Chapter 18
Carboxylic Acids and Their Derivatives. Nucleophilic Addition-Elimination at the Acyl Carbon
Introduction

The carboxyl group (-CO₂H) is the parent group of a family of compounds called acyl compounds or carboxylic acid derivatives.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acyl (or acid) chloride</td>
<td></td>
<td>Amide</td>
</tr>
</tbody>
</table>
| R
\(\text{C} = \text{Cl}\) | Acid anhydride | R
\(\text{C} = \text{NH}_2\) |      |
| R
\(\text{C} = \text{O}\) | Ester         | R
\(\text{C} = \text{NHR}'\) |      |
| R
\(\text{C} = \text{O}\) | Nitrile       | R
\(\text{C} = \text{NR}'\text{R''}\) |      |
Nomenclature and Physical Properties

- In IUPAC nomenclature, the name of a carboxylic acid is obtained by changing the -e of the corresponding parent alkane to -oic acid. The carboxyl carbon is assigned position 1 and need not be explicitly numbered.

- The common names for many carboxylic acids remain in use. Methanoic and ethanoic acid are usually referred to as formic and acetic acid.

- Carboxylic acids can form strong hydrogen bonds with each other and with water. Carboxylic acids with up to 4 carbons are miscible with water in all proportions.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Systematic Name</th>
<th>Common Name</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
<th>Water Solubility (g 100 mL(^{-1}) H(_2)O), 25°C</th>
<th>pK(_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCO(_2)H</td>
<td>Methanoic acid</td>
<td>Formic acid</td>
<td>8</td>
<td>100.5</td>
<td>∞</td>
<td>3.75</td>
</tr>
<tr>
<td>CH(_3)CO(_2)H</td>
<td>Ethanoic acid</td>
<td>Acetic acid</td>
<td>16.6</td>
<td>118</td>
<td>∞</td>
<td>4.76</td>
</tr>
<tr>
<td>CH(_3)CH(_2)CO(_2)H</td>
<td>Propanoic acid</td>
<td>Propionic acid</td>
<td>−21</td>
<td>141</td>
<td>∞</td>
<td>4.87</td>
</tr>
<tr>
<td>CH(_2)(CH(_2))(_2)CO(_2)H</td>
<td>Butanoic acid</td>
<td>Butyric acid</td>
<td>−6</td>
<td>164</td>
<td>∞</td>
<td>4.81</td>
</tr>
<tr>
<td>CH(_2)(CH(_2))(_3)CO(_2)H</td>
<td>Pentanoic acid</td>
<td>Valeric acid</td>
<td>−34</td>
<td>187</td>
<td>4.97</td>
<td>4.82</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_4)CO(_2)H</td>
<td>Hexanoic acid</td>
<td>Caproic acid</td>
<td>−3</td>
<td>205</td>
<td>1.08</td>
<td>4.84</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_5)CO(_2)H</td>
<td>Octanoic acid</td>
<td>Caprylic acid</td>
<td>16</td>
<td>239</td>
<td>0.07</td>
<td>4.89</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_6)CO(_2)H</td>
<td>Decanoic acid</td>
<td>Capric acid</td>
<td>31</td>
<td>269</td>
<td>0.015</td>
<td>4.84</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_10)CO(_2)H</td>
<td>Dodecanoic acid</td>
<td>Lauric acid</td>
<td>44</td>
<td>179(^{18})</td>
<td>0.006</td>
<td>5.30</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_12)CO(_2)H</td>
<td>Tetradecanoic acid</td>
<td>Myristic acid</td>
<td>59</td>
<td>200(^{20})</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_14)CO(_2)H</td>
<td>Hexadecanoic acid</td>
<td>Palmitic acid</td>
<td>63</td>
<td>219(^{17})</td>
<td>0.0007</td>
<td>6.46</td>
</tr>
<tr>
<td>CH(_3)(CH(_2))(_16)CO(_2)H</td>
<td>Octadecanoic acid</td>
<td>Stearic acid</td>
<td>70</td>
<td>383</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>CH(_3)CICO(_2)H</td>
<td>Chloroethanoic acid</td>
<td>Chloroacetic acid</td>
<td>63</td>
<td>189</td>
<td>Very soluble</td>
<td>2.86</td>
</tr>
<tr>
<td>CHCl(_2)CO(_2)H</td>
<td>Dichloroethanoic acid</td>
<td>Dichloroacetic acid</td>
<td>10.8</td>
<td>192</td>
<td>Very soluble</td>
<td>1.48</td>
</tr>
<tr>
<td>CCl(_3)CO(_2)H</td>
<td>Trichloroethanoic acid</td>
<td>Trichloroacetic acid</td>
<td>56.3</td>
<td>198</td>
<td>Very soluble</td>
<td>0.70</td>
</tr>
<tr>
<td>CH(_2)CHCICO(_2)H</td>
<td>2-Chloropropanoic acid</td>
<td>α-Chloropropionic acid</td>
<td>56.3</td>
<td>198</td>
<td>Very soluble</td>
<td>2.83</td>
</tr>
<tr>
<td>CH(_2)CICH(_2)CO(_2)H</td>
<td>3-Chloropropanoic acid</td>
<td>β-Chloropropionic acid</td>
<td>61</td>
<td>204</td>
<td>Soluble</td>
<td>3.98</td>
</tr>
<tr>
<td>C(_6)H(_5)CO(_2)H</td>
<td>Benzoic acid</td>
<td>Benzoic acid</td>
<td>122</td>
<td>250</td>
<td>0.34</td>
<td>4.19</td>
</tr>
<tr>
<td>p-C(_6)H(_5)CH(_2)CO(_2)H</td>
<td>4-Methylenbenzoic acid</td>
<td>p-Toluic acid</td>
<td>160</td>
<td>275</td>
<td>0.03</td>
<td>4.36</td>
</tr>
<tr>
<td>p-C(_6)H(_5)CO(_2)H</td>
<td>4-Chlorobenzoic acid</td>
<td>p-Chlorobenzoic acid</td>
<td>242</td>
<td>250</td>
<td>0.009</td>
<td>3.98</td>
</tr>
<tr>
<td>p-NO(_2)C(_6)H(_5)CO(_2)H</td>
<td>4-Nitrobenzoic acid</td>
<td>p-Nitrobenzoic acid</td>
<td>242</td>
<td>250</td>
<td>0.03</td>
<td>3.41</td>
</tr>
<tr>
<td>CO(_2)H</td>
<td>1-Naphthoic acid</td>
<td>α-Naphthoic acid</td>
<td>160</td>
<td>300</td>
<td>Insoluble</td>
<td>3.70</td>
</tr>
<tr>
<td>CO(_2)H</td>
<td>2-Naphthoic acid</td>
<td>β-Naphthoic acid</td>
<td>185</td>
<td>−300</td>
<td>Insoluble</td>
<td>4.17</td>
</tr>
</tbody>
</table>
Acidity of Carboxylic Acids

