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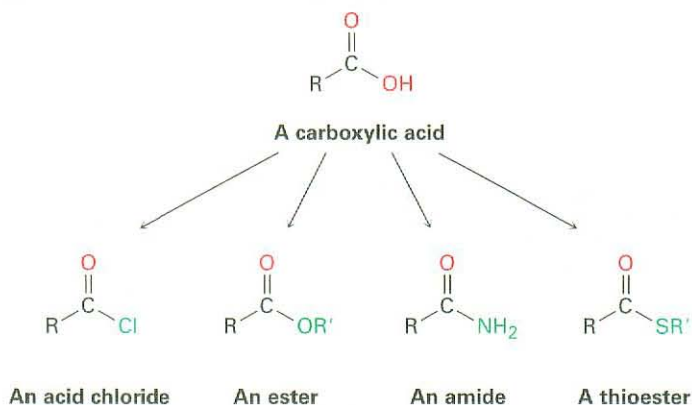
Carboxylic Acids and Nitriles

Organic KNOWLEDGE TOOLS

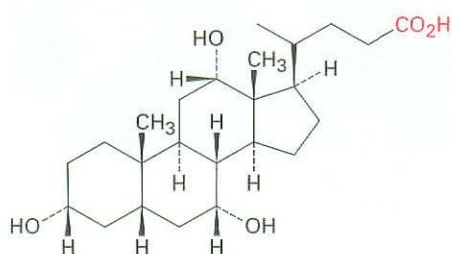
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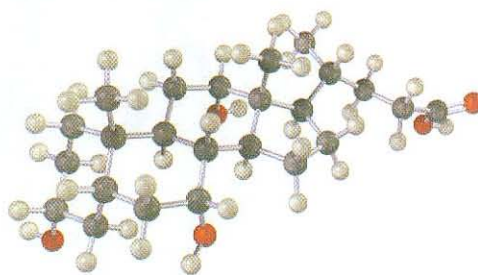
Carboxylic acids, RCO_2H , occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous *acyl derivatives* such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways. We'll look both at acids and at their close relatives, *nitriles* ($\text{RC}\equiv\text{N}$), in this chapter and at acyl derivatives in the next chapter.



A great many carboxylic acids are found in nature: acetic acid, $\text{CH}_3\text{CO}_2\text{H}$, is the chief organic component of vinegar; butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, is responsible for the rancid odor of sour butter; and hexanoic acid (caproic acid), $\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$, is responsible for the unmistakable aroma of goats and dirty gym socks (the name comes from the Latin *capere*, meaning “goat”). Other examples are cholic acid, a major component of human bile, and long-chain aliphatic acids such as palmitic acid, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$, a biological precursor of fats and vegetable oils.



Cholic acid



Approximately 2.5 million tons of acetic acid is produced each year in the United States for a variety of purposes, including preparation of the vinyl acetate polymer used in paints and adhesives. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.



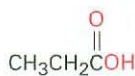
WHY THIS CHAPTER?

Carboxylic acids are present in many industrial processes and most biological pathways and are the starting materials from which other acyl derivatives are made. Thus, an understanding of their properties and reactions is fundamental to understanding organic chemistry. In this chapter, we'll look both at acids and at their close relatives, *nitriles* ($\text{RC}\equiv\text{N}$). In the next chapter, we'll look at acyl derivatives.

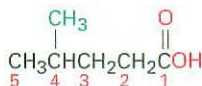
20.1 Naming Carboxylic Acids and Nitriles

Carboxylic Acids, RCO_2H

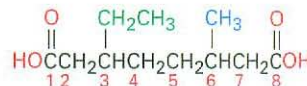
Simple carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. The $-\text{CO}_2\text{H}$ carbon atom is numbered C1.



Propanoic acid



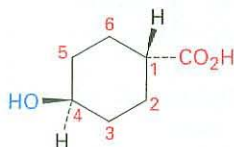
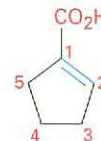
4-Methylpentanoic acid



3-Ethyl-6-methyloctanedioic acid

ThomsonNOW[™] Click *Organic Interactive* to use a web-based palette to draw structures of carboxylic acids based on their IUPAC names.


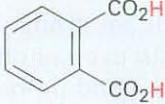
Compounds that have a $-\text{CO}_2\text{H}$ group bonded to a ring are named using the suffix *-carboxylic acid*. The CO_2H carbon is attached to C1 in this system and is not itself numbered. As a substituent, the CO_2H group is called a **carboxyl group**.

*trans*-4-Hydroxycyclohexanecarboxylic acid

1-Cyclopentene-2-carboxylic acid

Because many carboxylic acids were among the first organic compounds to be isolated and purified, a large number of common names exist (Table 20.1). Biological chemists, in particular, make frequent use of these names. We'll use systematic names in this book, with a few exceptions such as formic (methanoic) acid and acetic (ethanoic) acid, whose names are accepted by IUPAC and are so well known that it makes little sense to refer to them any other way. Also listed in Table 20.1 are the common names used for acyl groups derived from the parent acids. Except for the small handful at the top of Table 20.1, acyl groups are named by changing the *-ic acid* or *-oic acid* ending to *-oyl*.

Table 20.1 Common Names of Some Carboxylic Acids and Acyl Groups

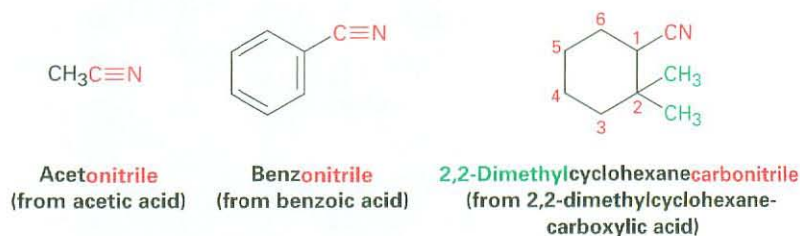
Structure	Name	Acyl group
HCO_2H	Formic	Formyl
$\text{CH}_3\text{CO}_2\text{H}$	Acetic	Acetyl
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	Propionic	Propionyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Butyric	Butyryl
$\text{HO}_2\text{CCO}_2\text{H}$	Oxalic	Oxalyl
$\text{HO}_2\text{CCH}_2\text{CO}_2\text{H}$	Malonic	Malonyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Succinic	Succinyl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	Glutaric	Glutaryl
$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	Adipic	Adipoyl
$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	Acrylic	Acryloyl
$\text{HO}_2\text{CCH}=\text{CHCO}_2\text{H}$	Maleic (cis)	Maleoyl
	Fumaric (trans)	Fumaroyl
$\text{HOCH}_2\text{CO}_2\text{H}$	Glycolic	Glycoloyl
$\begin{array}{c} \text{OH} \\ \\ \text{CH}_3\text{CHCO}_2\text{H} \end{array}$	Lactic	Lactoyl
$\begin{array}{c} \text{O} \\ \\ \text{CH}_3\text{CCO}_2\text{H} \end{array}$	Pyruvic	Pyruvoyl
$\begin{array}{c} \text{OH} \\ \\ \text{HOCH}_2\text{CHCO}_2\text{H} \end{array}$	Glyceric	Glyceroyl
$\begin{array}{c} \text{OH} \\ \\ \text{HO}_2\text{CCHCH}_2\text{CO}_2\text{H} \end{array}$	Malic	Maloyl
$\begin{array}{c} \text{O} \\ \\ \text{HO}_2\text{CCCH}_2\text{CO}_2\text{H} \end{array}$	Oxaloacetic	Oxaloacetyl
	Benzoic	Benzoyl
	Phthalic	Phthaloyl

Nitriles, $\text{RC}\equiv\text{N}$

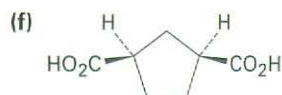
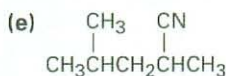
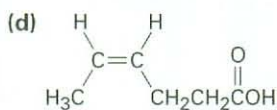
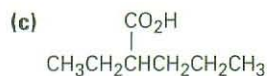
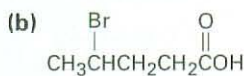
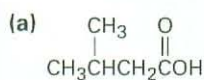
Compounds containing the $-\text{C}\equiv\text{N}$ functional group are called **nitriles** and undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding *-nitrile* as a suffix to the alkane name, with the nitrile carbon numbered C1.



Nitriles can also be named as derivatives of carboxylic acids by replacing the *-ic acid* or *-oic acid* ending with *-onitrile*, or by replacing the *-carboxylic acid* ending with *-carbonitrile*. The nitrile carbon atom is attached to C1 but is not itself numbered.



Problem 20.1 Give IUPAC names for the following compounds:



Problem 20.2 Draw structures corresponding to the following IUPAC names:

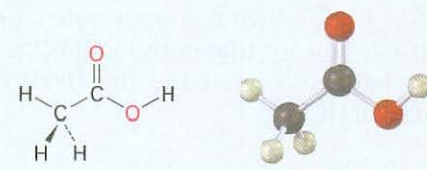
- | | |
|--|-----------------------------------|
| (a) 2,3-Dimethylhexanoic acid | (b) 4-Methylpentanoic acid |
| (c) <i>trans</i> -1,2-Cyclobutanedicarboxylic acid | (d) <i>o</i> -Hydroxybenzoic acid |
| (e) (9Z,12Z)-9,12-Octadecadienoic acid | (f) 2-Pentenenitrile |

20.2 Structure and Properties of Carboxylic Acids

Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2 -hybridized, and carboxylic acid groups are therefore planar with $\text{C}-\text{C}=\text{O}$ and $\text{O}=\text{C}-\text{O}$ bond angles of approximately 120° (Table 20.2).

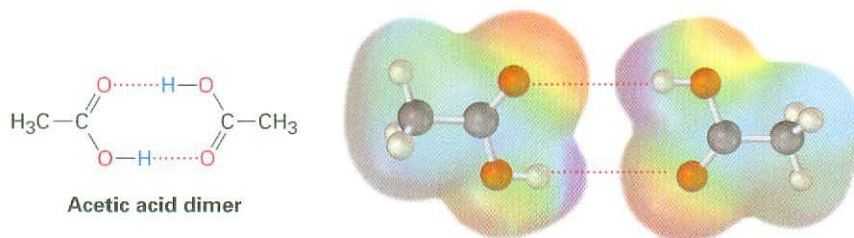
Like alcohols, carboxylic acids are strongly associated because of hydrogen bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen bonding has a noticeable effect on boiling points, making carboxylic acids much higher boiling than the corresponding

Table 20.2 Physical Parameters for Acetic Acid

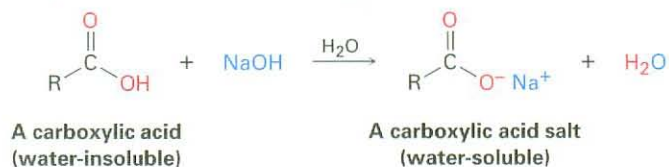


Bond angle	(degrees)	Bond length	(pm)
C-C=O	119	C-C	152
C-C-OH	119	C=O	125
O=C-OH	122	C-OH	131

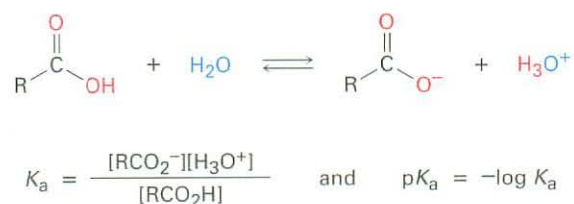
alcohols. Acetic acid, for instance, has a boiling point of 117.9 °C, versus 78.3 °C for ethanol, even though both compounds have two carbons.



The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*. They therefore react with bases such as NaOH and NaHCO₃ to give metal carboxylate salts, RCO₂⁻ M⁺. Carboxylic acids with more than six carbons are only slightly soluble in water, but the alkali metal salts of carboxylic acids are often highly water-soluble. In fact, it's often possible to purify an acid by extracting its salt into aqueous base, then reacidifying and extracting the pure acid back into an organic solvent.




Like other Brønsted–Lowry acids discussed in Section 2.7, carboxylic acids dissociate slightly in dilute aqueous solution to give H₃O⁺ and the corresponding carboxylate anions, RCO₂⁻. The extent of dissociation is given by an acidity constant, K_a.



