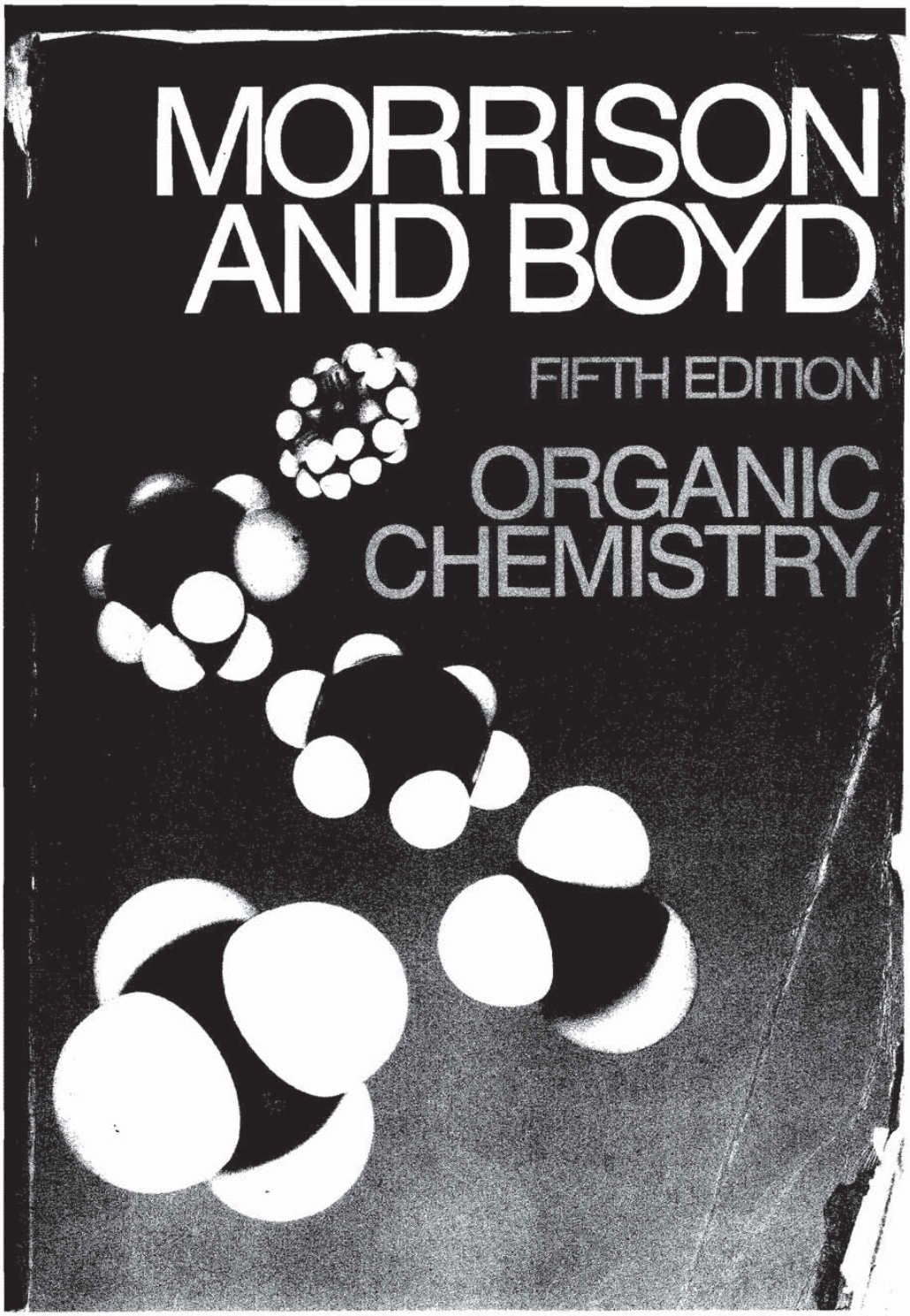

Organic Chemistry

Fifth Edition

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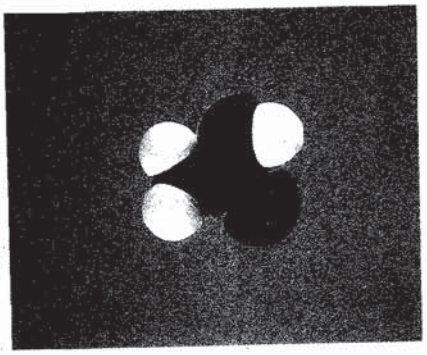
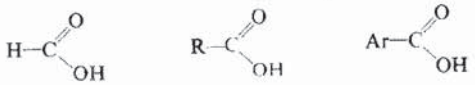
23

Carboxylic Acids



23.1 Structure

Of the organic compounds that show appreciable acidity, by far the most important are the carboxylic acids. These compounds contain the **carboxyl group**

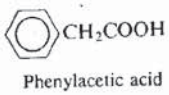


attached to hydrogen (HCOOH), an alkyl group (RCOOH), or an aryl group (ArCOOH). (See Fig. 23.1, p. 818.) For example:

HCOOH	CH_3COOH	$CH_3(CH_2)_{10}COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$
Formic acid	Acetic acid	Lauric acid	Oleic acid
Methanoic acid	Ethanoic acid	Dodecanoic acid	*cis*-9-Octadecenoic acid

Benzoic acid

p-Nitrobenzoic acid



Phenylacetic acid

$CH_3-CH(Br)-COOH$

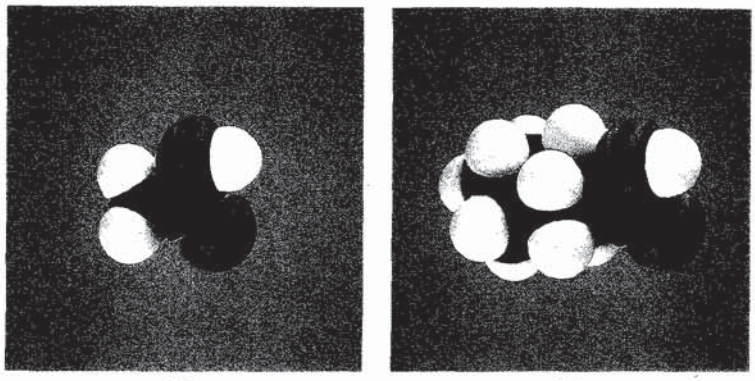
α-Bromopropionic acid
2-Bromopropanoic acid

Cyclohexanecarboxylic acid

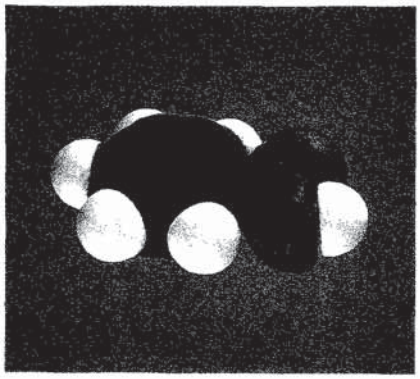
$CH_2=CHCOOH$

Acrylic acid
Propenoic acid

Whether the group is aliphatic or aromatic, saturated or unsaturated, substituted or unsubstituted, the properties of the carboxyl group are essentially the same.



(*a*) (*b*)



(*c*)

Figure 23.1 Models of some carboxylic acids: (*a*) acetic acid, CH_3COOH; (*b*) cyclohexanecarboxylic acid, *cyclo*-$C_6H_{11}COOH$; (*c*) benzoic acid, C_6H_5COOH.

23.2 Nomenclature

The aliphatic carboxylic acids have been known for a long time, and as a result have common names that refer to their sources rather than to their chemical structures. The **common names** of the more important acids are shown in Table 23.1. *Formic acid*, for example, adds the sting to the bite of an ant (Latin: *formica*,

Table 23.1 CARBOXYLIC ACIDS

Name	Formula	M.p., °C	B.p., °C	Solubility g/100 g H_2O
Formic	HCOOH	8	100.5	∞
Acetic	CH_3COOH	16.6	118	∞
Propionic	CH_3CH_2COOH	−22	141	∞
Butyric	$CH_3(CH_2)_2COOH$	− 6	164	∞
Valeric	$CH_3(CH_2)_3COOH$	−34	187	3.7
Caproic	$CH_3(CH_2)_4COOH$	− 3	205	1.0
Caprylic	$CH_3(CH_2)_6COOH$	16	239	0.7
Capric	$CH_3(CH_2)_8COOH$	31	269	0.2
Lauric	$CH_3(CH_2)_{10}COOH$	44	225^{100}	i.
Myristic	$CH_3(CH_2)_{12}COOH$	54	251^{100}	i.
Palmitic	$CH_3(CH_2)_{14}COOH$	63	269^{100}	i.
Stearic	$CH_3(CH_2)_{16}COOH$	70	287^{100}	i.
Oleic	*cis*-9-Octadecenoic	16	223^{10}	i.
Linoleic	*cis,cis*-9,12-Octadecadienoic	− 5	230^{16}	i.
Linolenic	*cis,cis,cis*-9,12,15-Octadecatrienoic	−11	232^{17}	i.
Cyclohexanecarboxylic	*cyclo*-$C_6H_{11}COOH$	31	233	0.20
Phenylacetic	$C_6H_5CH_2COOH$	77	266	1.66
Benzoic	C_6H_5COOH	122	250	0.34
o-Toluic	*o*-$CH_3C_6H_4COOH$	106	259	0.12
m-Toluic	*m*-$CH_3C_6H_4COOH$	112	263	0.10
p-Toluic	*p*-$CH_3C_6H_4COOH$	180	275	0.03
o-Chlorobenzoic	*o*-ClC_6H_4COOH	141		0.22
m-Chlorobenzoic	*m*-ClC_6H_4COOH	154		0.04
p-Chlorobenzoic	*p*-ClC_6H_4COOH	242		0.009
o-Bromobenzoic	*o*-BrC_6H_4COOH	148		0.18
m-Bromobenzoic	*m*-BrC_6H_4COOH	156		0.04
p-Bromobenzoic	*p*-BrC_6H_4COOH	254		0.006
o-Nitrobenzoic	*o*-$O_2NC_6H_4COOH$	147		0.75
m-Nitrobenzoic	*m*-$O_2NC_6H_4COOH$	141		0.34
p-Nitrobenzoic	*p*-$O_2NC_6H_4COOH$	242		0.03
Phthalic	*o*-$C_6H_4(COOH)_2$	231		0.70
Isophthalic	*m*-$C_6H_4(COOH)_2$	348		0.01
Terephthalic	*p*-$C_6H_4(COOH)_2$	300 *subl.*		0.002
Salicylic	*o*-HOC_6H_4COOH	159		0.22
p-Hydroxybenzoic	*p*-HOC_6H_4COOH	213		0.65
Anthranilic	*o*-$H_2NC_6H_4COOH$	146		0.52
m-Aminobenzoic	*m*-$H_2NC_6H_4COOH$	179		0.77
p-Aminobenzoic	*p*-$H_2NC_6H_4COOH$	187		0.3
o-Methoxybenzoic	*o*-$CH_3OC_6H_4COOH$	101		0.5
m-Methoxybenzoic	*m*-$CH_3OC_6H_4COOH$	110		s. hot
p-Methoxybenzoic (Anisic)	*p*-$CH_3OC_6H_4COOH$	184		0.04

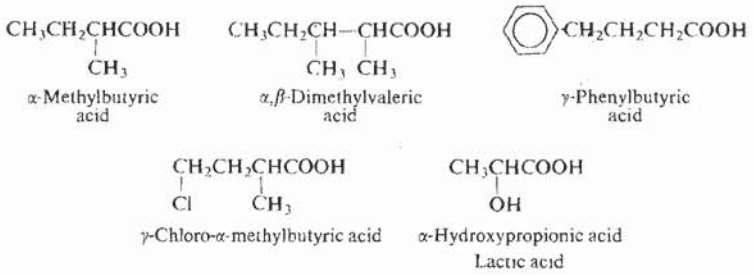
ant); *butyric acid* gives rancid butter its typical smell (Latin: *butyrum*, butter); and *caproic*, *caprylic*, and *capric acids* are all found in goat fat (Latin: *caper*, goat).

Branched-chain acids and substituted acids are named as derivatives of the straight-chain acids. To indicate the position of attachment, the Greek letters, α-, β-, γ-, δ-, etc., are used; the α-carbon is the one bearing the carboxyl group.

$$\overset{\delta}{C}-\overset{\gamma}{C}-\overset{\beta}{C}-\overset{\alpha}{C}-COOH$$

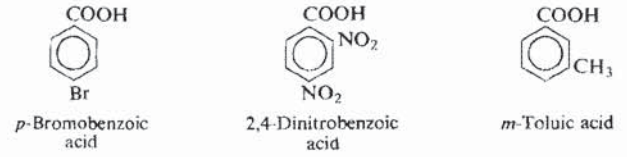
Used in common names

For example:

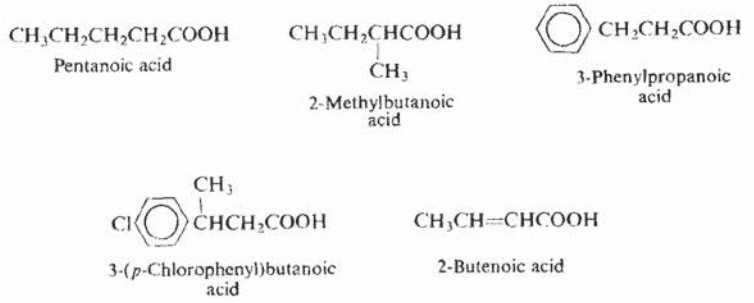


Generally the parent acid is taken as the one of longest carbon chain, although some compounds are named as derivatives of acetic acid.

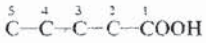
Aromatic acids, ArCOOH, are usually named as derivatives of the parent acid, **benzoic acid**, C_6H_5COOH. The methylbenzoic acids are given the special name of *toluic acids*.



The **IUPAC names** follow the usual pattern. The longest chain carrying the carboxyl group is considered the parent structure, and is named by replacing the *-e* of the corresponding alkane with **-oic acid**. For example:



The position of a substituent is indicated as usual by a number. We should notice



Used in IUPAC names

that the carboxyl carbon is always considered as C–1, and hence C–2 corresponds to α of the common names, C–3 to β, and so on. (*Caution*: Do not mix Greek letters with IUPAC names, or Arabic numerals with common names.)

The name of a **salt** of a carboxylic acid consists of the name of the cation (*sodium*, *potassium*, *ammonium*, etc.) followed by the name of the acid with the ending *-ic acid* changed to **-ate**. For example:

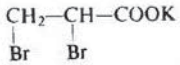
Sodium benzoate

$(CH_3COO)_2Ca$

Calcium acetate

$HCOONH_4$

Ammonium formate



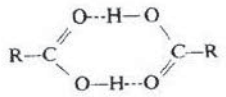
Potassium α,β-dibromopropionate
Potassium 2,3-dibromopropanoate

23.3 Physical properties

As we would expect from their structure, carboxylic acid molecules are polar, and like alcohol molecules can form hydrogen bonds with each other and with other kinds of molecules. The aliphatic acids therefore show very much the same solubility behavior as the alcohols: the first four are miscible with water, the five-carbon acid is partly soluble, and the higher acids are virtually insoluble. Water solubility undoubtedly arises from hydrogen bonding between the carboxylic acid and water. The simplest aromatic acid, benzoic acid, contains too many carbon atoms to show appreciable solubility in water.

Carboxylic acids are soluble in less polar solvents like ether, alcohol, benzene, etc.

We can see from Table 23.1 that as a class the carboxylic acids are even higher boiling than alcohols. For example, propionic acid (b.p. 141 °C) boils more than 20 °C higher than the alcohol of comparable molecular weight, *n*-butyl alcohol (b.p. 118 °C). These very high boiling points are due to the fact that a pair of carboxylic acid molecules are held together not by one but by two hydrogen bonds:



Problem 23.1 At 110 °C and 454 mm pressure, 0.11 g acetic acid vapor occupies 63.7 mL; at 156 °C and 458 mm, 0.081 g occupies 66.4 mL. Calculate the molecular weight of acetic acid in the vapor phase at each temperature. How do you interpret these results?

The odors of the lower aliphatic acids progress from the sharp, irritating odors of formic and acetic acids to the distinctly unpleasant odors of butyric, valeric, and caproic acids; the higher acids have little odor because of their low volatility.

23.4 Salts of carboxylic acids

Although much weaker than the strong mineral acids (sulfuric, hydrochloric, nitric), the carboxylic acids are tremendously more acidic than the very weak organic acids (alcohols, acetylene) we have so far studied; they are much stronger acids than water. Aqueous hydroxides therefore readily convert carboxylic acids into their salts; aqueous mineral acids readily convert the salts back into the carboxylic acids. Since we can do little with carboxylic acids without encountering

$$\underset{\text{Acid}}{RCOOH} \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} \underset{\text{Salt}}{RCOO^-}$$

this conversion into and from their salts, it is worthwhile for us to examine the properties of these salts.

Salts of carboxylic acids--like all salts—are crystalline non-volatile solids made up of positive and negative ions; their properties are what we would expect of such structures. The strong electrostatic forces holding the ions in the crystal lattice can be overcome only by heating to a high temperature, or by a very polar solvent. The temperature required for melting is so high that before it can be reached carbon–carbon bonds break and the molecule decomposes, generally in the neighborhood of 300–400 °C. A decomposition point is seldom useful for the identification of a compound, since it usually reflects the rate of heating rather than the identity of the compound.

The alkali metal salts of carboxylic acids (sodium, potassium, ammonium) are soluble in water but insoluble in non-polar solvents; most of the heavy metal salts (iron, silver, copper, etc.) are insoluble in water.

Thus we see that, except for the acids of four carbons or fewer, which are soluble both in water and in organic solvents, *carboxylic acids and their alkali metal salts show exactly opposite solubility behavior*. Because of the ready interconversion of acids and their salts, this difference in solubility behavior may be used in two important ways; for *identification* and for *separation*.

A water-insoluble organic compound that dissolves in cold dilute aqueous sodium hydroxide must be either a carboxylic acid or one of the few other kinds of organic compounds more acidic than water; that it is indeed a carboxylic acid can then be shown in other ways.

$$\underset{\substack{\text{Stronger acid}\\ \textit{Insoluble in } H_2O}}{RCOOH} + NaOH \longrightarrow \underset{\substack{\textit{Soluble in}\\ H_2O}}{RCOONa} + \underset{\substack{\text{Weaker}\\ \text{acid}}}{H_2O}$$

Instead of sodium hydroxide, we can use aqueous sodium bicarbonate; even if the unknown is water-soluble, its acidity is shown by the evolution of bubbles of CO_2.

$$\underset{\textit{Insoluble in } H_2O}{RCOOH} + NaHCO_3 \longrightarrow \underset{\textit{Soluble in } H_2O}{RCOONa} + H_2O + CO_2\uparrow$$

We can separate a carboxylic acid from non-acidic compounds by taking advantage of its solubility and their insolubility in aqueous base; once the separation has been accomplished, we can regenerate the acid by acidification of the aqueous solution. If we are dealing with solids, we simply stir the mixture with

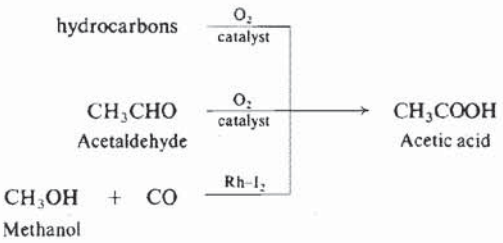
aqueous base and then filter the solution from insoluble, non-acidic materials; addition of mineral acid to the filtrate precipitates the carboxylic acid, which can be collected on a filter. If we are dealing with liquids, we shake the mixture with aqueous base in a separatory funnel and separate the aqueous layer from the insoluble organic layer; addition of acid to the aqueous layer again liberates the carboxylic acid, which can then be separated from the water. For completeness of separation and ease of handling, we often add a water-insoluble solvent like ether to the acidified mixture. The carboxylic acid is extracted from the water by the ether, in which it is more soluble; the volatile ether is readily removed by distillation from the comparatively high-boiling acid.

For example, an aldehyde prepared by the oxidation of a primary alcohol (Sec. 18.6) may very well be contaminated with the carboxylic acid; this acid can be simply washed out with dilute aqueous base. The carboxylic acid prepared by oxidation of an alkylbenzene (Sec. 15.11) may very well be contaminated with unreacted starting material; the carboxylic acid can be taken into solution by aqueous base, separated from the insoluble hydrocarbon, and regenerated by addition of mineral acid.

Since separations of this kind are more clear-cut and less wasteful of material, they are preferred wherever possible over recrystallization or distillation.

23.5 Industrial source

Acetic acid, by far the most important of all carboxylic acids, has been prepared chiefly by catalytic air oxidation of various hydrocarbons or of acetaldehyde. A newer method involves reaction between methanol and carbon monoxide in the

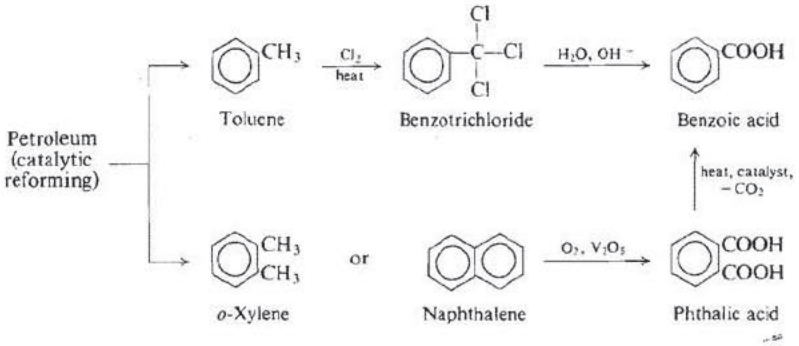


presence of an iodine–rhodium catalyst—still another example of catalysis by a transition metal complex (see Secs. 8.3, 17.6, and 20.5–20.8).

Large amounts of acetic acid are also produced as the dilute aqueous solution known as *vinegar*. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (*Acetobacter*) enzymes.

The most important sources of aliphatic carboxylic acids are the animal and vegetable **fats** (Secs. 37.2–37.4). From fats there can be obtained, in purity of over 90%, straight-chain carboxylic acids of even carbon number ranging from six to eighteen carbon atoms. These acids can be converted into the corresponding alcohols (Sec. 23.18), which can then be used, in the ways we have already studied (Sec. 18.8), to make a great number of other compounds containing long, straight-chain units.

The most important of the aromatic carboxylic acids, **benzoic acid** and the **phthalic acids**, are prepared on an industrial scale by a reaction we have already encountered: oxidation of alkylbenzenes (Sec. 15.11). The toluene and xylenes required are readily obtained from petroleum by catalytic reforming of aliphatic hydrocarbons (Sec. 15.5); much smaller amounts of these arenes are isolated directly from coal tar. Another precursor of phthalic acid (the *ortho* isomer) is the aromatic hydrocarbon *naphthalene*, also found in coal tar. Cheap oxidizing agents like chlorine or even air (in the presence of catalysts) are used.



Problem 23.2 In the presence of peroxides, carboxylic acids (or esters) react with 1-alkenes to yield more complicated acids. For example:

$$n\text{-}C_4H_9CH{=}CH_2 + CH_3CH_2CH_2COOH \xrightarrow{\text{peroxides}} n\text{-}C_4H_9CH_2CH_2CHCOOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad C_2H_5$$

1-Hexene — *n*-Butyric acid — 2-Ethyloctanoic acid (*70% yield*)

(a) Outline all steps in a likely mechanism for this reaction. (*Hint*: See Sec. 8.20.) Predict the products of similar reactions between: (b) 1-octene and propionic acid; (c) 1-decene and isobutyric acid; (d) 1-octene and ethyl malonate, $CH_2(COOC_2H_5)_2$.

Problem 23.3 (a) Carbon monoxide converts a sulfuric acid solution of each of the following into 2,2-dimethylbutanoic acid: 2-methyl-2-butene, *tert*-pentyl alcohol, neopentyl alcohol. Suggest a likely mechanism for this method of synthesizing carboxylic acids. (b) *n*-Butyl alcohol and *sec*-butyl alcohol give the same product. What would you expect it to be?

23.6 Preparation

The straight-chain aliphatic acids up to C_6 and those of even carbon number up to C_{18} are commercially available, as are the simple aromatic acids. Other carboxylic acids can be prepared by the methods outlined below.

PREPARATION OF CARBOXYLIC ACIDS

1. **Oxidation of primary alcohols.** Discussed in Sec. 18.6.

$$R{-}CH_2OH \xrightarrow{KMnO_4} R{-}COOH$$

Examples:

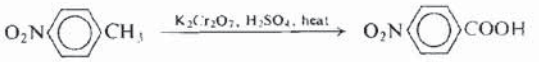
2-Methyl-1-butanol — 2-Methylbutanoic acid

Isobutyl alcohol — Isobutyric acid

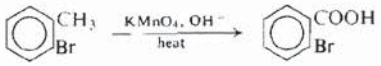
2. **Oxidation of alkylbenzenes.** Discussed in Sec. 15.11.

$$Ar{-}R \xrightarrow{KMnO_4 \text{ or } K_2Cr_2O_7} Ar{-}COOH$$

Examples:



p-Nitrotoluene — *p*-Nitrobenzoic acid



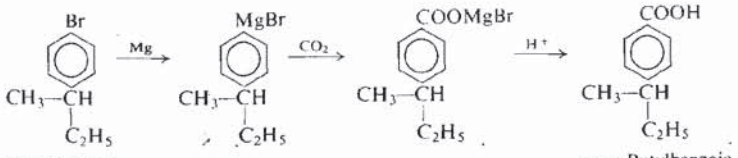
o-Bromotoluene — *o*-Bromobenzoic acid

3. **Carbonation of Grignard reagents.** Discussed in Sec. 23.7.

$$R{-}X \xrightarrow{Mg} R{-}MgX \xrightarrow{CO_2} R{-}COOMgX \xrightarrow{H^+} R{-}COOH$$

(or Ar—X) (or Ar—COOH)

Examples:



p-Bromo-*sec*-butylbenzene — *p*-*sec*-Butylbenzoic acid

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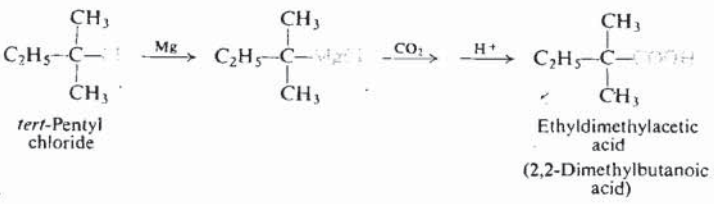
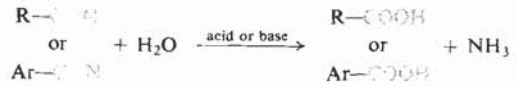
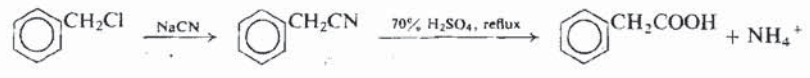
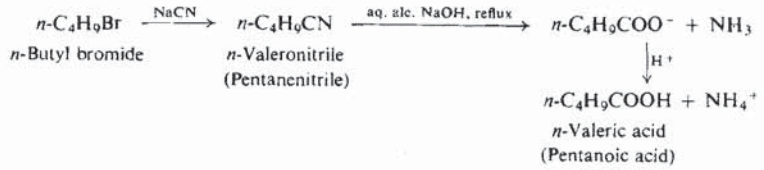


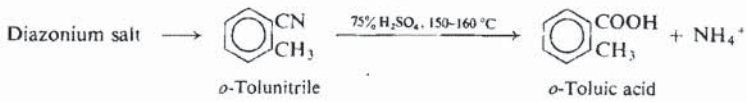
4. Hydrolysis of nitriles. Discussed in Sec. 23.8.



Examples:







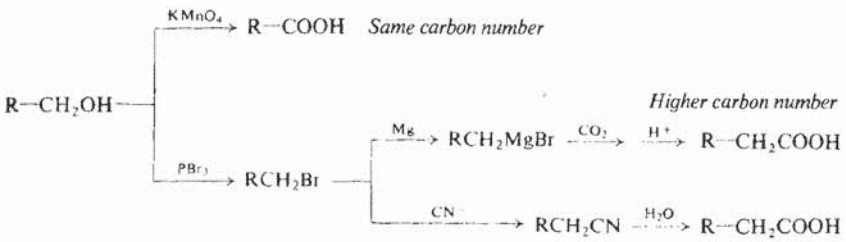
5. Malonic ester synthesis. Discussed in Sec. 30.2.

6. Special methods for phenolic acids. Discussed in Sec. 28.11.

All the methods listed are important; our choice is governed by the availability of starting materials.

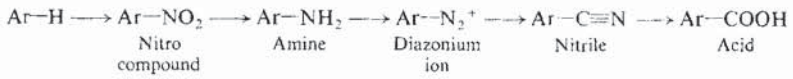
Oxidation is the most direct and is generally used when possible, some lower aliphatic acids being made from the available alcohols, and substituted aromatic acids from substituted toluenes.

