Lecture 5

Carboxylic Acids and their Derivatives I

Instructor: Dr. Tanatorn Khotavivattana
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:
**Carboxyl** = **carbonyl** group + **hydroxyl** group

- Compounds containing the carboxyl group are distinctly **acidic** and are called **carboxylic acids**

\[
\begin{align*}
\text{Formic acid} & \quad \text{H}_{2}\text{C} \equiv \text{OH} \\
\text{Methanoic acid} & \quad \text{H} \equiv \text{C} \equiv \text{OH} \\
\text{Acetic acid} & \quad \text{H}_{3}\text{C} \equiv \text{C} \equiv \text{OH} \\
\text{Ethanoic acid} & \quad \text{H}_{3}\text{C} \equiv \text{C} \equiv \text{OH}
\end{align*}
\]
Carboxylic Acid

- **Aliphatic** acid has an **alkyl** group bonded to the carboxyl group, and an **aromatic** acid has an **aryl** group.

  ![Chemical structures](image)

  - Formic acid
  - Propionic acid (an aliphatic acid)
  - Benzoic acid (an aromatic acid)
  - Stearic acid (a fatty acid)

- A carboxylic acid donates protons by heterolytic cleavage of the acidic O—H bond to give a **proton** and a **carboxylate ion**.

  ![Reactions](image)

  \[
  \text{carboxylic acid} + \text{H}_2\text{O} \leftrightarrow \text{carboxylate ion} + \text{H}_3\text{O}^+ 
  \]
Nomenclature – IUPAC Names

- Uses the name of the alkane that corresponds to the **longest continuous chain** of carbon atoms
- The final -e in the alkane name is replaced by the suffix -oic acid
- The chain is **numbered, starting with the carboxyl carbon atom**, to give positions of substituents along the chain

![Examples of IUPAC naming](image)

- The carboxyl group takes priority over any of the other functional groups

*Chapter 20 – Wade - Prentice Hall*
Nomenclature – IUPAC Names

- Unsaturated acids are named using the name of the corresponding alkene, with the final -e replaced by -oic acid.
- Cycloalkanes with –COOH substituents are named as cycloalkanecarboxylic acids.
- Aromatic acids of the form Ar-COOH are named as derivatives of benzoic acid.
- ortho-, meta-, and para- may be used to give the positions of substituents.
### Nomenclature – Common Names

<table>
<thead>
<tr>
<th>IUPAC Name</th>
<th>Common Name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>methanoic</td>
<td>formic</td>
<td>HCOOH</td>
</tr>
<tr>
<td>ethanoic</td>
<td>acetic</td>
<td>CH₃COOH</td>
</tr>
<tr>
<td>propanoic</td>
<td>propionic</td>
<td>CH₃CH₂COOH</td>
</tr>
<tr>
<td>prop-2-enoic</td>
<td>acrylic</td>
<td>H₂C═CH—COOH</td>
</tr>
<tr>
<td>butanoic</td>
<td>butyric</td>
<td>CH₃(CH₂)₂COOH</td>
</tr>
<tr>
<td>2-methylpropanoic</td>
<td>isobutyric</td>
<td>(CH₃)₂CHCOOH</td>
</tr>
<tr>
<td>trans-but-2-enoic</td>
<td>crotonic</td>
<td>CH₃—CH═CH—COOH</td>
</tr>
<tr>
<td>pentanoic</td>
<td>valeric</td>
<td>CH₃(CH₂)₃COOH</td>
</tr>
<tr>
<td>2,2-dimethylpropanoic</td>
<td>pivalic</td>
<td>(CH₃)₃C—COOH</td>
</tr>
<tr>
<td>hexanoic</td>
<td>caproic</td>
<td>CH₃(CH₂)₄COOH</td>
</tr>
<tr>
<td>octanoic</td>
<td>caprylic</td>
<td>CH₃(CH₂)₆COOH</td>
</tr>
<tr>
<td>decanoic</td>
<td>capric</td>
<td>CH₃(CH₂)₈COOH</td>
</tr>
<tr>
<td>dodecanoic</td>
<td>lauric</td>
<td>CH₃(CH₂)₁₀COOH</td>
</tr>
<tr>
<td>tetradecanoic</td>
<td>myristic</td>
<td>CH₃(CH₂)₁₂COOH</td>
</tr>
<tr>
<td>hexadecanoic</td>
<td>palmitic</td>
<td>CH₃(CH₂)₁₄COOH</td>
</tr>
<tr>
<td>octadecanoic</td>
<td>stearic</td>
<td>CH₃(CH₂)₁₆COOH</td>
</tr>
<tr>
<td>benzoic</td>
<td>benzoic</td>
<td>C₆H₅COOH</td>
</tr>
</tbody>
</table>
Problem #1

Name the following carboxylic acids (when possible, give both a common name and a systematic name).