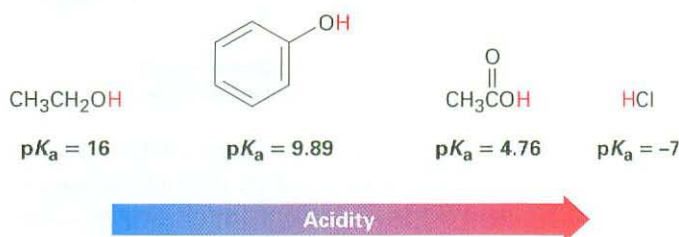
A list of K_a values for various carboxylic acids is given in Table 20.3. For most, K_a is approximately 10^{-4} to 10^{-5} . Acetic acid, for instance, has $K_a = 1.75 \times 10^{-5}$, which corresponds to a pK_a of 4.76. In practical terms, a K_a value near 10^{-5} means that only about 0.1% of the molecules in a 0.1 M solution are dissociated, as opposed to the 100% dissociation found with strong mineral acids like HCl.

Table 20.3 Acidity of Some Carboxylic Acids

Structure	K_a	pK_a
$\text{CF}_3\text{CO}_2\text{H}$	0.59	0.23
HCO_2H	1.77×10^{-4}	3.75
$\text{HOCH}_2\text{CO}_2\text{H}$	1.5×10^{-4}	3.84
$\text{C}_6\text{H}_5\text{CO}_2\text{H}$	6.46×10^{-5}	4.19
$\text{H}_2\text{C}=\text{CHCO}_2\text{H}$	5.6×10^{-5}	4.25
$\text{CH}_3\text{CO}_2\text{H}$	1.75×10^{-5}	4.76
$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	1.34×10^{-5}	4.87
$\text{CH}_3\text{CH}_2\text{OH}$ (ethanol)	(1.00×10^{-16})	(16.00)

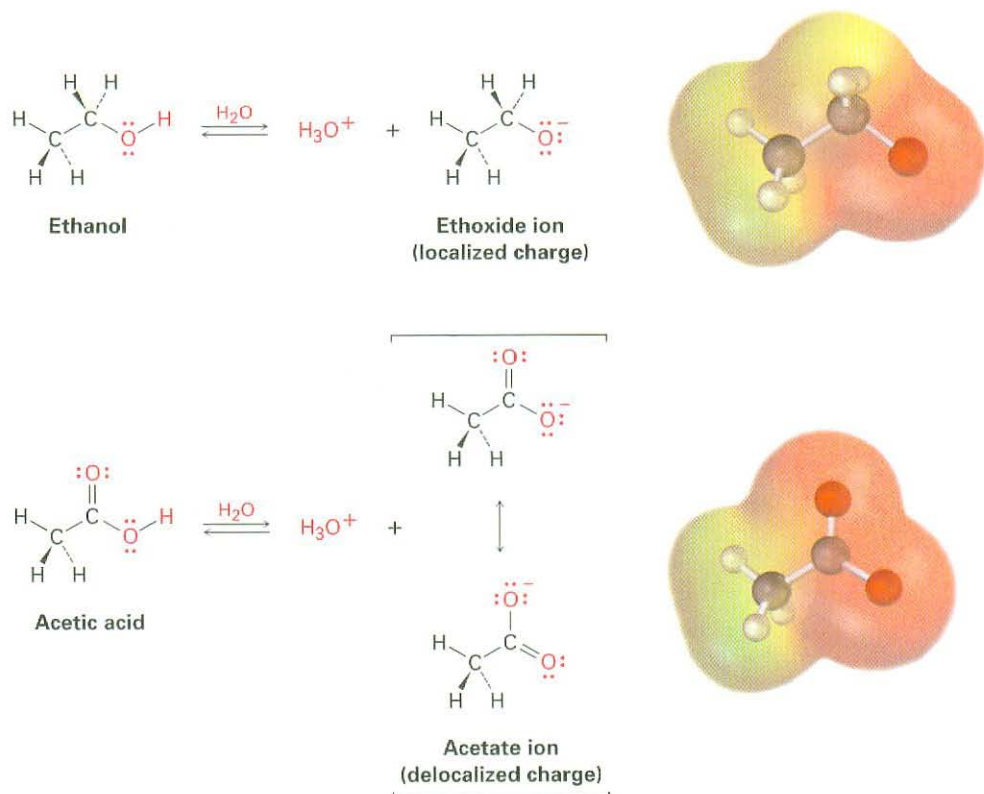


Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The K_a of ethanol, for example, is approximately 10^{-16} , making ethanol a weaker acid than acetic acid by a factor of 10^{11} .



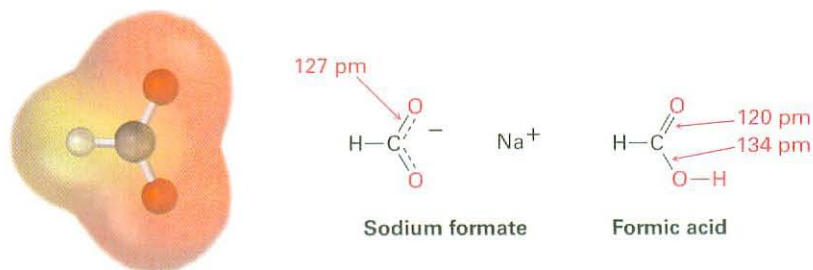
Why are carboxylic acids so much more acidic than alcohols, even though both contain $-\text{OH}$ groups? An alcohol dissociates to give an alkoxide ion, in which the negative charge is localized on a single electronegative atom. A carboxylic acid, however, gives a carboxylate ion, in which the negative charge is delocalized over *two* equivalent oxygen atoms (Figure 20.1). In resonance terms (Section 2.4), a carboxylate ion is a stabilized resonance hybrid of *two* equivalent

structures. Since a carboxylate ion is more stable than an alkoxide ion, it is lower in energy and more favored in the dissociation equilibrium.



Active Figure 20.1 An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.

Experimental evidence for the equivalence of the two carboxylate oxygens comes from X-ray crystallographic studies on sodium formate. Both carbon-oxygen bonds are 127 pm in length, midway between the C=O bond (120 pm) and C-O bond (134 pm) of formic acid. An electrostatic potential map of the formate ion also shows how the negative charge (red) is dispersed equally over both oxygens.



Problem 20.3 Assume you have a mixture of naphthalene and benzoic acid that you want to separate. How might you take advantage of the acidity of one component in the mixture to effect a separation?

Problem 20.4 The K_a for dichloroacetic acid is 3.32×10^{-2} . Approximately what percentage of the acid is dissociated in a 0.10 M aqueous solution?

20.3 Biological Acids and the Henderson–Hasselbalch Equation

In acidic solution at low pH, a carboxylic acid is completely undissociated and exists entirely as RCO_2H . In basic solution at high pH, a carboxylic acid is completely dissociated and exists entirely as RCO_2^- . Inside living cells, however, the pH is neither acidic nor basic but is instead buffered to nearly neutral pH—in humans, to $\text{pH} = 7.3$, a value often referred to as *physiological pH*. In what form, then, do carboxylic acids exist inside cells? The question is an important one for understanding the acid catalysts so often found in biological reactions.

If the $\text{p}K_a$ value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using what is called the **Henderson–Hasselbalch equation**.

For any acid HA, we have

$$\begin{aligned} \text{p}K_a &= -\log \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} = -\log[\text{H}_3\text{O}^+] - \log \frac{[\text{A}^-]}{[\text{HA}]} \\ &= \text{pH} - \log \frac{[\text{A}^-]}{[\text{HA}]} \end{aligned}$$

which can be rearranged to give

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]} \quad \text{Henderson–Hasselbalch equation}$$

$$\text{so} \quad \log \frac{[\text{A}^-]}{[\text{HA}]} = \text{pH} - \text{p}K_a$$

This equation says that the logarithm of the concentration of dissociated acid $[\text{A}^-]$ divided by the concentration of undissociated acid $[\text{HA}]$ is equal to the pH of the solution minus the $\text{p}K_a$ of the acid. Thus, if we know both the pH of the solution and the $\text{p}K_a$ of the acid, we can calculate the ratio of $[\text{A}^-]$ to $[\text{HA}]$. Furthermore, when $\text{pH} = \text{p}K_a$, the two forms HA and A^- are present in equal amounts because $\log 1 = 0$.

As an example of how to use the Henderson–Hasselbalch equation, let's find out what species are present in a 0.0010 M solution of acetic acid at $\text{pH} = 7.3$. According to Table 20.3, the $\text{p}K_a$ of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\begin{aligned} \log \frac{[\text{A}^-]}{[\text{HA}]} &= \text{pH} - \text{p}K_a = 7.3 - 4.76 = 2.54 \\ \frac{[\text{A}^-]}{[\text{HA}]} &= \text{antilog}(2.54) = 3.5 \times 10^2 \quad \text{so} \quad [\text{A}^-] = (3.5 \times 10^2) [\text{HA}] \end{aligned}$$

In addition, we know that

$$[\text{A}^-] + [\text{HA}] = 0.0010 \text{ M}$$

Solving the two simultaneous equations gives $[A^-] = 0.0010 \text{ M}$ and $[HA] = 3 \times 10^{-6} \text{ M}$. In other words, at a physiological pH of 7.3, essentially 100% of acetic acid molecules in a 0.0010 M solution are dissociated to the acetate ion.

What is true for acetic acid is also true for other carboxylic acids: at the physiological pH that exists inside cells, carboxylic acids are almost entirely dissociated. To reflect this fact, we always refer to cellular carboxylic acids by the name of their anion—acetate, lactate, citrate, and so forth, rather than acetic acid, lactic acid, and citric acid.

Problem 20.5 Calculate the percentages of dissociated and undissociated forms present in the following solutions:

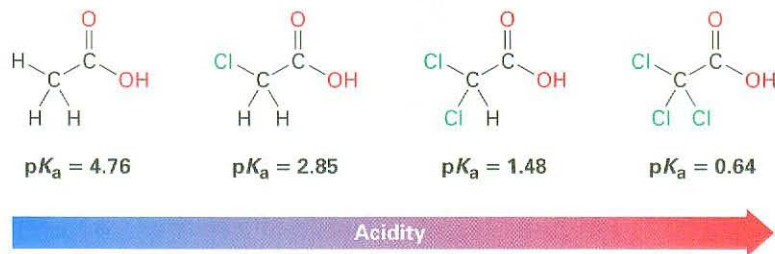
(a) 0.0010 M glycolic acid ($\text{HOCH}_2\text{CO}_2\text{H}$; $\text{p}K_a = 3.83$) at pH = 4.50

(b) 0.0020 M propanoic acid ($\text{p}K_a = 4.87$) at pH = 5.30

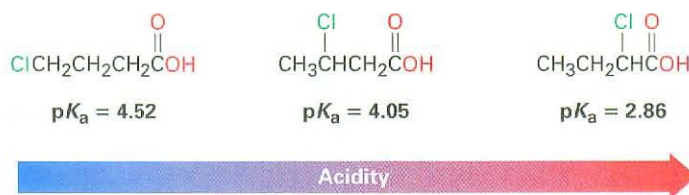
20.4 Substituent Effects on Acidity

The listing of $\text{p}K_a$ values shown previously in Table 20.3 indicates that there are substantial differences in acidity from one carboxylic acid to another. For example, trifluoroacetic acid ($K_a = 0.59$) is 33,000 times as strong as acetic acid ($K_a = 1.75 \times 10^{-5}$). How can we account for such differences?

Because the dissociation of a carboxylic acid is an equilibrium process, any factor that stabilizes the carboxylate anion relative to undissociated carboxylic acid will drive the equilibrium toward increased dissociation and result in increased acidity. An electron-withdrawing chlorine atom, for instance, makes chloroacetic acid ($K_a = 1.4 \times 10^{-3}$) approximately 80 times as strong as acetic acid; introduction of two chlorines makes dichloroacetic acid 3000 times as strong as acetic acid, and introduction of three chlorines makes trichloroacetic acid more than 12,000 times as strong.




Because inductive effects operate through σ bonds and are dependent on distance, the effect of halogen substitution decreases as the substituent moves farther from the carboxyl. Thus, 2-chlorobutanoic acid has $\text{p}K_a = 2.86$, 3-chlorobutanoic acid has $\text{p}K_a = 4.05$, and 4-chlorobutanoic acid has $\text{p}K_a = 4.52$, similar to that of butanoic acid itself.



