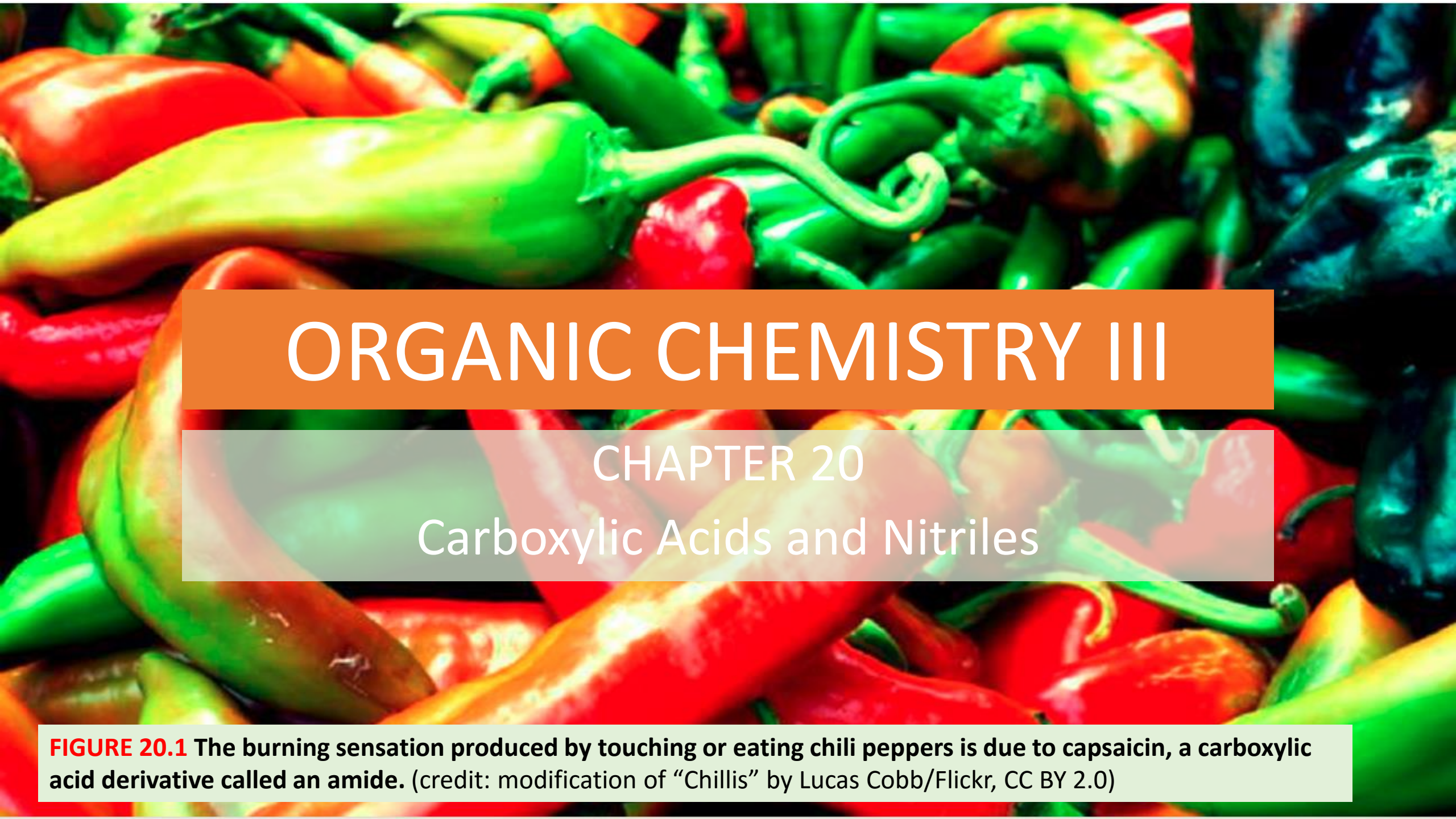


ORGANIC CHEMISTRY III

CHAPTER 20

Carboxylic Acids and Nitriles

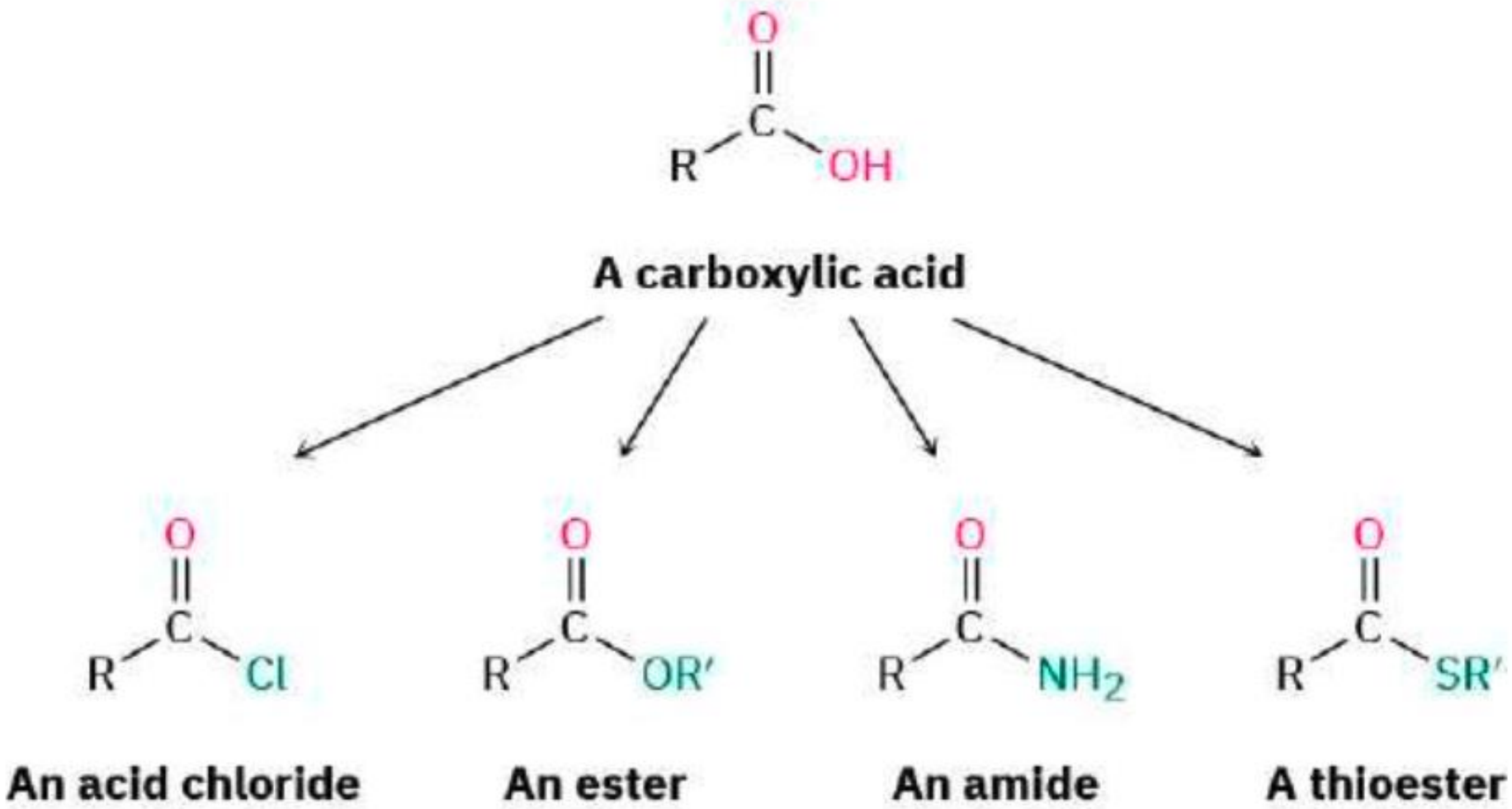
FIGURE 20.1 The burning sensation produced by touching or eating chili peppers is due to capsaicin, a carboxylic acid derivative called an amide. (credit: modification of “Chillis” by Lucas Cobb/Flickr, CC BY 2.0)

CHAPTER CONTENTS

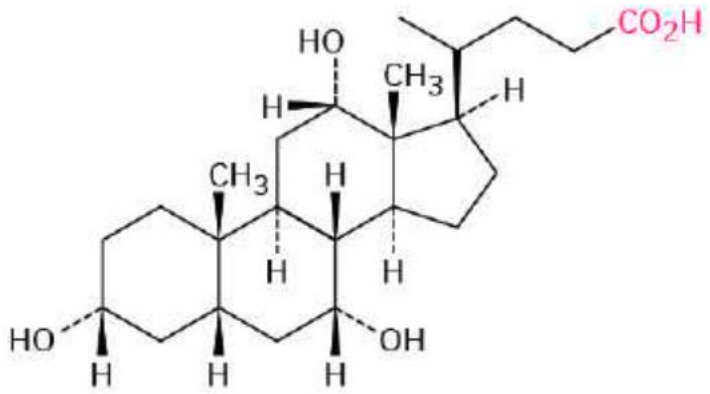
WHY THIS CHAPTER?

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. We'll look both at acids and at their close relatives, nitriles (RC≡N), in this chapter and at carboxylic acid derivatives in the next chapter.

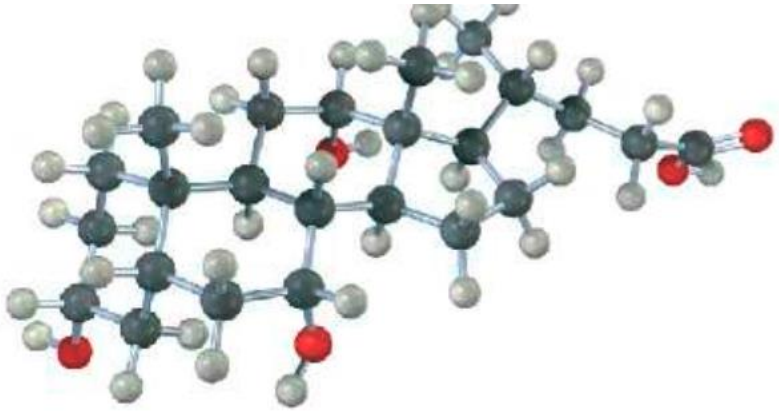
Carboxylic acids, RCO_2H, occupy a central place among carbonyl compounds. Not only are they valuable in themselves, they also serve as starting materials for preparing numerous carboxylic acid derivatives such as acid chlorides, esters, amides, and thioesters. In addition, carboxylic acids are present in the majority of biological pathways.

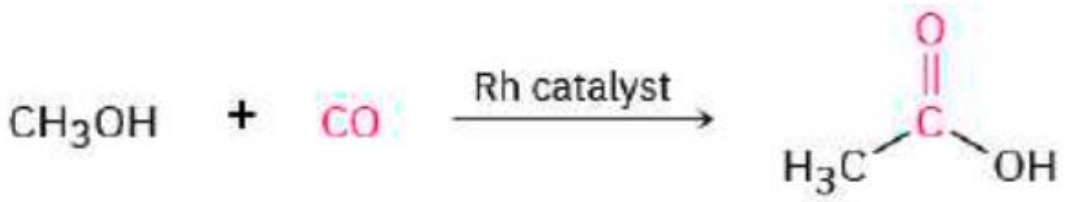

O
C
R
OH
A carboxylic acid
O
C
R
Cl
An acid chloride
O
C
R
OR′
An ester
O
C
R
NH2
An amide
O
C
R
SR′
A thioester

A great many carboxylic acids are found in nature: acetic acid, CH3CO2H, is the chief organic component of vinegar; Other examples are cholic acid, a major component of human bile



Cholic acid

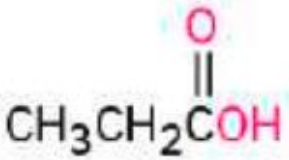




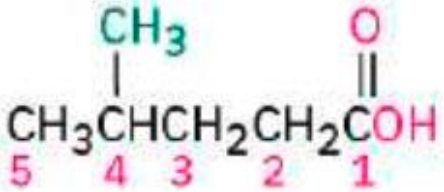
Approximately 20 million tons of acetic acid is produced worldwide each year for a variety of purposes. About 20% of the acetic acid synthesized industrially is obtained by oxidation of acetaldehyde. Much of the remaining 80% is prepared by the rhodium-catalyzed reaction of methanol with carbon monoxide.

