companion experiment carried out on the trans stereoisomer of the ketone, only the trans acetate was formed.

As unusual as the Baeyer–Villiger reaction may seem, what is even more remarkable is that an analogous reaction occurs in living systems. Certain bacteria, including those of the *Pseudomonas* and *Acinetobacter* type, can use a variety of organic compounds, even hydrocarbons, as a carbon source. With cyclohexane, for example, the early stages proceed by oxidation to cyclohexanone, which then undergoes the "biological Baeyer–Villiger reaction."



Cyclohexane Cyclohexanone 6-Hexanolide

The product (6-hexanolide) is a cyclic ester or *lactone* (Section 19.15). Like the Baeyer–Villiger oxidation, an oxygen atom is inserted between the carbonyl group and the carbon attached to it. But peroxy acids are not involved in any way; the oxidation of cyclohexanone is catalyzed by an enzyme called *cyclohexanone monooxygenase* with the aid of certain coenzymes.

17.17 SPECTROSCOPIC ANALYSIS OF ALDEHYDES AND KETONES

Infrared: Carbonyl groups are among the easiest functional groups to detect by infrared spectroscopy. The C=O stretching vibration of aldehydes and ketones gives rise to strong absorption in the region 1710–1750 cm^{-1} as illustrated for butanal in Figure 17.13. In addition to a peak for C=O stretching, the CH=O group of an aldehyde exhibits two weak bands for C—H stretching near 2720 and 2820 cm^{-1}.

^{1}H NMR: Aldehydes are readily identified by the presence of a signal for the hydrogen of CH=O at δ 9–10 ppm. This is a region where very few other protons ever appear. Figure 17.14 shows the ^{1}H NMR spectrum of 2-methylpropanal [$(CH_3)_2CHCH{=}O$)],

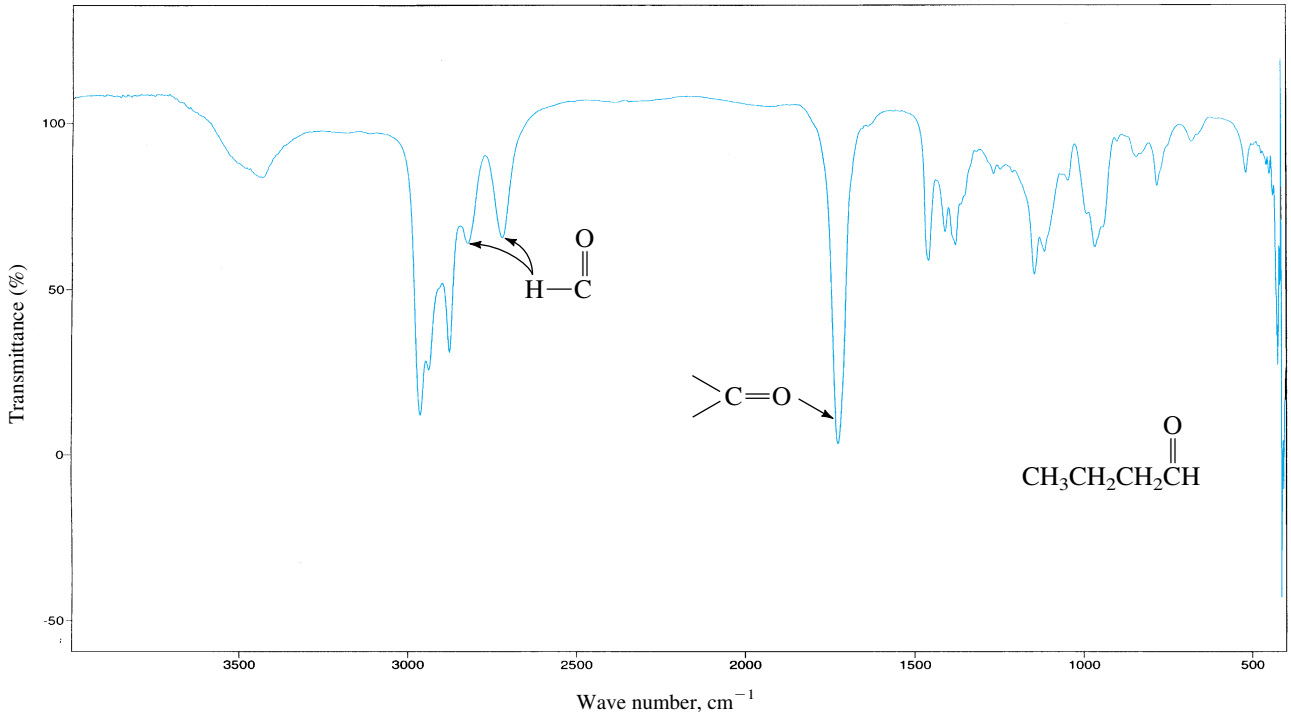


FIGURE 17.13 Infrared spectrum of butanal showing peaks characteristic of the CH═O unit at 2720 and 2820 cm^{-1} (C—H) and at 1720 cm^{-1} (C═O).

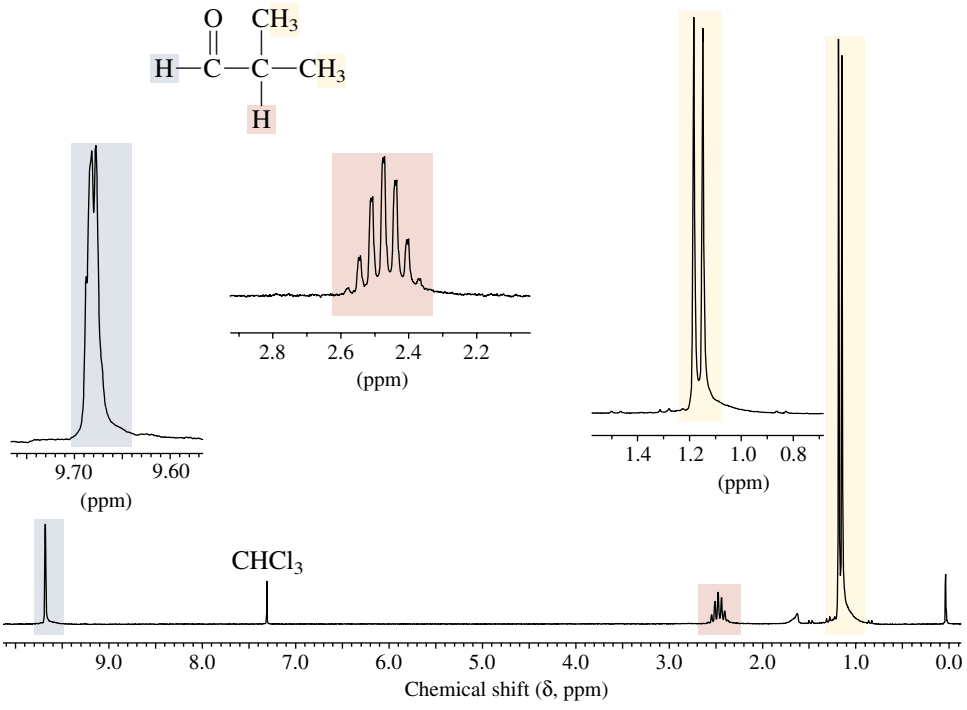


FIGURE 17.14 The 200-MHz ^{1}H NMR spectrum of 2-methylpropanal, showing the aldehyde proton as a doublet at low field strength (9.7 ppm).

where the large chemical shift difference between the aldehyde proton and the other protons in the molecule is clearly evident. As seen in the expanded-scale inset, the aldehyde proton is a doublet, split by the proton as C-2. Coupling between the protons in HC—CH=O is much smaller than typical vicinal couplings, making the multiplicity of the aldehyde peak difficult to see without expanding the scale.

Methyl ketones, such as 2-butanone in Figure 17.15, are characterized by sharp singlets near δ 2 ppm for the protons of $CH_3C{=}O$. Similarly, the deshielding effect of the carbonyl causes the protons of $CH_2C{=}O$ to appear at lower field (δ 2.4 ppm) than in a CH_2 group of an alkane.

^{13}C NMR: The signal for the carbon of C=O in aldehydes and ketones appears at very low field, some 190–220 ppm downfield from tetramethylsilane. Figure 17.16 illustrates this for 3-heptanone, in which separate signals appear for each of the seven carbons. The six sp^3-hybridized carbons appear in the range δ 8–42 ppm, while the carbon of the C=O group is at δ 210 ppm. Note, too, that the intensity of the peak for the C=O carbon is much less than all the others, even though each peak corresponds to a single carbon. This decreased intensity is a characteristic of Fourier transform (FT) spectra for carbons that don't have attached hydrogens.

UV-VIS: Aldehydes and ketones have two absorption bands in the ultraviolet region. Both involve excitation of an electron to an antibonding π*. In one, called a π→π*

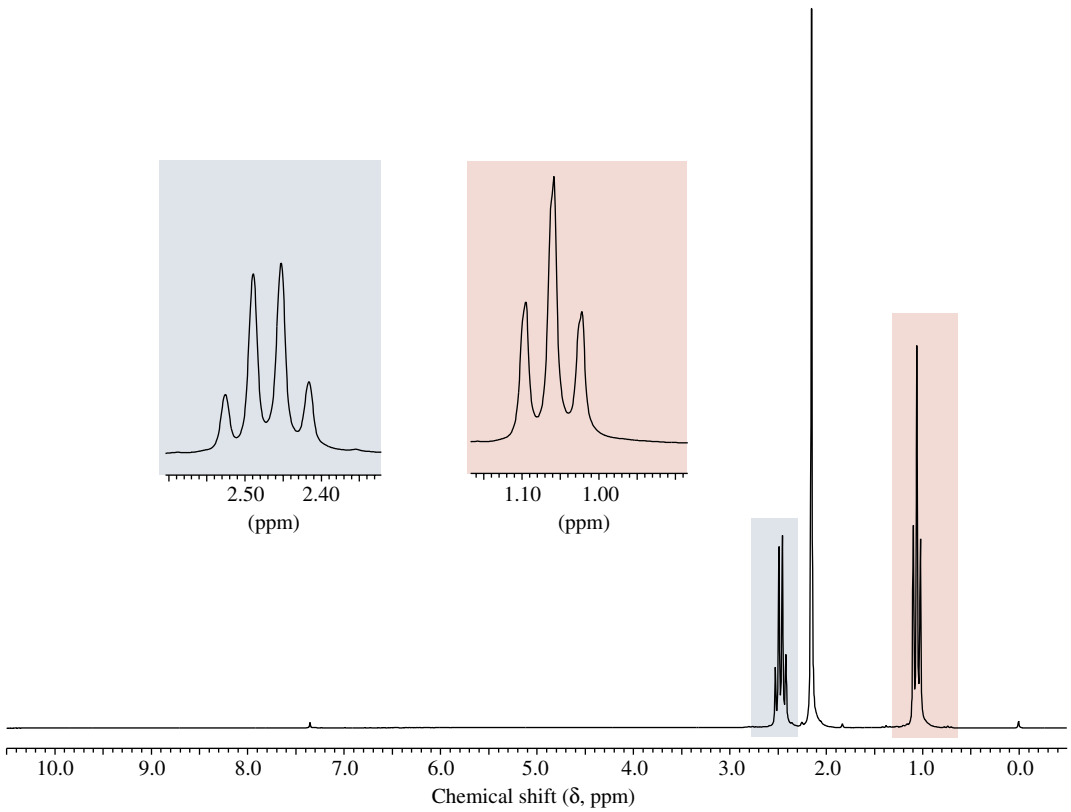
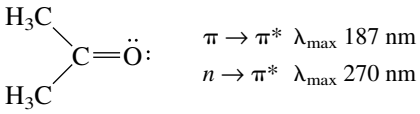


FIGURE 17.15 The 200-MHz ^{1}H NMR spectrum of 2-butanone. The triplet–quartet pattern of the ethyl group is more clearly seen in the scale-expanded insets.

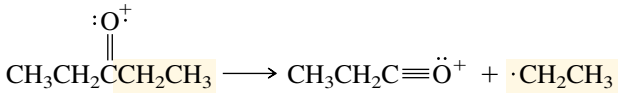
transition, the electron is one of the π electrons of the C═O group. In the other, called an $n \rightarrow \pi^*$ transition, it is one of the oxygen lone-pair electrons. Since the π electrons are more strongly held than the lone-pair electrons, the $\pi \rightarrow \pi^*$ transition is of higher energy and shorter wavelength than the $n \rightarrow \pi^*$ transition. For simple aldehydes and ketones, the $\pi \rightarrow \pi^*$ transition is below 200 nm and of little use in structure determination. The $n \rightarrow \pi^*$ transition, although weak, is of more diagnostic value.



Acetone

$\pi \rightarrow \pi^*$ λ_{max} 187 nm
$n \rightarrow \pi^*$ λ_{max} 270 nm

Mass Spectrometry: Aldehydes and ketones typically give a prominent molecular ion peak in their mass spectra. Aldehydes also exhibit an M-1 peak. A major fragmentation pathway for both aldehydes and ketones leads to formation of acyl cations (acylium ions) by cleavage of an alkyl group from the carbonyl. The most intense peak in the mass spectrum of diethyl ketone, for example, is *m/z* 57, corresponding to loss of ethyl radical from the molecular ion.



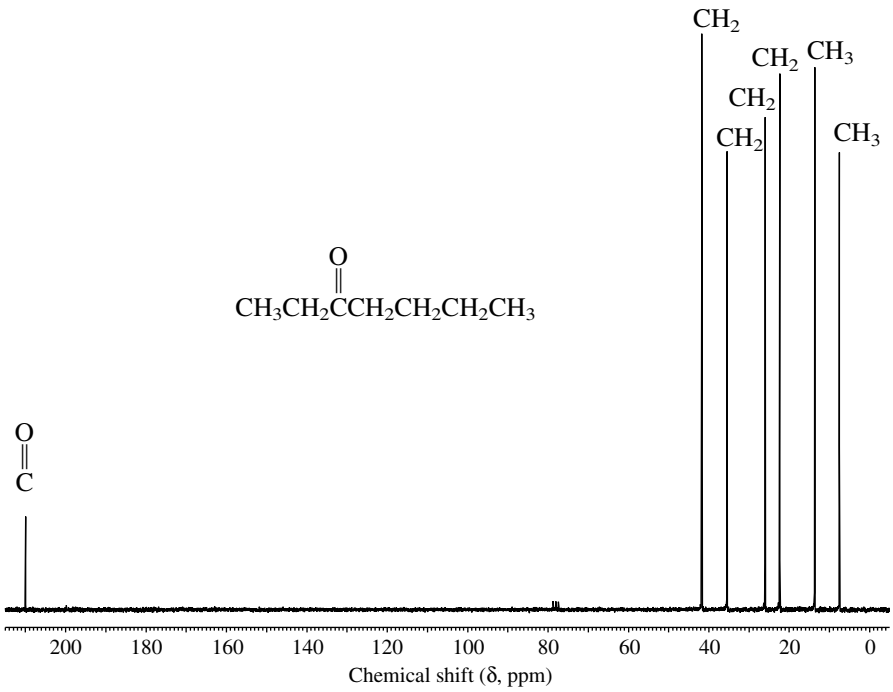
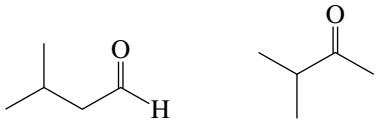


FIGURE 17.16 The ^{13}C NMR spectrum of 3-heptanone. Each signal corresponds to a single carbon. The carbonyl carbon is the least shielded and appears at δ 210 ppm.

17.18 SUMMARY

The chemistry of the carbonyl group is probably the single most important aspect of organic chemical reactivity. Classes of compounds that contain the carbonyl group include many derived from carboxylic acids (acyl chlorides, acid anhydrides, esters, and amides) as well as the two related classes discussed in this chapter—*aldehydes* and *ketones.*

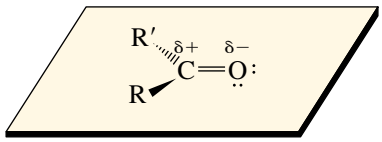
Section 17.1 The substitutive IUPAC names of aldehydes and ketones are developed by identifying the longest continuous chain that contains the carbonyl group and replacing the final *-e* of the corresponding alkane by *-al* for aldehydes and *-one* for ketones. The chain is numbered in the direction that gives the lowest locant to the carbon of the carbonyl group.



3-Methylbutanal 3-Methyl-2-butanone

Ketones are named using functional class IUPAC nomenclature by citing the two groups attached to the carbonyl in alphabetical order followed by the word "ketone." Thus, 3-methyl-2-butanone (substitutive) becomes isopropyl methyl ketone (functional class).

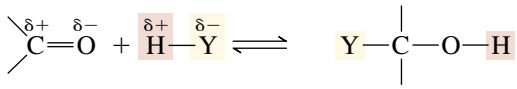
Section 17.2 The carbonyl carbon is sp^2-hybridized, and it and the atoms attached to it are coplanar (Section 17.2).



Section 17.3 Aldehydes and ketones are polar molecules. Nucleophiles attack C═O at carbon (positively polarized) and electrophiles, especially protons, attack oxygen (negatively polarized).

Section 17.4 The numerous reactions that yield aldehydes and ketones discussed in earlier chapters and reviewed in Table 17.1 are sufficient for most syntheses.

Sections 17.5–17.13 The characteristic reactions of aldehydes and ketones involve *nucleophilic addition* to the carbonyl group and are summarized in Table 17.5. Reagents of the type HY react according to the general equation

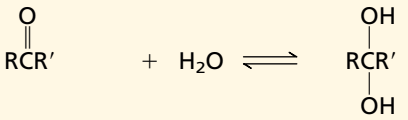
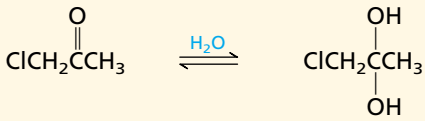
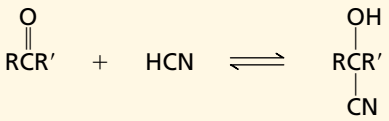
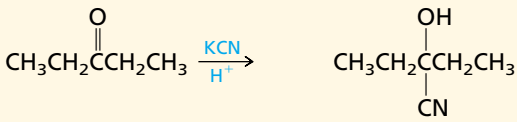
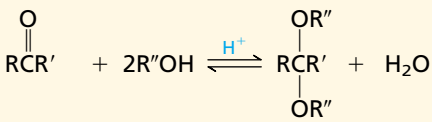
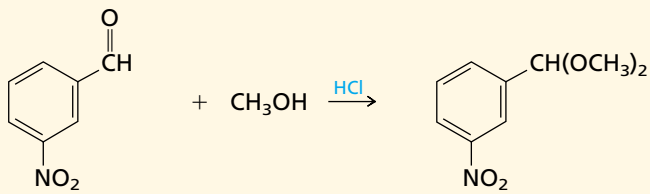
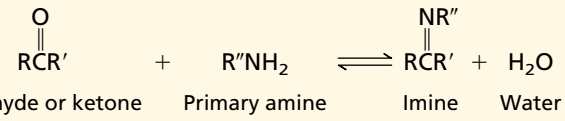
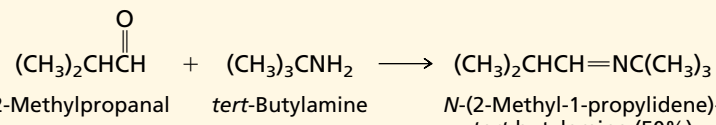


Aldehyde or ketone Product of nucleophilic addition to carbonyl group

Aldehydes undergo nucleophilic addition more readily and have more favorable equilibrium constants for addition than do ketones.

The step in which the nucleophile attacks the carbonyl carbon is

TABLE 17.5 Nucleophilic Addition to Aldehydes and Ketones

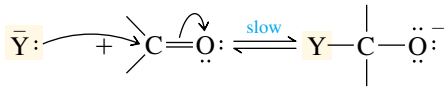
Reaction (section) and comments	General equation and typical example
Hydration (Section 17.6) Can be either acid- or base-catalyzed. Equilibrium constant is normally unfavorable for hydration of ketones unless R, R′, or both are strongly electron-withdrawing.	 Aldehyde or ketone — Water — Geminal diol  Chloroacetone (90% at equilibrium) — Chloroacetone hydrate (10% at equilibrium)
Cyanohydrin formation (Section 17.7) Reaction is catalyzed by cyanide ion. Cyanohydrins are useful synthetic intermediates; cyano group can be hydrolyzed to $—CO_2H$ or reduced to $—CH_2NH_2$.	 Aldehyde or ketone — Hydrogen cyanide — Cyanohydrin  3-Pentanone — 3-Pentanone cyanohydrin (75%)
Acetal formation (Sections 17.8–17.9) Reaction is acid-catalyzed. Equilibrium constant normally favorable for aldehydes, unfavorable for ketones. Cyclic acetals from vicinal diols form readily.	 Aldehyde or ketone — Alcohol — Acetal — Water  *m*-Nitrobenzaldehyde — Methanol — *m*-Nitrobenzaldehyde dimethyl acetal (76–85%)
Reaction with primary amines (Section 17.10) Isolated product is an imine (Schiff's base). A carbinolamine intermediate is formed, which undergoes dehydration to an imine.	 Aldehyde or ketone — Primary amine — Imine — Water  2-Methylpropanal — *tert*-Butylamine — *N*-(2-Methyl-1-propylidene)-*tert*-butylamine (50%)

(Continued)

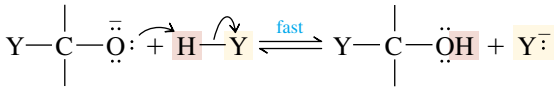
TABLE 17.5 Nucleophilic Addition to Aldehydes and Ketones *(Continued)*

Reaction (section) and comments	General equation and typical example
Reaction with secondary amines (Section 17.11) Isolated product is an enamine. Carbinolamine intermediate cannot dehydrate to a stable imine.	$RCCH_2R' + R''_2NH \rightleftharpoons RC{=}CHR' + H_2O$ Aldehyde or ketone; Secondary amine; Enamine; Water Cyclohexanone + Morpholine $\xrightarrow[\text{heat}]{\text{benzene}}$ 1-Morpholinocyclohexene (85%)
The Wittig reaction (Sections 17.12–17.13) Reaction of a phosphorus ylide with aldehydes and ketones leads to the formation of an alkene. A versatile method for the preparation of alkenes.	$RCR' + (C_6H_5)_3\overset{+}{P}-\overset{-}{C}(A)B \longrightarrow R'R{=}CAB + (C_6H_5)_3\overset{+}{P}-O^-$ Aldehyde or ketone; Wittig reagent (an ylide); Alkene; Triphenylphosphine oxide $CH_3CCH_3 + (C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCH_2CH_2CH_2CH_3 \xrightarrow{\text{DMSO}}$ Acetone; 1-Pentylidenetriphenylphosphorane $(CH_3)_2C{=}CHCH_2CH_2CH_2CH_3 + (C_6H_5)_3\overset{+}{P}-O^-$ 2-Methyl-2-heptene (56%); Triphenylphosphine oxide

rate-determining in both base-catalyzed and acid-catalyzed nucleophilic addition. In the base-catalyzed mechanism this is the first step.

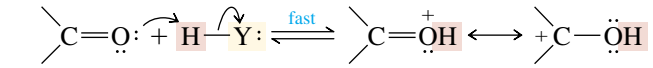


Nucleophile; Aldehyde or ketone



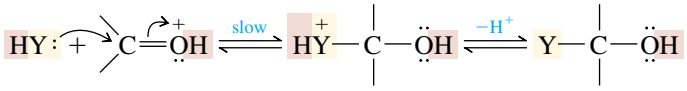
Product of nucleophilic addition

Under conditions of acid catalysis, the nucleophilic addition step follows protonation of the carbonyl oxygen. Protonation increases the carbocation character of a carbonyl group and makes it more electrophilic.



Aldehyde or ketone

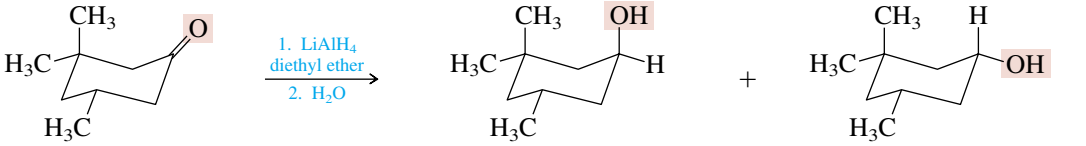
Resonance forms of protonated aldehyde or ketone



Product of nucleophilic addition

Often the product of nucleophilic addition is not isolated but is an intermediate leading to the ultimate product. Most of the reactions in Table 17.5 are of this type.

Section 17.14 Nucleophilic addition to the carbonyl group is *stereoselective*. When one direction of approach to the carbonyl group is less hindered than the other, the nucleophile normally attacks at the less hindered face.

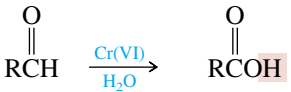


3,3,5-Trimethylcyclohexanone

trans-3,3,5-Trimethylcyclohexanol (83%)

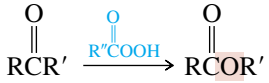
cis-3,3,5-Trimethylcyclohexanol (17%)

Section 17.15 Aldehydes are easily oxidized to carboxylic acids.



Aldehyde Carboxylic acid

Section 17.16 The oxidation of ketones with peroxy acids is called the *Baeyer–Villiger oxidation* and is a useful method for preparing esters.



Ketone Ester

Section 17.17 A strong peak near 1700 cm^{-1} in the infrared is characteristic of compounds that bear a C═O group. The ^{1}H and ^{13}C NMR spectra of aldehydes and ketones are affected by the deshielding of a C═O group. The proton of an H—C═O group appears in the δ 8–10 ppm range. The carbon of a C═O group is at δ 190–210 ppm.

PROBLEMS

17.19 (a) Write structural formulas and provide IUPAC names for all the isomeric aldehydes and ketones that have the molecular formula $C_5H_{10}O$. Include stereoisomers.

(b) Which of the isomers in part (a) yield chiral alcohols on reaction with sodium borohydride?

(c) Which of the isomers in part (a) yield chiral alcohols on reaction with methylmagnesium iodide?

17.20 Each of the following aldehydes or ketones is known by a common name. Its substitutive IUPAC name is provided in parentheses. Write a structural formula for each one.

(a) Chloral (2,2,2-trichloroethanal)

(b) Pivaldehyde (2,2-dimethylpropanal)

(c) Acrolein (2-propenal)

(d) Crotonaldehyde [(*E*)-2-butenal]

(e) Citral [(*E*)-3,7-dimethyl-2,6-octadienal]

(f) Diacetone alcohol (4-hydroxy-4-methyl-2-pentanone)

(g) Carvone (5-isopropenyl-2-methyl-2-cyclohexenone)

(h) Biacetyl (2,3-butanedione)

17.21 Predict the product of the reaction of propanal with each of the following:

(a) Lithium aluminum hydride

(b) Sodium borohydride

(c) Hydrogen (nickel catalyst)

(d) Methylmagnesium iodide, followed by dilute acid

(e) Sodium acetylide, followed by dilute acid

(f) Phenyllithium, followed by dilute acid

(g) Methanol containing dissolved hydrogen chloride

(h) Ethylene glycol, *p*-toluenesulfonic acid, benzene

(i) Aniline ($C_6H_5NH_2$)

(j) Dimethylamine, *p*-toluenesulfonic acid, benzene

(k) Hydroxylamine

(l) Hydrazine

(m) Product of part (l) heated in triethylene glycol with sodium hydroxide

(n) *p*-Nitrophenylhydrazine

(o) Semicarbazide

(p) Ethylidenetriphenylphosphorane [$(C_6H_5)_3\overset{+}{P}-\ddot{\overset{-}{C}}HCH_3$]

(q) Sodium cyanide with addition of sulfuric acid

(r) Chromic acid

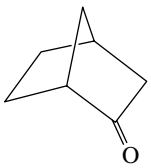
17.22 Repeat the preceding problem for cyclopentanone instead of propanal.

17.23 Hydride reduction (with $LiAlH_4$ or $NaBH_4$) of each of the following ketones has been reported in the chemical literature and gives a mixture of two diastereomeric alcohols in each case. Give the structures or build molecular models of both alcohol products for each ketone.

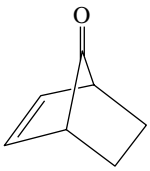
(a) (*S*)-3-Phenyl-2-butanone

(b) 4-*tert*-Butylcyclohexanone

(c)



(d)



17.24 Choose which member in each of the following pairs reacts faster or has the more favorable equilibrium constant for reaction with the indicated reagent. Explain your reasoning.

(a) C_6H_5CH (O) or $C_6H_5CCH_3$ (O) (rate of reduction with sodium borohydride)

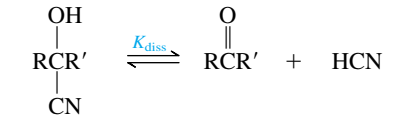
(b) Cl_3CCH (O) or CH_3CH (O) (equilibrium constant for hydration)

(c) Acetone or 3,3-dimethyl-2-butanone (equilibrium constant for cyanohydrin formation)

(d) Acetone or 3,3-dimethyl-2-butanone (rate of reduction with sodium borohydride)

(e) $CH_2(OCH_2CH_3)_2$ or $(CH_3)_2C(OCH_2CH_3)_2$ (rate of acid-catalyzed hydrolysis)

17.25 Equilibrium constants for the dissociation (K_{diss}) of cyanohydrins according to the equation



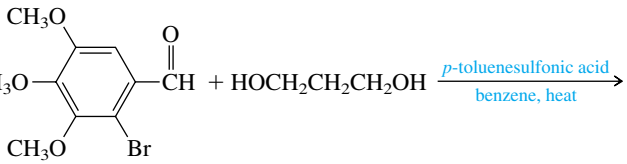
Cyanohydrin — Aldehyde or ketone — Hydrogen cyanide

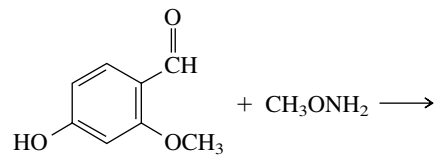
have been measured for a number of cyanohydrins. Which cyanohydrin in each of the following pairs has the greater dissociation constant?

(a) $CH_3CH_2CH(OH)CN$ or $(CH_3)_2C(OH)CN$

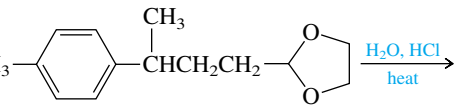
(b) $C_6H_5CH(OH)CN$ or $C_6H_5C(OH)(CH_3)CN$

17.26 Each of the following reactions has been reported in the chemical literature and gives a single organic product in good yield. What is the principal product in each reaction?

(a) 

(b) 

(c) $CH_3CH_2CH(=O) + (CH_3)_2NNH_2 \longrightarrow$

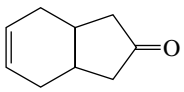
(d) 

(e) $C_6H_5CCH_3$ (O) $\xrightarrow[HCl]{NaCN}$

(f) $C_6H_5CCH_3$ (O) + HN O $\xrightarrow[\text{benzene, heat}]{p\text{-toluenesulfonic acid}}$

(g) $CH_3CH_2C(CH_3)(C_6H_5)CCH_3$ (O) + C_6H_5COOH $\xrightarrow{CHCl_3}$

17.27 Wolff–Kishner reduction (hydrazine, KOH, ethylene glycol, 130°C) of the compound shown gave compound A. Treatment of compound A with *m*-chloroperoxybenzoic acid gave compound B, which on reduction with lithium aluminum hydride gave compound C. Oxidation of compound C with chromic acid gave compound D ($C_9H_{14}O$). Identify compounds A through D in this sequence.

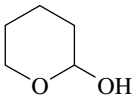


17.28 On standing in ^{17}O-labeled water, both formaldehyde and its hydrate are found to have incorporated the ^{17}O isotope of oxygen. Suggest a reasonable explanation for this observation.

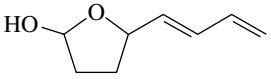
17.29 Reaction of benzaldehyde with 1,2-octanediol in benzene containing a small amount of *p*-toluenesulfonic acid yields almost equal quantities of two products in a combined yield of 94%. Both products have the molecular formula $C_{15}H_{22}O_2$. Suggest reasonable structures for these products.

17.30 Compounds that contain both carbonyl and alcohol functional groups are often more stable as cyclic hemiacetals or cyclic acetals than as open-chain compounds. Examples of several of these are shown. Deduce the structure of the open-chain form of each.

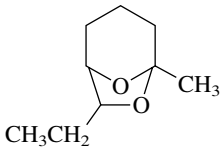
(a)



(b)

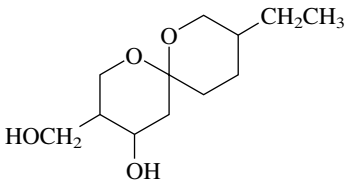


(c)



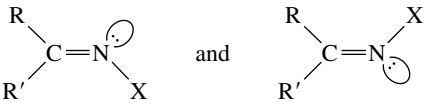
Brevicomin (sex attractant of Western pine beetle)

(d)



Talaromycin A (a toxic substance produced by a fungus that grows on poultry house litter)

17.31 Compounds that contain a carbon–nitrogen double bond are capable of stereoisomerism much like that seen in alkenes. The structures



are stereoisomeric. Specifying stereochemistry in these systems is best done by using *E*–*Z* descriptors and considering the nitrogen lone pair to be the lowest priority group. Write the structures or build molecular models, clearly showing stereochemistry, of the following:

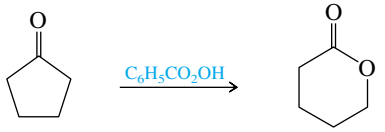
(a) (*Z*)-$CH_3CH{=}NCH_3$

(b) (*E*)-Acetaldehyde oxime

(c) (*Z*)-2-Butanone hydrazone

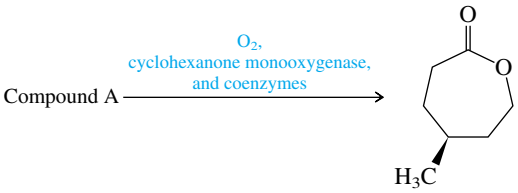
(d) (*E*)-Acetophenone semicarbazone

17.32 Compounds known as *lactones*, which are cyclic esters, are formed on Baeyer–Villiger oxidation of cyclic ketones. Suggest a mechanism for the Baeyer–Villiger oxidation shown.



Cyclopentanone 5-Pentanolide (78%)

17.33 Organic chemists often use enantiomerically homogeneous starting materials for the synthesis of complex molecules (see *Chiral Drugs,* p. 273). A novel preparation of the *S* enantiomer of compound B has been described using a bacterial cyclohexanone monooxygenase enzyme system.

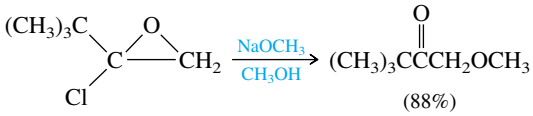


Compound B

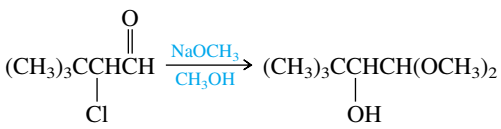
(a) What is compound A?

(b) How would the product obtained by treatment of compound A with peroxyacetic acid differ from that shown in the equation?

17.34 Suggest reasonable mechanism for each of the following reactions:

(a) 

(88%)

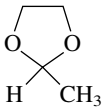
(b) 

(72%)

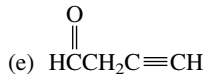
17.35 *Amygdalin,* a substance present in peach, plum, and almond pits, is a derivative of the *R* enantiomer of benzaldehyde cyanohydrin. Give the structure of (*R*)-benzaldehyde cyanohydrin.

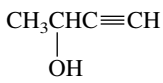
17.36 Using ethanol as the source of all the carbon atoms, describe efficient syntheses of each of the following, using any necessary organic or inorganic reagents:

(a) $CH_3CH(OCH_2CH_3)_2$

(b) 

(c) 

(e) 

(d) 

(f) $CH_3CH_2CH_2CH_2OH$

17.37 Describe reasonable syntheses of benzophenone,  , from each of the following starting materials and any necessary inorganic reagents.

(a) Benzoyl chloride and benzene

(b) Benzyl alcohol and bromobenzene

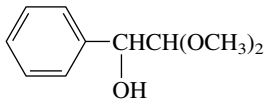
(c) Bromodiphenylmethane, $(C_6H_5)_2CHBr$

(d) Dimethoxydiphenylmethane, $(C_6H_5)_2C(OCH_3)_2$

(e) 1,1,2,2-Tetraphenylethene, $(C_6H_5)_2C{=}C(C_6H_5)_2$

17.38 The sex attractant of the female winter moth has been identified as the tetraene $CH_3(CH_2)_8CH{=}CHCH_2CH{=}CHCH_2CH{=}CHCH{=}CH_2$. Devise a synthesis of this material from 3,6-hexadecadien-1-ol and allyl alcohol.

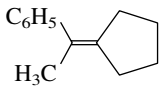
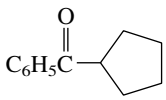
17.39 Hydrolysis of a compound A in dilute aqueous hydrochloric acid gave (along with methanol) a compound B, mp 164–165°C. Compound B had the molecular formula $C_{16}H_{16}O_4$; it exhibited hydroxyl absorption in its infrared spectrum at 3550 cm^{-1} but had no peaks in the carbonyl region. What is a reasonable structure for compound B?

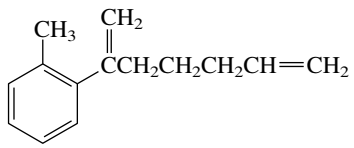


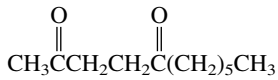
Compound A

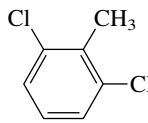
17.40 Syntheses of each of the following compounds have been reported in the chemical literature. Using the indicated starting material and any necessary organic or inorganic reagents, describe short sequences of reactions that would be appropriate for each transformation.

(a) 1,1,5-Trimethylcyclononane from 5,5-dimethylcyclononanone

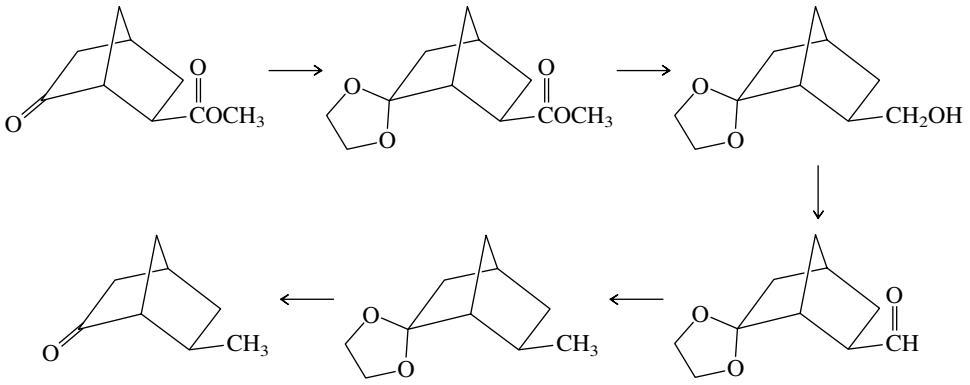
(b)  from 

(c)  from *o*-bromotoluene and 5-hexenal

(d)  from $HC{\equiv}CCH_2CH_2CH_2OH$

(e)  from 3-chloro-2-methylbenzaldehyde

17.41 The following five-step synthesis has been reported in the chemical literature. Suggest reagents appropriate for each step.



17.42 Increased "single-bond character" in a carbonyl group is associated with a decreased carbon–oxygen stretching frequency. Among the three compounds benzaldehyde, 2,4,6-trimethoxybenzaldehyde, and 2,4,6-trinitrobenzaldehyde, which one will have the lowest frequency carbonyl absorption? Which one will have the highest?

17.43 A compound has the molecular formula C_4H_8O and contains a carbonyl group. Identify the compound on the basis of its ^1H NMR spectrum shown in Figure 17.17.

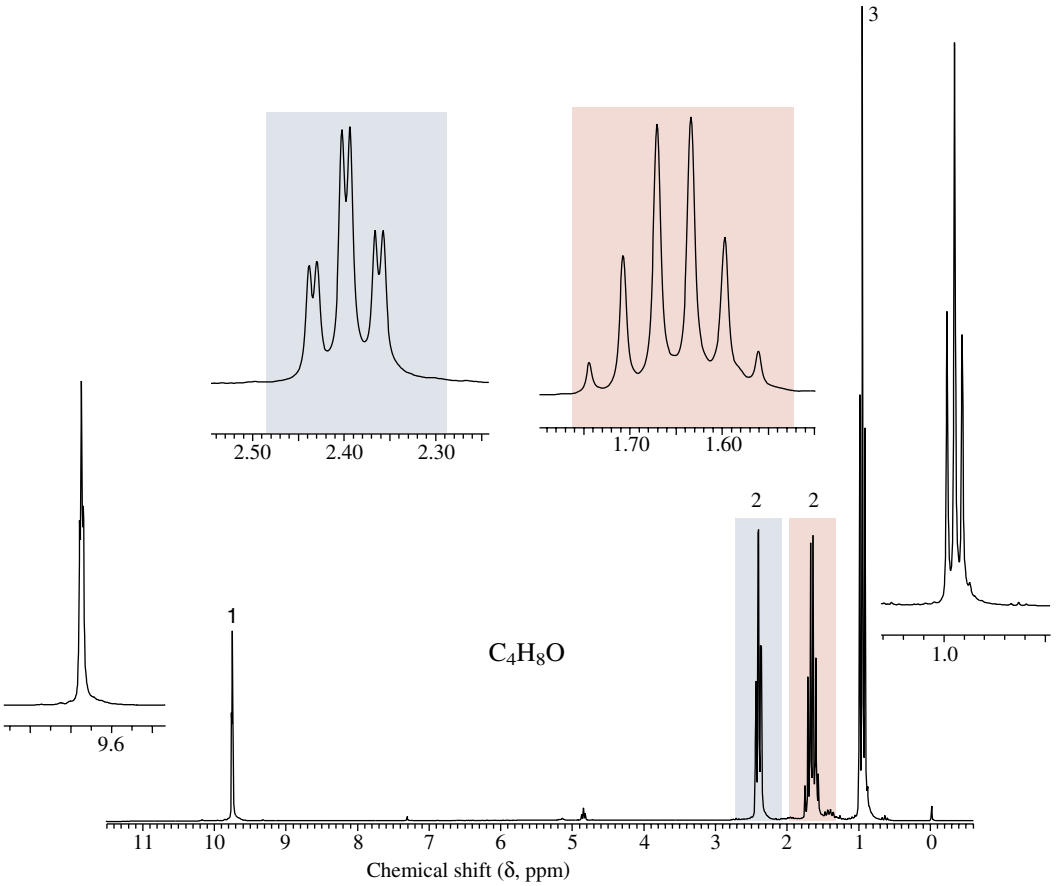


FIGURE 17.17 The 200-MHz ^1H NMR spectrum of a compound (C_4H_8O) (Problem 17.43).

17.44 A compound ($C_7H_{14}O$) has a strong peak in its infrared spectrum at 1710 cm^{-1}. Its ^1H NMR spectrum consists of three singlets in the ratio 9:3:2 at δ 1.0, 2.1, and 2.3 ppm, respectively. Identify the compound.

17.45 Compounds A and B are isomeric diketones of molecular formula $C_6H_{10}O_2$. The ^1H NMR spectrum of compound A contains two signals, both singlets, at δ 2.2 (6 protons) and 2.8 ppm (4 protons). The ^1H NMR spectrum of compound B contains two signals, one at δ 1.3 ppm (triplet, 6 protons) and the other at δ 2.8 ppm (quartet, 4 protons). What are the structures of compounds A and B?

17.46 A compound ($C_{11}H_{14}O$) has a strong peak in its infrared spectrum near 1700 cm^{-1}. Its 200-MHz ^1H NMR spectrum is shown in Figure 17.18. What is the structure of the compound?

17.47 A compound is a ketone of molecular formula $C_7H_{14}O$. Its ^{13}C NMR spectrum is shown in Figure 17.19. What is the structure of the compound?

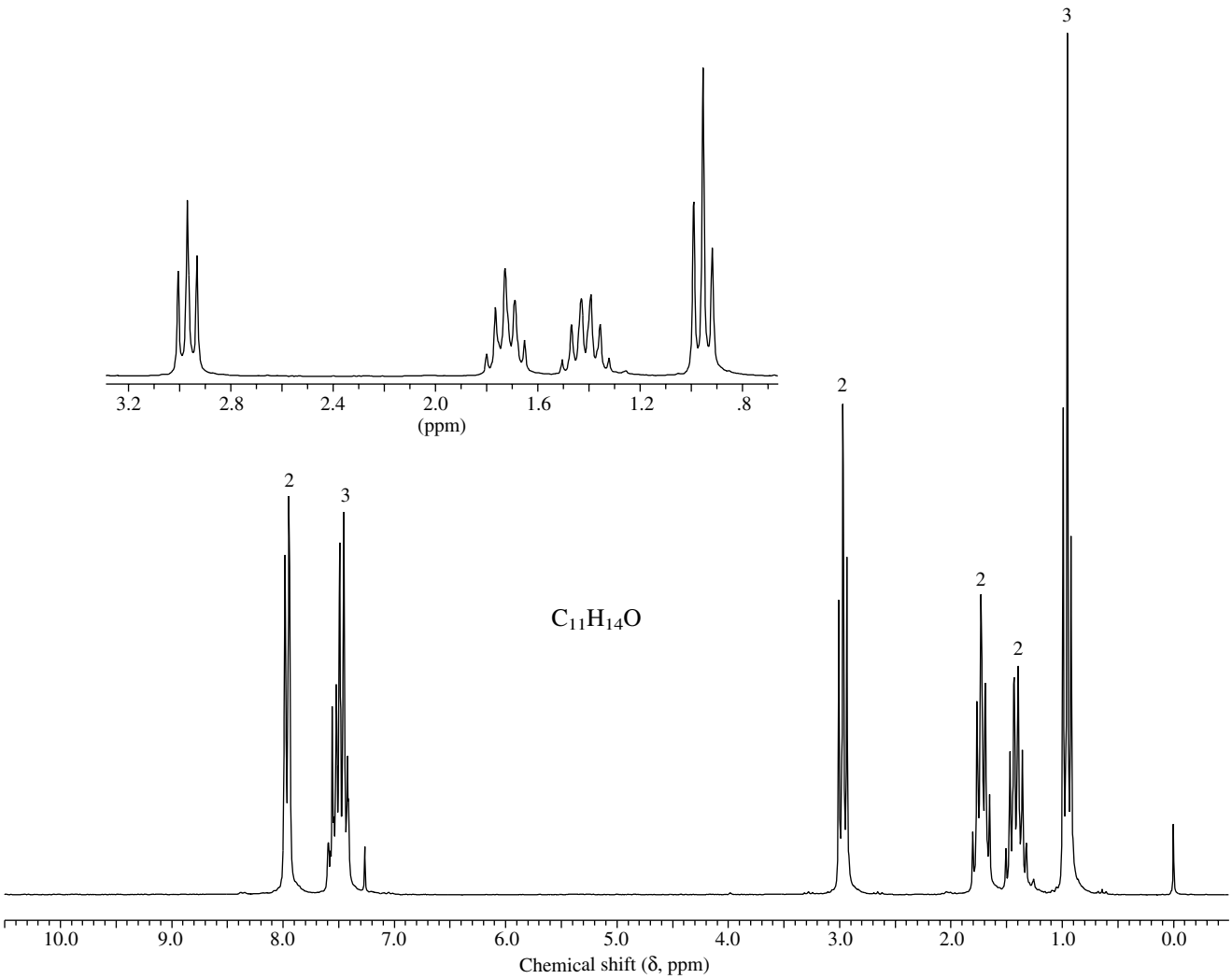


FIGURE 17.18 The 200-MHz ^1H NMR spectrum of a compound ($C_{11}H_{14}O$) (Problem 17.46).

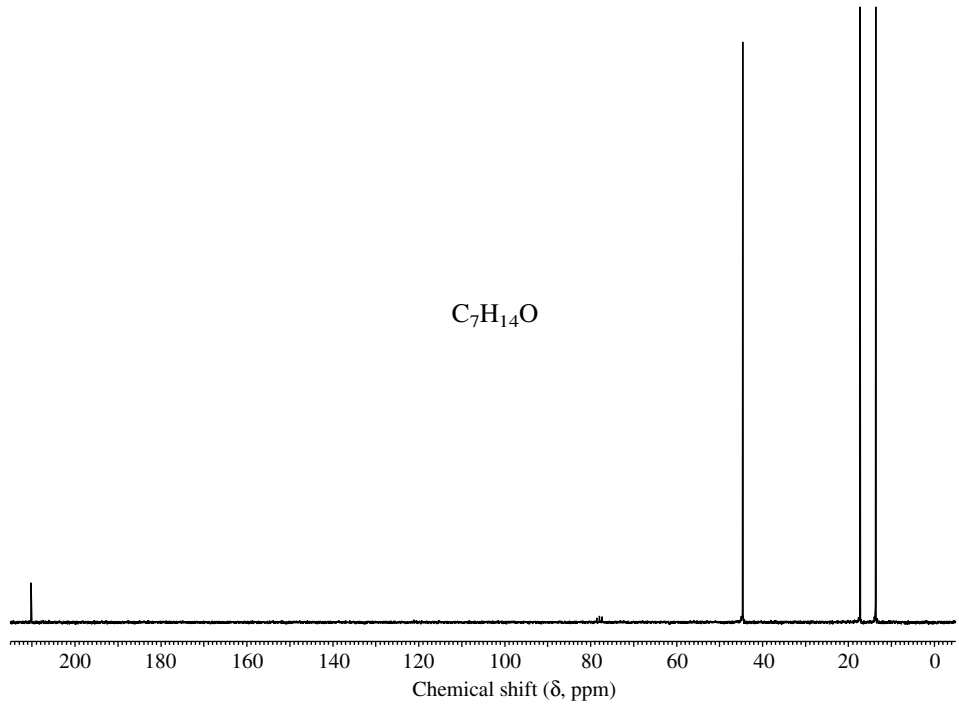


FIGURE 17.19 The ^{13}C NMR spectrum of an unknown compound ($C_7H_{14}O$) (Problem 17.47).

17.48 Compound A and compound B are isomers having the molecular formula $C_{10}H_{12}O$. The mass spectrum of each compound contains an abundant peak at *m/z* 105. The ^{13}C NMR spectra of compound A (Figure 17.20) and compound B (Figure 17.21) are shown. Identify these two isomers.

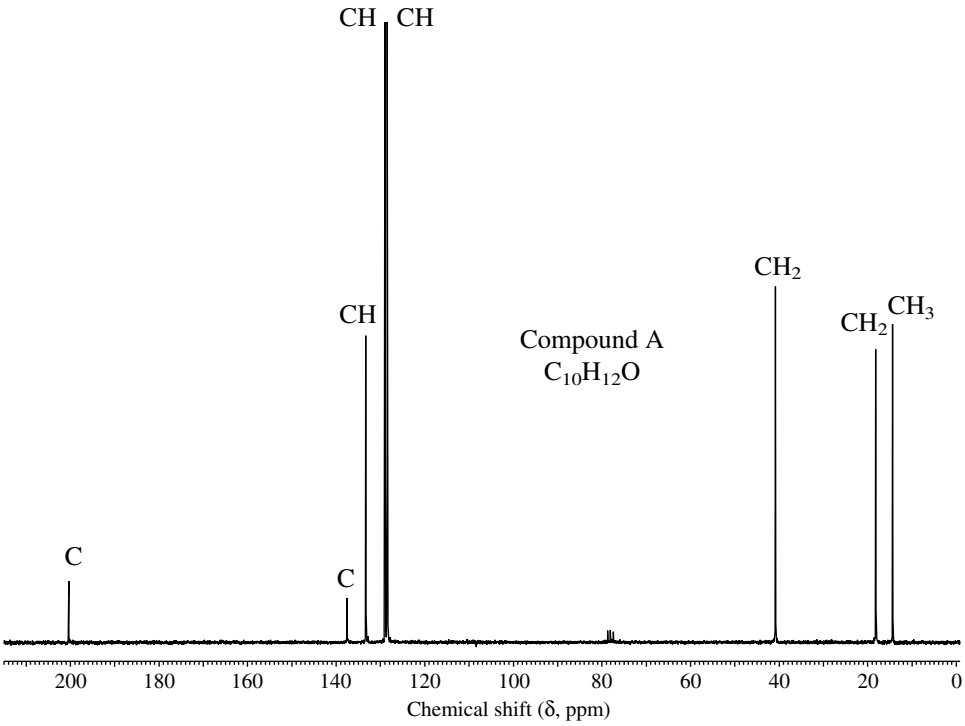


FIGURE 17.20 The ^{13}C NMR spectrum of compound A ($C_{10}H_{12}O$) (Problem 17.48).

