Chapter
22

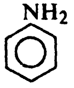
Amines I. Preparation and Physical Properties

22.1 Structure

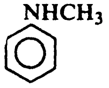
Nearly all the organic compounds that we have studied so far are bases, although very weak ones. Much of the chemistry of alcohols, ethers, esters, and even of alkenes and aromatic hydrocarbons is understandable in terms of the basicity of these compounds.

Of the organic compounds that show appreciable basicity (for example, those strong enough to turn litmus blue), by far the most important are the **amines.** An amine has the general formula RNH_2, R_2NH, or R_3N, where R is any alkyl or aryl group. For example:

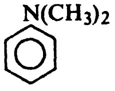
CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$H_2NCH_2CH_2NH_2$
Methylamine	Dimethylamine	Trimethylamine	Ethylenediamine
(1°)	(2°)	(3°)	(1°)



Aniline
(1°)



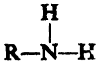
N-Methylaniline
(2°)



N,N-Dimethylaniline
(3°)

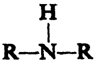
22.2 Classification

Amines are classified as **primary**, **secondary**, or **tertiary**, according to the number of groups attached to the nitrogen atom.



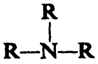
$$R-\overset{\displaystyle H}{\overset{|}{N}}-H$$

Primary
1°



$$R-\overset{\displaystyle H}{\overset{|}{N}}-R$$

Secondary
2°



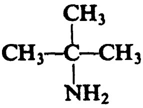
$$R-\overset{\displaystyle R}{\overset{|}{N}}-R$$

Tertiary
3°

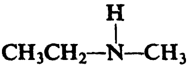
In their fundamental properties—*basicity* and the accompanying *nucleophilicity*—amines of different classes are very much the same. In many of their reactions, however, the final products depend upon the number of hydrogen atoms attached to the nitrogen atom, and hence are different for amines of different classes.

22.3 Nomenclature

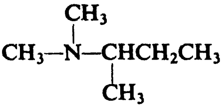
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:


$CH_3-\overset{CH_3}{\underset{NH_2}{C}}-CH_3$

tert-Butylamine
(1°)


$CH_3CH_2-\overset{H}{N}-CH_3$

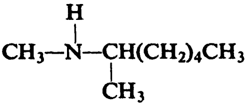
Methylethylamine
(2°)


$CH_3-\overset{CH_3}{N}-\underset{CH_3}{C}HCH_2CH_3$

Dimethyl-*sec*-butylamine
(3°)

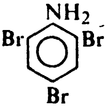
$H_2NCH_2CH_2CH_2COOH$
γ-Aminobutyric acid
(1°)

$H_2NCH_2CH_2OH$
2-Aminoethanol
(Ethanolamine)
(1°)

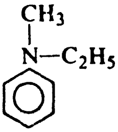

$CH_3-\overset{H}{N}-\underset{CH_3}{C}H(CH_2)_4CH_3$

2-(N-Methylamino)heptane
(2°)

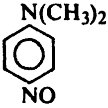
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



2,4,6-Tribromoaniline
(1°)

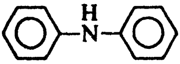


N-Methyl-N-ethylaniline
(3°)

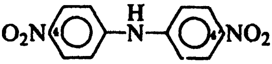


p-Nitroso-N,N-dimethylaniline
(3°)

p-Toluidine
(1°)



Diphenylamine
(2°)



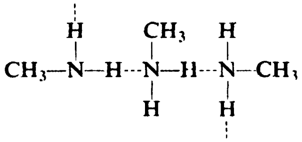
4,4′-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing *-amine* by *-ammonium* (or *-aniline* by *-anilinium*), and adding the name of the anion (*chloride*, *nitrate*, *sulfate*, etc.). For example:

$(C_2H_5NH_3^+)_2SO_4^{--}$	$(CH_3)_3NH^+NO_3^-$	$C_6H_5NH_3^+Cl^-$
Ethylammonium sulfate	Trimethylammonium nitrate	Anilinium chloride

22.4 Physical properties of amines

Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. Amines have higher boiling points than non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids.



$$\begin{array}{ccccccccc} & & \vdots & & & & & & \\ & & H & & CH_3 & & H & & \\ & & | & & | & & | & & \\ CH_3 & - & N & -H\cdots & N & -H\cdots & N & - & CH_3 \\ & & & & | & & | & & \\ & & & & H & & H & & \\ & & & & & & \vdots & & \end{array}$$

Amines of all three classes are capable of forming hydrogen bonds with water. As a result, smaller amines are quite soluble in water, with borderline solubility