20.1 Naming Carboxylic Acids and Nitriles

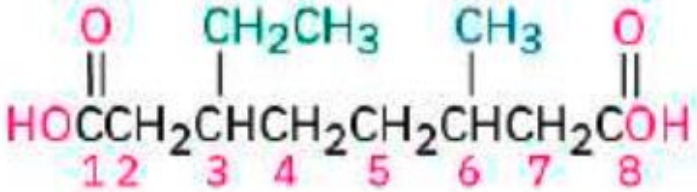
Carboxylic Acids, RCO_2H



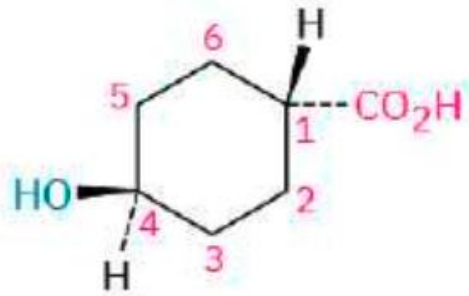
Propanoic acid



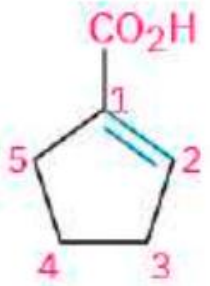
4-Methylpentanoic acid



3-Ethyl-6-methyloctanedioic acid



***trans*-4-Hydroxycyclohexanecarboxylic acid**



1-Cyclopentenecarboxylic acid

TABLE 20.1 Common Names of Some Carboxylic Acids and Acyl Groups

Structure	Name	Acyl group
HCO_2H	Formic	Formyl
CH_3CO_2H	Acetic	Acetyl
$CH_3CH_2CO_2H$	Propionic	Propionyl
$CH_3CH_2CH_2CO_2H$	Butyric	Butyryl
HO_2CCO_2H	Oxalic	Oxalyl
$HO_2CCH_2CO_2H$	Malonic	Malonyl
$HO_2CCH_2CH_2CO_2H$	Succinic	Succinyl

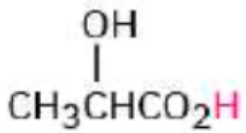
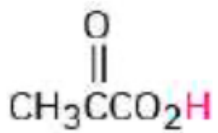
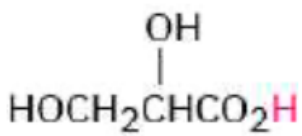
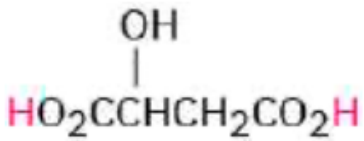
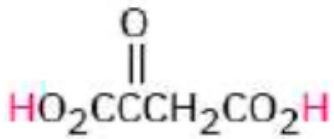
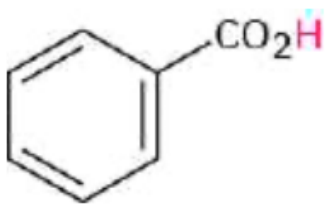
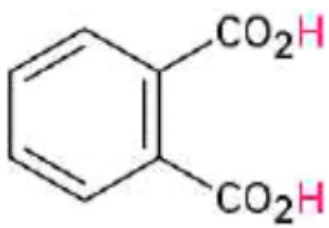
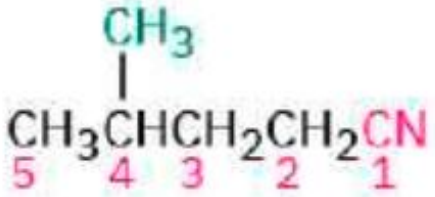
$HO_2CCH_2CH_2CH_2CO_2H$	Glutaric	Glutaryl
$HO_2CCH_2CH_2CH_2CH_2CO_2H$	Adipic	Adipoyl
$H_2C{=}CHCO_2H$	Acrylic	Acryloyl
$HO_2CCH{=}CHCO_2H$	Maleic (cis) Fumaric (trans)	Maleoyl Fumaroyl
$HOCH_2CO_2H$	Glycolic	Glycoloyl
	Lactic	Lactoyl
	Pyruvic	Pyruvoyl
	Glyceric	Glyceroyl

TABLE 20.1 Common Names of Some Carboxylic Acids and Acyl Groups

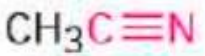
Structure	Name	Acyl group
	Malic	Maloyl
	Oxaloacetic	Oxaloacetyl
	Benzoic	Benzoyl
	Phthalic	Phthaloyl

Nitriles, RC≡N

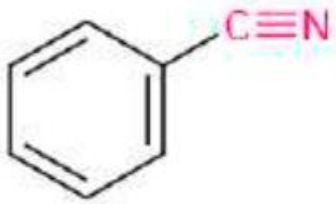
Compounds containing the -C≡N functional group are called **Nitrile** and can undergo some chemistry similar to that of carboxylic acids. Simple open-chain nitriles are named by adding -nitrile as a suffix to the alkane name, with the nitrile carbon numbered C1.



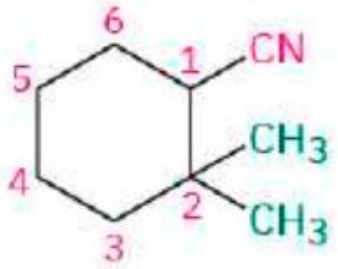
4-Methylpentanenitrile



Acetonitrile
(from acetic acid)

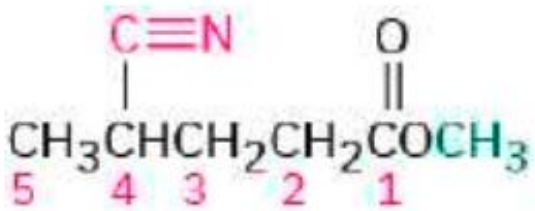


Benzonitrile
(from benzoic acid)



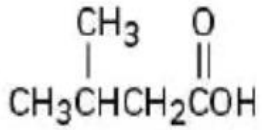
2,2-Dimethylcyclohexanecarbonitrile
(from 2,2-dimethylcyclohexane-carboxylic acid)

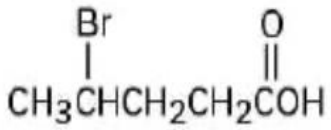
If another carboxylic acid derivative is present in the same molecule, the prefix cyano- is used for the group.

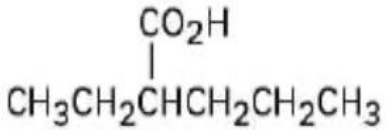


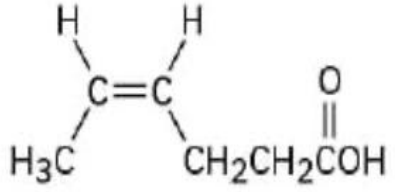
Methyl 4-cyanopentanoate

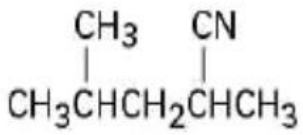
PROBLEM 20-1 Give IUPAC names for the following compounds:

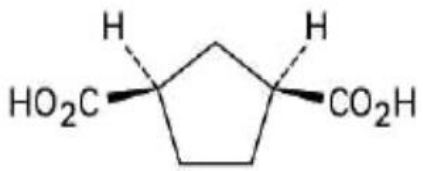
(a)


(b)


(c)


(d)


(e)


(f)


PROBLEM 20-2 Draw structures corresponding to the following IUPAC names:

(a) 2,3-Dimethylhexanoic acid **(b)** 4-Methylpentanoic acid

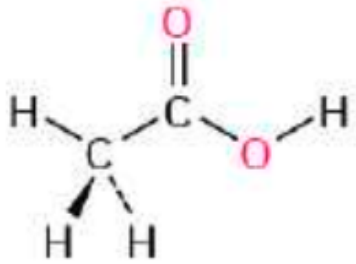
(c) trans-1,2-Cyclobutanedicarboxylic acid **(d)** o-Hydroxybenzoic acid

(e) (9Z,12Z)-9,12-Octadecadienoic acid **(f)** 2-Pentenenitrile

20.2 Structure and Properties of Carboxylic Acids

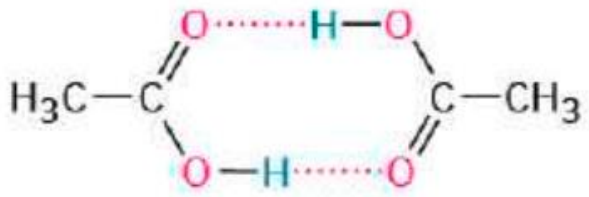
Carboxylic acids are similar in some respects to both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2-hybridized, and carboxylic acid groups are therefore planar with and approximately 120° (**TABLE 20.2**).

TABLE 20.2 Physical Parameters for Acetic Acid

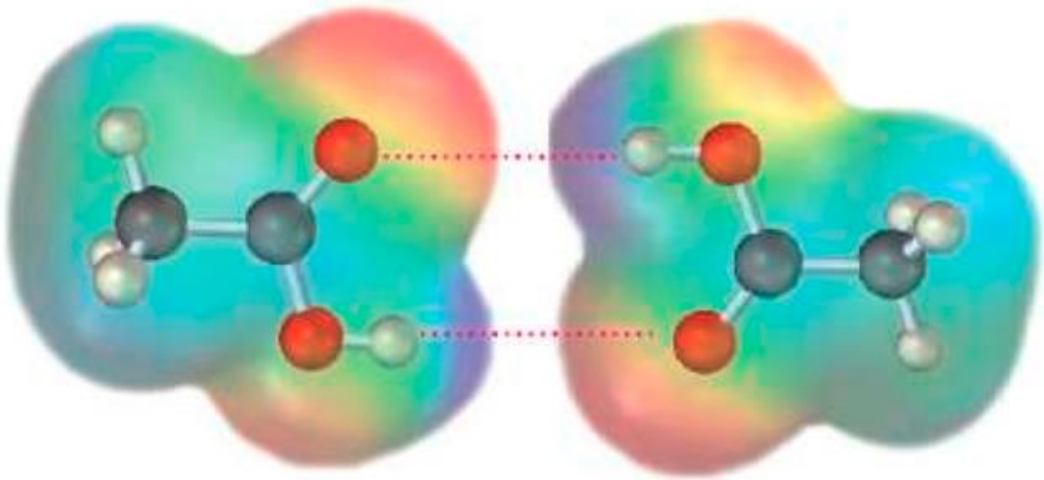


Bond angle	(degrees)	Bond length	(pm)
C–C=O	119	C–C	152
C–C–OH	119	C=O	125
O=C–OH	122	C–OH	131

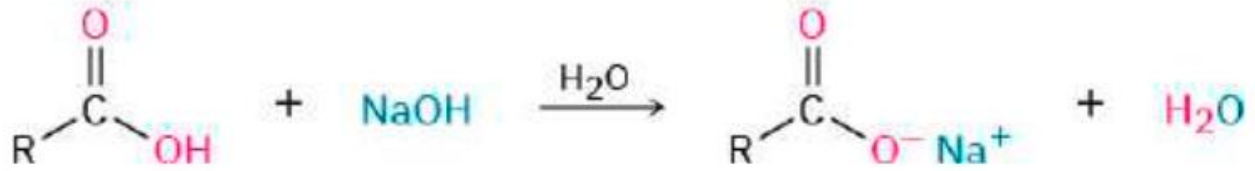
Like alcohols, carboxylic acids are strongly associated because of hydrogen-bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This strong hydrogen-bonding has a noticeable effect on boiling points, making carboxylic acids boil far less easily than their corresponding 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.



Acetic acid dimer

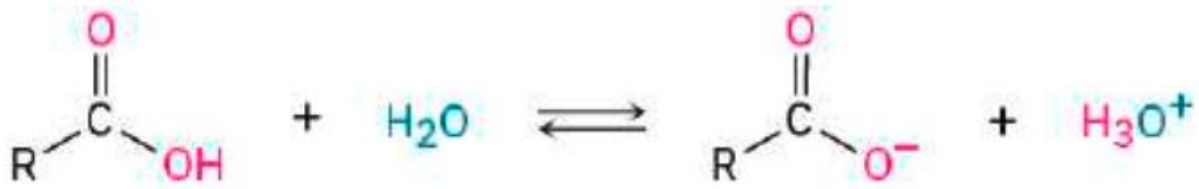


The most obvious property of carboxylic acids is implied by their name: carboxylic acids are *acidic*.



A carboxylic acid (water-insoluble) **A carboxylic acid salt (water-soluble)**

Like other Brønsted–Lowry acids discussed in **Section 2.7**, carboxylic acids dissociate slightly in dilute aqueous solution to give H_3O^+ and the corresponding carboxylate anions, RCO^{2-}. The extent of dissociation is given by an acidity constant, *Ka*.

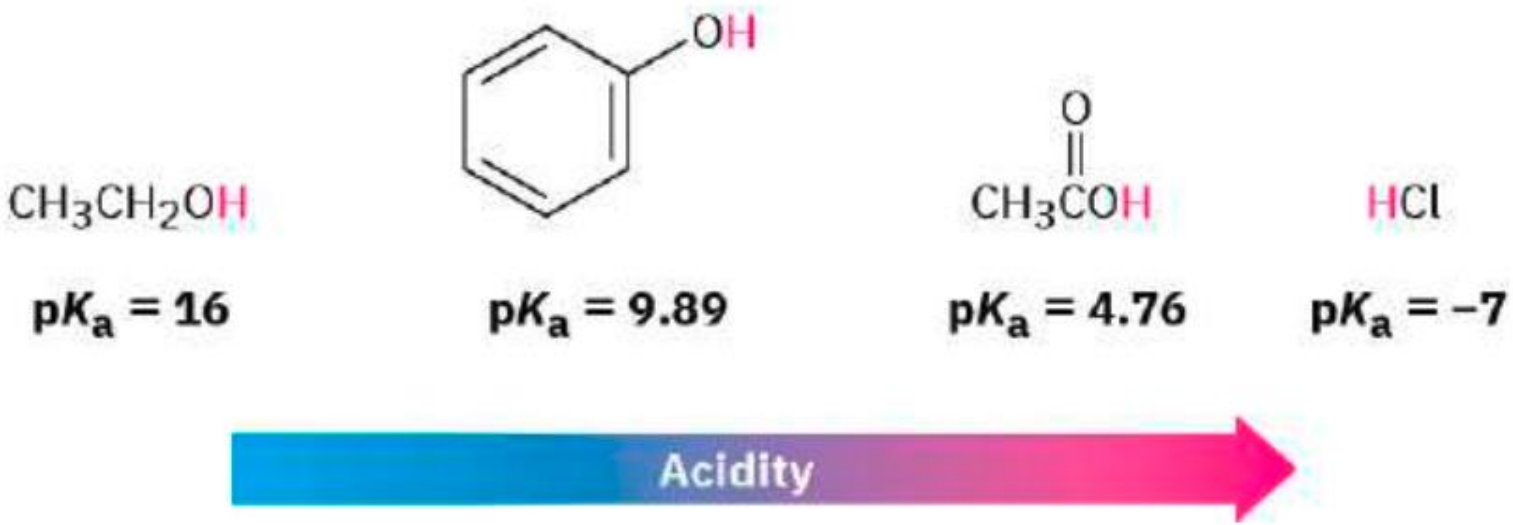


$$K_a = \frac{[RCO_2^-][H_3O^+]}{[RCO_2H]} \quad \text{and} \quad pK_a = -\log K_a$$