-The carboxyl proton of most carboxylic acids has a $pK_a = 4 - 5$

Carboxylic acids are readily deprotonated by sodium hydroxide or sodium bicarbonate to form carboxylate salts.

Carboxylate salts are more water soluble than the corresponding carboxylic acid.

Electron-withdrawing groups near the carboxyl group increase the carboxylic acid’s acidity.

They stabilize the carboxylate anion by inductive delocalization of charge.
### Dicarboxylic Acids

Dicarboxylic acids are named as alkanedioic acids in the IUPAC system. Common names are often used for simple dicarboxylic acids.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Common Name</th>
<th>mp (°C)</th>
<th>$pK_a$ (at 25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO$_2$C—CO$_2$H</td>
<td>Oxalic acid</td>
<td>189 dec</td>
<td>1.2</td>
</tr>
<tr>
<td>HO$_2$CCH$_2$CO$_2$H</td>
<td>Malonic acid</td>
<td>136</td>
<td>2.9</td>
</tr>
<tr>
<td>HO$_2$C(CH$_2$)$_2$CO$_2$H</td>
<td>Succinic acid</td>
<td>187</td>
<td>4.2</td>
</tr>
<tr>
<td>HO$_2$C(CH$_2$)$_3$CO$_2$H</td>
<td>Glutaric acid</td>
<td>98</td>
<td>4.3</td>
</tr>
<tr>
<td>HO$_2$C(CH$_2$)$_4$CO$_2$H</td>
<td>Adipic acid</td>
<td>153</td>
<td>4.4</td>
</tr>
<tr>
<td>cis-HO$_2$C—CH=CH—CO$_2$H</td>
<td>Maleic acid</td>
<td>131</td>
<td>1.9</td>
</tr>
<tr>
<td>trans-HO$_2$C—CH=CH—CO$_2$H</td>
<td>Fumaric acid</td>
<td>287</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Phthalic acid</td>
<td>206–208 dec</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Isophthalic acid</td>
<td>345–348</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>Terephthalic acid</td>
<td>Sublimes</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Chapter 18

**Esters**

- The names of esters are derived from the names of the corresponding carboxylic acid and alcohol from which the ester would be made.
  - The alcohol portion is named first and has the ending -yl.
  - The carboxylic acid portion follows and its name ends with -ate or -oate.

