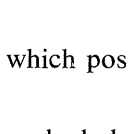
18

CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Almost all of the basic *types* of reactions now have been covered: addition, elimination, substitution, and rearrangement by polar, radical, and concerted mechanisms. Indeed, if you have been looking for similarities, you will have seen that most of the reactions discussed in the preceding three chapters are variations on basic types we have discussed earlier. Furthermore, most of the basic structural effects that determine chemical reactivity also have been covered in previous chapters: bond energies, steric hindrance, electronegativity, electron delocalization, hydrogen bonding, solvation, and conformational influences.

You might well ask what is left. The answer is, a great deal—but now we will be concerned mostly with putting concepts together, moving from the simple to the complex. For example, in this chapter we will be trying to understand the ways that carboxylic acids, which possess the  functional group, are similar to and different from alcohols, which have the OH group, and aldehydes and ketones, which have C=O bonds.

Subsequently we will look at acids that also possess OH or NH_2 substituent groups (or both) and develop a rationale for the behavior of these combinations in terms of effects we already have discussed. Insofar as possible, you should try to do this yourself whenever you encounter a substance with a new set of combinations of functional groups on its molecules. You often will be in error (as many experts will be), because even if you take

account of all of the structural effects, as well as the possible reactions or interactions, the overall result of these frequently is very difficult to judge in advance. In one case, steric hindrance may dominate, in another, electron delocalization, and so on. Still, trying to assess the effects and possible reactions leads to understanding and recognition of what the alternatives are, even if the resultant of them is difficult to assess.[1] Continuing study can be expected to develop an instinct for what is "good" chemistry and what is not.

We have described previously the acidic properties of several types of compounds: alkynes, alkenes, and alkanes (Sections 11-8 and 13-5B); halides (Section 14-7B); alcohols (Section 15-4A); and carbonyl compounds (Section 17-1A). Now we come to compounds that we actually call *acids*—the **carboxylic acids,** RCO_2H. Are these acids different in kind, or only in degree, from other acidic compounds discussed before? This is not a simple question and deserves some thought. In the most widely used sense, acids are proton donors but, as we have seen, their abilities to donate a proton to water vary over an enormous range: CH_4 has a K_a of $<10^{-40}$, whereas HI has a K_a of $\sim 10^9$. This represents a difference in ionization energies of more than 70 kcal mole^{-1}. The differences in K_a are only differences in degree, because examples are available of acids with K_a values in all parts of the range of K_a values. An important difference in kind was mentioned in Section 17-1B, namely, that acids with the same K_a values can differ greatly in the *rates* at which they give up a proton to a given base, such as water. Carbon acids, in which the proton comes from a C–H bond, may react *more than 10^{10} times slower* than an oxygen acid with the same K_a in which the proton is given up from an O–H bond.

Tradition reserves the use of the name "acid" for substances that transfer protons measurably to water. Thus the carboxylic acids stand out from alkynes, halides, alcohols, and simple aldehydes and ketones in giving water solutions that are "acidic" to indicator papers or pH meters as the result of proton transfers from the carboxyl groups:

$$RCO_2H + H_2O \rightleftharpoons RCO_2^{\ominus} + H_3O^{\oplus}$$

Even so, carboxylic acids are not very strong acids and, in a 1*M* water solution, a typical carboxylic acid is converted to ions to the extent of only about 0.5%.

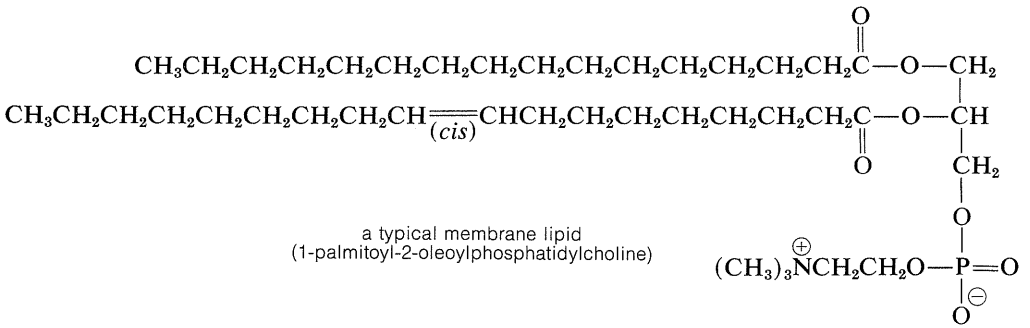
The nomenclature of carboxylic acids and their derivatives was discussed in Section 7-6. Many carboxylic acids have trivial names and often are referred to as "fatty acids." This term applies best to the naturally occurring straight-chain saturated and unsaturated aliphatic acids, which, as esters, are constituents of the fats, waxes, and oils of plants and animals. The most abundant of these fatty acids are palmitic, stearic, oleic, and linoleic acids.

[1]The major problem with assessing the resultant to be expected from opposing factors in chemical reactions is that relatively small energy differences can cause great differences in which product is favored. For an equilibrium such as A $\rightleftharpoons$ B at 25°C, a 5.5 kcal mole^{-1} change in ΔG^0 (Section 4-4A) can cause the equilibrium to shift from 99% in favor of A to 99% in favor of B.

They occur as **glycerides,** which are esters of the trihydric alcohol, 1,2,3-propanetriol (glycerol):

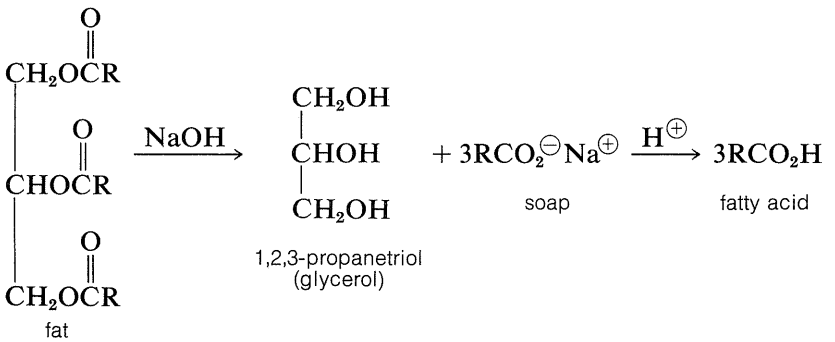
$CH_3(CH_2)_{14}CO_2H$	hexadecanoic (palmitic) acid
$CH_3(CH_2)_{16}CO_2H$	octadecanoic (stearic) acid
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	*cis*-9-octadecenoic (oleic) acid
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	*cis*-9-*cis*-12-octadecadienoic (linoleic) acid

Fats or glycerides belong to a class of biomolecules known as **lipids.** The traditional definition of *a lipid is a water-insoluble organic compound that can be extracted from cells and tissues by nonpolar solvents* (chloroform, ether, benzene). Compounds that meet this definition are substantially hydrocarbon-like, although they may differ widely in structure. They include not only esters of long-chain fatty acids but steroids (Section 30-4), terpenes (Section 30-3), and prostaglandins (Section 30-7). These nonpolar substances serve a variety of different biological functions, but lipids derived from fatty acids are most important for energy storage (Sections 18-8F and 20-10) and as components of membranes. **Phosphoglycerides** represent an important class of membrane lipids derived from glycerol. The hydroxyl groups of glycerol are esterified with two fatty-acid chains and one phosphate-ester residue. One of the phosphate-ester groups carries a highly *polar* $-N(CH_3)_3^{\oplus}$ group, the importance of which is indicated in Section 18-2F:



a typical membrane lipid
(1-palmitoyl-2-oleoylphosphatidylcholine)

Hydrolysis of fats with alkali (e.g., sodium hydroxide) yields salts of the fatty acids, and those of the alkali metals, such as sodium or potassium, are useful as soaps:



fat

1,2,3-propanetriol
(glycerol)

soap

fatty acid

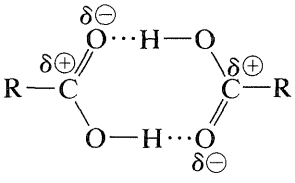
The properties of salts of long-chain carboxylic acids that make them useful as soaps will be discussed in Section 18-2F.

General methods for the preparation of carboxylic acids are summarized in Table 18-5, at the end of the chapter.

18-1 PHYSICAL PROPERTIES OF CARBOXYLIC ACIDS

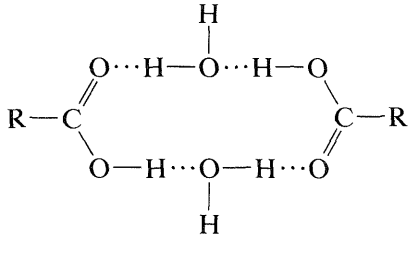
18-1A Hydrogen Bonding

Carboxylic acids show a high degree of association through hydrogen bonding. We have encountered such bonding previously with alcohols; however, acids form stronger hydrogen bonds than alcohols because their O–H bonds are more strongly polarized as $\overset{\delta\ominus}{-O}-\overset{\delta\oplus}{H}$. Furthermore, carboxylic acids are able to form hydrogen bonds to the negative oxygen of the carbonyl dipole rather than just to the oxygen of another hydroxyl group. Carboxylic acids in the solid and liquid states mostly exist as cyclic dimers, and these dimeric structures persist to some extent even in the vapor state and in dilute solution in hydrocarbon solvents:



The physical properties of some representative carboxylic acids are listed in Table 18-1. The substantially higher melting points and boiling points of acids relative to alcohols, aldehydes, ketones, and chlorides can be attributed to the strength and degree of hydrogen bonding. These differences in volatility are shown more strikingly in Figure 18-1, which is a plot of boiling point versus n (the total number of carbon atoms) for the homologous series $CH_3(CH_2)_{n-2}X$, in which X is $-CO_2H$, $-CH_2OH$, or $-CH_2Cl$.

Hydrogen bonding also is responsible for the high water solubility of the simple carboxylic acids with less than five carbons; water molecules can solvate the carbonyl group through hydrogen bonds. Nonetheless, as the chain length of the hydrocarbon residue R increases, the solubility decreases markedly, because the proportion of polar to nonpolar groups becomes smaller.



solvation of a carboxylic acid by water through hydrogen bonding

Table 18-1
Physical Properties of Representative Carboxylic Acids

Acid	Structure	Solubility, g/100 g H_2O	mp, °C	bp, °C	K_a (H_2O) at 25°C
methanoic (formic)	HCO_2H	∞	8.4	100.7	1.77×10^{-4}
ethanoic (acetic)	CH_3CO_2H	∞	16.6	118.1	1.75×10^{-5}
propanoic (propionic)	$CH_3CH_2CO_2H$	∞	−22	141.1	1.3×10^{-5}
butanoic (butyric)	$CH_3CH_2CH_2CO_2H$	∞	−8	163.5	1.5×10^{-5}
2-methylpropanoic (isobutyric)	$(CH_3)_2CHCO_2H$	20^{20}	−47	154.5	1.4×10^{-5}
pentanoic (valeric)	$CH_3(CH_2)_3CO_2H$	3.3^{16}	−34.5	187	1.6×10^{-5}
hexadecanoic (palmitic)	$CH_3(CH_2)_{14}CO_2H$	insol.	64	390	
octadecanoic (stearic)	$CH_3(CH_2)_{16}CO_2H$	0.034^{25}	69.4	360 d	
chloroethanoic (chloroacetic)	$ClCH_2CO_2H$	sol.	63	189	1.4×10^{-3}
dichloroethanoic (dichloroacetic)	Cl_2CHCO_2H	8.63	5–6	194	5×10^{-2}
trichloroethanoic (trichloroacetic)	Cl_3CCO_2H	120^{25}	58	195.5	1×10^{-1}
trifluoroethanoic (trifluoroacetic)	F_3CCO_2H	∞	−15	72.4	strong[a]
2-chlorobutanoic (α-chlorobutyric)(D,L)	$CH_3CH_2CHClCO_2H$	sol. hot		$101^{15\,mm}$	1.4×10^{-3}
3-chlorobutanoic (β-chlorobutyric)(D,L)	$CH_3CHClCH_2CO_2H$		44	$116^{22\,mm}$	8.9×10^{-5}
4-chlorobutanoic (γ-chlorobutyric)	$ClCH_2CH_2CH_2CO_2H$		16	$196^{22\,mm}$	3.0×10^{-5}
5-chloropentanoic (δ-chlorovaleric)	$ClCH_2(CH_2)_3CO_2H$		18	130^{11mm}	2×10^{-5}
methoxyethanoic (methoxyacetic)	$CH_3OCH_2CO_2H$	sol.		203	3.3×10^{-4}
cyanoethanoic (cyanoacetic)	$N{\equiv}CCH_2CO_2H$	sol.	66	$108^{0.15\,mm}$	4×10^{-3}
3-butenoic (vinylacetic)	$CH_2{=}CHCH_2CO_2H$	sol.	−39	163	3.8×10^{-5}
benzenecarboxylic (benzoic)	$C_6H_5CO_2H$	0.27^{18}	122	249	6.5×10^{-5}
phenylethanoic (phenylacetic)	$C_6H_5CH_2CO_2H$	1.66^{20}	76.7	265	5.6×10^{-5}

[a]The term "strong" acid implies essentially complete dissociation to $RCO_2^{\ominus}$ and $H_3O^{\oplus}$ in aqueous solution.

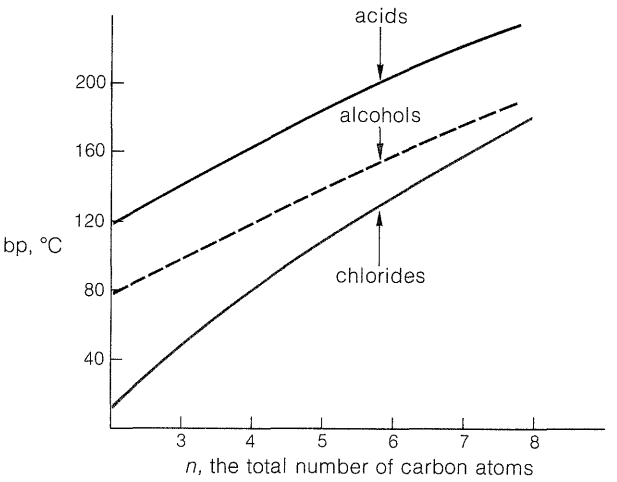


Figure 18-1 Boiling points of acids, $CH_3(CH_2)_{n-2}CO_2H$; alcohols, $CH_3(CH_2)_{n-2}CH_2OH$; and alkyl chlorides, $CH_3(CH_2)_{n-2}CH_2Cl$

18-1B Spectra of Carboxylic Acids

The *infrared spectra* of carboxylic acids provide clear evidence for the hydrogen bonding discussed in the preceding section. This is illustrated in Figure 18-2, which shows the spectrum of ethanoic acid in carbon tetrachloride solution, together with those of ethanol and ethanal for comparison.

The spectrum of ethanol has two absorption bands that are characteristic of the OH bond; one is a sharp band at 3640 cm^{-1}, which corresponds to free or unassociated hydroxyl groups, and the other is a broad band centered on 3350 cm^{-1} due to hydrogen-bonded groups. The spectrum of ethanoic acid shows no absorption from free hydroxyl groups but, like that of ethanol, has a very broad intense absorption ascribed to associated OH groups. However, the frequency of absorption, 3000 cm^{-1}, is shifted appreciably from that of ethanol and reflects stronger hydrogen bonding than in ethanol. The absorption due to the carbonyl group of ethanoic acid (1740 cm^{-1}) is broad, but is at about the same position as the carbonyl absorption in ethanal.

The carboxyl function does absorb *ultraviolet* radiation, but the wavelengths at which this occurs are appreciably shorter than for carbonyl compounds such as aldehydes and ketones, and, in fact, are out of the range of most commercial ultraviolet spectrometers. Some idea of how the hydroxyl substituent modifies the absorption properties of the carbonyl group in carboxylic acids can be seen from Table 18-2, in which are listed the wavelengths of maximum light absorption (λ_{max}) and the extinction coefficients at maximum absorption (ϵ_{max}) of several carboxylic acids, aldehydes, and ketones.

In the *nuclear magnetic resonance spectra* of carboxylic acids, the carboxyl proton is seen to absorb at unusually low magnetic fields. This is illustrated in Figure 18-3 by the spectra of phenylethanoic acid ($C_6H_5CH_2CO_2H$)

and phenylmethanol ($C_6H_5CH_2OH$). The chemical shift of the carboxylic acid proton is here about 9 ppm toward lower magnetic fields than that of the hydroxyl proton of the alcohol. This behavior parallels that of the enol hydrogens of 1,3-dicarbonyl compounds and is similarly related to hydrogen-bond formation (Section 17-1D).

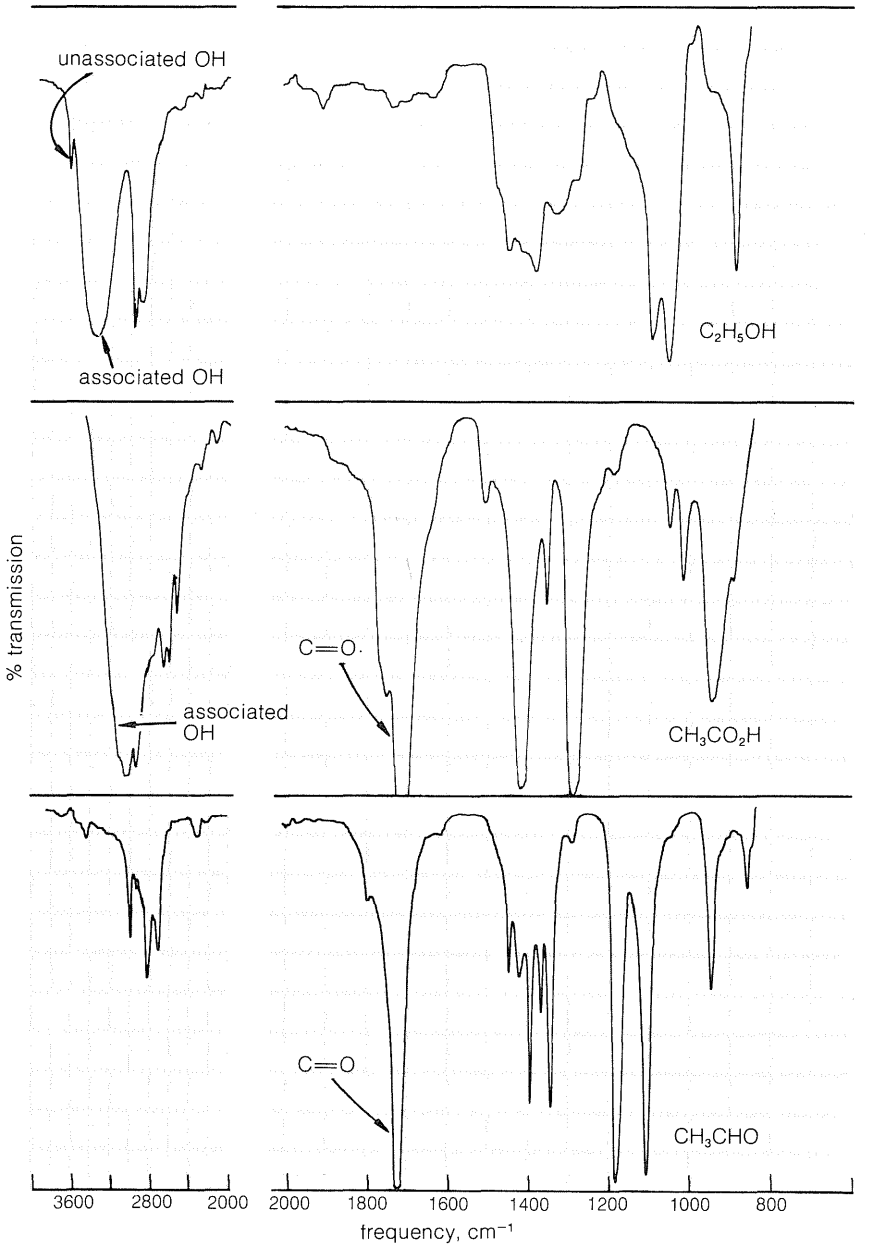


Figure 18-2 Infrared spectra of ethanol, ethanoic acid, and ethanal as 10% solutions in carbon tetrachloride

Table 18-2
Wavelengths for Maximum Ultraviolet Absorption of Some Carboxylic Acids, Aldehydes, and Ketones ($n \longrightarrow \pi^*$)

Compound	λ_{max}, nm	ϵ_{max}	Solvent	Compound	λ_{max}, nm	ϵ_{max}	Solvent
ethanoic acid	204	40	water	2-propanone	270	16	alcohol
ethanoic acid	197	60	hexane	butanoic acid	207	74	water
ethanal	293	12	hexane	butanal	290	18	hexane

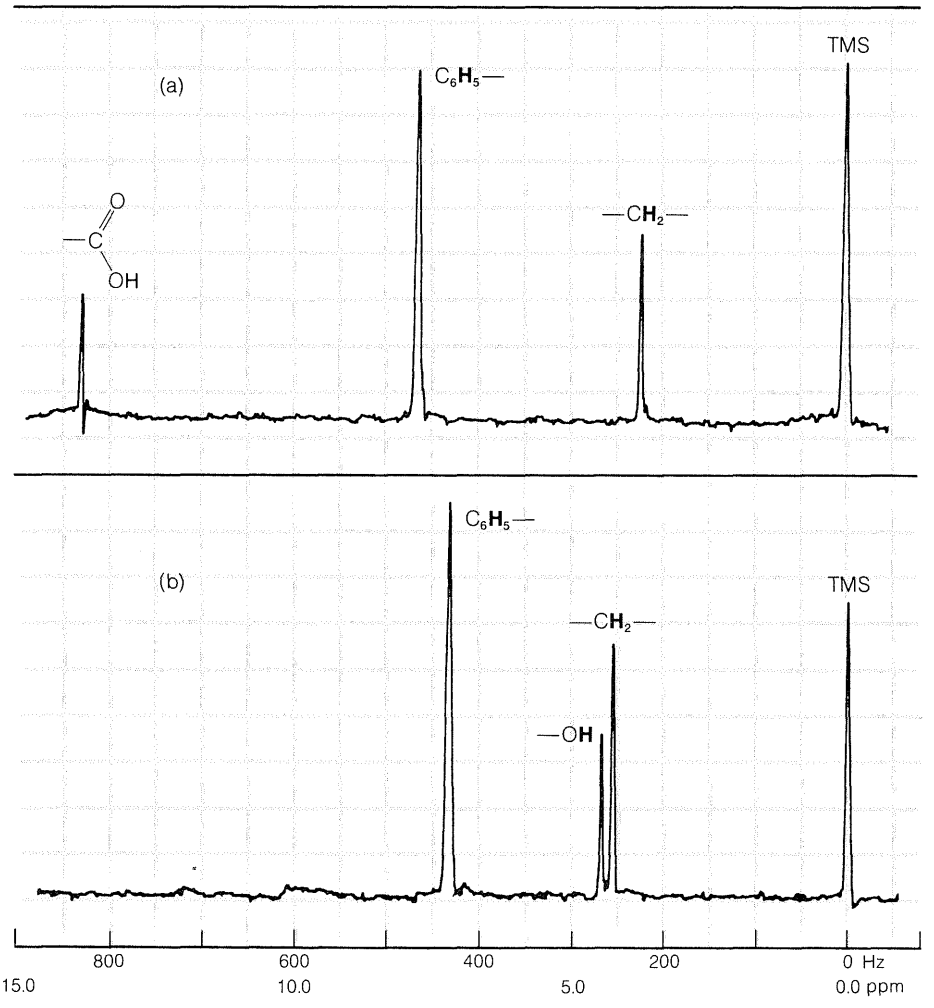
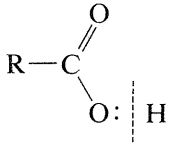


Figure 18-3 Proton nmr spectra of (a) phenylethanoic acid and (b) phenylmethanol in carbon tetrachloride solution at 60 MHz relative to TMS

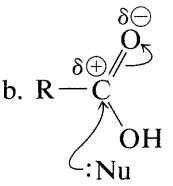
Exercise 18-1 Explain why the proton line position of the acidic hydrogen of a carboxylic acid, dissolved in a nonpolar solvent such as carbon tetrachloride, changes much less with concentration than does that of the OH proton of an alcohol under the same conditions (Section 9-10E).

