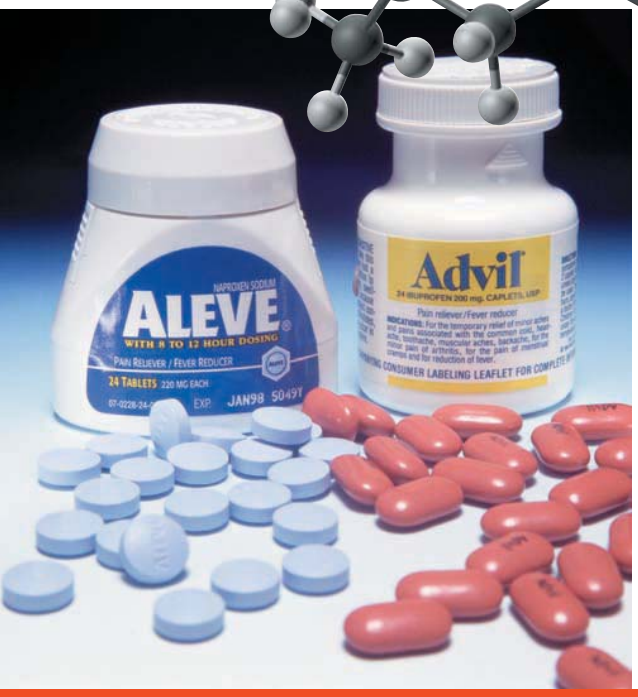
13

Carboxylic Acids



The active ingredients in these two nonprescription pain relievers are derivatives of arylpropanoic acids. See Chemical Connections 13A, "From Willow Bark to Aspirin and Beyond." Inset: A model of (*S*)-ibuprofen. (Charles D. Winters)

KEY QUESTIONS

HOW TO

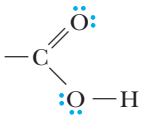
CHEMICAL CONNECTIONS

CARBOXYLIC ACIDS ARE another class of organic compounds containing the carbonyl group. Their occurrence in nature is widespread, and they are important components of foodstuffs such as vinegar, butter, and vegetable oils. The most important chemical property of carboxylic acids is their acidity. Furthermore, carboxylic acids form numerous important derivatives, including esters, amides, anhydrides, and acid halides. In this chapter, we study carboxylic acids themselves; in Chapters 14 and 15, we study their derivatives.

13.1 What Are Carboxylic Acids?

Carboxyl group A —COOH group.

The functional group of a carboxylic acid is a **carboxyl group**, so named because it is made up of a **carb**onyl group and a hydr**oxyl** group (Section 1.7D). Following is a Lewis structure of the carboxyl group, as well as two alternative representations of it:



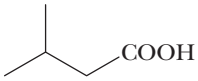
—COOH —CO_2H

The general formula of an aliphatic carboxylic acid is RCOOH; that of an aromatic carboxylic acid is ArCOOH.

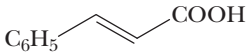
13.2 How Are Carboxylic Acids Named?

A. IUPAC System

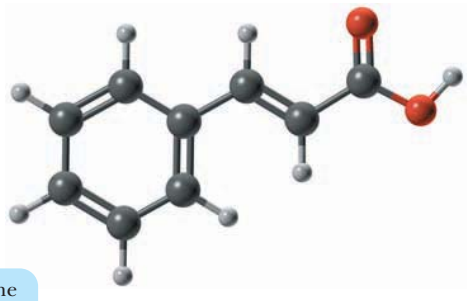
We derive the IUPAC name of a carboxylic acid from that of the longest carbon chain that contains the carboxyl group by dropping the final *-e* from the name of the parent alkane and adding the suffix *-oic*, followed by the word *acid* (Section 3.5). We number the chain beginning with the carbon of the carboxyl group. Because the carboxyl carbon is understood to be carbon 1, there is no need to give it a number. If the carboxylic acid contains a carbon–carbon double bond, we change the infix from *-an-* to *-en-* to indicate the presence of the double bond, and we show the location of the double bond by a number. In the following examples, the common name of each acid is given in parentheses:



3-Methylbutanoic acid
(Isovaleric acid)

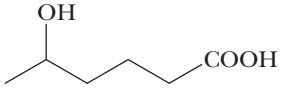


trans-3-Phenylpropenoic acid
(Cinnamic acid)

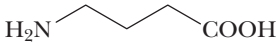


it is not necessary to indicate that the alkene occurs at position 2 because there is no other position where it can occur

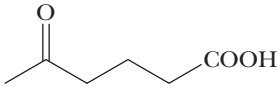
In the IUPAC system, a carboxyl group takes precedence over most other functional groups (Table 12.1), including hydroxyl and amino groups, as well as the carbonyl groups of aldehydes and ketones. As illustrated in the following examples, an —OH group of an alcohol is indicated by the prefix *hydroxy-*, an $—NH_2$ group of an amine by *amino-*, and an =O group of an aldehyde or ketone by *oxo-*:



5-Hydroxyhexanoic acid

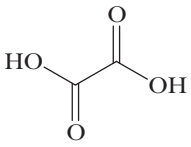


4-Aminobutanoic acid

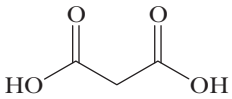


5-Oxohexanoic acid

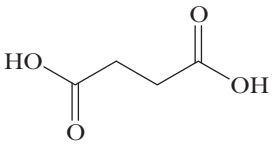
Dicarboxylic acids are named by adding the suffix *-dioic*, followed by the word *acid*, to the name of the carbon chain that contains both carboxyl groups. Because the two carboxyl groups can be only at the ends of the parent chain, there is no need to number them. Following are IUPAC names and common names for several important aliphatic dicarboxylic acids:



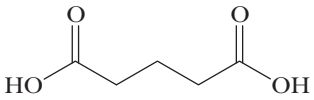
Ethanedioic acid
(Oxalic acid)



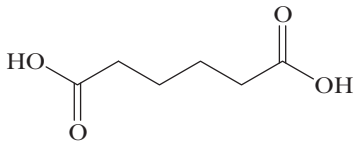
Propanedioic acid
(Malonic acid)



Butanedioic acid
(Succinic acid)



Pentanedioic acid
(Glutaric acid)



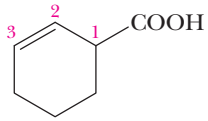
Hexanedioic acid
(Adipic acid)

The name *oxalic acid* is derived from one of its sources in the biological world, namely, plants of the genus *Oxalis*, one of which is rhubarb. Oxalic acid also occurs in human and animal urine, and calcium oxalate (the calcium salt of oxalic acid) is a major component of kidney stones. Adipic acid is one of the two monomers required for the synthesis of the polymer nylon 66. The U.S. chemical industry produces approximately 1.8 billion pounds of adipic acid annually, solely for the synthesis of nylon 66 (Section 16.4A).

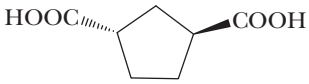
Lisa Kyle Young/Getty Images, Inc.

Leaves of the rhubarb plant contain oxalic acid as its potassium and sodium salts.

A carboxylic acid containing a carboxyl group bonded to a cycloalkane ring is named by giving the name of the ring and adding the suffix *-carboxylic acid*. The atoms of the ring are numbered beginning with the carbon bearing the —COOH group:

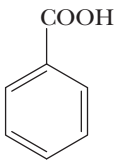


2-Cyclohexenecarboxylic acid

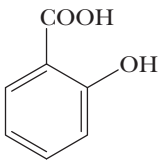


trans-1,3-Cyclopentanedicarboxylic acid

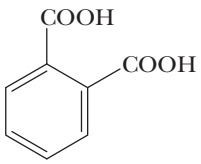
The simplest aromatic carboxylic acid is benzoic acid. Derivatives are named by using numbers and prefixes to show the presence and location of substituents relative to the carboxyl group. Certain aromatic carboxylic acids have common names by which they are more usually known. For example, 2-hydroxybenzoic acid is more often called salicylic acid, a name derived from the fact that this aromatic carboxylic acid was first obtained from the bark of the willow, a tree of the genus *Salix*. Aromatic dicarboxylic acids are named by adding the words *dicarboxylic acid* to *benzene*. Examples are 1,2-benzenedicarboxylic acid and 1,4-benzenedicarboxylic acid. Each is more usually known by its common name: phthalic acid and terephthalic acid, respectively. Terephthalic acid is one of the two organic components required for the synthesis of the textile fiber known as Dacron® polyester (Section 16.4B).



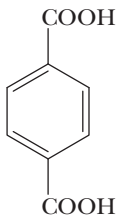
Benzoic acid



2-Hydroxybenzoic acid
(Salicylic acid)



1,2-Benzenedicarboxylic acid
(Phthalic acid)



1,4-Benzenedicarboxylic acid
(Terephthalic acid)

B. Common Names

Aliphatic carboxylic acids, many of which were known long before the development of structural theory and IUPAC nomenclature, are named according to their source or for

Fotosearch RF/Getty Images, Inc.

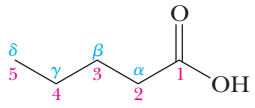
Formic acid was first obtained in 1670 from the destructive distillation of ants, whose genus is *Formica*. It is one of the components of the venom of stinging ants.

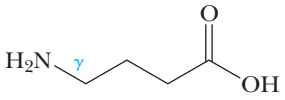
TABLE 13.1 Several Aliphatic Carboxylic Acids and Their Common Names

Structure	IUPAC Name	Common Name	Derivation
HCOOH	Methanoic acid	Formic acid	Latin: *formica*, ant
CH_3COOH	Ethanoic acid	Acetic acid	Latin: *acetum*, vinegar
CH_3CH_2COOH	Propanoic acid	Propionic acid	Greek: *propion*, first fat
$CH_3(CH_2)_2COOH$	Butanoic acid	Butyric acid	Latin: *butyrum*, butter
$CH_3(CH_2)_3COOH$	Pentanoic acid	Valeric acid	Latin: *valere*, to be strong
$CH_3(CH_2)_4COOH$	Hexanoic acid	Caproic acid	Latin: *caper*, goat
$CH_3(CH_2)_6COOH$	Octanoic acid	Caprylic acid	Latin: *caper*, goat
$CH_3(CH_2)_8COOH$	Decanoic acid	Capric acid	Latin: *caper*, goat
$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid	Latin: *laurus*, laurel
$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid	Greek: *myristikos*, fragrant
$CH_3(CH_2)_{14}COOH$	Hexadecanoic acid	Palmitic acid	Latin: *palma*, palm tree
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid	Greek: *stear*, solid fat
$CH_3(CH_2)_{18}COOH$	Icosanoic acid	Arachidic acid	Greek: *arachis*, peanut

some characteristic property. Table 13.1 lists several of the unbranched aliphatic carboxylic acids found in the biological world, along with the common name of each. Those with 16, 18, and 20 carbon atoms are particularly abundant in fats and oils (Section 19.1) and the phospholipid components of biological membranes (Section 19.3).

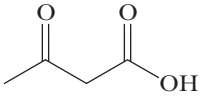
When common names are used, the Greek letters α, β, γ, δ, and so forth are often added as a prefix to locate substituents. The α-position in a carboxylic acid is the position next to the carboxyl group; an α-substituent in a common name is equivalent to a 2-substituent in an IUPAC name. *GABA*, short for *g*amma-*a*mino*b*utyric *a*cid, is an inhibitory neurotransmitter in the central nervous system of humans:





4-Aminobutanoic acid
(γ-Aminobutyric acid, GABA)

In common nomenclature, the prefix *keto-* indicates the presence of a ketone carbonyl in a substituted carboxylic acid (as illustrated by the common name β-ketobutyric acid):



3-Oxobutanoic acid
(β-Ketobutyric acid;
Acetoacetic acid)

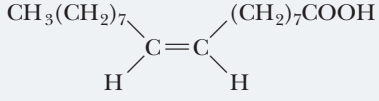
Acetyl group
(Aceto group)

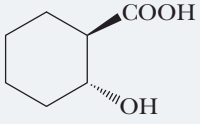
Aceto group A $CH_3C(=O)$— group.

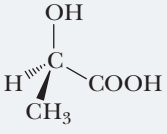
An alternative common name for 3-oxobutanoic acid is acetoacetic acid. In deriving this common name, this ketoacid is regarded as a substituted acetic acid, and the $CH_3C(=O)$— substituent is named an **aceto group**.

EXAMPLE 13.1

Write the IUPAC name for each carboxylic acid:

(a) 

(b) 

(c) 

(d) $ClCH_2COOH$

STRATEGY

Identify the longest chain of carbon atoms that contains the carboxyl group to determine the root name. The suffix *-e* is then changed to *-anoic acid*. For cyclic carboxylic acids, *carboxylic acid* is appended to the name of the cycloalkane (without dropping the suffix *-e*). As usual, remember to note stereochemistry (*E*/*Z*, *cis*/*trans*, or *R*/*S*) where appropriate.

