Chapter 17

- Carboxylic Acids and Their Derivatives
  Nucleophilic Addition–Elimination
  at the Acyl Carbon
1. Introduction

- Carboxylic Acid Derivatives

- Carboxylic acid: $\text{R-COOH}$
- Acid chloride: $\text{R-COCl}$
- Acid anhydride: $\text{R-COOR'}$ $\text{R-COOR'}$
- Ester: $\text{R-COOR'}$
- Amide: $\text{R-CO-NR'$_2$}$
2. Nomenclature and Physical Properties

- Nomenclature of Carboxylic Acids and Derivatives
  - Rules
    - Carboxylic acid as parent (suffix): ending with “-oic acid”
    - Carboxylate as parent (suffix): ending with “-oate”
Most anhydrides are named by dropping the word **acid** from the name of the carboxylic acid and then adding the word “**anhydride**”

- Acid chloride as parent (suffix): ending with “−oyl chloride”
- Ester as parent (suffix): ending with “−oate”
- Amide as parent (suffix): ending with “amide”
- Nitrile as parent (suffix): ending with “nitrile”
Examples

- Ethanoic acid (acetic acid)
- Methyl propanoate
- Ethanoic anhydride (acetic anhydride)
- Ethanamide
Examples

- **Sodium benzoate**
  - Chemical structure: ![Sodium benzoate](image)
  - Formula: $\text{C}_6\text{H}_5\text{CO}_2\text{Na}$

- **Benzoyl chloride**
  - Chemical structure: ![Benzoyl chloride](image)
  - Formula: $\text{C}_6\text{H}_5\text{C}=\text{O}$

- **Ethylenenitrile**
  - Chemical structure: ![Ethylenenitrile](image)
  - Formula: $\text{C}_2\text{H}_3\text{C}≡\text{N}$

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2C. Acidity of Carboxylic Acids

\[ R\text{COOH} \]

\[ pK_a \sim 4-5 \]

- Compare
  - $pK_a$ of $\text{H}_2\text{O} \sim 16$
  - $pK_a$ of $\text{H}_2\text{CO}_3 \sim 7$
  - $pK_a$ of $\text{HF} \sim 3$
When comparing acidity of organic compounds, we compare the stability of their conjugate bases. The more stable the conjugate base, the stronger the acid.

\[
\begin{align*}
\text{CH}_3\text{COOH} & \quad 4.75 \\
\text{CH}_3\text{CH}_2\text{OH} & \quad 16
\end{align*}
\]
$\text{CH}_3\text{O} - \text{H} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{O} - \text{H}^+ + \text{H}_3\text{O}^+$

$\text{CH}_3\text{CH}_2\text{O} - \text{H} + \text{H}_2\text{O} \rightleftharpoons \text{CH}_3\text{CH}_2\text{O} - \text{H}^+ + \text{H}_3\text{O}^+$
The conjugate base $B_1$ is more stable (the anion is more delocalized) than $B_2$ due to resonance stabilization.

Thus, $A_1$ is a stronger acid than $A_2$. 
Acidity of Carboxylic Acids, Phenols and Alcohols

- $pK_a = 4.20$
- $pK_a = \sim 10$
- $pK_a = \sim 17$
Acidity of Carboxylic Acids, Phenols and Alcohols
Acidity of Carboxylic Acids, Phenols and Alcohols

\[
\text{H}_2\text{O}^+ \rightleftharpoons \text{H}_3\text{O}^+ + \text{H}_2\text{O}
\]
Acidity of Carboxylic Acids, Phenols and Alcohols

\[
\begin{align*}
\text{O} & \quad \text{H} \\
+ \quad \text{H}_2\text{O} & \quad \text{\Leftrightarrow} & \quad \text{O}^- \\
\quad & \quad + \quad \text{H}_3\text{O}^+ \\
\end{align*}
\]

(NO resonance stabilization)
Question

If you are given three unknown samples: one is benzoic acid; one is phenol; and one is cyclohexyl alcohol; how would you distinguish them by simple chemical tests?

