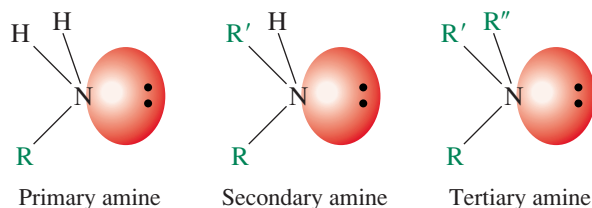


22.20 SUMMARY

Section 22.1 Alkylamines are compounds of the type shown, where R, R', and R'' are alkyl groups. One or more of these groups is an aryl group in arylamines.

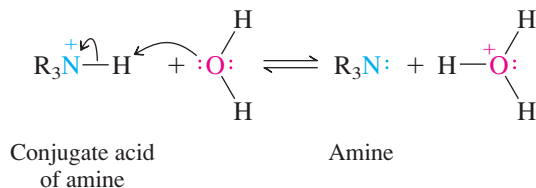


Alkylamines are named in two ways. One method adds the ending *-amine* to the name of the alkyl group. The other applies the principles of substitutive nomenclature by replacing the *-e* ending of an alkane name by *-amine* and uses appropriate locants to identify the position of the amino group. Arylamines are named as derivatives of aniline.

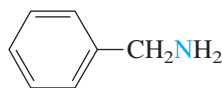
Section 22.2 Nitrogen's unshared electron pair is of major importance in understanding the structure and properties of amines. Alkylamines have a pyramidal arrangement of bonds to nitrogen, and the unshared electron pair resides in an sp^3 -hybridized orbital. The geometry at nitrogen in arylamines is somewhat flatter than in alkylamines, and the unshared electron pair is delocalized into the π system of the ring. Delocalization binds the electron pair more strongly in arylamines than in alkylamines. Arylamines are less basic and less nucleophilic than alkylamines.

Section 22.3 Amines are less polar than alcohols. Hydrogen bonding in amines is weaker than in alcohols because nitrogen is less electronegative than oxygen. Amines have lower boiling points than alcohols, but higher boiling points than alkanes. Primary amines have higher boiling points than isomeric secondary amines; tertiary amines, which cannot form intermolecular hydrogen bonds, have the lowest boiling points. Amines resemble alcohols in their solubility in water.

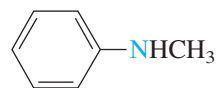
Section 22.4 The basicity of amines is conveniently expressed in terms of the pK_a of their conjugate acids.



The stronger base is associated with the weaker conjugate acid. The greater the pK_a of the conjugate acid, the stronger the base. The pK_a 's of the conjugate acids of alkylamines lie in the 9–11 range. Arylamines are much weaker bases than alkylamines. The pK_a 's of the conjugate acids of arylamines are usually 3–5. Strong electron-withdrawing groups can weaken the basicity of arylamines even more.



Benzylamine

(alkylamine: pK_a of conjugate acid = 9.3)*N*-Methylaniline(arylamine: pK_a of conjugate acid = 3.2)

Section 22.5 Quaternary ammonium salts, compounds of the type $R_4N^+ X^-$, find application in a technique called **phase-transfer catalysis**. A small amount of a quaternary ammonium salt promotes the transfer of an anion from aqueous solution, where it is highly solvated, to an organic solvent, where it is much less solvated and much more reactive.

Sections 22.6–22.10 Methods for the preparation of amines are summarized in Table 22.5.

TABLE 22.5 Preparation of Amines

Reaction (section) and comments	General equation and specific example
Alkylation methods	
<p>Alkylation of ammonia (Section 22.7) Ammonia can act as a nucleophile toward primary and some secondary alkyl halides to give primary alkylamines. Yields tend to be modest because the primary amine is itself a nucleophile and undergoes alkylation. Alkylation of ammonia can lead to a mixture containing a primary amine, a secondary amine, a tertiary amine, and a quaternary ammonium salt.</p>	$RX + 2NH_3 \longrightarrow RNH_2 + NH_4X$ <p>Alkyl halide Ammonia Alkylamine Ammonium halide</p> <p> $C_6H_5CH_2Cl \xrightarrow{NH_3 (8 \text{ mol})} C_6H_5CH_2NH_2 + (C_6H_5CH_2)_2NH$ Benzyl chloride (1 mol) Benzylamine (53%) Dibenzylamine (39%) </p>
<p>Alkylation of phthalimide. The Gabriel synthesis (Section 22.8) The potassium salt of phthalimide reacts with alkyl halides to give <i>N</i>-alkylphthalimide derivatives. Hydrolysis or hydrazinolysis of this derivative yields a primary alkylamine.</p>	$RX + \text{Phthalimide}^-K^+ \longrightarrow \text{N-Alkylphthalimide}$ <p>Alkyl halide <i>N</i>-Potassiophthalimide <i>N</i>-Alkylphthalimide</p> <p> $\text{N-Alkylphthalimide} + H_2NNH_2 \longrightarrow RNH_2 + \text{Phthalhydrazide}$ <i>N</i>-Alkylphthalimide Hydrazine Primary amine Phthalhydrazide </p> <p> $CH_3CH=CHCH_2Cl \xrightarrow[2. H_2NNH_2, \text{ ethanol}]{1. N\text{-potassiophthalimide, DMF}} CH_3CH=CHCH_2NH_2$ 1-Chloro-2-butene 2-Buten-1-amine (95%) </p>