Table 22.1 AMINES

Name	M.p., °C	B.p., °C	Solub., g/100 g H_2O	K_b
Methylamine	− 92	− 7.5	v.sol.	4.5×10^{-4}
Dimethylamine	− 96	7.5	v.sol.	5.4
Trimethylamine	−117	3	91	0.6
Ethylamine	− 80	17	∞	5.1
Diethylamine	− 39	55	v sol.	10.0
Triethylamine	−115	89	14	5.6
n-Propylamine	− 83	49	∞	4.1
Di-*n*-propylamine	− 63	110	s.sol.	10
Tri-*n*-propylamine	− 93	157	s.sol.	4.5
Isopropylamine	−101	34	∞	4
n-Butylamine	− 50	78	v.sol.	4.8
Isobutylamine	− 85	68	∞	3
sec-Butylamine	−104	63	∞	4
tert-Butylamine	− 67	46	∞	5
Cyclohexylamine		134	s.sol.	5
Benzylamine		185	∞	0.2
α-Phenylethylamine		187	4.2	
β-Phenylethylamine		195	s.	
Ethylenediamine	8	117	s.	
Tetramethylenediamine [$H_2N(CH_2)_4NH_2$]	27	158	v.sol.	0.85
Hexamethylenediamine	39	196	v.sol.	5
Tetramethylammonium hydroxide	63	135*d*	220	strong base

Table 22.1 AMINES (*continued*)

Name	M.p., °C	B.p., °C	Solub., g/100 g H_2O	K_b
Aniline	− 6	184	3.7	4.2 × 10^{-10}
Methylaniline	− 57	196	v.sl.sol.	7.1
Dimethylaniline	3	194	1.4	11.7
Diphenylamine	53	302	i.	0.0006
Triphenylamine	127	365	i.	
o-Toluidine	− 28	200	1.7	2.6
m-Toluidine	− 30	203	s.sol.	5
p-Toluidine	44	200	0.7	12
o-Anisidine (*o*-$CH_3OC_6H_4NH_2$)	5	225	s.sol.	3
m-Anisidine		251	s.sol.	2
p-Anisidine	57	244	v.sl.sol.	20
o-Chloroaniline	− 2	209	i.	0.05
m-Chloroaniline	− 10	236		0.3
p-Chloroaniline	70	232		1
o-Bromoaniline	32	229	s.sol.	0.03
m-Bromoaniline	19	251	v.sl.sol.	0.4
p-Bromoaniline	66	*d*	i.	0.7
o-Nitroaniline	71	284	0.1	0.00006
m-Nitroaniline	114	307*d*	0.1	0.029
p-Nitroaniline	148	332	0.05	0.001
2,4-Dinitroaniline	187		s.sol.	
2,4,6-Trinitroaniline (picramide)	188		0.1	
o-Phenylenediamine [*o*-$C_6H_4(NH_2)_2$]	104	252	3	3
m-Phenylenediamine	63	287	25	10
p-Phenylenediamine	142	267	3.8	140
Benzidine	127	401	0.05	9
p-Aminobenzoic acid	187		0.3	0.023
Sulfanilic acid	288*d*		1	0.17
Sulfanilamide	163		0.4	

Name	Formula	M.p., °C
Acetanilide	$C_6H_5NHCOCH_3$	114
Benzanilide	$C_6H_5NHCOC_6H_5$	163
Aceto-*o*-toluidide	*o*-$CH_3C_6H_4NHCOCH_3$	110
Aceto-*m*-toluidide	*m*-$CH_3C_6H_4NHCOCH_3$	66
Aceto-*p*-toluidide	*p*-$CH_3C_6H_4NHCOCH_3$	147
o-Nitroacetanilide	*o*-$O_2NC_6H_4NHCOCH_3$	93
m-Nitroacetanilide	*m*-$O_2NC_6H_4NHCOCH_3$	154
p-Nitroacetanilide	*p*-$O_2NC_6H_4NHCOCH_3$	216

being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.

Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.

Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

22.5 Salts of amines

Aliphatic amines are about as basic as ammonia; aromatic amines are considerably less basic. Although amines are much weaker bases than hydroxide ion or ethoxide ion, they are much stronger bases than alcohols, ethers, esters, etc.; they are much stronger bases than water. Aqueous mineral acids or carboxylic acids readily convert amines into their salts; aqueous hydroxide ion readily converts the salts back into the free amines. As with the carboxylic acids, we can

$$\underset{\textit{Insoluble in water}}{\left.\begin{array}{r}\mathrm{RNH_2}\\ 1^\circ\text{ amine}\\ \mathrm{R_2NH}\\ 2^\circ\text{ amine}\\ \mathrm{R_3N}\\ 3^\circ\text{ amine}\end{array}\right\}}\ \underset{\mathrm{OH^-}}{\overset{\mathrm{H^+}}{\rightleftarrows}}\ \underset{\textit{Soluble in water}}{\left\{\begin{array}{l}\mathrm{RNH_3^+}\\ \text{salt}\\ \mathrm{R_2NH_2^+}\\ \text{salt}\\ \mathrm{R_3NH^+}\\ \text{salt}\end{array}\right.}$$

do little with amines without encountering this conversion into and from their salts; it is therefore worthwhile to look at the properties of these salts.

In Sec. 18.4 we contrasted physical properties of carboxylic acids with those of their salts; amines and their salts show the same contrast. Amine salts are typical ionic compounds. They are non-volatile solids, and when heated generally decompose before the high temperature required for melting is reached. The halides, nitrates, and sulfates are soluble in water but are insoluble in non-polar solvents.

The difference in solubility behavior between amines and their salts can be used both to detect amines and to separate them from non-basic compounds. A water-insoluble organic compound that dissolves in cold, dilute aqueous hydrochloric acid must be appreciably basic, which means almost certainly that it is an amine. An amine can be separated from non-basic compounds by its solubility in acid; once separated, the amine can be regenerated by making the aqueous solution alkaline. (See Sec. 18.4 for a comparable situation for carboxylic acids.)