The **Grignard synthesis** and the **nitrile synthesis** have the special advantage of increasing the length of a carbon chain, and thus extending the range of available materials. In the aliphatic series both Grignard reagents and nitriles are prepared from halides, which in turn are usually prepared from alcohols. The syntheses thus amount to the preparation of acids from alcohols containing one less carbon atom.



Problem 23.4 Which carboxylic acid can be prepared from *p*-bromotoluene: (a) by direct oxidation? (b) by free-radical chlorination followed by the nitrile synthesis?

Aromatic nitriles generally cannot be prepared from the unreactive aryl halides (Sec. 29.5). Instead they are made from diazonium salts by a reaction we shall discuss later (Sec. 27.14). Diazonium salts are prepared from aromatic amines, which in turn are prepared from nitro compounds. Thus the carboxyl group eventually occupies the position on the ring where a nitro group was originally introduced by direct nitration (Sec. 14.8).

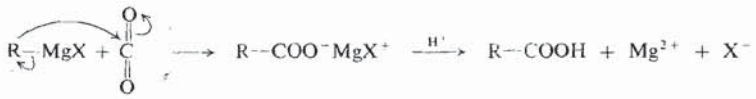


For the preparation of quite complicated acids, the most versatile method of all is used, the *malonic ester synthesis* (Sec. 30.2).

23.7 Grignard synthesis

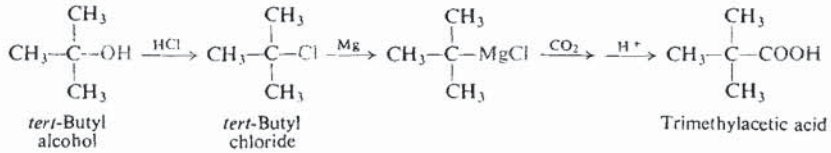
The Grignard synthesis of a carboxylic acid is carried out by bubbling gaseous CO_2 into the ether solution of the Grignard reagent, or by pouring the Grignard reagent on crushed Dry Ice (solid CO_2); in the latter method Dry Ice serves not only as reagent but also as cooling agent.

The Grignard reagent adds to the carbon–oxygen double bond just as in the reaction with aldehydes and ketones (Sec. 17.14). The product is the magnesium salt of the carboxylic acid, from which the free acid is liberated by treatment with mineral acid.

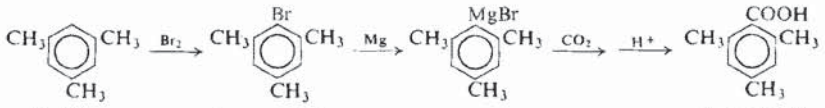


The Grignard reagent can be prepared from primary, secondary, tertiary, or aromatic halides; the method is limited only by the presence of other reactive

groups in the molecule (Sec. 17.17). The following syntheses illustrate the application of this method:



tert-Butyl alcohol — *tert*-Butyl chloride — Trimethylacetic acid



Mesitylene — Bromomesitylene — Mesitoic acid (2,4,6-Trimethylbenzoic acid)

23.8 Nitrile synthesis

Aliphatic nitriles are prepared by treatment of alkyl halides with sodium cyanide in a solvent that will dissolve both reactants; in dimethyl sulfoxide, reaction occurs rapidly and exothermically at room temperature. The resulting nitrile is then hydrolyzed to the acid by boiling aqueous alkali or acid.

$$R{-}X + CN^- \longrightarrow R{-}C{\equiv}N + X^-$$

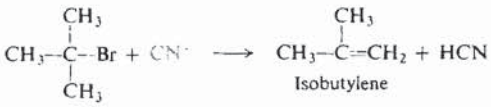
$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+} R{-}COOH + NH_4^+$$

$$R{-}C{\equiv}N + H_2O \xrightarrow{OH^-} R{-}COO^- + NH_3$$

The reaction of an alkyl halide with cyanide ion involves nucleophilic substitution (Sec. 5.8). The fact that HCN is a very weak acid tells us that cyanide ion is a strong base; as we might expect, this strongly basic ion can abstract hydrogen ion and thus cause elimination as well as substitution. Indeed, with tertiary halides

$CH_3CH_2CH_2CH_2Br + CN^- \longrightarrow CH_3CH_2CH_2CH_2CN$ — 1° halide: *substitution*

n-Butyl bromide — Valeronitrile



tert-Butyl bromide — Isobutylene — 3° halide: *elimination*

elimination is the principal reaction; even with secondary halides the yield of substitution product is poor. Here again we find a nucleophilic substitution reaction that is of synthetic importance *only when primary halides are used.*

As already mentioned, aromatic nitriles are made, not from the unreactive aryl halides, but from diazonium salts (Sec. 27.14).

Although nitriles are sometimes named as *cyanides* or as *cyano* compounds, they generally take their names from the acids they yield upon hydrolysis. They are named by dropping *-ic acid* from the common name of the acid and adding **-nitrile**; usually for euphony an "o" is inserted between the root and the ending (e.g., *acetonitrile*). In the IUPAC system they are named by adding *-nitrile* to the name of the parent hydrocarbon (e.g., *ethanenitrile*). For example:

23.9 Reactions

The characteristic chemical behavior of carboxylic acids is, of course, determined by their functional group, **carboxyl**, —COOH. This group is made up of a carbonyl group (C=O) and a hydroxyl group (—OH). As we shall see, it is the —OH that actually undergoes nearly every reaction—loss of H^+, or replacement by another group—but *it does so in a way that is possible only because of the effect of the* C=O.

The rest of the molecule undergoes reactions characteristic of its structure; it may be aliphatic or aromatic, saturated or unsaturated, and may contain a variety of other functional groups.

REACTIONS OF CARBOXYLIC ACIDS

1. Acidity. Salt formation. Discussed in Secs. 23.4, 23.10–23.14.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

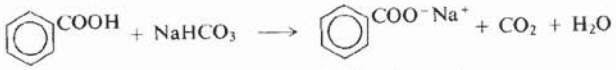
Examples:

$$2CH_3COOH + Zn \longrightarrow (CH_3COO^-)_2Zn^{2+} + H_2$$

Acetic acid — Zinc acetate

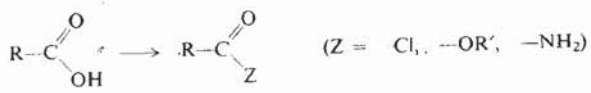
$$CH_3(CH_2)_{10}COOH + NaOH \longrightarrow CH_3(CH_2)_{10}COO^-Na^+ + H_2O$$

Lauric acid — Sodium laurate



Benzoic acid — Sodium benzoate

2. Conversion into functional derivatives



(Z = Cl, —OR′, —NH_2)

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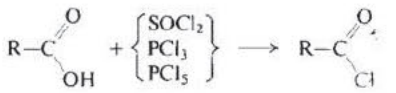
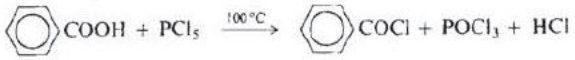
(a) Conversion into acid chlorides. Discussed in Sec. 23.15.

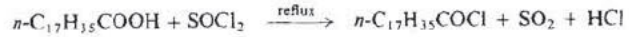


Acid chloride

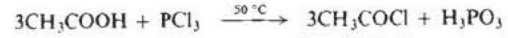
Examples:



Benzoic acid — Benzoyl chloride

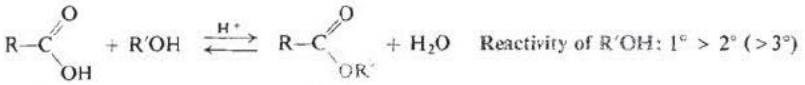


Stearic acid — Thionyl chloride — Stearoyl chloride

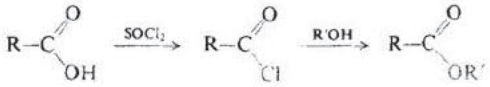


Acetic acid — Acetyl chloride

(b) Conversion into esters. Discussed in Secs. 23.16 and 24.15.

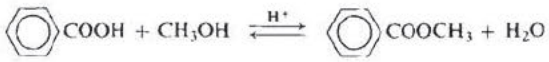


An ester

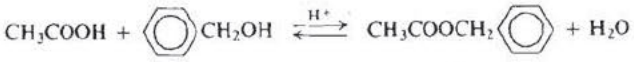


An acid chloride — An ester

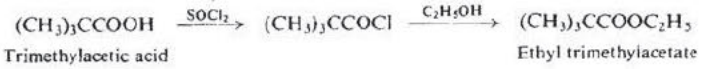
Examples:



Benzoic acid — Methanol — Methyl benzoate



Acetic acid — Benzyl alcohol — Benzyl acetate



Trimethylacetic acid — Ethyl trimethylacetate

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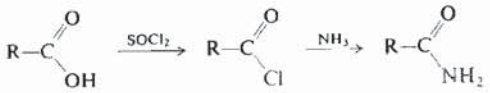
(c) **Conversion into amides.** Discussed in Sec. 23.17.



An acid chloride An amide

Example:

$C_6H_5CH_2COOH \xrightarrow{SOCl_2} C_6H_5CH_2COCl \xrightarrow{NH_3} C_6H_5CH_2CONH_2$

Phenylacetic acid — Phenylacetyl chloride — Phenylacetamide

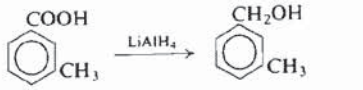
3. **Reduction.** Discussed in Sec. 23.18.

$R{-}COOH \xrightarrow{LiAlH_4} R{-}CH_2OH$ 1° alcohol *Also reduced via esters* (Sec. 24.22)

Examples:

$4(CH_3)_3CCOOH + 3LiAlH_4 \xrightarrow{ether} [(CH_3)_3CCH_2O]_4AlLi + 2LiAlO_2 + 4H_2 \xrightarrow{H^+} (CH_3)_3CCH_2OH$

Trimethylacetic acid — Neopentyl alcohol (2,2-Dimethyl-1-propanol)



m-Toluic acid *m*-Methylbenzyl alcohol

4. **Substitution in alkyl or aryl group**

(a) **Alpha-halogenation of aliphatic acids. Hell–Volhard–Zelinsky reaction.** Discussed in Sec. 23.19.

$RCH_2COOH + X_2 \xrightarrow{P} RCHCOOH + HX \qquad X_2 = Cl_2, Br_2$ (X = An α-halo acid)

Examples:

$CH_3COOH \xrightarrow{Cl_2, P} ClCH_2COOH \xrightarrow{Cl_2, P} Cl_2CHCOOH \xrightarrow{Cl_2, P} Cl_3CCOOH$

Acetic acid — Chloroacetic acid — Dichloroacetic acid — Trichloroacetic acid

Isovaleric acid α-Bromoisovaleric acid

CONTINUED

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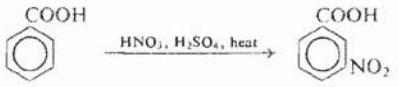
(b) **Ring substitution in aromatic acids.** Discussed in Secs. 14.5 and 14.15.

—COOH: deactivates, and directs *meta* in electrophilic substitution.

Example:



Benzoic acid *m*-Nitrobenzoic acid ■

The most characteristic property of the carboxylic acids is the one that gives them their name: **acidity**. Their tendency to give up a hydrogen ion is such that in aqueous solution a measurable equilibrium exists between acid and ions; they are thus much more acidic than any other class of organic compounds we have studied so far.

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

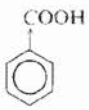
The OH of an acid can be replaced by a Cl, OR', or NH_2 group to yield an *acid chloride*, an *ester*, or an *amide*. These compounds are called **functional derivatives** of acids; they all contain the **acyl group**:

The functional derivatives are all readily reconverted into the acid by simple hydrolysis, and are often converted one into another.

One of the few reducing agents capable of reducing an acid directly to an alcohol is *lithium aluminum hydride*, $LiAlH_4$.

The hydrocarbon portion of an aliphatic acid can undergo the free-radical halogenation characteristic of alkanes, but because of the random nature of the substitution it is seldom used. The presence of a small amount of phosphorus, however, causes halogenation (by a heterolytic mechanism) to take place *exclusively at the alpha position*. This reaction is known as the **Hell–Volhard–Zelinsky reaction**, and it is of great value in synthesis.

An aromatic ring bearing a carboxyl group undergoes the aromatic electrophilic substitution reactions expected of a ring carrying a deactivating, *meta*-directing group. Deactivation is so strong that the Friedel–Crafts reaction does not take place. We have already accounted for this effect of the —COOH group on the basis of its strong electron-withdrawing tendencies (Sec. 14.16).



—COOH withdraws electrons: deactivates, directs meta in electrophilic substitution

Decarboxylation, that is, elimination of the —COOH group as CO_2, is of limited importance for aromatic acids, and highly important for certain substituted aliphatic acids: malonic acids (Sec. 30.2) and β-keto acids (Sec. 30.3). It is worthless for most simple aliphatic acids, yielding a complicated mixture of hydrocarbons.

23.10 Ionization of carboxylic acids. Acidity constant

In aqueous solution a carboxylic acid exists in equilibrium with the carboxylate anion and the hydrogen ion (actually, of course, the hydronium ion, H_3O^+).

$$RCOOH + H_2O \rightleftharpoons RCOO^- + H_3O^+$$

As for any equilibrium, the concentrations of the components are related by the expression

$$K_{eq} = \frac{[RCOO^-][H_3O^+]}{[H_2O][RCOOH]}$$

Since the concentration of water, the solvent, remains essentially constant, we can combine it with K_{eq} to obtain the expression

$$K_a = \frac{[RCOO^-][H_3O^+]}{[RCOOH]}$$

in which K_a equals $K_{eq}[H_2O]$. This new constant, K_a, is called the **acidity constant.**

Every carboxylic acid has its characteristic K_a, which indicates how strong an acid it is. Since the acidity constant is the ratio of ionized to un-ionized material, the larger the K_a the greater the extent of the ionization (under a given set of conditions) and the stronger the acid. We use the K_a values, then, to compare in an exact way the strengths of different acids.

We see in Table 23.2 (p. 839) that unsubstituted aliphatic and aromatic acids have K_a values of about 10^{-4} to 10^{-5} (0.0001 to 0.00001). This means that they are weakly acidic, with only a slight tendency to release protons.

By the same token, carboxylate anions are moderately basic, with an appreciable tendency to combine with protons. They react with water to increase the concentration of hydroxide ions, a reaction often referred to as *hydrolysis*. As a

$$RCOO^- + H_2O \rightleftharpoons RCOOH + OH^-$$

result aqueous solutions of carboxylate salts are slightly alkaline. (The basicity of an aqueous solution of a carboxylate salt is due chiefly, of course, to the carboxylate anions, not to the comparatively few hydroxide ions they happen to generate.)

We may now expand the series of relative acidities and basicities:

Acidity $RCOOH > HOH > ROH > HC{\equiv}CH > NH_3 > RH$

Basicity $RCOO^- < HO^- < RO^- < HC{\equiv}C^- < NH_2^- < R^-$

Certain substituted acids are much stronger or weaker than a typical acid like CH_3COOH. We shall see that the acid-strengthening or acid-weakening effect of a substituent can be accounted for in a reasonable way; however, we must first learn a little more about equilibrium in general.

23.11 Equilibrium

So far we have dealt very little with the problem of equilibrium. Under the conditions employed, most of our reactions have been essentially irreversible; that is, they have been one-way reactions. With a few exceptions—1,4-addition, for example (Sec. 10.27)—the products obtained, and their relative yields, have been determined by how fast reactions go and not by how nearly to completion they proceed before equilibrium is reached. Consequently, we have been concerned with the relationship between structure and rate; now we shall turn to the relationship between structure and equilibrium.

Let us consider the reversible reaction between A and B to form C and D. The

$$A + B \rightleftharpoons C + D$$

yield of C and D does not depend upon how fast A and B react, but rather upon how completely they have reacted when equilibrium is reached.

The concentrations of the various components are related by the familiar expression

$$K_{eq} = \frac{[C][D]}{[A][B]}$$

in which K_{eq} is the equilibrium constant. The more nearly a reaction has proceeded to completion when it reaches equilibrium, the larger is [C][D] compared with [A][B], and hence the larger the K_{eq}. The value of K_{eq} is therefore a measure of the tendency of the reaction to go to completion.

The value of K_{eq} is determined by the change in *free energy*, G, on proceeding from reactants to products (Fig. 23.2). The exact relationship is given by the expression

$$\Delta G^\circ = -2.303RT \log K_{eq}$$

where ΔG° is the *standard free energy change*.

Free energy change is related to our familiar quantity ΔH (precisely ΔH°, which is only slightly different) by the expression,

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

where ΔS° is the *standard entropy change*. Entropy corresponds, roughly, to the *randomness* of the system. To the extent that $T\Delta S^\circ$ contributes to ΔG°, equilibrium tends to shift toward the side in which fewer restrictions are placed on the positions of atoms and molecules. ("Die Energie der Welt ist constant. Die Entropie der Welt strebt einem Maximum zu."—*Clausius, 1865.*)

Under the same experimental conditions two reversible reactions have K_{eq} values of different sizes because of a difference in ΔG°. In attempting to understand the effect of structure on position of equilibrium, we shall estimate differences in relative stabilities of reactants and products. Now, what we estimate in this way are not differences in free energy change but differences in potential energy change. It turns out that very often these differences are *proportional to* differences in ΔG°. So long as we compare closely related compounds, the predictions we make by this approach are generally good ones.

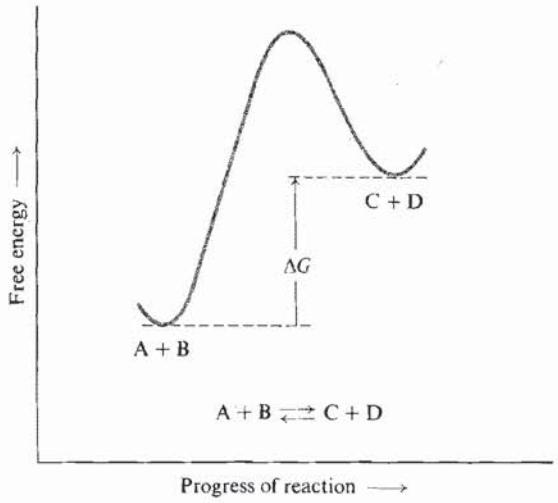


Figure 23.2 Free energy curve for a reversible reaction.

These predictions are good ones despite the fact that the free energy changes on which they depend are made up to varying degrees of ΔH and $\Delta S°$. For example, *p*-nitrobenzoic acid is a stronger acid than benzoic acid. We attribute this (Sec. 23.14) to stabilization of the *p*-nitrobenzoate anion (relative to the benzoate anion) through dispersal of charge by the electron-withdrawing nitro group. Yet, in this case, the greater acidity is due about as much to a more favorable $\Delta S°$ as to a more favorable ΔH. How can our simple "stabilization by dispersal of charge" account for an effect that involves the randomness of a system?

Stabilization *is* involved, but it appears partly in the $\Delta S°$ for this reason. Ionization of an acid is possible only because of solvation of the ions produced: the many ion–dipole bonds provide the energy needed for dissociation. But solvation requires that molecules of solvent leave their relatively unordered arrangement to cluster in some ordered fashion about the ions. This is good for the ΔH but bad for the $\Delta S°$. Now, because of its greater intrinsic stability, the *p*-nitrobenzoate anion does not *need* as many solvent molecules to help stabilize it as the benzoate anion does. The $\Delta S°$ is thus more favorable. We can visualize the *p*-nitrobenzoate ion accepting only as many solvent molecules as it has to, and stopping when the gain in stability (decrease in enthalpy) is no longer worth the cost in entropy.

(In the same way, it has been found that very often a more polar solvent speeds up a reaction—as, for example, an S_N1 reaction of alkyl halides (Sec. 6.5)—not so much by lowering E_{act} as by bringing about a more favorable entropy of activation. A more polar solvent is already rather ordered, and its clustering about the ionizing molecule amounts to very little loss of randomness—indeed, it may even amount to an *increase* in randomness.)

In dealing with rates, we compare the stability of the reactants with the stability of the transition state. In dealing with equilibria, we shall compare the stability of the reactants with the stability of the products. For closely related reactions, we are justified in assuming that the more stable the products relative to the reactants, the further reaction proceeds toward completion.

By the organic chemist's approach we can make *very* good predictions indeed. We can not only account for, say, the relative acidities of a set of acids, but we can correlate these acidities *quantitatively* with the relative acidities of another set of acids, or even with the relative rates of a set of reactions. These relationships are summarized in the Hammett equation (named for Louis P. Hammett of Columbia University),

$$\log\frac{K}{K_0} = \rho\sigma \qquad \text{or} \qquad \log\frac{k}{k_0} = \rho\sigma$$

where K or k refers to the reaction of a *m*- or *p*-substituted phenyl compound (say, ionization of a substituted benzoic acid) and K_0 or k_0 refers to the same reaction of the unsubstituted compound (say, ionization of benzoic acid).

The *substituent constant* (σ, *sigma*) is a number (+ or −) indicating the relative electron-withdrawing or electron-releasing effect of a particular substituent. The *reaction constant* (ρ, *rho*) is a number (+ or −) indicating the relative *need* of a particular reaction for electron withdrawal or electron release.

A vast amount of research has shown that the Hammett relationship holds for *hundreds of sets of reactions*. (Ionization of 40-odd *p*-substituted benzoic acids, for example, is *one* set.) By use of just two tables—one of σ constants and one of ρ constants—we can calculate the relative K_{eq} values or relative rates for thousands of individual reactions. For example, from the σ value for *m*-NO_2 (+ 0.710) and the ρ value for ionization of benzoic acids in water at 25 °C (+ 1.000), we can calculate that K_a for *m*-nitrobenzoic acid is 5.13 times as big as the K_a for benzoic acid. Using the same σ value, and the ρ value for acid-catalyzed hydrolysis of benzamides in 60% ethanol at 80 °C (−0.298), we can calculate that *m*-nitrobenzamide will be hydrolyzed only 0.615 times as fast as benzamide.

The Hammett relationship is called a *linear free energy relationship* since it is based on—and reveals—the fact that a linear relationship exists between free energy change and the effect exerted by a substituent. Other linear free energy relationships are known, which take into account steric as well as electronic effects, and which apply to *ortho* substituted phenyl compounds as well as *meta* and *para*, and to aliphatic as well as aromatic compounds. Together they make up what is perhaps the greatest accomplishment of physical organic chemistry.

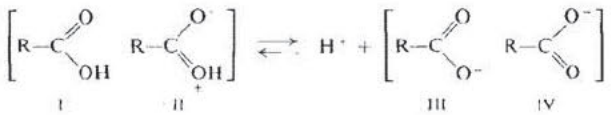
23.12 Acidity of carboxylic acids

Let us see how the acidity of carboxylic acids is related to structure. In doing this we shall assume that acidity is determined chiefly by the difference in stability between the acid and its anion.

First, and most important, there is the fact that carboxylic acids are acids at all. How can we account for the fact that the —OH of a carboxylic acid tends to release a hydrogen ion so much more readily than the —OH of, say, an alcohol? Let us examine the structures of the reactants and products in these two cases.

We see that the alcohol and alkoxide ion are each represented satisfactorily by a single structure. However, we can draw two reasonable structures (I and II) for the carboxylic acid and two reasonable structures (III and IV) for the carboxylate anion. Both acid and anion are resonance hybrids. But is resonance equally

$$R{-}O{-}H \rightleftharpoons H^+ + R{-}O^-$$



I II III IV

Non-equivalent: *resonance less important*

Equivalent: *resonance more important*

important in the two cases? By the principles of Sec. 10.10 we know that resonance is much more important between the exactly equivalent structures III and IV than between the non-equivalent structures I and II. As a result, although both acid and anion are stabilized by resonance, stabilization is far greater for the anion than for the acid (see Fig. 23.3). Equilibrium is shifted in the direction of increased ionization, and K_a is increased.

Strictly speaking, resonance is less important for the acid because the contributing structures are of *different stability*, whereas the equivalent structures for the ion must necessarily be of *equal stability*. In structure II two atoms of similar electronegativity carry opposite charges; since energy must be supplied to separate opposite charges, II should contain more energy and hence be less stable than I. Consideration of *separation of charge* is one of the rules of thumb (Sec. 10.10) that can be used to estimate relative stability and hence relative importance of a contributing structure.

The acidity of a carboxylic acid is thus due to the powerful resonance stabilization of its anion. *This stabilization and the resulting acidity are possible only because of the presence of the carbonyl group.*

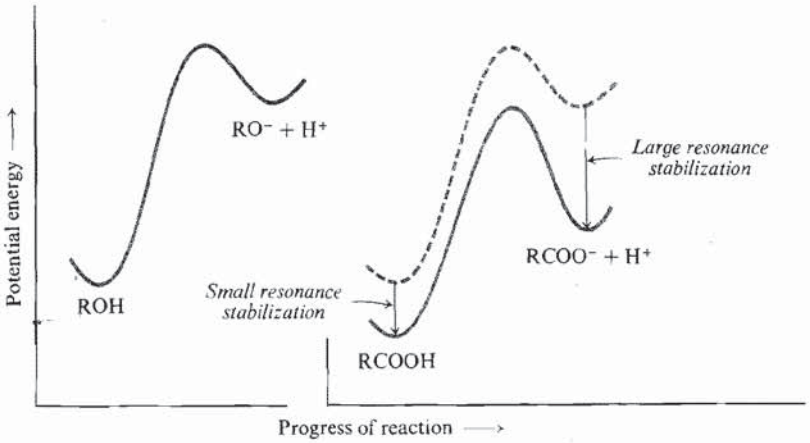
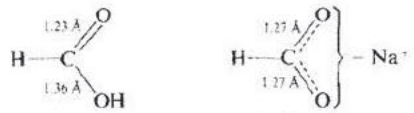


Figure 23.3 Molecular structure and position of equilibrium. A carboxylic acid yields a resonance-stabilized anion; it is a stronger acid than an alcohol. (The plots are aligned with each other for easy comparison.)

23.13 Structure of carboxylate ions

According to the resonance theory, then, a carboxylate ion is a hybrid of two structures which, being of equal stability, contribute equally. Carbon is joined to each oxygen by a "one-and-a-half" bond. The negative charge is evenly distributed over both oxygen atoms.

That the anion is indeed a resonance hybrid is supported by the evidence of bond length. Formic acid, for example, contains a carbon–oxygen double bond and a carbon–oxygen single bond; we would expect these bonds to have different lengths. Sodium formate, on the other hand, if it is a resonance hybrid, ought to contain two equivalent carbon–oxygen bonds; we would expect these to have the same length, intermediate between double and single bonds. X-ray and electron diffraction show that these expectations are correct. Formic acid contains one carbon–oxygen bond of 1.36 Å (single bond) and another of 1.23 Å (double bond); sodium formate contains two equal carbon–oxygen bonds, each 1.27 Å long.



Formic acid Sodium formate

Problem 23.5 How do you account for the fact that the three carbon–oxygen bonds in $CaCO_3$ have the same length, and that this length (1.31 Å) is greater than that found in sodium formate?

What does this resonance mean in terms of orbitals? Carboxyl carbon is joined to the three other atoms by σ bonds (Fig. 23.4); since these bonds utilize sp^2 orbitals (Sec. 7.2), they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps equally well p orbitals from *both* of the oxygens, to form hybrid bonds (compare benzene, Sec. 13.8). In this way the electrons are bound not just

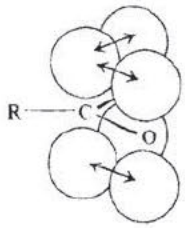


Figure 23.4 Carboxylate ion. Overlap of p orbitals in both directions: delocalization of π electrons, and dispersal of charge.

to one or two nuclei but to *three* nuclei (one carbon and two oxygens); they are therefore held more tightly, the bonds are stronger, and the anion is more stable. This participation of electrons in more than one bond, this smearing-out or delocalization of the electron cloud, is what is meant by representing the anion as a resonance hybrid of two structures.

Problem 23.6 How do you account for the fact that the α-hydrogens of an aldehyde (say, *n*-butyraldehyde) are much more acidic than any other hydrogens in the molecule? (Check your answer in Sec. 25.1.)

$$\overset{\gamma}{CH_3}\overset{\beta}{CH_2}\overset{\alpha}{CH_2}\overset{}{C}(H)=O$$

n-Butyraldehyde

23.14 Effect of substituents on acidity

Next, let us see how changes in the structure of the group bearing the —COOH affect the acidity. Any factor that stabilizes the anion more than it stabilizes the acid should increase the acidity; any factor that makes the anion less stable should decrease acidity. From what we have learned about carbocations, we know what we might reasonably expect. Electron-withdrawing substituents should disperse the negative charge, stabilize the anion, and thus increase acidity. Electron-releasing substituents should intensify the negative charge, destabilize the anion, and thus decrease acidity.

stabilizes anion, strengthens acid

destabilizes anion, weakens acid

The K_a values listed in Table 23.2 are in agreement with this prediction.