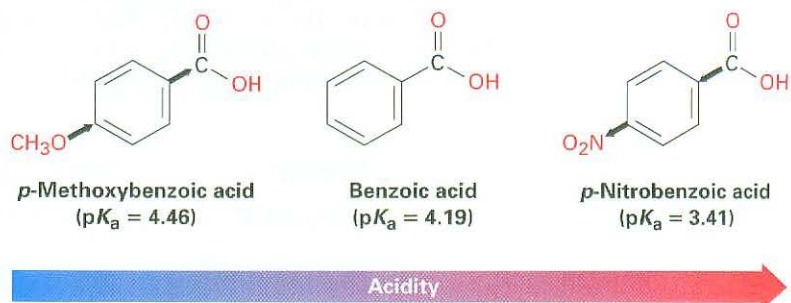
Substituent effects on acidity are also found in substituted benzoic acids. We saw during the discussion of electrophilic aromatic substitution in Section 16.4 that substituents on the aromatic ring dramatically affect reactivity. Aromatic rings with electron-donating groups are activated toward further electrophilic substitution, and aromatic rings with electron-withdrawing groups are deactivated. Exactly the same effects are noticed on the acidity of substituted benzoic acids (Table 20.4).

Table 20.4 Substituent Effects on Acidity of *p*-Substituted Benzoic Acids

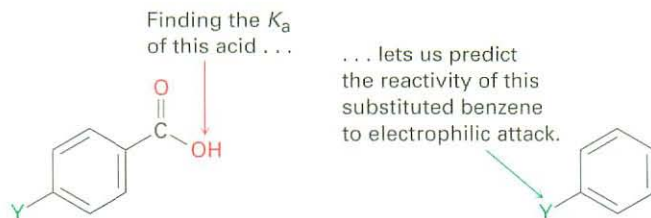


	Y	$K_a \times 10^{-5}$	pK_a	
Stronger acid ↑	-NO ₂	39	3.41	Deactivating groups
	-CN	28	3.55	
	-CHO	18	3.75	
	-Br	11	3.96	
	-Cl	10	4.0	
	-H	6.46	4.19	
Weaker acid ↓	CH ₃	4.3	4.34	Activating groups
	-OCH ₃	3.5	4.46	
	-OH	3.3	4.48	

As Table 20.4 shows, an electron-withdrawing (deactivating) group such as nitro increases acidity by stabilizing the carboxylate anion, and an electron-donating (activating) group such as methoxy decreases acidity by destabilizing the carboxylate anion.



Because it's much easier to measure the acidity of a substituted benzoic acid than it is to determine the relative reactivity of an aromatic ring toward electrophilic substitution, the correlation between the two effects is useful for predicting reactivity. If we want to know the effect of a certain substituent on electrophilic reactivity, we can simply find the acidity of the corresponding benzoic acid. Worked Example 20.1 gives an example.

**WORKED EXAMPLE 20.1****Predicting the Effect of a Substituent on the Reactivity of an Aromatic Ring toward Electrophilic Substitution**

The pK_a of *p*-(trifluoromethyl)benzoic acid is 3.6. Is the trifluoromethyl substituent an activating or deactivating group in electrophilic aromatic substitution?

Strategy Decide whether *p*-(trifluoromethyl)benzoic acid is stronger or weaker than benzoic acid. A substituent that strengthens the acid is a deactivating group because it withdraws electrons, and a substituent that weakens the acid is an activating group because it donates electrons.

Solution A pK_a of 3.6 means that *p*-(trifluoromethyl)benzoic acid is stronger than benzoic acid, whose pK_a is 4.19. Thus, the trifluoromethyl substituent favors dissociation by helping stabilize the negative charge. Trifluoromethyl must therefore be an electron-withdrawing, deactivating group.

Problem 20.6 Which would you expect to be a stronger acid, the lactic acid found in tired muscles or acetic acid? Explain.



Problem 20.7 Dicarboxylic acids have two dissociation constants, one for the initial dissociation into a monoanion and one for the second dissociation into a dianion. For oxalic acid, $\text{HO}_2\text{C}-\text{CO}_2\text{H}$, the first ionization constant has $pK_{a1} = 1.2$ and the second ionization constant has $pK_{a2} = 4.2$. Why is the second carboxyl group so much less acidic than the first?

Problem 20.8 The pK_a of *p*-cyclopropylbenzoic acid is 4.45. Is cyclopropylbenzene likely to be more reactive or less reactive than benzene toward electrophilic bromination? Explain.

Problem 20.9 Rank the following compounds in order of increasing acidity. Don't look at a table of pK_a data to help with your answer.

- (a) Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid
 (b) *p*-Nitrobenzoic acid, acetic acid, benzoic acid

20.5 Preparation of Carboxylic Acids

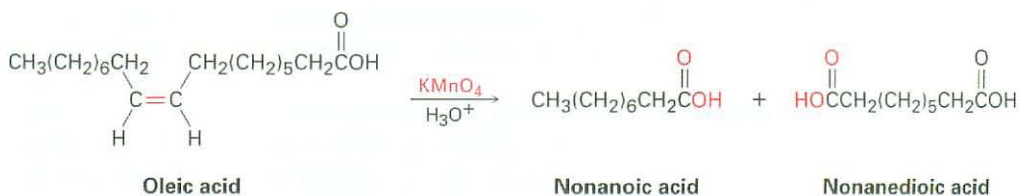
ThomsonNOW Click *Organic Interactive* to use your problem-solving skills to design syntheses of carboxylic acids.

Let's review briefly some of the methods for preparing carboxylic acids that we've seen in past chapters.

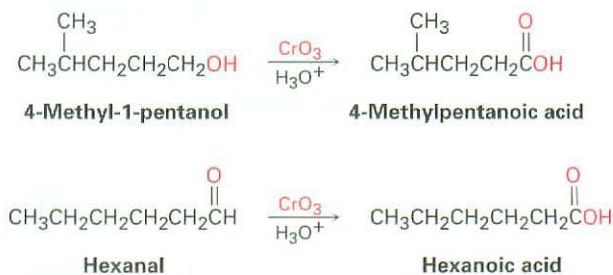
- Oxidation of a substituted alkylbenzene with KMnO_4 or $\text{Na}_2\text{Cr}_2\text{O}_7$ gives a substituted benzoic acid (Section 16.9). Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.



- Oxidative cleavage of an alkene with KMnO_4 gives a carboxylic acid if the alkene has at least one vinylic hydrogen (Section 7.9).



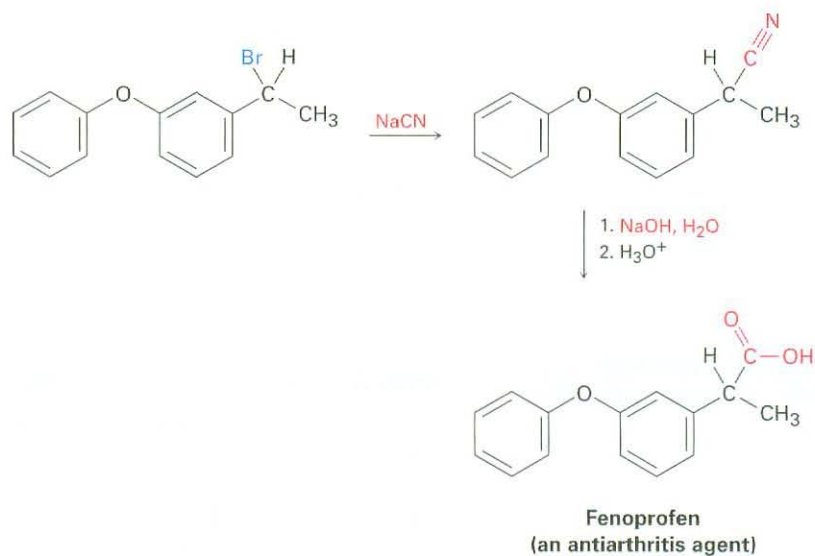
- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid (Sections 17.7 and 19.3). Primary alcohols are often oxidized with CrO_3 in aqueous acid, and aldehydes are oxidized with either acidic CrO_3 or basic silver oxide (Tollens' reagent).



Hydrolysis of Nitriles

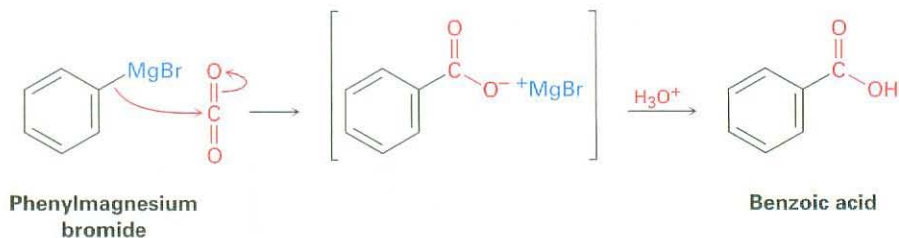
Carboxylic acids can be prepared from nitriles by reaction with hot aqueous acid or base by a mechanism that we'll see in Section 20.9. Since nitriles themselves are usually made by $\text{S}_{\text{N}}2$ reaction of a primary or secondary alkyl halide with CN^- , the two-step sequence of cyanide displacement followed by nitrile hydrolysis is a good way to make a carboxylic acid from an alkyl halide ($\text{RBr} \rightarrow \text{RC}\equiv\text{N} \rightarrow \text{RCO}_2\text{H}$).

Note that the product acid has one more carbon than the starting alkyl halide. An example occurs in the commercial synthesis of fenopropfen, a nonsteroidal anti-inflammatory drug, or NSAID, marketed under the trade name Nalfon. (See Chapter 15 *Focus On*.)



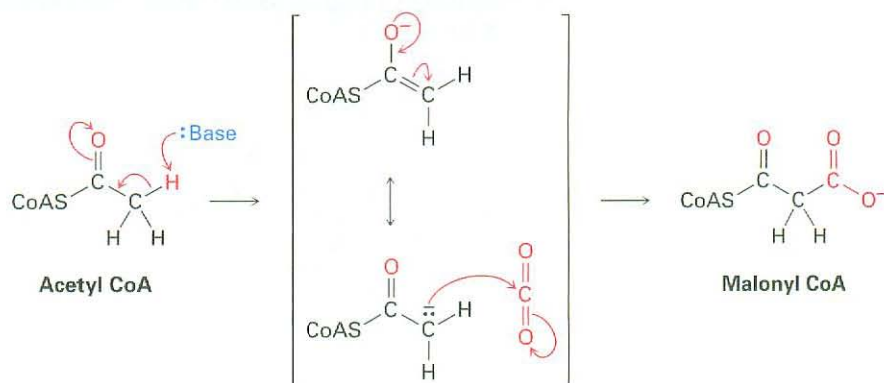
Carboxylation of Grignard Reagents

Another method for preparing carboxylic acids is by reaction of a Grignard reagent with CO_2 to yield a metal carboxylate, followed by protonation to give the carboxylic acid. This **carboxylation** reaction is usually carried out by bubbling a stream of dry CO_2 gas through a solution of the Grignard reagent. The organomagnesium halide adds to a $\text{C}=\text{O}$ bond of carbon dioxide in a typical nucleophilic carbonyl addition reaction, and protonation of the carboxylate by addition of aqueous HCl in a separate step then gives the free carboxylic acid. For example



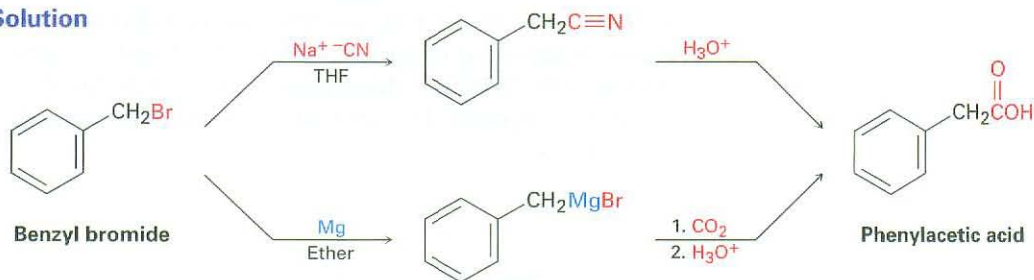
There are, of course, no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated. One of the

initial steps in fatty-acid biosynthesis, for instance, involves formation of a carbanion from acetyl CoA, followed by carboxylation to yield malonyl CoA.