![Chemical structures of esters]

- Esters cannot hydrogen bond to each other and therefore have lower boiling points than carboxylic acids.
  - Esters can hydrogen bond to water and have appreciable water solubility.
<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
<th>Solubility in Water (g 100 mL$^{-1}$ at 20°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl formate</td>
<td>HCO$_2$CH$_3$</td>
<td>−99</td>
<td>31.5</td>
<td>Very soluble</td>
</tr>
<tr>
<td>Ethyl formate</td>
<td>HCO$_2$CH$_2$CH$_3$</td>
<td>−79</td>
<td>54</td>
<td>Soluble</td>
</tr>
<tr>
<td>Methyl acetate</td>
<td>CH$_3$CO$_2$CH$_3$</td>
<td>−99</td>
<td>57</td>
<td>24.4</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>CH$_3$CO$_2$CH$_2$CH$_3$</td>
<td>−82</td>
<td>77</td>
<td>7.39 (25°C)</td>
</tr>
<tr>
<td>Propyl acetate</td>
<td>CH$_3$CO$_2$CH$_2$CH$_2$CH$_3$</td>
<td>−93</td>
<td>102</td>
<td>1.89</td>
</tr>
<tr>
<td>Butyl acetate</td>
<td>CH$_3$CO$_2$CH$_2$(CH$_2$)$_2$CH$_3$</td>
<td>−74</td>
<td>125</td>
<td>1.0 (22°C)</td>
</tr>
<tr>
<td>Ethyl propanoate</td>
<td>CH$_3$CH$_2$CO$_2$CH$_2$CH$_3$</td>
<td>−73</td>
<td>99</td>
<td>1.75</td>
</tr>
<tr>
<td>Ethyl butanoate</td>
<td>CH$_3$(CH$_2$)$_2$CO$_2$CH$_2$CH$_3$</td>
<td>−93</td>
<td>120</td>
<td>0.51</td>
</tr>
<tr>
<td>Ethyl pentanoate</td>
<td>CH$_3$(CH$_2$)$_3$CO$_2$CH$_2$CH$_3$</td>
<td>−91</td>
<td>145</td>
<td>0.22</td>
</tr>
<tr>
<td>Ethyl hexanoate</td>
<td>CH$_3$(CH$_2$)$_4$CO$_2$CH$_2$CH$_3$</td>
<td>−68</td>
<td>168</td>
<td>0.063</td>
</tr>
<tr>
<td>Methyl benzoate</td>
<td>C$_6$H$_5$CO$_2$CH$_3$</td>
<td>−12</td>
<td>199</td>
<td>0.15</td>
</tr>
<tr>
<td>Ethyl benzoate</td>
<td>C$_6$H$_5$CO$_2$CH$_2$CH$_3$</td>
<td>−35</td>
<td>213</td>
<td>0.08</td>
</tr>
<tr>
<td>Phenyl acetate</td>
<td>CH$_3$CO$_2$C$_6$H$_5$</td>
<td>196</td>
<td></td>
<td>Slightly soluble</td>
</tr>
<tr>
<td>Methyl salicylate</td>
<td>o-HOC$_6$H$_4$CO$_2$CH$_3$</td>
<td>−9</td>
<td>223</td>
<td>0.74 (30°C)</td>
</tr>
</tbody>
</table>
• Acid Anhydrides

⇒ Most anhydrides are named by dropping the word *acid* from the carboxylic acid name and adding the word *anhydride*

![Acetic anhydride](image1)
![Succinic anhydride](image2)
![Phthalic anhydride](image3)
![Maleic anhydride](image4)

Acetic anhydride (ethanoic anhydride)  
mp −73°C

Succinic anhydride  
mp 121°C

Phthalic anhydride  
mp 131°C

Maleic anhydride  
mp 53°C

• Acid Chlorides

⇒ Acid chlorides are named by dropping the *-ic acid* from the name of the carboxylic acid and adding *-yl chloride*

![Acetyl chloride](image5)
![Propanoyl chloride](image6)
![Benzoyl chloride](image7)

Acetyl chloride (ethanoyl chloride)  
mp −112°C; bp 51°C

Propanoyl chloride  
mp −94°C; bp 80°C

Benzoyl chloride  
mp −1°C; bp 197°C
Amides

Amides with no substituents on nitrogen are named by replacing -ic acid in the name with amide. Groups on the nitrogen are named as substituents and are given the locants N- or N,N-.