Table 23.2 ACIDITY CONSTANTS OF CARBOXYLIC ACIDS

	K_a		K_a
HCOOH	17.7×10^{-5}	$CH_3CHClCH_2COOH$	8.9×10^{-5}
CH_3COOH	1.75 ,,	$ClCH_2CH_2CH_2COOH$	2.96 ,,
$ClCH_2COOH$	136 ,,	FCH_2COOH	260 ,,
$Cl_2CHCOOH$	5530 ,,	$BrCH_2COOH$	125 ,,
Cl_3CCOOH	23200 ,,	ICH_2COOH	67 ,,
$CH_3CH_2CH_2COOH$	1.52 ,,	$C_6H_5CH_2COOH$	4.9 ,,
$CH_3CH_2CHClCOOH$	139 ,,	$p\text{-}O_2NC_6H_4CH_2COOH$	14.1 ,,

ACIDITY CONSTANTS OF SUBSTITUTED BENZOIC ACIDS

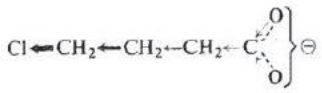
K_a of benzoic acid = 6.3×10^{-5}

	K_a		K_a		K_a
$p\text{-}NO_2$	36×10^{-5}	$m\text{-}NO_2$	32×10^{-5}	$o\text{-}NO_2$	670×10^{-5}
p-Cl	10.3 ,,	m-Cl	15.1 ,,	o-Cl	120 ,,
$p\text{-}CH_3$	4.2 ,,	$m\text{-}CH_3$	5.4 ,,	$o\text{-}CH_3$	12.4 ,,
$p\text{-}OCH_3$	3.3 ,,	$m\text{-}OCH_3$	8.2 ,,	$o\text{-}OCH_3$	8.2 ,,
p-OH	2.6 ,,	m-OH	8.3 ,,	o-OH	105 ,,
$p\text{-}NH_2$	1.4 ,,	$m\text{-}NH_2$	1.9 ,,	$o\text{-}NH_2$	1.6 ,,

Looking first at the aliphatic acids, we see that the electron-withdrawing halogens strengthen acids: chloroacetic acid is 100 times as strong as acetic acid, dichloroacetic acid is still stronger, and trichloroacetic acid is more than 10 000 times as strong as the unsubstituted acid. The other halogens exert similar effects.

Problem 23.7 (a) What do the K_a values of the monohaloacetic acids tell us about the relative strengths of the inductive effects of the different halogens? (b) On the basis of Table 23.2, what kind of inductive effect does the phenyl group, $-C_6H_5$, appear to have?

α-Chlorobutyric acid is about as strong as chloroacetic acid. As the chlorine is moved away from the —COOH, however, its effect rapidly dwindles: β-chlorobutyric acid is only six times as strong as butyric acid, and γ-chlorobutyric acid is only twice as strong. It is typical of inductive effects that they decrease rapidly with distance, and are seldom important when acting through more than four atoms.



Inductive effect: *decreases with distance*

The aromatic acids are similarly affected by substituents: $-CH_3$, —OH, and $-NH_2$ make benzoic acid weaker, and —Cl and $-NO_2$ make benzoic acid stronger. We recognize the acid-weakening groups as the ones that activate the ring toward electrophilic substitution (and deactivate toward nucleophilic substitution). The acid-strengthening groups are the ones that deactivate toward electrophilic substitution (and activate toward nucleophilic substitution). Furthermore, the groups that have the largest effects on reactivity—whether activating or deactivating—have the largest effects on acidity.

The —OH and $-OCH_3$ groups display both kinds of effect we have attributed to them (Sec. 14.18): from the *meta* position, an electron-withdrawing acid-strengthening inductive effect; and from the *para* position, an electron-releasing acid-weakening resonance effect (which at this position outweighs the inductive effect). Compare the two effects exerted by halogen on electrophilic aromatic substitution (Sec. 14.19).

ortho-Substituted acids do not fit into the pattern set by their *meta* and *para* isomers, and by aliphatic acids. Nearly all *ortho* substituents exert an effect of the same kind—acid-strengthening—whether they are electron-withdrawing or electron-releasing, and the effect is unusually large. (Compare, for example, the effects of *o*-NO_2 and *o*-CH_3, of *o*-NO_2 and *m*- or *p*-NO_2.) This *ortho* effect undoubtedly has to do with the *nearness* of the groups involved, but is more than just steric hindrance arising from their bulk.

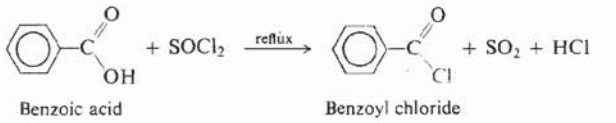
Thus we see that the same concepts—inductive effect and resonance—that we found so useful in dealing with rates of reaction are also useful in dealing with equilibria. By using these concepts to estimate the stabilities of anions, we are able to predict the relative strengths of acids; in this way we can account not only for the effect of substituents on the acid strength of carboxylic acids but also for the very fact that the compounds are acids.

Problem 23.8 There is evidence that certain groups like *p*-methoxy weaken the acidity of benzoic acids not so much by destabilizing the anion as by stabilizing the acid. Draw structures to show the kind of resonance that might be involved. Why would you expect such resonance to be more important for the acid than for the anion?

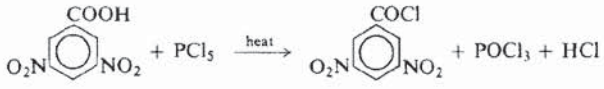
23.15 Conversion into acid chlorides

A carboxylic acid is perhaps more often converted into the acid chloride than into any other of its functional derivatives. From the highly reactive acid chloride there can then be obtained many other kinds of compounds, including esters and amides (Sec. 24.8).

An acid chloride is prepared by substitution of —Cl for the —OH of a carboxylic acid. Three reagents are commonly used for this purpose: *thionyl chloride*, $SOCl_2$; *phosphorus trichloride*, PCl_3; and *phosphorus pentachloride*, PCl_5. (Of what inorganic acids might we consider these reagents to be the acid chlorides?) For example:



Benzoic acid — Benzoyl chloride

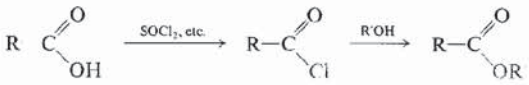


3,5-Dinitrobenzoic acid — 3,5-Dinitrobenzoyl chloride

Thionyl chloride is particularly convenient, since the products formed besides the acid chloride are gases and thus easily separated from the acid chloride; any excess of the low-boiling thionyl chloride (79 °C) is easily removed by distillation.

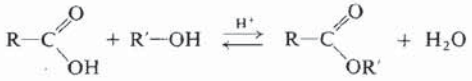
23.16 Conversion into esters

Acids are frequently converted into their esters via the acid chlorides:



Acid — Acid chloride — Ester

A carboxylic acid is converted directly into an ester when heated with an alcohol in the presence of a little mineral acid, usually concentrated sulfuric acid or dry hydrogen chloride. This reaction is reversible, and generally reaches equilibrium when there are appreciable quantities of both reactants and products present.



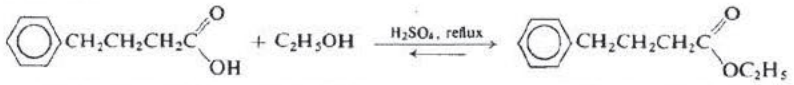
Acid — Alcohol — Ester

For example, when we allow one mole of acetic acid and one mole of ethyl alcohol to react in the presence of a little sulfuric acid until equilibrium is reached (after several hours), we obtain a mixture of about two-thirds mole each of ester and water, and one-third mole each of acid and alcohol. We obtain this same equilibrium

mixture, of course, if we start with one mole of ester and one mole of water, again in the presence of sulfuric acid. *The same catalyst, hydrogen ion, that catalyzes the forward reaction, esterification, necessarily catalyzes the reverse reaction, hydrolysis.*

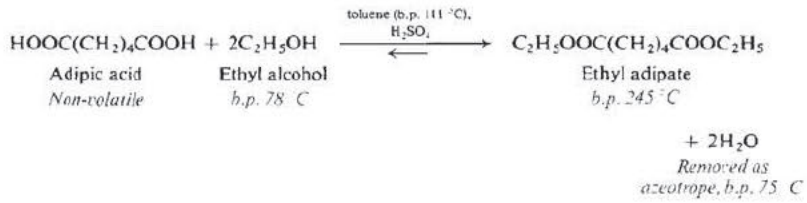
This reversibility is a disadvantage in the preparation of an ester directly from an acid; the preference for the acid chloride route is due to the fact that both steps—preparation of acid chloride from acid, and preparation of ester from acid chloride—are essentially irreversible and go to completion.

Direct esterification, however, has the advantage of being a single-step synthesis; it can often be made useful by application of our knowledge of equilibria. If either the acid or the alcohol is cheap and readily available, it can be used in large excess to shift the equilibrium toward the products and thus to increase the yield of ester. For example, it is worthwhile to use eight moles of cheap ethyl alcohol to convert one mole of valuable γ-phenylbutyric acid more completely into the ester:



γ-Phenylbutyric acid (*1 mole*) + Ethyl alcohol (*8 moles*) $\xrightleftharpoons{H_2SO_4,\ \text{reflux}}$ Ethyl γ-phenylbutyrate (*85–88% yield*) + H_2O

Sometimes the equilibrium is shifted by removing one of the products. An elegant way of doing this is illustrated by the preparation of ethyl adipate. The dicarboxylic acid adipic acid, an excess of ethyl alcohol, and toluene are heated with a little sulfuric acid under a distillation column. The lowest boiling component (b.p. 75 °C) of the reaction mixture is an azeotrope of water, ethyl alcohol, and toluene (compare Sec. 17.7); consequently, as fast as water is formed it is removed as the azeotrope by distillation. In this way a 95–97% yield of ester is obtained:



$HOOC(CH_2)_4COOH + 2C_2H_5OH \xrightleftharpoons{\text{toluene (b.p. 111 °C), } H_2SO_4} C_2H_5OOC(CH_2)_4COOC_2H_5 + 2H_2O$

Adipic acid (*Non-volatile*) + Ethyl alcohol (*b.p. 78 °C*) → Ethyl adipate (*b.p. 245 °C*) + $2H_2O$ (*Removed as azeotrope, b.p. 75 °C*)

The equilibrium is particularly unfavorable when phenols (ArOH) are used instead of alcohols; yet, if water is removed during the reaction, phenolic esters (RCOOAr) are obtained in high yield.

The presence of bulky groups near the site of reaction, whether in the alcohol or in the acid, slows down esterification (as well as its reverse, hydrolysis). This

Reactivity in esterification

$CH_3OH > 1° > 2° (> 3°)$

$HCOOH > CH_3COOH > RCH_2COOH > R_2CHCOOH > R_3CCOOH$

steric hindrance can be so marked that special methods are required to prepare esters of tertiary alcohols or esters of acids like 2,4,6-trimethylbenzoic acid (mesitoic acid). (See Fig. 23.5.)

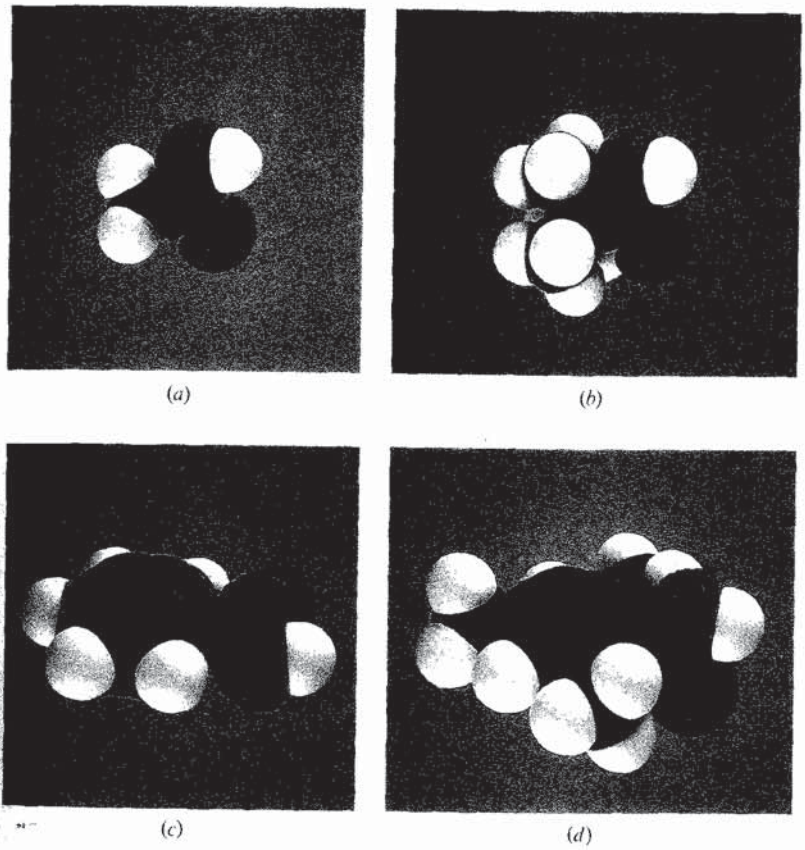


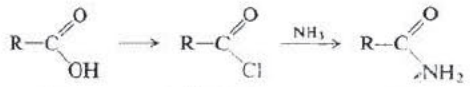
Figure 23.5 Molecular structure and reactivity: the steric factor in esterification. Crowding about the carboxyl group. Compare (*a*) acetic acid with (*b*) trimethylacetic acid, and (*c*) benzoic acid with (*d*) 2,4,6-trimethylbenzoic acid.

The mechanism of esterification is necessarily the exact reverse of the mechanism of hydrolysis of esters. We shall discuss both mechanisms when we take up the chemistry of esters (Sec. 24.18), after we have learned a little more about the carbonyl group.

Problem 23.9 (a) In the formation of an acid chloride, which bond of a carboxylic acid is broken, C—OH or CO—H? (b) When labeled methanol, $CH_3{}^{18}OH$, was allowed to react with ordinary benzoic acid, the methyl benzoate produced was found to be enriched in ^{18}O, whereas the water formed contained only ordinary oxygen. In this esterification, which bond of the carboxylic acid is broken, C—OH or CO—H? Which bond of the alcohol?

23.17 Conversion into amides

Amides are compounds in which the —OH of the carboxylic acid has been



Acid Acid chloride Amide

replaced by $-NH_2$. These are generally prepared by reaction of ammonia with acid chlorides.

23.18 Reduction of acids to alcohols

Conversion of alcohols into acids (Sec. 23.6) is important because, in general, alcohols are more available than acids. This is not always true, however; long straight-chain acids from fats are more available than are the corresponding alcohols, and here the reverse process becomes important: reduction of acids to alcohols.

Lithium aluminum hydride, $LiAlH_4$, is one of the few reagents that can reduce an acid to an alcohol; the initial product is an alkoxide from which the alcohol is liberated by hydrolysis:

$$4R{-}COOH + 3LiAlH_4 \longrightarrow 4H_2 + 2LiAlO_2 + (RCH_2O)_4AlLi \xrightarrow{H_2O} \underset{1^\circ \text{ alcohol}}{4R{-}CH_2OH}$$

Because of the excellent yields it gives, $LiAlH_4$ is widely used in the laboratory for the reduction of not only acids but many other classes of compounds. Since it is somewhat expensive, it can be used in industry only for the reduction of small amounts of valuable raw materials, as in the synthesis of certain drugs and hormones.

As an alternative to direct reduction, acids are often converted into alcohols by a two-step process: esterification, and reduction of the ester. Esters can be reduced in a number of ways (Sec. 24.22) that are adaptable to both laboratory and industry.

We have seen (Sec. 23.5) that in the carboxylic acids obtained from fats we have available long straight-chain units for use in organic synthesis. Reduction of these acids to alcohols (either directly or as esters) is a fundamental step in the utilization of these raw materials, since from the alcohols, as we know, a host of other compounds can be prepared (Sec. 18.8). Although only acids of even carbon number are available, it is possible, of course, to increase the chain length and thus prepare compounds of odd carbon number. (For an alternative source of long, straight-chain, primary alcohols, see Sec. 36.6.)

Problem 23.10 Outline the synthesis from lauric acid (n-$C_{11}H_{23}COOH$, dodecanoic acid) of the following compounds:

(a) 1-bromododecane
(b) tridecanoic acid (C_{13} acid)
(c) 1-tetradecanol
(d) 1-dodecene

(e) dodecane
(f) 1-dodecyne
(g) *n*-decyl methyl ketone
(h) 2-dodecanol
(i) undecanoic acid
(j) 2-tetradecanol
(k) 2-methyl-2-tetradecanol

23.19 Halogenation of aliphatic acids. Substituted acids

In the presence of a small amount of phosphorus, aliphatic carboxylic acids react smoothly with chlorine or bromine to yield a compound in which α-hydrogen has been replaced by halogen. This is the **Hell–Volhard–Zelinsky reaction**. Because of its specificity—*only alpha halogenation*—and the readiness with which it takes place, it is of considerable importance in synthesis.

$$CH_3COOH \xrightarrow{Cl_2,\,P} ClCH_2COOH \xrightarrow{Cl_2,\,P} Cl_2CHCOOH \xrightarrow{Cl_2,\,P} Cl_3CCOOH$$

$$CH_3CH_2COOH \xrightarrow{Br_2,\,P} CH_3CHBrCOOH \xrightarrow{Br_2,\,P} CH_3CBr_2COOH \xrightarrow{Br_2,\,P} \text{no further substitution}$$

The function of the phosphorus is ultimately to convert a little of the acid into acid halide. In this form (for reasons we cannot go into here) each molecule of acid sooner or later undergoes α-halogenation.

$$P + X_2 \longrightarrow PX_3$$

$$RCH_2COOH + PX_3 \longrightarrow RCH_2COX$$

$$RCH_2COX + X_2 \longrightarrow \underset{\displaystyle X}{RCHCOX} + HX$$

$$\underset{\displaystyle X}{RCHCOX} + RCH_2COOH \rightleftharpoons \underset{\displaystyle X}{RCHCOOH} + RCH_2COX$$

α-Halo acid

The halogen of these halogenated acids undergoes *nucleophilic displacement* and *elimination* much as it does in the simpler alkyl halides (Secs. 5.8 and 7.12). Halogenation is therefore the first step in the conversion of a carboxylic acid into many important substituted carboxylic acids:

$$\underset{\displaystyle Br}{RCHCOOH} + \text{large excess of } NH_3 \longrightarrow \underset{\displaystyle NH_2}{RCHCOOH}$$

An α-halogenated acid — An α-amino acid

$$\underset{\displaystyle Br}{RCHCOOH} + NaOH \longrightarrow \underset{\displaystyle OH}{RCHCOONa} \xrightarrow{H^+} \underset{\displaystyle OH}{RCHCOOH}$$

An α-hydroxy acid

$$RCH_2CHCOOH + KOH\ (alc) \longrightarrow RCH{=}CHCOO^- \xrightarrow{H^+} RCH{=}CHCOOH$$
(Br)

An α,β-unsaturated acid

These new substituents can, in turn, undergo *their* characteristic reactions.

Problem 23.11 Predict the product of each of the following reactions:
(a) $CH_3{-}CHCOOH + H_2/Ni$
(b) *trans*-$CH_3CH{=}CHCOOH + Br_2/CCl_4$
(c) $C_6H_5CH(OH)CH_2COOH + H^+$, heat $\longrightarrow C_9H_8O_2$
(d) *o*-$HOOCC_6H_4CH_2OH + H^+$, heat $\longrightarrow C_8H_6O_2$

23.20 Dicarboxylic acids

If the substituent is a second carboxyl group, we have a *dicarboxylic acid*. For example:

$HOOCCH_2COOH$	$HOOCCH_2CH_2COOH$	$HOOCCH_2CH_2CH_2CH_2COOH$
Malonic acid Propanedioic acid	Succinic acid Butanedioic acid	Adipic acid Hexanedioic acid

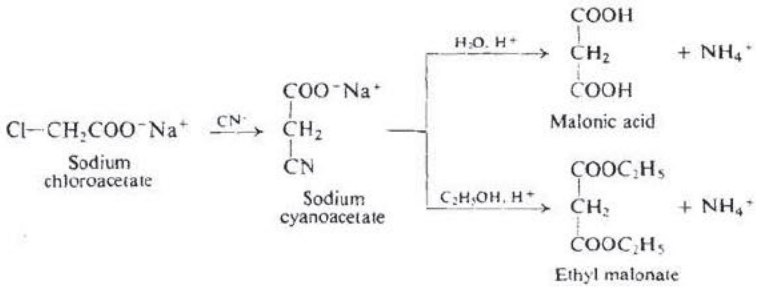
$HOOCCH_2CH_2CHCOOH$ (Br)	$HOOCCH_2\overset{CH_3}{\overset{\vert}{C}}CH_2COOH$ (CH_3)	$HOOC\overset{Cl}{\overset{\vert}{C}}HCH_2\overset{Cl}{\overset{\vert}{C}}HCOOH$
α-Bromoglutaric acid 2-Bromopentanedioic acid	β,β-Dimethylglutaric acid 3,3-Dimethylpentanedioic acid	α,α-Dichloroglutaric acid 2,4-Dichloro-pentanedioic acid

We have already encountered the benzenedicarboxylic acids, the *phthalic acids* (Sec. 15.11).

Table 23.3 DICARBOXYLIC ACIDS

Name	Formula	M.p., °C	Solubility g/100 g H_2O at 20 °C	K_1	K_2
Oxalic	HOOC—COOH	189	9	5400×10^{-5}	5.2×10^{-5}
Malonic	$HOOCCH_2COOH$	136	74	140	0.20
Succinic	$HOOC(CH_2)_2COOH$	185	6	6.4	0.23
Glutaric	$HOOC(CH_2)_3COOH$	98	64	4.5	0.38
Adipic	$HOOC(CH_2)_4COOH$	151	2	3.7	0.39
Maleic	*cis*-HOOCCH=CHCOOH	130.5	79	1000	0.055
Fumaric	*trans*-HOOCCH=CHCOOH	302	0.7	96	4.1
Phthalic	1,2-$C_6H_4(COOH)_2$	231	0.7	110	0.4
Isophthalic	1,3-$C_6H_4(COOH)_2$	348.5	0.01	24	2.5
Terephthalic	1,4-$C_6H_4(COOH)_2$	300 *subl*	0.002	29	3.5

Most dicarboxylic acids are prepared by adaptation of methods used to prepare monocarboxylic acids. Where hydrolysis of a nitrile yields a monocarboxylic acid, hydrolysis of a dinitrile or a cyanocarboxylic acid yields a dicarboxylic acid; where oxidation of a methylbenzene yields a benzoic acid, oxidation of a dimethylbenzene yields a phthalic acid. For example:



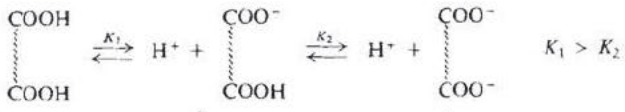
Problem 23.12 Why is chloroacetic acid converted into its salt before treatment with cyanide in the above preparation?

Problem 23.13 Outline a synthesis of: (a) pentanedioic acid from 1,3-propanediol (available from a fermentation of glycerol); (b) nonanedioic acid from *cis*-9-octadecenoic acid (oleic acid, obtained from fats); (c) succinic acid from 1,4-butynediol (available from acetylene and formaldehyde).

In general, dicarboxylic acids show the same chemical behavior as monocarboxylic acids. It is possible to prepare compounds in which only one of the carboxyl groups has been converted into a derivative; it is possible to prepare compounds in which the two carboxyl groups have been converted into different derivatives.

Problem 23.14 Predict the products of the following reactions:
(a) adipic acid (146 g) + 95% ethanol (146 g) + benzene + conc. H_2SO_4, 100 °C
(b) adipic acid (146 g) + 95% ethanol (50 g) + benzene + conc. H_2SO_4, 100 °C
(c) succinic acid + $LiAlH_4$
(d) pentanedioic acid + 1 mol Br_2, P
(e) terephthalic acid + excess $SOCl_2$
(f) maleic acid (*cis*-butenedioic acid) + Br_2/CCl_4

As with other acids containing more than one ionizable hydrogen (H_2SO_4, H_2CO_3, H_3PO_4, etc.), ionization of the second carboxyl group occurs less readily than ionization of the first (compare K_1 values with K_2 values in Table 23.3). More energy is required to separate a positive hydrogen ion from the doubly charged anion than from the singly charged anion.



Problem 23.15 Compare the acidity (first ionization) of oxalic acid with that of formic acid; of malonic acid with that of acetic acid. How do you account for these differences?

Problem 23.16 Arrange oxalic, malonic, succinic, and glutaric acids in order of acidity (first ionization). How do you account for this order?

Certain reactions of dicarboxylic acids, while fundamentally the same as those undergone by any carboxylic acid, lead to unusual results simply because there *are* two carboxyl groups in each molecule (Sec. 36.7). In addition, some dicarboxylic acids undergo certain special reactions that are possible only because the two carboxyl groups are located in a particular way with respect to each other (Sec. 30.4).

Problem 23.17 Give a likely structure for the product of each of the following reactions:

(a) oxalic acid + ethylene glycol $\longrightarrow C_4H_4O_4$
(b) succinic acid + heat $\longrightarrow C_4H_4O_3$
(c) terephthalic acid + ethylene glycol $\longrightarrow (C_{10}H_8O_4)_n$, the polymer Dacron

23.21 Analysis of carboxylic acids. Neutralization equivalent

Carboxylic acids are recognized through their acidity. They dissolve in aqueous sodium hydroxide and in aqueous sodium bicarbonate. The reaction with bicarbonate releases bubbles of carbon dioxide (see Sec. 23.4).

(Phenols, Sec. 28.7, are more acidic than water, but—with certain exceptions—are considerably weaker than carboxylic acids; they dissolve in aqueous sodium hydroxide, but *not* in aqueous sodium bicarbonate. Sulfonic acids are even more acidic than carboxylic acids, but they contain sulfur, which can be detected by elemental analysis.)

Once characterized as a carboxylic acid, an unknown is identified as a particular acid on the usual basis of its physical properties and the physical properties of derivatives. The derivatives commonly used are *amides* (Secs. 24.11 and 27.7) and *esters* (Sec. 24.15).

Problem 23.18 Expand the table you made in Problem 21.17, p. 787, to include carboxylic acids.

Particularly useful both in identification of previously studied acids and in proof of structure of new ones is the **neutralization equivalent**: *the equivalent weight of the acid as determined by titration with standard base.* A weighed sample of the acid is dissolved in water or aqueous alcohol, and the volume of standard base needed to neutralize the solution is measured. For example, a 0.224-g sample of an unknown acid (m.p. 139–140 °C) required 13.6 mL of 0.104 N sodium hydroxide solution for neutralization (to a phenolphthalein end point). Since each 1000 mL

of the base contains 0.104 equivalents, and since the number of equivalents of base required equals the number of equivalents of acid present,

$$\frac{13.6}{1000} \times 0.104 \text{ equivalent of acid} = 0.224 \text{ g}$$

and

$$1 \text{ equivalent of acid} = 0.224 \times \frac{1000}{13.6} \times \frac{1}{0.104} = 158 \text{ g}$$

Problem 23.19 Which of the following compounds might the above acid be: (a) *o*-chlorobenzoic acid (m.p. 141 °C) or (b) 2,6-dichlorobenzoic acid (m.p. 139 °C)?

Problem 23.20 A 0.187-g sample of an acid (b.p. 203–205 °C) required 18.7 mL of 0.0972 N NaOH for neutralization. (a) What is the neutralization equivalent? (b) Which of the following acids might it be: *n*-caproic acid (b.p. 205 °C), methoxyacetic acid (b.p. 203 °C), or ethoxyacetic acid (b.p. 206 °C)?

Problem 23.21 (a) How many equivalents of base would be neutralized by one mole of phthalic acid? What is the neutralization equivalent of phthalic acid? (b) What is the relation between neutralization equivalent and the number of acidic hydrogens per molecule of acid? (c) What is the neutralization equivalent of 1,3,5-benzenetricarboxylic acid? Of mellitic acid, $C_6(COOH)_6$?

A metal salt of a carboxylic acid is recognized through these facts: (a) it leaves a residue when strongly heated (*ignition test*); (b) it decomposes at a fairly high temperature, instead of melting; and (c) it is converted into a carboxylic acid upon treatment with dilute mineral acid.

Problem 23.22 The residue left upon ignition of a sodium salt of a carboxylic acid was white, soluble in water, turned moist litmus blue, and reacted with dilute hydrochloric acid with the formation of bubbles. What was its probable chemical composition?

23.22 Spectroscopic analysis of carboxylic acids

Infrared The carboxyl group is made up of a carbonyl group (C=O) and a hydroxyl group (OH), and the infrared spectrum of carboxylic acids reflects both these structural units. For hydrogen-bonded (dimeric) acids, O—H stretching gives a strong, broad band in the 2500–3000 cm^{-1} range (see Fig. 23.6, on the next page).