(a) \(\text{CH}_3\text{C}(\text{I})(\text{COOH})\)
(b) \(\text{CH}_2\text{CH}_3\text{C}(<\text{CH})\text{COOH}\)
(c) \(\text{C}(\text{NO}_2)\text{COOH}\)

(d) \(\text{C}(\text{COOH})(\text{COOH})\)
(e) \(\text{C}(\text{COOH})\text{Cl}\)
(f) \(\text{H}_3\text{C}(\text{COOH})(\text{COOH})\)
Structure of Carboxylic Group

- The $sp^2$ hybrid carbonyl carbon atom is planar, with nearly trigonal bond angles.

- One of the unshared electron pairs on the hydroxyl oxygen atom is delocalised into the electrophilic pi system of the carbonyl group.
Boiling Points

- Carboxylic acids boil at considerably **higher temperatures** than do alcohols, ketones, or aldehydes of similar molecular weights.

  \[
  \text{CH}_3\text{C} \equiv \text{OH} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \quad \text{CH}_3\text{CH}_2\text{C} \equiv \text{H} \\
  \text{acetic acid, bp 118 °C} \quad \text{propan-1-ol, bp 97 °C} \quad \text{propionaldehyde, bp 49 °C}
  \]

- The high boiling points of carboxylic acids result from formation of a stable, **hydrogen bonded dimer**; effectively doubling the molecular weight.
Solubilities

- Carboxylic acids form **hydrogen bonds** with water and alcohol
- The lower molecular-weight acids are **miscible** with water
- As the length of the hydrocarbon chain increases, water solubility decreases until acids with more than **10 carbon atoms are nearly insoluble** in water

<table>
<thead>
<tr>
<th>IUPAC Name</th>
<th>Common Name</th>
<th>Formula</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
<th>Solubility (g/100 g H₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methanoic</td>
<td>formic</td>
<td>HCOOH</td>
<td>8</td>
<td>101</td>
<td>∞ (miscible)</td>
</tr>
<tr>
<td>ethanoic</td>
<td>acetic</td>
<td>CH₃COOH</td>
<td>17</td>
<td>118</td>
<td>∞</td>
</tr>
<tr>
<td>propanoic</td>
<td>propionic</td>
<td>CH₃CH₂COOH</td>
<td>−21</td>
<td>141</td>
<td>∞</td>
</tr>
<tr>
<td>prop-2-enoic</td>
<td>acrylic</td>
<td>H₂C═CH—COOH</td>
<td>14</td>
<td>141</td>
<td>∞</td>
</tr>
<tr>
<td>butanoic</td>
<td>butyric</td>
<td>CH₃(CH₂)₂COOH</td>
<td>−6</td>
<td>163</td>
<td>∞</td>
</tr>
<tr>
<td>2-methylpropanoic</td>
<td>isobutyric</td>
<td>(CH₃)₂CHCOOH</td>
<td>−46</td>
<td>155</td>
<td>23.0</td>
</tr>
<tr>
<td><em>trans</em>-but-2-enoic</td>
<td>crotonic</td>
<td>CH₃—CH═CH—COOH</td>
<td>71</td>
<td>185</td>
<td>8.6</td>
</tr>
<tr>
<td>pentanoic</td>
<td>valeric</td>
<td>CH₃(CH₂)₃COOH</td>
<td>−34</td>
<td>186</td>
<td>3.7</td>
</tr>
<tr>
<td>2,2-dimethylproanoic</td>
<td>pivalic</td>
<td>(CH₃)₃C—COOH</td>
<td>35</td>
<td>164</td>
<td>2.5</td>
</tr>
<tr>
<td>hexanoic</td>
<td>caproic</td>
<td>CH₃(CH₂)₄COOH</td>
<td>−4</td>
<td>206</td>
<td>1.0</td>
</tr>
<tr>
<td>octanoic</td>
<td>caprylic</td>
<td>CH₃(CH₂)₆COOH</td>
<td>16</td>
<td>240</td>
<td>0.7</td>
</tr>
<tr>
<td>decanoic</td>
<td>capric</td>
<td>CH₃(CH₂)₈COOH</td>
<td>31</td>
<td>269</td>
<td>0.2</td>
</tr>
</tbody>
</table>

