Chapter Two
Amines

2.1. Introduction

Amines are organic derivatives of ammonia with one or more alkyl or aryl groups bonded to the nitrogen atom. As a class, amines include some of the most important biological compounds. Amines serve many functions in living organisms, such as bioregulation, neurotransmission, and defense against predators. Because of their high degree of biological activity, many amines are used as drugs and medicines. The structures and uses of some important biologically active amines are shown in **Figure 2-1.**

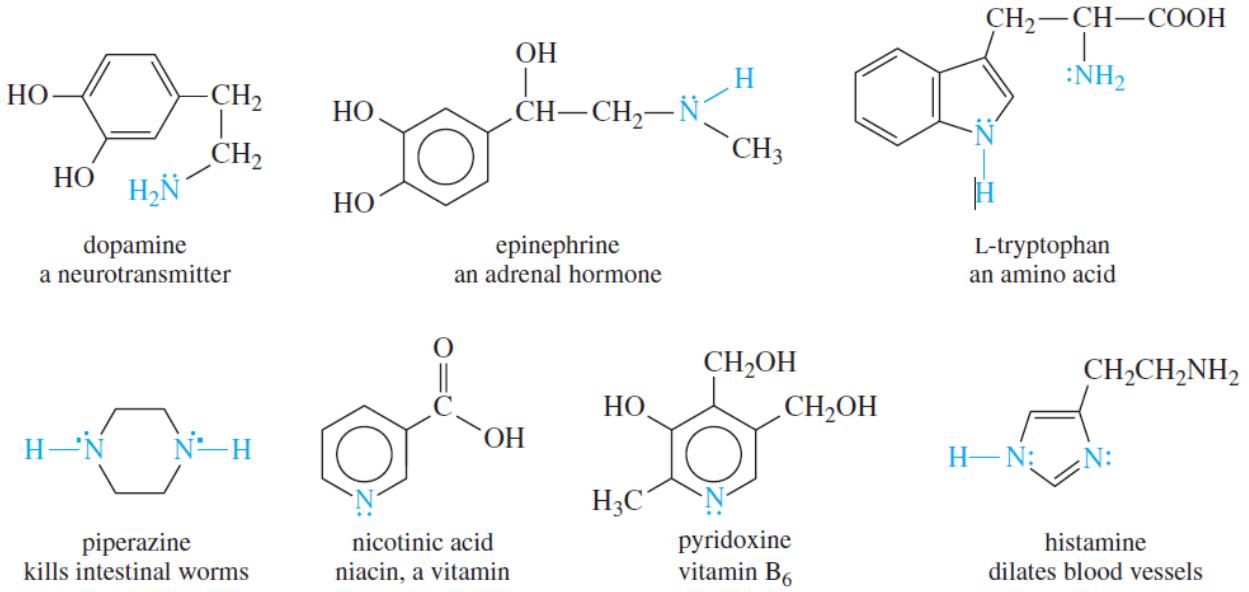


Figure 2-1: Examples of some biologically active amines.

The *alkaloids* are an important group of biologically active amines, mostly synthesized by plants to protect them from being eaten by insects and other animals. The structures of some representative alkaloids are shown in **Figure 2-2.** Although some alkaloids are used medicinally (chiefly as painkillers), all alkaloids are toxic and cause death if taken in large quantities. The Greeks chose the alkaloid coniine to kill Socrates, although morphine, nicotine, or cocaine would have served equally well. Mild cases of alkaloid poisoning can produce psychological effects that resemble peacefulness, euphoria, or hallucinations.

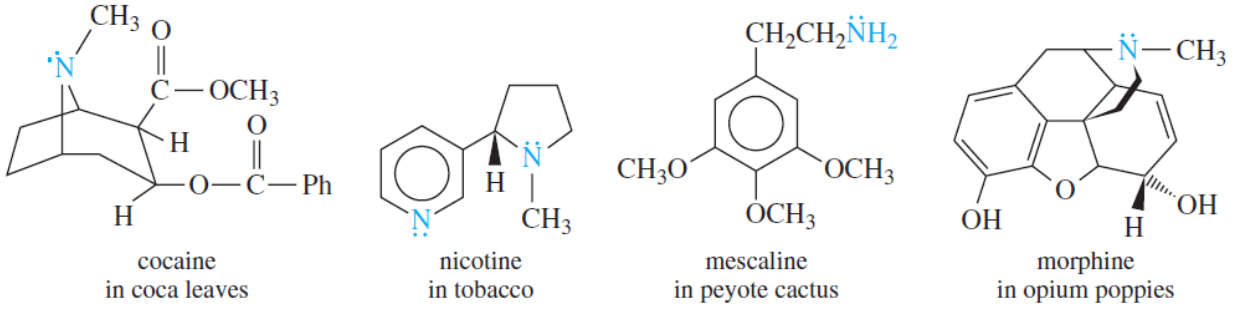
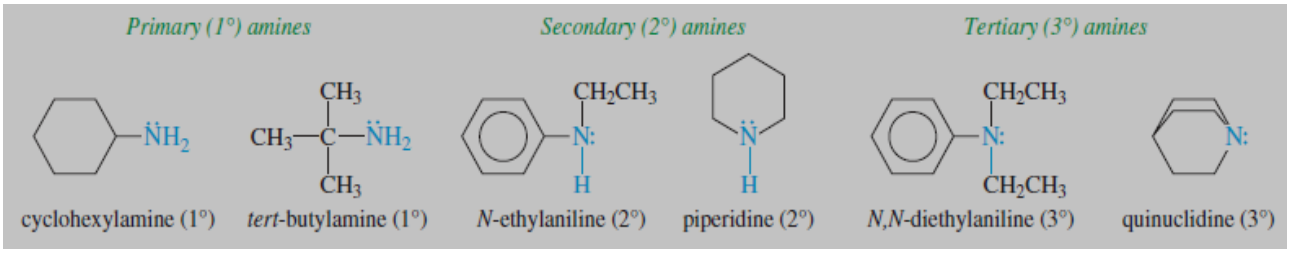


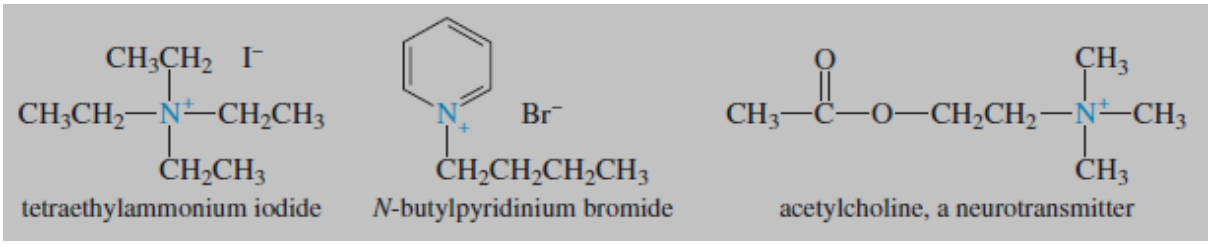
Figure 2-2: Some representative alkaloids.

2.2. Nomenclature

Amines are classified as **primary** (1°), **secondary** (2°), or **tertiary** (3°), corresponding to one, two, or three alkyl or aryl groups bonded to nitrogen. In a heterocyclic amine, the nitrogen atom is part of an aliphatic or aromatic ring.

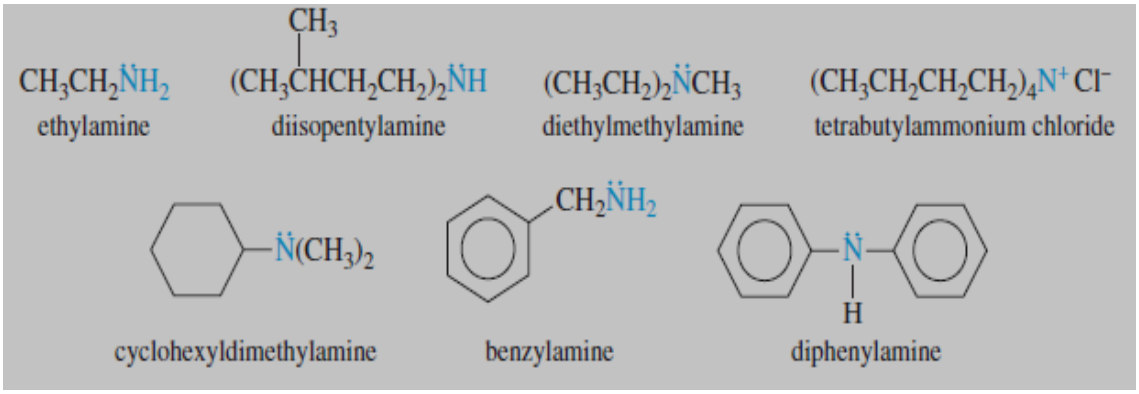


Quaternary ammonium salts have four alkyl or aryl bonds to a nitrogen atom. The nitrogen atom bears a positive charge, just as it does in simple ammonium salts such as ammonium chloride. The following are examples of quaternary (4°) ammonium salts.