- Recall: acidity of

\[
\begin{align*}
\text{benzoic acid} & < \text{phenol} < \text{cyclohexyl alcohol}
\end{align*}
\]
\[
\text{R} - \text{O} - \text{H} + \text{Na}^+ \overset{\text{OH}}{\longrightarrow} \text{R} - \text{O}^\text{-Na}^+ + \text{H}_2\text{O}
\]
(soluble in water)

\[
\text{C}_6\text{H}_5\text{O} - \text{H} + \text{NaOH} \overset{\text{Na}^+}{\longrightarrow} \text{C}_6\text{H}_5\text{O}^\text{-Na}^+
\]
(soluble in water)

\[
\text{C}_6\text{H}_{12}\text{O} - \text{H} + \text{NaOH} \nrightarrow \text{No Reaction}
\]
(immiscible with H\text{H}_2\text{O})
Stability of conjugate bases

$pK_a$ values:

- Chloroacetic acid: 0.70
- Dichloroacetic acid: 1.48
- Trichloroacetic acid: 2.86
- Propanoic acid: 4.76
4-Chlorobutanoic acid ($pK_a = 4.50$)

2-Chlorobutanoic acid ($pK_a = 2.85$)

3-Chlorobutanoic acid ($pK_a = 4.05$)

4-Chlorobutanoic acid ($pK_a = 4.50$)
# 2D. 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>
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<tr>
<td>HO$_2$C(CH$_2$)$_4$CO$_2$H</td>
<td>Adipic acid</td>
<td>153</td>
<td>4.4</td>
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<tr>
<td></td>
<td>Phththalic acid</td>
<td>206-208 dec</td>
<td>2.9</td>
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</table>
2J. Spectroscopic Properties of Acyl Compounds

- IR Spectra
  - The C=O stretching band occurs at different frequencies for acids, esters, and amides, and its precise location is often helpful in structure determination.
  - Conjugation and electron-donating groups bonded to the carbonyl shift the location of the C=O absorption to lower frequencies.
IR Spectra

- Electron-withdrawing groups bonded to the carbonyl shift the C=O absorption to higher frequencies.
- The hydroxyl groups of carboxylic acids also give rise to a broad peak in the 2500-3100-cm\(^{-1}\) region arising from O–H stretching vibrations.
- The N–H stretching vibrations of amides absorb between 3140 and 3500 cm\(^{-1}\).
<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Approximate Frequency Range (cm⁻¹)</th>
<th>1840</th>
<th>1820</th>
<th>1800</th>
<th>1780</th>
<th>1760</th>
<th>1740</th>
<th>1720</th>
<th>1700</th>
<th>1680</th>
<th>1660</th>
<th>1640</th>
<th>1620</th>
<th>1600</th>
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<tbody>
<tr>
<td>Acid chloride</td>
<td>1815–1785</td>
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<td>1800–1770 (conj.)</td>
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<tr>
<td>Acid anhydride</td>
<td>1820–1750</td>
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<td>1775–1720 (conj.)</td>
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<td>Ester/lactone</td>
<td>1750–1735</td>
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<td>1730–1715 (conj.)</td>
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<td>Carboxylic acid</td>
<td>~1760 or 1720–1705</td>
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<td>1710–1680 (conj.)</td>
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<td>Aldehyde</td>
<td>1740–1720</td>
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<td>1710–1685 (conj.)</td>
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<td>Ketone</td>
<td>1720–1710</td>
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<td>1685–1665 (conj.)</td>
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<tr>
<td>Amide/lactam</td>
<td>1700–1620</td>
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<tr>
<td>Carboxylate salt</td>
<td>1650–1550</td>
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</table>

*Orange bars represent absorption ranges for conjugated species.

Figure 17.2  Approximate carbonyl IR absorption frequencies. (Frequency ranges based on Silverstein and Webster, reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds, Sixth Edition*. Copyright 1998.)
Figure 17.3  The infrared spectrum of propanoic acid.
\[ ^1 \text{H NMR Spectra} \]

- The acidic protons of carboxylic acids are highly deshielded and absorb far downfield in the $\delta$ 10-12 region.