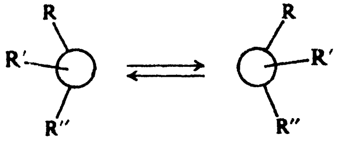
Problem 22.1 Describe exactly how you would go about separating a mixture of the three water-insoluble liquids, aniline (b.p. 184°), *n*-butylbenzene (b.p. 183°), and *n*-valeric acid (b.p. 187°), recovering each compound pure and in essentially quantitative yield. Do the same for a mixture of the three water-insoluble solids, *p*-toluidine, *o*-bromobenzoic acid, and *p*-nitroanisole.

22.6 Stereochemistry of nitrogen

So far in our study of organic chemistry, we have devoted considerable time to the spatial arrangement of atoms and groups attached to carbon atoms, that is, to the stereochemistry of carbon. Now let us look briefly at the stereochemistry of nitrogen.

Amines are simply ammonia in which one or more hydrogen atoms have been replaced by organic groups. Nitrogen uses sp^3 orbitals, which are directed to the corners of a tetrahedron. Three of these orbitals overlap *s* orbitals of hydrogen or carbon; the fourth contains an unshared pair of electrons (see Fig. 1.11, p. 18). Amines, then, are like ammonia, pyramidal, and with very nearly the same bond angles (108° in trimethylamine, for example).

From an examination of models, we can see that a molecule in which nitrogen carries three different groups is not superimposable on its mirror image; it is chiral and should exist in two enantiomeric forms (I and II) each of which—



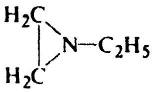
I II

separated from the other—might be expected to show optical activity.

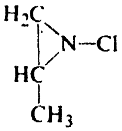
But such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly interconverted. Just as rapid rotation about carbon–carbon single bonds prevents isolation of conformational enantiomers (Sec. 4.20), so rapid *inversion* about nitrogen prevents isolation of enantiomers like I and II. Evidently, an unshared pair of electrons of nitrogen cannot ordinarily serve as a fourth group to maintain configuration.

Next, let us consider the quaternary ammonium salts, compounds in which four alkyl groups are attached to nitrogen. Here all four sp^3 orbitals are used to form bonds, and quaternary nitrogen is tetrahedral. Quaternary ammonium salts in which nitrogen holds four different groups have been found to exist as *configurational* enantiomers, capable of showing optical activity: methylallylphenylbenzylammonium iodide, for example.

Problem 22.2 At room temperature, the nmr spectrum of 1-ethylaziridine (III) shows the triplet-quartet of an ethyl group, and two other signals of equal peak area. When the temperature is raised to 120°, the latter two signals merge into a single signal. How do you interpret these observations?



III



IV

Problem 22.3 Account for the following, drawing all pertinent stereochemical formulas. (a) 1-Chloro-2-methylaziridine (IV, above) was prepared in two isomeric forms separable at 25° by ordinary gas chromatography. (b) The reaction of $(C_6H_5)_2C{=}NCH_3$ with R-(+)-2-phenylperoxypropionic acid gave a product, $C_{14}H_{13}ON$, with [α] +12.5°, which showed no loss of optical activity up to (at least) 90°.

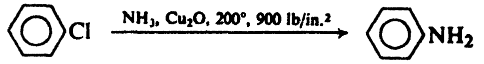
Problem 22.4 Racemization in certain free-radical and carbonium ion reactions has been attributed (Secs. 7.10 and 14.13) to loss of configuration in a *flat* intermediate. Account for the fact that the formation of alkyl carbanions, R: —which are believed to be *pyramidal*—can also lead to racemization.

22.7 Industrial source

Some of the simplest and most important amines are prepared on an industrial scale by processes that are not practicable as laboratory methods.

The most important of all amines, **aniline**, is prepared in several ways: (a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation, Sec. 22.9); (b) treatment of chlorobenzene with ammonia at high temperatures and high pressures in the presence of a catalyst. Process (b), we shall see (Chap. 25), involves nucleophilic aromatic substitution.

Nitrobenzene Anilinium chloride **Aniline**



Chlorobenzene Aniline

Methylamine, dimethylamine, and trimethylamine are synthesized on an industrial scale from methanol and ammonia:

$$\underset{\text{Ammonia}}{NH_3} \xrightarrow[Al_2O_3,\ 450^\circ]{CH_3OH} \underset{\text{Methylamine}}{CH_3NH_2} \xrightarrow[Al_2O_3,\ 450^\circ]{CH_3OH} \underset{\text{Dimethylamine}}{(CH_3)_2NH} \xrightarrow[Al_2O_3,\ 450^\circ]{CH_3OH} \underset{\text{Trimethylamine}}{(CH_3)_3N}$$

Alkyl halides are used to make some higher alkylamines, just as in the laboratory (Sec. 22.10). The acids obtained from fats (Sec. 33.4) can be converted into long-chain 1-aminoalkanes of even carbon number via reduction of nitriles (Sec. 22.8).

$$\underset{\text{Acid}}{RCOOH} \xrightarrow{NH_3,\ heat} \underset{\text{Amide}}{RCONH_2} \xrightarrow{heat} \underset{\text{Nitrile}}{RC{\equiv}N} \xrightarrow{H_2,\ cat.} \underset{\text{Amine}}{RCH_2NH_2}$$

22.8 Preparation

Some of the many methods that are used to prepare amines in the laboratory are outlined on the following pages.