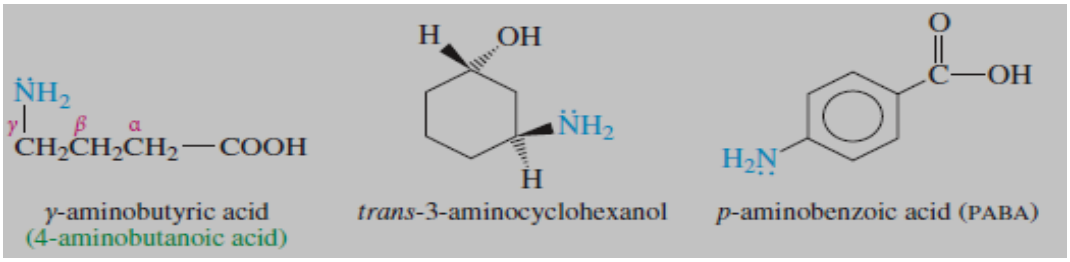


2.2.1. Common Names

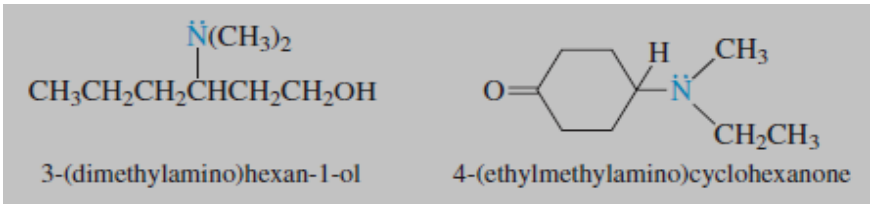
Common names of amines are formed from the names of the alkyl groups bonded to nitrogen, followed by the suffix *-amine*. The prefixes *di-*, *tri-*, and *tetra-* are used to describe two, three, or four identical substituents.



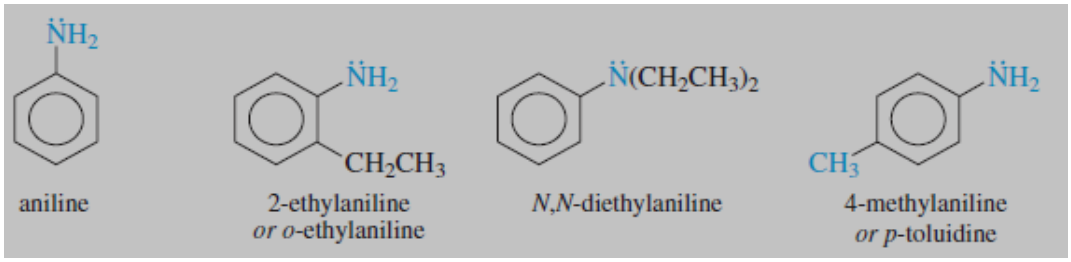
In naming amines with more complicated structures (multi-functional groups), the $-NH_2$ group is called the **amino** group. It is treated like any other substituent, with a number or other symbol indicating its position on the ring or carbon chain.



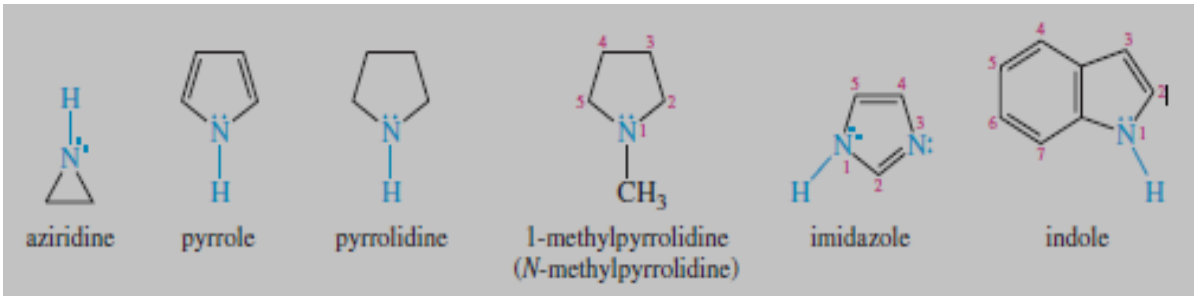
Using this system, secondary and tertiary amines are named by classifying the nitrogen atom (together with its alkyl groups) as an alkylamino group. The largest or most complicated alkyl group is taken to be the parent molecule.

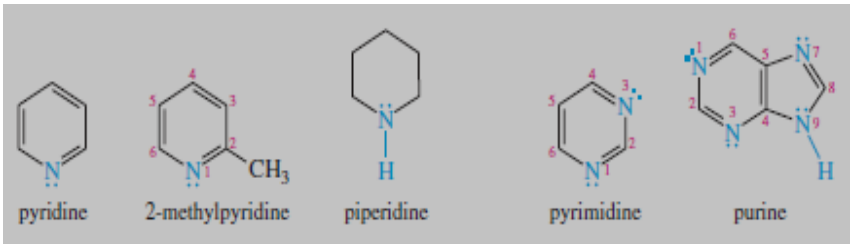


Aromatic and heterocyclic amines are generally known by historical names. Phenylamine is called *aniline*, for example, and its derivatives are named as derivatives of aniline.



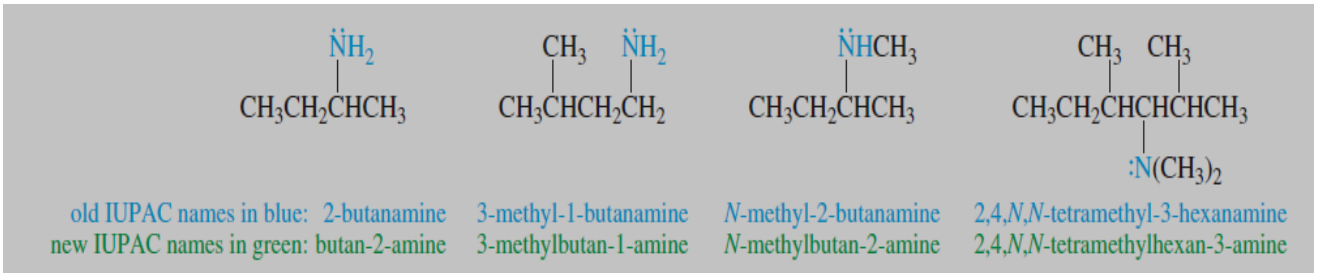
Heterocyclic amines are when nitrogen is part of the ring. The names and structures of some common ones are shown here. The heteroatom (N) is usually assigned position number 1.





2.2.2. IUPAC Names

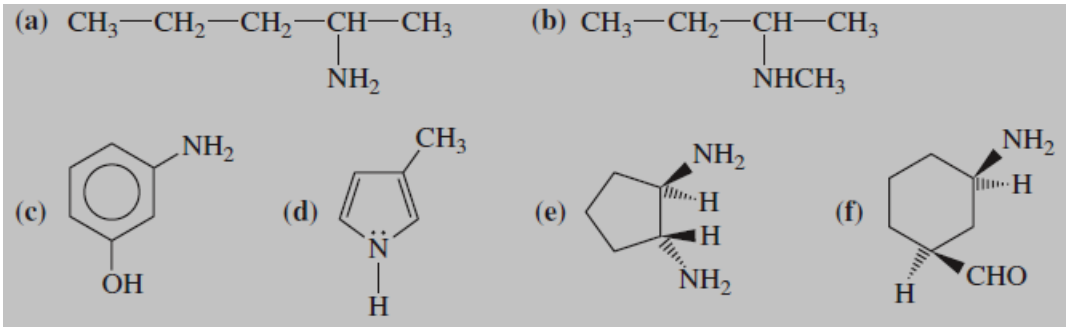
The IUPAC nomenclature for amines is similar to that for alcohols. The longest continuous chain of carbon atoms determines the root name. The *-e* ending in the alkane name is changed to *amine*, and a number shows the position of the amino group along the chain. Other substituents on the carbon chain are given numbers, and the prefix *N*- is used for each substituent on nitrogen.



Exercise 2.1

1. Draw the structures of the following compounds:
   (a) *tert*-butylamine **(b)** **α**-aminopropionaldehyde
   (c) 4-(dimethylamino)pyridine **(d)** 2-methylaziridine
   (e) *N*-ethyl-*N*-methylhexan-3-amine **(f)** *m*-chloroaniline

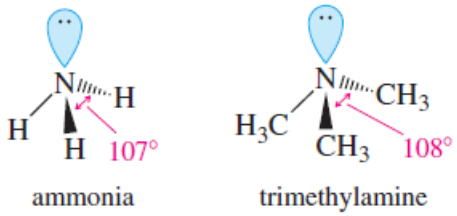
2. Give correct names for the following amines:



2.3. Structure of Amines

Ammonia has a slightly distorted tetrahedral shape. A lone pair of nonbonding electrons occupies one of the tetrahedral positions. This geometry is represented by sp^3 hybridization of nitrogen, with the bulky lone pair compressing the H-N-H bond angles to 107° from the "ideal" sp^3 bond angle of 109.5°.

Trimethylamine shows less angle compression because the bulky methyl groups open the angle slightly.



A tetrahedral amine with three different substituents (and a lone pair) is nonsuperimposable on its mirror image, and appears to be a chirality center. In most cases, however, we cannot resolve such an amine into two enantiomers because the enantiomers interconvert rapidly (see Figure 2-3). This interconversion takes place by **nitrogen inversion,** in which the lone pair moves from one face of the molecule to the other. The nitrogen atom is sp^2 hybridized in the transition state, and the nonbonding electrons occupy a *p* orbital. Interconversion of (*R*)- and (*S*)-ethylmethylamine is shown in **Figure 2-3**. In naming the enantiomers of chiral amines, the **Cahn–Ingold–Prelog convention** is used, with the nonbonding electron pair having the lowest priority.