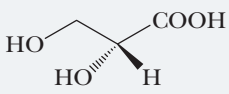
SOLUTION

(a) *cis*-9-Octadecenoic acid (oleic acid)
(b) *trans*-2-Hydroxycyclohexanecarboxylic acid
(c) (*R*)-2-Hydroxypropanoic acid [(*R*)-lactic acid]
(d) Chloroethanoic acid (chloroacetic acid)

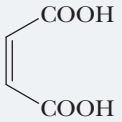
See problems 13.9–13.12, 13.15

PROBLEM 13.1

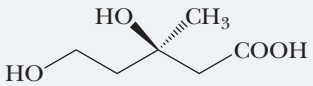
Each of the following compounds has a well-recognized common name. A derivative of glyceric acid is an intermediate in glycolysis (Section 21.3). Maleic acid is an intermediate in the tricarboxylic acid (TCA) cycle. Mevalonic acid is an intermediate in the biosynthesis of steroids (Section 19.4B).

(a) 

Glyceric acid

(b) 

Maleic acid

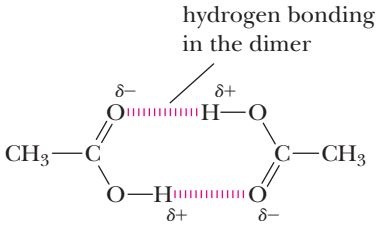
(c) 

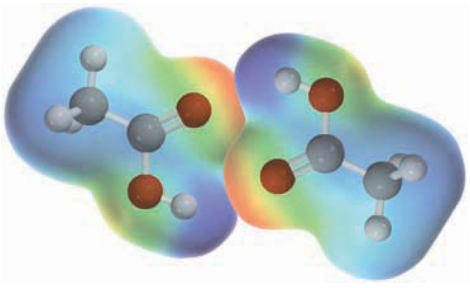
Mevalonic acid

Write the IUPAC name for each compound. Be certain to show the configuration of each.

13.3 What Are the Physical Properties of Carboxylic Acids?

In the liquid and solid states, carboxylic acids are associated by intermolecular hydrogen bonding into dimers, as shown for acetic acid:





Carboxylic acids have significantly higher boiling points than other types of organic compounds of comparable molecular weight, such as alcohols, aldehydes, and ketones. For example, butanoic acid (Table 13.2) has a higher boiling point than either 1-pentanol or pentanal. The higher boiling points of carboxylic acids result from their polarity and from the fact that they form very strong intermolecular hydrogen bonds.

Carboxylic acids also interact with water molecules by hydrogen bonding through both their carbonyl and hydroxyl groups. Because of these hydrogen-bonding interactions, carboxylic acids are more soluble in water than are alcohols, ethers, aldehydes, and ketones with comparable molecular weight. The solubility of a carboxylic acid in water decreases as its molecular weight increases. We account for this trend in the following way: A carboxylic acid consists of two regions of different polarity—a polar hydrophilic carboxyl group and, except

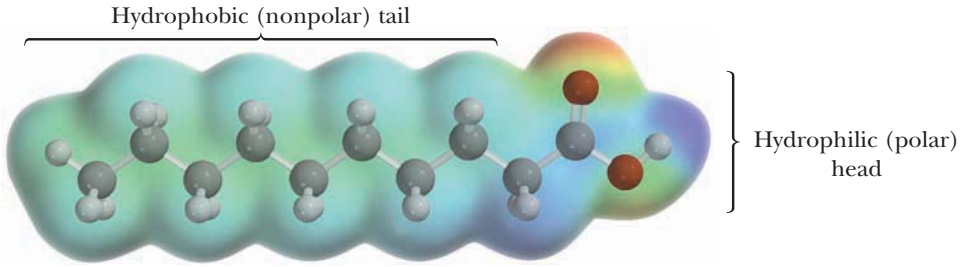
TABLE 13.2 Boiling Points and Solubilities in Water of Selected Carboxylic Acids, Alcohols, and Aldehydes of Comparable Molecular Weight

Structure	Name	Molecular Weight	Boiling Point (°C)	Solubility (g/100 mL H_2O)
CH_3COOH	acetic acid	60.5	118	infinite
$CH_3CH_2CH_2OH$	1-propanol	60.1	97	infinite
CH_3CH_2CHO	propanal	58.1	48	16
$CH_3(CH_2)_2COOH$	butanoic acid	88.1	163	infinite
$CH_3(CH_2)_3CH_2OH$	1-pentanol	88.1	137	2.3
$CH_3(CH_2)_3CHO$	pentanal	86.1	103	slight
$CH_3(CH_2)_4COOH$	hexanoic acid	116.2	205	1.0
$CH_3(CH_2)_5CH_2OH$	1-heptanol	116.2	176	0.2
$CH_3(CH_2)_5CHO$	heptanal	114.1	153	0.1

Hydrophilic From the Greek, meaning "water loving."

Hydrophobic From the Greek, meaning "water hating."

for formic acid, a nonpolar hydrophobic hydrocarbon chain. The **hydrophilic** carboxyl group increases water solubility; the **hydrophobic** hydrocarbon chain decreases water solubility.



Decanoic acid
(0.2 g/100 mL H_2O)

The first four aliphatic carboxylic acids (formic, acetic, propanoic, and butanoic acids) are infinitely soluble in water because the hydrophilic character of the carboxyl group more than counterbalances the hydrophobic character of the hydrocarbon chain. As the size of the hydrocarbon chain increases relative to the size of the carboxyl group, water solubility decreases. The solubility of hexanoic acid in water is 1.0 g/100 g water; that of decanoic acid is only 0.2 g/100 g water.

One other physical property of carboxylic acids must be mentioned: The liquid carboxylic acids, from propanoic acid to decanoic acid, have extremely foul odors, about as bad as those of thiols, though different. Butanoic acid is found in stale perspiration and is a major component of "locker room odor." Pentanoic acid smells even worse, and goats, which secrete C_6, C_8, and C_{10} acids, are not famous for their pleasant odors.

13.4 What Are the Acid–Base Properties of Carboxylic Acids?

A. Acid Ionization Constants

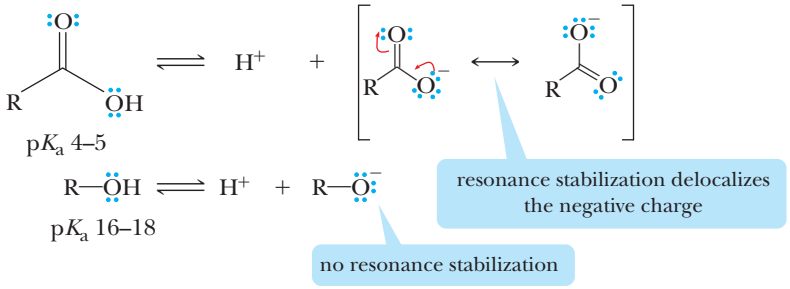
Carboxylic acids are weak acids. Values of K_a for most unsubstituted aliphatic and aromatic carboxylic acids fall within the range from 10^{-4} to 10^{-5}. The value of K_a for acetic acid, for example, is 1.74×10^{-5}, and the pK_a of acetic acid is 4.76:

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

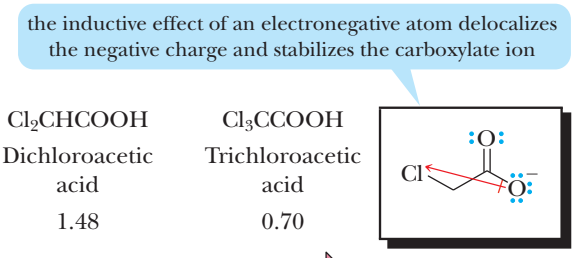
$$K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.74 \times 10^{-5}$$

$$pK_a = 4.76$$

As we discussed in Section 2.5B, carboxylic acids (pK_a 4–5) are stronger acids than alcohols (pK_a 16–18) because resonance stabilizes the **carboxylate** anion by delocalizing its negative charge. No comparable resonance stabilization exists in alkoxide ions.



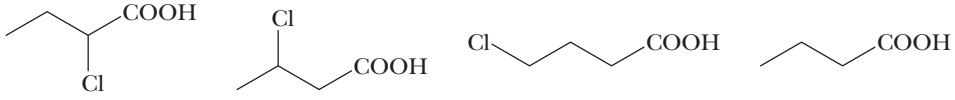
Substitution at the α-carbon of an atom or a group of atoms of higher electronegativity than carbon increases the acidity of carboxylic acids, often by several orders of magnitude (Section 2.5C). Compare, for example, the acidities of acetic acid (pK_a 4.76) and chloroacetic acid (pK_a 2.86). A single chlorine substituent on the α-carbon increases acid strength by nearly 100! Both dichloroacetic acid and trichloroacetic acid are stronger acids than phosphoric acid (pK_a 2.1):



Formula:	CH_3COOH	$ClCH_2COOH$	$Cl_2CHCOOH$	Cl_3CCOOH
Name:	Acetic acid	Chloroacetic acid	Dichloroacetic acid	Trichloroacetic acid
pK_a:	4.76	2.86	1.48	0.70

Increasing acid strength

The acid-strengthening effect of halogen substitution falls off rather rapidly with increasing distance from the carboxyl group. Although the acid ionization constant for 2-chlorobutanoic acid (pK_a 2.83) is 100 times that for butanoic acid, the acid ionization constant for 4-chlorobutanoic acid (pK_a 4.52) is only about twice that for butanoic acid:

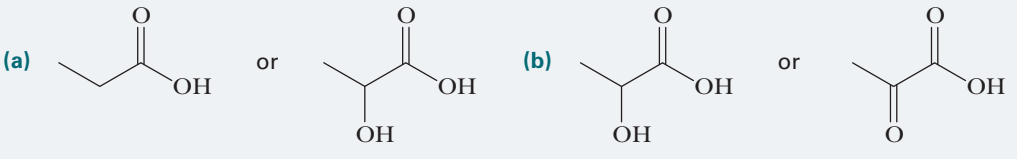


2-Chlorobutanoic acid (pK_a 2.83) | 3-Chlorobutanoic acid (pK_a 3.98) | 4-Chlorobutanoic acid (pK_a 4.52) | Butanoic acid (pK_a 4.82)

Decreasing acid strength

EXAMPLE 13.2

Which acid in each set is the stronger?



(a) Propanoic acid or 2-Hydroxypropanoic acid (Lactic acid)

(b) 2-Hydroxypropanoic acid (Lactic acid) or 2-Oxopropanoic acid (Pyruvic acid)

STRATEGY

Draw the conjugate base of each acid and look for possible stabilization of the ion via resonance or inductive effects. The conjugate base that is more greatly stabilized will indicate the more acidic carboxylic acid.

SOLUTION

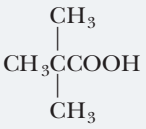
(a) 2-Hydroxypropanoic acid (pK_a 3.85) is a stronger acid than propanoic acid (pK_a 4.87) because of the electron-withdrawing inductive effect of the hydroxyl oxygen.

(b) 2-Oxopropanoic acid (pK_a 2.06) is a stronger acid than 2-hydroxypropanoic acid (pK_a 3.08) because of the greater electron-withdrawing inductive effect of the carbonyl oxygen compared with that of the hydroxyl oxygen.

See problems 13.20–13.22, 13.48

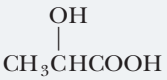
PROBLEM 13.2

Match each compound with its appropriate pK_a value:



2,2-Dimethylpropanoic acid

Trifluoroacetic acid

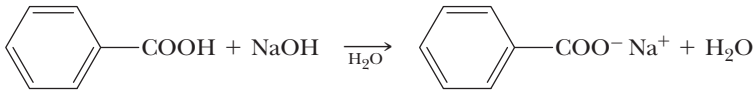


2-Hydroxypropanoic acid (Lactic acid)

pK_a values= 5.03, 3.85, and 0.22.

B. Reaction with Bases

All carboxylic acids, whether soluble or insoluble in water, react with NaOH, KOH, and other strong bases to form water-soluble salts:

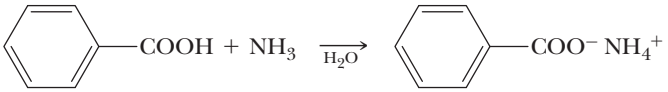


Benzoic acid (slightly soluble in water)

Sodium benzoate (60 g/100 mL water)

Sodium benzoate, a fungal growth inhibitor, is often added to baked goods "to retard spoilage." Calcium propanoate is used for the same purpose.

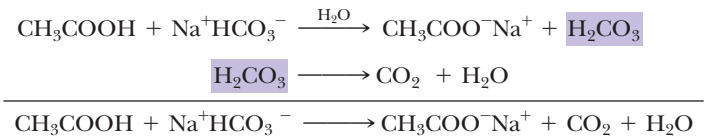
Carboxylic acids also form water-soluble salts with ammonia and amines:



Benzoic acid (slightly soluble in water)

Ammonium benzoate (20 g/100 mL water)

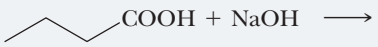
As described in Section 2.2, carboxylic acids react with sodium bicarbonate and sodium carbonate to form water-soluble sodium salts and carbonic acid (a relatively weak acid). Carbonic acid, in turn, decomposes to give water and carbon dioxide, which evolves as a gas:

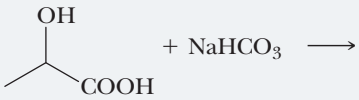


Salts of carboxylic acids are named in the same manner as are salts of inorganic acids: Name the cation first and then the anion. Derive the name of the anion from the name of the carboxylic acid by dropping the suffix *-ic acid* and adding the suffix *-ate*. For example, the name of $CH_3CH_2COO^-Na^+$ is sodium propanoate, and that of $CH_3(CH_2)_{14}COO^-Na^+$ is sodium hexadecanoate (sodium palmitate).