- Most carboxylic acids are also quite soluble in relatively **nonpolar solvents** such as chloroform because the acid continues to exist in its **dimeric form**
Acidities

- A carboxylic acid may dissociate in water to give a proton and a carboxylate ion:

\[
\begin{align*}
\text{R–C–O–H} + \text{H}_2\text{O} & \rightleftharpoons \text{R–C–O}^- + \text{H}_3\text{O}^+ \\
K_a & = \frac{[\text{R–CO}_2^-][\text{H}_3\text{O}^+]}{[\text{R–CO}_2\text{H}]} \\
pK_a & = -\log_{10} K_a
\end{align*}
\]

- The equilibrium constant $K_a$ is called the acid-dissociation constant.

- The $pK_a$ of an acid is the negative logarithm of $K_a$ and we commonly use as an indication of the relative acidities of different acids.

- Lower $pK_a$ value = Stronger acid
### Acidities

#### Table 20-3: Values of $K_a$ and $pK_a$ for Carboxylic Acids and Dicarboxylic Acids

<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>$K_a$ (at 25 °C)</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCOOH</td>
<td>formic acid</td>
<td>$1.77 \times 10^{-4}$</td>
<td>3.75</td>
</tr>
<tr>
<td>CH$_3$COOH</td>
<td>acetic acid</td>
<td>$1.76 \times 10^{-5}$</td>
<td>4.74</td>
</tr>
<tr>
<td>CH$_3$CH$_2$COOH</td>
<td>propionic acid</td>
<td>$1.34 \times 10^{-5}$</td>
<td>4.87</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_2$COOH</td>
<td>butyric acid</td>
<td>$1.54 \times 10^{-5}$</td>
<td>4.82</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_3$COOH</td>
<td>pentanoic acid</td>
<td>$1.52 \times 10^{-5}$</td>
<td>4.81</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_4$COOH</td>
<td>hexanoic acid</td>
<td>$1.31 \times 10^{-5}$</td>
<td>4.88</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_6$COOH</td>
<td>octanoic acid</td>
<td>$1.28 \times 10^{-5}$</td>
<td>4.89</td>
</tr>
<tr>
<td>CH$_3$(CH$_2$)$_8$COOH</td>
<td>decanoic acid</td>
<td>$1.43 \times 10^{-5}$</td>
<td>4.84</td>
</tr>
<tr>
<td>C$_6$H$_5$COOH</td>
<td>benzoic acid</td>
<td>$6.46 \times 10^{-5}$</td>
<td>4.19</td>
</tr>
<tr>
<td>$p$-CH$_3$C$_6$H$_4$COOH</td>
<td>$p$-toluic acid</td>
<td>$4.33 \times 10^{-5}$</td>
<td>4.36</td>
</tr>
<tr>
<td>$p$-ClC$_6$H$_4$COOH</td>
<td>$p$-chlorobenzoic acid</td>
<td>$1.04 \times 10^{-4}$</td>
<td>3.98</td>
</tr>
<tr>
<td>$p$-NO$_2$C$_6$H$_4$COOH</td>
<td>$p$-nitrobenzoic acid</td>
<td>$3.93 \times 10^{-4}$</td>
<td>3.41</td>
</tr>
</tbody>
</table>
Acidities

- Carboxylic acids \( (pK_a \approx 5) \) are \( 10^{11} \) times more acidic than alcohols \( (pK_a \approx 16) \).

- Dissociation of a carboxylic acid gives a \textbf{carboxylate ion} with the negative charge spread out equally over two oxygen atoms, compared with just one oxygen in an alkoxide ion.
Acidities – Substituent Effects

• Any substituent that stabilises the negatively charged carboxylate ion (i.e. electron withdrawing) promotes dissociation and results in a stronger acid

- Acetic acid: $pK_a = 4.74$
- Chloroacetic acid: $pK_a = 2.86$
- Dichloroacetic acid: $pK_a = 1.26$
- Trichloroacetic acid: $pK_a = 0.64$

• The magnitude of a substituent effect depends on its distance from the carboxyl group