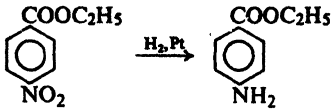
PREPARATION OF AMINES

1. **Reduction of nitro compounds.** Discussed in Sec. 22.9.

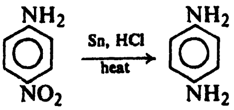
$$\underset{\text{Nitro compound}}{ArNO_2 \text{ or } RNO_2} \xrightarrow{\text{metal, } H^+\text{; or } H_2\text{, catalyst}} \underset{1° \text{ amine}}{ArNH_2 \text{ or } RNH_2}$$

Chiefly for aromatic amines

Examples:



Ethyl *p*-nitrobenzoate   Ethyl *p*-aminobenzoate



p-Nitroaniline   *p*-Phenylenediamine

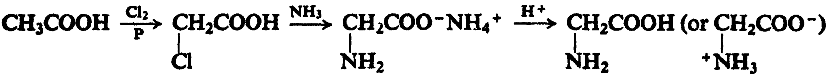
$$\underset{\text{1-Nitropropane}}{CH_3CH_2CH_2NO_2} \xrightarrow{\text{Fe, HCl}} \underset{n\text{-Propylamine}}{CH_3CH_2CH_2NH_2}$$

2. **Reaction of halides with ammonia or amines.** Discussed in Secs. 22.10 and 22.13.

$$NH_3 \xrightarrow{RX} \underset{1° \text{ amine}}{RNH_2} \xrightarrow{RX} \underset{2° \text{ amine}}{R_2NH} \xrightarrow{RX} \underset{3° \text{ amine}}{R_3N} \xrightarrow{RX} \underset{\text{Quaternary ammonium salt (4°)}}{R_4N^+X^-}$$

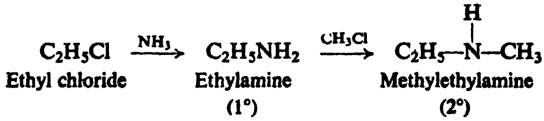
RX *must be alkyl, or aryl with electron-withdrawing substituents*

Examples:

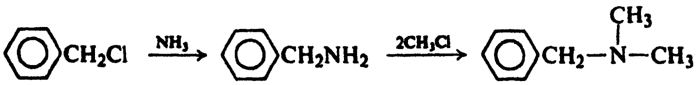


$$\underset{\text{Acetic acid}}{CH_3COOH} \xrightarrow[P]{Cl_2} \underset{\text{Chloroacetic acid}}{\underset{Cl}{CH_2COOH}} \xrightarrow{NH_3} \underset{NH_2}{CH_2COO^-NH_4^+} \xrightarrow{H^+} \underset{NH_2}{CH_2COOH} \text{ (or } \underset{^+NH_3}{CH_2COO^-})$$

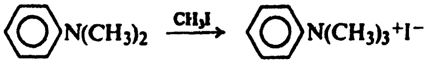
Aminoacetic acid
(Glycine; an amino acid)
(1°)



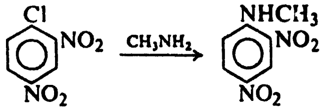
$$\underset{\text{Ethyl chloride}}{C_2H_5Cl} \xrightarrow{NH_3} \underset{\text{Ethylamine (1°)}}{C_2H_5NH_2} \xrightarrow{CH_3Cl} \underset{\text{Methylethylamine (2°)}}{C_2H_5{-}\overset{H}{N}{-}CH_3}$$



Benzyl chloride   Benzylamine (1°)   Benzyldimethylamine (3°)



N,N-Dimethylaniline (3°) Phenyltrimethylammonium iodide (4°)



2,4-Dinitrochlorobenzene N-Methyl-2,4-dinitroaniline (2°)

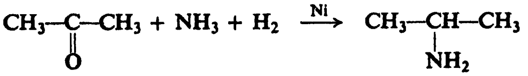
3. **Reductive amination.** Discussed in Sec. 22.11.

$$>C{=}O + NH_3 \xrightarrow[\text{or NaBH}_3\text{CN}]{H_2,\ Ni} >CH{-}NH_2 \qquad 1° \text{ amine}$$

$$+ RNH_2 \xrightarrow[\text{or NaBH}_3\text{CN}]{H_2,\ Ni} >CH{-}NHR \qquad 2° \text{ amine}$$

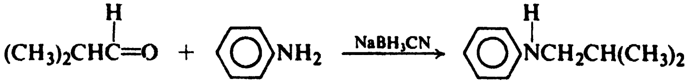
$$+ R_2NH \xrightarrow[\text{or NaBH}_3\text{CN}]{H_2,\ Ni} >CH{-}NR_2 \qquad 3° \text{ amine}$$

Examples:

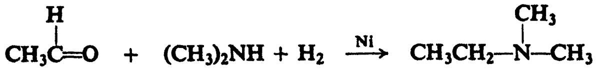


$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}CH_3 + NH_3 + H_2 \xrightarrow{Ni} CH_3{-}\underset{\underset{NH_2}{|}}{CH}{-}CH_3$$