**WORKED EXAMPLE 20.2****Devising a Synthesis Route for a Carboxylic Acid**

How would you prepare phenylacetic acid (PhCH₂CO₂H) from benzyl bromide (PhCH₂Br)?

Strategy We've seen two methods for preparing carboxylic acids from alkyl halides: (1) cyanide ion displacement followed by hydrolysis and (2) formation of a Grignard reagent followed by carboxylation. The first method involves an S_N2 reaction and is therefore limited to use with primary and some secondary alkyl halides. The second method involves formation of a Grignard reagent and is therefore limited to use with organic halides that have no acidic hydrogens or reactive functional groups elsewhere in the molecule. In the present instance, either method would work well.

Solution

Problem 20.10 How would you prepare the following carboxylic acids?

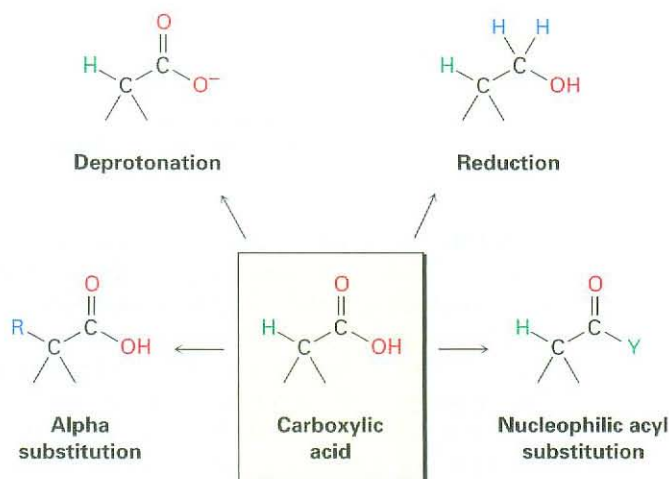
- (CH₃)₃CCO₂H from (CH₃)₃CCl
- CH₃CH₂CH₂CO₂H from CH₃CH₂CH₂Br

20.6 Reactions of Carboxylic Acids: An Overview

We commented earlier in this chapter that carboxylic acids are similar in some respects to both alcohols and ketones. Like alcohols, carboxylic acids can be deprotonated to give anions, which are good nucleophiles in S_N2 reactions. Like ketones,

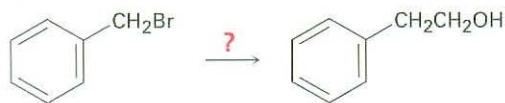
carboxylic acids undergo addition of nucleophiles to the carbonyl group. In addition, carboxylic acids undergo other reactions characteristic of neither alcohols nor ketones. Figure 20.2 shows some of the general reactions of carboxylic acids.

Figure 20.2 Some general reactions of carboxylic acids.



Reactions of carboxylic acids can be grouped into the four categories indicated in Figure 20.2. Of the four, we've already discussed the acidic behavior of carboxylic acids in Sections 20.2 through 20.4, and we mentioned reduction by treatment of the acid with LiAlH_4 in Section 17.4. The remaining two categories are examples of fundamental carbonyl-group reaction mechanisms—nucleophilic acyl substitution and α substitution—that will be discussed in detail in Chapters 21 and 22.

Problem 20.11 How might you prepare 2-phenylethanol from benzyl bromide? More than one step is needed.



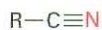
Problem 20.12 How might you carry out the following transformation? More than one step is needed.



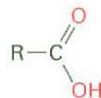
20.7 Chemistry of Nitriles

Nitriles are analogous to carboxylic acids in that both have a carbon atom with three bonds to an electronegative atom, and both contain a π bond. Thus, some reactions of nitriles and carboxylic acids are similar. Both kinds of

compounds are electrophiles, for instance, and both undergo nucleophilic addition reactions.

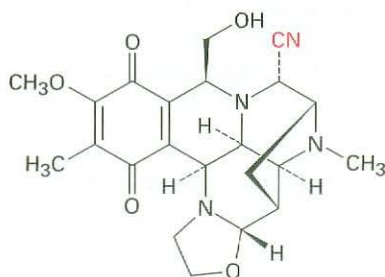


A nitrile—three
bonds to nitrogen

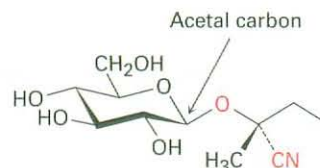


An acid—three
bonds to two oxygens

Nitriles occur infrequently in living organisms, although several hundred examples of their occurrence are known. Cyanocycline A, for instance, has been isolated from the bacterium *Streptomyces lavendulae* and found to have both antimicrobial and antitumor activity. In addition, more than 1000 compounds called *cyanogenic glycosides* are known. Derived primarily from plants, cyanogenic glycosides contain a sugar with an acetal carbon, one oxygen of which is bonded to a nitrile-bearing carbon (sugar-O-C-CN). On hydrolysis with aqueous acid, the acetal is cleaved (Section 19.10), generating a cyanohydrin (HO-C-CN), which releases hydrogen cyanide. It's thought that the primary function of cyanogenic glycosides is to protect the plant by poisoning any animal foolish enough to eat it. Lotaustralin from the cassava plant is an example.



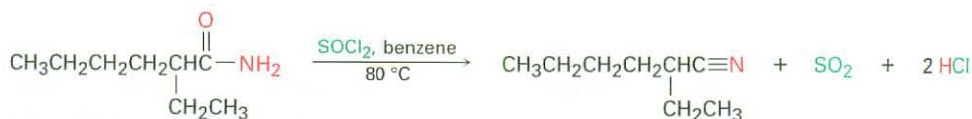
Cyanocycline A



Lotaustralin
(a cyanogenic glycoside)

Preparation of Nitriles

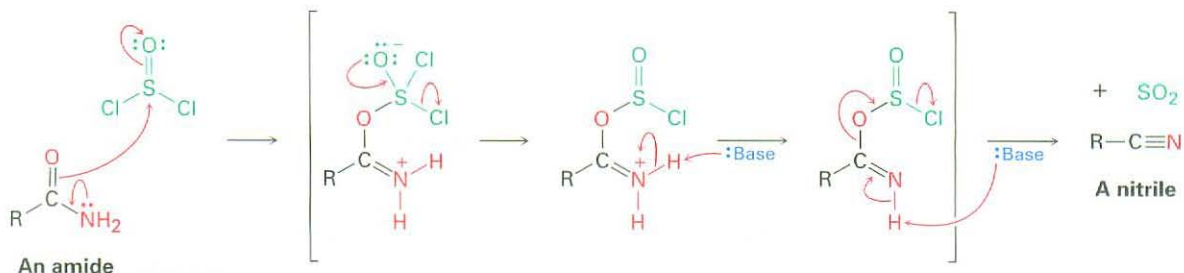
The simplest method of nitrile preparation is the S_N2 reaction of CN^- with a primary or secondary alkyl halide, as discussed in Section 20.5. Another method for preparing nitriles is by dehydration of a primary amide, RCONH_2 . Thionyl chloride is often used for the reaction, although other dehydrating agents such as POCl_3 also work.



2-Ethylhexanamide

2-Ethylhexanenitrile (94%)

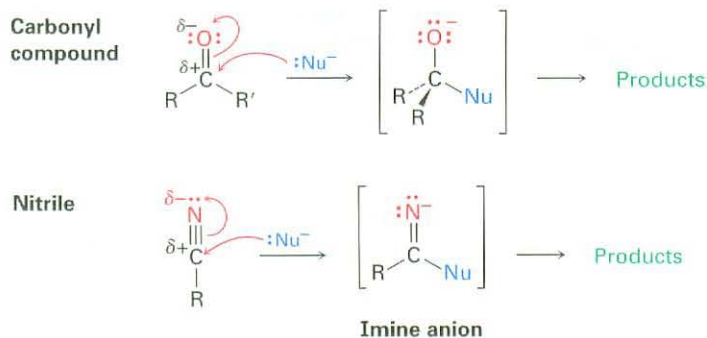
The dehydration occurs by initial reaction of SOCl_2 on the nucleophilic amide oxygen atom, followed by deprotonation and a subsequent E2-like elimination reaction.



Both methods of nitrile synthesis— $\text{S}_{\text{N}}2$ displacement by CN^- on an alkyl halide and amide dehydration—are useful, but the synthesis from amides is more general because it is not limited by steric hindrance.

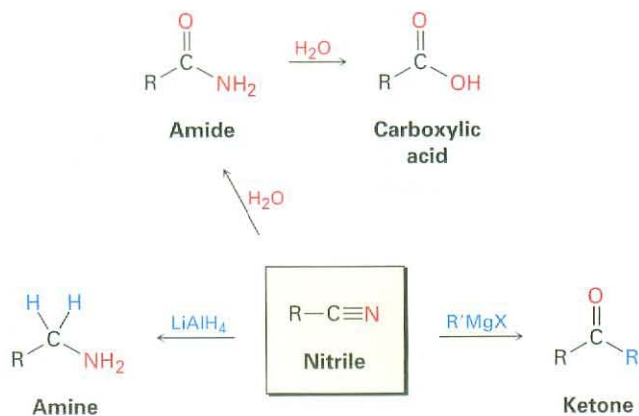
Reactions of Nitriles

Like a carbonyl group, a nitrile group is strongly polarized and has an electrophilic carbon atom. Nitriles therefore react with nucleophiles to yield sp^2 -hybridized imine anions in a reaction analogous to the formation of an sp^3 -hybridized alkoxide ion by nucleophilic addition to a carbonyl group.

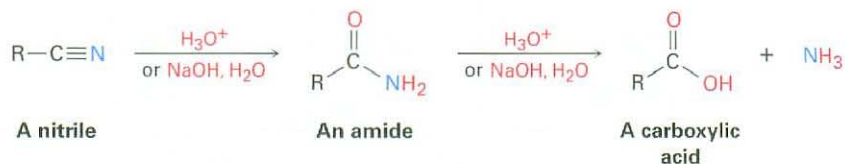


Among the most useful reactions of nitriles are hydrolysis to yield first an amide and then a carboxylic acid plus ammonia, reduction to yield an amine, and Grignard reaction to yield a ketone (Figure 20.3).

Figure 20.3 Some reactions of nitriles.

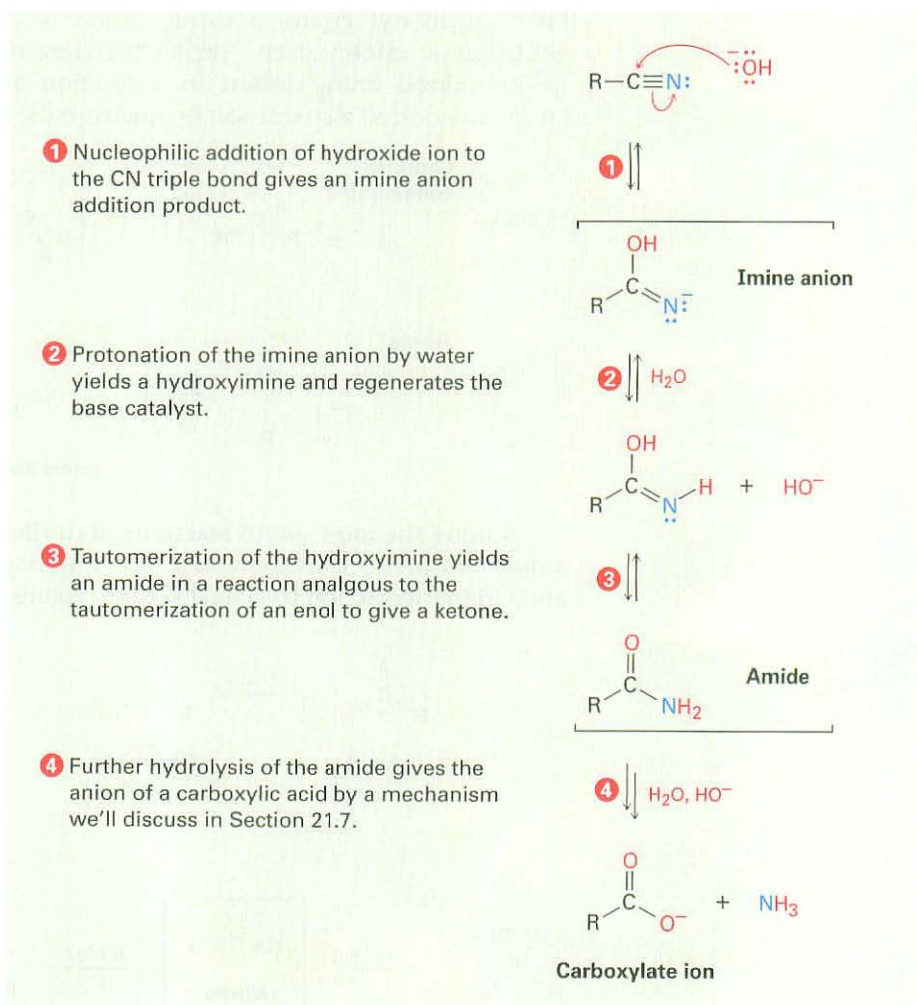


Hydrolysis: Conversion of Nitriles into Carboxylic Acids A nitrile is hydrolyzed in either basic or acidic aqueous solution to yield a carboxylic acid plus ammonia or an amine.