Chapter 20 – Wade - Prentice Hall
# Acidities – Substituent Effects

## Table 20-4

<table>
<thead>
<tr>
<th>Acid</th>
<th>$K_a$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{F}_3\text{C}\text{COOH}$</td>
<td>$5.9 \times 10^{-1}$</td>
<td>0.23</td>
</tr>
<tr>
<td>$\text{Cl}_3\text{C}\text{COOH}$</td>
<td>$2.3 \times 10^{-1}$</td>
<td>0.64</td>
</tr>
<tr>
<td>$\text{Cl}_2\text{CHC}\text{COOH}$</td>
<td>$5.5 \times 10^{-2}$</td>
<td>1.26</td>
</tr>
<tr>
<td>$\text{O}_2\text{N}\text{—CH}_2\text{COOH}$</td>
<td>$2.1 \times 10^{-2}$</td>
<td>1.68</td>
</tr>
<tr>
<td>$\text{NCCH}_2\text{COOH}$</td>
<td>$3.4 \times 10^{-3}$</td>
<td>2.46</td>
</tr>
<tr>
<td>$\text{FCH}_2\text{COOH}$</td>
<td>$2.6 \times 10^{-3}$</td>
<td>2.59</td>
</tr>
<tr>
<td>$\text{ClCH}_2\text{COOH}$</td>
<td>$1.4 \times 10^{-3}$</td>
<td>2.86</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{CHCl}\text{COOH}$</td>
<td>$1.4 \times 10^{-3}$</td>
<td>2.86</td>
</tr>
<tr>
<td>$\text{BrCH}_2\text{COOH}$</td>
<td>$1.3 \times 10^{-3}$</td>
<td>2.90</td>
</tr>
<tr>
<td>$\text{ICH}_2\text{COOH}$</td>
<td>$6.7 \times 10^{-4}$</td>
<td>3.18</td>
</tr>
<tr>
<td>$\text{CH}_3\text{OCH}_2\text{COOH}$</td>
<td>$2.9 \times 10^{-4}$</td>
<td>3.54</td>
</tr>
<tr>
<td>$\text{HOCH}_2\text{COOH}$</td>
<td>$1.5 \times 10^{-4}$</td>
<td>3.83</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CHClCH}_2\text{COOH}$</td>
<td>$8.9 \times 10^{-5}$</td>
<td>4.05</td>
</tr>
<tr>
<td>$\text{PhCOOH}$</td>
<td>$6.46 \times 10^{-5}$</td>
<td>4.19</td>
</tr>
<tr>
<td>$\text{PhCH}_2\text{COOH}$</td>
<td>$4.9 \times 10^{-5}$</td>
<td>4.31</td>
</tr>
<tr>
<td>$\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COOH}$</td>
<td>$3.0 \times 10^{-5}$</td>
<td>4.52</td>
</tr>
<tr>
<td>$\text{CH}_3\text{COOH}$</td>
<td>$1.8 \times 10^{-5}$</td>
<td>4.74</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$</td>
<td>$1.5 \times 10^{-5}$</td>
<td>4.82</td>
</tr>
</tbody>
</table>

*Stronger acids are indicated by an arrow.*
Salts of Carboxylic Acids

- A strong base can completely deprotonate a carboxylic acid. The products are a carboxylate ion, the cation remaining from the base, and water. The combination of a carboxylate ion and a cation is a salt of a carboxylic acid.

\[
\text{R―C―O―H} + M^+\text{-OH} \rightleftharpoons \text{R―C―O}^- \ M^+ + \text{H}_2\text{O}
\]

**Example**

\[
\text{CH}_3\text{―C―O―H} + \text{Na}^+\text{-OH} \rightleftharpoons \text{CH}_3\text{―C―O}^- \ \text{Na}^+ + \text{H}_2\text{O}
\]

- Addition of a mineral acid (more acidic) converts a carboxylic acid salt back to the original carboxylic acid.

\[
\text{CH}_3\text{―C―O}^- \ \text{Na}^+ + \text{H}^+ \text{Cl}^- \rightleftharpoons \text{CH}_3\text{―C―O―H} + \text{Na}^+ \text{Cl}^-
\]

**Example**

\[
\text{CH}_3\text{―C―O}^- \ \text{Na}^+ + \text{H}^+ \text{Cl}^- \rightleftharpoons \text{CH}_3\text{―C―O―H} + \text{Na}^+ \text{Cl}^-
\]
Salts of Carboxylic Acids – Properties

- **Solids** with little odour; melt at high temperatures; often decompose before reaching their melting points

- Carboxylate salts of the **alkali metals** (Li⁺, Na⁺, K⁺) and **ammonium** (NH₄⁺) generally **soluble in water** but relatively insoluble in nonpolar organic solvents

- **Soap** is a common example of carboxylate salts, consisting of the soluble sodium salts of long-chain fatty acids