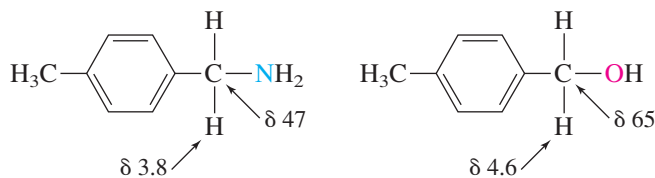
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TABLE 22.5 Preparation of Amines (*Continued*)

Reaction (section) and comments	General equation and specific example
Reduction methods	
<p>Reduction of alkyl azides (Section 22.9) Alkyl azides, prepared by nucleophilic substitution by azide ion in primary or secondary alkyl halides, are reduced to primary alkylamines by lithium aluminum hydride or by catalytic hydrogenation.</p>	$\text{R}\ddot{\text{N}}=\text{N}=\ddot{\text{N}}\text{:} \xrightarrow{\text{reduce}} \text{R}\ddot{\text{N}}\text{H}_2$ <p>Alkyl azide Primary amine</p> $\text{CF}_3\text{CH}_2\underset{\text{N}_3}{\text{CH}}\text{CO}_2\text{CH}_2\text{CH}_3 \xrightarrow{\text{H}_2, \text{Pd}} \text{CF}_3\text{CH}_2\underset{\text{NH}_2}{\text{CH}}\text{CO}_2\text{CH}_2\text{CH}_3$ <p>Ethyl 2-azido-4,4,4-trifluorobutanoate Ethyl 2-amino-4,4,4-trifluorobutanoate (96%)</p>
<p>Reduction of nitriles (Section 22.9) Nitriles are reduced to primary amines by lithium aluminum hydride or by catalytic hydrogenation.</p>	$\text{RC}\equiv\text{N} \xrightarrow{\text{reduce}} \text{RCH}_2\text{NH}_2$ <p>Nitrile Primary amine</p> $\text{Cyclopropyl-CN} \xrightarrow[2. \text{H}_2\text{O}]{1. \text{LiAlH}_4} \text{Cyclopropyl-CH}_2\text{NH}_2$ <p>Cyclopropyl cyanide Cyclopropylmethanamine (75%)</p>
<p>Reduction of aryl nitro compounds (Section 22.9) The standard method for the preparation of an arylamine is by nitration of an aromatic ring, followed by reduction of the nitro group. Typical reducing agents include iron or tin in hydrochloric acid or catalytic hydrogenation.</p>	$\text{ArNO}_2 \xrightarrow{\text{reduce}} \text{ArNH}_2$ <p>Nitroarene Arylamine</p> $\text{C}_6\text{H}_5\text{NO}_2 \xrightarrow[2. \text{HO}^-]{1. \text{Fe}, \text{HCl}} \text{C}_6\text{H}_5\text{NH}_2$ <p>Nitrobenzene Aniline (97%)</p>
<p>Reduction of amides (Section 22.9) Lithium aluminum hydride reduces the carbonyl group of an amide to a methylene group. Primary, secondary, or tertiary amines may be prepared by proper choice of the starting amide. R and R' may be either alkyl or aryl.</p>	$\text{RC(=O)NR}'_2 \xrightarrow{\text{reduce}} \text{RCH}_2\text{NR}'_2$ <p>Amide Amine</p> $\text{CH}_3\text{C(=O)NHC(CH}_3)_3 \xrightarrow[2. \text{H}_2\text{O}]{1. \text{LiAlH}_4} \text{CH}_3\text{CH}_2\text{NHC(CH}_3)_3$ <p><i>N</i>-<i>tert</i>-Butylacetamide <i>N</i>-Ethyl-<i>tert</i>-butylamine (60%)</p>
<p>Reductive amination (Section 22.10) Reaction of ammonia or an amine with an aldehyde or a ketone in the presence of a reducing agent is an effective method for the preparation of primary, secondary, or tertiary amines. The reducing agent may be either hydrogen in the presence of a metal catalyst or sodium cyanoborohydride. R, R', and R'' may be either alkyl or aryl.</p>	$\text{RCR}'\text{C(=O)R}'' + \text{R}'''\text{NH}_2 \xrightarrow{\text{reducing agent}} \text{RCR}'\text{CH}_2\text{NR}'''$ <p>Aldehyde or ketone Ammonia or an amine Amine</p> $\text{CH}_3\text{C(=O)CH}_3 + \text{Cyclohexyl-NH}_2 \xrightarrow{\text{H}_2, \text{Pt}} \text{CH}_3\text{CH}_2\text{NHCyclohexyl}$ <p>Acetone Cyclohexylamine <i>N</i>-Isopropylcyclohexylamine (79%)</p>

Sections 22.11–22.18 The reactions of amines are summarized in Tables 22.6 and 22.7.

Section 22.19 The N—H stretching frequency of primary and secondary amines appears in the infrared in the 3000–3500 cm^{-1} region. In the NMR spectra of amines, protons and carbons of the type H—C—N are more shielded than H—C—O.



Amines have odd-numbered molecular weights, which helps identify them by mass spectrometry. Fragmentation tends to be controlled by the formation of a nitrogen-stabilized cation.

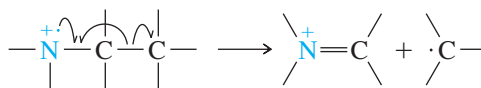


TABLE 22.6 Reactions of Amines Discussed in This Chapter

Reaction (section) and comments	General equation and specific example
Alkylation (Section 22.12) Amines act as nucleophiles toward alkyl halides. Primary amines yield secondary amines, secondary amines yield tertiary amines, and tertiary amines yield quaternary ammonium salts.	$\text{RNH}_2 \xrightarrow{\text{R}'\text{CH}_2\text{X}} \text{RNHCH}_2\text{R}'$ <p>Primary amine Secondary amine</p> $\downarrow \text{R}'\text{CH}_2\text{X}$ $\text{RN}(\text{CH}_2\text{R}')_2 \xleftarrow{\text{R}'\text{CH}_2\text{X}} \text{RN}(\text{CH}_2\text{R}')_3^+ \text{X}^-$ <p>Tertiary amine Quaternary ammonium salt</p> <p>2-Chloromethylpyridine + Pyrrolidine $\xrightarrow{\text{heat}}$ 2-(Pyrrolidinylmethyl)pyridine (93%)</p>
Hofmann elimination (Section 22.13) Quaternary ammonium hydroxides undergo elimination on being heated. It is an anti elimination of the E2 type. The regioselectivity of the Hofmann elimination is opposite to that of the Zaitsev rule and leads to the less highly substituted alkene.	$\text{RCH}_2\text{CHR}'\text{HO}^- \xrightarrow{\text{heat}} \text{RCH}=\text{CHR}' + \text{:N}(\text{CH}_3)_3 + \text{H}_2\text{O}$ <p style="text-align: center;"> \uparrow $\text{N}(\text{CH}_3)_3^+$ </p> <p>Alkyltrimethylammonium hydroxide Alkene Trimethylamine Water</p> <p>Cycloheptyltrimethylammonium hydroxide $\xrightarrow{\text{heat}}$ Cycloheptene (87%)</p>

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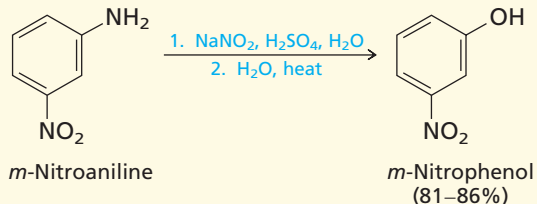
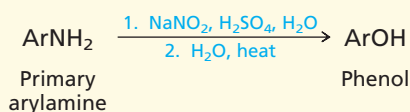
TABLE 22.6 Reactions of Amines Discussed in This Chapter (*Continued*)