EXAMPLE 13.3

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

(a) 

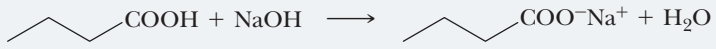
(b) 

STRATEGY

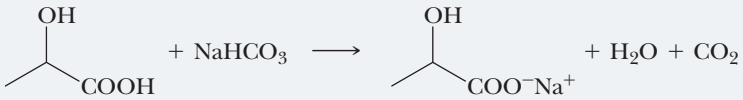
Identify the base and the most acidic hydrogen of the acid. Remember that sodium bicarbonate ($NaHCO_3$) typically reacts to yield carbonic acid, which subsequently decomposes to give CO_2 and H_2O.

SOLUTION

Each carboxylic acid is converted to its sodium salt. In (b), carbonic acid is formed (not shown) and decomposes to carbon dioxide and water:

(a) 

Butanoic acid — Sodium butanoate

(b) 

2-Hydroxypropanoic acid (Lactic acid) — Sodium 2-hydroxypropanoate (Sodium lactate)

See problems 13.23, 13.34

PROBLEM 13.3

Write an equation for the reaction of each acid in Example 13.3 with ammonia, and name the salt formed.

A consequence of the water solubility of carboxylic acid salts is that we can convert water-insoluble carboxylic acids to water-soluble alkali metal or ammonium salts and then extract them into aqueous solution. In turn, we can transform the salt into the free carboxylic acid by adding HCl, H_2SO_4, or some other strong acid. These reactions allow us to separate water-insoluble carboxylic acids from water-insoluble neutral compounds.

Figure 13.1 shows a flowchart for the separation of benzoic acid, a water-insoluble carboxylic acid, from benzyl alcohol, a water-insoluble nonacidic compound. First, we dissolve the mixture of benzoic acid and benzyl alcohol in diethyl ether. Next, we shake the ether solution with aqueous NaOH to convert benzoic acid to its water-soluble sodium salt. Then we separate the ether from the aqueous phase. Distillation of the ether solution yields first diethyl ether (bp 35 °C) and then benzyl alcohol (bp 205 °C). When we acidify the aqueous solution with HCl, benzoic acid precipitates as a water-insoluble solid (mp 122 °C) and is recovered by filtration. The ability to separate compounds based on their acid–base properties is very important in laboratory and industrial chemistry.

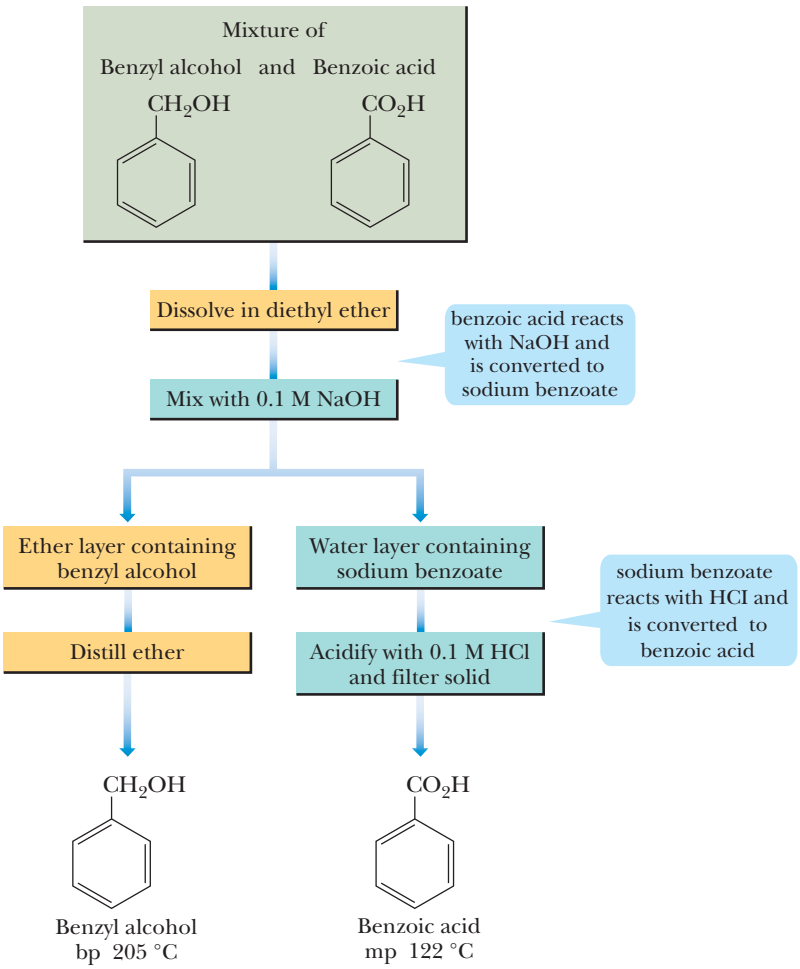


FIGURE 13.1
Flowchart for separation of benzoic acid from benzyl alcohol.

13.5 How Are Carboxyl Groups Reduced?

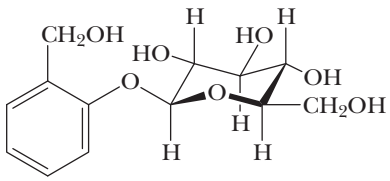
The carboxyl group is one of the organic functional groups that is most resistant to reduction. It is not affected by catalytic reduction (H_2/M) under conditions that easily reduce aldehydes and ketones to alcohols and that reduce alkenes to alkanes. The most common reagent for the reduction of a carboxylic acid to a primary alcohol is the very powerful reducing agent lithium aluminum hydride (Section 12.10).

Chemical Connections 13A

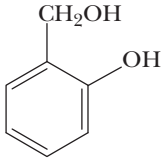
FROM WILLOW BARK TO ASPIRIN AND BEYOND

The first drug developed for widespread use was aspirin, today's most common pain reliever. Americans alone consume approximately 80 billion tablets of aspirin a year! The story of the development of this modern pain reliever goes back more than 2,000 years: In 400 B.C.E., the Greek physician Hippocrates recommended chewing bark of the willow tree to alleviate the pain of childbirth and to treat eye infections.

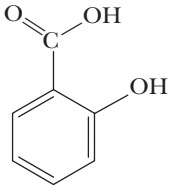
The active component of willow bark was found to be salicin, a compound composed of salicyl alcohol joined to a unit of β-D-glucose (Section 17.2). Hydrolysis of salicin in aqueous acid gives salicyl alcohol, which can then be oxidized to salicylic acid, an even more effective reliever of pain, fever, and inflammation than salicin and one without its extremely bitter taste:



Salicin



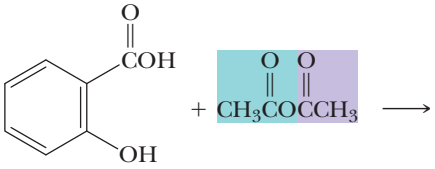
Salicyl alcohol



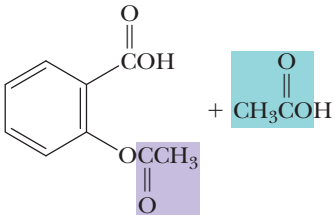
Salicylic acid

Unfortunately, patients quickly recognized salicylic acid's major side effect: It causes severe irritation of the mucous membrane lining the stomach.

In the search for less irritating, but still effective, derivatives of salicylic acid, chemists at the Bayer division of I. G. Farben in Germany prepared acetylsalicylic acid in 1883 and gave it the name *aspirin*, a word derived from the German *spirsäure* (salicylic acid), with the initial *a* for the acetyl group:



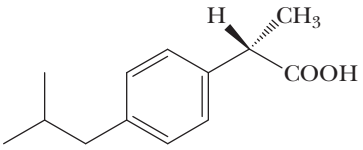
Salicylic acid Acetic anhydride



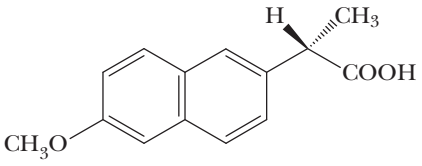
Acetyl salicylate (Aspirin)

Aspirin proved to be less irritating to the stomach than salicylic acid and also more effective in relieving the pain and inflammation of rheumatoid arthritis. Bayer began large-scale production of aspirin in 1899.

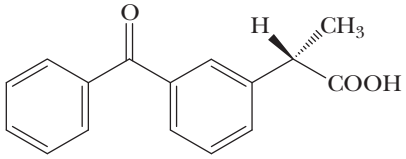
In the 1960s, in a search for even more effective and less irritating analgesics and anti-inflammatory drugs, the Boots Pure Drug Company in England studied compounds related in structure to salicylic acid. They discovered an even more potent compound, which they named ibuprofen, and soon thereafter, Syntex Corporation in the United States developed naproxen and Rhone–Poulenc in France developed ketoprofen:



(*S*)-Ibuprofen



(*S*)-Naproxen



(*S*)-Ketoprofen

Notice that each compound has one stereocenter and can exist as a pair of enantiomers. For each drug, the physiologically active form is the *S* enantiomer. Even though the *R* enantiomer of ibuprofen has none of the analgesic or anti-inflammatory activity, it is converted in the body to the active *S* enantiomer.

In the 1960s, scientists discovered that aspirin acts by inhibiting cyclooxygenase (COX), a key enzyme in the conversion of arachidonic acid to prostaglandins (Section 19.5). With this discovery, it became clear why only one enantiomer of ibuprofen, naproxen, and ketoprofen is active: Only the *S* enantiomer of each has the correct handedness to bind to COX and inhibit its activity.

The discovery that these drugs owe their effectiveness to the inhibition of COX opened an entirely new avenue for drug research. If we know more about the structure and function of this key enzyme, might it be possible to design and discover even more effective nonsteroidal anti-inflammatory drugs for the treatment of rheumatoid arthritis and other inflammatory diseases?

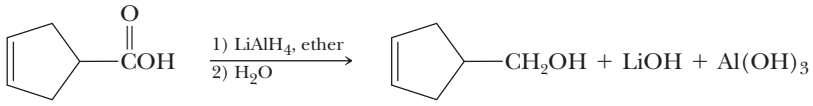
And so continues the story that began with the discovery of the beneficial effects of chewing willow bark.

Question

Draw the product of the reaction of salicylic acid with (a) one equivalent of NaOH, (b) two equivalents of NaOH, and (c) two equivalents of $NaHCO_3$.

A. Reduction of a Carboxyl Group

Lithium aluminum hydride, $LiAlH_4$, reduces a carboxyl group to a primary alcohol in excellent yield. Reduction is most commonly carried out in diethyl ether or tetrahydrofuran (THF). The initial product is an aluminum alkoxide, which is then treated with water to give the primary alcohol and lithium and aluminum hydroxides:



3-Cyclopentene-carboxylic acid

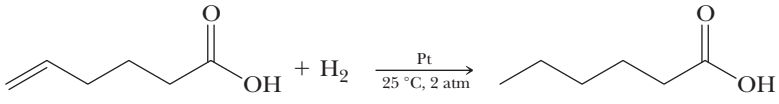
4-Hydroxymethyl-cyclopentene

These hydroxides are insoluble in diethyl ether or THF and are removed by filtration. Evaporation of the solvent yields the primary alcohol.

Alkenes are generally not affected by metal hydride-reducing reagents. These reagents function as hydride ion donors; that is, they function as nucleophiles, and alkenes are not normally attacked by nucleophiles.

B. Selective Reduction of Other Functional Groups

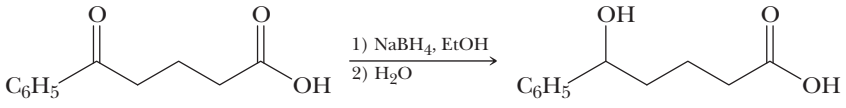
Catalytic hydrogenation (at least under the same conditions used to reduce ketones and aldehydes) does not reduce carboxyl groups, but does reduce alkenes to alkanes. Therefore, we can use H_2/M to reduce this functional group selectively in the presence of a carboxyl group:



5-Hexenoic acid

Hexanoic acid

We saw in Section 12.10 that aldehydes and ketones are reduced to alcohols by both $LiAlH_4$ and $NaBH_4$. Only $LiAlH_4$, however, reduces carboxyl groups. Thus, it is possible to reduce an aldehyde or a ketone carbonyl group selectively in the presence of a carboxyl group by using the less reactive $NaBH_4$ as the reducing agent:



5-Oxo-5-phenylpentanoic acid

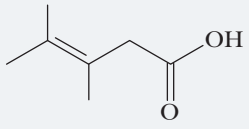
5-Hydroxy-5-phenylpentanoic acid

EXAMPLE 13.4

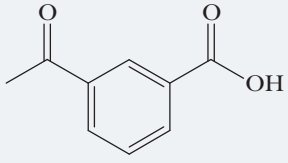
Provide the product formed when each of the following is treated with:
(i) H_2/Pd **(ii)** 1. $LiAlH_4$, ether 2. H_2O **(iii)** 1. $NaBH_4$, EtOH 2. H_2O

In each reaction, assume an excess of reagent is available for reaction.