- Carboxylate salts of most other metal ions are **insoluble** in water. For example, when soap is used in “**hard**” water containing calcium, magnesium, or iron ions, the insoluble carboxylate salts **precipitate** out as “hard-water scum.”

\[
2 \text{CH}_3(\text{CH}_2)_6\text{C}––\text{O}^- \text{Na}^+ + \text{Ca}^{2+} \rightarrow \left[\text{CH}_3(\text{CH}_2)_6\text{C}––\text{O}\right]_2\text{Ca} \downarrow + 2 \text{Na}^+ \\
\text{a soap} \\
\text{“hard-water scum”}
\]
Salts of Carboxylic Acids – Extraction

- Extraction is a **purification** method that takes advantage of the **different solubilities** of acids and their salts.

  - Impurities can be removed from a carboxylic acid using acid–base extractions.

  **Diagram:**
  - **Ether phase:**
    - $\text{RCOOH}$ + other organics
    - (1) remove H$_2$O phase
    - (2) add dilute NaOH (or NaHCO$_3$)
  - **H$_2$O phase:**
    - salts, etc.
  - NaOH (aq) to R–C–OH: soluble in ether, but not in H$_2$O
  - R–C–O$^-$ Na$^+$: soluble in H$_2$O, but not in ether
  - HCl (aq) to R–C–OH: soluble in ether, but not in H$_2$O

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Suppose you have just synthesized heptanoic acid from heptan-1-ol. The product is contaminated by sodium dichromate, sulfuric acid, heptan-1-ol, and possibly heptanal. Explain how you would use acid–base extractions to purify the heptanoic acid. Use a chart to show where the impurities are at each stage.
Reactions of Carboxylic Acids

1) Fischer Esterification – Condensation of Acids with Alcohols

- converts **carboxylic acids** and **alcohols** directly to **esters** by an **acid-catalysed nucleophilic acyl substitution**
- The net reaction is replacement of the acid –OH group by the –OR group

\[
\text{R–C–OH (acid)} + \text{R’–OH (alcohol)} \xrightleftharpoons{\text{H}^+} \text{R–C–O–R’ (ester)} + \text{H}_2\text{O}
\]

**Examples**

\[
\begin{align*}
\text{CH}_3\text{C–OH} &+ \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{H}_2\text{SO}_4, K_{eq} = 3.38} \text{CH}_3\text{C–O–CH}_2\text{CH}_3 + \text{H}_2\text{O} \\
\text{phthalic acid} &\xrightarrow{\text{excess CH}_3\text{OH, H}^+} \text{dimethyl phthalate}
\end{align*}
\]
1) Fischer Esterification – Mechanism

**Part 1: Acid-catalyzed addition of the alcohol to the carbonyl group.**

Protonation activates the carbonyl. The alcohol adds. Deprotonation completes the reaction.

![Chemical reaction diagram](image)

(Species in brackets are resonance-stabilized.)

**Part 2: Acid-catalyzed dehydration.**

Protonation prepares the OH group to leave. Water leaves. Deprotonation completes the reaction.

![Chemical reaction diagram](image)
1) Fischer Esterification

- Fischer esterification is an **equilibrium**, and typical equilibrium constants for esterification are not very large

**Equilibrium mixture**

\[
\text{CH}_3\text{C} \equiv \text{OH} \quad \text{+} \quad \text{CH}_3\text{CH}_2\text{OH} \quad \xrightleftharpoons{K_{eq} = 3.38} \quad \text{CH}_3\text{C} \equiv \text{OCH}_2\text{CH}_3 \quad \text{+} \quad \text{H}_2\text{O}
\]

- 0.35 mole 0.35 mole 0.65 mole 0.65 mole

- Esterification may be driven to the right either by using an **excess of one of the reactants** or by **removing one of the products**

- **Water** may be removed either by **distilling it out** or by **adding a dehydrating agent** such as magnesium sulfate or molecular sieves

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Problem #3

Most of the Fischer esterification mechanism is identical with the mechanism of acetal formation. The difference is in the final step, where a carbocation loses a proton to give the ester. Write mechanisms for the following reactions, with the comparable steps directly above and below each other. Explain why the final step of the esterification (proton loss) cannot occur in acetal formation, and show what happens instead.
Problem #4

Ethyl orthoformate hydrolyzes easily in dilute acid to give formic acid and three equivalents of ethanol. Propose a mechanism for the hydrolysis of ethyl orthoformate.
Reactions of Carboxylic Acids

2) Condensation of Acids with Amines: Direct Synthesis of Amides

- Amides can be synthesized directly from carboxylic acids, using heat to drive off water and force the reaction to completion.

