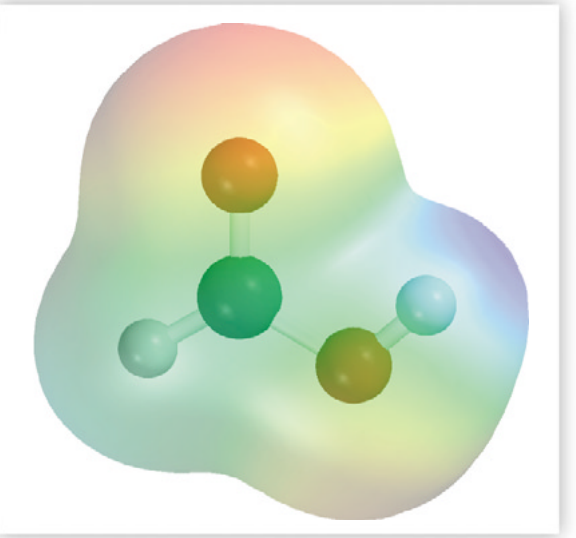
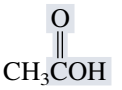


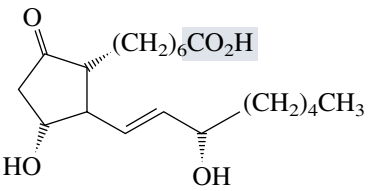
# CHAPTER 19

## CARBOXYLIC ACIDS

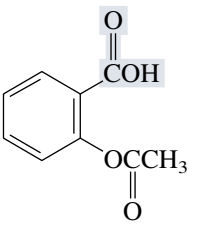
Carboxylic acids, compounds of the type $RC(=O)OH$, constitute one of the most frequently encountered classes of organic compounds. Countless natural products are carboxylic acids or are derived from them. Some carboxylic acids, such as acetic acid, have been known for centuries. Others, such as the 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-

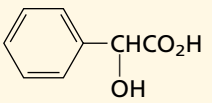
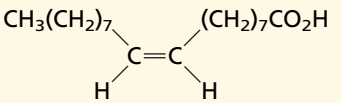
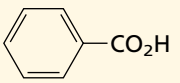
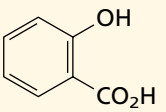
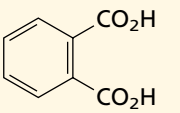
lowing this one. Together, this chapter and the next tell the story of some of the most fundamental structural types and functional group transformations in organic and biological chemistry.

## 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)

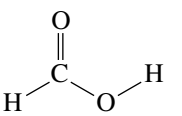
(d) $CH_3C_6H_4CO_2H$ (*p*-Toluic acid)

**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°.

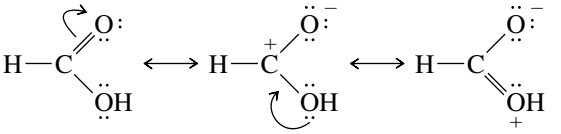
| *Bond Distances* | |
|---|---|
| C=O | 120 pm |
| C—O | 134 pm |



| *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.

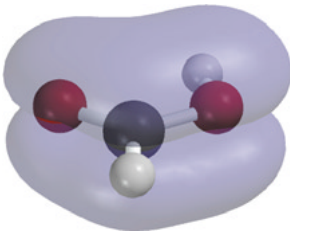
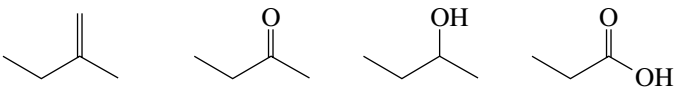


**FIGURE 19.1** Carbon and both oxygens are $sp^2$-hybridized in formic acid. The π component of the C═O group and the *p* orbital of the OH oxygen overlap to form an extended π system that includes carbon and the two oxygens.

## 19.3 PHYSICAL PROPERTIES

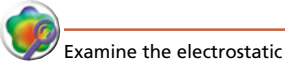
The melting points and boiling points of carboxylic acids are higher than those of hydrocarbons and oxygen-containing organic compounds of comparable size and shape and indicate strong intermolecular attractive forces.



| | 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.

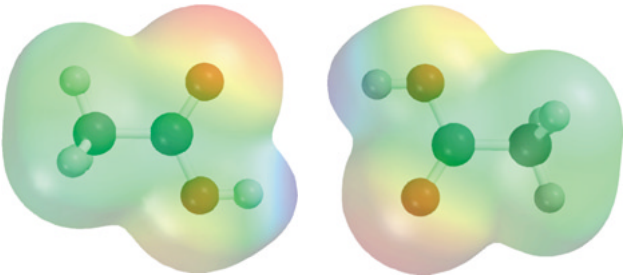


**FIGURE 19.2** Attractions between regions of positive (*blue*) and negative (*red*) electrostatic potential are responsible for intermolecular hydrogen bonding between two molecules of acetic acid.

## 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

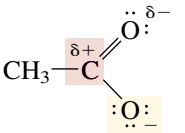
$$\Delta G^\circ = -RT \ln K_a$$

From these $K_a$ values, the calculated free energies of ionization ($\Delta G^\circ$) 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.

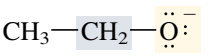
The large difference in the free energies of ionization of ethanol and acetic acid reflects a greater stabilization of acetate ion relative to ethoxide ion. Ionization of ethanol yields an alkoxide ion in which the negative charge is localized on oxygen. Solvation forces are the chief means by which 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.

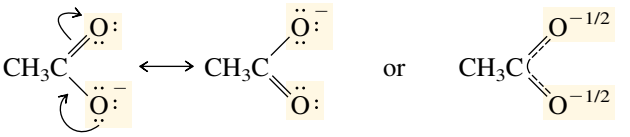
Positively polarized carbon attracts electrons from negatively charged oxygen.



$CH_2$ 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 ($CH_3C(=O)OOH$) is a weaker acid than acetic acid; its $K_a$ is $6.3 \times 10^{-9}$ ($pK_a$ 8.2) versus $1.8 \times 10^{-5}$ 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.

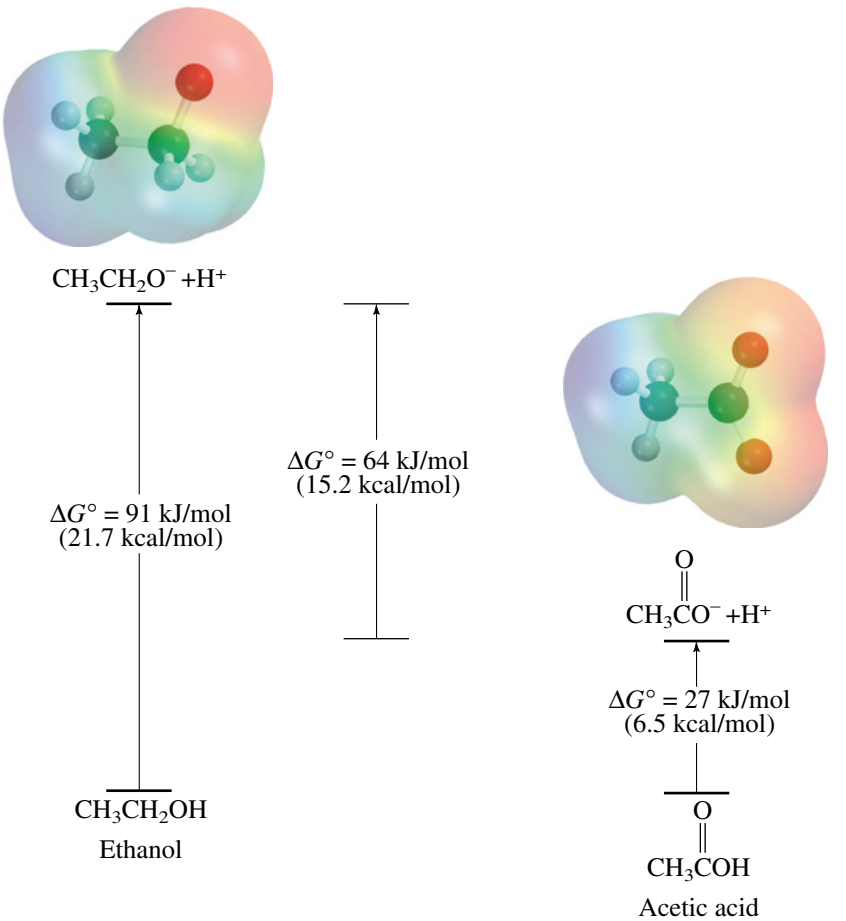
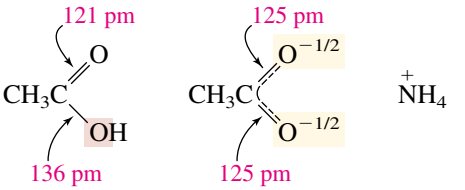



**FIGURE 19.3** Diagram comparing the free energies of ionization of ethanol and acetic acid in water. The electrostatic potential maps of ethoxide and acetate ion show the concentration of negative charge in ethoxide versus dispersal of charge in acetate.

