Chapter 20

Amines

Classification of amines

- Amines are organic nitrogen compounds, formed by replacing one or more hydrogen atoms of ammonia (NH₃) with alkyl groups.
- Amines are classified as 1°, 2°, or 3° based on the number of alkyl groups bonded to the nitrogen atom.

\[
\begin{align*}
\text{1° amine} & \quad \text{(1 R group on N)} \\
\text{2° amine} & \quad \text{(2 R groups on N)} \\
\text{3° amine} & \quad \text{(3 R groups on N)}
\end{align*}
\]

Introduction

- Like ammonia, the amine nitrogen atom has a nonbonded electron pair, making it both a base and a nucleophile.
- As a result, amines react with electrophiles to form quaternary ammonium salts—compounds with four bonds to nitrogen.

Structure and Bonding

- An amine N atom is sp³ hybridized and trigonal pyramidal, with bond angles of approximately 109.5°.
- Since an amine nitrogen has four different groups around it, it is technically a stereogenic center.
**Amines**

**Structure and Bonding**
- However, the chirality of the amine nitrogen can be ignored because the two enantiomers interconvert by passing through a trigonal planar (achiral) transition state.

![Image of amines structure and bonding]

**Amines**

**Structure and Bonding**
- In contrast, the chirality of a quaternary ammonium salt with four different groups cannot be ignored. Because there is no nonbonded electron pair on the nitrogen atom, interconversion cannot occur, and the N atom is just like a carbon atom with four different groups around it.

![Image of quaternary ammonium salt]

**Amines**

**Nomenclature**
- Amines are named using either systematic or common names.
- To assign a systematic name, find the longest continuous chain bonded to the amine nitrogen, and change the \(-e\) ending of the parent alkane to the suffix \(-amine\). Then use the usual rules of nomenclature to number the chain and name the substituents.
- To assign a common name, name the alkyl group bonded to the nitrogen atom and add the word amine, forming a single word.

| Examples | CH$_3$NH$_2$ | Systematic name: methanamine  Common name: methylamine | N$_2$H$_2$ | Systematic name: cyclonexanamine  Common name: cyclohexylamine |

**Amines**

**Nomenclature**
- Secondary and tertiary amines having identical alkyl groups are named using the prefix di- or tri- with the name of the primary amine.

| Secondary Amines | Diethylamine (N,N-diethyl-1,2-ethanamine) | Ethylmethylamine (N,N-diethylthetanamine) |
| Tertiary Amines | Tris(2,2-dimethylaminopropyl)amine (N,N,N-triethyl-1-propanamine) | Diproprylamine (N,N-diethyl-1,2-propanamine) |

**Amines**

**Nomenclature**
- Secondary and tertiary amines having more than one kind of alkyl group are named as N-substituted primary amines by listing all the constituents in an alphabetic order and putting prefix N before them.
Amines

Nomenclature

• The substituent NH₂ in the IUPAC system is called amino group.

2-Aminoethanol 3-Aminopropanoic acid

• Aromatic amines are named as derivatives of aniline.

Aniline N-ethylaniline o-bromotoluene

• There are many different nitrogen heterocycles, each with a different name. The N atom is considered to be at position “1”.

pyridine pyrrole pyrrole pyridazine

Interesting and Useful Amines

The neurotransmitter dopamine.

Cocaine, amphetamines, and several other addicting drugs (based on amines) increase the level of dopamine in the brain, which results in a pleasurable “high.” With time, the brain adapts to increased dopamine levels, so more drug is required to produce the same sensation.