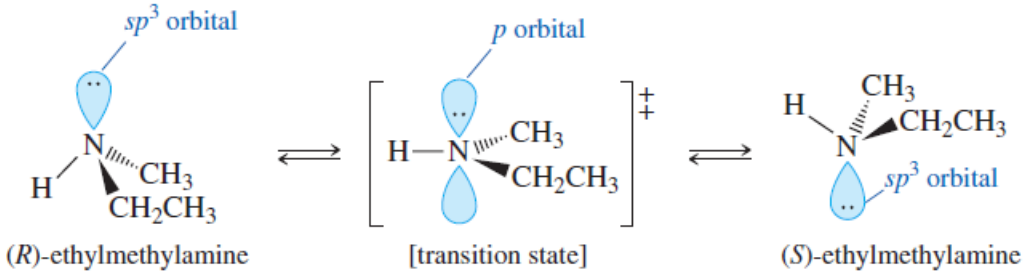
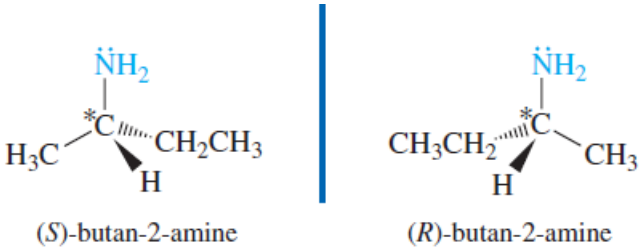


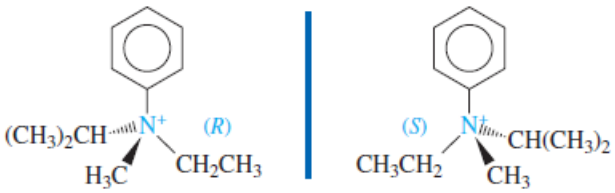
Figure 2-3: Nitrogen inversion interconverts the two enantiomers of a simple chiral amine.

Although most simple amines cannot be resolved into enantiomers, several types of chiral amines can be resolved.

1. *Amines whose chirality stems from the presence of asymmetric carbon atoms*.
   Most chiral amines fall into this group. Nitrogen inversion is irrelevant because nitrogen is not the chirality center. For example, butan-2-amine can be resolved into enantiomers because the 2-butyl group is chiral.



2. *Quaternary ammonium salts with asymmetric nitrogen atoms*.
Inversion of configuration is not possible because there is no lone pair to undergo nitrogen inversion. For example, the methyl ethyl isopropyl anilinium salts can be resolved into enantiomers.



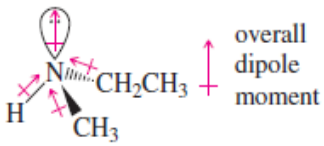
3. *Amines that cannot attain the sp^2 hybrid transition state for nitrogen inversion*.
If the nitrogen atom is contained in a small ring, for example, it is prevented from attaining the 120° bond angles that facilitate inversion. Such a compound has higher activation energy for inversion, the inversion is slow, and the enantiomers may be resolved. Chiral aziridines (three-membered rings containing a nitrogen) often may be resolved into enantiomers.

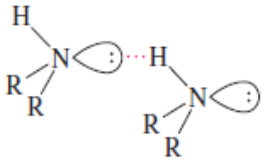
(*R*)-1,2,2-trimethylaziridine (*S*)-1,2,2-trimethylaziridine

2.4. Properties of Amines

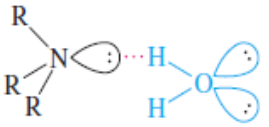
2.4.1. Physical Properties

Amines are strongly polar because the large dipole moment of the lone pair of electrons adds to the dipole moments of the C ↔ N and H ↔ N bonds. Primary and secondary amines have bonds, allowing them to form hydrogen bonds. Pure tertiary amines cannot engage in hydrogen bonding because they have no N-H bonds. They can, however, accept hydrogen bonds from molecules having O-H or N-H bonds.





1° or 2° amine:
hydrogen bond donor and acceptor



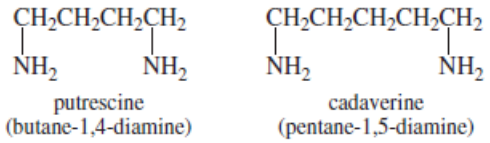
3° amine:
hydrogen bond acceptor only

Because nitrogen is less electronegative than oxygen, the N-H bond is less polar than the O-H bond. Therefore, amines form weaker hydrogen bonds than do alcohols of similar molecular weights. Primary and secondary amines have boiling points that are lower than those of alcohols, yet higher than those of ethers of similar molecular weights. With no hydrogen bonding, tertiary amines have lower boiling points than primary and secondary amines of similar molecular weights. **Table 2-1** compares the boiling points of an ether, an alcohol, and amines of similar molecular weights.

Table 2-1: How Hydrogen Bonding Affects Boiling Points

Compound	bp (°C)	Type	Molecular Weight
$(CH_3)_3N$:	3	tertiary amine	59
$CH_3—O—CH_2—CH_3$	8	ether	60
$CH_3—NH—CH_2—CH_3$	37	secondary amine	59
$CH_3CH_2CH_2—NH_2$	48	primary amine	59
$CH_3CH_2CH_2—OH$	97	alcohol	60

All amines, even tertiary ones, form hydrogen bonds with hydroxylic solvents such as water and alcohols. Therefore, amines tend to be soluble in alcohols, and the lowermolecular-weight amines (up to about four carbon atoms) are relatively soluble in water.
Perhaps the most obvious property of amines is their characteristic odor of rotting fish. Some of the diamines are particularly pungent; the following diamines have common names that describe their odors:



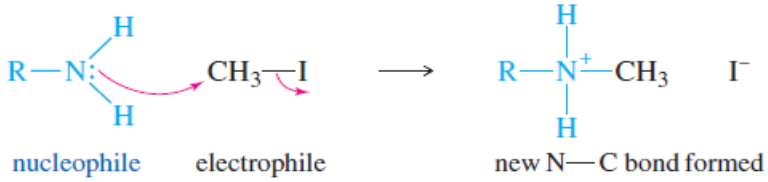
2.4.2. Chemical Properties of amines

These properties include the reactions and synthesis of amines. The lone pair on the nitrogen of an amine causes it to be nucleophilic as well as basic which is very useful in both reactions and syntheses of amines.

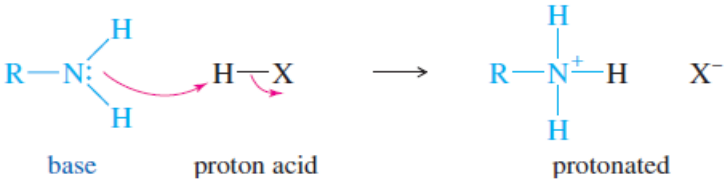
2.5. Basicity and Acidity of Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen, which makes amines both basic and nucleophilic. An amine is a nucleophile (a Lewis base) because its lone pair of nonbonding electrons can form a bond with an electrophile. An amine can also act as a Brønsted–Lowry base by accepting a proton from a proton acid.

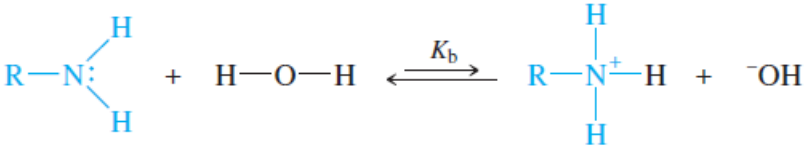
Reaction of an amine as a nucleophile



Reaction of an amine as a proton base



Because amines are fairly strong bases, their aqueous solutions are basic. An amine can abstract a proton from water, giving an ammonium ion and a hydroxide ion. The equilibrium constant for this reaction is called the **base-dissociation constant** for the amine, symbolized by K_b.



$$K_b = \frac{[RNH_3^+][^-OH]}{[RNH_2]} \qquad pK_b = -\log_{10} K_b$$

Stronger bases have smaller values of pK_b.
In practice, K_b values are not often used. Instead, the most convenient way to measure the basicity of an amine (RNH_2) is to look at the acidity of the corresponding ammonium ion (RNH_3^+).

For the reaction

$$RNH_3^+ + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}$$

so

$$K_a \cdot K_b = \left[\frac{[RNH_2]\,[H_3O^+]}{[RNH_3^+]}\right]\left[\frac{[RNH_3^+]\,[OH^-]}{[RNH_2]}\right]$$

$$= [H_3O^+]\,[OH^-] = K_w = 1.00 \times 10^{-14}$$

Thus

$$K_a = \frac{K_w}{K_b} \quad \text{and} \quad K_b = \frac{K_w}{K_a}$$

and

$$pK_a + pK_b = 14$$

These equations state that the K_b of an amine multiplied by the K_a of the corresponding ammonium ion is equal to K_w, the ion-product constant for water (1.00×10^{-14}). Thus, if we know K_a for an ammonium ion, we also know K_b for the corresponding amine base because $K_b = K_w/K_a$. The more acidic the ammonium ion, the less tightly the proton is held and the weaker the corresponding base. That is, a weaker base has an ammonium ion with a smaller pK_a and a stronger base has an ammonium ion with a larger pK_a.

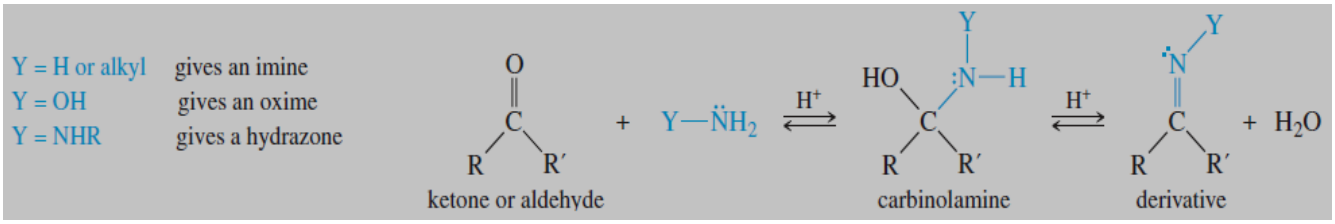
Generally, a strongly basic amine has a weakly acidic ammonium ion and a weakly basic amine has a strongly acidic ammonium ion. Most simple alkylamines are similar in their base strength, with pK_a's for their ammonium ions in the narrow range 10 to 11. Arylamines, however, are considerably less basic than alkylamines, as are the heterocyclic amines pyridine and pyrrole and this less basic is due to electron delocalization.