Acetone Isopropylamine (1°)



Isobutyraldehyde Aniline (1°) N-Isobutylaniline (2°)



$$CH_3\overset{\overset{H}{|}}{C}{=}O + (CH_3)_2NH + H_2 \xrightarrow{Ni} CH_3CH_2{-}\overset{\overset{CH_3}{|}}{N}{-}CH_3$$

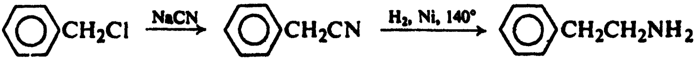
Acetaldehyde Dimethylamine (2°) Dimethylethylamine (3°)

4. **Reduction of nitriles.** Discussed in Sec. 22.8.

$$RC{\equiv}N \xrightarrow{2H_2,\ \text{catalyst}} RCH_2NH_2$$

Nitrile 1° amine

Examples:



Benzyl chloride Phenylacetonitrile (Benzyl cyanide) β-Phenylethylamine (1°)

$$ClCH_2CH_2CH_2CH_2Cl \xrightarrow{NaCN} NC(CH_2)_4CN \xrightarrow{H_2,\ Ni} H_2NCH_2(CH_2)_4CH_2NH_2$$

1,4-Dichlorobutane
Adiponitrile
Hexamethylenediamine
(1,6-Diaminohexane)
(1°)

5. Hofmann degradation of amides. Discussed in Secs. 22.13 and 28.2–28.5.

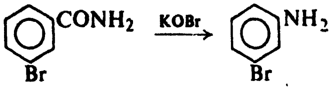
$$RCONH_2 \text{ or } ArCONH_2 \xrightarrow{OBr^-} RNH_2 \text{ or } ArNH_2 + CO_3^{--}$$

Amide
1° amine

Examples:

$$CH_3(CH_2)_4CONH_2 \xrightarrow{KOBr} CH_3(CH_2)_4NH_2$$

Caproamide
(Hexanamide)
n-Pentylamine



m-Bromobenzamide
m-Bromoaniline

Reduction of aromatic nitro compounds is by far the most useful method of preparing amines, since it uses readily available starting materials, and yields the most important kind of amines, *primary aromatic amines.* These amines can be converted into aromatic diazonium salts, which are among the most versatile class of organic compounds known (see Secs. 23.11–23.17). The sequence

$$\text{nitro compound} \longrightarrow \text{amine} \longrightarrow \text{diazonium salt}$$

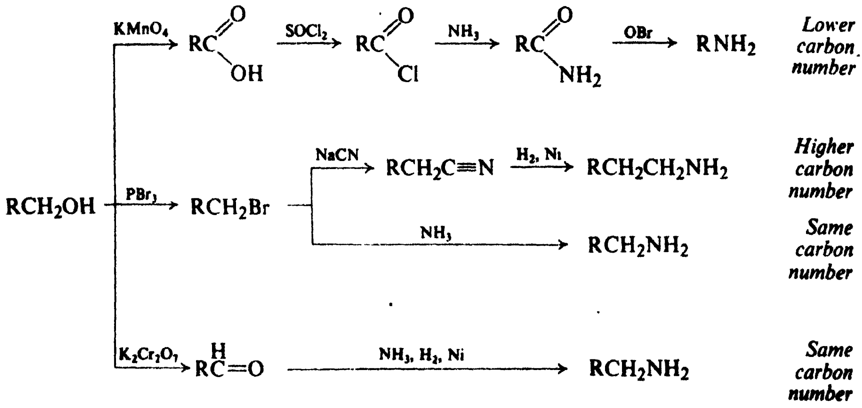
provides the best possible route to dozens of kinds of aromatic compounds.

Reduction of aliphatic nitro compounds is limited by the availability of the starting materials.

Ammonolysis of halides is usually limited to the aliphatic series, because of the generally low reactivity of aryl halides toward nucleophilic substitution. (However, see Chap. 25.) Ammonolysis has the disadvantage of yielding a mixture of different classes of amines. It is important to us as one of the most general methods of introducing the amino ($—NH_2$) group into molecules of all kinds; it can be used, for example, to convert bromoacids into amino acids. The exactly analogous reaction of halides with amines permits the preparation of every class of amine (as well as quaternary ammonium salts, $R_4N^+X^-$).

Reductive amination, the catalytic or chemical reduction of aldehydes (RCHO) and ketones (R_2CO) in the presence of ammonia or an amine, accomplishes much the same purpose as the reaction of halides. It too can be used to prepare any class of amine, and has certain advantages over the halide reaction. The formation of mixtures is more readily controlled in reductive amination than in ammonolysis of halides. Reductive amination of ketones yields amines containing a *sec*-alkyl group; these amines are difficult to prepare by ammonolysis because of the tendency of *sec*-alkyl halides to undergo elimination rather than substitution.

Synthesis via **reduction of nitriles** has the special feature of *increasing the length of a carbon chain*, producing a primary amine that has one more carbon atom than the alkyl halide from which the nitrile was made. The **Hofmann degradation of amides** has the feature of *decreasing the length of a carbon chain* by one carbon atom; it is also of interest as an example of an important class of reactions involving rearrangement.

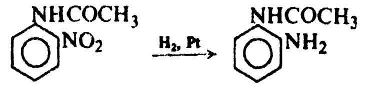


Problem 22.5 Show how *n*-pentylamine can be synthesized from available materials by the four routes just outlined.

22.9 Reduction of nitro compounds

Like many organic compounds, nitro compounds can be reduced in two general ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction, usually by a metal and acid.

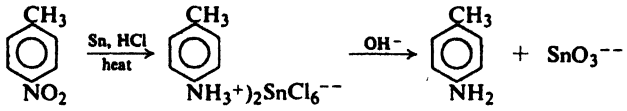
Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. For example:



o-Nitroacetanilide *o*-Aminoacetanilide

This method cannot be used when the molecule also contains some other easily hydrogenated group, such as a carbon–carbon double bond.

Chemical reduction in the laboratory is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from the reaction



p-Nitrotoluene *p*-Toluidine

mixture. The crude amine is generally contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, and the nitro compound is not.

Reduction of nitro compounds to amines is an essential step in what is probably the most important synthetic route in aromatic chemistry. Nitro compounds are readily prepared by direct nitration; when a mixture of *o*- and *p*-isomers is obtained, it can generally be separated to yield the pure isomers. The primary aromatic amines obtained by the reduction of these nitro compounds are readily converted into diazonium salts; the diazonium group, in turn, can be replaced by a large number of other groups (Sec. 23.11). In most cases this sequence is the best method of introducing these other groups into the aromatic ring. In addition, diazonium salts can be used to prepare the extremely important class of compounds. the *azo dyes.*

$$\mathrm{ArH} \longrightarrow \mathrm{ArNO_2} \longrightarrow \mathrm{ArNH_2} \longrightarrow \mathrm{ArN_2^+} \begin{cases} \rightarrow \mathrm{ArX} \\ \rightarrow \mathrm{ArOH} \\ \rightarrow \mathrm{ArCN} \\ \rightarrow \text{azo dyes} \end{cases}$$

22.10 Ammonolysis of halides

Many organic halogen compounds are converted into amines by treatment with aqueous or alcoholic solutions of ammonia. The reaction is generally carried out either by allowing the reactants to stand together at room temperature or by heating them under pressure. Displacement of halogen by NH_3 yields the amine salt, from which the free amine can be liberated by treatment with hydroxide ion.

$$\mathrm{RX + NH_3 \longrightarrow RNH_3^+X^-}$$

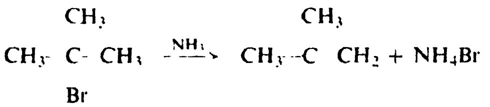
$$\mathrm{RNH_3^+X^- + OH^- \longrightarrow RNH_2 + H_2O + X^-}$$

Ammonolysis of halides belongs to the class of reactions that we have called nucleophilic substitution. The organic halide is attacked by the nucleophilic ammonia molecule in the same way that it is attacked by hydroxide ion, alkoxide ion, cyanide ion, acetylide ion, and water:

$$\mathrm{H_3N\!: + R{-}X} \longrightarrow \left[\mathrm{H_3}\overset{\delta+}{\mathrm{N}}\cdots\mathrm{R}\cdots\overset{\delta-}{\mathrm{X}}\right] \longrightarrow \mathrm{H_3}\overset{+}{\mathrm{N}}\mathrm{{-}R + X^-}$$

Like these other nucleophilic substitution reactions, ammonolysis is limited chiefly to alkyl halides or substituted alkyl halides. As with other reactions of this kind, elimination tends to compete (Sec. 14.23) with substitution: ammonia can attack hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

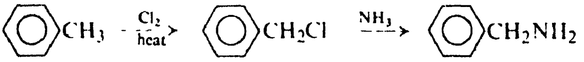
$$CH_3CH_2CH_2CH_2Br \xrightarrow{NH_3} CH_3CH_2CH_2CH_2NH_3{}^+Br^- \qquad \textit{Substitution}$$



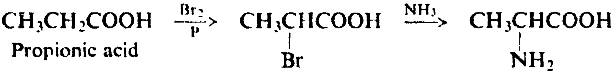
$$CH_3-\underset{Br}{\overset{CH_3}{C}}-CH_3 \xrightarrow{NH_3} CH_3-\overset{CH_3}{C}=CH_2 + NH_4Br \qquad \textit{Elimination}$$

Because of their generally low reactivity, aryl halides are converted into amines only (a) if the ring carries $-NO_2$ groups, or other strongly electron-withdrawing groups, at positions *ortho* and *para* to the halogen, or (b) if a high temperature or a strongly basic reagent is used (Chap. 25).

