Chapter 24: Amines

Amines: Nitrogen containing organic compounds

Organic derivatives of ammonia, \( \text{NH}_3 \),
Nitrogen atom have a lone pair of electrons, which potentially make amines both basic and nucleophilic.

There are many naturally occurring organic compounds that contain nitrogen (alkaloids)

24.1: Naming Amines

Alkyl-substituted (alkylamines) or aryl-substituted (arylamines)

Classified: \( 1^\circ \) (R NH\(_2\)), \( 2^\circ \) (R\(_2\)NH), \( 3^\circ \) (R\(_3\)N) and \( 4^\circ \) (R\(_4\)N\(^+\))

Although the terminology is the same, this designation of amines is different from that of alcohols.
**Amine nomenclature:**
The nomenclature for primary amines is similar to that of alcohols, the suffix \(-\text{amine}\) can be used in place of the final \(-\text{ol}\). Consider the \(-\text{NH}_2\) group as an \(\text{amino}\) substituent on the parent chain.

<table>
<thead>
<tr>
<th>Chain</th>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
</table>
| \(\text{CH}_3\text{CH}_2\text{CH}_3\) | butane         | ![butane](attachment)
| \(\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}\) | 1-butanol       | ![1-butanol](attachment)
| \(\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2\) | 1-butanamine    | ![1-butanamine](attachment) (butylamine)
| \(\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2\) | 2-butanamine    | ![2-butanamine](attachment) (2-aminobutane)
| \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2\) | 1,4-diaminobutane | ![1,4-diaminobutane](attachment) (putrescine)
| \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2\) | 1,5-diaminopentane | ![1,5-diaminopentane](attachment) (cadaverine)
| \(\text{C}_6\text{H}_5\text{NH}_2\) | aniline         | ![aniline](attachment)
| \(\text{C}_6\text{H}_5\text{OH}\) | \(\alpha\)-toluidine | ![\(\alpha\)-toluidine](attachment)
| \(\text{C}_6\text{H}_5\text{NH}_2\) | \(p\)-phenylenediamine | ![\(p\)-phenylenediamine](attachment)

**Symmetrical secondary and tertiary amines** are named by adding the prefix \(\text{di-}\) or \(\text{tri-}\) to the alkyl group. **Unsymmetrical secondary and tertiary amines** are named as \(N\)-substituted primary amines. The largest alkyl group is the parent name, and other alkyl groups are considered \(N\)-substituents.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="attachment" alt="diphenylamine" /></td>
<td>diphenylamine</td>
</tr>
<tr>
<td><img src="attachment" alt="diisopropylamine" /></td>
<td>diisopropylamine</td>
</tr>
<tr>
<td><img src="attachment" alt="triethylamine" /></td>
<td>triethylamine</td>
</tr>
<tr>
<td><img src="attachment" alt="N,N-dimethylpropylamine" /></td>
<td>(N,N)-dimethylpropylamine</td>
</tr>
<tr>
<td><img src="attachment" alt="N-ethyl-N-methylcyclohexylamine" /></td>
<td>(N)-ethyl-(N)-methylcyclohexylamine</td>
</tr>
</tbody>
</table>

Many arylamines go by non-systematic nomenclature.
The nomenclature of heterocyclic amines is highly specialized and often non-systematic.

\[
\text{pyridine} \quad \text{pyrrole} \quad \text{quinoline} \quad \text{imidazole} \quad \text{pyrimidine} \\
\text{indole} \quad \text{quinoxoline} \quad \text{pyrrolidine} \quad \text{piperidine} \quad \text{morpholine}
\]

### 24.2 Structure and Bonding in Amines

The nitrogen of alkylamines is \(sp^3\) hybridized and tetrahedral.

In principle an amine with three different substituents on the nitrogen is chiral with the lone pair of electrons being the fourth substituent; however, for most amines the *pyramidal inversion* of nitrogen is a racemization mechanism.

