Chapter 16:
Amines and Amides

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Amines are derivatives of ammonia, NH$_3$, where one or more hydrogen atoms have been replaced by an organic (R) group.

<table>
<thead>
<tr>
<th>Subclass</th>
<th>General Formula</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (1°)</td>
<td>R – N – H</td>
<td>CH$_3$ – N – H</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>CH$_3$ – N – CH$_3$</td>
</tr>
<tr>
<td>Secondary (2°)</td>
<td>R – N – R’</td>
<td>CH$_3$ – N – CH$_3$</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>Tertiary (3°)</td>
<td>R – N – R’</td>
<td>CH$_3$ – N – CH$_3$</td>
</tr>
<tr>
<td></td>
<td>R’</td>
<td>CH$_3$</td>
</tr>
</tbody>
</table>
COMMON NAMING FOR AMINES

- Alphabetically link the names of the alkyl or aromatic groups bonded to the nitrogen and attach the suffix –amine so the name is one word.

- Use di- or tri- prefixes for identical alkyl groups.

- Examples:

  \[
  \text{CH}_3\text{—NH}_2\quad \text{CH}_3\text{—NH—CH}_3\quad \text{CH}_3\text{CH}_2\text{—NH—CH}_3
  \]

  methylamine  dimethylamine  ethylmethylamine
IUPAC NAMING FOR PRIMARY AMINES

• The –NH₂ group is treated as a chain substituent called the amino group.

• Examples:

\[
\begin{align*}
\text{NH}_2 & \quad | \quad \text{Br} \\
\text{CH}_3 - \text{CH} - \text{CH}_3 & \quad | \\
\text{2-aminopropanol} & \quad | \\
\text{HO} - \text{CH}_2 - \text{CH} - \text{CH}_2 - \text{CH}_2 & \quad | \\
\text{4-amino-2-bromo-1-butanol} & \quad |
\end{align*}
\]
IUPAC NAMING FOR AMINES

- Name the longest chain attached to the nitrogen.
- Replace the final –e with –amine.
- Number the chain so the carbon bonded to the nitrogen has the lowest possible number.
- Number the other substituents on the carbon chain.
- An italic “N” is used as a prefix for a substituent on nitrogen.

Examples:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_3 \quad \text{CH}_3\quad \text{NH}_2 \quad \text{NHCH}_3
\]

2-pentanamine \quad 3-methyl-1-butanimine \quad N-methyl-2-butanimine
NAMING AROMATIC AMINES

- Aniline is the simplest aromatic amine.
- Compounds are named as substituted anilines.
- An italic “N” is used to indicate that an alkyl group is attached to the nitrogen and not to the ring.

Examples:

- Aniline
- 2-ethyl-N-methylaniline
PHYSICAL PROPERTIES OF AMINES

• The N-H bond is not quite as polar as the O-H bond.

• **Primary** and **secondary amines** can form hydrogen bonds between molecules.

• The hydrogen bonds are not as strong as those of alcohols, so **amine** boiling points are somewhat lower than those of alcohols.

• Simple, low molecular weight **amines** are gases at room temperature.

• Heavier, more complex compounds are liquids or solids.
### Table 16.2 Properties of Some Amines

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Melting Point (°C)</th>
<th>Boiling Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylamine</td>
<td>CH₃ — NH₂</td>
<td>−94</td>
<td>−6</td>
</tr>
<tr>
<td>ethylamine</td>
<td>CH₃CH₂ — NH₂</td>
<td>−81</td>
<td>17</td>
</tr>
<tr>
<td>dimethylamine</td>
<td>CH₃ — NH — CH₃</td>
<td>−93</td>
<td>7</td>
</tr>
<tr>
<td>diethylamine</td>
<td>CH₃CH₂ — NH — CH₂CH₃</td>
<td>−48</td>
<td>56</td>
</tr>
<tr>
<td>trimethylamine</td>
<td>CH₃ — N — CH₃</td>
<td>−117</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH₃</td>
<td></td>
</tr>
<tr>
<td>triethylamine</td>
<td>CH₃CH₂ — N — CH₂CH₃</td>
<td>−114</td>
<td>89</td>
</tr>
</tbody>
</table>
**Amines** can hydrogen bond with water, making smaller amine molecules (less than 6 carbon atoms) usually water soluble.

- 1° amine
- 2° amine
- 3° amine
Low molecular weight **amines** have an unpleasant odor reminiscent of decaying fish.