Some examples of the application of ammonolysis to synthesis are:



Toluene Benzyl chloride Benzylamine



$$\underset{\text{Propionic acid}}{CH_3CH_2COOH} \xrightarrow[P]{Br_2} \underset{\alpha\text{-Bromopropionic acid}}{CH_3\underset{Br}{C}HCOOH} \xrightarrow{NH_3} \underset{\substack{\text{Alanine}\\(\alpha\text{-Aminopropionic acid})}}{CH_3\underset{NH_2}{C}HCOOH}$$

$$\underset{\text{Ethylene}}{CH_2{=}CH_2} \xrightarrow{Cl_2} \underset{\text{Ethylene chloride}}{ClCH_2CH_2Cl} \xrightarrow{2NH_3} \underset{\text{Ethylenediamine}}{H_2NCH_2CH_2NH_2}$$

A serious disadvantage to the synthesis of amines by ammonolysis is the formation of more than one class of amine. The primary amine salt, formed by

$$RX + NH_3 \longrightarrow \underset{1^\circ\text{ amine salt}}{RNH_3{}^+X^-}$$

the initial substitution, reacts with the reagent ammonia to yield the ammonium salt and the free primary amine; the following equilibrium thus exists:

$$RNH_3{}^+ + NH_3 \rightleftarrows \underset{1^\circ\text{ amine}}{RNH_2} + NH_4{}^+$$

The free primary amine, like the ammonia from which it was made, is a nucleophilic reagent; it too can attack the alkyl halide, to yield the salt of a secondary amine:

$$\underset{1^\circ\text{ amine}}{RNH_2} + RX \longrightarrow R_2NH_2{}^+X^- \overset{NH_3}{\rightleftarrows} \underset{2^\circ\text{ amine}}{R_2NH}$$

The secondary amine, which is in equilibrium with its salt, can in turn attack the alkyl halide to form the salt of a tertiary amine:

$$\underset{\text{2° amine}}{R_2NH} + RX \longrightarrow R_3NH^+X^- \underset{}{\overset{NH_3}{\rightleftharpoons}} \underset{\text{3° amine}}{R_3N}$$

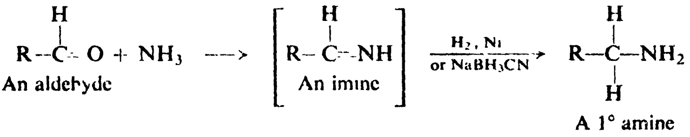
Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula $R_4N^+X^-$, called a *quaternary ammonium salt* (discussed in Sec. 23.5):

$$\underset{\text{3° amine}}{R_3N} + RX \longrightarrow \underset{\substack{\text{Quaternary ammonium salt}\\ (4°)}}{R_4N^+X^-}$$

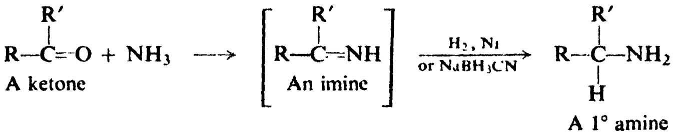
The presence of a large excess of ammonia lessens the importance of these last reactions and increases the yield of primary amine; under these conditions, a molecule of alkyl halide is more likely to encounter, and be attacked by, one of the numerous ammonia molecules rather than one of the relatively few amine molecules. At best, the yield of primary amine is always cut down by the formation of the higher classes of amines. Except in the special case of methylamine, the primary amine can be separated from these by-products by distillation.

22.11 Reductive amination

Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. Reaction involves reduction of an intermediate compound (an *imine*, RCH=NH or $R_2C{=}NH$) that contains a carbon-nitrogen double bond.



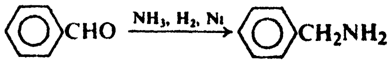
$$\underset{\text{An aldehyde}}{R-\overset{\displaystyle H}{\overset{|}{C}}=O} + NH_3 \longrightarrow \left[\underset{\text{An imine}}{R-\overset{\displaystyle H}{\overset{|}{C}}=NH}\right] \xrightarrow[\text{or } NaBH_3CN]{H_2,\ Ni} \underset{\text{A 1° amine}}{R-\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle H}{\underset{|}{C}}}}-NH_2}$$



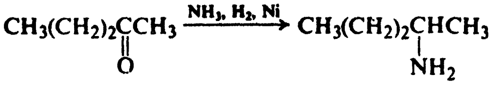
$$\underset{\text{A ketone}}{R-\overset{\displaystyle R'}{\overset{|}{C}}=O} + NH_3 \longrightarrow \left[\underset{\text{An imine}}{R-\overset{\displaystyle R'}{\overset{|}{C}}=NH}\right] \xrightarrow[\text{or } NaBH_3CN]{H_2,\ Ni} \underset{\text{A 1° amine}}{R-\overset{\displaystyle R'}{\overset{|}{\underset{\displaystyle H}{\underset{|}{C}}}}-NH_2}$$

Reductive amination has been used successfully with a wide variety of aldehydes and ketones, both aliphatic and aromatic. For example:

$$\underset{\substack{\text{Heptaldehyde}\\ \text{(Heptanal)}}}{CH_3(CH_2)_5CHO} \xrightarrow{NH_3,\ H_2,\ Ni} \underset{\substack{n\text{-Heptylamine}\\ \text{(1-Aminoheptane)}}}{CH_3(CH_2)_5CH_2NH_2}$$