(a)



(b)



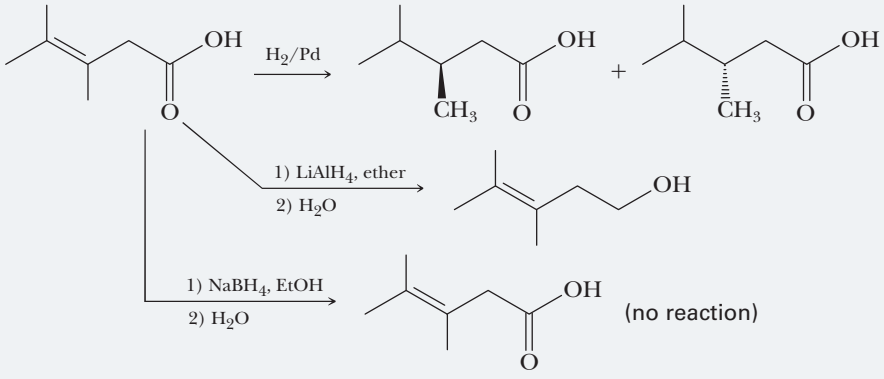
STRATEGY

Remember that carboxyl groups are only reduced by $LiAlH_4$, alkenes are only reduced by H_2/M, aldehydes and ketones are reduced by all metal hydride reducing agents, and benzene rings are resistant to each of these reducing reagents. Remember to consider stereochemistry in the outcome of each reaction.

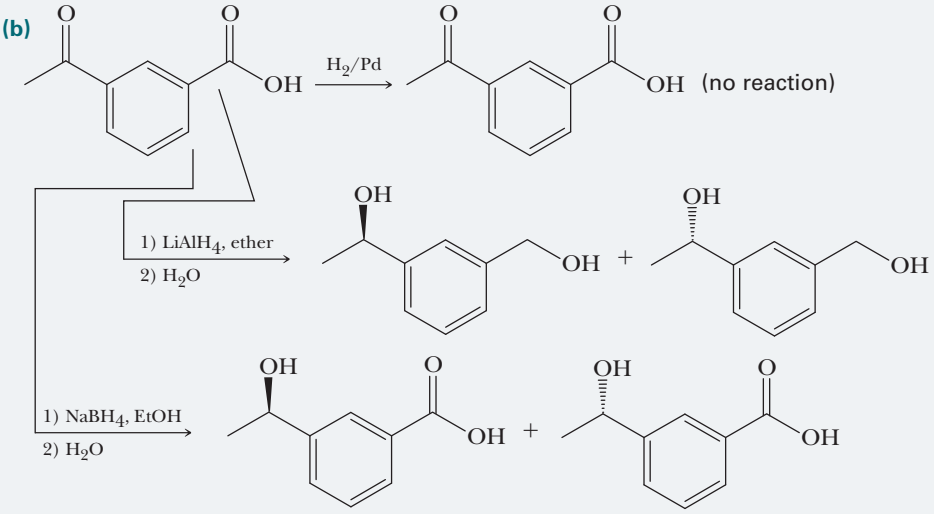
SOLUTION

Here are structural formulas for the major product produced in each reaction:

(a)



(b)



See problems 13.30–13.32, 13.47

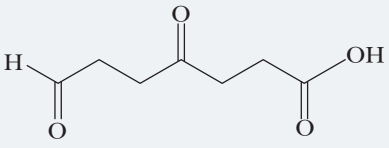
PROBLEM 13.4

Provide the product formed when each of the following is treated with:

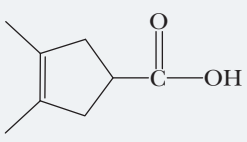
(i) H_2/Pd **(ii)** 1. $LiAlH_4$, ether 2. H_2O **(iii)** 1. $NaBH_4$, EtOH 2. H_2O

Presume that an excess of reagent is available for each reaction.

(a)



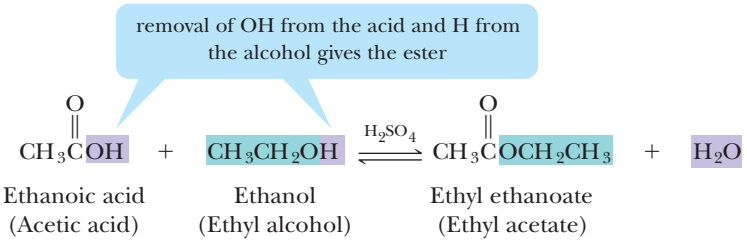
(b)



13.6 What Is Fischer Esterification?

Fischer esterification The process of forming an ester by refluxing a carboxylic acid and an alcohol in the presence of an acid catalyst, commonly sulfuric acid.

Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst—most commonly, concentrated sulfuric acid—gives an ester. This method of forming an ester is given the special name **Fischer esterification** after the German chemist Emil Fischer (1852–1919). As an example of Fischer esterification, treating acetic acid with ethanol in the presence of concentrated sulfuric acid gives ethyl acetate and water:



Ken Karp for John Wiley & Sons

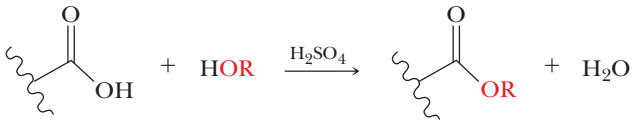
These products all contain ethyl acetate as a solvent.

We study the structure, nomenclature, and reactions of esters in detail in Chapter 14. In the present chapter, we discuss only their preparation from carboxylic acids.

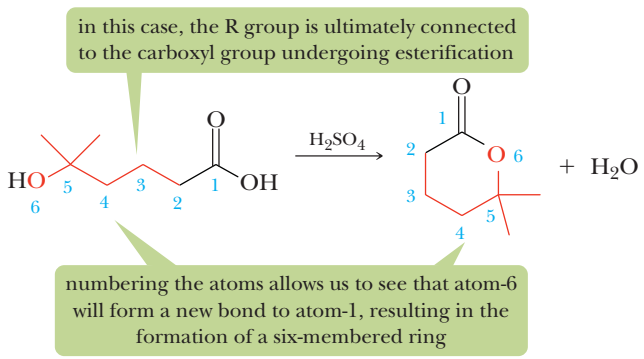
Acid-catalyzed esterification is reversible, and generally, at equilibrium, the quantities of remaining carboxylic acid and alcohol are appreciable. By controlling the experimental conditions, however, we can use Fischer esterification to prepare esters in high yields. If the alcohol is inexpensive compared with the carboxylic acid, we can use a large excess of the alcohol to drive the equilibrium to the right and achieve a high conversion of carboxylic acid to its ester.

HOW TO 13.1 Predict the Product of a Fischer Esterification

(a) In the Fischer esterification, the —OR portion of an alcohol replaces the —OH portion of a carboxylic acid.

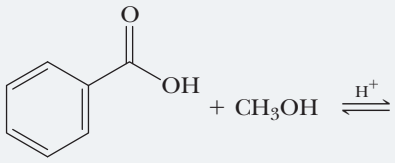


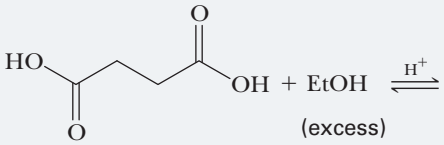
(b) This simple fact of the mechanism allows us to predict the product of any type of Fischer esterification. For example, in the following Fischer esterification, the alcohol is already a part of the molecule. In cases of intramolecular Fischer esterifications, it is often helpful to number the atoms in the molecule.



EXAMPLE 13.5

Complete these Fischer esterification reactions:

(a) 

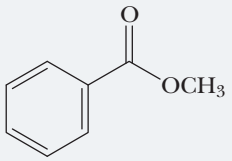
(b) 

STRATEGY

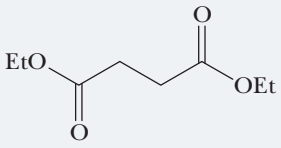
In a Fischer esterification, each carboxyl group is converted to an ester in which the —OR group originates from the alcohol reagent.

SOLUTION

Here is a structural formula for the ester produced in each reaction:

(a) 

Methyl benzoate

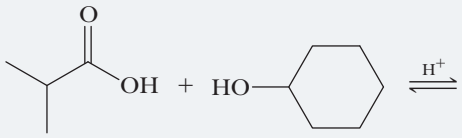
(b) 

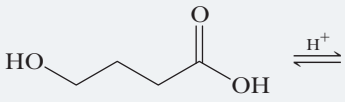
Diethyl butanedioate
(Diethyl succinate)

See problems 13.30, 13.33, 13.39, 13.40, 13.47

PROBLEM 13.5

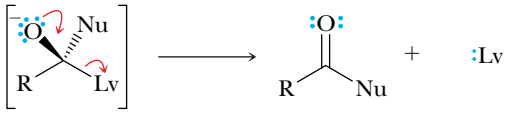
Complete these Fischer esterification reactions:

(a) 

(b) 
(a cyclic ester)

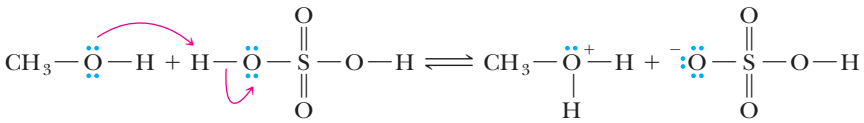
In Section 5.2C, we defined five common mechanistic patterns that we have subsequently seen in a variety of organic reactions. It is now time to define a sixth mechanistic pattern, one that we will encounter often in our study of carboxylic acids and functional derivatives of carboxylic acids (Chapter 14).

Pattern 6: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group. After addition of a nucleophile (Nu) to a carbonyl, one possible mechanism is for the tetrahedral carbonyl intermediate to collapse back to a C=O while ejecting a leaving group (Lv). We will see, in this and the chapters to come, that both Nu and Lv can take many forms.



Tetrahedral carbonyl addition intermediate

Following is a mechanism for Fischer esterification, and we urge you to study it carefully. It is important that you understand this mechanism thoroughly because it is a model for many of the reactions of the functional derivatives of carboxylic acids presented in Chapter 14. Note that, although we show the acid catalyst as H_2SO_4 when we write Fisher esterification reactions, the actual proton-transfer acid that initiates the reaction is the oxonium formed by the transfer of a proton from H_2SO_4 (the stronger acid) to the alcohol (the stronger base) used in the esterification reaction:



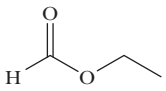
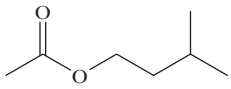
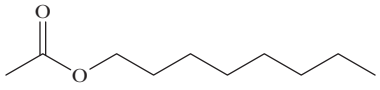
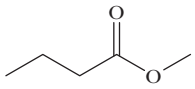
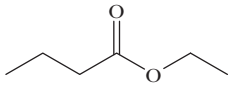
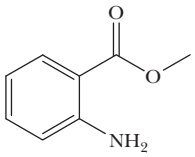
Chemical Connections 13B

ESTERS AS FLAVORING AGENTS

Flavoring agents are the largest class of food additives. At present, over a thousand synthetic and natural flavors are available. The majority of these are concentrates or extracts from the material whose flavor is desired and are often complex mixtures of from tens to hundreds of compounds. A number of ester flavoring agents are synthesized industrially. Many have flavors very close to the target flavor, and adding only one or a few of them is sufficient to make ice cream, soft drinks, or candy taste natural. (Isopentane is the common name for 2-methylbutane.) The table shows the structures of a few of the esters used as flavoring agents:

Question

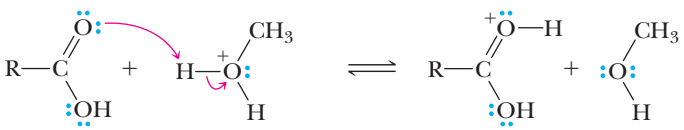
Show how each of the esters in the table can be synthesized using a Fischer esterification reaction.