Reaction (section) and comments	General equation and specific example
Electrophilic aromatic substitution (Section 22.14) Arylamines are very reactive toward electrophilic aromatic substitution. It is customary to protect arylamines as their <i>N</i> -acyl derivatives before carrying out ring nitration, chlorination, bromination, sulfonation, or Friedel–Crafts reactions.	$\text{ArH} + \text{E}^+ \longrightarrow \text{ArE} + \text{H}^+$ <p>Arylamine Electrophile Product of electrophilic aromatic substitution Proton</p> <p><i>p</i>-Nitroaniline 2,6-Dibromo-4-nitroaniline (95%)</p>
Nitrosation (Section 22.15) Nitrosation of amines occurs when sodium nitrite is added to a solution containing an amine and an acid. <i>Primary amines</i> yield alkyl diazonium salts. Alkyl diazonium salts are very unstable and yield carbocation-derived products. Aryl diazonium salts are exceedingly useful synthetic intermediates. Their reactions are described in Table 22.7.	$\text{RNH}_2 \xrightarrow[\text{H}_3\text{O}^+]{\text{NaNO}_2} \text{RN}\equiv\text{N}^+$ <p>Primary amine Diazonium ion</p> <p><i>m</i>-Nitroaniline <i>m</i>-Nitrobenzenediazonium hydrogen sulfate</p>
<i>Secondary alkylamines</i> and <i>secondary arylamines</i> yield <i>N</i> -nitroso amines.	$\text{R}_2\text{NH} \xrightarrow[\text{H}_3\text{O}^+]{\text{NaNO}_2} \text{R}_2\text{N}-\text{N}=\text{O}$ <p>Secondary amine <i>N</i>-Nitroso amine</p> <p>2,6-Dimethylpiperidine 2,6-Dimethyl-<i>N</i>-nitrosopiperidine (72%)</p>
<i>Tertiary alkylamines</i> illustrate no useful chemistry on nitrosation. <i>Tertiary arylamines</i> undergo nitrosation of the ring by electrophilic aromatic substitution.	<p><i>N,N</i>-Dimethylaniline <i>N,N</i>-Dimethyl-4-nitrosoaniline (80–89%)</p>

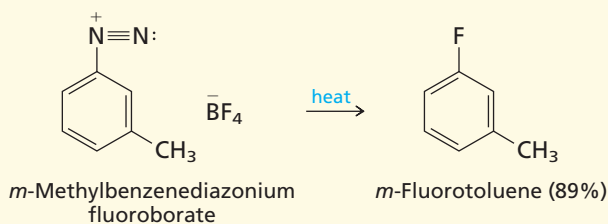
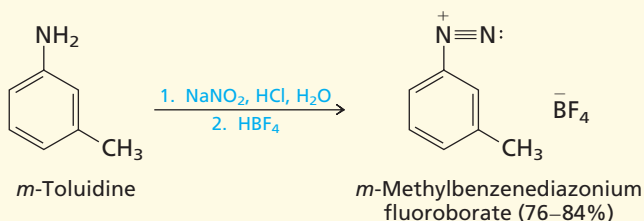
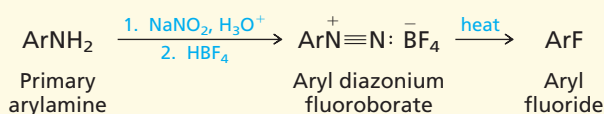
TABLE 22.7 Synthetically Useful Transformations Involving Aryl Diazonium Ions

Reaction and comments
General equation and specific example

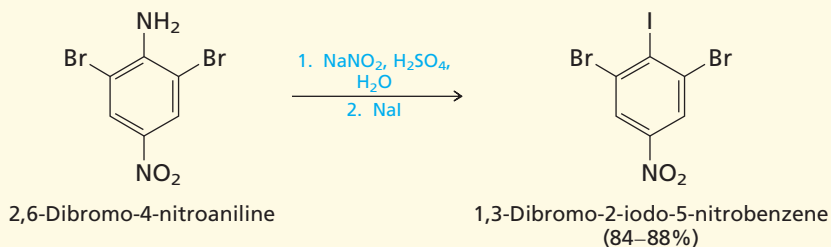
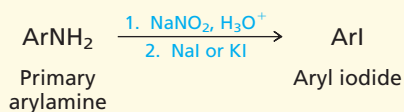
Preparation of phenols Heating its aqueous acidic solution converts a diazonium salt to a phenol. This is the most general method for the synthesis of phenols.



Preparation of aryl fluorides Addition of fluoroboric acid to a solution of a diazonium salt causes the precipitation of an aryl diazonium fluoroborate. When the dry aryl diazonium fluoroborate is heated, an aryl fluoride results. This is the Schiemann reaction; it is the most general method for the preparation of aryl fluorides.



Preparation of aryl iodides Aryl diazonium salts react with sodium or potassium iodide to form aryl iodides. This is the most general method for the synthesis of aryl iodides.



(Continued)