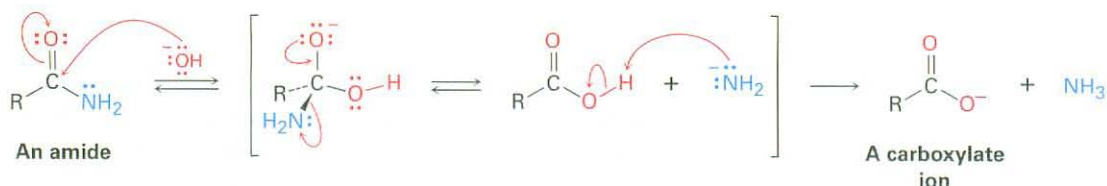


Base catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar $\text{C}\equiv\text{N}$ bond to give an imine anion in a process similar to nucleophilic addition to a polar $\text{C}=\text{O}$ bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes (Section 8.4) to an amide in a step similar to the tautomerization of an enol to a ketone. The mechanism is shown in Figure 20.4.

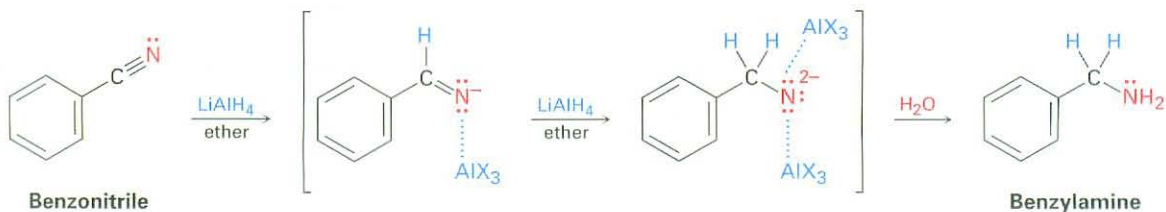
Active Figure 20.4 MECHANISM: Mechanism of the basic hydrolysis of a nitrile to yield an amide, which is subsequently hydrolyzed further to a carboxylic acid anion. Sign in at www.thomsonedu.com to see a simulation based on this figure and to take a short quiz.



Following formation of the amide intermediate, a second nucleophilic addition of hydroxide ion to the amide carbonyl group then yields a tetrahedral alkoxide ion, which expels amide ion, NH_2^- , as leaving group and gives the carboxylate ion, thereby driving the reaction toward products. Subsequent acidification in a separate step yields the carboxylic acid. We'll look at this process in more detail in Section 21.7.



Reduction: Conversion of Nitriles into Amines Reduction of a nitrile with LiAlH_4 gives a primary amine, RNH_2 . The reaction occurs by nucleophilic addition of hydride ion to the polar $\text{C}\equiv\text{N}$ bond, yielding an imine anion, which still contains a $\text{C}=\text{N}$ bond and therefore undergoes a second nucleophilic addition of hydride to give a dianion. Both monoanion and dianion intermediates are undoubtedly stabilized by Lewis acid–base complexation to an aluminum species, facilitating the second addition that would otherwise be difficult. Protonation of the dianion by addition of water in a subsequent step gives the amine.

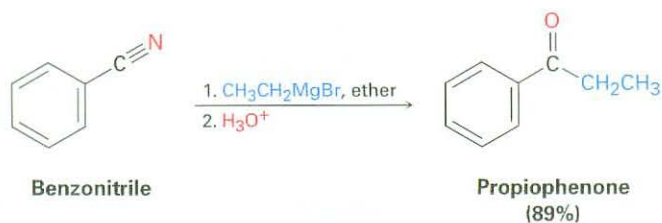


Reaction of Nitriles with Organometallic Reagents Grignard reagents add to a nitrile to give an intermediate imine anion that is hydrolyzed by addition of water to yield a ketone.



ThomsonNOW Click *Organic Interactive* to use a web-based palette to predict products from a variety of reactions involving carboxylic acids and nitriles.

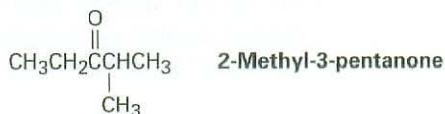
The reaction is similar to the reduction of a nitrile to an amine, except that only one nucleophilic addition occurs rather than two, and the attacking nucleophile is a carbanion (R'^-) rather than a hydride ion. For example:



WORKED EXAMPLE 20.3

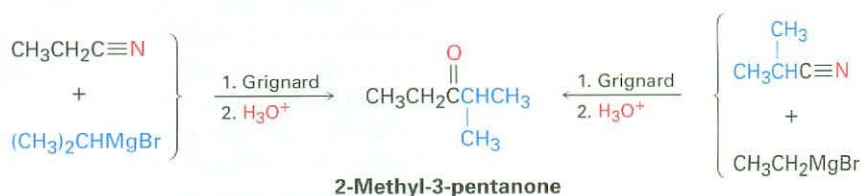
Synthesizing a Ketone from a Nitrile

How would you prepare 2-methyl-3-pentanone from a nitrile?

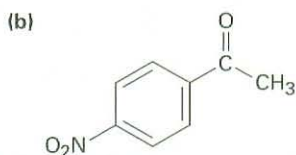
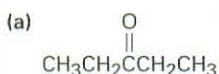


Strategy A ketone results from the reaction between a Grignard reagent and a nitrile, with the $\text{C}\equiv\text{N}$ carbon of the nitrile becoming the carbonyl carbon. Identify the two groups attached to the carbonyl carbon atom in the product. One will come from the Grignard reagent, and the other will come from the nitrile.

Solution There are two possibilities.



Problem 20.13 How would you prepare the following carbonyl compounds from a nitrile?



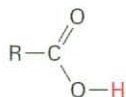
Problem 20.14 How would you prepare 1-phenyl-2-butanone, $\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_2\text{CH}_3$, from benzyl bromide, $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$? More than one step is required.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

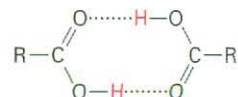
Infrared Spectroscopy

Carboxylic acids have two characteristic IR absorptions that make the $-\text{CO}_2\text{H}$ group easily identifiable. The $\text{O}-\text{H}$ bond of the carboxyl group gives rise to a very broad absorption over the range 2500 to 3300 cm^{-1} , and the $\text{C}=\text{O}$ bond shows an absorption between 1710 and 1760 cm^{-1} . The exact position of $\text{C}=\text{O}$ absorption depends both on the structure of the molecule and on whether the acid is free (monomeric) or hydrogen-bonded (dimeric). Free carboxyl groups absorb at 1760 cm^{-1} , but the more commonly encountered dimeric carboxyl groups absorb in a broad band centered around 1710 cm^{-1} .

Free carboxyl
(uncommon),
 1760 cm^{-1}



Associated carboxyl
(usual case),
 1710 cm^{-1}



Both the broad O–H absorption and the C=O absorption at 1710 cm^{-1} (dimeric) are identified in the IR spectrum of butanoic acid shown in Figure 20.5.

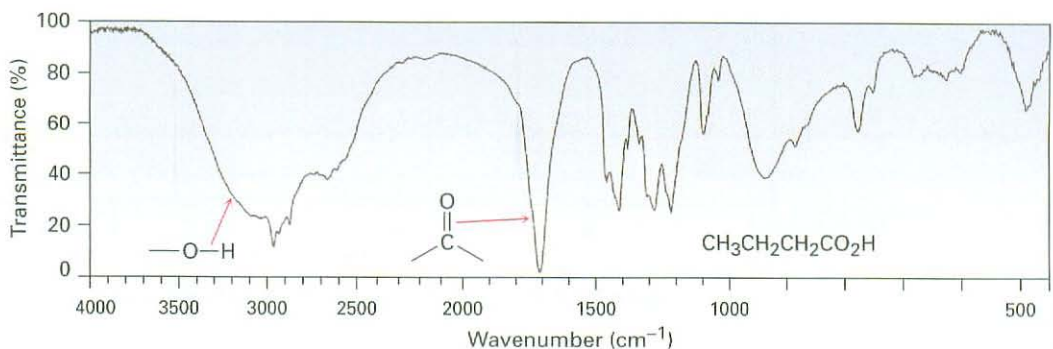


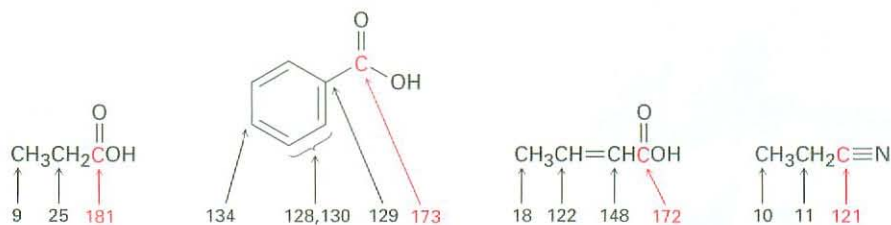
Figure 20.5 IR spectrum of butanoic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$.

Nitriles show an intense and easily recognizable $\text{C}\equiv\text{N}$ bond absorption near 2250 cm^{-1} for saturated compounds and 2230 cm^{-1} for aromatic and conjugated molecules. Since few other functional groups absorb in this region, IR spectroscopy is highly diagnostic for nitriles.

Problem 20.15 Cyclopentanecarboxylic acid and 4-hydroxycyclohexanone have the same formula ($\text{C}_6\text{H}_{10}\text{O}_2$), and both contain an –OH and a C=O group. How could you distinguish between them by IR spectroscopy?

Nuclear Magnetic Resonance Spectroscopy

Carboxylic acid groups can be detected by both ^1H and ^{13}C NMR spectroscopy. Carboxyl carbon atoms absorb in the range 165 to $185\ \delta$ in the ^{13}C NMR spectrum, with aromatic and α,β -unsaturated acids near the upfield end of the range ($\sim 165\ \delta$) and saturated aliphatic acids near the downfield end ($\sim 185\ \delta$). Nitrile carbons absorb in the range 115 to $130\ \delta$.



In the ^1H NMR spectrum, the acidic $-\text{CO}_2\text{H}$ proton normally absorbs as a singlet near $12\ \delta$. As with alcohols (Section 17.11), the $-\text{CO}_2\text{H}$ proton can be replaced by deuterium when D_2O is added to the sample tube, causing the absorption to disappear from the NMR spectrum. Figure 20.6 shows the ^1H NMR spectrum of phenylacetic acid. Note that the carboxyl proton absorption occurs at $12.0\ \delta$.

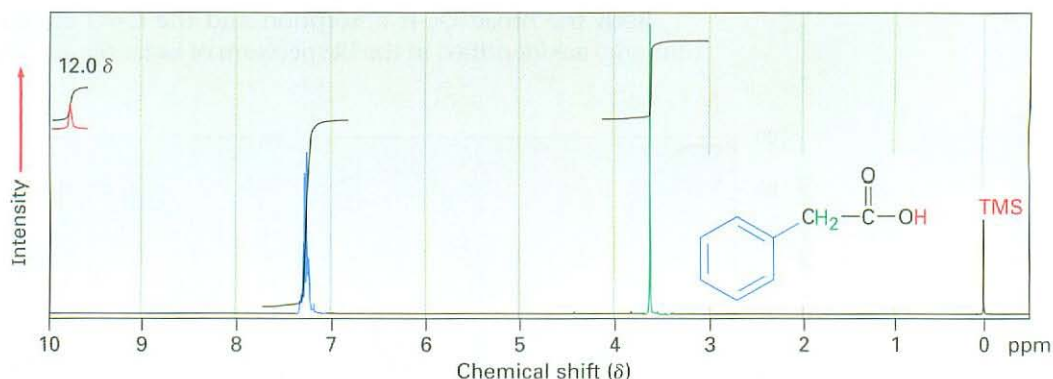


Figure 20.6 Proton NMR spectrum of phenylacetic acid, $C_6H_5CH_2CO_2H$.