O—H stretching, *strong, broad*	
—COOH and enols	2500–3000 cm^{-1}
ROH and ArOH	3200–3600 cm^{-1}

With acids we encounter again absorption due to stretching of the carbonyl group. As we saw for aldehydes and ketones (Sec. 21.16), this strong band appears in a region that is usually free of other strong absorption, and by its exact frequency

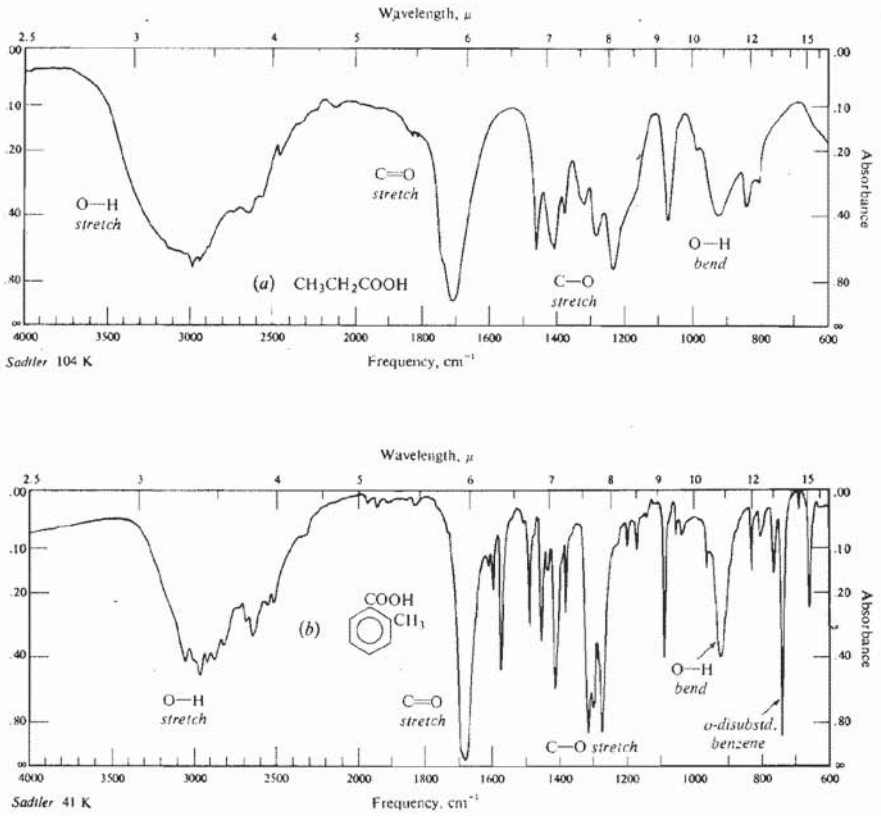


Figure 23.6 Infrared spectra of (*a*) propionic acid and (*b*) *o*-toluic acid.

gives much information about structure. For (hydrogen-bonded) acids, the C=O band is at about 1700 cm^{-1}.

C=O stretching, *strong*

R—C(=O)—OH	1700–1725 cm^{-1}	C=C—C(=O)—OH	1680–1700 cm^{-1}
Ar—C(=O)—OH	1680–1700 cm^{-1}	—C=CH—C(=O)— (OH·····O) (enols)	1540–1640 cm^{-1}

Acids also show a C O stretching band at about 1250 cm^{-1} (compare alcohols, Sec. 18.11, and ethers, Sec. 19.18), and bands for O—H bending near 1400 cm^{-1} and 920 cm^{-1} (*broad*).

Enols, too, show both O H and C=O absorption; these can be distinguished by the particular frequency of the C=O band. Aldehydes, ketones, and esters show

carbonyl absorption, but the O—H band is missing. (For a comparison of certain oxygen compounds, see Table 24.3, p. 890.)

NMR The outstanding feature of the NMR spectrum of a carboxylic acid is the absorption far downfield (δ 10.5–12) by the proton of —COOH. (Compare the absorption by the acid proton of phenols, ArOH, in Sec. 28.14.)

CMR In the CMR spectrum of a carboxylic acid we see the far downfield absorption by carbonyl carbon, δ 165–185. This is in the same general region as for functional derivatives of carboxylic acids, but somewhat upfield from the absorption by aldehydes and ketones.

PROBLEMS

1. Give the common names and IUPAC names for the straight-chain saturated carboxylic acids containing the following numbers of carbon atoms: 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18.

2. Give the structural formula and, where possible, a second name (by a different system) for each of the following:

(a) isovaleric acid
(b) trimethylacetic acid
(c) α,β-dimethylcaproic acid
(d) 2-methyl-4-ethyloctanoic acid
(e) phenylacetic acid
(f) γ-phenylbutyric acid
(g) adipic acid
(h) *p*-toluic acid
(i) phthalic acid
(j) isophthalic acid
(k) terephthalic acid
(l) *p*-hydroxybenzoic acid
(m) potassium α-methylbutyrate
(n) magnesium 2-chloropropanoate
(o) maleic acid
(p) α,α'-dibromosuccinic acid
(q) isobutyronitrile
(r) 2,4-dinitrobenzonitrile

3. Write equations to show how each of the following compounds could be converted into benzoic acid:

(a) toluene
(b) bromobenzene
(c) benzonitrile
(d) benzyl alcohol
(e) benzotrichloride
(f) acetophenone (*Hint*: See Sec. 18.9.)

4. Write equations to show how each of the following compounds could be converted into *n*-butyric acid:

(a) *n*-butyl alcohol
(b) *n*-propyl alcohol
(c) *n*-propyl alcohol (a second way)
(d) methyl *n*-propyl ketone

Which of the above methods could be used to prepare trimethylacetic acid?

5. Write equations to show how tetrahydrofuran could be converted into:

(a) succinic acid (b) glutaric acid (c) adipic acid

6. Write equations to show the reaction (if any) of benzoic acid with:

(a) KOH
(b) Al
(c) CaO
(d) Na_2CO_3
(e) NH_3(aq)
(f) H_2, Ni, 20 °C, 1 atm.
(g) $LiAlH_4$
(h) hot $KMnO_4$
(i) PCl_5
(j) PCl_3
(k) $SOCl_2$
(l) Br_2/Fe
(m) $Br_2 + P$
(n) HNO_3/H_2SO_4
(o) fuming sulfuric acid
(p) CH_3Cl, $AlCl_3$
(q) *n*-propyl alcohol, H^+

7. Answer Problem 6 for *n*-valeric acid.

8. Write equations to show how isobutyric acid could be converted into each of the following, using any needed reagents:

(a) ethyl isobutyrate
(b) isobutyryl chloride
(c) isobutyramide
(d) magnesium isobutyrate
(e) isobutyl alcohol

9. Write equations to show all steps in the conversion of benzoic acid into:

(a) sodium benzoate
(b) benzoyl chloride
(c) benzamide
(d) benzene
(e) *n*-propyl benzoate
(f) *p*-tolyl benzoate
(g) *m*-bromophenyl benzoate
(h) benzyl alcohol

10. Write equations to show how phenylacetic acid could be converted into each of the following, using any needed reagents.

(a) sodium phenylacetate
(b) ethyl phenylacetate
(c) phenylacetyl chloride
(d) phenylacetamide
(e) *p*-bromophenylacetic acid
(f) *p*-nitrophenylacetic acid
(g) β-phenylethyl alcohol
(h) α-bromophenylacetic acid
(i) α-aminophenylacetic acid
(j) α-hydroxyphenylacetic acid
(k) phenylmalonic acid, $C_6H_5CH(COOH)_2$

11. Complete the following, giving the structures and names of the principal organic products.

(a) $C_6H_5CH{=}CHCOOH + KMnO_4 + OH^- + \text{heat}$
(b) $p\text{-}CH_3C_6H_4COOH + HNO_3 + H_2SO_4$
(c) succinic acid + $LiAlH_4$, followed by H^+
(d) $C_6H_5COOH + C_6H_5CH_2OH + H^+$
(e) product (d) + $HNO_3 + H_2SO_4$
(f) *n*-butyric acid + Br_2, P
(g) cyclo-$C_6H_{11}MgBr + CO_2$, followed by H_2SO_4
(h) product (g) + $C_2H_5OH + H^+$
(i) product (g) + $SOCl_2$ + heat
(j) $m\text{-}CH_3C_6H_4OCH_3 + KMnO_4 + OH^-$
(k) mesitylene + $K_2Cr_2O_7 + H_2SO_4$
(l) isobutyric acid + isobutyl alcohol + H^+
(m) salicylic acid ($o\text{-}HOC_6H_4COOH$) + Br_2, Fe
(n) sodium acetate + *p*-nitrobenzyl bromide
(o) linolenic acid + excess H_2, Ni
(p) oleic acid + $KMnO_4$, heat
(q) linoleic acid + O_3, then H_2O, Zn
(r) benzoic acid ($C_7H_6O_2$) + H_2, Ni, heat, pressure $\longrightarrow C_7H_{12}O_2$
(s) benzoic acid + ethylene glycol + $H^+ \longrightarrow C_{16}H_{14}O_4$
(t) phthalic acid + ethyl alcohol + $H^+ \longrightarrow C_{12}H_{14}O_4$
(u) oleic acid + Br_2/CCl_4
(v) product (u) + KOH (alcoholic)
(w) oleic acid + HCO_2OH

12. Outline a possible laboratory synthesis of the following labeled compounds, using $Ba^{14}CO_3$ or $^{14}CH_3OH$ as the source of ^{14}C.

(a) $CH_3CH_2CH_2{}^{14}COOH$
(b) $CH_3CH_2{}^{14}CH_2COOH$
(c) $CH_2{}^{14}CH_2CH_2COOH$
(d) $^{14}CH_3CH_2CH_2COOH$

13. Outline all steps in a possible laboratory synthesis of each of the following compounds from toluene and any needed aliphatic and inorganic reagents.

(a) benzoic acid
(b) phenylacetic acid
(c) *p*-toluic acid
(d) *m*-chlorobenzoic acid
(e) *p*-chlorobenzoic acid
(f) *p*-bromophenylacetic acid
(g) α-chlorophenylacetic acid

14. Outline a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) ethyl α-methylbutyrate
(b) 3,5-dinitrobenzoyl chloride
(c) α-amino-*p*-bromophenylacetic acid
(d) α-hydroxypropionic acid
(e) p-$HO_3SC_6H_4COOH$
(f) 2-pentenoic acid
(g) *p*-toluamide
(h) *n*-hexyl benzoate
(i) 3-bromo-4-methylbenzoic acid
(j) α-methylphenylacetic acid
(k) 2-bromo-4-nitrobenzoic acid
(l) 1,2,4-benzenetricarboxylic acid

15. Without referring to tables, arrange the compounds of each set in order of acidity:

(a) butanoic acid, 2-bromobutanoic acid, 3-bromobutanoic acid, 4-bromobutanoic acid
(b) benzoic acid, *p*-chlorobenzoic acid, 2,4-dichlorobenzoic acid, 2,4,6-trichlorobenzoic acid
(c) benzoic acid, *p*-nitrobenzoic acid, *p*-toluic acid
(d) α-chlorophenylacetic acid, *p*-chlorophenylacetic acid, phenylacetic acid, α-phenylpropionic acid
(e) *p*-nitrobenzoic acid, *p*-nitrophenylacetic acid, β-(*p*-nitrophenyl)propionic acid
(f) acetic acid, acetylene, ammonia, ethane, ethanol, sulfuric acid, water
(g) acetic acid, malonic acid, succinic acid

16. Arrange the monosodium salts of the acids in Problem 15(f) in order of basicity.

17. The two water-insoluble solids, benzoic acid and *o*-chlorobenzoic acid, can be separated by treatment with an aqueous solution of sodium formate. What reaction takes place? (*Hint*: Look at the K_a values in Table 23.2.)

18. Arrange the compounds of each set in order of reactivity in the indicated reaction:

(a) esterification by benzoic acid: *sec*-butyl alcohol, methanol, *tert*-pentyl alcohol, *n*-propyl alcohol
(b) esterification by ethyl alcohol: benzoic acid, 2,6-dimethylbenzoic acid, *o*-toluic acid
(c) esterification by methanol: acetic acid, formic acid, isobutyric acid, propionic acid, trimethylacetic acid

19. Give stereochemical formulas of compounds A–F:

(a) racemic β-bromobutyric acid + one mole Br_2, P $\longrightarrow$ A + B
(b) fumaric acid + HCO_2OH $\longrightarrow$ C ($C_4H_6O_6$)
(c) 1,4-cyclohexadiene + $CHBr_3$/*t*-BuOK $\longrightarrow$ D ($C_7H_8Br_2$)
D + $KMnO_4$ $\longrightarrow$ E ($C_7H_8Br_2O_4$)
E + H_2, Ni(base) $\longrightarrow$ F ($C_7H_{10}O_4$)

20. Give structures of compounds G–J:

$$\text{acetylene} + CH_3MgBr \longrightarrow G + CH_4$$

$$G + CO_2 \longrightarrow H \xrightarrow{H^+} I\ (C_3H_2O_2)$$

$$I \xrightarrow{H_2O,\ H_2SO_4,\ HgSO_4} J\ (C_3H_4O_3)$$

$$J + KMnO_4 \longrightarrow CH_2(COOH)_2$$

21. Describe simple chemical tests (other than color change of an indicator) that would serve to distinguish between:

(a) propionic acid and *n*-pentyl alcohol
(b) isovaleric acid and *n*-octane
(c) ethyl *n*-butyrate and isobutyric acid
(d) propionyl chloride and propionic acid
(e) *p*-aminobenzoic acid and benzamide
(f) $C_6H_5CH{=}CHCOOH$ and $C_6H_5CH{=}CHCH_3$

Tell exactly what you would *do* and *see*.

22. Compare benzoic acid and sodium benzoate with respect to:

(a) volatility
(b) melting point
(c) solubility in water and (d) in ether
(e) degree of ionization of solid
(f) degree of ionization in water
(g) acidity and basicity

Does this comparison hold generally for acids and their salts?

23. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form:

(a) caproic acid and ethyl caproate
(b) di-*n*-butyl ether and *n*-butyric acid
(c) isobutyric acid and 1-hexanol
(d) sodium benzoate and triphenylmethanol

Tell exactly what you would *do* and *see*.

24. An unknown compound is believed to be one of the following. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible, use simple chemical tests; where necessary, use more elaborate chemical methods like quantitative hydrogenation, cleavage, neutralization equivalent, etc. Make use of any needed tables of physical constants.

(a) acrylic acid (CH_2=$CHCOOH$, b.p. 142 °C) and propionic acid (b.p. 141 °C)
(b) mandelic acid ($C_6H_5CHOHCOOH$, m.p. 120 °C) and benzoic acid (m.p. 122 °C)
(c) *o*-chlorobenzoic acid (m.p. 141 °C), mesotartaric acid (m.p. 140 °C), *m*-nitrobenzoic acid (m.p. 141 °C), and suberic acid ($HOOC(CH_2)_6COOH$, m.p. 144 °C)
(d) chloroacetic acid (b.p. 189 °C), α-chloropropionic acid (b.p. 186 °C), dichloroacetic acid (b.p. 194 °C), and *n*-valeric acid (b.p. 187 °C)
(e) 3-nitrophthalic acid (m.p. 220 °C) and 2,4,6-trinitrobenzoic acid (m.p. 220 °C)
(f) *p*-chlorobenzoic acid (m.p. 242 °C), *p*-nitrobenzoic acid (m.p. 242 °C), *o*-nitrocinnamic acid (o-$O_2NC_6H_4CH$=$CHCOOH$, m.p. 240 °C)
(g) The following compounds, all of which boil within a few degrees of each other:

o-chloroanisole	isodurene
β-chlorostyrene	linalool (see Problem 27, p. 692)
p-cresyl ethyl ether	4-methylpentanoic acid
cis-decalin (see Problem 8, p. 473)	α-phenylethyl chloride
2,4-dichlorotoluene	*o*-toluidine (o-$CH_3C_6H_4NH_2$)

25. By use of Table 23.4 (below) tell which acid or acids each of the following is likely to be. Tell what further steps you would take to identify it or to confirm your identification.

K: m.p. 155–7 °C; positive halogen test; *p*-nitrobenzyl ester, m.p. 104–6 °C; neutralization equivalent, 158 ± 2

Table 23.4 DERIVATIVES OF SOME CARBOXYLIC ACIDS

	Acid M.p., °C	Amide M.p., °C	Anilide M.p., °C	*p*-Nitrobenzyl ester M.p., °C
trans-Crotonic (CH_3CH=$CHCOOH$)	72	161	118	67
Phenylacetic	77	156	118	65
Arachidic (n-$C_{19}H_{39}COOH$)	77	108	92	—
α-Hydroxyisobutyric	79	98	136	80
Glycolic ($HOCH_2COOH$)	80	120	97	107
β-Iodopropionic	82	101	—	—
Iodoacetic	83	95	143	—
Adipic ($HOOC(CH_2)_4COOH$)	151	220	241	106
p-Nitrophenylacetic	153	198	198	—
2,5-Dichlorobenzoic	153	155	—	—
m-Chlorobenzoic	154	134	122	107
2,4,6-Trimethylbenzoic	155	—	—	188
m-Bromobenzoic	156	155	136	105
p-Chlorophenoxyacetic	158	133	125	—
Salicylic (o-HOC_6H_4COOH)	159	142	136	98

L: m.p. 152–4 °C; negative tests for halogen and nitrogen
M: m.p. 153–5 °C; positive chlorine test; neutralization equivalent, 188 ± 4
N: m.p. 72–3 °C; anilide, m.p. 117–8 °C; amide, m.p. 155–7 °C
O: m.p. 79–80 °C; amide, m.p. 97–9 °C
P: m.p. 78–80 °C; negative tests for halogen and nitrogen; positive test with CrO_3/H_2SO_4

26. An unknown acid was believed to be either *o*-nitrobenzoic acid (m.p. 147 °C) or anthranilic acid (m.p. 146 °C). A 0.201-g sample neutralized 12.4 mL of 0.098 N NaOH. Which acid was it?

27. Carboxylic acid Q contained only carbon, hydrogen, and oxygen, and had a neutralization equivalent of 149 ± 3. Vigorous oxidation by $KMnO_4$ converted Q into R, m.p. 345–50 °C, neutralization equivalent 84 ± 2.

When Q was heated strongly with soda lime a liquid S of b.p. 135–7 °C distilled. Vigorous oxidation by $KMnO_4$ converted S into T, m.p. 121–2 °C, neutralization equivalent 123 ± 2.

U, an isomer of Q, gave upon oxidation V, m.p. 375–80 °C, neutralization equivalent 70 ± 2.

What were compounds Q through V? (Make use of any needed tables of physical constants.)

28. *Tropic acid* (obtained from the alkaloid atropine, found in deadly nightshade, *Atropa belladona*), $C_9H_{10}O_3$, gives a positive CrO_3/H_2SO_4 test and is oxidized by hot $KMnO_4$ to benzoic acid. Tropic acid is converted by the following sequence of reactions into *hydratropic acid*:

$$\text{tropic acid} \xrightarrow{HBr} C_9H_9O_2Br \xrightarrow{OH^-} C_9H_8O_2 \text{ (atropic acid)}$$

$$\text{atropic acid} \xrightarrow{H_2, Ni} \text{hydratropic acid } (C_9H_{10}O_2)$$

(a) What structure or structures are possible at this point for hydratropic acid? For tropic acid?

(b) When α-phenylethyl chloride is treated with magnesium in ether, the resulting solution poured over dry ice, and the mixture then acidified, there is obtained an acid whose amide has the same melting point as the amide of hydratropic acid. A mixed melting point determination shows no depression. Now what is the structure of hydratropic acid? Of tropic acid?

29. Give a structure or structures consistent with each of the following sets of proton NMR data:

(a) $C_3H_5ClO_2$
a doublet, δ 1.73, 3H
b quartet, δ 4.47, 1H
c singlet, δ 11.22, 1H

(b) $C_3H_5ClO_2$
a singlet, δ 3.81, 3H
b singlet, δ 4.08, 2H

(c) $C_4H_7BrO_2$
a triplet, δ 1.30, 3H
b singlet, δ 3.77, 2H
c quartet, δ 4.23, 2H

(d) $C_4H_7BrO_2$
a triplet, δ 1.08, 3H
b quintet, δ 2.07, 2H
c triplet, δ 4.23, 1H
d singlet, δ 10.97, 1H

(e) $C_4H_8O_3$
a triplet, δ 1.27, 3H
b quartet, δ 3.66, 2H
c singlet, δ 4.13, 2H
d singlet, δ 10.95, 1H

30. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 23.7 (p. 856)?

n-butyric acid
crotonic acid ($CH_3CH{=}CHCOOH$)
malic acid ($HOOCCHOHCH_2COOH$)
benzoic acid
p-nitrobenzoic acid
mandelic acid ($C_6H_5CHOHCOOH$)
p-nitrobenzyl alcohol

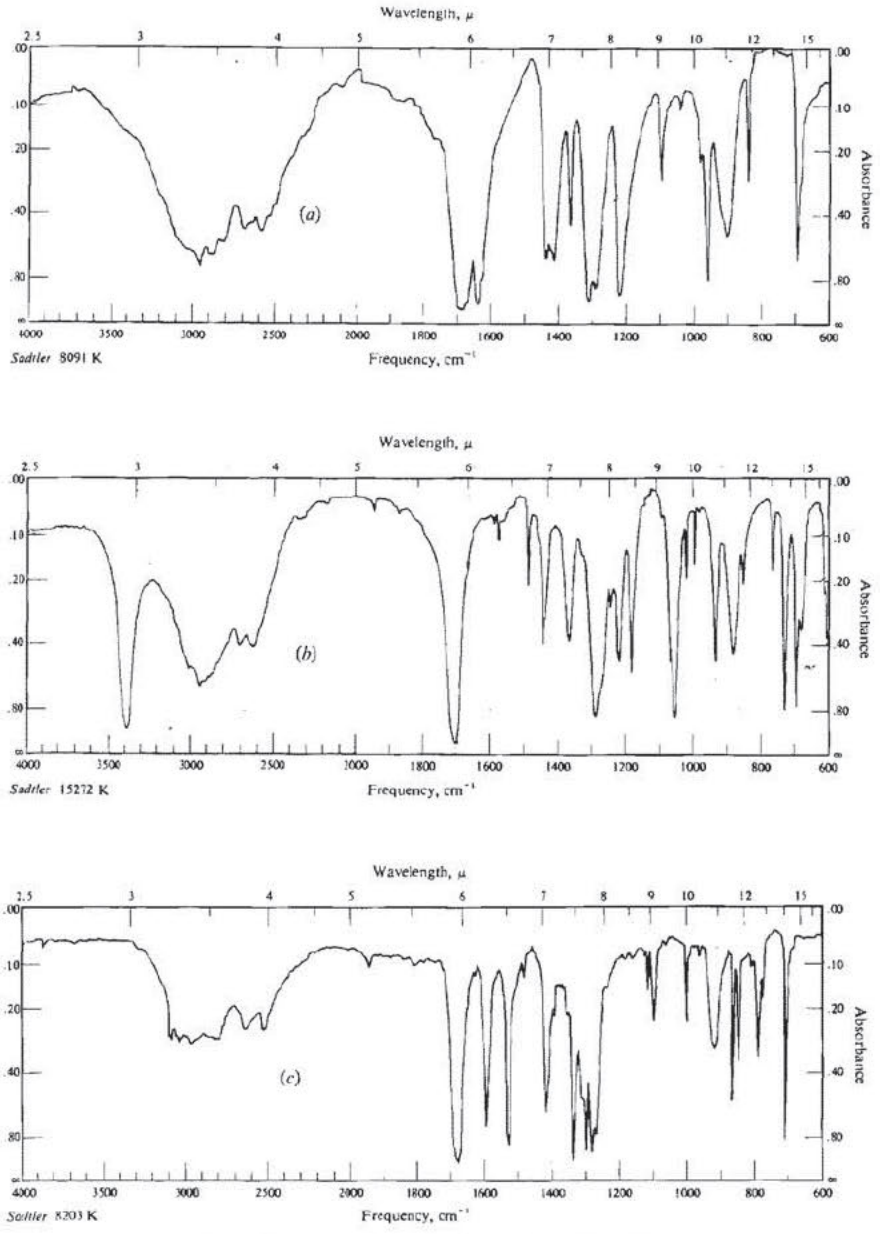
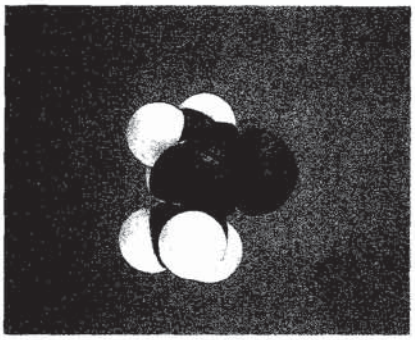


Figure 23.7 Infrared spectra for Problem 30, p. 855.

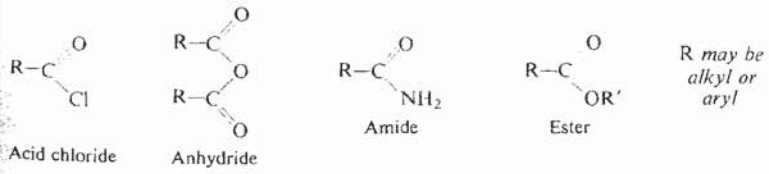
24

Functional Derivatives of Carboxylic Acids

Nucleophilic Acyl Substitution



Closely related to the carboxylic acids and to each other are a number of chemical families known as **functional derivatives of carboxylic acids**: *acid chlorides*, *anhydrides*, *amides*, and *esters*. These derivatives are compounds in which the —OH of a carboxyl group has been replaced by —Cl, —OOCR, —NH_2, or —OR′.

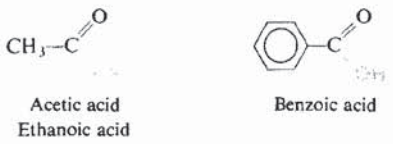


Acid chloride Anhydride Amide Ester

They all contain the **acyl group**, R—C(=O)—.

Like the acid to which it is related, an acid derivative may be aliphatic or aromatic, substituted or unsubstituted; whatever the structure of the rest of the molecule, the properties of the functional group remain essentially the same.

The names of acid derivatives are taken in simple ways from either the common name or the IUPAC name of the corresponding carboxylic acid. For example:



Acetic acid
Ethanoic acid

Benzoic acid

Acetyl chloride
Ethanoyl chloride

Benzoyl chloride

Change:
-ic acid to *-yl chloride*

Acetic anhydride
Ethanoic anhydride

Benzoic anhydride

acid to *anhydride*

Acetamide
Ethanamide

Benzamide

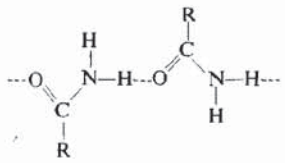
-ic acid of common name
(or *-oic acid* of IUPAC name)
to *-amide*

Ethyl acetate
Ethyl ethanoate

Ethyl benzoate

-ic acid to *-ate*,
preceded by name of
alcohol or phenol group

The presence of the C=O group makes the acid derivatives polar compounds. Acid chlorides and anhydrides (Table 24.1) and esters (Table 24.2, p. 873) have boiling points that are about the same as those of aldehydes or ketones of comparable molecular weight (see Sec. 17.5). Amides (Table 24.1) have quite high boiling points because they are capable of strong intermolecular hydrogen bonding.



The border line for solubility in water ranges from three to five carbons for the esters to five or six carbons for the amides. The acid derivatives are soluble in the usual organic solvents.

Volatile esters have pleasant, rather characteristic odors; they are often used in the preparation of perfumes and artificial flavorings. Acid chlorides have sharp, irritating odors, at least partly due to their ready hydrolysis to HCl and carboxylic acids.

Table 24.1 ACID CHLORIDES, ANHYDRIDES, AND AMIDES

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Acetyl chloride	−112	51	Succinic anhydride	120	
Propionyl chloride	− 94	80	Maleic anhydride	60	
n-Butyryl chloride	− 89	102			
n-Valeryl chloride	−110	128	Formamide	3	200*d*
Stearoyl chloride	23	215[15]	Acetamide	82	221
Benzoyl chloride	− 1	197	Propionamide	79	213
p-Nitrobenzoyl chloride	72	154[15]	*n*-Butyramide	116	216
			n-Valeramide	106	232
3,5-Dinitrobenzoyl chloride	74	196[12]	Stearamide	109	251[12]
			Benzamide	130	290
Acetic anhydride	− 73	140	Succinimide	126	
Phthalic anhydride	131	284	Phthalimide	238	

24.4 Nucleophilic acyl substitution. Role of the carbonyl group

Before we take up each kind of acid derivative separately, it will be helpful to outline certain general patterns into which we can then fit the rather numerous individual facts.

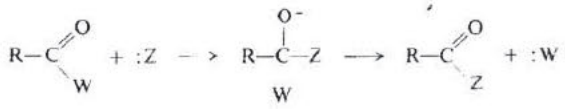
Each derivative is nearly always prepared—directly or indirectly—from the corresponding carboxylic acid, and can be readily converted into the carboxylic acid by simple hydrolysis. Much of the chemistry of acid derivatives involves their conversion one into another, and into the parent acid. In addition, each derivative has certain characteristic reactions of its own.