Structure	Name	Flavor
	Ethyl formate	Rum
	Isopentyl acetate	Banana
	Octyl acetate	Orange
	Methyl butanoate	Apple
	Ethyl butanoate	Pineapple
	Methyl 2-aminobenzoate (Methyl anthranilate)	Grape

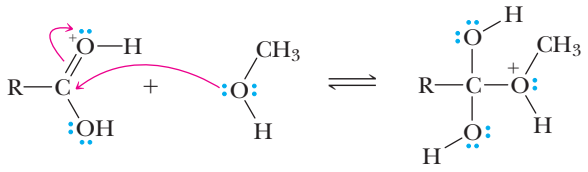
Mechanism

Fischer Esterification

STEP 1: Add a proton. Proton transfer from the acid catalyst to the carbonyl oxygen increases the electrophilicity of the carbonyl carbon:

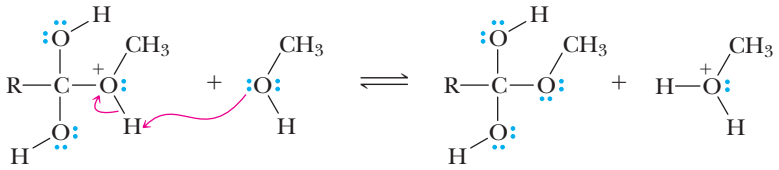


STEP 2: Reaction of a nucleophile and an electrophile to form a new covalent bond. The carbonyl carbon is then attacked by the nucleophilic oxygen atom of the alcohol to form an oxonium ion:

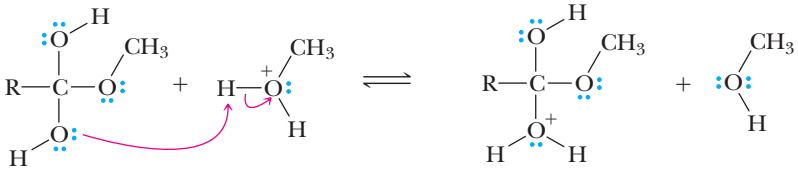


(an electrophile) (a nucleophile) (oxonium ion)

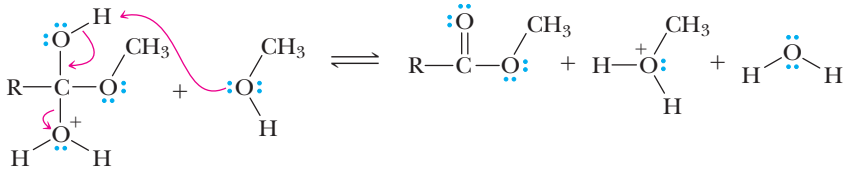
STEP 3: Take a proton away. Proton transfer from the oxonium ion to a second molecule of alcohol gives a tetrahedral carbonyl addition intermediate (TCAI):



STEP 4: Add a proton. Proton transfer to one of the —OH groups of the TCAI gives a new oxonium ion:

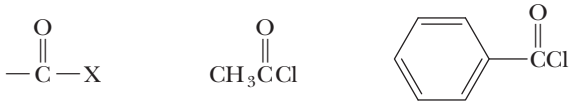


STEP 5: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group. Loss of water from this oxonium ion gives the ester and regenerates the acid catalyst:



13.7 What Are Acid Chlorides?

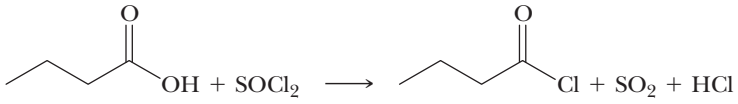
The functional group of an acid halide is a carbonyl group bonded to a halogen atom. Among the acid halides, acid chlorides are the most frequently used in the laboratory and in industrial organic chemistry:



Functional group of an acid halide | Acetyl chloride | Benzoyl chloride

We study the nomenclature, structure, and characteristic reactions of acid halides in Chapter 14. In this chapter, our concern is only with their synthesis from carboxylic acids.

The most common way to prepare an acid chloride is to treat a carboxylic acid with thionyl chloride, the same reagent that converts an alcohol to a chloroalkane (Section 8.2D):



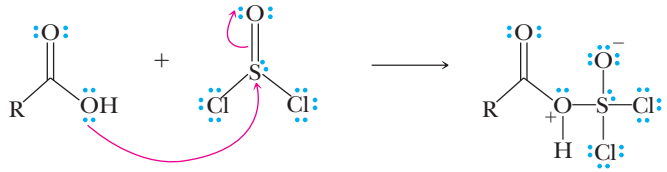
Butanoic acid — Thionyl chloride — Butanoyl chloride

The mechanism of this reaction consists of four steps.

Mechanism

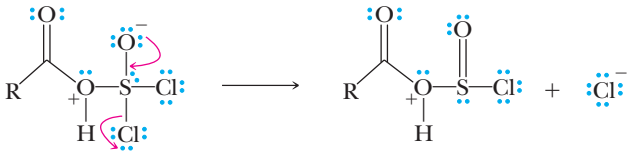
Acid Chloride Formation Using Thionyl Chloride

STEP 1: Reaction of a nucleophile and an electrophile to form a new covalent bond. The carboxyl group adds to the sulfur atom of thionyl chloride to generate a tetrahedral sulfur intermediate.

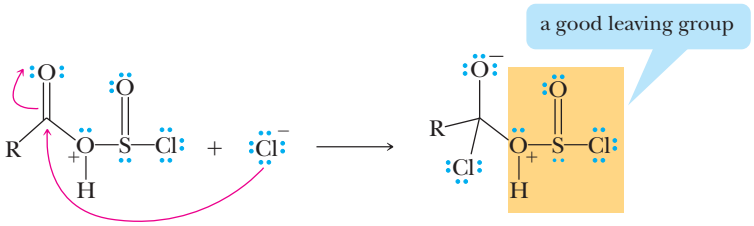


(a nucleophile) (an electrophile) (tetrahedral sulfur intermediate)

STEP 2: Collapse of the tetrahedral sulfur intermediate to eject a leaving group and regenerate the carbonyl group. Loss of chloride from the tetrahedral sulfur intermediate regenerates the sulfonyl group:



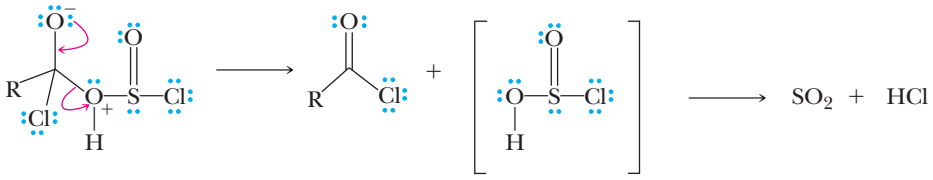
STEP 3: Reaction of a nucleophile and an electrophile to form a new covalent bond. The chloride ion attacks the carbonyl carbon, forming a tetrahedral carbonyl addition intermediate.



Tetrahedral carbonyl addition intermediate

STEP 4: Collapse of the tetrahedral carbonyl intermediate to eject a leaving group and regenerate the carbonyl group. The sulfonyl group highlighted in Step 3 is an excellent leaving group. This allows a lone pair of electrons to collapse back toward the bond to regenerate the carbonyl carbon while expelling the leaving group sulfochloridous acid. This sulfur-based acid is unstable and breaks down to yield sulfur

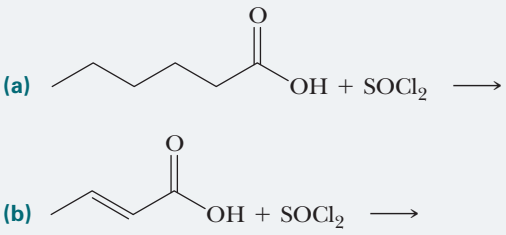
dioxide and HCl. The mechanism shown below is a common mode of reactivity for functional derivatives of carboxylic acids (Chapter 14).



Sulfochloridous acid

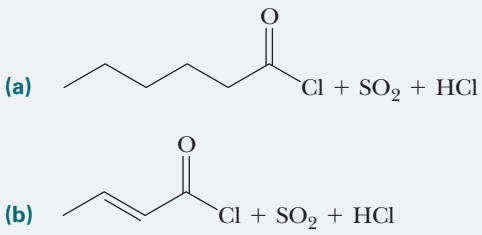
EXAMPLE 13.6

Complete each equation:



SOLUTION

Following are the products for each reaction:



See problems 13.30, 13.47

PROBLEM 13.6

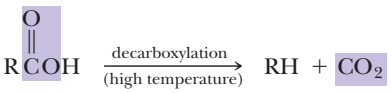
Complete each equation:

13.8 What Is Decarboxylation?

A. β-Ketoacids

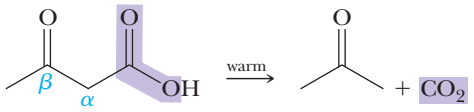
Decarboxylation is the loss of CO_2 from a carboxyl group. Almost any carboxylic acid, heated to a very high temperature, undergoes decarboxylation:

Decarboxylation Loss of CO_2 from a carboxyl group.



Most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation. Exceptions are carboxylic acids that have a carbonyl group β to the carboxyl group. This type of carboxylic acid undergoes decarboxylation quite readily

on mild heating. For example, when 3-oxobutanoic acid (acetoacetic acid) is heated moderately, it undergoes decarboxylation to give acetone and carbon dioxide:



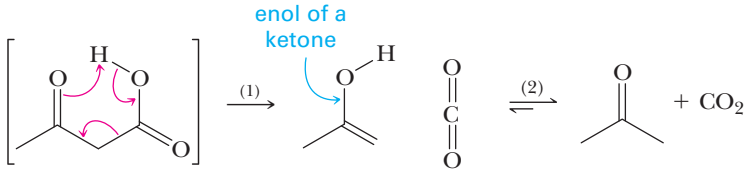
3-Oxobutanoic acid (Acetoacetic acid) — Acetone

Decarboxylation on moderate heating is a unique property of 3-oxocarboxylic acids (β-ketoacids) and is not observed with other classes of ketoacids.

Mechanism

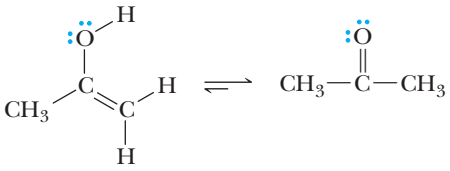
Decarboxylation of a β-Ketocarboxylic Acid

STEP 1: Rearrangement of bonds. Redistribution of six electrons in a cyclic six-membered transition state gives carbon dioxide and an enol:



(A cyclic six-membered transition state)

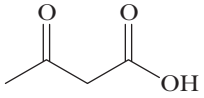
STEP 2: Keto–enol tautomerism. Tautomerism (Section 12.8A) of the enol gives the more stable keto form of the product:



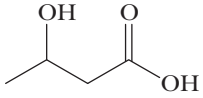
Chemical Connections 13C

KETONE BODIES AND DIABETES

3-Oxobutanoic acid (acetoacetic acid) and its reduction product, 3-hydroxybutanoic acid, are synthesized in the liver from acetyl-CoA, a product of the metabolism of fatty acids (Section 21.5C) and certain amino acids:



3-Oxobutanoic acid (Acetoacetic acid)



3-Hydroxybutanoic acid (β-Hydroxybutyric acid)

3-Hydroxybutanoic acid and 3-oxobutanoic acid are known collectively as ketone bodies.

The concentration of ketone bodies in the blood of healthy, well-fed humans is approximately 0.01 mM/L. However, in persons suffering from starvation or diabetes mellitus, the concentration of ketone bodies may increase to as much as 500 times normal. Under these conditions, the concentration of acetoacetic acid increases to the point where it undergoes spontaneous decarboxylation to form acetone and carbon dioxide. Acetone is not

metabolized by humans and is excreted through the kidneys and the lungs. The odor of acetone is responsible for the characteristic "sweet smell" on the breath of severely diabetic patients.

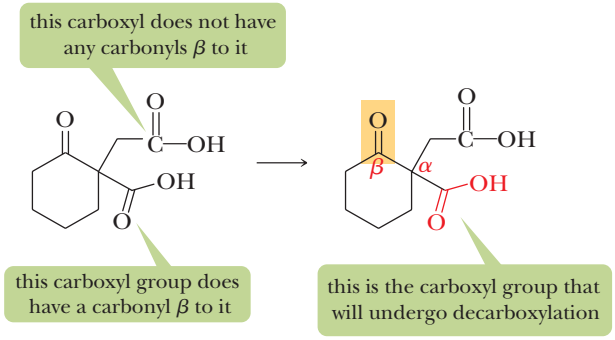
Question

Show the mechanism for the decarboxylation of acetoacetic acid. Explain why 3-hydroxybutanoic acid cannot undergo decarboxylation.

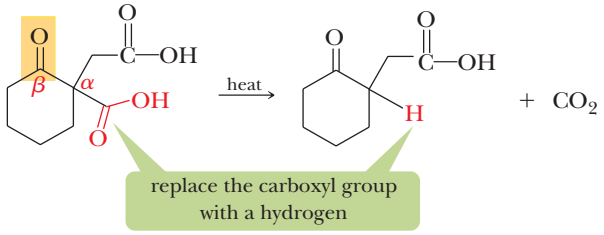
HOW TO 13.2

Predict the Product of a β-Decarboxylation Reaction

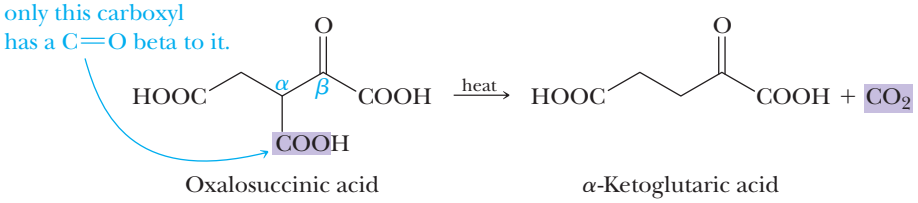
(a) The most important criterion of a decarboxylation reaction is that the carbonyl group be at the β-position relative to a carboxyl group. Therefore, identify each carboxyl group in a molecule and determine whether a carbonyl is β to it.