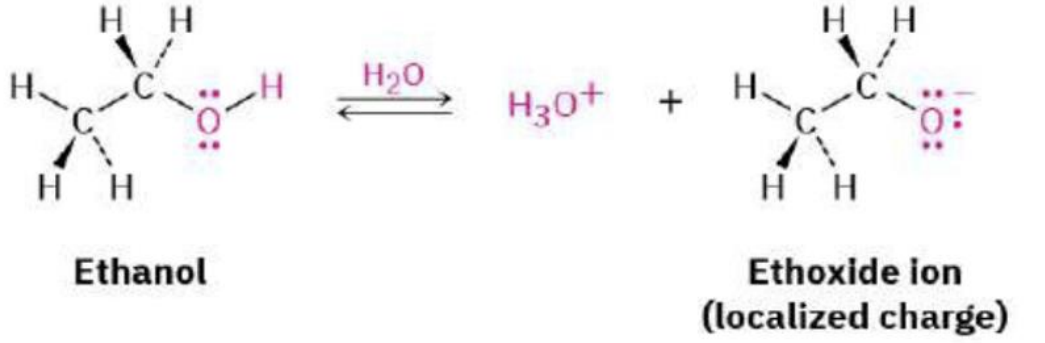
TABLE 20.3 Acidity of Some Carboxylic Acids

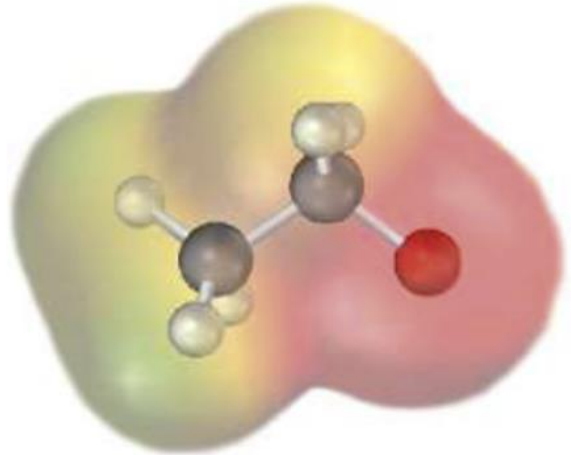
Structure	K_a	pK_a	
CF_3CO_2H	0.59	0.23	
HCO_2H	1.77×10^{-4}	3.75	Stronger acid
$HOCH_2CO_2H$	1.5×10^{-4}	3.84	
$C_6H_5CO_2H$	6.46×10^{-5}	4.19	
$H_2C{=}CHCO_2H$	5.6×10^{-5}	4.25	
CH_3CO_2H	1.75×10^{-5}	4.76	
$CH_3CH_2CO_2H$	1.34×10^{-5}	4.87	Weaker acid
CH_3CH_2OH (ethanol)	(1×10^{-16})	(16)	

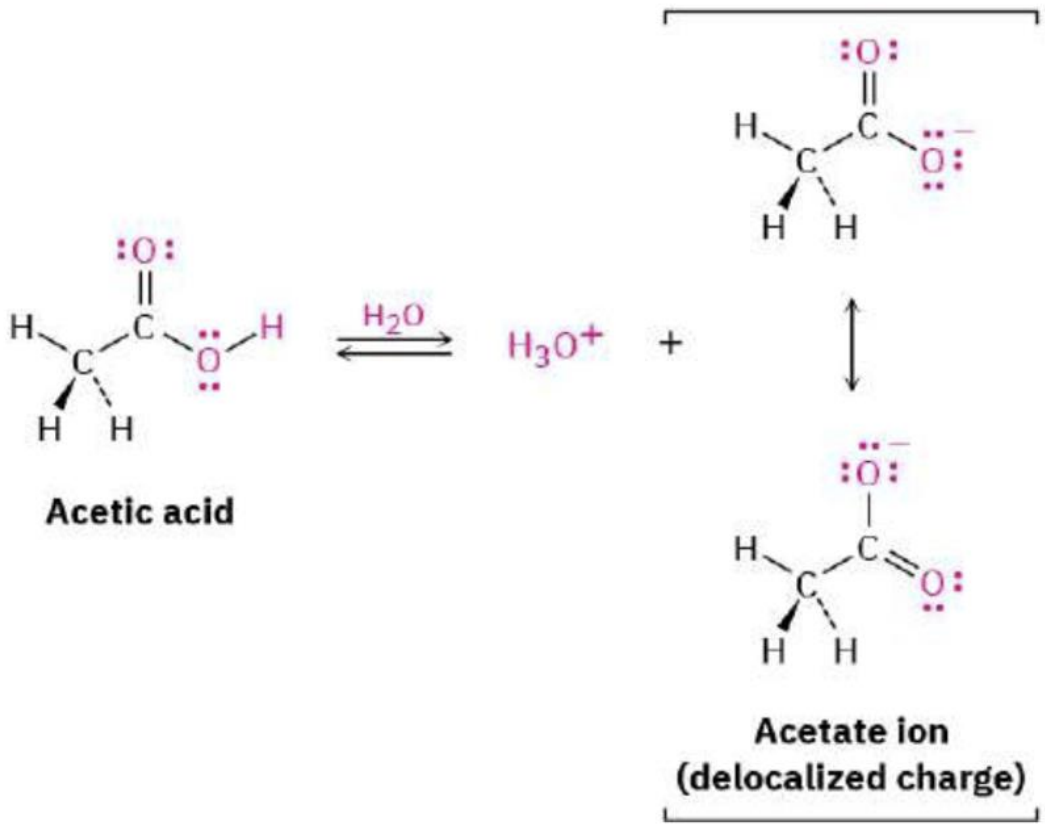
Although much weaker than mineral acids, carboxylic acids are nevertheless much stronger acids than alcohols and phenols. The *K*a of ethanol, for example, is approximately 10^{-16}, making it a weaker acid than acetic acid by a factor of 10^{11}.



Why are carboxylic acids so much more acidic than alcohols, even though both contain –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 20.2**).







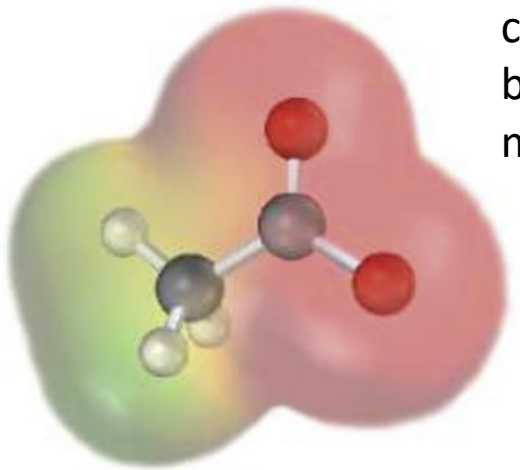
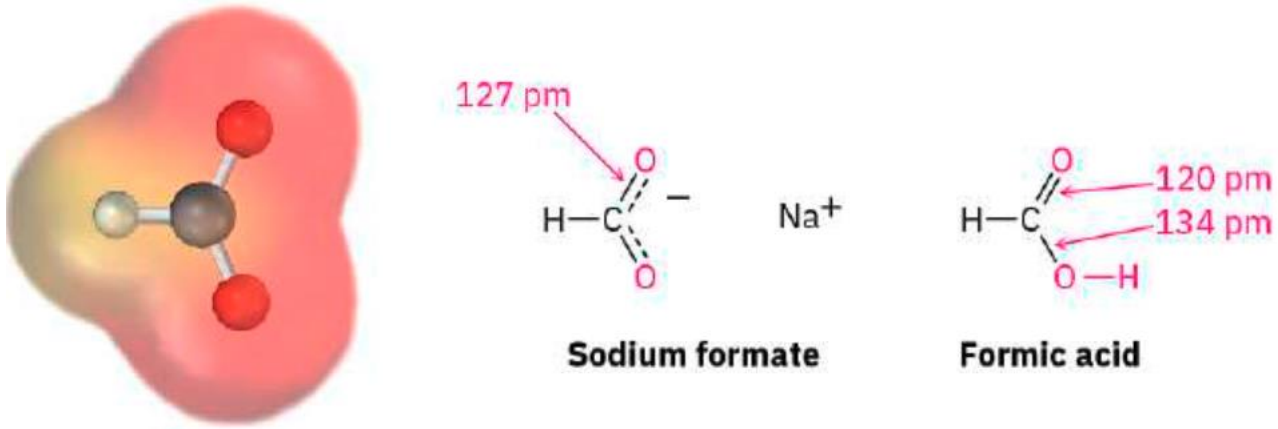


FIGURE 20.2 An alkoxide ion has its charge localized on one oxygen atom and is less stable, while a carboxylate ion has the charge spread equally over both oxygens and is therefore more stable.

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 double bond (120 pm) and the C–O single bond (134 pm) of formic acid. An electrostatic potential map of the formate ion also shows how the negative charge (red) is spread 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 Ka 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 RCOH. 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 a nearly neutral pH of 3.5–4.5 in humans, 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 pKa value of a given acid and the pH of the medium are known, the percentages of dissociated and undissociated forms can be calculated using the **Henderson–Hasselbalch equation**.

For any acid HA, we have

$$pK_a = -\log \frac{[H_3O^+][A^-]}{[HA]} = -\log[H_3O^+] - \log \frac{[A^-]}{[HA]}$$

$$= pH - \log \frac{[A^-]}{[HA]}$$

which can be rearranged to give

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ Henderson-Hasselbalch equation

so

$$\log \frac{[A^-]}{[HA]} = pH - pK_a$$

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 pH = 7.3. According to Table 20-3, the pKa of acetic acid is 4.76. From the Henderson–Hasselbalch equation, we have

$$\log \frac{[A^-]}{HA} = pH - pK_a = 7.3 - 4.76 = 2.54$$

$$\frac{[A^-]}{HA} = \text{antilog}\,(2.54) = 3.5 \times 10^2 \quad \text{so} \quad [A^-] = (3.5 \times 10^2)\,[HA]$$

In addition, we know that

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

Solving the two simultaneous equations gives $[A^-] = 0.0010$ M and $[HA] = 3 \times 10^{-6}$ 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.

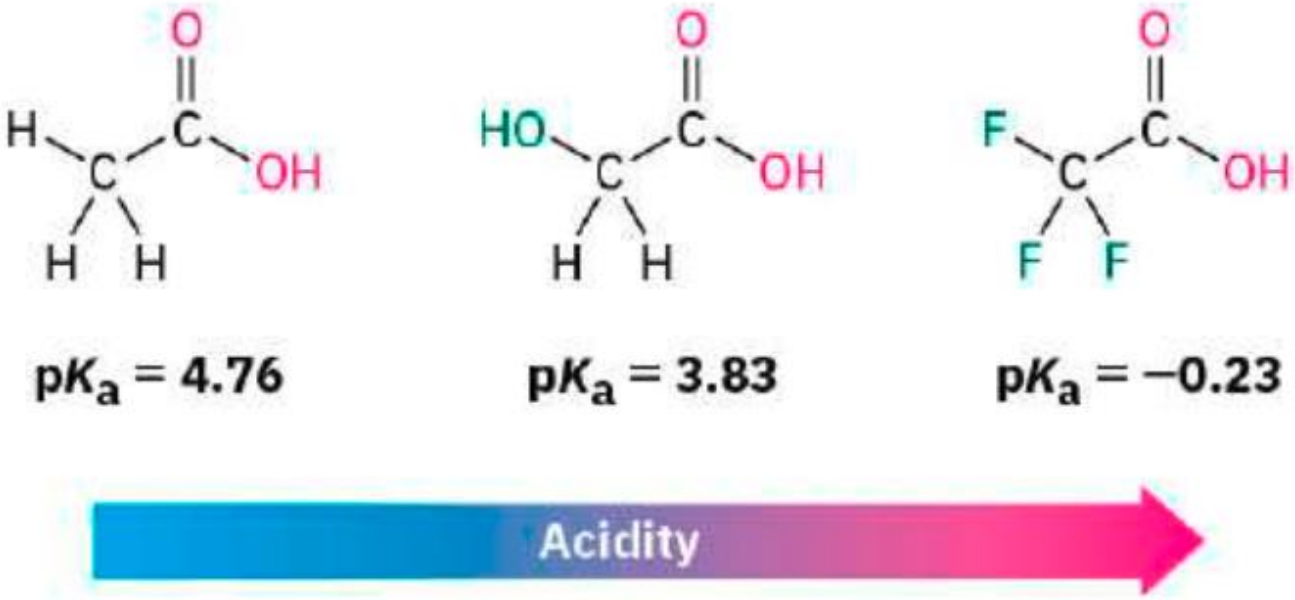
PROBLEM 20-5 Calculate the percentages of dissociated and undissociated forms present in the following solutions:

(a) 0.0010 M glycolic acid ($HOCH_2CO_2H$; pKa = 3.83) at pH = 4.50

(b) 0.0020 M propanoic acid (pKa = 4.87) at pH = 5.30

20.4 Substituent Effects on Acidity

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.



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 pKa = 2.86, 3-chlorobutanoic acid has pKa = 4.05, and 4-chlorobutanoic acid has pKa = 4.52, similar to that of butanoic acid itself.

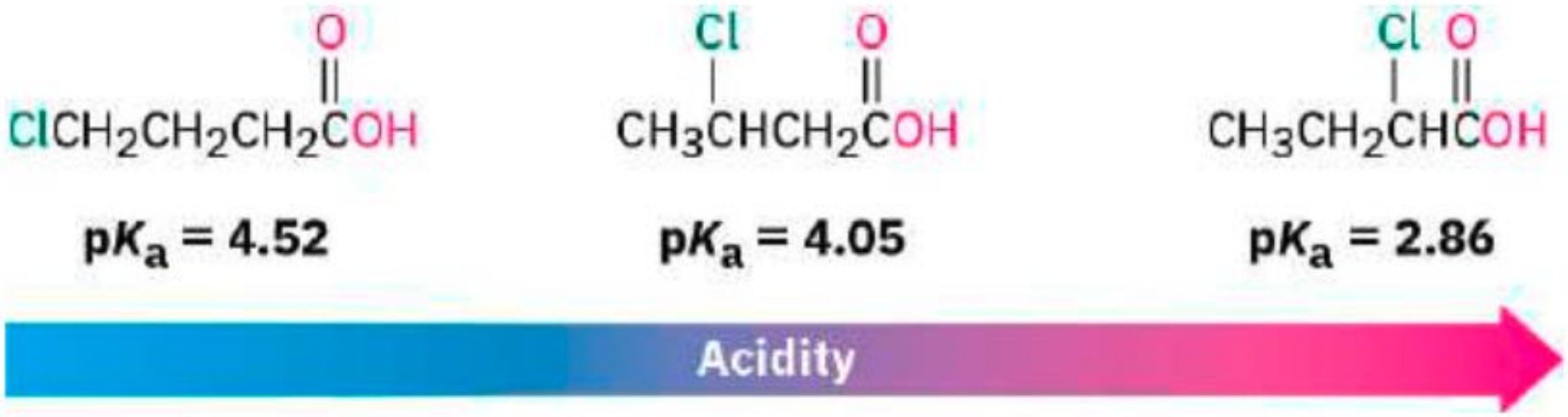
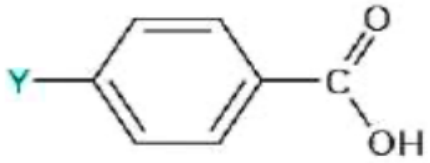
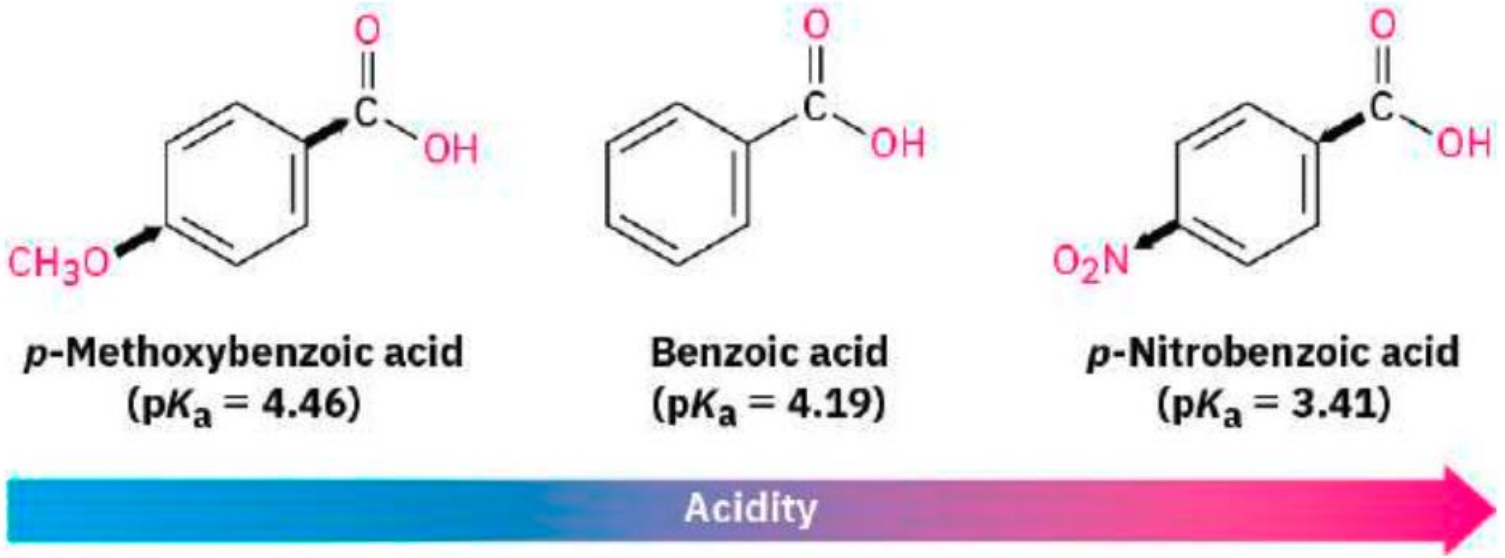


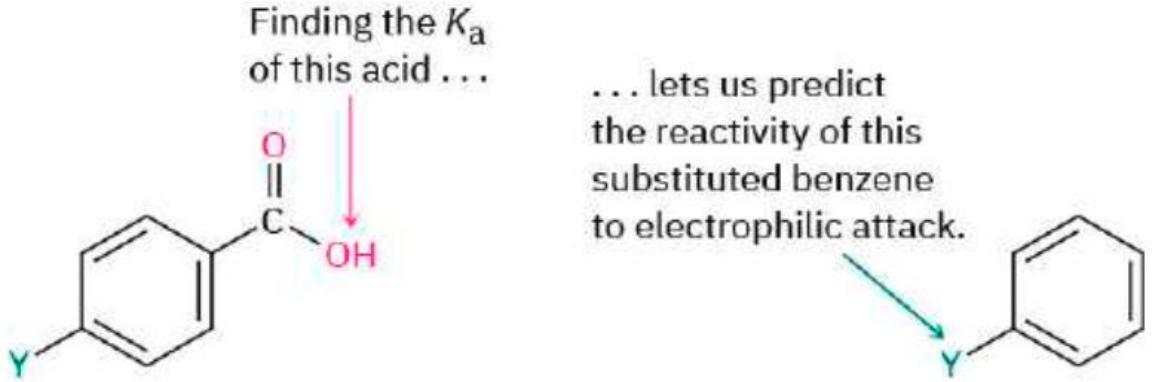
TABLE 20.4
Substituent Effects on the Acidity of *p*-Substituted Benzoic Acids



	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	
	$-CH_3$	4.3	4.34	Activating groups
	$-OCH_3$	3.5	4.46	
Weaker acid	$-OH$	3.3	4.48	

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





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?

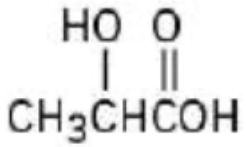
Strategy

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.



Lactic acid

PROBLEM 20-7 Dicarboxylic acids have two dissociation constants, one for the initial dissociation into a mono anion and one for the second dissociation into a dianion. For oxalic acid,$HO_2C–CO_2H$, the first ionization constant is pKa1 = 1.2 and the second ionization constant is pKa2 = 4.2. Why is the second carboxyl group far less acidic than the first?

PROBLEM 20-8 The pKa of *p*-cyclopropylbenzoic acid is 4.45. Is cyclopropyl benzene likely to be more reactive or less reactive than benzene toward electrophilic bromination? Explain.

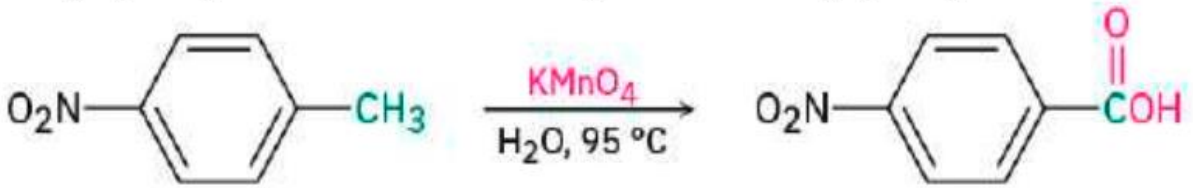
PROBLEM 20-9 Rankt he following compounds in order of increasing acidity. Don't look at a table of pKa data to help with your answer.

(a) Benzoic acid, *p*-methylbenzoic acid, *p*-chlorobenzoic acid

(b) Acid, acetic acid, *p*-Nitrobenzoic, benzoic acid

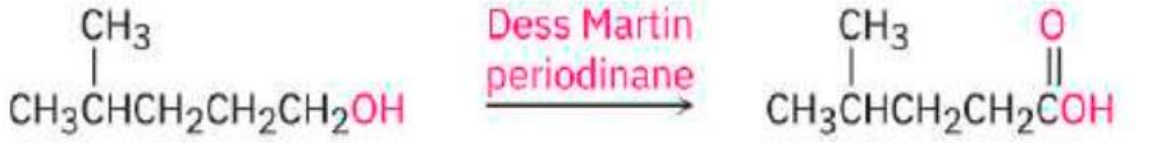
20.5 Preparing Carboxylic Acids

- Oxidation of a substituted alkylbenzene with $KMnO_4$ gives a substituted benzoic acid (**Section 16.8**). Both primary and secondary alkyl groups can be oxidized, but tertiary groups are not affected.

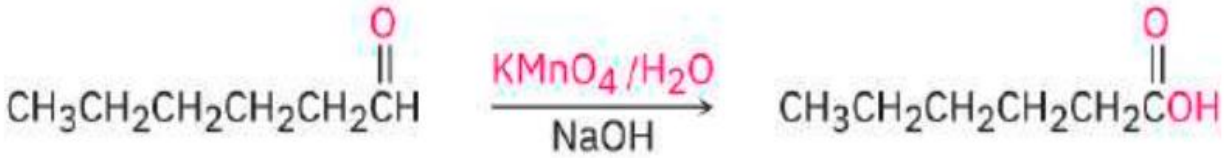


***p*-Nitrotoluene** **p-Nitrobenzoic acid (88%)**

- Oxidation of a primary alcohol or an aldehyde yields a carboxylic acid (**Section 17.7** and **Section 19.3**). Primary alcohols are often oxidized with the Dess Martin periodinane, and aldehydes are similarly oxidized with alkaline $KMnO_4$.