The derivatives of carboxylic acids, like the acids themselves, contain the carbonyl group, C=O. This group is retained in the products of most reactions undergone by these compounds, and does not suffer any permanent changes itself. But by its presence in the molecule it determines the characteristic reactivity of these compounds, and is the key to the understanding of their chemistry.

Here, too, as in aldehydes and ketones, the carbonyl group performs two functions: (a) it provides a site for nucleophilic attack, and (b) it increases the acidity of hydrogens attached to the *alpha* carbon.

(We shall discuss reactions resulting from the acidity of α-hydrogens in Secs. 25.11–25.12, and 30.1–30.3.)

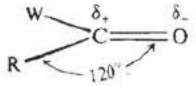
Acyl compounds—carboxylic acids and their derivatives—typically undergo **nucleophilic substitution** in which —OH, —Cl, —OOCR, —NH_2, or —OR′ is replaced by some other basic group. Substitution takes place much more readily than at a saturated carbon atom; indeed, many of these substitutions do not usually take place at all in the absence of the carbonyl group, as, for example, replacement of —NH_2 by —OH.



—W = —OH, —Cl, —OOCR, —NH_2, —OR′

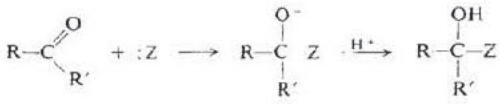
To account for the properties of acyl compounds, let us turn to the carbonyl group. We have encountered this group in our study of aldehydes and ketones (Secs. 21.1 and 21.7), and we know what it is like and what in general to expect of it.

Carbonyl carbon is joined to three other atoms by σ bonds; since these bonds utilize sp^2 orbitals (Sec. 1.10), they lie in a plane and are 120° apart. The remaining p orbital of the carbon overlaps a p orbital of oxygen to form a π bond; carbon and oxygen are thus joined by a double bond. The part of the molecule immediately surrounding carbonyl carbon is *flat*; oxygen, carbonyl carbon, and the two atoms directly attached to carbonyl carbon lie in a plane:

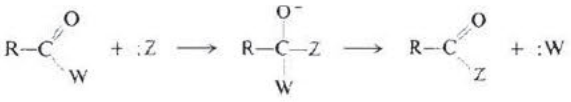


We saw before that both electronic and steric factors make the carbonyl group particularly susceptible to nucleophilic attack at the carbonyl carbon: (a) the tendency of oxygen to acquire electrons even at the expense of gaining a negative charge; and (b) the relatively unhindered transition state leading from the trigonal reactant to the tetrahedral intermediate. These factors make acyl compounds, too, susceptible to nucleophilic attack (Fig. 24.1).

It is in the second step of the reaction that acyl compounds differ from aldehydes and ketones. The tetrahedral intermediate from an aldehyde or ketone gains a proton, and the result is *addition*. The tetrahedral intermediate from an acyl compound ejects the :W group, returning to a trigonal compound, and thus the result is *substitution*.



Aldehyde or ketone
Addition



Acyl compound
Substitution

We can see why the two classes of compounds differ as they do. The ease with which :W is lost depends upon its basicity: the weaker the base, the better the

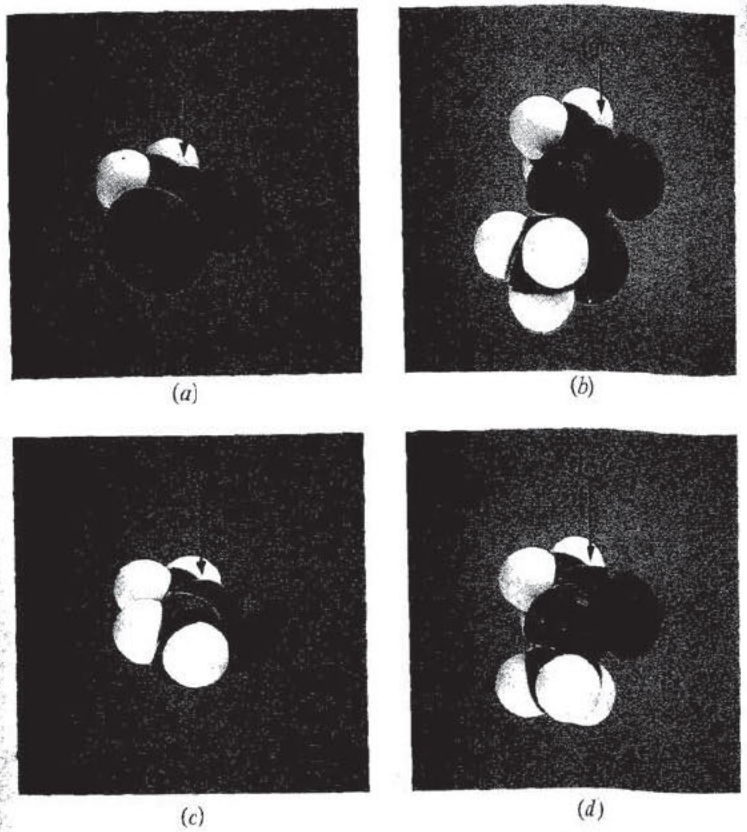


Figure 24.1 Molecular structure and reactivity: nucleophilic attack on the acyl group. Models of: (*a*) acetyl chloride, CH_3COCl; (*b*) acetic anhydride, $(CH_3CO)_2O$; (*c*) acetamide, CH_3CONH_2; (*d*) methyl acetate, CH_3COOCH_3. The flat carbonyl group is open to attack from above (or below).

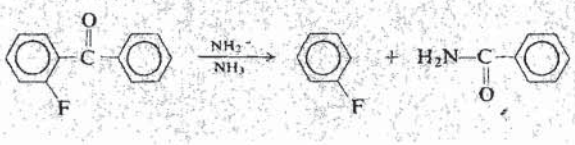
leaving group. For acid chlorides, acid anhydrides, esters, and amides, :W is, respectively: the very weak base Cl^-; the moderately weak base $RCOO^-$; and the strong bases $R'O^-$ and NH_2^-. But for an aldehyde or ketone to undergo substitution, the leaving group would have to be hydride ion ($:H^-$) or alkide ion ($:R^-$) which, as we know, are the strongest bases of all. (Witness the low acidity of H_2 and RH.) And so with aldehydes and ketones addition almost always takes place instead.

Problem 24.1 Suggest a likely mechanism for each of the following reactions, and account for the behavior shown:

(a) The last step in the haloform reaction (Sec. 18.9),

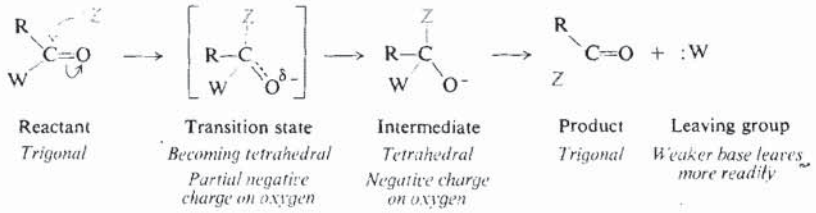
$$OH^- + R-\underset{\underset{O}{\|}}{C}-CX_3 \xrightarrow{H_2O} RCOO^- + CHX_3$$

(b) The reaction of *o*-fluorobenzophenone with amide ion,



Thus, nucleophilic acyl substitution proceeds by two steps, with the intermediate formation of a tetrahedral compound. Generally, the overall rate is affected by the rate of both steps, but the *first* step is the more important. The first step, formation of the tetrahedral intermediate, is affected by the same factors as in

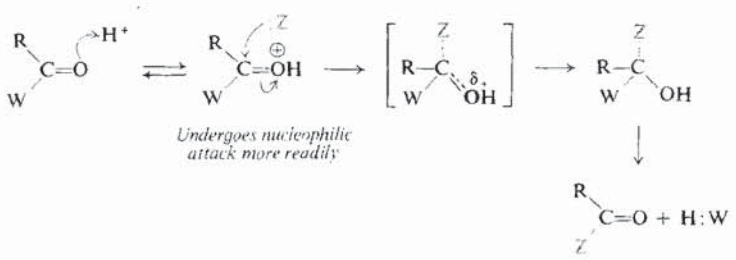
Nucleophilic acyl substitution



addition to aldehydes and ketones (Sec. 21.7): it is favored by electron withdrawal, which stabilizes the developing negative charge; and it is hindered by the presence of bulky groups, which become crowded together in the transition state. The second step depends, as we have seen, on the basicity of the leaving group, :W.

If acid is present, H^+ becomes attached to carbonyl oxygen, thus making the

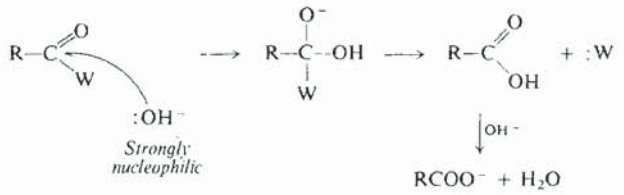
Acid-catalyzed nucleophilic acyl substitution



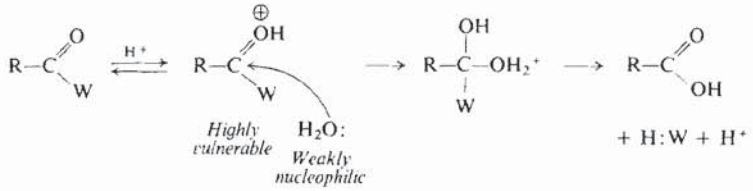
carbonyl group even more susceptible to the nucleophilic attack; oxygen can now acquire the π electrons without having to accept a negative charge.

It is understandable that acid derivatives are hydrolyzed more readily in either alkaline or acidic solution than in neutral solution: alkaline solutions provide hydroxide ion, which acts as a strongly nucleophilic reagent; acid solutions provide hydrogen ion, which attaches itself to carbonyl oxygen and thus renders the molecule vulnerable to attack by the weakly nucleophilic reagent, water.

Alkaline hydrolysis

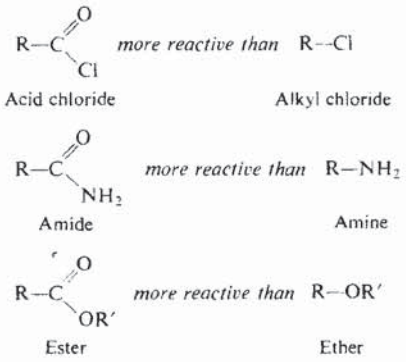


Acidic hydrolysis



24.5 Nucleophilic substitution: alkyl *vs.* acyl

As we have said, nucleophilic substitution takes place much more readily at an acyl carbon than at saturated carbon. Thus, toward nucleophilic attack acid chlorides are more reactive than alkyl chlorides, amides are more reactive than amines (RNH_2), and esters are more reactive than ethers.



Reactivity in nucleophilic displacement

It is, of course, the carbonyl group that makes acyl compounds more reactive than alkyl compounds. Nucleophilic attack (S_N2) on a tetrahedral alkyl carbon invoives a badly crowded transition state containing pentavalent carbon; a bond must be partly broken to permit the attachment of the nucleophile:

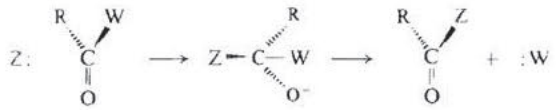
Alkyl nucleophilic substitution

Tetrahedral C
Attack hindered

Pentavalent C
Unstable

Nucleophilic attack on a flat acyl compound involves a relatively unhindered transition state leading to a tetrahedral intermediate that is actually a compound; since the carbonyl group is unsaturated, attachment of the nucleophile requires

Acyl nucleophilic substitution



Trigonal C
Attack relatively unhindered

Tetrahedral C
Stable

breaking only of the weak π bond, and places a negative charge on an atom quite willing to accept it, oxygen.

ACID CHLORIDES

24.6 Preparation of acid chlorides

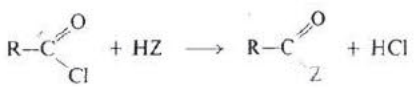
Acid chlorides are prepared from the corresponding acids by reaction with thionyl chloride, phosphorus trichloride, or phosphorus pentachloride, as discussed in Sec. 23.15.

24.7 Reactions of acid chlorides

Like other acid derivatives, acid chlorides typically undergo nucleophilic substitution. Chlorine is expelled as chloride ion or hydrogen chloride, and its place is taken by some other basic group. Because of the carbonyl group these reactions take place much more rapidly than the corresponding nucleophilic substitution reactions of the alkyl halides. Acid chlorides are the most reactive of the derivatives of carboxylic acids.

REACTIONS OF ACID CHLORIDES

1. **Conversion into acids and derivatives.** Discussed in Sec. 24.8.



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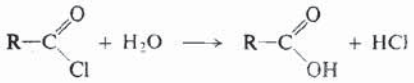
(a) **Conversion into acids. Hydrolysis**

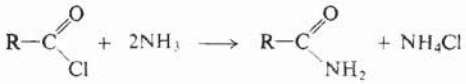


An acid

Example:

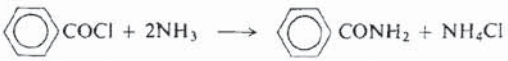
Benzoyl chloride — Benzoic acid

(b) **Conversion into amides. Ammonolysis**



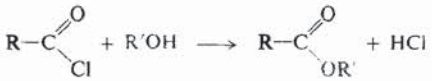
An amide

Example:



Benzoyl chloride — Benzamide

(c) **Conversion into esters. Alcoholysis**

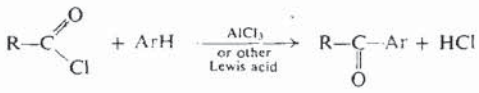


An ester

Example:

Benzoyl chloride — Ethyl alcohol — Ethyl benzoate

2. **Formation of ketones. Friedel–Crafts acylation.** Discussed in Sec. 21.5.



A ketone

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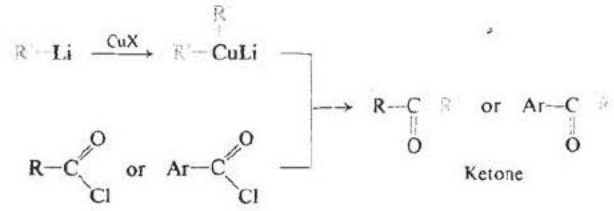
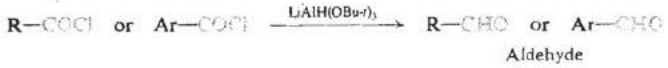
3. Formation of ketones. Reaction with organocopper compounds. Discussed in Sec. 21.6.

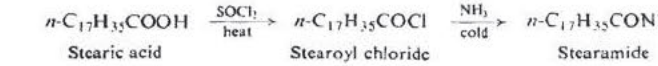


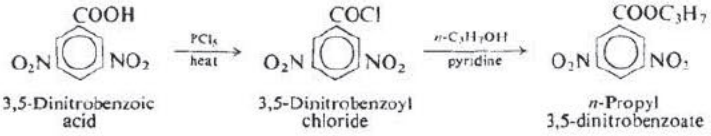
4. Formation of aldehydes by reduction. Discussed in Sec. 21.4.

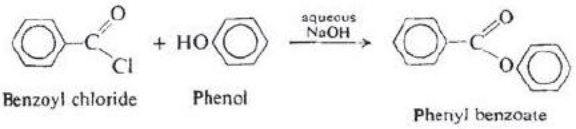


24.8 Conversion of acid chlorides into acid derivatives

In the laboratory, amides and esters are usually prepared from the acid chloride rather than from the acid itself. Both the preparation of the acid chloride and its reactions with ammonia or an alcohol are rapid, essentially irreversible reactions. It is more convenient to carry out these two steps than the single slow, reversible reaction with the acid. For example:







Aromatic acid chlorides (ArCOCl) are considerably less reactive than the aliphatic acid chlorides. With cold water, for example, acetyl chloride reacts almost explosively, whereas benzoyl chloride reacts only very slowly. The reaction of aromatic acid chlorides with an alcohol or a phenol is often carried out using the **Schotten–Baumann** technique: the acid chloride is added in portions (followed by vigorous shaking) to a mixture of the hydroxy compound and a base, usually aqueous sodium hydroxide or pyridine (an organic base, Sec. 35.11). Base serves not only to neutralize the hydrogen chloride that would otherwise be liberated, but also to catalyze the reaction. Pyridine, in particular, seems to convert the acid chloride into an even more powerful acylating agent.

ACID ANHYDRIDES

24.9 Preparation of acid anhydrides

Only one monocarboxylic acid anhydride is encountered very often; however, this one, **acetic anhydride**, is immensely important. It is prepared by the reaction of acetic acid with **ketene**, $CH_2{=}C{=}O$, which itself is prepared by high-temperature dehydration of acetic acid.

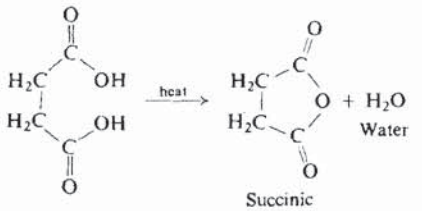
$$CH_3COOH \xrightarrow[700\ ^\circ C]{AlPO_4} H_2O + \underset{\text{Ketene}}{CH_2{=}C{=}O} \xrightarrow{CH_3COOH} \underset{\text{Acetic anhydride}}{(CH_3CO)_2O}$$

Ketene is an extremely reactive, interesting compound, which we have already encountered as a source of *methylene* (Sec. 12.16). It is made in the laboratory by

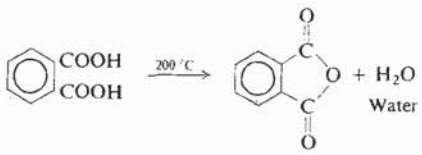
$$CH_3COCH_3 \xrightarrow{700\text{–}750\ ^\circ C} CH_4 + \underset{\text{Ketene}}{CH_2{=}C{=}O}$$

pyrolysis of acetone, and ordinarily used as soon as it is made.

In contrast to monocarboxylic acids, certain *di*carboxylic acids yield anhydrides on simple heating: in those cases where a five- or six-membered ring is produced. For example:

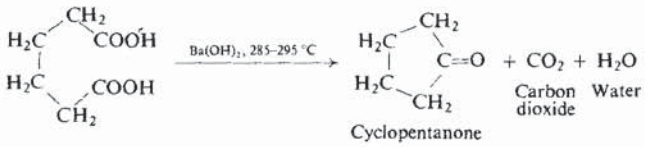


Succinic anhydride



Phthalic anhydride

Ring size is crucial: with adipic acid, for example, anhydride formation would produce a seven-membered ring, and does not take place. Instead, carbon dioxide is lost and cyclopentanone, a ketone with a five-membered ring, is formed:



Cyclopentanone

Problem 24.2 Cyclic anhydrides can be formed from only the *cis*-1,2-cyclopentanedicarboxylic acid, but from both the *cis*- and *trans*-1,2-cyclohexanedicarboxylic acids. How do you account for this?

24.10 Reactions of acid anhydrides

Acid anhydrides undergo the same reactions as acid chlorides, but a little more slowly; where acid chlorides yield a molecule of HCl, anhydrides yield a molecule of carboxylic acid.

Compounds containing the acetyl group are often prepared from acetic anhydride; it is cheap, readily available, less volatile and more easily handled than acetyl chloride, and it does not form corrosive hydrogen chloride. It is widely used industrially for the esterification of the polyhydroxy compounds known as *carbohydrates*, especially cellulose (Chap. 39).

REACTIONS OF ACID ANHYDRIDES

1. Conversion into acids and acid derivatives. Discussed in Sec. 24.10.

$$(RCO)_2O + HZ \longrightarrow RCOZ + RCOOH$$

(a) Conversion into acids. Hydrolysis

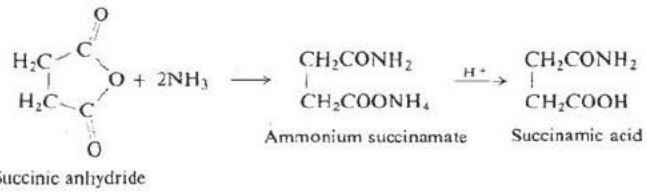
Example:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + H_2O \longrightarrow \underset{\text{Acetic acid}}{2CH_3COOH}$$

(b) Conversion into amides. Ammonolysis

Examples:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + 2NH_3 \longrightarrow \underset{\text{Acetamide}}{CH_3CONH_2} + \underset{\text{Ammonium acetate}}{CH_3COO^-NH_4^+}$$



Succinic anhydride — Ammonium succinamate — Succinamic acid

(c) Conversion into esters. Alcoholysis

Examples:

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + CH_3OH \longrightarrow \underset{\substack{\text{Methyl acetate}\\\text{(An ester)}}}{CH_3COOCH_3} + \underset{\text{Acetic acid}}{CH_3COOH}$$

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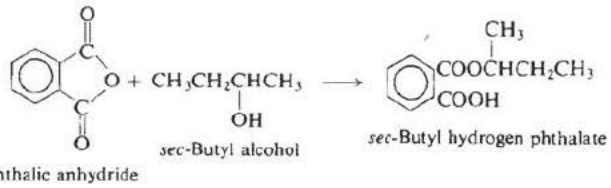
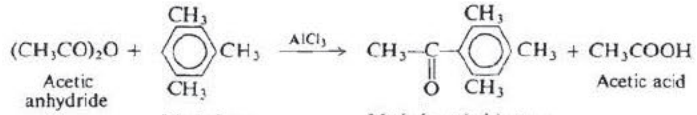


Phthalic anhydride — *sec*-Butyl alcohol — *sec*-Butyl hydrogen phthalate

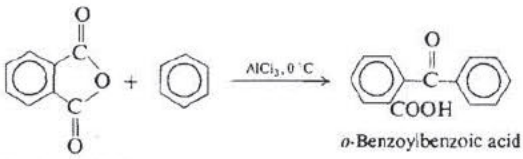
2. Formation of ketones. Friedel–Crafts acylation. Discussed in Sec. 21.5.

$$(RCO_2)O + ArH \xrightarrow[\text{or other Lewis acid}]{AlCl_3} R{-}\overset{\overset{O}{\|}}{C}{-}Ar + RCOOH$$

A ketone



Acetic anhydride — Mesitylene — Methyl mesityl ketone — Acetic acid



Phthalic anhydride — *o*-Benzoylbenzoic acid ■

Only "half" of the anhydride appears in the acyl product; the other "half" forms a carboxylic acid. A cyclic anhydride, we see, undergoes exactly the same reactions as any other anhydride. However, since both "halves" of the anhydride are attached to each other by carbon–carbon bonds, the acyl compound and the carboxylic acid formed will have to be part of the same molecule. Cyclic anhydrides can thus be used to make compounds containing both the acyl group and the carboxyl group: compounds that are, for example, both acids and amides, both acids and esters, etc. These difunctional compounds are of great value in further synthesis.

Problem 24.3 (a) The two 1,3-cyclobutanedicarboxylic acids (p. 457) have been assigned configurations on the basis of the fact that one can be converted into an anhydride and the other cannot. Which configuration would you assign to the one that can form the anhydride, and why? (b) The method of (a) cannot be used to assign configurations to the 1,2-cyclohexanedicarboxylic acids, since *both* give anhydrides. Why is this? (c) Could the method of (a) be used to assign configurations to the 1,3-cyclohexanedicarboxylic acids?

Problem 24.4 Give structural formulas for compounds A through G.

Benzene + succinic anhydride $\xrightarrow{AlCl_3}$ A ($C_{10}H_{10}O_3$)

A + Zn(Hg) $\xrightarrow{HCl}$ B ($C_{10}H_{12}O_2$)

B + $SOCl_2$ $\longrightarrow$ C ($C_{10}H_{11}OCl$)

C $\xrightarrow{AlCl_3}$ D ($C_{10}H_{10}O$)

D + H_2 $\xrightarrow{Pt}$ E ($C_{10}H_{12}O$)

E + H_2SO_4 $\xrightarrow{heat}$ F ($C_{10}H_{10}$)

F $\xrightarrow{Pt,\ heat}$ G ($C_{10}H_8$) + H_2

Problem 24.5 (a) What product will be obtained if D of the preceding problem is treated with C_2H_5MgBr and then water? (b) What will you finally get if the product from (a) replaces E in the preceding problem?

Problem 24.6 When heated with acid (e.g., concentrated H_2SO_4), *o*-benzoylbenzoic acid yields a product of formula $C_{14}H_8O_2$. What is the structure of this product? What general type of reaction has taken place?

Problem 24.7 Predict the products of the following reactions:
(a) toluene + phthalic anhydride + $AlCl_3$
(b) the product from (a) + conc. H_2SO_4 + heat

Problem 24.8 Alcohols are the class of compounds most commonly resolved (Sec. 4.27), despite the fact that they are not acidic enough or basic enough to form (stable) salts. Outline all steps in a procedure for the resolution of *sec*-butyl alcohol, using as resolving agent the base (−)-B.

AMIDES

24.11 Preparation of amides

In the laboratory amides are prepared by the reaction of ammonia with acid chlorides or, when available, acid anhydrides (Secs. 24.8 and 24.10). In industry they are often made by heating the ammonium salts of carboxylic acids.

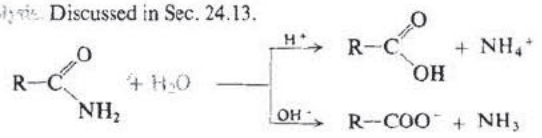
24.12 Reactions of amides

An amide is hydrolyzed when heated with aqueous acids or aqueous bases. The products are ammonia and the carboxylic acid, although one product or the other is obtained in the form of a salt, depending upon the acidity or basicity of the medium.

Another reaction of importance, the Hofmann degradation of amides, will be discussed later (Secs. 26.12 and 32.2–32.5).

REACTIONS OF AMIDES

1. Hydrolysis. Discussed in Sec. 24.13.



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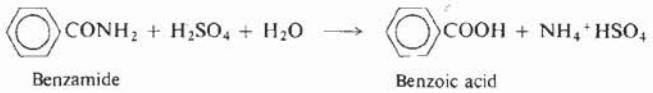
Examples:



Benzamide — Benzoic acid

$$CH_3CH_2CH_2CONH_2 + NaOH + H_2O \longrightarrow CH_3CH_2CH_2COO^-Na^+ + NH_3$$

Butyramide — Sodium butyrate

[illegible]. Discussed in Sec. 24.14.

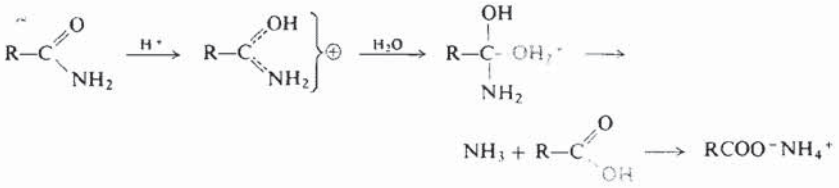
[illegible]. Discussed in Secs. 26.12 and 32.2–32.5.

$$R{-}CONH_2 \text{ or } Ar{-}CONH_2 \xrightarrow{OBr^-} R{-}NH_2 \text{ or } Ar{-}NH_2 + CO_3^{2-}$$

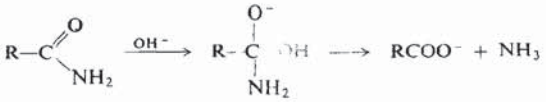
Amide — 1° amine

24.13 Hydrolysis of amides

Hydrolysis of amides is typical of the reactions of carboxylic acid derivatives. It involves nucleophilic substitution, in which the $-NH_2$ group is replaced by $-OH$. Under acidic conditions hydrolysis involves attack by water on the protonated amide:



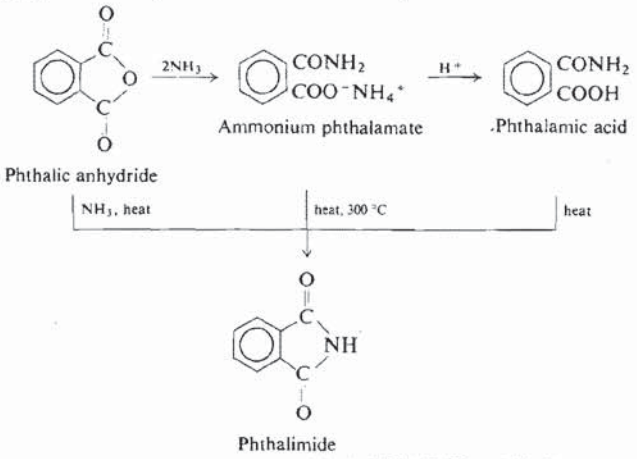
Under alkaline conditions hydrolysis involves attack by the strongly nucleophilic hydroxide ion on the amide itself:



24.14 Imides

Like other anhydrides, cyclic anhydrides react with ammonia to yield amides; in this case the product contains both $-CONH_2$ and $-COOH$ groups. If this acid-amide is heated, a molecule of water is lost, a ring forms, and a product is obtained in which two acyl groups have become attached to nitrogen; compounds

of this sort are called **imides**. Phthalic anhydride gives *phthalamic acid* and *phthalimide*:



Problem 24.9 Outline all steps in the synthesis of *succinimide* from succinic acid.

Problem 24.10 Account for the following sequence of acidities. (*Hint*: See Sec. 23.12.)