Problem 20.16 | How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by 1H and ^{13}C NMR spectroscopy? (See Problem 20.14.)

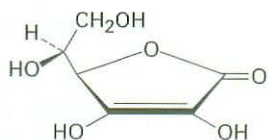
Focus On . . .

Vitamin C

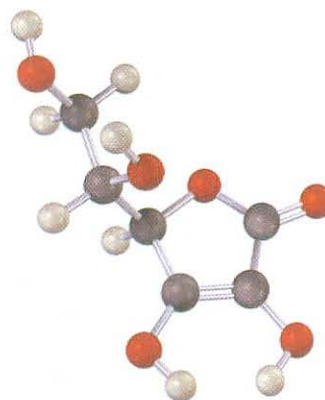


In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency.

Vitamin C, or ascorbic acid, is surely the best known of all vitamins. It was the first vitamin to be discovered (1928), the first to be structurally characterized (1933), and the first to be synthesized in the laboratory (1933). Over 200 million pounds of vitamin C are now synthesized worldwide each year, more than the total amount of all other vitamins combined. In addition to its use as a vitamin supplement, vitamin C is used as a food preservative, a “flour improver” in bakeries, and an animal food additive.



Vitamin C
(ascorbic acid)



(continued)

Vitamin C is perhaps most famous for its antiscorbutic properties, meaning that it prevents the onset of scurvy, a bleeding disease affecting those with a deficiency of fresh vegetables and citrus fruits in their diet. Sailors in the Age of Exploration were particularly susceptible to scurvy, and the death toll was high. The Portuguese explorer Vasco da Gama lost more than half his crew to scurvy during his 2-year voyage around the Cape of Good Hope in 1497–1499.

In more recent times, large doses of vitamin C have been claimed to prevent the common cold, cure infertility, delay the onset of symptoms in acquired immunodeficiency syndrome (AIDS), and inhibit the development of gastric and cervical cancers. None of these claims have been backed by medical evidence, however. In the largest study yet done of the effect of vitamin C on the common cold, a meta-analysis of more than 100 separate trials covering 40,000 people found no difference in the incidence of colds between those who took supplemental vitamin C regularly and those who did not. When taken during a cold, however, vitamin C does appear to decrease the cold's duration by 8%.

The industrial preparation of vitamin C involves an unusual blend of biological and laboratory organic chemistry. The Hoffmann-La Roche company synthesizes ascorbic acid from glucose through the five-step route shown in Figure 20.7. Glucose, a pentahydroxy aldehyde, is first reduced to sorbitol, which is then oxidized by the microorganism *Acetobacter suboxydans*. No chemical reagent is known that is selective enough to oxidize only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used. Treatment with acetone and an acid catalyst then protects four of the remaining hydroxyl groups in acetal linkages, and the unprotected hydroxyl group is chemically oxidized to the carboxylic acid by reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetal groups and causes an internal ester-forming reaction to take place to give ascorbic acid. Each of the five steps takes place in better than 90% yield.

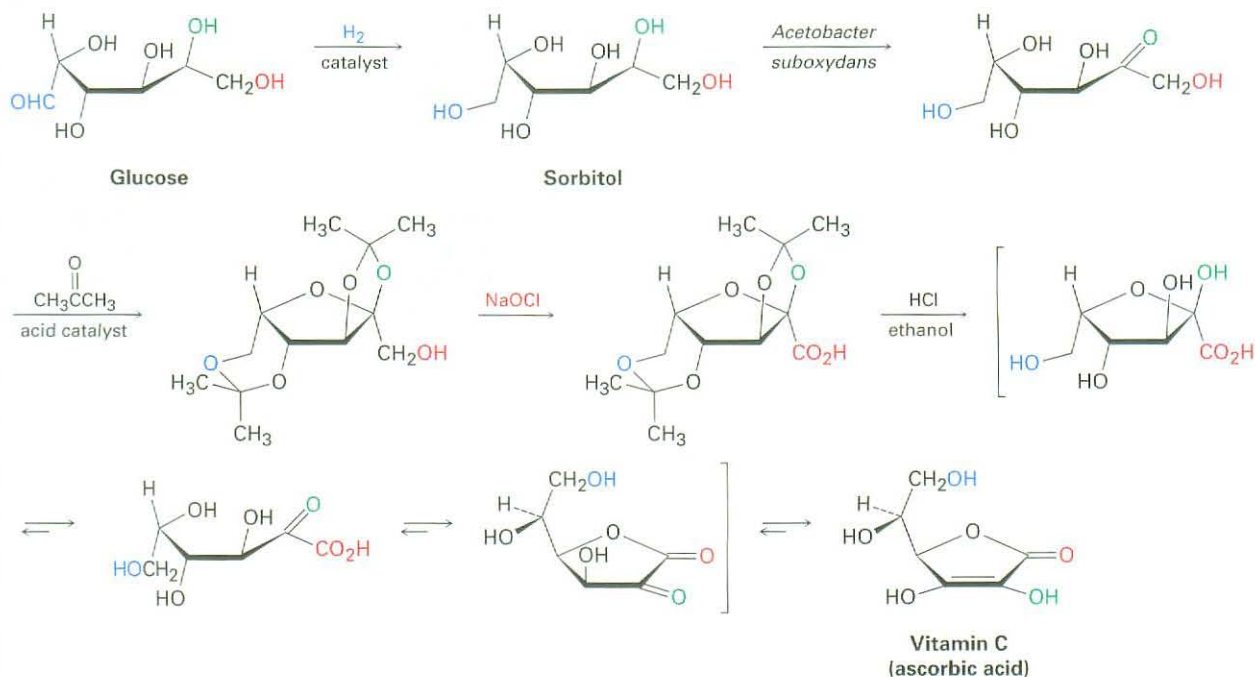


Figure 20.7 The industrial synthesis of ascorbic acid from glucose.

SUMMARY AND KEY WORDS

carboxyl group, 752
 carboxylation, 763
 carboxylic acid (RCO₂H), 751
 Henderson–Hasselbalch equation, 758
 nitrile (RC≡N), 754

Carboxylic acids are among the most useful building blocks for synthesizing other molecules, both in nature and in the chemical laboratory. They are named systematically by replacing the terminal *-e* of the corresponding alkane name with *-oic acid*. Like aldehydes and ketones, the carbonyl carbon atom is *sp*²-hybridized; like alcohols, carboxylic acids are associated through hydrogen-bonding and therefore have high boiling points.

The distinguishing characteristic of carboxylic acids is their acidity. Although weaker than mineral acids such as HCl, carboxylic acids dissociate much more readily than alcohols because the resultant carboxylate ions are stabilized by resonance between two equivalent forms.

Most carboxylic acids have *pK*_a values near 5, but the exact *pK*_a of a given acid depends on structure. Carboxylic acids substituted by electron-withdrawing groups are more acidic (have a lower *pK*_a) because their carboxylate ions are stabilized. Carboxylic acids substituted by electron-donating groups are less acidic (have a higher *pK*_a) because their carboxylate ions are destabilized. The extent of dissociation of a carboxylic acid in a buffered solution of a given pH can be calculated with the **Henderson–Hasselbalch equation**. Inside living cells, where the physiological pH = 7.3, carboxylic acids are entirely dissociated and exist as their carboxylate anions.

Methods of synthesis for carboxylic acids include (1) oxidation of alkylbenzenes, (2) oxidative cleavage of alkenes, (3) oxidation of primary alcohols or aldehydes, (4) hydrolysis of nitriles, and (5) reaction of Grignard reagents with CO₂ (**carboxylation**). General reactions of carboxylic acids include (1) loss of the acidic proton, (2) nucleophilic acyl substitution at the carbonyl group, (3) substitution on the α carbon, and (4) reduction.

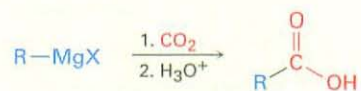
Nitriles are similar in some respects to carboxylic acids and are prepared either by S_N2 reaction of an alkyl halide with cyanide ion or by dehydration of an amide. Nitriles undergo nucleophilic addition to the polar C≡N bond in the same way that carbonyl compounds do. The most important reactions of nitriles are their hydrolysis to carboxylic acids, reduction to primary amines, and reaction with organometallic reagents to yield ketones.

Carboxylic acids and nitriles are easily distinguished spectroscopically. Acids show a characteristic IR absorption at 2500 to 3300 cm⁻¹ due to the O–H and another at 1710 to 1760 cm⁻¹ due to the C=O; nitriles have an absorption at 2250 cm⁻¹. Acids also show ¹³C NMR absorptions at 165 to 185 δ and ¹H NMR absorptions near 12 δ; nitriles have a ¹³C NMR absorption in the range 115 to 130 δ.

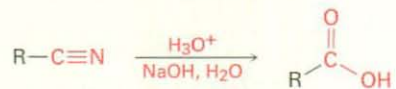
SUMMARY OF REACTIONS

1. Preparation of carboxylic acids (Section 20.5)

(a) Carboxylation of Grignard reagents

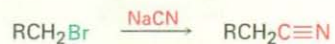


(b) Hydrolysis of nitriles

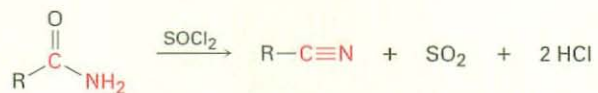


2. Preparation of nitriles (Section 20.7)

(a) S_N2 reaction of alkyl halides

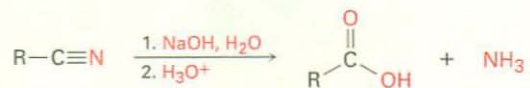


(b) Dehydration of amides

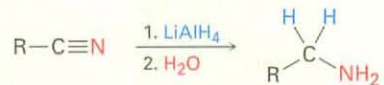


3. Reactions of nitriles (Section 20.7)

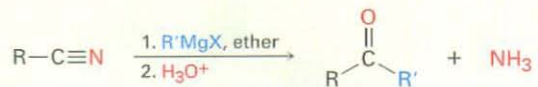
(a) Hydrolysis to yield carboxylic acids



(b) Reduction to yield primary amines



(c) Reaction with Grignard reagents to yield ketones



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at www.thomsonedu.com to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.



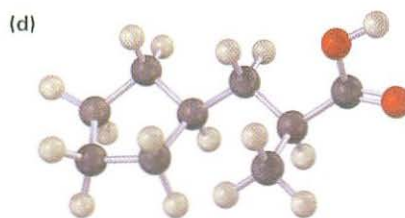
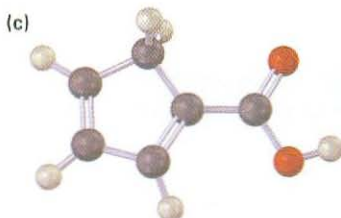
Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

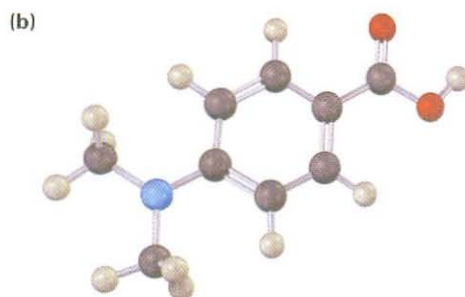
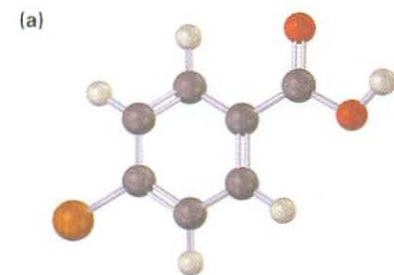
VISUALIZING CHEMISTRY

(Problems 20.1–20.16 appear within the chapter.)