2.6. Reactions of Amines

The lone pair on the nitrogen of an amine causes it to be nucleophilic as well as basic, so amines act as nucleophiles in a number of different kinds of reactions.

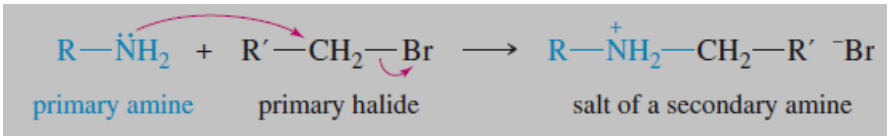
2.6.1. Reactions of amines with Aldehydes and ketones

Amines attack ketones and aldehydes. When this nucleophilic attack is followed by dehydration, an **imine** (Schiff base) results. The analogous reaction of a hydrazine derivative gives a **hydrazone**, and the reaction with hydroxylamine gives an **oxime.**

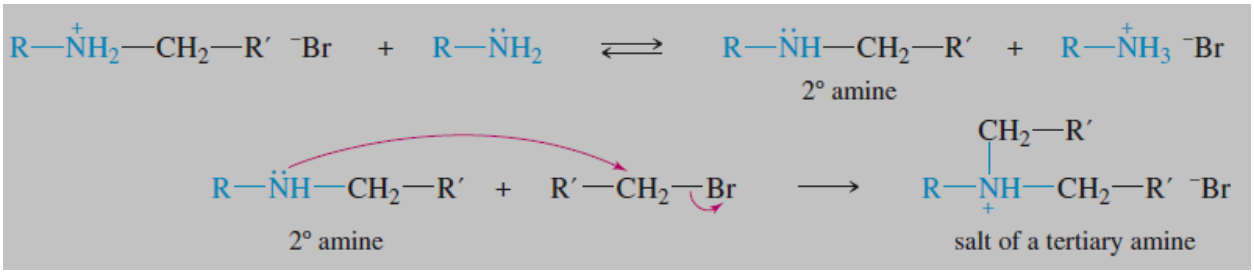


2.6.2. Alkylation of Amines

Amines react with primary alkyl halides to give alkylated ammonium halides. Alkylation proceeds by the S_N2 mechanism, so it is not feasible with tertiary halides because they are too hindered. Secondary halides often give poor yields, with elimination predominating over substitution.

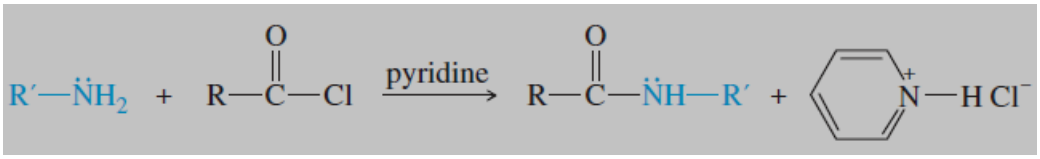


Unfortunately, the initially formed salt may become deprotonated. The resulting secondary amine is nucleophilic, and it can react with another molecule of the halide.



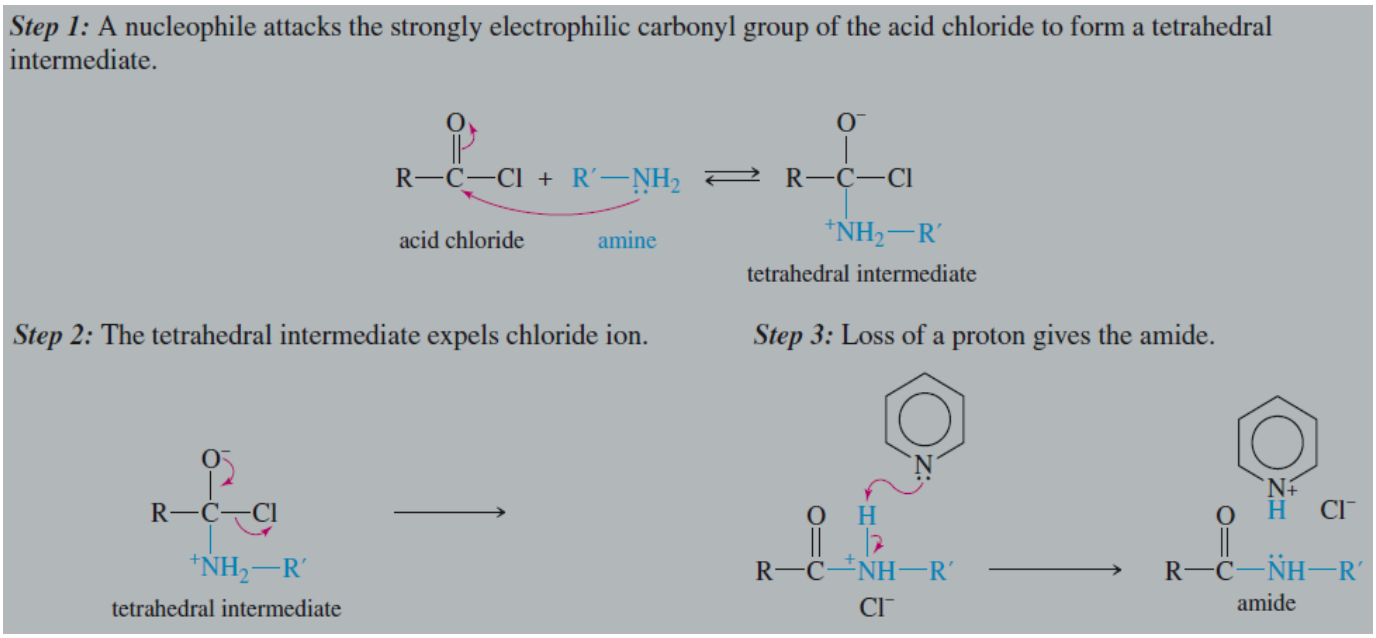
2.6.3. Acylation of Amines

Primary and secondary amines react with acid halides to form amides. This reaction is a *nucleophilic acyl substitution*: the replacement of a leaving group on a carbonyl carbon by a nucleophile. In this case, the amine replaces halide ion.

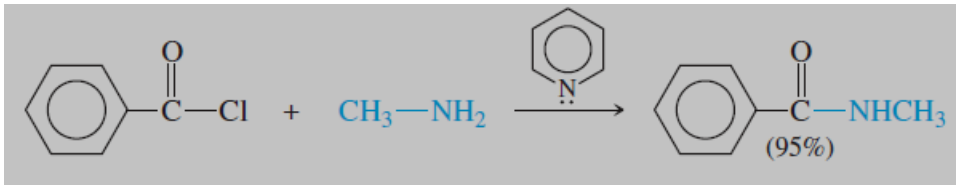


The amine attacks the carbonyl group of an acid chloride much like it attacks the carbonyl group of a ketone or aldehyde. The acid chloride is more reactive than a ketone or an aldehyde because the electronegative chlorine atom draws electron density away from the carbonyl carbon, making it more electrophilic. The chlorine atom in the tetrahedral intermediate is a good leaving group. The tetrahedral intermediate expels chloride to give the amide. A base such as pyridine or NaOH is often added to neutralize the HCl produced.