	K_a
Ammonia	10^{-33}
Benzamide	10^{-14} to 10^{-15}
Phthalimide	5×10^{-9}

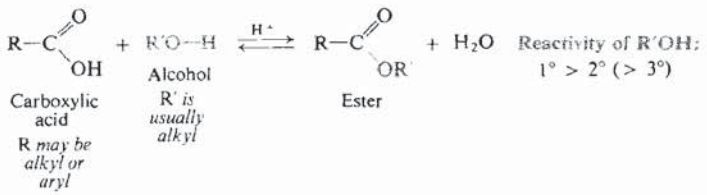
ESTERS

24.15 Preparation of esters

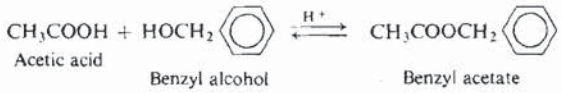
Esters are usually prepared by the reaction of alcohols or phenols with acids or acid derivatives. The most common methods are outlined below.

PREPARATION OF ESTERS

1. From acids. Discussed in Secs. 23.16 and 24.15.



Examples:



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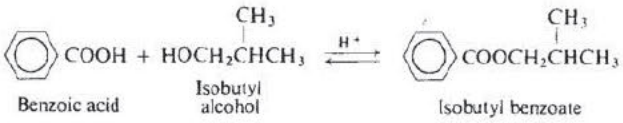
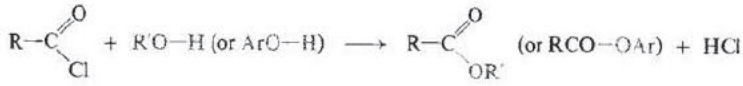
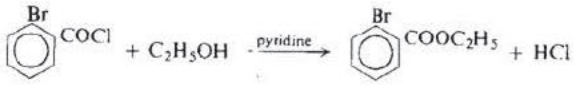


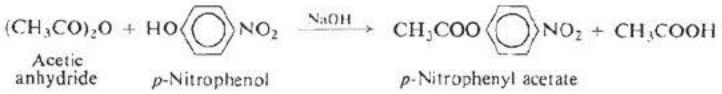
2. From acid chlorides or anhydrides. Discussed in Secs. 24.8 and 24.10.



$$(RCO)_2O + R'OH \text{ (or ArOH)} \longrightarrow RCOOR' \text{ (or RCOOAr)} + RCOOH$$

Examples:





3. From esters. Transesterification. Discussed in Sec. 24.20.

The direct reaction of alcohols or phenols with acids involves an equilibrium and—especially in the case of phenols—requires effort to drive to completion (see Sec. 23.16). In the laboratory, reaction with an acid chloride or anhydride is more commonly used.

The effect of the structure of the alcohol and of the acid on ease of esterification has already been discussed (Sec. 23.16).

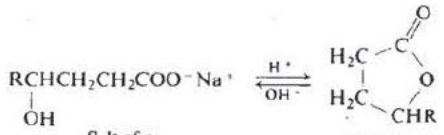
Table 24.2 ESTERS OF CARBOXYLIC ACIDS

Name	M.p., °C	B.p., °C	Name	M.p., °C	B.p., °C
Methyl acetate	−98	57.5	Ethyl formate	−80	54
Ethyl acetate	−84	77	Ethyl acetate	−84	77
n-Propyl acetate	−92	102	Ethyl propionate	−74	99
n-Butyl acetate	−77	126	Ethyl *n*-butyrate	−93	121
n-Pentyl acetate		148	Ethyl *n*-valerate	−91	146
Isopentyl acetate	−78	142	Ethyl stearate	34	215^{15}
Benzyl acetate	−51	214	Ethyl phenylacetate		226
Phenyl acetate		196	Ethyl benzoate	−35	213

As was mentioned earlier, esterification using aromatic acid chlorides, ArCOCl, is often carried out in the presence of base (the Schotten–Baumann technique, Sec. 24.8).

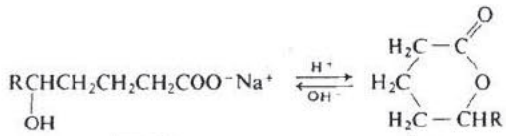
Problem 24.11 When benzoic acid is esterified by methanol in the presence of a little sulfuric acid, the final reaction mixture contains five substances: benzoic acid, methanol, water, methyl benzoate, sulfuric acid. Outline a procedure for the separation of the pure ester.

A hydroxy acid is both alcohol and acid. In those cases where a five- or six-membered ring can be formed, *intramolecular* esterification occurs. Thus, a γ- or δ-hydroxy acid loses water spontaneously to yield a cyclic ester known as a **lactone**. Treatment with base (actually hydrolysis of an ester) rapidly opens the lactone ring



Salt of a γ-hydroxy acid — A γ-lactone

A cyclic ester: five-membered ring



Salt of a δ-hydroxy acid — A δ-lactone

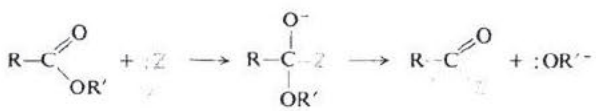
A cyclic ester: six-membered ring

to give the open-chain salt. We shall encounter lactones again in our study of carbohydrates (Sec. 38.8).

Problem 24.12 Suggest a likely structure for the product formed by heating each of these acids. (a) *Lactic acid*, $CH_3CHOHCOOH$, gives *lactide*, $C_6H_8O_4$. (b) 10-Hydroxydecanoic acid gives a material of high molecular weight (1000–9000).

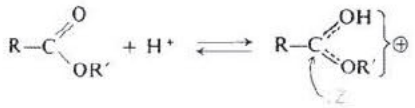
24.16 Reactions of esters

Esters undergo the nucleophilic substitution that is typical of carboxylic acid derivatives. Attack occurs at the electron-deficient carbonyl carbon, and results in the replacement of the $-OR'$ group by $-OH$, $-OR''$, or $-NH_2$:



$:Z = :OH^-,\ :OR''^-,\ :NH_3$

These reactions are sometimes carried out in the presence of acid. In these acid-catalyzed reactions, H^+ attaches itself to the oxygen of the carbonyl group, and thus renders carbonyl carbon even more susceptible to nucleophilic attack.

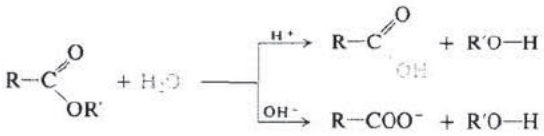


Acid catalysis: makes carbon more susceptible to nucleophilic attack

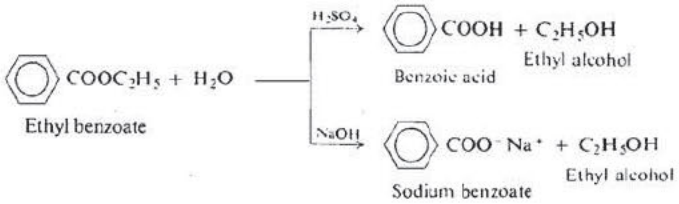
REACTIONS OF ESTERS

1. Conversion into acids and acid derivatives

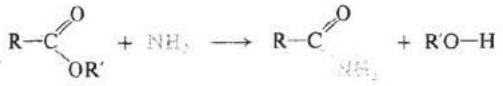
(a) Conversion into acids. Hydrolysis. Discussed in Secs. 24.17 and 24.18.



Example:



(b) Conversion into amides. Ammonolysis. Discussed in Sec. 24.19.

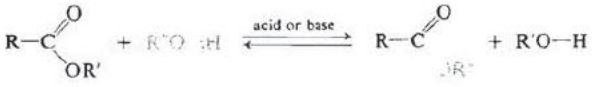


Example:

$$CH_3COOC_2H_5 + NH_3 \longrightarrow CH_3CONH_2 + C_2H_5OH$$

Ethyl acetate — Acetamide — Ethyl alcohol

(c) Conversion into esters. Transesterification. Acidolysis. Discussed in Sec. 24.20.



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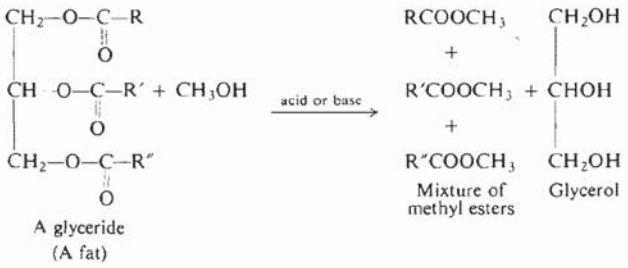
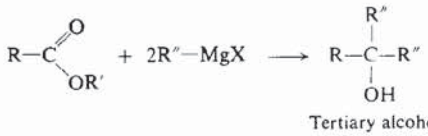
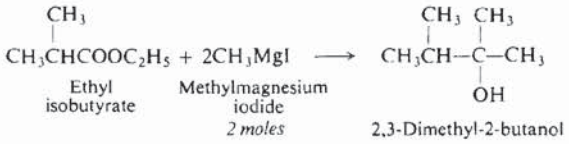
Example:



2. **Reaction with Grignard reagents.** Discussed in Sec. 24.21.

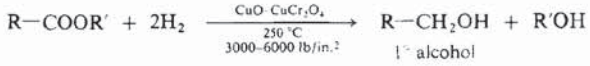


Example:

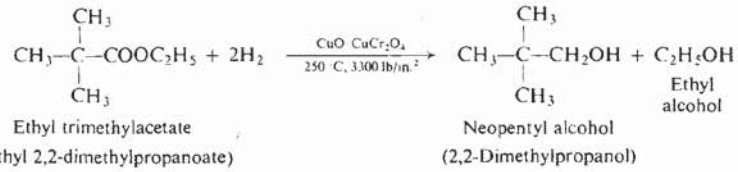


3. **Reduction to alcohols.** Discussed in Sec. 24.22.

(a) **Catalytic hydrogenation. Hydrogenolysis**



Example:



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(b) Chemical reduction

$$4R{-}COOR' + 2LiAlH_4 \xrightarrow{\text{anhyd. ether}} \left\{\begin{matrix} LiAl(OCH_2R)_4 \\ + \\ LiAl(OR')_4 \end{matrix}\right\} \xrightarrow{H^+} \left\{\begin{matrix} R{-}CH_2OH \\ + \\ R'OH \end{matrix}\right\}$$

Example:

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOCH_3 \xrightarrow{LiAlH_4} \xrightarrow{H^+} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

Methyl oleate (Methyl *cis*-9-octadecenoate) — Oleyl alcohol (*cis*-9-Octadecen-1-ol)

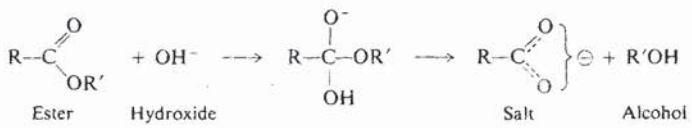
4. **Reaction with carbanions. Claisen condensation.** Discussed in Secs. 25.11 and 25.12.

A β-keto ester ■

24.17 Alkaline hydrolysis of esters

A carboxylic ester is hydrolyzed to a carboxylic acid and an alcohol or phenol when heated with aqueous acid or aqueous base. Under alkaline conditions, of course, the carboxylic acid is obtained as its salt, from which it can be liberated by addition of mineral acid.

Base promotes hydrolysis of esters by providing the strongly nucleophilic



Ester — Hydroxide — Salt — Alcohol

reagent OH^-. This reaction is essentially irreversible, since a resonance-stabilized carboxylate anion (Sec. 23.13) shows little tendency to react with an alcohol.

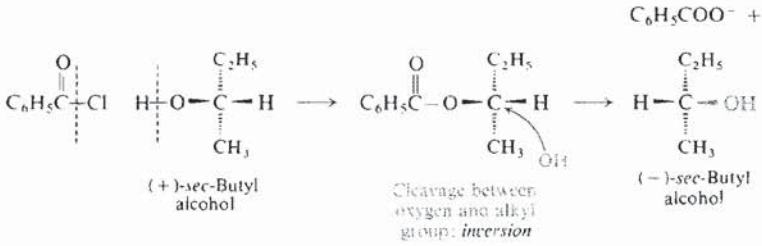
Let us look at the various aspects of the mechanism we have written, and see what evidence there is for each of them.

First, reaction involves attack on the ester by hydroxide ion. This is consistent with the **kinetics**, which is second-order, with the rate depending on both ester concentration and hydroxide concentration.

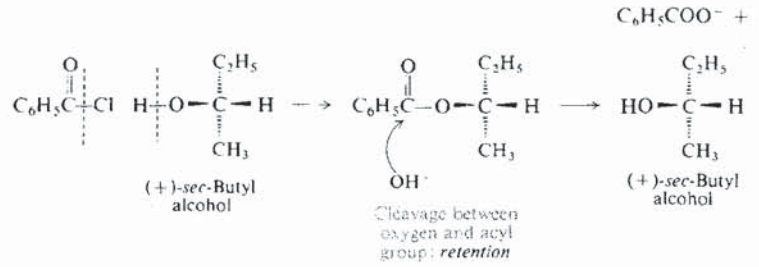
Next hydroxide attacks at the carbonyl carbon and displaces alkoxide ion. That is to say, reaction involves cleavage of the bond between oxygen and the acyl group, RCO–OR'. For this there are two lines of evidence, the first being the **stereochemistry**.

Let us consider, for example, the formation and subsequent hydrolysis of an ester of optically active *sec*-butyl alcohol. Reaction of (+)-*sec*-butyl alcohol with

benzoyl chloride must involve cleavage of the hydrogen–oxygen bond and hence cannot change the configuration about the chiral center (see Sec. 4.23). If hydrolysis of this ester involves cleavage of the bond between oxygen and the *sec*-butyl group, we would expect almost certainly inversion (or inversion plus racemization if the reaction goes by an S_N1 type of mechanism):

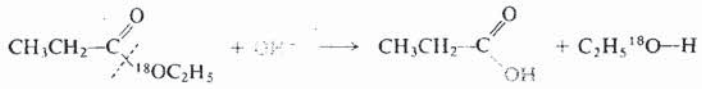


If, on the other hand, the bond between oxygen and the *sec*-butyl group remains intact during hydrolysis, then we would expect to obtain *sec*-butyl alcohol of the same configuration as the starting material:



When *sec*-butyl alcohol of rotation $+13.8°$ was actually converted into the benzoate and the benzoate was hydrolyzed in alkali, there was obtained *sec*-butyl alcohol of rotation $+13.8°$. This complete retention of configuration strongly indicates that bond cleavage occurs between oxygen and the acyl group.

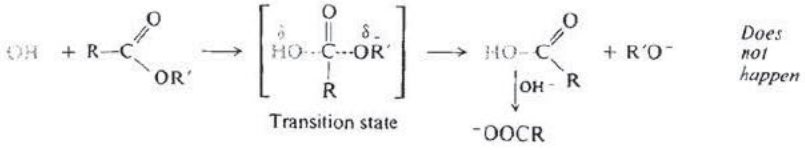
Tracer studies have confirmed the kind of bond cleavage indicated by the stereochemical evidence. When ethyl propionate labeled with ^{18}O was hydrolyzed by base in ordinary water, the ethanol produced was found to be enriched in ^{18}O; the propionic acid contained only the ordinary amount of ^{18}O:



The alcohol group retained the oxygen that it held in the ester; cleavage occurred between oxygen and the acyl group.

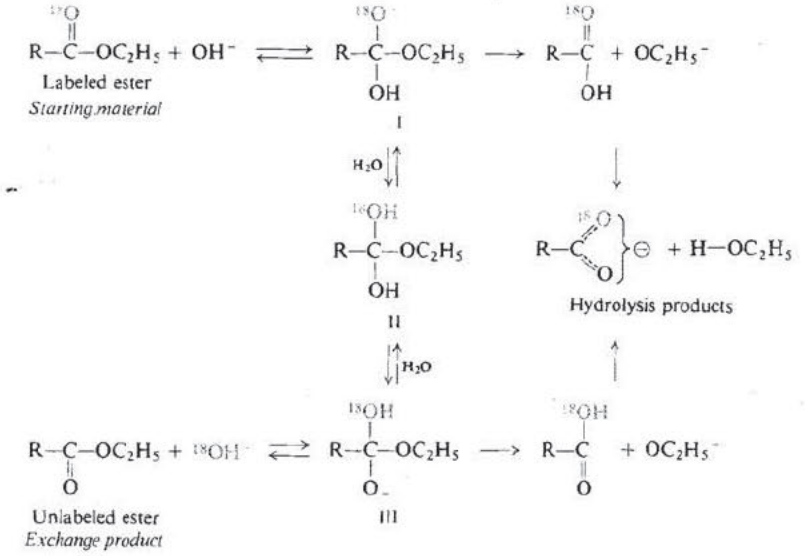
The study of a number of other hydrolyses by both tracer and stereochemical methods has shown that cleavage between oxygen and the acyl group is the usual one in ester hydrolysis. This behavior indicates that the preferred point of nucleophilic attack is the carbonyl carbon rather than the alkyl carbon; this is, of course, what we might have expected in view of the generally greater reactivity of carbonyl carbon (Sec. 24.5).

Finally, according to the mechanism, attack by hydroxide ion on carbonyl carbon does not displace alkoxide ion in one step,



but rather in *two steps* with the intermediate formation of a tetrahedral compound. These alternative mechanisms were considered more or less equally likely until 1950 when elegant work on **isotopic exchange** was reported by Myron Bender (now at Northwestern University).

Bender carried out the alkaline hydrolysis of carbonyl-labeled ethyl benzoate, $C_6H_5C^{18}OOC_2H_5$, in ordinary water, and focused his attention, not on the product, but on the *reactant*. He interrupted the reaction after various periods of time, and isolated the unconsumed ester and analyzed it for ^{18}O content. He found that in the alkaline solution the ester was undergoing not only hydrolysis but also *exchange of its* ^{18}O *for ordinary oxygen from the solvent*.



Oxygen exchange is not consistent with the one-step mechanism, which provides no way for it to happen. Oxygen exchange is consistent with a two-step mechanism in which intermediate I is not only formed, but partly reverts into starting material and partly is converted (probably via the neutral species II) into III—an intermediate that is equivalent to I except for the position of the label. If all this is so, the "reversion" of intermediate III into "starting material" yields ester that has lost its ^{18}O.

Bender's work does not *prove* the mechanism we have outlined. Conceivably, oxygen exchange—and hence the tetrahedral intermediate—simply represent a blind-alley down which ester molecules venture but which does not lead to hydrolysis. Such coincidence is

unlikely, however, particularly in light of certain kinetic relationships between oxygen exchange and hydrolysis.

Similar experiments have indicated the reversible formation of tetrahedral intermediates in hydrolysis of other esters, amides, anhydrides, and acid chlorides, and are the basis of the general mechanism we have shown for nucleophilic acyl substitution.

Exchange experiments are also the basis of our estimate of the relative importance of the two steps: differences in rate of hydrolysis of acyl derivatives depend chiefly on how fast intermediates are formed, and also on what fraction of the intermediate goes on to product. As we have said, the rate of formation of the intermediate is affected by both electronic and steric factors: in the transition state, a negative charge is developing and carbon is changing from trigonal toward tetrahedral.

Even in those cases where oxygen exchange cannot be detected, we cannot rule out the possibility of an intermediate; it may simply be that it goes on to hydrolysis products much faster than it does anything else.

Problem 24.13 The relative rates of alkaline hydrolysis of ethyl *p*-substituted benzoates, *p*-$GC_6H_4COOC_2H_5$, are:

$$\begin{array}{ccccccc} G = & NO_2 & > & Cl & > & H & > & CH_3 & > & OCH_3 \\ & 110 & & 4 & & 1 & & 0.5 & & 0.2 \end{array}$$

(a) How do you account for this order of reactivity? (b) What kind of effect, activating or deactivating, would you expect from *p*-Br? from *p*-NH_2? from *p*-$C(CH_3)_3$? (c) Predict the order of reactivity toward alkaline hydrolysis of: *p*-aminophenyl acetate, *p*-methylphenyl acetate, *p*-nitrophenyl acetate, phenyl acetate.

Problem 24.14 The relative rates of alkaline hydrolysis of alkyl acetates, CH_3COOR, are:

$$\begin{array}{ccccccc} R = & CH_3 & > & C_2H_5 & > & (CH_3)_2CH & > & (CH_3)_3C \\ & 1 & & 0.6 & & 0.15 & & 0.008 \end{array}$$

(a) What two factors might be at work here? (b) Predict the order of reactivity toward alkaline hydrolysis of: methyl acetate, methyl formate, methyl isobutyrate, methyl propionate, and methyl trimethylacetate.

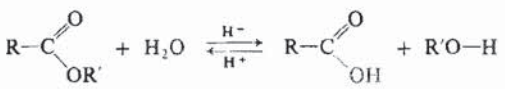
Problem 24.15 Exchange experiments show that the fraction of the tetrahedral intermediate that goes on to products follows the sequence:

acid chloride > acid anhydride > ester > amide

What is one factor that is probably at work here?

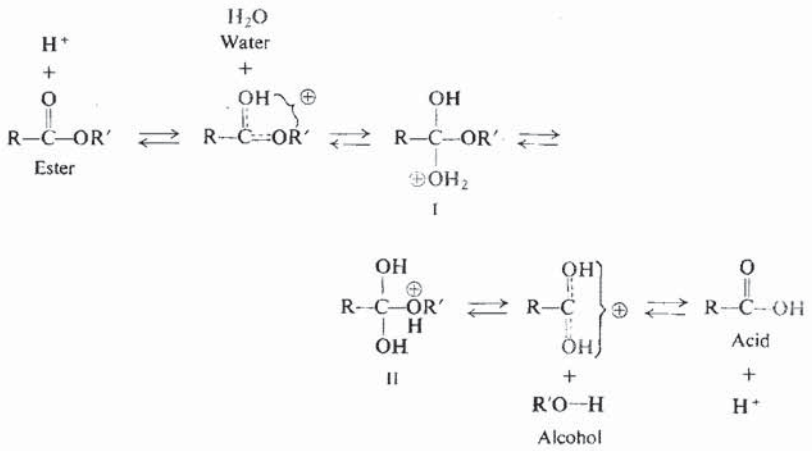
24.18 Acidic hydrolysis of esters

Hydrolysis of esters is promoted not only by base but also by acid. Acidic hydrolysis, as we have seen (Sec. 23.16), is reversible,



and hence the mechanism for hydrolysis is also—taken in the opposite direction—the mechanism for esterification. Any evidence about one reaction must apply to both.

The mechanism for acid-catalyzed hydrolysis and esterification is contained in the following equilibria:



Mineral acid speeds up both processes by protonating carbonyl oxygen and thus rendering carbonyl carbon more susceptible to nucleophilic attack (Sec. 24.4). In hydrolysis, the nucleophile is a water molecule and the leaving group is an alcohol; in esterification, the roles are exactly reversed.

As in alkaline hydrolysis, there is almost certainly a tetrahedral intermediate—or, rather, several of them. The existence of more than one intermediate is required by, among other things, the reversible nature of the reaction. Looking only at hydrolysis, intermediate II is *likely*, since it permits separation of the weakly basic alcohol molecule instead of the strongly basic alkoxide ion; but consideration of esterification shows that II almost certainly *must* be involved, since it is the product of attack by alcohol on the protonated acid.

The evidence for the mechanism is much the same as in alkaline hydrolysis. The position of cleavage, RCO$\dagger$OR′ and RCO$\dagger$OH, has been shown by ^{18}O studies of both hydrolysis and esterification. The existence of the tetrahedral intermediates was demonstrated, as in the alkaline reaction, by ^{18}O exchange between the carbonyl oxygen of the ester and the solvent.

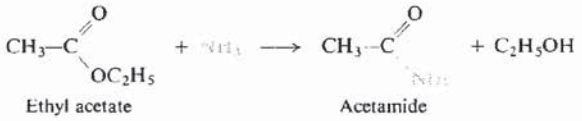
Problem 24.16 Write the steps to account for exchange between $RC^{18}OOR'$ and H_2O in acidic solution. There is reason to believe that a key intermediate here is identical with one in alkaline hydrolysis. What might this intermediate be?

Problem 24.17 Account for the fact (Sec. 23.16) that the presence of bulky substituents in either the alcohol group or the acid group slows down both esterification and hydrolysis.

Problem 24.18 Acidic hydrolysis of *tert*-butyl acetate in water enriched in ^{18}O has been found to yield *tert*-butyl alcohol enriched in ^{18}O and acetic acid containing ordinary oxygen. Acidic hydrolysis of the acetate of optically active 3,7-dimethyl-3-octanol has been found to yield alcohol of much lower optical purity than the starting alcohol, and having the opposite sign of rotation. (a) How do you interpret these two sets of results? (b) Is it surprising that these particular esters should show this kind of behavior?

24.19 Ammonolysis of esters

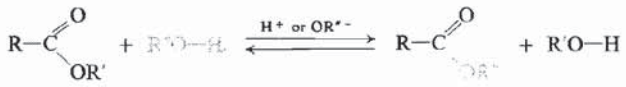
Treatment of an ester with ammonia, generally in ethyl alcohol solution, yields the amide. This reaction involves nucleophilic attack by a base, ammonia, on the electron-deficient carbon; the alkoxy group, —OR′, is replaced by $—NH_2$. For example:



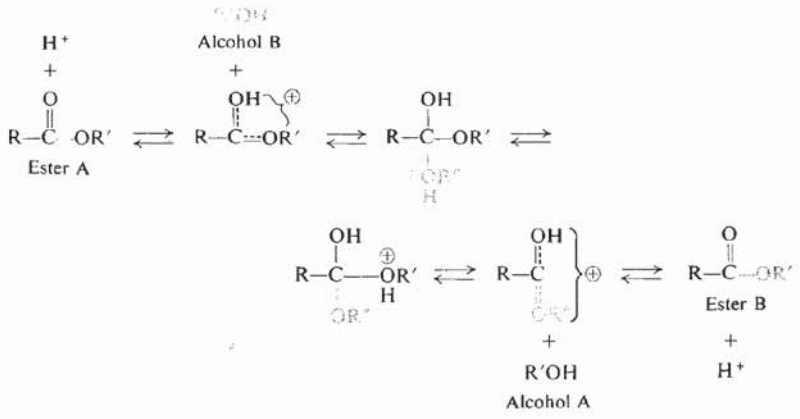
Ethyl acetate Acetamide

24.20 Transesterification

In the esterification of an acid, an alcohol acts as a nucleophilic reagent; in hydrolysis of an ester, an alcohol is displaced by a nucleophilic reagent. Knowing this, we are not surprised to find that one alcohol is capable of displacing another alcohol from an ester. This *alcoholysis* (cleavage by an alcohol) of an ester is called **transesterification**.



Transesterification is catalyzed by acid (H_2SO_4 or dry HCl) or base (usually alkoxide ion). The mechanisms of these two reactions are exactly analogous to those we have already studied. For acid-catalyzed transesterification:



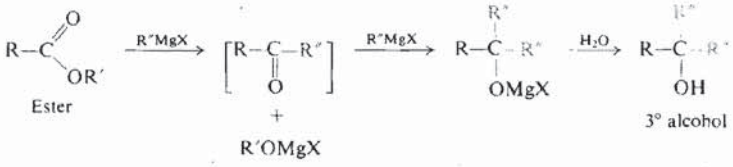
Ester A Alcohol A Ester B

For base-catalyzed transesterification:

Transesterification is an equilibrium reaction. To shift the equilibrium to the right, it is necessary to use a large excess of the alcohol whose ester we wish to make, or else to remove one of the products from the reaction mixture. The second approach is the better one when feasible, since in this way the reaction can be driven to completion.

24.21 Reaction of esters with Grignard reagents

The reaction of carboxylic esters with Grignard reagents is an excellent method for preparing tertiary alcohols. As in the reaction with aldehydes and ketones (Sec. 21.10), the nucleophilic (basic) alkyl or aryl group of the Grignard reagent attaches itself to the electron-deficient carbonyl carbon. Expulsion of the alkoxide group would yield a ketone, and in certain special cases ketones are indeed isolated from this reaction. However, as we know, ketones themselves readily react with Grignard reagents to yield tertiary alcohols (Sec. 17.15); in the present case the products obtained correspond to the addition of the Grignard reagent to such a ketone:



Two of the three groups attached to the carbon bearing the hydroxyl group in the alcohol come from the Grignard reagent and hence must be identical; this, of course, places limits upon the alcohols that can be prepared by this method. But, where applicable, reaction of a Grignard reagent with an ester is preferred to reaction with a ketone because esters are generally more accessible.

Problem 24.19 Starting from valeric acid, and using any needed reagents, outline the synthesis of 3-ethyl-3-heptanol via the reaction of a Grignard reagent with: (a) a ketone; (b) an ester.

Problem 24.20 (a) Esters of which acid would yield *secondary* alcohols on reaction with Grignard reagents? (b) Starting from alcohols of four carbons or fewer, outline all steps in the synthesis of 4-heptanol.