(*a*) (*b*)

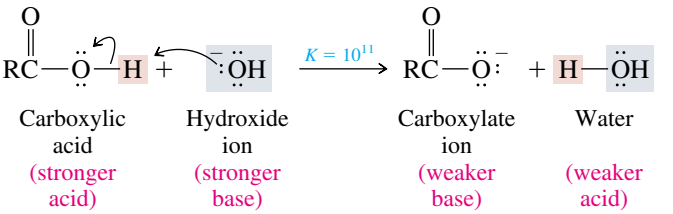
**FIGURE 19.4** Electrostatic potential maps of (*a*) acetic acid and (*b*) acetate ion. The negative charge (*red*) is equally distributed between both oxygens of acetate ion.




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_a$16), 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.

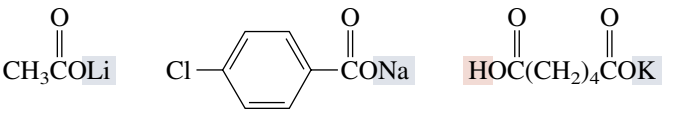
This difference in behavior for acetic acid in pure water versus water buffered at pH = 7.0 has some important practical consequences. Biochemists usually do not talk about acetic acid (or lactic acid, or salicylic acid, etc.). They talk about acetate (and lactate, and salicylate). Why? It's because 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



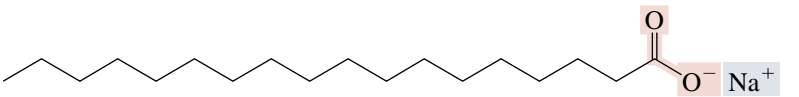
Sodium *p*-chlorobenzoate



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

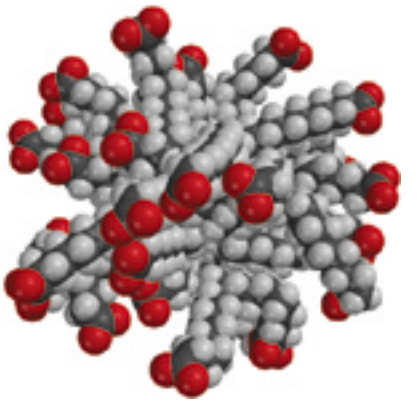


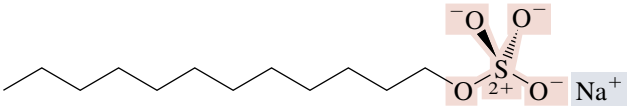
**FIGURE 19.5** A space-filling model of a micelle formed by association of carboxylate ions derived from a fatty acid. In general, the hydrophobic carbon chains are inside and the carboxylate ions on the surface, but the micelle is irregular, and contains voids, channels, and tangled carbon chains. 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)

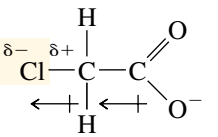
Detergents are designed to be effective in hard water, meaning water containing calcium salts that form insoluble calcium carboxylates with soaps. These precipitates rob the soap of its cleansing power and form an unpleasant scum. The calcium salts of synthetic detergents such as sodium lauryl sulfate, 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 $K_a$* | p$K_a$ |
|---|---|---|---|
| **Standard of comparison.** | | | |
| Acetic acid | $CH_3CO_2H$ | $1.8 \times 10^{-5}$ | 4.7 |
| **Alkyl substituents have a negligible effect on acidity.** | | | |
| Propanoic acid | $CH_3CH_2CO_2H$ | $1.3 \times 10^{-5}$ | 4.9 |
| 2-Methylpropanoic acid | $(CH_3)_2CHCO_2H$ | $1.6 \times 10^{-5}$ | 4.8 |
| 2,2-Dimethylpropanoic acid | $(CH_3)_3CCO_2H$ | $0.9 \times 10^{-5}$ | 5.1 |
| Heptanoic acid | $CH_3(CH_2)_5CO_2H$ | $1.3 \times 10^{-5}$ | 4.9 |
| **α-Halogen substituents increase acidity.** | | | |
| Fluoroacetic acid | $FCH_2CO_2H$ | $2.5 \times 10^{-3}$ | 2.6 |
| Chloroacetic acid | $ClCH_2CO_2H$ | $1.4 \times 10^{-3}$ | 2.9 |
| Bromoacetic acid | $BrCH_2CO_2H$ | $1.4 \times 10^{-3}$ | 2.9 |
| Dichloroacetic acid | $Cl_2CHCO_2H$ | $5.0 \times 10^{-2}$ | 1.3 |
| Trichloroacetic acid | $Cl_3CCO_2H$ | $1.3 \times 10^{-1}$ | 0.9 |
| **Electron-attracting groups increase acidity.** | | | |
| Methoxyacetic acid | $CH_3OCH_2CO_2H$ | $2.7 \times 10^{-4}$ | 3.6 |
| Cyanoacetic acid | $N{\equiv}CCH_2CO_2H$ | $3.4 \times 10^{-3}$ | 2.5 |
| Nitroacetic acid | $O_2NCH_2CO_2H$ | $2.1 \times 10^{-2}$ | 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 |
| $K_a = 1.4 \times 10^{-3}$ | $K_a = 1.0 \times 10^{-4}$ | $K_a = 3.0 \times 10^{-5}$ |
| p$K_a$ = 2.9 | p$K_a$ = 4.0 | p$K_a$ = 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.

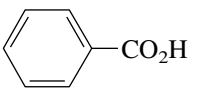
It is a curious fact that substituents affect the entropy of ionization more than they do the enthalpy term in the expression

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

The enthalpy term $\Delta H^\circ$ is close to zero for the ionization of most carboxylic acids, regardless of their strength. The free energy of ionization $\Delta G^\circ$ 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; $\Delta S^\circ$ 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

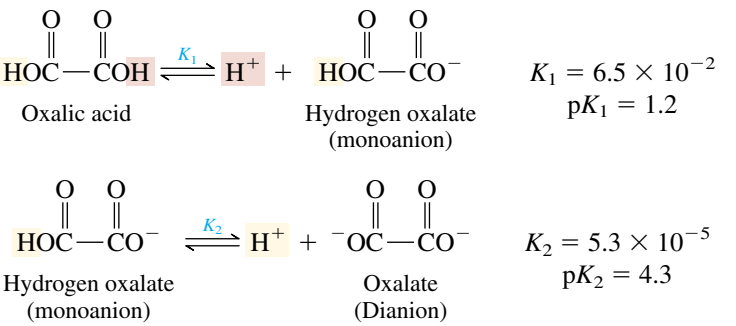
| Substituent in $XC_6H_4CO_2H$ | $K_a$ ($pK_a$)* for different positions of substituent X | | |
|---|---|---|---|
| | Ortho | Meta | Para |
| 1. H | $6.3 \times 10^{-5}$ (4.2) | $6.3 \times 10^{-5}$ (4.2) | $6.3 \times 10^{-5}$ (4.2) |
| 2. $CH_3$ | $1.2 \times 10^{-4}$ (3.9) | $5.3 \times 10^{-5}$ (4.3) | $4.2 \times 10^{-5}$ (4.4) |
| 3. F | $5.4 \times 10^{-4}$ (3.3) | $1.4 \times 10^{-4}$ (3.9) | $7.2 \times 10^{-5}$ (4.1) |
| 4. Cl | $1.2 \times 10^{-3}$ (2.9) | $1.5 \times 10^{-4}$ (3.8) | $1.0 \times 10^{-4}$ (4.0) |
| 5. Br | $1.4 \times 10^{-3}$ (2.8) | $1.5 \times 10^{-4}$ (3.8) | $1.1 \times 10^{-4}$ (4.0) |
| 6. I | $1.4 \times 10^{-3}$ (2.9) | $1.4 \times 10^{-4}$ (3.9) | $9.2 \times 10^{-5}$ (4.0) |
| 7. $CH_3O$ | $8.1 \times 10^{-5}$ (4.1) | $8.2 \times 10^{-5}$ (4.1) | $3.4 \times 10^{-5}$ (4.5) |
| 8. $O_2N$ | $6.7 \times 10^{-3}$ (2.2) | $3.2 \times 10^{-4}$ (3.5) | $3.8 \times 10^{-4}$ (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 |
| $K_1$ $6.5 \times 10^{-2}$ | $K_1$ $1.4 \times 10^{-3}$ | $K_1$ $3.1 \times 10^{-5}$ |
| ($pK_1$ 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 $4.3 \times 10^{-7}$ ($pK_a < 6.4$). 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, $4.3 \times 10^{-7}$, 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 $3.6 \times 10^7$ 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 $5.6 \times 10^{-11}$ ($pK_a$ 10.2). Bicarbonate is a weaker acid than carboxylic acids but a stronger acid than water and alcohols.