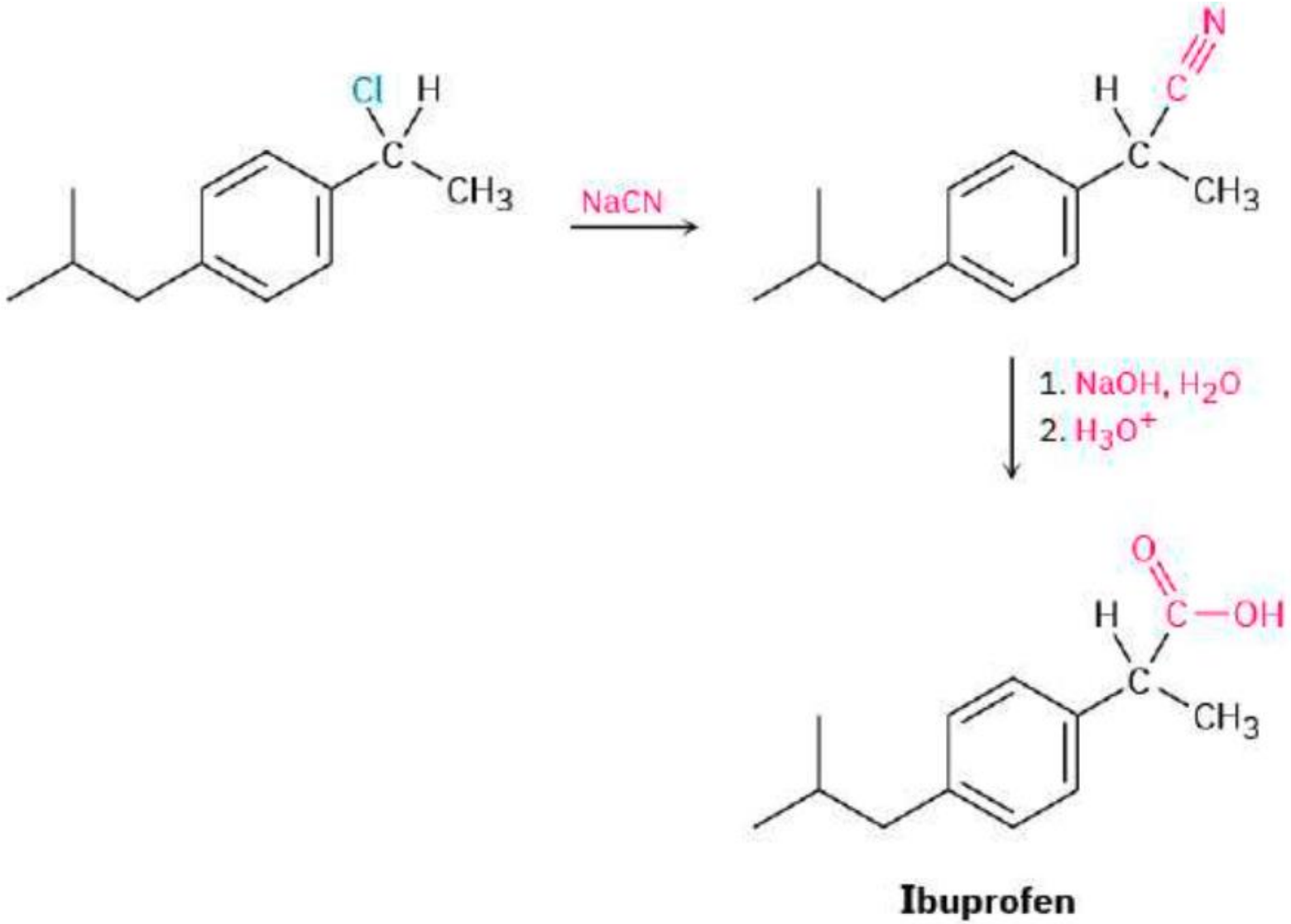


4-Methyl-1-pentanol **4-Methylpentanoic acid**

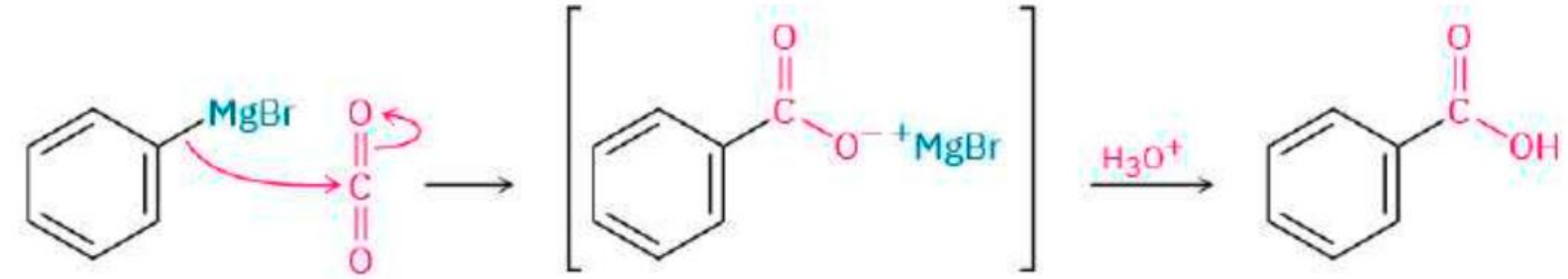


Hexanal **Hexanoic acid**

1.Hydrolysis of Nitriles



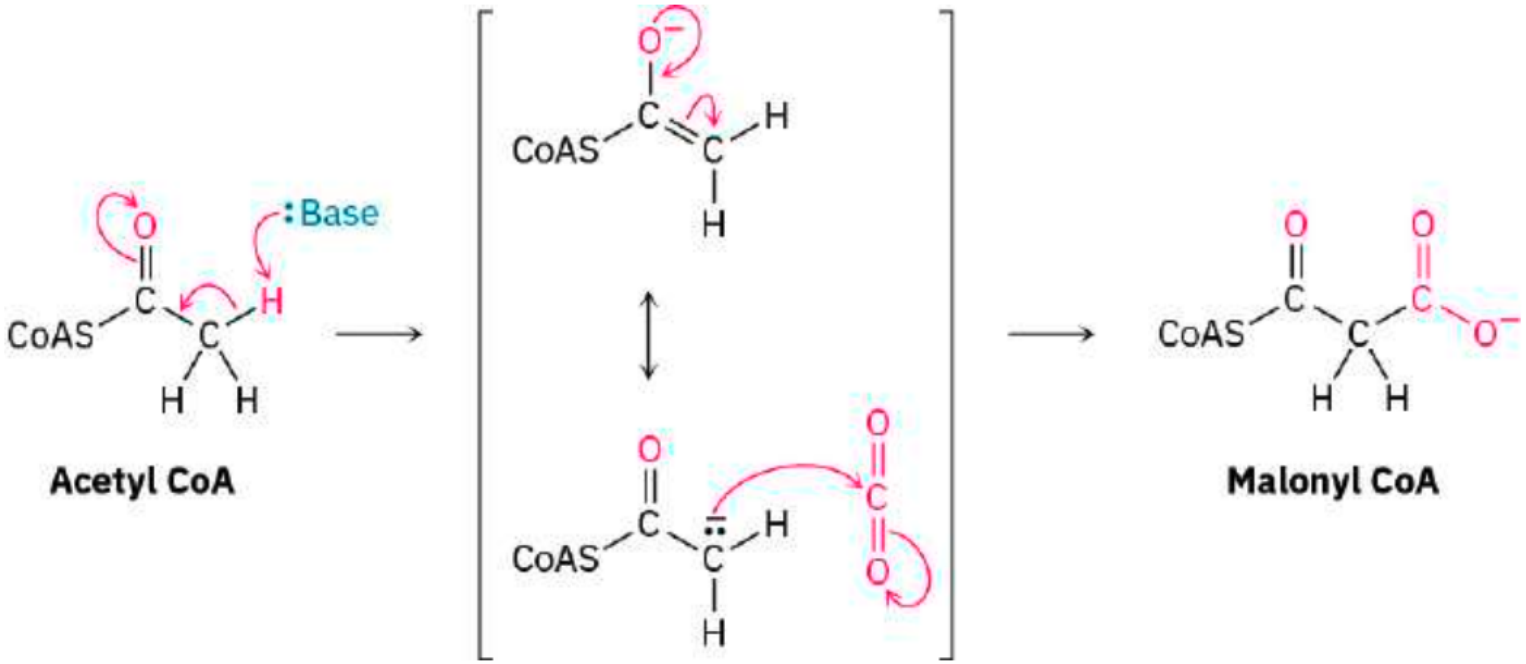
Ibuprofen



Phenylmagnesium bromide

Benzoic acid

As noted previously, there are no Grignard reagents inside living cells, but there are other types of stabilized carbanions that are often carboxylated.



Acetyl CoA

Malonyl CoA

WORKED EXAMPLE 20.2

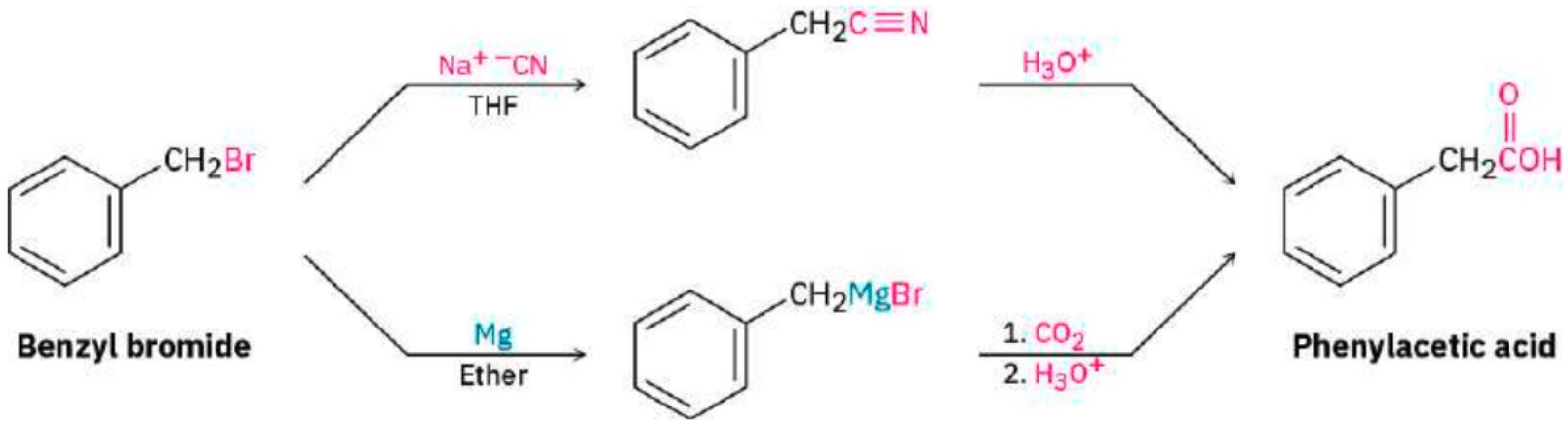
Devising a Synthesis Route for a Carboxylic Acid

How would you prepare phenylacetic acid ($PhCH_2CO_2H$) from benzyl bromide ($PhCH_2Br$)?

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?

(a) $(CH_3)_3CCO_2H$ from $(CH_3)_3CCl$ **(b)** $CH_3CH_2CH_2CO_2H$ from $CH_3CH_2CH_2Br$

20.6 Reactions of Carboxylic Acids: An Overview

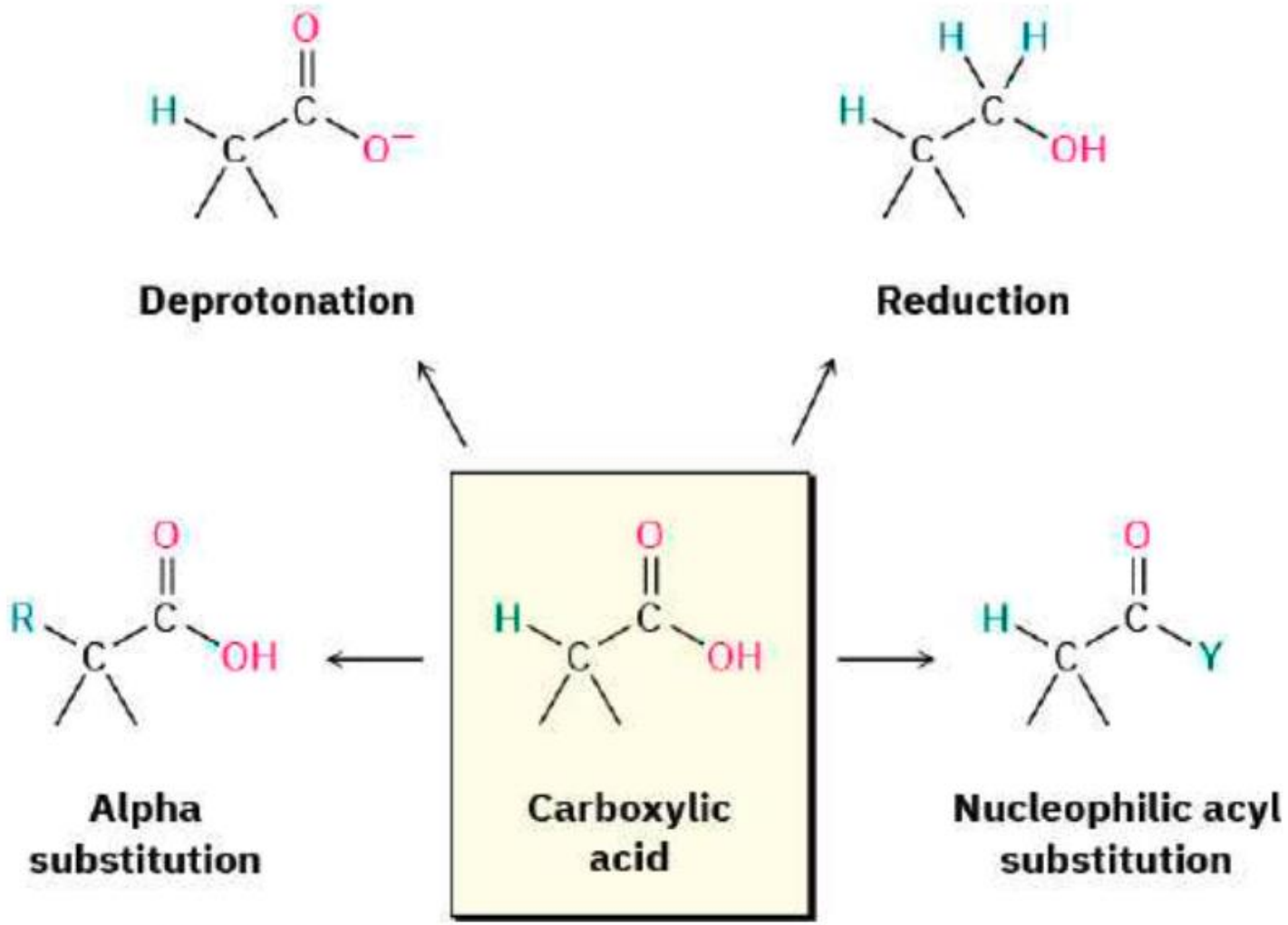
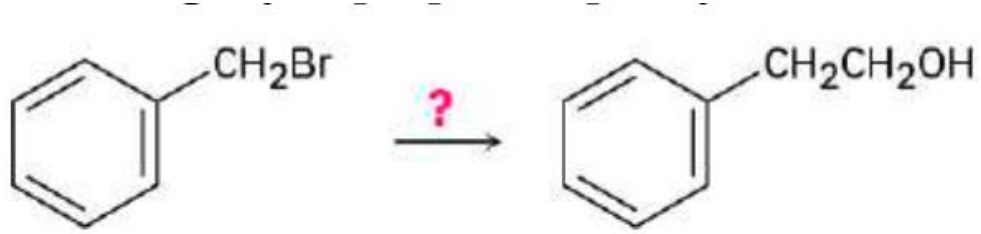
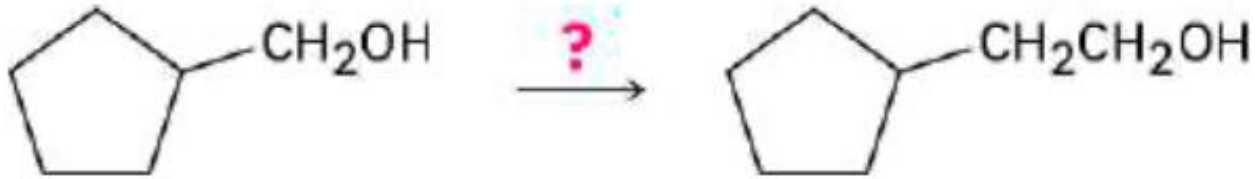


FIGURE 20.3 Some general reactions of carboxylic acids.

PROBLEM 20-11
How might you prepare 2-phenylethanol from benzyl bromide? More than one step is needed.

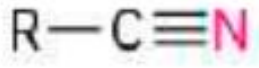


PROBLEM 20-12 How might you carry out the following transformation? More than one step is needed.

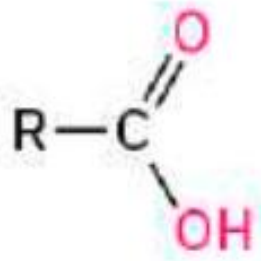


20.7 Chemistry of Nitriles

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.

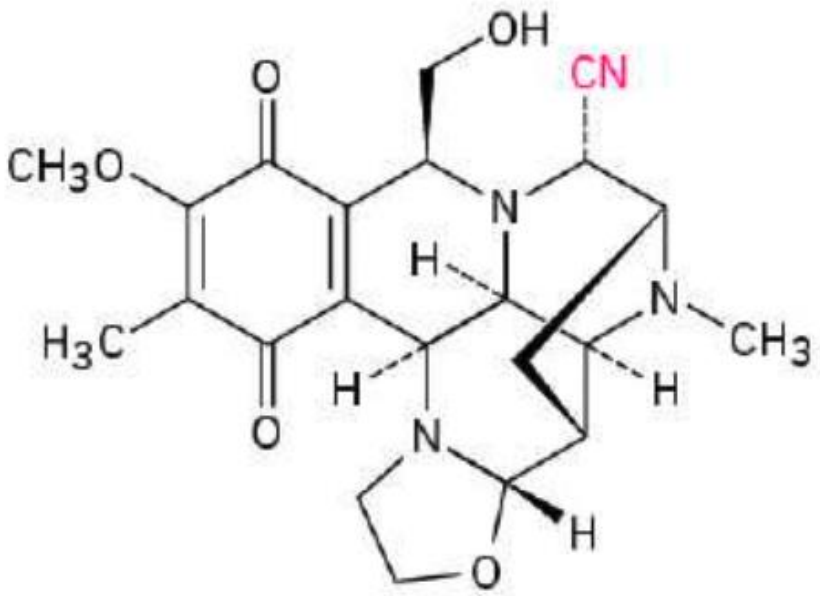


A nitrile—three bonds to nitrogen



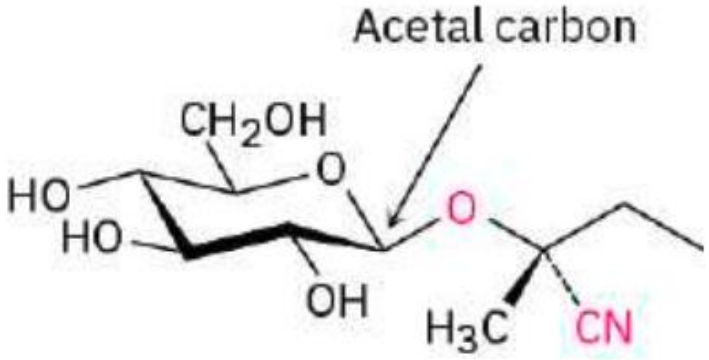
An acid—three bonds to two oxygens

isolated from the bacterium *Streptomyces lavendulae* and was found to have both antimicrobial and antitumor activity.