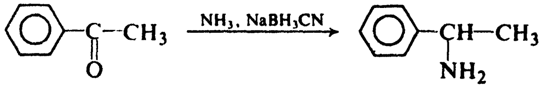


Benzaldehyde **Benzylamine**



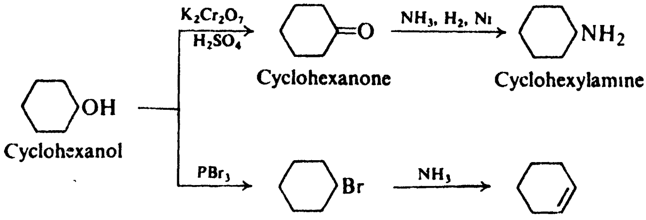
$$CH_3(CH_2)_2\underset{\underset{O}{\|}}{C}CH_3 \xrightarrow{NH_3,\ H_2,\ Ni} CH_3(CH_2)_2\underset{\underset{NH_2}{|}}{C}HCH_3$$

2-Pentanone (Methyl *n*-propyl ketone) 2-Aminopentane



Acetophenone (Methyl phenyl ketone) α-Phenylethylamine

Reductive amination of ketones yields amines containing a *sec*-alkyl group; such amines are difficult to obtain by ammonolysis because of the tendency for *sec*-alkyl halides to undergo elimination. For example, cyclohexanone is converted into cyclohexylamine in good yield, whereas ammonolysis of bromocyclohexane yields only cyclohexene.

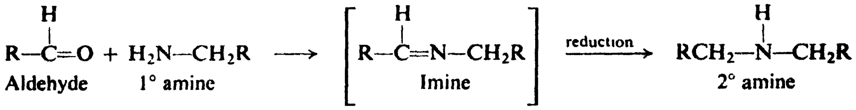


Cyclohexanol

Cyclohexanone Cyclohexylamine

Bromocyclohexane Cyclohexene

During reductive amination the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine. The tendency for the reaction to go



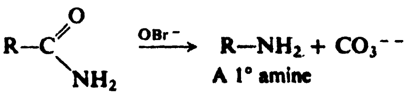
$$R{-}\overset{\overset{H}{|}}{C}{=}O + H_2N{-}CH_2R \longrightarrow \left[R{-}\overset{\overset{H}{|}}{C}{=}N{-}CH_2R\right] \xrightarrow{\text{reduction}} RCH_2{-}\overset{\overset{H}{|}}{N}{-}CH_2R$$

Aldehyde 1° amine Imine 2° amine

beyond the desired stage can be fairly well limited by the proportions of reactants employed and is seldom a serious handicap.

22.12 Hofmann degradation of amides

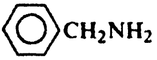
As a method of synthesis of amines, the Hofmann degradation of amides has the special feature of yielding a product containing one less carbon than the starting material. As we can see, reaction involves migration of a group from carbonyl

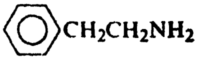


An amide A 1° amine

carbon to the adjacent nitrogen atom, and thus is an example of a *molecular rearrangement*. We shall return to the Hofmann degradation (Secs. 28.2–28.5) and discuss its mechanism in detail.

Problem 22.6 Using a different method in each case, show how the following amines could be prepared from *toluene* and any aliphatic reagents:

(a)


(c)


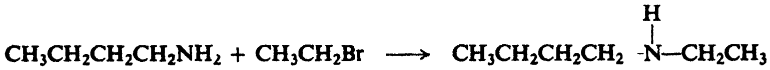
(b)


(d)


(e)

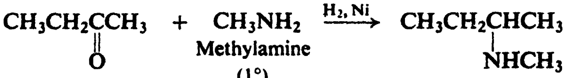

22.13 Synthesis of secondary and tertiary amines

So far we have been chiefly concerned with the synthesis of primary amines. Secondary and tertiary amines are prepared by adaptations of one of the processes already described: ammonolysis of halides or reductive amination. For example:



$$CH_3CH_2CH_2CH_2NH_2 + CH_3CH_2Br \longrightarrow CH_3CH_2CH_2CH_2\overset{H}{\overset{|}{N}}—CH_2CH_3$$

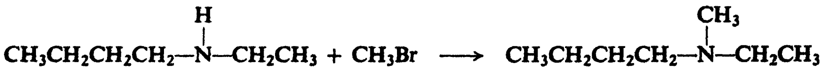
n-Butylamine (1°) Ethyl bromide Ethyl-*n*-butylamine (2°)



$$\underset{\underset{O}{\|}}{CH_3CH_2CCH_3} + CH_3NH_2 \xrightarrow{H_2, Ni} \underset{\underset{NHCH_3}{|}}{CH_3CH_2CHCH_3}$$

Butanone (Methyl ethyl ketone) Methylamine (1°) Methyl-*sec*-butylamine (2°)

Aniline (1°) N-Methylaniline (2°) N,N-Dimethylaniline (3°)



$$CH_3CH_2CH_2CH_2—\overset{H}{\overset{|}{N}}—CH_2CH_3 + CH_3Br \longrightarrow CH_3CH_2CH_2CH_2—\overset{CH_3}{\overset{|}{N}}—CH_2CH_3$$

Ethyl-*n*-butylamine (2°) Methyl bromide Methylethyl-*n*-butylamine (3°)

Where ammonia has been used to produce a primary amine, a primary amine can be used to produce a secondary amine, or a secondary amine can be used to produce a tertiary amine. In each of these syntheses there is a tendency for reaction to proceed beyond the first stage and to yield an amine of a higher class than the one that is wanted.