(b) Once all the carboxyl groups with β-carbonyls are identified, it is a simple matter of replacing the carboxyl groups with a hydrogen.



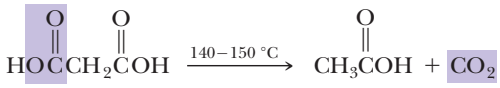
An important example of decarboxylation of a β-ketoacid in the biological world occurs during the oxidation of foodstuffs in the tricarboxylic acid (TCA) cycle. Oxalosuccinic acid, one of the intermediates in this cycle, undergoes spontaneous decarboxylation to produce α-ketoglutaric acid. Only one of the three carboxyl groups of oxalosuccinic acid has a carbonyl group in the position β to it, and it is this carboxyl group that is lost as CO_2:



B. Malonic Acid and Substituted Malonic Acids

The presence of a ketone or an aldehyde carbonyl group on the carbon β to the carboxyl group is sufficient to facilitate decarboxylation. In the more general reaction, decarboxylation is facilitated by the presence of any carbonyl group on the β carbon, including that

of a carboxyl group or an ester. Malonic acid and substituted malonic acids, for example, undergo decarboxylation on heating, as illustrated by the decarboxylation of malonic acid when it is heated slightly above its melting point of 135–137 °C:



Propanedioic acid
(Malonic acid)

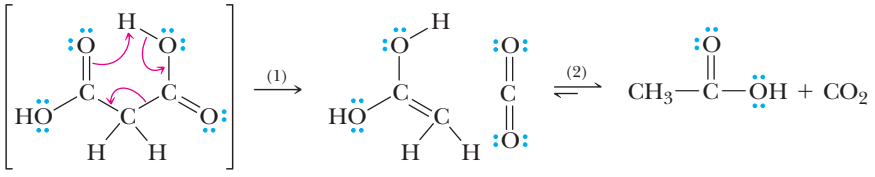
The mechanism for decarboxylation of malonic acids is similar to what we have just studied for the decarboxylation of β-ketoacids. The formation of a cyclic, six-membered transition state involving a redistribution of three electron pairs gives the enol form of a carboxylic acid, which, in turn, isomerizes to the carboxylic acid.

Mechanism

Decarboxylation of a β-Dicarboxylic Acid

STEP 1: Rearrangement of bonds. Rearrangement of six electrons in a cyclic six-membered transition state gives carbon dioxide and the enol form of a carboxyl group.

STEP 2: Keto–enol tautomerism. Tautomerism (Section 12.8A) of the enol gives the more stable keto form of the carboxyl group.



A cyclic six-membered transition state

Enol of a carboxyl group

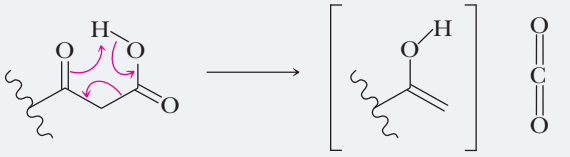
EXAMPLE 13.7

Each of these carboxylic acids undergoes thermal decarboxylation:

Draw a structural formula for the enol intermediate and final product formed in each reaction.

STRATEGY

It is often helpful to draw the full Lewis structure of the β-carboxyl group and to position it to allow a cyclic six-membered transition state:



A cyclic six-membered transition state

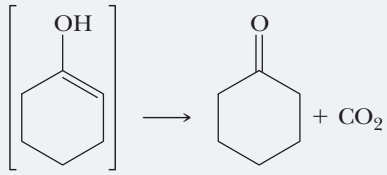
Enol

CO_2

By carefully keeping track of the movement of electrons, the bonds made and the bonds broken, one can arrive at the enol intermediate. Predicting the final product is a simple matter of replacing the —COOH group that is β to a carbonyl in the molecule with a hydrogen atom.

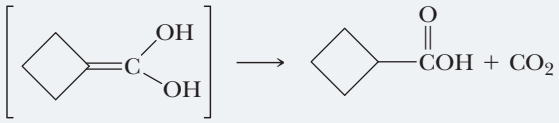
SOLUTION

(a)



Enol intermediate

(b)

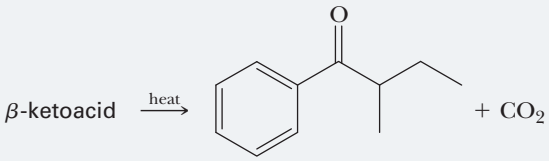


Enol intermediate

See problems 13.41, 13.47

PROBLEM 13.7

Draw the structural formula for the indicated β-ketoacid:



SUMMARY OF KEY QUESTIONS

13.1 What Are Carboxylic Acids?

- The functional group of a **carboxylic acid** is the **carboxyl group**, —**COOH**.

13.2 How Are Carboxylic Acids Named?

- IUPAC names of carboxylic acids are derived from the parent alkane by dropping the suffix *-e* and adding *-oic acid*.
- Dicarboxylic acids are named as *-dioic acids*.

13.3 What Are the Physical Properties of Carboxylic Acids?

- Carboxylic acids are polar compounds that associate by hydrogen bonding into **dimers** in the liquid and solid states.
- Carboxylic acids have higher boiling points and are more soluble in water than alcohols, aldehydes, ketones, and ethers of comparable molecular weight.
- A carboxylic acid consists of two regions of different polarity: a polar, **hydrophilic** carboxyl group, which increases solubility in water, and a nonpolar, **hydrophobic** hydrocarbon chain, which decreases solubility in water.
- The first four **aliphatic carboxylic acids** are infinitely soluble in water because the hydrophilic carboxyl group more than counterbalances the hydrophobic hydrocarbon chain.
- As the size of the carbon chain increases, the hydrophobic group becomes dominant, and solubility in water decreases.

13.4 What Are the Acid–Base Properties of Carboxylic Acids?

- Values of $\mathbf{pK_a}$ for aliphatic carboxylic acids are in the 4.0 to 5.0 range.
- Electron-withdrawing substituents near the carboxyl group increase acidity in both aliphatic and aromatic carboxylic acids.

13.5 How Are Carboxyl Groups Reduced?

- The carboxyl group is one of the organic functional groups that is most resistant to reduction. They do not react with H_2/M or $NaBH_4$.
- Lithium aluminum hydride, $LiAlH_4$, reduces a carboxyl group to a primary alcohol.

13.6 What Is Fischer Esterification?

- **Fischer esterification** is a method of forming an ester by treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst.

13.7 What Are Acid Chlorides?

- The functional group of an **acid chloride** is a carbonyl group bonded to a chlorine atom.
- The most common way to prepare an acid chloride is to treat a carboxylic acid with **thionyl chloride**.

13.8 What Is Decarboxylation?

- **Decarboxylation** is the loss of CO_2 from a carboxyl group.
- Carboxylic acids that have a carbonyl group β to the carboxyl group readily undergo decarboxylation on mild heating.

QUICK QUIZ

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

1. In naming carboxylic acids, it is always necessary to indicate the position at which the carboxyl group occurs. (13.2)
2. 2-Propylpropanedioic acid can undergo decarboxylation at relatively moderate temperatures. (13.8)
3. Fischer esterification is reversible. (13.6)
4. The hydrophilic group of a carboxylic acid decreases water solubility. (13.3)
5. Both alcohols and carboxylic acids react with $SOCl_2$. (13.7)
6. Fischer esterification involves the reaction of a carboxylic acid with another carboxylic acid. (13.6)
7. An electronegative atom on a carboxylic acid can potentially increase the acid's acidity. (13.4)
8. A carboxyl group is reduced to a 1° alcohol by H_2/Pt. (13.5)
9. A carboxyl group is reduced to a 1° alcohol by $NaBH_4$. (13.5)
10. A carboxyl group that has been deprotonated is called a carboxylate group. (13.4)
11. A carboxyl group is reduced to a 1° alcohol by $LiAlH_4$. (13.5)
12. The conjugate base of a carboxylic acid is resonance-stabilized. (13.4)
13. Carboxylic acids possess both a region of polarity and a region of nonpolarity. (13.3)
14. Carboxylic acids are less acidic than phenols. (13.4)
15. 4-Oxopentanoic acid can undergo decarboxylation at relatively moderate temperatures. (13.8)
16. The γ position of a carboxylic acid refers to carbon-4 of the chain. (13.2)

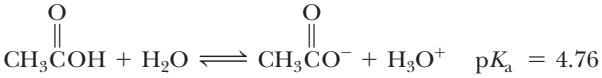
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

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

KEY REACTIONS

1. **Acidity of Carboxylic Acids (Section 13.4A)**

   Values of pK_a for most unsubstituted aliphatic and aromatic carboxylic acids are within the range from 4 to 5:



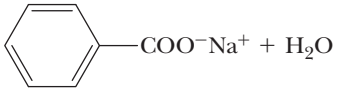
$$CH_3\overset{\overset{O}{\|}}{C}OH + H_2O \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}O^- + H_3O^+ \qquad pK_a = 4.76$$

   Substitution by electron-withdrawing groups decreases pK_a (increases acidity).

2. **Reaction of Carboxylic Acids with Bases (Section 13.4B)**

   Carboxylic acids form water-soluble salts with alkali metal hydroxides, carbonates, and bicarbonates, as well as with ammonia and amines:

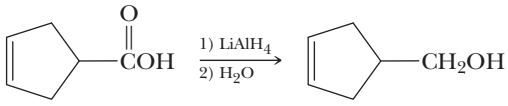
$$\text{C}_6\text{H}_5\text{COOH} + \text{NaOH} \xrightarrow{H_2O}$$



$$\text{C}_6\text{H}_5\text{COO}^-\text{Na}^+ + H_2O$$

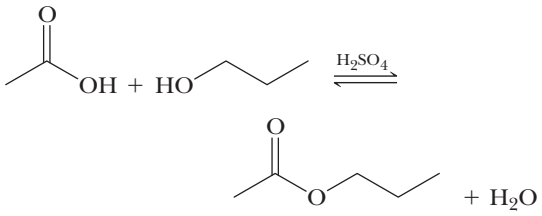
3. **Reduction by Lithium Aluminum Hydride (Section 13.5)**

Lithium aluminum hydride reduces a carboxyl group to a primary alcohol:



4. **Fischer Esterification (Section 13.6)**

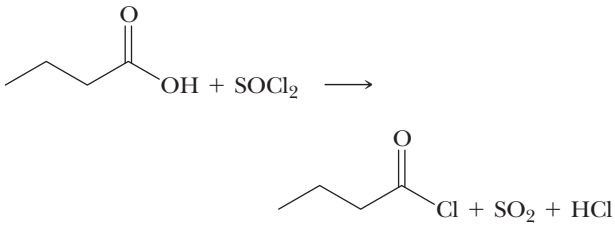
Fischer esterification is reversible:



One way to force the equilibrium to the right is to use an excess of the alcohol.

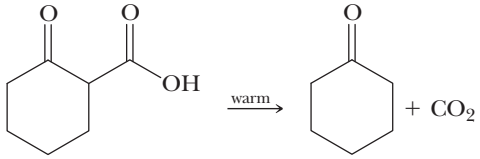
5. **Conversion to Acid Halides (Section 13.7)**

Acid chlorides, the most common and widely used of the acid halides, are prepared by treating carboxylic acids with thionyl chloride:



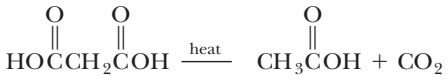
6. **Decarboxylation of β-Ketoacids (Section 13.8A)**

The mechanism of decarboxylation involves the redistribution of bonding electrons in a cyclic, six-membered transition state:



7. **Decarboxylation of β-Dicarboxylic Acids (Section 13.8B)**

The mechanism of decarboxylation of a β-dicarboxylic acid is similar to that of decarboxylation of a β-ketoacid:



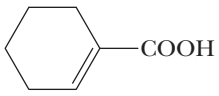
PROBLEMS

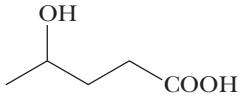
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

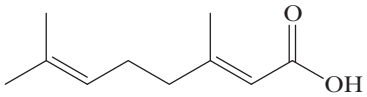
Section 13.2 Structure and Nomenclature

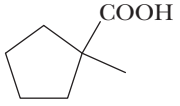
13.8 Name and draw structural formulas for the four carboxylic acids with molecular formula $C_5H_{10}O_2$. Which of these carboxylic acids is chiral?