- Acetamide (ethanamide) mp 82°C; bp 221°C
- N,N-Dimethylacetamide mp −20°C; bp 166°C
- N-Ethylacetamide bp 205°C
- N-Phenyl-N-propylacetamide mp 49°C; bp 266°C at 712 torr
- Benzamide mp 130°C; bp 290°C

Amides with one or two hydrogens on nitrogen form very strong hydrogen bonds and have high melting and boiling points. N,N-disubstituted amides cannot form hydrogen bonds to each other and have lower melting and boiling points.
Hydrogen bonding between amides in proteins and peptides is an important factor in determining their 3-dimensional shape

- Nitriles
  - Acyclic nitriles are named by adding the suffix *-nitrile* to the alkane name
    - The nitrile carbon is assigned position 1
    - Ethanenitrile is usually called acetonitrile

![Chemical structures of ethanenitrile and propenenitrile](image)

\[
\begin{align*}
\text{Ethanenitrile} & \quad \text{(acetonitrile)} \\
\text{Propenenitrile} & \quad \text{(acrylonitrile)}
\end{align*}
\]
**Spectroscopic Properties of Acyl Compounds**

**IR Spectra**

- The carbonyl stretching frequency varies according to the type of carboxylic acid derivative present.
- O-H stretching vibrations of the carboxylic acid give a broad band at 2500-3100 cm\(^{-1}\).
- N-H stretching vibrations of amides appear at 3140-3500 cm\(^{-1}\).

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Approximate Frequency Range (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid chloride</td>
<td>1815–1785 1800–1770 (conj.)</td>
</tr>
<tr>
<td>Acid anhydride</td>
<td>1820–1750 1775–1720 (conj.)</td>
</tr>
<tr>
<td>Ester/Lactone</td>
<td>1750–1735 1730–1715 (conj.)</td>
</tr>
<tr>
<td>Carboxylic acid</td>
<td>~1760 or 1720–1705 1710–1680 (conj.)</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>1740–1720 1710–1685 (conj.)</td>
</tr>
<tr>
<td>Ketone</td>
<td>1720–1710 1685–1665 (conj.)</td>
</tr>
<tr>
<td>Amide/lactam</td>
<td>1650–1640</td>
</tr>
<tr>
<td>Carboxylate salt</td>
<td>1650–1550 1650–1550 (solid) (solution)</td>
</tr>
</tbody>
</table>

*Orange bars represent absorption ranges for conjugated species.*
**1H NMR Spectra**

- The α hydrogens of carboxylic acids and their derivatives appear at δ 2.0-2.5
- The carboxyl group proton appears downfield at δ 10-12

**13C NMR Spectra**

- The carbonyl carbon signal for carboxylic acids and their derivatives appears at δ 160 to 180

13C NMR chemical shifts for the carbonyl or nitrile carbon atom
♦ Preparation of Carboxylic Acids

- By Oxidation of Alkanes

\[
RCH=CHR' \xrightarrow{(1) \text{ KMnO}_4, \text{OH}^- \text{ heat} } RCO_2H + R'CO_2H \\
RCH=CHR' \xrightarrow{(1) O_3 \text{ (2) H}_2\text{O}_2} RCO_2H + R'CO_2H
\]

- By Oxidation of Aldehydes and Primary Alcohols

\[
R-\text{CHO} \xrightarrow{(1) \text{ Ag}_2\text{O or Ag(NH}_3)_2^{+}\text{OH}^- \text{ (2) H}_2\text{O}^+ } RCO_2H \\
RCH_2\text{OH} \xrightarrow{(1) \text{ KMnO}_4, \text{OH}^- \text{ heat} } RCO_2H \\
R-\text{CHO or RCH}_2\text{OH} \xrightarrow{\text{H}_2\text{CrO}_4} RCO_2H
\]

- By Oxidation of Alkylbenzenes

\[
\begin{align*}
\text{Ar-CH}_3 & \xrightarrow{(1) \text{ KMnO}_4, \text{OH}^- \text{ heat} } \text{Ar-CO}_2\text{H} \\
& \xrightarrow{(2) \text{ H}_3\text{O}^+} 
\end{align*}
\]
• By Oxidation of the Benzene Ring

\[
\text{R} - \text{C}_6\text{H}_5 \xrightarrow{(1) \text{O}_3, \text{CH}_3\text{CO}_2\text{H}} \text{R} \xrightarrow{(2) \text{H}_2\text{O}_2} \text{R} - \text{COH}
\]