## 19.10 SOURCES OF CARBOXYLIC ACIDS

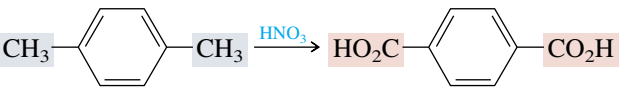
Many carboxylic acids were first isolated from natural sources and were given names based on their origin. Formic acid (Latin *formica,* "ant") was obtained by distilling ants. Since ancient times acetic acid (Latin *acetum,* "vinegar") has been known to be present in wine that has turned sour. Butyric 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 $3 \times 10^9$ 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 $5 \times 10^9$ 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)

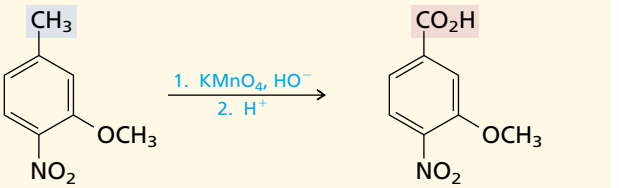
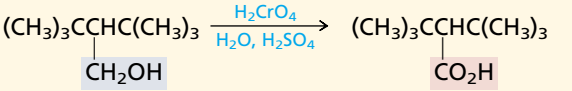
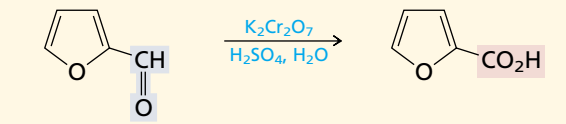
You will recognize the side-chain oxidation of *p*-xylene to terephthalic acid as a reaction type discussed previously (Section 11.13). Examples of other reactions encountered earlier that can be applied to the synthesis of carboxylic acids are collected in Table 19.4.

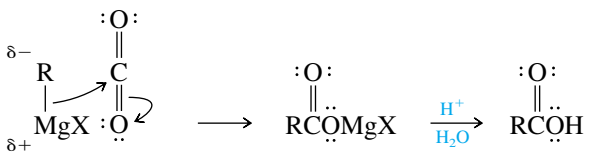
The examples in the table give carboxylic acids that have the same number of carbon atoms as the starting material. The reactions to be described in the next two sections permit carboxylic acids to be prepared by extending a chain by one carbon atom and are of great value in laboratory syntheses of carboxylic 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.

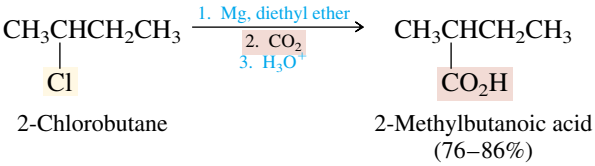
**TABLE 19.4** Summary of Reactions Discussed in Earlier Chapters That Yield Carboxylic Acids

| 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. | $ArCHR_2 \xrightarrow[K_2Cr_2O_7,\ H_2SO_4]{KMnO_4\ or} ArCO_2H$<br>Alkylbenzene → Arenecarboxylic acid<br>  <br>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. | $RCH_2OH \xrightarrow[K_2Cr_2O_7,\ H_2SO_4]{KMnO_4\ or} RCO_2H$<br>Primary alcohol → Carboxylic acid<br>  <br>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. | $RCH{=}O \xrightarrow{\text{oxidizing agent}} RCO_2H$<br>Aldehyde → Carboxylic acid<br>  <br>Furan-2-carbaldehyde (furfural) → Furan-2-carboxylic acid (furoic acid) (75%) |

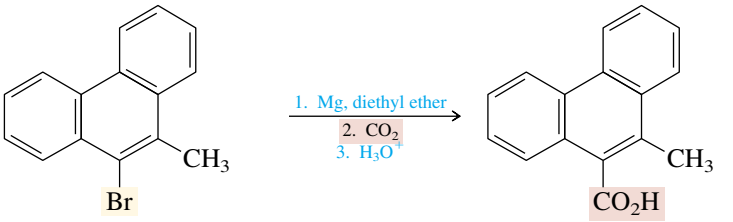



Grignard reagent acts as a nucleophile toward carbon dioxide → Halomagnesium carboxylate → Carboxylic acid

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%)

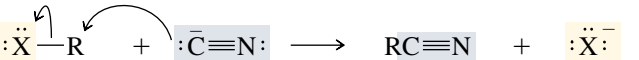



9-Bromo-10-methylphenanthrene — 10-Methylphenanthrene-9-carboxylic acid (82%)

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.



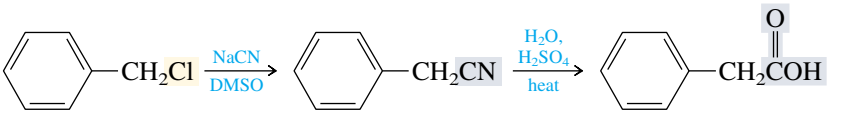

Primary or secondary alkyl halide — Cyanide ion — Nitrile (alkyl cyanide) — Halide ion

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.

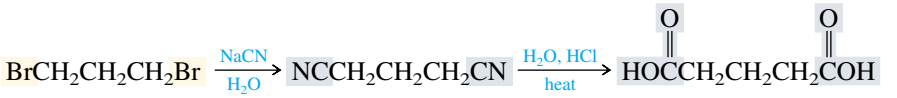
The mechanism of nitrile hydrolysis will be described in Section 20.19.


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%)

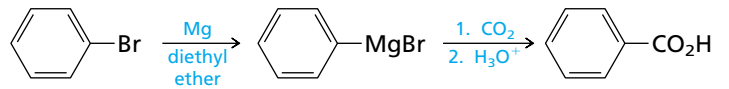
**PROBLEM 19.7** Of the two procedures just described, preparation and carboxylation of a Grignard reagent or formation and hydrolysis of a nitrile, only one is appropriate to each of the following RX → $RCO_2H$ conversions. Identify the correct procedure in each case, and specify why the other will fail.

(a) Bromobenzene → benzoic acid

(b) 2-Chloroethanol → 3-hydroxypropanoic acid

(c) *tert*-Butyl chloride → 2,2-dimethylpropanoic acid

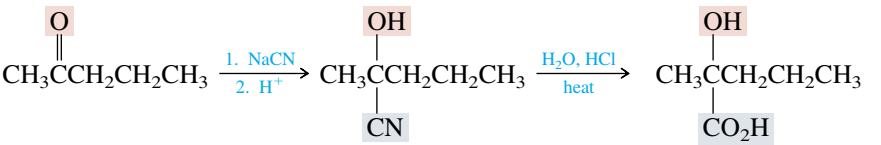
**SAMPLE SOLUTION** (a) Bromobenzene is an aryl halide and is unreactive toward nucleophilic substitution by cyanide ion. The route $C_6H_5Br \rightarrow C_6H_5CN \rightarrow C_6H_5CO_2H$ fails because the first step fails. The route proceeding through the Grignard reagent is perfectly satisfactory and 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.