18-2 SOME CHEMICAL PROPERTIES OF CARBOXYLIC ACIDS

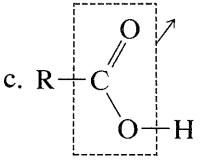
Most of the reactions of carboxylic acids belong to one of four principal classes, depending on the point in the molecule where the reaction occurs.

a. 

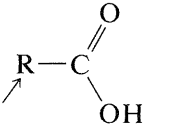
Reactions involving the O–H bond—these include acid dissociation and solvolytic reactions.

b. 

Reactions at the carbonyl carbon—most of which involve attack by a nucleophile :Nu on the carbonyl carbon with subsequent cleavage of a C–O bond. Examples are esterification, acyl chloride formation, and reduction with hydrides.

c. 

Decarboxylation—these are reactions in which the R–C bond is broken in such a way that CO_2 is lost and R–H is formed.

d. 

Substitution on the R group—substitutions for hydrogen or halogen at the 2-carbon are especially important.

We will emphasize the way in which the chemistry of carboxylic acids in each of these categories can be correlated with the principles outlined in previous chapters.

18-2A Dissociation of Carboxylic Acids. The Resonance Effect

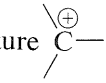
Compared with mineral acids such as hydrochloric, perchloric, nitric, and sulfuric acids, the carboxylic acids, $CH_3(CH_2)_nCO_2H$, are weak. The extent of

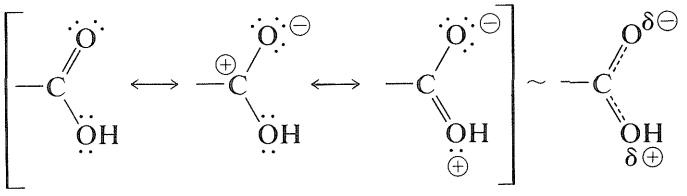
dissociation in aqueous solution is relatively small, the acidity constants, K_a, being approximately 10^{-5} (see Table 18-1).

$$RCO_2H + H_2O \rightleftharpoons RCO_2^{\ominus} + H_3O^{\oplus}$$

$$K_a = \frac{[RCO_2^{\ominus}][H_3O^{\oplus}]}{[RCO_2H]} \sim 10^{-5} \quad \text{for R} = CH_3(CH_2)_n-$$

Even though the carboxylic acids are weak acids, they are many orders of magnitude stronger than the corresponding alcohols, $CH_3(CH_2)_nCH_2OH$. Thus the K_a of ethanoic acid, CH_3CO_2H, is 10^{11} *times larger* than that of ethanol, CH_3CH_2OH.

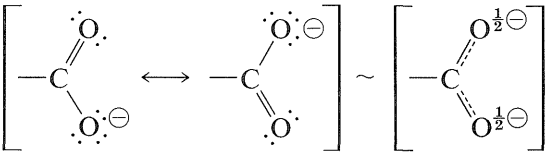
The acidity of the carboxyl group arises, at least in part, from the polar nature of the carbonyl group, the polarity of which can be ascribed to contributions of the structure  . For a carboxyl group, these structures and an additional possibility are shown by **1a**, **1b**, and **1c**:



1a **1b** **1c** **1**

Although the uncharged structure, **1a**, is of major importance, structures **1b** and **1c** make significant contributions. The stabilization is substantial and carboxylic acids are more stable than would be expected, from summing up their bond energies, by fully 18 kcal mole^{-1}.

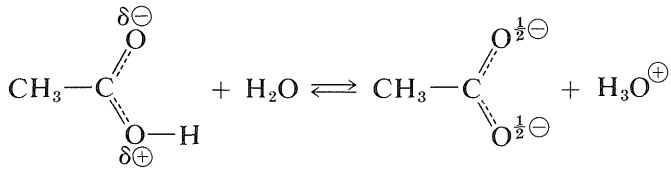
The stabilization energy of the carboxylate anion is substantially greater than that of the acid, because the anion is a resonance hybrid of two energetically *equivalent* structures, **2a** and **2b**, whereas the acid is represented by a hybrid of *nonequivalent* structures, **1a** through **1c**:



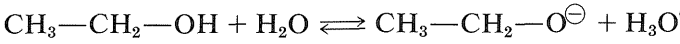
2a **2b** **2**

The rules for resonance stress that the greatest stabilization is expected when the contributing structures are equivalent (Section 6-5B). Therefore we can conclude that the resonance energy of a carboxylate anion should be

greater than that of the corresponding acid. Consequently we can say that there is a "driving force" (a gain in stability) that promotes the dissociation of carboxylic acids. The fact that alcohols are far weaker acids than carboxylic acids may be attributed to the lack of stabilization of alkoxide ions compared to that of carboxylate anions. The difference in energy corresponding to the dissociation of a carboxylic acid (Equation 18-1) relative to that of an alcohol (Equation 18-2) actually amounts to about 15 kcal mole^{-1}:



(18-1)



(18-2)

Exercise 18-2 Make atomic-orbital models of ethanoic acid and ethanol and of the ethanoate anion and ethoxide anion. Show how these models can be used to explain the greater acidity of ethanoic acid relative to ethanol.

Exercise 18-3 The K_a for the first ionization of carbonic acid, $O{=}C(OH)_2 + H_2O \rightleftharpoons O{=}C(OH)O^{\ominus} + H_3O^{\oplus}$, is about 1000 times *smaller* than K_a for ethanoic acid. Show how this fact can be rationalized by considering the expected relative stabilization energies of carbonic acid and the hydrogen carbonate ion compared to those of ethanoic acid and ethanoate anion.

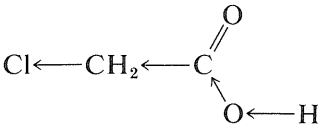
18-2B The Inductive Effect and Acid Strengths

You may have noticed that there are considerable differences between the strengths of some of the acids listed in Table 18-1. Methanoic acid and almost all the substituted ethanoic acids are stronger than ethanoic acid. In fact, trifluoroethanoic acid is similar in strength to hydrochloric acid. The substituent groups clearly can have a profound effect on acid strength by what commonly is called the **inductive effect,** an effect related to the electronegativity of the substituent. The inductive effect is different from resonance effects discussed in Section 18-2A in that it is associated with substitution on the *saturated* carbon atoms of the chain. The inductive effect of the substituent makes the acid stronger or weaker (relative to the unsubstituted acid), depending on whether the substituent is electron-attracting or electron-donating relative to hydrogen.

The electronegativity scale (Section 10-4B) shows chlorine to be more electron-attracting than hydrogen, and chloroethanoic acid is an 80-times

stronger acid than ethanoic acid itself. Substitution by more chlorines enhances the acidity. Dichloroethanoic acid is 3000 times and trichloroethanoic acid is 5000 times more acidic than ethanoic acid. Moving the position of substitution along the chain away from the carboxyl group makes the effect smaller, and 4-chlorobutanoic acid is only a two-times stronger acid than butanoic acid (Table 18-1).

The inductive effect of the substituent can be considered to be transmitted to the carboxyl group in two rather different ways. Most frequently, the substituent is regarded as causing shifts in the average distributions of the bonding electrons along the chain of atoms between it and the carboxyl proton. This produces a succession of electron shifts along the chain, which, for an electron-attracting substituent, increases the acid strength by making it more energetically feasible for the —OH hydrogen of the carboxyl group to leave as a proton:



Many other groups besides halogen exhibit electron-withdrawing acid-enhancing inductive effects. Among these are nitro ($—NO_2$), methoxy ($CH_3O—$), carbonyl ($\begin{pmatrix} \diagdown \\ C{=}O, \\ \diagup \end{pmatrix}$ as in aldehydes, ketones, acids, esters, and amides), cyano or nitrile ($—C{\equiv}N$), and trialkylammonium ($R_3\overset{\oplus}{N}—$). Alkyl groups—methyl, ethyl, isopropyl, and so on—are the only substituents listed in Table 18-1 that are acid-weakening relative to hydrogen (as can be seen by comparing the K_a values of the longer-chain acids with those of methanoic and ethanoic acids). We may take this to mean that alkyl groups *release* electrons to the carboxyl group.

18-2C The Electrostatic Interpretation of Acid Strengths

The other possible mode of transmission of the polar effect of a substituent group is a purely electrostatic one, sometimes called the "field effect," in which the dipole of the substituent produces an electrostatic field at the carboxyl proton, which helps or hinders ionization depending on the way in which the dipole is oriented with respect to the carboxyl group. It is easiest to visualize how the electrostatic theory operates by considering a proton midway between two well-separated carboxylate anions and deciding with which one the proton can combine more favorably. The more favorable one will correspond to the more basic carboxylate anion and the weaker carboxylic acid. With $CH_3CO_2^{\ominus}$ and $ClCH_2CO_2^{\ominus}$ as examples, and remembering that the Cl–C bond is polarized as $\overset{\delta\ominus}{Cl}—\overset{\delta\oplus}{C}$, we can write:

$$\overset{\delta\ominus}{Cl}—CH_2CO_2^{\ominus} \cdots\cdots H^{\oplus} \cdots\cdots {}^{\ominus}O_2CCH_3$$

The proton will be attracted by both $-CO_2^{\ominus}$ groups and the difference in electrostatic energy of its combination with one or the other of the carboxylate groups will depend on the influence of the $\overset{\delta\ominus}{Cl}-\overset{\delta\oplus}{CH_2}$ dipole. The $\overset{\delta\ominus}{Cl}$ end of the dipole will attract the proton, but the $\overset{\delta\oplus}{CH_2}$ end will repel it. The repulsion effect will be more important because the $\overset{\delta\oplus}{CH_2}$ is *closer* than $\overset{\delta\ominus}{Cl}$ to the final point of attachment of the proton to the carboxylate oxygen.[2] Thus, the proton will go more favorably to $CH_3CO_2^{\ominus}$ than to $ClCH_2CO_2^{\ominus}$, which means that $ClCH_2CO_2H$ is a stronger acid than CH_3CO_2H.

Quantitative application of electrostatic theory to the effect of substituents on the ionizations of carboxylic acids, such as chloroethanoic acid, is rendered difficult by the fact that the polarized $\overset{\delta\ominus}{Cl}-\overset{\delta\oplus}{CH_2}$ bond and the proton cannot be treated as if they were point charges in a vacuum. The intervening and surrounding matter must be taken into account. This is especially true for water solutions because a molecule of an organic acid in water is a cavity of low dielectric constant immersed in a medium of high dielectric constant. Therefore, when ionization occurs the proton goes from inside the cavity through the boundary into the water. At the same time, the nature of the cavity must change because it then contains an anion, not a neutral molecule.

Exercise 18-4 Which acid in each of the following pairs would you expect to be the stronger? Give your reasoning.

a. $(CH_3)_3\overset{\oplus}{N}CH_2CO_2H$ or $(CH_3)_2NCH_2CO_2H$

b. $(CH_3)_3\overset{\oplus}{N}CH_2CO_2H$ or $(CH_3)_2\overset{\oplus}{N}(O^{\ominus})CH_2CO_2H$

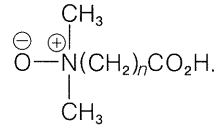
c. $(CH_3)_3CCO_2H$ or CH_3CO_2H

d. $CH_3OCH_2CO_2H$ or $CH_3SCH_2CO_2H$

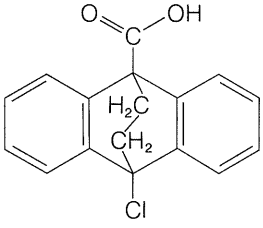
e. $CH_2{=}CH{-}CH_2CO_2H$ or $HC{\equiv}C{-}CH_2CO_2H$

Exercise 18-5* Simple electrostatic considerations suggest that the acidities of carboxylic acids of the type $(CH_3)_3\overset{\oplus}{N}(CH_2)_nCO_2H$ should decrease much more *slowly*

[2]The electrostatic energy involved in bringing two charges from a distance r_1 to a distance r_2 apart is given by $(e_1e_2/D)(1/r_1 - 1/r_2)$, where e_1 and e_2 are the magnitude of the charges and D is the dielectric constant of the medium (Section 8-7F). If e_1 and e_2 have the same sign, the energy is positive, and with opposite signs the energy is negative. For calibration, the electrostatic energy resulting from bringing a positive charge from a large distance ($1/r_1 \sim 0$) up to a negative charge at a distance of 1 A in a vacuum ($D = 1$) is -335 kcal mole^{-1}.

with increasing n than the acidities of acids of the type  . Explain why this should be so.

Exercise 18-6* The chloro acid **3** is a stronger acid than the acid without the chlorine, whereas the chloro acid **4** is a weaker acid than the corresponding acid with no chlorine. Explain why this can be expected from simple electrostatic theory. (Models may be helpful.)



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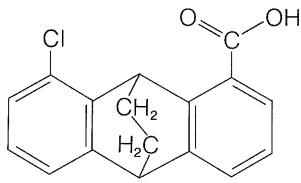


4

Exercise 18-7* Fluoroethanoic acid is only about twice as acidic as chloroethanoic acid, even though fluorine is much more electronegative than chlorine (Section 10-4B). The lengths of aliphatic C–F bonds are about 1.38 A, whereas those of C–Cl bonds are 1.78 A How could this difference in bond lengths tend to compensate for the differences in electronegativity between chlorine and fluorine and make the acids similar in strength?

18-2D What Part Does Entropy Play in the Dissociation of Carboxylic Acids?

We have discussed the influence of substituents on acid strengths of simple carboxylic acids as though the full electrostatic effect of the substituent were exerted solely on the ΔH of ionization. However, careful thermodynamic analysis of acidities in aqueous solution show that entropy effects (Section 4-4B) are very important. This may seem surprising because entropy effects ought to be small for *relative* acid strengths, which can be assessed by the constants for simple equilibria such as Equation 18-3, in which (1) there are the same number of molecules on each side of the equation, and (2) the constraints on the species involved hardly seem different from one side of the equation to the other:

$$CH_3CO_2H + ClCH_2CO_2^{\ominus} \rightleftharpoons CH_3CO_2^{\ominus} + ClCH_2CO_2H \qquad (18\text{-}3)$$

The entropy effects associated with these equilibria have to do with the "invisible" participant, water, which is involved in an intimate way, although

by convention we omit it from equations such as 18-3. Solvation of ions puts constraints on water molecules, and the same electrostatic effects that change the ease of removing the proton act to change the degree and nature of solvation, thereby requiring consideration of entropy effects on the equilibria.

If solvation entropy effects are important, how can we justify using simple electrostatic theory to account for changes in acid strengths produced by substituents? The answer lies in ΔG; whatever the electrostatic effects are doing to the balance between ΔH and ΔS, it is ΔG that determines the equilibrium constant and ΔG quite consistently follows the predictions of simple electrostatic considerations. Furthermore, the relative acid strengths of a number of substituted ethanoic acids have been determined in the gas phase by ion-cyclotron resonance (Section 27-8), under conditions where association and solvent effects are absent (Section 11-8A). In the gas phase, entropy effects are small and the relative acidities are in the order expected from the electronegativity scale, provided one corrects for the ion-size effect that we encountered previously with respect to the gas-phase acidities of alkynes and alcohols (Section 11-8B and 15-4A). Thus fluoroethanoic acid is weaker than chloroethanoic acid in the gas phase, whereas the reverse is true in water solution. The difference may be due simply to the fact that larger ions are in general more stable than smaller ions in the gas phase.

18-2E Carboxylic Acids as Bases

In addition to their acidic properties, carboxylic acids also can act as weak bases when the carbonyl oxygen accepts a proton from a strong acid, such as H_2SO_4, $HClO_4$, or $HSbF_6$ in SO_2 (Equation 18-4). Such protonation is an important step in acid-catalyzed esterification, as discussed in Section 15-4D:

$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH + H_2SO_4 \rightleftharpoons R{-}\overset{\displaystyle \oplus OH}{\overset{\|}{C}}{-}OH + HSO_4^{\ominus}} \qquad (18\text{-}4)$$

A proton also can add to the hydroxyl oxygen (Equation 18-5). The resulting conjugate acid normally is less favorable than its isomer with the proton on the carbonyl group. Nonetheless, this conjugate acid plays a role in esterification when the R group is particularly bulky and, in addition, has electron-donating properties, thereby favoring ionization to an acyl carbocation (as in Equation 18-6; see also Section 18-3A):

$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}OH + H_2SO_4 \rightleftharpoons R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\oplus}{O}H_2 + HSO_4^{\ominus}} \qquad (18\text{-}5)$$

$$\mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\overset{\oplus}{O}H_2 \rightleftharpoons \underset{\text{acyl carbocation}}{\overset{\displaystyle O}{\overset{\|}{R}}C\oplus} + H_2O} \qquad (18\text{-}6)$$

Exercise 18-8 Explain why the equilibrium of Equation 18-5 is *less* favorable than that of Equation 18-4.

18-2F Salts of Carboxylic Acids as Soaps. Micelle Formation

Carboxylic acids have an important practical use in the form of their metal salts as *soaps*. We have mentioned how fats, which are 1,2,3-propanetriol (glyceryl) esters of long-chain acids, can be hydrolyzed with alkali to give the corresponding carboxylate salts. It has been known as far back as Roman times (Pliny) that such substances have value for cleaning purposes.[3] These salts have a complicated interaction with water because they are very polar at the salt end of the molecule and very nonpolar at the long-chain hydrocarbon end of the molecule. These hydrocarbon ends are not compatible with a polar solvent such as water.[4]

When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are sizable aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water (Figure 18-4).

The cleansing action of soap is partly due to the way soap lowers the surface tension of the water thereby helping it to penetrate into fabrics, and also to the ability of the micelles to solubilize oils and greases by taking them into their hydrocarbon regions.

A major disadvantage of the simple carboxylate soaps is that they combine with the calcium and magnesium ions normally present in most tap water to form insoluble scums, which interfere with the cleansing process. Many so-called **detergents** have been developed that do not have this disadvantage—an

[3]Until the 19th century soaps were made by boiling animal or vegetable fats with wood ashes, which contain, besides silica, considerable amounts of potassium carbonate. The resulting mixture of potassium carboxylate salts gives a "soft" soap, and this can be converted to a "hard" soap by treatment with excess NaCl, which forms the less soluble sodium carboxylate salts. The KCl formed goes into the aqueous phase.

[4]One might well wonder why soap molecules do not simply crystallize out of water solution if the hydrocarbon chains are incompatible with water. However, the crystal packing of the polar salt parts of the molecule is not likely to be very compatible with the hydrocarbon parts and, furthermore, most soaps are salts of mixtures of aliphatic acids and this hardly helps crystallization to occur.

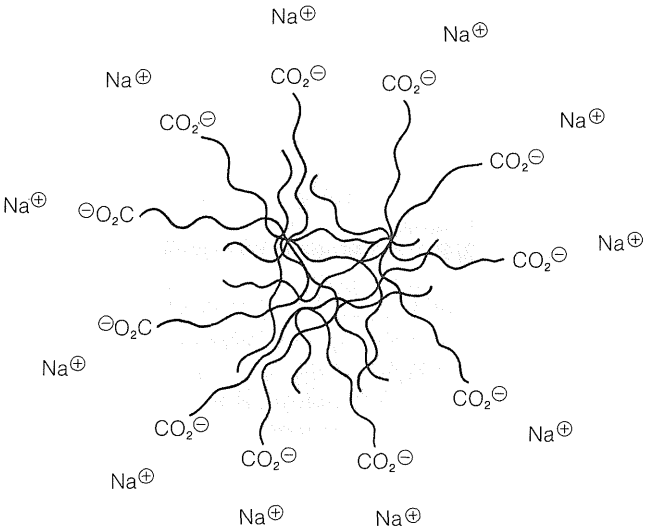
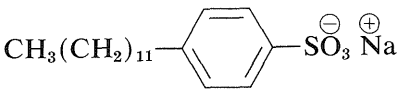


Figure 18-4 Schematic diagram of a soap micelle in water solution

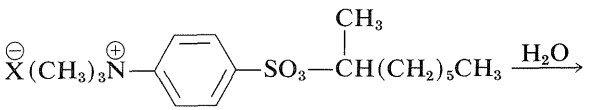
example is sodium 4-dodecanylbenzenesulfonate, whose calcium and magnesium salts are water soluble.



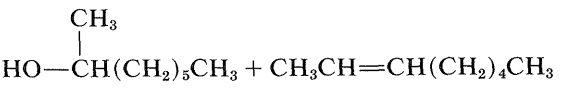
sodium 4-dodecanylbenzenesulfonate

When carboxylate salts are put into *nonpolar* solvents, **reversed micelles** often are formed, where the polar parts of the molecules are on the inside and the nonpolar parts are on the outside.

> Pronounced differences have been observed for the rates of chemical reactions in micelles as compared to pure water. For example, the solvolysis of the 1-methylheptyl sulfonate, **5**, in dilute water solution proceeds 70 times *slower* when sufficient sodium dodecanyl sulfate ($NaOSO_3C_{12}H_{25}$) is added to provide about twice as many dodecanyl sulfate ions in the micelle state as there are molecules of **5** present:



5



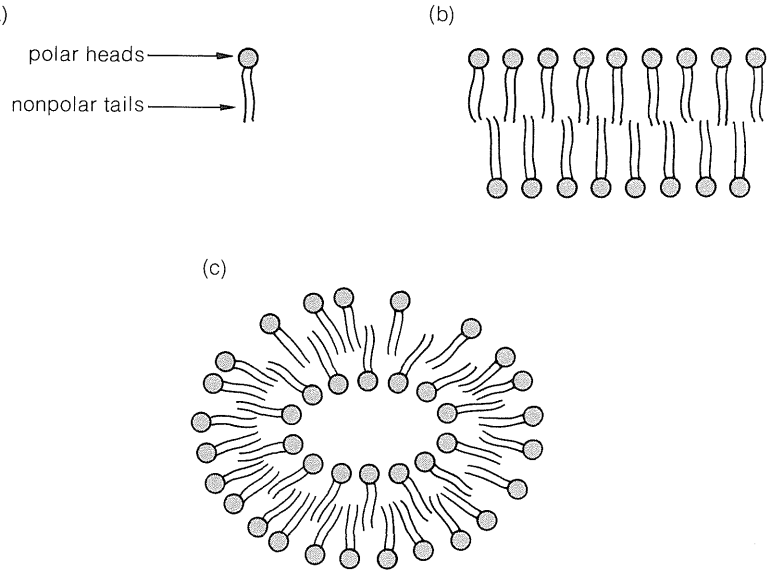


Figure 18-5 Schematic representation of (a) a membrane lipid, (b) a bilayer structure formed by lipid molecules in polar media; the interior of the bilayer is nonpolar, and (c) a continuous bilayer structure (liposome) with polar interior and exterior

This slowing of the solvolysis reaction by the alkyl sulfate requires that **5** be almost completely imprisoned by the micelles, because that part of **5** free in water would hydrolyze rapidly. An important result is in the stereochemistry of the reaction, which changes from 100% inversion with optically active **5** in pure water to only 56% inversion in the micelles. Micelles of the opposite polarity, made from hexadecyltrimethylammonium bromide, $C_{16}H_{33}\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{Br}$, have no effect on the rate of solvolysis of **5**.