• By Oxidation of Methyl Ketones (The Haloform Reaction)

\[
\text{Ar} - \text{C} - \text{CH}_3 \xrightarrow{(1) \text{X}_2/\text{NaOH}} \text{Ar} - \text{C} - \text{OH} + \text{CHX}_3
\]

• By Hydrolysis of Cyanohydrins and Other Nitriles

\[\text{Hydrolysis of a cyanohydrin yields an } \alpha\text{-hydroxy acid}\]

\[
\text{R} - \text{CN} + \text{HCN} \rightleftharpoons \text{R} - \text{O} - \text{CN} \xrightarrow{\text{HA, H}_2\text{O}} \text{R} - \text{C} - \text{CO}_2\text{H}
\]
Primary alkyl halides can react with cyanide to form nitriles and these can be hydrolyzed to carboxylic acids.

\[
\text{HOCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{NaCN}} \text{HOCH}_2\text{CH}_2\text{CN} \quad \xrightarrow{\text{OH}^-, \text{H}_2\text{O}} \quad \text{HOCH}_2\text{CH}_2\text{CO}_2\text{H}
\]

3-Hydroxypropanenitrile

3-Hydroxypropanoic acid

\[
\text{BrCH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaCN}} \text{NCCH}_2\text{CH}_2\text{CH}_2\text{CN} \xrightarrow{\text{H}_2\text{O}^+} \text{HO}_2\text{CCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\]

Pentanenitrile

Glutaric acid

**By Carbonation of Grignard Reagents**

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{Mg, Et}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{MgCl} \xrightarrow{\text{CO}_2, \text{H}_2\text{O}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\]

tert-Butyl chloride

2,2-Dimethylpropanoic acid (79–80% overall)

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{Mg, Et}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{MgCl} \xrightarrow{\text{CO}_2, \text{H}_2\text{O}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}
\]

Butyl chloride

Pentanoic acid (80% overall)

\[
\text{Br} \xrightarrow{\text{Mg, Et}_2\text{O}} \text{MgBr} \xrightarrow{\text{CO}_2, \text{H}_2\text{O}^+} \text{CO}_2\text{H}
\]

Benzoic acid (85%)
Nucleophilic Addition-Elimination at the Acyl Carbon

- Recall that aldehydes and ketones undergo nucleophilic addition to the carbon-oxygen double bond

\[
\text{R'}_2	ext{C}=\text{O}^- + \text{Nu}^- \rightarrow \text{R'}_2\text{C}-\text{O}^- \rightarrow \text{R'}_2\text{C}=\text{O}^- + \text{H}^+ + \text{Nu}^- \\
\text{Aldehyde or ketone}
\]

- The carbonyl group of carboxylic acids and their derivatives undergo nucleophilic addition-elimination
  - The nucleophile reacts at the carbonyl group to form a tetrahedral intermediate
  - The tetrahedral intermediate eliminates a leaving group (L)
  - The carbonyl group is regenerated; the net effect is an acyl substitution

\[
\text{R}_2\text{C}=\text{O}^- + \text{Nu}^- \rightarrow \text{R}_2\text{C}-\text{O}^- \rightarrow \text{R}_2\text{C}=\text{O}^- + \text{HL} \\
\text{An acyl compound} \quad \text{Tetrahedral intermediate} \quad \text{Another acyl compound}
\]

Chapter 18
To undergo nucleophilic addition-elimination the acyl compound must have a good leaving group or a group that can be converted into a good leaving group.

- Acid chlorides react with loss of chloride ion
- Anhydrides react with loss of a carboxylate ion

Specific Example
Esters, carboxylic acids and amides generally react with loss of the leaving groups alcohol, water and amine, respectively. These leaving groups are generated by protonation of the acyl compound.

Aldehydes and ketones cannot react by this mechanism because they lack a good leaving group.
• Relative Reactivity of Acyl Compounds

The relative reactivity of carboxylic acids and their derivatives is as follows:

\[
\begin{align*}
R'\quad \text{Acyl chloride} & \quad > \quad R\quad \text{Acid anhydride} \quad > \quad R'\quad \text{Ester} \quad > \quad R\quad \text{Amide}
\end{align*}
\]

In general, reactivity can be related to the ability of the leaving group (L) to depart

- Leaving group ability is inversely related to basicity
- Chloride is the weakest base and the best leaving group
- Amines are the strongest bases and the worst leaving groups

As a general rule, less reactive acyl compounds can be synthesized from more reactive ones