- The protons of the \( \alpha \) carbon of carboxylic acids absorb in the $\delta$ 2.0-2.5 region.
Figure 17.4 The 300-MHz $^1$H NMR spectrum of methyl propanoate. Expansions of the signals are shown in the offset plots.
13C NMR Spectra

- The carbonyl carbon of carboxylic acids and their derivatives occurs downfield in the $\delta$ 160-180 region (see the following examples), but not as far downfield as for aldehydes and ketones ($\delta$ 180-220)

- The nitrile carbon is not shifted so far downfield and absorbs in the $\delta$ 115-120 region
\[ \text{\textsuperscript{13}C NMR chemical shifts for the carbonyl or nitrile carbon atom} \]

\[ \begin{align*}
\text{H}_3\text{C} & \text{C} \quad \text{OH} & \delta 177.2 \\
\text{H}_3\text{C} & \text{C} \quad \text{OEt} & \delta 170.7 \\
\text{H}_3\text{C} & \text{C} \quad \text{Cl} & \delta 170.3 \\
\text{H}_3\text{C} & \text{C} \quad \text{NH}_2 & \delta 172.6 \\
\text{H}_3\text{C} & \text{C} \quad \text{N} & \delta 117.4
\end{align*} \]
3. Preparation of Carboxylic Acids

- By oxidation cleavage of alkenes
  - Using KMnO₄

\[
\text{Ph} \xrightarrow{\text{1. KMnO₄, OH}^-, \text{heat}} \text{Ph} \xrightarrow{\text{2. H}_3\text{O}^+} \text{Ph-} \xrightarrow{\text{OH}} \text{+ OH} \xrightarrow{\text{O}_3} \text{OH} \xrightarrow{\text{2. H}_2\text{O}_2} \text{+ OH}
\]

- Using ozonolysis
By oxidation of aldehydes & 1° alcohols

- e.g.

1. \(Ag_2O\)
2. \(H_3O^+\)

1. \(KMnO_4, OH^-, heat\)
2. \(H_3O^+\)

or

\(H_2CrO_4\)
By oxidation of alkyl benzene

(R = 1° or 2° alkyl groups)
By oxidation of benzene ring
• e.g.

1. O₃, CH₃COOH
2. H₂O₂
By hydrolysis of cyanohydrins and other nitriles

- e.g.

\[
\text{PhCH}_3 \text{CH}_3 \xrightarrow{\text{HCN}} \text{PhCH}_3 \text{CH}_3 \xrightarrow{\text{H}^+ \text{H}_2\text{O}} \text{PhCH}_3 \text{CH}_3
\]

\[
\text{CH}_3 \text{CH}_2 \text{Br} \xrightarrow{\text{HCN}} \text{CH}_3 \text{CH}_2 \text{CN} \xrightarrow{\text{H}^+ \text{H}_2\text{O, heat}} \text{CH}_3 \text{CH}_2 \text{COOH}
\]
- By carbonation of Grignard reagents
  - e.g.

\[
\begin{align*}
\text{Br} & \quad \text{Mg} \\
\text{Et}_2\text{O} & \quad \text{MgBr}
\end{align*}
\]
4. Acyl Substitution: Nucleophilic Addition-Elimination at the Acyl Carbon

This nucleophilic acyl substitution occurs through a nucleophilic addition-elimination mechanism.

(Y = leaving group, e.g. OR, NR₂, Cl)
This type of nucleophilic acyl substitution reaction is common for carboxylic acids and their derivatives.
Unlike carboxylic acids and their derivatives, aldehydes & ketones usually do not undergo this type of nucleophilic acyl substitution, due to the lack of an acyl leaving group.
Relative reactivity of carboxylic acid derivatives towards nucleophilic acyl substitution reactions

- There are 2 steps in a nucleophilic acyl substitution
  - The addition of the nucleophile to the carbonyl group
  - The elimination of the leaving group in the tetrahedral intermediate
• Usually the addition step (the first step) is the rate-determining step (r.d.s.). As soon as the tetrahedral intermediate is formed, elimination usually occurs spontaneously to regenerate the carbonyl group.
• Thus, both steric and electronic factors that affect the rate of the addition of a nucleophile control the reactivity of the carboxylic acid derivative.
● **Steric factor**

e.g.

reactivity of

\[
\begin{aligned}
\text{CH}_3\text{Cl} & > \\
\text{CH}_3\text{Cl} & > \\
\end{aligned}
\]

● **Electronic factor**

◆ The strongly polarized acid derivatives react more readily than less polar ones
• Thus, reactivity of

\[
\begin{align*}
R\overset{O}{\text{Cl}} & \quad > \quad R\overset{O}{\text{O}}\overset{O}{\text{O}}\overset{O}{\text{R}}\overset{O}{\text{R'}} \\
\text{most} & \quad \text{reactive} & \quad > \quad R\overset{O}{\text{O}}\overset{O}{\text{R}}\overset{O}{\text{R'}} & \quad > \quad R\overset{N}{\text{NR'}_2} \\
\text{least} & \quad \text{reactive}
\end{align*}
\]

• An important consequence of this reactivity

♦ It is usually possible to convert a more reactive acid derivative to a less reactive one, but not vice versa.
5. Acyl Chlorides

5A. Synthesis of Acyl Chlorides

- Conversion of carboxylic acids to acid chlorides

\[
\begin{align*}
\text{R-COOH} & \quad \rightarrow \quad \text{R-COOCl} \\
\end{align*}
\]

- Common reagents
  - \(\text{SOCl}_2\)
  - \((\text{COCl})_2\)
  - \(\text{PCl}_3\) or \(\text{PCl}_5\)
Mechanism

\[
\begin{align*}
R\text{CO}_2\text{OH} & \quad \xrightarrow{\text{Cl}^-} \quad \text{RCOCl}_2 \quad \xrightarrow{\text{Cl}^-} \quad \text{RCO}_2\text{Cl} + \text{CO}_2 + \text{CO} + \text{Cl}^- \\
\end{align*}
\]
Nucleophilic acyl substitution reactions of acid chlorides

- Conversion of acid chlorides to carboxylic acids

\[ R\text{-Cl} + \text{H}_2\text{O} \xrightarrow{\text{base}} R\text{-CO}_{2}\text{H} \]
• Mechanism

\[ \text{RCl} + \text{H}_2\text{O} \rightarrow \text{OH} \]

\[ \text{R} - \text{Cl} \text{O}^{\ominus} + \text{H} \rightarrow \text{OH} \]

\[ \text{R} + \text{OH} \rightarrow \text{R} - \text{OH} \]

\[ \text{R} - \text{OH} + \text{H} \rightarrow \text{R} - \text{OH}^{\oplus} \]

\[ \text{B} - \text{H} + \text{R} - \text{CO}_2\text{H} \rightarrow \text{R} - \text{CO}_2\text{H} \]

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Conversion of acid chlorides to other carboxylic derivatives

- **Ester**: Reaction with an alcohol (R'OH) in the presence of pyridine.
- **Amide**: Reaction with a secondary amine (R'_2NH).
- **Acid Anhydride**: Reaction with sodium hydride (NaH).

Chemical formulas:
- Ester: $R\text{CO}_2\text{OR'}$
- Amide: $R\text{CONR'}_2$
- Acid Anhydride: $R\text{C(OCR')_2}$
6. Carboxylic Acid Anhydrides

6A. Synthesis of Carboxylic Acid Anhydrides

\[
\begin{align*}
\text{RCOOH} + \text{R'Cl} + \text{PyCl}^- & \rightarrow \text{RCOOR'} + \text{PyCl}^- \\
\end{align*}
\]
\[
\begin{align*}
\text{CH}_3\text{CO}_2\text{Na}^- &+ \text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_3\text{CO}_2\text{CH}_2\text{CO}_2\text{CH}_3 + \text{Na}^+\text{Cl}^- \\
\text{Succinic acid} &\rightarrow \text{Succinic anhydride} + \text{H}_2\text{O} \\
\text{Phthalic acid} &\rightarrow \text{Phthalic anhydride} + \text{H}_2\text{O}
\end{align*}
\]
6B. Reactions of Carboxylic Acid Anhydrides

- Conversion of acid anhydrides to carboxylic acids

\[
R\text{O} \bigg\text{O} \quad \text{+ HO} \quad \xrightarrow[H^+]{\text{H}_2\text{O}} \quad R\text{O} \bigg\text{OH} \quad \text{+ HO} \quad \text{R'}\text{O} \bigg\text{O}
\]
- **Mechanism**

\[
\begin{align*}
\text{R'COOH} & \rightleftharpoons \text{R'CO}OH \\
\text{H_2O} & \rightleftharpoons \text{H}_2\text{O}^+ \\
\end{align*}
\]
Conversion of acid anhydrides to other carboxylic derivatives

\[ \text{R'OH} \rightarrow \text{ROR'} + \text{ROH} \]

\[ \text{ROR'} + \text{R'NH} \rightarrow \text{RNR'$_2$} + \text{ROO$^-$NR'$_2$H$_2$} \]
7. Esters

7A. Synthesis of Esters: Esterification

\[
\text{RCOOH} + \text{R'}OH \xrightarrow{\text{H}^+} \text{RCOOR'} + \text{H}_2\text{O}
\]
Esters from acyl chlorides

E.g.

Benzoyl chloride + EtOH + pyridine → Ethyl benzoate (80%) + pyridinium chloride
Esters from carboxylic acid anhydrides

e.g.

Acetic anhydride + Benzoyl alcohol → Benzoyl acetate + Acetic acid
7B. Base-Promoted Hydrolysis of Esters: Saponification

- Hydrolysis of esters under basic conditions: saponification

\[
\begin{align*}
\text{OR OR'} & \xrightarrow{\text{OH}^-} \text{R COO}^- + \text{R' OH} \\
\end{align*}
\]
Mechanism

\[ \text{ROR'} \rightarrow \Theta \text{OH} \]

\[ \Theta \text{OH} \rightarrow \text{ROR'} \]

\[ \text{ROR'} + \Theta \text{OH} \rightarrow \text{R'C} + \text{HO} \]

\[ \text{R'C} + \Theta \text{OH} \rightarrow \text{ROR'} \]

\[ \text{ROR'} + \text{H}^+ \rightarrow \text{R'OH} + \text{R'C} \]

\[ \text{R'C} + \Theta \text{OH} \rightarrow \text{ROR'} \]

\[ \text{ROR'} + \text{H}^+ \rightarrow \text{R'OH} + \text{R'C} \]
Hydrolysis of esters under acidic conditions

\[
R\text{OR} \xrightarrow{\text{H}^+} R\text{OH} + R'\text{OH}
\]

\[
\text{H}_2\text{O}
\]

\[
R\text{OR}'
\]

\[
R\text{O}H
\]
Mechanism

\[
\begin{align*}
R'OH & \xrightarrow{H^+} R'OH^+ \\
& \xrightarrow{H_2O} R'OH
\end{align*}
\]

\[
\begin{align*}
R'OH & \xrightarrow{H_2O} \text{esterification} \\
& \xrightarrow{R'OH} \text{hydration}
\end{align*}
\]
7C. **Lactones**

- Carboxylic acids whose molecules have a hydroxyl group on a $\gamma$ or $\delta$ carbon undergo an intramolecular esterification to give cyclic esters known as $\gamma$- or $\delta$-lactones
a δ-hydroxyacid

a δ-lactone
Lactones are hydrolyzed by aqueous base just as other esters are.

\[
\text{HA, slight excess} \quad \text{H}^+ / \text{H}_2\text{O} \quad \text{C}_6\text{H}_5\text{OH} \quad \text{C}_6\text{H}_5\text{C}_6\text{H}_5
\]

\[
\text{0}^\circ\text{C} \quad \text{HA, exactly 1 equiv.}
\]
8. Amides

8B. Amides from Acyl Chlorides

\[ \text{酰氯} + R'R''\text{NH}_2 \rightarrow \text{酰胺} \]

\[ \text{Cl}^- + R'R''\text{NH}_2 \rightarrow \text{酰胺} \]
8C. Amides from Carboxylic Anhydrides

R', R'' can be H, alkyl, or aryl.
Phthalamic anhydride + 2 NH₃ → warm H₂O → Phthalamic acid (81%) → Ammonium phthalamate (94%) → H₃O⁺ (- NH₄⁺)
Phthalamic acid $\xrightarrow{150-160^\circ C}$ Phthalimide

$+ \text{H}_2\text{O}$

(\sim 100\%)
8D. Amides from Esters

\[
\text{R' and/or R'' may be H.}
\]

e.g.

\[
\begin{align*}
\text{CH}_3\text{NH}_2 & \quad \text{heat} \\
\text{MeNH}_2 & \quad \text{heat}
\end{align*}
\]
8E. Amides from Carboxylic Acids and Ammonium Carboxylates

\[
\text{RCOOH} + \text{NH}_3 \rightleftharpoons \text{RCOONH}_4^+ \quad \text{heat} \quad \text{H}_2\text{O} + \text{RCONH}_2
\]
DCC-Promoted amide synthesis

\[ \text{RCOOH} \xrightarrow{1. \text{DCC}} \text{HCONHR'} + \text{DCU} \xrightarrow{2. \text{R'NH}_2} \text{RCO-NHR'} \]
Mechanism

Dicyclohexyl-carbodiimide (DCC)
Mechanism (Cont’d)

- **R' NH₂**
  - **R C O NHC₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**

- **proton transfer**
  - **R' NH₂**
  - **R C O NHC₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**

- **an amide**
  - **N,N'-Dicyclohexylurea (DCU)**

- **R C O NHC₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**

- **reactive intermediate**
  - **R C O NHC₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**

- **C₂H₅**
  - **C = O**
  - **C₂H₅**
  - **N = C₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**

- **H₂O**
  - **C₂H₅**
  - **C = O**
  - **C₂H₅**
  - **N = C₆H₁₁**
  - **NHC₆H₁₁**
  - **O → C**
8F. Hydrolysis of Amides

- Acid hydrolysis of amides

\[ \text{R-CONH}_2 \xrightarrow{\text{H}^+ \text{, } \text{H}_2\text{O, heat}} \text{R-COOH} + \text{NH}_4^+ \]
Mechanism

\[ \text{RCONH}_2 + \text{H}^+ \rightarrow \text{RCOOH} \]

\[ \text{RCOOH} + \text{NH}_3 \rightarrow \text{RCONH}_2 \]

\[ \text{RCONH}_2 + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{NH}_3 \]
Basic hydrolysis of amides

\[
\text{RCONH}_2 + \text{OH}^- + \text{H}_2\text{O}, \text{heat} \rightarrow \text{RCOO}^- + \text{NH}_3
\]
Mechanism

\[
\text{NH}_3 + \overset{\ominus}{\text{OH}} \leftrightarrow \overset{\ominus}{\text{O}} \overset{\ominus}{\text{H}} + \overset{\ominus}{\text{NH}_2}
\]

\[
\text{NH}_3 + \overset{\ominus}{\text{R}} \overset{\ominus}{\text{O}} \overset{\ominus}{\text{H}} + \overset{\ominus}{\text{NH}_2}
\]
8G. Nitriles from the Dehydration of Amides

This is a useful synthetic method for preparing nitriles that are not available by nucleophilic substitution reactions between alkyl halides and cyanide ions.
e.g. dehydration
Example

Synthesis of

\[ \text{1}^\circ \text{ alkyl bromide} \implies S_N2 \text{ reaction with} \]
\[ \theta \text{CN works fine} \]
But synthesis of

\[ \text{3}^\circ \text{ alkyl bromide} \Rightarrow \text{No } S_N2 \text{ reaction} \]
**Solution**

1. Mg, Et₂O
2. CO₂
3. H₃O⁺

**dehydration**

1. SOCl₂
2. NH₃
8H. Hydrolysis of Nitriles

Catalyzed by both acid and base
Examples

\[
\text{CN} \quad \xrightarrow{\text{H}_2\text{SO}_4, \Delta} \quad \text{OH}
\]

(82%)

1. NaOH, H\text{H}_2\text{O}, \Delta
2. H\text{H}_3\text{O}^+

(68%)
**Mechanism**

- **protonated nitrile**
- **amide tautomer**
- **protonated amide**
- **several steps (amide hydrolysis)**

Chemical equations:

\[
\text{R-C≡N} \quad \xleftrightarrow{\text{H}^+} \quad \text{R-C≡NH} \quad \xleftrightarrow{\text{H}^+} \quad \text{R-C≡NH} + \text{H}_2\text{O} \quad \xrightarrow{\text{slow}} \quad \text{H}^+ + \text{R-C=N}=\text{NH}_2 + \text{H}_2\text{O} \quad \xrightarrow{\text{several steps}} \quad \text{R-C=NH} \quad \xrightarrow{\text{amide hydrolysis}} \quad \text{R-COOH} + \text{NH}_4^+ \]

Ch. 17 - 83
8I. Lactams

- **α β-lactam**
- **α γ-lactam**
- **α δ-lactam**

Chemical structures of Penicillin G, Ampicillin, and Penicillin V.
9. Derivatives of Carbonic Acid

9A. Alkyl Chloroformates and Carbamates (Urethanes)

- Alkyl chloroformate

\[
\text{ROH} + \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \rightarrow \begin{array}{c}
\text{RO} \\
\text{Cl}
\end{array} + \text{HCl}
\]

alkyl chloroformate
e.g.

\[
\text{phenyl} \quad \text{OH} \quad + \quad \text{RO} \quad \text{Cl} \quad \rightarrow \quad \text{HCl} \quad + \quad \text{Benzyl} \quad \text{chloroformate}
\]

Ch. 17 - 87
Carbamates or urethanes

\[
\text{ROCl} + \text{R'}\text{NH}_2 \xrightarrow{\text{OH}^-} \text{RO-CONHR'}
\]

a carbamate (or urethane)
✧ Protection

\[ \text{R-NH}_2 + \text{benzyl chloride} \xrightarrow{\text{OH}^-} \text{protected amine} \]

✧ Deprotection

\[ \text{protected amine} \xrightarrow{\text{H}_2, \text{Pd}} \text{R-NH}_2 + \text{CO}_2 + \text{benzene} \]

\[ \text{protected amine} \xrightarrow{\text{HBr, CH}_2\text{CO}_2\text{H}} \text{R-NH}_3 + \text{CO}_2 + \text{Br-benzene} \]
10. Decarboxylation of Carboxylic Acids

**Decarboxylation**

\[ RCOOH \xrightarrow{\text{decarboxylation}} R\text{H} + CO_2 \]

100-150°C

**A β-keto acid**

\[ R\text{CH}_2\text{CH}_2\text{COOH} \xrightarrow{100-150^\circ C} R\text{CH}_2\text{CH}_2\text{CO}_2 + CO_2 \]
There are two reasons for this ease of decarboxylation:

- **β-keto acid**
  - Decarboxylation to form an enol, which can then isomerize to a ketone.

- **Acylacetate ion**
  - Decarboxylation to form a resonance-stabilized anion, which can then react with a proton to form a ketone.
11. Chemical Tests for Acyl Compounds

- Recall: acidity of

\[
\begin{align*}
\text{Acidity:} & \\
\text{Phenyl acetate} & > \text{Phenol} & > \text{Cyclohexanol}
\end{align*}
\]


\[
\text{R-CO}_2\text{H} + \text{Na}^+ \text{OH}^- \rightarrow \text{R-CO}_2\text{Na}^- + \text{H}_2\text{O}
\]

(soluable in water)

\[
\text{Ph-OH} + \text{NaOH} \rightarrow \text{Ph-ONa}^+
\]

(soluble in water)

\[
\text{Cyclohexene-OH} + \text{NaOH} \rightarrow \text{No Reaction}
\]

(immiscible with H\text{H}_2\text{O})
\[
\text{HCO}_3^- + \text{NaHCO}_3 \rightarrow \text{Na}^+ \text{CO}_2(\text{g}) + \text{H}_2\text{O} \\
\text{(gas evolved)}
\]

\[
\text{No Reaction}
\]

\[
\text{No Reaction}
\]
12. Polyesters and Polyamides: Step-Growth Polymers

Polyesters

\[
\text{HO} \quad \text{m} \quad \text{OH} \quad + \quad \text{HO} \quad \text{n} \quad \text{CO} \quad \text{OH}
\]

- H₂O

\[
\text{O} 
\]

(a polyester)
Polyamides

H₂N

N>H

O

Cl

O

Cl

N

O

H⁺

Cl⁻

N

H

O

H

O

N

H

O

(a polyamide)
Example: Nylon 66

(Nylon 66) + 2n H₂O

Applications: clothing, fibers, bearings
**Example: Dacron (Mylar)**

\[
\text{OCH}_3 \quad \text{OCH}_3 \quad + \quad n \quad \text{HO} - \text{CH}_2 - \text{OH}
\]

\[
\begin{align*}
\text{n} & \quad \text{n} \\
\text{CH}_3 & \quad \text{OCH}_3
\end{align*}
\]

\[
\text{200°C}
\]

\[
\begin{align*}
\text{O} - \text{CH}_2 - \text{O} & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O}
\end{align*}
\]

\[
\text{+ 2n CH}_3\text{OH}
\]

(Dacron)

- **Applications:** film, recording tape
13. Summary of the Reactions of Carboxylic Acids and Their Derivatives

- Reactions of carboxylic acids

- Reactions of carboxylic acids:
  1. P, X₂
  2. H₂O

- NaOH or NaHCO₃ or other bases

- R'O₅H, H⁺, Δ

- R'OH, H⁺, Δ

- SOCl₂ or PCl₃ or PCl₅

- O

- O

- O

- O

- O

- O

- O
Reactions of acyl chlorides

- R'\_2\text{NH}
- R'O
- H_2O
- R'O\text{OH}, base
- R'\text{COOH}
- base
- R'O\text{OR}'
Reactions of acyl chlorides (Cont’d)

- **Benzene**
  - **AlCl₃**

- **Acyl chloride**
  - **LiAlH₄**
  - **H₃O⁺**
  - **LiAlH(O^tBu)₃, -78°C**
  - **H₃O⁺**

- **Alcohol**
  - **H₂O**

- **Ester**
  - **R'OH**
  - **R'O**

- **Alkylation**
  - **R'MgX**
  - **H₃O⁺**

- **Carboxylic acid**
  - **R'CO₂H**
Reactions of acid anhydrides

\[
R'\text{HO} + \text{H}_2\text{O} \rightarrow R\text{OR'}
\]

\[
R\text{OH} + \text{R'O}_2\text{NH} \rightarrow R\text{NR'O}_2\text{H}_2
\]

\[
R\text{NR'O}_2\text{H}_2 + \text{R'O}_2\text{NR''}_2\text{H}_2 \rightarrow R\text{OR''} + \text{R'CO}_2\text{H}
\]
Reactions of esters

- **1.** $\text{R'H}$ (from ester hydrolysis)
  - $\text{H}_2\text{O}, \text{H}^+, \Delta$
- **2.** $\text{R'MgX}$ (from nucleophilic alkylation)
  - $\text{H}_3\text{O}^+$
- **3.** $\text{NH}_3$ (from fischer esterification)
  - $\text{R'H}$
- **4.** $\text{R''OH}$ (from nucleophilic substitution)
  - $\text{H}_2\text{O}, \text{H}^+$
- **5.** $\text{R''MgX}$ (from nucleophilic alkylation)
  - $\text{H}_3\text{O}^+$
Reactions of nitriles

1. LiAlH₄
2. H₃O⁺

R—NH₂

R—C≡N

1. LiAlH(OTBu)₃
or DIBAL, -78°C
2. H₃O⁺

R—COH

R—CO₂⁻

H⁺, H₂O, Δ

OH⁻, H₂O, Δ
Reactions of amides

\[ RCONH_2 + HNR_2' \]

1. LiAlH\(_4\)
2. H\(_3\)O\(^+\)

P\(_4\)O\(_{10}\) (P\(_2\)O\(_5\) or Ac\(_2\)O, D (R' = H only)

\[ R-CN \]