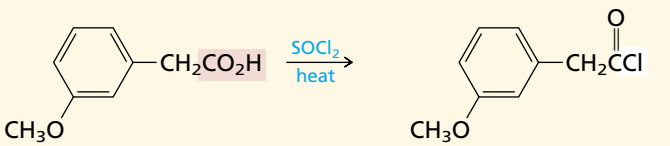
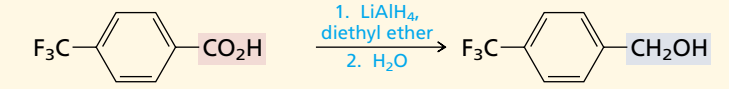
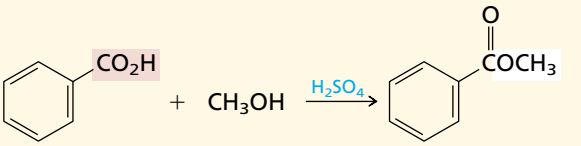



2-Pentanone — 2-Pentanone cyanohydrin — 2-Hydroxy-2-methylpentanoic acid (60% from 2-pentanone)

## 19.13 REACTIONS OF CARBOXYLIC ACIDS: A REVIEW AND A PREVIEW

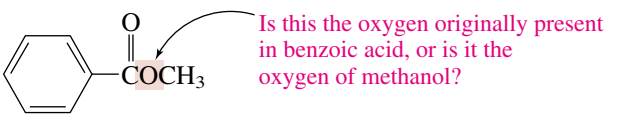
The most apparent chemical property of carboxylic acids, their acidity, has already been examined in earlier sections of this chapter. Three reactions of carboxylic acids—conversion to acyl chlorides, reduction, and esterification—have been encountered in previous chapters and are reviewed in Table 19.5. 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. | $RCO_2H + SOCl_2 \longrightarrow RCCl + SO_2 + HCl$<br>Carboxylic acid; Thionyl chloride; Acyl chloride; Sulfur dioxide; Hydrogen chloride<br>  <br>*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. | $RCO_2H \xrightarrow[2.\ H_2O]{1.\ LiAlH_4,\ \text{diethyl ether}} RCH_2OH$<br>Carboxylic acid; Primary alcohol<br>  <br>*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. | $RCO_2H + R'OH \overset{H^+}{\rightleftharpoons} RCOR' + H_2O$<br>Carboxylic acid; Alcohol; Ester; Water<br>  <br>Benzoic acid; Methanol; Methyl benzoate (70%) |

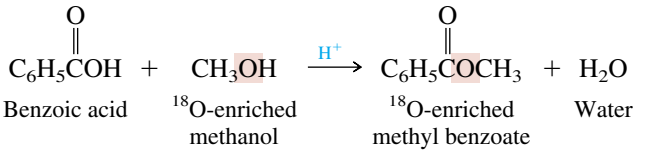
## 19.14 MECHANISM OF ACID-CATALYZED ESTERIFICATION

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.

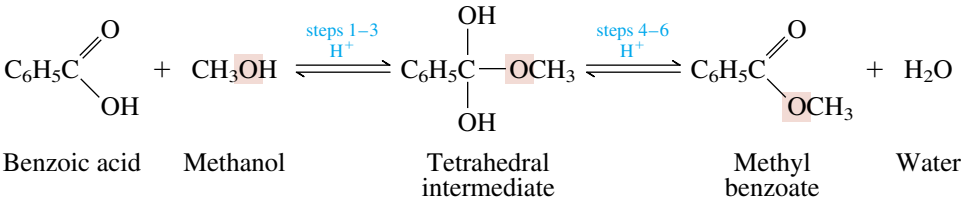
A clear-cut answer was provided by Irving Roberts and Harold C. Urey of Columbia University in 1938. They prepared methanol that had been enriched in the mass-18 isotope of oxygen. When this sample of methanol was esterified with benzoic acid, the methyl benzoate product contained all the $^{18}O$ label 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.

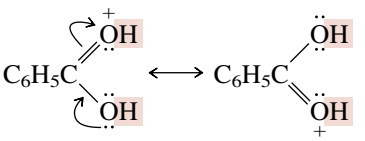
A mechanism consistent with these facts is presented in Figure 19.6. The six steps are best viewed as a combination of two distinct stages. *Formation* of a **tetrahedral intermediate** characterizes the first stage (steps 1–3), and *dissociation* of this tetrahedral intermediate characterizes the second (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.

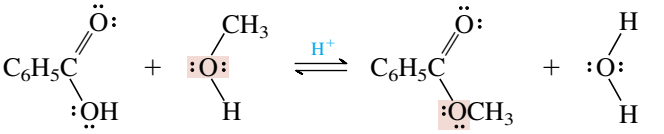
Notice, too, that the carbonyl oxygen of the carboxylic acid is protonated in the first step and not the hydroxyl oxygen. The species formed by protonation of the carbonyl oxygen is more stable, because it is stabilized by electron delocalization. The positive charge is shared equally by both oxygens.



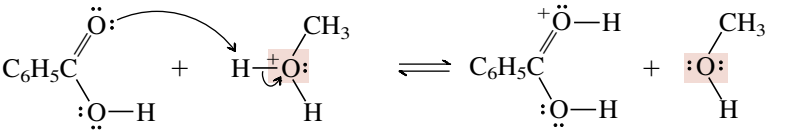
Electron delocalization in carbonyl-protonated benzoic acid

**FIGURE 19.6** The mechanism of acid-catalyzed esterification of benzoic acid with methanol.

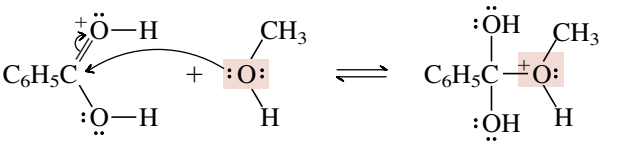
**The overall reaction:**



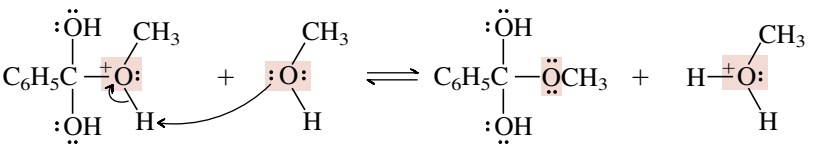

**Step 1:** The carboxylic acid is protonated on its carbonyl oxygen. The proton donor shown in the equation for this step is an alkyloxonium ion formed by proton transfer from the acid catalyst to the alcohol.




**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.

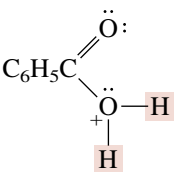



**Step 3:** The oxonium ion formed in step 2 loses a proton to give the tetrahedral intermediate in its neutral form. This step concludes the first stage in the mechanism.




—Cont.

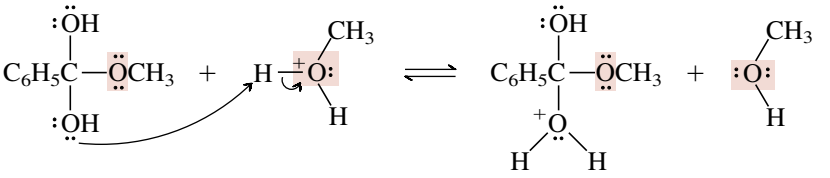
Protonation of the hydroxyl oxygen, on the other hand, yields a less stable cation:



Localized positive charge in hydroxyl-protonated benzoic acid

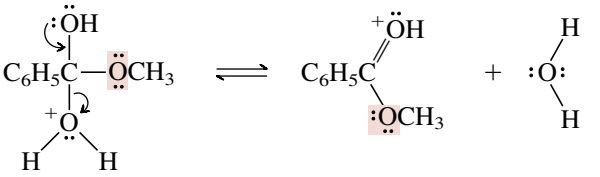
*(Continued)*

**Step 4:** The second stage begins with protonation of the tetrahedral intermediate on one of its hydroxyl oxygens.



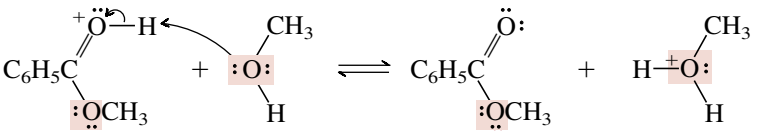
Tetrahedral intermediate | Methyloxonium ion | Hydroxyl-protonated tetrahedral intermediate | Methanol

**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.

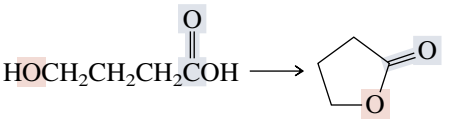
In the next chapter the three elements of the mechanism just described will be seen again as part of the general theme that unites the chemistry of carboxylic acid derivatives. These elements are

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

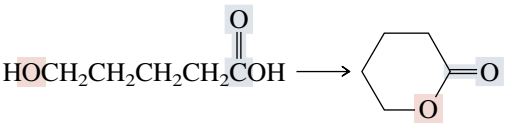
This sequence is one of the fundamental mechanistic patterns of organic chemistry.