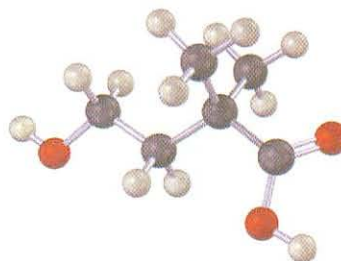
20.17 ■ Give IUPAC names for the following carboxylic acids (reddish brown = Br):



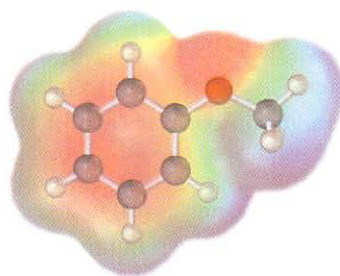
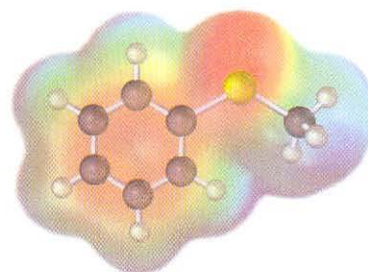
20.18 Would you expect the following carboxylic acids to be more acidic or less acidic than benzoic acid? Explain. (Reddish brown = Br.)



20.19 The following carboxylic acid can't be prepared from an alkyl halide by either the nitrile hydrolysis route or the Grignard carboxylation route. Explain.

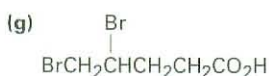
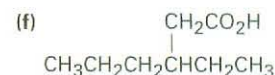
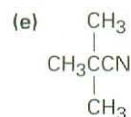
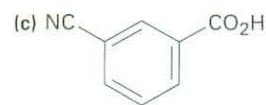
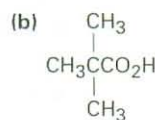
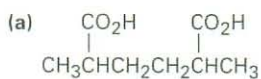


20.20 Electrostatic potential maps of anisole and thioanisole are shown. Which do you think is the stronger acid, *p*-methoxybenzoic acid or *p*-(methylthio)benzoic acid? Explain.

Anisole (C₆H₅OCH₃)Thioanisole (C₆H₅SCH₃)

ADDITIONAL PROBLEMS

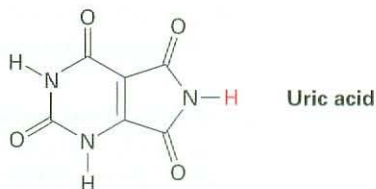
20.21 ■ Give IUPAC names for the following compounds:



20.22 ■ Draw structures corresponding to the following IUPAC names:

- | | |
|--|-----------------------------------|
| (a) <i>cis</i> -1,2-Cyclohexanedicarboxylic acid | (b) Heptanedioic acid |
| (c) 2-Hexen-4-ynoic acid | (d) 4-Ethyl-2-propyloctanoic acid |
| (e) 3-Chlorophthalic acid | (f) Triphenylacetic acid |
| (g) 2-Cyclobutenecarbonitrile | (h) <i>m</i> -Benzoylbenzonitrile |

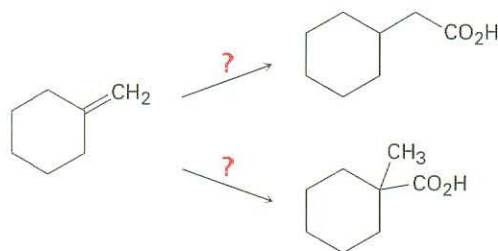
- 20.23** Draw and name the following:
 (a) The eight carboxylic acids with the formula $C_6H_{12}O_2$
 (b) Three nitriles with the formula C_5H_7N
- 20.24** Isocitric acid, an intermediate in the citric acid cycle of food metabolism, has the systematic name (2*R*,3*S*)-3-carboxy-2-hydroxypentanedioic acid. Draw the structure.
- 20.25** ■ Order the compounds in each of the following sets with respect to increasing acidity:
 (a) Acetic acid, oxalic acid, formic acid
 (b) *p*-Bromobenzoic acid, *p*-nitrobenzoic acid, 2,4-dinitrobenzoic acid
 (c) Fluoroacetic acid, 3-fluoropropanoic acid, iodoacetic acid
- 20.26** ■ Arrange the compounds in each of the following sets in order of increasing basicity:
 (a) Magnesium acetate, magnesium hydroxide, methylmagnesium bromide
 (b) Sodium benzoate, sodium *p*-nitrobenzoate, sodium acetylde
 (c) Lithium hydroxide, lithium ethoxide, lithium formate
- 20.27** ■ How could you convert butanoic acid into the following compounds? Write each step showing the reagents needed.
 (a) 1-Butanol (b) 1-Bromobutane (c) Pentanoic acid
 (d) 1-Butene (e) Octane
- 20.28** ■ How could you convert each of the following compounds into butanoic acid? Write each step showing all reagents.
 (a) 1-Butanol (b) 1-Bromobutane (c) 1-Butene
 (d) 1-Bromopropane (e) 4-Octene
- 20.29** ■ How could you convert butanenitrile into the following compounds? Write each step showing the reagents needed.
 (a) 1-Butanol (b) Butylamine (c) 2-Methyl-3-hexanone
- 20.30** ■ How would you prepare the following compounds from benzene? More than one step is required in each case.
 (a) *m*-Chlorobenzoic acid (b) *p*-Bromobenzoic acid
 (c) Phenylacetic acid, $C_6H_5CH_2CO_2H$
- 20.31** ■ Calculate pK_a 's for the following acids:
 (a) Lactic acid, $K_a = 8.4 \times 10^{-4}$ (b) Acrylic acid, $K_a = 5.6 \times 10^{-6}$
- 20.32** ■ Calculate K_a 's for the following acids:
 (a) Citric acid, $pK_a = 3.14$ (b) Tartaric acid, $pK_a = 2.98$
- 20.33** ■ Thioglycolic acid, $HSCH_2CO_2H$, a substance used in depilatory agents (hair removers) has $pK_a = 3.42$. What is the percent dissociation of thioglycolic acid in a buffer solution at $pH = 3.0$?
- 20.34** ■ In humans, the final product of purine degradation from DNA is uric acid, $pK_a = 5.61$, which is excreted in the urine. What is the percent dissociation of uric acid in urine at a typical $pH = 6.0$? Why do you think uric acid is acidic even though it does not have a CO_2H group?



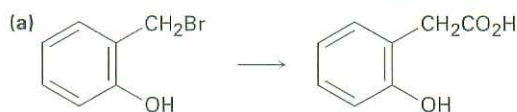
- 20.35** Shown here are some pK_a data for simple dibasic acids. How can you account for the fact that the difference between the first and second ionization constants decreases with increasing distance between the carboxyl groups?

Name	Structure	pK_1	pK_2
Oxalic	$\text{HO}_2\text{CCO}_2\text{H}$	1.2	4.2
Succinic	$\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO}_2\text{H}$	4.2	5.6
Adipic	$\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$	4.4	5.4

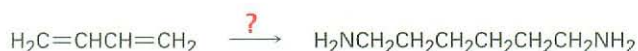
- 20.36** ■ Predict the product of the reaction of *p*-methylbenzoic acid with each of the following:
 (a) LiAlH_4 , then H_3O^+ (b) *N*-Bromosuccinimide in CCl_4
 (c) CH_3MgBr in ether, then H_3O^+ (d) KMnO_4 , H_3O^+
- 20.37** Using ^{13}C as your only source of labeled carbon, along with any other compounds needed, how would you synthesize the following compounds?
 (a) $\text{CH}_3\text{CH}_2^{13}\text{CO}_2\text{H}$ (b) $\text{CH}_3^{13}\text{CH}_2\text{CO}_2\text{H}$
- 20.38** How would you carry out the following transformations?



- 20.39** Which method—Grignard carboxylation or nitrile hydrolysis—would you use for each of the following reactions? Explain.

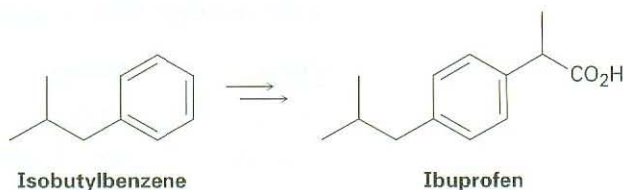


- 20.40** 1,6-Hexanediamine, a starting material needed for making nylon, can be made from 1,3-butadiene. How would you accomplish this synthesis?

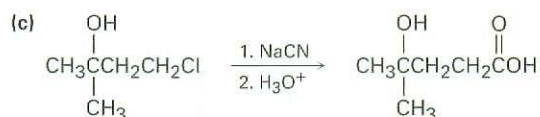
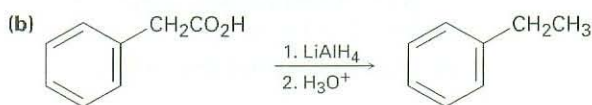
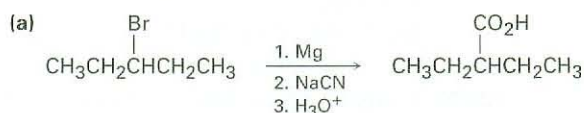


- 20.41** A chemist in need of 2,2-dimethylpentanoic acid decided to synthesize some by reaction of 2-chloro-2-methylpentane with NaCN , followed by hydrolysis of the product. After the reaction sequence was carried out, however, none of the desired product could be found. What do you suppose went wrong?

- 20.42** Show how you might prepare the anti-inflammatory agent ibuprofen starting from isobutylbenzene. More than one step is needed.

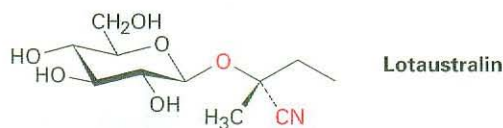


- 20.43** The following synthetic schemes all have at least one flaw in them. What is wrong with each?

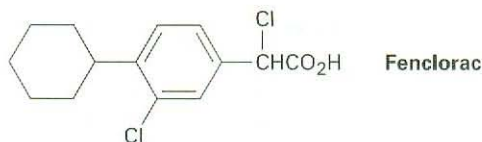


- 20.44** Naturally occurring compounds called *cyanogenic glycosides*, such as lotaustralin, release hydrogen cyanide, HCN, when treated with aqueous acid. The reaction occurs by hydrolysis of the acetal linkage to form a cyanohydrin, which then expels HCN and gives a carbonyl compound.

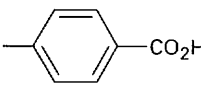
- (a) Show the mechanism of the acetal hydrolysis and the structure of the cyanohydrin that results.
 (b) Propose a mechanism for the loss of HCN, and show the structure of the carbonyl compound that forms.



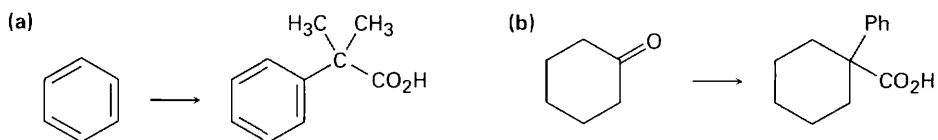
- 20.45** Acid-catalyzed hydrolysis of a nitrile to give a carboxylic acid occurs by initial protonation of the nitrogen atom, followed by nucleophilic addition of water. Review the mechanism of base-catalyzed nitrile hydrolysis in Section 20.7, and then write all the steps involved in the acid-catalyzed reaction, using curved arrows to represent electron flow in each step.
- 20.46** *p*-Aminobenzoic acid (PABA) is widely used as a sunscreen agent. Propose a synthesis of PABA starting from toluene.
- 20.47** Propose a synthesis of the anti-inflammatory drug Fenclorac from phenylcyclohexane.



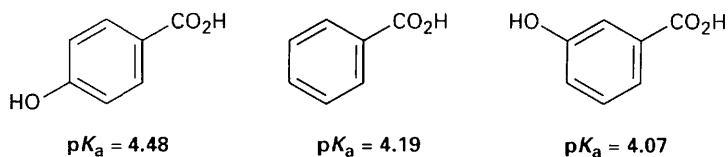
20.48 The pK_a 's of five *p*-substituted benzoic acids ($YC_6H_4CO_2H$) follow. Rank the corresponding substituted benzenes (YC_6H_5) in order of their increasing reactivity toward electrophilic aromatic substitution. If benzoic acid has $pK_a = 4.19$, which of the substituents are activators and which are deactivators?