- Synthesis of more reactive acyl derivatives from less reactive ones is difficult and requires special reagents (if at all possible)
Acid Chlorides

Synthesis of Acid Chlorides

Acid chlorides are made from carboxylic acids by reaction with thionyl chloride, phosphorus trichloride or phosphorus pentachloride. These reagents work because they turn the hydroxyl group of the carboxylic acid into an excellent leaving group.

\[
\text{RCOH} + \text{SOCl}_2 \rightarrow \text{RC} \equiv \text{Cl} + \text{SO}_2 + \text{HCl}
\]
Thionyl chloride

\[
3 \text{RCOH} + \text{PCl}_3 \rightarrow 3 \text{RCCl} + \text{H}_3\text{PO}_3
\]
Phosphorus trichloride

\[
\text{RCOH} + \text{PCl}_5 \rightarrow \text{RCCl} + \text{POCl}_3 + \text{HCl}
\]
Phosphorus pentachloride
Reactions of Acyl Chlorides

- Acyl chlorides are the most reactive acyl compounds and can be used to make any of the other derivatives.
- Since acyl chlorides are easily made from carboxylic acids they provide a way to synthesize any acyl compound from a carboxylic acid.
- Acyl chlorides react readily with water, but this is not a synthetically useful reaction.
Carboxylic Acid Anhydrides

Synthesis of Carboxylic Acid Anhydrides

- Acid chlorides react with carboxylic acids to form mixed or symmetrical anhydrides
  It is necessary to use a base such as pyridine

\[
\begin{align*}
\text{RCOOH} + \text{R'}\text{COCI} + \text{pyridine} & \rightarrow \text{RCOOR'} + \text{pyridinium chloride} \\
\end{align*}
\]

- Sodium carboxylates react readily with acid chlorides to form anhydrides

\[
\begin{align*}
\text{RCOONa} + \text{R'}\text{COCI} & \rightarrow \text{RCOOR'} + \text{NaCl} \\
\end{align*}
\]
Cyclic anhydrides with 5- and 6-membered rings can be synthesized by heating the appropriate diacid.

Reactions of Carboxylic Acid Anhydrides

- Carboxylic acid anhydrides are very reactive and can be used to synthesize esters and amides.
  - Hydrolysis of an anhydride yields the corresponding carboxylic acids.
Chapter 18

**Anhydride**

- **R'OH**
  - **RCOR'**
  - **RCOH**
  - **Ester**

- **NH₃**
  - **RCNH₂**
  - **RCO⁻NH₄⁺**
  - **Amide**

- **R'NH₂**
  - **RCNHR'**
  - **RCO⁻R'NH₃⁺**
  - **N-Substituted amide**

- **R'R''NH**
  - **RCNR'R''**
  - **RCO⁻R'R''NH₂⁺**
  - **N,N-Disubstituted amide**
  - **By-products**

**Anhydride**

- **H₂O**
  - **RCOH**
  - **HOCR'**

- **OH⁻/H₂O**
  - **RCO⁻**
  - **OCR'**
♦ Esters

● Synthesis of Esters: Esterification

→ Acid catalyzed reaction of alcohols and carboxylic acids to form esters is called Fischer esterification

→ Fischer esterification is an equilibrium process

♀ Ester formation is favored by use of a large excess of either the alcohol or carboxylic acid

♀ Ester formation is also favored by removal of water

\[
\begin{align*}
\text{R-CO-OR'} & \quad \text{(Ester)} \\
\text{R-COOH + R'-OH} & \quad \text{H}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{COH} + \text{CH}_3\text{CH}_2\text{OH} & \quad \text{H}_2\text{O} \\
\text{CH}_3\text{COCH}_2\text{CH}_3 & \quad \text{Acetate} \\
\text{C}_6\text{H}_5\text{COH} + \text{CH}_3\text{OH} & \quad \text{H}_2\text{O} \\
\text{C}_6\text{H}_5\text{COCH}_3 & \quad \text{Methyl benzoate}
\end{align*}
\]
Esterification with labeled methanol gives a product labeled only at the oxygen atom bonded to the methyl group.