## 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.**

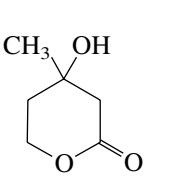


4-Hydroxybutanoic acid 4-Butanolide



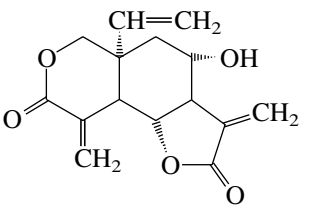
5-Hydroxypentanoic acid 5-Pentanolide

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



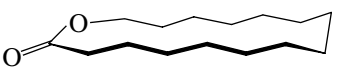
Mevalonolactone

(an intermediate in the biosynthesis of terpenes and steroids)



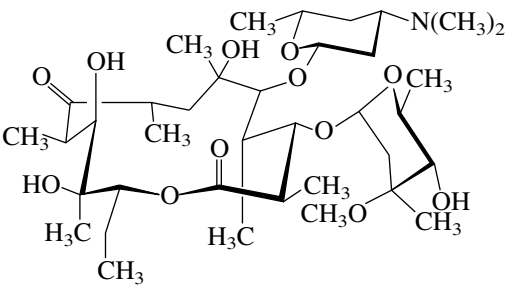
Vernolepin

(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)



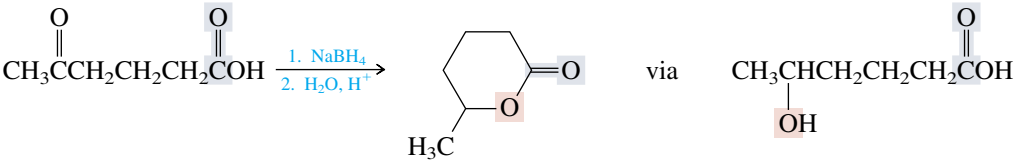
Erythromycin

(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.



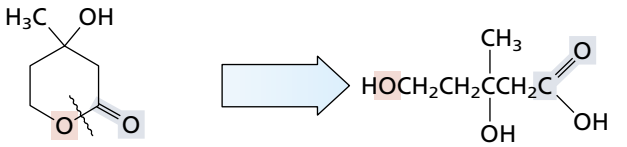

5-Oxohexanoic acid 5-Hexanolide (78%) 5-Hydroxyhexanoic acid

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.

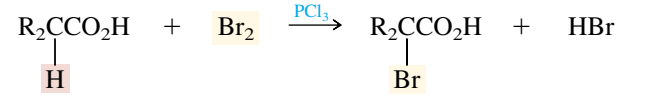
The compound *anisatin* is an example of a naturally occurring β-lactone. Its isolation and structure determination were described in the journal *Tetrahedron Letters* (1982), p. 5111.

## 19.16 α HALOGENATION OF CARBOXYLIC ACIDS: THE HELL–VOLHARD–ZELINSKY REACTION

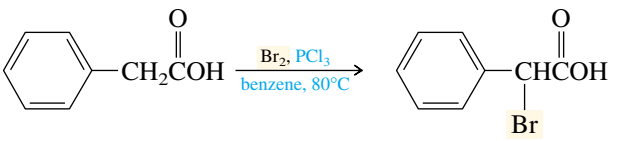
*Esterification* of carboxylic acids involves nucleophilic addition to the carbonyl group as a key step. In this respect the carbonyl group of a carboxylic acid resembles that of an aldehyde or a ketone. Do carboxylic acids resemble aldehydes and ketones in other ways? Do they, for example, form *enols,* 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.



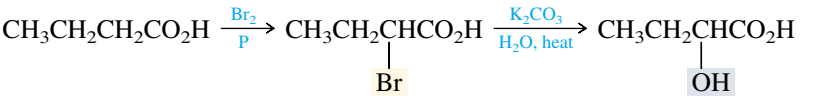

Carboxylic acid — Bromine — α-Bromo carboxylic acid — Hydrogen bromide




Phenylacetic acid — α-Bromophenylacetic acid (60–62%)

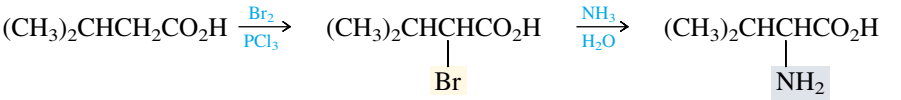
This method of α bromination of carboxylic acids is called the **Hell–Volhard–Zelinsky reaction.** This reaction is sometimes carried out by using a small amount of phosphorus instead of phosphorus trichloride. Phosphorus reacts with bromine to yield phosphorus tribromide as the active catalyst under these conditions.

The Hell–Volhard–Zelinsky reaction is of synthetic value in that the α halogen can be displaced by nucleophilic substitution:




Butanoic acid — 2-Bromobutanoic acid (77%) — 2-Hydroxybutanoic acid (69%)

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:




3-Methylbutanoic acid — 2-Bromo-3-methylbutanoic acid (88%) — 2-Amino-3-methylbutanoic acid (48%)

**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.

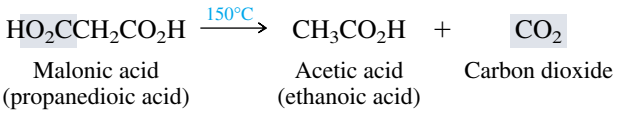
## 19.17 DECARBOXYLATION OF MALONIC ACID AND RELATED COMPOUNDS

The loss of a molecule of carbon dioxide from a carboxylic acid is known as **decarboxylation.**

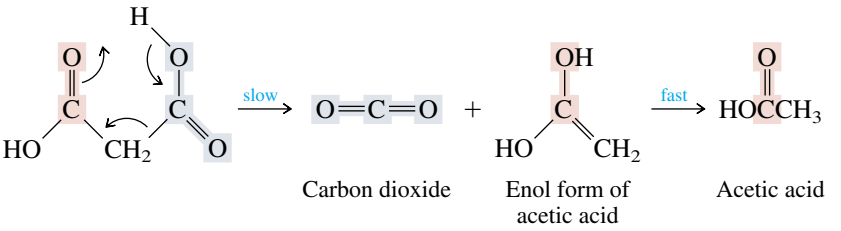

Carboxylic acid — Alkane — Carbon dioxide

Decarboxylation of simple carboxylic acids takes place with great difficulty and is rarely encountered.

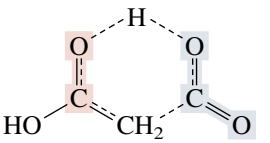
Compounds that readily undergo thermal decarboxylation include those related to malonic acid. On being heated above its melting point, malonic acid is converted to acetic acid and carbon dioxide.




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



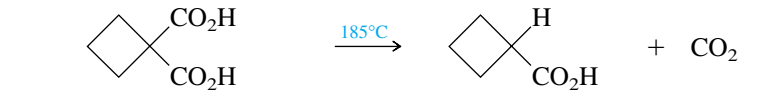

The transition state involves the carbonyl oxygen of one carboxyl group—the one that stays behind—acting as a proton acceptor toward the hydroxyl group of the carboxyl that is lost. Carbon–carbon bond cleavage leads to the enol form of acetic acid, along with a molecule of carbon dioxide.

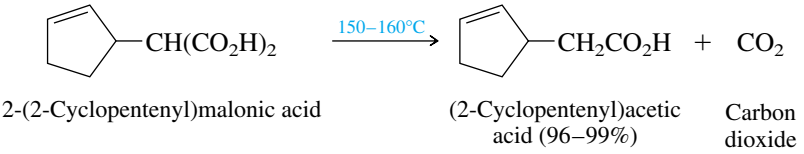


Representation of transition state in thermal decarboxylation of malonic acid

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.



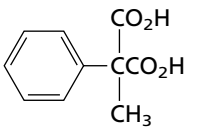



**PROBLEM 19.11** What will be the product isolated after thermal decarboxylation of each of the following? Using curved arrows, represent the bond changes that take place at the transition state.

(a) $(CH_3)_2C(CO_2H)_2$

(b) $CH_3(CH_2)_6CHCO_2H$ (with $CO_2H$ on the second carbon)

(c)

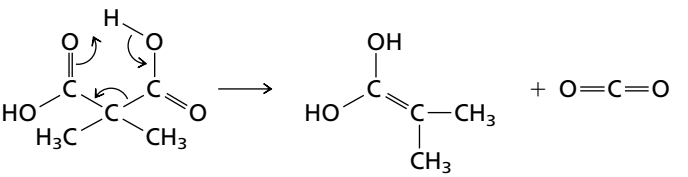


**SAMPLE SOLUTION** (a) Thermal decarboxylation of malonic acid derivatives leads to the replacement of one of the carboxyl groups by a hydrogen.

$$(CH_3)_2C(CO_2H)_2 \xrightarrow{\text{heat}} (CH_3)_2CHCO_2H + CO_2$$

2,2-Dimethylmalonic acid → 2-Methylpropanoic acid + Carbon dioxide

The transition state incorporates a cyclic array of six atoms:

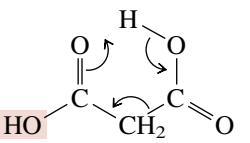


2,2-Dimethylmalonic acid → Enol form of 2-methylpropanoic acid + Carbon dioxide

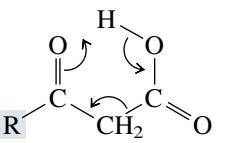
Tautomerization of the enol form to 2-methylpropanoic acid completes the process.