Basicity of Amines: Amine Salts

• Amines are weak bases

• Relative basicity of amines can be compared in terms of pKₐ values for their respective conjugate acids

\[ \text{RNH}_2 + \text{H}_2\text{O} \rightleftharpoons \text{RNH}_3^+ + \text{OH}^- \]

\[ K_b = \frac{[\text{RNH}_3^+][\text{OH}^-]}{[\text{RNH}_2]} \]

\[ \text{pK}_a = -\log K_b \]

• Primary alkyl amines are more basic than ammonia

Pictorial representation of the relationship between the strength of the amine and its conjugate acid.
In the gas phase, basicity in the family of methylamines increases with increasing methyl substitution. More alkyl substitution results in more stabilization of the alkylaminium ion.

\[ (\text{CH}_3)_2\text{N} > (\text{CH}_3)\text{NH} > \text{CH}_3\text{NH}_2 > \text{NH}_3 \]

In aqueous solution, trimethylamine is less basic than dimethyl- or methylamine. An alkylaminium ion in water is solvated and stabilized by hydrogen bonding of its hydrogens with water. The trimethylaminium ion has only one hydrogen with which to hydrogen bond to water. The trimethylaminium ion is solvated less well (and therefore stabilized less) than the dimethylaminium ion, which has two hydrogen atoms for hydrogen bonding.

\[ (\text{CH}_3)_2\text{NH} > \text{CH}_3\text{NH}_2 > (\text{CH}_3)_2\text{N} > \text{NH}_3 \]

### Basicity of Arylamines

Arylamines are weaker bases than the corresponding nonaromatic cyclohexylamines. Why?

- The unshared electron pair on nitrogen of an arylamine is delocalized to the ortho and para positions of the ring. The lone pair is less available for protonation, i.e., it is less basic.

Protonation of aniline is also disfavored because a protonated arylamine has only two resonance forms. Anilinium ion is not as well stabilized by resonance as aniline itself.

\[ \Delta \text{H}^\circ \text{ for protonation of aniline is larger than } \Delta \text{H}^\circ \text{ for protonation of cyclohexyl amine} \]

### Amines versus Amides

Amides are much less basic than amines. The pK_a of a protonated amide is typically about zero. One reason for this much lower basicity is that the amide is greatly stabilized by resonance but the protonated amide is not. Protonation at the oxygen allows resonance stabilization of the positive charge.
Amines as Bases

### Table 25.3: Table of pKₐ Values of Some Representative Organic Nitrogen Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKₐ of the</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH₃</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃NH₂</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>CH₃NH₂NH₂</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>CH₃N₂H₂</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃CONH₂</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>NH₂CONH₂</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Amines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCONH₂</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Preparations of Amines

- **By Nucleophilic Substitution Reactions**
  - **Alkylation of Ammonia**
    - Reaction of ammonia with an alkyl halide leads to an aminium salt
    - The salt is treated with base to give the primary amine
    - The method is limited because multiple alkylations usually occur
    - Using an excess of ammonia helps to minimize multiple alkylations

- **Alkylation of Azide Ion followed by Reduction**
  - A primary amine is prepared more efficiently by reaction of the azide ion with an alkyl halide and subsequent reduction of the alkylazide to the amine
  - Primary amines can also be made cleanly by the Gabriel Synthesis
  - The first step in the Gabriel synthesis is alkylation of potassium phthalimide
  - Reaction of the diethylphthalimide with hydrazine in boiling ethanol gives the primary amine

- **The Gabriel Synthesis**
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#### Aminium Salts and Quaternary Ammonium Salts

- **Protonation of amines with acids leads to formation of aminium salts**
  - Aminium salts are formed from 1°, 2° or 3° amines with acids. Note that aminium ions bear at least one hydrogen

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

- **Quaternary ammonium salts have four groups on the nitrogen**
  - The nitrogen atom is positively charged but does not bear a hydrogen atom

- **Aminium and quaternary ammonium halides are not basic because they do not have an unshared electron pair on nitrogen**
  - However, quaternary ammonium hydroxide salts act as strong bases

- **Many aminium chlorides, bromides, iodides and sulfates are water soluble**
Preparation of Aromatic Amines by Reduction of Nitro Compounds

Aromatic amines can be synthesized by reduction of the corresponding nitro compound.

\[
\text{Ar-NO}_2 + \text{H}_2 + \text{Pt} \rightarrow \text{Ar-NH}_2
\]

General Procedure

Specific Example

Preparation of Primary, Secondary and Tertiary Amines through Reductive Amination

Aldehydes and ketones react with ammonia, primary or secondary amines to yield imines or iminium ions.

The imines and iminium ions having C=N double bond can then be reduced to new primary, secondary or tertiary amines, respectively.

The reduction can be accomplished using catalytic hydrogenation or a hydride reducing reagent.

NaBH₃CN and LiBH₃CN are especially effective in reductive aminations.

Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

Reduction of nitriles or oximes yield primary amines.

Reduction of amides can yield primary, secondary or tertiary amines.

Amides can be prepared from acid chlorides, acid anhydrides, and esters (Section 15.4).
Reduction can be accomplished by using catalytic hydrogenation or LiAlH₄.

**INTERESTING:** Monoalkylation of an amine can be achieved by acylation of the amine and then reduction of the resulting amide.

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**Reactions of Amines (Reminder)**

*The lone pair of the amine nitrogen atom accounts for most chemistry of amines.*

**Acids-Bases Reactions**

An amine acting as a base:

**Alkylation**

An amine acting as a nucleophile in an alkylation reaction.

**The nitrogen lone pair can also make a carbon nucleophilic by resonance.**

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**Reactions of Amines with Nitrous Acid**

Nitrous acid (HONO) is a weak acid and is prepared in situ by reaction of sodium nitrite with a strong aqueous acid.

\[ \text{HONO} \quad \text{reaction of sodium nitrite with a strong aqueous acid} \]

**Reaction of Primary Aliphatic Amines with Nitrous Acid**

Primary amines undergo diazotization with nitrous acid.

- The unstable diazonium salts decompose to form carbocations.
- The carbocations react further to give alkenes, alcohols, and alkyl halides.

**General Reaction**

\[ R-NH_2 + \text{HONO} \rightarrow R-N_2+ + \text{H}_2\text{O} \]

**Primary aliphatic amine**

\[ R-NH_2 + \text{HONO} \rightarrow R-N_2+ + \text{H}_2\text{O} \]

**Aliphatic diazonium salt**

(Alkene, alcohol, alkyl halide)

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**Reaction of Primary Arylamines with Nitrous Acid**

Reaction of primary arylamines with nitrous acid results in the formation of relatively stable arenediazonium salts.

- This reaction occurs through the intermediacy of an N-nitrosoamine.
- The N-nitrosoamine is converted to a diazonium ion in a series of steps.

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Replacement Reactions of Arenediazonium Salts

- Aryldiazonium salts react readily with various nucleophilic reagents to give a wide variety of aromatic compounds.
  - The aryldiazonium salt is made from the corresponding arylamine.
  - The arylamine can be made by reduction of a nitroaromatic compound.

The mechanism of the Sandmeyer reaction is not well-understood but is thought to occur via radicals.

- The Sandmeyer Reaction: Replacement of the Diazonium Group by -Cl, -Br or -CN

- Replacement by -I
  - Reaction of arenediazonium salts with potassium iodide gives the aryl iodide.

- Replacement by -F
  - A diazonium fluoroborate is isolated, dried and heated until it decomposes to the fluoroaromatic product.

- Replacement by -OH
  - An aryl diazonium salt is placed in aqueous solution with a large excess of cupric nitrate and then treated with cuprous oxide.

Coupling Reactions of Arenediazonium Salts

- Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines.
  - The reaction is called a diazo coupling reaction.

- Coupling with phenol occurs best in slightly alkaline solution.
  - The alkaline solution produces a phenoxide ion that couples more rapidly.
  - If the solution is too alkaline, a nonreactive diazohydroxide is produced.
In 1935, Gerhard Domagk first used a synthetic dye, prontosil, to kill bacteria. Prontosil and other sulfur containing antibiotics are collectively known as sulfa drugs. Prontosil is not the active ingredient itself—In cells, it is metabolized to sulfanilamide, the active drug.