Substituent Y	pK_a of Y- 
$-\text{Si}(\text{CH}_3)_3$	4.27
$-\text{CH}=\text{CHC}\equiv\text{N}$	4.03
$-\text{HgCH}_3$	4.10
$-\text{OSO}_2\text{CH}_3$	3.84
$-\text{PCl}_2$	3.59

20.49 How would you carry out the following transformations? More than one step is required in each case.

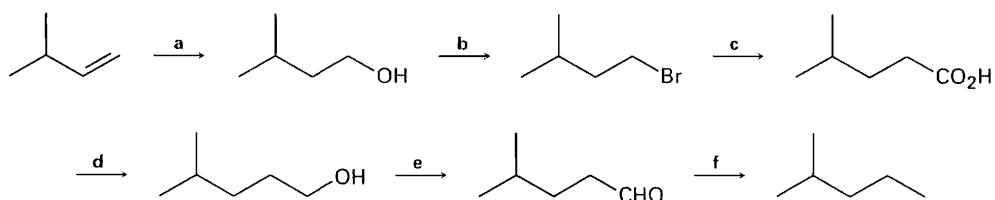


20.50 The following pK_a values have been measured. Explain why a hydroxyl group in the para position decreases the acidity while a hydroxyl group in the meta position increases the acidity.

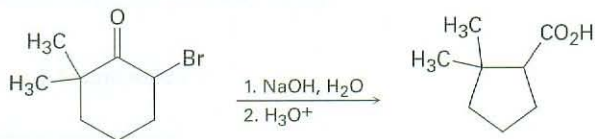


20.51 3-Methyl-2-hexenoic acid (mixture of *E* and *Z* isomers) has been identified as the substance responsible for the odor of human sweat. Synthesize the compound from starting materials having five or fewer carbons.

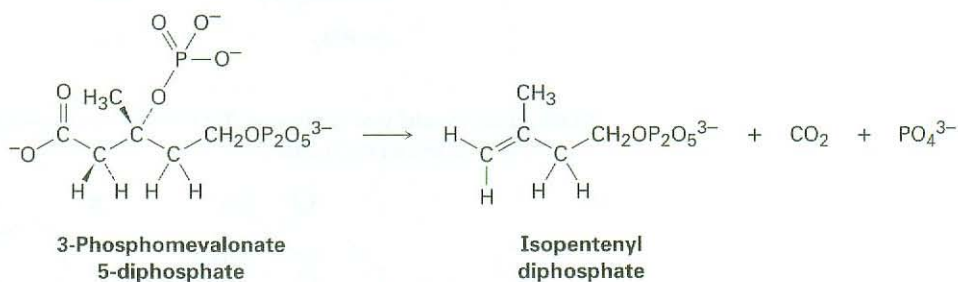
20.52 Identify the missing reagents a–f in the following scheme:



- 20.53** ■ 2-Bromo-6,6-dimethylcyclohexanone gives 2,2-dimethylcyclopentanecarboxylic acid on treatment with aqueous NaOH followed by acidification, a process called the *Favorskii reaction*. Propose a mechanism.

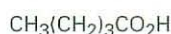


- 20.54** In plants, terpenes (see Chapter 6 *Focus On*) are biosynthesized by a pathway that involves loss of CO_2 from 3-phosphomevalonate 5-diphosphate to yield isopentenyl diphosphate. Use curved arrows to show the mechanism of this reaction.



- 20.55** ■ Propose a structure for a compound $\text{C}_6\text{H}_{12}\text{O}_2$ that dissolves in dilute NaOH and shows the following ^1H NMR spectrum: 1.08 δ (9 H, singlet), 2.2 δ (2 H, singlet), and 11.2 δ (1 H, singlet).

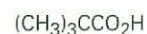
- 20.56** What spectroscopic method could you use to distinguish among the following three isomeric acids? Tell what characteristic features you would expect for each acid.



Pentanoic acid

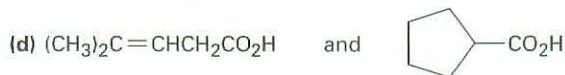
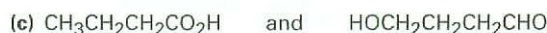
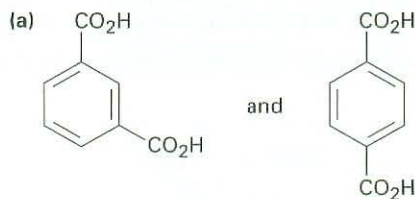


3-Methylbutanoic acid

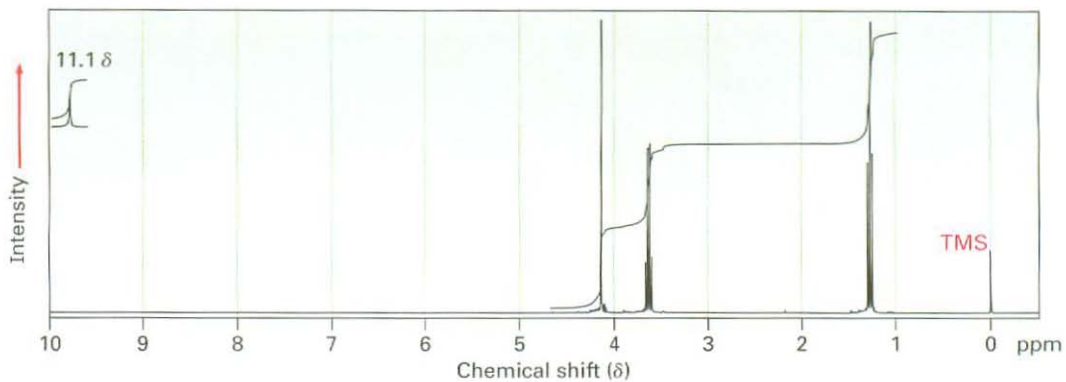


2,2-Dimethylpropanoic acid

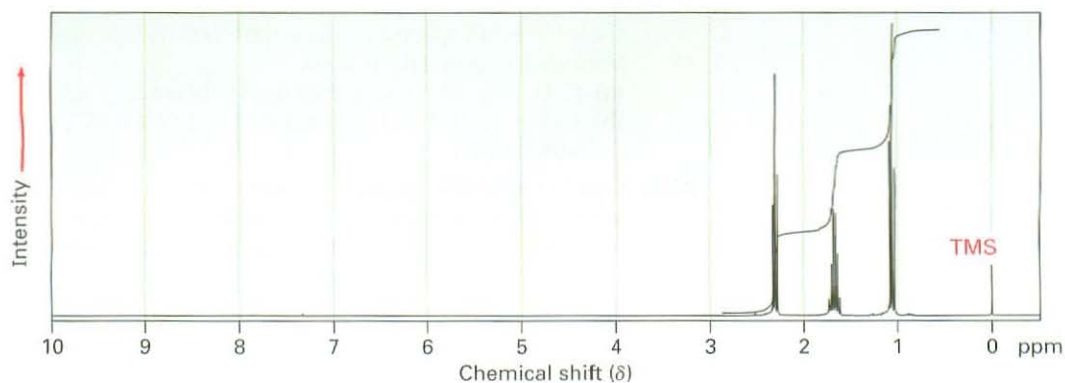
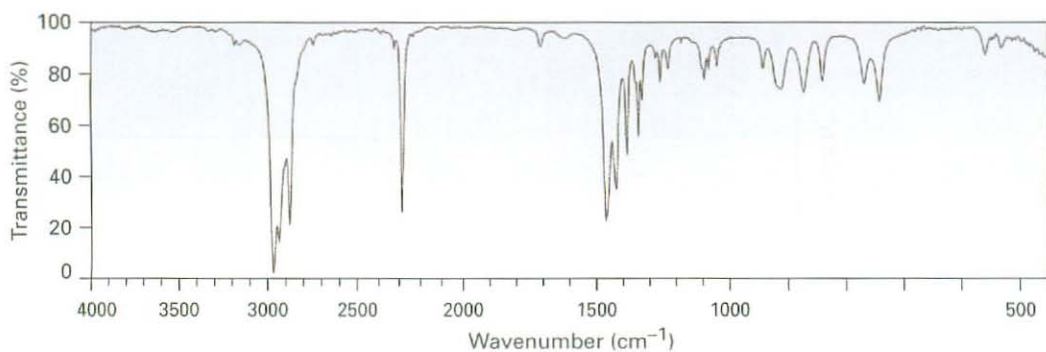
- 20.57** How would you use NMR (either ^{13}C or ^1H) to distinguish between the following pairs of isomers?



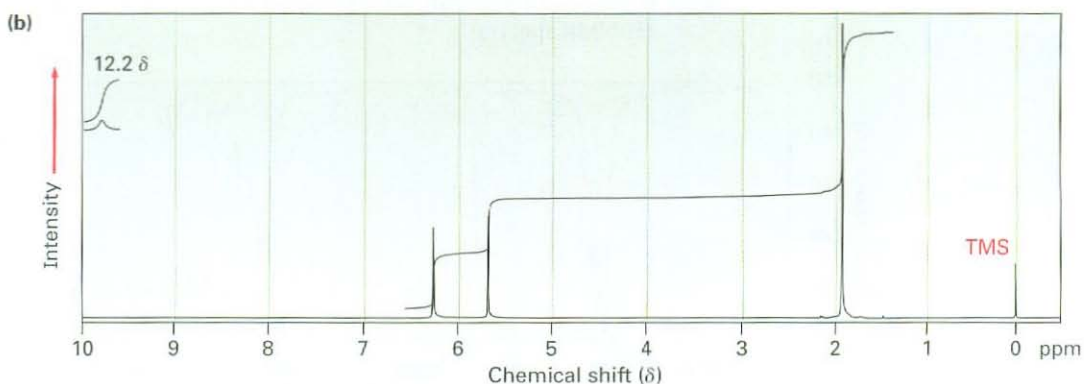
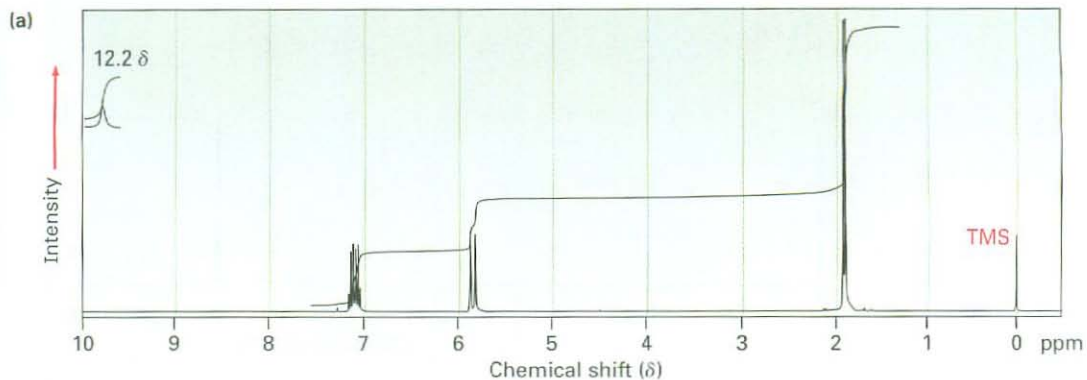
20.58 ■ Compound A, $C_4H_8O_3$, has infrared absorptions at 1710 and 2500 to 3100 cm^{-1} and has the ^1H NMR spectrum shown. Propose a structure for A.



20.59 ■ Propose a structure for a compound, C_4H_7N , that has the following IR and ^1H NMR spectra:



20.60 ■ The two ^1H NMR spectra shown here belong to crotonic acid (*trans*- $\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$) and methacrylic acid [$\text{H}_2\text{C}=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$]. Which spectrum corresponds to which acid? Explain.



20.61 ■ Propose structures for carboxylic acids that show the following peaks in their ^{13}C NMR spectra. Assume that the kinds of carbons (1° , 2° , 3° , or 4°) have been assigned by DEPT-NMR.

(a) $\text{C}_7\text{H}_{12}\text{O}_2$: 25.5 δ (2°), 25.9 δ (2°), 29.0 δ (2°), 43.1 δ (3°), 183.0 δ (4°)

(b) $\text{C}_8\text{H}_8\text{O}_2$: 21.4 δ (1°), 128.3 δ (4°), 129.0 δ (3°), 129.7 δ (3°), 143.1 δ (4°), 168.2 δ (4°)

20.62 Carboxylic acids having a second carbonyl group two atoms away lose CO_2 (*decarboxylate*) through an intermediate enolate ion when treated with base. Write the mechanism of this decarboxylation reaction using curved arrows to show the electron flow in each step.