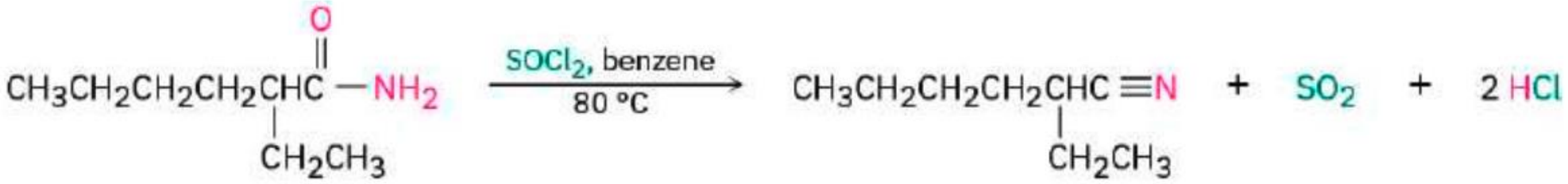
Cyanocycline A

to protect the plant by poisoning any animal foolish enough to eat it. Lotaustralin from the cassava plant is an example.

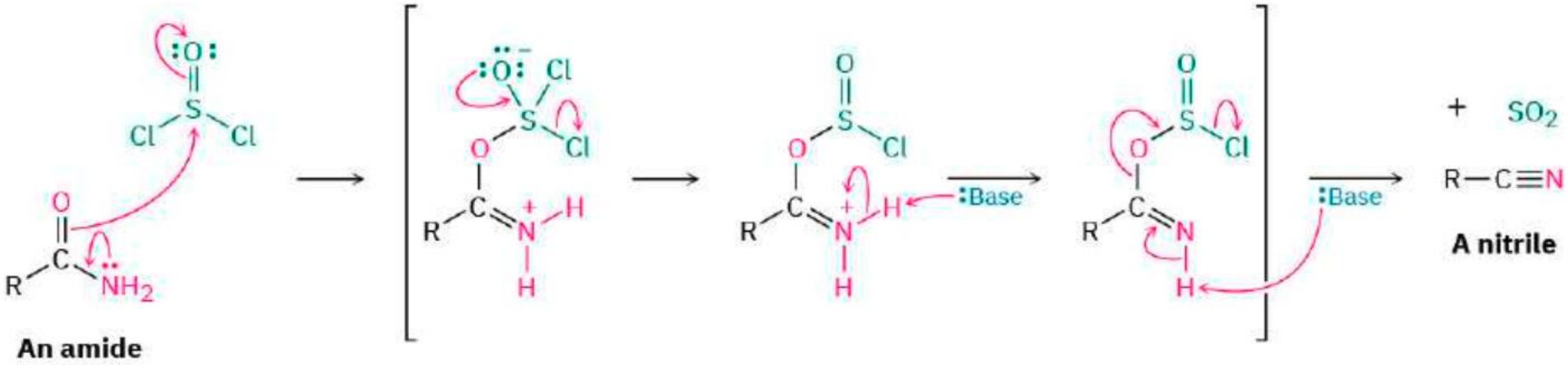


Lotaustralin
(a cyanogenic glycoside)

Preparation of Nitriles



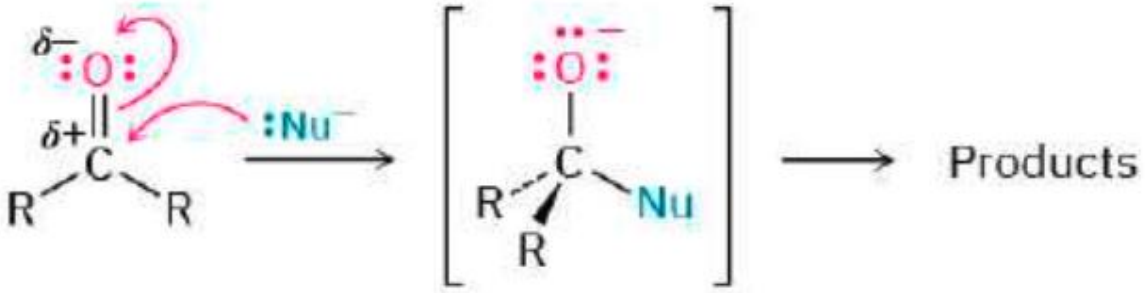
2-Ethylhexanamide **2-Ethylhexanenitrile (94%)**



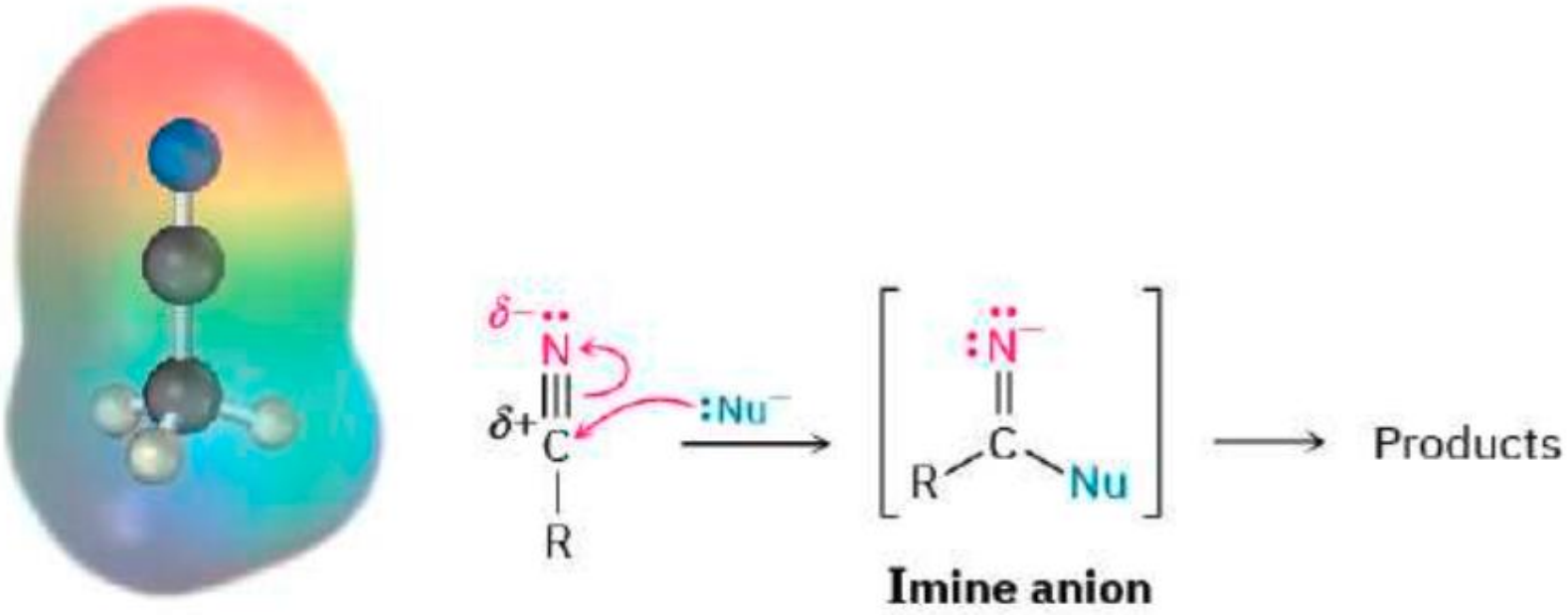
An amide **A nitrile**

Reactions of Nitriles

Carbonyl compound



Nitrile



Some general reactions of nitriles

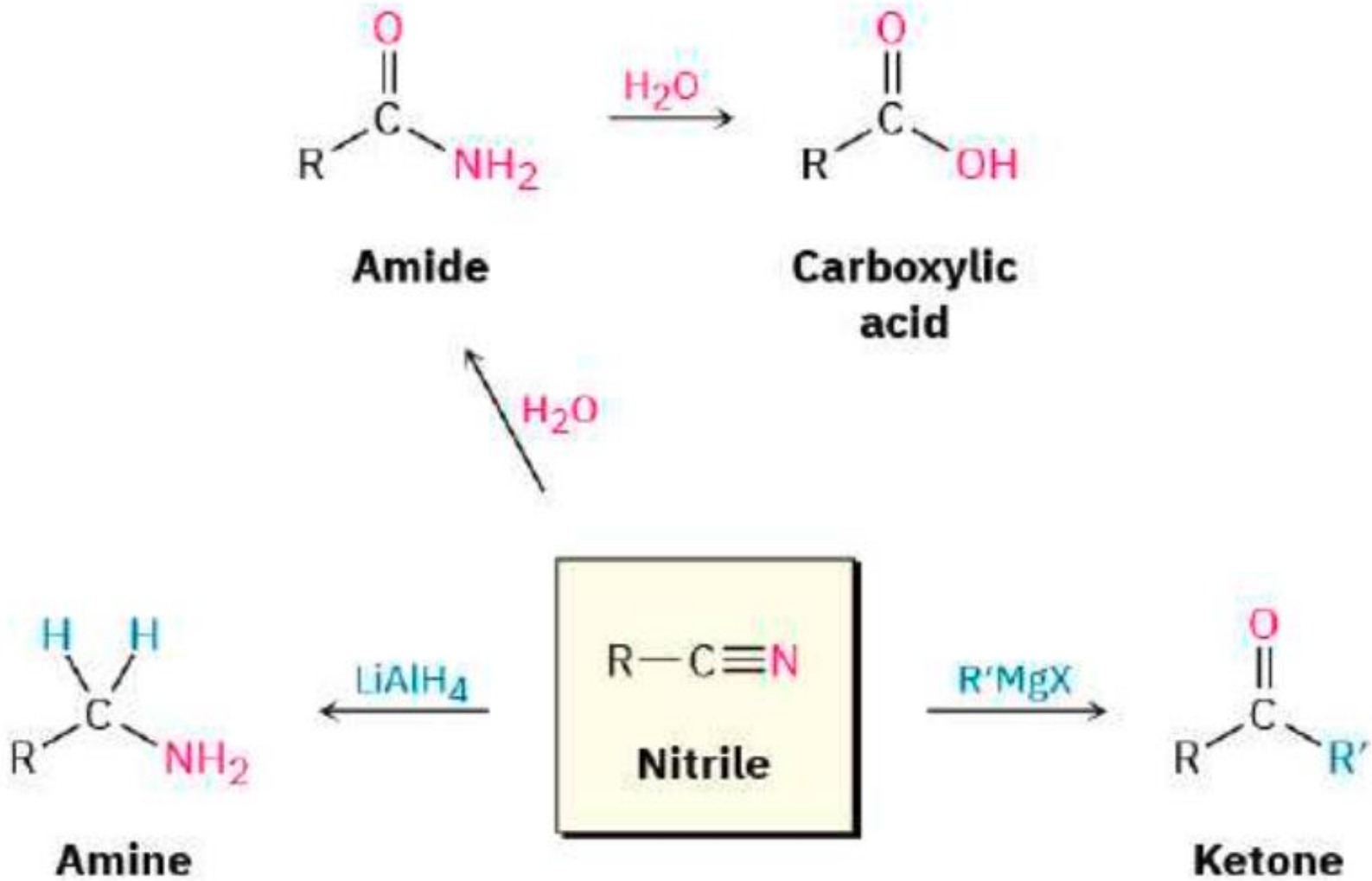
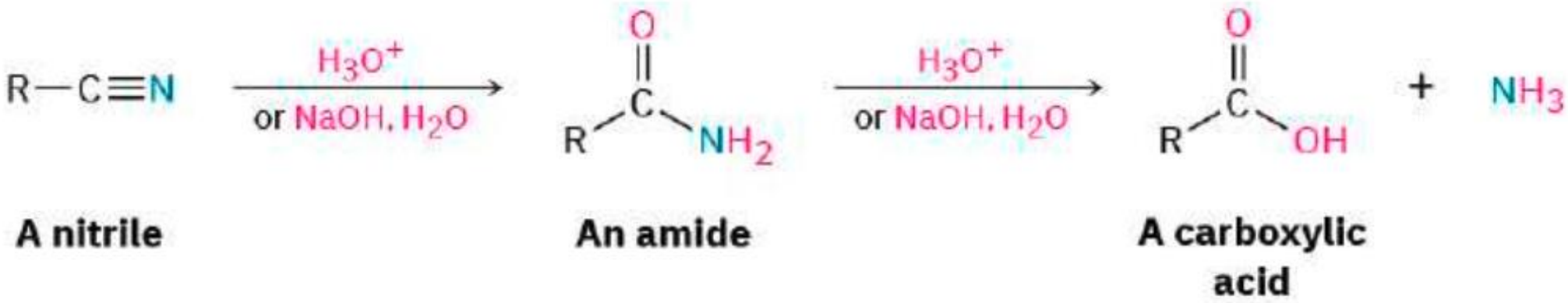


FIGURE 20.4 Some reactions of nitriles.