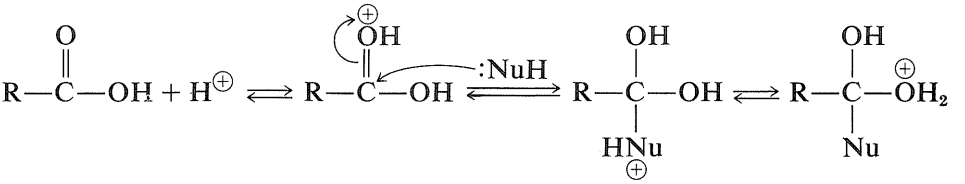
Studies of this type have been made on a number of systems and are of great interest because of the light they may shed on the structure and function of biological membranes.

There is a close resemblance between fatty-acid salts and phospholipids (p. 790) in that both possess long hydrocarbon tails and a polar head. Phospholipids also aggregate in a polar medium to form micelles *and* continuous bilayer structures such as shown in Figure 18-5. The bilayer lipid structure is very important to the self-sealing function of membranes and their impermeability to very polar molecules.

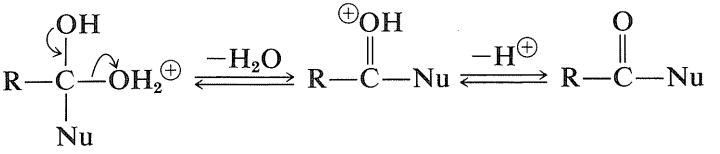
18-3 REACTIONS AT THE CARBONYL CARBON OF CARBOXYLIC ACIDS

Many important reactions of carboxylic acids involve attack on the carbon of the carbonyl group by nucleophilic species. These reactions frequently are catalyzed by acids, because addition of a proton or formation of a hydrogen

bond to the carbonyl oxygen makes the carbonyl carbon more vulnerable to nucleophilic attack. The following equations illustrate how an acid-catalyzed reaction operates with a neutral nucleophile (H—Nu:):



Subsequent cleavage of a C–O bond and loss of a proton yields a displacement product:

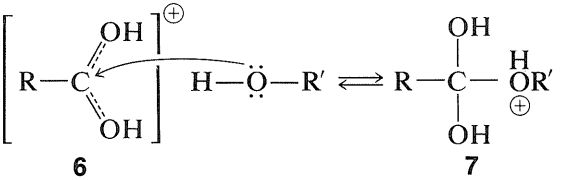


An important example of this type of reaction is the formation of esters, which was discussed previously in connection with the reactions of alcohols in Section 15-4D. Similar addition-elimination mechanisms occur in many reactions at the carbonyl groups of acid derivatives. A less obvious example of addition to carboxyl groups involves hydride ion ($H:^{\ominus}$) and takes place in lithium aluminum hydride reduction of carboxylic acids (Sections 16-4E and 18-3C).

Exercise 18-9 Use bond energies and the stabilization energy of ethanoic acid (18 kcal mole^{-1}, Section 18-2A) to calculate ΔH^0 for the addition of water to ethanoic acid to give 1,1,1-trihydroxyethane. Compare the value you obtain with a calculated ΔH^0 for the hydration of ethanal in the vapor phase. Would you expect the rate, the equilibrium constant, or both, for hydration of ethanoic acid in water solution to be increased in the presence of a strong acid such as sulfuric acid? Explain.

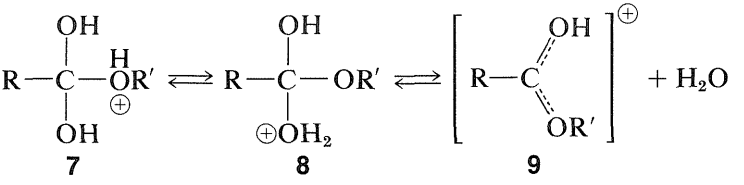
18-3A Esterification

Esters, RCO_2R', are formed from carboxylic acids and alcohols in the presence of acid catalysts. The key step in esterification is the nucleophilic attack of a neutral alcohol molecule, R′OH, at the carbonyl carbon of the conjugate acid of the carboxylic acid, $RC(OH)_2^{\oplus}$, **6**:



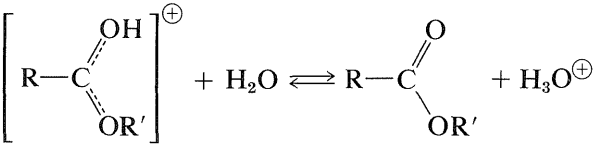
6 **7**

The intermediate, **7**, either can revert to the starting materials or form a second intermediate, **8**, by proton transfer. Loss of water from **8** leads to the conjugate acid of the ester, **9**:



7 **8** **9**

The final step in formation of the ester is proton transfer from **9** to the solvent:

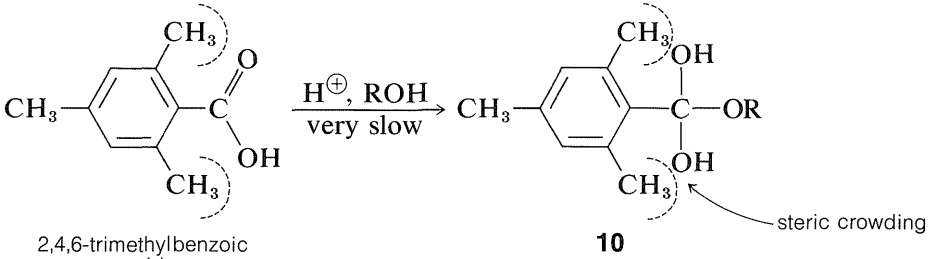


9

All the steps in ester formation are reversible, but the equilibrium in the C–O bond-making and -breaking processes are not very favorable, and an excess of one reactant (usually the alcohol) or removal of one product (most often water) is required to give a good yield of ester.

The usefulness of direct ester formation from alcohols and acids is limited to those alcohols or acids that do not undergo extensive side reactions in the presence of strong acids. Furthermore, if the alcohol is particularly bulky the reaction usually will not proceed satisfactorily because the intermediates **7** and **8** (as well as the product) are rendered unstable by crowding of the substituent groups.

Bulky groups in the esterifying acid also hinder the reaction. A classic example is 2,4,6-trimethylbenzoic (mesitoic) acid, which cannot be esterified readily under normal conditions because the methyl groups *ortho* to the carboxyl group make the transition state for formation of the intermediate **10** less favorable relative to the starting acid than would be the case for less hindered acids, such as ethanoic acid:



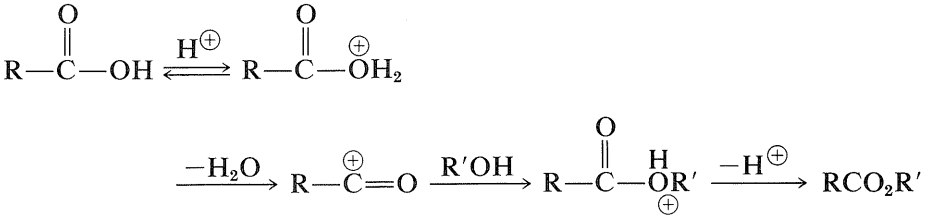
2,4,6-trimethylbenzoic acid

10

The important point is the *difference* in steric hindrance between the acid and the intermediate. If you make a scale model you will see that in the acid, the

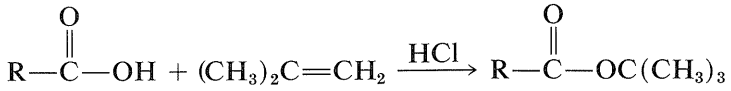
carboxyl group, being planar, can have reduced hindrance by turning about its bond to the ring so as to be between the methyl groups. However, no such relief is possible with **10**, in which the $-C(OH)_2OR$ carbon is tetrahedral.

Esterification of acids with bulky substituents, such as 2,4,6-trimethylbenzoic acid, can be achieved through formation of acyl cations. This is done by simply dissolving the carboxylic acid in strong sulfuric acid, whereby the acyl cation **11** is formed, and then pouring the solution into an excess of cold alcohol (see also Equations 18-5 and 18-6). This procedure works because it avoids the formation of a hindered tetrahedral intermediate similar to **10** and instead forms the conjugate acid directly:



11

Esterification of carboxylic acids with bulky alcohols is unsatisfactory. However, tertiary alkyl esters often can be prepared by addition of the acid to the appropriate *alkene* using an acid catalyst:



The success of such addition reactions depends on formation of a stable carbocation from the alkene under conditions where the most reactive nucleophile present is the carboxylic acid.

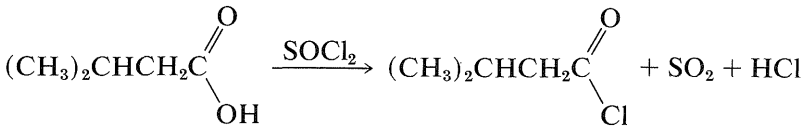
Exercise 18-10 Predict the outcome of an attempted esterification of ethanoic acid with *tert*-butyl alcohol in the presence of dry HCl.

Exercise 18-11 What would you expect to happen to the ^{18}O label in a mixture of ethanoic acid, hydrochloric acid, and $H_2{}^{18}O$? Explain.

Exercise 18-12 Benzoic acid is not esterified by the procedure that is useful for 2,4,6-trimethylbenzoic acid because, when benzoic acid is dissolved in sulfuric acid, it gives the conjugate acid and no acyl cation. Explain why the acyl cation, **11**, of 2,4,6-trimethylbenzoic acid might be more stable, relative to the conjugate acid of 2,4,6-trimethylbenzoic acid, than $C_6H_5CO^{\oplus}$ is, relative to the conjugate acid of benzoic acid. (Among other factors, consider the geometries of the various species involved.)

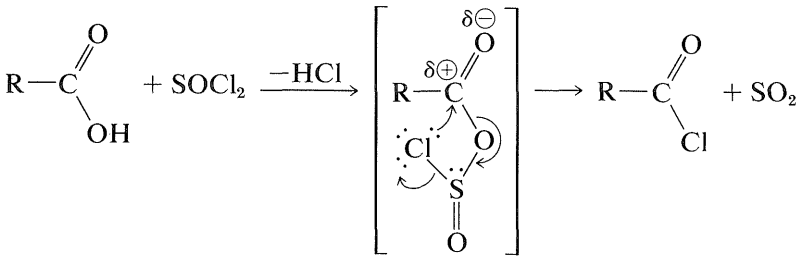
18-3B Acyl Chloride Formation

Carboxylic acids react with phosphorus trichloride, phosphorus pentachloride, or thionyl chloride with replacement of OH by Cl to form acyl chlorides, RCOCl:



3-methylbutanoic acid — 3-methylbutanoyl chloride

Although detailed mechanisms have not been established, the first step is thought to be formation of an unstable mixed anhydride, which then extrudes SO_2 and "collapses" with attack of chloride at the carbonyl carbon. A similar mechanism occurs in the formation of alkyl chlorides from alcohols and thionyl chloride (Section 15-5A):

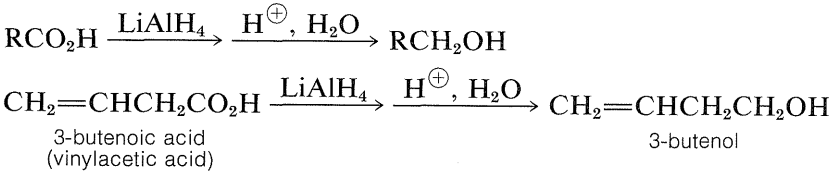


mixed anhydride of carboxylic and chlorosulfinic acids

Most acyl halides are stable, distillable liquids. However, methanoyl chloride, HCOCl, decomposes to carbon monoxide and hydrogen chloride at room temperature.

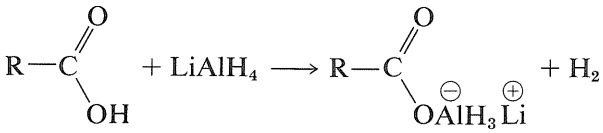
18-3C Reduction of Carboxylic Acids

Generally, carboxylic acids are difficult to reduce either by catalytic hydrogenation or by sodium and alcohol. Nonetheless, reduction to primary alcohols proceeds smoothly with lithium aluminum hydride, $LiAlH_4$:



3-butenoic acid (vinylacetic acid) — 3-butenol

The first step in lithium aluminum hydride reduction of carboxylic acids is formation of a complex aluminum salt of the acid and hydrogen:



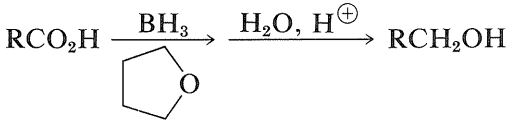
Reduction then proceeds by successive transfers of hydride ion, $H:^{\ominus}$, from aluminum to carbon. The first such transfer reduces the acid salt to the oxidation level of the aldehyde; reduction does not stop at this point, however, but continues rapidly to the alcohol. Insufficient information is available to permit very specific structures to be written for the intermediates in the lithium aluminum hydride reduction of carboxylic acids. However, the product is a complex aluminum alkoxide, from which the alcohol is freed by hydrolysis:

$$4RCO_2H + 3LiAlH_4 \longrightarrow [(RCH_2O)_4\overset{\ominus}{Al}]\overset{\oplus}{Li} + 4H_2 + 2LiAlO_2$$

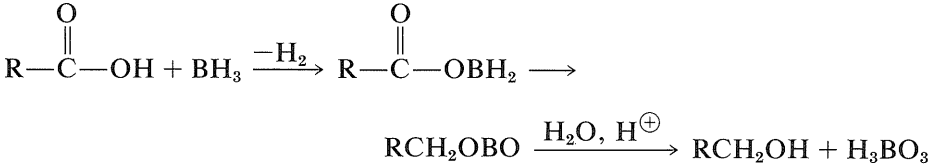
$$\downarrow H_2O,\ HCl$$

$$4RCH_2OH + AlCl_3 + LiCl$$

Sodium borohydride, $NaBH_4$, is too mild a reducing agent to transfer hydride to carboxylic acids, and one may suspect that borane, BH_3, also would be ineffective. However, this is not the case and borane in oxacyclopentane (tetrahydrofuran) reduces carboxylic acids more rapidly than it adds to alkene double bonds (see Table 16-5):

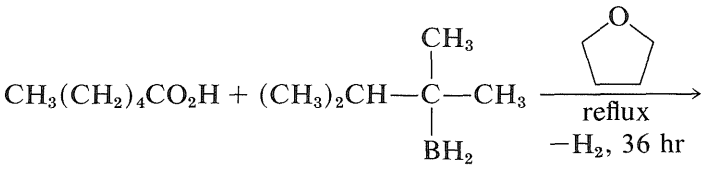


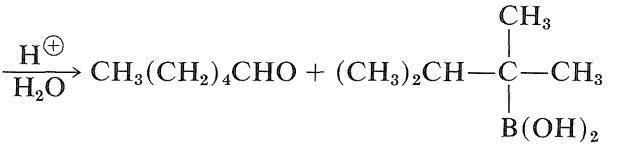
The reason for the high reactivity lies in the fact that the acid first converts the borane to an acyloxyborane, which then undergoes an intramolecular rearrangement in which the carbonyl group is reduced. Hydrolysis gives the alcohol:



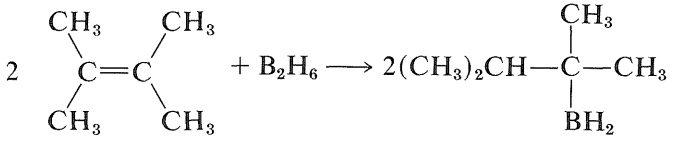
Special methods are required for the direct reduction of RCO_2H to RCHO. Aldehydes can be obtained directly by the slow reduction of carboxylic acids with 2,3-dimethyl-2-butylborane in oxacyclopentane solution.

One hydrogen of the borane is wasted through reaction with the acidic hydrogen of the carboxyl group to give hydrogen. An example is



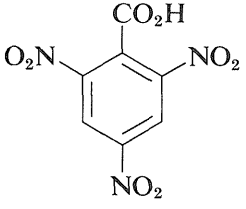


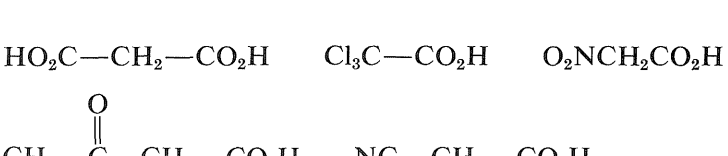
The borane is prepared through the addition of B_2H_6 to 2,3-dimethyl-2-butene and, because of steric hindrance, only the monoalkylborane is formed (Section 11-6A):



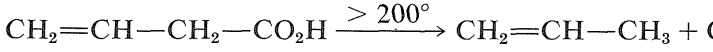
18-4 DECARBOXYLATION OF CARBOXYLIC ACIDS

The decarboxylation of RCO_2H to give RH and CO_2 can be calculated from bond energies and the stabilization energy of the carboxyl group to have $\Delta H^0 = -7$ kcal mole^{-1}. This does not mean that the reaction goes easily. Special structural features are required. The simple aliphatic carboxylic acids do not lose carbon dioxide on heating, but when there are strongly electron-attracting groups attached to the α carbon, decarboxylation often proceeds readily at 100–150°. Examples include

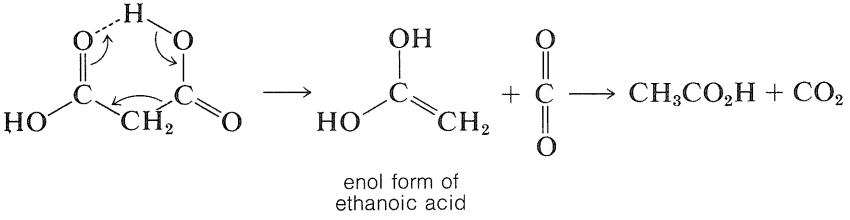




3-Butenoic acid also undergoes decarboxylation but has to be heated to above 200°:



The mechanisms of thermal decarboxylation probably are not the same for all cases, but when the acid has a *double-bonded* function such as O=C, N=C, O=N, or C=C attached to the α carbon then a cyclic elimination process appears to occur. For propanedioic acid the process is



enol form of ethanoic acid

Exercise 18-13 Predict the product of decarboxylation of 2-methyl-3-butenoic acid.

Exercise 18-14 Explain why decarboxylation of 2,2-dimethyl-3-oxobutanoic acid, $CH_3COC(CH_3)_2CO_2H$, in the presence of bromine gives 3-methyl-3-bromo-2-butanone, $CH_3COC(CH_3)_2Br$.

Stepwise decarboxylation also occurs, particularly in reactions in which the carboxylate radical ($RCO_2\cdot$) is formed. This radical usually decomposes to a hydrocarbon radical ($R\cdot$) and CO_2. The overall decarboxylation product is determined by what $R\cdot$ reacts with: If a good hydrogen donor is present, RH is formed; if a halogen donor such as Br_2 is present, RBr is formed:

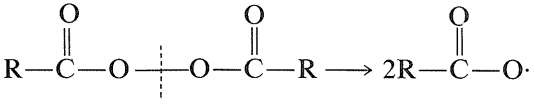
$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

$$R\cdot + R'H \longrightarrow RH + R'\cdot$$

$$R\cdot + Br_2 \longrightarrow RBr + Br\cdot$$

Exercise 18-15 What information would you need to calculate ΔH^0 for the reaction $CH_3CO_2\cdot \longrightarrow CO_2 + \cdot CH_3$?

Carboxylate radicals can be generated in several ways. One is the thermal decomposition of diacyl peroxides, which are compounds with rather weak O–O bonds:



Another method involves electrolysis of sodium or potassium carboxylate solutions, known as **Kolbe electrolysis,** in which carboxylate radicals are formed by transfer of an electron from the carboxylate ion to the anode. Decarboxylation may occur simultaneously with, or subsequent to, the formation of carboxylate radicals, leading to hydrocarbon radicals, which subsequently dimerize:

$$RCO_2^{\ominus} \longrightarrow RCO_2\cdot + e^{\ominus} \qquad \text{anode reaction}$$

$$e^{\ominus} + H_2O \longrightarrow \overset{\ominus}{OH} + \tfrac{1}{2}H_2 \qquad \text{cathode reaction}$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$

$$R\cdot + R\cdot \longrightarrow RR$$

An example is

$$2CH_3O_2C(CH_2)_8\overset{\ominus}{C}O_2 \xrightarrow[-2CO_2]{-2e^{\ominus}} CH_3O_2C(CH_2)_{16}CO_2CH_3 \qquad 70\%$$

Exercise 18-16 Why does Kolbe electrolysis not give RH by the reaction

$$RCO_2\cdot \xrightarrow{-CO_2} R\cdot \xrightarrow{H_2O} RH?$$

Exercise 18-17* At higher voltages than normally used in the Kolbe electrolysis, salts of carboxylic acids in hydroxylic solvents produce (at the anode) *alcohols* and *esters* of the type ROH and RCO_2R. Explain how this can occur.

Decarboxylation of the silver salts of carboxylic acids in the presence of bromine or chlorine, the **Hunsdiecker reaction,** often is useful for the synthesis of alkyl halides:

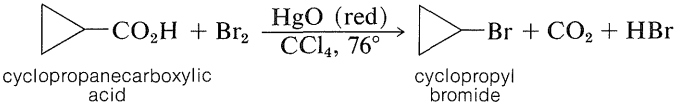
$$\underset{\substack{\text{silver salt of}\\ \text{phenylethanoic acid}}}{C_6H_5CH_2CO_2Ag} + Br_2 \xrightarrow[76^\circ]{\text{dry } CCl_4} \underset{\substack{\text{phenylmethyl}\\ \text{bromide}}}{C_6H_5CH_2Br} + CO_2 + AgBr$$

The mechanism of this reaction seems to involve formation of carboxylate radicals through decomposition of an acyl hypobromite intermediate, **12**:

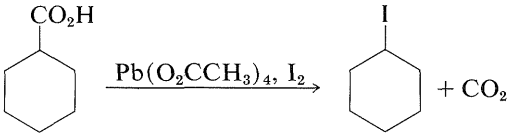
$$RCO_2Ag + Br_2 \xrightarrow{-AgBr} \underset{\textbf{12}}{R{-}C(=O){-}OBr} \longrightarrow R{-}C(=O){-}O\cdot + Br\cdot$$

$$RBr + CO_2 \longleftarrow R\cdot + CO_2 + Br\cdot$$

The Hunsdiecker reaction has certain disadvantages, mainly because it requires use of the pure *dry* silver salt, which is often difficult to prepare. With some acids, however, excellent results can be obtained using the acid itself and an excess of red mercuric oxide in place of the silver salt,



or by heating the acid with lead tetraethanoate, $Pb(O_2CCH_3)_4$, and iodine,



A somewhat similar decarboxylation reaction with formation of an alkene can be achieved by heating a carboxylic acid with lead tetraethanoate, $Pb(O_2CCH_3)_4$, in the presence of a catalytic amount of $Cu(OCH_3)_2$. A useful example is

$$HO_2C(CH_2)_6CO_2H + Pb(O_2CCH_3)_4 \xrightarrow{Cu(OCH_3)_2} CH_2{=}CH(CH_2)_4CO_2H + CO_2 + 2HO_2CCH_3 + Pb(O_2CCH_3)_2$$

There is some competing decarboxylation of the ethanoic acid, but the conversions in this kind of reaction are usually good. The key steps in the reaction probably are exchange of carboxylic acid groups on tetravalent lead, cleavage of the Pb–O bond to give the carboxylate radical, decarboxylation, oxidation of the alkyl radical by Cu(II) to give the cation [$R\cdot + Cu(II) \longrightarrow R^{\oplus} + Cu(I)$], and finally loss of a proton to form the alkene.