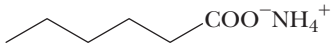
13.9 Write the IUPAC name for each compound: **(See Example 13.1)**

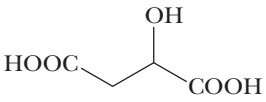
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

13.10 Draw a structural formula for each carboxylic acid: **(See Example 13.1)**

(a) 4-Nitrophenylacetic acid
(b) 4-Aminopentanoic acid
(c) 3-Chloro-4-phenylbutanoic acid
(d) *cis*-3-Hexenedioic acid
(e) 2,3-Dihydroxypropanoic acid
(f) 3-Oxohexanoic acid
(g) 2-Oxocyclohexanecarboxylic acid
(h) 2,2-Dimethylpropanoic acid

***13.11** Megatomoic acid, the sex attractant of the female black carpet beetle, has the structure **(See Example 13.1)**

$$CH_3(CH_2)_7CH{=}CHCH{=}CHCH_2COOH$$

Megatomoic acid

(a) What is the IUPAC name of megatomoic acid?
(b) State the number of stereoisomers possible for this compound.

***13.12** The IUPAC name of ibuprofen is 2-(4-isobutylphenyl) propanoic acid. Draw a structural formula of ibuprofen. **(See Example 13.1)**

***13.13** Draw structural formulas for these salts:

(a) Sodium benzoate (b) Lithium acetate
(c) Ammonium acetate (d) Disodium adipate
(e) Sodium salicylate (f) Calcium butanoate

***13.14** The monopotassium salt of oxalic acid is present in certain leafy vegetables, including rhubarb. Both oxalic acid and its salts are poisonous in high concentrations. Draw a structural formula of monopotassium oxalate.

***13.15** Potassium sorbate is added as a preservative to certain foods to prevent bacteria and molds from causing spoilage and to extend the foods' shelf life. The IUPAC name of potassium sorbate is potassium (2*E*,4*E*)-2,4-hexadienoate. Draw a structural formula of potassium sorbate. **(See Example 13.1)**

***13.16** Zinc 10-undecenoate, the zinc salt of 10-undecenoic acid, is used to treat certain fungal infections, particularly *tinea pedis* (athlete's foot). Draw a structural formula of this zinc salt.

Section 13.3 Physical Properties

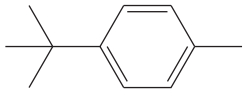
13.17 Arrange the compounds in each set in order of increasing boiling point:

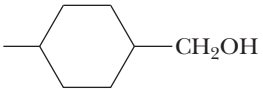
(a) $CH_3(CH_2)_5COOH$ $CH_3(CH_2)_6CHO$ $CH_3(CH_2)_6CH_2OH$
(b) CH_3CH_2COOH $CH_3CH_2CH_2CH_2OH$ $CH_3CH_2OCH_2CH_3$

Section 13.4 Preparation of Carboxylic Acids

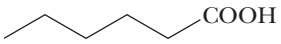
13.18 Draw a structural formula for the product formed by treating each compound with warm chromic acid, H_2CrO_4:

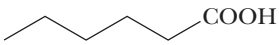
(a) $CH_3(CH_2)_4CH_2OH$

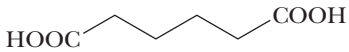
(b) 

(c) 

13.19 Draw a structural formula for a compound with the given molecular formula that, on oxidation by chromic acid, gives the carboxylic acid or dicarboxylic acid shown:

(a) $C_6H_{14}O \xrightarrow{\text{oxidation}}$ 

(b) $C_6H_{12}O \xrightarrow{\text{oxidation}}$ 

(c) $C_6H_{14}O_2 \xrightarrow{\text{oxidation}}$ 

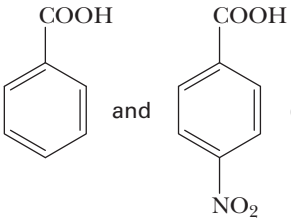
Acidity of Carboxylic Acids

13.20 Which is the stronger acid in each pair? **(See Example 13.2)**

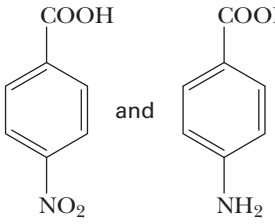
(a) Phenol (pK_a 9.95) or benzoic acid (pK_a 4.17)
(b) Lactic acid (K_a 1.4×10^{-4}) or ascorbic acid (K_a 6.8×10^{-5})

13.21 Arrange these compounds in order of increasing acidity: benzoic acid, benzyl alcohol, and phenol. **(See Example 13.2)**

13.22 Assign the acid in each set its appropriate pK_a: **(See Example 13.2)**

(a) 

and (pK_a 4.19 and 3.14)

(b) 

and (pK_a 4.92 and 3.14)

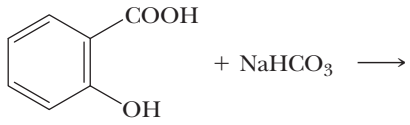
(c) $CH_3\overset{\overset{O}{\|}}{C}CH_2COOH$ and $CH_3\overset{\overset{O}{\|}}{C}COOH$
(pK_a 3.58 and 2.49)

(d) $CH_3\overset{\overset{OH}{|}}{C}HCOOH$ and CH_3CH_2COOH
(pK_a 3.85 and 4.78)

13.23 Complete these acid–base reactions: **(See Example 13.3)**

(a) 

(b) $CH_3CH{=}CHCH_2COOH + NaHCO_3 \longrightarrow$

(c)  $+ NaHCO_3 \longrightarrow$

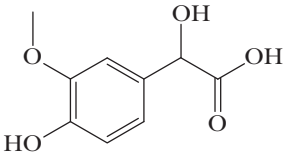
(d) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCOOH + H_2NCH_2CH_2OH \longrightarrow$

(e) $CH_3CH{=}CHCH_2COO^-Na^+ + HCl \longrightarrow$

***13.24** The normal pH range for blood plasma is 7.35–7.45. Under these conditions, would you expect the carboxyl group of lactic acid (pK_a 3.85) to exist primarily as a carboxyl group or as a carboxylate anion? Explain.

***13.25** The pK_a of salicylic acid (Section 13.2), is 2.97. Would you expect salicylic acid dissolved in blood plasma (pH 7.35–7.45) to exist primarily as salicylic acid or as salicylate anion? Explain.

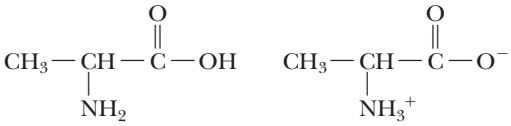
***13.26** Vanillylmandelic acid (pK_a 3.42) is a metabolite found in urine, the pH of which is normally in the range from 4.8 to 8.4. Provide the structure of vanillylmandelic acid that you would expect to find in urine with pH 5.8?



Vanillylmandelic acid

***13.27** The pH of human gastric juice is normally in the range from 1.0 to 3.0. What form of lactic acid (pK_a 3.85), lactic acid itself or its anion, would you expect to be present in the stomach?

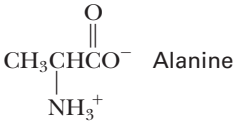
***13.28** Following are two structural formulas for the amino acid alanine (Section 18.2):



(A) (B)

Is alanine better represented by structural formula A or B? Explain.

***13.29** In Chapter 18, we discuss a class of compounds called amino acids, so named because they contain both an amino group and a carboxyl group. Following is a structural formula for the amino acid alanine in the form of an internal salt:

 Alanine

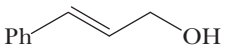
What would you expect to be the major form of alanine present in aqueous solution at (a) pH 2.0, (b) pH 5–6, and (c) pH 11.0? Explain.

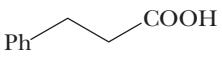
Sections 13.5–13.8 Reactions of Carboxylic Acids

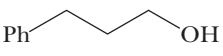
13.30 Give the expected organic products formed when phenylacetic acid, $PhCH_2COOH$, is treated with each of the following reagents: **(See Examples 13.4–13.6)**

(a) $SOCl_2$
(b) $NaHCO_3$, H_2O
(c) $NaOH$, H_2O
(d) NH_3, H_2O
(e) $LiAlH_4$, followed by H_2O
(f) $NaBH_4$, followed by H_2O
(g) $CH_3OH + H_2SO_4$ (catalyst)
(h) H_2/Ni at 25 °C and 3 atm pressure

13.31 Show how to convert *trans*-3-phenyl-2-propenoic acid (cinnamic acid) to these compounds: **(See Example 13.4)**

(a) 

(b) 

(c) 

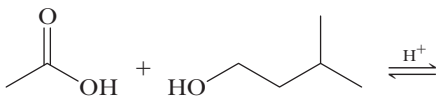
13.32 Show how to convert 3-oxobutanoic acid (acetoacetic acid) to these compounds: **(See Example 13.4)**

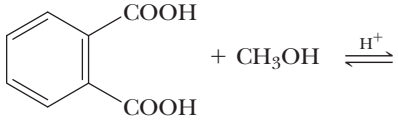
(a) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2COOH$

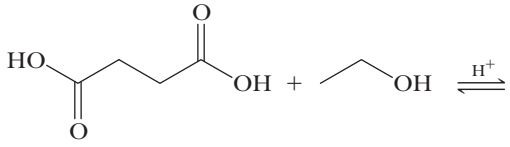
(b) $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2OH$

(c) $CH_3CH{=}CHCOOH$

13.33 Complete these examples of Fischer esterification (assume an excess of the alcohol): **(See Example 13.5)**

(a) 

(b) 

(c) 

*13.34 Formic acid is one of the components responsible for the sting of biting ants and is injected under the skin by bees and wasps. A way to relieve the pain is to rub the area of the sting with a paste of baking soda ($NaHCO_3$) and water, which neutralizes the acid. Write an equation for this reaction. **(See Example 13.3)**

*13.35 Methyl 2-hydroxybenzoate (methyl salicylate) has the odor of oil of wintergreen. This ester is prepared by the Fischer esterification of 2-hydroxybenzoic acid (salicylic acid) with methanol. Draw a structural formula of methyl 2-hydroxybenzoate.

*13.36 Benzocaine, a topical anesthetic, is prepared by treating 4-aminobenzoic acid with ethanol in the presence of an acid catalyst, followed by neutralization. Draw a structural formula of benzocaine.

*13.37 Examine the structural formulas of pyrethrin and permethrin. (See Chemical Connections 14D.)

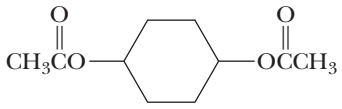
(a) Locate the ester groups in each compound.
(b) Is pyrethrin chiral? How many stereoisomers are possible for it?
(c) Is permethrin chiral? How many stereoisomers are possible for it?

*13.38 A commercial Clothing & Gear Insect Repellant gives the following information about permethrin, its active ingredient:

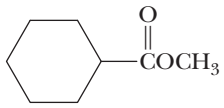
Cis/trans ratio: Minimum 35% (+/−) *cis* and maximum 65% (+/−) *trans*

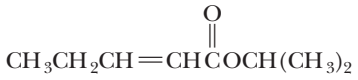
(a) To what does the *cis*/*trans* ratio refer?
(b) To what does the designation "(+/−)" refer?

13.39 From what carboxylic acid and alcohol is each of the following esters derived? **(See Example 13.5)**

(a) 

(b) 

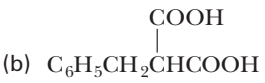
(c) 

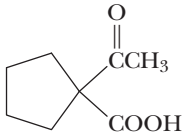
(d) 

13.40 When treated with an acid catalyst, 4-hydroxybutanoic acid forms a cyclic ester (a lactone). Draw the structural formula of this lactone. **(See Example 13.5)**

13.41 Draw a structural formula for the product formed on thermal decarboxylation of each of the following compounds: **(See Example 13.7)**

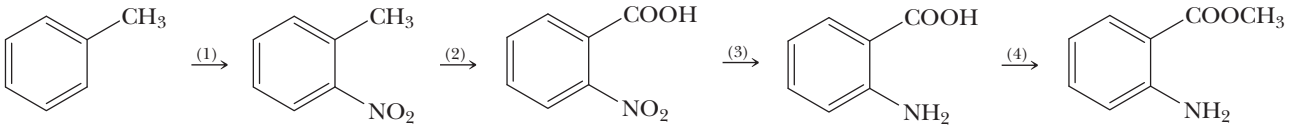
(a) 

(b) 

(c) 

Synthesis

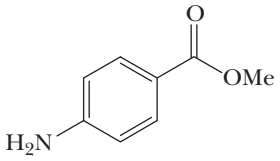
*13.42 Methyl 2-aminobenzoate, a flavoring agent with the taste of grapes (see Chemical Connections 13B), can be prepared from toluene by the following series of steps:



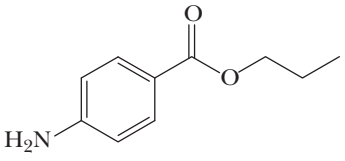
Toluene — Methyl 2-aminobenzoate

Show how you might bring about each step in this synthesis.