A mechanism consistent with this observation is shown below:

\[
\text{C}_6\text{H}_5\text{C} \equiv \text{OH} + \text{CH}_3^{18}\text{O} \equiv \text{H} \xrightarrow{\text{HA}} \text{C}_6\text{H}_5\text{C}^{18}\text{OCH}_3 + \text{H}_2\text{O}
\]

- The carboxylic acid accepts a proton from the strong acid catalyst.
- The alcohol attacks the protonated carbonyl group to give a tetrahedral intermediate.
- A proton is lost at one oxygen atom and gained at another.
- Loss of a molecule of water gives a protonated ester.
- Transfer of a proton to a base leads to the ester.
The reverse reaction is acid-catalyzed ester hydrolysis

\[ \text{Ester hydrolysis is favored by use of dilute aqueous acid} \]

\[ \text{R} \text{C} \text{OR'} + \text{H}_2\text{O} \xrightleftharpoons{\text{H}_3\text{O}^+} \text{R} \text{C} \text{OH} + \text{R'}\text{OH} \]

Esters from Acid Chlorides

\[ \text{Acid chlorides react readily with alcohols in the presence of a base (e.g. pyridine) to form esters} \]

\[ \text{R} \text{C} \text{Cl} + \text{R'}\text{OH} \xrightarrow{-\text{HCl}} \text{R} \text{C} \text{O} \text{R'} \]

Benzoyl chloride

\[ \text{C}_6\text{H}_5\text{C} \text{Cl} + \text{CH}_3\text{CH}_2\text{OH} + \text{N} \xrightarrow{\text{C}_6\text{H}_5\text{COCH}_2\text{CH}_3 + \text{N}^+\text{Cl}^-} \]

Ethyl benzoate (80%)
Esters from Carboxylic Acid Anhydrides

Alcohols react readily with anhydrides to form esters

\[
\begin{align*}
\text{RCOO} \quad + \quad &\text{R'OH} \quad \rightarrow \quad \text{RCO} \quad \text{O} \quad \text{O} \\
\text{RCOO} \quad + \quad &\text{RCO} \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\left(\text{CH}_3\text{C}=\text{O}\right)_2\text{O} \quad + \quad &\text{C}_6\text{H}_5\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{COCH}_2\text{C}_6\text{H}_5 \quad + \quad \text{CH}_3\text{CO}_2\text{H}
\end{align*}
\]

Acetic anhydride
Benzyl alcohol
Benzyl acetate

\[
\begin{align*}
\text{Phthalic anhydride} \quad + \quad &\text{CH}_3\text{CHCH}_2\text{CH}_3 \quad \rightarrow \quad \text{CH}_3\text{CHCH}_2\text{CH}_3
\end{align*}
\]

sec-Butyl alcohol
sec-Butyl hydrogen phthalate (97%)

Chapter 18
Base-Promoted Hydrolysis of Esters: Saponification

- Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol

\[
\text{RC-OR'} + \text{NaOH} \xrightarrow{\text{H}_2\text{O}} \text{RC-O}^-\text{Na}^+ + \text{R'}\text{OH}
\]

- The mechanism is reversible until the alcohol product is formed
- Protonation of the alkoxide by the initially formed carboxylic acid is irreversible
  - This step draws the overall equilibrium toward completion of the hydrolysis

A hydroxide ion attacks the carbonyl carbon atom.
The tetrahedral intermediate expels an alkoxide ion.

Transfer of a proton leads to the products of the reaction.
● Lactones

$\gamma$- or $\delta$-Hydroxyacids undergo acid catalyzed reaction to give cyclic esters known as $\gamma$- or $\delta$-lactones, respectively.

A $\delta$-hydroxy acid

A $\delta$-lactone
Lactones can be hydrolyzed with aqueous base

Acidification of the carboxylate product can lead back to the original lactone if too much acid is added.
Amides

- Synthesis of Amides
  - Amides From Acyl Chlorides
  
  * Ammonia, primary or secondary amines react with acid chlorides to form amides
  * An excess of amine is added to neutralize the HCl formed in the reaction
  * Carboxylic acids can be converted to amides via the corresponding acid chloride

Reactant
- Ammonia; R', R'' = H
- 1° Amine; R' = H, R'' = alkyl, aryl
- 2° Amine; R', R'' = alkyl, aryl

Product
- Unsubstituted amide; R', R'' = H
- N-Substituted amide; R' = H, R'' = alkyl, aryl
- N,N-Disubstituted amide; R', R'' = alkyl, aryl
Amides from Carboxylic Anhydrides

- Anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate

\[
\text{RC(=O)O + 2 R'NH → R'CONH R' + RCO_2^- R'R''NH}_2
\]

R', R'' can be H, alkyl or aryl

- Reaction of a cyclic anhydride with an amine, followed by acidification yields a product containing both amide and carboxylic acid functional groups

- Heating this product results in the formation of a cyclic imide
Amides from Carboxylic Acids and Ammonium Carboxylates