24.22 Reduction of esters

Like many organic compounds, esters can be reduced in two ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction. In either case, the ester is cleaved to yield (in addition to the alcohol or phenol from which it was derived) a primary alcohol corresponding to the acid portion of the ester.

$$\underset{\text{Ester}}{R{-}COOR'} \xrightarrow{\text{reduction}} \underset{1^\circ \text{ alcohol}}{R{-}CH_2OH} + R'OH$$

Hydrogenolysis (cleavage by hydrogen) of an ester requires more severe conditions than simple hydrogenation of (addition of hydrogen to) a carbon–carbon double bond. High pressures and elevated temperatures are required: the catalyst used most often is a mixture of oxides known as *copper chromite*, of approximately the composition $CuO.CuCr_2O_4$. For example:

$$\underset{\substack{\text{Methyl laurate}\\ \text{(Methyl dodecanoate)}}}{CH_3(CH_2)_{10}COOCH_3} \xrightarrow[150\ ^\circ C,\ 5000\ lb/in.^2]{H_2,\ CuO.CuCr_2O_4} \underset{\substack{\text{Lauryl alcohol}\\ \text{(1-Dodecanol)}}}{CH_3(CH_2)_{10}CH_2OH} + CH_3OH$$

Chemical reduction is carried out by use of sodium metal and alcohol, or more usually by use of lithium aluminum hydride. For example:

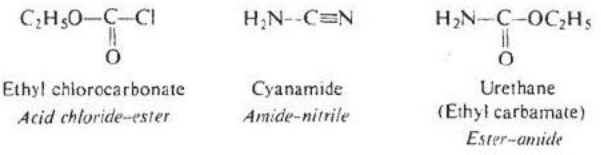
$$\underset{\substack{\text{Ethyl palmitate}\\ \text{(Ethyl hexadecanoate)}}}{CH_3(CH_2)_{14}COOC_2H_5} \xrightarrow{LiAlH_4} \xrightarrow{H^+} \underset{\text{1-Hexadecanol}}{CH_3(CH_2)_{14}CH_2OH}$$

Problem 24.21 Predict the products of the hydrogenolysis of *n*-butyl oleate over copper chromite.

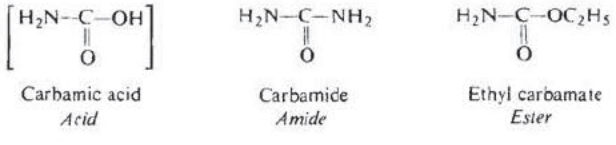
24.23 Functional derivatives of carbonic acid

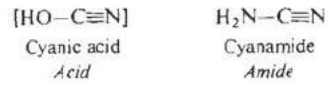
Much of the chemistry of the functional derivatives of carbonic acid is already quite familiar to us through our study of carboxylic acids. The first step in dealing with one of these compounds is to recognize just how it is related to the parent acid. Since carbonic acid is bifunctional, each of its derivatives, too, contains two functional groups; these groups can be the same or different. For example:

$\left[HO{-}\underset{\underset{O}{\|}}{C}{-}OH\right]$	$Cl{-}\underset{\underset{O}{\|}}{C}{-}Cl$	$H_2N{-}\underset{\underset{O}{\|}}{C}{-}NH_2$	$C_2H_5O{-}\underset{\underset{O}{\|}}{C}{-}OC_2H_5$
Carbonic acid	Phosgene (Carbonyl chloride)	Urea (Carbamide)	Ethyl carbonate
Acid	*Acid chloride*	*Amide*	*Ester*

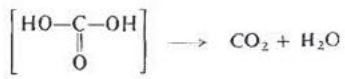


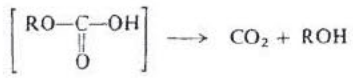
We use these functional relationships to carbonic acid simply for convenience. Many of these compounds could just as well be considered as derivatives of other acids, and, indeed, are often so named. For example:

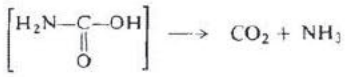


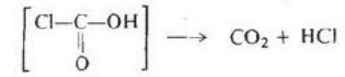


In general, a derivative of carbonic acid containing an —OH group is unstable, and decomposes to carbon dioxide. For example:



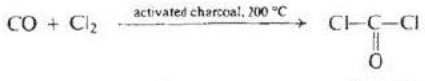




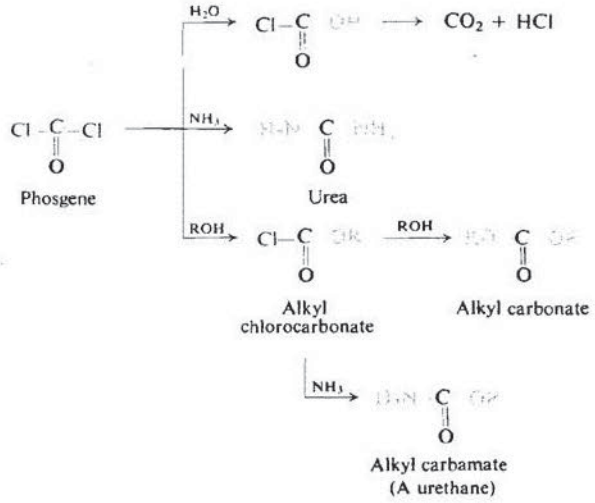


Most derivatives of carbonic acid are made from one of three industrially available compounds: phosgene, urea, or cyanamide.

Phosgene, $COCl_2$, a highly poisonous gas, is manufactured by the reaction between carbon monoxide and chlorine.

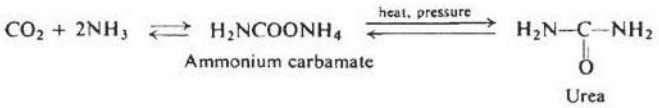


It undergoes the usual reactions of an acid chloride.

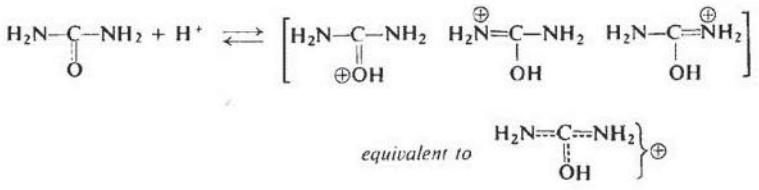


Problem 24.22 Suggest a possible synthesis of
(a) 2-pentylurethane, $H_2NCOOCH(CH_3)(n\text{-}C_3H_7)$, used as a hypnotic;
(b) benzyl chlorocarbonate (*carbobenzoxy chloride*), $C_6H_5CH_2OCOCl$, used in the synthesis of peptides (Sec. 40.10).

Urea, H_2NCONH_2, is excreted in the urine as the chief nitrogen-containing end product of protein metabolism. It is synthesized on a large scale for use as a fertilizer and as a raw material in the manufacture of urea–formaldehyde plastics and of drugs.

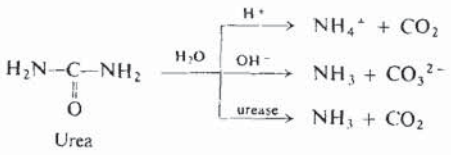


Urea is weakly basic, forming salts with strong acids. The fact that it is a stronger base than ordinary amides is attributed to resonance stabilization of the cation:



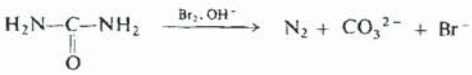
Problem 24.23 Account for the fact that *guanidine*, $(H_2N)_2C{=}NH$, is *strongly* basic.

Urea undergoes hydrolysis in the presence of acids, bases, or the enzyme *urease* (isolable from jack beans; generated by many bacteria, such as *Micrococcus ureae*).

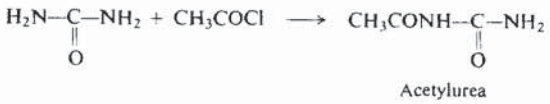


Urea reacts with nitrous acid to yield carbon dioxide and nitrogen; this is a useful way to destroy excess nitrous acid in diazotizations (Sec. 27.12).

Urea is converted by hypohalites into nitrogen and carbonate.

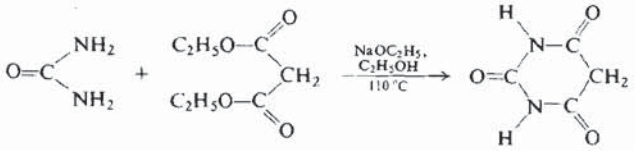


Treatment of urea with acid chlorides or anhydrides yields **ureides**. Of special



Acetylurea
A ureide

importance are the cyclic ureides formed by reaction with malonic esters; these are known as **barbiturates** and are important hypnotics (sleep-producers). For example:



Urea Ethyl malonate Barbituric acid
(Malonylurea)

Cyanamide, $H_2N{-}C{\equiv}N$, is obtained in the form of its calcium salt by the high-temperature reaction between calcium carbide and nitrogen. This reaction is

Calcium carbide — Calcium cyanamide

important as a method of nitrogen fixation; calcium cyanamide has been used as a fertilizer, releasing ammonia by the action of water.

Problem 24.24 Give the electronic structure of the cyanamide anion, $(NCN)^{2-}$. Discuss its molecular shape, bond lengths, and location of charge.

Problem 24.25 Give equations for the individual steps probably involved in the conversion of calcium cyanamide into ammonia in the presence of water. What other product or products will be formed in this process? Label each step with the name of the fundamental reaction type to which it belongs.

Problem 24.26 Cyanamide reacts with water in the presence of acid or base to yield urea; with methanol in the presence of acid to yield methylisourea, $H_2NC(=NH)OCH_3$; with hydrogen sulfide to yield *thiourea*, $H_2NC(=S)NH_2$; and with ammonia to yield *guanidine*, $H_2NC(=NH)NH_2$. (a) What functional group of cyanamide is involved in each of these reactions? (b) To what general class of reaction do these belong? (c) Show the most probable mechanisms for these reactions, pointing out the function of acid or base wherever involved.

24.24 Analysis of carboxylic acid derivatives. Saponification equivalent

Functional derivatives of carboxylic acids are recognized by their hydrolysis—under more or less vigorous conditions—to carboxylic acids. Just *which kind* of derivative it is is indicated by the other products of the hydrolysis.

Problem 24.27 Which kind (or kinds) of acid derivative: (a) rapidly forms a white precipitate (insoluble in HNO_3) upon treatment with alcoholic silver nitrate? (b) reacts with boiling aqueous NaOH to liberate a gas that turns moist litmus paper blue? (c) reacts immediately with cold NaOH to liberate a gas that turns moist litmus blue? (d) yields *only* a carboxylic acid upon hydrolysis? (e) yields an alcohol when heated with acid or base?

Identification or proof of structure of an acid derivative involves the identification or proof of structure of the carboxylic acid formed upon hydrolysis (Sec. 23.21). In the case of an ester, the alcohol that is obtained is also identified (Sec. 18.9). (In the case of a substituted amide, Sec. 27.7, the amine obtained is identified, Sec. 27.20.)

If an ester is hydrolyzed in a known amount of base (taken in excess), the amount of base used up can be measured and used to give the **saponification equivalent**: the equivalent weight of the ester, which is similar to the neutralization equivalent of an acid (see Sec. 23.21).

$$\underset{\textit{one equivalent}}{RCOOR'} + OH^- \longrightarrow \underset{\textit{one equivalent}}{RCOO^-} + R'OH$$

Problem 24.28 (a) What is the saponification equivalent of *n*-propyl acetate? (b) There are eight other simple aliphatic esters that have the same saponification equivalent. What are they? (c) In contrast, how many simple aliphatic acids have this equivalent weight? (d) Is saponification equivalent as helpful in identification as neutralization equivalent?

Problem 24.29 (a) How many equivalents of base would be used up by one mole of methyl phthalate, o-$C_6H_4(COOCH_3)_2$? What is the saponification equivalent of methyl phthalate? (b) What is the relation between saponification equivalent and the number of ester groups per molecule? (c) What is the saponification equivalent of glyceryl stearate (tristearoylglycerol)?

24.25 Spectroscopic analysis of carboxylic acid derivatives

Infrared The infrared spectrum of an acyl compound shows the strong band in the neighborhood of 1700 cm^{-1} that we have come to expect of C=O stretching (see Fig. 24.2).

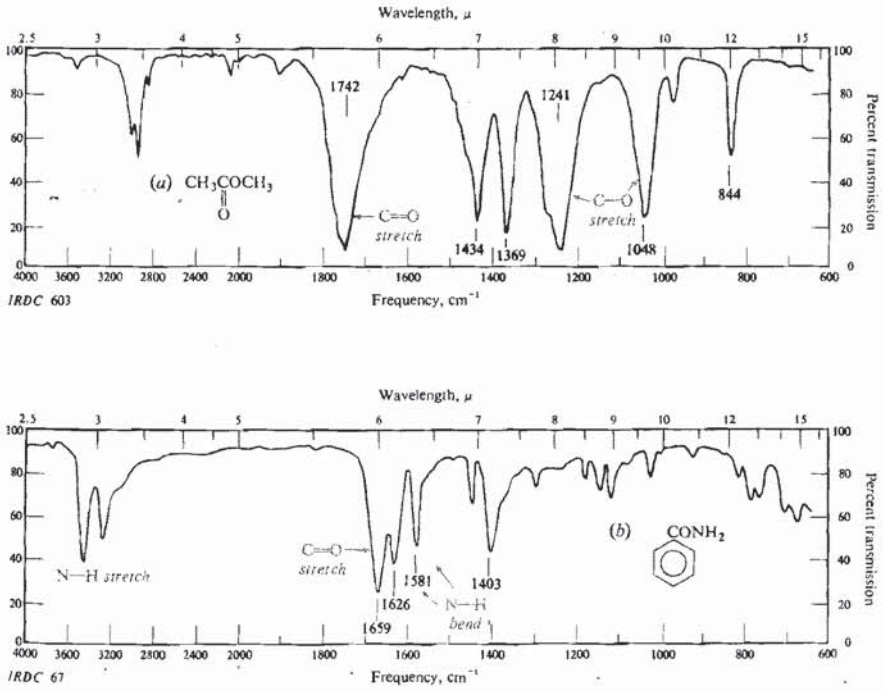


Figure 24.2 Infrared spectra of (*a*) methyl acetate and (*b*) benzamide.

The exact frequency depends on the family the compound belongs to (see Table 24.3) and, for a member of a particular family, on its exact structure. For esters, for example:

RCOOR 1740 cm^{-1} ArCOOR 1715–1730 cm^{-1} or $-\overset{|}{C}=\overset{|}{C}-COOR$ RCOOAr 1770 cm^{-1} or $RCOO\overset{|}{C}=\overset{|}{C}-$

Table 24.3 INFRARED ABSORPTION BY SOME OXYGEN COMPOUNDS

Compound	O—H	C—O	C=O
Alcohols	3200–3600 cm^{-1}	1000–1200 cm^{-1}	—
Phenols	3200–3600	1140–1230	—
Ethers, aliphatic	—	1060–1150	—
Ethers, aromatic	—	1200–1275 1020–1075	—
Aldehydes, ketones	—	—	1675–1725 cm^{-1}
Carboxylic acids	2500–3000	1250	1680–1725
Esters	—	1050–1300 (*two bands*)	1715–1740
Acid chlorides	—	—	1750–1810
Amides ($RCONH_2$)	(N—H 3050–3550)	—	1650–1690

Esters are distinguished from acids by the absence of the O—H band. They are distinguished from ketones by two strong C—O stretching bands in the 1050–1300 cm^{-1} region; the exact position of these bands, too, depends on the ester's structure.

Besides the carbonyl band, amides ($RCONH_2$) show absorption due to N—H stretching in the 3050–3550 cm^{-1} region (the number of bands and their location depending on the degree of hydrogen bonding), and absorption due to N—H bending in the 1600–1640 cm^{-1} region.

NMR As we can see in Table 16.4 (p. 585), the protons in the alkyl portion of an ester ($RCOOCH_2R'$) absorb farther downfield than the protons in the acyl portion (RCH_2COOR').

Absorption by the —CO—NH protons of an amide appears in the range δ 5–8, typically as a broad, low hump.

CMR The carbonyl carbon in these functional derivatives absorbs in the range δ 150–180, roughly the same region as for carboxylic acid.

PROBLEMS

1. Draw structures and give names of:

(a) nine isomeric esters of formula $C_5H_{10}O_2$
(b) six isomeric esters of formula $C_8H_8O_2$
(c) three isomeric methyl esters of formula $C_7H_{12}O_4$

2. Write balanced equations, naming all organic products, for the reaction (if any) of *n*-butyryl chloride with:

(a) H_2O
(b) isopropyl alcohol
(c) *p*-nitrophenol
(d) ammonia
(e) toluene, $AlCl_3$
(f) nitrobenzene, $AlCl_3$
(g) $NaHCO_3$(aq)
(h) alcoholic $AgNO_3$
(i) CH_3NH_2
(j) $(CH_3)_2NH$
(k) $(CH_3)_3N$
(l) $C_6H_5NH_2$
(m) $(C_6H_5)_2CuLi$
(n) C_6H_5MgBr

(Check your answers to (i) through (l) in Sec. 27.7.)

3. Answer Problem 2, parts (a) through (l), for acetic anhydride.

4. Write equations to show the reaction (if any) of succinic anhydride with:

(a) hot aqueous NaOH
(b) aqueous ammonia
(c) aqueous ammonia, then cold dilute HCl
(d) aqueous ammonia, then strong heat
(e) benzyl alcohol
(f) toluene, $AlCl_3$, heat

5. Write balanced equations, naming all organic products, for the reaction (if any) of phenylacetamide with: (a) hot HCl(aq), (b) hot NaOH(aq).

6. Answer Problem 5 for phenylacetonitrile.

7. Write balanced equations, naming all organic products, for the reaction (if any) of methyl *n*-butyrate with:

(a) hot H_2SO_4(aq)
(b) hot KOH(aq)
(c) isopropyl alcohol + H_2SO_4
(d) benzyl alcohol + $C_6H_5CH_2ONa$
(e) ammonia
(f) phenylmagnesium bromide
(g) isobutylmagnesium bromide
(h) $LiAlH_4$, then acid

8. Outline the synthesis of each of the following labeled compounds, using $H_2{}^{18}O$ as the source of ^{18}O.

(a) $C_6H_5-\overset{\overset{O}{\|}}{C}-{}^{18}OCH_3$ (b) $C_6H_5-\overset{\overset{{}^{18}O}{\|}}{C}-OCH_3$ (c) $C_6H_5-\overset{\overset{{}^{18}O}{\|}}{C}-{}^{18}OCH_3$

Predict the products obtained from each upon alkaline hydrolysis in ordinary H_2O.

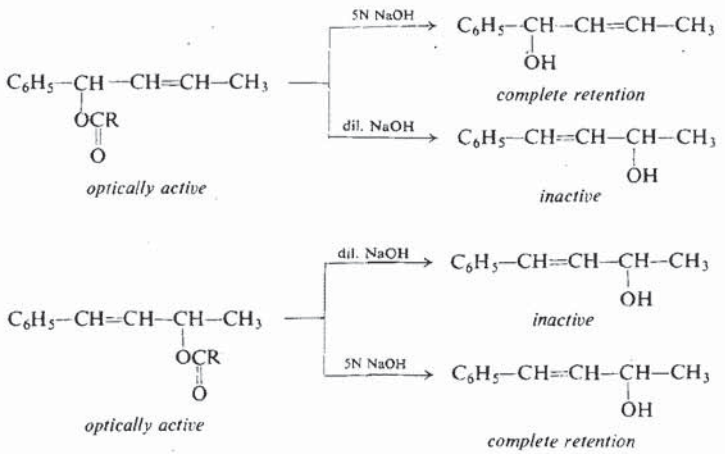
9. Outline the synthesis of each of the following labeled compounds, using $^{14}CO_2$ or $^{14}CH_3OH$ and $H_2{}^{18}O$ as the source of the "tagged" atoms.

(a) $CH_3CH_2{}^{14}COCH_3$
(b) $CH_3CH_2CO{}^{14}CH_3$
(c) $CH_3{}^{14}CH_2COCH_3$
(d) $^{14}CH_3CH_2COCH_3$
(e) $C_6H_5{}^{14}CH_2CH_3$
(f) $C_6H_5CH_2{}^{14}CH_3$
(g) $CH_3CH_2C{}^{18}OCH_3$

10. Predict the product of the reaction of γ-butyrolactone with (a) ammonia, (b) $LiAlH_4$, (c) $C_2H_5OH + H_2SO_4$.

11. When *sec*-butyl alcohol of rotation $+13.8°$ was treated with tosyl chloride, and the resulting tosylate was allowed to react with sodium benzoate, there was obtained *sec*-butyl benzoate. Alkaline hydrolysis of this ester gave *sec*-butyl alcohol of rotation $-13.4°$. In which step must inversion have taken place? How do you account for this?

12. Account for the following observations.



13. An unknown compound is believed to be one of the following, all of which boil within a few degrees of each other. Describe how you would go about finding out which of the possibilities the unknown actually is. Where possible use simple chemical tests; where necessary use more elaborate chemical methods like quantitative hydrogenation, cleavage, neutralization equivalent, saponification equivalent, etc. Make use of any needed tables of physical constants.

benzyl acetate	isopropyl benzoate	methyl *o*-toluate	methyl *p*-toluate
ethyl benzoate	methyl phenylacetate	methyl *m*-toluate	

14. Describe simple chemical tests that would serve to distinguish between:

(a) propionic acid and methyl acetate
(b) *n*-butyryl chloride and *n*-butyl chloride
(c) *p*-nitrobenzamide and ethyl *p*-nitrobenzoate
(d) glyceryl tristearate and glyceryl trioleate
(e) benzonitrile and nitrobenzene
(f) acetic anhydride and *n*-butyl alcohol
(g) glyceryl monopalmitate and glyceryl tripalmitate
(h) ammonium benzoate and benzamide
(i) *p*-bromobenzoic acid and benzoyl bromide

Tell exactly what you would *do* and *see*.

15. Tell how you would separate by chemical means the following mixtures, recovering each component in reasonably pure form: (a) benzoic acid and ethyl benzoate; (b) *n*-valeronitrile and *n*-valeric acid; (c) ammonium benzoate and benzamide. Tell exactly what you would *do* and *see*.

16. Carboxyl groups are often masked by reaction with dihydropyran (Sec. 19.9), which yields esters that are stable toward base but easily hydrolyzed by dilute aqueous acids. Account in detail both for the formation of these esters and for their ease of hydrolysis.

Dihydropyran (DHP) — Tetrahydropyranyl ester (RCOOTHP)

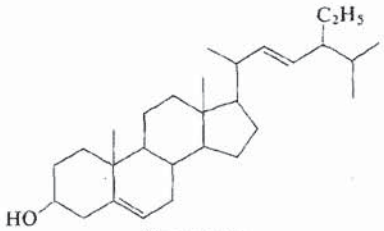
17. Treatment of 2,4-pentanedione with KCN and acetic acid, followed by hydrolysis, gives two products, A and B. Both A and B are dicarboxylic acids of formula $C_7H_{12}O_6$. A melts at 98 °C. When heated, B gives first a lactonic acid ($C_7H_{10}O_5$, m.p. 90 °C) and finally a dilactone ($C_7H_8O_4$, m.p. 105 °C). (a) What structure must B have that permits ready formation of both a monolactone and a dilactone? (b) What is the structure of A? (*Hint*: Use models.)

18. For many years esters have sometimes been synthesized by the reaction of sodium carboxylates with alkyl halides, but the method has not been a particularly good one. Recently, however, a simple modification in the experimental procedure has been found to increase yields dramatically. Can you suggest what this change is likely to have been?

19. Give the structures (including configurations where pertinent) of components C through O.

(a) urea (H_2NCONH_2) + hot dilute NaOH $\longrightarrow$ C + NH_3
(b) phosgene ($COCl_2$) + 1 mol C_2H_5OH, then + NH_3 $\longrightarrow$ D ($C_3H_7O_2N$)
(c) bromobenzene + Mg, ether $\longrightarrow$ E (C_6H_5MgBr)
E + ethylene oxide, followed by H^+ $\longrightarrow$ F ($C_8H_{10}O$)
F + PBr_3 $\longrightarrow$ G (C_8H_9Br)
G + NaCN $\longrightarrow$ H (C_9H_9N)
H + H_2SO_4, H_2O, heat $\longrightarrow$ I ($C_9H_{10}O_2$)
I + $SOCl_2$ $\longrightarrow$ J (C_9H_9OCl)
J + anhydrous HF $\longrightarrow$ K (C_9H_8O)
K + H_2, catalyst $\longrightarrow$ L ($C_9H_{10}O$)
L + H_2SO_4, warm $\longrightarrow$ M (C_9H_8)
(d) *trans*-2-methylcyclohexanol + acetyl chloride $\longrightarrow$ N
N + NaOH(aq) + heat $\longrightarrow$ O + sodium acetate

20. *Progesterone* is a hormone, secreted by the corpus luteum, that is involved in the control of pregnancy. Its structure was established, in part, by the following synthesis from the steroid *stigmasterol*, obtained from soybean oil.



Stigmasterol

stigmasterol ($C_{29}H_{48}O$) + $(CH_3CO)_2O$ $\longrightarrow$ P ($C_{31}H_{50}O_2$)
P + Br_2 $\longrightarrow$ Q ($C_{31}H_{50}O_2Br_2$)
Q + O_3, then Ag_2O $\longrightarrow$ R ($C_{24}H_{36}O_4Br_2$)
R + Zn/CH_3COOH $\longrightarrow$ S ($C_{24}H_{36}O_4$)
S + C_2H_5OH, H^+ $\longrightarrow$ T ($C_{26}H_{40}O_4$)
T + C_6H_5MgBr, then H_2O $\longrightarrow$ U ($C_{35}H_{46}O_3$)
U + acid, warm $\longrightarrow$ V ($C_{36}H_{44}O_2$)
V + Br_2; then CrO_3, H^+ $\longrightarrow$ W ($C_{23}H_{34}O_3Br_2$)
W + Zn/CH_3COOH $\longrightarrow$ X ($C_{23}H_{34}O_3$)
X + H_2O, H^+, heat $\longrightarrow$ Y ($C_{21}H_{32}O_2$), *pregnenolone*
Y + Br_2; then CrO_3, H^+ $\longrightarrow$ Z ($C_{21}H_{30}O_2Br_2$)
Z + Zn/CH_3COOH $\longrightarrow$ *progesterone* ($C_{21}H_{30}O_2$)

(a) Give structures for progesterone and the intermediates P–Z.
(b) Progesterone shows strong absorption in the near ultraviolet: λ_{max} 240 nm, ϵ_{max} 17 600. On this basis, what is the structure for progesterone?

21. On the basis of the following evidence assign structures to: (a) compounds AA to DD, isomers of formula $C_3H_8O_2$; (b) compounds EE to MM, isomers of formula $C_3H_6O_2$. (*Note*: α-Hydroxy ketones, —CHOH—CO—, give positive tests with Tollens' reagent and with Fehling's and Benedict's solutions (p. 1286), but negative Schiff's tests.)

	$NaHCO_3$	*Acetic anhydride*	*Tollens'*	*Schiff's*	HIO_4
(a) AA	–	$C_7H_{12}O_4$	–	–	–
BB	–	$C_7H_{12}O_4$	–	–	+
CC	–	$C_5H_{10}O_3$	–	–	–
DD	–	–	–[1]	–[1]	–
(b) EE	–	$C_5H_8O_3$	+	+	+
FF	–	$C_5H_8O_3$	+	–	+
GG	–	$C_5H_8O_3$	+	+	–
HH	CO_2	–	–	–	–
II	–[2]	–	+	–	–
JJ	–	–	–	–	–
KK	–	$C_7H_{10}O_4$	–	–	+
LL	–	–	–[1]	–[1]	–[1]
MM	–	$C_5H_8O_3$	–	–	–[1]

[1] After treatment with dilute acid, solution gives positive test.
[2] After treatment with NaOH, solution gives positive iodoform test.

22. 2,5-Dimethyl-1,1-cyclopentanedicarboxylic acid can be prepared as a mixture of two optically inactive substances of different physical properties, NN and OO. When each is heated and the reaction mixture worked up by fractional crystallization, NN yields a single product, PP, of formula $C_8H_{14}O_2$, and OO yields two products, QQ and RR, both of formula $C_8H_{14}O_2$.

(a) Give stereochemical formulas for NN, OO, PP, QQ, and RR. (b) Describe another method by which you could assign configurations to NN and OO.

23. (a) (−)-*Erythrose*, $C_4H_8O_4$, gives tests with Tollens' reagent and Benedict's solution (p. 1286), and is oxidized by bromine water to an optically active acid, $C_4H_8O_5$. Treatment with acetic anhydride yields $C_{10}H_{14}O_7$. Erythrose consumes three moles of HIO_4 and yields three moles of formic acid and one mole of formaldehyde. Oxidation of erythrose by nitric acid yields an *optically inactive* compound of formula $C_4H_6O_6$.

(−)-*Threose*, an isomer of erythrose, shows similar chemical behavior except that nitric acid oxidation yields an *optically active* compound of formula $C_4H_6O_6$.

On the basis of this evidence what structure or structures are possible for (−)-erythrose? For (−)-threose?