Exercise 18-18* Write a sequence of mechanistic steps that embody the suggestions given for conversion of $HO_2C(CH_2)_6CO_2H$ to $CH_2{=}CH(CH_2)_4CO_2H$ with $Pb(O_2CCH_3)_4$ and $Cu(OCH_3)_2$ as a catalyst. Complete the steps necessary to give all of the products and regenerate the catalyst. The role of Cu(II) in the oxidation of radicals is discussed briefly in Section 23-10B.

18-5 REACTIONS AT THE ALPHA CARBONS OF CARBOXYLIC ACIDS

18-5A Halogenation

Bromine reacts smoothly with carboxylic acids in the presence of small

quantities of phosphorus to form alpha-bromocarboxylic acids (**Hell-Volhard–Zelinsky reaction**):

$$CH_3CH_2COOH + Br_2 \xrightarrow{P} \underset{\text{2-bromopropanoic acid}}{CH_3CHBrCOOH} + HBr$$

The reaction is slow in the absence of phosphorus, whose function appears to be to form phosphorus tribromide, which then reacts with the acid to give the acyl bromide:

$$2P + 3Br_2 \longrightarrow 2PBr_3$$

$$CH_3CH_2CO_2H + PBr_3 \longrightarrow CH_3CH_2COBr + POBr + HBr$$

Formation of the acyl bromide speeds up the reaction because acid-catalyzed enolization of the acyl bromide occurs much more readily than enolization of the parent acid. Bromine probably reacts with the enol of the acyl bromide in the same way as it reacts with the enols of ketones (Section 17-2A).

The final step is the formation of the α-bromo acid by bromine exchange between the α-bromoacyl bromide and the parent acid; the acyl bromide, which is necessary for continued reaction, is thus regenerated:

$$CH_3CHBrC(=O)Br + CH_3CH_2CO_2H \longrightarrow CH_3CH_2C(=O)Br + CH_3CHBrCO_2H$$

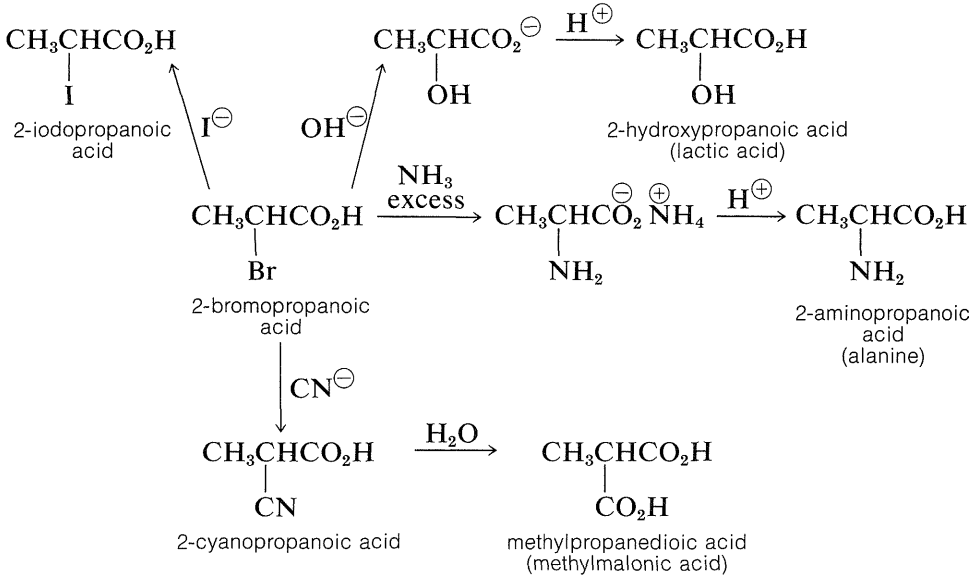
This bromination reaction results exclusively in alpha substitution and therefore is limited to carboxylic acids with α hydrogens. Chlorine with a trace of phosphorus reacts similarily but with less overall specificity, because concurrent free-radical chlorination can occur at all positions along the chain (as in hydrocarbon halogenation; see Section 4-6A).

Exercise 18-19 Write the steps in the phosphorus-catalyzed bromination of propanoic acid and explain why propanoyl bromide is expected to undergo acid-catalyzed bromination more readily than propanoic acid. (Review Section 17-1.)

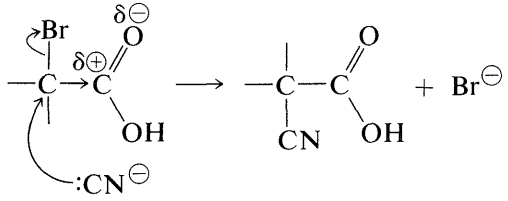
18-5B Substitution Reactions of α-Haloalkanoic Acids

The halogen of an α-haloalkanoic acid is replaced readily by nucleophilic reagents such as $CN^{\ominus}$, $OH^{\ominus}$, $I^{\ominus}$, and NH_3. Thus a variety of α-substituted

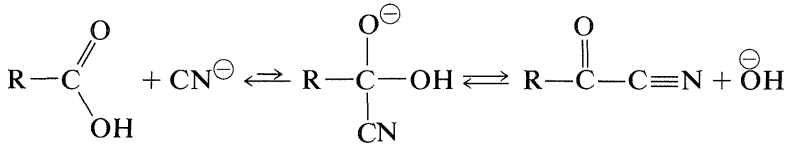
carboxylic acids may be prepared by reactions that are analogous to S_N2 substitution of alkyl halides:



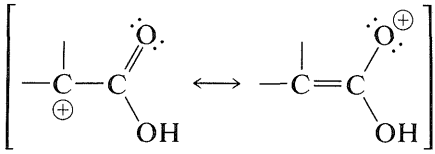
Facile S_N2 substitution reactions of halogens are expected from the electron-attracting characteristics of the neighboring carbonyl function, which should make the transition state for attack by a nucleophilic reagent more favorable:



Perhaps it may seem surprising that the carboxyl carbon is not attacked by the nucleophilic agents, because we have stressed earlier the susceptibility of carbonyl groups to nucleophilic reagents. No stable product results, however, from addition to the carbonyl group by the type of reagents considered here. Thus with cyanide ion the equilibrium constant for addition is unfavorable because of the associated loss of stabilization energy of the carboxyl group (see Exercise 18-9):



The S_N1 reactivity of α-haloalkanoic acids is particularly low. This is reasonable because formation of a cationic center at the α carbon should be difficult, because of the positive character of the carbonyl carbon. Furthermore, little, if any, help could be expected through electron delocalization because the corresponding valence-bond structure has a *positive,* single-bonded oxygen:



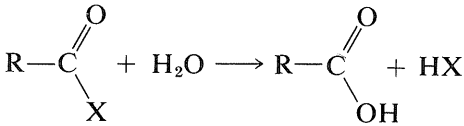
unfavorable

Similar considerations apply to the S_N1 and S_N2 reactions of α-halo aldehydes and α-halo ketones (Section 17-2C).

Exercise 18-20* Optically active sodium 2-bromopropanoate is converted to sodium 2-hydroxypropanoate in water solution. The product has the *same* stereochemical configuration at C2 as the starting material and the reaction rate is *independent* of added $OH^{\ominus}$ at moderate concentrations. At higher concentrations of $OH^{\ominus}$, the rate becomes *proportional* to the $OH^{\ominus}$ concentration and the 2-hydroxypropanoate formed has the *opposite* configuration to the starting material. Write appropriate mechanisms to explain these facts. Give your reasoning. (It may be helpful to review Sections 8-5 and 15-11.)

18-6 FUNCTIONAL DERIVATIVES OF CARBOXYLIC ACIDS

A **functional derivative** of a carboxylic acid is a substance formed by replacement of the hydroxyl group of the acid by some other group, X, such that it can be hydrolyzed back to the acid in accord with Equation 18-7:



(18-7)

By this definition, an amide, $RCONH_2$, but not a ketone, $RCOCH_3$, is a functional derivative of a carboxylic acid. Several derivatives of carboxylic acids are given in Table 18-3, and methods for preparation of these derivatives are summarized in Tables 18-6 and 18-7 at the end of the chapter.

Table 18-3
Functional Derivatives of Carboxylic Acids

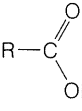
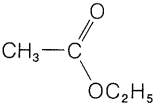
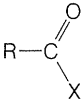
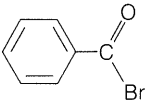
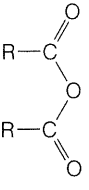
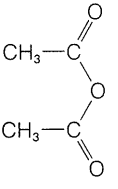
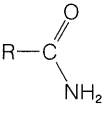
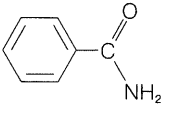
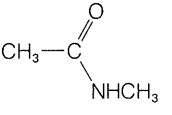
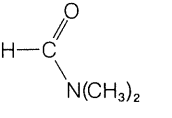
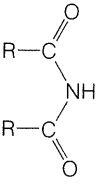
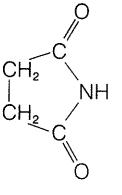
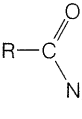
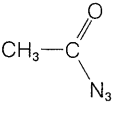
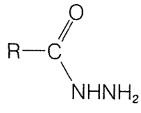
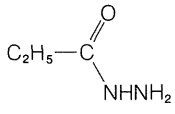
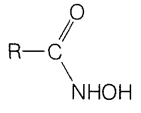
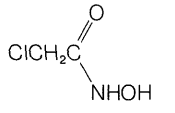
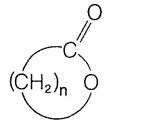
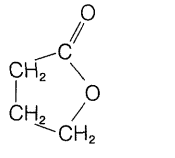
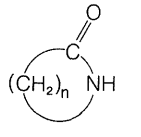
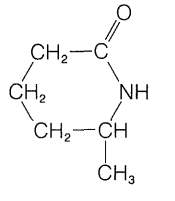
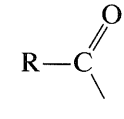
Derivative	Structure	Example	
		Structure	Name
esters			ethyl ethanoate (ethyl acetate)
acyl halides	 X = F, Cl, Br, I		benzenecarbonyl bromide (benzoyl bromide)
anhydrides			ethanoic anhydride (acetic anhydride)
amides (primary)			benzenecarboxamide (benzamide)
amides (secondary and tertiary)			*N*-methylethanamide (*N*-methylacetamide)
			*N*,*N*-dimethylmethanamide (*N*,*N*-dimethylformamide)
imides			butanimide (azacyclopenta-2,5-dione, succinimide)
acyl azides			ethanoyl azide (acetyl azide)

Table 18-3 (continued)
Functional Derivatives of Carboxylic Acids

Derivative	Structure	Example Structure	Example Name
hydrazides			diazanylethanone[a] (propionohydrazide)
hydroxamic acids			*N*-hydroxychloroethanamide (chloroacetylhydroxamic acid)
lactones (cyclic esters)	 most stable with $n = 3,4$		oxacyclopentan-2-one (γ-butyrolactone)
lactams (cyclic amides)	 most stable with $n = 3,4$		6-methylazacyclohexan-2-one (δ-caprolactam)

[a]This is a recommended but not widely used name. Without some thought, few organic chemists currently could write the proper structure that corresponds to it.

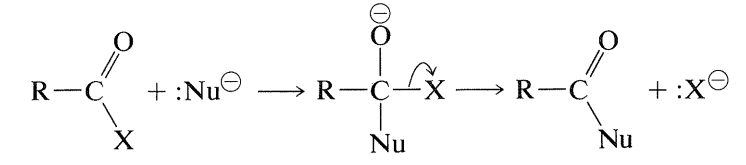
The common structural feature of the compounds listed in Table 18-3 is the acyl group  . However, nitriles, RC≡N, often are considered to be acid derivatives, even though the acyl group is not present as such, because hydrolysis of nitriles leads to carboxylic acids:

$$\underset{\text{ethanenitrile (acetonitrile)}}{CH_3C{\equiv}N} + 2H_2O \xrightarrow{H^{\oplus}} \underset{\text{ethanoic acid (acetic acid)}}{CH_3COOH} + NH_3$$

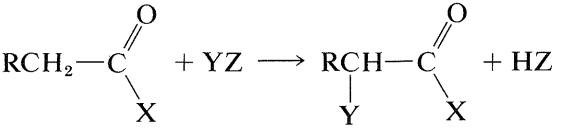
The chemistry of nitriles will be discussed in Section 24-5.

Exercise 18-21 The following substances have boiling points as indicated:
ethyl ethanoate (77°) ethanoic acid (118°)
ethanoic anhydride (140°) ethanamide (221°)
Account for these differences on the basis of molecular weight and hydrogen bonding.

The two main types of reactions of carboxylic acid derivatives with which we now shall be concerned are the replacement of X by attack of a nucleophile $:Nu^{\ominus}$ at the carbonyl carbon with subsequent cleavage of the C–X bond (Equation 18-8), and substitution at the α carbon facilitated by the carbonyl group (Equation 18-9):



(18-8)

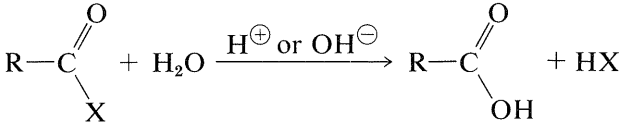


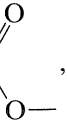
(18-9)

18-7 REACTIONS AT THE CARBONYL CARBON OF ACID DERIVATIVES

18-7A Displacement Reactions

Hydrolysis of most acid derivatives to the parent acids is acid- or base-catalyzed:

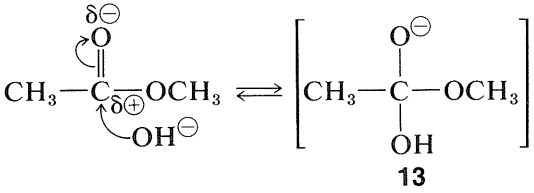


X = halogen, —OR,  , —NH_2, etc.

However, acyl halides and anhydrides usually hydrolyze rapidly without the aid of an acidic or basic catalyst, when *in solution.* It is important to recognize that an insoluble acyl halide or anhydride often reacts slowly with water.

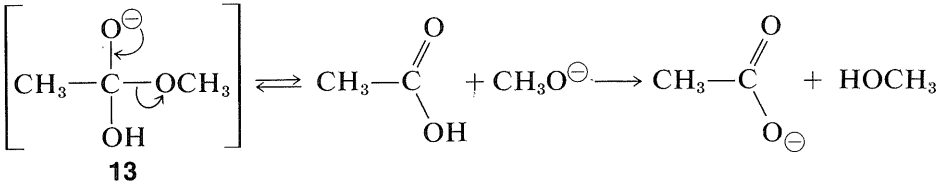
Esters and amides hydrolyze much more slowly, and for useful rates require a catalyst. The hydrolysis of amides is of exceptional importance in biochemistry and will be discussed in more detail in Chapters 24 and 25.

Acid-catalyzed hydrolysis of esters is the reverse of acid-catalyzed ester formation discussed previously. *Base-induced ester hydrolysis* (**saponification**) *is an irreversible reaction.* The initial step is the attack of hydroxide ion at the carbonyl carbon:



13

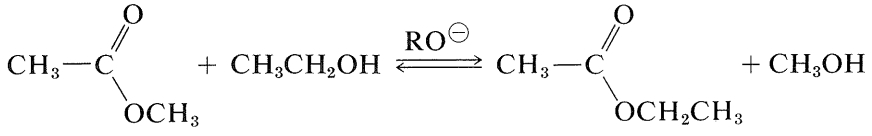
The intermediate anion, **13**, so formed then either loses $OH^{\ominus}$ and reverts to the original ester, or it loses $CH_3O^{\ominus}$ to form the acid. The overall reaction is irreversible because once the acid is formed, it immediately is converted to the carboxylate anion, which is stabilized to such a degree that it is not attacked by the alcohol and will not reform the starting ester. Consequently, the reaction goes to completion in the direction of hydrolysis:



13

Exercise 18-22 Why is a carboxylate anion more resistant to attack by nucleophilic agents, such as CH_3OH or $CH_3O^{\ominus}$, than is the corresponding ester?

Ester interchange is closely related to ester hydrolysis. This is a base-catalyzed reaction that is useful to replace the alcohol group of an ester with a different alcohol group. The catalyst is alkoxide ion and the equilibrium constant is close to unity, unless the alcohols differ greatly in size. An example is

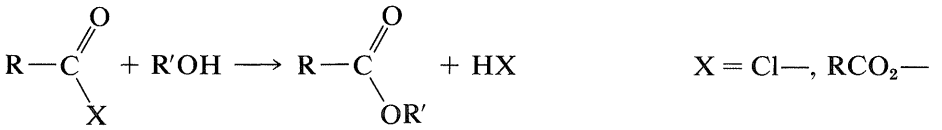


in which $RO^{\ominus}$ is either $CH_3O^{\ominus}$ or $CH_3CH_2O^{\ominus}$.

Exercise 18-23 **a.** Develop a mechanism for ester interchange between ethanol and methyl ethanoate catalyzed by alkoxide that is consistent with the mechanism of base-induced ester hydrolysis.
b. Why doesn't it matter whether one uses methoxide or ethoxide as the catalyst?
c. If one used D-2-butyl ethanoate as the starting ester and methanol as the exchanging alcohol, what would be the configuration of the 2-butanol formed with methoxide as a catalyst?

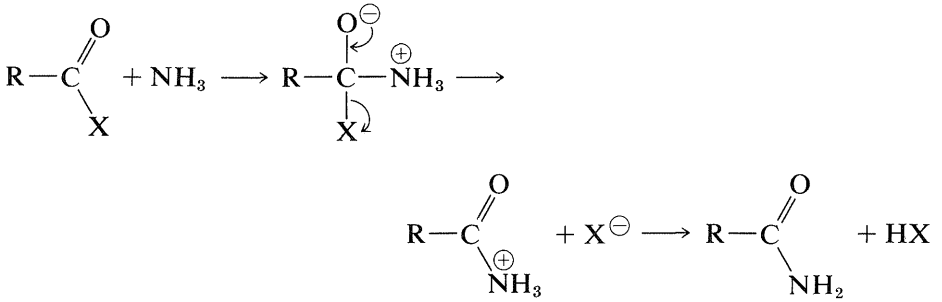
Exercise 18-24 Ester interchange also can proceed (but more slowly) with an acidic instead of a basic catalyst. Write a mechanism for this reaction consistent with acid-catalyzed ester formation (Section 18-3A).

The formation of esters from acid chlorides and anhydrides according to the following equation has been discussed:



$X = Cl—, RCO_2—$

Amides can be obtained from acyl halides, carboxylic anhydrides, or esters with amines or ammonia. The mechanisms of these reactions are very similar to the corresponding reactions of alcohols:



$X = Cl—, RCO_2—, R'O—$

We will discuss this kind of reaction further in Chapters 24 and 25.

Exercise 18-25 By analogy with the reaction mechanisms already discussed, propose a mechanism for each of the following reactions:

a. $C_6H_5CO_2CH_3 + C_2H_5OH \xrightarrow{H^\oplus} C_6H_5CO_2C_2H_5 + CH_3OH$
b. $CH_3COCl + CH_3CH_2OH \longrightarrow CH_3CO_2CH_2CH_3 + HCl$
c. $(CH_3CO)_2O + CH_3OH \xrightarrow{H^\oplus} CH_3CO_2CH_3 + CH_3CO_2H$

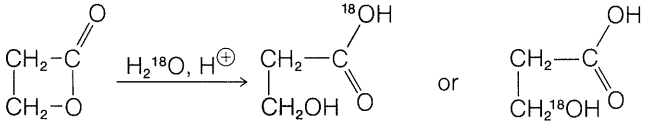
d. $CH_3CONH_2 + H_3O^{\oplus} \xrightarrow{H_2O} CH_3CO_2H + NH_4^{\oplus}$

e. $CH_3CONH_2 + {}^{\ominus}OH \longrightarrow CH_3CO_2^{\ominus} + NH_3$

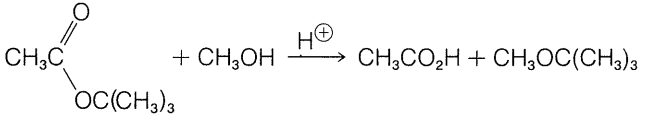
f. $CH_3COCl + 2NH_3 \longrightarrow CH_3CONH_2 + NH_4Cl$

g. $CH_3CO_2CH_3 + CH_3NH_2 \longrightarrow CH_3CONHCH_3 + CH_3OH$

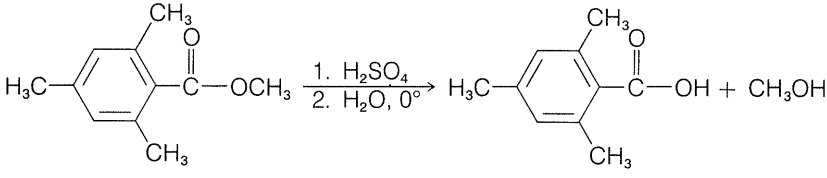
Exercise 18-26 What can you conclude about the mechanism of acid-catalyzed hydrolysis of oxacyclobutan-2-one (β-propiolactone) from the following equation:



Exercise 18-27 Write a plausible mechanism supported by analogy for the following reaction:

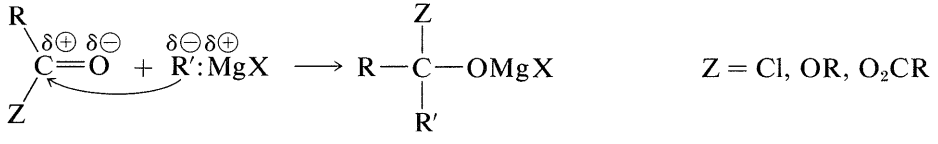


Exercise 18-28 Explain why the base-induced hydrolysis of methyl 2,4,6-trimethylbenzoate is unusually slow. Write a mechanism for the hydrolysis of methyl 2,4,6-trimethylbenzoate that occurs when the ester is dissolved in concentrated sulfuric acid and the solution poured into a mixture of ice and water (see Section 18-3A):

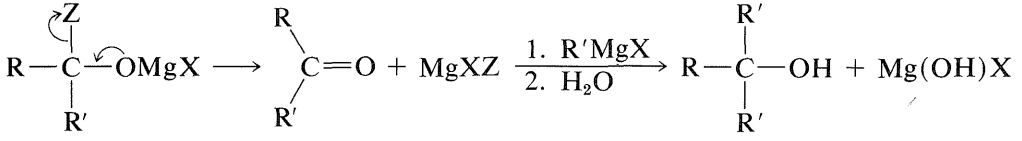


18-7B Reactions with Organometallic Compounds

The reactions of several carboxylic acid derivatives with organomagnesium and organolithium compounds were described in Section 14-12. The key step in these reactions is addition of the organometallic compound, as $R^{\delta\ominus}M^{\delta\oplus}$, to the carbonyl group. For a Grignard reagent,



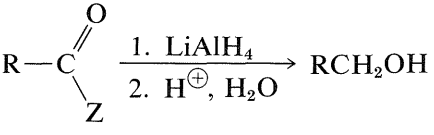
The reaction normally does not stop at this stage; MgXZ is eliminated and the resulting ketone rapidly reacts with another molecule of organometallic compound. On hydrolysis, a tertiary alcohol is formed with at least two identical alkyl groups on the tertiary carbon:



Exercise 18-29 Grignard reagents add to *N,N*-dialkylalkanamides, $RCONR_2'$, to give ketones after hydrolysis. With esters or acyl chlorides, a tertiary alcohol is the usual product. Explain why, on the basis of the stability of the RR'CZ(OMgX) intermediate, the amides may be expected to be less likely than esters or acyl chlorides to give tertiary alcohols. How could you use an *N,N*-dialkylalkanamide to prepare an aldehyde with the aid of a Grignard reagent?