Hydrolysis: Conversion of Nitriles into Carboxylic Acids

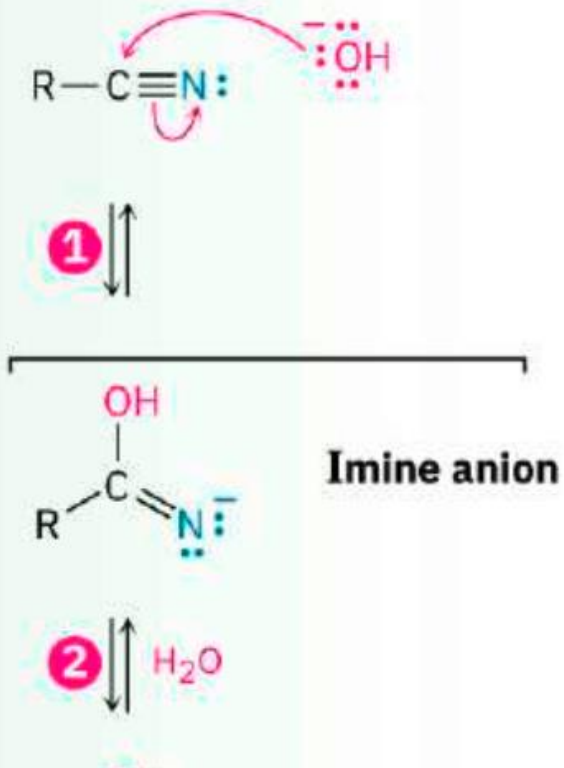
Among the most useful reactions of nitriles is their hydrolysis to yield first an amide and then a carboxylic acid plus ammonia or an amine. The reaction occurs in either basic or acidic aqueous solution:



As shown in **FIGURE 20.5**, base-catalyzed nitrile hydrolysis involves nucleophilic addition of hydroxide ion to the polar C≡N bond to give an imine anion in a process similar to the nucleophilic addition to a polar C=O bond to give an alkoxide anion. Protonation then gives a hydroxy imine, which tautomerizes (**Section 9.4**) to an amide in a step similar to the tautomerization of an enol to a ketone. Further hydrolysis gives a carboxylate ion.

FIGURE 20.5 MECHANISM

Mechanism for the basic hydrolysis of a nitrile to yield an amide, which is then hydrolyzed further to a carboxylic acid anion.

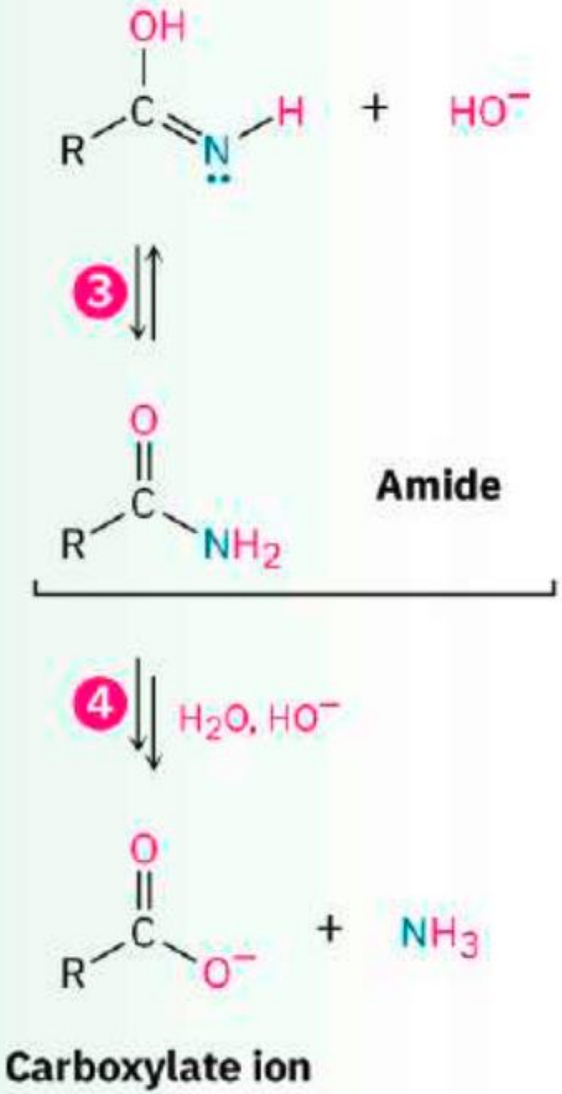


1. Nucleophilic addition of hydroxide ion to the CN triple bond gives an imine anion addition product.

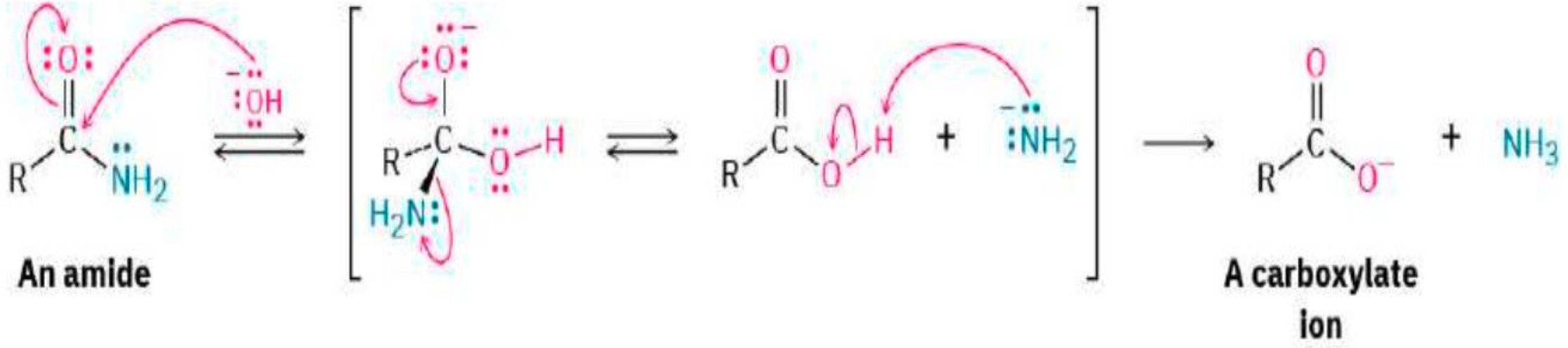
2. Protonation of the imine anion by water yields a hydroxyimine and regenerates the base catalyst.

3 Tautomerization of the hydroxyimine yields an amide in a reaction analogous to the tautomerization of an enol to give a ketone.

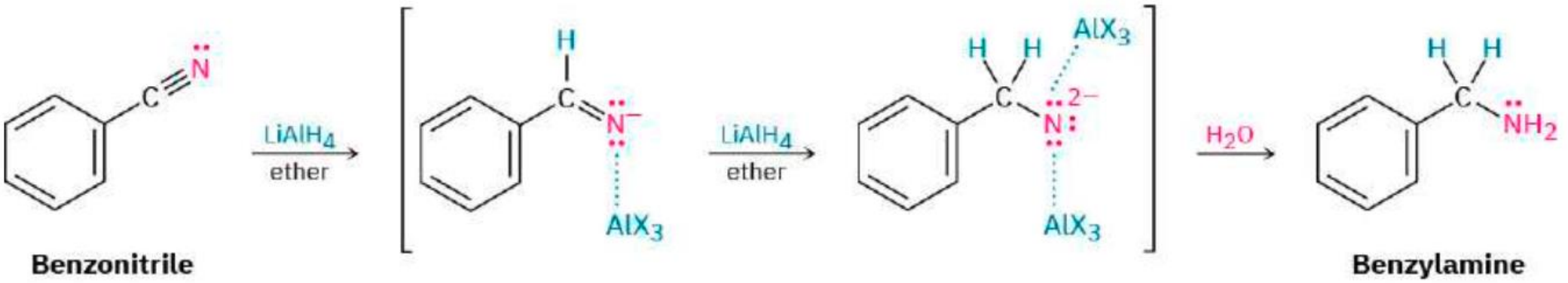
4 Further hydrolysis of the amide gives the anion of a carboxylic acid by a mechanism we'll discuss in **Section 21.7**.



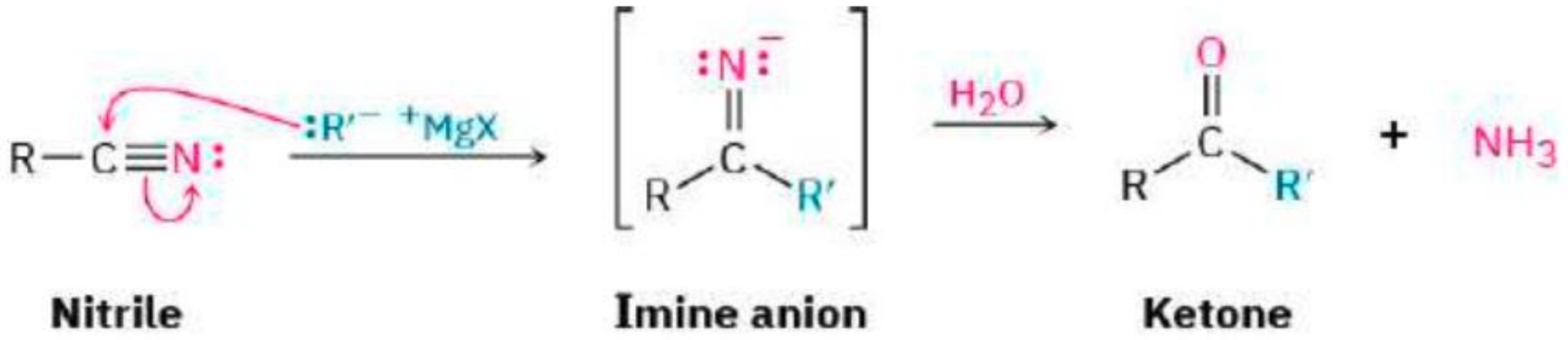
The further hydrolysis of the amide intermediate takes place by a nucleophilic addition of hydroxide ion to the amide carbonyl group, which yields a tetrahedral alkoxide ion. Expulsion of amide ion, NH2−, as leaving group gives the carboxylate ion, thereby driving the reaction toward the products. Subsequent acidification in a separate step yields the carboxylic acid. We'll look at this process in more detail in **Section 21.7**.



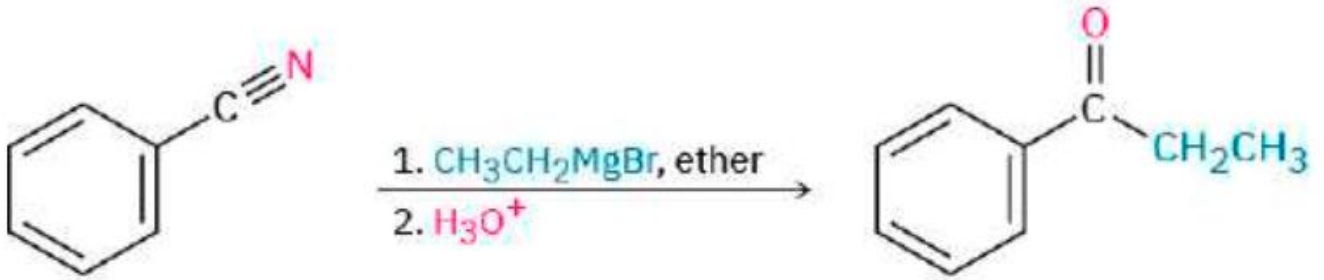
Reduction: Conversion of Nitriles into Amines



Reaction of Nitriles with Grignard Reagents



This 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:



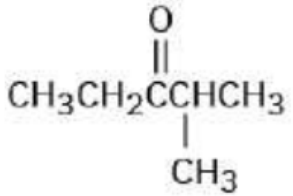
Benzonitrile

Propiophenone (89%)

WORKED EXAMPLE 20.3

Synthesizing a Ketone from a Nitrile

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



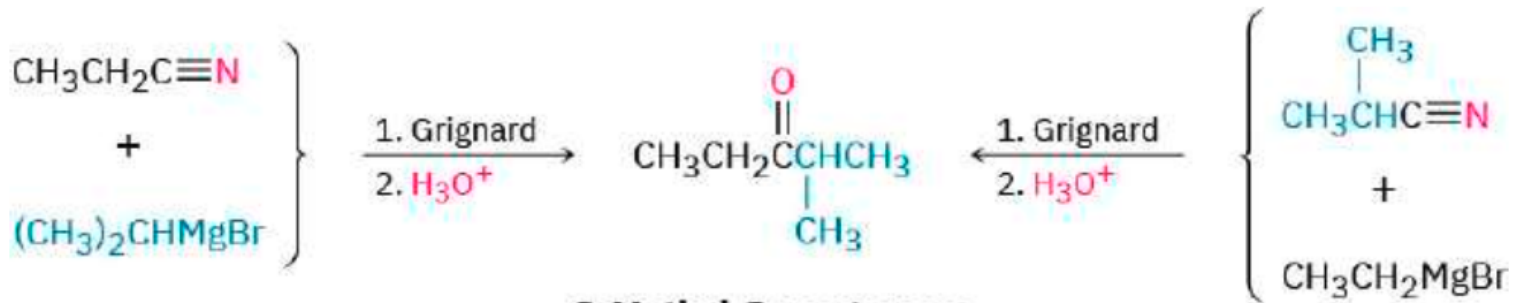
2-Methyl-3-pentanone

Strategy

A ketone results from the reaction between a Grignard reagent and a nitrile, with the C≡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.

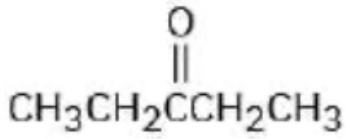


2-Methyl-3-pentanone

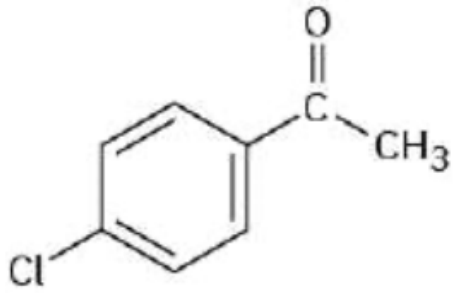
PROBLEM 20-13

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

(a)



(b)



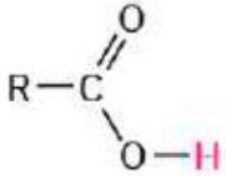
PROBLEM 20-14

How would you prepare 1-phenyl-2-butanone, $C_6H_5CH_2COCH_2CH_3$, from benzyl bromide, $C_6H_5CH_2Br$? More than one step is needed.