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.

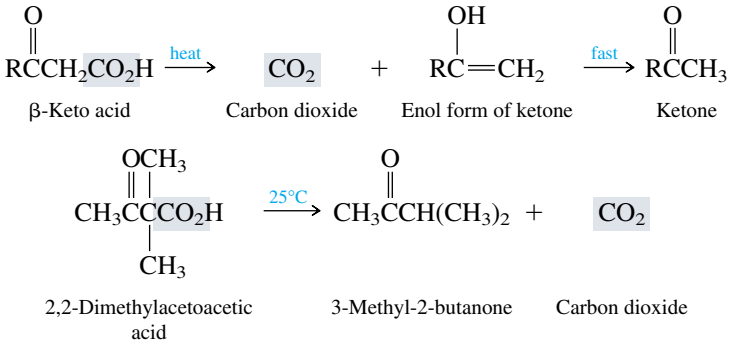


Bonding changes during decarboxylation of malonic acid



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.

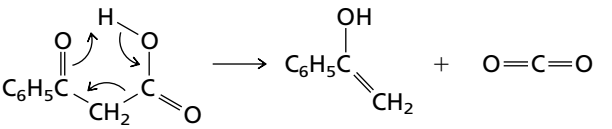



**PROBLEM 19.12** Show the bonding changes that occur, and write the structure of the intermediate formed in the thermal decarboxylation of

(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).

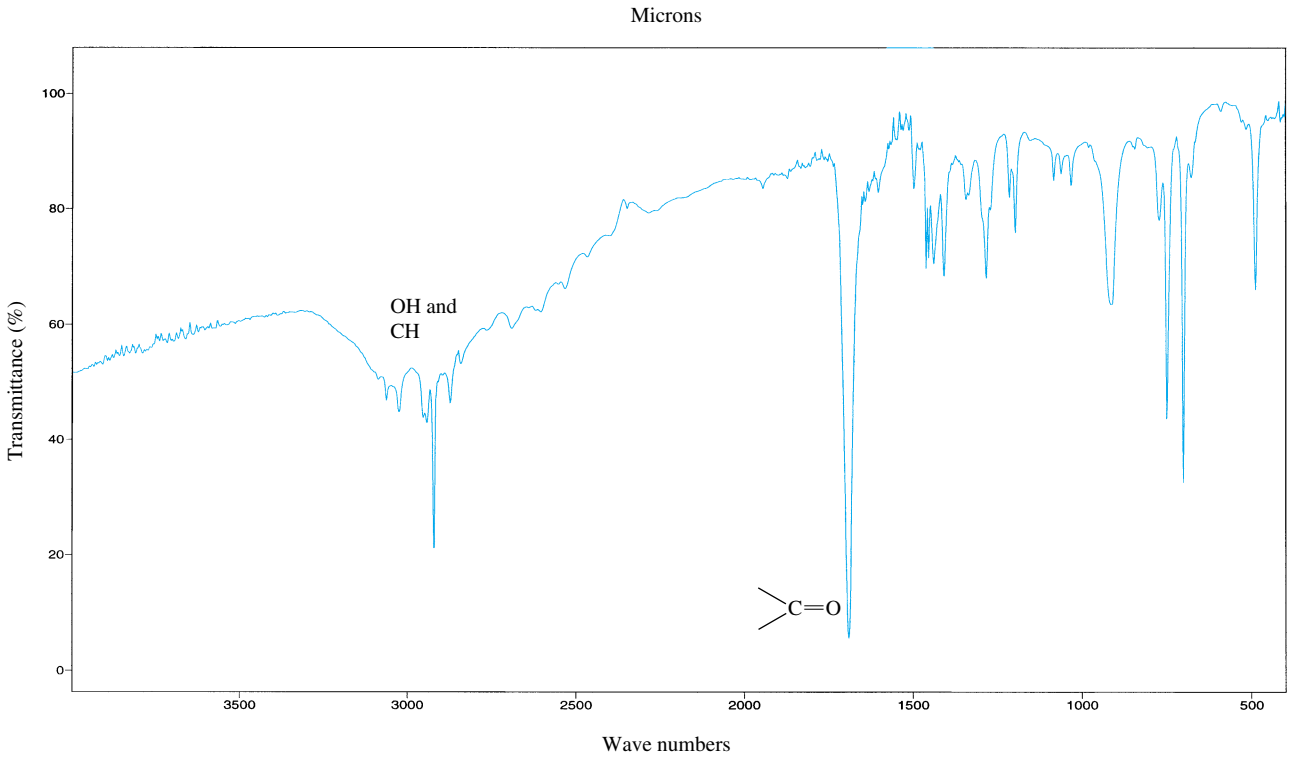



**FIGURE 19.8** The infrared spectrum of 4-phenylbutanoic acid.

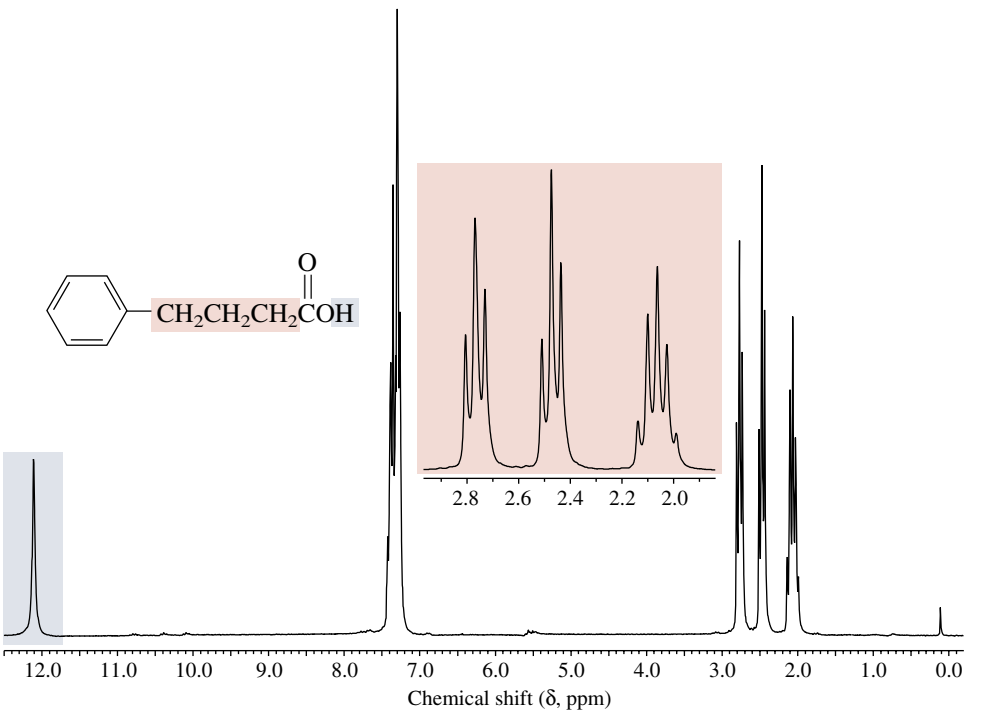
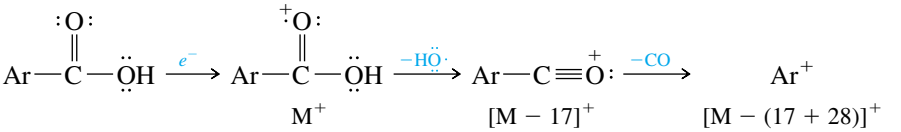



**FIGURE 19.9** The 200-MHz $^1$H NMR spectrum of 4-phenylbutanoic acid. The peak for the proton of the $CO_2H$ group is at δ 12 ppm.

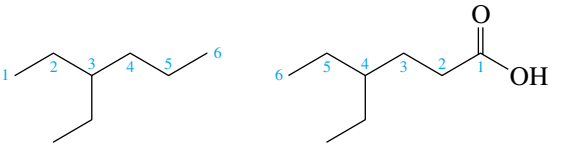
***UV-VIS:*** In the absence of any additional chromophores, carboxylic acids absorb at a wavelength (210 nm) that is not very useful for diagnostic purposes.

