Reactions of Amines

1. **Reaction as a proton base** (Section 19-5 and 19-6)

   \[
   \text{R-NH}_2 + \text{H}^+ \rightarrow \text{R-NH}_3^+ + \text{X}^-
   \]

   - Mechanism: Required (protonation)
   - Reverse Mechanism: Required (deprotonation)
   - Amines are completely converted to ammonium salts by acids
   - Ammonium salts are completely neutralized back to amines by bases
   - Patterns in base strength: Reflect stabilization/destabilization factors for both the amine and the ammonium
     - N lone pair: \( \text{sp}^3 > \text{sp}^2 > \text{p} \)
     - For \( \text{sp}^3 \) nitrogens, \( 3^\circ > 2^\circ > 1^\circ \)

2. **Reaction with Ketones or Aldehydes** (Section 18-16,17 and 19-10)

   \[
   \text{R}^\prime \text{R} \overset{\text{aldehyde or ketone}}{\rightleftharpoons} \text{ZNH}_2, \text{H}^+ \rightarrow \text{R}^\prime \text{R} \overset{\text{HNZ}}{\rightleftharpoons} \text{H}^+, \text{-H}_2\text{O} \rightarrow \text{R}^\prime \text{R} \overset{\text{imine}}{\rightleftharpoons}
   \]

   Notes:
   - “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
   - The “aminol” can’t be isolated, it’s only present at equilibrium.
   - Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
   - Mechanism: Learned for last test (not tested this time)
   - Must have at least 2 H’s on nitrogen \( 2^\circ, 3^\circ \) amines can’t do this
1. **Alkylation of 1º Alkyl Halides** (Section 19-12, 19-21A)

   \[
   \begin{align*}
   R-NH_2 + H_2O &\rightarrow R-NH_2 + 2H_2O \\
   R-NH_2 + H_2O &\rightarrow R-NH_2 + 2H_2O \\
   R-NH_2 + H_2O &\rightarrow R-NH_2 + 2H_2O \\
   \end{align*}
   \]

   - **3a. Polyalkylation** is routine.
     - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H’s on nitrogen, examples below).
     - Mechanism required for polylalkylations. The mechanism involves repetitive sequential S$_{N}^{2}$ alkylation-deprotonations.

   \[
   \begin{align*}
   \text{Ph-NH}_2 + 3 \text{CH}_3\text{Br} &\rightarrow \text{Ph-N}_3\text{Br} \\
   \text{NH} + 2 \text{CH}_2\text{CH}_2\text{Br} &\rightarrow \text{NH}_3\text{Br} \\
   \text{Et}_3\text{N} + \text{PhCH}_2\text{Br} &\rightarrow \text{Et}_3\text{N}-\text{CH}_2\text{Ph} \text{Br} \\
   \end{align*}
   \]

   - **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
     - Mechanism for monosubstitution required. This involves simple S$_{N}^{2}$, followed by deprotonation by the excess amine.

   \[
   \begin{align*}
   \text{NH}_2 + \text{excess NH}_3 &\rightarrow \text{NH}_2 \\
   \end{align*}
   \]

2. **Acylation with Acid Chlorides** to Amides: (Section 19-13, 20-15)

   \[
   \begin{align*}
   \text{R}_1\text{R}_2\text{N}-\text{H} + \text{Cl} &\rightarrow \text{R}_1\text{R}_2\text{N} + \text{Cl} \\
   \end{align*}
   \]

   - Mechanism: Required (addition-elimination-deprotonation)
   - Amine must have at least one hydrogen to begin. But 1º, 2º, or NH$_3$ all react well.
   - But 3º amines can’t work.
   - Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H’s (triethylamine, pyridine) can be used. Or else NaOH or NaHCO$_3$ can be used.
4b. **Acylation with Carboxylic Acids** to From Amides: (Section 20-12)

\[
R_1NH \xrightarrow{\text{heat}} R_1N\overset{\text{O}}{R}R_2
\]

- **Mechanism:** Not Required
- Fairly high temperatures often required, and yields aren’t as good as with acid chlorides
- Biologically amine + acid \(\rightarrow\) amide is routine, and is facilitated by complex enzyme mechanisms

3. **Substitution for Aromatic Amines via the Diazonium Salts** ("The Sandmeyer Reaction") (Section 19-17, 18)

\[
\begin{align*}
\text{ArNH}_2 & \xrightarrow{\text{NaNO}_2, \text{HCl}} \text{ArN}_2^+\text{Cl}^- \\
& \xrightarrow{\text{CuCN}} \text{ArCN} \\
& \xrightarrow{\text{CuBr}} \text{ArBr} \\
& \xrightarrow{\text{CuCl}} \text{ArCl} \\
& \xrightarrow{\text{H}_2\text{O, H}^+, \text{heat}} \text{ArOH} \\
& \xrightarrow{\text{H}_2\text{PO}_2} \text{ArH}
\end{align*}
\]

- **Mechanism:** Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces \(N_2\), a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven’t been able to make before.
Synthesis of Amines

6. **From Aldehydes or Ketones: Reductive Amination** (Section 19-19)

\[
\begin{align*}
\text{Ketone or aldehyde} + R_2\underset{NaBH_3CN}{\longrightarrow} & \text{cat. H}^+ & R_2\text{N}_2R_3
\end{align*}
\]

- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but \(R_2\) and/or \(R_3\) can be either a carbon or a hydrogen. Thus:
  - \(\text{NH}_3 \rightarrow 1\text{o RNH}_2\)
  - \(1\text{o RNH}_2 \rightarrow 2\text{o R}_2\text{NH}\)
  - \(2\text{o R}_2\text{NH} \rightarrow 3\text{o R}_3\text{N}\)
  - \(3\text{o R}_3\text{N} \text{ don’t react}\)

7. **Via Amides**: (Section 19-20)

\[
\begin{align*}
\text{Ketone or aldehyde} + R_2\underset{NaBH_3CN}{\longrightarrow} & \text{cat. H}^+ & R_2\text{NR}_2
\end{align*}
\]

- No mechanism required for the reduction
- Access: 1º, 2º, or 3º Amines.
- \(R_1\) and \(R_2\) can be either H or C. Thus, you can produce either 1º, 2º, or 3º amines in this way:
  - \(\text{RCONH}_2 \rightarrow 1\text{o RCH}_2\text{NH}_2\)
  - \(\text{RCONHR} \rightarrow 2\text{o RCH}_2\text{NHR}\)
  - \(\text{RCONR}_2 \rightarrow 3\text{o RCH}_2\text{NR}_2\)
8. **From Amines via Amides**: (Section 19-20)

\[
\text{R}^+\text{Cl} + \text{H}_2\text{N}^\text{R}_1^\text{R}_2 \xrightarrow{\text{acylation}} \text{R}^\text{N}^\text{R}_1^\text{R}_2 \xrightarrow{\text{LiAlH}_4} \text{R}^\text{N}^\text{R}_1^\text{R}_2
\]

\[
\text{R}^\text{O} + \text{H}_2\text{N}^\text{R}_1^\text{R}_2 \xrightarrow{\text{acylation, heat}} \text{R}^\text{N}^\text{R}_1^\text{R}_2 \xrightarrow{\text{LiAlH}_4} \text{R}^\text{N}^\text{R}_1^\text{R}_2
\]

- Access: 1º, 2º, or 3º Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.

9. **Reduction of nitro compounds**: (section 19-21C)

\[
\text{Fe, HCl} \quad \text{NO}_2 \quad \text{Fe, HCl} \quad \text{NH}_2
\]

- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H₂, Ni/H₂, Pt/H₂,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).

\[
\text{R}^\text{Br} \xrightarrow{\text{excess NH}_3} \text{R}^\text{N}^\text{H}_2
\]

- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH₃ prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)

\[
\text{R}^-\text{C}=\text{N} \xrightarrow{\text{LiAlH}_4} \text{R}^-\text{NH}_2
\]

- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)

\[
\text{R}^-\text{Br} \xrightarrow{1. \text{KCN}} \text{R}^-\text{CN} \xrightarrow{2. \text{LiAlH}_4} \text{R}^-\text{N}_2
\]

- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!
### Summary of Amine Syntheses

<table>
<thead>
<tr>
<th>Route</th>
<th>Reaction Number</th>
<th>Source/ Precursor</th>
<th>Reagent</th>
<th>Available Amines</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>#6</td>
<td>Aldehydes or Ketones</td>
<td>R₂NH₂, H⁺ NaBH₃CN</td>
<td>1°, 2°, or 3° Amines</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>#7, #8</td>
<td>Amides</td>
<td>LiAlH₄</td>
<td>1°, 2°, or 3° Amines</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>#7, #8</td>
<td>Amines (via Amide)</td>
<td>1. RCOCl (or RCO₂H, heat) 2. LiAlH₄</td>
<td>1° ArNH₂</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>#7, #8</td>
<td>Acid Chlorides or Acids (via Amide)</td>
<td>1. RNH₂ 2. LiAlH₄</td>
<td>1° ArNH₂</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>#9</td>
<td>ArNO₂</td>
<td>Fe/HCl</td>
<td>1° ArNH₂</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>#10</td>
<td>1° RCH₂Br (excess)</td>
<td>NH₃</td>
<td>1° only, with CH₂ next to nitrogen</td>
<td>Original carbon chain is not extended</td>
</tr>
<tr>
<td>7</td>
<td>#12</td>
<td>1° RCH₂Br (via nitrile)</td>
<td>1. KCN or NaCN 2. LiAlH₄</td>
<td>1° only, with CH₂ next to nitrogen</td>
<td>Original carbon chain is extended by one carbon</td>
</tr>
<tr>
<td>8</td>
<td>#11</td>
<td>RCH₂CN</td>
<td>LiAlH₄</td>
<td>1° only, with CH₂ next to nitrogen</td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms
1. Protonation

\[ \text{Ph-NH}_2 + \text{HCl} \rightarrow \text{Ph-NH}_3^+ \text{Cl}^- \]

1.-Reverse. Deprotonation

\[ \text{Ph-NH}_3^+ \rightarrow \text{Ph-NH}_2 + \text{OH}^- \]

3. Polyalkylation

Ex:

\[ \text{Ph-NH}_2 + 3 \text{Br} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \]

Mech:

\[ \text{Ph-NH}_2 + \text{Br} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{OH} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \]

3b. Monoalkylation

\[ \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{Br} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{OH} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{NH}_3 \]

\[ \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{NH}_3 \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{OH} \rightarrow \text{Ph-N}^+ \text{Et} \text{Et} \text{Et}^- \text{NH}_2 \]
4. Acylation

Ex:

\[
\text{NH}_2 \text{Cl} \xrightarrow{\text{NaOH}} \text{C} \xrightarrow{\text{O}} \text{H} \text{N} \]

Mech: 3 steps: Addition-Elimination-Deprotonation
Amines versus Amides

\[
\begin{align*}
\text{amine} & \quad \text{amide} & \quad \text{ammonia} \\
\begin{array}{c}
\text{R-N-H} \\
\text{H} \\
\text{1º Amine}
\end{array} & \quad \begin{array}{c}
\text{R-N-H} \\
\text{R} \\
\text{2º Amine}
\end{array} & \quad \begin{array}{c}
\text{R-N-R} \\
\text{3º Amine}
\end{array}
\end{align*}
\]

1º, 2º, 3º classification: based on how many of the three nitrogen attachments are carbons:

- 1º Amine: \( \text{R-N-H} \)
- 2º Amine: \( \text{R-N-R} \)
- 3º Amine: \( \text{R-N-R} \)

Note: 1º, 2º, 3º has a different sense than with alcohols.

1. In an alcohol, it’s based on how many carbon groups are attached to the hydroxy-bearing carbon.
   - The alcohol oxygen always has one carbon group.
2. But in amines, it’s how many carbon groups are attached to the nitrogen itself.
   - Because the nitrogen could have 0, 1, 2, or 3 carbon groups attached.

Amines versus Ammoniums: Neutral versus protonated/cationic

\[
\begin{align*}
\text{ammonia} & \quad \text{ammonium} \\
\begin{array}{c}
\text{H-N-H} \\
\text{H} \\
\text{ammonia}
\end{array} & \quad \begin{array}{c}
\text{H-N-H} \\
\text{H} \\
\text{ammonium}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{amine} & \quad \text{ammonium} \\
\begin{array}{c}
\text{R-N-H} \\
\text{R} \\
\text{quaternary ammonium}
\end{array}
\end{align*}
\]
19.2 **Formal Amine Nomenclature:** X-alkanamine, N-alkyl-X-alkanamine, etc.
1. For core name, choose longest C-chain to which nitrogen is attached, and call it X-alkanamine
   - Number from end nearer N
   - Be sure to specify with a number which **carbon** has the nitrogen
   - The nitrogen does **not** count as a number itself.
2. Substituents on the **nitrogen** (rather than on carbon) are designated as “N-alkyl”
   - The position of substituents on a carbon are always designated by the carbon’s number
   - this is the first time we’ve had a substituent on something other than carbon, so it’s location is designated by “N-” rather than by a number
3. NH₂ as a **Substituent:** “Amino”

**Draw the structure or provide the name for the following.**

1. N-methyl-3-phenyl-2-octanamine

2. Z-3-penten-1-amine

3. 3-hexanamine

4. 

5. 

**Common Naming** (for simple amines): Alkylamine, dialkylamine, trialkylamine….

**Three Common Amine Names to Memorize (Review from Aromatics Chapter)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aniline</td>
<td><img src="image" alt="Structure" /></td>
<td>Pyridine</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Pyrrole</td>
<td><img src="image" alt="Structure" /></td>
<td>Pyrrole</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

**Some Other Famous Common Amine Names (No memory requirement)**

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrrolidine</td>
<td><img src="image" alt="Structure" /></td>
<td>Pyridine</td>
<td><img src="image" alt="Structure" /></td>
</tr>
<tr>
<td>Purine</td>
<td><img src="image" alt="Structure" /></td>
<td>Pyrimidine</td>
<td><img src="image" alt="Structure" /></td>
</tr>
</tbody>
</table>

RNA, DNA, ATP, and ADP are made from derivatives of Purine and Pyrimidine
Test Keys:
1. Understand that amino acids are the building blocks for polymeric proteins, and that the biological information is specified by the identity and sequence of the side groups.
2. Understand what form an “amino acid” exists in, depending on whether the conditions are acidic, neutral, or basic pH.
   a. Acidic pH: both are in protonated acid forms. Overall Charge: POSITIVE
   b. Neutral pH: one in acid form, the other in base form. Overall Charge: NEUTRAL
   c. Basic pH: both are in deprotonated base form. Overall Charge: NEGATIVE

19.3 Structure and Hybridization
1. N atoms are typically either sp³ hybridized (normal) or sp² hybridized
   a. sp³ is the default (when no double bonds/conjugation require a p orbital)
   b. sp² in either of two cases:
      ▪ N atom is itself double bonded
      ▪ N atom is conjugated to a double bond

2. N lone pair is either:
   a. sp³ is the default (when no double bonds/conjugation require a p orbital)
   b. sp² when the N atom is itself double bonded
      ▪ the p orbital is used to make the double bond
      ▪ the lone pair is left in an sp² hybrid
   c. p when the N atom is conjugated to a double bond but is not itself double bonded
      ▪ the lone pair sits in the p orbital so that it can overlap with the adjacent p orbital/π bond

Practice: For the nitrogens on page 10, identify the lone pair hybridization and bond angles.
19.4 Physical Properties

Key: hydrogen bond strength depends on acidity of the hydrogen and basicity of the N or O

1. **Water Solubility:** All amines hydrogen-bond water → impacts solubility
   a. Because $R_3N\cdots \text{H}_2\text{O}$ bond is stronger (due to amine lone-pair basicity) than $\text{ROH}\cdots \text{H}_2\text{O}$, amines tend to better H-bond water and are more soluble than oxygen analogs
   b. Based on basicity (the acidity of water’s hydrogen is common)

2. **Boiling Point:** $1^\circ$ and $2^\circ$ amines hydrogen bond themselves, but $3^\circ$ amines don’t
   a. Boiling point for similar mw amines: $1^\circ$, $2^\circ$ amines > $3^\circ$ amines
   b. Amines generally have lower boiling points than analogous oxygen compounds
      • Boiling point for similar mw: $\text{RCO}_2\text{H}$ > $\text{RCH}_2\text{OH}$ > $\text{RCH}_2\text{NH}_2$
   c. For boiling point, the weaker acidity of the N-H hydrogens weakens the hydrogen-bonding strength more than the greater basicity of the Nitrogen lone pair.

3. Amines stink! (ammoniums don’t)

1. **Boiling Points.** Rank the following in terms of boiling point, 1 being highest, 4 being lowest.

   ![Boiling Points](image)

2. **Water Solubility.** Rank the following in terms of water solubility, 1 being most water soluble, 5 being least water soluble.

   ![Water Solubility](image)

B. **Basicity of Amines: Reactivity of the Nitrogen Lone Pair (19.5.6)**

- The nitrogen lone pair dominates amine reactivity
- Trends in base strength, nucleophile strength, and redox strength follow similar patterns, based on lone pair stability/reactivity

Neutral amine bases are stronger than:
1. Neutral oxygens (water, alcohol, ketones…)
2. Carboxylate anions (resonance stabilized)

Neutral amine bases are weaker than:
1. Anionic hydroxide or alkoxides
2. Anionic nitrogen or carbon bases
### Acidity/Basicity Table 19.1: Neutral Acids and Anionic Bases

<table>
<thead>
<tr>
<th>Class</th>
<th>Neutral Acid Structure</th>
<th>$K_a$</th>
<th>Acid Strength</th>
<th>Anion Base</th>
<th>Base Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Acids</td>
<td>H-Cl, H$_2$SO$_4$</td>
<td>$10^2$</td>
<td></td>
<td>Cl$^-$, HO-SO$_3^-$</td>
<td></td>
</tr>
<tr>
<td>Carboxylic Acid</td>
<td>R-COOH</td>
<td>$10^{-5}$</td>
<td></td>
<td>R-COO$^-$</td>
<td></td>
</tr>
<tr>
<td>Phenol</td>
<td>phenol</td>
<td>$10^{-10}$</td>
<td></td>
<td>phenol$^-$</td>
<td></td>
</tr>
<tr>
<td>1,3-Dicarbonyl</td>
<td>O=CH$_2$OMe</td>
<td>$10^{-12}$</td>
<td></td>
<td>O=CH$_2$O$^-$</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>HOH</td>
<td>$10^{-16}$</td>
<td></td>
<td>HO$^-$</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>ROH</td>
<td>$10^{-17}$</td>
<td></td>
<td>RO$^-$</td>
<td></td>
</tr>
<tr>
<td>Ketones and Aldehydes</td>
<td>O$_\alpha$H</td>
<td>$10^{-20}$</td>
<td></td>
<td>O$_\alpha$</td>
<td></td>
</tr>
<tr>
<td>Amine (N-H)</td>
<td>(iPr)$_2$N-H</td>
<td>$10^{-33}$</td>
<td></td>
<td>(iPr)$_2$N$^-$Li$^+$</td>
<td></td>
</tr>
<tr>
<td>Alkane (C-H)</td>
<td>RCH$_3$</td>
<td>$10^{-50}$</td>
<td></td>
<td>RCH$_2$</td>
<td></td>
</tr>
</tbody>
</table>

**Quick Checklist of Acid/Base Factors**
1. Charge
2. Electronegativity
3. Resonance/Conjugation
4. Hybridization
5. Impact of Electron Donors/Withdrawers
6. Amines/Ammoniums

- When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.
- When a neutral acids are involved, it’s often best to draw the conjugate anionic bases, and to think from the anion stability side.
## Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases

<table>
<thead>
<tr>
<th>Class</th>
<th>Structure</th>
<th>$K_a$</th>
<th>Acid Strength</th>
<th>Base</th>
<th>Base Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Acids</td>
<td>H-Cl, H$_2$SO$_4$</td>
<td>$10^2$</td>
<td></td>
<td>$\text{Cl}^-$, H$_2$O-$\text{SO}_4^-$</td>
<td>Smell Awful!</td>
</tr>
<tr>
<td>Hydronium</td>
<td>H$_3$O$^+$, ROH$^+$</td>
<td>$10^0$</td>
<td></td>
<td>H$_2$O, HOR</td>
<td>Humans</td>
</tr>
<tr>
<td>Carboxylic Acid</td>
<td>R-(\text{O})</td>
<td>$10^{-5}$</td>
<td></td>
<td>R-(\text{O}^-)</td>
<td>Cuz</td>
</tr>
<tr>
<td>Phenol</td>
<td>(\text{O})-(\text{OH})</td>
<td>$10^{-10}$</td>
<td></td>
<td>(\text{O}^-)-(\text{Ph})</td>
<td>People</td>
</tr>
<tr>
<td>Ammonium Ion (Charged)</td>
<td><img src="image" alt="" /></td>
<td>$10^{-12}$</td>
<td>Charged, but only weakly acidic!</td>
<td>Neutral, but basic</td>
<td>Against</td>
</tr>
<tr>
<td>Water</td>
<td>HOH</td>
<td>$10^{-16}$</td>
<td></td>
<td>HO$^-$</td>
<td>Working</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ROH</td>
<td>$10^{-17}$</td>
<td></td>
<td>RO$^-$</td>
<td>Are</td>
</tr>
<tr>
<td>Ketones and Aldehydes</td>
<td>O-(\alpha)-H</td>
<td>$10^{-20}$</td>
<td></td>
<td>O-(\alpha)</td>
<td>Kingdoms</td>
</tr>
<tr>
<td>Amine (N-H)</td>
<td>(iPr)$_2$N-H</td>
<td>$10^{-33}$</td>
<td></td>
<td>(iPr)$_2$N$^-\text{Li}^+$</td>
<td>Animal</td>
</tr>
<tr>
<td>Alkane (C-H)</td>
<td>RCH$_3$</td>
<td>$10^{-50}$</td>
<td></td>
<td>RCH$_2^-$</td>
<td>All</td>
</tr>
</tbody>
</table>

Notes to remember

1. Average neutral amine a thousand billion times **more basic than a neutral oxygen** (electronegativity factor)
2. An average neutral amine is thousands of times **less basic than** non-resonance stabilized hydroxide or alkoxide anions (charge factor)
3. But average neutral amine **millions** of times **more basic** than highly resonance-stabilized carboxylate anion (resonance factor trumps charge factor in this case)
4. **Ammonium cations** are million of times **less acidic than** neutral carboxylic acids, but are **more acidic than neutral water/alcohol**!
5. Neutral amine can completely deprotonate carboxylic acids, but not water or alcohols.
6. Therefore hydroxide can deprotonate ammoniums, but carboxylates cannot.
More Detailed Discussion of Acid/Base Patterns/Factors to remember

1. Charge
   - Nonfactor on Table 19.1, since all of the “acids” have the same charge (neutral)
   - In Table 19.1, all of the “bases” have the same charge (anion, single negative charge)
   - Normally, all else equal, cations are more acidic than neutrals, and anions more basic than neutrals. (See Table 19.2)

2. Electronegativity:
   - Acidity: \( \text{H-X (halogen)} > \text{H-O} > \text{H-N} > \text{H-C} \)
     - Basicity: \( X^\ominus < O^\ominus < N^\ominus < C^\ominus \)
     - Anion Stability: \( X^\ominus > O^\ominus > N^\ominus > C^\ominus \)

3. Resonance/Conjugation:
   - Oxygen Series:
     - Acidity: sulfuric acid > carboxylic acid > phenol > alcohol
     - Anion Basicity: \( \text{HO-S-O} < \text{O-O} < \text{C} < \text{N} \)
     - Anion Stability: \( \text{HO-S-O} > \text{O-O} > \text{C} > \text{N} \)
   - Carbon Series:
     - Acidity: 1,3-dicarbonyl > ketone (monocarbonyl) > alkane
     - Anion Basicity: \( \text{O-O} < \text{O-O} < \text{O-O} \)
     - Anion Stability: \( \text{O-O} > \text{O-O} > \text{O-O} \)
   - Nitrogen Series:
     - Acidity: amide > amine
     - Anion Basicity: \( \text{O-N-H} < \text{N-H} \)
     - Anion Stability: \( \text{O-N-H} > \text{N-H} \)
   - Note: Resonance is often useful as a tiebreaker (for example, molecules in which both have O-H bonds and both have equal charge, so that neither the charge factor nor the electronegativity factor could predict acidity/basicity)
   - NOTE: Resonance can sometimes (not always) trump electronegativity or even charge.
     - Example of resonance versus electronegativity: a C-H with carbonyl resonance (ketone/enolate case) is more acidic than an N-H with no resonance help but less acidic than an O-H with no resonance help. A C-H with two carbonyl resonances (a 1,3-dicarbonyl case) is more acidic than even an O-H that has no resonance help.
Example of resonance versus charge: A carboxylate anion, with serious resonance stabilization, ends up being so stabilized that it is even less basic than a neutral, uncharged amine! A hydrogen sulfate anion from sulfuric acid is less basic than not only neutral amines but also neutral oxygen (water, etc.)

4. Hybridization:
   - For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$

   ![Hybridization Diagram](Diagram.png)

   - This means that for acidity, alkynes > alkenes > alkanes

5. Electron donating/electron withdrawing substituents:
   - Electron withdrawing substituents will stabilize negatively charged anions, but will destabilize positively charged cations.
     - This means a withdrawer will increase the acidity of a neutral acid because it will stabilize the resulting anion.
     - This means a withdrawer will decrease the basicity of a neutral base because it will destabilize the resulting cation
   - Electron donating substituents will stabilize positively charged cations, but will destabilize negatively charged anions.
     - This means a donor will increase the basicity of a neutral base because it will stabilize the resulting cation. The resulting cation will be less acidic.

   ![Electron Donating/Electronic Withdrawing Substituents](Diagram.png)

   - This means a donor will decrease the acidity of a neutral acid because it will destabilize the resulting anion, and will increase the basicity of the anion

6. Ammonium Cations as Acids and Neutral Amines as Bases
   - Neutral amines are more basic than any neutral oxygen (electronegativity factor)
   - Neutral amines are less basic than most anionic oxygens, including alkoxides, hydroxides (charge factor)
   - However, neutral amines are more basic than highly resonance-stabilized carboxylate anions (in this case, resonance factor trumps the charge factor).
Table 9.3  Relative Basicity of Different Classes of Neutral Nitrogen Compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure of Amine Base</th>
<th>Base Strength</th>
<th>Lone Pair Hybrid</th>
<th>Impact On Base Strength</th>
<th>Structure of Ammonium Acid</th>
<th>$K_a$</th>
<th>Acid Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH</td>
<td>P</td>
<td>Aromatic, Conjugated</td>
<td>Decrease</td>
<td>$\text{NH}_2$</td>
<td>$10^1$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$\text{O} \text{NH}_2$</td>
<td>P</td>
<td>Conjugated, Electron-Withdrawing Carbonyl</td>
<td>Decrease</td>
<td>$\text{NH}_3$</td>
<td>$10^5$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NH$_2$</td>
<td>P</td>
<td>Conjugated</td>
<td>Decrease</td>
<td>$\text{N}_3$</td>
<td>$10^{-4}$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>sp$^2$</td>
<td>Reference</td>
<td></td>
<td>$\text{NH}_3$</td>
<td>$10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NH$_3$</td>
<td>sp$^3$</td>
<td>Reference</td>
<td>$\text{NH}_4$</td>
<td>$10^{-9.3}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>EtNH$_2$</td>
<td>sp$^3$</td>
<td>Alkyl Donor</td>
<td>Increase</td>
<td>$\text{EtNH}_3$</td>
<td>$10^{-10.6}$</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Et$_2$NH</td>
<td>sp$^3$</td>
<td>Alkyl Donor</td>
<td>Increase</td>
<td>$\text{Et}_2\text{NH}_2$</td>
<td>$10^{-10.8}$</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Et$_3$N</td>
<td>sp$^3$</td>
<td>Alkyl Donor</td>
<td>Increase</td>
<td>$\text{Et}_3\text{NH}$</td>
<td>$10^{-11.0}$</td>
<td></td>
</tr>
</tbody>
</table>

**General Amine Basicity Patterns.**

a. Relative basicity correlates Lone pair hybridization: sp$^3$ (entries 5-8) > sp$^2$ (entry 4) > p (entries 1-3) (hybridization factor)
b. Within the sp$^3$ amines, increasing alkyl substitution increases basicity (entries 5-8): $3^\circ > 2^\circ > 1^\circ > \text{NH}_3$ (electron donating group factor)

to: patterns (a) and (b) essentially cover everything.

c. Amides are much less basic than amines, or even other nitrogens with p-lone pairs (less than amines reflects hybridization and conjugation; amides are less basic than other p-hybrid conjugated lone pairs because or the electron-withdrawing group factor).
d. Conjugated nitrogens are in general less basic than isolated nitrogens (both hybridization and conjugation factors)

- Note: The **acidity of conjugate ammonium cations (conjugate acids relative to the amines) is directly and inversely related to the basicity of the neutral amines**.
- **Key:** remember patterns (a) and (b) above. That should help you solve relative basicity problems. If given ammoniums, draw the related conjugate neutral amines, rank them as bases, and realize that the strongest amine base relates to the weakest ammonium acid.
- You should be able to handle any ranking problems involving either amines as bases or their conjugate ammoniums as acids. This should include relative to non-nitrogen acids and bases.
Explanation for Basicity Pattern: Acidity/Basicity is an equilibrium measurement, and thus reflects both product stability and starting material stability.

- Anything that **stabilizes the cation increases the basicity** of the nitrogen
- Anything that **destabilizes the cation decreases the basicity** of the nitrogen
- Anything that **stabilizes the amine decreases the basicity** of the nitrogen (especially if that stabilizing factor is sacrificed upon protonation)
- Anything that **destabilizes the amine** increases it’s basicity
- When lone pair is p, that always reflects stabilizing conjugation and reduced basicity. This is the origin of both the p-hybridization factor and the resonance/conjugation factor.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conjugate Cation</th>
<th>Substituent And it’s Impact</th>
<th>Why: Which Side Is Stabilized or Destabilized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>NH₃</td>
<td>NH₄⁺</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>6-8</td>
<td>Et₃N</td>
<td>Et₃NH⁺</td>
<td>Alkyl Groups Increase Basicity</td>
<td>Cation side stabilized by alkyl groups (electron donors, cation stabilizers)</td>
</tr>
<tr>
<td>1</td>
<td>NH₂</td>
<td>NH₂⁺NH₂</td>
<td>Being part of Aromatic ring Reduces Basicity</td>
<td>Neutral side is stabilized by aromaticity. (Aromaticity is lost following protonation.)</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>NH₃</td>
<td>Acyl/Amide Conjugated To Carbonyl</td>
<td>Neutral side is stabilized by conjugation to the carbonyl. That conjugation is lost following protonation. Second, the cation side is destabilized by the strongly electron withdrawing carbonyl group.</td>
</tr>
<tr>
<td>3</td>
<td>NH₂</td>
<td>NH₃</td>
<td>Conjugated To Aromatic</td>
<td>Neutral side is stabilized by conjugation. (That conjugation is lost following protonation.)</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>N⁺H</td>
<td>Aromatic. Part of Aromatic Ring</td>
<td>Amine side is stabilized by the sp² hybridization of the lone pair. An sp² lone pair is shorter than an sp³ orbital. The shorter sp² orbital means the electrons are nearer and held more tightly by the nitrogen nucleus, and are thus more stable.</td>
</tr>
</tbody>
</table>
Choose the More Acidic for Each of the Following Pairs: Single Variable Problems

1. \( \text{NH}_3 \) \( \oplus \text{NH}_4 \)

2. \( \text{HO}_2 \) \( \text{HO} \)

3. \( \text{OH} \) \( \text{NH}_2 \)

4. \( \text{OH} \) \( \text{OH} \)

5. \( \text{NH}_2 \text{C}_3 \) \( \text{NH}_2 \)

6. \( \text{PhNO}_2 \) \( \text{PhOCO} \)

Choose the More Basic for Each of the Following Pairs (Single Variable)

7. \( \text{NH}_3 \) \( \text{NaNH}_2 \)

8. \( \text{NaOH} \) \( \text{H}_2\text{O} \)

9. \( \text{NH}_3 \) \( \text{H}_2\text{O} \)

10. \( \text{PhO} \) \( \text{PhC} \)

11. \( \text{PhNO}_2 \) \( \text{PhOCO} \)

12. \( \text{NH}_2 \text{NH}_3 \) \( \text{O}_2\text{N-NH}_2 \)

Choose the More Basic for Each of the Following (Multiple Variables, apples and oranges…)

13. \( \text{NH}_3 \) \( \text{O}^- \)

14. \( \text{O}^- \) \( \text{PhC}^- \)

15. \( \text{O}^- \) \( \text{PhOCO} \)
Choose the More Basic for Each of the Following Pairs

16. \( \text{NH}_3 \) \( \text{NaNH}_2 \)

17. \( \text{NH}_3 \) \( \text{NaOH} \)

18. \( \text{NH}_3 \) \( \text{H}_2\text{O} \)

19. \( \text{NH}_3 \) \( \text{CH}_3\text{OH} \)

20. \( \text{NH}_3 \) \( \text{O}^- \)

21. \( \text{NH}_3 \) \( \text{Cl}^- \text{ or } \text{HO}-\text{SO}_3^- \)

22. \( \text{NH}_3 \) \( \text{CH}_3\text{MgBr} \)

23. \( \text{NH}_3 \) \( \text{CH}_3\text{NH}_2 \)

24. \( \text{NH}_3 \) \( \text{CH}_3\text{NH}_2 \)

25. For the following sets of bases, rank them, 1 being the most basic.

a. \( \text{CH}_3\text{MgBr} \) \( \text{CH}_3\text{NHNa} \) \( \text{CH}_3\text{NH}_2 \) \( \text{CH}_3\text{OH} \)

b. \( \text{O}^- \) \( \text{CH}_3\text{NH}_2 \) \( \text{OH} \)
26. **Amine Basicity**. For the following pairs or sets of bases, rank them, 1 being the most basic.

a. ![Structure](image1.png)

b. ![Structure](image2.png)

c. benzamide [PhC(O)NH₂]  aniline (PhNH₂)  pyridine  triethylamine

d. triethylamine  ethylamine  ammonia

e. dimethylamine  methylamine  aniline (PhNH₂)

f. ![Structure](image3.png)

g. ![Structure](image4.png)

h. triethylamine  NaOH

i. methanol  methylamine  methane

j. CH₃MgBr  CH₃NHNa  CH₃ONa  CH₃NH₂  CH₃CO₂Na  CH₃OH
27. Rank the acidity of the following compounds, 1 being most acidic.

a. \( \text{H}_3\text{O}^+ \) \( \text{NH}_4^+\text{Cl}^- \) water \( \text{acetic acid (CH}_3\text{CO}_2\text{H}) \) \( \text{NH}_3 \)

b. \( \text{H}_3\text{O}^+ \) \( \text{acetic acid (CH}_3\text{CO}_2\text{H}) \) \( \text{Me}_3\text{NH}^+\text{Cl}^- \) ethanol

c. \( \text{NH}_4^+\text{Cl}^- \) \( \text{Me}_3\text{NH}^+\text{Cl}^- \) \( \text{PhNH}_3^+\text{Cl}^- \)

28. Suppose all of the molecules A-D are dissolved in diethyl ether.

a. Which one or ones will extract (dissolve) into aqueous sodium hydroxide? (And why?)

b. Which, if any, will extract into aqueous hydrochloric acid? (And why?)

c. Which, if any, will extract into neutral water? (Why or why not?)

d. Explain how you could use an extraction scheme to separate D from A.
C. Reactions of Amines (other than as bases)

2. Reaction with Ketones or Aldehydes (Section 19.10)

\[
\text{R'OH} + \text{ZNH}_2 \xrightarrow{\text{H}^+} \text{R'NHz} \xrightarrow{\text{H}^+, \text{H}_2\text{O}} \text{R'N=Z} \xrightarrow{\text{H}^+, \text{H}_2\text{O}} \text{R'N=Z} + \text{H}_2\text{O}
\]

Notes:
- “Z” can be a carbon, nitrogen, oxygen, or hydrogen atom/group.
- The “aminol” can’t be isolated, it’s only present at equilibrium.
- Equilibrium factors apply. Water drives to the carbonyl side; removal of water drives to the imine side.
- Mechanism: Learned for last test (not tested this time)
- Must have at least 2 H’s on nitrogen \( \rightarrow \) 2º, 3º amines can’t do this

Draw the Products of the following Amine reactions.

1. \( \text{PhNH}_2 + 4\text{-phenyl-2-hexanone, H}^+ \)

2. \( \text{Cyclohexanone + H}_2\text{NNH}_2 \)

3. Alkylation of 1º Alkyl Halides (Section 19.12)

- 3a. Polyalkylation is routine.
  - With excess alkyl halide and base, keep on alkylating until it becomes the quaternary ammonium salt (no surviving H’s on nitrogen, examples below).
  - Mechanism required for polyalkylations. The mechanism involves repetitive sequential S\(_\text{N}2\) alklylation-deprotonations.

\[
\text{PhNH}_2 + 3\text{CH}_3\text{Br} \xrightarrow{\text{NaHCO}_3} \text{PhNCH}_3\text{CH}_3 \xrightarrow{\text{H}_3\text{C}} \text{PhNCH}_3\text{CH}_3 \xrightarrow{\text{Br}} \]

Notes

1. All amines are nucleophilic
   - 3° > 2° > 1° > NH₃
   - structural effects parallel basicity
2. Limited synthetic utility, due to frequent overalkylation
3. Due to Sₜₙ₂ mechanism, limited to alkylation of 1° R-X

- **3b. Monosubstitution** is possible when excess ammonia (or other cheap amines) is used.
  - Mechanism for monosubstitution required. This involves simple Sₜₙ₂, followed by deprotonation by the excess amine.

Synthetically Useful Alkylation Scenarios:
1. Exhaustive Alkylation to Intentionally produce quaternary ammonium salts
2. Reaction 10. **From 1° Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A)

Draw the Products and mechanisms of the following Amine reactions.

1. Me₃N + PhCH₂I
2. Ph- NH₂ NaOH
Draw the Products and mechanisms of the following Amine reactions.

1. \[
\text{PhCH}_2\text{Br} \quad \xrightarrow{\text{Excess NH}_3} \quad \text{H}_2\text{N} - \text{Br}
\]

2. \[
\text{NaOH} \quad \xrightarrow{\text{H}_2\text{N} - \text{Br}}
\]

Why do you not get clean monoalkylation if you do a 1:1 mixture of RNH\textsubscript{2} and R-X?

4. **Acylation with Acid Chlorides** to From Amides: (Section 19-13, 20-15)

\[
\text{R}_1\text{N} - \text{R}_2 \quad \xrightarrow{\text{Cl}_2\text{O}} \quad \text{R}_1\text{N} - \text{R}_2
\]

- Mechanism: Required (addition-elimination-deprotonation)
- Amine must have at least one hydrogen to begin. But 1º, 2º, or NH\textsubscript{3} all react well.
- But 3º amines can’t work.
- Some base is required for the deprotonation step and to absorb the HCl. For cheap amines, excess amine can simply be used. Alternatively, amines with no H’s (triethylamine, pyridine) can be used. Or else NaOH or NaHCO\textsubscript{3} can be used.

\[
\text{NH}_2 \quad \xrightarrow{\text{Cl}_2\text{O}} \quad \text{O}
\]

Mech: 3 steps: Addition-Elimination-Deprotonation
Draw the Products of the following Amine reactions, and the mechanism for the first one.

1. $\text{PhNH}_2 + \text{ClO}_2 \xrightarrow{\text{NaOH}}$  

2. $\text{PhCl} + \text{N-methylbutanamine} \xrightarrow{\text{NaHCO}_3}$

4b. **Acylation with Carboxylic Acids** to Form Amides: (Section 20-12)

- Mechanism: Not Required
- Fairly high temperatures often required, and yields aren’t as good as with acid chlorides
- Biologically amine $+$ acid $\rightarrow$ amide is routine, and is facilitated by complex enzyme mechanisms

1. $\text{R}_1\text{N} - \text{H} + \text{HOOCR} \xrightarrow{\text{heat}} \text{R}_1\text{NO} - \text{R}$
5. **Substitution for Aromatic Amines via the Diazonium Salts** (“The Sandmeyer Reaction”)  
(Section 19-17, 18)

- Mechanism: Not Required
- Qualitatively, can think of this as a nucleophilic substitution: a nucleophile replaces \( \text{N}_2 \), a premier leaving group. The actual mechanism is probably radical, however.
- Application in synthesis: The amine (an o/p director) is often derived from a nitro (a meta director). Using the nitro group to direct meta, then reducing and converting the nitrogen into CN, Br, Cl, OH, or H, provides products we haven’t been able to make before.

**Lewis bases** (lone pair electron donors) all function as:
1. Bases (give electrons to H\(^+\))
2. Nucleophiles (give electrons to some other electrophile)
3. Reducing agents (give electrons to oxidizing agents)

Amines can be oxidized

\( \text{NaNO}_2/\text{HCl} \) is a strong oxidizing agent, converts \( \text{RNH}_2 \) to \( \text{RN}_2^+ \), and \( \text{ArNH}_2 \) to \( \text{ArN}_2^+ \)
- “Diazonium salts”

\( \text{RN}_2^+ \) has the best leaving group known, because the leaving group is highly stable, neutral \( \text{N}_2 \) gas
1. Alkyl \( \text{RN}_2^+ \) are highly unstable, give cations, and usually give mixtures of E1, S\(_N\)1, and cation rearrangement product mixtures
2. Not much use synthetically
3. However, \( \text{N}_2 \) is such a great leaving group that even 1\(^{st}\) carbocations can be formed/studied

| Reactivity: | \( \text{RN}_2^+ > \text{ROH}_2^+ > \text{ROts} > \text{RI} > \text{RBr} > \text{RCl} \) |
| Leaving group ability: | \( \text{N}_2 > \text{H}_2\text{O} > \text{TsO anion} > \text{Iodide anion} > \text{Bromide anion} > \text{Chloride anion} \) |

1. Unlike Alkyl diazoniums \( \text{RN}_2^+ \), aryl \( \text{ArN}_2^+ \) are very useful
2. A variety of substitutions for the nitrogen can be done
3. While the reactions look like ionic substitutions, most are really complex radical mechanisms
**Synthetic Use:**
1. $\text{NO}_2$ (meta director) $\rightarrow$ $\text{NH}_2$ $\rightarrow$ $\text{N}_2^+$ $\rightarrow$ Cl, Br, OH, CN, H
2. Easy to get meta relationships, even when you end with things that are not meta directors

**Draw the products**

1. $\text{HNO}_3, \text{H}_2\text{SO}_4$
2. $\text{Br}_2, \text{Fe}$
3. $\text{Fe}, \text{HCl}$
4. $\text{NaNO}_2, \text{HCl}$
5. $\text{CuCl}$

1. $\text{HNO}_3, \text{H}_2\text{SO}_4$
2. $\text{Fe}, \text{HCl}$
3. $\text{NaNO}_2, \text{HCl}$
4. $\text{CuCN}$
5. $\text{KMnO}_4$

3. $\text{Br}_2\text{N}_2\text{H}_2$ $\rightarrow$ $\text{NaNO}_2, \text{HCl}$
   1. $\text{H}_3\text{PO}_2$

4. $\text{H}_3\text{C}\text{NH}_2$ $\rightarrow$ $\text{NaNO}_2, \text{HCl}$
   1. $\text{H}_2\text{O}, \text{H}_2\text{SO}_4, \text{heat}$

**Design Synthesis**

5. \[ \text{C}_6\text{H}_5 \rightarrow \text{Br} \]

6. Nitrobenzene $\rightarrow$ 

\[ \text{Cl} \]
19.14 Reaction with Sulfonyl Chlorides (Not tested)

\[
\begin{align*}
\text{N} & \quad \text{H} \quad \text{CH} \quad \text{S} \quad \text{R} \quad -\text{HCl} \quad \text{N} \quad \text{O} \quad \text{S} \quad \text{R} \\
& \quad \text{Sulfonamide}
\end{align*}
\]

- Exactly as for amide formation
- Many antibiotic drugs: sulfonamides are so similar to amides that they occupy enzyme active sites → prevent bacterial growth
D. Synthesis of Amines

6. From Aldehydes or Ketones: Reductive Amination (Section 19-19)

\[
\text{Ketone or aldehyde} + \text{amine} \overset{\text{NaBH}_3\text{CN, cat. H}^+}{\rightarrow} \text{ammonia} \rightarrow \text{amino group}
\]

- Access: 1º, 2º, or 3º Amines
- Mechanism: Not required. (Basic workup)
- The carbonyl reactant can be an aldehyde or a ketone
- The amine reactant must have at least one hydrogen, as shown above; but R₂ and/or R₃ can be either a carbon or a hydrogen. Thus:
  - NH₃ → 1º RNH₂
  - 1º RNH₂ → 2º R₂NH
  - 2º R₂NH → 3º R₃N
  - 3º R₃N don’t react

Note: book gives several other variants, but this is really the one universal method, and the one I’ll use for my tests.

Synthesis of Amines: Draw the products for the following reactions.

1. \[\text{O} + \text{MeNH}_2 \overset{\text{NaBH}_3\text{CN, H}^+}{\rightarrow}\]

2. \[\text{O} + \text{NH}_3 \overset{\text{NaBH}_3\text{CN, H}^+}{\rightarrow}\]
1. NaBH₃CN functions as a hydride H⁻ source, similar to NaBH₄ and LiAlH₄
2. Formation of imminium cation is key
   - Highly electrophilic, much more so than neutral imine
3. NaBH₃CN is a special, mild H⁻ source, much more stable and less reactive than NaBH₄ and LiAlH₄
   - So much so that it can coexist with acid (thus enabling imminium ion formation)
   - So much so that it does not reduce neutral ketones and aldehydes (thus allowing the aldehydes and ketones to sit around and equilibrate with imminium ion)
7. **Via Amides:** (Section 19-20)

\[
\begin{align*}
R^1 N R^2 & \xrightarrow{\text{LiAlH}_4} R^1 N R^2 \\
R^1 N R^2 & \xrightarrow{\text{Liglation}} R^1 N R^2 \\
R^1 N R^2 & \xrightarrow{\text{heat}} R^1 N R^2 \\
\end{align*}
\]

- No mechanism required for the reduction
- Access: 1°, 2°, or 3° Amines.
- \( R_1 \) and \( R_2 \) can be either H or C. Thus, you can produce either 1°, 2°, or 3° amines in this way:
  - \( RCONH_2 \to 1° RCH_2NH_2 \)
  - \( RCONHR \to 2° RCH_2NHR \)
  - \( RCONR_2 \to 3° RCH_2NR_2 \)

8. **From Amines via Amides:** (Section 19-20)

\[
\begin{align*}
R^1 N R^2 & \xrightarrow{\text{LiAlH}_4} R^1 N R^2 \\
R^1 N R^2 & \xrightarrow{\text{Liglation}} R^1 N R^2 \\
R^1 N R^2 & \xrightarrow{\text{heat}} R^1 N R^2 \\
\end{align*}
\]

- Access: 1°, 2°, or 3° Amines
- Acylation mechanism required (see reaction 4) but reduction mechanism not required.
9. **Reduction of nitro compounds**: (section 19-21C)

\[
\text{NO}_2 \xrightarrow{\text{Fe, HCl}} \text{NH}_2
\]

- Access: 1º Amines only (especially aromatic amines)
- No mechanism required.
- There are many other recipes for reduction of nitro compounds:
  - Pd/H₂, Ni/H₂, Pt/H₂,
  - Fe/HCl, Zn/HCl, Sn/HCl

10. **From 1º Alkyl Halides: Alkylation of Ammonia** (Section 19-12, 19-21A) (See reaction 3).

\[
\text{RBr} \xrightarrow{\text{excess NH}_3} \text{RNH}_2
\]

- Access: 1º Amines only
- Mechanism required. (see reaction 3b)
- No change in number of carbons.
- Excess NH₃ prevents polysubstitution.

11. **From Nitriles: Reduction of Nitriles** (Section 19-21B)

\[
\text{R-CN} \xrightarrow{\text{LiAlH}_4} \text{R-NH}_2
\]

- Access: 1º amines
- Mechanism not required.

12. **From Alkyl Halides: Via the Nitrile** (Section 19-21B)

\[
\text{RBr} \xrightarrow{1. \text{KCN}} \xrightarrow{2. \text{LiAlH}_4} \text{R-NH}_2
\]

- Access: 1º Amines only
- Mechanism not required.
- One-Carbon chain extension!
# Summary of Amine Syntheses

<table>
<thead>
<tr>
<th>Route</th>
<th>Reaction Number</th>
<th>Source/ Precursor</th>
<th>Reagent</th>
<th>Available Amines</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>#6</td>
<td>Aldehydes or Ketones</td>
<td>R₂NH, H⁺ NaBH₃CN,</td>
<td>1º, 2º, or 3º Amines</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>#7, #8</td>
<td>Amides</td>
<td>LiAlH₄</td>
<td>1º, 2º, or 3º Amines</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>#7, #8</td>
<td>Amines (via Amide)</td>
<td>3. RCOCl (or RCO₂H, heat) 4. LiAlH₄</td>
<td>1º ArNH₂</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>#7, #8</td>
<td>Acid Chlorides or Acids (via Amide)</td>
<td>3. RNH₂ 4. LiAlH₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>#9</td>
<td>ArNO₂</td>
<td>Fe/HCl</td>
<td>1º ArNH₂</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>#10</td>
<td>1º RCH₂Br</td>
<td>NH₃ (excess)</td>
<td>1º only, with CH₂ next to nitrogen</td>
<td>Original carbon chain is not extended</td>
</tr>
<tr>
<td>7</td>
<td>#12</td>
<td>1º RCH₂Br (via nitrile)</td>
<td>3. KCN 4. LiAlH₄</td>
<td>1º only, with CH₂ next to nitrogen</td>
<td>Original carbon chain is extended by one carbon</td>
</tr>
<tr>
<td>8</td>
<td>#11</td>
<td>RCH₂CN</td>
<td>LiAlH₄</td>
<td>1º only, with CH₂ next to nitrogen</td>
<td></td>
</tr>
</tbody>
</table>
1. Come up with various pathways (4 good ones) to the following 1º amine:

2. Come up with pathways (4 good ones) to the following 2º amine:
Provide Reagents for the following Transformations.

1. \( \text{O} \) \( \rightarrow \) \( \text{NH} \)

2. \( \text{CH}_2\text{OH} \) \( \rightarrow \) \( \text{CH}_2\text{NMMe}_2 \)

3. \( \text{PhCOCl} \) \( \rightarrow \) \( \text{PhNH}_2 \)

4. \( \text{Ph} \) \( \rightarrow \) \( \text{PhCO} \) \( \rightarrow \) \( \text{PhNH}_2 \)

5. \( \text{PhBr} \) \( \rightarrow \) \( \text{PhNH}_2 \)

6. \( \text{PhBr} \) \( \rightarrow \) \( \text{PhNH}_2 \)
Synthesis of Carboxylic Acids

1. **From 1º Alcohols and Aldehydes: Oxidation** (Section 11-2B and 18-20)

   
   \[
   \begin{align*}
   \text{1º Alcohol} & \xrightarrow{\text{H}_2\text{CrO}_4} \text{Aldehyde} & \xrightarrow{\text{H}_2\text{CrO}_4} \text{Carboxylic Acid} \\
   \end{align*}
   \]

   - No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage** (Section 8-15A and 9-10)

   
   \[
   \begin{align*}
   \text{Alkenes} & \xrightarrow{\text{KMnO}_4} \text{Acid} + \text{Ketone} \\
   \end{align*}
   \]

   - No mechanism required for the reaction
   - Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
   - RCH=CHR would give two acids; RCH=CH\textsubscript{2} would give an acid and carbonic acid (H\textsubscript{2}CO\textsubscript{3}), etc..

3. **From Aromatics: Oxidation of Alkylbenzenes** (Section 17-14A)

   
   \[
   \begin{align*}
   \text{Aromatic} & \xrightarrow{\text{KMnO}_4} \text{Carboxylic Acid} \\
   \end{align*}
   \]

   - No mechanism required for the reduction
   - While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation** (Chapter 22)

   
   \[
   \begin{align*}
   \text{Diesters} & \xrightarrow{1. \text{NaOR}} \xrightarrow{2. \text{R-X}} \xrightarrow{\text{H}_2\text{O}^+, \text{heat}} \text{Acids} \\
   \end{align*}
   \]

   - Mechanism: Deprotonation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)
5. **From Grignard Reagents: Via Carboxylation**: (Section 20-8B)

\[
R\text{-MgX} \xrightarrow{\text{1. CO}_2} R\text{-CO}_2\text{H}
\]

\[
R\xrightarrow{\text{ether}} \xrightarrow{\text{Mg}} R\text{-MgX} \xrightarrow{\text{1. CO}_2} R\text{-CO}_2\text{H} \xrightarrow{\text{2. H}^+} R\text{-CO}_2\text{H}
\]

- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 20-8C)

\[
R\text{-C≡N} \xrightarrow{\text{H}^+, \text{H}_2\text{O}} R\text{-OH}
\]

- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**

\[
R\text{-X} \xrightarrow{\text{Mg}} R\text{-MgX} \xrightarrow{\text{1. CO}_2} R\text{-CO}_2\text{H} \xrightarrow{\text{2. H}^+} R\text{-CO}_2\text{H}
\]

If R-X is 1º alkyl halide:

\[
R\text{-C≡N} \xrightarrow{\text{H}^+, \text{H}_2\text{O}} R\text{-OH}
\]

- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via S_N2
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents
8. From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis (Section 20-8C)
   a) “Downhill” hydrolysis: From acids or anhydrides with NEUTRAL WATER alone
      • mechanism required: addition-elimination-deprotonation

      \[ \text{HCl} + \text{CH}_2\text{C}=\text{O} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{OH}^- \]

      \[ \text{RCOCl} + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{HCl} \]

      b) “Lateral” hydrolysis: From esters with water and acid catalysis (ACID WATER)
      • mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)
      • These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester

      \[ \text{RCO}_2\text{H} + \text{H}_2\text{O} \rightarrow \text{RCO}_2\text{CH}_3 + \text{H}_2\text{O} \]

      \[ \text{RCO}_2\text{H} + \text{H}_2\text{O} \rightarrow \text{RCO}_2\text{H} + \text{H}_2\text{O} \]

   c) “Basic” hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H⁺ workup
      • mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation
      • Since the reaction with NaOH is always downhill, all of these reactions work

      \[ \text{RCOCl} + \text{NaOH} + \text{H}_2\text{O} \rightarrow \text{RCOOH} + \text{NaCl} \]

      \[ \text{RCOCl} + \text{NaOH} \rightarrow \text{RCOO}^-\text{Na}^+ + \text{HCl} \]

      \[ \text{RCO}_2\text{H} + \text{NaOH} \rightarrow \text{RCOO}^-\text{Na}^+ + \text{H}_2\text{O} \]

      \[ \text{R}_2\text{NH} + \text{NaOH} \rightarrow \text{RNH}_2 + \text{NaCl} \]
Reactions of Carboxylic Acids

9. **Reaction as a proton Acid** (Section 20-4, 20-5)

\[
\begin{align*}
\text{R} & \quad \text{NaOH (or other bases, including amines)} \\
\text{OH} & \quad \text{H-X (proton acid)} \\
\rightarrow & \quad \text{Na}^+ \\
\text{carboxylate salt} & \quad \text{(basic)}
\end{align*}
\]

- Mechanism: Required (deprotonation)
- Reverse Mechanism: Required (protonation)
- Carboxylic acids are completely converted to carboxylate salts by base
- Carboxylate salts are completely neutralized back to carboxylic acids by strong acid
- The resonanance stabilization makes carboxylates much more stable than hydroxide or alkoxide anions, which is why the parents are carboxylic “acids”
- Carboxylic acids are more acidic than ammonium salts
- Patterns in acid strength: Reflect stabilization/destabilization factors on the carboxylate
  - Electron donors destabilize the carboxylate anion, so make the parent acid less acidic
  - Electron withdrawers stabilize the carboxylate anion, so make the parent acid more acidic

10. **Conversion to Acid Chlorides** (Section 20-11, 21-5)

\[
\begin{align*}
\text{R} & \quad \text{SOCl}_2 \\
\text{OH} & \quad \text{Cl} \\
\rightarrow & \quad \text{Cl}
\end{align*}
\]

- Mechanism: Not Required
- Easy (but smelly) reaction. Side products HCl and SO₂ are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. **Indirect Conversion to Anhydrides** (Section 21-5)

\[
\begin{align*}
\text{R} & \quad \text{SOCl}_2 \\
\text{OH} & \quad \left[ \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \right] \\
\rightarrow & \quad \text{Cl}
\end{align*}
\]

- mechanism required for acid chloride to anhydride conversion: addition-elimination-deprotonation
- Conversion of the acid chloride to the anhydride is a “downhill” reaction energetically.
- Conversion of the acid to the anhydride directly would be an “uphill” reaction
12. **Direct Conversion to Esters** (Sections 20-10-12, 21-5)

\[
\begin{align*}
R\text{OH} & \xrightarrow{\text{R'OH, H}^+} [R\text{OH}] \xrightarrow{\text{H}_2\text{O, H}^+} R\text{OR}' \\
\end{align*}
\]

- **mechanism required:** protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)
- These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a “lateral” reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b

13. **Indirect Conversion to Esters via Acid Chlorides** (Sections 20-10-12, 21-5)

\[
\begin{align*}
\text{ROH} & \xrightarrow{1. \text{SOCl}_2} [\text{RCl}] \xrightarrow{2. \text{R'OH}} \text{ROR'} \\
\end{align*}
\]

- **mechanism required for acid chloride to ester conversion:** addition-elimination-deprotonation
- Conversion of the acid chloride to the ester is a “downhill” reaction energetically.

14. **Direct Conversion to Amides** (Sections 20-11, 20-13, 21-5)

\[
\begin{align*}
\text{R\text{OH}} & \xrightarrow{\text{RNH}_2, \text{heat}} \text{R\text{NHR}} \\
\end{align*}
\]

- **mechanism not required**
- This is a “downhill” reaction energetically, but is complicated and retarded by acid-base reactions. Normally the “indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.

15. **Indirect Conversion to Amides** (Sections 20-11, 20-13, 21-5)

\[
\begin{align*}
\text{R\text{OH}} & \xrightarrow{1. \text{SOCl}_2} [\text{RCl}] \xrightarrow{2. \text{RNH}_2} \text{RNHR} \\
\end{align*}
\]

- **mechanism required for acid chloride to amide conversion:** addition-elimination-deprotonation
- This reaction sequence works very well in the laboratory
16. **Reduction to Primary Alcohol** (Sections 10-11, 20-14)

\[
\begin{align*}
\text{RCHO} & \quad 1. \text{LiAlH}_4 \\
& \quad 2. \text{H}^+ \\
\text{ROH} & \\
\end{align*}
\]

- mechanism not required

17. **Alkylation to Form Ketones** (Section 18-19, 20-15)

\[
\begin{align*}
\text{PhCOOH} & \quad 1. 2\text{RLi} \\
& \quad 2. \text{H}^+ \\
\text{PhCOR} & \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCOOH} & \quad 1. 2\text{RLi} \\
& \quad 2. \text{H}^+ \\
\text{carboxylate anion} & \quad \text{tetrahedral dianion} & \quad \text{tetrahedral "hydrate"} & \quad \text{acid} \\
\text{LiO}_{\text{Ph}}\text{OLi} & \\
\text{acid} & \\
\text{PhCOR} & \\
\end{align*}
\]

- mechanism not required
18. **Interconversions of Acids and Acid Derivatives** (Section 21-5 and many others)

- “Cl-A-vE-N-O” Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any “lateral” step (acid to ester or vice-versa) can be done with acid
- Any “uphill” sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl₂ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)
Mechanisms
A. Miscellaneous
5. From Grignard Reagents: Via Carboxylation:

- exactly like any Grignard reaction

9. Reaction as a Proton Acid

B. Any “Downhill” Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

Examples

Reaction 8a

Reaction 8c (Note: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)

Reaction 13

Reaction 15
C. “Lateral” Interconversions (8b/12): Acid-Catalyzed conversion from Ester to Acid (8b) or From Acid to Ester (12): (ACID WATER)

- General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)

**Examples**

**Reaction 8b: Ester to Acid**

**Reaction 12: Acid to Ester**
**Nomenclature** (20.2)  
Formal: **alkanoic acid** (space in between)
-highest priority of any functional group

<table>
<thead>
<tr>
<th>Formal</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOH</td>
<td>Methanoic acid</td>
</tr>
<tr>
<td>H₃C-C-OH</td>
<td>Ethanoic acid</td>
</tr>
<tr>
<td>Ph-OH</td>
<td>Benzoic acid</td>
</tr>
<tr>
<td>-COOH</td>
<td>Pentanoic acid</td>
</tr>
<tr>
<td>H₂N₂-OH</td>
<td>(S)-2-aminobutanoic acid</td>
</tr>
</tbody>
</table>

1. Nomenclature. Provide names or structures for the following.
   a. 3-phenylbutanoic acid
   b. 2,2-dichloropropanoic acid
   c. 2-hydroxy-3-propanoyl-4-ethoxy-5-amino-6-hydroxyheptanoic acid

**Physical Properties (Section 20.3)**

Boiling Points: (weight being equal): acid > alcohol > 1,2º amines > non-H-bonders
- Acids boil about 20º higher than same-weight alcohols
- First four acids are completely water soluble

Water solubility (weight being equal): amines > acids ? ketones, alcohols, ethers >> alkanes
- Basicity is more important than acidity

2. Circle the one with higher boiling point, and square the one with the greater solubility in water.
### Acidity/Basicity Table 19.2: With both Neutral and Cationic Acids and both Neutral and Anionic Bases (Section 20-4)

<table>
<thead>
<tr>
<th>Class</th>
<th>Structure</th>
<th>$K_a$</th>
<th>Acid Strength</th>
<th>Base</th>
<th>Base Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Acids</td>
<td>H-Cl, H$_2$SO$_4$</td>
<td>$10^2$</td>
<td></td>
<td>Cl$^-$, HO-</td>
<td>Smell Awful!</td>
</tr>
<tr>
<td>Hydronium</td>
<td>H$_3$O$^+$, ROH$^+$ cationic</td>
<td>$10^0$</td>
<td></td>
<td>H$_2$O, HOR neutral</td>
<td>Humans</td>
</tr>
<tr>
<td>Carboxylic Acid</td>
<td><a href="#">Structure</a></td>
<td>$10^{-5}$</td>
<td></td>
<td><a href="#">Structure</a></td>
<td>Cuz</td>
</tr>
<tr>
<td>Phenol</td>
<td><a href="#">Structure</a></td>
<td>$10^{-10}$</td>
<td></td>
<td><a href="#">Structure</a></td>
<td>People</td>
</tr>
<tr>
<td>Ammonium Ion (Charged)</td>
<td><a href="#">Structure</a></td>
<td>$10^{-12}$</td>
<td>Charged, but only weakly acidic!</td>
<td><a href="#">Structure</a></td>
<td>Against</td>
</tr>
<tr>
<td>Water</td>
<td>HOH</td>
<td>$10^{-16}$</td>
<td></td>
<td>HO$^-$</td>
<td>Working</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ROH</td>
<td>$10^{-17}$</td>
<td></td>
<td>RO$^-$</td>
<td>Are</td>
</tr>
<tr>
<td>Ketones and Aldehydes</td>
<td><a href="#">Structure</a></td>
<td>$10^{-20}$</td>
<td></td>
<td><a href="#">Structure</a></td>
<td>Kingdoms</td>
</tr>
<tr>
<td>Amine (N-H)</td>
<td>(iPr)$_2$N-H</td>
<td>$10^{-33}$</td>
<td></td>
<td>(iPr)$_2$N$^-$Li$^+$</td>
<td>Animal</td>
</tr>
<tr>
<td>Alkane (C-H)</td>
<td>RCH$_3$</td>
<td>$10^{-50}$</td>
<td></td>
<td>RCH$_2^-$</td>
<td>All</td>
</tr>
</tbody>
</table>

**Quick Checklist of Acid/Base Factors**
1. **Charge**
2. **Electronegativity**
3. **Resonance/Conjugation**
4. **Hybridization**
5. **Impact of Electron Donors/Withdrawers**
6. **Amines/Ammoniums**
   - When comparing/ranking any two acids or bases, go through the above checklist to see which factors apply and might differentiate the two.
   - When a neutral acid is involved, it's often best to draw the conjugate anionic bases, and to think from the anion stability side.
**Acidity (20-4)**

\[
\begin{align*}
\text{ROH} & \quad \text{O} \quad \text{H}^{+} & \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{O} \\
& \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{O} \\
& \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{R} \quad \text{O} \quad \text{O}
\end{align*}
\]

- Anion is stabilized by conjugation/resonance
- Charge dispersal
- Carboxylate is an anion, so is stabilized by electron withdrawing groups (increasing acidity) and destabilized by electron donating groups (decreasing acidity)

<table>
<thead>
<tr>
<th>Carboxylic Acid</th>
<th>(10^{-5})</th>
<th>Ammonium Ion (Charged)</th>
<th>(10^{-12})</th>
<th>Alcohol</th>
<th>(10^{-17})</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Diagram]</td>
<td></td>
<td>[Diagram]</td>
<td></td>
<td>[Diagram]</td>
<td></td>
</tr>
</tbody>
</table>

- Acids are a million times more acidic than average ammoniums (despite charge)
- Acids are trillions more acidic than alcohols

**Amino Acids:**
- Which way does the equilibrium lie?
- Equilibrium always favors the weaker acid and weaker base?
- What happens under acid conditions, and what happens under base conditions?

38. Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. acetic acid ethanol phenol

b. propanoic acid \(\text{CH}_3\text{NH}_3\text{Cl}\) \((\text{CH}_3)_3\text{NHCl}\)
Substituent Effects (20.4B)
• Withdrawers stabilize anions, increase acidity
• Donors destabilize anions, reduce acidity
• Opposite from the effect of donors and withdrawers on amines and ammoniums

1. Carboxylic Acids as Acids. Rank the acidity of the following groups, 1 being most acidic and 3 being least acidic. [Remember: the best guideline for acidity is the stability of the anion!]

a. propanoic acid 3-Chloropropanoic acid 2-fluoropropanoic acid

b. benzoic acid p-methylbenzoic acid p-nitrobenzoic acid

2. For each of the following acid/base reactions, draw a circle around the weakest base, and draw an arrow to show whether the reaction would proceed from left to right, or from right to left.

a. \( \text{OH} + \text{NaOH} \quad \text{ONa} + \text{HOH} \)

\[ \text{Ka} = 10^{-5} \]

b. \( \text{Ph-OH} + \text{NaOH} \quad \text{Ph-ONa} + \text{HOH} \)

c. \( \text{O} + \text{NaOH} \quad \text{ONa} + \text{HOH} \)

d. \( \text{O} + \text{NaHCO}_3 \quad \text{ONa} + \text{H}_2\text{CO}_3 \)

\[ \text{Ka} = 10^{-7} \]
20.5 Carboxylate Salts

\[ \text{RCO}_2\text{H} + \text{NaOH} \rightarrow \text{RCO}_2\text{Na} + \text{H}_2\text{O} \]  Produces weaker acid and base

- Easy to make
- Ionic \( \rightarrow \) water soluble

\[ \text{Acids are soluble in NaOH/water or NaHCO}_3/\text{H}_2\text{O} \]

- Weak bases, react with HCl \( \rightarrow \) RCO₂H
- Named: sodium alkanoate

Purification Schemes for Acids from other Organics Based on Acidity

a. Dissolve acid and neutral organic in ether
b. Treat with NaOH/water
   - Neutral stays neutral, goes in ether layer
   - Acid is deprotonated to \( \text{RCO}_2\text{Na} \), goes into water layer
c. Concentrate ether layer \( \rightarrow \) pure neutral organic
d. Add HCl to aqueous layer, results in: \( \text{RCO}_2\text{Na} + \text{HCl} \rightarrow \text{RCO}_2\text{H} \)
e. Neutral \( \text{RCO}_2\text{H} \) now has low solubility in water, so can be harvested by filtration (if solid) or by organic extraction

1. Design a solubility flow chart to separate benzoic acid ("A") from acetophenone \( \text{PhC(O)CH}_3 \) ("B"). Make sure that your plan enables you to isolate both “A” and “B”.

[Diagram of benzoic acid (A) and acetophenone (B)]

Soaps (20.6, 25.4) (not for test)
RCO₂Na with variable long alkyl chains
Ex: \( \text{C}_{17}\text{H}_{35}\text{CO}_2 \oplus \text{Na} \oplus \)

Carboxylate head: hydrophilic \( \rightarrow \) water soluble
Hydrocarbon tail: hydrophobic \( \rightarrow \) can dissolve grease and organic materials

Form “micelles” in water

[Diagram of micelles in water]

The hydrophobic hydrocarbon tails (strings) self-aggregate, while the ionic heads (circles) keep the microdroplet soluble in water. Organic materials can be dissolved inside the organic center, and carried through the water. Thus grease gets dissolved, and dirt protected by grease is freed.
B. Synthesis of Carboxylic Acids

Synthesis of Carboxylic Acids

Review (20.8)

1. **From 1º Alcohols and Aldehydes: Oxidation** (Section 11-2B and 18-20)

   \[ R\text{-}\text{OH} \xrightarrow{\text{H}_2\text{Cr}_4\text{O}_7} R\text{-}\text{CO}_2\text{H} \]

   • No mechanism required for the reaction

2. **From Alkenes: Oxidative Cleavage**: (Section 8-15A and 9-10)

   \[ \text{R} = \text{CHR}_1\text{CH}=\text{CHR}_2 \xrightarrow{\text{KMnO}_4} \text{酸} \quad \text{R}_1\text{CO}_2\text{H} \quad \text{酸} \quad \text{R}_2\text{CO}_2\text{H} \]

   • No mechanism required for the reaction
   • Where C=C begins, C=O ends. But where an attached H begins, an OH ends.
   • RCH=CHR would give two acids; RCH=CH₂ would give an acid and carbonic acid (H₂CO₃), etc..

3. **From Aromatics: Oxidation of Alkylbenzenes** (Section 17-14A)

   \[ \text{苯} \xrightarrow{\text{KMnO}_4} \text{苯} \text{CO}_2\text{H} \]

   • No mechanism required for the reduction
   • While toluenes (methylbenzenes) oxidize especially well, other alkyl benzenes can also be oxidized in this way.

4. **From 1,3-Diesters: Via Hydrolysis/Decarboxylation**: (Chapter 22)

   \[ \text{RCO}_2\text{OR} \xrightarrow{1. \text{NaOR}} \text{RCO}_2\text{R} \xrightarrow{2. \text{R-X}} \text{HO}_2\text{CO}_2\text{R} \xrightarrow{\text{H}_2\text{O}^+, \text{heat}} \text{HO} \quad \text{酸} \]

   • Mechanism: Deprotonation/Alkylation covered previously. The hydrolysis of the esters to acids will be required (see reaction 8b)
New Routes

5. **From Grignard Reagents: Via Carboxylation:** (Section 20-8B)

\[
R-MgX \xrightarrow{1. \text{ CO}_2} R-CO_2H \\
R-MgX + \text{ether} \xrightarrow{1. \text{ CO}_2} R-CO_2H
\]

- Access: Alkyl or Aryl Acids
- Alkyl group can be 1º, 2º, or 3º
- Mechanism required. (From Grignard on.)

6. **From Nitriles: Hydrolysis** (Section 20-8C)

\[
R-C\equiv N \xrightarrow{H^+, H_2O} R-CO_2H
\]

- Mechanism not required.

7. **From Halides: Either via Formation and Carboxylation of Grignards (Reaction 5) or via Formation and Hydrolysis of Nitriles (Reaction 6)**

- Formation/Hydrolysis of Nitriles Requires a 1º Alkyl Halide to begin, since the formation of the nitrile proceeds via $S_N2$
- Reaction via the Grignard has no such limitation
- For 1º alkyl halides, the formation/hydrolysis of the nitrile is technically easier, since there is no need to handle air-sensitive Grignard reagents
Problems
1. Preparation of Carboxylic Acids. Fill in the blanks for the following reactions.

a. \( (C_3H_8O) \) \( \xrightarrow{H_2CrO_4} \) \( \text{carboxylic acid} \)

b. Bromobenzene \( \xrightarrow{1. \text{Mg} \ 2. \text{epoxide; H}_2\text{O} \ 3. \text{H}_2\text{CrO}_4} \) \( \text{carboxylic acid} \)

c. \( \text{Ph} = \text{C} = \text{Ph} \) \( \xrightarrow{1. \text{KMnO}_4/\text{NaOH/heat} \ 2. \text{H}^+} \) \( + \text{carbonic acid} \)

d. Benzene \( \xrightarrow{\text{Br}_2, \text{FeBr}_3} \) \( \xrightarrow{\text{Mg}} \) \( \xrightarrow{1. \text{CO}_2 \ 2. \text{H}^+} \) \( \text{carboxylic acid} \)

e. \( \text{OH} \) \( \xrightarrow{1. \ \text{2.}} \) \( \text{CN} \) \( \xrightarrow{\text{H}_3\text{O}^+} \) \( \text{carboxylic acid} \)

f. \( \text{Ph} - \text{Br} \) \( \xrightarrow{1. \text{NaCN} \ 2. \text{H}_3\text{O}^+} \) \( \text{carboxylic acid} \)
8. From Acid Chlorides, Anhydrides, Esters, or Amides: Hydrolysis (Section 20-8C)
   a) “Downhill” hydrolysis: From acids or anhydrides with NEUTRAL WATER alone
      • mechanism required: addition-elimination-deprotonation

      \[
      \text{Cl} \quad \overset{\text{H}_2\text{O}}{\text{R-Cl}} \rightarrow \text{R-OH} + \text{H-Cl}
      \]
      \[
      \text{A} \quad \overset{\text{H}_2\text{O}}{\text{R-O} \text{R'}} \rightarrow \text{R-OH} + \text{H-O} \text{R}'
      \]

   b) “Lateral” hydrolysis: From esters with water and acid catalysis (ACID WATER)
      • mechanism required: protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to acid)
      • These reactions are under equilibrium control. With excess water, you go to the acid. With removal of water and/or excess alcohol, the equilibrium favors the ester

      \[
      \text{E} \quad \overset{\text{H}_2\text{O}, \text{H}^+}{\text{RO} \text{R}_1} \rightleftharpoons \text{R-OH} + \text{R'O} \text{H} \quad \text{via} \quad \text{R-OH} \text{R}_1, \text{H}^+ \text{hemiacetal}
      \]

   c) “Basic” hydrolysis using NaOH (BASIC WATER) (always downhill) followed by H\(^{+}\) workup
      • mechanism required: addition-elimination-deprotonation (to carboxylate intermediate) followed by protonation
      • Since the reaction with NaOH is always downhill, all of these reactions work
Interconversions and Reactivity of Acids and Acid Derivatives (Section 21-5 and others)

- “Cl-A-vE-N-O” Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- Any downhill step can be done directly
- Any “lateral” step (acid to ester or vice-versa) can be done with acid
- Any “uphill” sequence requires protonation or going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl₂ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)

“Cl-A-vE-N-O” applied to Hydrolysis
1. Chlorides and Anhydrides are “above” acids, so can be converted to acids by direct hydrolysis with neutral water
2. Esters are “lateral” to acids, so can be hydrolyzed to acids by acid-catalyzed hydrolysis
3. Chloride, anhydrides, esters, and amides can all be base-hydrolyzed (NaOH/water) to carboxylates.
   - Subsequent acid workup protonates the carboxylate and produces the acid
   - Base hydrolysis always works
4. For amides, basic hydrolysis is the only way to do it
1. For the following problems, draw the starting materials that would give the indicated hydrolysis products.

- Note: All of these are drawn as basic hydrolysies, but some could also be done using neutral water or acidic water. Mark which could proceed using neutral hydrolysis or acid-catalyzed hydrolysis in addition to via basic hydrolysis.

Mechanism: General Mechanism for Any “Downhill” CI-A-vE-N-O Interconversions (8a, 8c, 11, 13, 15, 18): All Proceed by Addition-Elimination-Deprotonation

Base Case, Using Anionic Hydroxide: Slightly different because hydroxide nucleophile is anionic, not neutral; and product carboxylate is anionic, not neutral)
Acid-Catalyzed conversion from Ester to Acid (8b): (ACID WATER)

- General Mechanism: protonation-addition-deprotonation (acid-catalyzed addition to a carbonyl to produce the tetrahedral hemiacetal intermediate) followed by protonation-elimination-deprotonation (acid catalyzed elimination)

\[
\begin{align*}
\text{Ester} & \quad \text{Protonate} \quad \text{Add} \quad \text{Deprotonate} \\
\text{Acid} & \quad \text{Protonate} \quad \text{Deprotonate} \quad \text{Eliminate}
\end{align*}
\]

Draw the Mechanisms for the following Hydrolyses

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

Where will the \(^{18}\text{O}\) label end up?

\[
\begin{align*}
\text{O}^{18} & \quad \text{Ph} - \text{OMe} \\
\text{H}_2\text{O} & \quad \text{Ph} - \text{OH} + \text{HMe}
\end{align*}
\]
C. Reactions of Carboxylic Acids

20.9, 21.5 Interconversions with Derivatives: Cl-A-vE-N-O

- “Cl-A-vE-N-O” Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any “lateral” step (acid to ester or vice-versa) can be done with acid
- Any “uphill” sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl₂ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)
Acid Chlorides: Preparation and Uses (Sections 20.11 and 21.5)

10. Conversion of acids or Carboxylates to Acid Chlorides (Section 20-11, 21-5)

\[
\begin{align*}
\text{O} & \quad \text{SOCl}_2 & \quad \text{O} & \quad \text{Cl} \\
\text{O} & \quad \text{Na} & \quad \text{SOCl}_2 & \quad \text{O} \\
R^- & \quad \text{O} & \quad \text{Cl} & \quad R^- \\
R^- & \quad \text{O} & \quad \text{Cl} & \quad R^- \\
\end{align*}
\]

- Mechanism: Not Required
- Easy (but smelly) reaction.
  - Side products HCl and SO\(_2\) are gases, so can just evaporate away leaving clean, useful product. So no workup is required, nice!
- Extremely useful because the acid chlorides are so reactive, and can be converted into esters, anhydrides, or amides.

11. Indirect Conversion to Anhydrides (Section 21-5)

\[
\begin{align*}
\text{O} & \quad \text{SOCl}_2 & \quad \text{O} & \quad \text{Cl} & \quad \text{O} & \quad \text{Cl} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\end{align*}
\]

- mechanism required for acid chloride to anhydride conversion: addition-elimination-deprotonation
- Conversion of the acid chloride to the anhydride is a “downhill” reaction energetically.
- Conversion of the acid to the anhydride directly would be an “uphill” reaction
- Base often present to absorb the HCl

13. Indirect Conversion to Esters via Acid Chlorides (Sections 20-10-12, 21-5)

\[
\begin{align*}
\text{O} & \quad \text{SOCl}_2 & \quad \text{O} & \quad \text{Cl} & \quad \text{O} & \quad \text{R}^- & \quad \text{OH} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\end{align*}
\]

- mechanism required for acid chloride to ester conversion: addition-elimination-deprotonation
- Conversion of the acid chloride to the ester is a “downhill” reaction energetically.
- Base often present to absorb the HCl

15. Indirect Conversion to Amides (Sections 20-11, 20-13, 21-5)

\[
\begin{align*}
\text{O} & \quad \text{SOCl}_2 & \quad \text{O} & \quad \text{Cl} & \quad \text{O} & \quad \text{NHR} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\text{R}^- & \quad \text{OH} & \quad \text{R}^- & \quad \text{H} & \quad \text{R}^- & \quad \text{OH} \\
\end{align*}
\]

- mechanism required for acid chloride to amide conversion: addition-elimination-deprotonation
- This reaction sequence works very well in the laboratory
- Base often present to absorb the HCl
Condensation/Hydrolysis: Interconversions between Acids and Esters (20.10, 13, 21.7)

12. **Direct Conversion to Esters** (Sections 20-10-12, 21-5)

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

- **mechanism required:** protonation-addition-deprotonation (to hemiacetal intermediate) followed by protonation-elimination-deprotonation (hemiacetal to ester)
- These reactions are under equilibrium control.
  1. With excess water, you go to the acid.
  2. With removal of water and/or excess alcohol, the equilibrium favors the ester
- This is a “lateral” reaction, neither uphill nor downhill energetically
- This is the exact reverse of reaction 8b
- Under base conditions, the equilibrium always goes completely away from the ester and goes to the acid side
  1. The base deprotonates the carboxylic acid, so LeChatellier’s principle says that the equilibrium keeps driving from ester towards acid to compensate

2. Draw the mechanism for the following reaction.

\[
\text{O} \quad \xrightarrow{\text{HOMe, H}^+} \quad \text{O} \quad \text{OMe} \quad \text{(+ H}_2\text{O)}
\]

14. **Direct Conversion to Amides** (Sections 20-11, 20-13, 21-5)

\[
\text{R} \quad \text{OH} \quad \xrightarrow{\text{RNH}_2, \text{heat}} \quad \text{R} \quad \text{NHR}
\]

- **mechanism not required**
- This is a “downhill” reaction energetically, but is complicated and retarded by acid-base reactions. Normally the “indirect) conversion is more clean in the laboratory
- This reaction occurs routinely under biological conditions, in which enzymes catalyze the process rapidly even at mild biological temperatures.
Problems
1. Synthesis of Acid derivatives. Draw the products for the following reactions.

a. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{\text{SOCl}_2} \hspace{1cm} \text{Ph} \hspace{1cm} \text{SOCl}_2 \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

b. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{1-butanol} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

c. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{\text{ethanol, H}^+} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

d. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{cyclopentanol} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

e. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{2-butanol} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

f. \[
\text{H} \hspace{1cm} \text{OH} \hspace{1cm} \text{Ph} \hspace{1cm} \xrightarrow{\text{H}^+} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

g. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{diethylamine} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

h. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{NH}_3 \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

i. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{1. \text{SOCl}_2} \hspace{1cm} 2. \text{2-butanamine} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]

j. \[
\text{Ph} \hspace{1cm} \text{OH} \hspace{1cm} \xrightarrow{\text{diethylamine, heat}} \hspace{1cm} \text{Ph} \hspace{1cm} \text{Cl} \hspace{1cm} \text{OH}
\]
1. Draw the mechanism.

b. \[
\begin{align*}
\text{Cl} & \text{O} \\
\text{Cl} & \text{O} \\
\text{N} & \\
\text{NH}_2 \\
\end{align*}
\]

2. Draw the products for the following reactions.

a. \[
\begin{align*}
\text{Ph} & \text{O} \\
\text{Ph} & \text{O} \\
\text{H} & \\
\text{H} & \\
\end{align*}
\]

1. LiAlH\(_4\)

2. H\(_3\)O\(^+\)

b. \[
\begin{align*}
\text{Ph} & \text{O} \\
\text{Ph} & \text{O} \\
\text{H} & \\
\text{H} & \\
\end{align*}
\]

1. MeLi (excess)

2. H\(_3\)O\(^+\)

Ch. 21 Carboxylic Acid Derivatives:
- Cl chloride
- A anhydride
- E ester
- N amide
- O: carboxylate

21.1.2 Structure, Names, Notes
- all are subject to hydrolysis
- All hydrolyze to acids (actually, to carboxylate anion) upon treatment with NaOH/H\(_2\)O
- Some (Cl and A) hydrolyze to acids under straight water treatment
- Esters hydrolyze to acids under acid catalysis

<table>
<thead>
<tr>
<th></th>
<th>General</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Alkanoyl</td>
<td>Butanoyl</td>
</tr>
<tr>
<td>Cl</td>
<td>chloride</td>
<td>chloride</td>
</tr>
<tr>
<td></td>
<td>Alkanoyl Anhydride</td>
<td>Propanoic anhydride</td>
</tr>
<tr>
<td></td>
<td>Alkyl Alkanoate</td>
<td>Ethyl Benzoate</td>
</tr>
<tr>
<td>R</td>
<td>Alkanamide</td>
<td>N-isopropyl pentanamide</td>
</tr>
</tbody>
</table>

- High reactivity
- Named as if ionic
1. Draw the structures for the following esters.

a. propyl benzoate

b. methyl ethanoate

c. ethyl butanoate

21.5 Interconversion of Acid Derivatives: Cl-A-vE-N-O

- “Cl-A-vE-N-O” Chlorides-Anhydrides-Esters (and Acids)-Amides-Carboxylates
- All can be interconverted by substitution procedures: 1, 2, or 3 steps
- Any downhill step can be done directly
- Any “lateral” step (acid to ester or vice-versa) can be done with acid
- Any “uphill” sequence requires going up through the Acid Chloride, either directly (from an acid or a carboxylate) or indirectly (conversion to carboxylate; react with SOCl₂ to get to the top; then go downhill from there.)
- Mechanism is required for any downhill conversion and is the same: protonation-addition-deprotonation (addition to produce the hemiacetal intermediate) followed by protonation-elimination-deprotonation (elimination)
1. Rank the acidity of the following molecules, 1 being most acidic and 4 being least acidic.

\[ \text{HCl} \quad \text{HO} \quad \text{HOCH}_3 \quad \text{NH}_2\text{CH}_3 \]

2. Rank the reactivity of the following toward hydrolysis. Do you see a similarity between your rankings for this question relative to your answers for question 8?

\[ \text{OCl} \quad \text{OOC} \quad \text{OCH}_3 \quad \text{NHCH}_3 \]

Notes:
- Any “downhill” reaction can be done in one laboratory step
- Any “downhill” reaction involves a 3-step mechanism: addition-elimination-deprotonation

\[ \text{Add} \quad \text{Z-H} \quad \text{r}_1 \quad \text{Elim} \quad \text{r}_1 \]

- The overall reactivity correlates the leaving ability of the Y for two reasons
  1. This affects the kinetic r_2/r_1 partition. If r_2 is slow, the addition is simply reversible
  2. The same factors that make Y a good leaving group also make the initial carbonyl more reactive toward addition (step 1, r_1).
  3. Thus good leaving groups have benefits at both r_1 and r_2

- Memory
  - Think anion stability
  - Cliff Cl-A-vE-N-O

B. “Uphill” Reaction Sequences: 3-steps

\[ \text{O} \quad \text{R} \quad \text{Y} \quad 1. \text{NaOH, H}_2\text{O} \quad 2. \text{SOCl}_2 \quad 3. \text{HZ} \]

Ex:

- PhO\text{NH}_2 + \text{OH} \quad 1. \text{NaOH, H}_2\text{O} \quad 2. \text{SOCl}_2 \quad 3. \text{HOCH}_3

- PhO\text{OCl} + \text{NH}_3 \quad 1. \text{NaOH, H}_2\text{O} \quad 2. \text{SOCl}_2 \quad 3. \text{HOCH}_3

- PhO\text{OCH}_3 \quad 1. \text{NaOH, H}_2\text{O} \quad 2. \text{SOCl}_2 \quad 3. \text{HOCH}_3

- PhO\text{OEt}_3
1. Which will proceed easily/directly? ("downhill") Add Appropriate Reactant(s) and Side Product. If it doesn’t go directly, give indirect route.

a. \( \text{PhCl} + \text{NH}_3 \rightarrow \text{PhNH}_2 \)

b. \( \text{CO}_2 \text{H} + \rightarrow \text{CO}_2 \text{H} + \)

c. \( \text{Cl} + \text{H}_2\text{O} \rightarrow \text{Cl} \quad \text{and} \quad \text{H}_2\text{O} \)

d. \( \text{CO}_2\text{HOC}_2\text{H} + \text{HCl} \rightarrow \text{Cl} + \text{H}_2\text{O} \)

e. \( \text{CO}_2\text{HOC}_2\text{H} + \text{H-NMe}_2 \rightarrow \text{ClNMMe}_2 + \text{HOCH}_3 \)

f. \( \text{CO}_2\text{HOC}_2\text{H} + \text{NaOH} \rightarrow \text{ClNa} + \text{HOCH}_3 \)

g. \( \text{ClNMMe}_2 + \text{NaOH} \rightarrow \text{ClNa} + \text{HNMMe}_2 \)

h. \( \text{ClNMMe}_2 + \rightarrow \text{ClMe} \)

i. \( \text{CO}_2\text{HOC}_2\text{H} + \rightarrow \text{CO}_2\text{H} + \)
1. Provide products for the following transformations.

   a. \[
   \text{PhO} \quad \text{SOCl}_2 \quad \text{PhOH}
   \]

   b. \[
   \text{PhO} \quad \text{1. SOCl}_2 \rightarrow \text{PhOH} \quad \text{2. Acetic acid, pyridine}
   \]

   c. \[
   \text{PhO} \quad \text{Ph NH}_2 \quad \text{PhOMe}
   \]

   d. \[
   \text{PhN} \quad \text{1. NaOH, H}_2\text{O; H}^+ \rightarrow \text{PhNH}_2 \quad \text{2. SOCl}_2 \quad \text{3. MeOH, pyridine}
   \]

   e. \[
   \text{PhO} \quad \text{ethanol, pyridine} \quad \text{PhOMe}
   \]

   f. \[
   \text{Ph-CN} \quad \text{1. H}_3\text{O}^+ \rightarrow \text{Ph-CN} \quad \text{2. MeOH, H}^+
   \]

2. Draw the mechanism for the following reaction.

\[
\text{PhO} + \text{HOH} \rightarrow \text{PhOCH}_2\text{CH}_3 + \text{HO} \quad (3 \text{ steps})
\]
1. Provide reagents for the following transformations.

   a. 
   
   b. 
   
   c. 
   
   d. 
   
   e. 
   
   f. 
   
   g. 
   
   h. 
   

(Method 1)
2. Provide products for the following condensation or hydrolysis transformations.

a. \( \text{Ph-COOH} + \text{MeOH} \rightarrow \text{Ph-COMe} \)

b. \( \text{CH}_3\text{COOH} + \text{PhNH}_2 \rightarrow \text{PhCONHCH}_3 \)

c. \( \text{CH}_3\text{COOCH}_2\text{CH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOCH}_2\text{CH}_2\text{OH} \)

d. \( \text{Ph-NHCH}_2\text{Ph} \rightarrow \text{Ph-NHCH}_2\text{Ph} \rightarrow \text{Ph-NHCH}_2\text{Ph} + \text{H}_2\text{O} \)

e. \( \text{Ph-COOH} \rightarrow \text{Ph-COOH} \rightarrow \text{Ph-COOH} + \text{H}_2\text{O} \)

f. \( \text{CH}_3\text{CH(OH)}\text{CH}_2\text{CH(OH)}\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CH(OH)}\text{CH}_2\text{CH(OH)}\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CH(OH)}\text{CH}_2\text{CH(OH)}\text{CH}_2\text{CH}_3 \)

g. \( \text{MeO} \rightarrow \text{MeO} \rightarrow \text{MeO} + \text{H}_2\text{O} \)
3. Cyclic Esters and Amides: Provide products or starting reactants for the following condensation or hydrolysis reactions involving cyclic esters or amides.

a. 

\[ \text{HO} \quad \text{OH} \quad \xrightarrow{H^+} \]

b. 

\[ \text{O} \quad \text{O} \quad \xrightarrow{1. \text{NaOH}} \quad 1. \text{NaOH} \quad \xrightarrow{2. \text{H}_3\text{O}^+} \]

c. 

\[ \text{O} \quad \text{N} \quad \text{Cl} \quad \xrightarrow{1. \text{NaOH}} \quad 1. \text{NaOH} \quad \xrightarrow{2. \text{H}_3\text{O}^+} \]

\[
\text{Heat} \quad \xrightarrow{\text{Me}} \quad \text{HN} \quad \text{Me}
\]

d. 

4. Rank the following as acids or bases.

a. 

\[ \text{F} \quad \text{O} \quad \text{OH} \quad \text{CH}_3\text{NH}_3 \quad \text{NH}_3 \]

b. 

\[ \text{H}_2\text{O} \quad \text{PhNH}_3 \quad \text{CH}_3\text{NH}_3 \quad \text{NH}_3 \]

c. 

\[ \text{Et}_3\text{N} \quad \text{EtNH}_2 \quad \text{PhMgBr} \]
5. Provide reagents for the following transformations. There may be more than one solution.

a. 

b. 

c. 

d. 

e. 

f. 

6. Provide reagents for the following transformations. There may be more than one solution.

a. \[
\text{CH}_3\text{OCH}_3 \rightarrow \text{COOH}
\]

b. \[
\text{CH}_3\text{OCH}_3 \rightarrow \text{CON(CH}_3)_2
\]

c. \[
\text{CH}_3\text{OCH}_3 \rightarrow \text{C}_2\text{OPh}
\]

d. \[
\text{CH}_2\text{OH} \rightarrow \text{COCl}
\]

e. \[
\text{CH}_2\text{OH} \rightarrow \text{COOH}
\]

f. \[
\text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{COOH}
\]
7. Provide mechanism for the following reactions.

a. \(\text{CH}_3\text{OCH}_3\) \(\xrightarrow{\text{H}^+, \text{H}_2\text{O}}\) \(\text{CO}_2\text{H}\)

b. \(\text{CO}_2\text{H}\) \(\xrightarrow{1. \text{NaOH, H}_2\text{O}}\) \(\xrightarrow{2. \text{H}^+}\) \(\text{HO}_2\text{CO}_2\text{H}\)

c. \(\text{ClO}_2\text{H}\) \(\xrightarrow{\text{H}_2\text{O}}\) \(\text{CO}_2\text{H}\)

d. \(\text{CH}_3\text{NH}_2\) \(\xrightarrow{3 \text{CH}_3\text{Br, NaOH}}\) \((\text{CH}_3)_4\text{N}^+\) \(\text{Br}^-\)