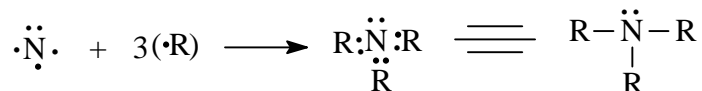


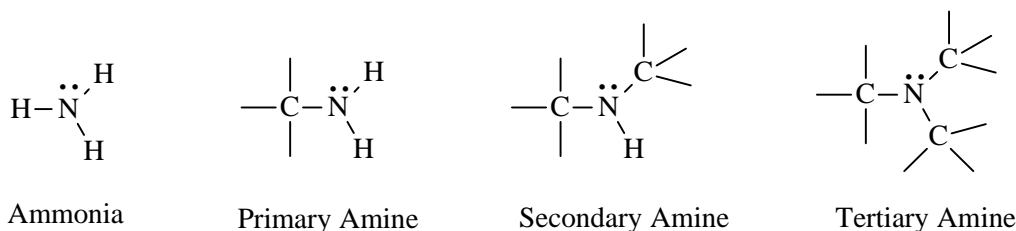
AMINES AND QUATERNARY AMMONIUM COMPOUNDS

I. Introduction

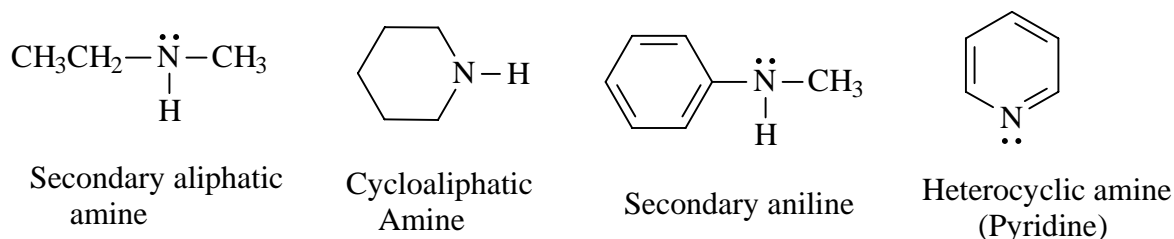
Amines are hydrocarbon derivatives of ammonia. Nitrogen has five valence electrons and therefore requires three electrons or bonds to complete its octet. Based on this valence and bonding order, nitrogen forms three bonds in its neutral (uncharged) state and maintains one pair of non-bonded electrons (NBEs):



Amines are sub-classified as primary, secondary and tertiary based on the degree of hydrocarbon substitution as shown below. Amines with four hydrocarbon substituents are positively charged and exist as "permanent cations" referred to as quaternary ammonium compounds. These will be discussed in more detail at the end of this section:

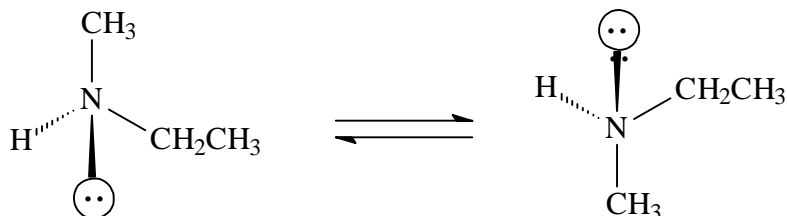


Amines also can be sub-classified as "aliphatic", "cycloaliphatic", "aromatic" or "heterocyclic" based on the nature of the N-substituent and bonding patterns. Aliphatic amines have simple hydrocarbon substituents (alkyl groups) while aromatic amines, more commonly referred to as "anilines", have at least one aromatic (benzene) ring substituent. Anilines also are sub-classified as primary, secondary and tertiary based on the total number of carbon-containing substituents as illustrated in the examples below. In heterocyclic amines the nitrogen atom is part of a heterocyclic ring which may be partially or fully unsaturated. While qualitatively similar in their chemical properties, anilines and heterocyclic amines differ from aliphatic amines in a number of important ways that are discussed in the following sections.



Amines are sp^3 hybridized and thus amines bearing four different substituents (one "substituent" being the lone pair of electrons on nitrogen) are chiral. However, due to rapid pyramidal inversion (see below), the individual enantiomers are not usually separable (resolvable). On the

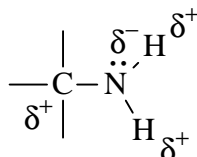
other hand, amines that contain an asymmetrically substituted nitrogen atom in a ring system, particularly at a bridgehead position, may not undergo facile inversion, and thus it is possible to resolve distinct stereoisomers. This phenomena is described in more detail in the *Stereochemistry Tutorials*.



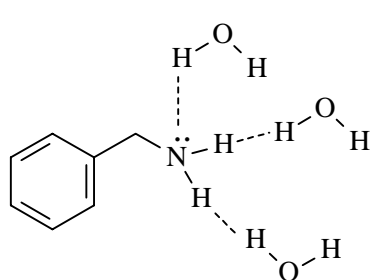
The amine functionality is the most common functional group found in drug molecules. The primary physicochemical property of importance in the drug chemistry of the amino group is its basicity. Because most amines are basic, salts forms can be generated to facilitate water solubility or solubility in other vehicles for drug administration. Also the protonated amino group present in many drug compounds provides a cationic center required for binding to many drug targets including receptors and enzymes. In addition to basicity, amines are capable of functioning as nucleophiles and participating in displacement reactions with electrophilic compounds. These chemical properties are discussed in more detail in the sections that follow.

II. Amine Solubility

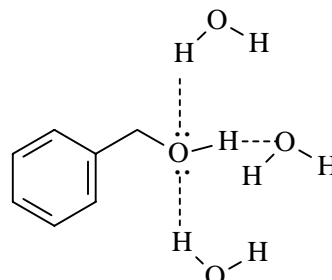
Due to the presence of C-N and N-H dipoles (electronegative N and electropositive C and Hs) primary and secondary compounds amines are considered to be somewhat polar organic compounds:



Amines with relatively small hydrocarbon substituents (lower molecular weight amines) are only moderately soluble in water since the N-H dipole is relatively weak, particularly compared to the O-H dipole of alcohols and acids, and since N is not as electronegative as O. The free pair of electrons available on N promotes water solubility as a H-bond acceptor:



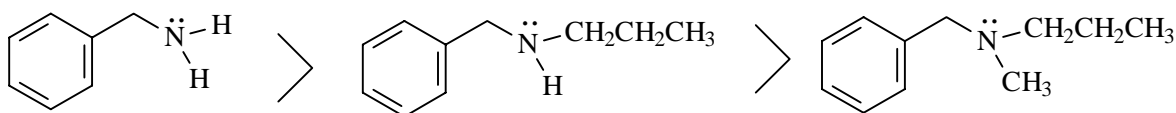
Amines: H-bonding



Alcohols: H-bonding

Amines substituted with larger hydrocarbon substituents have lower water solubility due to the presence of more non-polar functionality. Tertiary amines have even more limited water solubility since they do not have a N-H dipole to contribute H-bonds to water:

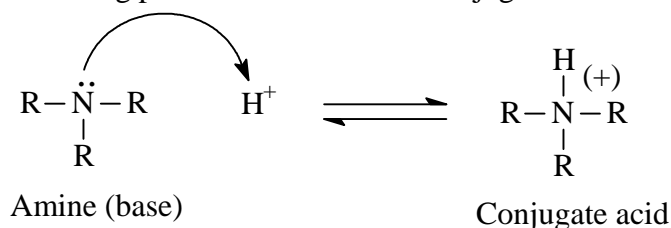
Relative water solubilities of several amines:



Another important factor that determines the water solubility of amines is basicity. Since amines are basic they may be converted to salt forms which have substantially higher water solubility than the parent amine. This is discussed more in the following section.

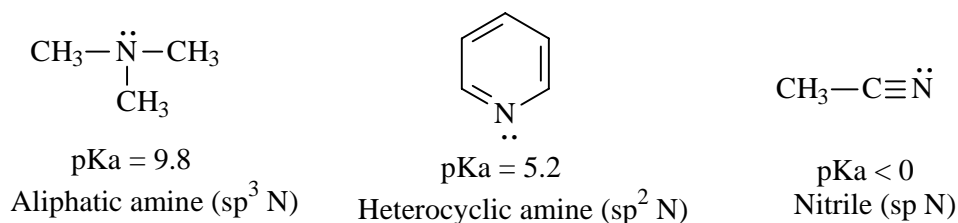
III. Amine Basicity Reactivity

An extremely important property of the amines is their **basicity** and their ability to ionize at pHs below their pKas and to form salts with mineral and organic acids. The basicity of the amine functional group results from the presence of the non-bonded pair of electrons (NBEs) on nitrogen and the relatively low electronegativity of this atom. Thus nitrogen is able to "share" its free electron pair to form a bond with a proton (and other electrophilic atoms). The free amine in this reaction is a base and the resulting protonated amine is its conjugate acid:

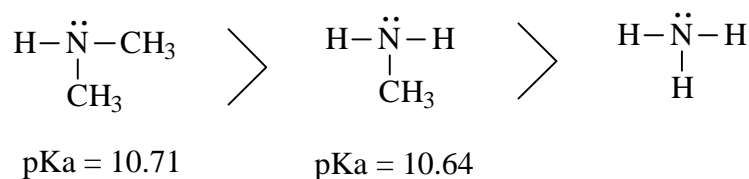


Based on this chemical reaction and mechanism, the "strength" or relative basicity of an amine is a function of its ability to share its NBEs. The ability of an amine to share its NBEs is a function of the compounds electronic (inductive and resonance) and steric properties. The contribution of each of these factors is discussed below with examples. *It is important to remember that amines do not completely ionize in neutral water as do bases such as hydroxide. Thus amines are classified as weak bases, while bases such as sodium hydroxide are classified as strong bases:*

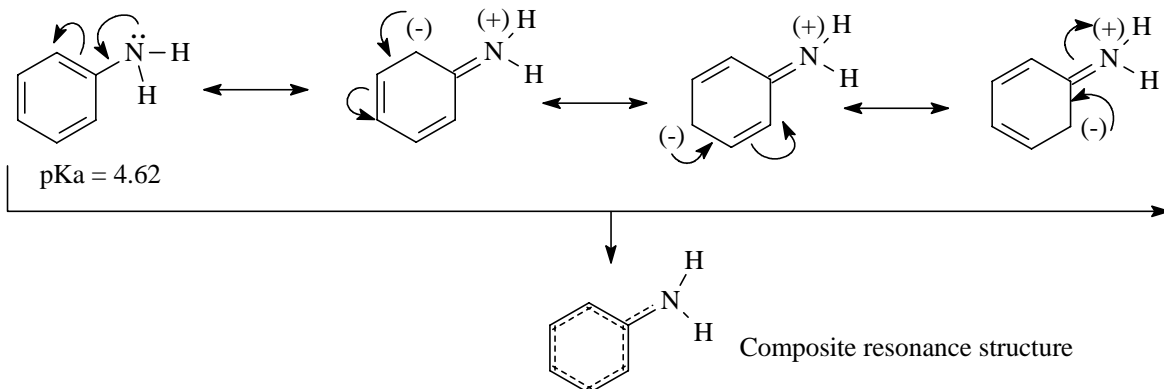
- Basicity and Nitrogen Hybridization:** The hybridization state and bonding order of a nitrogen atom is an important determinant of potential basicity as indicated by the examples below. Generally, as the "s" character of a nitrogen atom increases, basicity or the ability to coordinate the NBEs with an acid (proton) decreases. This is because "s" electrons are more tightly held by the nucleus of the nitrogen atom and less readily shared. Therefore, typical aliphatic amines which are sp^3 hybridized (25% "s" character) are more basic than aromatic heterocyclic amines which are sp^2 hybridized (33% "s" character), and these are more basic than nitriles in which the nitrogen atom is sp hybridized (50% "s" character):



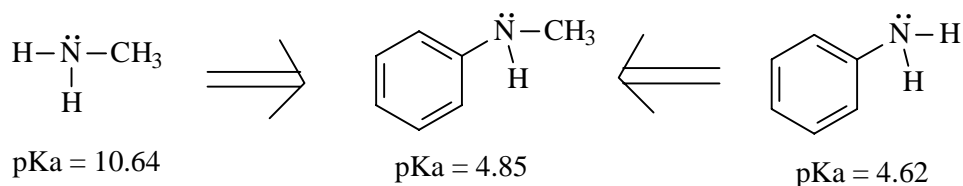
- Basicity and Electronic Factors:** Groups attached to the amine function that are electron-donating groups increase base strength (increase pKa) and assist in stabilizing the positively charged conjugate acid of an amine. Conversely, groups that are electron-withdrawing decrease base strength (decrease pKa) and destabilize the conjugate acid. As discussed in the *Resonance and Induction Tutorial*, functional groups can donate or withdraw electron density by resonance or induction. A properly positioned electron donating substituent can enhance basicity by inductive mechanisms (+I) by "pushing" electron density toward nitrogen, enabling the nitrogen to share its NBEs more readily with a proton. Such is the case with simple alkyl groups (+I). Note that dimethylamine (with two +I methyl groups on nitrogen) is more basic than methylamine (with one +I methyl group) and both compounds are more basic than simple ammonia:



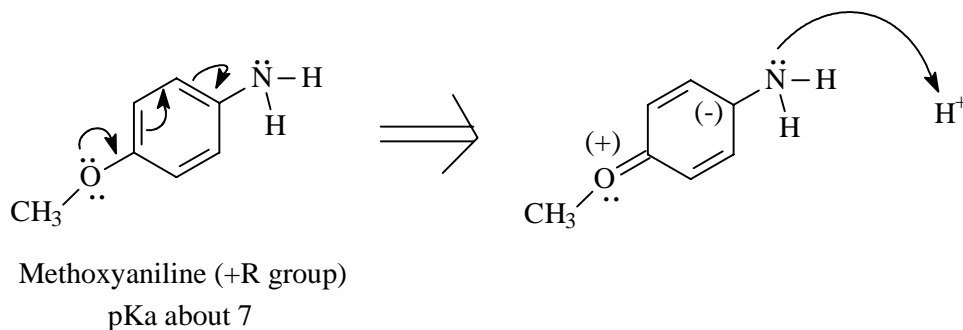
Resonance effects also play a major role in the relative basicities of various amines. Consider the example of methylamine and aniline. As discussed above, methylamine is more basic than ammonia because of the presence of an electron donating (+I) methyl group. In the case of aniline, the aromatic ring can serve as an electron withdrawer by resonance (an "electron sink"), pulling electron density away from nitrogen and thereby reducing its ability to coordinate with a proton. This is illustrated in the resonance structures below which show that the NBEs of nitrogen actually can be delocalized into the aromatic pi system of the benzene ring and "less available" to bind with a proton (act as a base). For this reason, aniline is less basic than methamine!



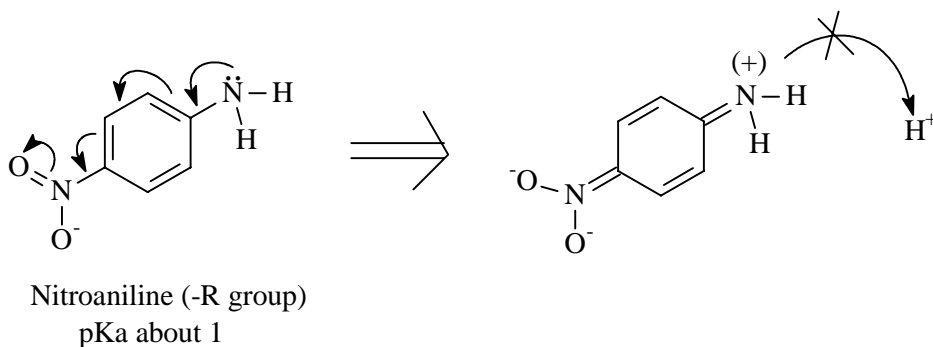
Often it is necessary to consider a variety of substituents with differing electronic properties to make an estimate of relative basicity. Consider the example of N-methylaniline. The methyl group is +I and enhances basicity. But the aromatic ring is a -R group and reduces basicity! The net effect of these two groups is a compound that is less basic than methylamine, but more basic than aniline; N-methylaniline has a pKa of 4.85 compared to a pKa of 4.62 for aniline. These examples also illustrate that resonance effects have a greater impact on basicity (pKa) than inductive effects. Note the magnitude of the reduction in pKa from methylamine (pKa 10.64) to aniline (pKa 4.62):



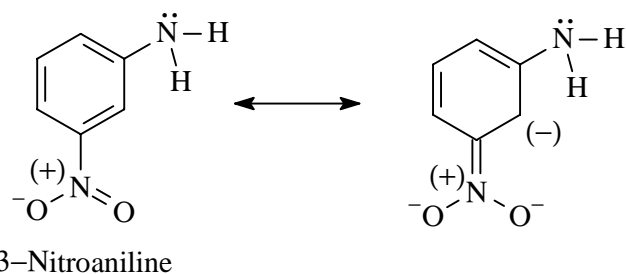
Basicity may also vary within a closely related series of amine compounds depending on the electronic nature of differing substituents. Such is the case among the substituted anilines. Anilines substituted with a substituent capable of donating electron density to nitrogen by resonance (+R) are more basic than comparable anilines containing a substituent capable of withdrawing electron density by resonance. Consider the examples of "methoxyaniline" and nitroaniline shown below. When positioned appropriately on the aromatic ring (at the 2- or 4-positions), +R substituents such as methoxy can release electron density into the ring and toward nitrogen, freeing the NBEs of nitrogen to coordinate with a proton. This is illustrated in the figure below. As a result, methoxy aniline is more basic than aniline:



Conversely, when positioned appropriately on the aromatic ring (at the 2- or 4-positions), -R substituents, such as a nitro, can withdraw electron density into the ring and away from nitrogen, occupying the NBEs of nitrogen and hindering the coordination with a proton. This is illustrated in the figure below. As a result, nitroaniline is less basic (pKa 1.0) than aniline:



As stated repeated in the examples above, for resonance effects to be optimal, substituents must be positioned appropriately. In the example above positioning is critical because the substituents must be "conjugated" with the amino moiety to allow for optimal electron withdrawal. For example, in 3-nitroaniline the nitro group is not in direct conjugation with the amino group, so the full -R effect is not observed. 3-Nitroaniline thus is a stronger base than 4-nitroaniline. It is still weaker than aniline, however, and this is a result of the electron withdrawing effect on the aromatic ring which has an indirect withdrawing effect on the NBEs



of the amino group:

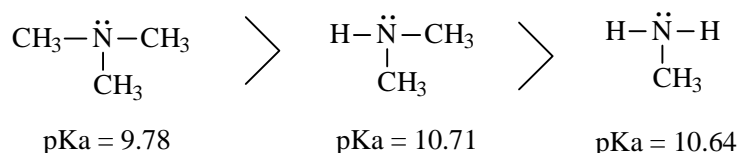
Thus both the position and the electronic nature of the functionality linked to an amino group are important determinants of relative basicity. This may be best illustrated by consideration of a related functional group, the amide. Amides may be viewed as amine derivatives where one nitrogen substituent is a carbonyl moiety as shown below. In this case a "conjugated system" is present - the NBEs of nitrogen are in conjugation with the C=O of the carbonyl. The strongly electron withdrawing nature of the carbonyl group by resonance (due to the presence of the double bond involving an electronegative oxygen atom) allows for delocalization of the NBEs of nitrogen by resonance. The electron withdrawal created by this conjugated system limits the ability of nitrogens NBEs to coordinate with a proton (act as a base) and renders amides essentially "non-basic":



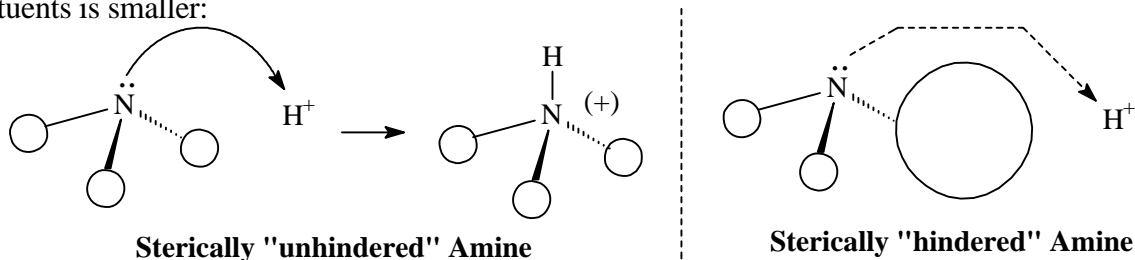
Amides and resonance delocalization

It should be noted that such resonance delocalization does not necessarily render a system non-basic. As illustrated by the example of guanidine at the end of this tutorial, conjugated nitrogen systems may be very basic, depending on the nature of their overall structure.