- The initial acid–base reaction of a carboxylic acid with an amine gives an ammonium carboxylate salt. The carboxylate ion is a poor electrophile, and the ammonium ion is not nucleophilic. Therefore, heat is required!

\[
\begin{align*}
\text{R–C–OH} & \quad \text{+ R’–NH}_2 & \text{\textbullet} \quad \text{heat} & \quad \rightarrow \quad \text{R–C–O}^- \quad \text{H}_3\text{N}^+\text{–R’} \\
\text{acid} & \quad \text{amine} & \text{an ammonium carboxylate salt} & \quad \rightarrow \quad \text{R–C–NH}–\text{R’} \quad \text{+ H}_2\text{O}\uparrow \\
& & & \text{amide}
\end{align*}
\]

Example

\[
\begin{align*}
\text{benzoic acid} & \quad \text{+ CH}_3\text{CH}_2\text{NH}_2 & \text{\textbullet} \quad \text{heat} & \quad \rightarrow \quad \text{N-ethylbenzamide} \\
& & & \text{+ H}_2\text{O}\uparrow
\end{align*}
\]
Problem #5

Show how to synthesize the following compounds, using appropriate carboxylic acids and amines.

(a) $\text{CH}_3\text{C} = \text{N(CH}_2\text{CH}_3)_2$

$N,N$-diethyl-meta-toluamide

(DEET insect repellent)

(b) $\text{NH} - \text{C} - \text{CH}_3$

acetanilide

(c) $\text{H} - \text{C} - \text{N(CH}_3)_2$

$N,N$-dimethylformamide (DMF)
3) Reduction of Carboxylic Acids

- **Lithium aluminum hydride** (LiAlH₄ or LAH) reduces carboxylic acids to primary alcohols.

  \[
  \text{O} \quad \begin{array}{c}
  \text{R} \quad \text{C} \quad \text{OH} \\
  \text{acid}
  \end{array}
  \xrightarrow{(1) \text{LiAlH}_4} \xrightarrow{(2) \text{H}_3\text{O}^+} \begin{array}{c}
  \text{R} \quad \text{CH}_2 \quad \text{OH} \\
  \text{primary alcohol}
  \end{array}
  \]

  **Example**

  \[
  \begin{array}{c}
  \text{O} \\
  \text{phenylacetic acid}
  \end{array}
  \xrightarrow{(1) \text{LiAlH}_4} \xrightarrow{(2) \text{H}_3\text{O}^+} \begin{array}{c}
  \text{O} \\
  \text{2-phenylethanol (75%)}
  \end{array}
  \]

- The aldehyde is an intermediate in this reduction, but it cannot be isolated because it is reduced more easily than the original acid.
3) Reduction of Carboxylic Acids – Mechanism

1. LAH is a strong base, and the first step is deprotonation of the acid.

\[
\text{R–C–O–H} + \text{Li}^+ + \text{H–Al–H} \rightarrow \text{H}_2↑ + \text{R–C–O}^- + \text{Li} + \text{AlH}_3
\]

2. AlH₃ adds to the carbonyl group of the lithium carboxylate salt.

3. Elimination gives an aldehyde, which is quickly reduced to a lithium alkoxide.

4. Water protonates the alkoxide to the primary alcohol.
Reactions of Carboxylic Acids

4) Alkylation of Carboxylic Acids

- Carboxylic acids react with **two equivalents of an organolithium reagent** to give ketones

\[
\begin{align*}
\text{O} & \quad \text{R—C—O—H} & \quad \text{(1) } 2 \text{ R’—Li} & \quad \text{(2) H}_2\text{O} & \quad \text{R—C—R’} & \quad + & \quad \text{R’—H} \\
\end{align*}
\]

- The **first equivalent** of the organolithium reagent simply **deprotonates** the acid
- The **second equivalent** adds to the carbonyl to give a **stable dianion**
- Hydrolysis of the dianion (by adding water) gives the hydrate of a ketone
Reactions of Carboxylic Acids

4) Alkylation of Carboxylic Acids

- Hydrolysis of the dianion (by adding water) gives the hydrate of a ketone

\[
\begin{align*}
\text{dianion} & \quad \text{H}_2\text{O}^+ \quad \text{hydrate of ketone} \\
\text{R} = \text{C} = \text{O} \quad \text{OH} \\
\text{H}_2\text{O} & \quad \text{R} = \text{C} = \text{R'} \\
\text{hydrate of ketone} & \quad + \quad \text{H}_2\text{O}
\end{align*}
\]

Example

benzoic acid

\[
\begin{align*}
\text{benzoic acid} \quad & \xrightarrow{(1) 2 \text{CH}_3\text{CH}_2\text{Li}} \quad \text{propiophenone} \\
& \xrightarrow{(2) \text{H}_2\text{O}} \\
\end{align*}
\]
Problem #6

Show how the following ketones might be synthesized from the indicated acids, using any necessary reagents.