(b) When *R*-glyceraldehyde, $CH_2OHCHOHCHO$, is treated with cyanide and the resulting product is hydrolyzed, two monocarboxylic acids are formed (see Problem 11, p. 790). These acids are identical with the acids obtained by oxidation with bromine water of (−)-threose and (−)-erythrose.

Assign a single structure to (−)-erythrose and to (−)-threose.

24. At room temperature, *N*,*N*-dimethylacetamide gives three sharp singlets of equal area in the proton NMR spectrum. As the temperature is raised, two of the peaks (but not the third) broaden and finally, at 110 °C, form one sharp singlet. (a) How do you account for this? What does it indicate about the structure of the amide? (b) What would you expect to see in the CMR spectrum of this compound at room temperature? At 110 °C?

25. Which (if any) of the following compounds could give rise to each of the infrared spectra shown in Fig. 24.3 (p. 896)?

ethyl acetate
ethyl acrylate (CH_2=$CHCOOC_2H_5$)
isobutyric acid
methacrylic acid [CH_2=$C(CH_3)COOH$]
methacrylamide [CH_2=$C(CH_3)CONH_2$]
phenylacetamide

26. Give a structure or structures consistent with each of the proton NMR spectra shown in Fig. 24.4 (p. 897).

27. Give a structure or structures consistent with the proton NMR spectrum shown in Fig. 24.5, p. 898.

28. Give a structure or structures consistent with each of the CMR spectra shown in Fig. 24.6, p. 898.

29. Give a structure or structures consistent with each of the CMR spectra shown in Fig. 24.7, p. 899.

30. Give the structure of compounds SS, TT, and UU on the basis of their infrared spectra (Fig. 24.8, p. 900) and their proton NMR spectra (Fig. 24.9, p. 901).

31. Give the structure of compound VV on the basis of its infrared, CMR, and proton NMR spectra shown in Fig. 24.10, p. 902.

32. Give a structure or structures consistent with each of the NMR spectra shown in Fig. 24.11, p. 903.

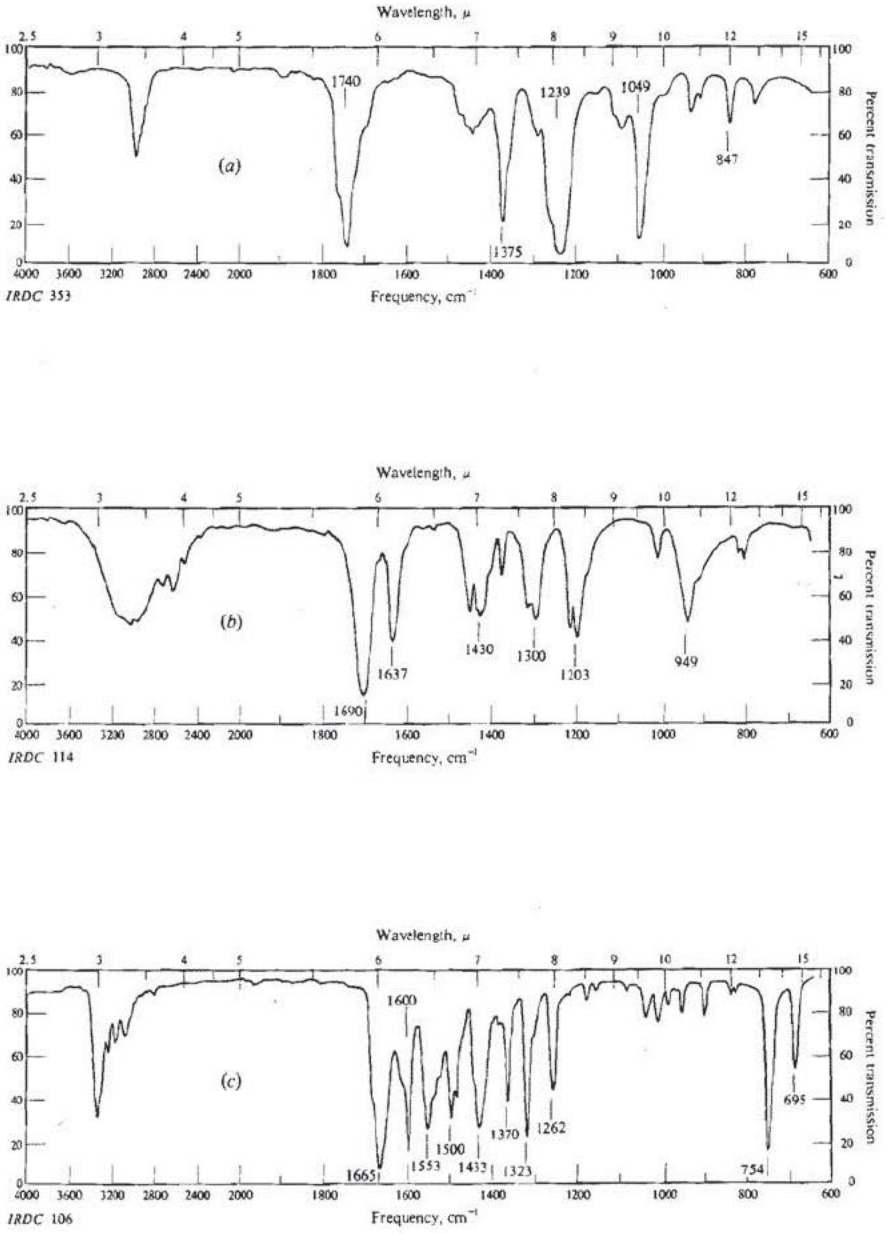


Figure 24.3 Infrared spectra for Problem 25, p. 894.

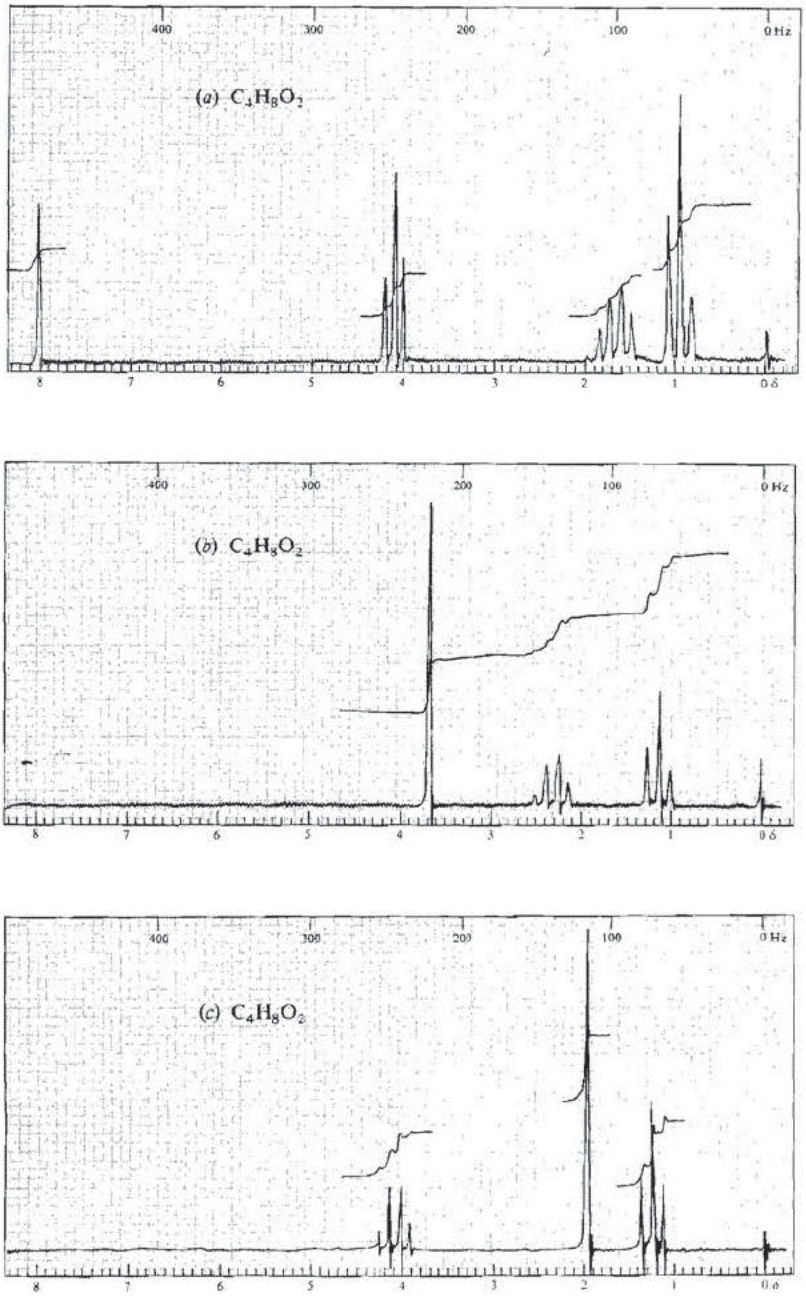


Figure 24.4 Proton NMR spectra for Problem 26, p. 895.

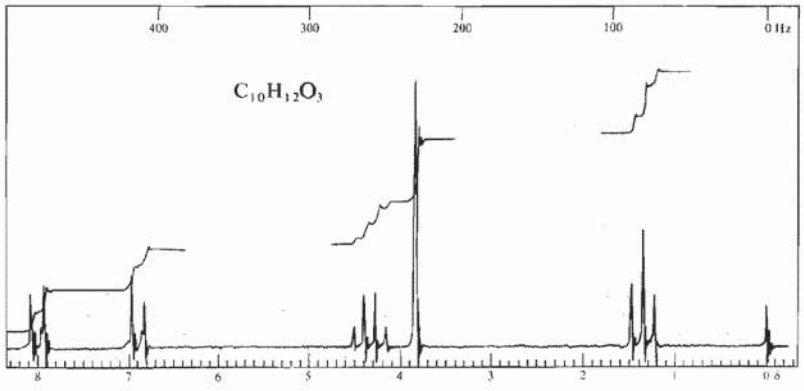
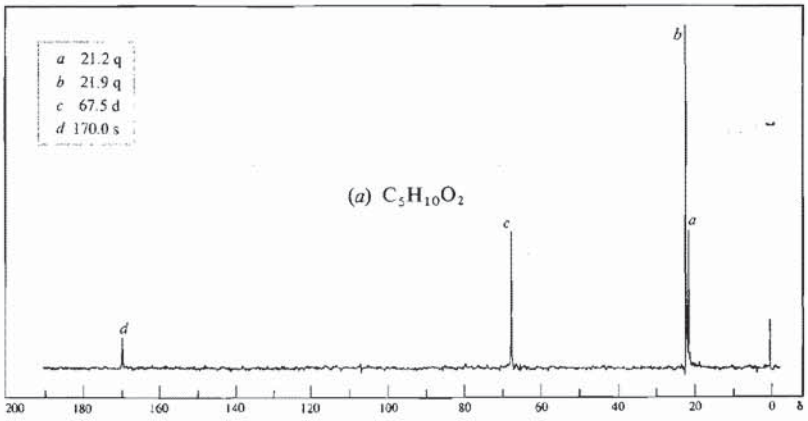


Figure 24.5 Proton NMR spectrum for Problem 27, p. 895.



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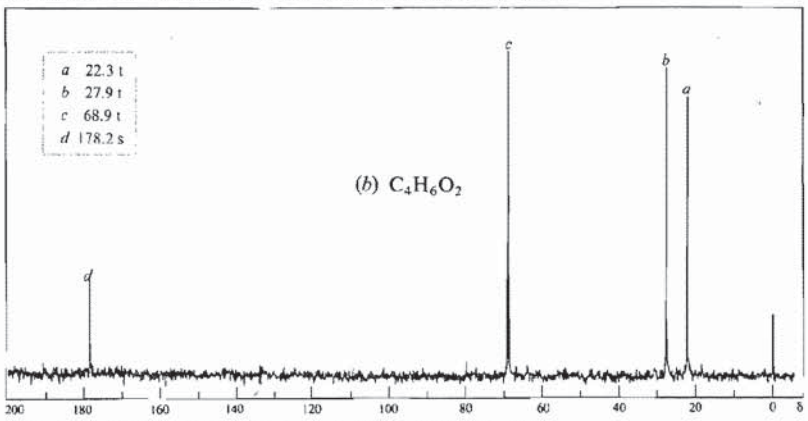

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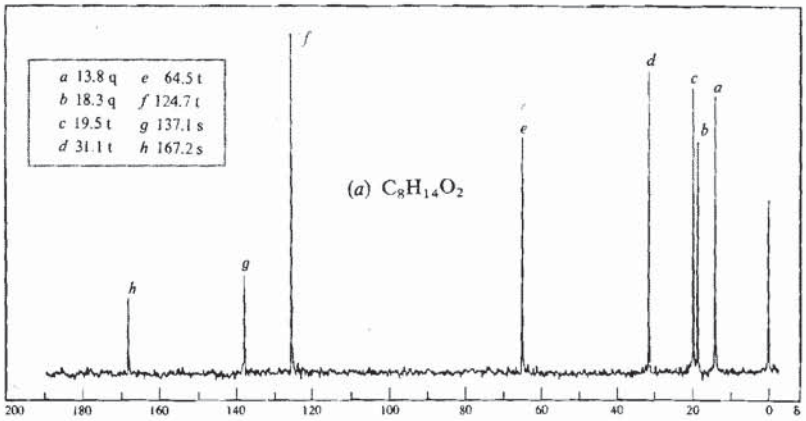
Figure 24.6 CMR spectra for Problem 28, p. 895.



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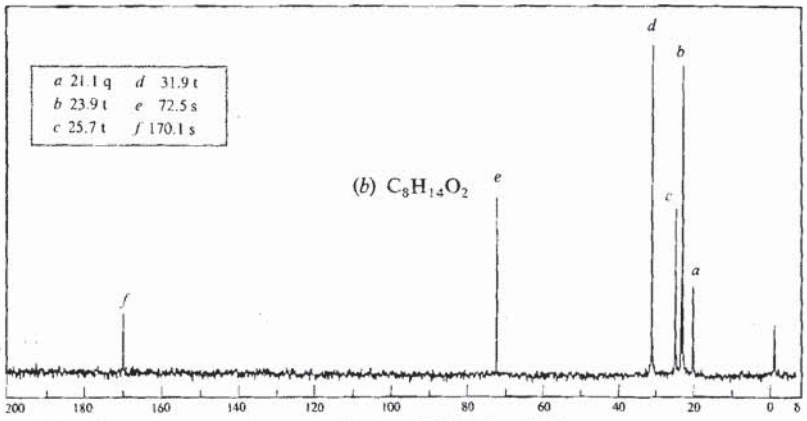

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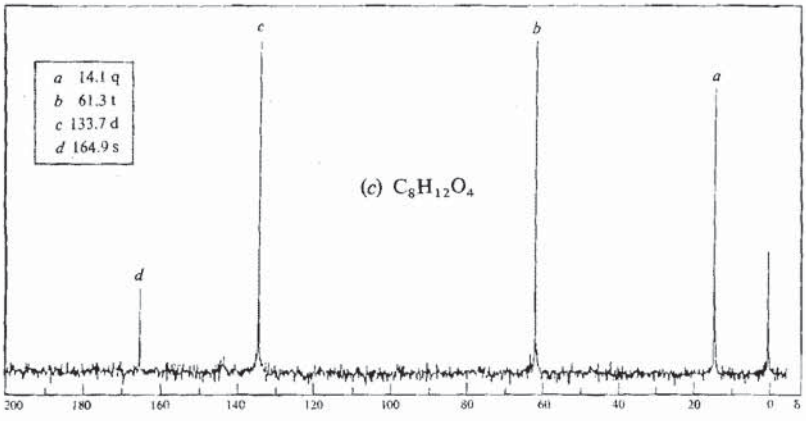

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Figure 24.7 CMR spectra for Problem 29, p. 895.

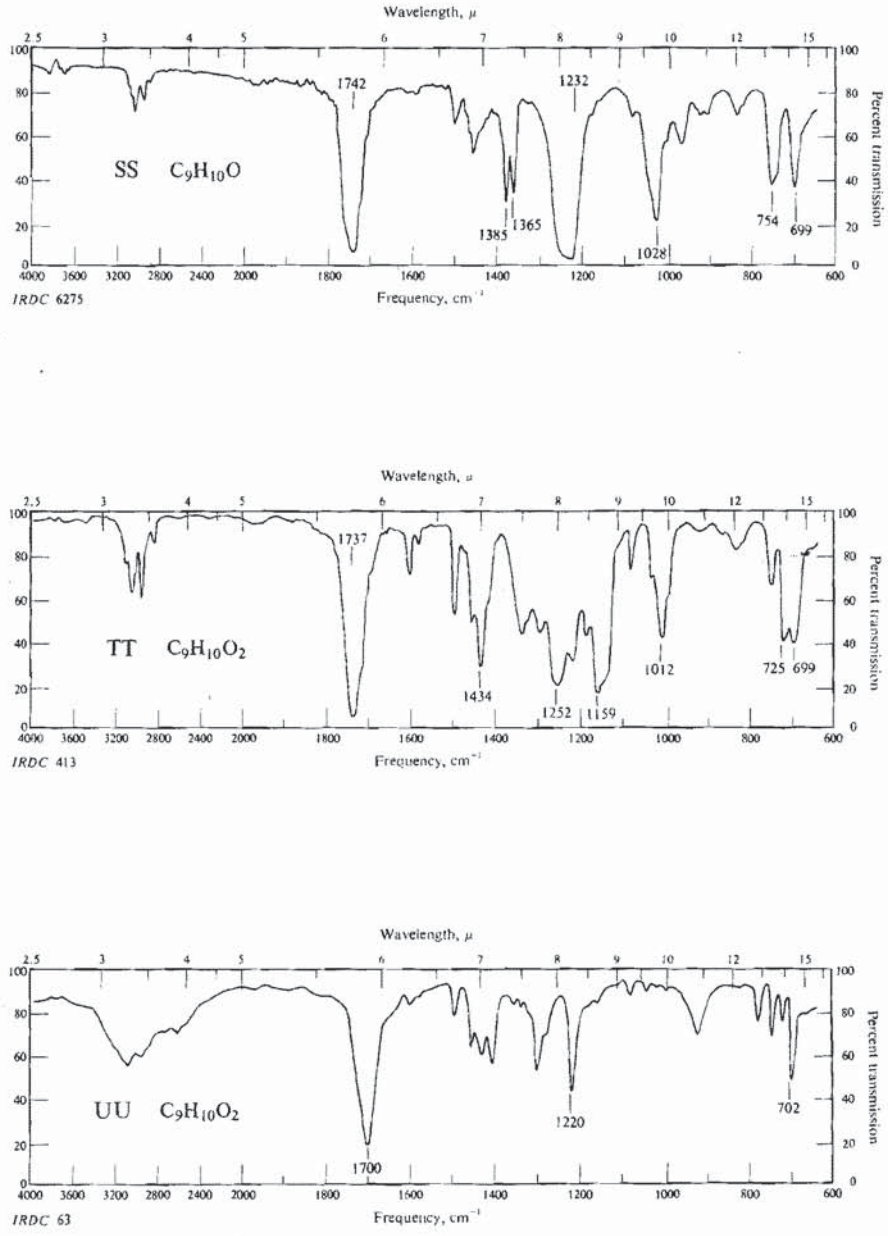


Figure 24.8 Infrared spectra for Problem 30, p. 895.

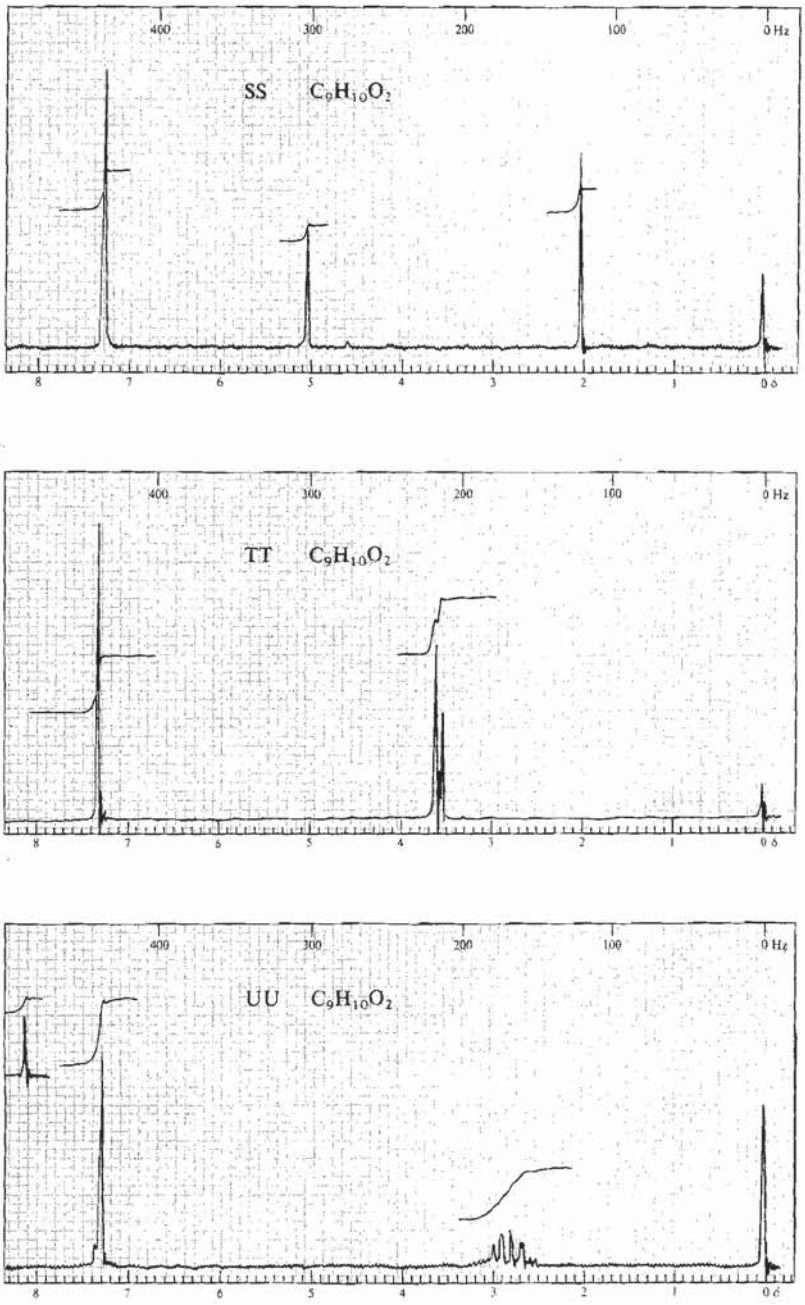
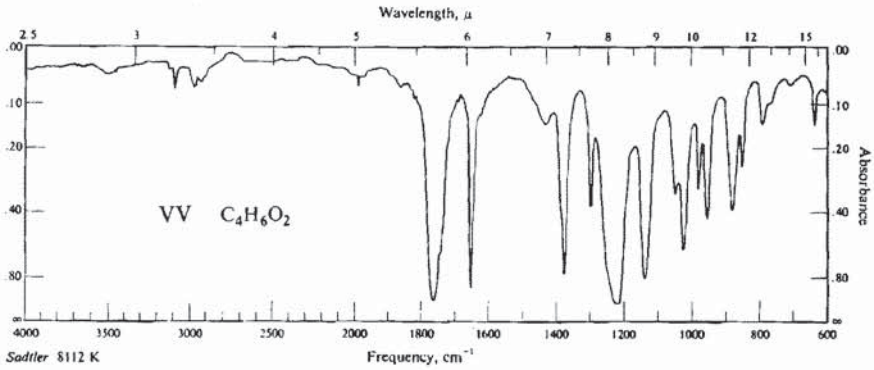
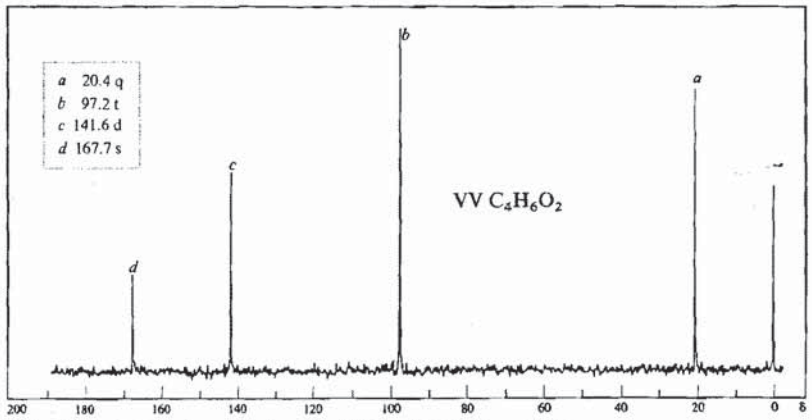


Figure 24.9 Proton NMR spectra for Problem 30, p. 895.





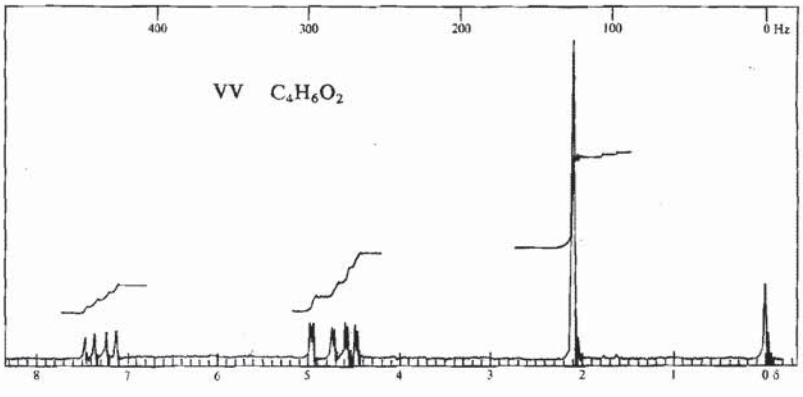
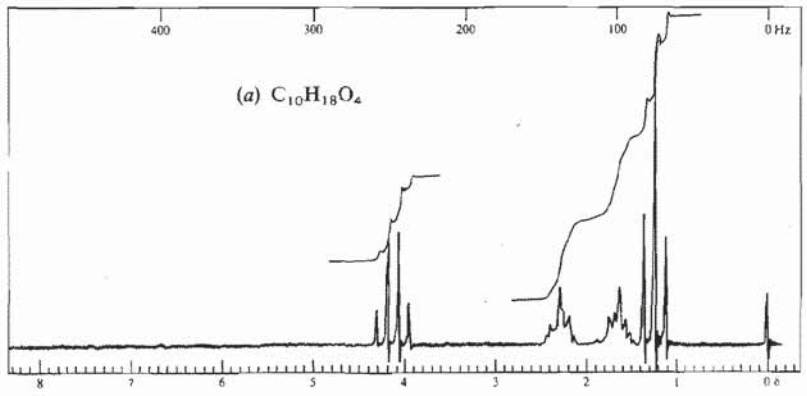
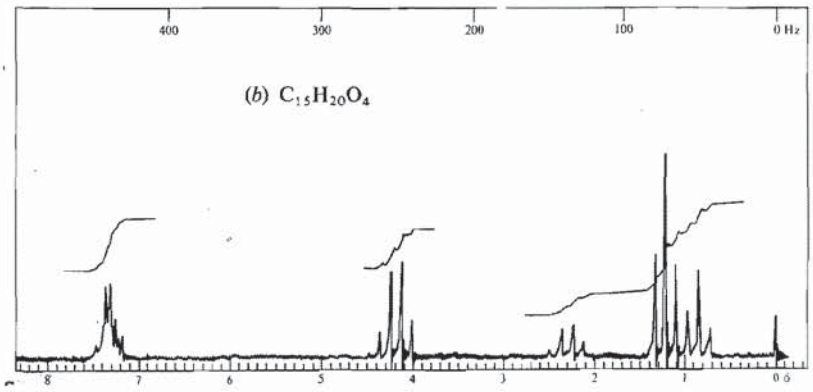


Figure 24.10 Infrared, CMR, and proton NMR spectra for Problem 31, p. 895.





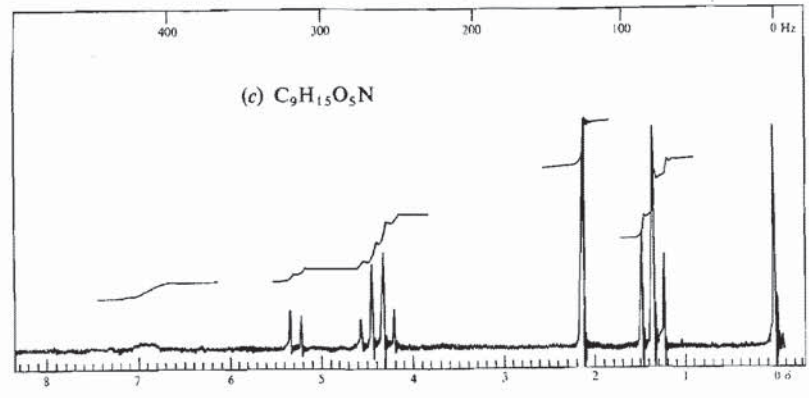


Figure 24.11 Proton NMR spectra for Problem 32, p. 895.