- Direct reaction of carboxylic acids and ammonia yields ammonium salts

\[
\begin{align*}
\text{RCO}_2\text{H} + \text{NH}_3 & \rightleftharpoons \text{RCO}_2\text{O}^{-}\text{NH}_4^+\\
\text{An ammonium carboxylate}
\end{align*}
\]

- Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures

- This is generally a poor method of amide synthesis

\[
\begin{align*}
\text{RCO}_2\text{O}^{-}\text{NH}_4^+ (\text{solid}) & \xrightarrow{\text{heat}} \text{RCO} + \text{H}_2\text{O} \\
\text{NH}_2
\end{align*}
\]

- A good way to synthesize an amide is to convert a carboxylic acid to an acid chloride and to then react the acid chloride with ammonia or an amine
Dicyclohexylcarbodiimide (DCC) is a reagent used to form amides from carboxylic acids and amines.

DCC activates the carbonyl group of a carboxylic acid toward nucleophilic addition-elimination.
Hydrolysis of Amides

Heating an amide in concentrated aqueous acid or base causes hydrolysis.

\[ R\text{CONH}_2 + H_3O^+ \xrightarrow{\text{H}_2O \text{ heat}} R\text{COOH} + \text{NH}_4^+ \]

\[ R\text{CONH}_2 + \text{Na}^+\text{OH}^- \xrightarrow{\text{H}_2O \text{ heat}} R\text{COONa}^- + \text{NH}_3 \]

Hydrolysis of an amide is slower than hydrolysis of an ester.
The amide carbonyl accepts a proton from the aqueous acid.

A water molecule attacks the protonated carbonyl to give a tetrahedral intermediate.

A proton is lost at one oxygen and gained at the nitrogen.

Loss of a molecule of ammonia gives a protonated carboxylic acid.

Transfer of a proton to ammonia leads to the carboxylic acid and an ammonium ion.
A hydroxide ion attacks the acyl carbon of the amide. A hydroxide ion removes a proton to give a dianion. The dianion loses a molecule of ammonia (or an amine); this step is synchronized with a proton transfer from water due to the basicity of $\text{NH}_2^-$.

$\text{R}^+\text{C}^\text{O}^-\text{NH}_2 + \cdot\text{OH}^- \rightleftharpoons \text{R}^-\text{C}^\text{O}^-\text{H} \rightleftharpoons \text{R}^-\text{C}^-\text{O}^-\text{NH}_2 \rightleftharpoons \text{R}^-\text{C}^-\text{O}^-\text{H} + \cdot\text{OH}^- \rightleftharpoons \text{R}^-\text{C}^-\text{O}^- + \cdot\text{NH}_3 + \cdot\text{OH}^-$
• **Nitriles from the Dehydration of Amides**
  ➔ A nitrile can be formed by reaction of an amide with phosphorous pentoxide or boiling acetic anhydride

\[
\begin{align*}
R-CN\overset{\text{P}_4\text{O}_{10} \text{ or } (\text{CH}_3\text{CO})_2\text{O}}{\text{heat}} \quad &\rightarrow \quad R-\overset{\text{Nitrile}}{\text{C} = \text{N}} + \text{H}_3\text{PO}_4 \quad \text{or} \quad \text{CH}_3\text{CO}_2\text{H}
\end{align*}
\]

• **Hydrolysis of Nitriles**
  ➔ A nitrile is the synthetic equivalent of a carboxylic acid because it can be converted to a carboxylic acid by hydrolysis

\[
\begin{align*}
R-CN\overset{\text{H}_2\text{O}^+, \text{H}_2\text{O}, \text{heat}}{\rightarrow} \quad &\rightarrow \quad \overset{\text{RCO}_2\text{H}}{\text{RCO}_2\text{H}}
\end{align*}
\]

\[
\begin{align*}
R-CN\overset{\text{OH}^-, \text{H}_2\text{O}, \text{heat}}{\rightarrow} \quad &\rightarrow \quad \overset{\text{RCO}_2^-}{\text{RCO}_2^-}
\end{align*}
\]
Decarboxylation of Carboxylic Acids

- β-Keto carboxylic acids and their salts decarboxylate readily when heated
  - Some even decarboxylate slowly at room temperature

\[ \text{RCCH}_2\text{COH} \quad 100-150^\circ\text{C} \quad \text{RCCH}_3 + \text{CO}_2 \]
A β-keto acid

- The mechanism of β-keto acid decarboxylation proceeds through a 6-membered ring transition state
Carboxylate anions decarboxylate rapidly because they form a resonance-stabilized enolate.

Malonic acids also decarboxylate readily.