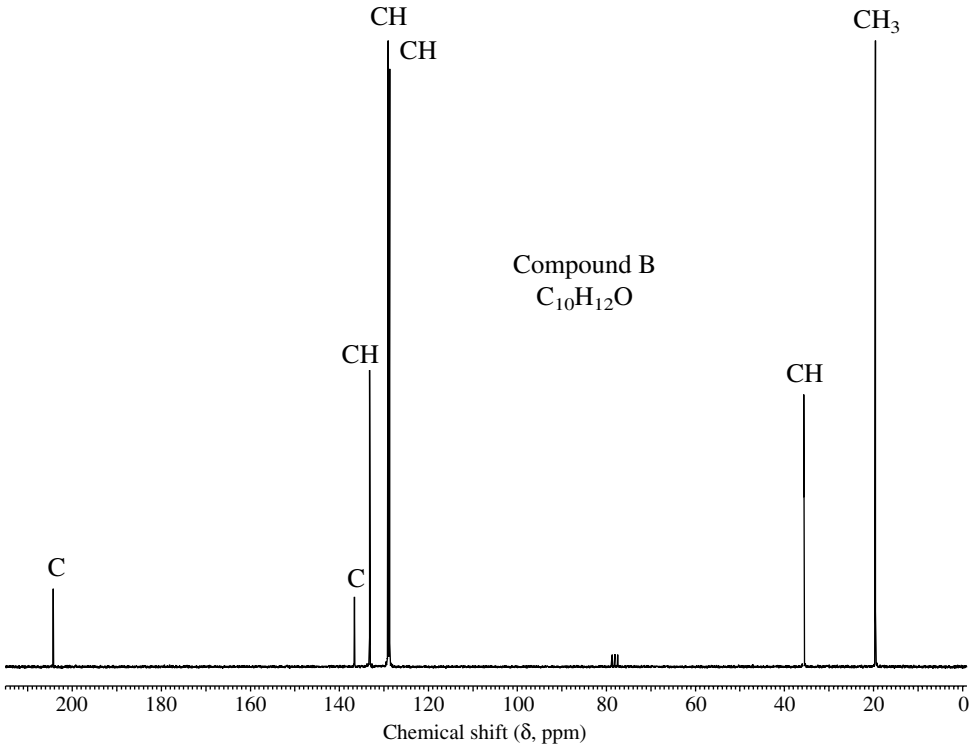
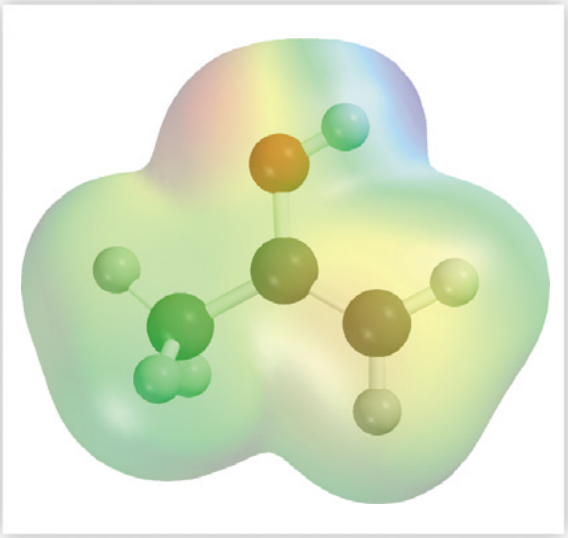


FIGURE 17.21 The ^{13}C NMR spectrum of compound B ($C_{10}H_{12}O$) (Problem 17.48).

17.49 The most stable conformation of acetone has one of the hydrogens of each methyl group eclipsed with the carbonyl oxygen. Construct a model of this conformation.

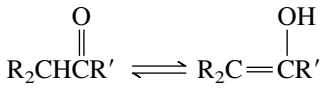
17.50 Construct a molecular model of cyclohexanone. Do either of the hydrogens of C-2 eclipse the carbonyl oxygen?



CHAPTER 18

ENOLS AND ENOLATES

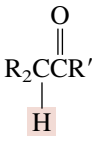
In the preceding chapter you learned that nucleophilic addition to the carbonyl group is one of the fundamental reaction types of organic chemistry. In addition to its own reactivity, a carbonyl group can affect the chemical properties of aldehydes and ketones in other ways. Aldehydes and ketones are in equilibrium with their **enol** isomers.



Aldehyde or ketone — Enol

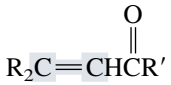
In this chapter you'll see a number of processes in which the enol, rather than the aldehyde or a ketone, is the reactive species.

There is also an important group of reactions in which the carbonyl group acts as a powerful electron-withdrawing substituent, increasing the acidity of protons on the adjacent carbons.



This proton is far more acidic than a hydrogen in an alkane.

As an electron-withdrawing group on a carbon–carbon double bond, a carbonyl group renders the double bond susceptible to nucleophilic attack:

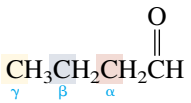


Normally, carbon–carbon double bonds are attacked by electrophiles; a carbon–carbon double bond that is conjugated to a carbonyl group is attacked by nucleophiles.

The presence of a carbonyl group in a molecule makes possible a number of chemical reactions that are of great synthetic and mechanistic importance. This chapter is complementary to the preceding one; the two chapters taken together demonstrate the extraordinary range of chemical reactions available to aldehydes and ketones.

18.1 THE α-CARBON ATOM AND ITS HYDROGENS

It is convenient to use the Greek letters α, β, γ, and so forth, to locate the carbons in a molecule in relation to the carbonyl group. The carbon atom adjacent to the carbonyl is the α-carbon atom, the next one down the chain is the β carbon, and so on. Butanal, for example, has an α carbon, a β carbon, and a γ carbon.



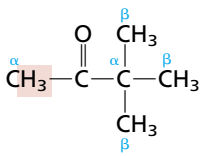
Carbonyl group is reference point; no Greek letter assigned to it.

Hydrogens take the same Greek letter as the carbon atom to which they are attached. A hydrogen connected to the α-carbon atom is an α hydrogen. Butanal has two α protons, two β protons, and three γ protons. No Greek letter is assigned to the hydrogen attached directly to the carbonyl group of an aldehyde.

PROBLEM 18.1 How many α hydrogens are there in each of the following?

(a) 3,3-Dimethyl-2-butanone
(b) 2,2-Dimethylpropanal
(c) Benzyl methyl ketone
(d) Cyclohexanone

SAMPLE SOLUTION (a) This ketone has two different α carbons, but only one of them has hydrogen substituents. There are three equivalent α hydrogens. The other nine hydrogens are attached to β-carbon atoms.

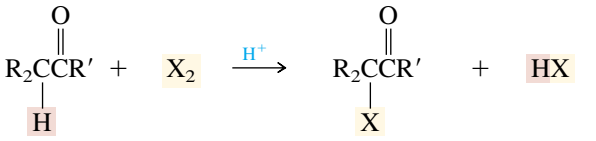


3,3-Dimethyl-2-butanone

Other than nucleophilic addition to the carbonyl group, the most important reactions of aldehydes and ketones involve substitution of an α hydrogen. A particularly well studied example is halogenation of aldehydes and ketones.

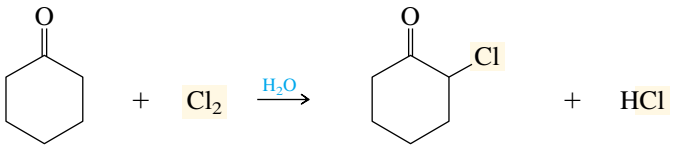
18.2 α HALOGENATION OF ALDEHYDES AND KETONES

Aldehydes and ketones react with halogens by *substitution* of one of the α hydrogens:



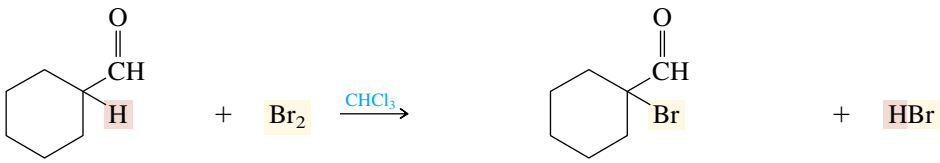
Aldehyde or ketone — Halogen — α-Halo aldehyde or ketone — Hydrogen halide

The reaction is *regiospecific* for substitution of an α hydrogen. None of the hydrogens farther removed from the carbonyl group are affected.



Cyclohexanone — Chlorine — 2-Chlorocyclohexanone (61–66%) — Hydrogen chloride

Nor is the hydrogen directly attached to the carbonyl group in aldehydes affected. Only the α hydrogen is replaced.



Cyclohexanecarbaldehyde — Bromine — 1-Bromocyclohexanecarbaldehyde (80%) — Hydrogen bromide

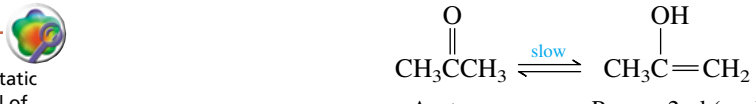
PROBLEM 18.2 Chlorination of 2-butanone yields two isomeric products, each having the molecular formula C_4H_7ClO. Identify these two compounds.

α Halogenation of aldehydes and ketones can be carried out in a variety of solvents (water and chloroform are shown in the examples, but acetic acid and diethyl ether are also often used). The reaction is catalyzed by acids. Since one of the reaction products, the hydrogen halide, is an acid and therefore a catalyst for the reaction, the process is said to be **autocatalytic.** Free radicals are *not* involved, and the reactions occur at room temperature in the absence of initiators. Mechanistically, acid-catalyzed halogenation of aldehydes and ketones is much different from free-radical halogenation of alkanes. Although both processes lead to the replacement of a hydrogen by a halogen, they do so by completely different pathways.

18.3 MECHANISM OF α HALOGENATION OF ALDEHYDES AND KETONES

In one of the earliest mechanistic investigations in organic chemistry, Arthur Lapworth discovered in 1904 that the rates of chlorination and bromination of acetone were the same. Later he found that iodination of acetone proceeded at the same rate as chlorination

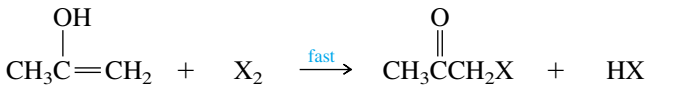
and bromination. Moreover, the rates of all three halogenation reactions, although first-order in acetone, are independent of the halogen concentration. *Thus, the halogen does not participate in the reaction until after the rate-determining step.* These kinetic observations, coupled with the fact that substitution occurs exclusively at the α-carbon atom, led Lapworth to propose that the rate-determining step is the conversion of acetone to a more reactive form, its enol isomer:



Acetone — Propen-2-ol (enol form of acetone)

The graphic that opened this chapter is an electrostatic potential map of the enol of acetone.

Once formed, this enol reacts rapidly with the halogen to form an α-halo ketone:

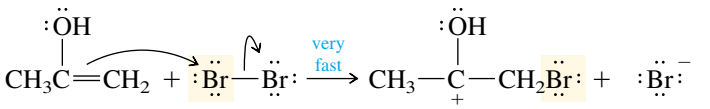


Propen-2-ol (enol form of acetone) — Halogen — α-Halo derivative of acetone — Hydrogen halide

PROBLEM 18.3 Write the structures of the enol forms of 2-butanone that react with chlorine to give 1-chloro-2-butanone and 3-chloro-2-butanone.

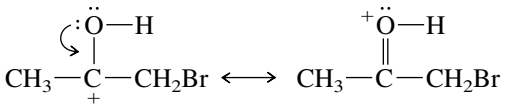
Lapworth was far ahead of his time in understanding how organic reactions occur. For an account of Lapworth's contributions to mechanistic organic chemistry, see the November 1972 issue of the *Journal of Chemical Education,* pp. 750–752.

Both parts of the Lapworth mechanism, enol formation and enol halogenation, are new to us. Let's examine them in reverse order. We can understand enol halogenation by analogy to halogen addition to alkenes. An enol is a very reactive kind of alkene. Its carbon–carbon double bond bears an electron-releasing hydroxyl group, which activates it toward attack by electrophiles.



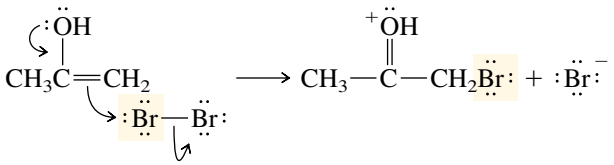
Propen-2-ol (enol form of acetone) — Bromine — Stabilized carbocation — Bromide ion

The hydroxyl group stabilizes the carbocation by delocalization of one of the unshared electron pairs of oxygen:



Less stable resonance form; 6 electrons on positively charged carbon. — More stable resonance form; all atoms (except hydrogen) have octets of electrons.

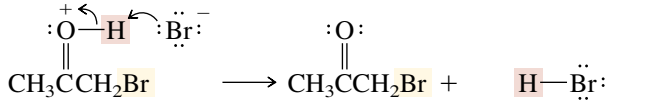
Participation by the oxygen lone pairs is responsible for the rapid attack on the carbon–carbon double bond of an enol by bromine. We can represent this participation explicitly:



Writing the bromine addition step in this way emphasizes the increased nucleophilicity of the enol double bond and identifies the source of that increased nucleophilicity as the enolic oxygen.

PROBLEM 18.4 Represent the reaction of chlorine with each of the enol forms of 2-butanone (see Problem 18.3) according to the curved arrow formalism just described.

The cationic intermediate is simply the protonated form (conjugate acid) of the α-halo ketone. Deprotonation of the cationic intermediate gives the products.



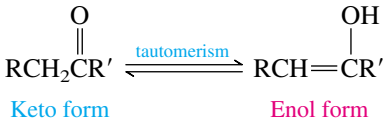
Cationic intermediate Bromoacetone Hydrogen bromide

Having now seen how an enol, once formed, reacts with a halogen, let us consider the process of enolization itself.

18.4 ENOLIZATION AND ENOL CONTENT

Enols are related to an aldehyde or a ketone by a proton-transfer equilibrium known as **keto–enol tautomerism.** (*Tautomerism* refers to an interconversion between two structures that differ by the placement of an atom or a group.)

The keto and enol forms are constitutional isomers. Using older terminology they are referred to as *tautomers* of each other.



Keto form Enol form

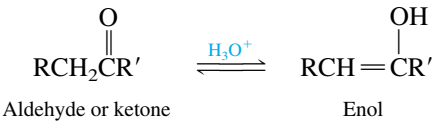
The mechanism of enolization involves two separate proton-transfer steps rather than a one-step process in which a proton jumps from carbon to oxygen. It is relatively slow in neutral media. The rate of enolization is catalyzed by acids as shown by the mechanism in Figure 18.1. In aqueous acid, a hydronium ion transfers a proton to the carbonyl oxygen in step 1, and a water molecule acts as a Brønsted base to remove a proton from the α-carbon atom in step 2. The second step is slower than the first. The first step involves proton transfer between oxygens, and the second is a proton transfer from carbon to oxygen.

You have had earlier experience with enols in their role as intermediates in the hydration of alkynes (Section 9.12). The mechanism of enolization of aldehydes and ketones is precisely the reverse of the mechanism by which an enol is converted to a carbonyl compound.

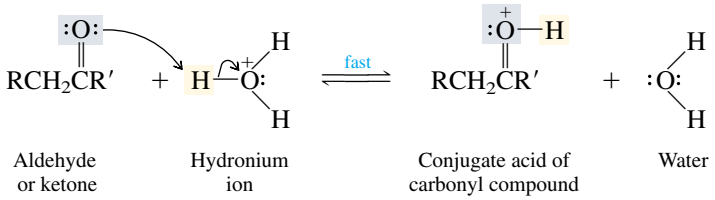
The amount of enol present at equilibrium, the *enol content,* is quite small for simple aldehydes and ketones. The equilibrium constants for enolization, as shown by the following examples, are much less than 1.

FIGURE 18.1 Mechanism of acid-catalyzed enolization of an aldehyde or ketone in aqueous solution.

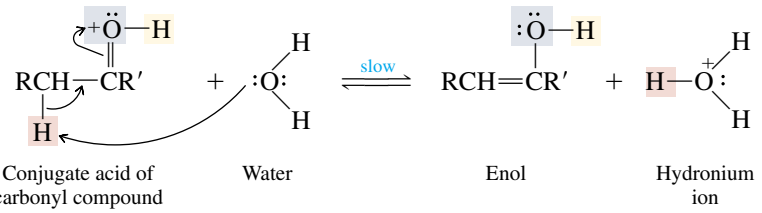
Overall reaction:

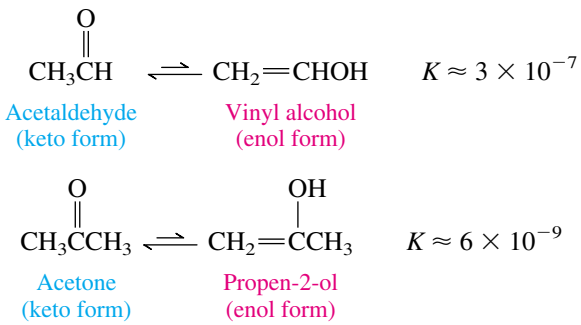


Step 1: A proton is transferred from the acid catalyst to the carbonyl oxygen.



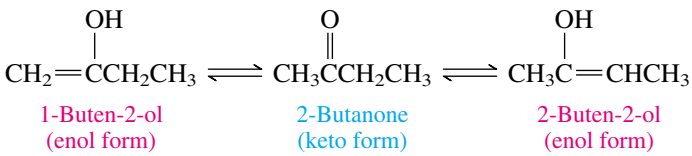
Step 2: A water molecule acts as a Brønsted base to remove a proton from the α carbon atom of the protonated aldehyde or ketone.





In these and numerous other simple cases, the keto form is more stable than the enol by some 45–60 kJ/mol (11–14 kcal/mol). The chief reason for this difference is that a carbon–oxygen double bond is stronger than a carbon–carbon double bond.

With unsymmetrical ketones, enolization may occur in either of two directions:



The ketone is by far the most abundant species present at equilibrium. Both enols are also present, but in very small concentrations.

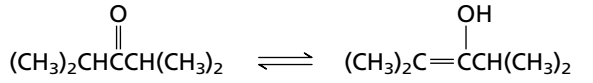
PROBLEM 18.5 Write structural formulas corresponding to

(a) The enol form of 2,4-dimethyl-3-pentanone

(b) The enol form of acetophenone

(c) The two enol forms of 2-methylcyclohexanone

SAMPLE SOLUTION (a) Remember that enolization involves the α-carbon atom. The ketone 2,4-dimethyl-3-pentanone gives a single enol, since the two α carbons are equivalent.

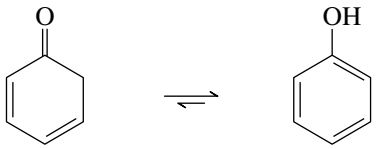


2,4-Dimethyl-3-pentanone (keto form) ⇌ 2,4-Dimethyl-2-penten-3-ol (enol form)

It is important to recognize that an enol is a real substance, capable of independent existence. An enol is *not* a resonance form of a carbonyl compound; the two are constitutional isomers of each other.

18.5 STABILIZED ENOLS

Certain structural features can make the keto–enol equilibrium more favorable by stabilizing the enol form. Enolization of 2,4-cyclohexadienone is one such example:

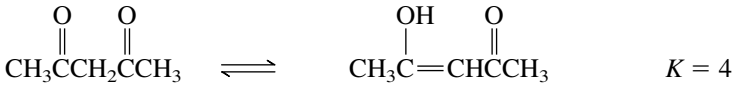


2,4-Cyclohexadienone (keto form, not aromatic) ⇌ Phenol (enol form, aromatic)

K is too large to measure.

The enol is *phenol,* and the stabilization gained by forming an aromatic ring is more than enough to overcome the normal preference for the keto form.

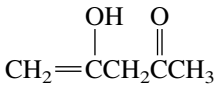
A 1,3 arrangement of two carbonyl groups (compounds called **β-diketones**) leads to a situation in which the keto and enol forms are of comparable stability.



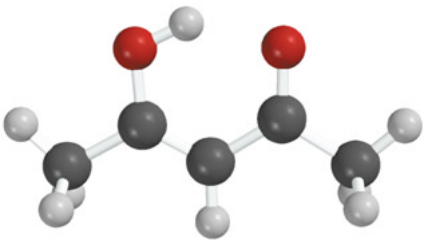
2,4-Pentanedione (20%) (keto form) ⇌ 4-Hydroxy-3-penten-2-one (80%) (enol form) $K = 4$

The two most important structural features that stabilize the enol of a β-dicarbonyl compound are (1) conjugation of its double bond with the remaining carbonyl group and (2) the presence of a strong intramolecular hydrogen bond between the enolic hydroxyl group and the carbonyl oxygen (Figure 18.2).

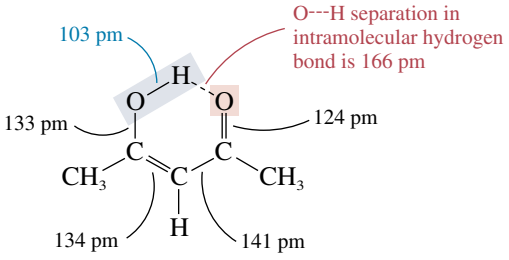
In β-diketones it is the methylene group flanked by the two carbonyls that is involved in enolization. The alternative enol



4-Hydroxy-4-penten-2-one



(*a*)



(*b*)

FIGURE 18.2 (*a*) A molecular model and (*b*) bond distances in the enol form of 2,4-pentanedione.

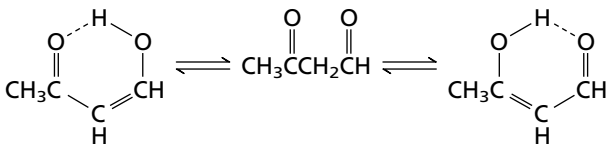
does not have its carbon–carbon double bond conjugated with the carbonyl group, is not as stable, and is present in negligible amounts at equilibrium.

PROBLEM 18.6 Write structural formulas corresponding to

(a) The two most stable enol forms of CH_3CCH_2CH (O, O)

(b) The two most stable enol forms of 1-phenyl-1,3-butanedione

SAMPLE SOLUTION (a) Enolization of this 1,3-dicarbonyl compound can involve either of the two carbonyl groups:

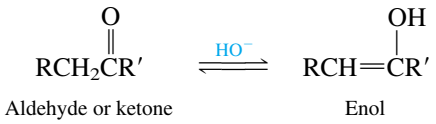


Both enols have their carbon–carbon double bonds conjugated to a carbonyl group and can form an intramolecular hydrogen bond. They are of comparable stability.

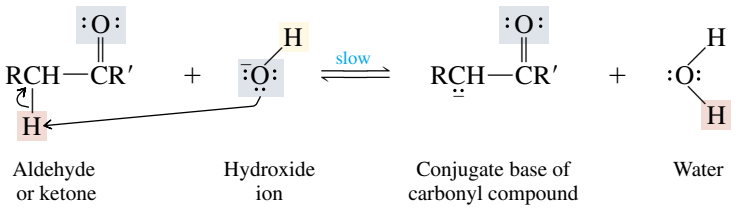
18.6 BASE-CATALYZED ENOLIZATION: ENOLATE ANIONS

The proton-transfer equilibrium that interconverts a carbonyl compound and its enol can be catalyzed by bases as well as by acids. Figure 18.3 illustrates the roles of hydroxide ion and water in a base-catalyzed enolization. As in acid-catalyzed enolization, protons are transferred sequentially rather than in a single step. First (step 1), the base abstracts

Overall reaction:



Step 1: A proton is abstracted by hydroxide ion from the α carbon atom of the carbonyl compound.



Step 2: A water molecule acts as a Brønsted acid to transfer a proton to the oxygen of the enolate ion.

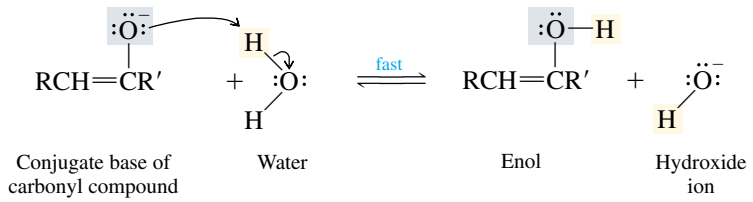
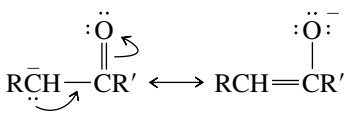


FIGURE 18.3 Mechanism of the base-catalyzed enolization of an aldehyde or ketone in aqueous solution.

a proton from the α-carbon atom to yield an anion. This anion is a resonance-stabilized species. Its negative charge is shared by the α-carbon atom and the carbonyl oxygen.



Electron delocalization in conjugate base of ketone

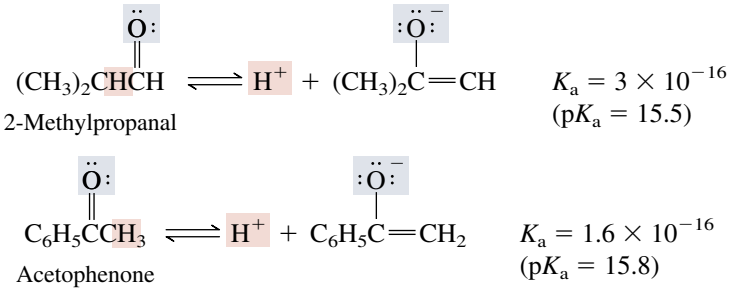
Protonation of this anion can occur either at the α carbon or at oxygen. Protonation of the α carbon simply returns the anion to the starting aldehyde or ketone. Protonation of oxygen, as shown in step 2 of Figure 18.3, produces the enol.

The key intermediate in this process, the conjugate base of the carbonyl compound, is referred to as an **enolate ion,** since it is the conjugate base of an enol. The term "enolate" is more descriptive of the electron distribution in this intermediate in that oxygen bears a greater share of the negative charge than does the α-carbon atom.

The slow step in base-catalyzed enolization is formation of the enolate ion. The second step, proton transfer from water to the enolate oxygen, is very fast, as are almost all proton transfers from one oxygen atom to another.

Examine the enolate of acetone on *Learning By Modeling.* How is the negative charge distributed between oxygen and the α carbon?

Our experience to this point has been that C—H bonds are not very acidic. Compared with most hydrocarbons, however, aldehydes and ketones have relatively acidic protons on their α-carbon atoms. Equilibrium constants for enolate formation from simple aldehydes and ketones are in the 10^{-16} to 10^{-20} range (pK_a = 16–20).

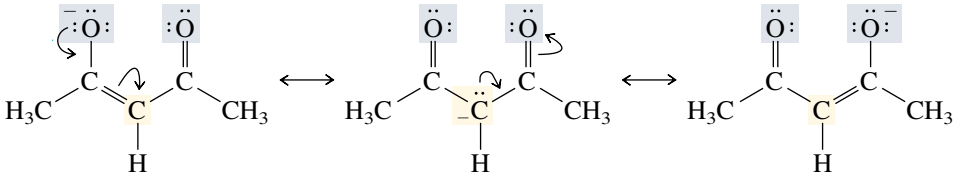


Delocalization of the negative charge onto the electronegative oxygen is responsible for the enhanced acidity of aldehydes and ketones. With K_a's in the 10^{-16} to 10^{-20} range, aldehydes and ketones are about as acidic as water and alcohols. Thus, hydroxide ion and alkoxide ions are sufficiently strong bases to produce solutions containing significant concentrations of enolate ions at equilibrium.

β-Diketones, such as 2,4-pentanedione, are even more acidic:

Learning By Modeling contains molecular models of the enolates of acetone and 2,4-pentanedione. Compare the two with respect to the distribution of negative charge.

In the presence of bases such as hydroxide, methoxide, and ethoxide, these β-diketones are converted completely to their enolate ions. Notice that it is the methylene group flanked by the two carbonyl groups that is deprotonated. Both carbonyl groups participate in stabilizing the enolate by delocalizing its negative charge.

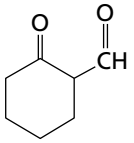


PROBLEM 18.7 Write the structure of the enolate ion derived from each of the following β-dicarbonyl compounds. Give the three most stable resonance forms of each enolate.

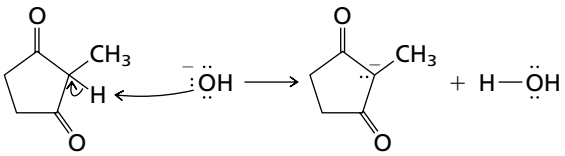
(a) 2-Methyl-1,3-cyclopentanedione

(b) 1-Phenyl-1,3-butanedione

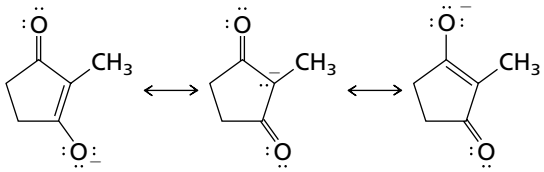
(c)



SAMPLE SOLUTION (a) First identify the proton that is removed by the base. It is on the carbon between the two carbonyl groups.



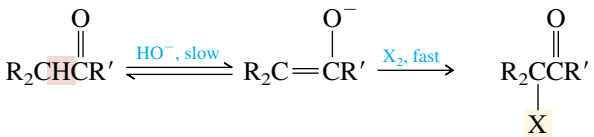
The three most stable resonance forms of this anion are



Enolate ions of β-dicarbonyl compounds are useful intermediates in organic synthesis. We shall see some examples of how they are employed in this way later in the chapter.

18.7 THE HALOFORM REACTION

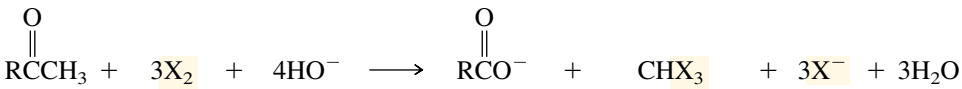
Rapid halogenation of the α-carbon atom takes place when an enolate ion is generated in the presence of chlorine, bromine, or iodine.



Aldehyde or ketone	Enolate	α-Halo aldehyde or ketone

As in the acid-catalyzed halogenation of aldehydes and ketones, the reaction rate is independent of the concentration of the halogen; chlorination, bromination, and iodination all occur at the same rate. Formation of the enolate is rate-determining, and, once formed, the enolate ion reacts rapidly with the halogen.

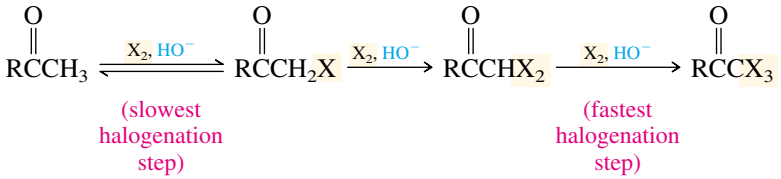
Unlike its acid-catalyzed counterpart, α halogenation in base cannot normally be limited to monohalogenation. Methyl ketones, for example, undergo a novel polyhalogenation and cleavage on treatment with a halogen in aqueous base.



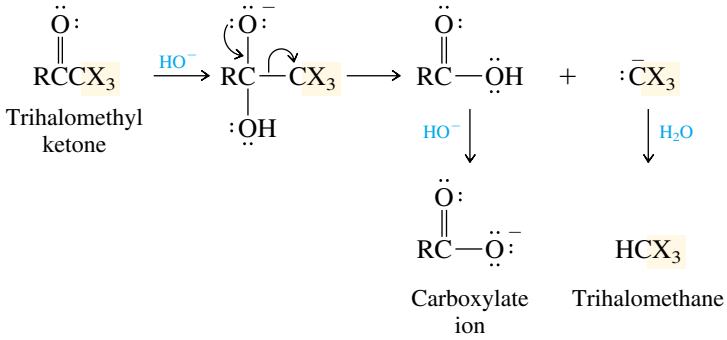
Methyl ketone	Halogen	Hydroxide ion	Carboxylate ion	Trihalomethane	Halide ion	Water

This is called the *haloform reaction* because the trihalomethane produced is chloroform, bromoform, or iodoform, depending, of course, on the halogen used.

The mechanism of the haloform reaction begins with α halogenation via the enolate. The electron-attracting effect of an α halogen increases the acidity of the protons on the carbon to which it is bonded, making each subsequent halogenation *at that carbon* faster than the preceding one.

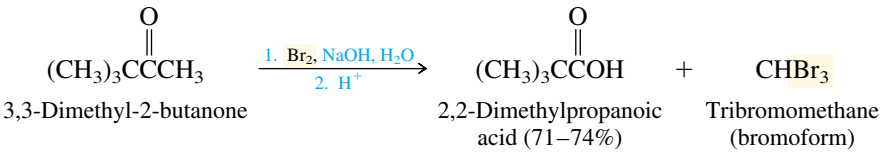


The trihalomethyl ketone ($RCCX_3$) so formed then undergoes nucleophilic addition of hydroxide ion to its carbonyl group, triggering its dissociation.



The three electron-withdrawing halogen substituents stabilize the negative charge of the trihalomethide ion ($^{-}$:CX_3), permitting it to act as a leaving group in the carbon–carbon bond cleavage step.

The haloform reaction is sometimes used for the preparation of carboxylic acids from methyl ketones.



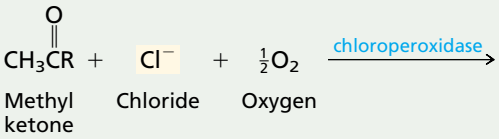
The methyl ketone shown in the example can enolize in only one direction and typifies the kind of reactant that can be converted to a carboxylic acid in synthetically acceptable yield by the haloform reaction. When C-3 of a methyl ketone bears enolizable hydrogens, as in $CH_3CH_2CCH_3$, the first halogenation step is not very regioselective and the isolated yield of $CH_3CH_2CO_2H$ is only about 50%.

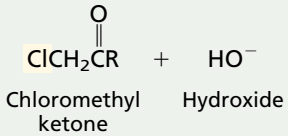
The haloform reaction, using iodine, was once used as an analytical test in which the formation of a yellow precipitate of iodoform was taken as evidence that a substance was a methyl ketone. This application has been superseded by spectroscopic methods of structure determination. Interest in the haloform reaction has returned with the realization that chloroform and bromoform occur naturally and are biosynthesized by an analogous process. (See the boxed essay "The Haloform Reaction and the Biosynthesis of Trihalomethanes.")

THE HALOFORM REACTION AND THE BIOSYNTHESIS OF TRIHALOMETHANES

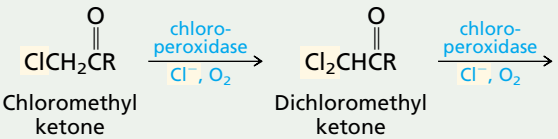
Until scientists started looking specifically for them, it was widely believed that naturally occurring organohalogen compounds were rare. We now know that more than 2000 such compounds occur naturally, with the oceans being a particularly rich source.* Over 50 organohalogen compounds, including $CHBr_3$, $CHBrClI$, $BrCH_2CH_2I$, CH_2I_2, $Br_2CHCH{=}O$, I_2CHCO_2H, and $(Cl_3C)_2C{=}O$, have been found in a single species of Hawaiian red seaweed, for example. It is not surprising that organisms living in the oceans have adapted to their halide-rich environment by incorporating chlorine, bromine, and iodine into their metabolic processes. Chloromethane (CH_3Cl), bromomethane (CH_3Br), and iodomethane (CH_3I) are all produced by marine algae and kelp, but land-based plants and fungi also contribute their share to the more than 5 million tons of the methyl halides formed each year by living systems. The ice plant, which grows in arid regions throughout the world and is cultivated as a ground cover along coastal highways in California, biosynthesizes CH_3Cl by a process in which nucleophilic attack by chloride ion (Cl^-) on the methyl group of *S*-adenosylmethionine is the key step (Section 16.17).

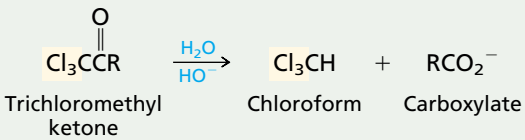
Interestingly, the trihalomethanes chloroform ($CHCl_3$), bromoform ($CHBr_3$), and iodoform (CHI_3) are biosynthesized by an entirely different process, one that is equivalent to the haloform reaction (Section 18.7) and begins with the formation of an α-halo ketone. Unlike the biosynthesis of methyl halides, which requires attack by a halide nucleophile (X^-), α halogenation of a ketone requires attack by an electrophilic form of the halogen. For chlorination, the electrophilic form of the halogen is generated by oxidation of Cl^- in the presence of the enzyme *chloroperoxidase.* Thus, the overall equation for the enzyme-catalyzed chlorination of a methyl ketone may be written as





Further chlorination of the chloromethyl ketone gives the corresponding trichloromethyl ketone, which then undergoes hydrolysis to form chloroform.





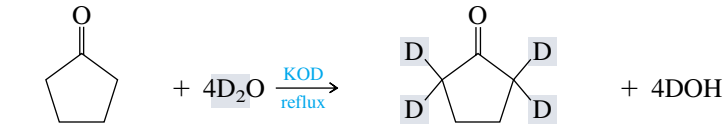
Purification of drinking water, by adding Cl_2 to kill bacteria, is a source of electrophilic chlorine and contributes a nonenzymatic pathway for α chlorination and subsequent chloroform formation. Although some of the odor associated with tap water may be due to chloroform, more of it probably results from chlorination of algae-produced organic compounds.

*The November 1994 edition of the *Journal of Chemical Education* contains as its cover story the article "Natural Organohalogens. Many More Than You Think!"

18.8 SOME CHEMICAL AND STEREOCHEMICAL CONSEQUENCES OF ENOLIZATION

A number of novel reactions involving the α-carbon atom of aldehydes and ketones involve enol and enolate anion intermediates.

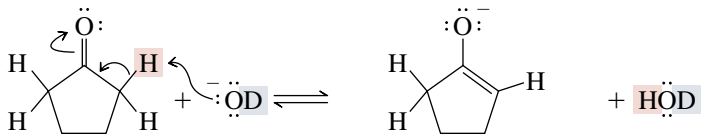
Substitution of deuterium for hydrogen at the α-carbon atom of an aldehyde or a ketone is a convenient way to introduce an isotopic label into a molecule and is readily carried out by treating the carbonyl compound with deuterium oxide (D_2O) and base.



Cyclopentanone Cyclopentanone-2,2,5,5-d_4

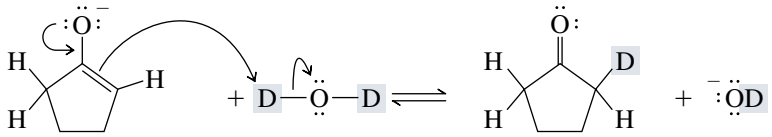
Only the α hydrogens are replaced by deuterium in this reaction. The key intermediate is the enolate ion formed by proton abstraction from the α-carbon atom of cyclopentanone. Transfer of deuterium from the solvent D_2O to the enolate gives cyclopentanone containing a deuterium atom in place of one of the hydrogens at the α carbon.

Formation of the enolate



Cyclopentanone Enolate of cyclopentanone

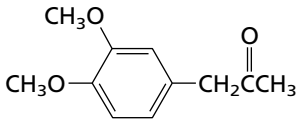
Deuterium transfer to the enolate



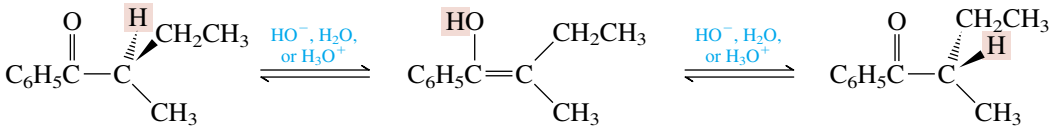
Enolate of cyclopentanone Cyclopentanone-2-d_1

In excess D_2O the process continues until all four α protons are eventually replaced by deuterium.

PROBLEM 18.8 After the compound shown was heated in D_2O containing K_2CO_3 at 70°C the only signals that could be found in its ^1H NMR spectrum were at δ 3.9 ppm (6H) and δ 6.7–6.9 ppm (3H). What happened?



If the α-carbon atom of an aldehyde or a ketone is a stereogenic center, its stereochemical integrity is lost on enolization. Enolization of optically active *sec*-butyl phenyl ketone leads to its racemization by way of the achiral enol form.



(*R*)-*sec*-Butyl phenyl ketone

Enol form [achiral; may be converted to either (*R*)- or (*S*)-*sec*-butyl phenyl ketone]

(*S*)-*sec*-Butyl phenyl ketone

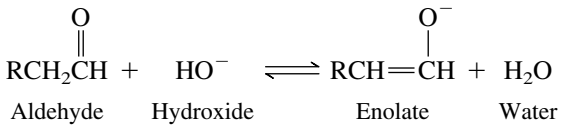
Each act of proton abstraction from the α-carbon atom converts a chiral molecule to an achiral enol or enolate anion. Careful kinetic studies have established that the rate of loss

of optical activity of *sec*-butyl phenyl ketone is equal to its rate of hydrogen–deuterium exchange, its rate of bromination, and its rate of iodination. In each case, the rate-determining step is conversion of the starting ketone to the enol or enolate anion.

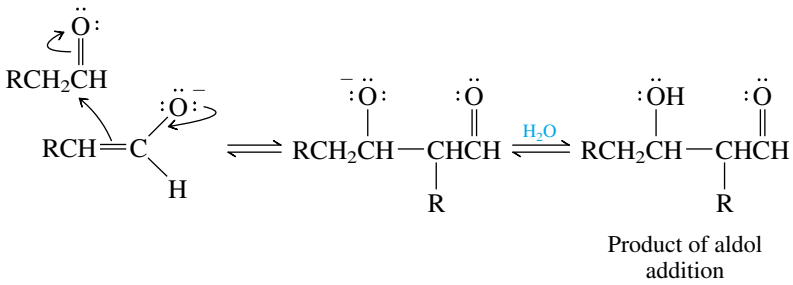
PROBLEM 18.9 Is the product from the α chlorination of (*R*)-*sec*-butyl phenyl ketone with Cl_2 in acetic acid chiral? Is it optically active?

18.9 THE ALDOL CONDENSATION

As noted earlier, an aldehyde is partially converted to its enolate anion by bases such as hydroxide ion and alkoxide ions.



In a solution that contains both an aldehyde and its enolate ion, the enolate undergoes nucleophilic addition to the carbonyl group. This addition is analogous to the addition reactions of other nucleophilic reagents to aldehydes and ketones described in Chapter 17.



The alkoxide formed in the nucleophilic addition step then abstracts a proton from the solvent (usually water or ethanol) to yield the product of **aldol addition.** This product is known as an *aldol* because it contains both an aldehyde function and a hydroxyl group *(ald + ol = aldol).*

An important feature of aldol addition is that carbon–carbon bond formation occurs between the α-carbon atom of one aldehyde and the carbonyl group of another. This is because carbanion (enolate) generation can involve proton abstraction *only* from the α-carbon atom. The overall transformation can be represented schematically, as shown in Figure 18.4.

Some of the earliest studies of the aldol reaction were carried out by Aleksander Borodin. Though a physician by training and a chemist by profession, Borodin is remembered as the composer of some of the most familiar works in Russian music. See pp. 326–327 in the April 1987 issue of the *Journal of Chemical Education* for a biographical sketch of Borodin.

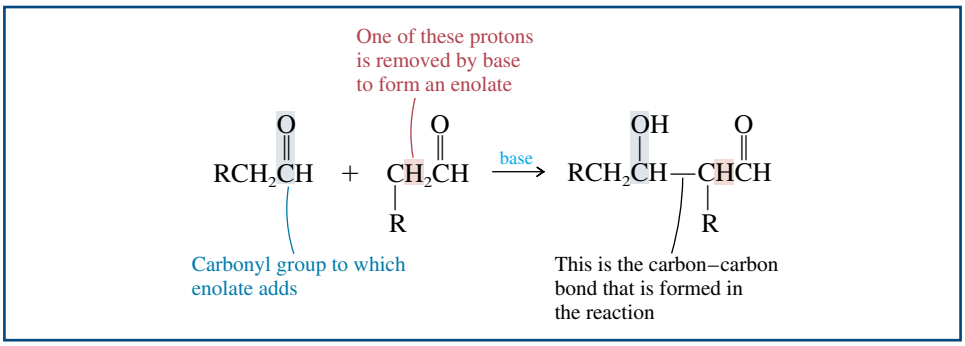
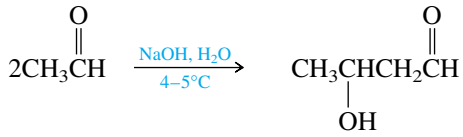
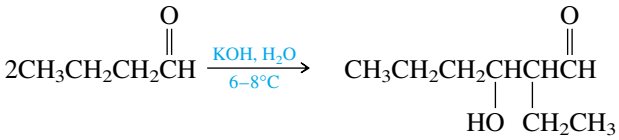


FIGURE 18.4 The reactive sites in aldol addition are the carbonyl group of one aldehyde molecule and the α-carbon atom of another.

Aldol addition occurs readily with aldehydes:



Acetaldehyde — 3-Hydroxybutanal (50%) (acetaldol)



Butanal — 2-Ethyl-3-hydroxyhexanal (75%)

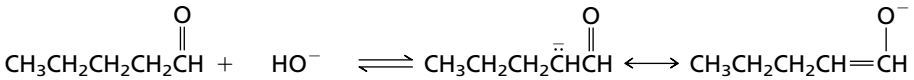
PROBLEM 18.10 Write the structure of the aldol addition product of

(a) Pentanal, $CH_3CH_2CH_2CH_2CH$

(b) 2-Methylbutanal, $CH_3CH_2CH(CH_3)CH$

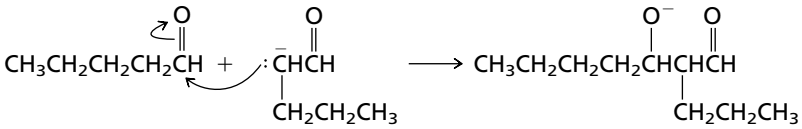
(c) 3-Methylbutanal, $(CH_3)_2CHCH_2CH$

SAMPLE SOLUTION (a) A good way to correctly identify the aldol addition product of any aldehyde is to work through the process mechanistically. Remember that the first step is enolate formation and that this *must* involve proton abstraction from the α carbon.

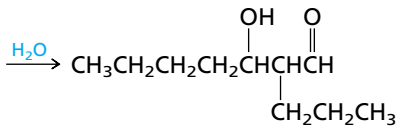


Pentanal — Hydroxide — Enolate of pentanal

Now use the negatively charged α carbon of the enolate to form a new carbon–carbon bond to the carbonyl group. Proton transfer from the solvent completes the process.

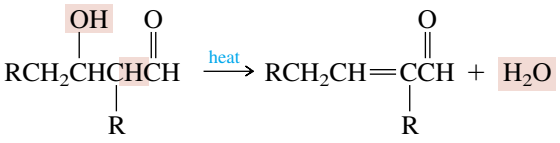


Pentanal — Enolate of pentanal



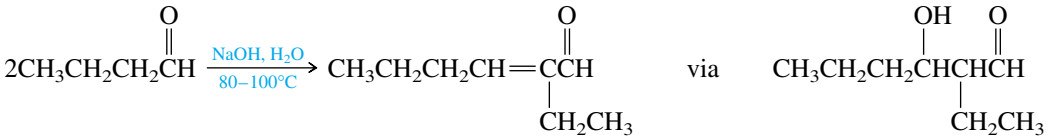
3-Hydroxy-2-propylheptanal (aldol addition product of pentanal)

The β-hydroxy aldehyde products of aldol addition undergo dehydration on heating, to yield *α,β-unsaturated aldehydes:*



β-Hydroxy aldehyde — α,β-Unsaturated aldehyde — Water

Conjugation of the newly formed double bond with the carbonyl group stabilizes the α,β-unsaturated aldehyde, provides the driving force for the dehydration, and controls its regioselectivity. Dehydration can be effected by heating the aldol with acid or base. Normally, if the α,β-unsaturated aldehyde is the desired product, all that is done is to carry out the base-catalyzed aldol addition reaction at elevated temperature. Under these conditions, once the aldol addition product is formed, it rapidly loses water to form the α,β-unsaturated aldehyde.



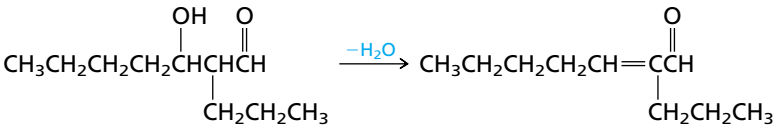
Butanal — 2-Ethyl-2-hexenal (86%) — 2-Ethyl-3-hydroxyhexanal (not isolated; dehydrates under reaction conditions)

Reactions in which two molecules of an aldehyde combine to form an α,β-unsaturated aldehyde and a molecule of water are called **aldol condensations.**

Recall from Section 15.7 that a condensation is a reaction in which two molecules combine to give a product along with some small (usually inorganic) molecule such as water.

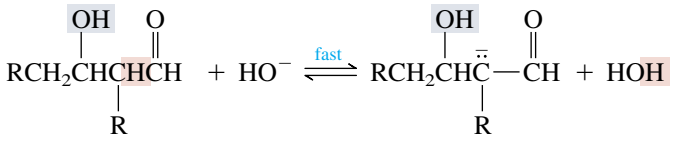
PROBLEM 18.11 Write the structure of the aldol condensation product of each of the aldehydes in Problem 18.10. One of these aldehydes can undergo aldol addition, but not aldol condensation. Which one? Why?

SAMPLE SOLUTION (a) Dehydration of the product of aldol addition of pentanal introduces the double bond between C-2 and C-3 to give an α,β-unsaturated aldehyde.

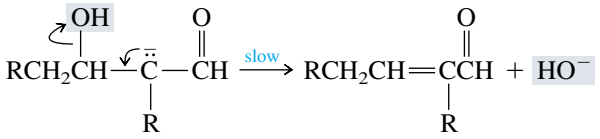


Product of aldol addition of pentanal (3-hydroxy-2-propylheptanal) — Product of aldol condensation of pentanal (2-propyl-2-heptenal)

The point was made earlier (Section 5.9) that alcohols require acid catalysis in order to undergo dehydration to alkenes. Thus, it may seem strange that aldol addition products can be dehydrated in base. This is another example of the way in which the enhanced acidity of protons at the α-carbon atom affects the reactions of carbonyl compounds. Elimination may take place in a concerted E2 fashion or it may be stepwise and proceed through an enolate ion.

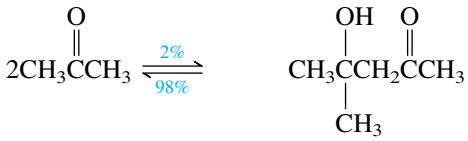


β-Hydroxy aldehyde — Enolate ion of β-hydroxy aldehyde



Enolate ion of β-hydroxy aldehyde — α,β-Unsaturated aldehyde

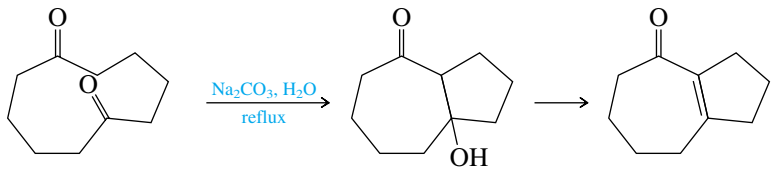
As with other reversible nucleophilic addition reactions, the equilibria for aldol additions are less favorable for ketones than for aldehydes. For example, only 2% of the aldol addition product of acetone is present at equilibrium.



Acetone — 4-Hydroxy-4-methyl-2-pentanone

The situation is similar for other ketones. Special procedures for aldol addition and self-condensation of ketones have been developed, but are rarely used.

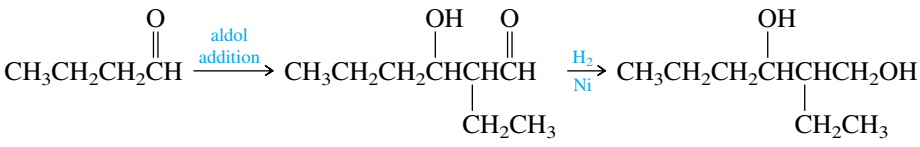
Aldol condensations of dicarbonyl compounds—even diketones—occur intramolecularly when five- or six-membered rings are possible.



1,6-Cyclodecanedione — Not isolated; dehydrates under reaction conditions — Bicyclo[5.3.0]dec-1(7)-en-2-one (96%)

Aldol condensations are one of the fundamental carbon–carbon bond-forming processes of synthetic organic chemistry. Furthermore, since the products of these aldol condensations contain functional groups capable of subsequent modification, access to a host of useful materials is gained.

To illustrate how aldol condensation may be coupled to functional group modification, consider the synthesis of 2-ethyl-1,3-hexanediol, a compound used as an insect repellent. This 1,3-diol is prepared by reduction of the aldol addition product of butanal:



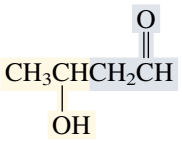
Butanal — 2-Ethyl-3-hydroxyhexanal — 2-Ethyl-1,3-hexanediol

PROBLEM 18.12 Outline a synthesis of 2-ethyl-1-hexanol from butanal.

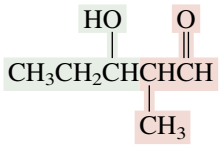
The carbon–carbon bond-forming potential of the aldol condensation has been extended beyond the self-condensations described in this section to cases in which two different carbonyl compounds react in what are called *mixed aldol condensations.*

18.10 MIXED ALDOL CONDENSATIONS

Mixed aldol condensations can be effective only if we limit the number of reaction possibilities. It would not be useful, for example, to treat a solution of acetaldehyde and propanal with base. A mixture of four aldol addition products forms under these conditions. Two of the products are those of self-addition:

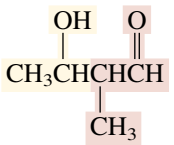


3-Hydroxybutanal
(from addition of enolate
of acetaldehyde to acetaldehyde)

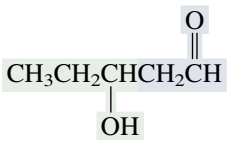


3-Hydroxy-2-methylpentanal
(from addition of enolate
of propanal to propanal)

Two are the products of mixed addition:



3-Hydroxy-2-methylbutanal
(from addition of enolate
of propanal to acetaldehyde)

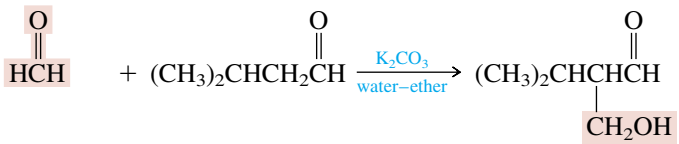


3-Hydroxypentanal
(from addition of enolate
of acetaldehyde to propanal)

The mixed aldol condensations that are the most synthetically useful are those in which:

1. Only one of the reactants can form an enolate; or
2. One of the reactants is more reactive toward nucleophilic addition than the other.

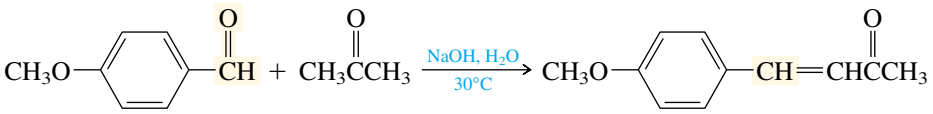
Formaldehyde, for example, cannot form an enolate but can react with the enolate of an aldehyde or ketone that can.