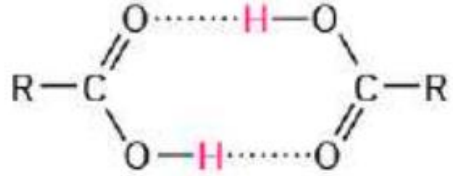
20.8 Spectroscopy of Carboxylic Acids and Nitriles

Infrared Spectroscopy

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 20.6**.

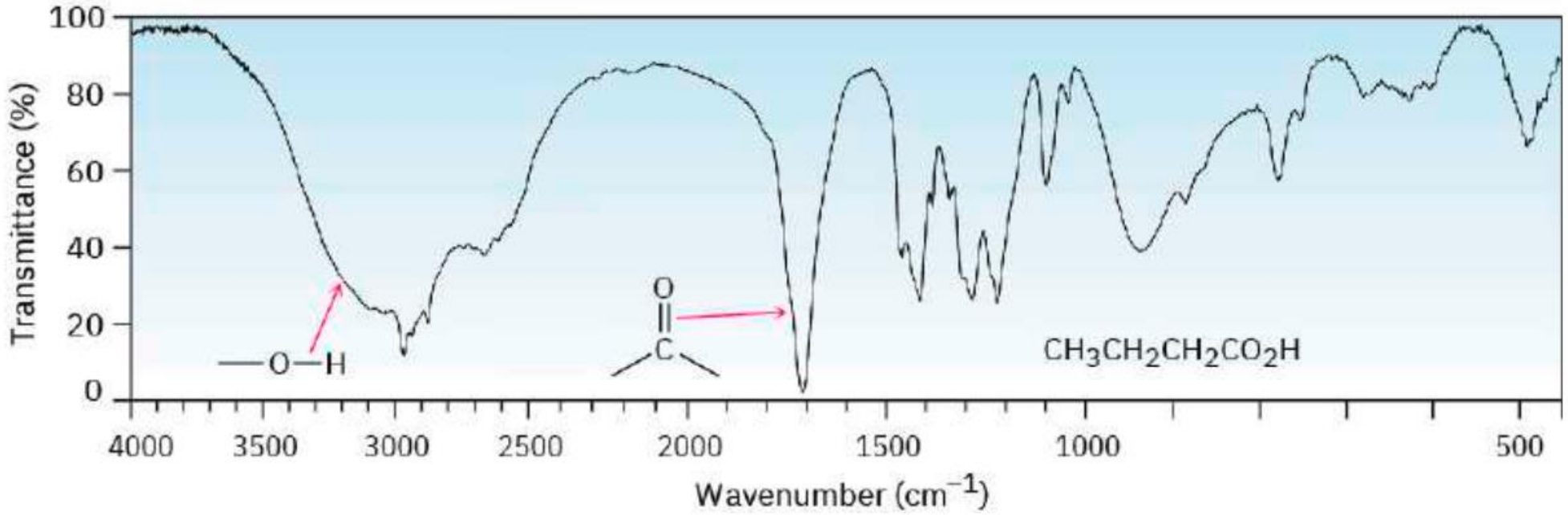


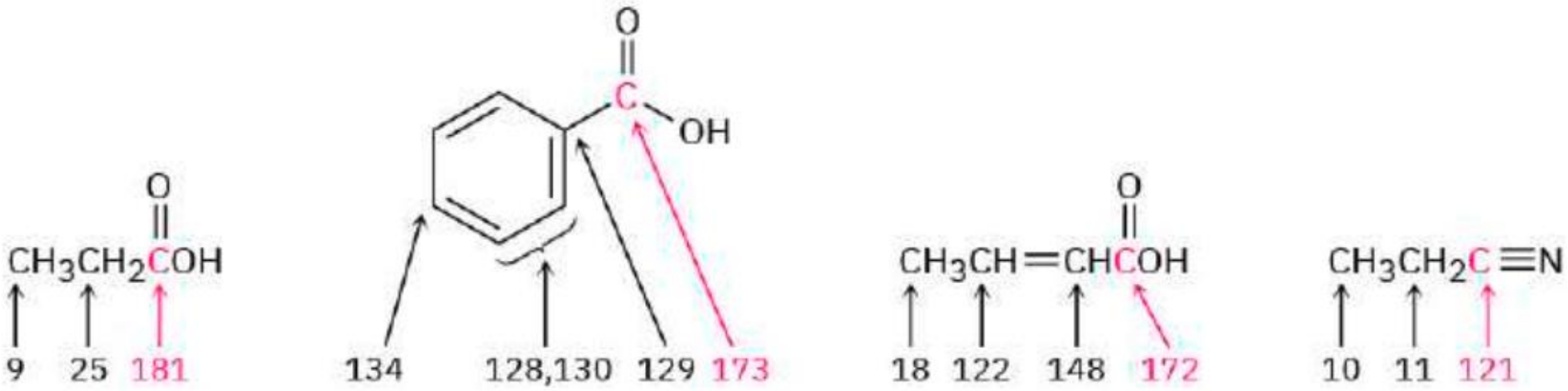
FIGURE 20.6 IR spectrum of butanoic acid, $CH_3CH_2CH_2CO_2H$.

Nitriles show an intense and easily recognizable bond absorption near 2250 cm–1 for saturated compounds and 2230 cm–1 for aromatic and conjugated molecules. Few other functional groups absorb in this region, so IR spectroscopy is highly diagnostic for nitriles.

PROBLEM 20-15 Cyclopentane carboxylic acid and 4-hydroxy cyclo hexanone have the same formula ($C_6H_{10}O_2$), and both contain an –OH and a C═O group. How could you distinguish between them using IR spectroscopy?

Nuclear Magnetic Resonance Spectroscopy

Carboxyl carbon atoms absorb in the range 165 to 185 δ in the ^{13}C NMR spectrum, with aromatic and α,β-unsaturated acids near the upfield end of the range (~165 δ) and saturated aliphatic acids near the downfield end (~185 δ). Nitrile carbons absorb in the range 115 to 130 δ.



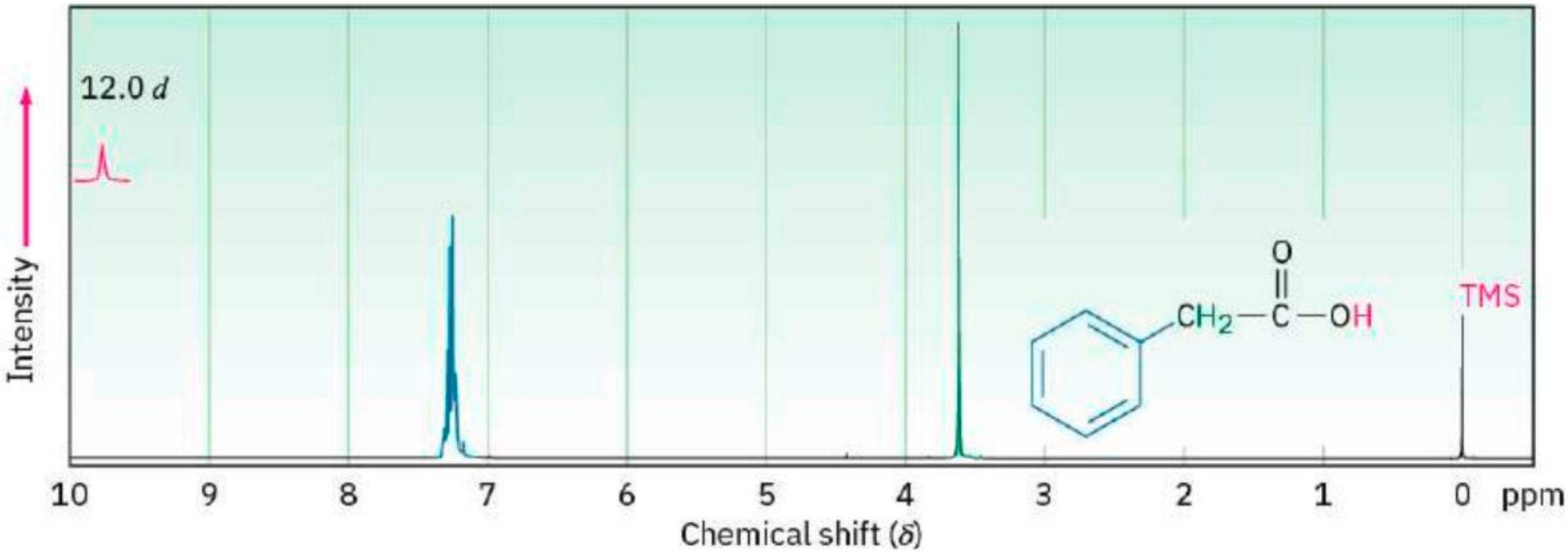
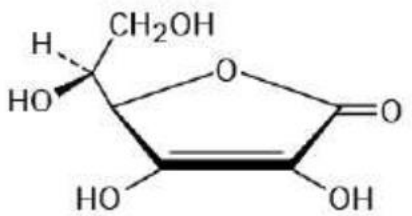


FIGURE 20.7 Proton NMR spectrum of phenylacetic acid, $C_6H_5CH_2CO_2H$.

PROBLEM 20-16 How could you distinguish between the isomers cyclopentanecarboxylic acid and 4-hydroxycyclohexanone by 1H and 13C NMR spectroscopy? (See Problem 20-15.)

CHEMISTRY MATTERS

Vitamin C



Vitamin C
(ascorbic acid)

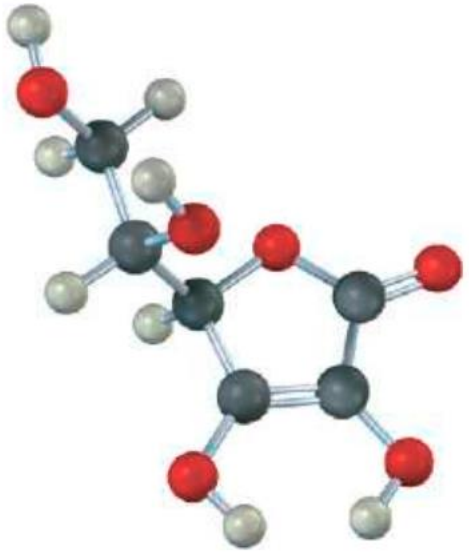


FIGURE 20.8 In addition to the hazards of weather, participants in early polar expeditions often suffered from scurvy, caused by a dietary vitamin C deficiency

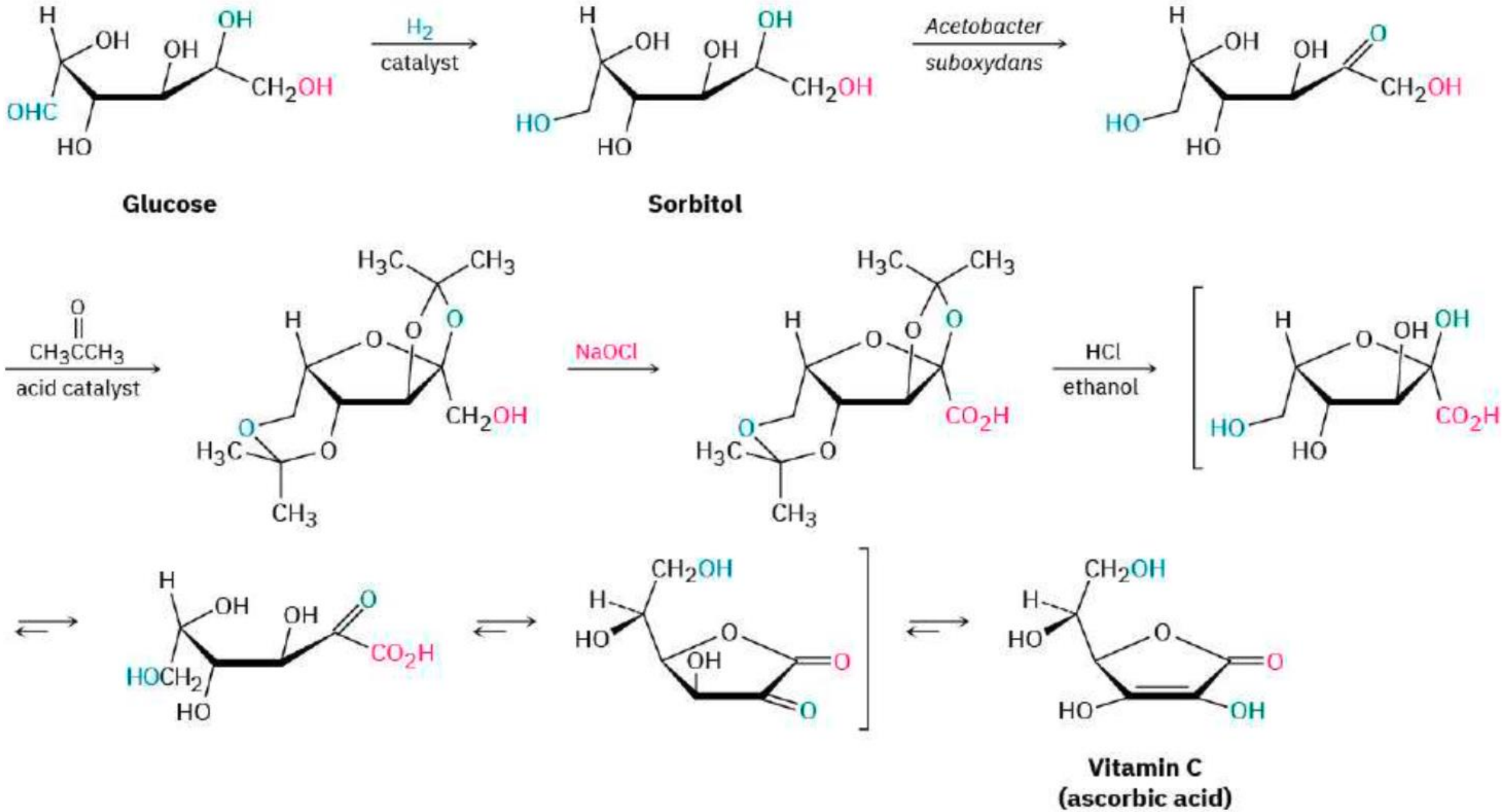


FIGURE 20.9 The industrial synthesis of ascorbic acid from glucose.