*13.43 Methylparaben and propylparaben are used as preservatives in foods, beverages, and cosmetics:



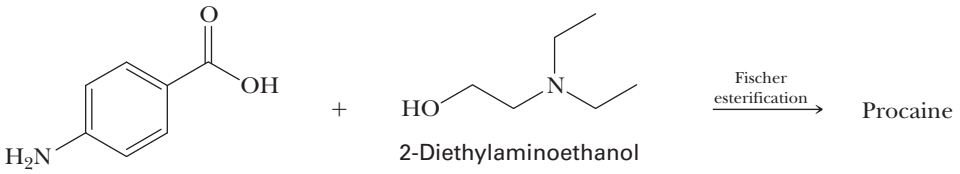
Methyl 4-aminobenzoate (Methylparaben)



Propyl 4-aminobenzoate (Propylparaben)

Show how the synthetic scheme in Problem 13.42 can be modified to give each of these compounds.

***13.44** Procaine (its hydrochloride is marketed as Novocaine®) was one of the first local anesthetics developed for infiltration and regional anesthesia. It is synthesized by the following Fischer esterification:

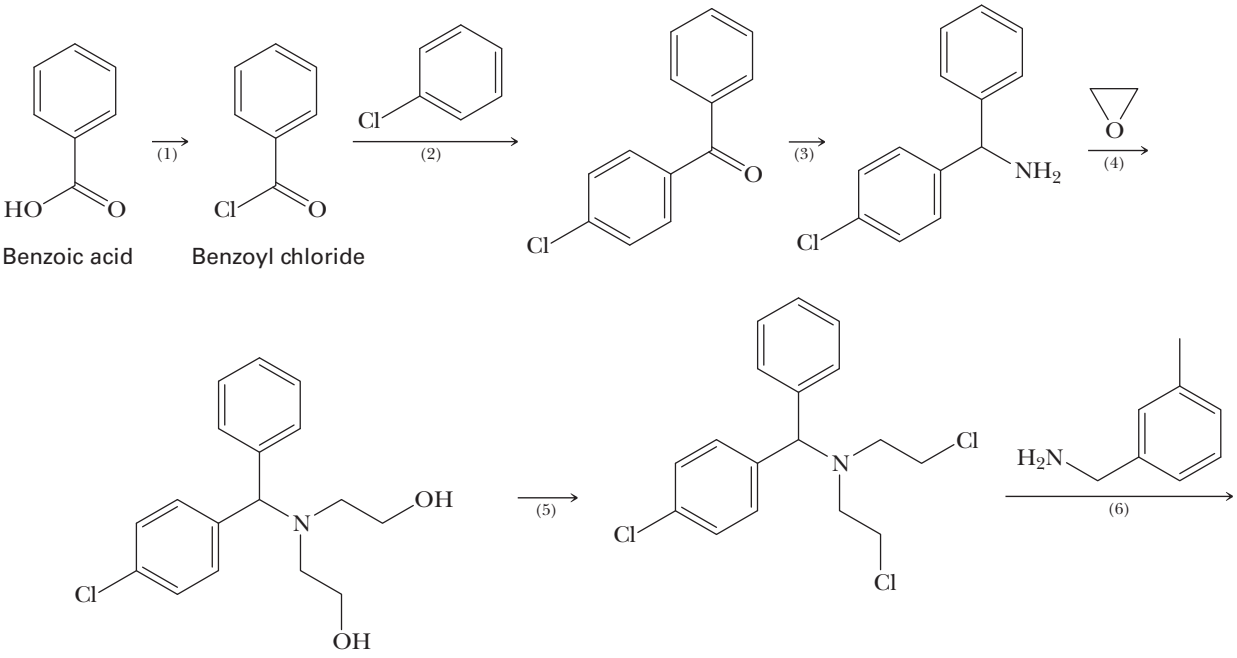


p-Aminobenzoic acid

2-Diethylaminoethanol

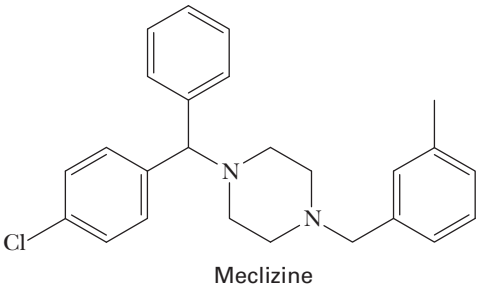
Draw a structural formula for procaine.

***13.45** Meclizine is an antiemetic: It helps prevent, or at least lessen, the vomiting associated with motion sickness, including seasickness. Among the names of the over-the-counter preparations of meclizine are Bonine®, Sea-Legs, Antivert®, and Navicalm®. Meclizine can be synthesized by the following series of steps:



Benzoic acid

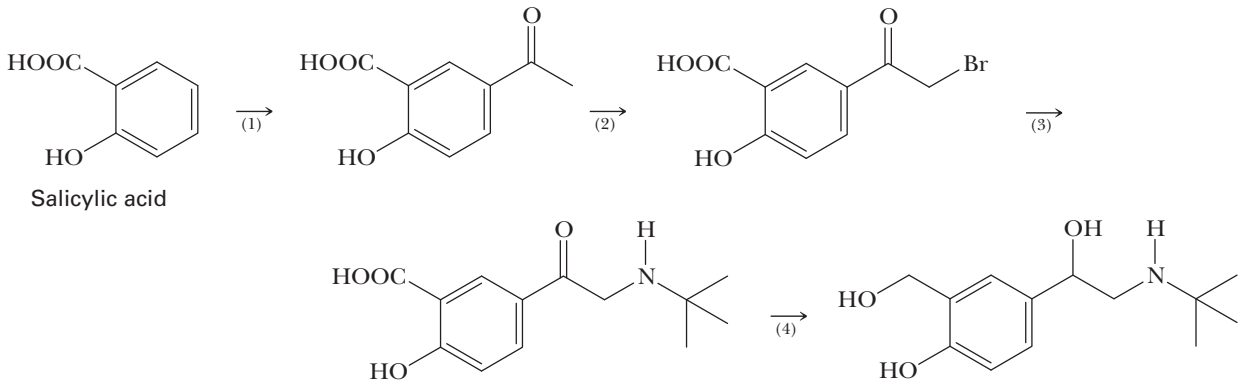
Benzoyl chloride



Meclizine

(a) Propose a reagent for Step 1.
(b) The catalyst for Step 2 is $AlCl_3$. Name the type of reaction that occurs in Step 2.
(c) Propose reagents for Step 3.
(d) Propose a mechanism for Step 4, and show that it is an example of nucleophilic aliphatic substitution.
(e) Propose a reagent for Step 5.
(f) Show that Step 6 is also an example of nucleophilic aliphatic substitution.

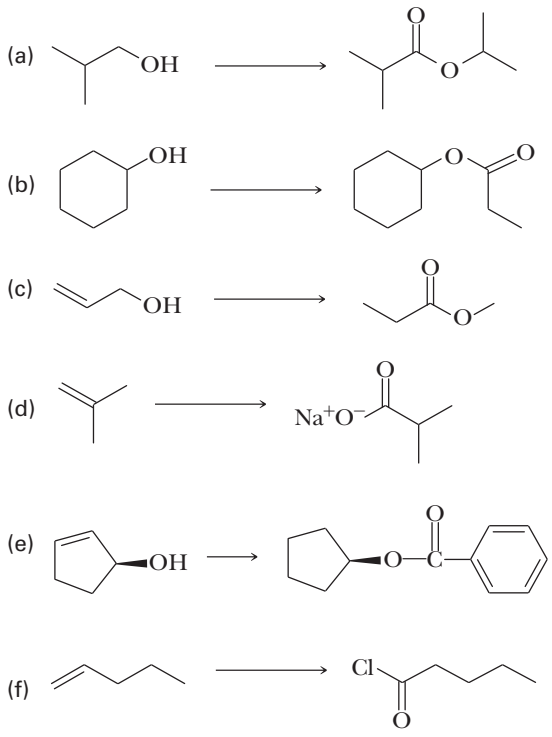
***13.46** Chemists have developed several syntheses for the antiasthmatic drug albuterol (Proventil). One of these syntheses starts with salicylic acid, the same acid that is the starting material for the synthesis of aspirin:

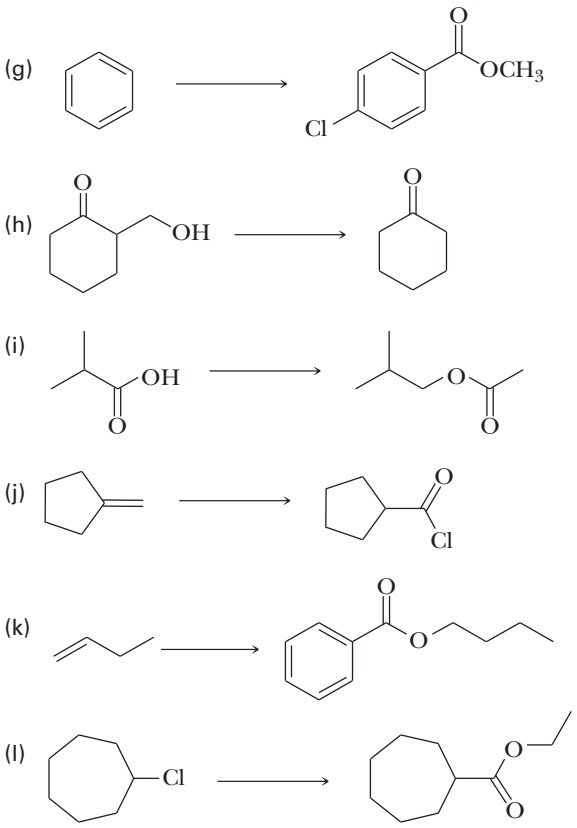


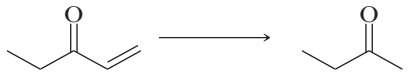
(a) Propose a reagent and a catalyst for Step 1. What name is given to this type of reaction?
(b) Propose a reagent for Step 2.
(c) Name the amine used to bring about Step 3.
(d) Step 4 is a reduction of two functional groups. Name the functional groups reduced and tell what reagent will accomplish the reduction.
(e) Is albuterol chiral? If so how many stereoisomers are possible?
(f) Would the albuterol formed in this synthesis be optically active or optically inactive? That is, would it be formed as a single enantiomer or as a racemic mixture?

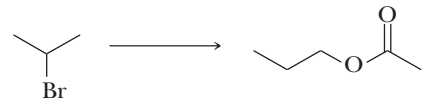
CHEMICAL TRANSFORMATIONS

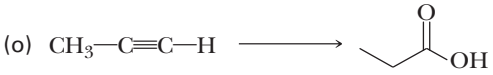
13.47 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note*: Some will require more than one step. **(See Examples 13.4–13.7)**

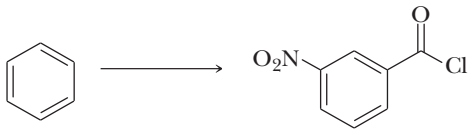




(m) 

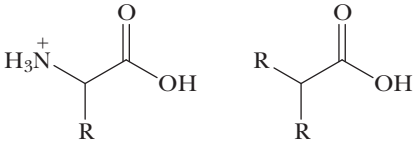
(n) 

(o) 

(p) 

LOOKING AHEAD

13.48 Explain why α-amino acids, the building blocks of proteins (Chapter 18), are nearly a thousand times more acidic than aliphatic carboxylic acids: (**See Example 13.2**)

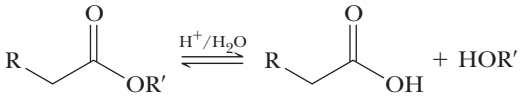


An α-amino acid
$pK_a \approx 2$

An aliphatic acid
$pK_a \approx 5$

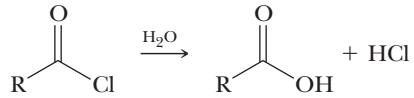
13.49 Which is more difficult to reduce with $LiAlH_4$, a carboxylic acid or a carboxylate ion?

13.50 Show how an ester can react with H^+/H_2O to give a carboxylic acid and an alcohol (*Hint:* This is the reverse of Fischer esterification):



13.51 In Chapter 12, we saw how Grignard reagents readily attack the carbonyl carbon of ketones and aldehydes. Should the same process occur with Grignards and carboxylic acids? With esters?

13.52 In Section 13.6, it was suggested that the mechanism for the Fischer esterification of carboxylic acids would be a model for many of the reactions of the functional derivatives of carboxylic acids. One such reaction, the reaction of an acid halide with water, is the following:



Suggest a mechanism for this reaction.

GROUP LEARNING ACTIVITIES

13.53 What acids are more acidic (lower pK_a) than carboxylic acids? What acids are less acidic (higher pK_a) than carboxylic acids? List and discuss any trends in this list of acids.

13.54 We learned that after it is formed by the attack of a nucleophile, the TCAI of a carboxylic acid can collapse to eject a leaving group and regenerate the carbonyl group. Discuss why the TCAIs of ketones and aldehydes don't undergo the same process.