***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.



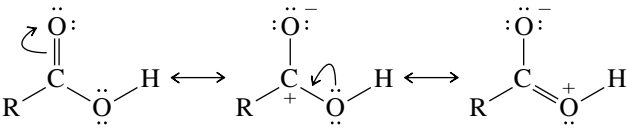

## 19.19 SUMMARY

**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.



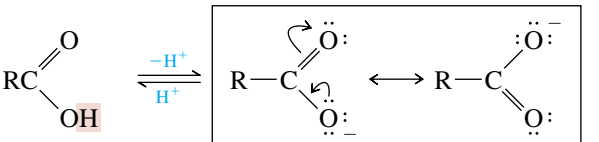

3-Ethylhexane 4-Ethylhexanoic acid

**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.

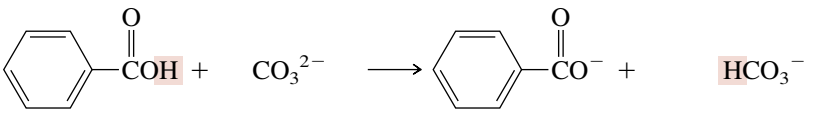
**Section 19.4** Carboxylic acids are weak acids and, in the absence of electron-attracting substituents, have dissociation constants $K_a$ of approximately $10^{-5}$ ($pK_a = 5$). Carboxylic acids are much stronger acids than alcohols because of the electron-withdrawing power of the carbonyl group (inductive effect) and its ability to delocalize negative charge in the carboxylate anion (resonance effect).




Carboxylic acid

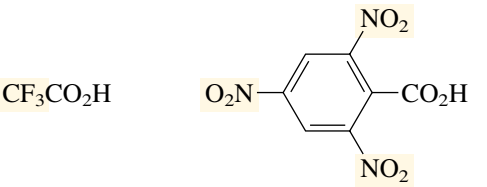
Resonance description of electron delocalization in carboxylate anion

**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)

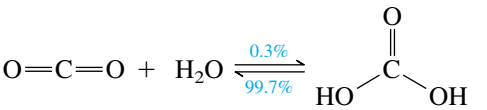
**Sections 19.6–19.7** Electronegative substituents, especially those within a few bonds of the carboxyl group, increase the acidity of carboxylic acids.




Trifluoroacetic acid $K_a = 5.9 \times 10^{-1}$ ($pK_a = 0.2$) — 2,4,6-Trinitrobenzoic acid $K_a = 2.2 \times 10^{-1}$ ($pK_a = 0.6$)

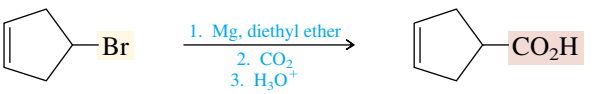
**Section 19.8** Dicarboxylic acids have separate $K_a$ values for their first and second ionizations.

**Section 19.9** Carbon dioxide and carbonic acid are in equilibrium in water. Carbon dioxide is the major component.



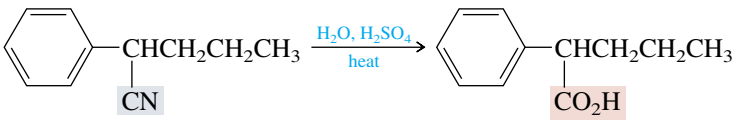

**Section 19.10** Several of the reactions introduced in earlier chapters can be used to prepare carboxylic acids (See Table 19.4).

**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.

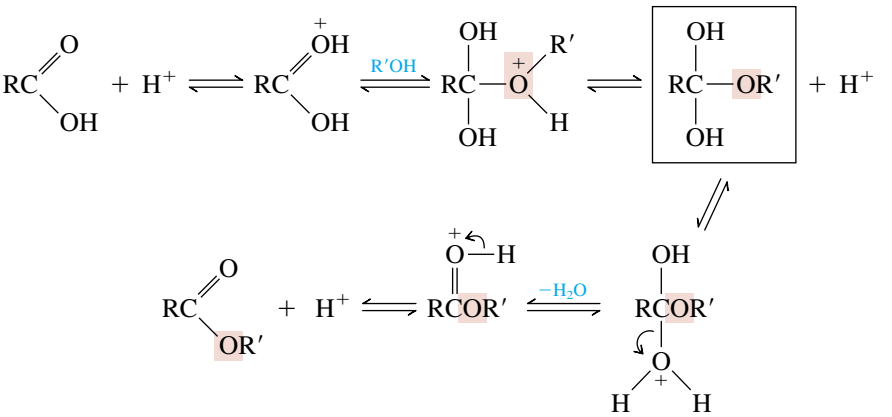



2-Phenylpentanenitrile — 2-Phenylpentanoic acid (52%)

Likewise, the cyano group of a cyanohydrin can be hydrolyzed to $—CO_2H$.

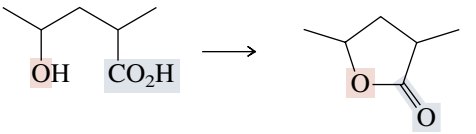
**Section 19.13** Among the reactions of carboxylic acids, their conversion to acyl chlorides, primary alcohols, and esters were introduced in earlier chapters and were reviewed in Table 19.5.

**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.



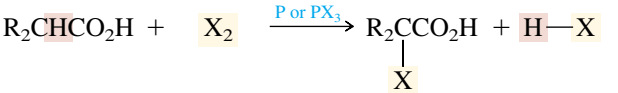

Protonation of the carbonyl oxygen activates the carbonyl group toward nucleophilic addition. Addition of an alcohol gives a tetrahedral intermediate (shown in the box in the preceding equation), which has the capacity to revert to starting materials or to undergo dehydration to yield an ester.

**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

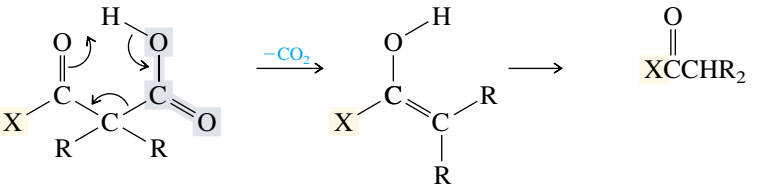
**Section 19.16** Halogenation at the α-carbon atom of carboxylic acids can be accomplished by the *Hell–Volhard–Zelinsky reaction.* An acid is treated with chlorine or bromine in the presence of a catalytic quantity of phosphorus or a phosphorus trihalide:




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*)

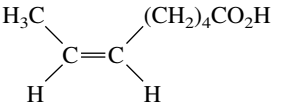
(j) *o*-Hydroxybenzenecarboxylic acid (better known as *salicylic acid,* it is obtained from willow bark)

**19.14** Give an acceptable IUPAC name for each of the following:

(a) $CH_3(CH_2)_6CO_2H$

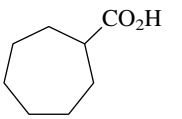
(b) $CH_3(CH_2)_6CO_2K$

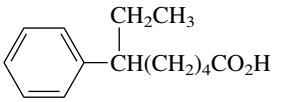
(c) $CH_2{=}CH(CH_2)_5CO_2H$

(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

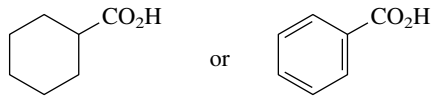
(d) Acetic acid, ethanol, trifluoroacetic acid, 2,2,2-trifluoroethanol, trifluoromethanesulfonic acid ($CF_3SO_2OH$)

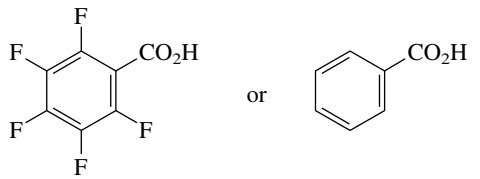
(e) Cyclopentanecarboxylic acid, 2,4-pentanedione, cyclopentanone, cyclopentene

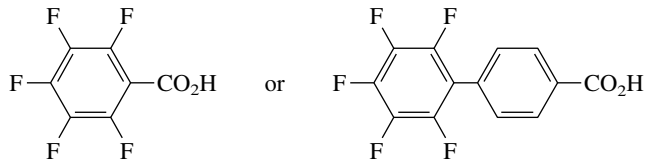
**19.16** Identify the more acidic compound in each of the following pairs:

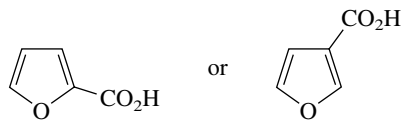
(a) $CF_3CH_2CO_2H$ or $CF_3CH_2CH_2CO_2H$

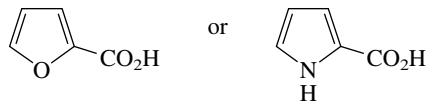
(b) $CH_3CH_2CH_2CO_2H$ or $CH_3C{\equiv}CCO_2H$

(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) $H\overset{*}{C}H$ (with O) (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) $HO_2CCH_2CO_2H$

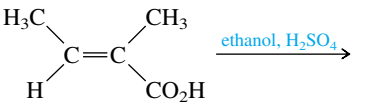
(e) $ICH_2CO_2H$

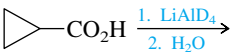
(f) $BrCH_2CO_2CH_2CH_3$

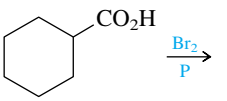
(g) $(C_6H_5)_3\overset{+}{P}-\overset{-}{\underset{\cdot\cdot}{C}}HCO_2CH_2CH_3$

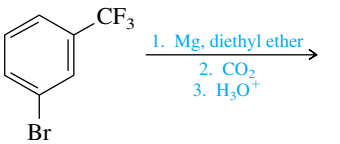
(h) $C_6H_5CH{=}CHCO_2CH_2CH_3$

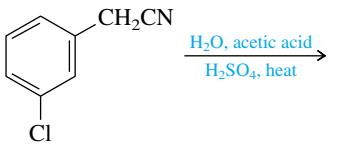
**19.22** Each of the following reactions has been reported in the chemical literature and gives a single product in good yield. What is the product in each reaction?

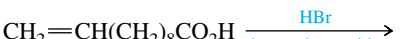
(a) 


(b) 


(c) 


(d) 


(e) 


(f) 


**19.23** Show by a series of equations how you could synthesize each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents:

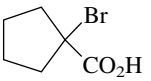
(a) 2-Methylpropanoic acid from *tert*-butyl alcohol

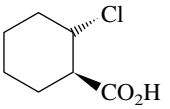
(b) 3-Methylbutanoic acid from *tert*-butyl alcohol

(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

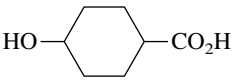
(g)  from (*E*)-ClCH=CHCO$_2$H

(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.

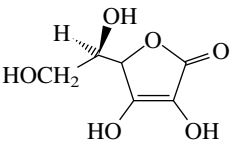
**19.25** Suggest reasonable explanations for each of the following observations.

(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.

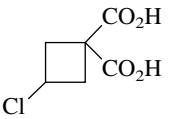
(c) The dissociation constant of *o*-hydroxybenzoic acid is greater (by a factor of 12) than that of *o*-methoxybenzoic acid.

(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?

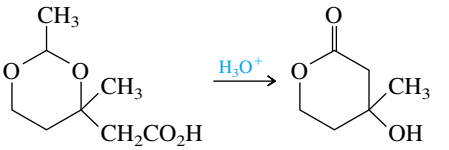


Compound A

**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 ($CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CO_2H$) 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?

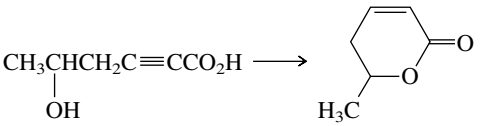
**19.29** On standing in dilute aqueous acid, compound A is smoothly converted to mevalonolactone.




Compound A Mevalonolactone

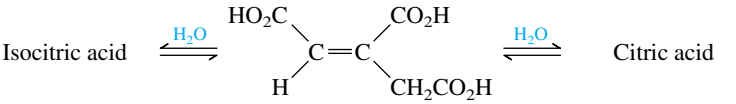
Suggest a reasonable mechanism for this reaction. What other organic product is also formed?

**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)

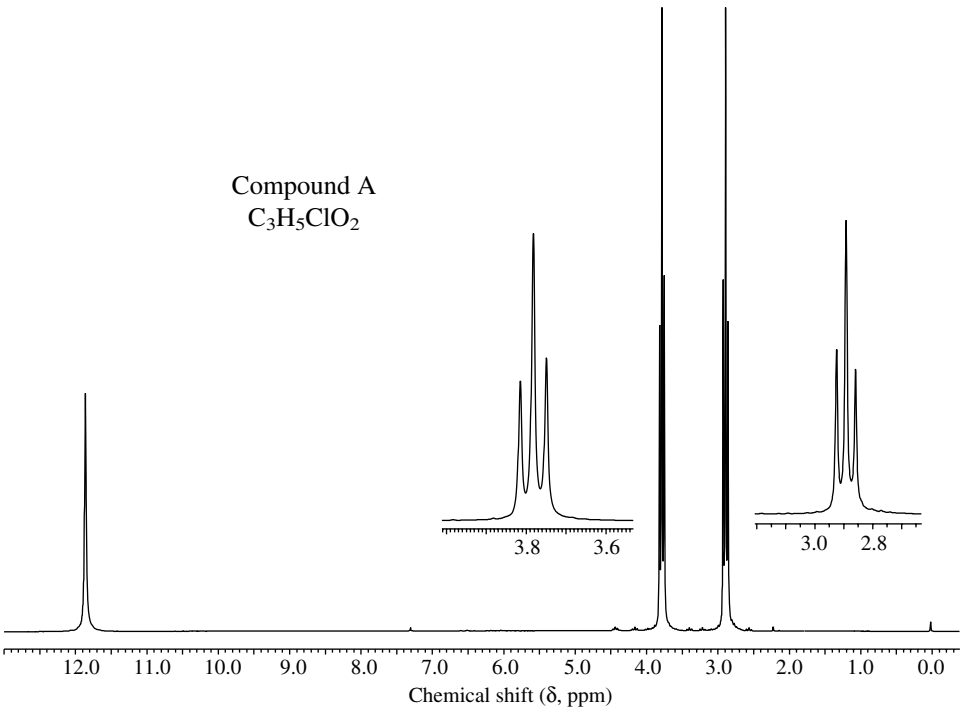



**FIGURE 19.10** The 200-MHz $^1$H NMR spectrum of compound A ($C_3H_5ClO_2$) (Problem 19.34a).

**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).

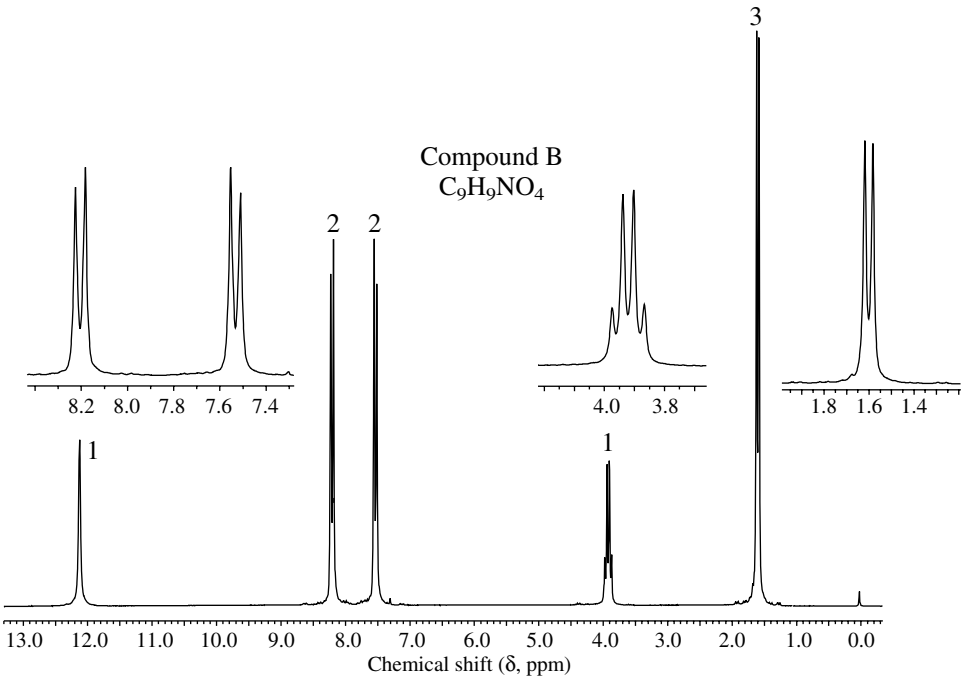



**FIGURE 19.11** The 200-MHz $^1$H NMR spectrum of compound B ($C_9H_9NO_4$) (Problem 19.34b).