Mechanism of acylation of an amine by an acid chloride



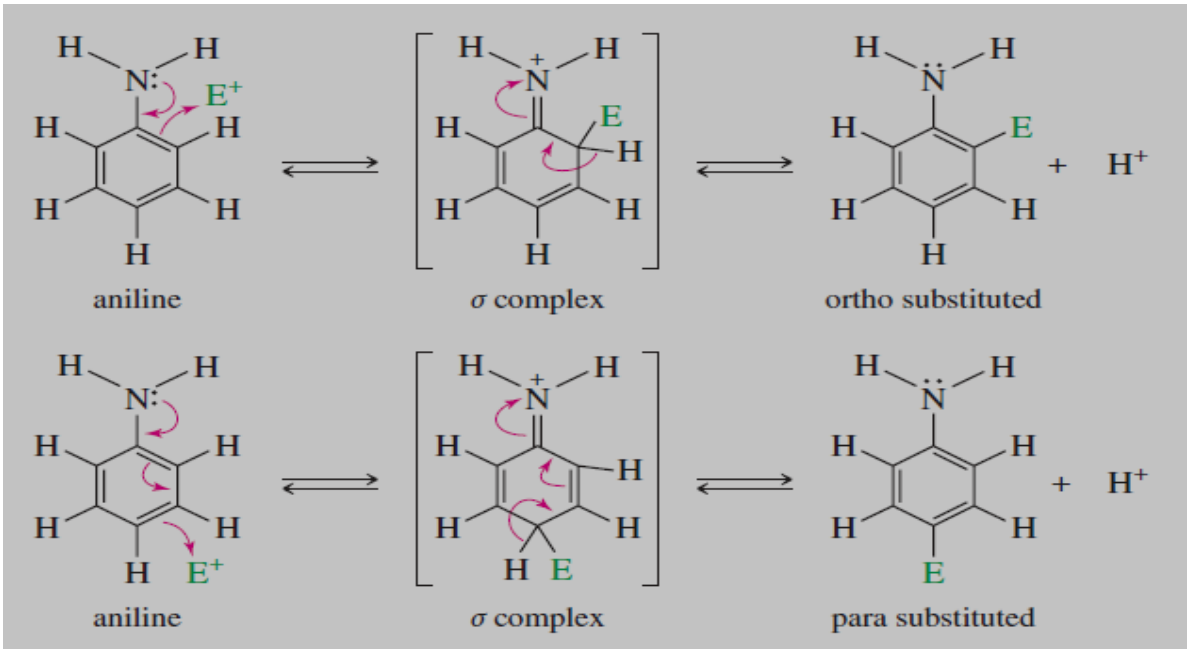
Example



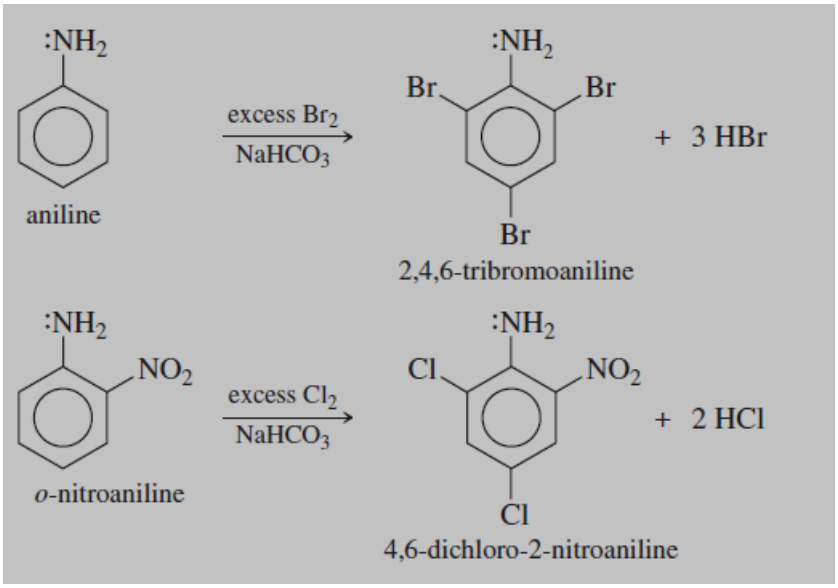
2.6.4. Aromatic Substitution of Arylamines and Pyridine

A) Electrophilic Aromatic Substitution of Arylamines

In an arylamine, the nonbonding electrons on nitrogen help stabilize intermediates (σ complexes) resulting from electrophilic attack at the positions ortho or para to the amine substituent. As a result, amino groups are strong activating groups and ortho, para directors.



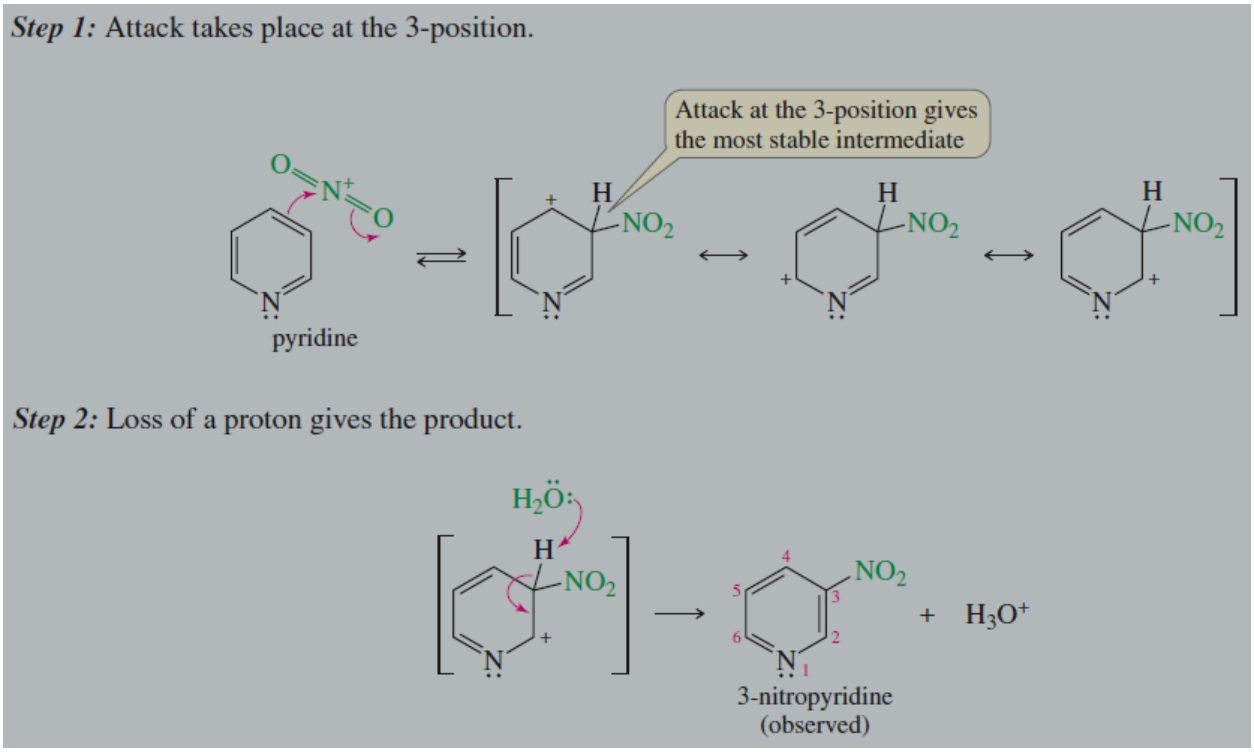
For example, the following reactions show halogenation of aniline derivatives, which occurs readily without a catalyst. If an excess of the reagent is used, all the unsubstituted positions ortho and para to the amino group become substituted.



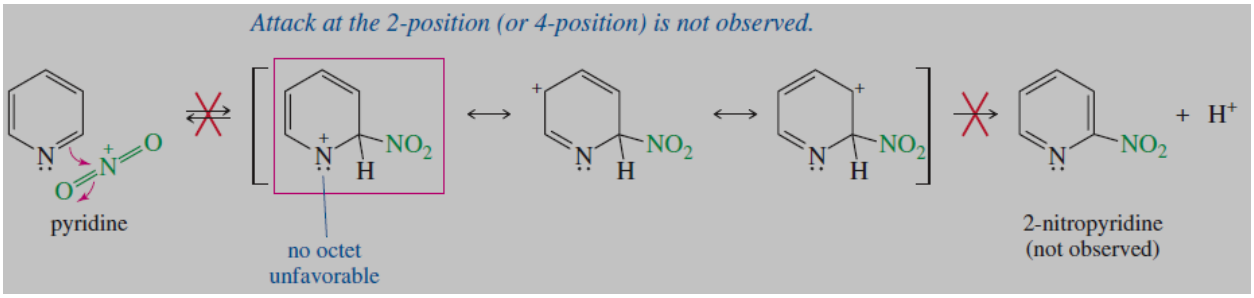
B) Electrophilic Aromatic Substitution of Pyridine

In its aromatic substitution reactions, pyridine resembles strongly deactivated benzene. Deactivation results from the electron-withdrawing effect of the electronegative nitrogen atom. Its nonbonding electrons are perpendicular to the π system, and they cannot stabilize the positively charged intermediate. When pyridine does react, it gives substitution at the 3-position, analogous to the meta substitution shown by deactivated benzene derivatives.

Mechanism of the Electrophilic Aromatic Substitution of Pyridine

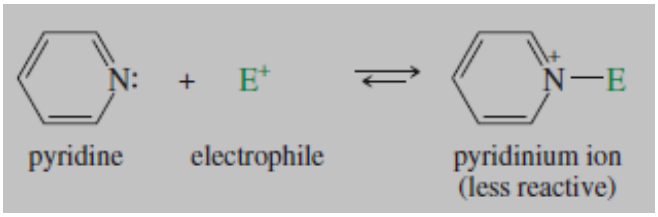


In comparison, consider the unfavorable intermediate that would be formed by attack at the 2-position.

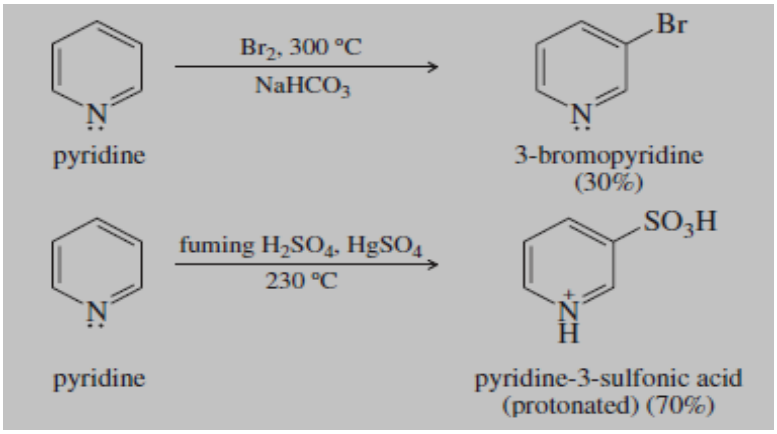


Electrophilic attack on pyridine at the 2-position gives an unstable intermediate, with one of the resonance structures showing a positive charge and only six electrons on nitrogen. In contrast, electrophilic attack at the 3-position gives a more stable intermediate with the positive charge spread over three carbon atoms and not on nitrogen.

Electrophilic substitution of pyridine is further hindered by the tendency of the nitrogen atom to attack electrophiles and take on a positive charge. The positively charged pyridinium ion is even more resistant than pyridine to electrophilic substitution.



Two electrophilic substitutions of pyridine are shown here. Notice that these reactions require severe conditions, and the yields are poor to fair.



Pyridine is deactivated toward electrophilic attack, but it is activated toward attack by electron-rich nucleophiles; that is, it is activated toward nucleophilic aromatic substitution. If there is a good leaving group at either the 2-position or the 4-position, a nucleophile can attack and displace the leaving group. The following reaction shows nucleophilic attack at the 2-position. The intermediate is stabilized by delocalization of the negative charge onto the electronegative nitrogen atom. This stabilization is not possible if attack occurs at the 3-position.

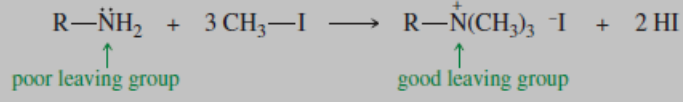
2.6.5. Hofmann and Cope Eliminations

A) Hofmann Elimination: Amines as Leaving Groups

Amines can be converted to alkenes by elimination reactions, much like alcohols and alkyl halides undergo elimination to give alkenes. An amine cannot undergo elimination directly, however, because the leaving group would be an amide ion ($^-NH_2$ or ^-NHR), which is a very strong base and a poor leaving group. An amino group can be converted to a good leaving group by exhaustive methylation, which converts it to a quaternary ammonium salt that can leave as a neutral amine. An amino group can be converted to a good leaving group by exhaustive methylation, which converts it to a quaternary ammonium salt that can leave as a neutral amine.

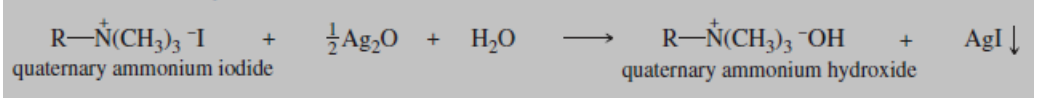
Exhaustive methylation is usually accomplished using methyl iodide.

Exhaustive methylation of an amine



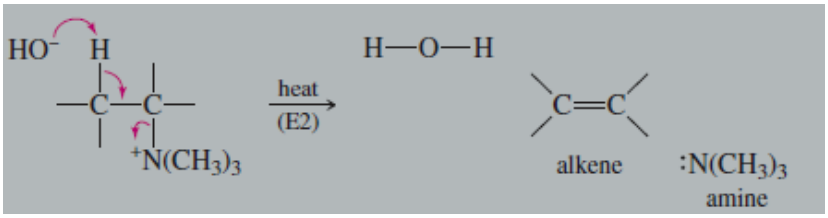
Elimination of the quaternary ammonium salt generally takes place by the E2 mechanism, which requires a strong base. To provide the base, the quaternary ammonium iodide is converted to the hydroxide salt by treatment with silver oxide (Ag_2O).

Conversion to the hydroxide salt



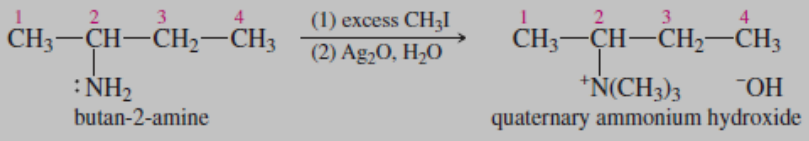
Heating of the quaternary ammonium hydroxide results in E2 elimination and formation of an alkene. This elimination of a quaternary ammonium hydroxide is called the **Hofmann elimination.**

Mechanism of Hofmann Elimination: The Hofmann elimination is a one-step, concerted E2 reaction using an amine as the leaving group.

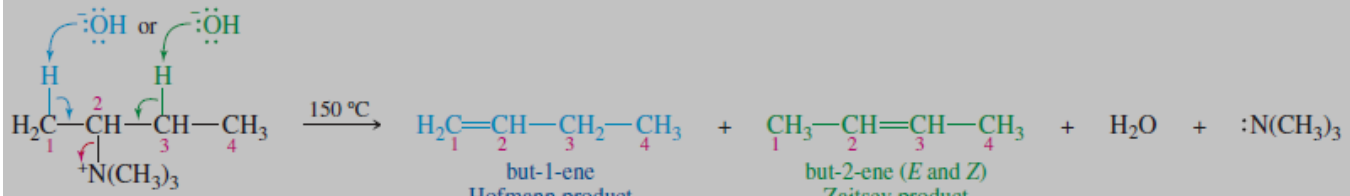


For example, when butan-2-amine is exhaustively methylated, converted to the hydroxide salt, and heated, elimination takes place to form a mixture of but-1-ene and but-2-ene.

Exhaustive methylation and conversion to the hydroxide salt

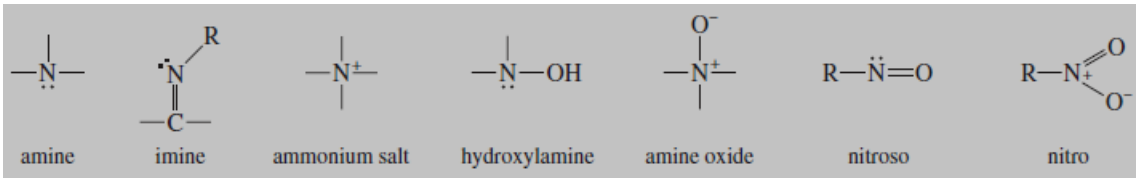


Heating and Hofmann elimination

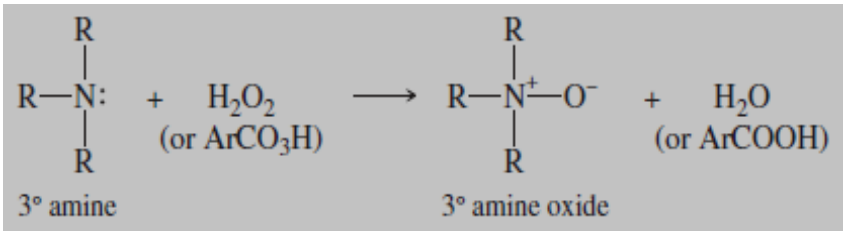


B) The Cope Elimination: Oxidation of Amines

Amines are notoriously easy to oxidize, and oxidation is often a side reaction in amine syntheses. Amines also oxidize during storage in contact with the air. Preventing air oxidation is one of the reasons for converting amines to their salts for storage or use as medicines. The following partial structures show some of the bonding and oxidation states of amines:

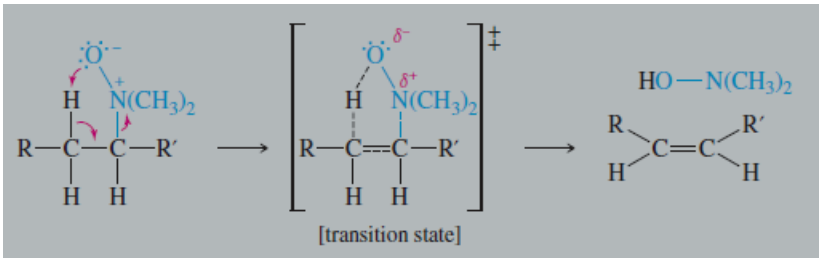


Depending on their specific structures, these states are generally more oxidized as you go from left to right. (Note the increasing number of bonds to oxygen.) Most amines are oxidized by common oxidants such as H_2O_2, permanganate, and peroxyacids. Primary and secondary amines are oxidized to primary and secondary hydroxylamine respectively. Tertiary amines are oxidized to **amine oxides,** often in good yields. Either H_2O_2 or a peroxyacid may be used for this oxidation.

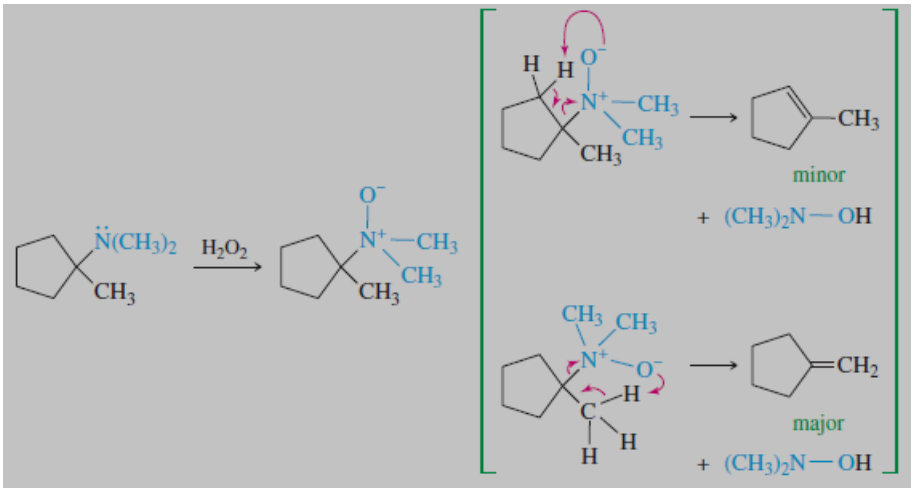


Because of the positive charge on nitrogen, the amine oxide may undergo a **Cope elimination,** much like the Hofmann elimination of a quaternary ammonium salt. The amine oxide acts as its own base through a cyclic transition state, so a strong base is not needed. The Cope elimination generally gives the same orientation as Hofmann elimination, resulting in the least-substituted alkene.

Mechanism of the Cope Elimination of an Amine Oxide: The Cope elimination is a one-step, concerted internal elimination (Ei) using an amine oxide as both the base and the leaving group. Syn stereochemistry is required for the Cope elimination.

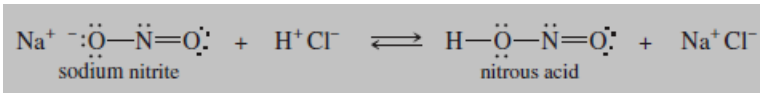


For example look at the following tertiary amine when it is treated with H_2O_2 and heated. Oxidation converts the tertiary amine to an amine oxide. Cope elimination can give either of two alkenes. We expect the less-hindered elimination to be favored, giving the Hofmann product.

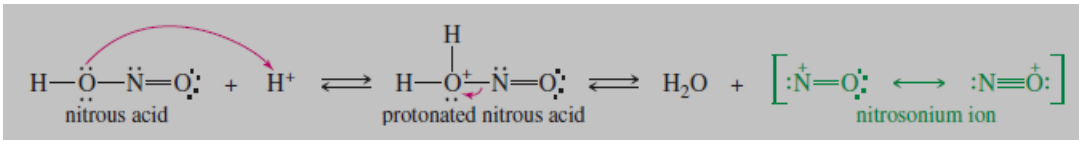


2.6.6. Reactions of Amines with Nitrous Acid

Reactions of amines with nitrous acid (H-O-N=O) are particularly useful for synthesis. Because nitrous acid is unstable, it is generated in situ (in the reaction mixture) by mixing sodium nitrite ($NaNO_2$) with cold, dilute hydrochloric acid.

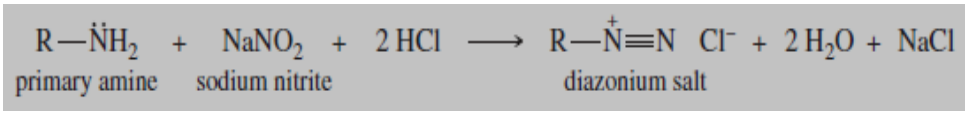


In an acidic solution, nitrous acid may protonate and lose water to give the nitrosonium ion, $^{+}N{=}O$. The nitrosonium ion appears to be the reactive intermediate in most reactions of amines with nitrous acid.



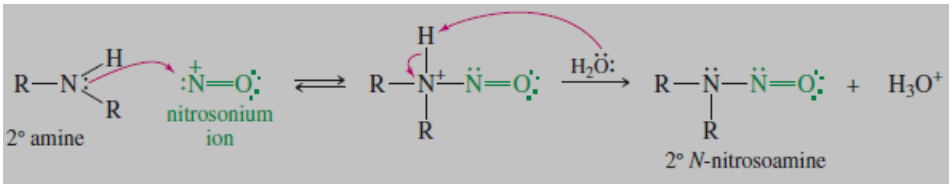
A) Reaction with Primary Amines: Formation of Diazonium Salts

Primary amines react with nitrous acid, via the nitrosonium ion, to give diazonium cations of the form $R\text{-}^{+}N{\equiv}N$. This procedure is called diazotization of an amine. Diazonium salts are the most useful products obtained from the reactions of amines with nitrous acid. The mechanism for diazonium salt formation begins with a nucleophilic attack on the nitrosonium ion to form an N-nitrosoamine.



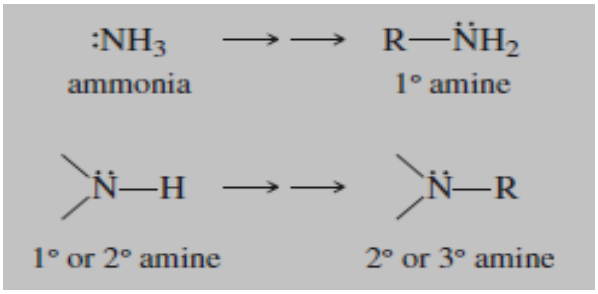
B) Reaction with Secondary Amines: Formation of N-Nitrosoamines

Secondary amines react with the nitrosonium ion to form secondary N-nitrosoamines, sometimes called nitrosamines.



2.7. Synthesis of Amines

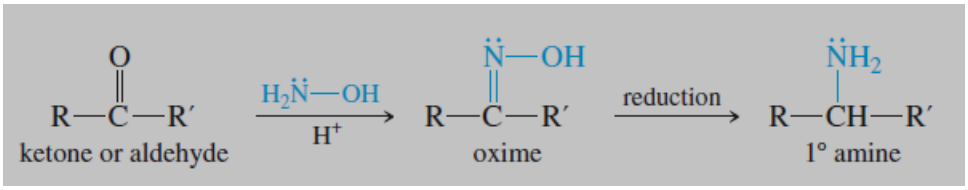
Many methods are available for making amines. Most of these methods derive from the reactions of amines covered in the preceding sections. The most common amine syntheses start with ammonia or an amine and add another alkyl group. Such a process converts ammonia to a primary amine, or a primary amine to a secondary amine, or a secondary amine to a tertiary amine.



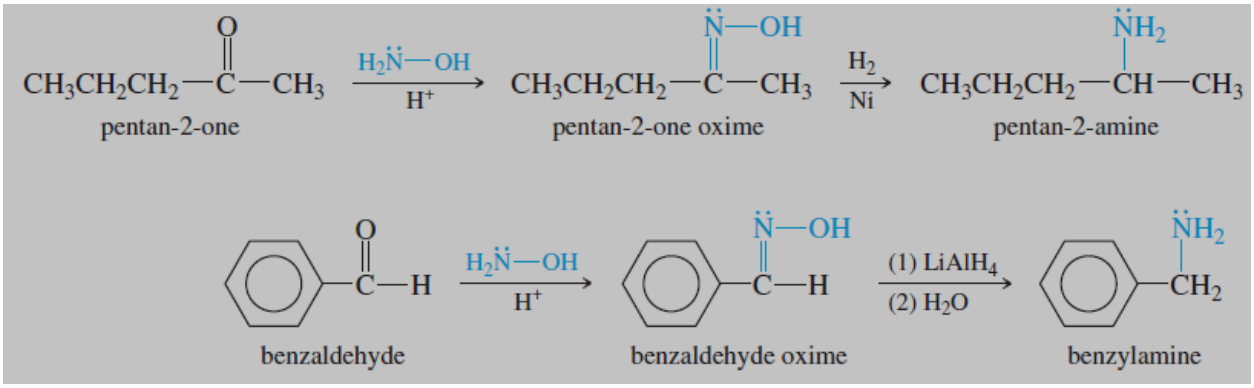
2.7.1. Synthesis of Amines by Reductive Amination

Reductive amination is the most general amine synthesis, capable of adding a primary or secondary alkyl group to an amine. Reductive amination is a two-step procedure. First we form an imine or oxime derivative of a ketone or aldehyde, and then reduce it to the amine. In effect, reductive amination adds one alkyl group to the nitrogen atom. The product can be a primary, secondary, or tertiary amine, depending on whether the starting amine had zero, one, or two alkyl groups.

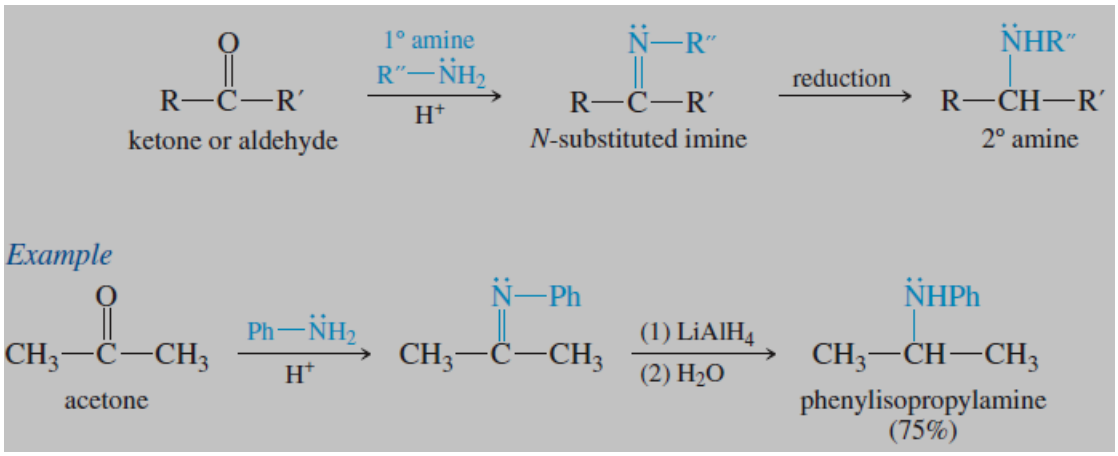
i) **Primary Amines**: Primary amines result from condensation of hydroxylamine (zero alkyl groups) with a ketone or an aldehyde, followed by reduction of the oxime. Hydroxylamine is used in place of ammonia because most oximes are stable, easily isolated compounds. The oxime is reduced using catalytic reduction, lithium aluminum hydride, or zinc and HCl.



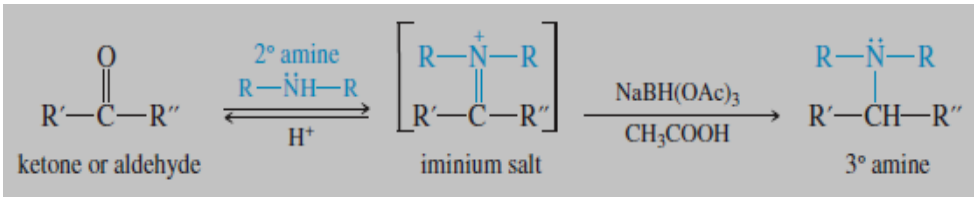
Examples

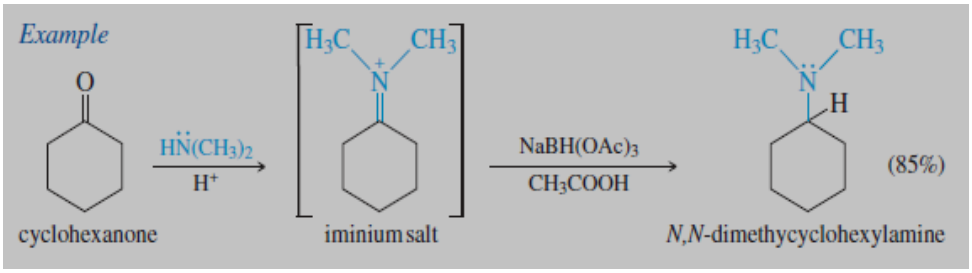


ii) **Secondary Amines:** Condensation of a primary amine with a ketone or aldehyde forms an *N*-substituted imine (a Schiff base). Reduction of the imine, using either $LiAlH_4$ or $NaBH_4$, gives a secondary amine.