The barrier to nitrogen inversion is about 25 KJ/mol (very rapid at room temperature).
24.3 Properties and Sources of Amines
Primary and secondary amines, like water and alcohols, can be hydrogen bond donors (N-H) and hydrogen bond acceptors (the lone pair).

24.5 Basicity of Amines
The chemistry of amines is dominated by the basicity of the nitrogen lone pair.

Alkyl amines are stronger bases than water, alcohols or ethers:

\[
\text{R}_3\text{N:} + \text{H}_2\text{O} \rightleftharpoons \text{R}_3\text{NH}^+ + \text{HO}^- \\
K_b = \frac{[\text{R}_3\text{NH}^+][\text{HO}^-]}{[\text{R}_3\text{N}]} \\
pK_b = -\log K_b
\]

pK_b values are rarely used. Amines basicity is measured by the pK_a of the conjugate acid. (pK_b + pK_a = 14)

The conjugate base of a weak acid is a strong base:
Higher pK_a = weaker acid = stronger conjugate base
The conjugate base of a strong acid is a weak base:
Lower pK_a = stronger acid = weaker conjugate base

\[
\text{R}_3\text{NH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{R}_3\text{N}: \\
\text{lower pK_a} \\
\text{R}_3\text{NH}^+ \text{ more acidic} \\
\text{R}_3\text{N less basic}
\]

\[
\text{higher pK_a} \\
\text{R}_3\text{NH}^+ \text{ less acidic} \\
\text{R}_3\text{N more basic}
\]
Table 24.1 (p. 899): pK\textsubscript{a} values of ammonium ions

Alkyl ammonium ions, \( R_3\text{NH}^+ X^- \), have pKa values in the range of 10-11 (ammonium ion, \( \text{H}_4\text{N}^+ X^- \), has a pK\textsubscript{a} \( \sim 9.25 \)).

The ammonium ions of aryl amines and heterocyclic aromatic amines are considerably less basic than alkyl amines (pK\textsubscript{a} \( \sim 5 \) or less). The nitrogen lone pair is less basic if it is in an \( sp^2 \) hybridized orbital (versus an \( sp^3 \)).

<table>
<thead>
<tr>
<th>Structure</th>
<th>pK\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{NH}_4^+ )</td>
<td>9.26</td>
</tr>
<tr>
<td>( \text{H}_3\text{CH}_2\text{C})\text{NH}_3^+ )</td>
<td>10.8</td>
</tr>
<tr>
<td>( \text{H}_3\text{CH}_2\text{C})_2\text{NH}_2^+ )</td>
<td>10.7</td>
</tr>
<tr>
<td>( \text{H}_3\text{CH}_2\text{C})_3\text{NH}^+ )</td>
<td>11.0</td>
</tr>
</tbody>
</table>

24.5 Basicity of Substituted Arylamines

The lone pair of electrons on the nitrogen of aniline are conjugated to the \( \pi \)-electrons of the aromatic ring and are therefore less available for acid-base chemistry. Protonation disrupts the conjugation.

Substituents can greatly influence the basicity of the aniline. The effect is dependent upon the nature and position of the substituent (recall the acidity of substituted phenols).
Electron-donating substituents (-CH$_3$, -OH, -OCH$_3$) make the substituted aniline more basic than aniline itself (the pKa of the anilinium ion is higher than 4.6)

Electron-withdrawing substituents (-Cl, -NO$_2$) make the substituted aniline less basic than aniline itself (the pKa of the anilinium ion is lower than 4.6)

See Table 24.2 (p. 903)

$$\text{Y} = \text{-NH}_2, \text{pK}_a = 6.15$$
$$\text{-OCH}_3, \text{pK}_a = 5.34$$
$$\text{-CH}_3, \text{pK}_a = 5.08$$
$$\text{-H}, \text{pK}_a = 4.63$$
$$\text{-Cl}, \text{pK}_a = 3.98$$
$$\text{-CN}, \text{pK}_a = 1.74$$
$$\text{-NO}_2, \text{pK}_a = 1.00$$