**Sulfa Drugs**

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**Reactions of Amines with Sulfonyl Chlorides**

- Primary and secondary amines react with sulfonyl chlorides to produce sulfonamides.
- A sulfonamide can be hydrolyzed to an amine by heating with aqueous acid.

**Spectroscopic Analysis**

- **Infrared Spectra**
  - Primary and secondary amines are characterized by N-H stretching vibrations in the 3300-3555 cm⁻¹ region.
  - Primary amines give two absorptions (from symmetric and asymmetric stretching); secondary amines give one absorption.

- **1H NMR Spectra**
  - Primary and secondary amines have broad, uncoupled N-H peaks at δ 6-7.
  - N-H protons will exchange with D₂O and disappear from the 1H spectrum.
  - Protons on carbons adjacent to the nitrogen appear at δ 2.2-2.9.

- **13C NMR Spectra**
  - Carbons bonded to nitrogen exhibit 13C signals not as far downfield (δ 20-70) as carbons bonded to oxygen (δ 40-80) due to the lesser electronegativity of nitrogen as compared to oxygen.
  - The deshielding effect of the nitrogen atom decreases with distance.

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Hofmann Elimination

- The Hofmann elimination converts an amine into an alkene.

- The Hofmann elimination consists of three steps, as shown for the conversion of propylamine to propene.

The general E2 mechanism for the Hofmann elimination is shown below.

All Hofmann elimination reactions result in the formation of a new \( \pi \) bond between the \( \alpha \) and \( \beta \) carbon atoms, as shown for cyclohexylamine and 2-phenethylamine.

Amines as Resolving Agents

- A chiral amine can be used to resolve a racemic mixture of carboxylic acids by formation of diastereomeric salts.
- Diastereomers can be separated on the basis of differences in physical properties.
- Acidification of the separated diastereomeric salts gives the resolved carboxylic acids.
Preparation of Primary Amines by the Hofmann and Curtius Rearrangements

An unsubstituted amide can be converted to a primary amine by formal loss of the amide carbonyl through the Hofmann rearrangement (also called the Hofmann degradation).

$$R-C-CONH_2 + Br_2 + 4 NaOH \rightarrow RCONH_2 + 2 NaBr + Na_2CO_3 + 2 H_2O$$

The first two steps of the mechanism result in N-bromination of the amide.

- The N-bromamide is deprotonated and rearranges to an isocyanate.
- The isocyanate is hydrolyzed to a carbamate which decarboxylates to the amine.

Oxidation of Amines

Primary and secondary amines undergo N-oxidation, but useful products are not obtained because of side-reactions.

Tertiary amines undergo clean N-oxidation.
**Replacement by Hydrogen: Deamination by Diazotization**

- An arenediazonium salt can react with hypophosphorous acid (H₃PO₂) to replace the diazonium group with a hydrogen atom.
  - This reaction can be used to remove an amino group that was important early in a synthesis as an ortho, para director.
  - Example: m-Bromotoluene cannot be made directly from either toluene or bromobenzene.
  - N-Acylation is used to reduce the activating effect of the amine.

**The Hinsberg Test**

- This test can distinguish between 1°, 2° and 3° amines.
  - An amine and benzenesulfonyl chloride are mixed with aqueous potassium hydroxide; the reaction is acidified in a second step.
  - The results are different depending on the class of amine.
  - A benzenesulfonamide from a primary amine is soluble in basic solution, but precipitates upon acidification.

**The Cope Elimination**

- A tertiary amine oxide will undergo elimination to the alkene when heated.
  - Tertiary amine oxides can be made from tertiary amines by reaction with hydrogen peroxide.
  - Amine oxide elimination is syn and proceeds via a cyclic transition state.