Formaldehyde 3-Methylbutanal 2-Hydroxymethyl-3-methylbutanal (52%)

Indeed, formaldehyde is so reactive toward nucleophilic addition that it suppresses the self-condensation of the other component by reacting rapidly with any enolate present.

Aromatic aldehydes cannot form enolates, and a large number of mixed aldol condensations have been carried out in which an aromatic aldehyde reacts with an enolate.



p-Methoxybenzaldehyde Acetone 4-*p*-Methoxyphenyl-3-buten-2-one (83%)

Mixed aldol condensations in which a ketone reacts with an aromatic aldehyde are known as *Claisen–Schmidt condensations.*

Recall that ketones do not readily undergo self-condensation. Thus, in the preceding example, the enolate of acetone reacts preferentially with the aromatic aldehyde and gives the mixed aldol condensation product in good yield. Mixed aldol condensations using aromatic aldehydes always involve dehydration of the product of mixed addition and yield a product in which the double bond is conjugated to both the aromatic ring and the carbonyl group.

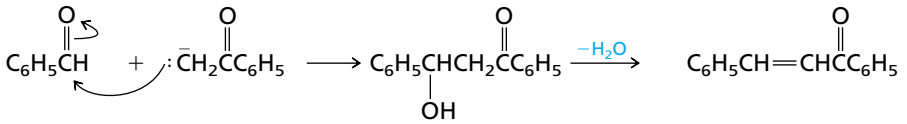
PROBLEM 18.13 Give the structure of the mixed aldol condensation product of benzaldehyde with

(a) Acetophenone, $C_6H_5CCH_3$ (O above the C)

(b) *tert*-Butyl methyl ketone, $(CH_3)_3CCCH_3$ (O above the C)

(c) Cyclohexanone

SAMPLE SOLUTION (a) The enolate of acetophenone reacts with benzaldehyde to yield the product of mixed addition. Dehydration of the intermediate occurs, giving the α,β-unsaturated ketone.



Benzaldehyde Enolate of acetophenone 1,3-Diphenyl-2-propen-1-one

As actually carried out, the mixed aldol condensation product, 1,3-diphenyl-2-propen-1-one, has been isolated in 85% yield on treating benzaldehyde with acetophenone in an aqueous ethanol solution of sodium hydroxide at 15–30°C.

18.11 EFFECTS OF CONJUGATION IN α,β-UNSATURATED ALDEHYDES AND KETONES

Aldol condensation offers an effective route to α,β-unsaturated aldehydes and ketones. These compounds have some interesting properties that result from conjugation of the carbon–carbon double bond with the carbonyl group. As shown in Figure 18.5, the π systems of the carbon–carbon and carbon–oxygen double bonds overlap to form an extended π system that permits increased electron delocalization.

This electron delocalization stabilizes a conjugated system. Under conditions chosen to bring about their interconversion, the equilibrium between a β,γ-unsaturated ketone and an α,β-unsaturated analog favors the conjugated isomer.

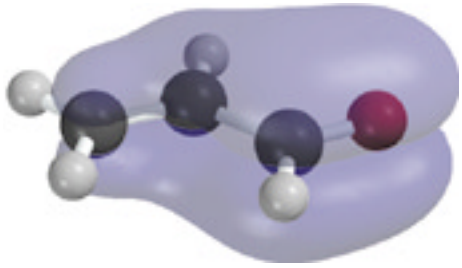
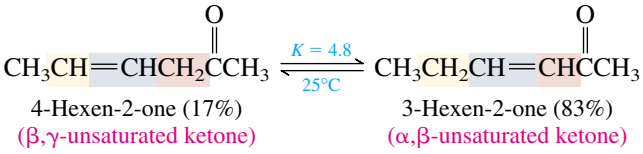


FIGURE 18.5 Acrolein ($H_2C{=}CHCH{=}O$) is a planar molecule. Oxygen and each carbon are sp^2-hybridized, and each contributes one electron to a conjugated π electron system analogous to that of 1,3-butadiene.



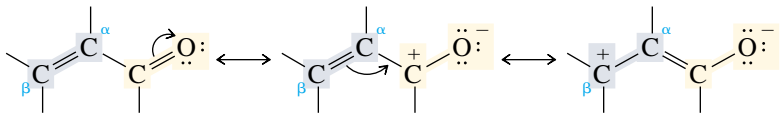
4-Hexen-2-one (17%)
(β,γ-unsaturated ketone)

3-Hexen-2-one (83%)
(α,β-unsaturated ketone)

Figure 3.17 (page 107) shows how the composition of an equilibrium mixture of two components varies according to the free-energy difference between them. For the equilibrium shown in the accompanying equation, $\Delta G° = -4$ kJ/mol (−1 kcal/mol).

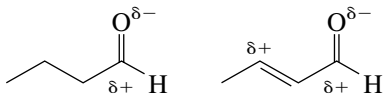
PROBLEM 18.14 Commercial mesityl oxide, $(CH_3)_2C{=}CHCCH_3$, is often contaminated with about 10% of an isomer having the same carbon skeleton. What is a likely structure for this compound?

In resonance terms, electron delocalization in α,β-unsaturated carbonyl compounds is represented by contributions from three principal resonance structures:



Most stable structure

The carbonyl group withdraws π electron density from the double bond, and both the carbonyl carbon and the β carbon are positively polarized. Their greater degree of charge separation makes the dipole moments of α,β-unsaturated carbonyl compounds significantly larger than those of comparable aldehydes and ketones.



Butanal
μ = 2.7 D

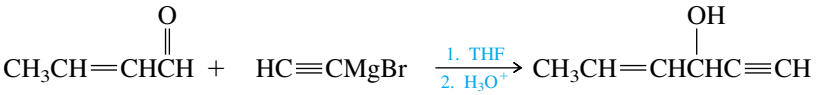
trans-2-Butenal
μ = 3.7 D

The diminished π electron density in the double bond makes α,β-unsaturated aldehydes and ketones less reactive than alkenes toward electrophilic addition. Electrophilic reagents—bromine and peroxy acids, for example—react more slowly with the carbon–carbon double bond of α,β-unsaturated carbonyl compounds than with simple alkenes.

On the other hand, the polarization of electron density in α,β-unsaturated carbonyl compounds makes their β-carbon atoms rather electrophilic. Some chemical consequences of this enhanced electrophilicity are described in the following section.

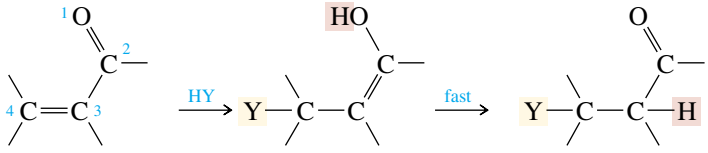
18.12 CONJUGATE ADDITION TO α,β-UNSATURATED CARBONYL COMPOUNDS

α,β-Unsaturated carbonyl compounds contain two electrophilic sites: the carbonyl carbon and the carbon atom that is β to it. Nucleophiles such as organolithium and Grignard reagents and lithium aluminum hydride tend to react by nucleophilic addition to the carbonyl group, as shown in the following example:

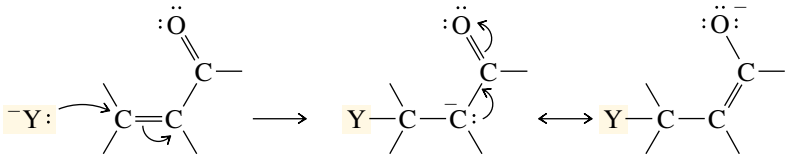


This is called *direct addition,* or *1,2 addition.* (The "1" and "2" do not refer to IUPAC locants but are used in a manner analogous to that employed in Section 10.10 to distinguish between direct and conjugate addition to conjugated dienes.)

With certain other nucleophiles, addition takes place at the carbon–carbon double bond rather than at the carbonyl group. Such reactions proceed via enol intermediates and are described as *conjugate addition,* or *1,4-addition,* reactions.



The nucleophilic portion of the reagent (Y in HY) becomes bonded to the β carbon. For reactions carried out under conditions in which the attacking species is the anion $:Y^-$, an enolate ion precedes the enol.

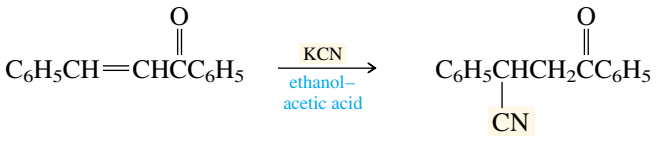


Enolate ion formed by nucleophilic addition of $:Y^-$ to β carbon

Ordinarily, nucleophilic addition to the carbon–carbon double bond of an alkene is very rare. It occurs with α,β-unsaturated carbonyl compounds because the carbanion that results is an enolate, which is more stable than a simple alkyl anion.

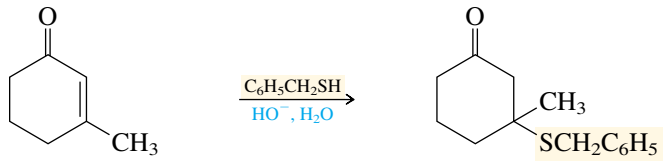
Hydrogen cyanide and alkanethiols have K_a values in the 10^{-9}–10^{-10} range (pK_a = 9–10), and K_a for acetylene is 10^{-26} (pK_a = 26).

Conjugate addition is most often observed when the nucleophile ($Y:^-$) is weakly basic. The nucleophiles in the two examples that follow are $^-:C{\equiv}N:$ and $C_6H_5CH_2\ddot{S}:^-$, respectively. Both are much weaker bases than acetylide ion, which was the nucleophile used in the example illustrating direct addition.



1,3-Diphenyl-2-propen-1-one

4-Oxo-2,4-diphenylbutanenitrile
(93–96%)



3-Methyl-2-cyclohexenone

3-Benzylthio-3-methylcyclohexanone
(58%)

One explanation for these observations is presented in Figure 18.6. Nucleophilic addition to α,β-unsaturated aldehydes and ketones may be governed either by *kinetic control* or by *thermodynamic control* (Section 10.10). 1,2 Addition is faster than 1,4 addition and, under conditions in which the 1,2- and 1,4-addition products do not equilibrate, is the predominant pathway. Kinetic control operates with strongly basic nucleophiles to give the 1,2-addition product. A weakly basic nucleophile, however, goes on and off the carbonyl carbon readily and permits the 1,2-addition product to equilibrate with the more slowly formed, but more stable, 1,4-addition product. Thermodynamic control is observed with weakly basic nucleophiles. The product of 1,4 addition, which retains the carbon–oxygen double bond, is more stable than the product of 1,2 addition, which retains the carbon–carbon double bond. In general, carbon–oxygen double bonds are more stable than carbon–carbon double bonds because the greater electronegativity of oxygen permits the π electrons to be bound more strongly.

PROBLEM 18.15 *Acrolein* ($CH_2{=}CHCH{=}O$) reacts with sodium azide (NaN_3) in aqueous acetic acid to form a compound, $C_3H_5N_3O$ in 71% yield. Propanal ($CH_3CH_2CH{=}O$), when subjected to the same reaction conditions, is recovered unchanged. Suggest a structure for the product formed from acrolein, and offer an explanation for the difference in reactivity between acrolein and propanal.

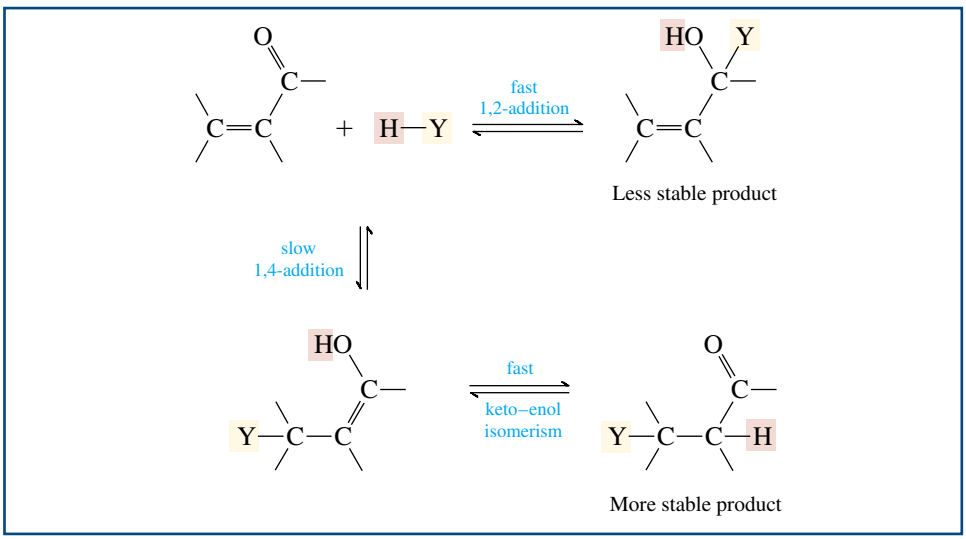
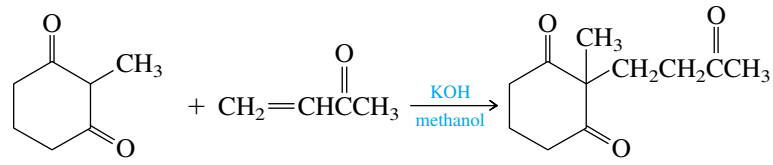


FIGURE 18.6 Nucleophilic addition to α,β-unsaturated aldehydes and ketones may take place either in a 1,2- or 1,4 manner. Direct addition (1,2) occurs faster than conjugate addition (1,4) but gives a less stable product. The product of 1,4 addition retains the carbon–oxygen double bond, which is, in general, stronger than a carbon–carbon double bond.

18.13 ADDITION OF CARBANIONS TO α,β-UNSATURATED KETONES: THE MICHAEL REACTION

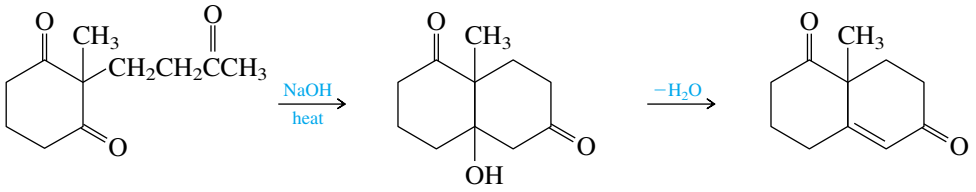
Arthur Michael, for whom the reaction is named, was an American chemist whose career spanned the period between the 1870s and the 1930s. He was independently wealthy and did much of his research in his own private laboratory.

A synthetically useful reaction known as the **Michael reaction,** or **Michael addition,** involves nucleophilic addition of carbanions to α,β-unsaturated ketones. The most common types of carbanions used are enolate ions derived from β-diketones. These enolates are weak bases (Section 18.6) and react with α,β-unsaturated ketones by *conjugate addition.*



2-Methyl-1,3-cyclohexanedione | Methyl vinyl ketone | 2-Methyl-2-(3′-oxobutyl)-1,3-cyclohexanedione (85%)

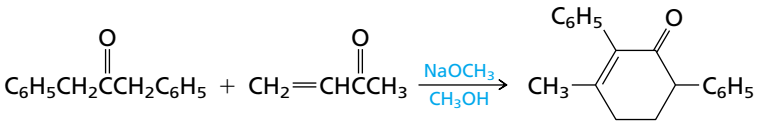
The product of Michael addition has the necessary functionality to undergo an intramolecular aldol condensation:



2-Methyl-2-(3′-oxobutyl)-1,3-cyclohexanedione | Intramolecular aldol addition product; not isolated | Δ^4-9-Methyloctalin-3,8-dione

The synthesis of cyclohexenone derivatives by Michael addition followed by intramolecular aldol condensation is called the **Robinson annulation,** after Sir Robert Robinson, who popularized its use. By *annulation* we mean the building of a ring onto some starting molecule. (The alternative spelling "annelation" is also often used.)

PROBLEM 18.16 Both the conjugate addition step and the intramolecular aldol condensation step can be carried out in one synthetic operation without isolating any of the intermediates along the way. For example, consider the reaction

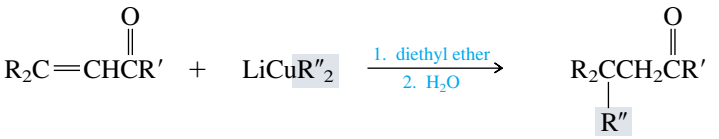


Dibenzyl ketone | Methyl vinyl ketone | 3-Methyl-2,6-diphenyl-2-cyclohexen-1-one (55%)

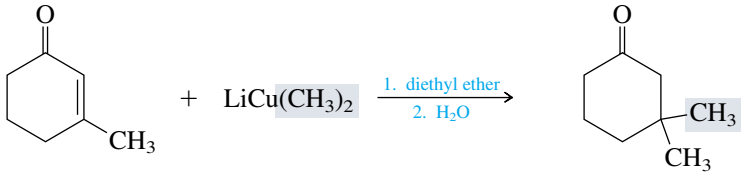
Write structural formulas corresponding to the intermediates formed in the conjugate addition step and in the aldol addition step.

18.14 CONJUGATE ADDITION OF ORGANOCOPPER REAGENTS TO α,β-UNSATURATED CARBONYL COMPOUNDS

The preparation and some synthetic applications of lithium dialkylcuprates were described earlier (Section 14.11). The most prominent feature of these reagents is their capacity to undergo conjugate addition to α,β-unsaturated aldehydes and ketones.



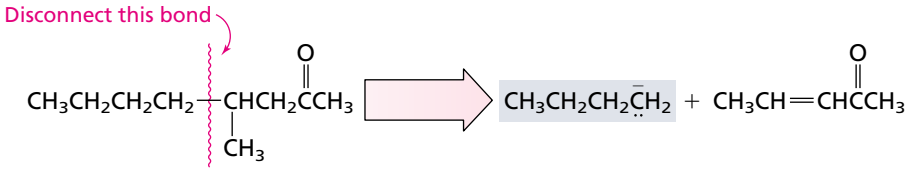
α,β-Unsaturated aldehyde or ketone | Lithium dialkylcuprate | Aldehyde or ketone alkylated at the β position



3-Methyl-2-cyclohexenone | Lithium dimethylcuprate | 3,3-Dimethylcyclohexanone (98%)

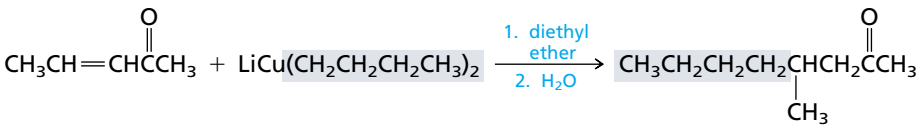
PROBLEM 18.17 Outline two ways in which 4-methyl-2-octanone can be prepared by conjugate addition of an organocuprate to an α,β-unsaturated ketone.

SAMPLE SOLUTION Mentally disconnect one of the bonds to the β carbon so as to identify the group that comes from the lithium dialkylcuprate.



4-Methyl-2-octanone

According to this disconnection, the butyl group is derived from lithium dibutylcuprate. A suitable preparation is



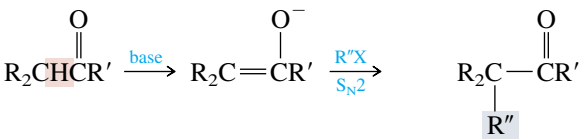
3-Penten-2-one | Lithium dibutylcuprate | 4-Methyl-2-octanone

Now see if you can identify the second possibility.

Like other carbon–carbon bond-forming reactions, organocuprate addition to enones is a powerful tool in organic synthesis.

18.15 ALKYLATION OF ENOLATE ANIONS

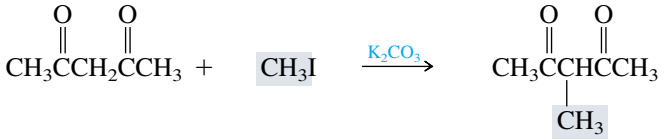
Since enolate anions are sources of nucleophilic carbon, one potential use in organic synthesis is their reaction with alkyl halides to give α-alkyl derivatives of aldehydes and ketones:



Aldehyde or ketone | Enolate anion | α-Alkyl derivative of an aldehyde or a ketone

Alkylation occurs by an S_N2 mechanism in which the enolate ion acts as a nucleophile toward the alkyl halide.

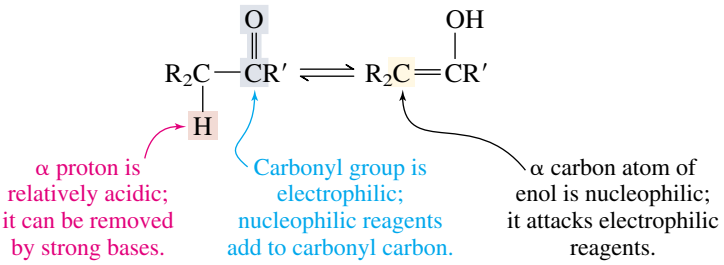
In practice, this reaction is difficult to carry out with simple aldehydes and ketones because aldol condensation competes with alkylation. Furthermore, it is not always possible to limit the reaction to the introduction of a single alkyl group. The most successful alkylation procedures use β-diketones as starting materials. Because they are relatively acidic, β-diketones can be converted quantitatively to their enolate ions by weak bases and do not self-condense. Ideally, the alkyl halide should be a methyl or primary alkyl halide.



18.16 SUMMARY

Section 18.1 Greek letters are commonly used to identify various carbons in aldehydes and ketones. Using the carbonyl group as a reference, the adjacent carbon is designated α, the next one β, and so on as one moves down the chain. Attached groups take the same Greek letter as the carbon to which they are connected.

Sections 18.2–18.15 Because aldehydes and ketones exist in equilibrium with their corresponding enol isomers, they can express a variety of different kinds of chemical reactivity.



Reactions that proceed via enol or enolate intermediates are summarized in Table 18.1.

PROBLEMS

18.18 (a) Write structural formulas or build molecular models for all the noncyclic aldehydes and ketones of molecular formula C_4H_6O.

(b) Are any of these compounds stereoisomeric?

(c) Are any of these compounds chiral?

(d) Which of these are α,β-unsaturated aldehydes or α,β-unsaturated ketones?

(e) Which of these can be prepared by a simple (i.e., not mixed) aldol condensation?

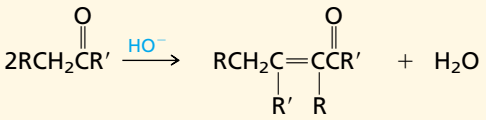
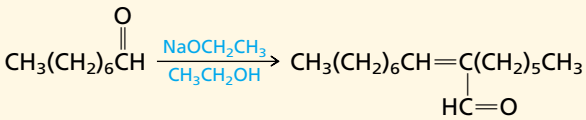
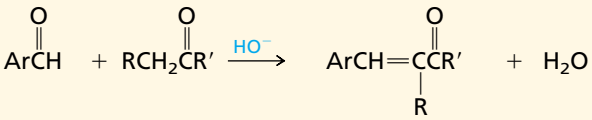
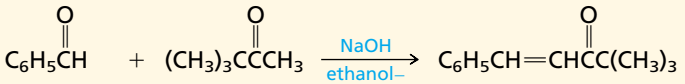
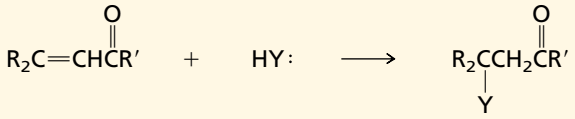
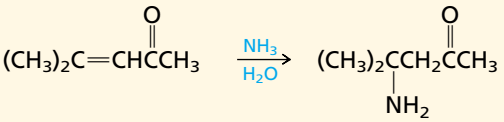
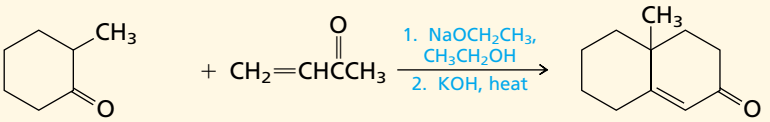
18.19 The main flavor component of the hazelnut is (2*E*,5*S*)-5-methyl-2-hepten-4-one. Write a structural formula or build a molecular model showing its stereochemistry.

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates

Reaction (section) and comments	General equation and typical example
α Halogenation (Sections 18.2 and 18.3) Halogens react with aldehydes and ketones by substitution; an α hydrogen is replaced by a halogen. Reaction occurs by electrophilic attack of the halogen on the carbon–carbon double bond of the enol form of the aldehyde or ketone. An acid catalyst increases the rate of enolization, which is the rate-determining step.	$R_2CHCR' + X_2 \longrightarrow R_2CCR' + HX$ (X) Aldehyde or ketone; Halogen; α-Halo aldehyde or ketone; Hydrogen halide $Br\text{-}C_6H_4\text{-}CCH_3 + Br_2 \xrightarrow{\text{acetic acid}} Br\text{-}C_6H_4\text{-}CCH_2Br + HBr$ *p*-Bromoacetophenone; Bromine; *p*-Bromophenacyl bromide (69–72%); Hydrogen bromide
Enolization (Sections 18.4 through 18.6) Aldehydes and ketones exist in equilibrium with their enol forms. The rate at which equilibrium is achieved is increased by acidic or basic catalysts. The enol content of simple aldehydes and ketones is quite small; β-diketones, however, are extensively enolized.	$R_2CH\text{—}CR' \rightleftharpoons R_2C{=}CR'$ (OH) Aldehyde or ketone; Enol Cyclopentanone $\overset{K}{\rightleftharpoons}$ Cyclopenten-1-ol (OH) $\quad K = 1 \times 10^{-8}$
Enolate ion formation (Section 18.6) An α proton of an aldehyde or a ketone is more acidic than most other protons bound to carbon. Aldehydes and ketones are weak acids, with K_a's in the range 10^{-16} to 10^{-20} (pK_a 16–20). Their enhanced acidity is due to the electron-withdrawing effect of the carbonyl group and the resonance stabilization of the enolate anion.	$R_2CHCR' + HO^- \rightleftharpoons R_2C{=}CR' + H_2O$ (:O:⁻) Aldehyde or ketone; Hydroxide ion; Enolate anion; Water $CH_3CH_2CCH_2CH_3 + HO^- \rightleftharpoons CH_3CH{=}CCH_2CH_3 + H_2O$ (:O:⁻) 3-Pentanone; Hydroxide ion; Enolate anion of 3-pentanone; Water
Haloform reaction (Section 18.7) Methyl ketones are cleaved on reaction with excess halogen in the presence of base. The products are a trihalomethane (haloform) and a carboxylate salt.	$RCCH_3 + 3X_2 \xrightarrow{HO^-} RCO^- + HCX_3$ Methyl ketone; Halogen; Carboxylate ion; Trihalomethane (haloform) $(CH_3)_3CCH_2CCH_3 \xrightarrow[2.\ H^+]{1.\ Br_2,\ NaOH} (CH_3)_3CCH_2CO_2H + CHBr_3$ 4,4-Dimethyl-2-pentanone; 3,3-Dimethylbutanoic acid (89%); Bromoform

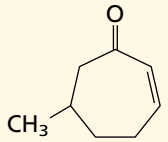
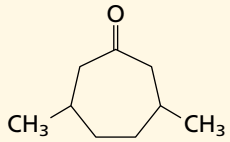
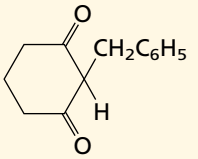
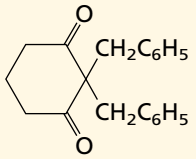
(Continued)

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates *(Continued)*

Reaction (section) and comments	General equation and typical example
Aldol condensation (Section 18.9) A reaction of great synthetic value for carbon–carbon bond formation. Nucleophilic addition of an enolate ion to a carbonyl group, followed by dehydration of the β-hydroxy aldehyde, yields an α,β-unsaturated aldehyde.	 Aldehyde — α,β-Unsaturated aldehyde — Water  Octanal — 2-Hexyl-2-decenal (79%)
Claisen–Schmidt reaction (Section 18.10) A mixed aldol condensation in which an aromatic aldehyde reacts with an enolizable aldehyde or ketone.	 Aromatic aldehyde — Aldehyde or ketone — α,β-Unsaturated carbonyl compound — Water  Benzaldehyde — 3,3-Dimethyl-2-butanone — 4,4-Dimethyl-1-phenyl-1-penten-3-one (88–93%)
Conjugate addition to α,β-unsaturated carbonyl compounds (Sections 18.11 through 18.14) The β-carbon atom of an α,β-unsaturated carbonyl compound is electrophilic; nucleophiles, especially weakly basic ones, yield the products of conjugate addition to α,β-unsaturated aldehydes and ketones.	 α,β-Unsaturated aldehyde or ketone — Nucleophile — Product of conjugate addition  4-Methyl-3-penten-2-one (mesityl oxide) — 4-Amino-4-methyl-2-pentanone (63–70%)
Robinson annulation (Section 18.13) A combination of conjugate addition of an enolate anion to an α,β-unsaturated ketone with subsequent intramolecular aldol condensation.	 2-Methylcyclohexanone — Methyl vinyl ketone — 6-Methylbicyclo[4.4.0]-1-decen-3-one (46%)

(Continued)

TABLE 18.1 Reactions of Aldehydes and Ketones That Involve Enol or Enolate Ion Intermediates *(Continued)*

Reaction (section) and comments	General equation and typical example
Conjugate addition of organocopper compounds (Section 18.14) The principal synthetic application of lithium dialkylcuprate reagents is their reaction with α,β-unsaturated carbonyl compounds. Alkyl-ation of the β carbon occurs.	$R_2C{=}CHCR' + R''_2CuLi \xrightarrow[2.\ H_2O]{1.\ \text{diethyl ether}} R_2C(R'')CH_2CR'$ (O) α,β-Unsaturated aldehyde or ketone; Lithium dialkylcuprate; β-Alkyl aldehyde or ketone  $\xrightarrow[2.\ H_2O]{1.\ LiCu(CH_3)_2}$  6-Methylcyclohept-2-enone; 3,6-Dimethylcycloheptanone (85%)
α Alkylation of aldehydes and ketones (Section 18.15) Alkylation of simple aldehydes and ketones via their enolates is difficult. β-Diketones can be converted quantitatively to their enolate anions, which react efficiently with primary alkyl halides.	$RCCH_2CR \xrightarrow{R'CH_2X,\ HO^-} RCCHCR$ (CH$_2$R′) β-Diketone; α-Alkyl-β-diketone  + $C_6H_5CH_2Cl \xrightarrow[\text{ethanol}]{KOCH_2CH_3}$  2-Benzyl-1,3-cyclohexanedione; Benzyl chloride; 2,2-Dibenzyl-1,3-cyclohexanedione (69%)

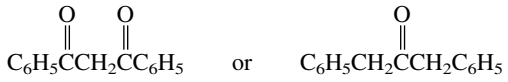
18.20 The simplest α,β-unsaturated aldehyde *acrolein* is prepared by heating glycerol with an acid catalyst. Suggest a mechanism for this reaction.

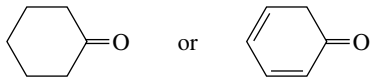
$$HOCH_2CH(OH)CH_2OH \xrightarrow[\text{heat}]{KHSO_4} CH_2{=}CHCH(O) + H_2O$$

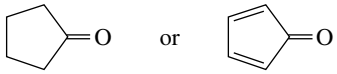
18.21 In each of the following pairs of compounds, choose the one that has the greater enol content, and write the structure of its enol form:

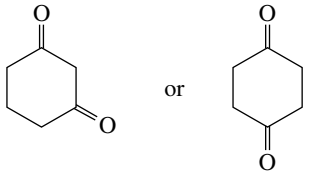
(a) $(CH_3)_3CCH(O)$ or $(CH_3)_2CHCH(O)$

(b) $C_6H_5CC(O)C_6H_5$ or $C_6H_5CH_2CCH_2C_6H_5$ (O)

(c) 

(d) 

(e) 

(f) 

18.22 Give the structure of the expected organic product in the reaction of 3-phenylpropanal with each of the following:

(a) Chlorine in acetic acid

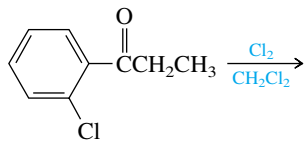
(b) Sodium hydroxide in ethanol, 10°C

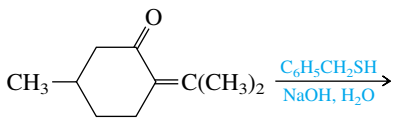
(c) Sodium hydroxide in ethanol, 70°C

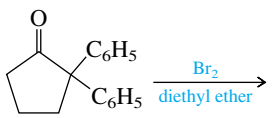
(d) Product of part (c) with lithium aluminum hydride; then H_2O

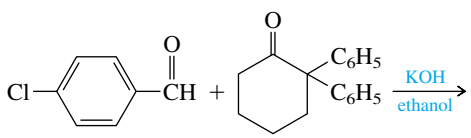
(e) Product of part (c) with sodium cyanide in acidic ethanol

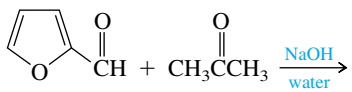
18.23 Each of the following reactions has been reported in the chemical literature. Write the structure of the product(s) formed in each case.

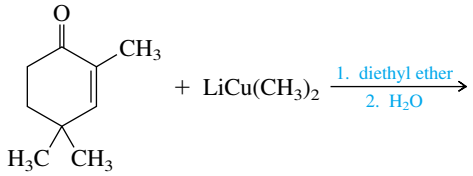
(a) 

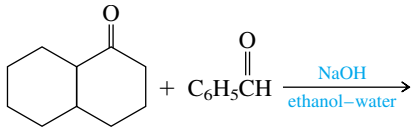
(b) 

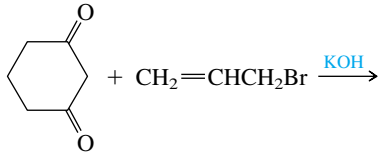
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

18.24 Show how each of the following compounds could be prepared from 3-pentanone. In most cases more than one synthetic transformation will be necessary.

(a) 2-Bromo-3-pentanone

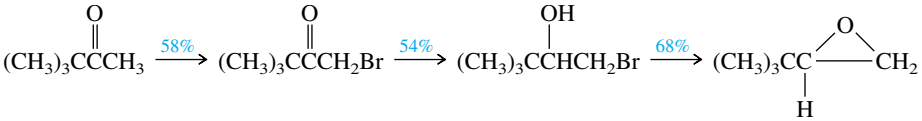
(b) 1-Penten-3-one

(c) 1-Penten-3-ol

(d) 3-Hexanone

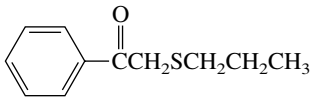
(e) 2-Methyl-1-phenyl-1-penten-3-one

18.25 (a) A synthesis that begins with 3,3-dimethyl-2-butanone gives the epoxide shown. Suggest reagents appropriate for each step in the synthesis.

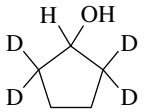


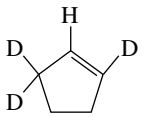
(b) The yield for each step as actually carried out in the laboratory is given above each arrow. What is the overall yield for the three-step sequence?

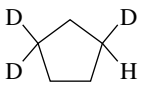
18.26 Using benzene, acetic anhydride, and 1-propanethiol as the source of all the carbon atoms, along with any necessary inorganic reagents, outline a synthesis of the compound shown.

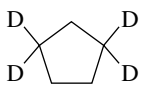


18.27 Show how you could prepare each of the following compounds from cyclopentanone, D_2O, and any necessary organic or inorganic reagents.

(a) 

(b) 

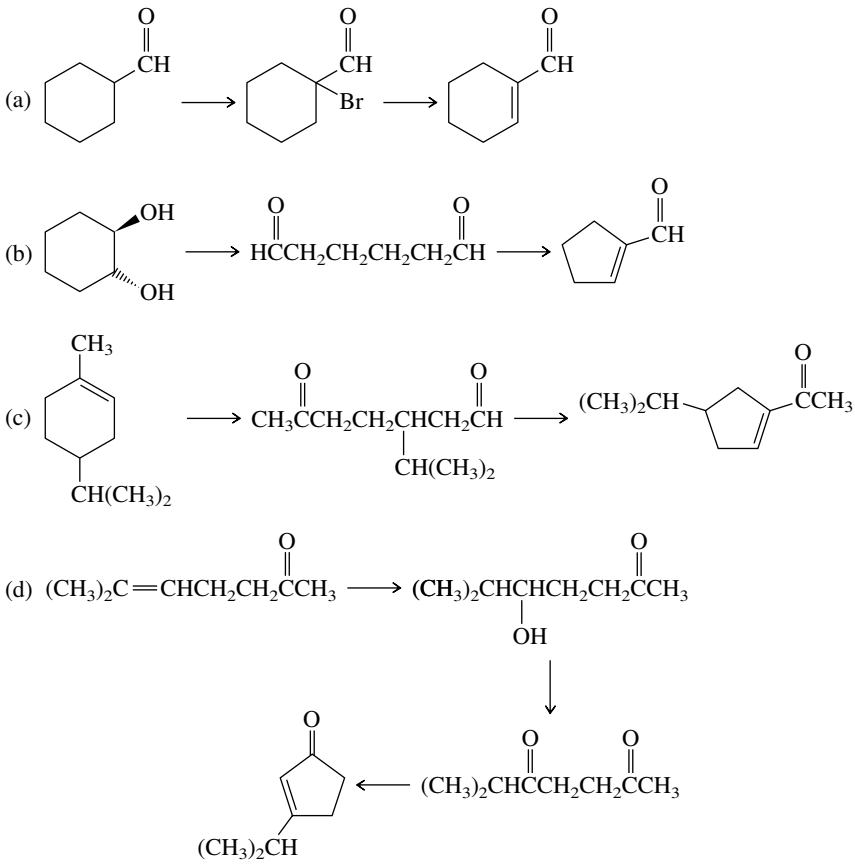
(c) 

(d) 

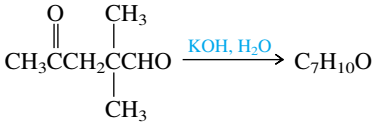
18.28 (a) At present, butanal is prepared industrially by hydroformylation of propene (Section 17.4). Write a chemical equation for this industrial synthesis.

(b) Before about 1970, the principal industrial preparation of butanal was from acetaldehyde. Outline a practical synthesis of butanal from acetaldehyde.

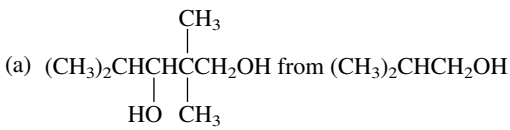
18.29 Identify the reagents appropriate for each step in the following syntheses:

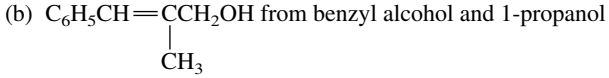


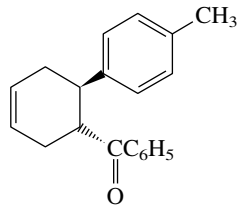
18.30 Give the structure of the product derived by intramolecular aldol condensation of the keto aldehyde shown:



18.31 Prepare each of the following compounds from the starting materials given and any necessary organic or inorganic reagents:

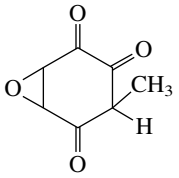




(c) 

from acetophenone, 4-methylbenzyl alcohol, and 1,3-butadiene

18.32 *Terreic acid* is a naturally occurring antibiotic substance. Its actual structure is an enol isomer of the structure shown. Write the two most stable enol forms of terreic acid, and choose which of those two is more stable.

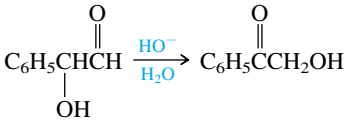


18.33 In each of the following, the indicated observations were made before any of the starting material was transformed to aldol addition or condensation products:

(a) In aqueous acid, only 17% of $(C_6H_5)_2CHCH{=}O$ is present as the aldehyde; 2% of the enol is present. Some other species accounts for 81% of the material. What is it?

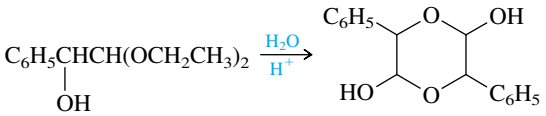
(b) In aqueous base, 97% of $(C_6H_5)_2CHCH{=}O$ is present as a species different from any of those in part (a). What is this species?

18.34 (a) For a long time attempts to prepare compound A were thwarted by its ready isomerization to compound B. The isomerization is efficiently catalyzed by traces of base. Write a reasonable mechanism for this isomerization.



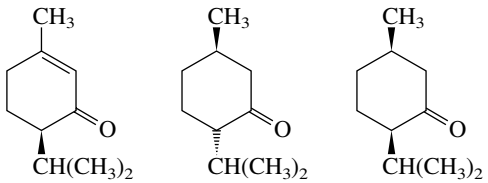
Compound A Compound B

(b) Another attempt to prepare compound A by hydrolysis of its diethyl acetal gave only the 1,4-dioxane derivative C. How was compound C formed?



Compound C

18.35 Consider the ketones piperitone, menthone, and isomenthone.



(−)-Piperitone Menthone Isomenthone

Suggest reasonable explanations for each of the following observations:

(a) Optically active piperitone ($\alpha_D - 32°$) is converted to racemic piperitone on standing in a solution of sodium ethoxide in ethanol.

(b) Menthone is converted to a mixture of menthone and isomenthone on treatment with 90% sulfuric acid.

18.36 Many nitrogen-containing compounds engage in a proton-transfer equilibrium that is analogous to keto–enol tautomerism:

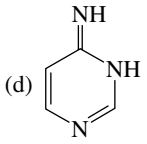
$$HX{-}N{=}Z \rightleftharpoons X{=}N{-}ZH$$

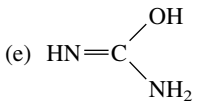
Each of the following compounds is the less stable partner of such a tautomeric pair. Write the structure of the more stable partner for each one.

(a) $CH_3CH_2N{=}O$

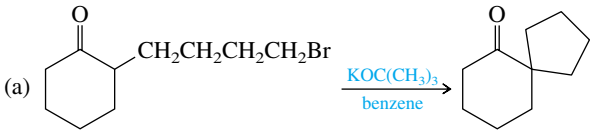
(b) $(CH_3)_2C{=}CHNHCH_3$

(c) $CH_3CH{=}\overset{+}{N}(O^-)OH$

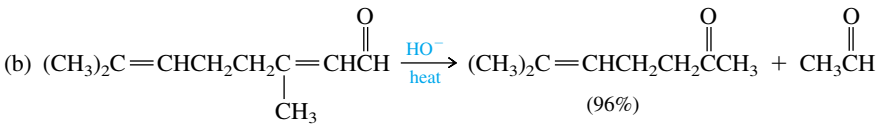
(d) 

(e) 

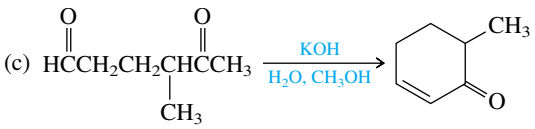
18.37 Outline reasonable mechanisms for each of the following reactions:

(a) 

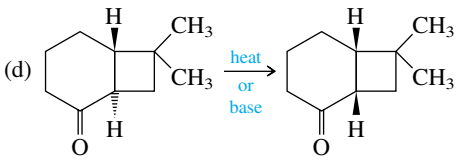
(76%)

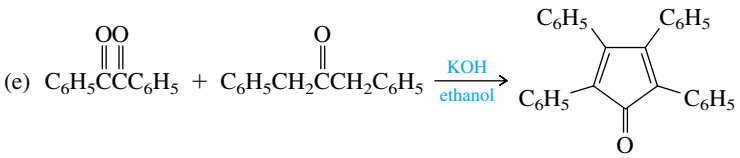
(b) 

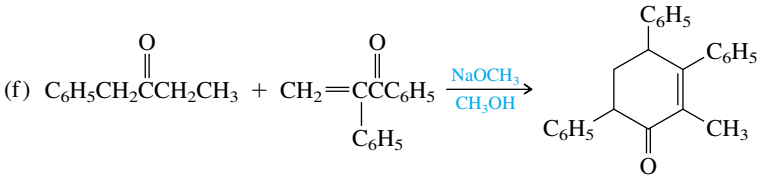
(96%)

(c) 

(40%)

(d) 

(e) 

(f) 

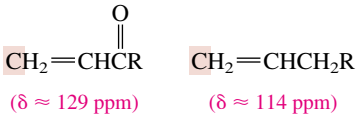
18.38 Suggest reasonable explanations for each of the following observations:

(a) The C═O stretching frequency of α,β-unsaturated ketones (about 1675 cm^{-1}) is less than that of typical dialkyl ketones (1710–1750 cm^{-1}).

(b) The C═O stretching frequency of cyclopropenone (1640 cm^{-1}) is lower than that of typical α,β-unsaturated ketones (1675 cm^{-1}).

(c) The dipole moment of diphenylcyclopropenone (μ = 5.1 D) is substantially larger than that of benzophenone (μ = 3.0 D)

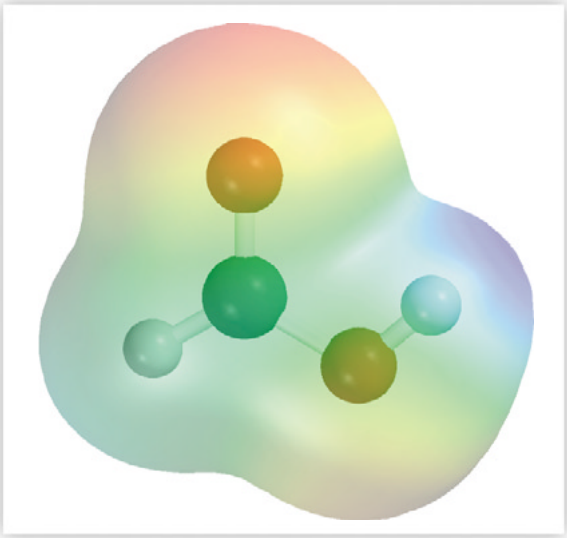
(d) The β carbon of an α,β-unsaturated ketone is less shielded than the corresponding carbon of an alkene. Typical ^{13}C NMR chemical shift values are



18.39 Bromination of 3-methyl-2-butanone yielded two compounds, each having the molecular formula C_5H_9BrO, in a 95:5 ratio. The ^1H NMR spectrum of the major isomer A was characterized by a doublet at δ 1.2 ppm (6 protons), a septet at δ 3.0 ppm (1 proton), and a singlet at δ 4.1 ppm (2 protons). The ^1H NMR spectrum of the minor isomer B exhibited two singlets, one at δ 1.9 ppm and the other at δ 2.5 ppm. The lower field singlet had half the area of the higher field one. Suggest reasonable structures for these two compounds.

18.40 Treatment of 2-butanone (1 mol) with Br_2 (2 mol) in aqueous HBr gave $C_4H_6Br_2O$. The ^1H NMR spectrum of the product was characterized by signals at δ 1.9 ppm (doublet, 3 protons), 4.6 ppm (singlet, 2 protons), and 5.2 ppm (quartet, 1 proton). Identify this compound.

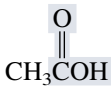
18.41 2-Phenylpropanedial [$C_6H_5CH(CHO)_2$] exists in the solid state as an enol in which the configuration of the double bond is *E*. In solution ($CDCl_3$), an enol form again predominates but this time the configuration is *Z*. Make molecular models of these two enols, and suggest an explanation for the predominance of the *Z* enol in solution. (*Hint:* Think about intermolecular versus intramolecular hydrogen bonding.)



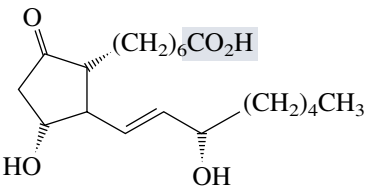
CHAPTER 19

CARBOXYLIC ACIDS

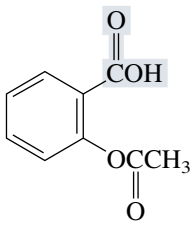
Carboxylic acids, compounds of the type $RC(=O)OH$, constitute one of the most frequently encountered classes of organic compounds. Countless natural products are carboxylic acids or are derived from them. Some carboxylic acids, such as acetic acid, have been known for centuries. Others, such as the prostaglandins, which are powerful regulators of numerous biological processes, remained unknown until relatively recently. Still others, aspirin for example, are the products of chemical synthesis. The therapeutic effects of aspirin, welcomed long before the discovery of prostaglandins, are now understood to result from aspirin's ability to inhibit the biosynthesis of prostaglandins.



Acetic acid (present in vinegar)



PGE_1 (a prostaglandin; a small amount of PGE_1 lowers blood pressure significantly)



Aspirin

The chemistry of carboxylic acids is the central theme of this chapter. The importance of carboxylic acids is magnified when we realize that they are the parent compounds of a large group of derivatives that includes acyl chlorides, acid anhydrides, esters, and amides. Those classes of compounds will be discussed in the chapter fol-

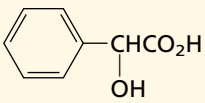
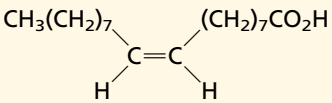
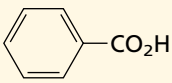
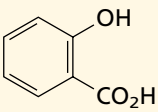
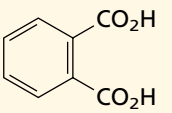
lowing this one. Together, this chapter and the next tell the story of some of the most fundamental structural types and functional group transformations in organic and biological chemistry.

19.1 CARBOXYLIC ACID NOMENCLATURE

Nowhere in organic chemistry are common names used more often than with the carboxylic acids. Many carboxylic acids are better known by common names than by their systematic names, and the framers of the IUPAC nomenclature rules have taken a liberal view toward accepting these common names as permissible alternatives to the systematic ones. Table 19.1 lists both the common and the systematic names of a number of important carboxylic acids.

Systematic names for carboxylic acids are derived by counting the number of carbons in the longest continuous chain that includes the carboxyl group and replacing the *-e* ending of the corresponding alkane by *-oic acid.* The first three acids in the table, methanoic (1 carbon), ethanoic (2 carbons), and octadecanoic acid (18 carbons), illustrate this point. When substituents are present, their locations are identified by number; numbering of the carbon chain always begins at the carboxyl group. This is illustrated in entries 4 and 5 in the table.

TABLE 19.1 Systematic and Common Names of Some Carboxylic Acids

	Structural formula	Systematic name	Common name
1.	HCO_2H	Methanoic acid	Formic acid
2.	CH_3CO_2H	Ethanoic acid	Acetic acid
3.	$CH_3(CH_2)_{16}CO_2H$	Octadecanoic acid	Stearic acid
4.	CH_3CHCO_2H (OH)	2-Hydroxypropanoic acid	Lactic acid
5.		2-Hydroxy-2-phenylethanoic acid	Mandelic acid
6.	$CH_2{=}CHCO_2H$	Propenoic acid	Acrylic acid
7.		(*Z*)-9-Octadecenoic acid	Oleic acid
8.		Benzenecarboxylic acid	Benzoic acid
9.		*o*-Hydroxybenzenecarboxylic acid	Salicylic acid
10.	$HO_2CCH_2CO_2H$	Propanedioic acid	Malonic acid
11.	$HO_2CCH_2CH_2CO_2H$	Butanedioic acid	Succinic acid
12.		1,2-Benzenedicarboxylic acid	Phthalic acid

Notice that compounds 4 and 5 are named as hydroxy derivatives of carboxylic acids, rather than as carboxyl derivatives of alcohols. We have seen earlier that hydroxyl groups take precedence over double bonds, and double bonds take precedence over halogens and alkyl groups, in naming compounds. Carboxylic acids outrank all the common groups we have encountered to this point.

Double bonds in the main chain are signaled by the ending *-enoic acid,* and their position is designated by a numerical prefix. Entries 6 and 7 are representative carboxylic acids that contain double bonds. Double-bond stereochemistry is specified by using either the cis–trans or the *E–Z* notation.

When a carboxyl group is attached to a ring, the parent ring is named (retaining the final *-e*) and the suffix *-carboxylic acid* is added, as shown in entries 8 and 9.

Compounds with two carboxyl groups, as illustrated by entries 10 through 12, are distinguished by the suffix *-dioic acid* or *-dicarboxylic acid* as appropriate. The final *-e* in the base name of the alkane is retained.

PROBLEM 19.1 The list of carboxylic acids in Table 19.1 is by no means exhaustive insofar as common names are concerned. Many others are known by their common names, a few of which follow. Give a systematic IUPAC name for each.

(a) $CH_2{=}C(CH_3)CO_2H$ (Methacrylic acid)

(b) $H_3C(H)C{=}C(H)CO_2H$ (Crotonic acid)

(c) HO_2CCO_2H (Oxalic acid)

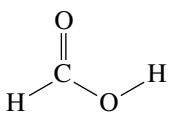
(d) $CH_3C_6H_4CO_2H$ (*p*-Toluic acid)

SAMPLE SOLUTION (a) Methacrylic acid is an industrial chemical used in the preparation of transparent plastics such as *Lucite* and *Plexiglas.* The carbon chain that includes both the carboxylic acid and the double bond is three carbon atoms in length. The compound is named as a derivative of *propenoic acid.* It is not necessary to locate the position of the double bond by number, as in "2-propenoic acid," because no other positions are structurally possible for it. The methyl group is at C-2, and so the correct systematic name for methacrylic acid is *2-methylpropenoic acid.*

19.2 STRUCTURE AND BONDING

The structural features of the carboxyl group are most apparent in formic acid. Formic acid is planar, with one of its carbon–oxygen bonds shorter than the other, and with bond angles at carbon close to 120°.

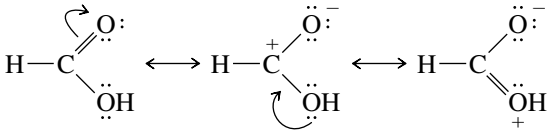
Bond Distances	
C=O	120 pm
C—O	134 pm



Bond Angles	
H—C=O	124°
H—C—O	111°
O—C=O	125°

This suggests sp^2 hybridization at carbon, and a $\sigma + \pi$ carbon–oxygen double bond analogous to that of aldehydes and ketones.

Additionally, sp^2 hybridization of the hydroxyl oxygen allows one of its unshared electron pairs to be delocalized by orbital overlap with the π system of the carbonyl group (Figure 19.1). In resonance terms, this electron delocalization is represented as:



Lone-pair donation from the hydroxyl oxygen makes the carbonyl group less electrophilic than that of an aldehyde or ketone. The graphic that opened this chapter is an electrostatic potential map of formic acid that shows the most electron-rich site to be the oxygen of the carbonyl group and the most electron-poor one to be, as expected, the OH proton.

Carboxylic acids are fairly polar, and simple ones such as acetic acid, propanoic acid, and benzoic acid have dipole moments in the range 1.7–1.9 D.

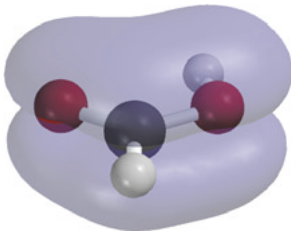
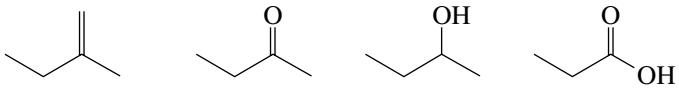


FIGURE 19.1 Carbon and both oxygens are sp^2-hybridized in formic acid. The π component of the C═O group and the *p* orbital of the OH oxygen overlap to form an extended π system that includes carbon and the two oxygens.

19.3 PHYSICAL PROPERTIES

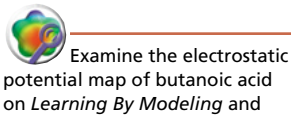
The melting points and boiling points of carboxylic acids are higher than those of hydrocarbons and oxygen-containing organic compounds of comparable size and shape and indicate strong intermolecular attractive forces.



	2-Methyl-1-butene	2-Butanone	2-Butanol	Propanoic acid
bp (1 atm):	31°C	80°C	99°C	141°C

A unique hydrogen-bonding arrangement, shown in Figure 19.2, contributes to these attractive forces. The hydroxyl group of one carboxylic acid molecule acts as a proton donor toward the carbonyl oxygen of a second. In a reciprocal fashion, the hydroxyl proton of the second carboxyl function interacts with the carbonyl oxygen of the first. The result is that the two carboxylic acid molecules are held together by *two* hydrogen bonds. So efficient is this hydrogen bonding that some carboxylic acids exist as hydrogen-bonded dimers even in the gas phase. In the pure liquid a mixture of hydrogen-bonded dimers and higher aggregates is present.

In aqueous solution intermolecular association between carboxylic acid molecules is replaced by hydrogen bonding to water. The solubility properties of carboxylic acids are similar to those of alcohols. Carboxylic acids of four carbon atoms or fewer are miscible with water in all proportions.



Examine the electrostatic potential map of butanoic acid on *Learning By Modeling* and notice how much more intense the blue color (positive charge) is on the OH hydrogen than on the hydrogens bonded to carbon.

A summary of physical properties of some representative carboxylic acids is presented in Appendix 1.

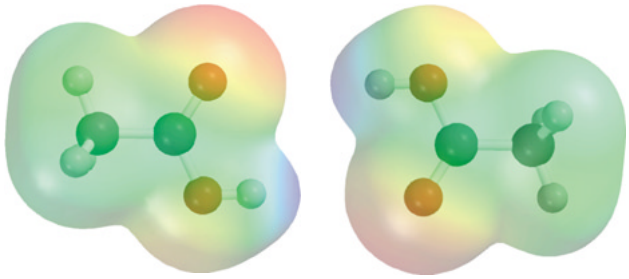


FIGURE 19.2 Attractions between regions of positive (*blue*) and negative (*red*) electrostatic potential are responsible for intermolecular hydrogen bonding between two molecules of acetic acid.

19.4 ACIDITY OF CARBOXYLIC ACIDS

Carboxylic acids are the most acidic class of compounds that contain only carbon, hydrogen, and oxygen. With ionization constants K_a on the order of 10^{-5} ($pK_a \approx 5$), they are much stronger acids than water and alcohols. The case should not be overstated, however. Carboxylic acids are weak acids; a 0.1 M solution of acetic acid in water, for example, is only 1.3% ionized.

To understand the greater acidity of carboxylic acids compared with water and alcohols, compare the structural changes that accompany the ionization of a representative alcohol (ethanol) and a representative carboxylic acid (acetic acid). The equilibria that define K_a are

Ionization of ethanol

$$\underset{\text{Ethanol}}{CH_3CH_2OH} \rightleftharpoons H^+ + \underset{\text{Ethoxide ion}}{CH_3CH_2O^-} \qquad K_a = \frac{[H^+][CH_3CH_2O^-]}{[CH_3CH_2OH]} = 10^{-16}$$

Ionization of acetic acid

$$\underset{\text{Acetic acid}}{CH_3COH} \rightleftharpoons H^+ + \underset{\text{Acetate ion}}{CH_3CO^-} \qquad K_a = \frac{[H^+][CH_3CO_2^-]}{[CH_3CO_2H]} = 1.8 \times 10^{-5}$$

Free energies of ionization are calculated from equilibrium constants according to the relationship

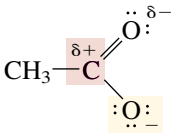
$$\Delta G^\circ = -RT \ln K_a$$

From these K_a values, the calculated free energies of ionization (ΔG°) are 91 kJ/mol (21.7 kcal/mol) for ethanol versus 27 kJ/mol (6.5 kcal/mol) for acetic acid. An energy diagram portraying these relationships is presented in Figure 19.3. Since it is *equilibria,* not *rates,* of ionization that are being compared, the diagram shows only the initial and final states. It is not necessary to be concerned about the energy of activation, since that affects only the rate of ionization, not the extent of ionization.

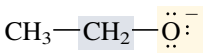
The large difference in the free energies of ionization of ethanol and acetic acid reflects a greater stabilization of acetate ion relative to ethoxide ion. Ionization of ethanol yields an alkoxide ion in which the negative charge is localized on oxygen. Solvation forces are the chief means by which ethoxide ion is stabilized. Acetate ion is also stabilized by solvation, but has two additional mechanisms for dispersing its negative charge that are not available to ethoxide ion:

1. *The inductive effect of the carbonyl group.* The carbonyl group of acetate ion is electron-withdrawing, and by attracting electrons away from the negatively charged oxygen, acetate anion is stabilized. This is an inductive effect, arising in the polarization of the electron distribution in the σ bond between the carbonyl carbon and the negatively charged oxygen.

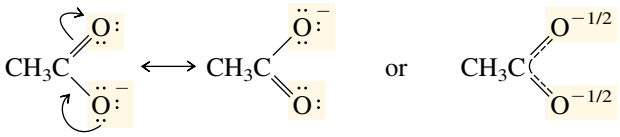
Positively polarized carbon attracts electrons from negatively charged oxygen.



CH_2 group has negligible effect on electron density at negatively charged oxygen.



2. *The resonance effect of the carbonyl group.* Electron delocalization, expressed by resonance between the following Lewis structures, causes the negative charge in acetate to be shared equally by both oxygens. Electron delocalization of this type is not available to ethoxide ion.



PROBLEM 19.2 Peroxyacetic acid $(CH_3\overset{\overset{O}{\|}}{C}OOH)$ is a weaker acid than acetic acid; its K_a is 6.3×10^{-9} (pK_a 8.2) versus 1.8×10^{-5} for acetic acid (pK_a 4.7). Why are peroxy acids weaker than carboxylic acids?

Electron delocalization in carboxylate ions is nicely illustrated with the aid of electrostatic potential maps. As Figure 19.4 shows, the electrostatic potential is different for the two different oxygens of acetic acid, but is the same for the two equivalent oxygens of acetate ion.

Likewise, the experimentally measured pattern of carbon–oxygen bond lengths in acetic acid is different from that of acetate ion. Acetic acid has a short C═O and a long C—O distance. In ammonium acetate, though, both carbon–oxygen distances are equal.

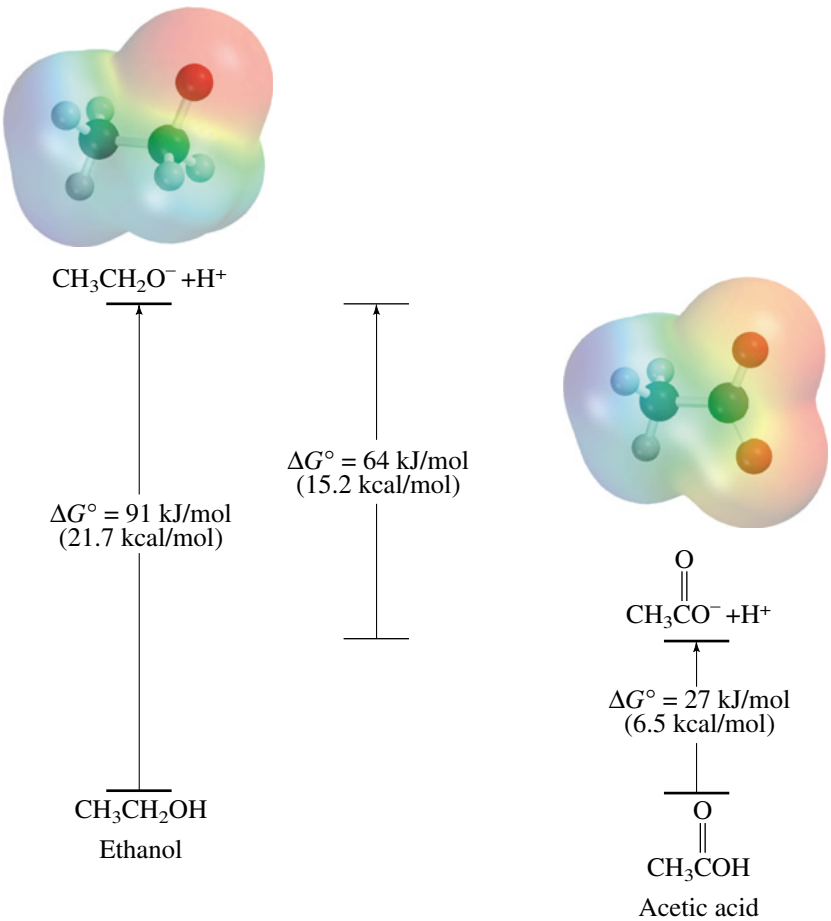
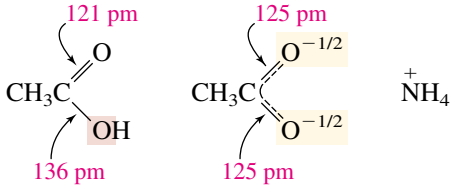


FIGURE 19.3 Diagram comparing the free energies of ionization of ethanol and acetic acid in water. The electrostatic potential maps of ethoxide and acetate ion show the concentration of negative charge in ethoxide versus dispersal of charge in acetate.

(*a*) (*b*)

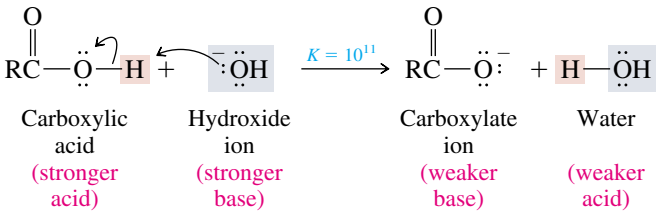
FIGURE 19.4 Electrostatic potential maps of (*a*) acetic acid and (*b*) acetate ion. The negative charge (*red*) is equally distributed between both oxygens of acetate ion.



For many years, resonance in carboxylate ions was emphasized when explaining the acidity of carboxylic acids. Recently, however, it has been suggested that the inductive effect of the carbonyl group may be more important. It seems clear that, even though their relative contributions may be a matter of debate, both play major roles.

19.5 SALTS OF CARBOXYLIC ACIDS

In the presence of strong bases such as sodium hydroxide, carboxylic acids are neutralized rapidly and quantitatively:



PROBLEM 19.3 Write an ionic equation for the reaction of acetic acid with each of the following, and specify whether the equilibrium favors starting materials or products:

(a) Sodium ethoxide
(b) Potassium *tert*-butoxide
(c) Sodium bromide
(d) Sodium acetylide
(e) Potassium nitrate
(f) Lithium amide

SAMPLE SOLUTION (a) This is an acid–base reaction; ethoxide ion is the base.

$$CH_3CO_2H + CH_3CH_2O^- \longrightarrow CH_3CO_2^- + CH_3CH_2OH$$

Acetic acid (stronger acid) + Ethoxide ion (stronger base) → Acetate ion (weaker base) + Ethanol (weaker acid)

The position of equilibrium lies well to the right. Ethanol, with a K_a of 10^{-16} (pK_a16), is a much weaker acid than acetic acid.

QUANTITATIVE RELATIONSHIPS INVOLVING CARBOXYLIC ACIDS

Suppose you take two flasks, one containing pure water and the other a buffer solution maintained at a pH of 7.0. If you add 0.1 mol of acetic acid to each one and the final volume in each flask is 1 L, how much acetic acid is present at equilibrium? How much acetate ion? In other words, what is the extent of ionization of acetic acid in an unbuffered medium and in a buffered one?

The first case simply involves the ionization of a weak acid and is governed by the expression that defines K_a for acetic acid:

$$K_a = \frac{[H^+][CH_3CO_2^-]}{[CH_3CO_2H]} = 1.8 \times 10^{-5}$$

Since ionization of acetic acid gives one H^+ for each $CH_3CO_2^-$, the concentrations of the two ions are equal, and setting each one equal to x gives:

$$K_a = \frac{x^2}{0.1 - x} = 1.8 \times 10^{-5}$$

Solving for x gives the acetate ion concentration as:

$$x = 1.3 \times 10^{-3}$$

Thus when acetic acid is added to pure water, the ratio of acetate ion to acetic acid is

$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{1.3 \times 10^{-3}}{0.1} = 0.013$$

Only 1.3% of the acetic acid has ionized. Most of it (98.7%) remains unchanged.

Now think about what happens when the same amount of acetic acid is added to water that is buffered at pH = 7.0. Before doing the calculation, let us recognize that it is the $[CH_3CO_2^-]/[CH_3CO_2H]$ ratio in which we are interested and do a little algebraic manipulation. Since

$$K_a = \frac{[H^+][CH_3CO_2^-]}{[CH_3CO_2H]}$$

then

$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{K_a}{[H^+]}$$

This relationship is one form of the **Henderson–Hasselbalch equation.** It is a useful relationship in chemistry and biochemistry. One rarely needs to calculate the pH of a solution—pH is more often measured than calculated. It is much more common that one needs to know the degree of ionization of an acid at a particular pH, and the Henderson–Hasselbalch equation gives that ratio.

For the case at hand, the solution is buffered at pH = 7.0. Therefore,

$$\frac{[CH_3CO_2^-]}{[CH_3CO_2H]} = \frac{1.8 \times 10^{-5}}{10^{-7}} = 180$$

A very different situation exists in an aqueous solution maintained at pH = 7.0 from the situation in pure water. We saw earlier that almost all the acetic acid in a 0.1 M solution in pure water was nonionized. At pH 7.0, however, hardly any nonionized acetic acid remains; it is almost completely converted to its carboxylate ion.

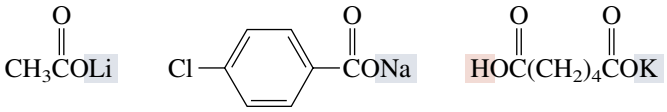
This difference in behavior for acetic acid in pure water versus water buffered at pH = 7.0 has some important practical consequences. Biochemists usually do not talk about acetic acid (or lactic acid, or salicylic acid, etc.). They talk about acetate (and lactate, and salicylate). Why? It's because biochemists are concerned with carboxylic acids as they exist in dilute aqueous solution at what is called *biological pH.* Biological fluids are naturally buffered. The pH of blood, for example, is maintained at 7.2, and at this pH carboxylic acids are almost entirely converted to their carboxylate anions.

An alternative form of the Henderson–Hasselbalch equation for acetic acid is

$$pH = pK_a + \log \frac{[CH_3CO_2^-]}{[CH_3CO_2H]}$$

From this equation it can be seen that when $[CH_3CO_2^-] = [CH_3CO_2H]$, then the second term is log 1 = 0, and pH = pK_a. This means that when the pH of a solution is equal to the pK_a of a weak acid, the concentration of the acid and its conjugate base are equal. This is a relationship worth remembering.

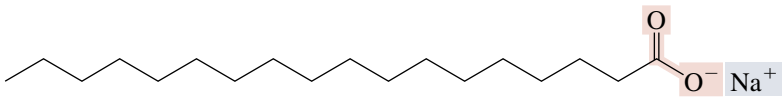
The metal carboxylate salts formed on neutralization of carboxylic acids are named by first specifying the metal ion and then adding the name of the acid modified by replacing *-ic acid* by *-ate*. Monocarboxylate salts of diacids are designated by naming both the cation and hydrogen as substituents of carboxylate groups.



Lithium acetate | Sodium *p*-chlorobenzoate | Potassium hydrogen hexanedioate

Metal carboxylates are ionic, and when the molecular weight isn't too high, the sodium and potassium salts of carboxylic acids are soluble in water. Carboxylic acids therefore may be extracted from ether solutions into aqueous sodium or potassium hydroxide.

The solubility behavior of salts of carboxylic acids having 12–18 carbons is unusual and can be illustrated by considering sodium stearate:



Sodium stearate
(sodium octadecanoate)

Sodium stearate has a polar carboxylate group at one end of a long hydrocarbon chain. The carboxylate group is **hydrophilic** ("water-loving") and tends to confer water solubility on the molecule. The hydrocarbon chain is **lipophilic** ("fat-loving") and tends to associate with other hydrocarbon chains. The compromise achieved by sodium stearate when it is placed in water is to form a colloidal dispersion of spherical aggregates called **micelles.** Each micelle is composed of 50–100 individual molecules. Micelles form spontaneously when the carboxylate concentration exceeds a certain minimum value called the **critical micelle concentration.** A representation of a micelle is shown in Figure 19.5.

Polar carboxylate groups dot the surface of the micelle. There they bind to water molecules and to sodium ions. The nonpolar hydrocarbon chains are directed toward the interior of the micelle, where individually weak but cumulatively significant induced-dipole/induced-dipole forces bind them together. Micelles are approximately spherical because a sphere encloses the maximum volume of material for a given surface area and

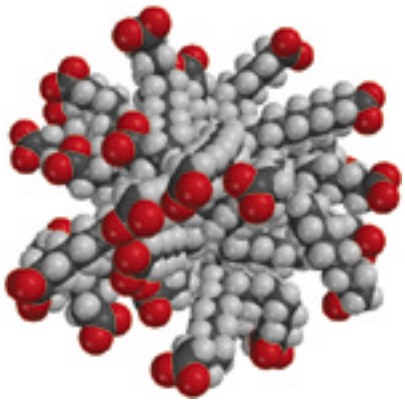


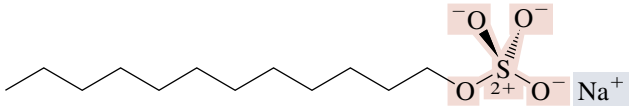
FIGURE 19.5 A space-filling model of a micelle formed by association of carboxylate ions derived from a fatty acid. In general, the hydrophobic carbon chains are inside and the carboxylate ions on the surface, but the micelle is irregular, and contains voids, channels, and tangled carbon chains. Each carboxylate is associated with a metal ion such as Na^+ (not shown).

disrupts the water structure least. Because their surfaces are negatively charged, two micelles repel each other rather than clustering to form higher aggregates.

It is the formation of micelles and their properties that are responsible for the cleansing action of soaps. Water that contains sodium stearate removes grease by enclosing it in the hydrocarbon-like interior of the micelles. The grease is washed away with the water, not because it dissolves in the water but because it dissolves in the micelles that are dispersed in the water. Sodium stearate is an example of a soap; sodium and potassium salts of other C_{12}–C_{18} unbranched carboxylic acids possess similar properties.

Detergents are substances, including soaps, that cleanse by micellar action. A large number of synthetic detergents are known. One example is sodium lauryl sulfate. Sodium lauryl sulfate has a long hydrocarbon chain terminating in a polar sulfate ion and forms soap-like micelles in water.

Compare the electrostatic potential maps of sodium lauryl sulfate and sodium stearate on *Learning By Modeling*.



Sodium lauryl sulfate
(sodium dodecyl sulfate)

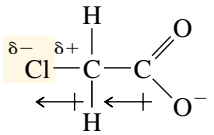
Detergents are designed to be effective in hard water, meaning water containing calcium salts that form insoluble calcium carboxylates with soaps. These precipitates rob the soap of its cleansing power and form an unpleasant scum. The calcium salts of synthetic detergents such as sodium lauryl sulfate, however, are soluble and retain their micelle-forming ability in water.

19.6 SUBSTITUENTS AND ACID STRENGTH

Alkyl groups have little effect on the acidity of a carboxylic acid. The ionization constants of all acids that have the general formula $C_nH_{2n+1}CO_2H$ are very similar to one another and equal approximately 10^{-5} (pK_a 5). Table 19.2 gives a few examples.

An electronegative substituent, particularly if it is attached to the α carbon, increases the acidity of a carboxylic acid. As the data in Table 19.2 show, all the monohaloacetic acids are about 100 times more acidic than acetic acid. Multiple halogen substitution increases the acidity even more; trichloroacetic acid is 7000 times more acidic than acetic acid!

The acid-strengthening effect of electronegative atoms or groups is easily seen as an inductive effect of the substituent transmitted through the σ bonds of the molecule. According to this model, the σ electrons in the carbon–chlorine bond of chloroacetate ion are drawn toward chlorine, leaving the α-carbon atom with a slight positive charge. The α carbon, because of this positive character, attracts electrons from the negatively charged carboxylate, thus dispersing the charge and stabilizing the anion. The more stable the anion, the greater the equilibrium constant for its formation.



Chloroacetate anion is stabilized by electron-withdrawing effect of chlorine.

Learning By Modeling contains molecular models of $CH_3CO_2^-$ (acetate) and $Cl_3CCO_2^-$ (trichloroacetate). Compare these two ions with respect to the amount of negative charge on their oxygens.

TABLE 19.2 Effect of Substituents on Acidity of Carboxylic Acids

Name of acid	Structure	Ionization constant K_a*	pK_a
Standard of comparison.			
Acetic acid	CH_3CO_2H	1.8×10^{-5}	4.7
Alkyl substituents have a negligible effect on acidity.			
Propanoic acid	$CH_3CH_2CO_2H$	1.3×10^{-5}	4.9
2-Methylpropanoic acid	$(CH_3)_2CHCO_2H$	1.6×10^{-5}	4.8
2,2-Dimethylpropanoic acid	$(CH_3)_3CCO_2H$	0.9×10^{-5}	5.1
Heptanoic acid	$CH_3(CH_2)_5CO_2H$	1.3×10^{-5}	4.9
α-Halogen substituents increase acidity.			
Fluoroacetic acid	FCH_2CO_2H	2.5×10^{-3}	2.6
Chloroacetic acid	$ClCH_2CO_2H$	1.4×10^{-3}	2.9
Bromoacetic acid	$BrCH_2CO_2H$	1.4×10^{-3}	2.9
Dichloroacetic acid	Cl_2CHCO_2H	5.0×10^{-2}	1.3
Trichloroacetic acid	Cl_3CCO_2H	1.3×10^{-1}	0.9
Electron-attracting groups increase acidity.			
Methoxyacetic acid	$CH_3OCH_2CO_2H$	2.7×10^{-4}	3.6
Cyanoacetic acid	$N{\equiv}CCH_2CO_2H$	3.4×10^{-3}	2.5
Nitroacetic acid	$O_2NCH_2CO_2H$	2.1×10^{-2}	1.7

*In water at 25°C.

Inductive effects fall off rapidly as the number of σ bonds between the carboxyl group and the substituent increases. Consequently, the acid-strengthening effect of a halogen decreases as it becomes more remote from the carboxyl group:

$ClCH_2CO_2H$	$ClCH_2CH_2CO_2H$	$ClCH_2CH_2CH_2CO_2H$
Chloroacetic acid	3-Chloropropanoic acid	4-Chlorobutanoic acid
$K_a = 1.4 \times 10^{-3}$	$K_a = 1.0 \times 10^{-4}$	$K_a = 3.0 \times 10^{-5}$
pK_a = 2.9	pK_a = 4.0	pK_a = 4.5

PROBLEM 19.4 Which is the stronger acid in each of the following pairs?

(a) $(CH_3)_3CCH_2CO_2H$ or $(CH_3)_3\overset{+}{N}CH_2CO_2H$

(b) $CH_3CH_2CO_2H$ or $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCO_2H$

(c) $CH_3\overset{\displaystyle O}{\overset{\|}{C}}CO_2H$ or $CH_2{=}CHCO_2H$

(d) $CH_3CH_2CH_2CO_2H$ or $CH_3\overset{\displaystyle O}{\overset{\|}{\underset{\displaystyle O}{\underset{\|}{S}}}}CH_2CO_2H$

SAMPLE SOLUTION (a) Think of the two compounds as substituted derivatives of acetic acid. A *tert*-butyl group is slightly electron-releasing and has only a modest effect on acidity. The compound $(CH_3)_3CCH_2CO_2H$ is expected to have an acid strength similar to that of acetic acid. A trimethylammonium substituent, on the other hand, is positively charged and is a powerful electron-withdrawing substituent. The compound $(CH_3)_3\overset{+}{N}CH_2CO_2H$ is expected to be a much stronger acid than $(CH_3)_3CCH_2CO_2H$. The measured ionization constants, shown as follows, confirm this prediction.

$(CH_3)_3CCH_2CO_2H$	$(CH_3)_3\overset{+}{N}CH_2CO_2H$
Weaker acid	Stronger acid
$K_a = 5 \times 10^{-6}$	$K_a = 1.5 \times 10^{-2}$
$(pK_a = 5.3)$	$(pK_a = 1.8)$

Another proposal advanced to explain the acid-strengthening effect of polar substituents holds that the electron-withdrawing effect is transmitted through the water molecules that surround the carboxylate ion rather than through successive polarization of σ bonds. This is referred to as a **field effect.** Both field and inductive contributions to the polar effect tend to operate in the same direction, and it is believed that both are important.

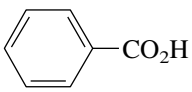
It is a curious fact that substituents affect the entropy of ionization more than they do the enthalpy term in the expression

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

The enthalpy term ΔH° is close to zero for the ionization of most carboxylic acids, regardless of their strength. The free energy of ionization ΔG° is dominated by the $-T\Delta S^\circ$ term. Ionization is accompanied by an increase in solvation forces, leading to a decrease in the entropy of the system; ΔS° is negative, and $-T\Delta S^\circ$ is positive. Anions that incorporate substituents capable of dispersing negative charge impose less order on the solvent (water), and less entropy is lost in their production.

19.7 IONIZATION OF SUBSTITUTED BENZOIC ACIDS

A considerable body of data is available on the acidity of substituted benzoic acids. Benzoic acid itself is a somewhat stronger acid than acetic acid. Its carboxyl group is attached to an sp^2-hybridized carbon and ionizes to a greater extent than one that is attached to an sp^3-hybridized carbon. Remember, carbon becomes more electron-withdrawing as its *s* character increases.

CH_3CO_2H	$CH_2{=}CHCO_2H$	
Acetic acid	Acrylic acid	Benzoic acid
$K_a = 1.8 \times 10^{-5}$	$K_a = 5.5 \times 10^{-5}$	$K_a = 6.3 \times 10^{-5}$
$(pK_a\ 4.8)$	$(pK_a\ 4.3)$	$(pK_a\ 4.2)$

PROBLEM 19.5 What is the most acidic neutral molecule characterized by the formula $C_3H_xO_2$?

Table 19.3 lists the ionization constants of some substituted benzoic acids. The largest effects are observed when strongly electron-withdrawing substituents are ortho to

TABLE 19.3 Acidity of Some Substituted Benzoic Acids

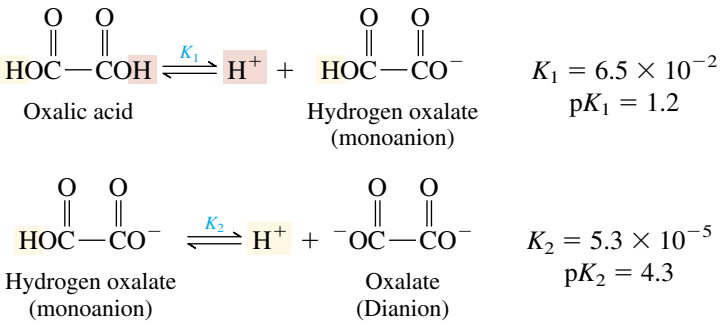
Substituent in $XC_6H_4CO_2H$	K_a (pK_a)* for different positions of substituent X		
	Ortho	Meta	Para
1. H	6.3×10^{-5} (4.2)	6.3×10^{-5} (4.2)	6.3×10^{-5} (4.2)
2. CH_3	1.2×10^{-4} (3.9)	5.3×10^{-5} (4.3)	4.2×10^{-5} (4.4)
3. F	5.4×10^{-4} (3.3)	1.4×10^{-4} (3.9)	7.2×10^{-5} (4.1)
4. Cl	1.2×10^{-3} (2.9)	1.5×10^{-4} (3.8)	1.0×10^{-4} (4.0)
5. Br	1.4×10^{-3} (2.8)	1.5×10^{-4} (3.8)	1.1×10^{-4} (4.0)
6. I	1.4×10^{-3} (2.9)	1.4×10^{-4} (3.9)	9.2×10^{-5} (4.0)
7. CH_3O	8.1×10^{-5} (4.1)	8.2×10^{-5} (4.1)	3.4×10^{-5} (4.5)
8. O_2N	6.7×10^{-3} (2.2)	3.2×10^{-4} (3.5)	3.8×10^{-4} (3.4)

*In water at 25°C.

the carboxyl group. An *o*-nitro substituent, for example, increases the acidity of benzoic acid 100-fold. Substituent effects are small at positions meta and para to the carboxyl group. In those cases the pK_a values are clustered in the range 3.5–4.5.

19.8 DICARBOXYLIC ACIDS

Separate ionization constants, designated K_1 and K_2, respectively, characterize the two successive ionization steps of a dicarboxylic acid.



Oxalic acid is poisonous and occurs naturally in a number of plants including sorrel and begonia. It is a good idea to keep houseplants out of the reach of small children, who might be tempted to eat the leaves or berries.

The first ionization constant of dicarboxylic acids is larger than K_a for monocarboxylic analogs. One reason is statistical. There are two potential sites for ionization rather than one, making the effective concentration of carboxyl groups twice as large. Furthermore, one carboxyl group acts as an electron-withdrawing group to facilitate dissociation of the other. This is particularly noticeable when the two carboxyl groups are separated by only a few bonds. Oxalic and malonic acid, for example, are several orders of magnitude stronger than simple alkyl derivatives of acetic acid. Heptanedioic acid, in which the carboxyl groups are well separated from each other, is only slightly stronger than acetic acid.

HO_2CCO_2H	$HO_2CCH_2CO_2H$	$HO_2C(CH_2)_5CO_2H$
Oxalic acid	Malonic acid	Heptanedioic acid
K_1 6.5×10^{-2}	K_1 1.4×10^{-3}	K_1 3.1×10^{-5}
(pK_1 1.2)	(pK_1 2.8)	(pK_1 4.3)

19.9 CARBONIC ACID

Through an accident of history, the simplest dicarboxylic acid, carbonic acid, $HOCOH$, is not even classified as an organic compound. Because many minerals are carbonate salts, nineteenth-century chemists placed carbonates, bicarbonates, and carbon dioxide in the inorganic realm. Nevertheless, the essential features of carbonic acid and its salts are easily understood on the basis of our knowledge of carboxylic acids.

Carbonic acid is formed when carbon dioxide reacts with water. Hydration of carbon dioxide is far from complete, however. Almost all the carbon dioxide that is dissolved in water exists as carbon dioxide; only 0.3% of it is converted to carbonic acid. Carbonic acid is a weak acid and ionizes to a small extent to bicarbonate ion.

The systematic name for bicarbonate ion is *hydrogen carbonate*. Thus, the systematic name for sodium bicarbonate ($NaHCO_3$) is *sodium hydrogen carbonate*.

$$\underset{\text{Carbon dioxide}}{CO_2} + \underset{\text{Water}}{H_2O} \rightleftharpoons \underset{\text{Carbonic acid}}{HOCOH} \rightleftharpoons H^+ + \underset{\text{Bicarbonate ion}}{HOCO^-}$$

The equilibrium constant for the overall reaction is related to an apparent equilibrium constant K_1 for carbonic acid ionization by the expression

$$K_1 = \frac{[H^+][HCO_3^-]}{[CO_2]} = 4.3 \times 10^{-7} \qquad pK_a = 6.4$$

These equations tell us that the reverse process, proton transfer from acids to bicarbonate to form carbon dioxide, will be favorable when K_a of the acid exceeds 4.3×10^{-7} ($pK_a < 6.4$). Among compounds containing carbon, hydrogen, and oxygen, only carboxylic acids are acidic enough to meet this requirement. They dissolve in aqueous sodium bicarbonate with the evolution of carbon dioxide. This behavior is the basis of a qualitative test for carboxylic acids.

PROBLEM 19.6 The value cited for the "apparent K_1" of carbonic acid, 4.3×10^{-7}, is the one normally given in reference books. It is determined by measuring the pH of water to which a known amount of carbon dioxide has been added. When we recall that only 0.3% of carbon dioxide is converted to carbonic acid in water, what is the "true K_1" of carbonic acid?

Carbonic anhydrase is an enzyme that catalyzes the hydration of carbon dioxide to bicarbonate. The uncatalyzed hydration of carbon dioxide is too slow to be effective in transporting carbon dioxide from the tissues to the lungs, and so animals have developed catalysts to speed this process. The activity of carbonic anhydrase is remarkable; it has been estimated that one molecule of this enzyme can catalyze the hydration of 3.6×10^7 molecules of carbon dioxide per minute.

As with other dicarboxylic acids, the second ionization constant of carbonic acid is far smaller than the first.

$$\underset{\text{Bicarbonate ion}}{HOCO^-} \overset{K_2}{\rightleftharpoons} H^+ + \underset{\text{Carbonate ion}}{{}^-OCO^-}$$

The value of K_2 is 5.6×10^{-11} (pK_a 10.2). Bicarbonate is a weaker acid than carboxylic acids but a stronger acid than water and alcohols.

19.10 SOURCES OF CARBOXYLIC ACIDS

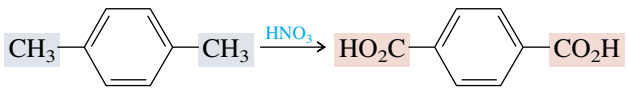
Many carboxylic acids were first isolated from natural sources and were given names based on their origin. Formic acid (Latin *formica,* "ant") was obtained by distilling ants. Since ancient times acetic acid (Latin *acetum,* "vinegar") has been known to be present in wine that has turned sour. Butyric acid (Latin *butyrum,* "butter") contributes to the odor of both rancid butter and ginkgo berries, and lactic acid (Latin *lac,* "milk") has been isolated from sour milk.

Although these humble origins make interesting historical notes, in most cases the large-scale preparation of carboxylic acids relies on chemical synthesis. Virtually none of the 3×10^9 lb of acetic acid produced in the United States each year is obtained from vinegar. Instead, most industrial acetic acid comes from the reaction of methanol with carbon monoxide.

$$\underset{\text{Methanol}}{CH_3OH} + \underset{\substack{\text{Carbon}\\\text{monoxide}}}{CO} \xrightarrow[\text{heat, pressure}]{\text{cobalt or rhodium catalyst}} \underset{\text{Acetic acid}}{CH_3CO_2H}$$

The principal end use of acetic acid is in the production of vinyl acetate for paints and adhesives.

The carboxylic acid produced in the greatest amounts is 1,4-benzenedicarboxylic acid (terephthalic acid). About 5×10^9 lb/year is produced in the United States as a starting material for the preparation of polyester fibers. One important process converts *p*-xylene to terephthalic acid by oxidation with nitric acid:



p-Xylene — 1,4-Benzenedicarboxylic acid (terephthalic acid)

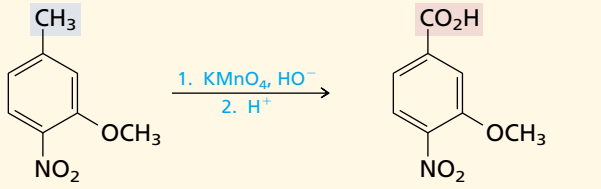
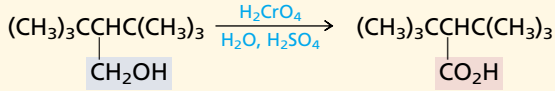
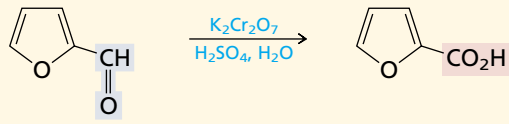
You will recognize the side-chain oxidation of *p*-xylene to terephthalic acid as a reaction type discussed previously (Section 11.13). Examples of other reactions encountered earlier that can be applied to the synthesis of carboxylic acids are collected in Table 19.4.

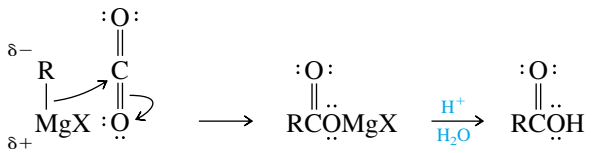
The examples in the table give carboxylic acids that have the same number of carbon atoms as the starting material. The reactions to be described in the next two sections permit carboxylic acids to be prepared by extending a chain by one carbon atom and are of great value in laboratory syntheses of carboxylic acids.

19.11 SYNTHESIS OF CARBOXYLIC ACIDS BY THE CARBOXYLATION OF GRIGNARD REAGENTS

We've seen how Grignard reagents add to the carbonyl group of aldehydes, ketones, and esters. Grignard reagents react in much the same way with *carbon dioxide* to yield magnesium salts of carboxylic acids. Acidification converts these magnesium salts to the desired carboxylic acids.

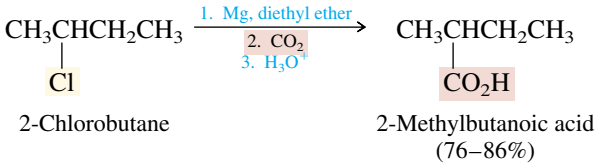
TABLE 19.4 Summary of Reactions Discussed in Earlier Chapters That Yield Carboxylic Acids

Reaction (section) and comments	General equation and specific example
Side-chain oxidation of alkylbenzenes (Section 11.13) A primary or secondary alkyl side chain on an aromatic ring is converted to a carboxyl group by reaction with a strong oxidizing agent such as potassium permanganate or chromic acid.	$ArCHR_2 \xrightarrow[K_2Cr_2O_7,\ H_2SO_4]{KMnO_4\ or} ArCO_2H$ Alkylbenzene → Arenecarboxylic acid  3-Methoxy-4-nitrotoluene → 3-Methoxy-4-nitrobenzoic acid (100%)
Oxidation of primary alcohols (Section 15.10) Potassium permanganate and chromic acid convert primary alcohols to carboxylic acids by way of the corresponding aldehyde.	$RCH_2OH \xrightarrow[K_2Cr_2O_7,\ H_2SO_4]{KMnO_4\ or} RCO_2H$ Primary alcohol → Carboxylic acid  2-*tert*-Butyl-3,3-dimethyl-1-butanol → 2-*tert*-Butyl-3,3-dimethylbutanoic acid (82%)
Oxidation of aldehydes (Section 17.15) Aldehydes are particularly sensitive to oxidation and are converted to carboxylic acids by a number of oxidizing agents, including potassium permanganate and chromic acid.	$RCH{=}O \xrightarrow{\text{oxidizing agent}} RCO_2H$ Aldehyde → Carboxylic acid  Furan-2-carbaldehyde (furfural) → Furan-2-carboxylic acid (furoic acid) (75%)

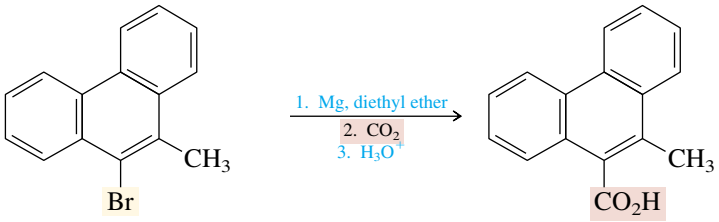


Grignard reagent acts as a nucleophile toward carbon dioxide → Halomagnesium carboxylate → Carboxylic acid

Overall, the carboxylation of Grignard reagents transforms an alkyl or aryl halide to a carboxylic acid in which the carbon skeleton has been extended by one carbon atom.



2-Chlorobutane — 2-Methylbutanoic acid (76–86%)

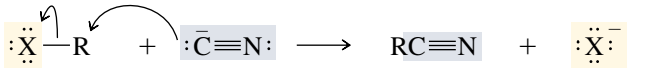


9-Bromo-10-methylphenanthrene — 10-Methylphenanthrene-9-carboxylic acid (82%)

The major limitation to this procedure is that the alkyl or aryl halide must not bear substituents that are incompatible with Grignard reagents, such as OH, NH, SH, or C═O.

19.12 SYNTHESIS OF CARBOXYLIC ACIDS BY THE PREPARATION AND HYDROLYSIS OF NITRILES

Primary and secondary alkyl halides may be converted to the next higher carboxylic acid by a two-step synthetic sequence involving the preparation and hydrolysis of *nitriles.* Nitriles, also known as *alkyl cyanides,* are prepared by nucleophilic substitution.

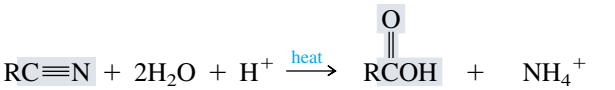


Primary or secondary alkyl halide — Cyanide ion — Nitrile (alkyl cyanide) — Halide ion

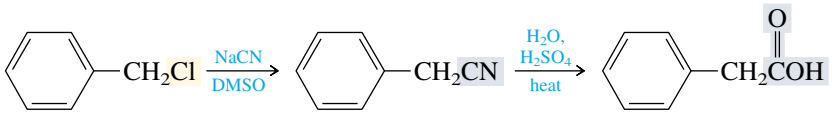
The reaction is of the S_N2 type and works best with primary and secondary alkyl halides. Elimination is the only reaction observed with tertiary alkyl halides. Aryl and vinyl halides do not react. Dimethyl sulfoxide is the preferred solvent for this reaction, but alcohols and water–alcohol mixtures have also been used.

Once the cyano group has been introduced, the nitrile is subjected to hydrolysis. Usually this is carried out in aqueous acid at reflux.

The mechanism of nitrile hydrolysis will be described in Section 20.19.

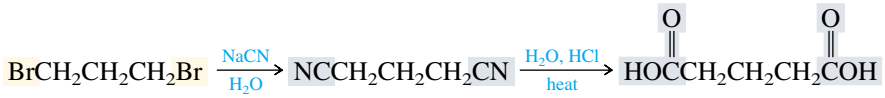


Nitrile — Water — Carboxylic acid — Ammonium ion



Benzyl chloride — Benzyl cyanide (92%) — Phenylacetic acid (77%)

Dicarboxylic acids have been prepared from dihalides by this method:



1,3-Dibromopropane — 1,5-Pentanedinitrile (77–86%) — 1,5-Pentanedioic acid (83–85%)

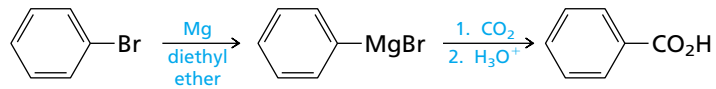
PROBLEM 19.7 Of the two procedures just described, preparation and carboxylation of a Grignard reagent or formation and hydrolysis of a nitrile, only one is appropriate to each of the following RX → RCO_2H conversions. Identify the correct procedure in each case, and specify why the other will fail.

(a) Bromobenzene → benzoic acid

(b) 2-Chloroethanol → 3-hydroxypropanoic acid

(c) *tert*-Butyl chloride → 2,2-dimethylpropanoic acid

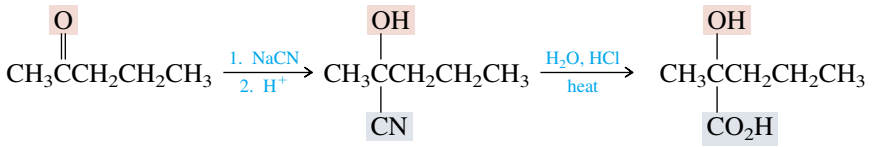
SAMPLE SOLUTION (a) Bromobenzene is an aryl halide and is unreactive toward nucleophilic substitution by cyanide ion. The route $C_6H_5Br \rightarrow C_6H_5CN \rightarrow C_6H_5CO_2H$ fails because the first step fails. The route proceeding through the Grignard reagent is perfectly satisfactory and appears as an experiment in a number of introductory organic chemistry laboratory texts.



Bromobenzene — Phenylmagnesium bromide — Benzoic acid

Nitrile groups in cyanohydrins are hydrolyzed under conditions similar to those of alkyl cyanides. Cyanohydrin formation followed by hydrolysis provides a route to the preparation of α-hydroxy carboxylic acids.

Recall the preparation of cyanohydrins in Section 17.7.

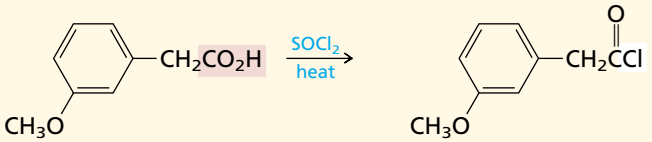
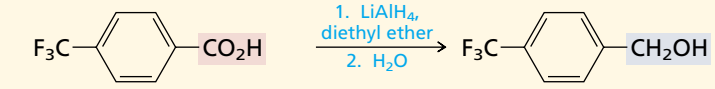
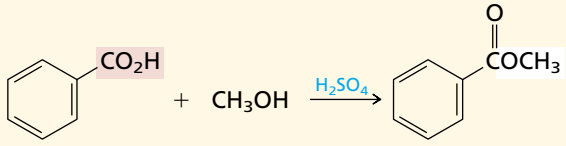


2-Pentanone — 2-Pentanone cyanohydrin — 2-Hydroxy-2-methylpentanoic acid (60% from 2-pentanone)

19.13 REACTIONS OF CARBOXYLIC ACIDS: A REVIEW AND A PREVIEW

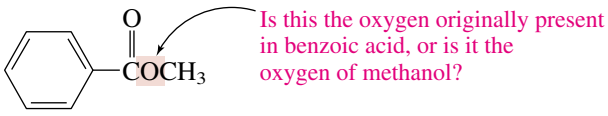
The most apparent chemical property of carboxylic acids, their acidity, has already been examined in earlier sections of this chapter. Three reactions of carboxylic acids—conversion to acyl chlorides, reduction, and esterification—have been encountered in previous chapters and are reviewed in Table 19.5. Acid-catalyzed esterification of carboxylic acids is one of the fundamental reactions of organic chemistry, and this portion of the chapter begins with an examination of the mechanism by which it occurs. Later, in Sections 19.16 and 19.17, two new reactions of carboxylic acids that are of synthetic value will be described.

TABLE 19.5 Summary of Reactions of Carboxylic Acids Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Formation of acyl chlorides (Section 12.7) Thionyl chloride reacts with carboxylic acids to yield acyl chlorides.	$RCO_2H + SOCl_2 \longrightarrow RCCl + SO_2 + HCl$ Carboxylic acid; Thionyl chloride; Acyl chloride; Sulfur dioxide; Hydrogen chloride  *m*-Methoxyphenylacetic acid; *m*-Methoxyphenylacetyl chloride (85%)
Lithium aluminum hydride reduction (Section 15.3) Carboxylic acids are reduced to primary alcohols by the powerful reducing agent lithium aluminum hydride.	$RCO_2H \xrightarrow[2.\ H_2O]{1.\ LiAlH_4,\ \text{diethyl ether}} RCH_2OH$ Carboxylic acid; Primary alcohol  *p*-(Trifluoromethyl)benzoic acid; *p*-(Trifluoromethyl)benzyl alcohol (96%)
Esterification (Section 15.8) In the presence of an acid catalyst, carboxylic acids and alcohols react to form esters. The reaction is an equilibrium process but can be driven to favor the ester by removing the water that is formed.	$RCO_2H + R'OH \underset{}{\overset{H^+}{\rightleftharpoons}} RCOR' + H_2O$ Carboxylic acid; Alcohol; Ester; Water  Benzoic acid; Methanol; Methyl benzoate (70%)

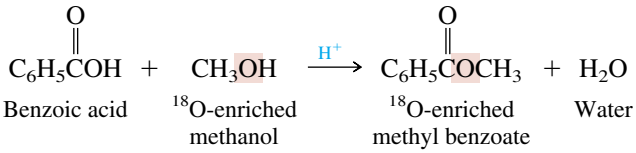
19.14 MECHANISM OF ACID-CATALYZED ESTERIFICATION

An important question about the mechanism of acid-catalyzed esterification concerns the origin of the alkoxy oxygen. For example, does the methoxy oxygen in methyl benzoate come from methanol, or is it derived from benzoic acid?



The answer to this question is critical because it tells us whether the carbon–oxygen bond of the alcohol or a carbon–oxygen of the carboxylic acid is broken during the esterification.

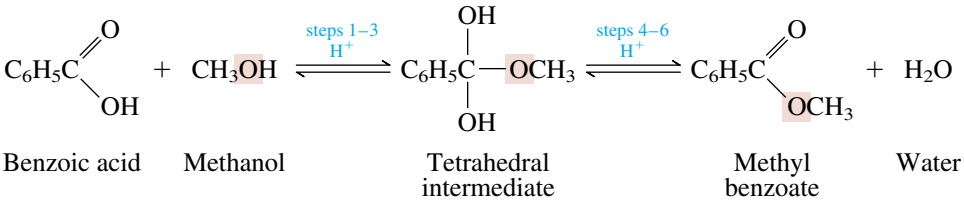
A clear-cut answer was provided by Irving Roberts and Harold C. Urey of Columbia University in 1938. They prepared methanol that had been enriched in the mass-18 isotope of oxygen. When this sample of methanol was esterified with benzoic acid, the methyl benzoate product contained all the ^{18}O label that was originally present in the methanol.



In this equation, the red-highlighted O signifies oxygen enriched in its mass -18 isotope; analysis of isotopic enrichment was performed by mass spectrometry.

The results of the Roberts–Urey experiment tell us that the C—O bond of the alcohol is preserved during esterification. The oxygen that is lost as a water molecule must come from the carboxylic acid.

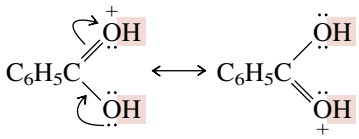
A mechanism consistent with these facts is presented in Figure 19.6. The six steps are best viewed as a combination of two distinct stages. *Formation* of a **tetrahedral intermediate** characterizes the first stage (steps 1–3), and *dissociation* of this tetrahedral intermediate characterizes the second (steps 4–6).



The species connecting the two stages is called a *tetrahedral intermediate* because the hybridization at carbon has changed from sp^2 in the carboxylic acid to sp^3 in the intermediate before returning to sp^2 in the ester product. *The tetrahedral intermediate is formed by nucleophilic addition of an alcohol to a carboxylic acid and is analogous to a hemiacetal formed by nucleophilic addition of an alcohol to an aldehyde or a ketone.* The three steps that lead to the tetrahedral intermediate in the first stage of esterification are analogous to those in the mechanism for acid-catalyzed nucleophilic addition of an alcohol to an aldehyde or a ketone. The tetrahedral intermediate cannot be isolated. It is unstable under the conditions of its formation and undergoes acid-catalyzed dehydration to form the ester.

Notice that the oxygen of methanol becomes incorporated into the methyl benzoate product according to the mechanism outlined in Figure 19.6, as the observations of the Roberts–Urey experiment require it to be.

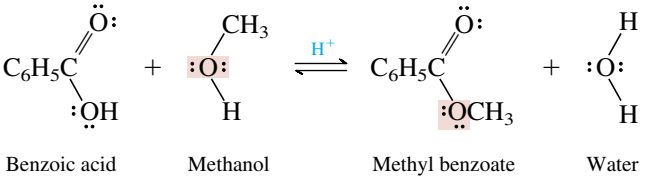
Notice, too, that the carbonyl oxygen of the carboxylic acid is protonated in the first step and not the hydroxyl oxygen. The species formed by protonation of the carbonyl oxygen is more stable, because it is stabilized by electron delocalization. The positive charge is shared equally by both oxygens.



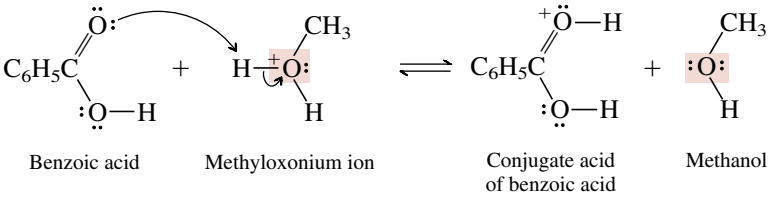
Electron delocalization in carbonyl-protonated benzoic acid

FIGURE 19.6 The mechanism of acid-catalyzed esterification of benzoic acid with methanol.

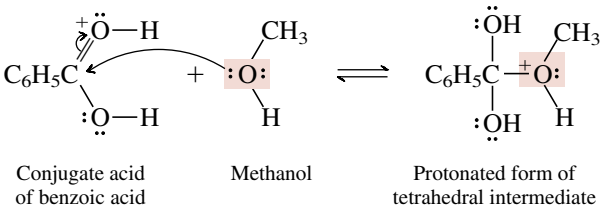
The overall reaction:



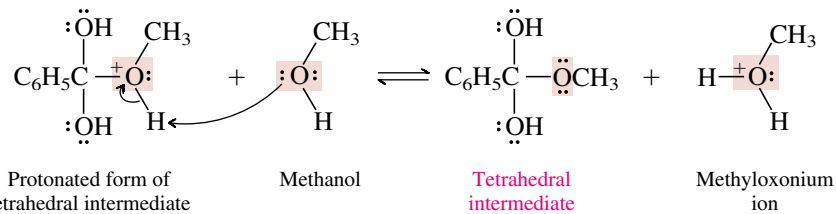
Step 1: The carboxylic acid is protonated on its carbonyl oxygen. The proton donor shown in the equation for this step is an alkyloxonium ion formed by proton transfer from the acid catalyst to the alcohol.



Step 2: Protonation of the carboxylic acid increases the positive character of its carbonyl group. A molecule of the alcohol acts as a nucleophile and attacks the carbonyl carbon.

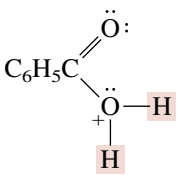


Step 3: The oxonium ion formed in step 2 loses a proton to give the tetrahedral intermediate in its neutral form. This step concludes the first stage in the mechanism.



—Cont.

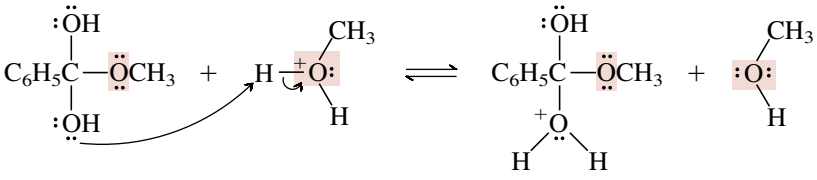
Protonation of the hydroxyl oxygen, on the other hand, yields a less stable cation:



Localized positive charge in hydroxyl-protonated benzoic acid

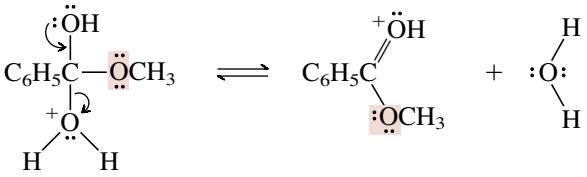
(Continued)

Step 4: The second stage begins with protonation of the tetrahedral intermediate on one of its hydroxyl oxygens.



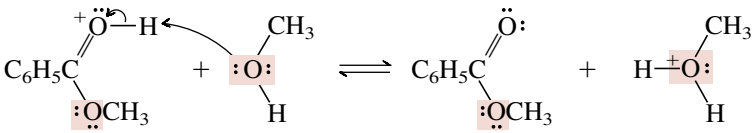
Tetrahedral intermediate | Methyloxonium ion | Hydroxyl-protonated tetrahedral intermediate | Methanol

Step 5: This intermediate loses a molecule of water to give the protonated form of the ester.



Hydroxyl-protonated tetrahedral intermediate | Conjugate acid of methyl benzoate | Water

Step 6: Deprotonation of the species formed in step 5 gives the neutral form of the ester product.



Conjugate acid of methyl benzoate | Methanol | Methyl benzoate | Methyloxonium ion

The positive charge in this cation cannot be shared by the two oxygens; it is localized on one of them. Since protonation of the carbonyl oxygen gives a more stable cation, that cation is formed preferentially.

PROBLEM 19.8 When benzoic acid is allowed to stand in water enriched in ^{18}O, the isotopic label becomes incorporated into the benzoic acid. The reaction is catalyzed by acids. Suggest an explanation for this observation.

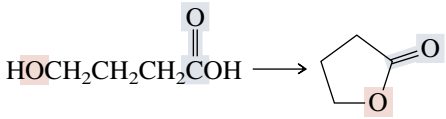
In the next chapter the three elements of the mechanism just described will be seen again as part of the general theme that unites the chemistry of carboxylic acid derivatives. These elements are

1. Activation of the carbonyl group by protonation of the carbonyl oxygen
2. Nucleophilic addition to the protonated carbonyl to form a tetrahedral intermediate
3. Elimination from the tetrahedral intermediate to restore the carbonyl group

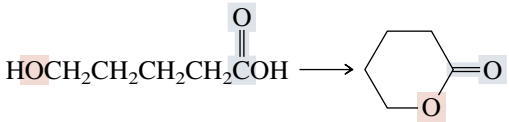
This sequence is one of the fundamental mechanistic patterns of organic chemistry.

19.15 INTRAMOLECULAR ESTER FORMATION: LACTONES

Hydroxy acids, compounds that contain both a hydroxyl and a carboxylic acid function, have the capacity to form cyclic esters called *lactones*. This intramolecular esterification takes place spontaneously when the ring that is formed is five membered or six membered. Lactones that contain a five-membered cyclic ester are referred to as **γ-lactones;** their six-membered analogs are known as **δ-lactones.**

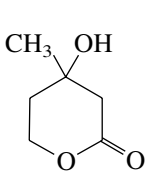


4-Hydroxybutanoic acid 4-Butanolide



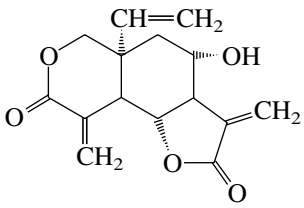
5-Hydroxypentanoic acid 5-Pentanolide

A lactone is named by replacing the *-oic acid* ending of the parent carboxylic acid by *-olide* and identifying its oxygenated carbon by number. This system is illustrated in



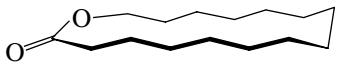
Mevalonolactone

(an intermediate in the biosynthesis of terpenes and steroids)



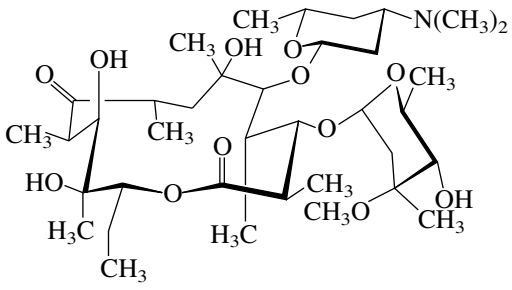
Vernolepin

(a tumor-inhibitory substance that incorporates both a γ-lactone and a δ-lactone into its tricyclic framework)



15-Pentadecanolide

(an odor-enhancing substance used in perfume)



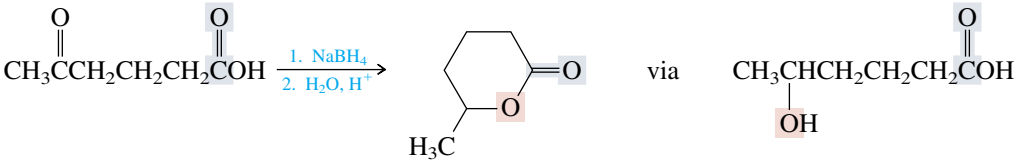
Erythromycin

(a macrolide antibiotic; drug production is by fermentation processes, but the laboratory synthesis of this complex substance has been achieved)

FIGURE 19.7 Some naturally occurring lactones.

the lactones shown in the preceding equations. Both 4-butanolide and 5-pentanolide are better known by their common names, γ-butyrolactone and δ-valerolactone, respectively, and these two common names are permitted by the IUPAC rules.

Reactions that are expected to produce hydroxy acids often yield the derived lactones instead if a five- or six-membered ring can be formed.



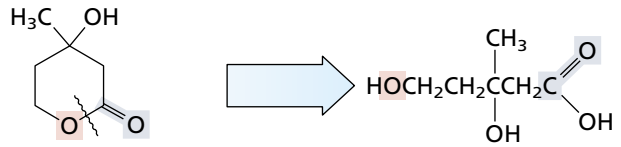
5-Oxohexanoic acid 5-Hexanolide (78%) 5-Hydroxyhexanoic acid

Many natural products are lactones, and it is not unusual to find examples in which the ring size is rather large. A few naturally occurring lactones are shown in Figure 19.7. The *macrolide antibiotics,* of which erythromycin is one example, are macrocyclic (large-ring) lactones. The lactone ring of erythromycin is 14 membered.

PROBLEM 19.9 Write the structure of the hydroxy acid corresponding to each of the following lactones. The structure of each lactone is given in Figure 19.7.

(a) Mevalonolactone
(b) Pentadecanolide
(c) Vernolepin

SAMPLE SOLUTION (a) The ring oxygen of the lactone is derived from the hydroxyl group of the hydroxy acid, whereas the carbonyl group corresponds to that of the carboxyl function. To identify the hydroxy acid, disconnect the O—C(O) bond of the ester.



Mevalonolactone (disconnect bond indicated) Mevalonic acid

Lactones whose rings are three or four membered (α-lactones and β-lactones) are very reactive, making their isolation difficult. Special methods are normally required for the laboratory synthesis of small-ring lactones as well as those that contain rings larger than six membered.

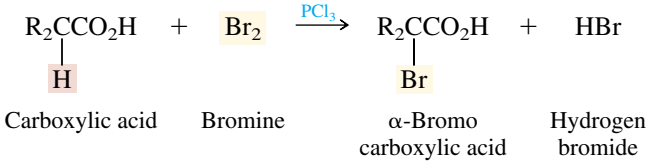
The compound *anisatin* is an example of a naturally occurring β-lactone. Its isolation and structure determination were described in the journal *Tetrahedron Letters* (1982), p. 5111.

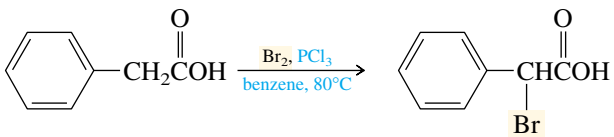
19.16 α HALOGENATION OF CARBOXYLIC ACIDS: THE HELL–VOLHARD–ZELINSKY REACTION

Esterification of carboxylic acids involves nucleophilic addition to the carbonyl group as a key step. In this respect the carbonyl group of a carboxylic acid resembles that of an aldehyde or a ketone. Do carboxylic acids resemble aldehydes and ketones in other ways? Do they, for example, form *enols,* and can they be halogenated at their α-carbon atom via an enol in the way that aldehydes and ketones can?

The enol content of a carboxylic acid is far less than that of an aldehyde or ketone, and introduction of a halogen substituent at the α-carbon atom requires a different set

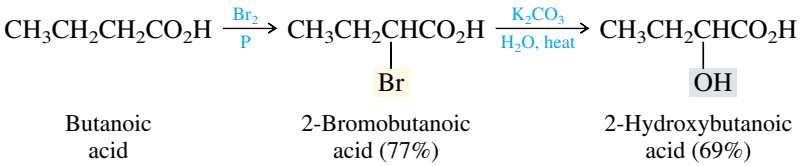
of reaction conditions. Bromination is the reaction that is normally carried out, and the usual procedure involves treatment of the carboxylic acid with bromine in the presence of a small amount of phosphorus trichloride as a catalyst.



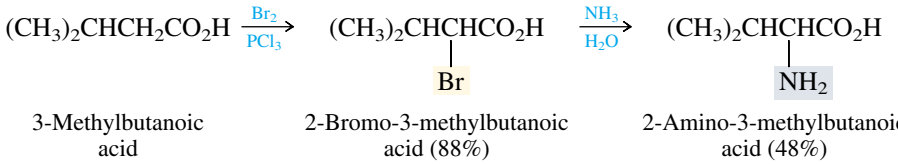


This method of α bromination of carboxylic acids is called the **Hell–Volhard–Zelinsky reaction.** This reaction is sometimes carried out by using a small amount of phosphorus instead of phosphorus trichloride. Phosphorus reacts with bromine to yield phosphorus tribromide as the active catalyst under these conditions.

The Hell–Volhard–Zelinsky reaction is of synthetic value in that the α halogen can be displaced by nucleophilic substitution:



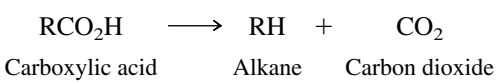
A standard method for the preparation of an α-amino acid uses α-bromo carboxylic acids as the substrate and aqueous ammonia as the nucleophile:



PROBLEM 19.10 α-Iodo acids are not normally prepared by direct iodination of carboxylic acids under conditions of the Hell–Volhard–Zelinsky reaction. Show how you could convert octadecanoic acid to its 2-iodo derivative by an efficient sequence of reactions.

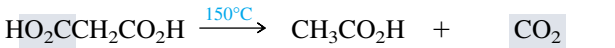
19.17 DECARBOXYLATION OF MALONIC ACID AND RELATED COMPOUNDS

The loss of a molecule of carbon dioxide from a carboxylic acid is known as **decarboxylation.**



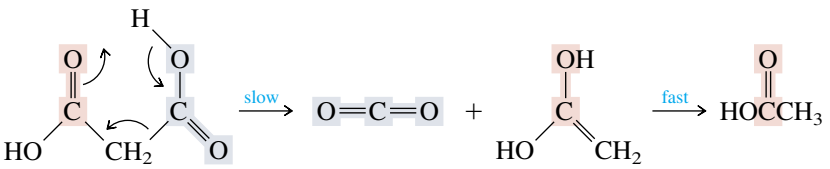
Decarboxylation of simple carboxylic acids takes place with great difficulty and is rarely encountered.

Compounds that readily undergo thermal decarboxylation include those related to malonic acid. On being heated above its melting point, malonic acid is converted to acetic acid and carbon dioxide.



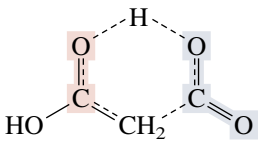
Malonic acid (propanedioic acid) | Acetic acid (ethanoic acid) | Carbon dioxide

It is important to recognize that only one carboxyl group is lost in this process. The second carboxyl group is retained. A mechanism recognizing the assistance that one carboxyl group gives to the departure of the other is represented by the equation



Carbon dioxide | Enol form of acetic acid | Acetic acid

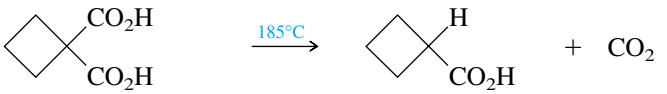
The transition state involves the carbonyl oxygen of one carboxyl group—the one that stays behind—acting as a proton acceptor toward the hydroxyl group of the carboxyl that is lost. Carbon–carbon bond cleavage leads to the enol form of acetic acid, along with a molecule of carbon dioxide.



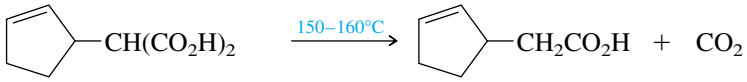
Representation of transition state in thermal decarboxylation of malonic acid

The enol intermediate subsequently tautomerizes to acetic acid.

The protons attached to C-2 of malonic acid are not directly involved in the process and so may be replaced by other substituents without much effect on the ease of decarboxylation. Analogs of malonic acid substituted at C-2 undergo efficient thermal decarboxylation.



1,1-Cyclobutanedicarboxylic acid | Cyclobutanecarboxylic acid (74%) | Carbon dioxide

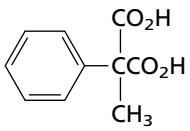


2-(2-Cyclopentenyl)malonic acid | (2-Cyclopentenyl)acetic acid (96–99%) | Carbon dioxide

PROBLEM 19.11 What will be the product isolated after thermal decarboxylation of each of the following? Using curved arrows, represent the bond changes that take place at the transition state.

(a) $(CH_3)_2C(CO_2H)_2$

(b) $CH_3(CH_2)_6CHCO_2H$ (with CO_2H on the CH)

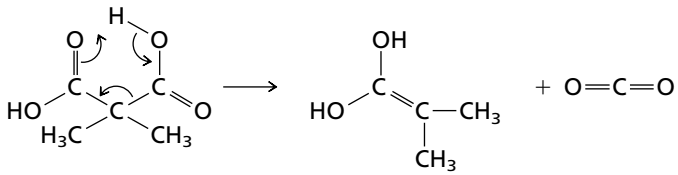
(c) 

SAMPLE SOLUTION (a) Thermal decarboxylation of malonic acid derivatives leads to the replacement of one of the carboxyl groups by a hydrogen.

$$(CH_3)_2C(CO_2H)_2 \xrightarrow{\text{heat}} (CH_3)_2CHCO_2H + CO_2$$

2,2-Dimethylmalonic acid → 2-Methylpropanoic acid + Carbon dioxide

The transition state incorporates a cyclic array of six atoms:

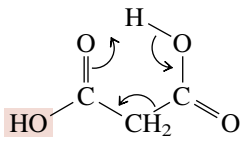


2,2-Dimethylmalonic acid → Enol form of 2-methylpropanoic acid + Carbon dioxide

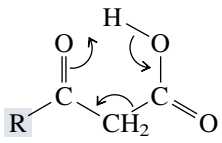
Tautomerization of the enol form to 2-methylpropanoic acid completes the process.

The thermal decarboxylation of malonic acid derivatives is the last step in a multistep synthesis of carboxylic acids known as the *malonic ester synthesis.* This synthetic method will be described in Section 21.7.

Notice that the carboxyl group that stays behind during the decarboxylation of malonic acid has a hydroxyl function that is not directly involved in the process. Compounds that have substituents other than hydroxyl groups at this position undergo an analogous decarboxylation.

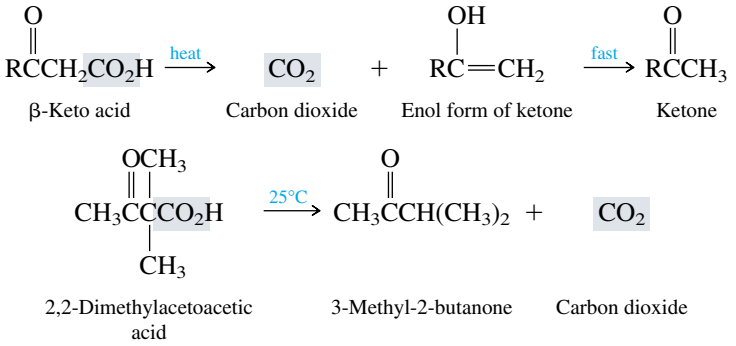


Bonding changes during decarboxylation of malonic acid



Bonding changes during decarboxylation of a β-keto acid

The compounds most frequently encountered in this reaction are β-keto acids, that is, carboxylic acids in which the β carbon is a carbonyl function. Decarboxylation of β-keto acids leads to ketones.

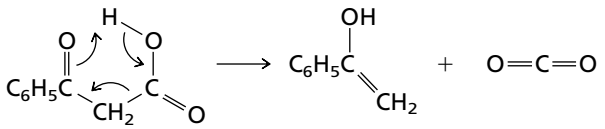


PROBLEM 19.12 Show the bonding changes that occur, and write the structure of the intermediate formed in the thermal decarboxylation of

(a) Benzoylacetic acid

(b) 2,2-Dimethylacetoacetic acid

SAMPLE SOLUTION (a) By analogy to the thermal decarboxylation of malonic acid, we represent the corresponding reaction of benzoylacetic acid as



Acetophenone is the isolated product; it is formed from its enol by proton-transfers.

The thermal decarboxylation of β-keto acids is the last step in a ketone synthesis known as the *acetoacetic ester synthesis.* The acetoacetic ester synthesis is discussed in Section 21.6.

19.18 SPECTROSCOPIC ANALYSIS OF CARBOXYLIC ACIDS

Infrared: The most characteristic peaks in the infrared spectra of carboxylic acids are those of the hydroxyl and carbonyl groups. As shown in the infrared spectrum of 4-phenylbutanoic acid (Figure 19.8) the O—H and C—H stretching frequencies overlap to produce a broad absorption in the 3500–2500 cm^{-1} region. The carbonyl group gives a strong band for C=O stretching at 1700 cm^{-1}.

^{1}H NMR: The hydroxyl proton of a CO_2H group is normally the least shielded of all the protons in an NMR spectrum, appearing 10–12 ppm downfield from tetramethylsilane, often as a broad peak. Figure 19.9 illustrates this for 4-phenylbutanoic acid. As with other hydroxyl protons, the proton of a carboxyl group can be identified by adding D_2O to the sample. Hydrogen–deuterium exchange converts $—CO_2H$ to $—CO_2D$, and the signal corresponding to the carboxyl group disappears.

^{13}C NMR: Like other carbonyl groups, the carbon of the $—CO_2H$ group of a carboxylic acid is strongly deshielded (δ 160–185 ppm), but not as much as that of an aldehyde or ketone (190–215 ppm).

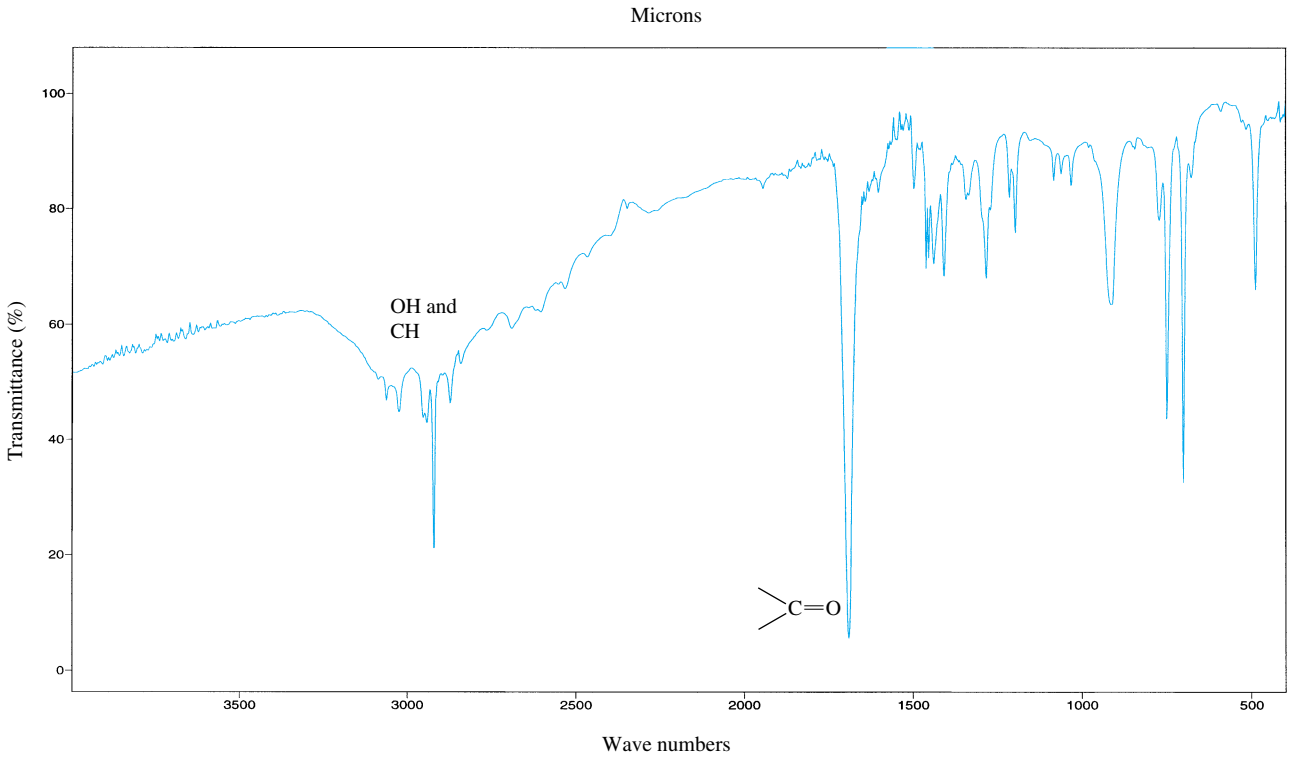


FIGURE 19.8 The infrared spectrum of 4-phenylbutanoic acid.

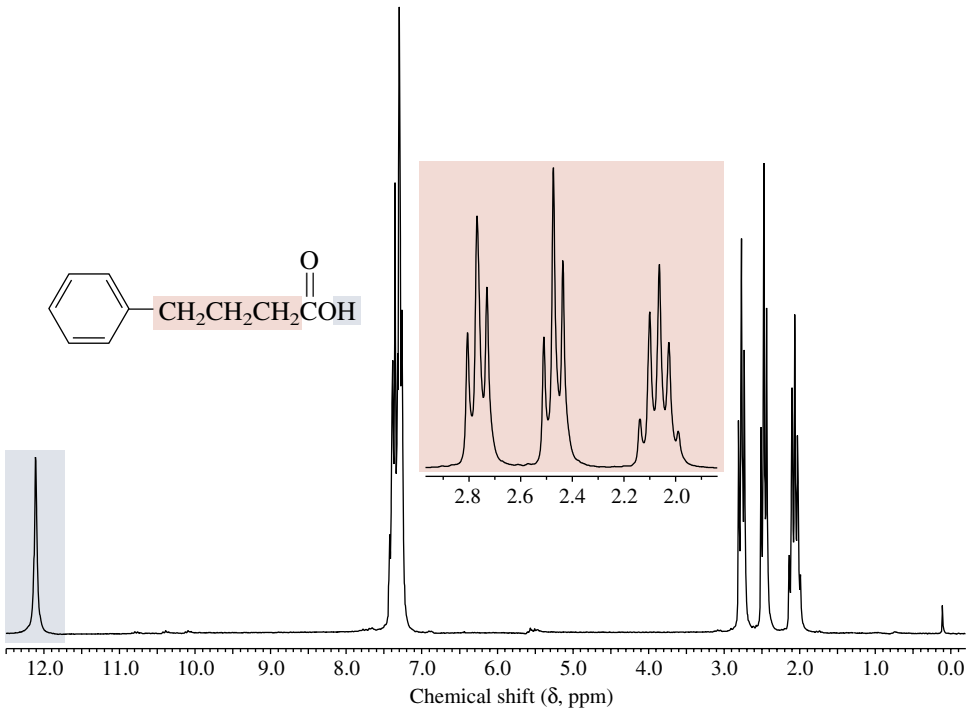
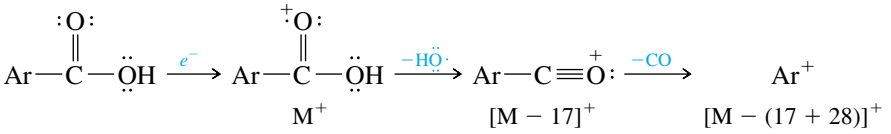


FIGURE 19.9 The 200-MHz ^{1}H NMR spectrum of 4-phenylbutanoic acid. The peak for the proton of the CO_2H group is at δ 12 ppm.

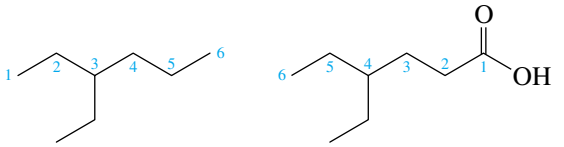
UV-VIS: In the absence of any additional chromophores, carboxylic acids absorb at a wavelength (210 nm) that is not very useful for diagnostic purposes.

Mass Spectrometry: Aside from a peak for the molecular ion, which is normally easy to pick out, aliphatic carboxylic acids undergo a variety of fragmentation processes. The dominant fragmentation in aromatic acids corresponds to loss of OH, then loss of CO.



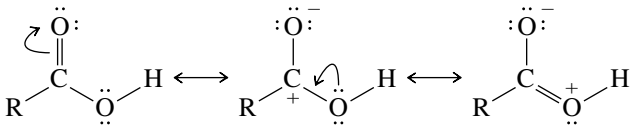
19.19 SUMMARY

Section 19.1 Carboxylic acids take their names from the alkane that contains the same number of carbons as the longest continuous chain that contains the $—CO_2H$ group. The *-e* ending is replaced by *-oic acid.* Numbering begins at the carbon of the $—CO_2H$ group.



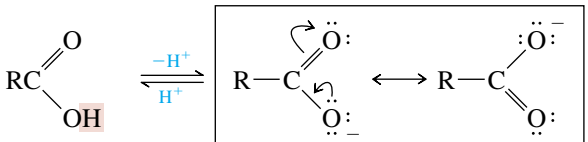
3-Ethylhexane 4-Ethylhexanoic acid

Section 19.2 Like the carbonyl group of aldehydes and ketones, the carbon of a C═O unit in a carboxylic acid is sp^2-hybridized. Compared with the carbonyl group of an aldehyde or ketone, the C═O unit of a carboxylic acid receives an extra degree of stabilization from its attached OH group.



Section 19.3 Hydrogen bonding in carboxylic acids raises their melting points and boiling points above those of comparably constituted alkanes, alcohols, aldehydes, and ketones.

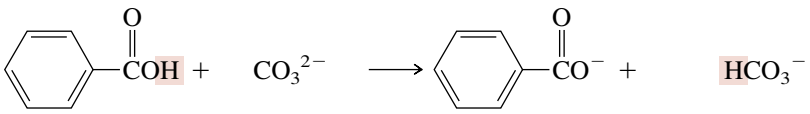
Section 19.4 Carboxylic acids are weak acids and, in the absence of electron-attracting substituents, have dissociation constants K_a of approximately 10^{-5} ($pK_a = 5$). Carboxylic acids are much stronger acids than alcohols because of the electron-withdrawing power of the carbonyl group (inductive effect) and its ability to delocalize negative charge in the carboxylate anion (resonance effect).



Carboxylic acid

Resonance description of electron delocalization in carboxylate anion

Section 19.5 Although carboxylic acids dissociate to only a small extent in water, they are deprotonated almost completely in basic solution.



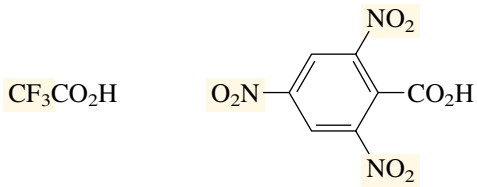
Benzoic acid
$K_a = 6.3 \times 10^{-5}$
(stronger acid)

Carbonate ion

Benzoate ion

Hydrogen carbonate ion
$K_a = 5 \times 10^{-11}$
(weaker acid)

Sections 19.6–19.7 Electronegative substituents, especially those within a few bonds of the carboxyl group, increase the acidity of carboxylic acids.

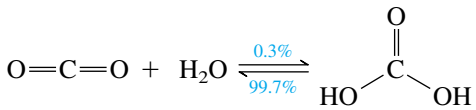


Trifluoroacetic acid
$K_a = 5.9 \times 10^{-1}$
($pK_a = 0.2$)

2,4,6-Trinitrobenzoic acid
$K_a = 2.2 \times 10^{-1}$
($pK_a = 0.6$)

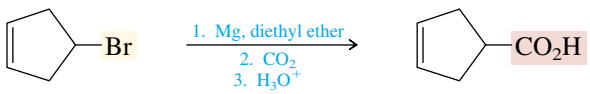
Section 19.8 Dicarboxylic acids have separate K_a values for their first and second ionizations.

Section 19.9 Carbon dioxide and carbonic acid are in equilibrium in water. Carbon dioxide is the major component.



Section 19.10 Several of the reactions introduced in earlier chapters can be used to prepare carboxylic acids (See Table 19.4).

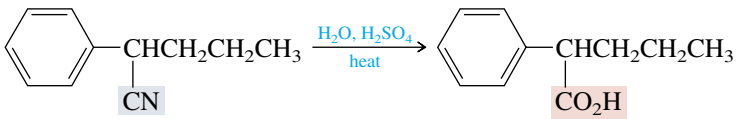
Section 19.11 Carboxylic acids can be prepared by the reaction of Grignard reagents with carbon dioxide.



4-Bromocyclopentene

Cyclopentene-4-carboxylic acid (66%)

Section 19.12 Nitriles, which can be prepared from primary and secondary alkyl halides by nucleophilic substitution with cyanide ion, can be converted to carboxylic acids by hydrolysis.



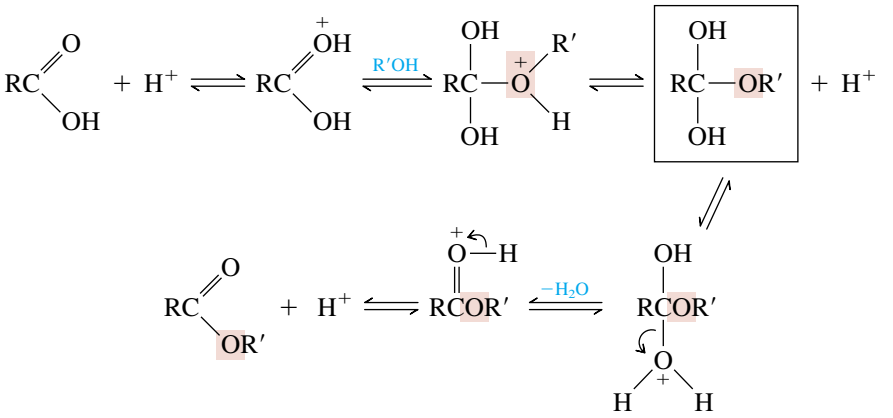
2-Phenylpentanenitrile

2-Phenylpentanoic acid (52%)

Likewise, the cyano group of a cyanohydrin can be hydrolyzed to —CO_2H.

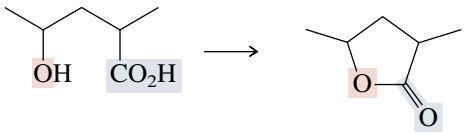
Section 19.13 Among the reactions of carboxylic acids, their conversion to acyl chlorides, primary alcohols, and esters were introduced in earlier chapters and were reviewed in Table 19.5.

Section 19.14 The mechanism of acid-catalyzed esterification involves some key features that are fundamental to the chemistry of carboxylic acids and their derivatives.



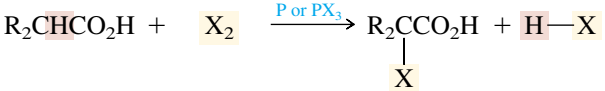
Protonation of the carbonyl oxygen activates the carbonyl group toward nucleophilic addition. Addition of an alcohol gives a tetrahedral intermediate (shown in the box in the preceding equation), which has the capacity to revert to starting materials or to undergo dehydration to yield an ester.

Section 19.15 An intramolecular esterification can occur when a molecule contains both a hydroxyl and a carboxyl group. Cyclic esters are called *lactones* and are most stable when the ring is five or six membered.



4-Hydroxy-2-methylpentanoic acid — 2-Methyl-4-pentanolide

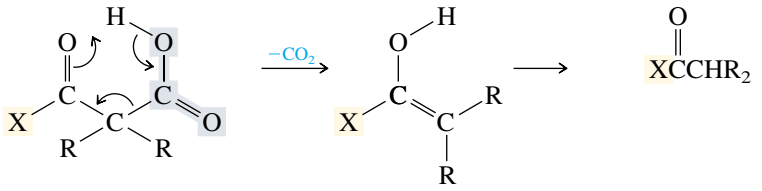
Section 19.16 Halogenation at the α-carbon atom of carboxylic acids can be accomplished by the *Hell–Volhard–Zelinsky reaction.* An acid is treated with chlorine or bromine in the presence of a catalytic quantity of phosphorus or a phosphorus trihalide:



Carboxylic acid — Halogen — α-Halo acid

This reaction is of synthetic value in that α-halo acids are reactive substrates in nucleophilic substitution reactions.

Section 19.17 1,1-Dicarboxylic acids and β-keto acids undergo thermal decarboxylation by a mechanism in which a β-carbonyl group assists the departure of carbon dioxide.



X = OH: malonic acid derivative
X = alkyl or aryl: β-keto acid

Enol form of product

X = OH: carboxylic acid
X = alkyl or aryl: ketone

Section 19.18 Carboxylic acids are readily identified by the presence of strong infrared absorptions at 1700 cm^{-1} (C=O) and between 2500 and 3500 cm^{-1} (OH), a ^1H NMR signal for the hydroxyl proton at δ 10–12 ppm, and a ^{13}C signal for the carbonyl carbon near δ 180 ppm.

PROBLEMS

19.13 Many carboxylic acids are much better known by their common names than by their systematic names. Some of these follow. Provide a structural formula for each one on the basis of its systematic name.

(a) 2-Hydroxypropanoic acid (better known as *lactic acid,* it is found in sour milk and is formed in the muscles during exercise)

(b) 2-Hydroxy-2-phenylethanoic acid (also known as *mandelic acid,* it is obtained from plums, peaches, and other fruits)

(c) Tetradecanoic acid (also known as *myristic acid,* it can be obtained from a variety of fats)

(d) 10-Undecenoic acid (also called *undecylenic acid,* it is used, in combination with its zinc salt, to treat fungal infections such as athlete's foot)

(e) 3,5-Dihydroxy-3-methylpentanoic acid (also called *mevalonic acid,* it is an important intermediate in the biosynthesis of terpenes and steroids)

(f) (*E*)-2-Methyl-2-butenoic acid (also known as *tiglic acid,* it is a constituent of various natural oils)

(g) 2-Hydroxybutanedioic acid (also known as *malic acid,* it is found in apples and other fruits)

(h) 2-Hydroxy-1,2,3-propanetricarboxylic acid (better known as *citric acid,* it contributes to the tart taste of citrus fruits)

(i) 2-(*p*-Isobutylphenyl)propanoic acid (an antiinflammatory drug better known as *ibuprofen*)

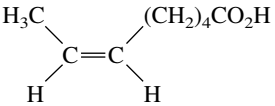
(j) *o*-Hydroxybenzenecarboxylic acid (better known as *salicylic acid,* it is obtained from willow bark)

19.14 Give an acceptable IUPAC name for each of the following:

(a) $CH_3(CH_2)_6CO_2H$

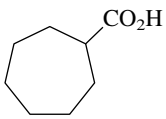
(b) $CH_3(CH_2)_6CO_2K$

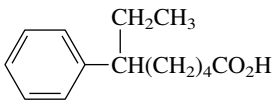
(c) $CH_2{=}CH(CH_2)_5CO_2H$

(d) 

(e) $HO_2C(CH_2)_6CO_2H$

(f) $CH_3(CH_2)_4CH(CO_2H)_2$

(g) 

(h) 

19.15 Rank the compounds in each of the following groups in order of decreasing acidity:

(a) Acetic acid, ethane, ethanol

(b) Benzene, benzoic acid, benzyl alcohol

(c) Propanedial, 1,3-propanediol, propanedioic acid, propanoic acid

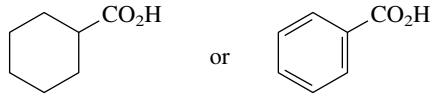
(d) Acetic acid, ethanol, trifluoroacetic acid, 2,2,2-trifluoroethanol, trifluoromethanesulfonic acid (CF_3SO_2OH)

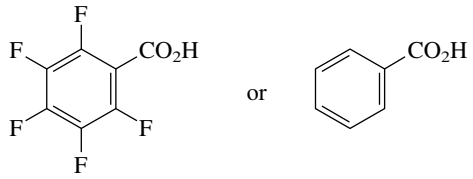
(e) Cyclopentanecarboxylic acid, 2,4-pentanedione, cyclopentanone, cyclopentene

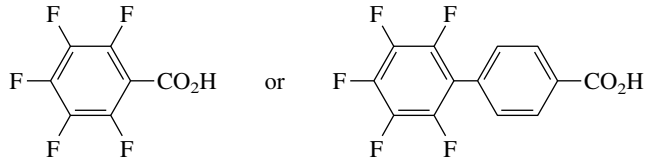
19.16 Identify the more acidic compound in each of the following pairs:

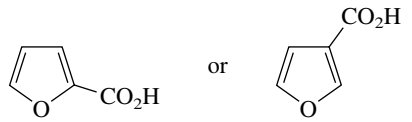
(a) $CF_3CH_2CO_2H$ or $CF_3CH_2CH_2CO_2H$

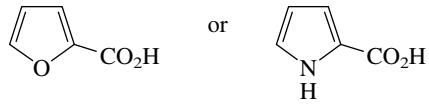
(b) $CH_3CH_2CH_2CO_2H$ or $CH_3C{\equiv}CCO_2H$

(c) 

(d) 

(e) 

(f) 

(g) 

19.17 Propose methods for preparing butanoic acid from each of the following:

(a) 1-Butanol

(b) Butanal

(c) 1-Butene

(d) 1-Propanol

(e) 2-Propanol

(f) Acetaldehyde

(g) $CH_3CH_2CH(CO_2H)_2$

19.18 It is sometimes necessary to prepare isotopically labeled samples of organic substances for probing biological transformations and reaction mechanisms. Various sources of the radioactive mass-14 carbon isotope are available. Describe synthetic procedures by which benzoic acid, labeled with ^{14}C at its carbonyl carbon, could be prepared from benzene and the following ^{14}C-labeled precursors. You may use any necessary organic or inorganic reagents. (In the formulas shown, an asterisk indicates ^{14}C.)

(a) $\overset{*}{C}H_3Cl$ (b) $H\overset{O}{\overset{\|}{\overset{*}{C}}}H$ (c) $\overset{*}{C}O_2$

19.19 Give the product of the reaction of pentanoic acid with each of the following reagents:

(a) Sodium hydroxide

(b) Sodium bicarbonate

(c) Thionyl chloride

(d) Phosphorus tribromide

(e) Benzyl alcohol, sulfuric acid (catalytic amount)

(f) Chlorine, phosphorus tribromide (catalytic amount)

(g) Bromine, phosphorus trichloride (catalytic amount)

(h) Product of part (g) treated with sodium iodide in acetone

(i) Product of part (g) treated with aqueous ammonia

(j) Lithium aluminum hydride, then hydrolysis

(k) Phenylmagnesium bromide

19.20 Show how butanoic acid may be converted to each of the following compounds:

(a) 1-Butanol

(b) Butanal

(c) 1-Chlorobutane

(d) Butanoyl chloride

(e) Phenyl propyl ketone

(f) 4-Octanone

(g) 2-Bromobutanoic acid

(h) 2-Butenoic acid

19.21 Show by a series of equations, using any necessary organic or inorganic reagents, how acetic acid can be converted to each of the following compounds:

(a) $H_2NCH_2CO_2H$

(b) $C_6H_5OCH_2CO_2H$

(c) $NCCH_2CO_2H$

(d) $HO_2CCH_2CO_2H$

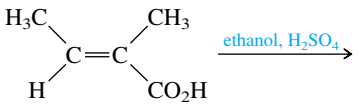
(e) ICH_2CO_2H

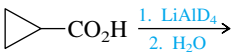
(f) $BrCH_2CO_2CH_2CH_3$

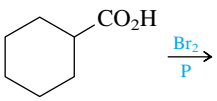
(g) $(C_6H_5)_3\overset{+}{P}—\overset{-}{\underset{\cdot\cdot}{C}}HCO_2CH_2CH_3$

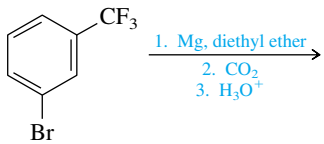
(h) $C_6H_5CH{=}CHCO_2CH_2CH_3$

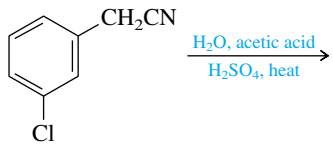
19.22 Each of the following reactions has been reported in the chemical literature and gives a single product in good yield. What is the product in each reaction?

(a) 

(b) 

(c) 

(d) 

(e) 

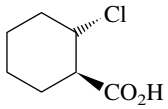
(f) $CH_2{=}CH(CH_2)_8CO_2H \xrightarrow[\text{benzoyl peroxide}]{\text{HBr}}$

(c) 3,3-Dimethylbutanoic acid from *tert*-butyl alcohol

(d) $HO_2C(CH_2)_5CO_2H$ from $HO_2C(CH_2)_3CO_2H$

(e) 3-Phenyl-1-butanol from CH_3CHCH_2CN (with C_6H_5 on the CH)

(f)  from cyclopentyl bromide

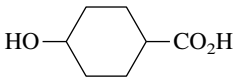
(g)  from (*E*)-ClCH=CHCO$_2$H

(h) 2,4-Dimethylbenzoic acid from *m*-xylene

(i) 4-Chloro-3-nitrobenzoic acid from *p*-chlorotoluene

(j) (*Z*)-$CH_3CH{=}CHCO_2H$ from propyne

19.24 (a) Which stereoisomer of 4-hydroxycyclohexanecarboxylic acid (cis or trans) can form a lactone? Make a molecular model of this lactone. What is the conformation of the cyclohexane ring in the starting hydroxy acid? In the lactone?



(b) Repeat part (a) for the case of 3-hydroxycyclohexanecarboxylic acid.

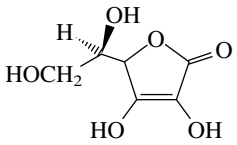
19.25 Suggest reasonable explanations for each of the following observations.

(a) Both hydrogens are anti to each other in the most stable conformation of formic acid.

(b) Oxalic acid has a dipole moment of zero in the gas phase.

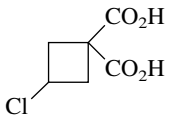
(c) The dissociation constant of *o*-hydroxybenzoic acid is greater (by a factor of 12) than that of *o*-methoxybenzoic acid.

(d) Ascorbic acid (vitamin C), although not a carboxylic acid, is sufficiently acidic to cause carbon dioxide liberation on being dissolved in aqueous sodium bicarbonate.



Ascorbic acid

19.26 When compound A is heated, two isomeric products are formed. What are these two products?

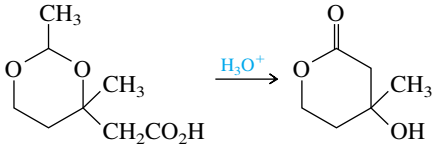


Compound A

19.27 A certain carboxylic acid ($C_{14}H_{26}O_2$), which can be isolated from whale blubber or sardine oil, yields nonanal and $O{=}CH(CH_2)_3CO_2H$ on ozonolysis. What is the structure of this acid?

19.28 When levulinic acid ($CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CO_2H$) was hydrogenated at high pressure over a nickel catalyst at 220°C, a single product, $C_5H_8O_2$, was isolated in 94% yield. This compound lacks hydroxyl absorption in its infrared spectrum and does not immediately liberate carbon dioxide on being shaken with sodium bicarbonate. What is a reasonable structure for the compound?

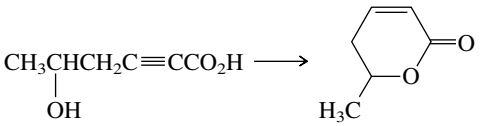
19.29 On standing in dilute aqueous acid, compound A is smoothly converted to mevalonolactone.



Compound A Mevalonolactone

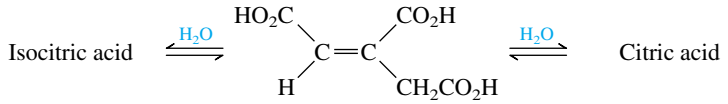
Suggest a reasonable mechanism for this reaction. What other organic product is also formed?

19.30 Suggest reaction conditions suitable for the preparation of compound A from 5-hydroxy-2-hexynoic acid.



5-Hydroxy-2-hexynoic acid Compound A

19.31 In the presence of the enzyme *aconitase,* the double bond of aconitic acid undergoes hydration. The reaction is reversible, and the following equilibrium is established:



($C_6H_8O_7$) (6% at equilibrium)

Aconitic acid (4% at equilibrium)

($C_6H_8O_7$) (90% at equilibrium)

(a) The major tricarboxylic acid present is *citric acid,* the substance responsible for the tart taste of citrus fruits. Citric acid is achiral. What is its structure?

(b) What must be the constitution of isocitric acid? (Assume that no rearrangements accompany hydration.) How many stereoisomers are possible for isocitric acid?

19.32 The ^{1}H NMR spectra of formic acid (HCO_2H), maleic acid (*cis*-$HO_2CCH{=}CHCO_2H$), and malonic acid ($HO_2CCH_2CO_2H$) are similar in that each is characterized by two singlets of equal intensity. Match these compounds with the designations A, B, and C on the basis of the appropriate ^{1}H NMR chemical shift data.

Compound A: signals at δ 3.2 and 12.1 ppm

Compound B: signals at δ 6.3 and 12.4 ppm

Compound C: signals at δ 8.0 and 11.4 ppm

19.33 Compounds A and B are isomers having the molecular formula $C_4H_8O_3$. Identify A and B on the basis of their ^{1}H NMR spectra.

Compound A: δ 1.3 ppm (3H, triplet); 3.6 ppm (2H, quartet); 4.1 ppm (2H, singlet); 11.1 ppm (1H, broad singlet)

Compound B: δ 2.6 ppm (2H, triplet); 3.4 ppm (3H, singlet); 3.7 ppm (2H triplet); 11.3 ppm (1H, broad singlet)

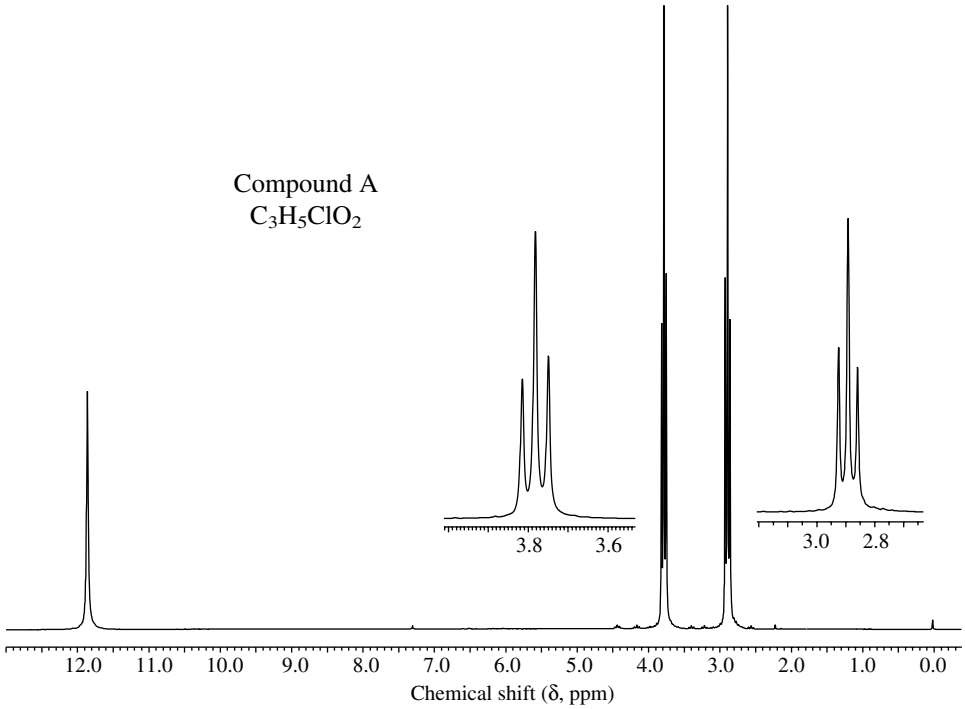


FIGURE 19.10 The 200-MHz ^{1}H NMR spectrum of compound A ($C_3H_5ClO_2$) (Problem 19.34a).

19.34 Compounds A and B are carboxylic acids. Identify each one on the basis of its ^{1}H NMR spectrum.

(a) Compound A ($C_3H_5ClO_2$) (Figure 19.10).

(b) Compound B ($C_9H_9NO_4$) has a nitro group attached to an aromatic ring (Figure 19.11).

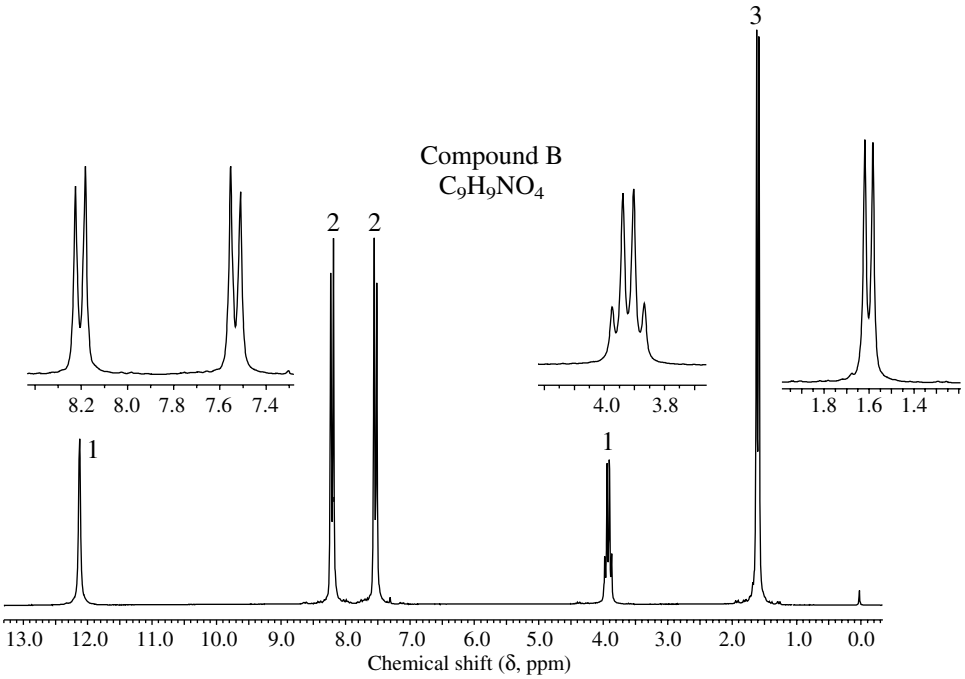
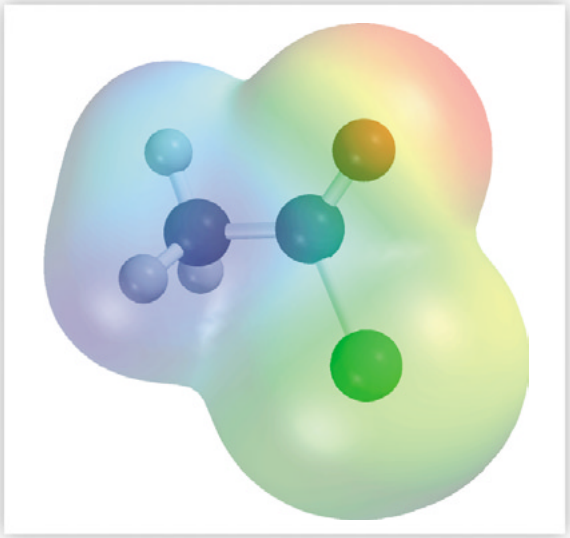


FIGURE 19.11 The 200-MHz ^{1}H NMR spectrum of compound B ($C_9H_9NO_4$) (Problem 19.34b).



CHAPTER 20

CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION

This chapter differs from preceding ones in that it deals with several related classes of compounds rather than just one. Included are

1. Acyl chlorides, $RC(=O)Cl$
2. Carboxylic acid anhydrides, $RC(=O)OC(=O)R$
3. Esters of carboxylic acids, $RC(=O)OR'$
4. Carboxamides, $RC(=O)NH_2$, $RC(=O)NHR'$, and $RC(=O)NR'_2$

These classes of compounds are classified as **carboxylic acid derivatives.** All may be converted to carboxylic acids by hydrolysis.

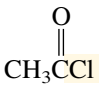
$$\underset{\text{Carboxylic acid derivative}}{RC(=O)X} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\text{Carboxylic acid}}{RC(=O)OH} + \underset{\text{Conjugate acid of leaving group}}{HX}$$

The hydrolysis of a carboxylic acid derivative is but one example of a **nucleophilic acyl substitution.** Nucleophilic acyl substitutions connect the various classes of carboxylic acid derivatives, with a reaction of one class often serving as preparation of another. These reactions provide the basis for a large number of functional group transformations both in synthetic organic chemistry and in biological chemistry.

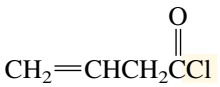
Also included in this chapter is a discussion of the chemistry of *nitriles,* compounds of the type RC≡N. Nitriles may be hydrolyzed to carboxylic acids or to amides and, so, are indirectly related to the other functional groups presented here.

20.1 NOMENCLATURE OF CARBOXYLIC ACID DERIVATIVES

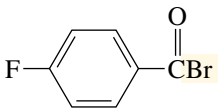
With the exception of nitriles (RC≡N), all carboxylic acid derivatives consist of an acyl group ($RC(=O)-$) attached to an electronegative atom. *Acyl groups* are named by replacing the *-ic acid* ending of the corresponding carboxylic acid by *-yl. Acyl halides* are named by placing the name of the appropriate halide after that of the acyl group.



Acetyl chloride



3-Butenoyl chloride

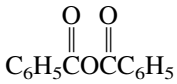


p-Fluorobenzoyl bromide

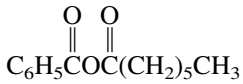
Although acyl fluorides, bromides, and iodides are all known classes of organic compounds, they are encountered far less frequently than are acyl chlorides. Acyl chlorides will be the only acyl halides discussed in this chapter.

In naming *carboxylic acid anhydrides* in which both acyl groups are the same, we simply specify the acyl group and add the word "anhydride." When the acyl groups are different, they are cited in alphabetical order.

Acetic anhydride

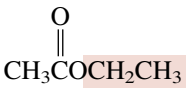


Benzoic anhydride

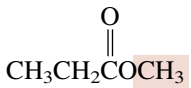


Benzoic heptanoic anhydride

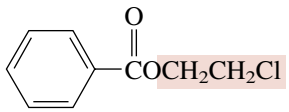
The alkyl group and the acyl group of an *ester* are specified independently. Esters are named as *alkyl alkanoates.* The alkyl group R′ of $RCOR'$ is cited first, followed by the acyl portion $RC(=O)-$. The acyl portion is named by substituting the suffix *-ate* for the *-ic* ending of the corresponding acid.



Ethyl acetate



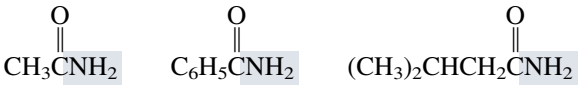
Methyl propanoate



2-Chloroethyl benzoate

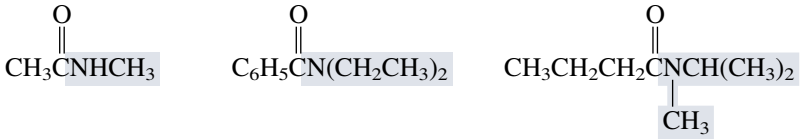
Aryl esters, that is, compounds of the type $RCOAr$, are named in an analogous way.

The names of *amides* of the type $RCNH_2$ are derived from carboxylic acids by replacing the suffix *-oic acid* or *-ic acid* by *-amide*.



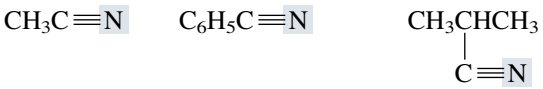
Acetamide | Benzamide | 3-Methylbutanamide

We name compounds of the type $RCNHR'$ and $RCNR'_2$ as *N*-alkyl- and *N,N*-dialkyl-substituted derivatives of a parent amide.



N-Methylacetamide | *N,N*-Diethylbenzamide | *N*-Isopropyl-*N*-methylbutanamide

Substitutive IUPAC names for *nitriles* add the suffix *-nitrile* to the name of the parent hydrocarbon chain that includes the carbon of the cyano group. Nitriles may also be named by replacing the *-ic acid* or *-oic acid* ending of the corresponding carboxylic acid with *-onitrile*. Alternatively, they are sometimes given functional class IUPAC names as alkyl cyanides.

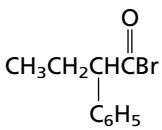


Ethanenitrile (acetonitrile) | Benzonitrile | 2-Methylpropanenitrile (isopropyl cyanide)

PROBLEM 20.1 Write a structural formula for each of the following compounds:

(a) 2-Phenylbutanoyl bromide
(b) 2-Phenylbutanoic anhydride
(c) Butyl 2-phenylbutanoate
(d) 2-Phenylbutyl butanoate
(e) 2-Phenylbutanamide
(f) *N*-Ethyl-2-phenylbutanamide
(g) 2-Phenylbutanenitrile

SAMPLE SOLUTION (a) A 2-phenylbutanoyl group is a four-carbon acyl unit that bears a phenyl substituent at C-2. When the name of an acyl group is followed by the name of a halide, it designates an *acyl halide.*



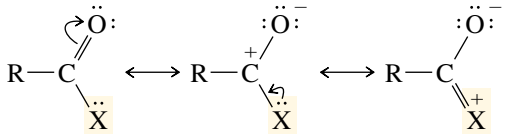
2-Phenylbutanoyl bromide

20.2 STRUCTURE OF CARBOXYLIC ACID DERIVATIVES

Figure 20.1 shows the structures and electrostatic potentials of the various derivatives of acetic acid–acetyl chloride, acetic anhydride, ethyl acetate, acetamide, and acetonitrile. Like the other carbonyl-containing compounds that we've studied, acyl chlorides, anhydrides, esters, and amides all have a planar arrangement of bonds to the carbonyl group.

An important structural feature of acyl chlorides, anhydrides, esters, and amides is that the atom attached to the acyl group bears an unshared pair of electrons that can interact with the carbonyl π system, as shown in Figure 20.2.

This electron delocalization can be represented in resonance terms by contributions from the following resonance structures:



Electron release from the substituent stabilizes the carbonyl group and decreases its electrophilic character. The extent of this electron delocalization depends on the electron-

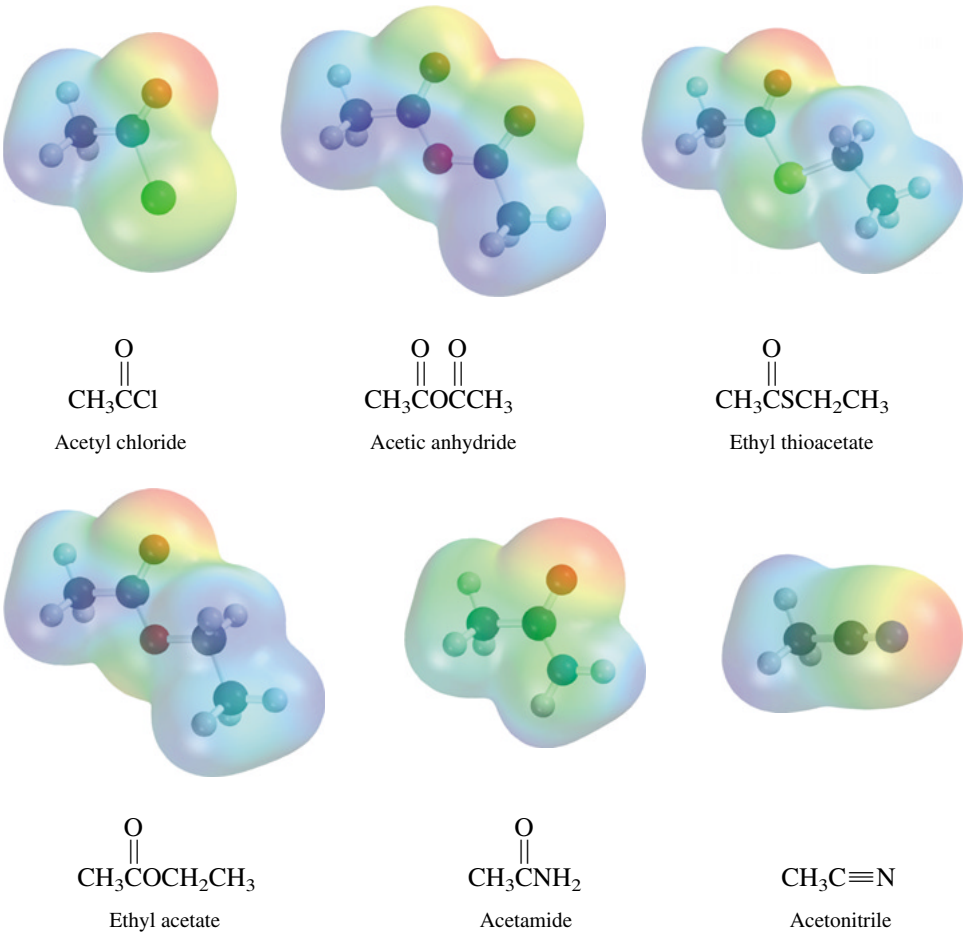
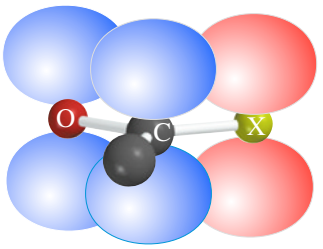


FIGURE 20.1 The structures and electrostatic potential maps of various derivatives of acetic acid. These models may be viewed on *Learning By Modeling.*

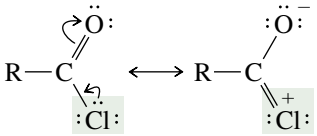


X = OH; carboxylic acid
X = Cl; acyl chloride
X = OCR; acid anhydride
X = OR; ester
X = NR_2; amide

FIGURE 20.2 The three σ bonds originating at the carbonyl carbon are coplanar. The *p* orbital of the carbonyl carbon, its oxygen, and the atom by which group X is attached to the acyl group overlap to form an extended π system through which the π electrons are delocalized.

donating properties of the substituent X. Generally, the less electronegative X is, the better it donates electrons to the carbonyl group and the greater its stabilizing effect.

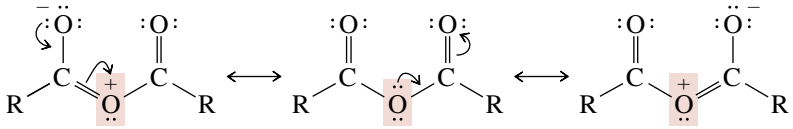
Resonance stabilization in acyl chlorides is not nearly as pronounced as in other derivatives of carboxylic acids:



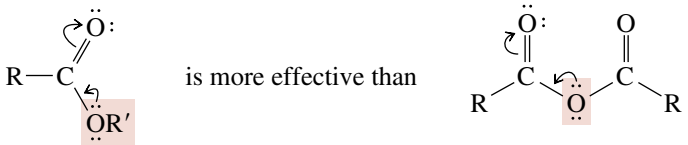
Weak resonance stabilization

Because the carbon–chlorine bond is so long—typically on the order of 180 pm for acyl chlorides—overlap between the 3*p* orbitals of chlorine and the π orbital of the carbonyl group is poor. Consequently, there is little delocalization of the electron pairs of chlorine into the π system. The carbonyl group of an acyl chloride feels the normal electron-withdrawing inductive effect of a chlorine substituent without a significant compensating electron-releasing effect due to lone-pair donation by chlorine. This makes the carbonyl carbon of an acyl chloride more susceptible to attack by nucleophiles than that of other carboxylic acid derivatives.

Acid anhydrides are better stabilized by electron delocalization than are acyl chlorides. The lone-pair electrons of oxygen are delocalized more effectively into the carbonyl group. Resonance involves both carbonyl groups of an acid anhydride.

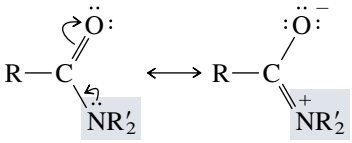


The carbonyl group of an ester is stabilized more than is that of an anhydride. Since both acyl groups of an anhydride compete for the oxygen lone pair, each carbonyl is stabilized less than the single carbonyl group of an ester.



Ester Acid anhydride

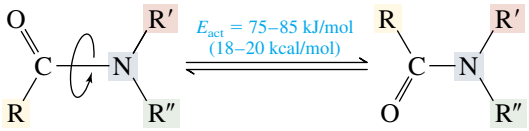
Esters are stabilized by resonance to about the same extent as carboxylic acids but not as much as amides. Nitrogen is less electronegative than oxygen and is a better electron-pair donor.



Very effective
resonance stabilization

Amide resonance is a powerful stabilizing force and gives rise to a number of structural effects. Unlike the pyramidal arrangement of bonds in ammonia and amines, the bonds to nitrogen in amides lie in the same plane. The carbon–nitrogen bond has considerable double-bond character and, at 135 pm, is substantially shorter than the normal 147-pm carbon–nitrogen single-bond distance observed in amines.

The barrier to rotation about the carbon–nitrogen bond in amides is 75 to 85 kJ/mol (18–20 kcal/mol).



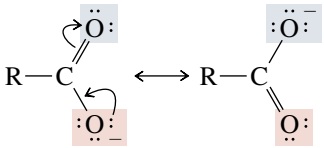
Recall that the rotational barrier in ethane is only 12 kJ/mol (3 kcal/mol).

This is an unusually high rotational energy barrier for a single bond and indicates that the carbon–nitrogen bond has significant double-bond character, as the resonance picture suggests.

PROBLEM 20.2 The ^{1}H NMR spectrum of *N,N*-dimethylformamide shows a separate signal for each of the two methyl groups. Can you explain why?

Electron release from nitrogen stabilizes the carbonyl group of amides and decreases the rate at which nucleophiles attack the carbonyl carbon. Nucleophilic reagents attack electrophilic sites in a molecule; if electrons are donated to an electrophilic site in a molecule by a substituent, then the tendency of that molecule to react with external nucleophiles is moderated.

An extreme example of carbonyl group stabilization is seen in carboxylate anions:



The negatively charged oxygen substituent is a powerful electron donor to the carbonyl group. Resonance in carboxylate anions is more effective than resonance in carboxylic acids, acyl chlorides, anhydrides, esters, and amides.

Table 20.1 summarizes the stabilizing effects of substituents on carbonyl groups to which they are attached. In addition to a qualitative ranking, quantitative estimates of the relative rates of hydrolysis of the various classes of acyl derivatives are given. A weakly stabilized carboxylic acid derivative reacts with water faster than does a more stabilized one.

Most methods for their preparation convert one class of carboxylic acid derivative to another, and the order of carbonyl group stabilization given in Table 20.1 bears directly on the means by which these transformations may be achieved. A reaction that converts one carboxylic acid derivative to another that lies below it in the table is practical; a reaction that converts it to one that lies above it in the table is not. This is another way of saying that *one carboxylic acid derivative can be converted to another if the reaction*

TABLE 20.1 Relative Stability and Reactivity of Carboxylic Acid Derivatives

Carboxylic acid derivative		Stabilization	Relative rate of hydrolysis*
Acyl chloride	$RCCl$ (O)	Very small	10^{11}
Anhydride	$RCOCR$ (O, O)	Small	10^{7}
Ester	$RCOR'$ (O)	Moderate	1.0
Amide	$RCNR'_2$ (O)	Large	$< 10^{-2}$
Carboxylate anion	RCO^- (O)	Very large	

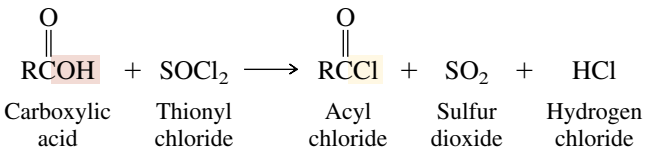
*Rates are approximate and are relative to ester as standard substrate at pH 7.

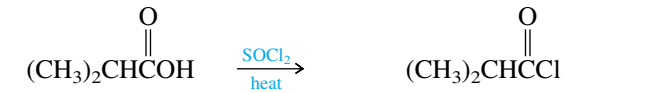
leads to a more stabilized carbonyl group. Numerous examples of reactions of this type will be presented in the sections that follow. We begin with reactions of acyl chlorides.

20.3 NUCLEOPHILIC SUBSTITUTION IN ACYL CHLORIDES

One of the most useful reactions of acyl chlorides was presented in Section 12.7. Friedel–Crafts acylation of aromatic rings takes place when arenes are treated with acyl chlorides in the presence of aluminum chloride.

Acyl chlorides are readily prepared from carboxylic acids by reaction with thionyl chloride (Section 12.7).



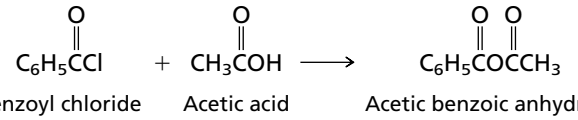


On treatment with the appropriate nucleophile, an acyl chloride may be converted to an acid anhydride, an ester, an amide, or a carboxylic acid. Examples are presented in Table 20.2.

PROBLEM 20.3 Apply the knowledge gained by studying Table 20.2 to help you predict the major organic product obtained by reaction of benzoyl chloride with each of the following:

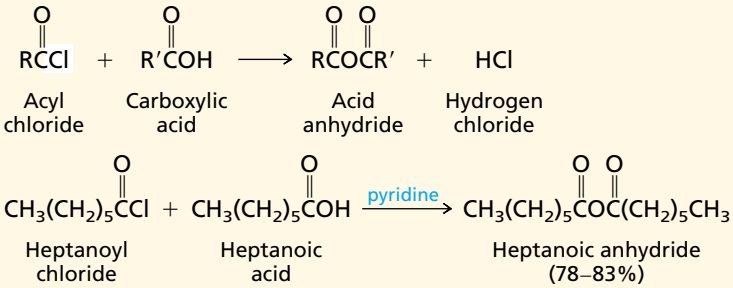
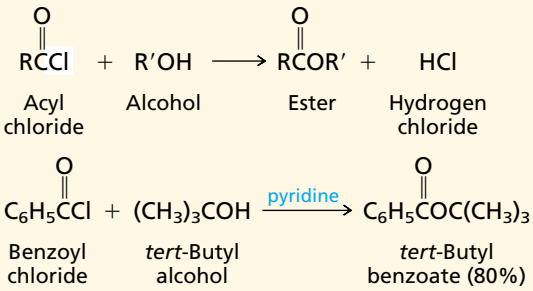
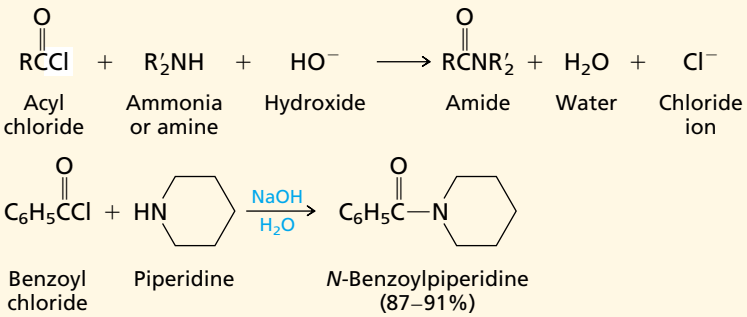
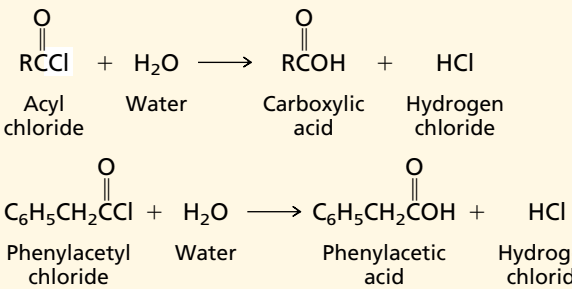
(a) Acetic acid
(b) Benzoic acid
(c) Ethanol
(d) Methylamine, CH_3NH_2
(e) Dimethylamine, $(CH_3)_2NH$
(f) Water

SAMPLE SOLUTION (a) As noted in Table 20.2, the reaction of an acyl chloride with a carboxylic acid yields an acid anhydride.

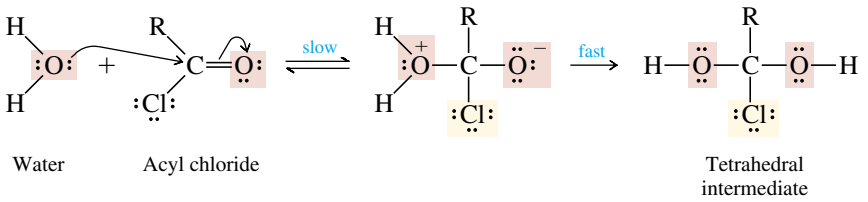


The product is a mixed anhydride. Acetic acid acts as a nucleophile and substitutes for chloride on the benzoyl group.

TABLE 20.2 Conversion of Acyl Chlorides to Other Carboxylic Acid Derivatives

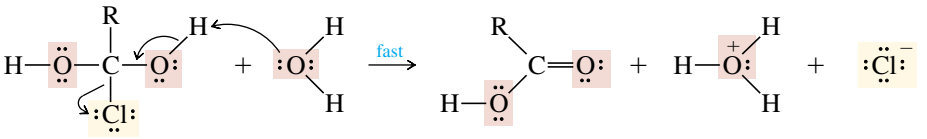
Reaction (section) and comments	General equation and specific example
Reaction with carboxylic acids (Section 20.4) Acyl chlorides react with carboxylic acids to yield acid anhydrides. When this reaction is used for preparative purposes, a weak organic base such as pyridine is normally added. Pyridine is a catalyst for the reaction and also acts as a base to neutralize the hydrogen chloride that is formed.	
Reaction with alcohols (Section 15.8) Acyl chlorides react with alcohols to form esters. The reaction is typically carried out in the presence of pyridine.	
Reaction with ammonia and amines (Section 20.13) Acyl chlorides react with ammonia and amines to form amides. A base such as sodium hydroxide is normally added to react with the hydrogen chloride produced.	
Hydrolysis (Section 20.3) Acyl chlorides react with water to yield carboxylic acids. In base, the acid is converted to its carboxylate salt. The reaction has little preparative value because the acyl chloride is nearly always prepared from the carboxylic acid rather than vice versa.	

First stage: Formation of the tetrahedral intermediate by nucleophilic addition of water to the carbonyl group



Water Acyl chloride Tetrahedral intermediate

Second stage: Dissociation of the tetrahedral intermediate by dehydrohalogenation



Tetrahedral intermediate Water Carboxylic acid Hydronium ion Chloride ion

FIGURE 20.3 Hydrolysis of acyl chloride proceeds by way of a tetrahedral intermediate. Formation of the tetrahedral intermediate is rate-determining.

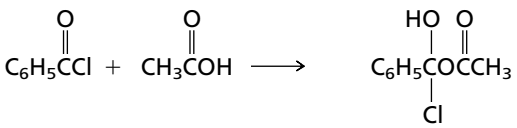
The mechanisms of all the reactions cited in Table 20.2 are similar to the mechanism of hydrolysis of an acyl chloride outlined in Figure 20.3. They differ with respect to the nucleophile that attacks the carbonyl group.

In the first stage of the mechanism, water undergoes nucleophilic addition to the carbonyl group to form a tetrahedral intermediate. This stage of the process is analogous to the hydration of aldehydes and ketones discussed in Section 17.6.

The tetrahedral intermediate has three potential leaving groups on carbon: two hydroxyl groups and a chlorine. In the second stage of the reaction, the tetrahedral intermediate dissociates. Loss of chloride from the tetrahedral intermediate is faster than loss of hydroxide; chloride is less basic than hydroxide and is a better leaving group. The tetrahedral intermediate dissociates because this dissociation restores the resonance-stabilized carbonyl group.

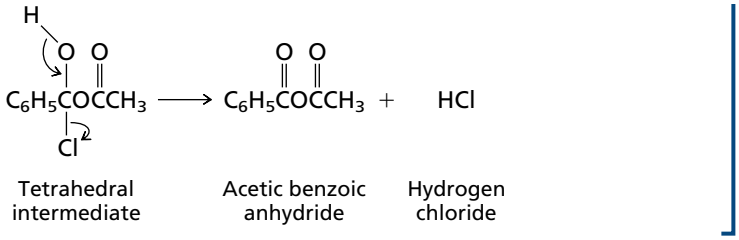
PROBLEM 20.4 Write the structure of the tetrahedral intermediate formed in each of the reactions given in Problem 20.3. Using curved arrows, show how each tetrahedral intermediate dissociates to the appropriate products.

SAMPLE SOLUTION (a) The tetrahedral intermediate arises by nucleophilic addition of acetic acid to benzoyl chloride.

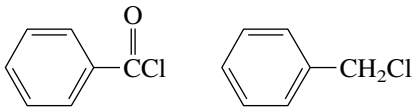


Benzoyl chloride Acetic acid Tetrahedral intermediate

Loss of a proton and of chloride ion from the tetrahedral intermediate yields the mixed anhydride.



Nucleophilic substitution in acyl chlorides is much faster than in alkyl chlorides.

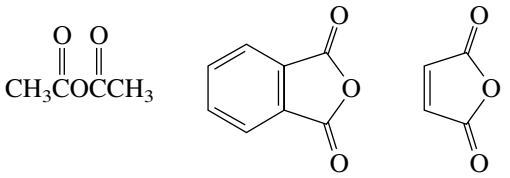


	Benzoyl chloride	Benzyl chloride
Relative rate of hydrolysis (80% ethanol–20% water; 25°C)	1,000	1

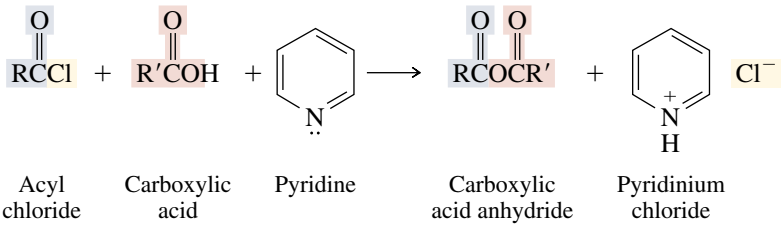
The sp^2-hybridized carbon of an acyl chloride is less sterically hindered than the sp^3-hybridized carbon of an alkyl chloride, making an acyl chloride more open toward nucleophilic attack. Also, unlike the S_N2 transition state or a carbocation intermediate in an S_N1 reaction, the tetrahedral intermediate in nucleophilic acyl substitution has a stable arrangement of bonds and can be formed via a lower energy transition state.

20.4 PREPARATION OF CARBOXYLIC ACID ANHYDRIDES

After acyl halides, acid anhydrides are the most reactive carboxylic acid derivatives. Three of them, acetic anhydride, phthalic anhydride, and maleic anhydride, are industrial chemicals and are encountered far more often than others. Phthalic anhydride and maleic anhydride have their anhydride function incorporated into a ring and are referred to as *cyclic anhydrides.*

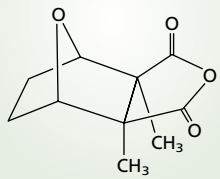


The customary method for the laboratory synthesis of acid anhydrides is the reaction of acyl chlorides with carboxylic acids (Table 20.2).



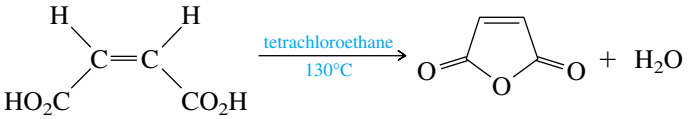
This procedure is applicable to the preparation of both symmetrical anhydrides (R and R′ the same) and mixed anhydrides (R and R′ different).

Acid anhydrides rarely occur naturally. One example is the putative aphrodisiac *cantharidin,* obtained from a species of beetle.



PROBLEM 20.5 Benzoic anhydride has been prepared in excellent yield by adding one molar equivalent of water to two molar equivalents of benzoyl chloride. How do you suppose this reaction takes place?

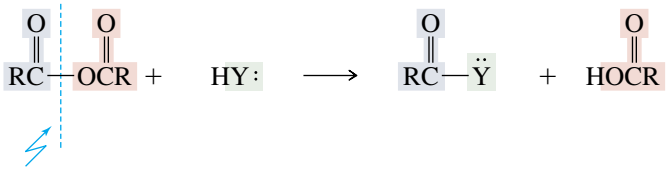
Cyclic anhydrides in which the ring is five- or six-membered are sometimes prepared by heating the corresponding dicarboxylic acids in an inert solvent:



Maleic acid — Maleic anhydride (89%) — Water

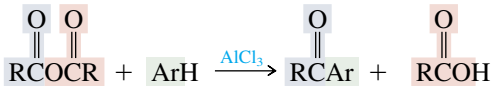
20.5 REACTIONS OF CARBOXYLIC ACID ANHYDRIDES

Nucleophilic acyl substitution in acid anhydrides involves cleavage of a bond between oxygen and one of the carbonyl groups. One acyl group is transferred to an attacking nucleophile; the other retains its single bond to oxygen and becomes the acyl group of a carboxylic acid.

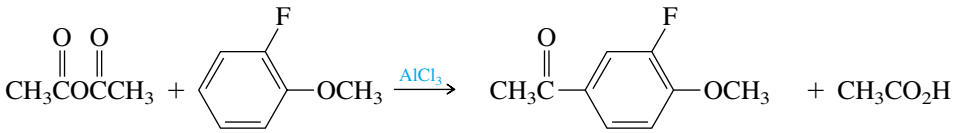


Bond cleavage occurs here in an acid anhydride. — Nucleophile — Product of nucleophilic acyl substitution — Carboxylic acid

One reaction of this type, Friedel–Crafts acylation (Section 12.7), is already familiar to us.



Acid anhydride — Arene — Ketone — Carboxylic acid



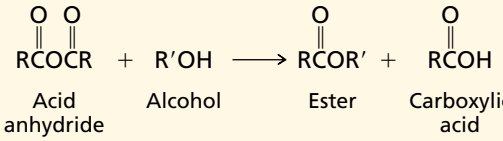
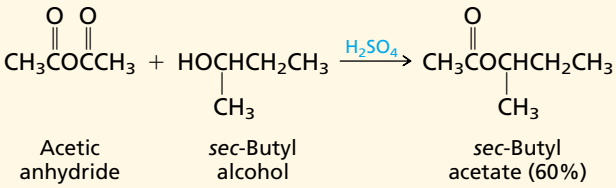
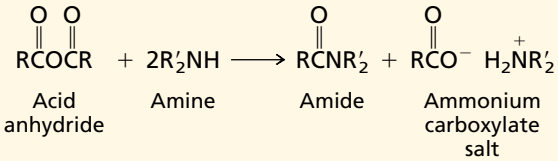
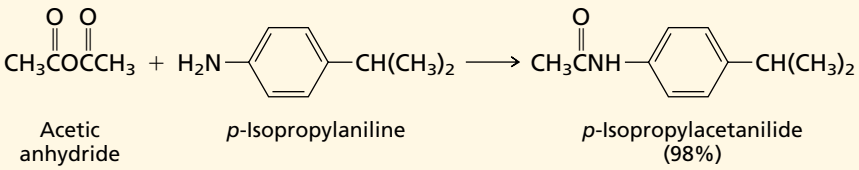
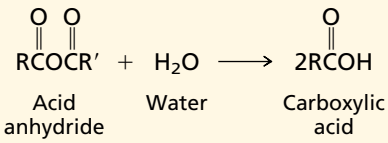
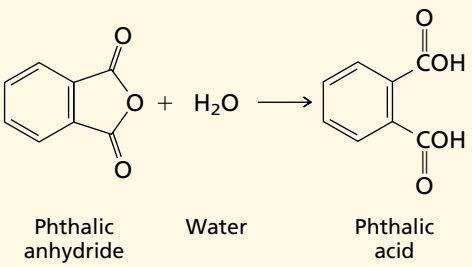
Acetic anhydride — *o*-Fluoroanisole — 3-Fluoro-4-methoxyacetophenone (70–80%) — Acetic acid

An acyl cation is an intermediate in Friedel–Crafts acylation reactions.

PROBLEM 20.6 Write a structural formula for the acyl cation intermediate in the preceding reaction.

Conversions of acid anhydrides to other carboxylic acid derivatives are illustrated in Table 20.3. Since a more highly stabilized carbonyl group must result in order for nucleophilic acyl substitution to be effective, acid anhydrides are readily converted to carboxylic acids, esters, and amides but not to acyl chlorides.

TABLE 20.3 Conversion of Acid Anhydrides to Other Carboxylic Acid Derivatives

Reaction (section) and comments	General equation and specific example
Reaction with alcohols (Section 15.8) Acid anhydrides react with alcohols to form esters. The reaction may be carried out in the presence of pyridine or it may be catalyzed by acids. In the example shown, only one acetyl group of acetic anhydride becomes incorporated into the ester; the other becomes the acetyl group of an acetic acid molecule.	 
Reaction with ammonia and amines (Section 20.13) Acid anhydrides react with ammonia and amines to form amides. Two molar equivalents of amine are required. In the example shown, only one acetyl group of acetic anhydride becomes incorporated into the amide; the other becomes the acetyl group of the amine salt of acetic acid.	 
Hydrolysis (Section 20.5) Acid anhydrides react with water to yield two carboxylic acid functions. Cyclic anhydrides yield dicarboxylic acids.	 

PROBLEM 20.7 Apply the knowledge gained by studying Table 20.3 to help you predict the major organic product of each of the following reactions:

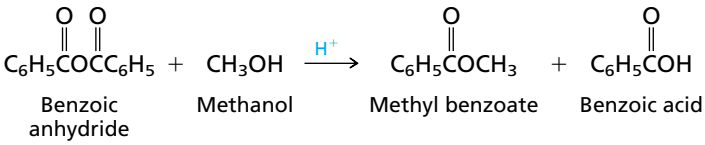
(a) Benzoic anhydride + methanol $\xrightarrow{H^+}$

(b) Acetic anhydride + ammonia (2 mol) ⟶

(c) Phthalic anhydride + $(CH_3)_2NH$ (2 mol) ⟶

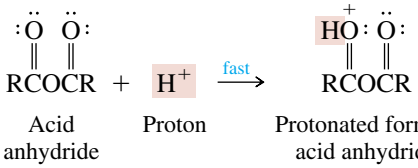
(d) Phthalic anhydride + sodium hydroxide (2 mol) ⟶

SAMPLE SOLUTION (a) Nucleophilic acyl substitution by an alcohol on an acid anhydride yields an ester.

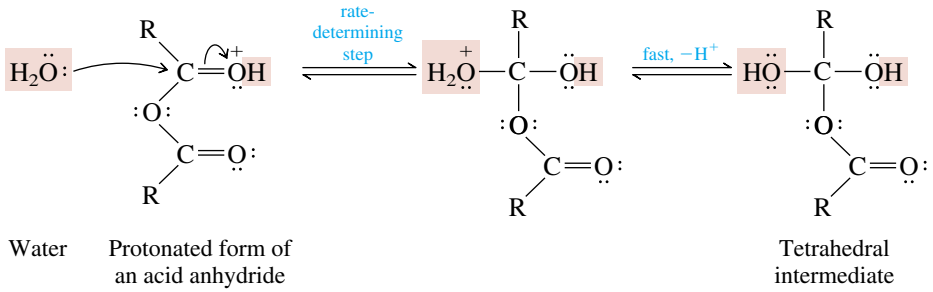


The first example in Table 20.3 introduces a new aspect of nucleophilic acyl substitution that applies not only to acid anhydrides but also to acyl chlorides, esters, and amides. Nucleophilic acyl substitutions can be catalyzed by acids.

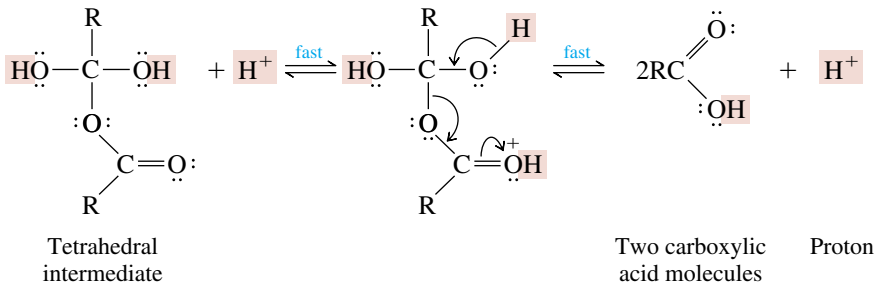
We can see how an acid catalyst increases the rate of nucleophilic acyl substitution by considering the hydrolysis of an acid anhydride. Formation of the tetrahedral intermediate is rate-determining and is the step that is accelerated by the catalyst. The acid anhydride is activated toward nucleophilic addition by protonation of one of its carbonyl groups:



The protonated form of the acid anhydride is present to only a very small extent, but it is quite electrophilic. Water (and other nucleophiles) add to a protonated carbonyl group much faster than they do to a neutral one. Thus, the rate-determining nucleophilic addition of water to form a tetrahedral intermediate takes place more rapidly in the presence of an acid than in its absence.



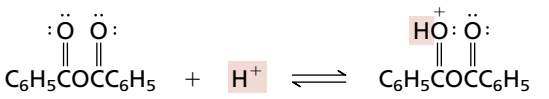
Acids also catalyze the dissociation of the tetrahedral intermediate. Protonation of its carbonyl oxygen permits the leaving group to depart as a neutral carboxylic acid molecule, which is a less basic leaving group than a carboxylate anion.



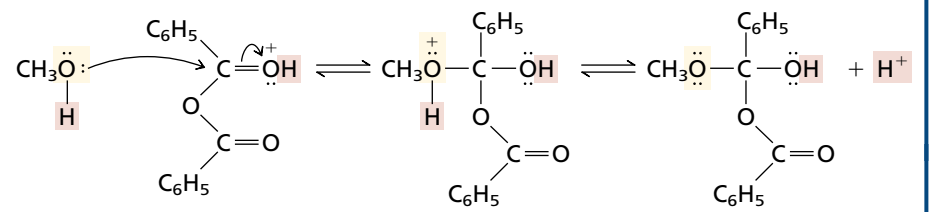
This pattern of increased reactivity resulting from carbonyl group protonation has been seen before in nucleophilic additions to aldehydes and ketones (Section 17.6) and in the mechanism of the acid-catalyzed esterification of carboxylic acids (Section 19.14). Many biological reactions involve nucleophilic acyl substitution and are catalyzed by enzymes that act by donating a proton to the carbonyl oxygen, the leaving group, or both.

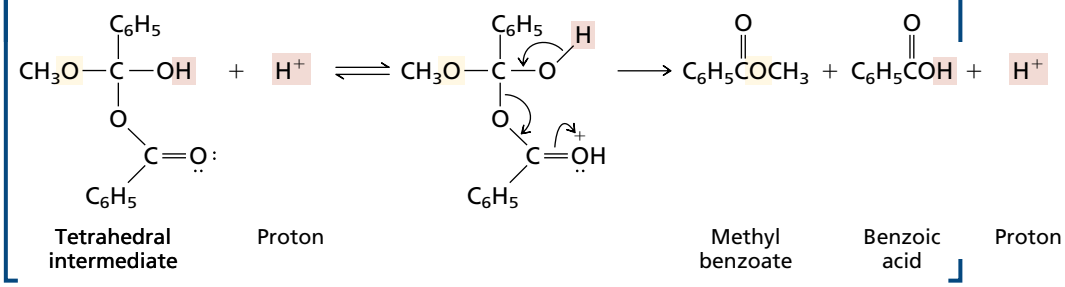
PROBLEM 20.8 Write the structure of the tetrahedral intermediate formed in each of the reactions given in Problem 20.7. Using curved arrows, show how each tetrahedral intermediate dissociates to the appropriate products.

SAMPLE SOLUTION (a) The reaction given is the acid-catalyzed esterification of methanol by benzoic anhydride. The first step is the activation of the anhydride toward nucleophilic addition by protonation.



The tetrahedral intermediate is formed by nucleophilic addition of methanol to the protonated carbonyl group.

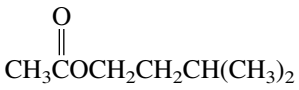




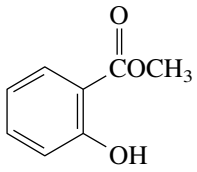
Acid anhydrides are more stable and less reactive than acyl chlorides. Acetyl chloride, for example, undergoes hydrolysis about 100,000 times more rapidly than acetic anhydride at 25°C.

20.6 SOURCES OF ESTERS

Many esters occur naturally. Those of low molecular weight are fairly volatile, and many have pleasing odors. Esters often form a significant fraction of the fragrant oil of fruits and flowers. The aroma of oranges, for example, contains 30 different esters along with 10 carboxylic acids, 34 alcohols, 34 aldehydes and ketones, and 36 hydrocarbons.



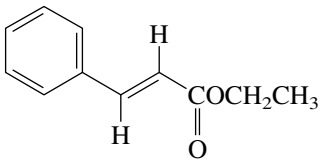
3-Methylbutyl acetate
(contributes to characteristic odor of bananas)



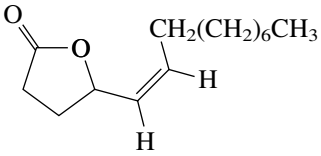
Methyl salicylate
(principal component of oil of wintergreen)

3-Methylbutyl acetate is more commonly known as isoamyl acetate.

Among the chemicals used by insects to communicate with one another, esters occur frequently.



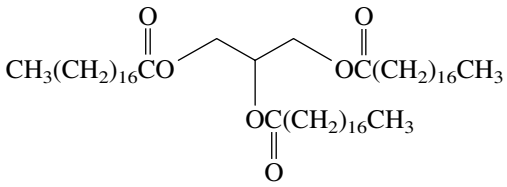
Ethyl cinnamate
(one of the constituents of the sex pheromone of the male oriental fruit moth)



(*Z*)-5-Tetradecen-4-olide
(sex pheromone of female Japanese beetle)

Notice that (*Z*)-5-tetradecen-4-olide is a cyclic ester. Recall from Section 19.15 that cyclic esters are called *lactones* and that the suffix *-olide* is characteristic of IUPAC names for lactones.

Esters of glycerol, called *glycerol triesters, triacylglycerols,* or *triglycerides,* are abundant natural products. The most important group of glycerol triesters includes those in which each acyl group is unbranched and has 14 or more carbon atoms.



Tristearin, a trioctadecanoyl ester of glycerol found in many animal and vegetable fats

A molecular model of tristearin is shown in Figure 26.2.

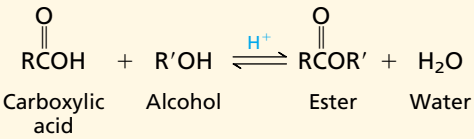
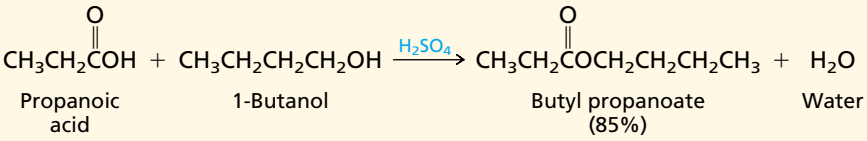
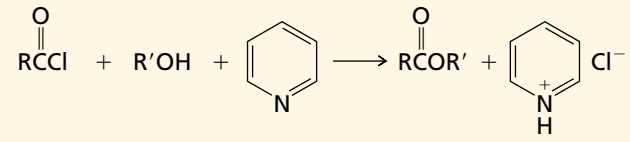
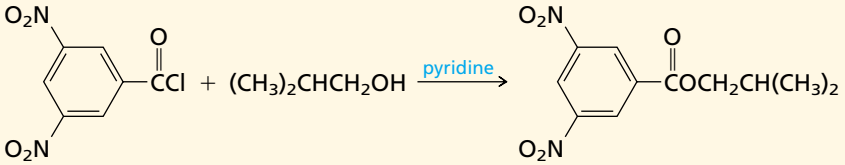
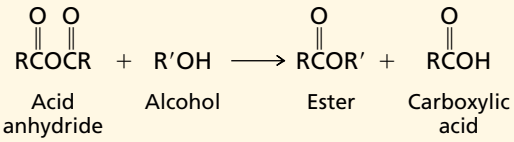
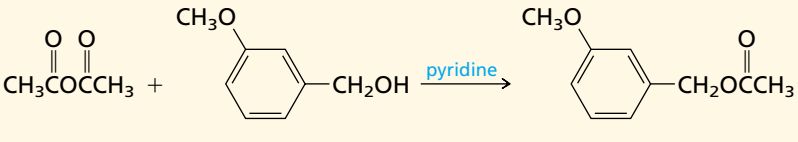
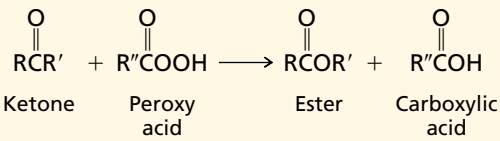
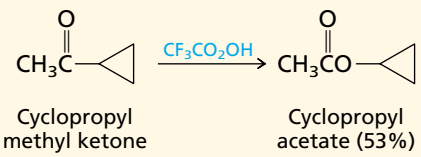
Fats and **oils** are naturally occurring mixtures of glycerol triesters. Fats are mixtures that are solids at room temperature; oils are liquids. The long-chain carboxylic acids obtained from fats and oils by hydrolysis are known as **fatty acids.**

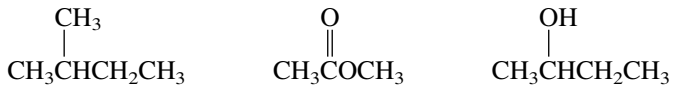
The chief methods used to prepare esters in the laboratory have all been described earlier, and are summarized in Table 20.4.

20.7 PHYSICAL PROPERTIES OF ESTERS

Esters are moderately polar, with dipole moments in the 1.5 to 2.0-D range. Dipole–dipole attractive forces give esters higher boiling points than hydrocarbons of similar shape and molecular weight. Because they lack hydroxyl groups, however, ester molecules cannot form hydrogen bonds to each other; consequently, esters have lower boiling points than alcohols of comparable molecular weight.

TABLE 20.4 Preparation of Esters

Reaction (section) and comments	General equation and specific example
From carboxylic acids (Sections 15.8 and 19.14) In the presence of an acid catalyst, alcohols and carboxylic acids react to form an ester and water. This is the Fischer esterification.	 
From acyl chlorides (Sections 15.8 and 20.3) Alcohols react with acyl chlorides by nucleophilic acyl substitution to yield esters. These reactions are typically performed in the presence of a weak base such as pyridine.	 
From carboxylic acid anhydrides (Sections 15.8 and 20.5) Acyl transfer from an acid anhydride to an alcohol is a standard method for the preparation of esters. The reaction is subject to catalysis by either acids (H_2SO_4) or bases (pyridine).	 
Baeyer–Villiger oxidation of ketones (Section 17.16) Ketones are converted to esters on treatment with peroxy acids. The reaction proceeds by migration of the group R′ from carbon to oxygen. It is the more highly substituted group that migrates. Methyl ketones give acetate esters.	 



2-Methylbutane: mol wt 72, bp 28°C | Methyl acetate: mol wt 74, bp 57°C | 2-Butanol: mol wt 74, bp 99°C

Esters can participate in hydrogen bonds with substances that contain hydroxyl groups (water, alcohols, carboxylic acids). This confers some measure of water solubility on low-molecular-weight esters; methyl acetate, for example, dissolves in water to the extent of 33 g/100 mL. Water solubility decreases as the carbon content of the ester increases. Fats and oils, the glycerol esters of long-chain carboxylic acids, are practically insoluble in water.

20.8 REACTIONS OF ESTERS: A REVIEW AND A PREVIEW

The reaction of esters with Grignard reagents and with lithium aluminum hydride, both useful in the synthesis of alcohols, were described earlier. They are reviewed in Table 20.5.

Nucleophilic acyl substitutions at the ester carbonyl group are summarized in Table 20.6. Esters are less reactive than acyl chlorides and acid anhydrides. Nucleophilic acyl substitution in esters, especially ester hydrolysis, has been extensively investigated from a mechanistic perspective. Indeed, much of what we know concerning the general topic

TABLE 20.5 Summary of Reactions of Esters Discussed in Earlier Chapters

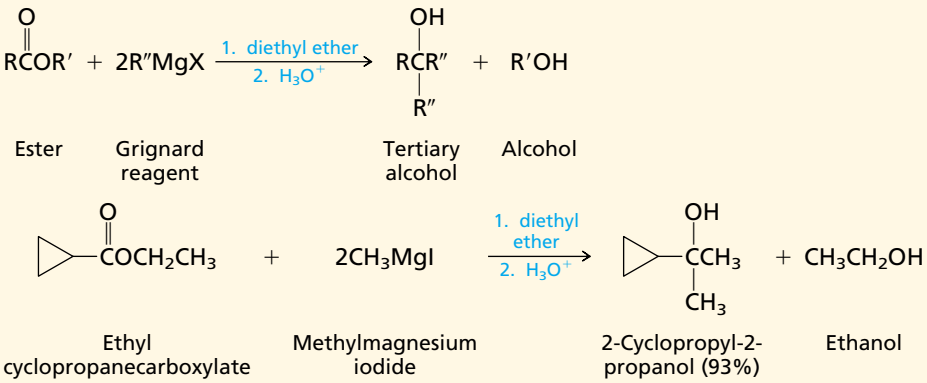
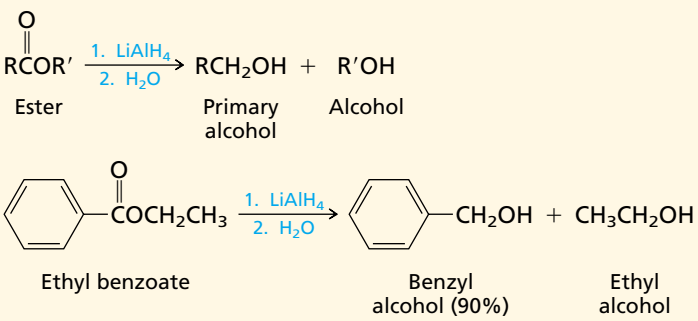
Reaction (section) and comments	General equation and specific example
Reaction with Grignard reagents (Section 14.10) Esters react with two equivalents of a Grignard reagent to produce tertiary alcohols. Two of the groups bonded to the carbon that bears the hydroxyl group in the tertiary alcohol are derived from the Grignard reagent.	 Ester; Grignard reagent; Tertiary alcohol; Alcohol. Ethyl cyclopropanecarboxylate; Methylmagnesium iodide; 2-Cyclopropyl-2-propanol (93%); Ethanol.
Reduction with lithium aluminum hydride (Section 15.3) Lithium aluminum hydride cleaves esters to yield two alcohols.	 Ester; Primary alcohol; Alcohol. Ethyl benzoate; Benzyl alcohol (90%); Ethyl alcohol.

TABLE 20.6 Conversion of Esters to Other Carboxylic Acid Derivatives

Reaction (section) and comments	General equation and specific example
Reaction with ammonia and amines (Section 20.13) Esters react with ammonia and amines to form amides. Methyl and ethyl esters are the most reactive.	$RCOR' + R''_2NH \longrightarrow RCNR''_2 + R'OH$ Ester · Amine · Amide · Alcohol $FCH_2COCH_2CH_3 + NH_3 \xrightarrow{H_2O} FCH_2CNH_2 + CH_3CH_2OH$ Ethyl fluoroacetate · Ammonia · Fluoroacetamide (90%) · Ethanol
Hydrolysis (Sections 20.9 and 20.10) Ester hydrolysis may be catalyzed either by acids or by bases. Acid-catalyzed hydrolysis is an equilibrium-controlled process, the reverse of the Fischer esterification. Hydrolysis in base is irreversible and is the method usually chosen for preparative purposes.	$RCOR' + H_2O \longrightarrow RCOH + R'OH$ Ester · Water · Carboxylic acid · Alcohol $O_2NC_6H_4COCH_3 \xrightarrow{1.\ H_2O,\ NaOH;\ 2.\ H^+} O_2NC_6H_4COH + CH_3OH$ Methyl *m*-nitrobenzoate · *m*-Nitrobenzoic acid (90–96%) · Methanol

of nucleophilic acyl substitution comes from studies carried out on esters. The following sections describe those mechanistic studies.

20.9 ACID-CATALYZED ESTER HYDROLYSIS

Ester hydrolysis is the most studied and best understood of all nucleophilic acyl substitutions. Esters are fairly stable in neutral aqueous media but are cleaved when heated with water in the presence of strong acids or bases. The hydrolysis of esters in dilute aqueous acid is the reverse of the Fischer esterification (Sections 15.8 and 19.14):

$$RCOR' + H_2O \underset{}{\overset{H^+}{\rightleftharpoons}} RCOH + R'OH$$

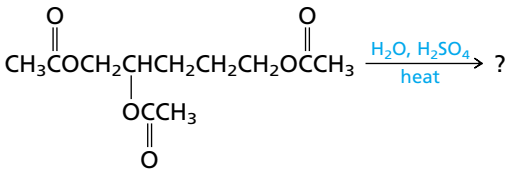
Ester · Water · Carboxylic acid · Alcohol

When esterification is the objective, water is removed from the reaction mixture to encourage ester formation. When ester hydrolysis is the objective, the reaction is carried out in the presence of a generous excess of water.

$$C_6H_5CH(Cl)COCH_2CH_3 + H_2O \xrightarrow[\text{heat}]{HCl} C_6H_5CH(Cl)COH + CH_3CH_2OH$$

Ethyl 2-chloro-2-phenylacetate · Water · 2-Chloro-2-phenylacetic acid (80–82%) · Ethyl alcohol

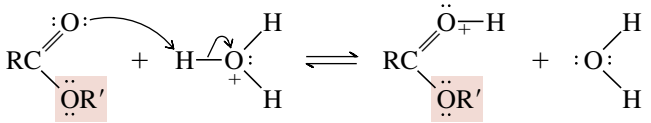
PROBLEM 20.9 The compound having the structure shown was heated with dilute sulfuric acid to give a product having the molecular formula $C_5H_{12}O_3$ in 63–71% yield. Propose a reasonable structure for this product. What other organic compound is formed in this reaction?



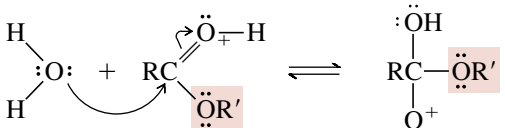
The mechanism of acid-catalyzed ester hydrolysis is presented in Figure 20.4. It is precisely the reverse of the mechanism given for acid-catalyzed ester formation in Section 19.14. Like other nucleophilic acyl substitutions, it proceeds in two stages. A tetrahedral intermediate is formed in the first stage, and this tetrahedral intermediate dissociates to products in the second stage.

A key feature of the first stage is the site at which the starting ester is protonated. Protonation of the carbonyl oxygen, as shown in step 1 of Figure 20.4, gives a cation that is stabilized by electron delocalization. The alternative site of protonation, the alkoxy oxygen, gives rise to a much less stable cation.

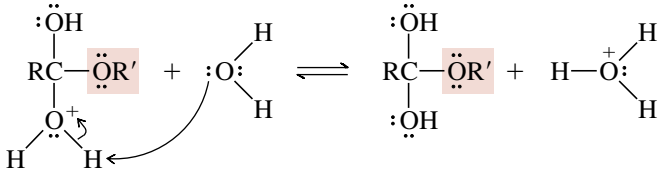
Step 1: Protonation of the carbonyl oxygen of the ester



Step 2: Nucleophilic addition of water to protonated form of ester



Step 3: Deprotonation of the oxonium ion to give the neutral form of the tetrahedral intermediate

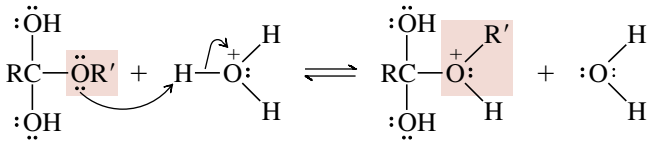


—Cont.

FIGURE 20.4 The mechanism of acid-catalyzed ester hydrolysis. Steps 1 through 3 show the formation of the tetrahedral intermediate. Dissociation of the tetrahedral intermediate is shown in steps 4 through 6.

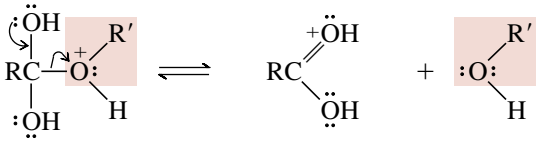
FIGURE 20.4 (*Continued*)

Step 4: Protonation of the tetrahedral intermediate at its alkoxy oxygen



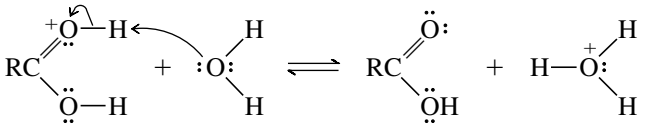
Tetrahedral intermediate | Hydronium ion | Oxonium ion | Water

Step 5: Dissociation of the protonated form of the tetrahedral intermediate to an alcohol and the protonated form of the carboxylic acid



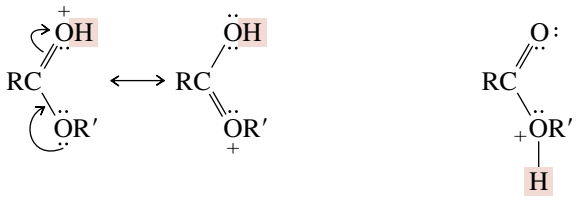
Oxonium ion | Protonated form of carboxylic acid | Alcohol

Step 6: Deprotonation of the protonated carboxylic acid



Protonated form of carboxylic acid | Water | Carboxylic acid | Hydronium ion

Protonation of carbonyl oxygen ***Protonation of alkoxy oxygen***



Positive charge is delocalized. Positive charge is localized on a single oxygen.

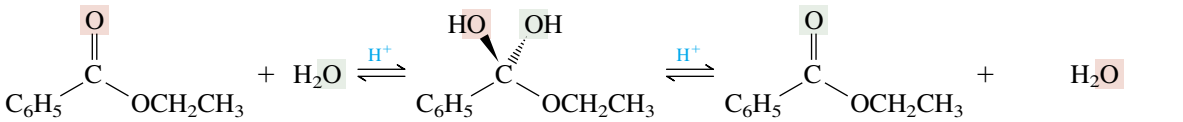
Protonation of the carbonyl oxygen, as emphasized earlier in the reactions of aldehydes and ketones, makes the carbonyl group more susceptible to nucleophilic attack. A water molecule adds to the carbonyl group of the protonated ester in step 2. Loss of a proton from the resulting oxonium ion gives the neutral form of the tetrahedral intermediate in step 3 and completes the first stage of the mechanism.

Once formed, the tetrahedral intermediate can revert to starting materials by merely reversing the reactions that formed it, or it can continue onward to products. In the second stage of ester hydrolysis, the tetrahedral intermediate dissociates to an alcohol and a carboxylic acid. In step 4 of Figure 20.4, protonation of the tetrahedral intermediate at

its alkoxy oxygen gives a new oxonium ion, which loses a molecule of alcohol in step 5. Along with the alcohol, the protonated form of the carboxylic acid arises by dissociation of the tetrahedral intermediate. Its deprotonation in step 6 completes the process.

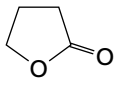
PROBLEM 20.10 On the basis of the general mechanism for acid-catalyzed ester hydrolysis shown in Figure 20.4, write an analogous sequence of steps for the specific case of ethyl benzoate hydrolysis.

The most important species in the mechanism for ester hydrolysis is the tetrahedral intermediate. Evidence in support of the existence of the tetrahedral intermediate was developed by Professor Myron Bender on the basis of isotopic labeling experiments he carried out at the University of Chicago. Bender prepared ethyl benzoate, labeled with the mass-18 isotope of oxygen at the carbonyl oxygen, then subjected it to acid-catalyzed hydrolysis in ordinary (unlabeled) water. He found that ethyl benzoate, recovered from the reaction before hydrolysis was complete, had lost a portion of its isotopic label. This observation is consistent only with the reversible formation of a tetrahedral intermediate under the reaction conditions:



The two OH groups in the tetrahedral intermediate are equivalent, and so either the labeled or the unlabeled one can be lost when the tetrahedral intermediate reverts to ethyl benzoate. Both are retained when the tetrahedral intermediate goes on to form benzoic acid.

PROBLEM 20.11 In a similar experiment, unlabeled 4-butanolide was allowed to stand in an acidic solution in which the water had been labeled with ^{18}O. When the lactone was extracted from the solution after 4 days, it was found to contain ^{18}O. Which oxygen of the lactone do you think became isotopically labeled?

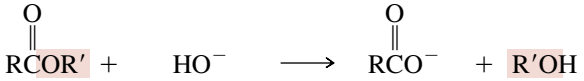


4-Butanolide

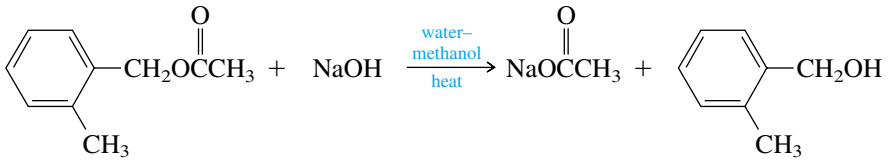
20.10 ESTER HYDROLYSIS IN BASE: SAPONIFICATION

Unlike its acid-catalyzed counterpart, ester hydrolysis in aqueous base is *irreversible.*

Since it is consumed, hydroxide ion is a reactant, not a catalyst.

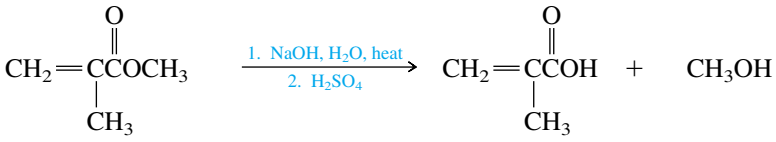


This is because carboxylic acids are converted to their corresponding carboxylate anions under these conditions, and these anions are incapable of acyl transfer to alcohols.



o-Methylbenzyl acetate | Sodium hydroxide | Sodium acetate | *o*-Methylbenzyl alcohol (95–97%)

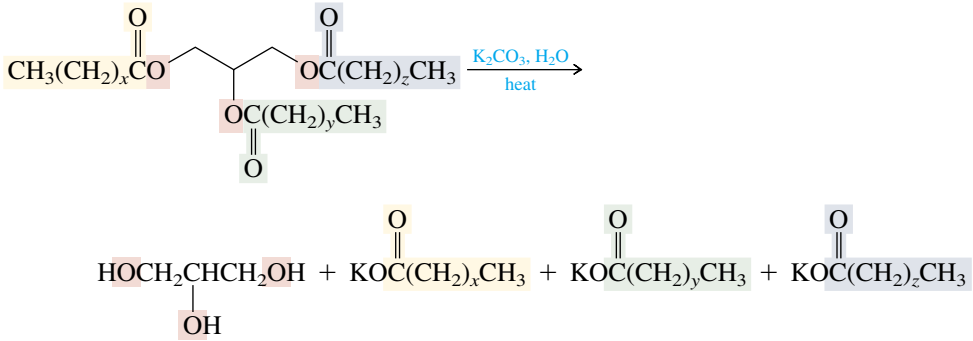
To isolate the carboxylic acid, a separate acidification step following hydrolysis is necessary. Acidification converts the carboxylate salt to the free acid.



Methyl 2-methylpropenoate (methyl methacrylate) | 2-Methylpropenoic acid (87%) (methacrylic acid) | Methyl alcohol

Ester hydrolysis in base is called **saponification,** which means "soap making." Over 2000 years ago, the Phoenicians made soap by heating animal fat with wood ashes. Animal fat is rich in glycerol triesters, and wood ashes are a source of potassium carbonate. Basic cleavage of the fats produced a mixture of long-chain carboxylic acids as their potassium salts.

Procedures for making a variety of soaps are given in the May 1998 issue of the *Journal of Chemical Education,* pp. 612–614.

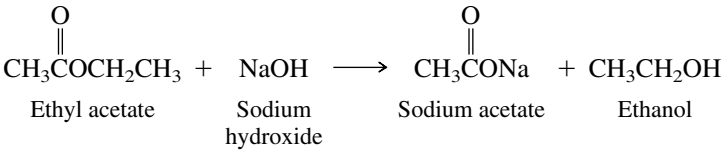


Glycerol | Potassium carboxylate salts

Potassium and sodium salts of long-chain carboxylic acids form micelles that dissolve grease (Section 19.5) and have cleansing properties. The carboxylic acids obtained by saponification of fats are called *fatty acids.*

PROBLEM 20.12 *Trimyristin* is obtained from coconut oil and has the molecular formula $C_{45}H_{86}O_6$. On being heated with aqueous sodium hydroxide followed by acidification, trimyristin was converted to glycerol and tetradecanoic acid as the only products. What is the structure of trimyristin?

In one of the earliest kinetic studies of an organic reaction, carried out in the 19th century, the rate of hydrolysis of ethyl acetate in aqueous sodium hydroxide was found to be first order in ester and first order in base.

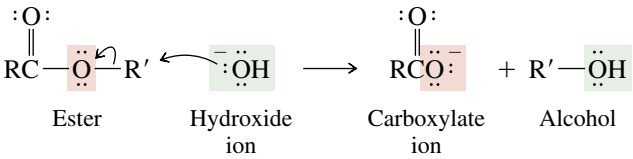


$$\text{Rate} = k[\text{CH}_3\text{COCH}_2\text{CH}_3][\text{NaOH}]$$

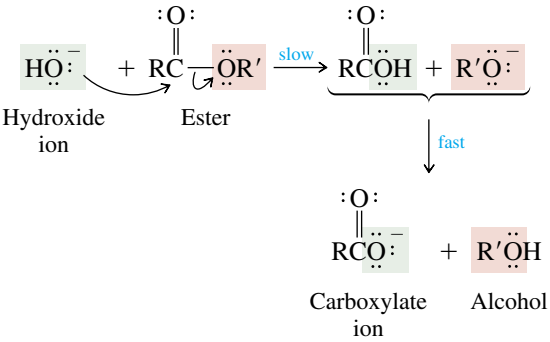
Overall, the reaction exhibits second-order kinetics. Both the ester and the base are involved in the rate-determining step or in a rapid step that precedes it.

Two processes that are consistent with second-order kinetics both involve hydroxide ion as a nucleophile but differ in the site of nucleophilic attack. One of these processes is an S_N2 reaction in which hydroxide displaces carboxylate from the alkyl group of the ester. We say that this pathway involves *alkyl–oxygen cleavage,* because it is the bond between oxygen and the alkyl group of the ester that breaks. The other process involves *acyl–oxygen cleavage,* with hydroxide attacking the carbonyl group.

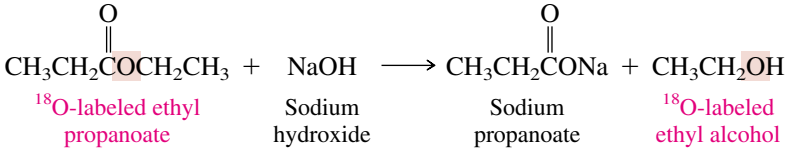
Alkyl–oxygen cleavage



Acyl–oxygen cleavage



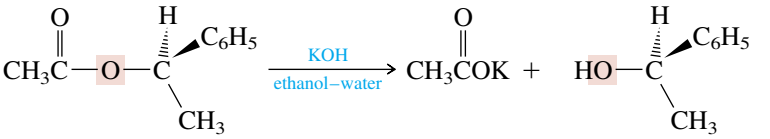
Convincing evidence that ester hydrolysis in base proceeds by the second of these two paths, namely, acyl–oxygen cleavage, has been obtained from several sources. In one experiment, ethyl propanoate labeled with ^{18}O in the ethoxy group was hydrolyzed. On isolating the products, all the ^{18}O was found in the ethyl alcohol; there was no ^{18}O enrichment in the sodium propanoate.



The carbon–oxygen bond broken in the process is therefore the one between oxygen and the acyl group. The bond between oxygen and the ethyl group remains intact.

PROBLEM 20.13 In a similar experiment, pentyl acetate was subjected to saponification with ^{18}O-labeled hydroxide in ^{18}O-labeled water. What product do you think became isotopically labeled here, acetate ion or 1-pentanol?

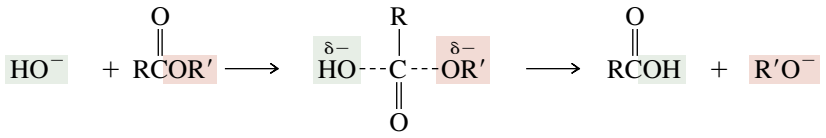
Identical conclusions in support of acyl–oxygen cleavage have been obtained from stereochemical studies. Saponification of esters of optically active alcohols proceeds with *retention of configuration.*



(*R*)-(+)-1-Phenylethyl acetate | Potassium acetate | (*R*)-(+)-1-Phenylethyl alcohol (80% yield; same optical purity as ester)

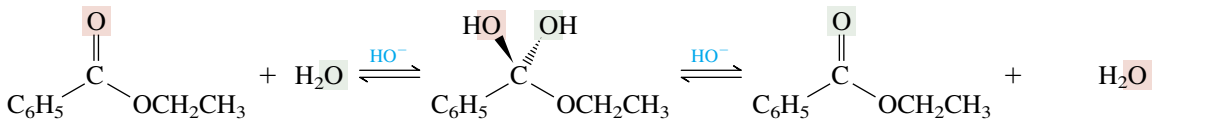
None of the bonds to the stereogenic center are broken when acyl–oxygen cleavage occurs. Had alkyl–oxygen cleavage occurred instead, it would have been accompanied by inversion of configuration at the stereogenic center to give (*S*)-(−)-1-phenylethyl alcohol.

Once it was established that hydroxide ion attacks the carbonyl group in basic ester hydrolysis, the next question to be addressed concerned whether the reaction is concerted or involves an intermediate. In a concerted reaction acyl–oxygen cleavage occurs at the same time that hydroxide ion attacks the carbonyl group.



Hydroxide ion | Ester | Representation of transition state for concerted displacement | Carboxylic acid | Alkoxide ion

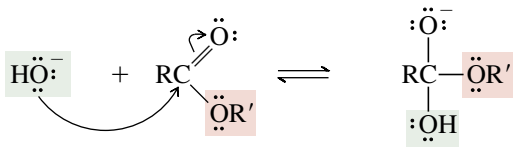
In an extension of the work described in the preceding section, Bender showed that basic ester hydrolysis was *not* concerted and, like acid hydrolysis, took place by way of a tetrahedral intermediate. The nature of the experiment was the same, and the results were similar to those observed in the acid-catalyzed reaction. Ethyl benzoate enriched in ^{18}O at the carbonyl oxygen was subjected to hydrolysis in base, and samples were isolated before saponification was complete. The recovered ethyl benzoate was found to have lost a portion of its isotopic label, consistent with the formation of a tetrahedral intermediate:



Ethyl benzoate (labeled with ^{18}O) | Water | Tetrahedral intermediate | Ethyl benzoate | Water (labeled with ^{18}O)

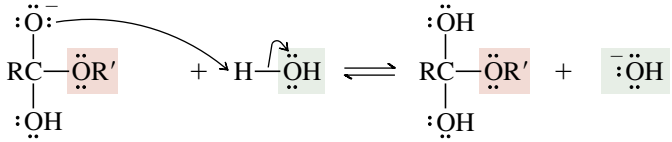
All these facts—the observation of second-order kinetics, acyl–oxygen cleavage, and the involvement of a tetrahedral intermediate—are accommodated by the reaction mechanism shown in Figure 20.5. Like the acid-catalyzed mechanism, it has two distinct

Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



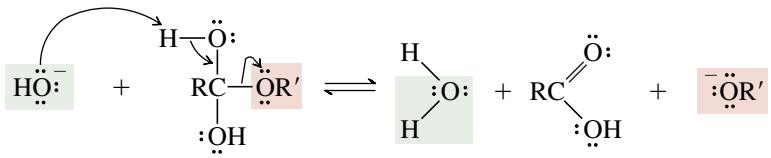
Hydroxide ion | Ester | Anionic form of tetrahedral intermediate

Step 2: Proton transfer to anionic form of tetrahedral intermediate



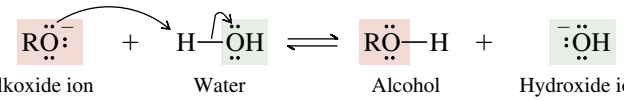
Anionic form of tetrahedral intermediate | Water | Tetrahedral intermediate | Hydroxide ion

Step 3: Dissociation of tetrahedral intermediate

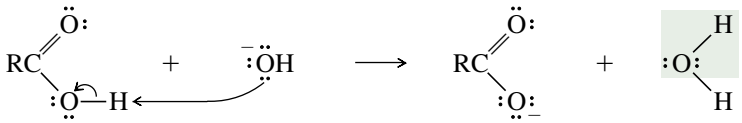


Hydroxide ion | Tetrahedral intermediate | Water | Carboxylic acid | Alkoxide ion

Step 4: Proton transfer steps yield an alcohol and a carboxylate anion



Alkoxide ion | Water | Alcohol | Hydroxide ion



Carboxylic acid (stronger acid) | Hydroxide ion (stronger base) | Carboxylate ion (weaker base) | Water (weaker acid)

FIGURE 20.5 The mechanism of ester hydrolysis in basic solution.

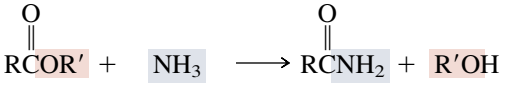
stages, namely, formation of the tetrahedral intermediate and its subsequent dissociation. All the steps are reversible except the last one. The equilibrium constant for proton abstraction from the carboxylic acid by hydroxide is so large that step 4 is, for all intents and purposes, irreversible, and this makes the overall reaction irreversible.

Steps 2 and 4 are proton-transfer reactions and are very fast. Nucleophilic addition to the carbonyl group has a higher activation energy than dissociation of the tetrahedral intermediate; step 1 is rate-determining.

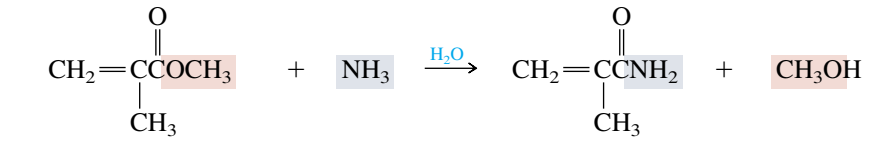
PROBLEM 20.14 On the basis of the general mechanism for basic ester hydrolysis shown in Figure 20.5, write an analogous sequence of steps for the saponification of ethyl benzoate.

20.11 REACTION OF ESTERS WITH AMMONIA AND AMINES

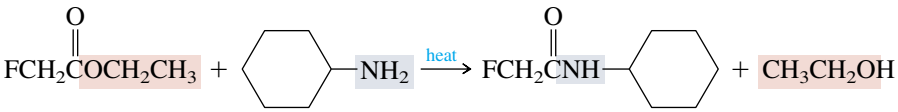
Esters react with ammonia to form amides.



Ammonia is more nucleophilic than water, making it possible to carry out this reaction using aqueous ammonia.

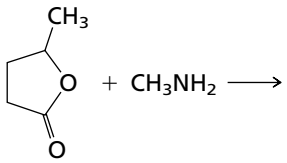


Amines, which are substituted derivatives of ammonia, react similarly:



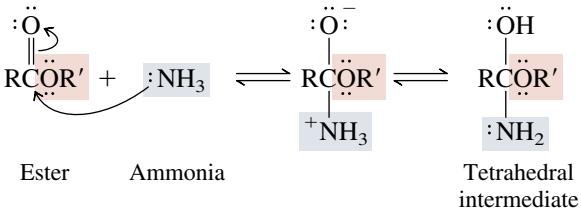
The amine must be primary (RNH_2) or secondary (R_2NH). Tertiary amines (R_3N) cannot form amides, because they have no proton on nitrogen that can be replaced by an acyl group.

PROBLEM 20.15 Give the structure of the expected product of the following reaction:

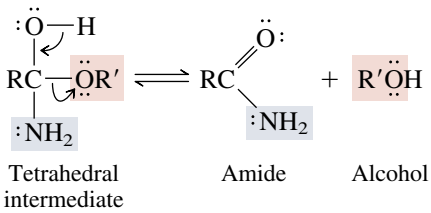


The reaction of ammonia and amines with esters follows the same general mechanistic course as other nucleophilic acyl substitution reactions. A tetrahedral intermediate is formed in the first stage of the process and dissociates in the second stage.

Formation of tetrahedral intermediate



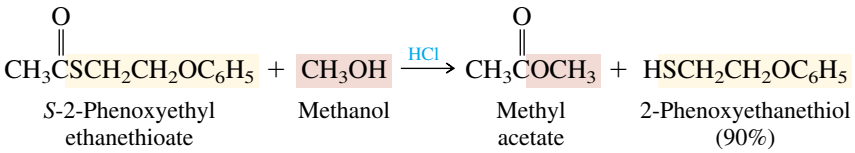
Dissociation of tetrahedral intermediate



Although both stages are written as equilibria, the overall reaction lies far to the right because the amide carbonyl is stabilized to a much greater extent than the ester carbonyl.

20.12 THIOESTERS

Thioesters, compounds of the type $RCSR'$, undergo the same kinds of reactions as esters and by similar mechanisms. Nucleophilic acyl substitution of a thioester gives a *thiol* along with the product of acyl transfer. For example:



PROBLEM 20.16 Write the structure of the tetrahedral intermediate formed in the reaction just described.

The carbon–sulfur bond of a thioester is rather long—typically on the order of 180 pm—and delocalization of the sulfur lone-pair electrons into the π orbital of the carbonyl group is not as effective as in esters. Nucleophilic acyl substitution reactions of thioesters occur faster than those of simple esters. A number of important biological processes involve thioesters; several of these are described in Chapter 26.

20.13 PREPARATION OF AMIDES

Amides are readily prepared by acylation of ammonia and amines with acyl chlorides, anhydrides, or esters.

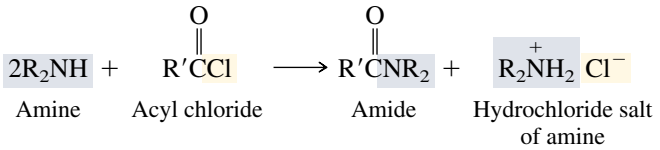
Acylation of *ammonia* (NH_3) yields an amide ($R'CNH_2$).

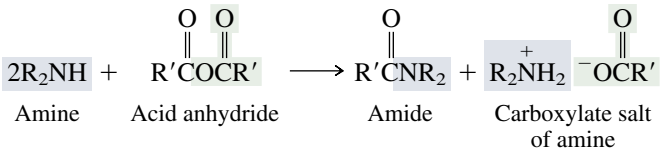
Primary amines (RNH_2) yield *N*-substituted amides ($R'CNHR$).

Secondary amines (R_2NH) yield *N,N*-disubstituted amides ($R'CNR_2$, with O).

Examples illustrating these reactions may be found in Tables 20.2, 20.3, and 20.6.

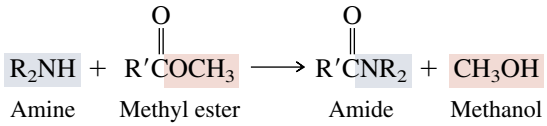
Two molar equivalents of amine are required in the reaction with acyl chlorides and acid anhydrides; one molecule of amine acts as a nucleophile, the second as a Brønsted base.





It is possible to use only one molar equivalent of amine in these reactions if some other base, such as sodium hydroxide, is present in the reaction mixture to react with the hydrogen chloride or carboxylic acid that is formed. This is a useful procedure in those cases in which the amine is a valuable one or is available only in small quantities.

Esters and amines react in a 1:1 molar ratio to give amides. No acidic product is formed from the ester, and so no additional base is required.



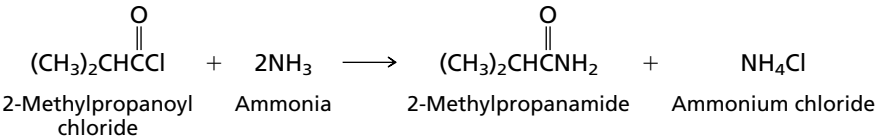
PROBLEM 20.17 Write an equation showing the preparation of the following amides from the indicated carboxylic acid derivative:

(a) $(CH_3)_2CHCNH_2$ (with O) from an acyl chloride

(b) CH_3CNHCH_3 (with O) from an acid anhydride

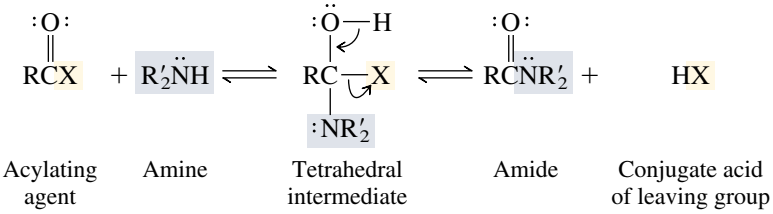
(c) $HCN(CH_3)_2$ (with O) from a methyl ester

SAMPLE SOLUTION (a) Amides of the type $RCNH_2$ (with O) are derived by acylation of ammonia.



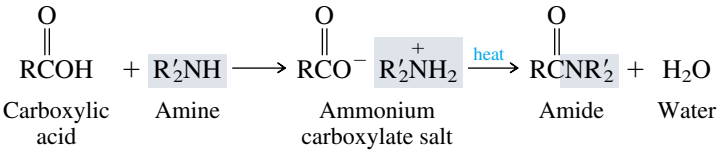
Two molecules of ammonia are needed because its acylation produces, in addition to the desired amide, a molecule of hydrogen chloride. Hydrogen chloride (an acid) reacts with ammonia (a base) to give ammonium chloride.

All these reactions proceed by nucleophilic addition of the amine to the carbonyl group. Dissociation of the tetrahedral intermediate proceeds in the direction that leads to an amide.

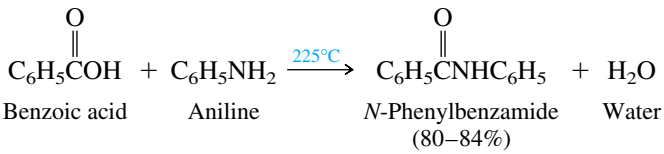


The carbonyl group of an amide is stabilized to a greater extent than that of an acyl chloride, anhydride, or ester; amides are formed rapidly and in high yield from each of these carboxylic acid derivatives.

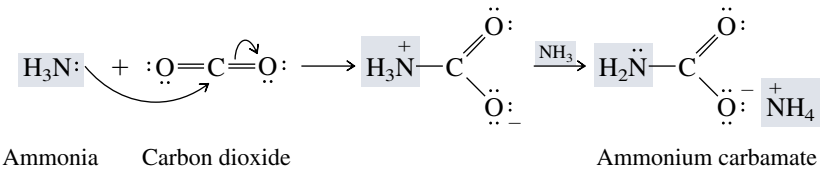
Amides are sometimes prepared directly from carboxylic acids and amines by a two-step process. The first step is an acid–base reaction in which the acid and the amine combine to form an ammonium carboxylate salt. On heating, the ammonium carboxylate salt loses water to form an amide.



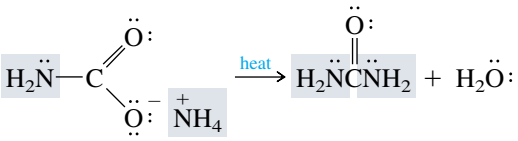
In practice, both steps may be combined in a single operation by simply heating a carboxylic acid and an amine together:



A similar reaction in which ammonia and carbon dioxide are heated under pressure is the basis of the industrial synthesis of *urea.* Here, the reactants first combine, yielding a salt called *ammonium carbamate:*



On being heated, ammonium carbamate undergoes dehydration to form urea:



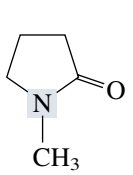
Ammonium carbamate Urea Water

Over 10^{10} lb of urea—most of it used as fertilizer—is produced annually in the United States by this method.

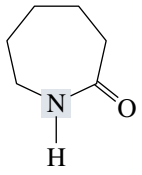
These thermal methods for preparing amides are limited in their generality. Most often amides are prepared in the laboratory from acyl chlorides, acid anhydrides, or esters, and these are the methods that you should apply to solving synthetic problems.

20.14 LACTAMS

Lactams are cyclic amides and are analogous to lactones, which are cyclic esters. Most lactams are known by their common names, as the examples shown illustrate.

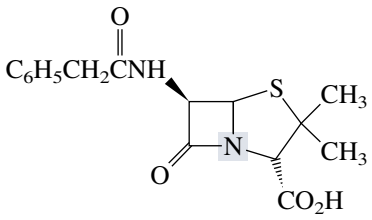


N-Methylpyrrolidone
(a polar aprotic solvent)

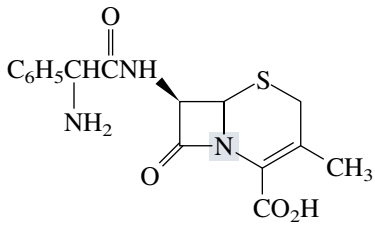


ϵ-Caprolactam
(industrial chemical used to prepare a type of nylon)

Just as amides are more stable than esters, lactams are more stable than lactones. Thus, although β-lactones are difficultly accessible (Section 19.15), β-lactams are among the best known products of the pharmaceutical industry. The penicillins and cephalosporins, which are so useful in treating bacterial infections, are β-lactams and are customarily referred to as *β-lactam antibiotics.*



Penicillin G

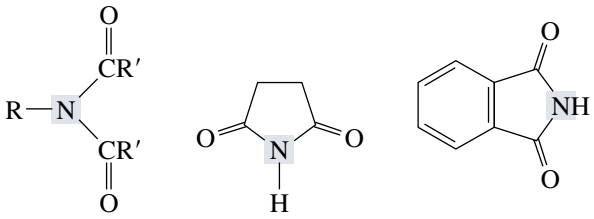


Cephalexin

These antibiotics inhibit a bacterial enzyme that is essential for cell wall formation. A nucleophilic site on the enzyme reacts with the carbonyl group in the four-membered ring, and the ring opens to acylate the enzyme. Once its nucleophilic site is acylated, the enzyme is no longer active and the bacteria die. The β-lactam rings of the penicillins and cephalosporins combine just the right level of stability in aqueous media with reactivity toward nucleophilic substitution to be effective acylating agents toward this critical bacterial enzyme.

20.15 IMIDES

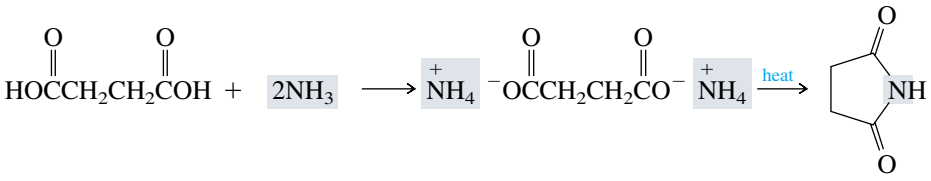
Compounds that have two acyl groups bonded to a single nitrogen are known as **imides.** The most common imides are cyclic ones:



Imide Succinimide Phthalimide

Cyclic imides can be prepared by heating the ammonium salts of dicarboxylic acids:

Replacement of the proton on nitrogen in succinimide by bromine gives *N*-bromosuccinimide, a reagent used for allylic and benzylic brominations (Sections 10.4 and 11.12).

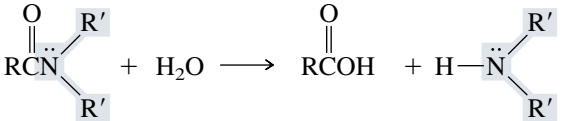


Succinic acid Ammonia Ammonium succinate Succinimide (82–83%)

PROBLEM 20.18 Phthalimide has been prepared in 95% yield by heating the compound formed on reaction of phthalic anhydride (Section 20.4) with excess ammonia. This compound has the molecular formula $C_8H_{10}N_2O_3$. What is its structure?

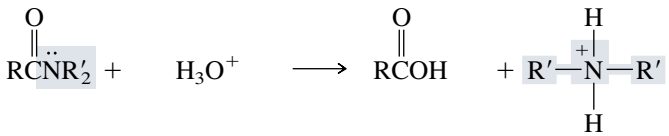
20.16 HYDROLYSIS OF AMIDES

The only nucleophilic acyl substitution reaction that amides undergo is hydrolysis. Amides are fairly stable in water, but the amide bond is cleaved on heating in the presence of strong acids or bases. Nominally, this cleavage produces an amine and a carboxylic acid.



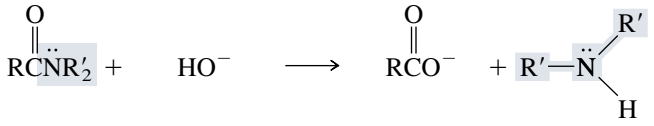
Amide Water Carboxylic acid Amine

In acid, however, the amine is protonated, giving an ammonium ion, $R'_2\overset{+}{N}H_2$:



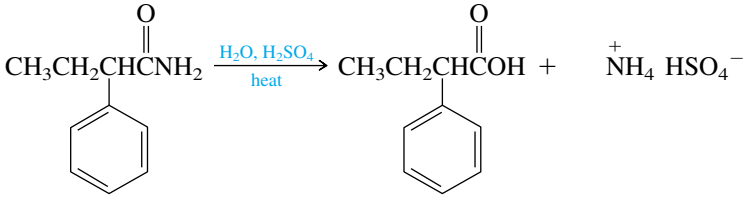
Amide Hydronium ion Carboxylic acid Ammonium ion

In base the carboxylic acid is deprotonated, giving a carboxylate ion:

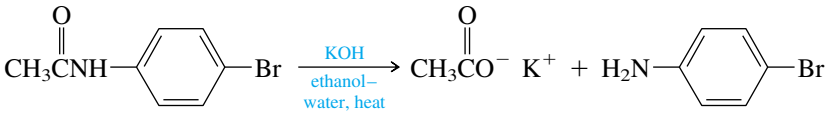


Amide Hydroxide ion Carboxylate ion Amine

The acid–base reactions that occur after the amide bond is broken make the overall hydrolysis irreversible in both cases. The amine product is protonated in acid; the carboxylic acid is deprotonated in base.



2-Phenylbutanamide 2-Phenylbutanoic acid (88–90%) Ammonium hydrogen sulfate

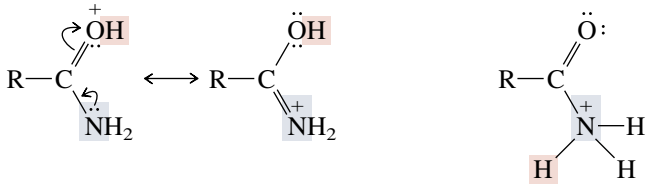


N-(4-Bromophenyl)acetamide (*p*-bromoacetanilide) Potassium acetate *p*-Bromoaniline (95%)

Mechanistically, amide hydrolysis is similar to the hydrolysis of other carboxylic acid derivatives. The mechanism of the hydrolysis in acid is presented in Figure 20.6. It proceeds in two stages; a tetrahedral intermediate is formed in the first stage and dissociates in the second.

The amide is activated toward nucleophilic attack by protonation of its carbonyl oxygen. The cation produced in this step is stabilized by resonance involving the nitrogen lone pair and is more stable than the intermediate in which the amide nitrogen is protonated.

Protonation of carbonyl oxygen ***Protonation of amide nitrogen***

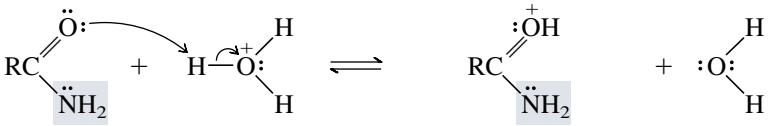


Most stable resonance forms of an *O*-protonated amide An acylammonium ion; the positive charge is localized on nitrogen

Once formed, the *O*-protonated intermediate is attacked by a water molecule in step 2. The intermediate formed in this step loses a proton in step 3 to give the neutral form of the tetrahedral intermediate. The tetrahedral intermediate has its amino group ($—NH_2$) attached to sp^3-hybridized carbon, and this amino group is the site at which protonation

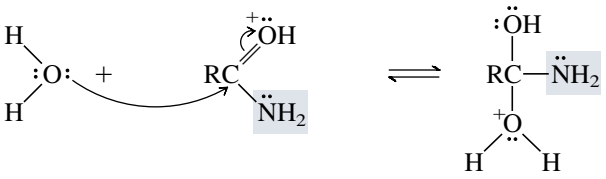
FIGURE 20.6 The mechanism of amide hydrolysis in acid solution. Steps 1 through 3 show the formation of the tetrahedral intermediate. Dissociation of the tetrahedral intermediate is shown in steps 4 through 6.

Step 1: Protonation of the carbonyl oxygen of the amide



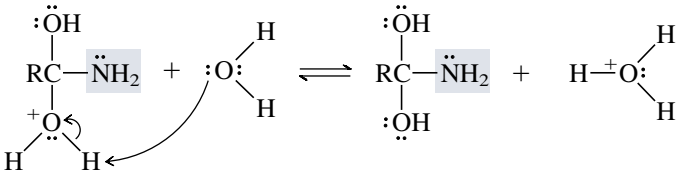
Amide | Hydronium ion | Protonated form of amide | Water

Step 2: Nucleophilic addition of water to the protonated form of the amide



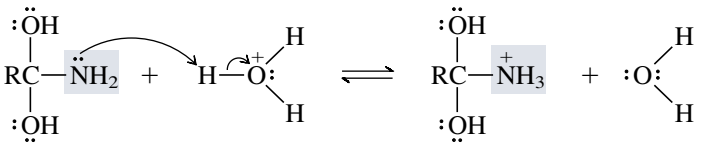
Water | Protonated form of amide | Oxonium ion

Step 3: Deprotonation of the oxonium ion to give the neutral form of the tetrahedral intermediate



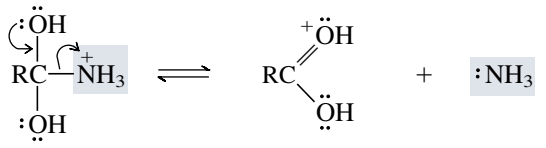
Oxonium ion | Water | Tetrahedral intermediate | Hydronium ion

Step 4: Protonation of the tetrahedral intermediate at its amino nitrogen



Tetrahedral intermediate | Hydronium ion | Ammonium ion | Water

Step 5: Dissociation of the *N*-protonated form of the tetrahedral intermediate to give ammonia and the protonated form of the carboxylic acid



Ammonium ion | Protonated form of carboxylic acid | Ammonia

—Cont.

Step 6: Proton transfer processes yielding ammonium ion and the carboxylic acid

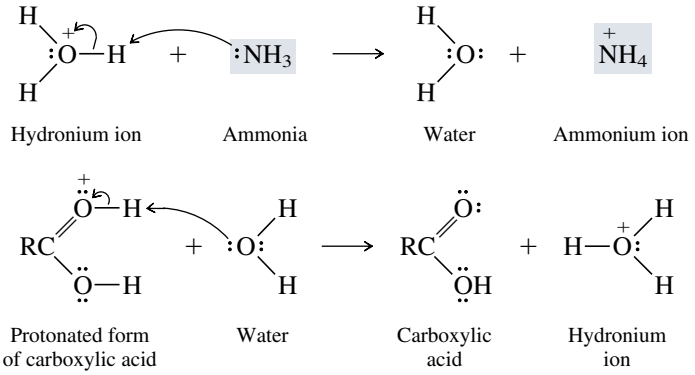


FIGURE 20.6 (*Continued*)

occurs in step 4. Cleavage of the carbon–nitrogen bond in step 5 yields the protonated form of the carboxylic acid, along with a molecule of ammonia. In acid solution ammonia is immediately protonated to give ammonium ion, as shown in step 6. This protonation step has such a large equilibrium constant that it makes the overall reaction irreversible.

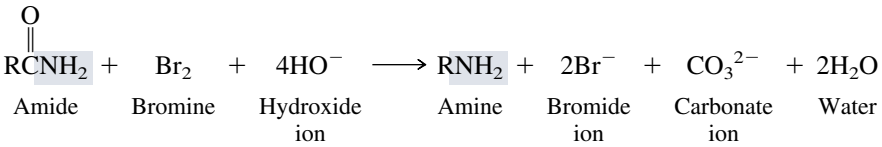
PROBLEM 20.19 On the basis of the general mechanism for amide hydrolysis in acidic solution shown in Figure 20.6, write an analogous sequence of steps for the hydrolysis of acetanilide, $CH_3CNHC_6H_5$.

In base the tetrahedral intermediate is formed in a manner analogous to that proposed for ester saponification. Steps 1 and 2 in Figure 20.7 show the formation of the tetrahedral intermediate in the basic hydrolysis of amides. In step 3 the basic amino group of the tetrahedral intermediate abstracts a proton from water, and in step 4 the derived ammonium ion undergoes basic dissociation. Conversion of the carboxylic acid to its corresponding carboxylate anion in step 5 completes the process and renders the overall reaction irreversible.

PROBLEM 20.20 On the basis of the general mechanism for basic hydrolysis shown in Figure 20.7, write an analogous sequence for the hydrolysis of *N,N*-dimethylformamide, $HCN(CH_3)_2$.

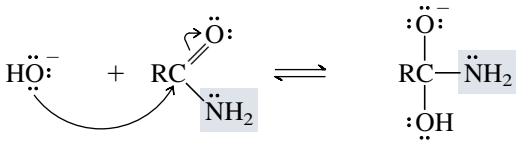
20.17 THE HOFMANN REARRANGEMENT

On treatment with bromine in basic solution, amides of the type $RCNH_2$ undergo an interesting reaction that leads to amines. This reaction was discovered by the nineteenth century German chemist August W. Hofmann and is called the **Hofmann rearrangement.**



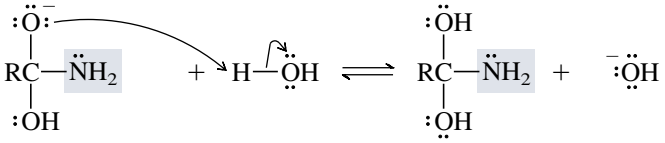
The group R attached to the carboxamide function may be alkyl or aryl.

Step 1: Nucleophilic addition of hydroxide ion to the carbonyl group



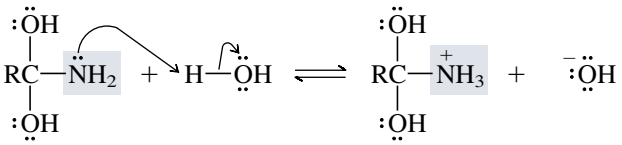
Hydroxide ion | Amide | Anionic form of tetrahedral intermediate

Step 2: Proton transfer to anionic form of tetrahedral intermediate



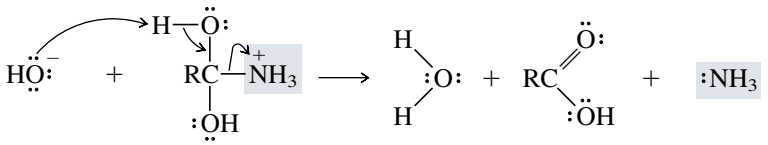
Anionic form of tetrahedral intermediate | Water | Tetrahedral intermediate | Hydroxide ion

Step 3: Protonation of amino nitrogen of tetrahedral intermediate



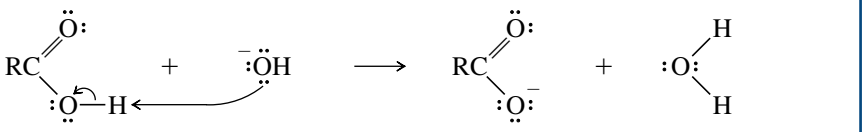
Tetrahedral intermediate | Water | Ammonium ion | Hydroxide ion

Step 4: Dissociation of *N*-protonated form of tetrahedral intermediate



Hydroxide ion | Ammonium ion | Water | Carboxylic acid | Ammonia

Step 5: Irreversible formation of carboxylate anion



Carboxylic acid (stronger acid) | Hydroxide ion (stronger base) | Carboxylate ion (weaker base) | Water (weaker acid)

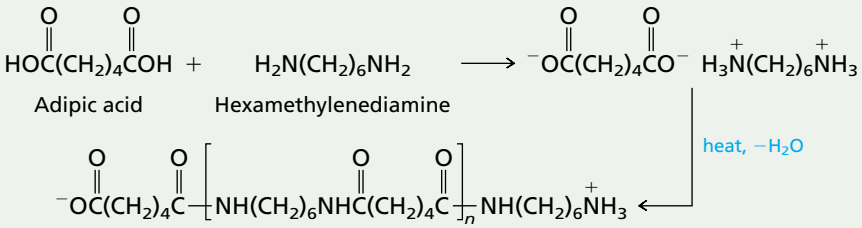
FIGURE 20.7 The mechanism of amide hydrolysis in basic solution.

CONDENSATION POLYMERS. POLYAMIDES AND POLYESTERS

All fibers are polymers of one kind or another. Cotton, for example, is cellulose, and cellulose is a naturally occurring polymer of glucose. Silk and wool are naturally occurring polymers of amino acids. An early goal of inventors and entrepreneurs was to produce fibers from other naturally occurring polymers. Their earliest efforts consisted of chemically modifying the short cellulose fibers obtained from wood so that they could be processed into longer fibers more like cotton and silk. These efforts were successful, and the resulting fibers of modified cellulose, known generically as *rayon,* have been produced by a variety of techniques since the late nineteenth century.

A second approach involved direct chemical synthesis of polymers by connecting appropriately chosen small molecules together into a long chain. In 1938, E. I. Du Pont de Nemours and Company announced the development of *nylon,* the first synthetic polymer fiber.

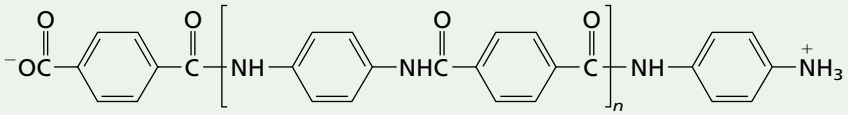
The leader of Du Pont's effort was Wallace H. Carothers,* who reasoned that he could reproduce the properties of silk by constructing a polymer chain held together, as is silk, by amide bonds. The necessary amide bonds were formed by heating a dicarboxylic acid with a diamine. Hexanedioic acid *(adipic acid)* and 1,6-hexanediamine *(hexamethylenediamine)* react to give a salt that, when heated, gives a **polyamide** called *nylon 66.* The amide bonds form by a condensation reaction, and nylon 66 is an example of a **condensation polymer.**



Nylon 66

The first "6" in nylon 66 stands for the number of carbons in the diamine, the second for the number of carbons in the dicarboxylic acid. Nylon 66 was an immediate success and fostered the development of a large number of related polyamides, many of which have also found their niche in the marketplace.

A slightly different class of polyamides is the *aramids (aromatic polyamides).* Like the nylons, the aramids are prepared from a dicarboxylic acid and a diamine, but the functional groups are anchored to benzene rings. An example of an aramid is *Kevlar,* which is a polyamide derived from 1,4-benzenedicarboxylic acid *(terephthalic acid)* and 1,4-benzenediamine *(p-phenylenediamine):*



Kevlar (a polyamide of the aramid class)

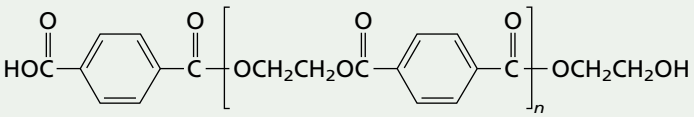
Kevlar fibers are very strong, which makes Kevlar a popular choice in applications where the ratio of strength to weight is important. For example, a cable made from Kevlar weighs only one fifth as much as a steel one but is just as strong. Kevlar is also used to make lightweight bulletproof vests.

Nomex is another aramid fiber. Kevlar and Nomex differ only in that the substitution pattern in the aromatic rings is para in Kevlar but meta in Nomex. Nomex is best known for its fire-resistant properties and is used in protective clothing for firefighters, astronauts, and race-car drivers.

*For an account of Carothers' role in the creation of nylon, see the September 1988 issue of the *Journal of Chemical Education* (pp. 803–808).

—Cont.

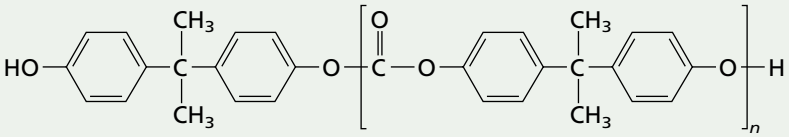
Polyesters are a second class of condensation polymers, and the principles behind their synthesis parallel those of polyamides. Ester formation between the functional groups of a dicarboxylic acid and a diol serve to connect small molecules together into a long polyester. The most familiar example of a polyester is *Dacron,* which is prepared from 1,4-benzenedicarboxylic acid and 1,2-ethanediol (*ethylene glycol*):



Dacron (a polyester)

The production of polyester fibers leads that of all other types. Annual United States production of polyester fibers is 1.6 million tons versus 1.4 million tons for cotton and 1.0 million tons for nylon. Wool and silk trail far behind at 0.04 and 0.01 million tons, respectively.

Not all synthetic polymers are used as fibers. *Mylar,* for example, is chemically the same as Dacron, but is prepared in the form of a thin film instead of a fiber. *Lexan* is a polyester which, because of its impact resistance, is used as a shatterproof substitute for glass. It is a **polycarbonate** having the structure shown:

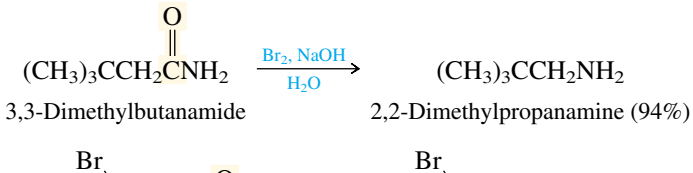


Lexan (a polycarbonate)

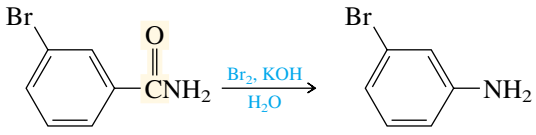
In terms of the number of scientists and engineers involved, research and development in polymer chemistry is the principal activity of the chemical industry. The initial goal of making synthetic materials that are the equal of natural fibers has been more than met; it has been far exceeded. What is also important is that all of this did not begin with a chance discovery. It began with a management decision to do basic research in a specific area, and to support it in the absence of any guarantee that success would be quickly achieved.[†]

[†]The April 1988 issue of the *Journal of Chemical Education* contains a number of articles on polymers, including a historical review entitled "Polymers Are Everywhere" (pp. 327–334) and a glossary of terms (pp. 314–319).

The relationship of the amine product to the amide reactant is rather remarkable. The overall reaction appears as if the carbonyl group had been plucked out of the amide, leaving behind a primary amine having one less carbon atom than the amide.



3,3-Dimethylbutanamide — 2,2-Dimethylpropanamine (94%)



m-Bromobenzamide — *m*-Bromoaniline (87%)

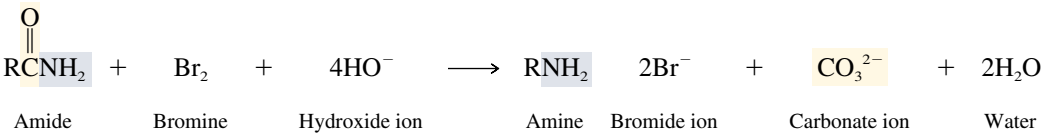
PROBLEM 20.21 Outline an efficient synthesis of 1-propanamine ($CH_3CH_2CH_2NH_2$) from butanoic acid.