Problem 24.4: Which compound is more basic?

a) \(\text{NaOH}\) - or - \(\text{H}_3\text{C} \text{NH}_2\)

b) \(\text{H}_2\text{CH}_2\text{C} \text{NH}_2\) - or - \(\text{NH}_2\) \(\text{Br}\)

c) \(\text{(CH}_2\text{OH})\text{NH}\) - or - \(\text{H}_3\text{C} \text{NH}_2\)

Problem 24.6: Rank the following in order of increasing basicity?

a) \(\text{O}_2\text{N} \text{NH}_2, \text{Br} \text{NH}_2, \text{NH}_2\) \(\text{H}_2\text{C} \text{NH}_2\)

b) \(\text{Cl} \text{NH}_2, \text{NH}_2, \text{H}_2\text{C} \text{NH}_2\)

c) \(\text{F}_2\text{C} \text{NH}_2, \text{H}_2\text{C} \text{NH}_2, \text{H}_2\text{FC} \text{NH}_2\)
24.6 Synthesis of Amines

Reduction of Nitriles, Amides and Nitro Compounds

R-Br $\xrightarrow{\text{NaCN}}$ R-CN $\xrightarrow{\text{LiAlH}_4}$ ether $\xrightarrow{\text{H}_2\text{O}^+}$ R-CH$_2$H $\xrightarrow{\text{1° amine}}$

R-Br $\xrightarrow{\text{Mg(0), CO$_2$ then H$_2$O$^+$}}$ ROH $\xrightarrow{\text{SOCl$_2$}}$ RCl $\xrightarrow{\text{H}_3\text{C-NH$_2$}}$ R-CH$_2$H $\xrightarrow{\text{LiAlH}_4}$ H$_2$O $\xrightarrow{\text{or-}}$ BH$_3$ $\xrightarrow{\text{1°, 2° or 3° amine}}$

S$_N^2$ reaction of alkyl halides and tosylates

Ammonia and other alkylamines are good nucleophiles and react with 1° and 2° alkyl halides or tosylates via and S$_N^2$ reaction to give alkyl amines.

1°, 2°, and 3° amines all have similar reactivity; the initially formed monoalkylation product can undergo further reaction to yield a mixture of alkylation products.
Synthesis of primary amines from the reaction of alkyl halides or tosylates with “ammonia equivalents”

Azide ion is a very strong nucleophile and react with $1^\circ$ or $2^\circ$ alkyl halides or tosylates via an $S_N^2$ reaction. The resulting azide can be reduced to a $1^\circ$ amine.

Gabriel amine synthesis: reaction of potassium phthalimide with alkyl halides or tosylates via an $S_N^2$ reaction. The resulting $N$-substituted phthalimide can be hydrolyzed to a $1^\circ$ amine.

Reductive amination: synthesis of an amine by the reduction of an imine from the condensation of an aldehyde or ketone with ammonia, $1^\circ$ or $2^\circ$ amine.
Sodium cyanoborohydride, Na+ N≡C-BH₃⁻: the cyano ligand makes cyanoborohydride a weak hydride source and it will react with only the most easily reduced functional groups, such as an imine. Does not reduce ketones and reduced aldehydes slowly.