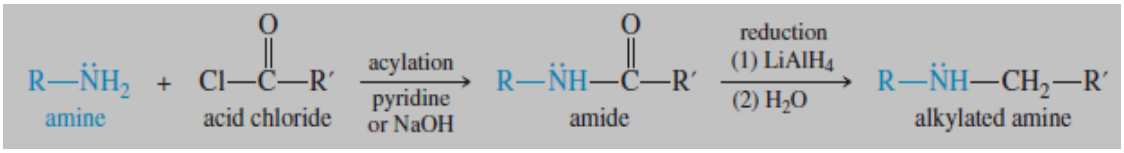
iii) **Tertiary Amines:** Condensation of a secondary amine with a ketone or aldehyde gives an iminium salt. Iminium salts are frequently unstable, so they are rarely isolated. A reducing agent in the solution reduces the iminium salt to a tertiary amine. The reducing agent must reduce the iminium salt, but it must not reduce the carbonyl group of the ketone or aldehyde. Sodium triacetoxyborohydride [$NaBH(OCOCH_3)_3$ or $NaBH(OAc)_3$] is less reactive than sodium borohydride, and it does not reduce the carbonyl group. Sodium triacetoxyborohydride has largely replaced the older, more toxic reagent, sodium cyanoborohydride ($NaBH_3CN$).





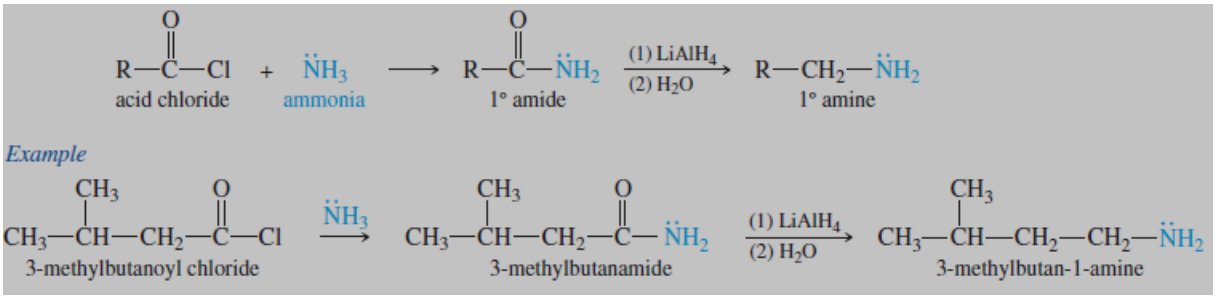
2.7.2. Synthesis of Amines by Acylation–Reduction

The second general synthesis of amines is acylation–reduction. Like reductive amination, acylation–reduction adds one alkyl group to the nitrogen atom of the starting amine. Acylation of the starting amine by an acid chloride gives an amide, which is much less nucleophilic and unlikely to over-acylate. Reduction of the amide by lithium aluminum hydride ($LiAlH_4$) gives the corresponding amine.

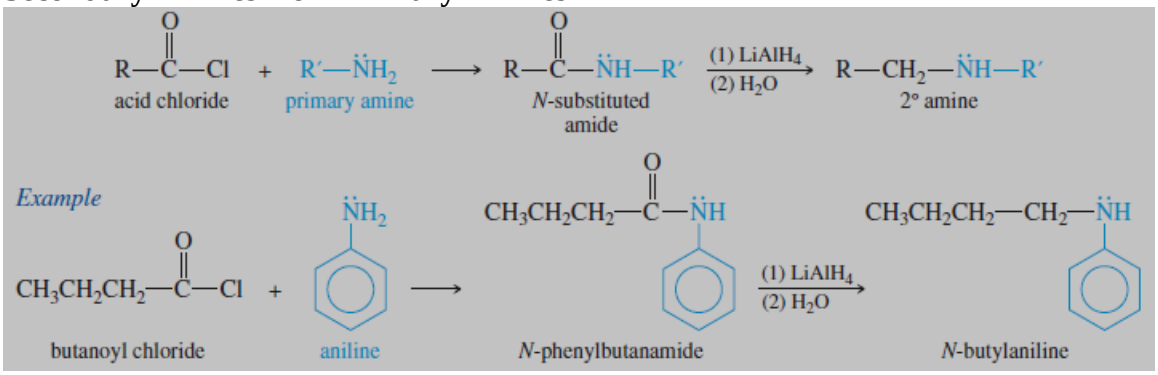


Acylation–reduction converts ammonia to a primary amine, a primary amine to a secondary amine, or a secondary amine to a tertiary amine. These reactions are quite general, with one restriction: The added alkyl group is always 1° because the carbon bonded to nitrogen is derived from the carbonyl group of the amide, reduced to a methylene (-CH_2-) group.

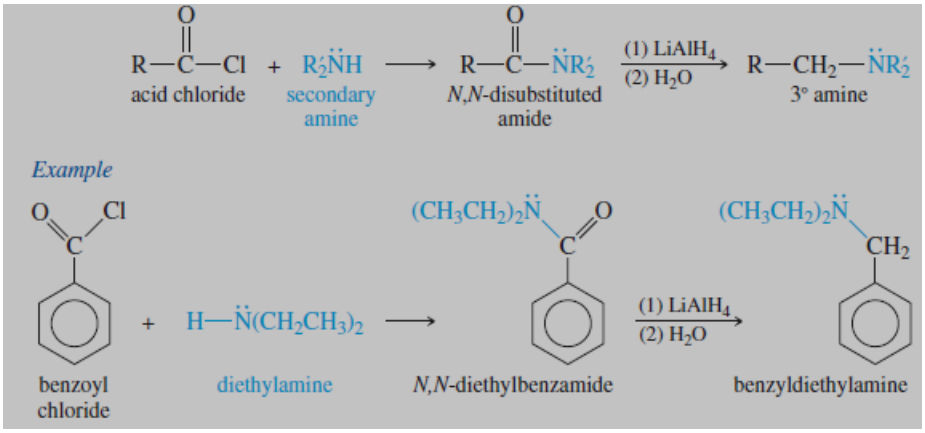
i) Primary Amines from Ammonia



ii) Secondary Amines from Primary Amines

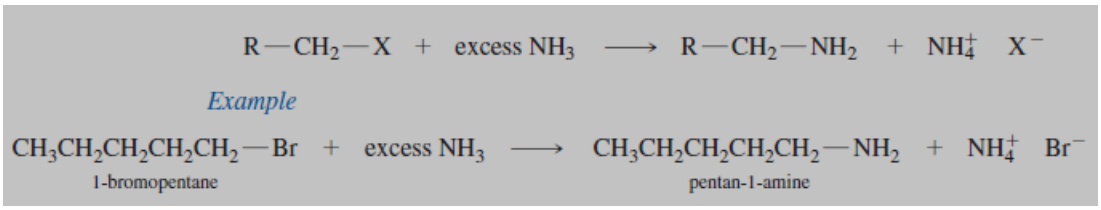


iii) Tertiary Amines from Secondary Amines

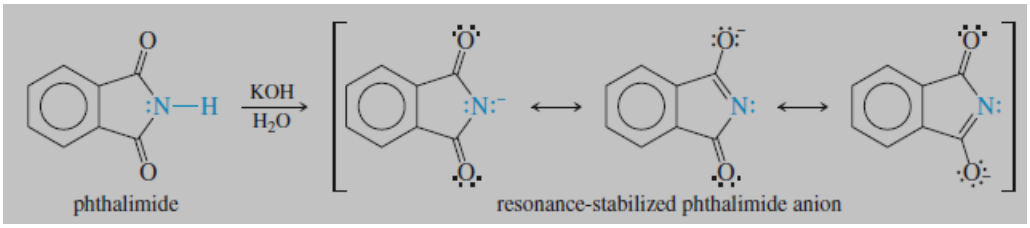


2.7.3. Direct Alkylation and Gabriel Synthesis

The S_N2 reaction of amines with alkyl halides is complicated by a tendency for overalkylation to form a mixture of monoalkylated and polyalkylated products. Simple primary amines can be synthesized, however, by adding a halide or tosylate (must be a good S_N2 substrate) to a large excess of ammonia. Because there is a large excess of ammonia present, the probability that a molecule of the halide will alkylate ammonia is much larger than the probability that it will over-alkylate the amine product.



In 1887, Siegmund Gabriel (at the University of Berlin) developed the **Gabriel amine synthesis** for making primary amines without danger of over-alkylation. He used the phthalimide anion as a protected form of ammonia that cannot alkylate more than once. Phthalimide has one acidic N-H proton (p*K*a=8.3) that is abstracted by potassium hydroxide to give the phthalimide anion.



The phthalimide anion is a strong nucleophile, displacing a halide or tosylate ion from a good S_N2 substrate. Heating the *N*-alkyl phthalimide with hydrazine displaces the primary amine, giving the very stable hydrazide of phthalimide.