The mechanism of the Hofmann rearrangement (Figure 20.8) involves three stages:

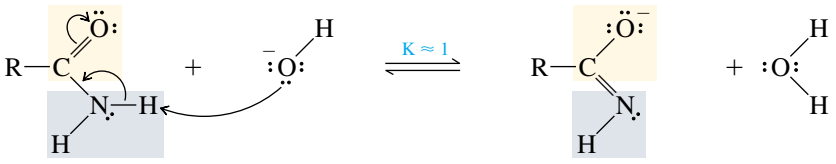
1. Formation of an *N*-bromo amide intermediate (steps 1 and 2)
2. Rearrangement of the *N*-bromo amide to an isocyanate (steps 3 and 4)
3. Hydrolysis of the isocyanate (steps 5 and 6)

FIGURE 20.8 The mechanism of the Hofmann rearrangement.

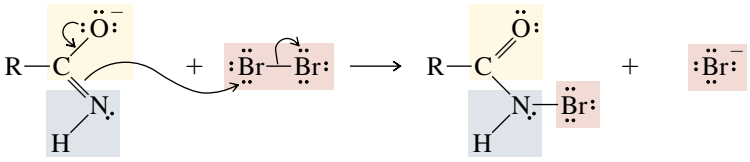
Overall Reaction



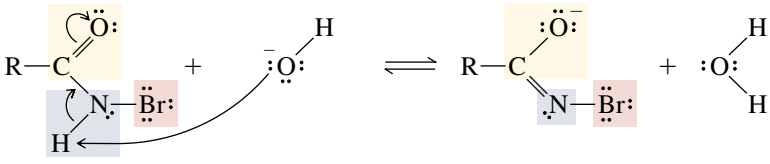
Step 1: Deprotonation of the amide. Amides of the type $RCNH_2$ are about as acidic as water, so appreciable quantities of the conjugate base are present at equilibrium in aqueous base. The conjugate base of an amide is stabilized by electron delocalization in much the same way that an enolate anion is.



Step 2: Reaction of the conjugate base of the amide with bromine. The product of this step is an *N*-bromo amide.

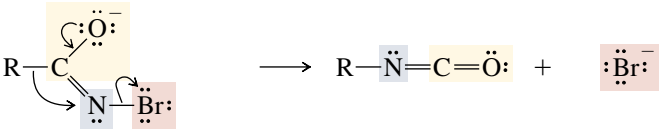


Step 3: Deprotonation of the *N*-bromo amide. The electron-withdrawing effect of the bromine substituent reinforces that of the carbonyl group and makes the *N*-bromo amide even more acidic than the starting amide.



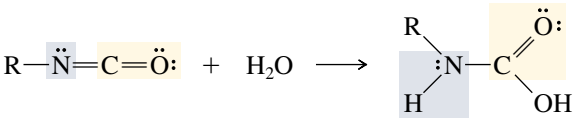
—Cont.

Step 4: Rearrangement of the conjugate base of the *N*-bromo amide. The group R migrates from carbon to nitrogen, and bromide is lost as a leaving group from nitrogen. The product of this rearrangement is an *N*-alkyl isocyanate.



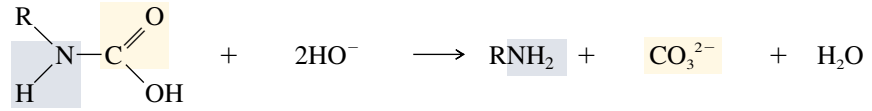
Conjugate base of *N*-bromo amide | *N*-Alkyl isocyanate | Bromide ion

Step 5: Hydrolysis of the isocyanate begins by base-catalyzed addition of water to form an *N*-alkylcarbamic acid.



N-Alkyl isocyanate | *N*-Alkylcarbamic acid

Step 6: The *N*-alkylcarbamic acid is unstable and dissociates to an amine and carbon dioxide. Carbon dioxide is converted to carbonate ion in base. (Several steps are actually involved; in the interests of brevity, they are summarized as shown.)



N-Alkylcarbamic acid | Hydroxide ion | Amine | Carbonate ion | Water

FIGURE 20.8 (*Continued*)

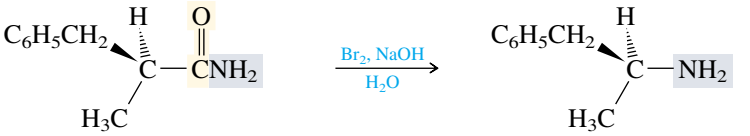
Formation of the *N*-bromo amide intermediate is relatively straightforward. The base converts the amide to its corresponding anion (step 1), which acts as a nucleophile toward bromine (step 2).

Conversion of the *N*-bromo amide to its conjugate base in step 3 is also easy to understand. It is an acid–base reaction exactly analogous to that of step 1. The anion produced in step 3 is a key intermediate; it rearranges in step 4 by migration of the alkyl (or aryl) group from carbon to nitrogen, with loss of bromide from nitrogen. The product of this rearrangement is an isocyanate. The isocyanate formed in the rearrangement step then undergoes basic hydrolysis in steps 5 and 6 to give the observed amine.

Among the experimental observations that contributed to elaboration of the mechanism shown in Figure 20.8 are the following:

1. Only amides of the type $RCNH_2$ (with O) undergo the Hofmann rearrangement. The amide nitrogen must have *two* protons attached to it, of which one is replaced by bromine to give the *N*-bromo amide, whereas abstraction of the second by base is necessary to trigger the rearrangement. Amides of the type $RCNHR'$ (with O) form *N*-bromo amides under the reaction conditions, but these *N*-bromo amides do not rearrange.

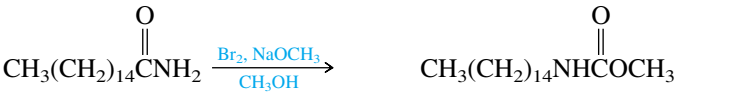
2. Rearrangement proceeds with *retention of configuration* at the migrating group.



(*S*)-(+)-2-Methyl-3-phenylpropanamide (*S*)-(+)-1-Phenyl-2-propanamine

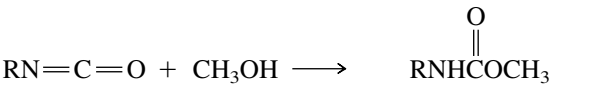
The new carbon–nitrogen bond is formed at the same face of the migrating carbon as the bond that is broken. The rearrangement step depicted in Figure 20.8 satisfies this requirement. Presumably, carbon–nitrogen bond formation is concerted with carbon–carbon bond cleavage.

3. Isocyanates are intermediates. When the reaction of an amide with bromine is carried out in methanol containing sodium methoxide instead of in aqueous base, the product that is isolated is a **carbamate.**



Hexadecanamide Methyl *N*-pentadecylcarbamate (84–94%)

Carbamates are esters of **carbamic acid** (H_2NCOH). Carbamates are also known as **urethans.** They are relatively stable and are formed by addition of alcohols to isocyanates.



Isocyanate Methanol Methyl *N*-alkylcarbamate

Carbamic acid itself (H_2NCOH) and *N*-substituted derivatives of carbamic acid are unstable; they decompose spontaneously to carbon dioxide and ammonia or an amine. Thus in aqueous solution, an isocyanate intermediate yields an amine via the corresponding carbamic acid; in methanol, an isocyanate is converted to an isolable methyl carbamate. If desired, the carbamate can be isolated, purified, and converted to an amine in a separate hydrolysis operation.

Although the Hofmann rearrangement is complicated with respect to mechanism, it is easy to carry out and gives amines that are sometimes difficult to prepare by other methods.

20.18 PREPARATION OF NITRILES

Nitriles are organic compounds that contain the —C≡N functional group. We have already discussed the two main procedures by which they are prepared, namely, the nucleophilic substitution of alkyl halides by cyanide and the conversion of aldehydes and ketones to cyanohydrins. Table 20.7 reviews aspects of these reactions. Neither of the reactions in Table 20.7 is suitable for aryl nitriles (ArC≡N); these compounds are readily prepared by a reaction to be discussed in Chapter 22.

TABLE 20.7 Preparation of Nitriles

Reaction (section) and comments	General equation and specific example
Nucleophilic substitution by cyanide ion (Sections 8.1, 8.13) Cyanide ion is a good nucleophile and reacts with alkyl halides to give alkyl nitriles. The reaction is of the S_N2 type and is limited to primary and secondary alkyl halides. Tertiary alkyl halides undergo elimination; aryl and vinyl halides do not react.	$:N\equiv\bar{C}: + R-X \longrightarrow RC\equiv N + X^-$ Cyanide ion; Alkyl halide; Nitrile; Halide ion $CH_3(CH_2)_8CH_2Cl \xrightarrow[\text{ethanol–water}]{KCN} CH_3(CH_2)_8CH_2CN$ 1-Chlorodecane; Undecanenitrile (95%)
Cyanohydrin formation (Section 17.7) Hydrogen cyanide adds to the carbonyl group of aldehydes and ketones.	$RCR' + HCN \longrightarrow RCR'(OH)(C\equiv N)$ Aldehyde or ketone; Hydrogen cyanide; Cyanohydrin $CH_3CH_2CCH_2CH_3 \xrightarrow[H^+]{KCN} CH_3CH_2C(OH)(CN)CH_2CH_3$ 3-Pentanone; 3-Pentanone cyanohydrin (75%)

Both alkyl and aryl nitriles are accessible by dehydration of amides.

$$RCNH_2 \longrightarrow RC\equiv N + H_2O$$

Amide (R may be alkyl or aryl); Nitrile (R may be alkyl or aryl); Water

Among the reagents used to effect the dehydration of amides is the compound P_4O_{10}, known by the common name *phosphorus pentoxide* because it was once thought to have the molecular formula P_2O_5. Phosphorus pentoxide is the anhydride of phosphoric acid and is used in a number of reactions requiring dehydrating agents.

$$(CH_3)_2CHCNH_2 \xrightarrow[200°C]{P_4O_{10}} (CH_3)_2CHC\equiv N$$

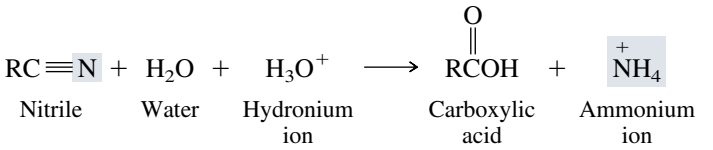
2-Methylpropanamide; 2-Methylpropanenitrile (69–86%)

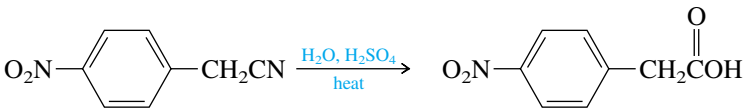
PROBLEM 20.22 Show how ethyl alcohol could be used to prepare (a) CH_3CN and (b) CH_3CH_2CN. Along with ethyl alcohol you may use any necessary inorganic reagents.

An important nitrile is *acrylonitrile,* $CH_2{=}CHCN$. It is prepared industrially from propene, ammonia, and oxygen in the presence of a special catalyst. Polymers of acrylonitrile have many applications, the most prominent being their use in the preparation of acrylic fibers.

20.19 HYDROLYSIS OF NITRILES

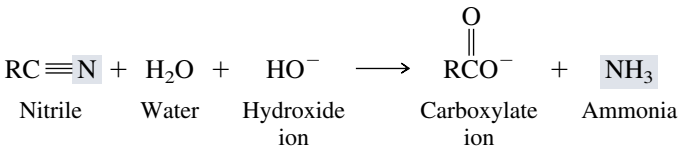
Nitriles are classified as carboxylic acid derivatives because they are converted to carboxylic acids on hydrolysis. The conditions required are similar to those for the hydrolysis of amides, namely, heating in aqueous acid or base for several hours. Like the hydrolysis of amides, nitrile hydrolysis is irreversible in the presence of acids or bases. Acid hydrolysis yields ammonium ion and a carboxylic acid.

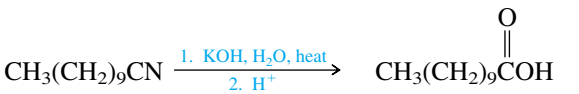




p-Nitrobenzyl cyanide *p*-Nitrophenylacetic acid (92–95%)

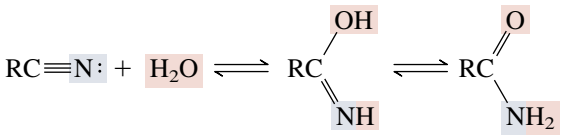
In aqueous base, hydroxide ion abstracts a proton from the carboxylic acid. In order to isolate the acid a subsequent acidification step is required.





Undecanenitrile Undecanoic acid (80%)

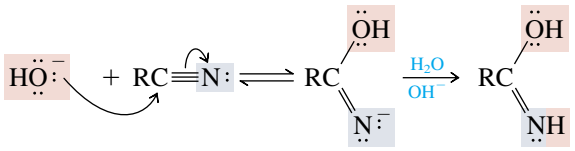
Nitriles are susceptible to nucleophilic addition. In their hydrolysis, water adds across the carbon–nitrogen triple bond. In a series of proton-transfer steps, an amide is produced:



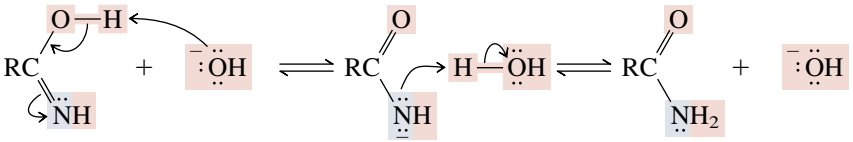
Nitrile Water Imino acid Amide

We already discussed both the acidic and basic hydrolysis of amides (see Section 20.16). All that remains to complete the mechanistic picture of nitrile hydrolysis is to examine the conversion of the nitrile to the corresponding amide.

Nucleophilic addition to the nitrile may be either acid- or base-catalyzed. In aqueous base, hydroxide adds to the carbon–nitrogen triple bond:



The imino acid is transformed to the amide by the sequence

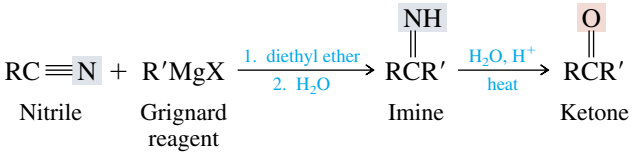


PROBLEM 20.23 Suggest a reasonable mechanism for the conversion of a nitrile (RCN) to the corresponding amide in aqueous acid.

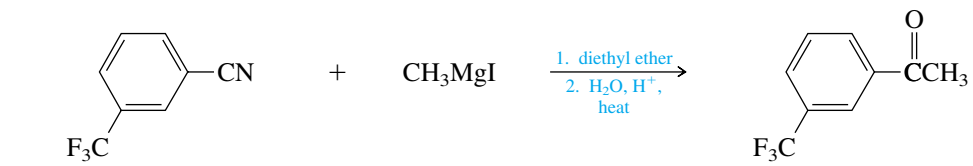
Nucleophiles other than water can also add to the carbon–nitrogen triple bond of nitriles. In the following section we will see a synthetic application of such a nucleophilic addition.

20.20 ADDITION OF GRIGNARD REAGENTS TO NITRILES

The carbon–nitrogen triple bond of nitriles is much less reactive toward nucleophilic addition than is the carbon–oxygen double bond of aldehydes and ketones. Strongly basic nucleophiles such as Grignard reagents, however, do react with nitriles in a reaction that is of synthetic value:



The imine formed by nucleophilic addition of the Grignard reagent to the nitrile is normally not isolated but is hydrolyzed directly to a ketone. The overall sequence is used as a means of preparing ketones.



m-(Trifluoromethyl)benzonitrile — Methylmagnesium iodide — *m*-(Trifluoromethyl)acetophenone (79%)

PROBLEM 20.24 Write an equation showing how you could prepare ethyl phenyl ketone from propanenitrile and a Grignard reagent. What is the structure of the imine intermediate?

Organolithium reagents react in the same way and are often used instead of Grignard reagents.

20.21 SPECTROSCOPIC ANALYSIS OF CARBOXYLIC ACID DERIVATIVES

Infrared: Infrared spectroscopy is quite useful in identifying carboxylic acid derivatives. The carbonyl stretching vibration is very strong, and its position is sensitive to the nature of the carbonyl group. In general, electron donation from the substituent decreases the double-bond character of the bond between carbon and oxygen and decreases the stretching frequency. Two distinct absorptions are observed for the symmetric and antisymmetrical stretching vibrations of the anhydride function.

The C=O stretching vibrations of these compounds may be viewed on *Learning By Modeling.*

CH_3CCl	CH_3COCCH_3	CH_3COCH_3	CH_3CNH_2
Acetyl chloride	Acetic anhydride	Methyl acetate	Acetamide
$\nu_{C=O} = 1822\ cm^{-1}$	$\nu_{C=O} = 1748\ cm^{-1}$ and $1815\ cm^{-1}$	$\nu_{C=O} = 1736\ cm^{-1}$	$\nu_{C=O} = 1694\ cm^{-1}$

Nitriles are readily identified by absorption due to —C≡N stretching in the 2210–2260 cm^{-1} region.

^{1}H NMR: Chemical-shift differences in their ^{1}H NMR spectra aid the structure determination of esters. Consider the two isomeric esters: ethyl acetate and methyl propanoate. As Figure 20.9 shows, the number of signals and their multiplicities are the same for both esters. Both have a methyl singlet and a triplet–quartet pattern for their ethyl group.

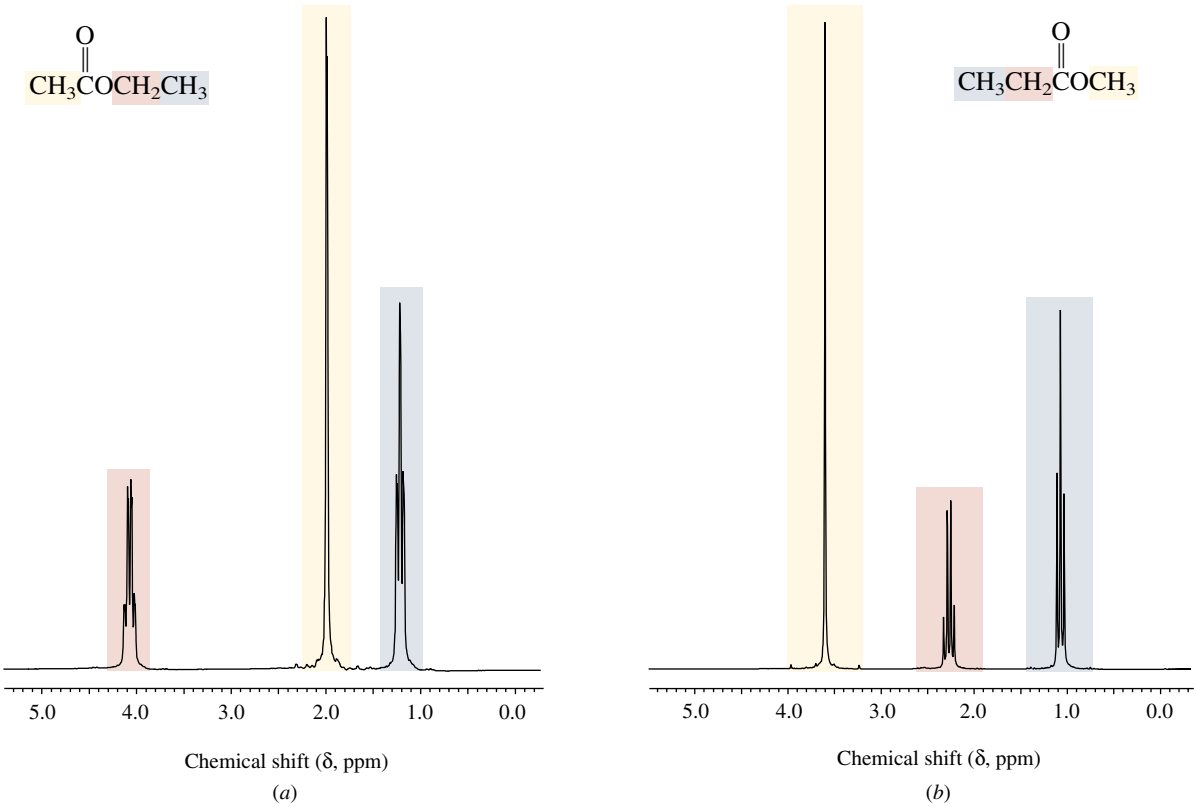
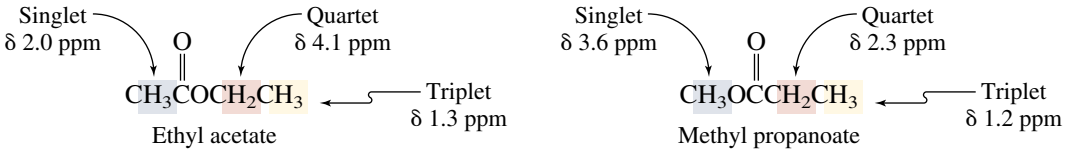


FIGURE 20.9 The 200-MHz ^{1}H NMR spectra of (*a*) ethyl acetate and (*b*) methyl propanoate.



Notice, however, that there is a significant difference in the chemical shifts of the corresponding signals in the two spectra. The methyl singlet is more shielded (δ 2.0 ppm) when it is bonded to the carbonyl group of ethyl acetate than when it is bonded to the oxygen of methyl propanoate (δ 3.6 ppm). The methylene quartet is more shielded (δ 2.3 ppm) when it is bonded to the carbonyl group of methyl propanoate than when it is bonded to the oxygen of ethyl acetate (δ 4.1 ppm). Analysis of the number of peaks and their splitting patterns will not provide an unambiguous answer to structure assignment in esters; chemical-shift data must also be considered.

The chemical shift of the N—H proton of amides appears in the range δ 5–8 ppm. It is often a very broad peak; sometimes it is so broad that it does not rise much over the baseline and can be lost in the background noise.

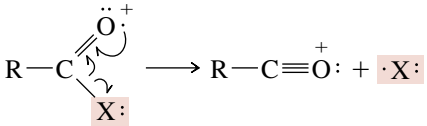
^{13}C NMR: The ^{13}C NMR spectra of carboxylic acid derivatives, like the spectra of carboxylic acids themselves, are characterized by a low-field resonance for the carbonyl carbon in the range δ 160–180 ppm. The carbonyl carbons of carboxylic acid derivatives are more shielded than those of aldehydes and ketones, but less shielded than the sp^2-hybridized carbons of alkenes and arenes.

The carbon of a C≡N group appears near δ 120 ppm.

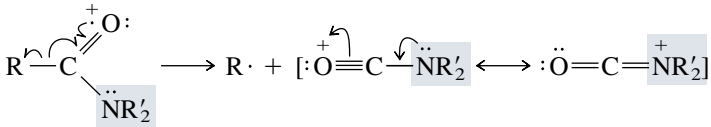
UV-VIS: The following values are typical for the $n \rightarrow \pi,^*$ absorption associated with the C=O group of carboxylic acid derivatives.

	CH_3CCl	CH_3COCCH_3	CH_3COCH_3	CH_3CNH_2
	Acetyl chloride	Acetic anhydride	Methyl acetate	Acetamide
λ_{max}	235nm	225nm	207nm	214nm

Mass Spectrometry: A prominent peak in the mass spectra of most carboxylic acid derivatives corresponds to an acylium ion derived by cleavage of the bond to the carbonyl group:

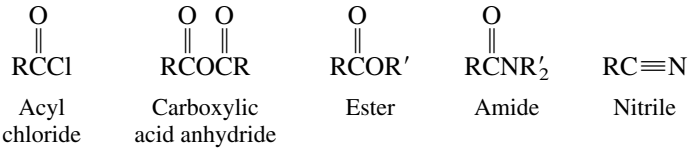


Amides, however, tend to cleave in the opposite direction to produce a nitrogen-stabilized acylium ion:

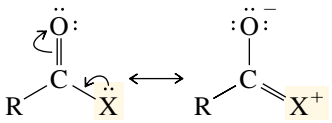


20.22 SUMMARY

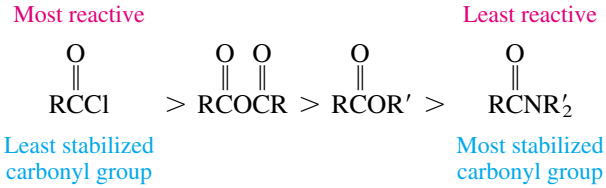
Section 20.1 This chapter concerns the preparation and reactions of *acyl chlorides, acid anhydrides, esters, amides,* and *nitriles.* These compounds are generally classified as carboxylic acid derivatives, and their nomenclature is based on that of carboxylic acids (Section 20.1).



Section 20.2 The structure and reactivity of carboxylic acid derivatives depend on how well the atom bonded to the carbonyl group donates electrons to it.

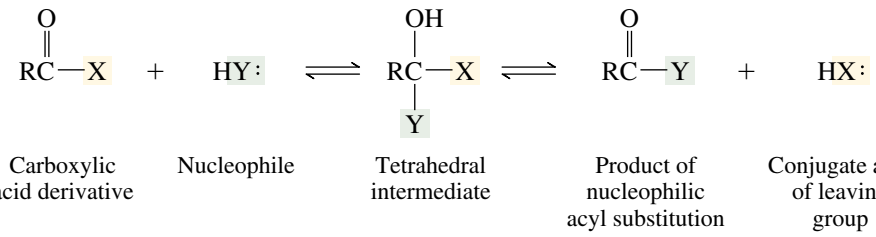


Electron-pair donation stabilizes the carbonyl group and makes it less reactive toward nucleophilic acyl substitution.

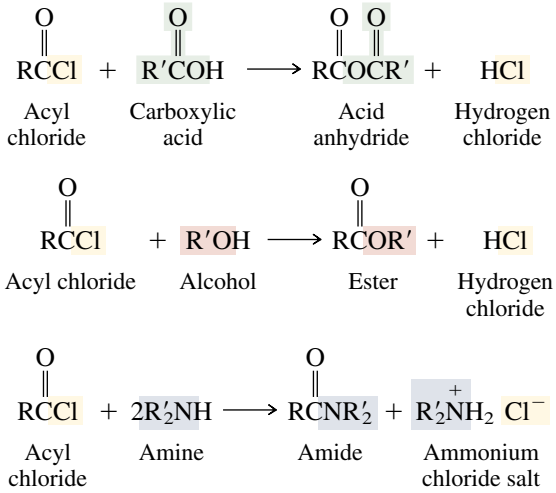


Nitrogen is a better electron-pair donor than oxygen, and amides have a more stabilized carbonyl than esters and anhydrides. Chlorine is the poorest electron-pair donor, and acyl chlorides have the least stabilized carbonyl group and are the most reactive.

Section 20.3 The characteristic reaction of acyl chlorides, acid anhydrides, esters, and amides is **nucleophilic acyl substitution.** Addition of a nucleophilic reagent HY: to the carbonyl group leads to a tetrahedral intermediate that dissociates to give the product of substitution:



Acyl chlorides are converted to anhydrides, esters, and amides by nucleophilic acyl substitution.



Examples of each of these reactions may be found in Table 20.2.

Section 20.4 Acid anhydrides may be prepared from acyl chlorides in the laboratory, but the most commonly encountered ones (acetic anhydride, phthalic anhydride, and maleic anhydride) are industrial chemicals prepared by specialized methods.

Section 20.5 Acid anhydrides are less reactive toward nucleophilic acyl substitution than acyl chlorides, but are useful reagents for preparing esters and amides.

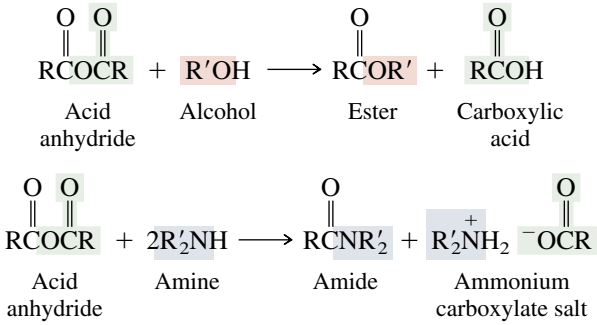


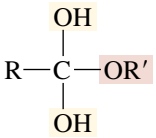
Table 20.3 presents examples of these reactions.

Section 20.6 Esters occur naturally or are prepared from alcohols by Fischer esterification or by acylation with acyl chlorides or acid anhydrides (see Table 20.4).

Section 20.7 Esters are polar and have higher boiling points than alkanes of comparable size and shape. Esters don't form hydrogen bonds to other ester molecules so have lower boiling points than analogous alcohols. They can form hydrogen bonds to water and so are comparable to alcohols with respect to their solubility in water.

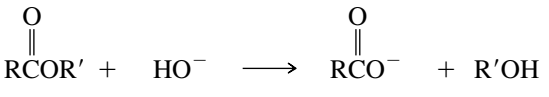
Section 20.8 Esters react with Grignard reagents and are reduced by lithium aluminum hydride (Table 20.5).

Section 20.9 Ester hydrolysis can be catalyzed by acids and its mechanism (Figure 20.4) is the reverse of the mechanism for Fischer esterification. The reaction proceeds via a tetrahedral intermediate.

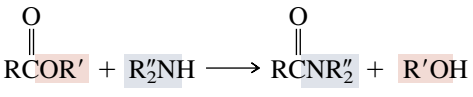


Tetrahedral intermediate
in ester hydrolysis

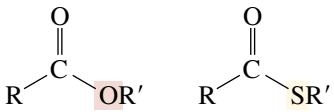
Section 20.10 Ester hydrolysis in basic solution is called *saponification* and proceeds through the same tetrahedral intermediate (Figure 20.5) as in acid-catalyzed hydrolysis. Unlike acid-catalyzed hydrolysis, saponification is irreversible because the carboxylic acid is deprotonated under the reaction conditions.



Section 20.11 Esters react with amines to give amides.



Section 20.12 Thioesters undergo reactions analogous to those of esters, but at faster rates. A sulfur atom stabilizes a carbonyl group less effectively than an oxygen.

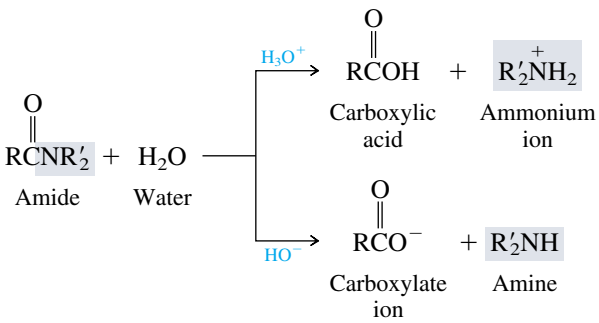


Section 20.13 Amides are normally prepared by the reaction of amines with acyl chlorides, anhydrides, or esters.

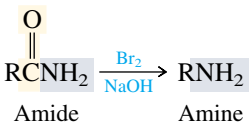
Section 20.14 Lactams are cyclic amides.

Section 20.15 Imides are compounds that have two acyl groups attached to nitrogen.

Section 20.16 Like ester hydrolysis, amide hydrolysis can be achieved in either aqueous acid or aqueous base. The process is irreversible in both media. In base, the carboxylic acid is converted to the carboxylate anion; in acid, the amine is protonated to an ammonium ion:

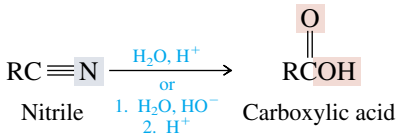


Section 20.17 The **Hofmann rearrangement** converts amides of the type $RC(=O)NH_2$ to primary amines (RNH_2). The carbon chain is shortened by one carbon with loss of the carbonyl group:

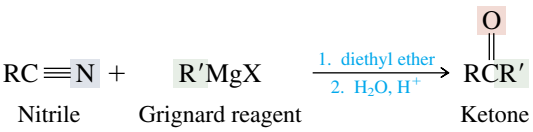


Section 20.18 Nitriles are prepared by nucleophilic substitution (S_N2) of alkyl halides with cyanide ion, by converting aldehydes or ketones to cyanohydrins (Table 20.7) or by dehydration of amides.

Section 20.19 The hydrolysis of nitriles to carboxylic acids is irreversible in both acidic and basic solution.



Section 20.20 Nitriles are useful starting materials for the preparation of ketones by reaction with Grignard reagents.



Section 20.21 Acyl chlorides, anhydrides, esters, and amides all show a strong band for C=O stretching in the infrared. The range extends from about 1820 cm^{-1} (acyl chlorides) to 1690 cm^{-1} (amides). Their ^{13}C NMR spectra are characterized by a peak near δ180 ppm for the carbonyl carbon. ^1H NMR spectroscopy is useful for distinguishing between the groups R and R′ in esters (RCO_2R'). The protons on the carbon bonded to O in R′ appear at lower field (less shielded) than those on the carbon bonded to C=O.

PROBLEMS

20.25 Write a structural formula for each of the following compounds:

(a) *m*-Chlorobenzoyl bromide

(b) Trifluoroacetic anhydride

(c) *cis*-1,2-Cyclopropanedicarboxylic anhydride

(d) Ethyl cycloheptanecarboxylate

(e) 1-Phenylethyl acetate

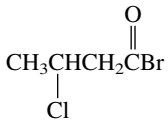
(f) 2-Phenylethyl acetate

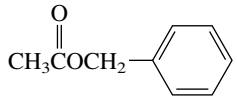
(g) *p*-Ethylbenzamide

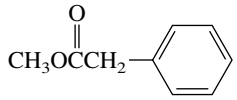
(h) *N*-Ethylbenzamide

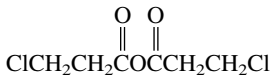
(i) 2-Methylhexanenitrile

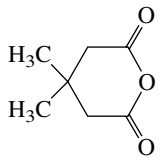
20.26 Give an acceptable IUPAC name for each of the following compounds:

(a) 

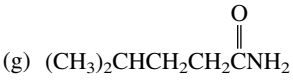
(b) 

(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

20.27 Write a structural formula for the principal organic product or products of each of the following reactions:

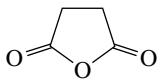
(a) Acetyl chloride and bromobenzene, $AlCl_3$

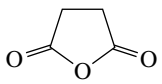
(b) Acetyl chloride and 1-butanethiol

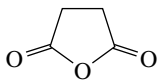
(c) Propanoyl chloride and sodium propanoate

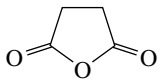
(d) Butanoyl chloride and benzyl alcohol

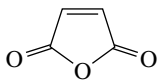
(e) *p*-Chlorobenzoyl chloride and ammonia

(f)  and water

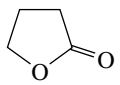
(g)  and aqueous sodium hydroxide

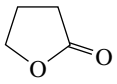
(h)  and aqueous ammonia

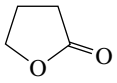
(i)  and benzene, $AlCl_3$

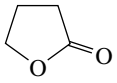
(j)  and 1,3-pentadiene

(k) Acetic anhydride and 3-pentanol

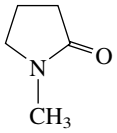
(l)  and aqueous sodium hydroxide

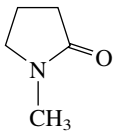
(m)  and aqueous ammonia

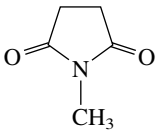
(n)  and lithium aluminum hydride, then H_2O

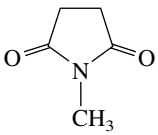
(o)  and excess methylmagnesium bromide, then H_3O^+

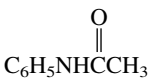
(p) Ethyl phenylacetate and methylamine (CH_3NH_2)

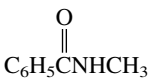
(q)  and aqueous sodium hydroxide

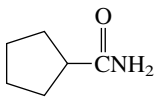
(r)  and aqueous hydrochloric acid, heat

(s)  and aqueous sodium hydroxide

(t)  and aqueous hydrochloric acid, heat

(u)  and aqueous hydrochloric acid, heat

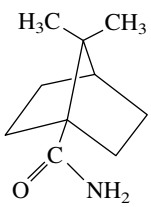
(v)  and aqueous sulfuric acid, heat

(w)  and P_4O_{10}

(x) $(CH_3)_2CHCH_2C{\equiv}N$ and aqueous hydrochloric acid, heat

(y) *p*-Methoxybenzonitrile and aqueous sodium hydroxide, heat

(z) Propanenitrile and methylmagnesium bromide, then H_3O^+

(aa)  + Br_2 $\xrightarrow[CH_3OH]{NaOCH_3}$

(bb) Product of (aa) $\xrightarrow{KOH,\ H_2O}$

20.28 Using ethanol as the ultimate source of all the carbon atoms, along with any necessary inorganic reagents, show how you could prepare each of the following:

(a) Acetyl chloride
(b) Acetic anhydride
(c) Ethyl acetate
(d) Ethyl bromoacetate
(e) 2-Bromoethyl acetate
(f) Ethyl cyanoacetate
(g) Acetamide
(h) Methylamine (CH_3NH_2)
(i) 2-Hydroxypropanoic acid

20.29 Using toluene as the ultimate source of all the carbon atoms, along with any necessary inorganic reagents, show how you could prepare each of the following:

(a) Benzoyl chloride
(b) Benzoic anhydride
(c) Benzyl benzoate
(d) Benzamide
(e) Benzonitrile
(f) Benzyl cyanide
(g) Phenylacetic acid
(h) *p*-Nitrobenzoyl chloride
(i) *m*-Nitrobenzoyl chloride
(j) Aniline

20.30 The saponification of ^{18}O-labeled ethyl propanoate was described in Section 20.10 as one of the significant experiments that demonstrated acyl–oxygen cleavage in ester hydrolysis. The ^{18}O-labeled ethyl propanoate used in this experiment was prepared from ^{18}O-labeled ethyl alcohol, which in turn was obtained from acetaldehyde and ^{18}O-enriched water. Write a series of equations showing the preparation of $CH_3CH_2C(=O)OCH_2CH_3$ (where O = ^{18}O) from these starting materials.

20.31 Suggest a reasonable explanation for each of the following observations:

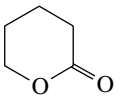
(a) The second-order rate constant k for saponification of ethyl trifluoroacetate is over 1 million times greater than that for ethyl acetate (25°C).

(b) The second-order rate constant for saponification of ethyl 2,2-dimethylpropanoate, $(CH_3)_3CCO_2CH_2CH_3$, is almost 100 times smaller than that for ethyl acetate (30°C).

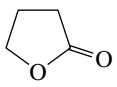
(c) The second-order rate constant k for saponification of methyl acetate is 100 times greater than that for *tert*-butyl acetate (25°C).

(d) The second-order rate constant k for saponification of methyl *m*-nitrobenzoate is 40 times greater than that for methyl benzoate (25°C).

(e) The second-order rate constant k for saponification of 5-pentanolide is over 20 times greater than that for 4-butanolide (25°C).

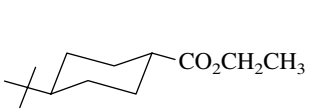


5-Pentanolide

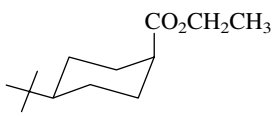


4-Butanolide

(f) The second-order rate constant k for saponification of ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate is 20 times greater than that for its cis diastereomer (25°C).

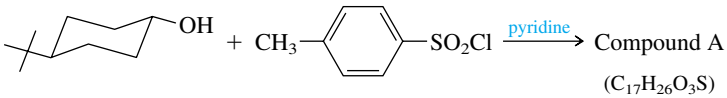


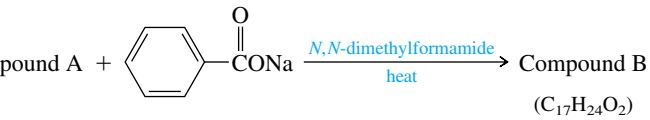
Ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate

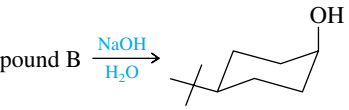


Ethyl *cis*-4-*tert*-butylcyclohexanecarboxylate

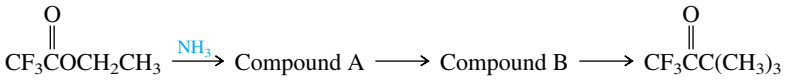
20.32 The preparation of *cis*-4-*tert*-butylcyclohexanol from its trans stereoisomer was carried out by the following sequence of steps. Write structural formulas, including stereochemistry, for compounds A and B.

Step 1: 

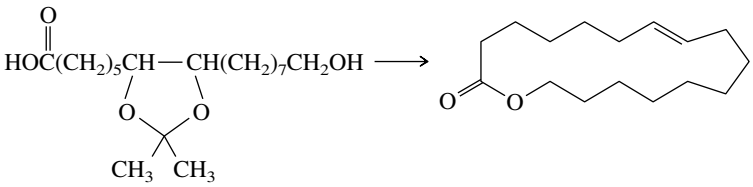
Step 2: 

Step 3: 

20.33 The ketone shown was prepared in a three-step sequence from ethyl trifluoroacetate. The first step in the sequence involved treating ethyl trifluoroacetate with ammonia to give a compound A. Compound A was in turn converted to the desired ketone by way of a compound B. Fill in the missing reagents in the sequence shown, and give the structures of compounds A and B.



20.34 *Ambrettolide* is obtained from hibiscus and has a musk-like odor. Its preparation from a compound A is outlined in the table that follows. Write structural formulas, ignoring stereochemistry, for compounds B through G in this synthesis. (*Hint:* Zinc, as used in step 4, converts vicinal dibromides to alkenes.)



Compound A Ambrettolide

Step	Reactant	Reagents	Product
1.	Compound A	H_2O, H^+, heat	Compound B ($C_{16}H_{32}O_5$)
2.	Compound B	HBr	Compound C ($C_{16}H_{29}Br_3O_2$)
3.	Compound C	Ethanol, H_2SO_4	Compound D ($C_{18}H_{33}Br_3O_2$)
4.	Compound D	Zinc, ethanol	Compound E ($C_{18}H_{33}BrO_2$)
5.	Compound E	Sodium acetate, acetic acid	Compound F ($C_{20}H_{36}O_4$)
6.	Compound F	KOH, ethanol, then H^+	Compound G ($C_{16}H_{30}O_3$)
7.	Compound G	Heat	Ambrettolide ($C_{16}H_{28}O_2$)

20.35 The preparation of the sex pheromone of the bollworm moth, (*E*)-9,11-dodecadien-1-yl acetate, from compound A has been described. Suggest suitable reagents for each step in this sequence.

(a) $HOCH_2CH{=}CH(CH_2)_7CO_2CH_3 \longrightarrow HC(=O)CH{=}CH(CH_2)_7CO_2CH_3$

Compound A (*E* isomer) — Compound B

(b) Compound B $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CO_2CH_3$

Compound C

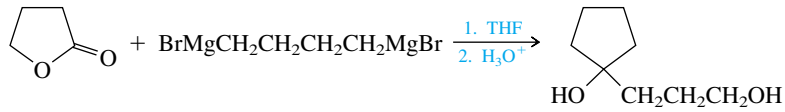
(c) Compound C $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CH_2OH$

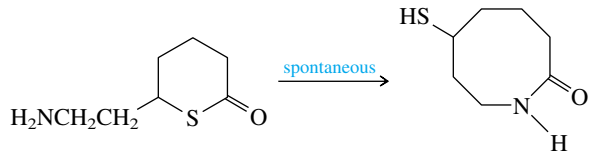
Compound D

(d) Compound D $\longrightarrow CH_2{=}CHCH{=}CH(CH_2)_7CH_2OC(=O)CH_3$

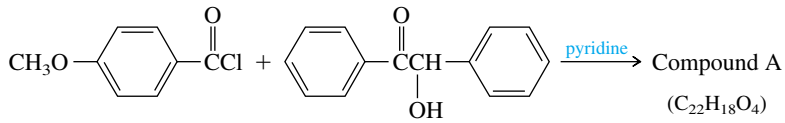
(*E*)-9,11-Dodecadien-1-yl acetate

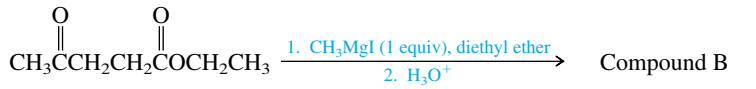
20.36 Outline reasonable mechanisms for each of the following reactions:

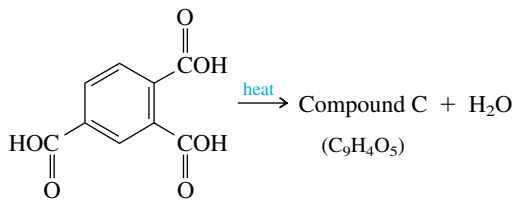
(a) 

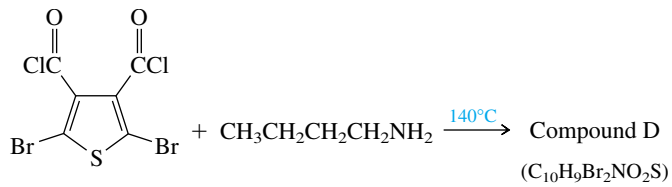
(b) 

20.37 Identify compounds A through D in the following equations:

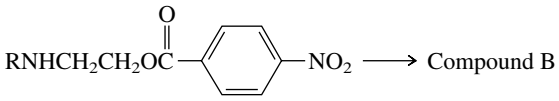
(a) 

(b) 

(c) 

(d) 

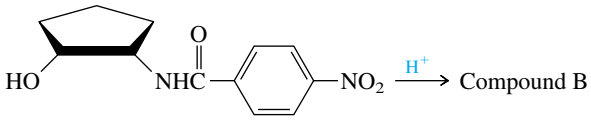
20.38 When compounds of the type represented by A are allowed to stand in pentane, they are converted to a constitutional isomer.



Compound A

Hydrolysis of either A or B yields $RNHCH_2CH_2OH$ and *p*-nitrobenzoic acid. Suggest a reasonable structure for compound B, and demonstrate your understanding of the mechanism of this reaction by writing the structure of the key intermediate in the conversion of compound A to compound B.

20.39 (a) In the presence of dilute hydrochloric acid, compound A is converted to a constitutional isomer, compound B.

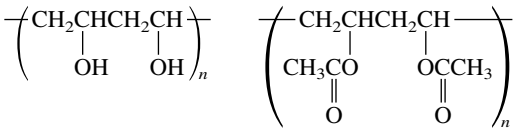


Compound A

Suggest a reasonable structure for compound B.

(b) The trans stereoisomer of compound A is stable under the reaction conditions. Why does it not rearrange?

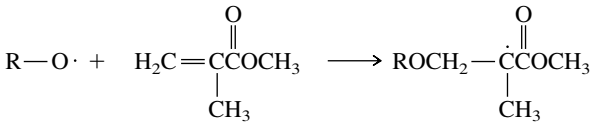
20.40 Poly(vinyl alcohol) is a useful water-soluble polymer. It cannot be prepared directly from vinyl alcohol, because of the rapidity with which vinyl alcohol ($CH_2{=}CHOH$) isomerizes to acetaldehyde. Vinyl acetate, however, does not rearrange and can be polymerized to poly(vinyl acetate). How could you make use of this fact to prepare poly(vinyl alcohol)?



Poly(vinyl alcohol) Poly(vinyl acetate)

20.41 *Lucite* is a polymer of methyl methacrylate.

(a) Assuming the first step in the polymerization of methyl methacrylate is as shown,

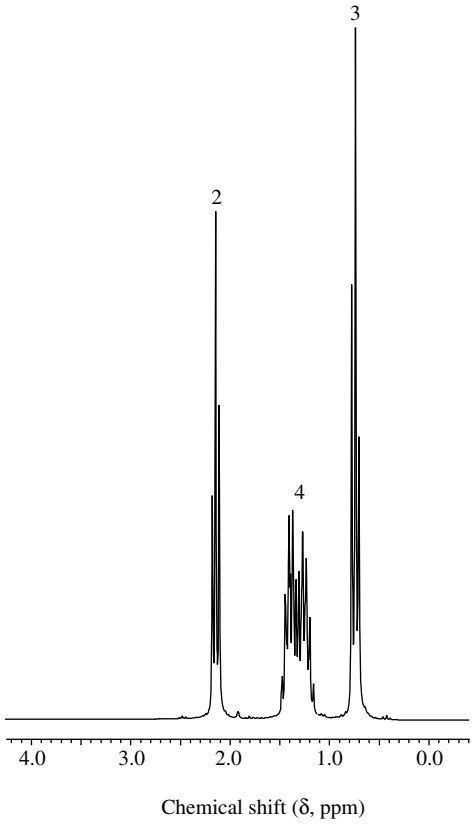


Methyl methacrylate

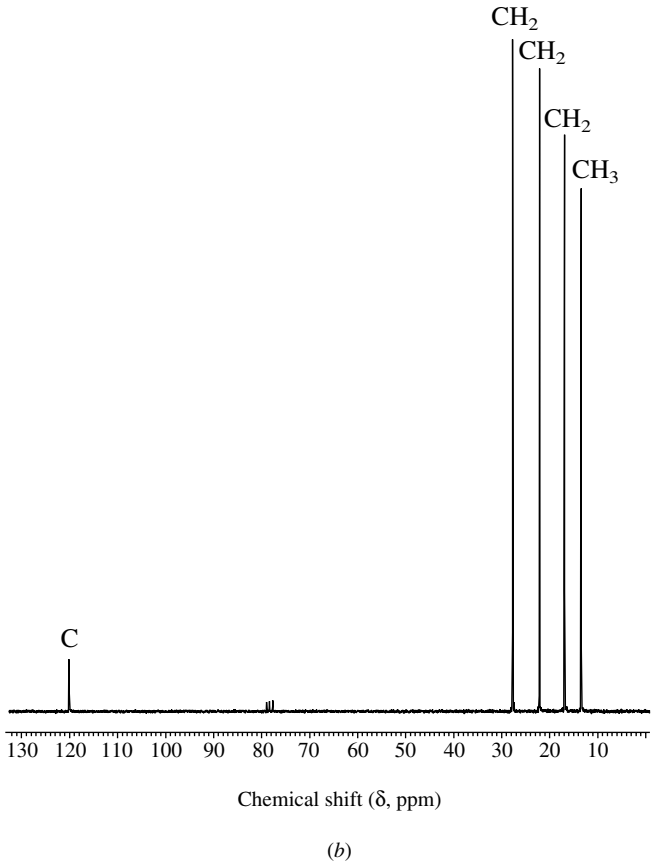
write a structural formula for the free radical produced after the next two propagation steps.

(b) Outline a synthesis of methyl methacrylate from acetone, sodium cyanide, and any necessary organic or inorganic reagents.

20.42 A certain compound has a molecular weight of 83 and contains nitrogen. Its infrared spectrum contains a moderately strong peak at 2270 cm^{-1}. Its ^1H and ^{13}C NMR spectra are shown in Figure 20.10. What is the structure of this compound?



(*a*)



(*b*)

FIGURE 20.10 The 200-MHz (*a*) ^{1}H and (*b*) ^{13}C NMR spectra of the compound in problem 20.42.

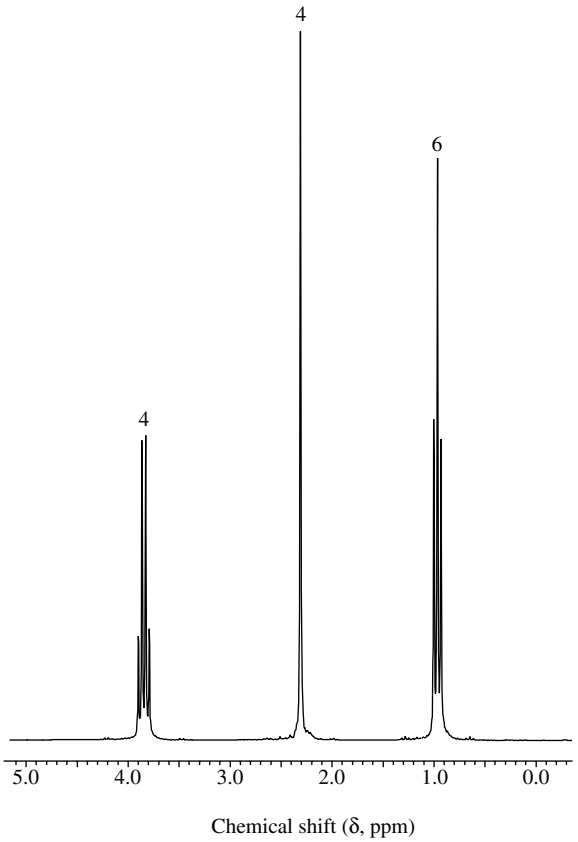


FIGURE 20.11 The 200-MHz ^{1}H NMR spectrum of the compound $C_8H_{14}O_4$ in problem 20.43.

20.43 A compound has a molecular formula of $C_8H_{14}O_4$, and its infrared spectrum contains an intense peak at 1730 cm^{-1}. The ^{1}H NMR spectrum of the compound is shown in Figure 20.11. What is its structure?

20.44 A compound ($C_4H_6O_2$) has a strong band in the infrared at 1760 cm^{-1}. Its ^{13}C NMR spectrum exhibits signals at δ 20.2 (CH_3), 96.8 (CH_2), 141.8 (CH), and 167.6 ppm (C). The ^{1}H NMR spectrum of the compound has a three-proton singlet at δ 2.1 ppm along with three other signals, each of which is a doublet of doublets, at δ 4.7, 4.9, and 7.3 ppm. What is the structure of the compound?

20.45 Excluding enantiomers, there are three isomeric cyclopropanedicarboxylic acids. Two of them, A and B, are constitutional isomers of each other, and each forms a cyclic anhydride on being heated. The third diacid, C, does not form a cyclic anhydride. C is a constitutional isomer of A and a stereoisomer of B. Identify A, B, and C. Construct molecular models of the cyclic anhydrides formed on heating A and B. Why doesn't C form a cyclic anhydride?