(a) propiophenone from propionic acid (two ways, using alkylation of the acid and using Friedel–Crafts acylation)
(b) methyl cyclohexyl ketone from cyclohexanecarboxylic acid
Reactions of Carboxylic Acids

5) Synthesis of Acid Chlorides

- The best reagents for converting carboxylic acids to acid chlorides are thionyl chloride (SOCl₂) and oxalyl chloride [(COCl)₂] because they form gaseous by-products that do not contaminate the product.

\[
\text{R-C-Cl} \quad \xrightarrow{\text{Cl-S-O}} \quad \text{Cl-C-Cl}
\]

**Examples**

\[\text{CH}_3(\text{CH}_2)_7\text{C}≡\text{C}(\text{CH}_2)_7\text{C-OH} \xrightarrow{\text{Cl-S-O}} \text{CH}_3(\text{CH}_2)_7\text{C}≡\text{C}(\text{CH}_2)_7\text{C-Cl} + \text{SO}_2↑ + \text{HCl}↑\]

oleic acid

oleoyl chloride (95%)
5) Synthesis of Acid Chlorides – Mechanism

- Oxygen atom of the acid can attack sulphur, replacing chloride

\[
\begin{align*}
\text{R-C-} & \quad \text{S-Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

- This reactive anhydride undergoes nucleophilic acyl substitution by chloride ion to give the acid chloride

\[
\begin{align*}
\text{R-C-} & \quad \text{S-Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]
Synthesis of Carboxylic Acids – Recap

1) Oxidation of Primary Alcohols and Aldehydes

- Common oxidising agents are **chromic acid** ($\text{H}_2\text{CrO}_4$) or **sodium hypochlorite** (bleach, NaOCl)

$$\text{R–CH}_2\text{–OH} \quad \xrightarrow{\text{H}_2\text{CrO}_4 \text{ (or NaOCl)}} \quad \text{R–C–H} \quad \xrightarrow{\text{H}_2\text{CrO}_4 \text{ (or NaOCl)}} \quad \text{R–C–OH}$$

\text{primary alcohol} \quad \text{aldehyde} \quad \text{carboxylic acid}

*Example*

$$\text{Ph–CH}_2\text{–CH}_2\text{–CH}_2\text{–OH} \quad \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4} \quad \text{Ph–CH}_2\text{–CH}_2\text{–C–OH}$$

3-phenylpropan-1-ol \quad 3-phenylpropanoic acid
2) Oxidative Cleavage

- **Warm, concentrated permanganate** solution cleaves the central carbon–carbon bond of **alkenes**, giving **ketones** or **acids** depending on the substitution of the double bond.

\[
\text{alkene} \xrightarrow{\text{concd. KMnO}_4} \begin{array} {c} \text{glycol (not isolated)} \\ \end{array} \rightarrow R\text{-COOH} + O=\text{C}R'
\]

- With **alkynes**, either **ozonolysis** or a vigorous **permanganate** oxidation cleaves the triple bond to give **carboxylic acids**.

\[
\text{alkyne} \xrightarrow{\text{concd. KMnO}_4 \text{ or (1) } O_3 \text{ or (2) } H_2O} \begin{array} {c} \text{(not isolated)} \\ \end{array} \rightarrow R\text{-COOH} + \text{HOOC}R'
\]
3) Oxidation of Alkylbenzenes

- Side chains of alkylbenzenes are oxidised to **benzoic acid** derivatives by treatment with **hot potassium permanganate** or **hot chromic acid**

![Chemical structure](image)

*Example*

- *p*-chloroisopropylbenzene


R(alkyl)

\[
\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{heat} \quad \text{or} \quad \text{KMnO}_4, \text{H}_2\text{O}, \text{heat}
\]

\[
\text{COOH}
\]

- a benzoic acid

\[
\text{an alkylbenzene} \\
(Z \text{ must be oxidation-resistant})
\]

- *p*-chlorobenzoic acid

**Chapter 20 – Wade - Prentice Hall**
4) Carboxylation of Grignard Reagents

• Grignard reagents add to carbon dioxide to form magnesium salts of carboxylic acids.

