Chapter 16

Carboxylic Acids
The functional group of a carboxylic acid is a carboxyl group

The general formula of an aliphatic carboxylic acid is $RCO_2H$; that of an aromatic carboxylic acid is $ArCO_2H$
Nomenclature - IUPAC

- IUPAC names: drop the -e from the parent alkane and add the suffix -oic acid
- If the compound contains a carbon-carbon double bond, change the infix -an- to -en-

\[
\text{Propenoic acid (Acrylic acid)}
\]

\[
\text{trans-3-Phenylpropenoic acid (Cinnamic acid)}
\]

\[
\text{trans-2-Butenoic acid (Crotonic acid)}
\]
The carboxyl group takes precedence over most other functional groups.

\[
\begin{align*}
\text{OH} & \\
\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} & \\
& \text{5-Hydroxyhexanoic acid}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} & \\
\text{CH}_3\text{CCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H} & \\
& \text{4-Aminobutanoic acid} & \text{5-Oxohexanoic acid}
\end{align*}
\]
Dicarboxylic acids: add the suffix -dioic acid to the name of the parent alkane containing both carboxyl groups.

- Ethanedioic acid (Oxalic acid)
- Propanedioic acid (Malonic acid)
- Butanedioic acid (Succinic acid)
If the carboxyl group is attached to a ring, name the ring compound and add the suffix -carboxylic acid.

- 2-Cyclohexene-carboxylic acid
- trans-1,3-Cyclopentane-dicarboxylic acid
The simplest aromatic carboxylic acid is benzoic acid. Derivatives are named using numbers to show the location of substituents relative to the carboxyl group.

- Benzoic acid
- 2-Hydroxybenzoic acid (Salicylic acid)
- 4-Aminobenzoic acid
Aromatic dicarboxylic acids are named by adding the words “dicarboxylic acid” to “benzene”

1,2-Benzenedicarboxylic acid (Phthalic acid)

1,4-Benzenedicarboxylic acid (Terephthalic acid)
When common names are used, the letters $\alpha$, $\beta$, $\gamma$, $\delta$, etc. are often used to locate substituents.

\[
\begin{array}{cccc}
\delta & \gamma & \beta & \alpha \\
\text{C-C-C-C-C-OH} & & & \\
5 & 4 & 3 & 2 & 1
\end{array}
\]

- 4-Hydroxybutanoic acid
  (\(\gamma\)-Hydroxybutyric acid)

- 2-Aminopropanoic acid
  (\(\alpha\)-Aminopropionic acid; Alanine)
In the liquid and solid states, carboxylic acids are associated by hydrogen bonding into dimeric structures.
Physical Properties

Carboxylic acids have significantly higher boiling points than other types of organic compounds of comparable molecular weight

- they are polar compounds and form very strong intermolecular hydrogen bonds

Carboxylic acids are more soluble in water than alcohols, ethers, aldehydes, and ketones of comparable molecular weight

- they form hydrogen bonds with water molecules through both the C=O and OH groups
Water solubility decreases as the relative size of the hydrophobic portion of the molecule increases.
Carboxylic acids are weak acids

- values of $pK_a$ for most aliphatic and aromatic carboxylic acids fall within the range 4 to 5

Two factors account for the greater acidity of carboxylic acids relative to alcohols, both compounds containing an -OH group

- the electron-withdrawing inductive effect of the adjacent carbonyl group weakens the O-H bond
- the carboxylate anion is stabilized by resonance
Electron-withdrawing substituents near the carboxyl group increase acidity through their inductive effect:

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Acid Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>4.76</td>
</tr>
<tr>
<td>CH$_2$CO$_2$H</td>
<td>3.18</td>
</tr>
<tr>
<td>CH$_2$CO$_2$H</td>
<td>2.90</td>
</tr>
<tr>
<td>CH$_2$CO$_2$H</td>
<td>2.86</td>
</tr>
<tr>
<td>CH$_2$CO$_2$H</td>
<td>2.59</td>
</tr>
</tbody>
</table>

Increasing acid strength
Multiple substitution of electron-withdrawing groups further increases acidity

<table>
<thead>
<tr>
<th></th>
<th>Acetic acid</th>
<th>Chloroacetic acid</th>
<th>Dichloroacetic acid</th>
<th>Trichloroacetic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ</td>
<td>4.76</td>
<td>2.86</td>
<td>1.48</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Increasing acid strength
Acidity

The inductive effect of an electron-withdrawing substituent falls off rapidly with its distance from the carboxyl group.

<table>
<thead>
<tr>
<th>Substituted Butanoic Acid</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Chlorobutanoic acid</td>
<td>4.52</td>
</tr>
<tr>
<td>3-Chlorobutanoic acid</td>
<td>3.98</td>
</tr>
<tr>
<td>2-Chlorobutanoic acid</td>
<td>2.83</td>
</tr>
</tbody>
</table>

Increasing acid strength
Carboxylic acids, whether soluble or insoluble in water, react with NaOH, KOH, and other strong bases to give water-soluble salts.

\[
\text{Benzoic acid (slightly soluble in water)} + \text{NaOH} \rightarrow \text{Sodium benzoate (60 g/100 mL water)}
\]
They also form water-soluble salts with ammonia and amines

\[
\text{Benzoic acid (slightly soluble in water)} + \text{NH}_3 \xrightarrow{\text{H}_2\text{O}} \text{Ammonium benzoate (20 g/100 mL water)}
\]
Carboxylic acids react with sodium bicarbonate and sodium carbonate to form water-soluble salts and carbonic acid.

\[ \text{CH}_3\text{CO}_2\text{H} + \text{NaHCO}_3 \xrightarrow{\text{H}_2\text{O}} \]

\[ \text{CH}_3\text{CO}_2^- \text{Na}^+ + \text{CO}_2 + \text{H}_2\text{O} \]
The most common fragmentation patterns are:

- **α-cleavage** of the carboxyl group to give the ion \([\text{CO}_2\text{H}]^+\) of m/z 45

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{-C-OH} & \xrightarrow{\alpha\text{-cleavage}} \text{CH}_3\text{CH}_2\text{CH}_2\cdot + \cdot:O=\text{C}=\text{O}^+\cdot\cdot\text{H} \\
& \text{m/z 45}
\end{align*}
\]
Mass Spectrometry

- and McLafferty rearrangement

\[
\begin{align*}
\text{H}_2\text{C} & \text{H} \quad \text{O} \\
\text{H}_2\text{C} & \quad \text{C} \quad \text{CH}_2 \quad \text{O} \\
\text{H}_2\text{C} & \quad \text{C} \quad \text{OH}
\end{align*}
\]

\[+\]

McLafferty rearrangement

\[
\begin{align*}
\text{H}_2\text{C} & + \\
\text{H}_2\text{C} & \text{CH}_2 \quad \text{OH}
\end{align*}
\]

m/z 60
$^{1}$H-NMR

- hydrogens on the $\alpha$-carbon to a carboxyl group appear in the range $\delta$ 2.0-2.5
- the hydrogen of the carboxyl group appears in the range $\delta$ 10-13

$^{13}$C-NMR

- the carboxyl carbon appears in the range $\delta$ 160-180, and is similar to that of carboxyl derivatives (esters, amides, and anhydrides) described in Section 17.3B
The carboxyl group gives two characteristic absorptions

- 1700 - 1725 cm\(^{-1}\) associated with the stretching vibration of the C=O group
- 2400 - 3400 cm\(^{-1}\) associated with the stretching vibration of the O-H group
The carboxyl groups is one of the organic functional groups most resistant to reduction

- it is not affected by catalytic hydrogenation under conditions that easily reduce aldehydes and ketones to alcohols, and reduce alkenes and alkynes to alkanes
- it is not reduced by NaBH₄
Lithium aluminum hydride reduces a carboxyl group to a 1° alcohol

- reduction is carried out in diethyl ether, THF, or other nonreactive, aprotic solvent

\[
\text{LiAlH}_4, \text{ether} \\
\text{2. } \text{H}_2\text{O}
\]

3-Cyclopentene-carboxylic acid

\[
\text{CH}_2\text{OH} + \text{LiOH} + \text{Al(OH)}_3
\]

4-Hydroxymethyl-cyclopentene
Using the less reactive NaBH$_4$, it is possible to reduce the carbonyl group of an aldehyde or ketone without affecting a carboxyl group.

5-Oxo-5-phenyl-pentanoic acid

\[
\text{O} \quad \text{CCH}_2\text{CH}_2\text{CH}_2\text{COH} \quad 1. \text{NaBH}_4 \quad 2. \text{H}_2\text{O}
\]

5-Hydroxy-5-phenyl-pentanoic acid
Esters can be prepared by treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst, commonly $\text{H}_2\text{SO}_4$ or gaseous $\text{HCl}$.

$$\text{CH}_3\text{COH} + \text{CH}_3\text{CH}_2\text{OH} \overset{\text{H}_2\text{SO}_4}{\rightleftharpoons} \text{CH}_3\text{COCH}_2\text{CH}_3 + \text{H}_2\text{O}$$

Ethanoic acid (Acetic acid) + Ethanol (Ethyl alcohol) $\rightleftharpoons$ Ethyl ethanoate (Ethyl acetate)
Fischer esterification is an equilibrium reaction, and by careful control of experimental conditions, it is possible to prepare esters in high yield.

- if the alcohol is inexpensive relative to the carboxylic acid, it can be used in excess to drive the equilibrium to the right.
- alternatively, water can be removed by azeotropic distillation and a Dean-Stark trap.
A key intermediate in Fischer esterification is the tetrahedral carbonyl addition intermediate formed by addition of ROH to the C=O group.

\[
\begin{align*}
\text{R} - \text{C} - \text{OH} & \quad + \quad \text{HOCH}_3 \quad \text{H}^+ \\
\text{R} - \text{C} - \text{OCH}_3 & \quad + \quad \text{HOH} \quad \text{H}^+
\end{align*}
\]

tetrahedral carbonyl addition intermediate
Diazomethane, \( \text{CH}_2\text{N}_2 \), a potentially explosive, toxic yellow gas, is best drawn as a hybrid of two contributing structures:

\[
\begin{array}{c}
\text{H} & \overset{\text{C}}{\text{-N}} & \overset{\text{+}}{\text{N}} & \overset{\text{-}}{\text{:}} \\
\text{H} & \overset{\text{C}}{\text{=N}} & \overset{\text{+}}{\text{N=N}} & \overset{\text{-}}{\text{:}} \\
\end{array}
\]

Treatment of a carboxylic acid with diazomethane gives a methyl ester:

\[
\text{RCOH} + \text{CH}_2\text{N}_2 \xrightarrow{\text{ether}} \text{RCOCH}_3 + \text{N}_2
\]

Diazomethane

A methyl ester
Esterification occurs in two steps

Step 1: proton transfer from the carboxyl group to diazomethane

\[
\text{R-C(OH)} + \cdot\text{CH}_2\text{N}^+\equiv\text{N}^- \rightarrow \text{R-C(O)}^- + \text{CH}_3\text{N}^+\equiv\text{N}^-
\]

A carboxylate anion
Step 2: nucleophilic displacement ($S_N^2$) of $N_2$, an extraordinarily good leaving group, by the carboxylate anion.

\[
\begin{align*}
\text{O} & \quad - \quad \text{R--C--O}^{-} \quad \text{+} \quad \text{CH}_3\text{C}^{+}\text{N} \equiv \text{N}^{-} \quad \xrightarrow{S_N^2} \quad \text{O} \\
& \quad \quad \quad \quad \quad \quad \text{R--C--O}^{-} \quad \text{CH}_3 \quad + \quad \cdot \text{N} \equiv \text{N}^{-}
\end{align*}
\]
The functional group of an acid halide is a carbonyl group bonded to a halogen atom.

Among the acid halides, acid chlorides are by far the most common and the most widely used.

Functional group of an acid halide

Acetyl chloride

Benzoyl chloride
Acid chlorides are most often prepared by treatment of a carboxylic acid with thionyl chloride:

\[
\text{Butanoic acid} + \text{Thionyl chloride} \rightarrow \text{Butanoyl chloride}
\]

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{COH} & + \text{SOCl}_2 \\
\text{Butanoic acid} & \quad \text{Thionyl chloride} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CCl} & + \text{SO}_2 + \text{HCl} \\
\text{Butanoyl chloride} & 
\end{align*}
\]
The mechanism for this reaction is divided into two steps.

Step 1: -OH, a poor leaving group, is transformed into a chlorosulfite group, a good leaving group.

\[
\text{R-C-OH} + \text{Cl-S-Cl} \rightarrow \text{R-C-O} - \overset{\text{S}}{\text{Cl}} + \text{HCl}
\]

A chlorosulfite group
Step 2: attack of chloride ion gives a tetrahedral carbonyl addition intermediate, which collapses to give the acid chloride

\[
\begin{align*}
\text{R-} & \text{C-Cl} + \text{Cl}^- \\
\xrightarrow{O} & \\
\xrightarrow{O} & \\
\text{R-C-O-S-Cl} + \text{Cl}^- & \rightarrow \text{R-C-Cl} + \text{SO}_2 + \text{Cl}^-
\end{align*}
\]

A tetrahedral carbonyl addition intermediate
Decarboxylation: loss of $\text{CO}_2$ from a carboxyl group

Most carboxylic acids, if heated to a very high temperature, undergo thermal decarboxylation.

Most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation.
Exceptions are carboxylic acids that have a carbonyl group beta to the carboxyl group.

- this type of carboxylic acid undergoes decarboxylation on mild heating.

$$
\text{CH}_3\beta-C-\text{CH}_2-C-OH \xrightarrow{\text{warm}} \text{CH}_3\alpha-C-\text{CH}_3 + \text{CO}_2
$$

3-Oxobutanoic acid (Acetoacetic acid)

Acetone
Thermal decarboxylation of a β-ketoacid involves rearrangement of six electrons in a cyclic six-membered transition state.

(A cyclic six-membered transition state)
Decarboxylation occurs if there is any carbonyl group beta to the carboxyl.

Malonic acid and substituted malonic acids, for example, also undergo thermal decarboxylation.

\[
\begin{align*}
\text{Propanedioic acid} & \quad \text{(Malonic acid)} \\
\text{HOCCH}_2\text{COH} & \quad 140-150^\circ\text{C} \\
\text{CH}_3\text{COH} & + \quad \text{CO}_2
\end{align*}
\]
Thermal decarboxylation of malonic acids also involves rearrangement of six electrons in a cyclic six-membered transition state.

A cyclic six-membered transition state

enol of a carboxylic acid

CH$_3$-C-OH $+$ CO$_2$
Carboxylic Acids

End Chapter 16