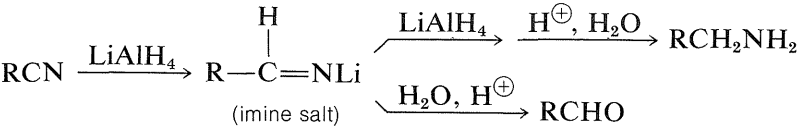
18-7C Reduction of Acid Derivatives

Esters, chlorides, and anhydrides are reduced by lithium aluminum hydride in the same general way as the parent acids (Section 18-3C), the difference being that no hydrogen is evolved. The products after hydrolysis are primary alcohols:



$Z = Cl, OR, O_2CR$

Nitriles can be reduced to amines by lithium aluminum hydride. An imine salt is an intermediate product; if the reaction is carried out under the proper conditions, this salt is the major product and provides an aldehyde on hydrolysis (see Section 16-4C):



Amides are reduced to primary amines, and *N*-substituted amides to secondary and tertiary amines:

$$\left.\begin{matrix}RCONH_2\\RCONHR'\\RCONR_2'\end{matrix}\right\} \xrightarrow[2.\ H^{\oplus},\ H_2O]{1.\ LiAlH_4} \left\{\begin{matrix}RCH_2NH_2\\RCH_2NHR'\\RCH_2NR_2'\end{matrix}\right.$$

Borane also will reduce esters, amides, and nitriles to the same products as does $LiAlH_4$, but with reduced reactivity (Table 16-6).

Although lithium aluminum hydride and boranes are very useful reagents, they are expensive and impractical to employ on a large scale. Other methods of reduction then may be necessary. Of these, the most important are reduction of esters with sodium and ethanol (acids do not react readily),

$$RCO_2R' + 4Na + 4C_2H_5OH \xrightarrow{C_2H_5OH} RCH_2OH + R'OH + 4C_2H_5O^{\ominus}Na^{\oplus}$$

and high-pressure hydrogenation over a copper chromite catalyst,

$$RCO_2R' + 2H_2 \xrightarrow[\text{copper chromite}]{200^\circ} RCH_2OH + R'OH$$

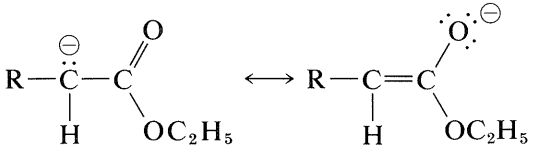
18-8 REACTIONS AT THE ALPHA CARBONS OF CARBOXYLIC ACID DERIVATIVES

18-8A The Acidic Properties of Esters with α Hydrogens

Many important synthetic reactions in which C–C bonds are formed involve esters and are brought about by basic reagents. This is possible because the α hydrogens of an ester, such as $RCH_2CO_2C_2H_5$, are weakly acidic, and a strong base, such as sodium ethoxide, can produce a significant concentration of the ester anion at equilibrium:

$$RCH_2CO_2C_2H_5 + C_2H_5O^{\ominus} \rightleftharpoons \overset{\ominus}{\ddot{C}}HCO_2C_2H_5 + C_2H_5OH$$

The acidity of α hydrogens is attributed partly to the electron-attracting inductive effects of the ester oxygens, and partly to resonance stabilization of the resulting anion (Section 17-1A):



When the α carbon of the ester carries a second strongly electron-attracting group, the acidity of α hydrogen is greatly enhanced. Examples of such compounds follow:

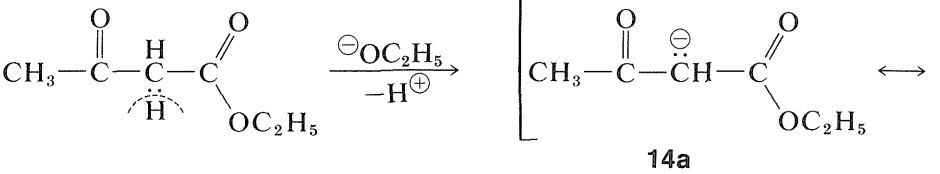
$O_2NCH_2CO_2C_2H_5$
ethyl nitroethanoate
(ethyl nitroacetate)
$pK_a = 5.8$

$C_2H_5O_2CCH_2CO_2C_2H_5$
diethyl propanedioate
(diethyl malonate)
$pK_a = 13.3$

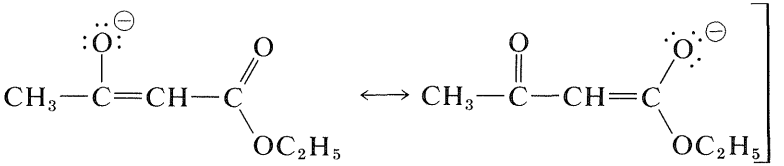
$N{\equiv}CCH_2CO_2C_2H_5$
ethyl cyanoethanoate
(ethyl cyanoacetate)
$pK_a \sim 13$

$CH_3COCH_2CO_2C_2H_5$
ethyl 3-oxobutanoate
(ethyl acetoacetate)
$pK_a = 10.7$

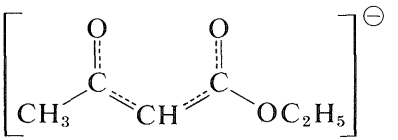
The stabilization of the anions of these specially activated esters is greater than for simple esters because of the electron-withdrawing inductive effects of the substituents but more importantly because the negative charge can be distributed over more than two centers. Thus for the anion of ethyl 3-oxobutanoate we can regard all three of the valence-bond structures, **14a** through **14c**, as important in contributing to the hybrid, **14**:



14a



14b **14c**



14

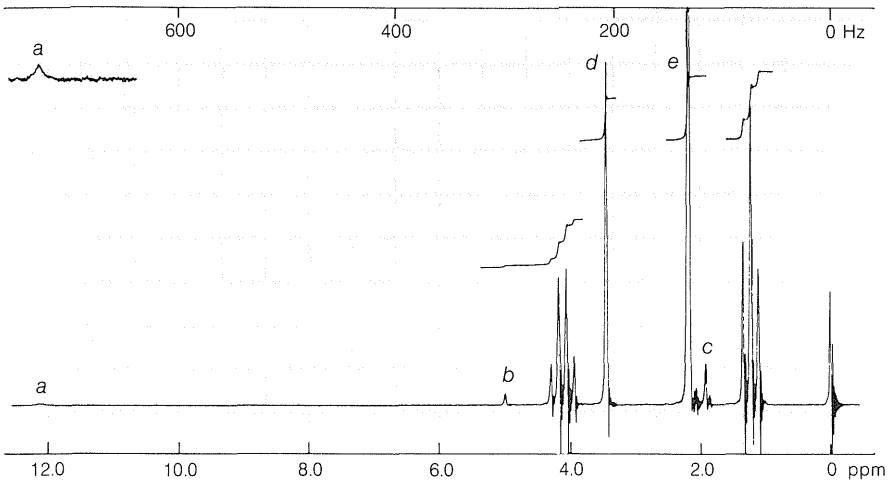
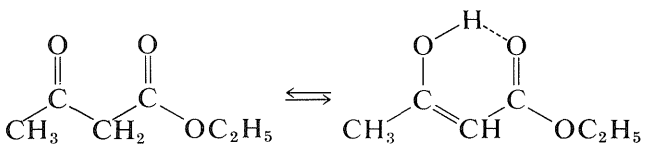


Figure 18-6 Proton nmr spectrum of ethyl 3-oxobutanoate (ethyl acetoacetate) at 60 MHz; calibrations are relative to tetramethylsilane at 0.00 ppm. Peaks marked *a*, *b*, and *c* are assigned, respectively, to the OH, alkenyl, and methyl protons of the enol form, whereas peaks *d* and *e* are assigned to the α-CH_2 and methyl protons, respectively, of the keto form. The quartet of lines at 4.2 ppm and the triplet at 1.3 ppm result from the ethyl groups of both keto and enol forms.

The anion, **14**, is sufficiently stable relative to the ester that the K_a is about 10^{-11} in water solution (Table 17-1).

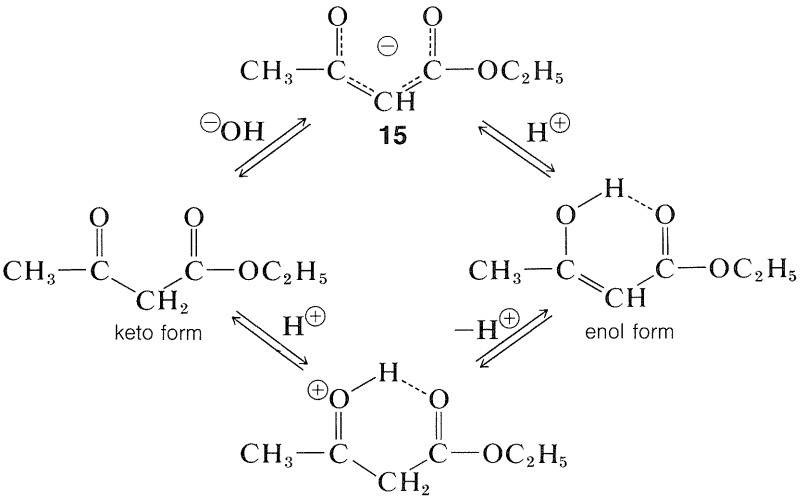
Ethyl 3-oxobutanoate exists at room temperature as an equilibrium mixture of keto and enol tautomers in the ratio of 92.5 to 7.5. The presence of enol can be shown by rapid titration with bromine, but is more evident from the proton nmr spectrum (Figure 18-6), which shows absorption of the hydroxyl, alkenyl, and methyl protons of the enol form, in addition to absorptions expected for the keto form:



keto form, 92.5% enol form, 7.5%

Interconversion of the enol and keto forms of ethyl 3-oxobutanoate is powerfully catalyzed by bases through the anion, **15**, and less so by acids

through the conjugate acid of the keto form:



Nonetheless, if contact with acidic and basic substances is rigidly excluded to the extent of using quartz equipment in place of glass (glass normally has a slightly alkaline surface), then interconversion is slow enough that it is possible to separate the lower-boiling enol from the keto form by fractional distillation under reduced pressure. The separated isomers are indefinitely stable when stored at −80° in quartz vessels.

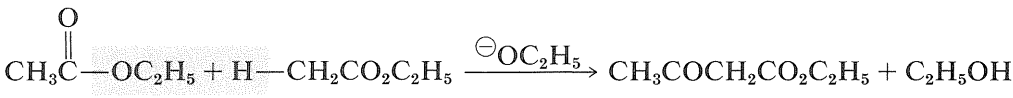
Exercise 18-30 Explain why 2,4-pentanedione can be expected to contain much more enol at equilibrium than does ethyl 3-oxobutanoate. How much enol would you expect to find in diethyl propanedioate? In 3-oxobutanal? Explain.

Exercise 18-31 Arguing from the factors that appear to regulate the ratio of C- to O-alkylation of enolate anions (Section 17-4), show how you could decide whether the reaction of the sodium enolate salt of ethyl 3-oxobutanoate with a strong acid would give, as the *initial* product, mostly the enol form, mostly the keto form, or the equilibrium mixture.

Exercise 18-32 When a small amount of sodium ethoxide is added to ethyl 3-oxobutanoate, the proton nmr peaks marked *a*, *b*, and *c* in Figure 18-6 disappear. Explain why this should be so. (You may wish to review Section 9-10E.)

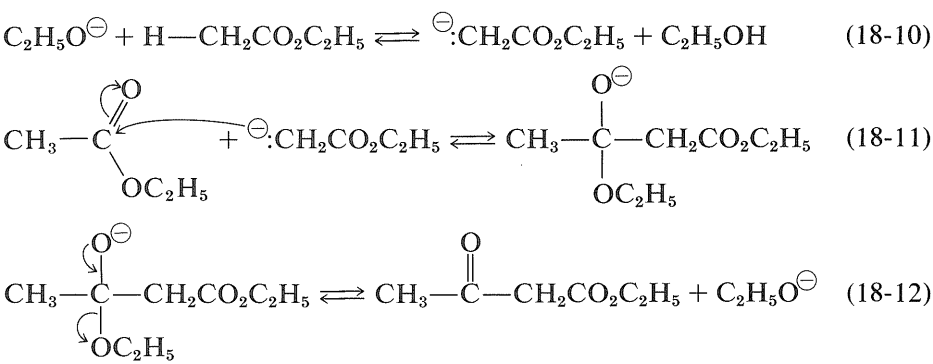
18-8B The Claisen Condensation

One of the most useful of the base-induced reactions of esters is illustrated by the self-condensation of ethyl ethanoate under the influence of sodium ethoxide to give ethyl 3-oxobutanoate:



This reaction, called the **Claisen condensation,** is interesting because, from consideration of bond and stabilization energies, it is expected to be unfavorable thermodynamically with ΔH^0 (vapor) equal to 6 kcal mole^{-1}. This expectation is realized in practice, and much effort has been expended to determine conditions by which practical yields of the condensation product can be obtained.

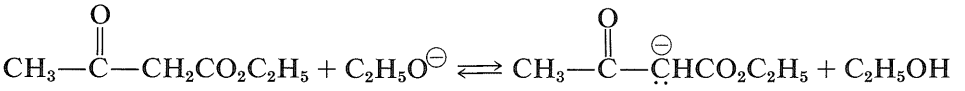
The Claisen condensation resembles *both* the aldol addition (Section 17-3) and carbonyl additions of acid derivatives discussed previously (Sections 16-4 and 18-7). The first step, as shown in Equation 18-10, is the formation of the anion of ethyl ethanoate which, being a powerful nucleophile, attacks the carbonyl carbon of a second ester molecule (Equation 18-11). Elimination of ethoxide ion then leads to the β-keto ester, ethyl 3-oxobutanoate (Equation 18-12):



The sum of these steps represents an unfavorable equilibrium, and satisfactory yields of the β-keto ester are obtained only if the equilibrium can be shifted by removal of one of the products.

One simple way of doing this is to remove the ethanol by distillation as it is formed; however, this may be difficult to carry to completion and, in any case, is self-defeating if the starting ester is low-boiling. Alternatively, one can use a large excess of sodium ethoxide. This is helpful because ethanol is a weaker acid than the ester enol, and *excess ethoxide shifts the equilibrium to*

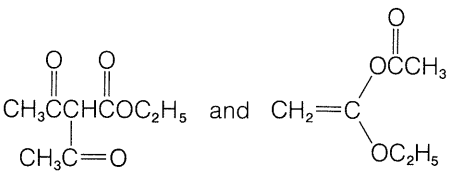
the right through conversion of the β-keto ester to the enolate salt (Equation 18-13).



(18-13)

Obviously, the condensation product must be recovered from the enol salt and isolated under conditions that avoid reversion to starting materials. The best procedure is to quench the reaction mixture by pouring it into an excess of cold dilute acid.

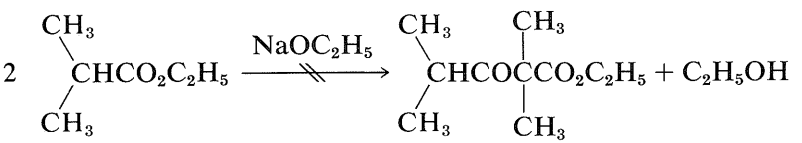
Exercise 18-33 Possible by-products of the Claisen condensation of ethyl ethanoate are



Explain how these products may be formed and why they are not formed in significant amounts.

Exercise 18-34 Ethanol has a K_a of 10^{-18} and ethyl 3-oxobutanoate has $K_a = 10^{-11}$. Calculate ΔG^0 for the reaction of sodium ethoxide with the ester as per Equation 18-13. (See Section 4-4A.)

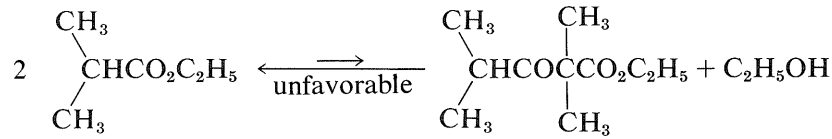
A limitation on the Claisen condensation is that although the starting ester need have only *one* α hydrogen for Reactions 18-10 through 18-12 to occur, *two* α hydrogens are necessary for a favorable equilibrium utilizing the ionization reaction of Equation 18-13. As a result, it is not surprising to find that ethyl 2-methylpropanoate fails to condense with itself in the presence of sodium ethoxide, because the condensation product has no α hydrogen next to the ester group:



ethyl 2-methylpropanoate

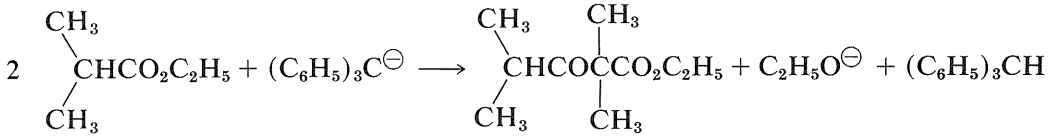
ethyl 2,2,4-trimethyl 3-oxopentanoate

However, if an excess of a very much stronger base than sodium ethoxide is used [such as triphenylmethylsodium, $(C_6H_5)_3C^{\ominus}Na^{\oplus}$], this same condensation does take place in reasonable yields. The reason is that the base is now strong enough to convert the alcohol formed in the reaction to sodium ethoxide, thus shifting the equilibrium to the right:

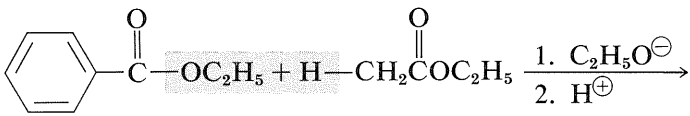


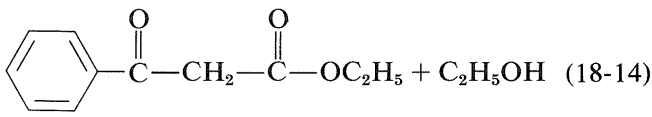
$$C_2H_5OH + (C_6H_5)_3C^{\ominus} \underset{\text{favorable}}{\rightleftharpoons} C_2H_5O^{\ominus} + (C_6H_5)_3CH$$

The overall reaction then is

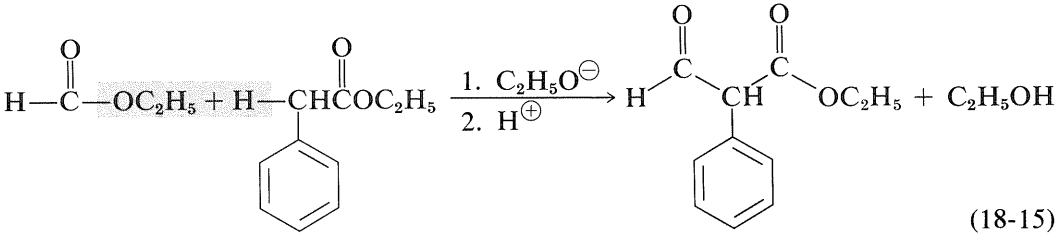


Claisen condensations can be carried out between two *different* esters but, because there are four possible products, mixtures often result. Less difficulty is encountered if one of the esters has no α hydrogen and reacts readily with a carbanion according to Equations 18-11 and 18-12. The reaction then has considerable resemblance to the mixed aldol additions discussed in Section 17-3C. Among the useful esters without α hydrogens, and with the requisite electrophilic reactivity, are those of benzenecarboxylic, methanoic, ethanedioic, and carbonic acids. Several practical examples of mixed Claisen condensations are shown in Equations 18-14 through 18-16 (all of the products exist to the extent of 10% or so as the enol forms):

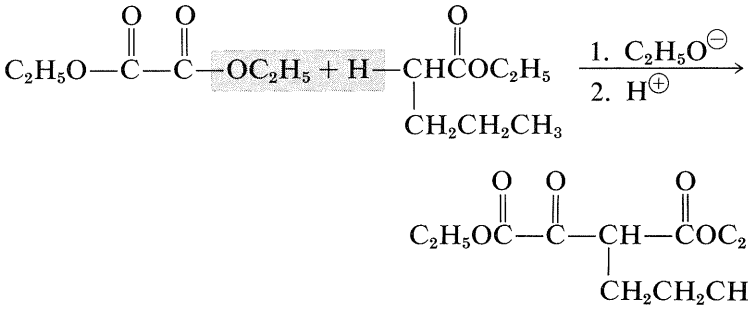




(18-14)

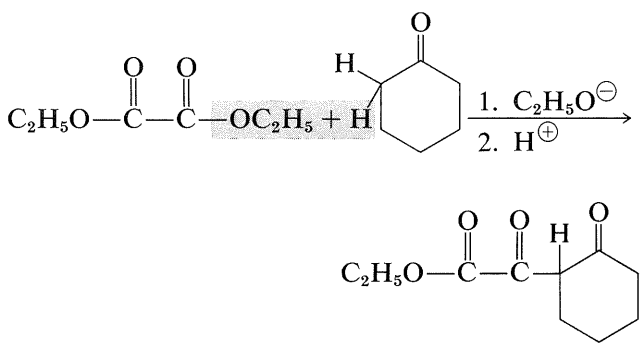


(18-15)



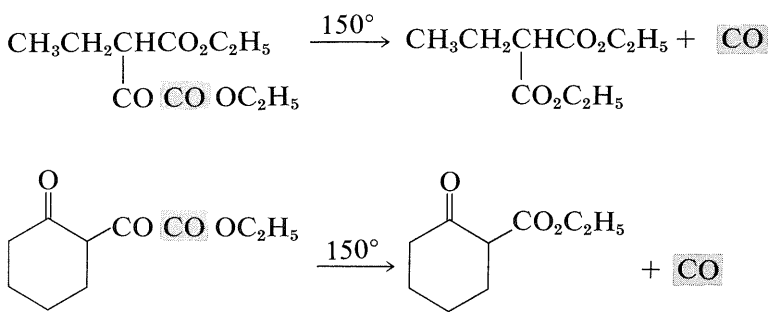
(18-16)

An important variation on the Claisen condensation is to use a ketone as the anionic reagent. This often works well because ketones usually are more acidic than simple esters and the base-induced self-condensation of ketones (aldol addition) is thermodynamically unfavorable (Section 17-3C). A typical example is the condensation of cyclohexanone with diethyl ethanedioate (diethyl oxalate):



(18-17)

α-Keto esters of the type formed according to Equations 18-16 and 18-17 have synthetic utility in that they lose carbon monoxide when strongly heated:



A somewhat similar decarbonylation reaction was mentioned previously for diphenylpropanetrione (Section 17-10).