• Addition of dilute acid protonates these magnesium salts to give carboxylic acids.

\[
\begin{align*}
R-X & \xrightarrow{\text{ether}} R-MgX & \xrightarrow{\text{O=C=O}} R-C-O^- + MgX & \xrightarrow{H^+} R-C-OH \\
(\text{alkyl or aryl halide}) & & & \\
\end{align*}
\]

Example

bromocyclohexane \xrightarrow{\text{ether}} MgBr \xrightarrow{\text{O=C=O}} \xrightarrow{H^+} COOH
cyclohexanecarboxylic acid
5) Formation and Hydrolysis of Nitriles

- Convert an alkyl halide (or tosylate) to a carboxylic acid with an additional carbon atom by displacing the halide with sodium cyanide to give nitrile

- **Acidic or basic hydrolysis** of the nitrile gives a carboxylic acid

\[
\begin{align*}
R-\text{CH}_2-X & \xrightarrow{\text{NaCN, acetone}} R-\text{CH}_2-C≡\text{N} : \quad \text{or } H^+, \text{H}_2\text{O} \text{or } -\text{OH}, \text{H}_2\text{O} \\
& \quad \xrightarrow{} R-\text{CH}_2-\text{C}=\text{O} + \text{NH}_4^+
\end{align*}
\]

**Example**

- benzyl bromide
- phenylacetonitrile
- phenylacetic acid

- Limited to halides and tosylates that are **good S\text{N}2 electrophiles**: usually primary and unhindered
Problem #7

Show how you would synthesize the following carboxylic acids, using the indicated starting materials.

(a) oct-4-yne $\rightarrow$ butanoic acid  
(b) $trans$-cyclodecene $\rightarrow$ decanedioic acid 
(c) bromobenzene $\rightarrow$ phenylacetic acid  
(d) butan-2-ol $\rightarrow$ 2-methylbutanoic acid 
(e) $p$-xylene $\rightarrow$ terephthalic acid  
(f) allyl iodide $\rightarrow$ but-3-enoic acid
Homework – 1

Give the IUPAC names of the following compounds.
(a) CH₃CH₂C≡CCOOH   (b) CH₃CH(NH₂)CH(OH)COOH   (c) (CH₃)C≡CHCOOH

Homework – 2

Arrange each group of compounds in order of increasing acidity.
(a) phenol, ethanol, acetic acid
(b) F-COH  Cl-COH  Br-COH
Predict the products, if any, of the following reactions.

(a) \( \text{COOH} \) \( \xrightarrow{(1) \text{LiAlH}_4} \) \( \text{CH}_2\text{Br} \) \( \xrightarrow{(2) \text{H}_3\text{O}^+} \)

(b) \( \text{CH}_2\text{Br} \) \( \xrightarrow{(1) \text{NaCN}} \) \( \text{H}_3\text{O}^+, \text{heat} \)

(c) \( \text{COOH} \) \( \xrightarrow{(1) \text{SOCl}_2} \) \( \text{AlCl}_3 \)

(d) \( \text{oct-4-yne} \) \( \xrightarrow{\text{KMnO}_4, \text{H}_2\text{O}} \) (warm, concd.)

(e) \( \text{CH}_2\text{OH} \) \( \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4} \)

(f) \( \text{Ph} \) \( \xrightarrow{(1) \text{BH}_3, \text{THF}} \) \( \text{CH}_3\text{CH}_2\text{CH}==\text{COOH} \) \( \xrightarrow{(2) \text{H}_3\text{O}^+} \)
Show how you would accomplish the following multistep syntheses. You may use any additional reagents and solvents you need.

(a) $\text{PhCH}_2\text{CH}_2\text{OH} \rightarrow \text{PhCH}_2\text{CH}_2\text{COOH}$

(b) $\text{CH}_2\text{C}\text{H}_2 \rightarrow \text{CH}_3\text{COOH}$

(c) $\text{CH}_2\text{C}\text{H}_2 \rightarrow \text{CH}_2\text{COOH}$

(d) $\text{Br} \rightarrow \text{COOH}$

(e) $\text{COOH} \rightarrow \text{O}_3$  

(f) $2\times\text{C}=\text{OH} \rightarrow \text{O}$