22.7
Reactions of Amines:
A Review and a Preview
Two questions to answer:

1) How is the C—N bond to be formed?
2) How do we obtain the correct oxidation state of nitrogen (and carbon)?
Methods for C—N Bond Formation

Nucleophilic substitution by azide ion (N₃⁻) (Section 8.1, 8.13)

Nitration of arenes (Section 12.3)

Nucleophilic ring opening of epoxides by ammonia (Section 16.12)

Nucleophilic addition of amines to aldehydes and ketones (Sections 17.10, 17.11)

Nucleophilic substitution by ammonia on a-halo acids (Section 19.16)

Nucleophilic acyl substitution (Sections 20.3, 20.5, and 20.11)

Hofmann rearrangement (Section 20.17)
22.8
Preparation of Amines
by Alkylation of Ammonia
Alkylation of Ammonia

Desired reaction is:

$$2 \text{NH}_3 + \text{R}–\text{X} \rightarrow \text{R}–\text{NH}_2 + \text{NH}_4\text{X}$$
Alkylation of Ammonia

Desired reaction is:

\[ 2 \text{NH}_3 + R-X \rightarrow R-\text{NH}_2 + \text{NH}_4X \]

via:

\[ \text{H}_3\text{N}: + R-X \rightarrow \text{H}_3\text{N-R} + \text{X}^- \]

then:

\[ \text{H}_3\text{N}: + \text{H}^+ + R \rightarrow \text{H}_3\text{N-H} + \text{N-R} \]
Alkylation of Ammonia

But the method doesn't work well in practice. Usually gives a mixture of primary, secondary, and tertiary amines, plus the quaternary salt.

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NH₃ + RX → RNH₂
RₙNH₂ + RX → R₂NH
RₙN⁺ X⁻ + RX → Rₙ₊₁N⁺ X⁻
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As octylamine is formed, it competes with ammonia for the remaining 1-bromooctane. Reaction of octylamine with 1-bromooctane gives N,N-dioctylamine.
As octylamine is formed, it competes with ammonia for the remaining 1-bromooctane. Reaction of octylamine with 1-bromooctane gives N,N-dioctylamine.
22.9
The Gabriel Synthesis of Primary Alkylamines
Gabriel Synthesis

gives primary amines without formation of secondary, etc. amines as byproducts

uses an $S_N$2 reaction on an alkyl halide to form the C—N bond

the nitrogen-containing nucleophile is $N$-potassiophthalimide
gives primary amines without formation of secondary, etc. amines as byproducts

uses an $S_N2$ reaction on an alkyl halide to form the C─N bond

the nitrogen-containing nucleophile is $N$-potassioophthalimide
The $pK_a$ of phthalimide is 8.3

*N*-potassiophthalimide is easily prepared by the reaction of phthalimide with KOH

\[
\text{Phthalimide} + \text{KOH} \rightarrow \text{N-Potassiophthalimide} + \text{H}_2\text{O}
\]
N-Potassiophthalimide as a nucleophile

\[
\text{N-Potassiophthalimide} + R\text{X} \rightarrow \text{N-Potassiophthalimide-R} + \text{X}^-
\]
Cleavage of Alkylated Phthalimide

\[
\text{imide hydrolysis is nucleophilic acyl substitution}
\]

\[
\text{acid or base}
\]
Cleavage of Alkylated Phthalimide

Hydrazinolysis is an alternative method of releasing the amine from its phthalimide derivative.

\[
\text{Phthalimide derivative} + \text{H}_2\text{NNNH}_2 \rightarrow \text{Hydrazine} + \text{NH}_2\text{RNH}_2
\]
Example

\[
\text{N}^- \quad \text{K}^+ \quad + \quad \text{C}_6\text{H}_5\text{CH}_2\text{Cl} \quad \text{DMF}
\]
Example

\[
\text{Compound A}^\text{N} \quad \text{K}^+ \quad + \quad \text{C}_6\text{H}_5\text{CH}_2\text{Cl} \quad \text{DMF} \quad \text{Compound B}^\text{N} - \text{CH}_2\text{C}_6\text{H}_5 \quad (74\%) 
\]
Example

\[
\text{[Chemical Structure]}
\]

\[
\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2 \ (97\%) \quad \text{+} \quad \text{H}_2\text{NNH}_2
\]

\[
\text{[Chemical Structure]}
\]
22.10
Preparation of Amines by Reduction
almost any nitrogen-containing compound can be reduced to an amine, including:

- azides
- nitriles
- nitro-substituted benzene derivatives
- amides
$S_N2$ reaction, followed by reduction, gives a primary alkylamine.

$$\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaN}_3} \text{CH}_2\text{CH}_2\text{N}_3$$

(74%)

1. LiAlH$_4$
2. H$_2$O

$$\text{CH}_2\text{CH}_2\text{NH}_2$$

(89%)
$S_N2$ reaction, followed by reduction, gives a primary alkylamine.

Azides may also be reduced by catalytic hydrogenation.
**Synthesis of Amines via Nitriles**

$\text{S}_2$ reaction, followed by reduction, gives a primary alkylamine.

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{NaCN} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CN} \quad (69\%)
\]

\[
\text{H}_2 (100 \text{ atm}), \text{Ni} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \quad (56\%)
\]
$S_N 2$ reaction, followed by reduction, gives a primary alkylamine.

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaCN}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CN} \quad (69\%)$$

Nitriles may also be reduced by lithium aluminum hydride

$$\text{H}_2 (100 \text{ atm}), \text{Ni}$$

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \quad (56\%)$$
$S_N2$ reaction, followed by reduction, gives a primary alkylamine.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaCN}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CN} \quad (69\%) \]

The reduction also works with cyanohydrins.

\[ \text{H}_2 (100 \text{ atm}), \text{Ni} \]

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \quad (56\%) \]
Synthesis of Amines via Nitroarenes

1. Fe, HCl
2. NaOH

(95%)

(88-95%)
Synthesis of Amines via Nitroarenes

nitro groups may also be reduced with tin (Sn) + HCl or by catalytic hydrogenation

1. Fe, HCl
2. NaOH

(88-95%)

(95%)
Synthesis of Amines via Amides

1. LiAlH₄
2. H₂O

(88%)

1. SOCl₂
2. (CH₃)₂NH

(86-89%)
Synthesis of Amines via Amides

only LiAlH₄ is an appropriate reducing agent for this reaction
22.11
Reductive Amination
In reductive amination, an aldehyde or ketone is subjected to catalytic hydrogenation in the presence of ammonia or an amine.

\[
R\backslash\begin{array}{c}
C\equiv O
\end{array} + \begin{array}{c}NH_3\end{array} \overset{fast}{\leftrightarrow} \begin{array}{c}R\end{array}\backslash\begin{array}{c}C\equiv NH\end{array} + \begin{array}{c}H_2O\end{array}
\]

The aldehyde or ketone equilibrates with the imine faster than hydrogenation occurs.

**Synthesis of Amines via Reductive Amination**
The imine undergoes hydrogenation faster than the aldehyde or ketone. An amine is the product.
Example: Ammonia gives a primary amine.

\[
\text{Cyclohexanone} + \text{NH}_3 \xrightarrow{\text{H}_2, \text{Ni}} \text{(80\%)} \xrightarrow{\text{ethanol}} \text{Cyclohexane} \text{amine}
\]
Example: Primary amines give secondary amines

\[
\text{CH}_3(\text{CH}_2)_5\text{CH} + \text{H}_2\text{N}-\text{C}_6\text{H}_5 \xrightarrow{\text{H}_2, \text{Ni}} \text{ethanol} \\
\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{NH}-\text{C}_6\text{H}_5 \quad (65\%)
\]
Example: Primary amines give secondary amines

$$\text{CH}_3(\text{CH}_2)_5\text{CH} + \text{H}_2\text{N}$$

$$\text{H}_2, \text{Ni} \quad \text{ethanol}$$

$$\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{NH}$$

(65%)

via:

$$\text{CH}_3(\text{CH}_2)_5\text{CH}==\text{N}$$
Example: Secondary amines give tertiary amines

$\text{H}_2, \text{Ni, ethanol}$

$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 + \text{N}_2\text{H}_2 \rightarrow \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (93%)
Example: Secondary amines give tertiary amines

Possible intermediates include:

- HO-CHCH₂CH₂CH₃
- CHCH₂CH₂CH₃
- CH=CHCH₂CH₃