Exercise 18-35 Write structures for all of the Claisen condensation products that reasonably may be expected to be formed from the following ester mixtures and sodium ethoxide:

a. ethyl ethanoate and ethyl propanoate
b. diethyl carbonate and 2-propanone
c. diethyl ethanedioate and ethyl 2,2-dimethylpropanoate

Exercise 18-36 Show how the following substances may be synthesized by Claisen-type condensations from the indicated starting materials. Specify the reagents and reaction conditions as completely as possible.

a. ethyl 2-methyl-3-oxopentanoate from ethyl propanoate
b. ethyl 2,4-dioxopentanoate from 2-propanone
c. diethyl 2-phenylpropanedioate from ethyl phenylethanoate
d. 2,4-pentanedione from 2-propanone
e. 2,2,6,6-tetramethyl-3,5-heptanedione from 3,3-dimethyl-2-butanone
f. ethyl 2,2-dimethyl-3-phenyl-3-oxopropanoate from 2-methylpropanoate.

Exercise 18-37 What advantages and disadvantages may sodium hydride (NaH) have as the base used in the Claisen condensation?

18-8C Alkylation of Ester Anions

The anions of esters such as ethyl 3-oxobutanoate and diethyl propanedioate can be alkylated with alkyl halides. These reactions are important for the synthesis of carboxylic acids and ketones and are similar in character to the alkylation of ketones discussed previously (Section 17-4A). The ester is converted by a strong base to the enolate anion, Equation 18-18, which then is alkylated in an S_N2 reaction with the alkyl halide, Equation 18-19. Usually, C-alkylation predominates:

$$CH_3COCH_2CO_2C_2H_5 + C_2H_5O^{\ominus} \rightleftharpoons CH_3C\overset{\ominus}{O}CHCO_2C_2H_5 + C_2H_5OH \qquad (18\text{-}18)$$

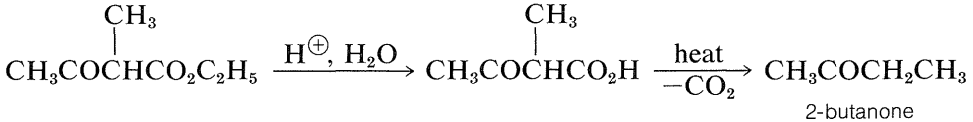
$$CH_3I + CH_3C\overset{\ominus}{O}CHCO_2C_2H_5 \longrightarrow CH_3COCHCO_2C_2H_5 + I^{\ominus} \qquad (18\text{-}19)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

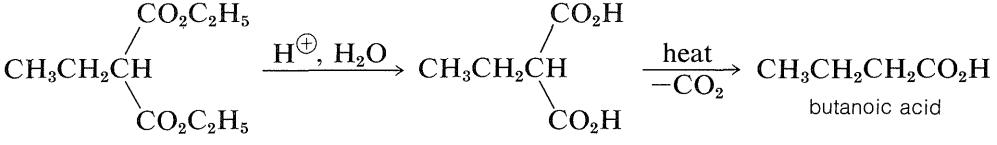
Esters of propanedioic (malonic) acid can be alkylated in a similar fashion (Equation 18-20):

$$H_2C\begin{<}{CO_2C_2H_5}{CO_2C_2H_5} \xrightarrow{NaOC_2H_5} \xrightarrow{CH_3CH_2Br} CH_3CH_2{-}CH\begin{<}{CO_2C_2H_5}{CO_2C_2H_5} \qquad (18\text{-}20)$$

Unfortunately, monoalkylation seldom occurs cleanly by the above sequence whenever the monoalkylation product has an α hydrogen located so as to permit dialkylation to occur. In practice, alkylation reactions, using one mole of ester, one mole of sodium ethoxide, and one mole of an alkyl halide (e.g., CH_3I), give a mixture of the starting ester, its mono- and dialkylation products. The situation is more favorable when large alkyl groups are introduced, because then the physical properties and reactivities of the starting materials and of mono- and dialkylation produces differ considerably. Usually dialkylation is inhibited by having a bulky alkyl group in the monoalkylation product.

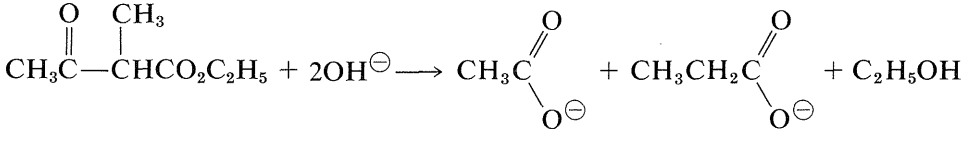
Alkyl-substituted 3-oxobutanoic and propanedioic esters can be hydrolyzed under acidic conditions to the corresponding acids, and when these are heated they readily decarboxylate (Section 18-4). *Alkyl 3-oxobutanoic esters thus yield methyl alkyl ketones, whereas alkylpropanedioic esters produce carboxylic acids:*





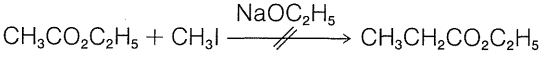
These reactions commonly are known as the **acetoacetic-ester ketone** and the **malonic-ester acid** syntheses, respectively.

Alkyl 3-oxobutanoic esters react with concentrated alkali by a *different* path to reverse the Claisen condensation:



(18-21)

Exercise 18-38 Why does the following reaction fail to give ethyl propanoate?



Exercise 18-39 Show a synthesis of 3-ethyl-2-pentanone from ethyl 3-oxobutanoate. What advantage would this route have over alkylation of 2-pentanone with sodium amide and ethyl iodide? (Section 17-4A.)

Exercise 18-40 How could you prepare diethyl methylpropanedioate that is *free* of diethyl propanedioate and diethyl dimethylpropanedioate? (Review Section 18-8B to find an alternative synthesis not involving alkylation.)

Exercise 18-41 Show how one could prepare cyclobutanecarboxylic acid from diethyl propanedioate and a suitable dihalide.

Exercise 18-42 Write a mechanism based on analogy with other reactions in this chapter that will account for the strong alkali-induced cleavage of ethyl 2-methyl-3-oxobutanoate in accord with Equation 18-21.

18-8D Acylation of Ester Anions

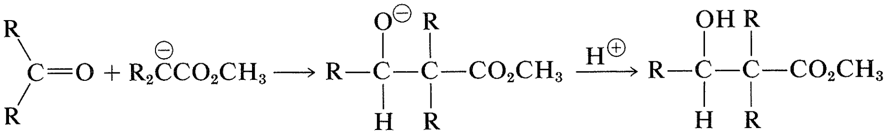
Enolate anions of esters, such as ethyl 3-oxobutanoate or diethyl propanedioate, react with acyl halides or anhydrides to give *acylation* products. These reactions are carried out best using sodium hydride instead of sodium ethoxide for production of the enol salt, because then no alcohol is liberated to react with the acyl halide or anhydride:

$$CH_3COCH_2CO_2C_2H_5 + \overset{\oplus}{Na}\,\overset{\ominus}{H} \longrightarrow [CH_3CO\overset{\ominus}{\ddot{C}}HCO_2C_2H_5]\overset{\oplus}{Na} + H_2$$

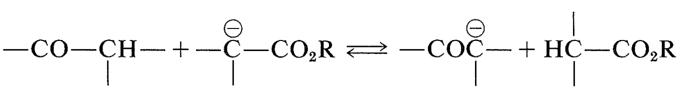
$$CH_3CO\overset{\ominus}{\ddot{C}}HCO_2C_2H_5 + C_6H_5COCl \longrightarrow CH_3CO\underset{\substack{|\\COC_6H_5}}{C}HCO_2C_2H_5 + Cl^{\ominus}$$

18-8E Aldol-Type Additions of Ester Anions and the Reformatsky Reaction

Addition of an ester anion to the carbonyl group of an aldehyde or ketone is a type of *aldol* addition (Section 17-3):



There are certain difficulties in achieving this type of aldol reaction. First, alkali-induced ester hydrolysis would compete with addition. Second, a Claisen condensation of the ester might intervene, and third, the ester anion is a *stronger base* than the enolate anions of either aldehydes or ketones, which means reaction could be defeated by proton transfer of the type



However, a useful synthetic reaction can be achieved in the following way. First, the ester anion is formed in the absence of water without causing a Claisen condensation or other carbonyl addition. This can be done with ethyl ethanoate by treating it with lithium bis(trimethylsilyl)amide in oxacyclopentane solution at −80°:

$$CH_3CO_2C_2H_5 + LiN[Si(CH_3)_3]_2 \xrightarrow{-80^\circ} LiCH_2CO_2C_2H_5 + HN[Si(CH_3)_3]_2 \quad (18\text{-}22)$$

The advantage of $LiN[Si(CH_3)_3]_2$ as the base in this reaction is that $\overset{\ominus}{N}[Si(CH_3)_3]_2$ is a reasonably strong base; it is bulky, which inhibits addition to the carbonyl; and it also forms a weakly basic amine, $HN[Si(CH_3)_3]_2$, which does not interfere in the subsequent reactions.

The solution of ethyl lithioethanoate must be kept cold and treated promptly with an aldehyde or ketone. Thus, with 2-propanone,

$$LiCH_2CO_2C_2H_5 + CH_3COCH_3 \xrightarrow{-80^\circ} LiO-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2CO_2C_2H_5$$

$$\xrightarrow{H^\oplus,\ H_2O} H-O-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_2CO_2C_2H_5 \quad 90\% \quad (18\text{-}23)$$

For the reaction to be successful, the carbonyl addition has to be faster than the proton transfer reaction, $LiCH_2CO_2C_2H_5 + CH_3COCH_3 \longrightarrow CH_3CO_2C_2H_5 + LiCH_2COCH_3$ and, at −80°, this is the case. This synthesis of β-hydroxy esters is a beautiful example of how rates of competing reactions can be manipulated to obtain a high yield of a desired addition product that may not be the most thermodynamically favorable one.

A closely related synthesis of β-hydroxy esters is provided by the Reformatsky reaction. This synthesis starts with an aldehyde or ketone, RCOR′, and an α-bromo ester, such as ethyl bromoethanoate. Zinc in a nonhydroxylic solvent (usually benzene) transforms the bromo ester into an organozinc compound, which then adds to the aldehyde or ketone carbonyl. Hydrolysis produces the β-hydroxy ester:

$$BrCH_2CO_2C_2H_5 \xrightarrow[C_6H_6]{Zn} \overset{\delta\oplus\ \ \delta\ominus}{BrZn-CH_2CO_2C_2H_5} \xrightarrow{RR'C=O}$$

$$RR'\overset{OZnBr}{\overset{|}{C}}CH_2CO_2C_2H_5 \xrightarrow[H_2O]{NH_4Cl} RR'\overset{OH}{\overset{|}{C}}CH_2CO_2C_2H_5$$

As do aldols, β-hydroxy esters dehydrate (usually readily) to α,β-unsaturated carbonyl compounds.

$$RR'\overset{OH}{\overset{|}{C}}CH_2CO_2C_2H_5 \xrightarrow{H^\oplus,\ -H_2O} RR'C=CHCO_2C_2H_5$$

Exercise 18-43* a. In the formation of $LiCH_2CO_2C_2H_5$ (Equation 18-22), would it be better to add the ester to the solution of the base in oxacyclopentane, or the reverse? Give your reasoning.

b. Suppose a solution formed in accord with Equation 18-23 were allowed to stand (before adding acid and water) until equilibrium is established between the various possible Claisen, mixed-Claisen, and aldol-addition products described in Sections 18-8B and 17-3C. What products would you then expect to be formed on hydrolysis with dilute acid and water? Which would be expected to predominate? Give your reasoning.

c. Show how you could synthesize methyl 2-(1-cyclohexenyl)ethanoate from cyclohexanone by the reactions described in this section.

18-8F Biological Claisen Condensations and Aldol Additions. Fatty Acid Metabolism

The overall result of a Claisen condensation is the transfer of an acyl group $\left(R-C\begin{matrix}O\\ \diagup\\ \diagdown\end{matrix}\right)$ from one ester molecule to another:

$$R-\overset{O}{\overset{\|}{C}}-OC_2H_5 + CH_3\overset{O}{\overset{\|}{C}}-OC_2H_5 \rightleftharpoons R-\overset{O}{\overset{\|}{C}}-CH_2\overset{O}{\overset{\|}{C}}-OC_2H_5 + C_2H_5OH \qquad (18\text{-}24)$$

In biological systems, related reactions of acyl transfer occur by way of *thioesters,* $R-\overset{O}{\overset{\|}{C}}-SR'$, derived from carboxylic acids and a thiol known as **coenzyme A** (**HSCoA**).[5] The full structure of coenzyme A is shown in Figure 18-7. Although it is large and complex, the reactive part for our discussion here

[5]Considerable confusion is possible because of the way in which biochemists use abbreviated names and formulas for the acyl derivatives of coenzyme A. To emphasize the vital —SH group, coenzyme A is usually written as **CoASH**. However, the acyl derivatives most often are called acetyl **CoA** and the like, not acetyl **SCoA**, and you could well get the erroneous impression that the sulfur has somehow disappeared in forming the acyl derivative. We will include the sulfur in formulas such as $CH_3COSCoA$, but use the customary names such as acetyl **CoA** without including the sulfur. To make clear that **CoA** does not contain cobalt, **CoA** is printed in this text in boldface type.

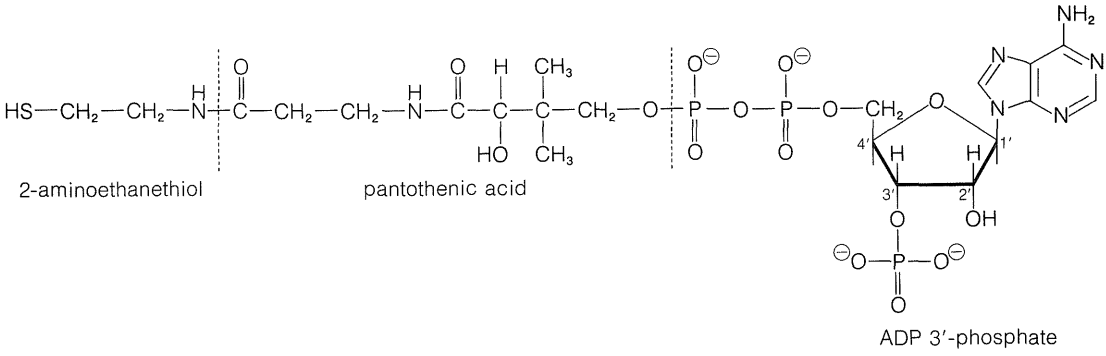


Figure 18-7 The structure of coenzyme A (HSCoA) showing the segments of which it can be considered to be constructed. The thiol group at the left end of the molecule reacts to form *thioesters* of the type R—C(=O)—SCoA. The other parts of the coenzyme A molecule provide the structural elements that permit a high degree of specificity for interactions with enzymes.

is the thiol (SH) group. The thioester equivalent of the Claisen condensation of Equation 18-24 is

$$\mathrm{R{-}C(=O){-}SCoA + CH_3C(=O){-}SCoA \rightleftharpoons R{-}C(=O){-}CH_2C(=O){-}SCoA + HSCoA}$$

The reverse of the above reaction is a key step in the *oxidative degradation* of fatty acids. This reverse Claisen condensation (catalyzed by *thiolase*) involves the cleavage of a carbon–carbon bond of a β-keto ester of coenzyme A by another molecule of coenzyme A to give a new acyl derivative (RCO—**SCoA**) and ethanoyl (acetyl) derivative (CH_3CO—**SCoA**):

$$\mathrm{R{-}C(=O){-}CH_2{-}C(=O){-}SCoA \xrightarrow{\text{thiolase}} R{-}C(=O){-}SCoA + CH_3C(=O){-}SCoA}$$
(HS—CoA)

For further degradation of RCO—**SCoA**, it first must be oxidized to a β-keto thioester. The reactions that accomplish this oxidation are shown in Figure 18-8 and involve a sequence of enzymatic transformations of the type

$$\mathrm{-CH_2CH_2- \longrightarrow -CH{=}CH- \longrightarrow -CH(OH){-}CH_2- \longrightarrow -CO{-}CH_2-}$$

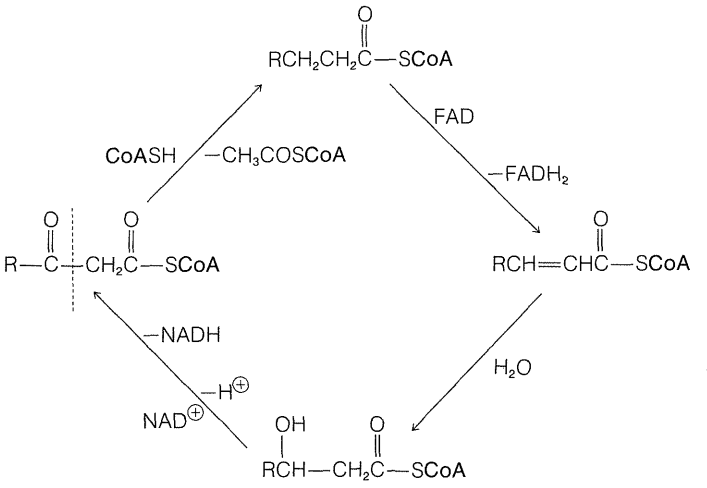


Figure 18-8 Steps in the metabolic oxidation of a fatty acid. In each cycle of reactions, one mole of $CH_3COSCoA$ is formed and the alkyl group R is shortened by two carbons.

After formation of the β-keto thioester, it is cleaved by **CoASH**, and the resulting thioester goes back into the sequence *two carbons shorter* than before. In this way, a fatty acid is degraded from the carboxyl end, two carbons at a time.

Exercise 18-44* The formation of an acyl coenzyme A, RCO—SCoA, from coenzyme A and a carboxylic acid is coupled to a cleavage reaction of ATP to give AMP:

$$RCO_2H + ATP + CoA—SH \rightleftharpoons RCO—SCoA + AMP + PP$$

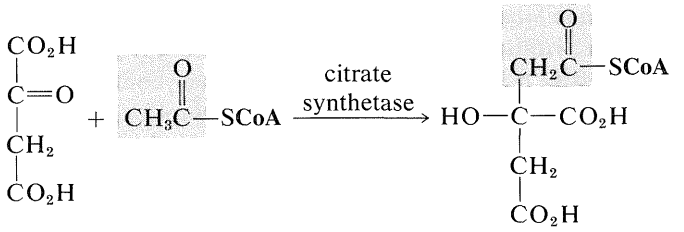
Write the possible steps involved in this esterification reaction. (Review Section 15-5F.)

There are two principle pathways for utilization of the ethanoyl coenzyme A (CH_3CO—**SCoA**) formed in each turn of the oxidation cycle of Figure 18-8. Either it is used to synthesize larger molecules such as fatty acids, steroids, and so on, as will be described in Section 30-5A, or the acyl group is oxidized to CO_2 and H_2O:

$$CH_3CO—SCoA \xrightarrow{[O]} 2CO_2 + H_2O + HSCoA$$

The oxidation of the acyl group of coenzyme A is the net outcome of the **citric acid** or **Krebs cycle** (Section 20-10B). We will be interested here in the

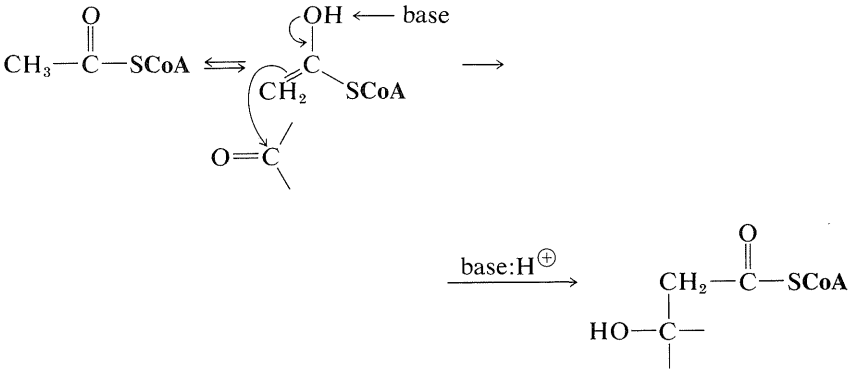
entry point of the cycle whereby ethanoyl coenzyme A is employed in a reaction that builds the C_6 chain of citric acid (3-carboxy-3-hydroxypentanedioic acid) from C_2 and C_4 pieces:



2-oxobutanedioic acid (oxaloacetic acid)

citryl CoA

This reaction is quite special in that it is an *aldol-type addition* in which a thioester is the donor (nucleophile) and a keto acid is the acceptor (electrophile). From the discussion in Section 18-8E, you will see that reactions of this kind involving an ester as the donor and an aldehyde or ketone as the acceptor can be achieved in the laboratory only under rather special conditions. For the thioester to function as a nucleophile at the α carbon under the restraints imposed by having the reaction occur at the physiological pH, the catalyzing enzyme almost certainly must promote formation of the enol form of the thioester. The enol then could add to the ketone carbonyl with the assistance of a basic group on the enzyme. This kind of catalysis by enzymes is discussed in Section 25-9C.



18-9 REACTIONS OF UNSATURATED CARBOXYLIC ACIDS AND THEIR DERIVATIVES

Unsaturated carboxylic acids of the type $RCH{=}CH(CH_2)_nCOOH$ usually exhibit the properties characteristic of isolated double bonds and isolated carboxyl groups when n is large and the functional groups are far apart. As

expected, exceptional behavior is found most commonly when the groups are sufficiently close together to interact strongly, as in α,β-unsaturated acids, $\overset{\beta}{\text{R}}\text{CH}{=}\overset{\alpha}{\text{C}}\text{HCO}_2\text{H}$. We shall emphasize those properties that are exceptional in the following discussion.

18-9A Migration of the Double Bond

In the presence of strong base, α,β- and β,γ-unsaturated carboxylic acids tend to interconvert by migration of the double bond:

$$\underset{\beta,\gamma\text{-unsaturated}}{\text{RCH}{=}\text{CH}{-}\text{CH}_2\text{CO}_2^{\ominus}} \xrightleftharpoons{\text{NaOH}} \underset{\alpha,\beta\text{-unsaturated}}{\text{RCH}_2\text{CH}{=}\text{CHCO}_2^{\ominus}}$$

Ester derivatives, $\text{RCH}{=}\text{CH}{-}\text{CH}_2\text{COOR}'$, and the corresponding unsaturated aldehydes and ketones, $\text{RCH}{=}\text{CH}{-}\text{CH}_2\text{COR}'$, are much more prone to this type of rearrangement than are the acids.

Exercise 18-45 Write a mechanism for the base-catalyzed equilibration of α,β- and β,γ-unsaturated esters. Which isomer would you expect to predominate? Why does this type of isomerization proceed less readily for the carboxylate anions than for the esters? Would γ,δ-unsaturated esters rearrange readily to the α,β-unsaturated esters? Why, or why not?

18-9B Hydration and Hydrogen Bromide Addition

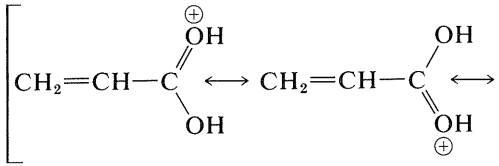
Like alkenes, the double bonds of α,β-unsaturated acids can be brominated, hydroxylated, hydrated, and hydrobrominated, although the reactions often are relatively slow. In the addition of unsymmetrical reagents the direction of addition is *opposite* to that observed for alkenes (anti-Markownikoff). Thus propenoic (acrylic) acid adds hydrogen bromide and water to form 3-bromo- and 3-hydroxypropanoic acids:

$$\text{CH}_2{=}\text{CHCOOH} \quad \text{propenoic acid}$$

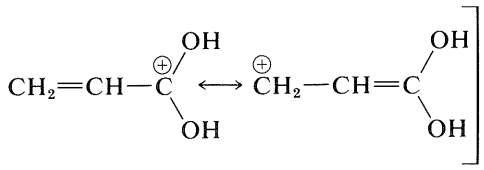
$$\xrightarrow{\text{HBr}} \text{BrCH}_2\text{CH}_2\text{COOH} \quad \text{3-bromopropanoic acid}$$

$$\xrightarrow[\text{H}^{\oplus}]{\text{H}_2\text{O}} \underset{\text{OH}}{\text{CH}_2\text{CH}_2\text{COOH}} \quad \text{3-hydroxypropanoic acid}$$

These additions are analogous to the addition of halogens and halogen acids to 1,3-butadiene (Section 13-2). In the first step, a proton is transferred to the carbonyl oxygen. The resulting conjugate acid can be regarded as a resonance hybrid of structures **16a–16d**:

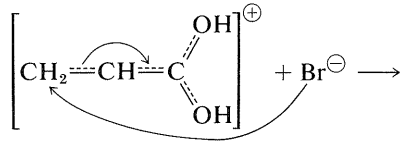


16a **16b**

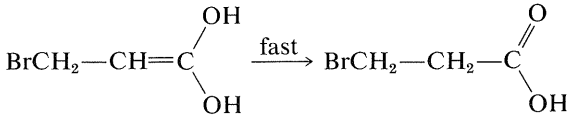


16c **16d**

In the second step, a nucleophile (such as $Br^{\ominus}$ or a water molecule) attacks an electron-deficient carbon of the hybrid **16**. Attack at the carboxyl carbon may occur but does not lead to a stable product. Attack of the nucleophile at the β carbon, however, produces the enol form of the β-substituted acid, which then is converted rapidly to the normal carboxylic acid:



16

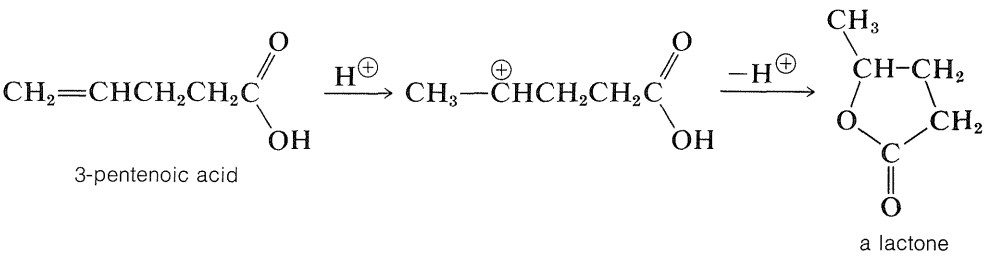


18-9C Lactone Formation

When the double bond of an unsaturated acid is farther down the carbon chain than between the alpha and beta positions, the so-called "conjugate addition" is not possible. Nonetheless, the double bond and carboxyl group frequently interact in the presence of acidic catalysts because the carbocation that results from addition of a proton to the double bond has a built-in nucleophile (the

carboxyl group), which may attack the cationic center to form a cyclic ester called a *lactone*.

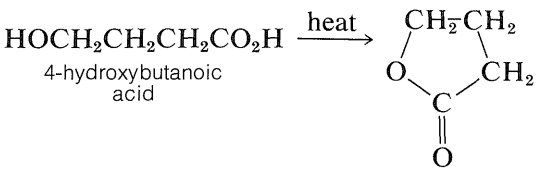
Lactone formation only occurs readily by this mechanism when a five- or six-membered ring can be formed:



3-pentenoic acid

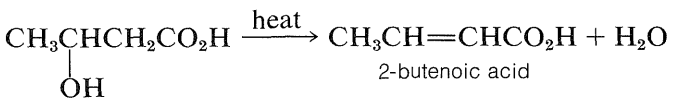
a lactone

Five- or six-membered lactones also are formed by internal esterification when either γ- or δ-hydroxy acids are heated. Under similar conditions, β-hydroxy acids are dehydrated to α,β-unsaturated acids, whereas α-hydroxy acids undergo bimolecular esterification to substances with six-membered dilactone rings called **lactides:**



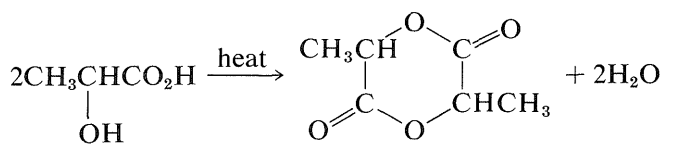
4-hydroxybutanoic acid

oxacyclopentan-2-one



3-hydroxybutanoic acid

2-butenoic acid



2-hydroxypropanoic acid (lactic acid)

a lactide

Exercise 18-46 Would you expect 3-butenoic acid to form a lactone with a five- or a four-membered ring when heated with a catalytic amount of sulfuric acid?

18-9D More on the Michael Addition

The foregoing examples of addition to the double bonds of unsaturated carboxylic acids all involve activation by an electrophilic species such as $H^{\oplus}$. Conjugate addition also may occur by nucleophilic attack on acid derivatives, the most important being the base-catalyzed Michael addition (Section 17-5B) and 1,4-addition of organometallic compounds (Section 14-12D). In all of these reactions a nucleophilic agent, usually a carbanion, attacks the double bond of an α,β-unsaturated acid derivative, or more generally an α,β-unsaturated carbonyl compound, or an unsaturated compound in which the double bond is conjugated with, and activated by, a strongly electronegative unsaturated group (such as —CN, $—NO_2$, etc.) In the Michael addition, the carbanion usually is an enolate salt.

The overall reaction is illustrated here by the specific example of the addition of diethyl propanedioate (diethyl malonate) to ethyl 3-phenylpropenoate (ethyl cinnamate):

$$C_6H_5CH{=}CHCO_2C_2H_5 + CH_2(CO_2C_2H_5)_2 \xrightarrow{\ominus OC_2H_5} C_6H_5\underset{\displaystyle CH(CO_2C_2H_5)_2}{\underset{|}{C}}HCH_2CO_2C_2H_5$$

The mechanism of this kind of transformation, with diethyl propanedioate as the addend, is outlined in Equations 18-25 and 18-26. The basic catalyst required for the Michael addition (here symbolized as B:) serves by forming the corresponding anion:

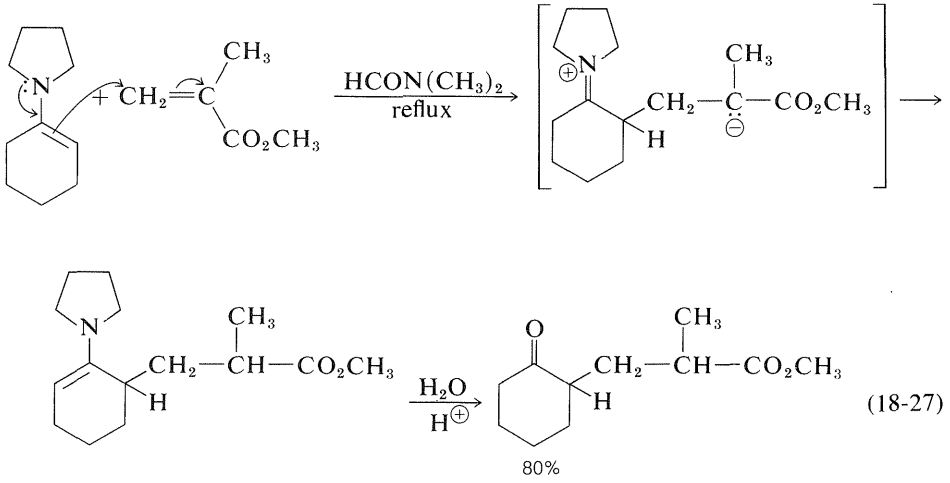
$$CH_2(CO_2C_2H_5) + B: \rightleftharpoons :\overset{\ominus}{C}H(CO_2C_2H_5)_2 + \overset{\oplus}{B}:H \qquad (18\text{-}25)$$

$$\diagdown C{=}C{-}C{=}O \diagup + :\overset{\ominus}{C}H(CO_2C_2H_5)_2 \longrightarrow \left[-C-C{=}C{=}O \;\; (CH(CO_2C_2H_5)_2)\right]^{\ominus} \xrightarrow{BH^{\oplus}}$$

$$-C-CH-C{=}O \quad (CH(CO_2C_2H_5)_2) \qquad (18\text{-}26)$$

A variety of nucleophilic agents can be used; propanedinitrile, 3-oxobutanoate esters, and cyanoethanoate esters all form relatively stable carbanions and function well in Michael addition reactions. Obviously, if the carbanion is *too* stable, it will have little or no tendency to attack the double bond of the α,β-unsaturated acid derivative. The utility of the Michael addition for preparing 1,5-dicarbonyl compounds is illustrated by the examples in Exercise 18-49.

Enamines (Sections 16-4C and 17-4B) are excellent addends in many Michael-type reactions. An example is provided by the addition of *N*-(1-cyclohexenyl)-azacyclopentane to methyl 2-methylpropenoate:



(18-27)

Exercise 18-47 Explain why the Michael addition of diethyl propanedioate to 3-phenylpropenoic acid is unlikely to be successful.

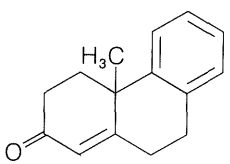
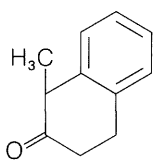
Exercise 18-48* The Michael-addition product that results from ethyl 3-phenylpropenoate and diethyl propanedioate, in principle, also can be formed by sodium ethoxide-catalyzed addition of ethyl ethanoate to ethyl (2-carbethoxy)-3-phenylpropenoate. Work out the course of this reaction along the lines of Equations 18-25 and 18-26 and explain why it is less likely to be successful than the addition of diethyl propanedioate to ethyl 3-phenylpropenoate. It will be helpful to compare the various possible acid-base equilibria involved in the two possible routes to the same Michael-addition product.

Exercise 18-49 Show how the following substances can be prepared by syntheses based on Michael additions. In some cases, additional transformations may be required.

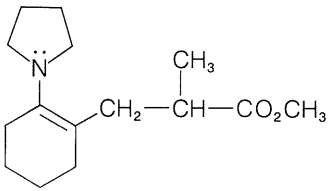
a. 3-phenylpentanedioic acid from ethyl 3-phenylpropenoate

b. 3,5-diphenyl-5-oxopentanenitrile from 1,3-diphenylpropenone (benzalacetophenone)

c. 4,4-(dicarbethoxy)heptanedinitrile from propenenitrile (acrylonitrile)

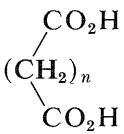
d.  from  and 3-butene-2-one

Exercise 18-50 Explain how steric hindrance would lead one to expect that the proton-transfer product in the addition of *N*-(1-cyclohexenyl)azacyclopentane to methyl 2-methylpropenoate would have the structure shown in Equation 18-27, rather than the following:



18-10 DICARBOXYLIC ACIDS

Acids in which there are two carboxyl groups separated by a chain of more than five carbon atoms ($n > 5$) for the most part have unexceptional properties, and the carboxyl groups behave more or less independently of one another.



However, when the carboxyl groups are closer together the possibilities for interaction increase; we shall be interested primarily in such acids. A number of important dicarboxylic acids are listed in Table 18-4 together with their physical properties, methods of manufacture, and commercial uses.

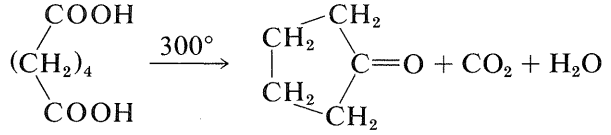
18-10A Acidic Properties of Dicarboxylic Acids

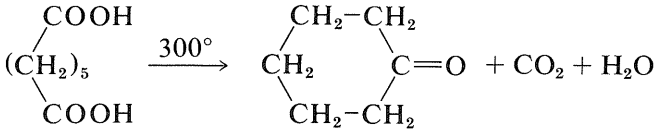
The inductive effect of one carboxyl group is expected to enhance the acidity of the other. In Table 18-4 we see that the acid strength of the dicarboxylic acids, as measured by the first acid-dissociation constant, K_1, is higher than that of ethanoic acid ($K_a = 1.5 \times 10^{-5}$) and decreases with increasing number of bonds between the two carboxyl groups. The second acid-dissociation constant, K_2, is smaller than K_a for ethanoic acid (with the exception of oxalic acid) because it is more difficult to remove a proton under the electrostatic attraction of the nearby carboxylate anion (see Section 18-2C).

18-10B Thermal Behavior of Dicarboxylic Acids

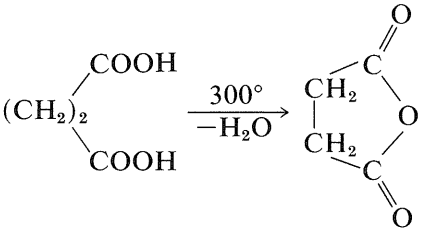
The reactions that occur when dicarboxylic acids are heated depend critically upon the chain length separating the carboxyl groups. Cyclization usually is

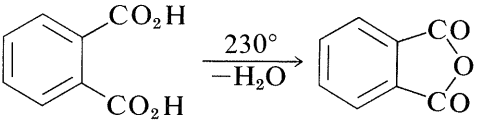
favored if a strainless five- or six-membered ring can be formed. Thus hexanedioic and heptanedioic acids decarboxylate and cyclize to cyclopentanone and cyclohexanone, respectively:

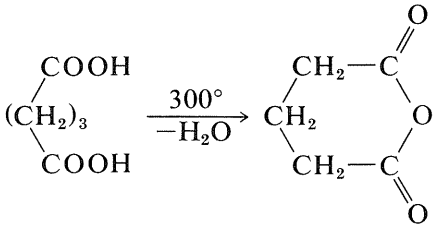


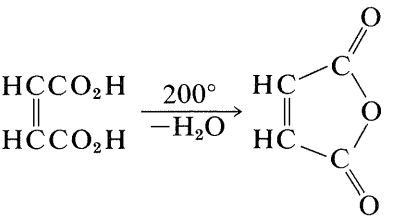


Butanedioic and pentanedioic acids take a different course. Rather than form the strained cyclic ketones, cyclopropanone and cyclobutanone, both acids form cyclic anhydrides that have five- and six-membered rings, respectively. 1,2-Benzenedicarboxylic (phthalic) and *cis*-1,4-butenedicarboxylic (maleic) acids behave similarly:

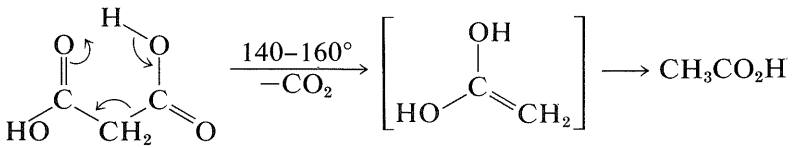








Because of their short chains, propanedioic and ethanedioic acids simply decarboxyate when heated (Section 18-4):



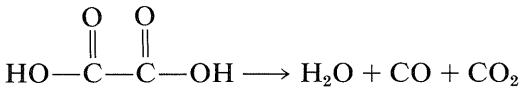
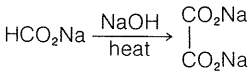
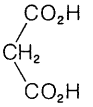
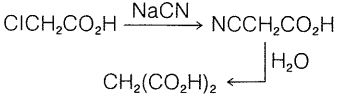
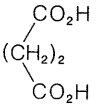
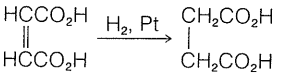
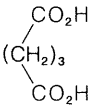
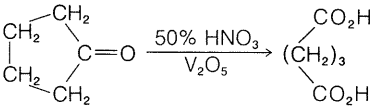
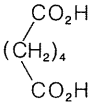
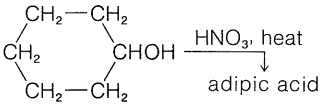
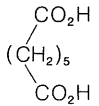
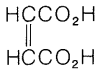
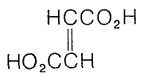
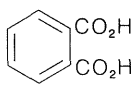
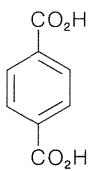


Table 18-4
Dicarboxylic Acids

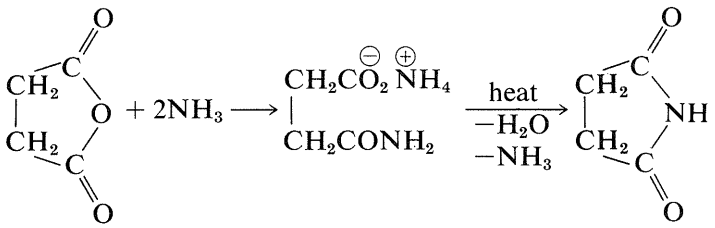
Acid	Formula	Mp, °C	$K_1 \times 10^5$ at 25°	$K_2 \times 10^5$ at 25°	Commercial preparation	Principal commercial uses
ethanedioic (oxalic)		189	3500	5.3		analytical, reducing, and bleaching agent; rust, paint, varnish, and ink remover
propanedioic (malonic)		136 dec.	171	0.22		employed as ethyl ester in synthesis of carboxylic acids and manufacture of barbiturates
butanedioic (succinic)		185	6.6	0.25		manufacture of lacquers and dyes
pentanedioic (glutaric)		98	4.7	0.29		
hexanedioic (adipic)		152	3.7	0.24		important in condensation polymerization, particularly for manufacture of nylon and urethane foams

heptanedioic (pimelic)		105	3.4	0.26	reverse Claisen condensation of 2-carbethoxycyclohexanone	
cis-butenedioic (maleic)		130	1170	0.026	catalytic oxidation of benzene to the anhydride	mainly used in the form of the anhydride in Diels–Alder diene synthesis; polymers, particularly fiberglass compositions
trans-butenedioic (fumaric)		sub. 200	93	2.9	from glucose by bacterial action	
1,2-benzenedicarboxylic (phthalic)		231	130	0.39[18]	air oxidation of naphthalene and 1,2-dimethylbenzene	used as anhydride in organic synthesis and in manufacture of coating materials such as polyester
1,4-benzenedicarboxylic (terephthalic)		>300	31	1.5	air oxidation of 1,4-dimethyl-benzene	polyester fibers such as Dacron

Exercise 18-51 The *cis*- and *trans*-butenedioic acids give the same anhydride on heating, but the *trans* acid must be heated to much higher temperatures than the *cis* acid to achieve anhydride formation. Explain. Write a reasonable mechanism for both reactions.

18-10C Imides from Dicarboxylic Acids

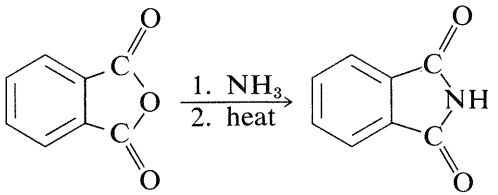
The cyclic anhydride of butanedioic acid reacts with ammonia, as may be expected for a typical anhydride; but the product, when strongly heated, forms a cyclic imide (butanimide):



butanedioic anhydride (succinic anhydride)

butanimide (succinimide)

1,2-Benzenedicarboxylic (phthalic) anhydride behaves similarly, giving 1,2-benzenedicarboximide (phthalimide):

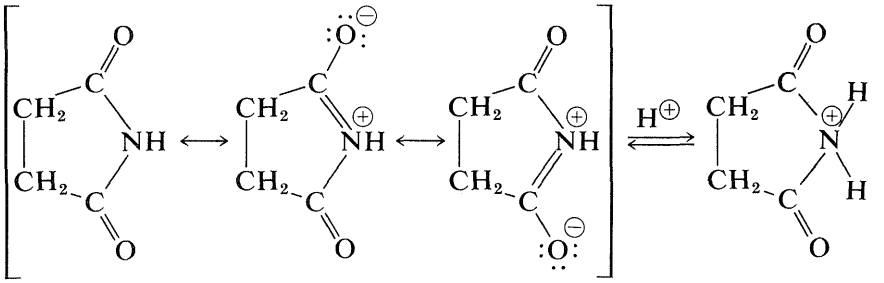


1,2-benzenedicarboxylic (phthalic) anhydride

1,2-benzenedicarboximide (phthalimide)

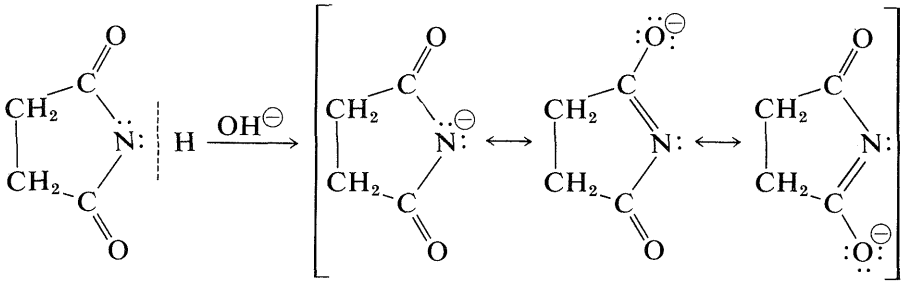
Unlike amines, imides do not have basic properties in water solution; the electron pair of nitrogen is partly delocalized over the carbonyl groups,

as indicated by **17a** to **17c**. This stabilization is lost if a proton is added to nitrogen to give the conjugate acid, **18**:



17a **17b** **17c** **18**

Imides are, in fact, quite acidic and readily dissolve in alkali-metal hydroxide solutions to give salts. Like carboxylic acids and 1,3-dicarbonyl compounds, imides are acidic primarily because the stabilization of the anion is greater than that of the acid. This can be seen by comparison of the resonance structures that may be written for the imide, **17**, with those of the anion, **18**. Separation of positive and negative charge, as in Structures **17b** and **17c**, increases the energy of such structures. There is no charge separation in the anion; thus **19b** and **19c** are more important with respect to their hybrid than are **17b** and **17c** to their hybrid. (You may wish to review the corresponding argument for the acidity of carboxylic acids, Section 18-2A.)



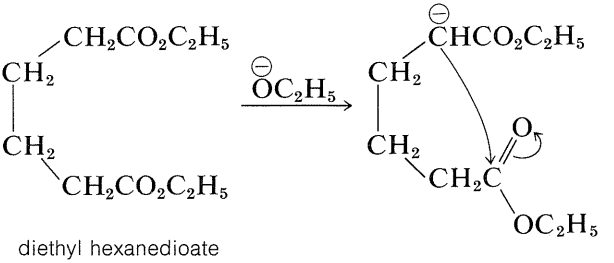
17 **19a** **19b** **19c**

The salts of imides are useful in synthesis, as is described in Section 23-9D.

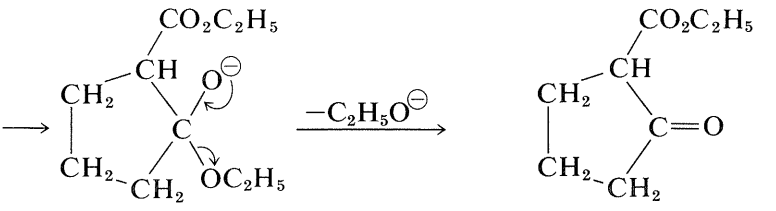
18-10D The Dieckmann Condensation

Esters of most dicarboxylic acids, except propanedioic esters, undergo the Claisen condensation in much the same way as do esters of monocarboxylic

acids (see Section 18-8B). However, when a strainless five- or six-membered ring can be formed, an intramolecular Claisen condensation, called the **Dieckmann condensation,** may take place which would result in the formation of a cyclic β-keto ester:



diethyl hexanedioate



2-(ethoxycarbonyl)cyclopentanone

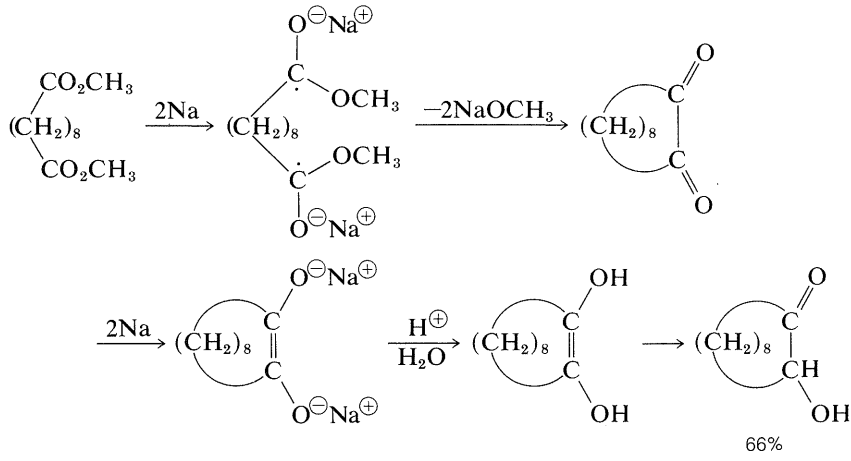
18-10E The Acyloin Reaction

A useful method of forming carbon–carbon bonds involves reduction of esters with sodium metal in aprotic solvents such as ether or benzene and is called the **acyloin reaction:**

$$2CH_3(CH_2)_3CO_2C_2H_5 \xrightarrow[2.\ H^{\oplus},\ H_2O]{1.\ Na,\ ether} \underset{65\%}{CH_3(CH_2)_3C(=O)-CH(OH)(CH_2)_3CH_3}$$

This interesting reaction is especially useful for the synthesis of medium- and large-ring compounds from dicarboxylic esters, and is effective for ring sizes that cannot be made by the Dieckmann condensation or decarboxylation (Section 18-10B). Radical anions formed by addition of sodium to the ester

groups appear to be the key intermediates for carbon–carbon bond formation. Thus, for dimethyl decanedioate,



Additional Reading

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G. V. Calder and T. J. Barton, "Actual Effects Controlling the Acidity of Carboxylic Acids," *J. Chem. Educ.* **48,** 338 (1971).

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Table 18-5
Methods of Preparation of Carboxylic Acids[a]

Reaction	Comment
1. *Hydrolysis of nitriles* $RCN \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCONH_2 \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCO_2H$	Acid or base catalyzed; amide is formed first, then hydrolyzed to the acid; a useful laboratory synthesis if the nitrile is accessible as by S_N2 reactions of RX (Section 8-7F).
2. *Hydrolysis of esters and amides* $RCO_2R' \xrightarrow[H^{\oplus} \text{ or } OH^{\ominus}]{H_2O} RCO_2H + R'OH$ $RCONH_2 \xrightarrow{H^{\oplus} \text{ or } OH^{\ominus}} RCO_2H + NH_3$	Useful where the starting material can be prepared by alkylation of 3-oxobutanoate or propanedioate esters and similar reactions.
3. *Carbonation of organometallic compounds* $RMgX \xrightarrow{CO_2} RCO_2MgX \xrightarrow{H_2O,\ H^{\oplus}} RCO_2H$ $RLi \xrightarrow{CO_2} RCO_2Li \xrightarrow{H_2O,\ H^{\oplus}} RCO_2H$	Usually carried out by pouring solution of organometallic compound over powdered Dry Ice and stirring efficiently; an important and versatile reaction (see Section 14-12B).
4. *Malonic ester synthesis* $RX + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} RCH(CO_2C_2H_5)_2$ $\xrightarrow[2.\ \text{heat } (-CO_2)]{1.\ H_2O,\ H^{\oplus}} RCH_2CO_2H$ $R'X + RCH(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5} RR'C(CO_2C_2H_5)_2$ $\xrightarrow[2.\ \text{heat } (-CO_2)]{1.\ H_2O,\ H^{\oplus}} RR'CHCO_2H$	An important reaction for synthesis of alkyl and dialkylethanoic acids (RX and R'X are primary or secondary alkyl halides); *dicarboxylic acids* (RX = haloester); unsaturated acids (RX = an unsaturated halide, best for allylic halides); β-keto acids (R = acyl chloride); (see Sections 18-8C and 18-8D).
5. *Acetoacetic ester syntheses* $RX + CH_3COCH_2CO_2C_2H_5 \xrightarrow{NaOC_2H_5} CH_3COCHCO_2C_2H_5$ (R) $\xrightarrow[2.\ H^{\oplus}]{1.\ OH^{\ominus}} RCH_2CO_2H$ $R'X + CH_3COCHCO_2C_2H_5$ (R) $\xrightarrow{NaOC_2H_5} CH_3COCCO_2C_2H_5$ (R, R') $\xrightarrow[2.\ H^{\oplus}]{1.\ OH^{\ominus}} RR'CHCO_2H$	No particular advantage over 4; in fact, ketones may be formed in competition with acids in acetoacetic-ester synthesis (see Section 18-8B).

Table 18-5 (continued)
Methods of Preparation of Carboxylic Acids[a]

Reaction	Comment
6. *Arndt–Eistert reaction* $RCOCl + \underset{\text{diazomethane}}{CH_2N_2} \longrightarrow \underset{\text{diazoketone}}{RCOCHN_2} \xrightarrow[Ag_2O]{H_2O} RCH_2CO_2H$	Useful method of preparing next-higher homologue of an acid (see Sections 16-4A and 24-7C).
7. *Oxidation of primary alcohols and aldehydes* $RCH_2OH \xrightarrow{[O]} RCHO \xrightarrow{[O]} RCO_2H$	Oxidizing agents are $KMnO_4$ ($H^{\oplus}$ or $OH^{\ominus}$), CrO_3, HNO_3, and Ag_2O. (Ag_2O only works for aldehydes.)
8. *Oxidation of alkenes* $RCH{=}CH_2 \xrightarrow{[O]} RCO_2H$	Oxidizing agents are $KMnO_4$ ($H^{\oplus}$ or $OH^{\ominus}$), CrO_3, and HNO_3; used mainly for structure determination; further degradation may occur.
9. *Oxidation of methyl ketones (haloform reaction)* $RCOCH_3 \xrightarrow{Br_2,\ NaOH} [RCOCBr_3] \xrightarrow[2.\ H^{\oplus}]{1.\ NaOH} RCO_2H + CHBr_3$	Hypochlorites may be used in place of Br_2 and NaOH; limited by possible substitution of halogen in R radical (see Section 17-2B).
10. *Cannizzaro reaction* $2RCHO \xrightarrow{NaOH} RCH_2OH + RCO_2H$	Useful only when aldehyde has no α hydrogen and cannot then undergo an aldol condensation (see Section 16-4E).
11. *Baeyer–Villiger oxidation of ketones with peracids* $RCOR + R'\overset{O}{\overset{\|}{C}}{-}O{-}O{-}H \longrightarrow RCO_2R + R'CO_2H$ $\downarrow H^{\oplus}, H_2O$ $RCO_2H + ROH$	Generally useful method for aliphatic and aryl ketones without double bonds; oxidizing agents commonly used are peroxybenzoic acid ($C_6H_5CO_3H$), peroxyethanoic acid (CH_3CO_3H), and trifluoroperoxyethanoic acid (CF_3CO_3H); the last is prepared from trifluoroethanoic anhydride and H_2O_2 and used in the presence of NaH_2PO_4 as a buffering agent (Section 16-7).

[a]Methods specific for the preparation of aromatic acids are discussed in Chapter 26.

Table 18-6
Methods of Preparation of Carboxylic Esters

Reaction	Comment
1. *From carboxylic acids and primary alcohols* $RCO_2H + R'OH \overset{H^{\oplus}}{\rightleftharpoons} RCO_2R' + H_2O$	Generally limited to primary alcohols; acidic catalysts include H_2SO_4, HCl, BF_3; for details and mechanism see Sections 15-4D and 18-3A.
2. *From acid chlorides and alcohols* $RCOCl + R'OH \longrightarrow RCO_2R' + HCl$	Versatile reaction; works well with *prim., sec.,* and *tert.* alcohols; a base may be necessary to remove HCl, because *tert*-aliphatic alcohols may give alkenes and *tert*-butyl chlorides.
3. *From anhydrides and alcohols* $(RCO)_2O + R'OH \xrightarrow{H^{\oplus}} RCO_2R' + RCO_2H$ $\xrightarrow[H^{\oplus}]{R'OH} RCO_2R' + H_2O$	Widely applicable; acid-catalyzed.
4. *Ester interchange* $RCO_2R' + R''OH \overset{H^{\oplus} \text{ or } OH^{\ominus}}{\rightleftharpoons} RCO_2R'' + R'OH$	Acid- and base-catalyzed; generally limited to primary alcohols (for discussion, see Section 18-7A).
5. *From carboxylate salts, thionyl chloride, and alcohols* $R'OH + SOCl_2 \longrightarrow \underset{\text{alkyl chlorosulfite}}{R'OSOCl} + HCl$ $RCO_2Na + R'OSOCl \longrightarrow RCO_2R' + SO_2 + NaCl$	Limited to primary alcohols; it amounts to an S_N2 displacement of chlorosulfite group by carboxylate ion; steric hindrance in the carboxylate salt seems unimportant.
6. *From carboxylate salts and alkyl halides* $RCO_2Na + R'X \longrightarrow RCO_2R' + NaX$	Restricted to primary halides with high S_N2 reactivity.
7. *Alcoholysis of nitriles* $RCN + R'OH \xrightarrow{H^{\oplus},\ H_2O} RCO_2R' + NH_4^{\oplus}$	Analogous to hydrolysis of nitriles, Method 1, Table 18-5.
8. *Diazomethane and carboxylic acids* $RCO_2H + CH_2N_2 \longrightarrow RCO_2CH_3 + N_2$	High yield, clean reaction, but diazomethane is a reactive, explosive, and toxic compound; useful for methyl esters of rare or acid-sensitive carboxylic acids.

Table 18-7
Methods of Preparation of Acyl Halides, Anhydrides, Amides, and Related Compounds

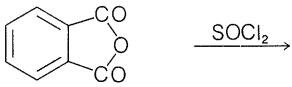
Reaction	Comment
ACYL HALIDES	
1. *From thionyl chloride and carboxylic acids* $RCO_2H + SOCl_2 \longrightarrow RCOCl + HCl + SO_2$	Most acyl chlorides are prepared by this method; anhydride formation is sometimes an objectionable side reaction.
2. *From phosphorus halides and carboxylic acids* $3RCO_2H + PBr_3 \longrightarrow 3RCOBr + H_3PO_3$ $RCO_2H + PCl_5 \longrightarrow RCOCl + POCl_3 + HCl$	Separation difficulties from H_3PO_3 and $POCl_3$ sometimes occur.
3. *From thionyl chloride and anhydrides*  1,2-benzenedicarboxylic anhydride 1,2-benzenedicarbonyl dichloride	Useful only when anhydride is more accessible than the parent acid.
4. *Acyl fluorides, bromides, and iodides from chlorides* $RCOCl + HX \longrightarrow RCOX + HCl$ in which HX = HF, HBr, or HI	Sometimes the only route available to halides other than the chloride.
5. *From ethanedioyl dichloride* $RCO_2H + \underset{\underset{COCl}{\vert}}{COCl} \longrightarrow RCOCl + CO + CO_2 + HCl$	Usually an excellent method.
ANHYDRIDES	
1. *From acid halides and carboxylic acids* $RCO_2H + R'COCl \xrightarrow{\text{pyridine}} RCO{-}O{-}COR' + HCl$	The most frequently used method; simple or mixed anhydrides can be prepared.
2. *From acid halides and carboxylic salts* $RCO_2Na + R'COCl \longrightarrow RCO{-}O{-}COR' + NaCl$	
3. *From ketene and carboxylic acids* $CH_2{=}C{=}O + RCO_2H \longrightarrow RCO{-}O{-}COCH_3$	Commercial preparation of ethanoic anhydride (Section 17-6B).

Table 18-7 (continued)
Methods of Preparation of Acyl Halides, Anhydrides, Amides, and Related Compounds

Reaction	Comment
AMIDES	
1. *From acyl chlorides and ammonia or amines* $RCOCl + 2NH_3 \longrightarrow RCONH_2 + \overset{\oplus}{N}H_4\overset{\ominus}{Cl}$ $RCOCl + 2R'NH_2 \longrightarrow RCONHR' + R'\overset{\oplus}{N}H_3\overset{\ominus}{Cl}$	Most amides are prepared by this method; use base to convert $R'NH_3Cl$ to RNH_2 (Sections 23-9A and 24-3).
2. *From carboxylic acids and ammonia or amines* $RCO_2H + NH_3 \longrightarrow RCO_2\overset{\ominus}{N}H_4\overset{\oplus}{} \xrightarrow{\text{heat}} RCONH_2 + H_2O$ $RCO_2H + R'NH_2 \longrightarrow RCO_2\overset{\ominus}{N}H_3R\overset{\oplus}{} \xrightarrow{\text{heat}} RCONHR + H_2O$	Requires relatively high temperatures.
3. *From anhydrides and ammonia or amines* $(RCO)_2O + NH_3 \longrightarrow RCO_2\overset{\ominus}{N}H_4\overset{\oplus}{} + RCONH_2$ $\xrightarrow[-H_2O]{\text{heat}} RCONH_2$	Important method for preparation of cyclic imides from cyclic anhydrides.
4. *Hydrolysis of nitriles* $RCN + H_2O \xrightarrow[H_2O_2,\ OH^{\ominus}]{H^{\oplus}} RCONH_2$	Hydrolysis stops at amide stage if R is a *tert*-alkyl group; H_2O_2 accelerates the hydrolysis reaction in alkaline solution (Section 24-3B).
5. *Addition of nitriles to alkenes (Ritter reaction)* $R_2C{=}CH_2 + R'CN \xrightarrow{H_2SO_4} R_2C(CH_3)-N{=}C(R')-OSO_3H \xrightarrow{H_2O} R'CONHCR_2(CH_3)$	Gives *N*-alkylamides; good only for alkenes (or alcohols) that form relatively stable carbonium ions; useful for preparation of amines with *tert*-alkyl groups by hydrolysis of amides (Section 24-3B).
6. *Hydrazides* $RCO_2C_2H_5 + \underset{\text{hydrazine}}{NH_2NH_2} \longrightarrow \underset{\text{hydrazide}}{RCONHNH_2} + C_2H_5OH$	
7. *Hydroxamic acids (acylazanols)* $RCO_2C_2H_5 + \underset{\text{hydroxylammonium chloride}}{\overset{\oplus}{N}H_3OH\overset{\ominus}{Cl}} \longrightarrow RCONHOH + C_2H_5OH + HCl$	
8. *Acyl azides* $RCOCl + \underset{\text{sodium azide}}{NaN_3} \longrightarrow RCON_3 + NaCl$	

Supplementary Exercises

18-52 Write equations for a practical laboratory synthesis of each of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions.

a. butanoic acid from 1-propanol

b. 2,2-dimethylpropanoic acid from *tert*-butyl chloride

c. 2-methylpropanoic acid from 2-methylpropene

d. 2-bromo-3,3-dimethylbutanoic acid from *tert*-butyl chloride

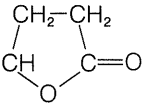
e. cyclobutylmethanol-1-^{14}C, $(CH_2)_3CH^{14}CH_2OH$, from cyclobutanecarboxylic acid and $Ba^{14}CO_3$

f. 4-pentenamide from 3-chloropropene

g. 2,2-dimethylpropyl 2,2-dimethylpropanoate from *tert*-butyl chloride

18-53 Write reasonable mechanisms for each of the following reactions:

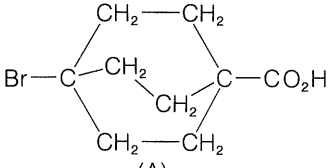
a. *cis*-$CH_3CH{=}CHCO_2H \xrightarrow[2.\ H^{\oplus}]{1.\ \overset{\ominus}{O}H,\ 100^\circ}$ *trans*-$CH_3CH{=}CHCO_2H$

b. $CH_2{=}CHCH_2CH_2CO_2H \xrightarrow{HOBr}$ 

c. $CH_3\overset{O}{\overset{\|}{C}}{-}OCH_3 + CH_3CH_2CO_2H \overset{H^{\oplus}}{\rightleftharpoons} CH_3CH_2\overset{O}{\overset{\|}{C}}{-}O{-}CH_3 + CH_3CO_2H$

The order of reactivity for CH_3CO_2R is R = CH_3— > CH_3CH_2— ≫ $(CH_3)_2CH$—.

18-54 4-Bromobicyclo[2.2.2]octane-1-carboxylic acid (A) is a considerably stronger acid than 5-bromopentanoic acid (B). Explain. (*Hint:* Consider the possible conformations and modes of transmission of the electrical effect of the C—Br dipole.)



(A)

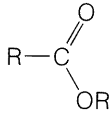
$Br{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2H$

(B)

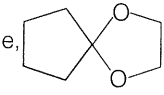
18-55 *tert*-Butyl ethanoate is converted to methyl ethanoate by sodium methoxide in methanol about *one tenth as fast* as ethyl ethanoate is converted to methyl ethanoate under the same conditions. With dilute HCl in methanol, *tert*-butyl ethanoate is *rapidly* converted to 2-methoxy-2-methylpropane and ethanoic acid, whereas ethyl ethanoate goes *more slowly* to ethanol and methyl ethanoate.

a. Write reasonable mechanisms for each of the reactions and show how the relative-rate data agree with your mechanisms.

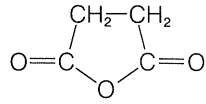
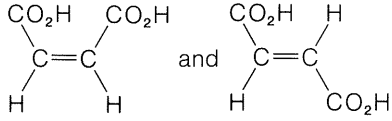
b. How could one use ^{18}O as a tracer to substantiate your proposed mechanisms?

18-56 It has been reported that esters (RCO_2R') in ^{18}O water containing sodium hydroxide are converted to  in competition with alkaline hydrolysis. The rates of both exchange and hydrolysis reactions are proportional to $OH^{\ominus}$ concentration. Explain what these facts mean with regard to the mechanism of ester hydrolysis.

18-57 Write equations for a practical laboratory synthesis of each of the following substances from the indicated starting materials (several steps may be required). Give reagents and conditions.

a. 2-chloroethyl bromoethanoate from ethanol and/or ethanoic acid
b. 2-methoxy-2-methylpropanamide from 2-methylpropanoic acid
c. 3,5,5-trimethyl-3-hexanol from 2,4,4-trimethyl-1-pentene (commercially available)
d. 3,3-dimethylbutanal from 2,2-dimethylpropanoic acid
e. 2,3,3-trimethyl-2-butanol from 2,3-dimethyl-2-butene
f. the 1,2-ethanediol ketal of cyclopentanone,  , from hexanedioic acid

18-58 For each of the following pairs of compounds give a chemical test, preferably a test-tube reaction, that will distinguish between the two substances. Write an equation for each reaction.

a. HCO_2H and H_3CCO_2H
b. $CH_3CO_2C_2H_5$ and $CH_3OCH_2CO_2H$
c. $CH_2{=}CHCO_2H$ and $CH_3CH_2CO_2H$
d. CH_3COBr and $BrCH_2CO_2H$
e. $BrCH_2CH_2CH_2CO_2CH_3$ and $CH_3CH_2CHBrCO_2CH_3$
f. $(CH_3CH_2CO)_2O$ and 
g. 
h. $HC{\equiv}CCO_2CH_3$ and $CH_2{=}CHCO_2CH_3$
i. $CH_3CO_2NH_4$ and CH_3CONH_2
j. $CH_2{=}CH{-}CH_2CH_2CO_2H$ and $CH_3CH_2CH{=}CHCO_2H$
k. $(CH_3CO)_2O$ and $CH_3CO_2CH_2CH_3$

18-59 Explain how you could distinguish between the pairs of compounds listed in Exercise 18-58 by spectroscopic means. Be *specific* about what would be observed.

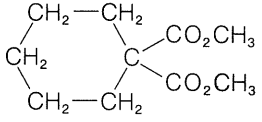
18-60 Suppose you were given four bottles, each containing a different isomer (2-, 3-, 4-, or 5-) of hydroxypentanoic acid. Explain in detail how you could distinguish the various isomers by chemical reactions.

18-61 Compound A ($C_4H_8O_3$) was optically active, quite soluble in water (giving a solution acidic to litmus), and, on strong heating, yielded B ($C_4H_6O_2$), which was optically *inactive,* rather water-soluble (acidic to litmus), and reacted much more readily with $KMnO_4$ than did A. When A was oxidized with dilute chromic acid solution, it was converted to a volatile liquid C (C_3H_6O), which did not react with $KMnO_4$, and gave a yellow precipitate with I_2 and NaOH solution.

Write appropriate structures for the lettered compounds and equations for all of the reactions mentioned. Is Compound A uniquely defined by the above description? Explain.

18-62 Name each of the following substances by the IUPAC system:

a.



b. $CH_3COCH[CH(CH_3)_2]CO_2C_2H_5$

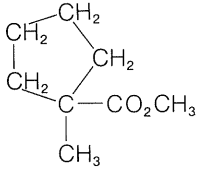
c. $CH_3CH_2COC(CH_3)_2CON(CH_3)_2$

d. $HOCH{=}CHCO_2C_2H_5$

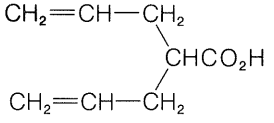
e. $C_2H_5OCOCOCH_2CO_2C_2H_5$

f. $C_2H_5O_2CCH_2CH(CO_2C_2H_5)COCO_2C_2H_5$

g.



h.



i. $CH_3CH_2COCH(CH_3)CH_2CH_2CH(CH_3)_2$

j. $CH_3CH_2CH_2CH(CH_2CH{=}CH_2)CO_2H$

k. $CH_3COCH(CO_2C_2H_5)_2$

l. $C_6H_5CH{=}CH{-}CH(OH)CH_2CO_2C_2H_5$

18-63 Write equations for the synthesis of each of the substances in Exercise 18-62 a–l from compounds with fewer carbon atoms, using the type of reactions discussed in Sections 18-9, 18-10, and 18-11. You may wish to review Sections 13-6 to 13-9 before beginning.

18-64 Direct reduction of aldehydes with 2,3-dimethyl-2-butylborane proceeds rapidly and gives the corresponding alcohol. Nonetheless, reduction of carboxylic acids with the same borane (Section 18-3C) proceeds slowly and gives high yields of aldehydes. Explain why the reaction of RCO_2H with the 2,3-dimethyl-2-butylborane produces RCHO instead of RCH_2OH.