Reductive amination with NaB(CN)H₃: one-pot reaction

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine (R-C=O) + H₂C-NH₂</td>
<td>[CH₃CH(NH₂)CH₂CH₂CH₂]NH₂</td>
</tr>
<tr>
<td>Phenylalanine (R-NH₂) + H₂C=O</td>
<td>[CH₃CH(NH₂)CH₂CH₂CH₂]NH₂</td>
</tr>
</tbody>
</table>

practice problem 24.1 (p. 908)

Hoffmann and Curtius rearrangements (please read)

**24.7: Reactions of Amines**

Acylation: ammonia, 1° and 2° amines react with acid chlorides and anhydrides to give amides (Chapt. 21.4, 21.5 & 21.8)

- **Unsubstituted (1°) amide**
- **Mono-substituted (2°) amide**
- **Di-substituted (3°) amide**
Hofmann elimination: E2 elimination of a trimethyl ammonium group to give an alkene

\[
\text{NH}_2 + (\text{H}_3\text{C})_3\text{CO} \cdot \text{K}^+ \rightarrow \text{No reaction} \quad \text{(H}_2\text{N}^- \text{is a very poor leaving group)}
\]

\[
\text{NH}_2 \cdot (\text{H}_3\text{C})_3\text{CO} \cdot \text{K}^+ \rightarrow \text{CH}_3 + (\text{H}_3\text{C})_3\text{CO}
\]

(major) (minor)

Hofmann elimination gives the less substituted alkene, where E2 elimination of an alkyl halide or tosylate will follow Zaitsev rule to give the more substituted alkene

24.8 Reactions of Arylamines
Electrophilic aromatic substitution: an amino group is a very strong activating group and an ortho/para director.
The amino group is incompatible with the Friedel-Crafts reactions (Ch. 16.3).

Electrophilic aromatic substitution of phenyl acetamides (amides of aniline).

The acetamide group is still a strong activator and an ortho/para director. (see Fig. 16.10, page 541)
Advantages of the acetamide over the amino group for electrophilic aromatic substitution:
Anilines are so activated that multiple substitution reactions can be a problem. The reactivity of the acetamide is attenuated so that mono substitution is achieved.

The acetamide group is compatible with the Friedel-Crafts reactions.

Diazonium salts: The Sandmeyer reaction primary arylamines (anilines) react with nitrous acid (HNO₂, generated from the reaction of NaNO₂ and H₂SO₄) to form a stable aryl diazonium salt.

Aryl diazonium salts react with nucleophiles in a substitution reaction. N₂ is one of the best leaving groups.

What is the mechanism? rate = k [Ar-N=N⁺]
Synthesize 3,5-dibromotoluene from bromobenzene or toluene

Some reactions of aryl diazonium salts

\[
\text{Na} &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{I} \\
\text{HBF}_4 &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{F} \\
\text{H}_2\text{PO}_2 &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{H}
\]

Some more reactions of aryl diazonium substitution reactions promoted by Cu(I) salts (Sandmeyer reaction).

\[
\text{Cl} &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{Cl} \\
\text{Br} &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{Br} \\
\text{CN} &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{CN} \\
\text{OH} &\xrightarrow{\cdot \cdot \cdot \cdot \cdot \cdot} \text{OH}
\]

The mechanism of the Sandmeyer reaction (Cu$^+$ promoted) involves an aryl radical intermediate.
Diazonium coupling reaction (please read)

24.9 Tetraalkylammonium Salts as Phase-Transfer Catalysts (please read)

24.10 Spectroscopy of Amines
IR: N-H stretches in the range of 3300 - 3500 cm\(^{-1}\)
same range as O-H stretch, but N-H stretches are sharper and less intense.

Synthesize 2-iodoethylbenzene from benzene:

![Chemical structure of benzene and 2-iodoethylbenzene](image)
Mass Spectrum:

**Nitrogen rule**: small organic compounds with an odd number of nitrogen atoms have an odd mass; compounds with an even number of nitrogen atoms have an even mass.

NMR: Hydrogens on the carbon attached to a nitrogen of an amine have a chemical shift of $\delta$ 2.2 - 3.0

$^{13}$C NMR: Carbons attached to a nitrogen of an amine are deshielded about 20 ppm downfield from where they would absorb in an alkane.
C₉H₁₃NO
[α]D +23°

13C NMR: 138.6, 129.1, 128.5, 126.3, 65.9, 54.2, 40.6

IR: