SECTION 20 – CARBOXYLIC ACID DERIVATIVES and NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

20-1 -- General Classes and Nomenclature of Carboxylic Acid Derivatives
- Acid Halides (“Alkanoyl Halides”)
- Acid Anhydrides
- Esters: Straight-Chained Esters and Cyclic Esters (“Lactones”)
- Amides (“Alkanamides”; 1°, 2°, and 3°)
- Cyclic Amides (“Lactams”)
- Imides – 2 Fused Amides
- Nitriles, R-ĊN: (“Alkanenitriles”)

20-5 -- Priority Order of Principle Groups in Carboxylic Acid Derivatives
- Main Chain vs. Substituents (“Branches”)
- Some Common Substituents

20-5 -- Structures, Properties, & Spectroscopy of Carboxylic Acid Derivatives
- Esters Prefer to be Planar (Z-conformation vs. E-conformation)
- IR Spectroscopy of Esters
- IR Spectroscopy of Acid Anhydrides (asymmetric stretch & symmetric stretch)
- Amides Prefer to be Planar
- IR and ¹H NMR for Amides

20-8 -- Reactions of Carboxylic Acid Derivatives (BIG TOPIC) – thru p.20-26
- The Mechanism of Acyl Substitution Reactions Under Basic Conditions
- The Mechanism of Acyl Substitution Reactions Under Acidic Conditions
- Tetrahedral Intermediates, Reaction Rates, and Relative Stabilities
- Relative Reactivities of Carboxylic Acid Derivatives

20-9 -- Hydrolysis Reactions (Addition of H₂O)
- Acid Halides + H₂O → ?
- Acid Anhydrides + H₂O → ?
- Esters (and Lactones) + H₂O → ? (acid-catalyzed vs. base-catalyzed)
- Amides (and Lactams) + H₂O → ? (acid-catalyzed vs. base-catalyzed)
- Nitriles + H₂O → ?

20-12 -- Reactions with Nucleophiles Other than Water
- Acid Chlorides → Esters (via use of Pyridine)
- Acid Chlorides → Amides
- Acid Chlorides → Anhydrides (involves use of a Carboxylate Salt)
- Mixed Anhydrides
- Dehydration of 2 Carboxylic Acids Produces an Anhydride
- Anhydrides → Esters
• Cyclic Anhydrides → One Half-Ester + One Half-Acid
• Transesterification: Converting One Ester to Another Ester
• Transesterification can be Acid-Catalyzed or Base-Catalyzed
• Esters → Amides
• Acids → Acid Chlorides
• Use of SOCl₂ (Thionyl Chloride) and PCl₃ or PBr₃
• Acids → Anhydrides (via use of P₂O₅)
• Acids → Esters (via acid-catalyzed mechanism only)

20-19 -- Summary of Carbonyl Substitution Reactions

20-19 -- Reactions of –COOH Derivatives with Carbanionic Nucleophiles, “:R”
• R-MgX (Grignard Reagent), R-Li (Alkylithium Reagent), and R₂CuLi Reagent
• Acid Chlorides + Carbanionic Nucleophiles → ?
• Esters + Carbanionic Nucleophiles → ?
• Carboxylic Acids + Carbanionic Nucleophiles → ?

20-21 -- Reactions with Hydride Equivalents (“:H”) as Nucleophiles
• “Reductions”
• LiAlH₄ (Lithium Aluminum Hydride) and NaBH₄ (Sodium Borohydride)
• Acid Chlorides → Alcohols or Aldehydes
• Use of LiAlH(ÔBu)₃ – Bulkier Version of LiAlH₄
• Anhydrides → 2 Alcohols
• Esters → Alcohols or Aldehydes
• Use of DIBAH (Diisobutylaluminum hydride)
• Acids → Alcohols (via LiAlH₄ or borane, BH₃)
• Amides → Amines (using LiAlH₄)

20-26 – The Chemistry of Nitriles, R-CEN:
• Preparation of Nitriles (via S₂N₂, or P₂O₅, or SOCl₂, or POCl₃)

20-26 – Reactions of Nitriles
• Reduction with LiAlH₄ or DIBAH
• Reduction with Grignard Reagent (R′-MgX)
General Classes and Nomenclature - "Carboxylic Acid Derivatives"

1. **Acid Halides.**
   - **Alkanoyl halide** (IUPAC)
   - \[ \text{ex: } \text{CH}_3\text{C} = \text{Cl} \rightarrow \text{acetyl chloride (common name)} \]
   - or
   - **ethanoyl chloride** (IUPAC)
   - \[ \text{ex: } \text{CH}_2\text{C} = \text{Cl} \rightarrow \text{propanoyl chloride} \]

2. **Acid Anhydrides.**
   - \[ \text{ex: if } R = R' = \text{-CH}_3, \text{ then it's acetic anhydride.} \]
   - \[ \text{ex: } \text{CH}_3\text{CH}_2\text{C} = \text{Pr} \rightarrow \text{propanoic butanoic anhydride.} \]

3. **Esters.**
   - a) Straight-chained esters
   - b) Cyclic esters

\{ covered on next page... \}
a). **Straight-Chain Esters.**

- "Esters" \[ \overset{0}{\text{O}} \text{C}_\text{o} \text{R}^\prime \] named as alkyl carboxylates ("alkyl alkanoate")

- See the difference?
  - \[ \text{ex: } \text{CH}_3\text{CH}_2\overset{0}{\text{C}_\text{o}}\text{CH}_3 \rightarrow \text{methyl propanoate} \]
  - \[ \text{ex: } \text{CH}_3\text{CH}_2\overset{0}{\text{O}} \text{CH}_3 \rightarrow \text{ethyl acetate} \]
  - \[ \text{ex: } \overset{0}{\text{O}} \text{C}_\text{o} \rightarrow \text{phenyl acetate} \] \[ \rightarrow \text{not a cyclic ester!} \]
  - \[ \rightarrow \text{because "ester part" is not in the ring.} \]

b). **Cyclic Esters**

- Called "lactones" \[ \rightarrow \text{designated } \alpha, \beta, \gamma, \text{ etc. according to the point of attachment of ring } \overset{0}{\text{O}} \text{ to the carbon chain.} \]

- \[ \text{ex: } \overset{\gamma}{\text{O}} \overset{\beta}{\text{Y}} \overset{\gamma}{\text{Y}} \rightarrow \alpha \overset{\gamma}{\text{Y}} \text{ lactone} \]
  - "gamma"

- \[ \text{ex: } \overset{\alpha}{\text{O}} \rightarrow \alpha \overset{\delta}{\text{Y}} \text{ lactone} \]
  - "delta"
Amides ⇒ \[
\begin{array}{c}
\text{R-C-N} \\
\text{I}
\end{array} \]

= "alkanamide"

a). Straight-chained amides:

can be 1\textsuperscript{o} amide, 2\textsuperscript{o} amide, or 3\textsuperscript{o} amide (primary), (secondary), or (tertiary)

\[
\begin{align*}
\text{R-C-NH}_2 & \quad \text{R-C-NH-R'} \\
\text{R-C-C-N} & \quad \text{R-C-N-R'}
\end{align*}
\]

\[
\begin{align*}
\text{ex: CH}_3\text{CH}_2\text{CH}_2-C-NH_2 & \rightarrow \text{butanamide} \\
(1\textsuperscript{o} \text{ amide})
\end{align*}
\]

\[
\begin{align*}
\text{ex: } & \quad \text{denotes that ethyl group} \\
& \quad \text{is "off the N".}
\end{align*}
\]

\[
\begin{align*}
\text{ex: N-ethylpropanamide} & \rightarrow \text{propanamide part} \\
(2\textsuperscript{o} \text{ amide})
\end{align*}
\]

\[
\begin{align*}
\text{ex: } & \quad \text{N,N-diethylpropanamide} \\
& \quad (3\textsuperscript{o} \text{ amide})
\end{align*}
\]

\[
\begin{align*}
\text{ex: } & \quad \text{cyclopentanecarboxamide} \\
& \quad \text{NOT a "cyclic amide" -- see next page...}
\end{align*}
\]
b) Cyclic Amides.
   \[ \text{called "lactams" - named exactly like lactones} \]

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{N}\\
\text{H}\\
\text{H}
\end{array}
\end{array} \rightarrow \alpha \beta-\text{lactam} \]
\[ \beta-\text{propiolactam} \]

---

c) Imides \[ \Rightarrow \] 2 fused amides:

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{N}\\
\text{H}\\
\text{H}
\end{array}
\end{array} = \text{succinimide (common name)} \]

---

5) Nitriles \[ \Rightarrow \] \[ R-\text{C} \equiv \text{N}: \]
   \[ \equiv \] "alkanenitriles"

\[ \xrightarrow{\text{can be hydrolyzed to carboxylic acids}} \]
\[ \xrightarrow{\text{via}} \left( H_3O^+ \right) \]
\[ \xrightarrow{\text{leaves in form}} \text{of } NH_3 \] (ammonia).

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{C}\\
\text{C}\\
\text{C}\\
\text{C}
\end{array}
\end{array} \rightarrow \text{hexanenitrile} \]

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{CH}_3\\
\text{C}\\
\text{C}\\
\text{C}
\end{array}
\end{array} \rightarrow \text{acetonitrile (common name)} \]
\[ \text{or} \]
\[ \text{ethanenitrile (IUPAC)} \]

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{Ph}\\
\text{C}\\
\text{C}
\end{array}
\end{array} \rightarrow \text{benzonitrile} \]

\[ \xrightarrow{\text{ex:}} \begin{array}{c}
\begin{array}{c}
\text{NC}\\
\text{C}\\
\text{C}
\end{array}
\end{array} \rightarrow \text{malononitrile (common name)} \]
\[ \text{or} \]
\[ \text{propanedinitrile (IUPAC)} \]
- The 5 classes of carboxylic acid derivatives just discussed are all principle groups:
  - in the "main chain"
  - i.e. not a substituent (branch)

**Priority Order:**

\[
\text{-COOH} > \text{-COO}^- > \text{-COOR} > \text{-CONH}_2 > \text{-CN}
\]

When named as a branch:

- **cyano**
- **hydroxy**
- **oxo**

**Example:**

\[
\text{HO-CH}_2-\text{CH(COOH)}-\text{CH}_2-\text{CH}_2\text{OH}
\]

**7-hydroxy-4-oxooctanoic acid**

\[\rightarrow \text{a carboxylic acid}\]

*Some common substituents:*

- Acetoxy branch
- Acetamide branch

**Structures, Properties, and Spectroscopy of Carboxylic Acid Derivatives:**

\[\rightarrow \text{we'll cover 3 of the 5 general classes:}\]

1. Esters
2. Anhydrides
3. Amides
1. **Esters**: prefer to be planar to satisfy (or maximize) resonance stabilization.

![Chemical structure](image)

\[ \text{Z-conformation} \]

Esters prefer planarity due to small res. structure contribution from the dipolar res. structure (the one on the right)

**Z-conformation** = slightly better than the E-configuration for steric reasons:

\[ \text{E-configuration is more sterically hindered.} \]

**IR** for esters \( \rightarrow \) C=O stretch \( \sim 1730-1750 \) cm\(^{-1} \)

2. **Acid Anhydrides**.

\( \rightarrow \) often just referred to as **"anhydrides"**

**IR** \( \Rightarrow \) 2 \( \neq 0 \) stretches. Can see 2 peaks

- a). Symmetric stretch:
  
  ![Symmetric stretch](image)

- b). Asymmetric stretch:
  
  ![Asymmetric stretch](image)

\( \Rightarrow \) combination bands at \( \sim 1760 \) cm\(^{-1} \), \( \sim 1820 \) cm\(^{-1} \)

*Note: E/Z chemistry covered in Section 5.*
Amides:

\[
\begin{array}{c}
\text{O}^+ \quad \text{O}^+ \\
\text{C} - \text{C} - \text{N}^- \\
\end{array}
\leftrightarrow
\begin{array}{c}
\text{O}^- \quad \text{O}^- \\
\text{C} - \text{C} - \text{N}^+ \\
\end{array}
\]

→ not as important, but it is a more important res. structure than analogous structure for esters on p. 20-6.

→ prefers planarity.

→ 2 bonds having "partial double bond character" make amide group planar.

* barrier for rotation around the C-N bond is relatively large (≈ 17 kcal/mol) due to partial d.b. character.

* for Z° amides, "Z-conformation" preferred:

\[
\begin{array}{c}
\text{O}^- \\
\text{R} - \text{C} - \text{N}^- \\
\text{H} \\
\end{array}
\text{vs.}
\begin{array}{c}
\text{O}^- \\
\text{R} - \text{C} - \text{N}^+ \\
\text{H} \\
\end{array}
\]

Z

\[
\text{E}
\]

steric hindrance of R+R' isn't good for stability.

* IR for amides.

\[
\begin{array}{c}
\text{C=O stretch} \\
\rightarrow
\end{array}
\sim 1650 - 1700 \text{ cm}^{-1}
\]

\[
\begin{array}{c}
\text{N-H stretch} \\
\rightarrow
\end{array}
\sim 3300 - 3400 \text{ cm}^{-1}
\]

note: 1° amides show 2 N-H bands:

\[
\begin{array}{c}
\text{H} \\
\text{N} \quad \text{H} \\
\end{array}
\text{symmetrical}
\]

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\end{array}
\text{asymmetrical}
\]
"\[ ^1H \text{NMR for amides.}\]

\[
\begin{align*}
\text{C} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{H} & \quad \delta = 7.9 \text{ ppm (broad)}
\end{align*}
\]

\text{note: } ^1H \text{ NMR was covered in section 12.}

\[ \star \star \star \text{Reactions of Carboxylic Acid Derivatives.}\]

\[ \text{HUGE Topic. } \rightarrow [A-D], \text{ pages 20-8 thru 20-26} \]

\[ \star \text{All reactions are essentially acyl substitution reactions.} \]

1) \text{mech: basic conditions.}

\[ \begin{array}{ccc}
\text{R-C} & \rightleftharpoons & \text{R-C-Y} \\
\text{nucleophile} & \rightarrow & \text{tetrahedral intermediate}
\end{array} \]

2) \text{mech: acidic conditions.}

\[ \begin{array}{ccc}
\text{R-C} & \rightleftharpoons & \text{R-C-Y} \\
\text{strong Lewis acid} & \rightarrow & \text{tetrahedral intermediate}
\end{array} \]

\[ \text{carbon becomes a lot more electrophilic} \]
tetrahedral intermediates are the highest-E forms/points of the reaction mechanism.

In general, reaction rate depends on the relative stabilities of the carbonyl comp'd and the tetrahedral intermediate.

**Note:** Groups that destabilize the carbonyl group will accelerate the reaction.

Relative Reactivities.

- Least reactive $\Rightarrow R-C=\text{N}$:

A = Hydrolysis Reactions: Water acts as the nucleophile and a carboxylic acid is formed.

1. Acid Halides $\xrightarrow{\text{H}_2\text{O}}$ very reactive. $\Rightarrow$ react even faster under basic or acidic conditions.

$$ R-C-\text{Cl} \xrightarrow{\text{H}_2\text{O}} R-C-OH + \text{HCl} \quad \text{mech. on next page...} $$
2. Anhydrides \( \xrightarrow{H_2O} \) makes two carboxylic acids in hydrolysis with water. The mechanism is identical to 1 (acid chlorides) -- see top of page.

\[
\begin{align*}
R-C=O \quad & \xrightarrow{H_2O} \quad \boxed{\begin{array}{c}
R-C-OH \\
+ \quad \boxed{\begin{array}{c}
R'-C-OH
\end{array}}
\end{array}} \\
\end{align*}
\]

3. Esters (and Lactones) \( \xrightarrow{H_2O} \)

(a) Base-catalyzed = generates carboxylate ion.

\[
R-C-OR' \xrightarrow{OH^- \text{ (H}_2\text{O)}} \boxed{\begin{array}{c}
R-C-O^{-} \\
+ \quad \text{HOR}'
\end{array}}\quad \text{(alcohol)}
\]

Mechanism:

\[
\begin{align*}
\xrightarrow{\text{OH}^-} \\
\end{align*}
\]

R-C-OR' \xrightarrow{\text{OH}^-} \boxed{\begin{array}{c}
R-C-OH \\
+ \quad \text{OR}'
\end{array}}\quad \text{(irreversible last step)}
\]

(b) Acid-catalyzed = reversible the whole way.

\[
R-C-OR' \xrightarrow{H^+ \text{ (H}_2\text{O)}} \boxed{\begin{array}{c}
R-C-OH \\
+ \quad \text{HOR}'
\end{array}}\quad \text{(alcohol)}
\]

Mechanism on the next page.

Excess of \( H_2O \) drives reaction to the right.

Excess of alcohol, or removal of \( H_2O \) drives reaction equilibrium to the left.
SECTION 20 – CARBOXYLIC ACID DERIVATIVES and NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

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