Some **amines** are partially responsible for the odor of decaying animal tissue.

\[
\text{H}_2\text{N}—\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2—\text{NH}_2
\]

*putrescine*  
*(1,4-diaminobutane)*

\[
\text{H}_2\text{N}—\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2—\text{NH}_2
\]

*cadaverine*  
*(1,5-diaminopentane)*
AMINE REACTIONS

- All amines behave as weak bases in water (similar to ammonia).

General reaction: $\text{R—NH}_2 + \text{H}_2\text{O} \Leftrightarrow \text{R—NH}_3^+ + \text{OH}^-$

- Example:

  $\text{CH}_3—\text{NH}_2 + \text{H}_2\text{O} \Leftrightarrow \text{CH}_3—\text{NH}_3^+ + \text{OH}^-$

  methylamine  methylammonium ion
AMINE REACTIONS (continued)

- All amines behave as weak bases and form salts when they react with acids such as HCl.

General reaction: \[ R\text{―NH}_2 + HCl \rightarrow R\text{―NH}_3^+\text{Cl}^- \]

- Example:

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

methylamine methylammonium chloride
• All **amines** behave as weak bases and form salts when they react with sulfuric, nitric, phosphoric, and carboxylic acids as well.

• Example:

\[
\text{CH}_3\text{CH}_2\text{—NH}_2 + \text{CH}_3\text{COOH} \rightarrow \text{CH}_3\text{CH}_2\text{—NH}_3^+\text{CH}_3\text{COO}^-
\]

ethylamine  acetic acid  ethylammonium acetate
AMINE SALTS

• Name as an **amine**, but change “amine” to “ammonium” and add the anion name.

• Examples:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 - N - H^+ Br^- \\
\text{CH}_2\text{CH}_3 & \\
\text{ethyltrimethylammonium bromide} & \quad (\text{CH}_3\text{CH}_2)_{3}\text{NH}^+ \text{CH}_3\text{COO}^- \\
\text{triethylammonium acetate}
\end{align*}
\]
• **Amine** salts are more water soluble than the parent **amine**, which is a useful characteristic for administering **amine** drugs.

• Example:

\[
\text{CH}_3\text{N} + \text{H}_2\text{SO}_4 \rightarrow \text{CH}_3\text{N}^+\text{HSO}_4^- 
\]

morphine (water insoluble) + H$_2$SO$_4$ → morphine sulfate (water soluble)
• Amine salts can be converted back to amine form by adding a strong base.

\[ R\text{–}NH_3^+\text{Cl}^- + \text{NaOH} \rightarrow R\text{–}NH_2 + H_2O + \text{NaCl} \]

• The form in which amines occur in solutions is pH dependent, just as is the case for carboxylic acids.

\[
\begin{align*}
\text{H}^+ & \\
R\text{–}NH_2 & \rightleftharpoons R\text{–}NH_3^+ \\
\text{OH}^- & \\
\text{amine} & \quad \text{amine salt}\\
\text{(high pH)} & \quad \text{(low pH)}
\end{align*}
\]
• **Quaternary ammonium salts** have four alkyl groups attached to the nitrogen.

• Unlike other **amine salts**, **quaternary salts** contain no hydrogen attached to the nitrogen that can be removed by adding a base.

• **Quaternary salts** are present in solution in only one form, which is independent of the pH of the solution.
Important \textbf{quaternary ammonium salts} include:

- choline – component of certain lipids
- acetylcholine – involved in transmission of nerve impulses from one cell to another
- benzalkonium chloride (Zephiran®) – well-known antiseptic compound that kills many pathogenic (disease-causing) bacteria and fungi on contact
AMINE SALTS (continued)

• benzalkonium chloride (Zephiran®) – well-known antiseptic compound that kills many pathogenic (disease-causing) bacteria and fungi on contact
  • detergent action destroys the membranes that coat and protect the microorganisms
  • recommended as a disinfectant solution for skin and hands prior to surgery and for sterile storage of instruments

• other anti-infectives that contain quaternary ammonium salts:
  • Phemerol®, Bactine®, and Ceepryn®
• Amines react with acid chlorides or acid anhydrides to form amides.
The amide linkage can be thought of as separating an ammonia or amine portion and a portion derived from a carboxylic acid.

Note: The reaction of an amine with a carboxylic acid normally produces a salt and not an amide.
**AMIDE FORMATION (continued)**

- **Primary** and **secondary amines** can form **amides**.
- **Tertiary amines** do not react to form **amides**.

![Chemical Reaction Diagram]

\[
\text{O} \\
\text{R—C—Cl} + \text{R’—N—H} \rightarrow \text{R—C—N—R’} + \text{HCl}
\]

酸酐 羧酸

\[
\text{酸酐} + \text{胺} \rightarrow \text{酸胺} + \text{羧酸}
\]
• Examples:

\[
\begin{align*}
\text{CH}_3\text{C} &= \text{O} \quad \text{CH}_3\text{O} \\
\text{O} \quad \text{O} &\quad \text{CH}_3
\end{align*}
\]

\[
\quad + \quad \text{H} - \text{N} - \text{H} \quad \rightarrow \quad \text{CH}_3\text{C} - \text{N} - \text{H} + \quad \text{CH}_3\text{C} - \text{O} \quad \text{H}
\]

acetic anhydride  ammonia  acetamide  acetic acid

\[
\begin{align*}
\quad \text{O} \quad \text{C} - \text{Cl} \\
\text{H} - \text{N} - \text{CH}_3
\end{align*}
\]

\[
\quad + \quad \text{H} - \text{N} - \text{CH}_3 \quad \rightarrow \quad \text{N} - \text{C} - \text{NH} - \text{CH}_3 + \quad \text{HCl}
\]

benzoyl chloride  methylamine  \(\text{N-methylbenzamide}\)
AMIDE FORMATION (continued)

\[
\text{benzoyl chloride} + \text{dimethylamine (a } 2^\circ \text{ amine)} \rightarrow \text{N,N-dimethylbenzamide} + \text{HCl}
\]
AMINE REACTION MAP

- **An ammonium ion (plus OH⁻)**
  - Reacts with **H₂O** to form **Amine**
  - Reacts with **HCl** to form **Salt**
  - Reacts with **Acid anhydride** to form **Amide (plus a carboxylic acid)**
  - Reacts with **Acid chloride** to form **Amide (plus HCl)**
POLYAMIDE FORMATION

- Reaction of diacid chlorides with diamines produces polyamides that, like polyesters, are condensation polymers.
- The repeating units in polyamides are held together by amide linkages.

\[
\begin{align*}
\text{adipoyl chloride} & \quad \text{hexamethylenediamine} \\
n\text{Cl} - \text{C}-(\text{CH}_2)_4 - \text{C} - \text{Cl} & \quad n\text{H}_2\text{N}-(\text{CH}_2)_6 - \text{NH}_2 \\
\text{o} & \quad \text{o} \\
\text{amide linkages} & \quad \text{amide linkage} \\
\text{polyamide nylon} & \quad n\text{HCl}
\end{align*}
\]
Three billion pounds of nylon and related polyamides are produced annually.
- 60% nylon fiber for home furnishings (e.g. carpet)
- ~40% textile fiber in clothing and tire cord
- minor uses: fasteners, rope, parachutes, paintbrushes, electrical parts, medical tubing, nylon sutures
- Proteins are polyamides (e.g. silk and wool).
A neurotransmitter is a substance that acts as a chemical bridge in nerve impulse transmission between nerve cells.
IMPORTANT AMINE NEUROTRANSMITTERS

- Acetylcholine
- Dopamine – synthesized from the amino acid tyrosine
- Norepinephrine – synthesized from dopamine, may be associated with mental illness
- Serotonin – synthesized from the amino acid tryptophan, may be associated with mental illness
Norepinephrine (NE):
- produces a feeling of elation when excess is formed in the brain.
- in extreme excess can induce a manic state.
- in low levels may cause depression.
- activates six different receptors in body.
- has a stimulant action (like epinephrine) that can be reduced by beta blockers, which are used to:
  - treat cardiac arrhythmias, angina, and hypertension,
  - and slightly decrease the force of each heartbeat.
  - Depression can be side effect.
- is synthesized in body from amino acid tyrosine.
Each step is catalyzed by at least one enzyme.
Each intermediate has physiological activity.
Note: Tyrosine is an essential amino acid because it must be obtained from the diet.
• Dopa is a treatment for Parkinson’s disease.

• Dopamine is used to treat low blood pressure.
Serotonin:

- is a neurotransmitter.
- is produced from the amino acid tryptophan.
- influences sleeping, regulation of body temperature, and sensory perception.
- mimicking drugs are used to treat depression, anxiety, and obsessive-compulsive disorder.
- blockers used to treat migraine headaches and relieve nausea from cancer chemotherapy.
OTHER BIOLOGICALLY IMPORTANT AMINES

• Epinephrine (adrenaline):
  • is more important as a hormone than a neurotransmitter.
  • is synthesized in the adrenal gland.
  • acts to increase the blood level of glucose for a sudden burst of energy.
  • is released in response to pain, anger, or fear.
  • is called the “fight-or-flight” hormone.

\[
\text{HO} - \text{CHCH}_2 - \text{NH} - \text{CH}_3
\]

epinephrine (adrenaline)
Epinephrine (continued):
- Raises blood pressure by increasing the rate and force of heart contractions and constricting peripheral blood vessels.
- Is a component of injectable local anesthetics.
- Is used to reduce hemorrhage, treat asthma attacks, and combat anaphylactic shock.

[Chemical structure of epinephrine (adrenaline)]
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

- Amphetamine (a.k.a. Benzedrine®):
  - is a powerful nervous system stimulant.
  - is similar in structure to epinephrine.
  - raises glucose level in the blood.
  - increases pulse rate and blood pressure.
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

- Other phenethylamine compounds:
  - also act as powerful nervous system stimulants.
  - are thought of as amphetamine derivatives.
  - are called **amphetamines**, which:
    - are used both legally and illegally.
    - have drug culture names: bennies, pep pills, reds, red devils, speed, dexies, and uppers.
    - some (STP, speed, mescaline) cause hallucinations.
    - when abused have severe detrimental effects on body and mind.

![Chemical structure](image)

*N-methylyphenylethylamine (Methedrine®, or “speed”)*
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

• **Amphetamines** (continued):
  • are addictive and concentrate in brain and nervous system.
  • produce long periods of sleeplessness, weight loss, and paranoia.
  • prompt the use of other drugs to prevent the “crash” brought on by discontinuation of use.
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

• **Alkaloids:**
  • are a class of nitrogen-containing organic compounds obtained from plants.
  
• Examples:
  • **Nicotine:**
    • is found in tobacco.
    • in small doses is a stimulant and not especially harmful.
    • is habit-forming.
    • addiction exposes habitual tobacco users to other harmful substances (tars, carbon monoxide, and polycyclic carcinogens).
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

• Caffeine:
  • is found in coffee, cola drinks, tea, chocolate, and cocoa.
  • is a mild stimulant of the respiratory and central nervous systems.
  • has side effects nervousness and insomnia.
  • is a mild diuretic.
  • is used in pain relievers, cold remedies, diet pills, and “stay-awake” pills.
  • should be prudently consumed by pregnant women because it:
    • enters the bloodstream,
    • crosses the placental barrier,
    • and reaches the fetus.
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

- Quinine is used to treat malaria.
- Atropine is a preoperative drug used to:
  - relax muscles,
  - reduce the secretion of saliva in surgical patients, and
  - dilate the pupil of the eye in patients undergoing eye examinations.
Other biologically important amines (continued)

- Opium:
  - is the dried juice of the poppy plant.
  - is used as a painkilling drug.
  - contains numerous alkaloids (e.g. morphine and codeine), which:
    - are central nervous system depressants.
    - exert a soothing effect on the body.
    - are useful as painkillers (e.g. morphine).
    - are useful to depress the action of cough center in brain (e.g. codeine in cough syrup).
  - are all addictive.
OTHER BIOLOGICALLY IMPORTANT AMINES (continued)

• Heroin:
  • is a derivative of morphine.
  • is one of more destructive hard illegal drugs.
  • addicts are likely to commit crimes to support their habits.

\[
\text{Heroin: } \text{CH}_3\text{C-O} \quad \text{N} \quad \text{CH}_3
\]

\[
\text{CH}_3\text{C-O} \quad \text{O} \quad \text{O} \quad \text{heroin}
\]
NAMING AMIDES

- Use the carboxylic acid’s name and drop the –ic ending (common name) or –oic ending (IUPAC name) and change to –amide.

- Examples:
  
  \[
  \begin{align*}
  \text{formic acid} & \quad \rightarrow \quad \text{formamidine} \\
  \text{methanoic acid} & \quad \rightarrow \quad \text{methanamide} \\
  \text{benzoic acid} & \quad \rightarrow \quad \text{benzamide}
  \end{align*}
  \]
NAMING AMIDES (continued)

• Use $N$ to denote alkyl groups attached to the nitrogen atom.

• Examples:

$\begin{align*}
\text{O} & \\
\| & \\
\text{H} - \text{C} - \text{NH} - \text{CH}_3 & \\
\end{align*}$

$\begin{align*}
\text{CH}_3 - \text{C} - \text{N} - \text{CH}_3 & \\
\| & \\
\text{CH}_3 & \\
\end{align*}$

$N$-methylformamide

$N$-methylmethanamide

$N,N$-dimethylacetamide

$N,N$-dimethylethanamide
PHYSICAL PROPERTIES OF AMIDES

- Hydrogen bonding between unsubstituted amides causes them to have high melting points.
- Formamide is a liquid at room temperature.
- All other unsubstituted amides are solids at room temperature.
• **Amides** can form hydrogen bonds with water, making smaller amide molecules (less than 6 carbon atoms) rather water soluble.
**AMIDE REACTIONS**

- **Amides** are neither acidic nor basic.
- **Amide** hydrolysis is the reverse of **amide** formation; an **amide** is cleaved to produce a carboxylic acid and an **amine** or ammonia.

\[
\text{R} - \text{C} - \text{NH} - \text{R'} + \text{H}_2\text{O} \xrightarrow{\text{Acid or base, Heat}} \text{R} - \text{C} - \text{OH} + \text{R'} - \text{NH}_2
\]

- **Amide** hydrolysis is a central reaction in the digestion of proteins and the breakdown of proteins within cells.
- In the body, this hydrolysis is catalyzed by enzymes.
The products of an amide hydrolysis depend on whether the reaction occurs in acidic or basic conditions.

One hydrolysis product must always be in the form of a salt.

\[
\text{amide} + \text{H}_2\text{O} + \text{HCl} \xrightarrow{\text{Heat}} \text{carboxylic acid} + \text{amine salt}
\]

\[
\text{amide} + \text{NaOH} \xrightarrow{\text{Heat}} \text{carboxylate salt} + \text{amine}
\]
AMIDE REACTIONS (continued)

- Examples:

  \[
  \text{O} \\
  \text{CH}_3\text{\textendash}C\text{\textendash}\text{NH}_2 + \text{H}_2\text{O} + \text{HCl} \xrightarrow{\text{Heat}} \text{CH}_3\text{\textendash}C\text{\textendash}\text{OH} + \text{NH}_4^+\text{Cl}^- \\
  \text{acetamide} \\
  \text{O} \\
  \text{CH}_3\text{\textendash}C\text{\textendash}\text{NH} - \text{CH}_3 + \text{H}_2\text{O} + \text{HCl} \xrightarrow{\text{Heat}} \text{CH}_3\text{\textendash}C\text{\textendash}\text{OH} + \text{CH}_3 - \text{NH}_3^+\text{Cl}^- \\
  \text{N-methylacetamide} \\
  \text{O} \\
  \text{CH}_3\text{\textendash}C\text{\textendash}\text{NH} - \text{CH}_3 + \text{NaOH} \xrightarrow{\text{Heat}} \text{CH}_3\text{\textendash}C\text{\textendash}\text{O}^-\text{Na}^+ + \text{CH}_3 - \text{NH}_2 \\
  \text{N-methylacetamide} \\
  \text{O} \\
  \text{CH}_3\text{\textendash}C\text{\textendash}\text{O}^-\text{Na}^+ + \text{CH}_3 - \text{NH}_2 \\
  \text{sodium acetate} \\
  \text{ammonium chloride} \\
  \text{acetic acid} \\
  \text{methylammonium chloride} \\
  \text{methylamine}
# IMPORTANT AMIDES IN MEDICINE

## Table 16.3 Some Important Amides in Medicine

<table>
<thead>
<tr>
<th>Structure</th>
<th>Generic Name (Trade Name)</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Thiopental Struct" /></td>
<td>thiopental (Pentothal®)</td>
<td>Intravenous anesthesia</td>
</tr>
<tr>
<td><img src="image2.png" alt="Amobarbital Struct" /></td>
<td>amobarbital (Amytal®)</td>
<td>Treatment of insomnia</td>
</tr>
</tbody>
</table>
## Table 16.3 Some Important Amides in Medicine

<table>
<thead>
<tr>
<th>Structure</th>
<th>Generic Name (Trade Name)</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>diazepam (Valium®)</td>
<td>Tranquilizer</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>ampicillin (Polycillin®)</td>
<td>Antibiotic</td>
</tr>
</tbody>
</table>