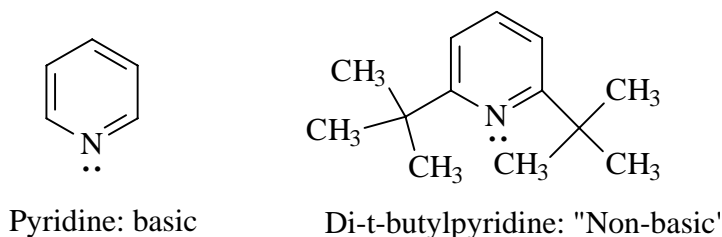
- **Basicity and Steric Factors:** Based on the electronic factors discussed above, it would be reasonable to predict amines with three alkyl groups (tertiary amines) would be more basic than comparable secondary amines (which are more basic than primary amines). However, this is not the case as is illustrated by the comparison of the pKas of trimethylamine, dimethylamine and methylamine show below:



The addition of the third methyl group as in trimethylamine actually results in a slight decrease in basicity! This reduction in pKa is a result of steric factors. The attachment of large and/or multiple substituents to the basic nitrogen of amines hinders bond formation with a proton and thereby reduces basicity. Steric factors also may destabilized the conjugate acid of an amine since this structure is tetrahedral vs. trigonal in the parent amine and intramolecular distances between substituents is smaller:

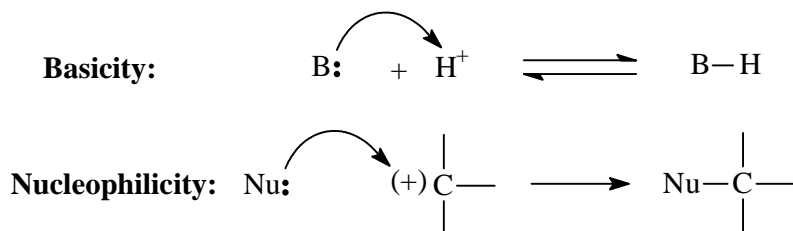


As a result of these steric phenomena, tertiary amines are typically less basic than comparable secondary amines. In some cases substitution of very bulky substituents around a sterically crowded center may render an otherwise basic nitrogen atom essentially non-basic, as illustrated by the pyridine derivative below where the nitrogen atom is flanked by two bulky t-butyl groups:

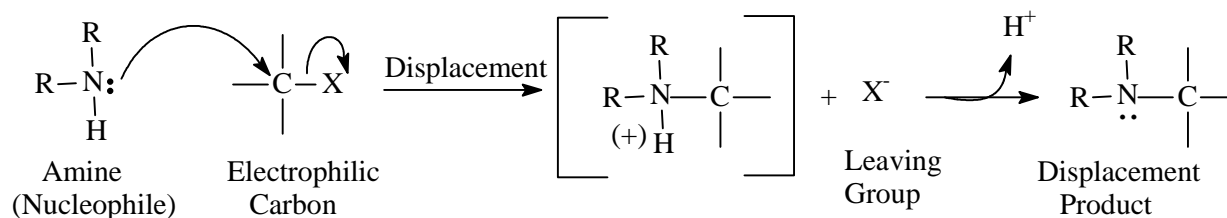


IV. Amine Nucleophilicity

Nucleophilicity may be defined as the ability of an atom to donate an electron pair to an electrophile (an electron deficient species) in a chemical reaction. Nucleophilicity is similar to basicity in that it is a measure of the ability of an atom to function as an electron donor. It differs however in that basicity refers to electron donation to a proton (or other acid) in a reversible or equilibrium reaction and is measured by association constants such as pKa. Nucleophilicity refers to electron donation, usually to an electrophilic carbon atom, in a non-equilibrium reaction and is measured by rate constants. The difference is illustrated by the two reactions below:

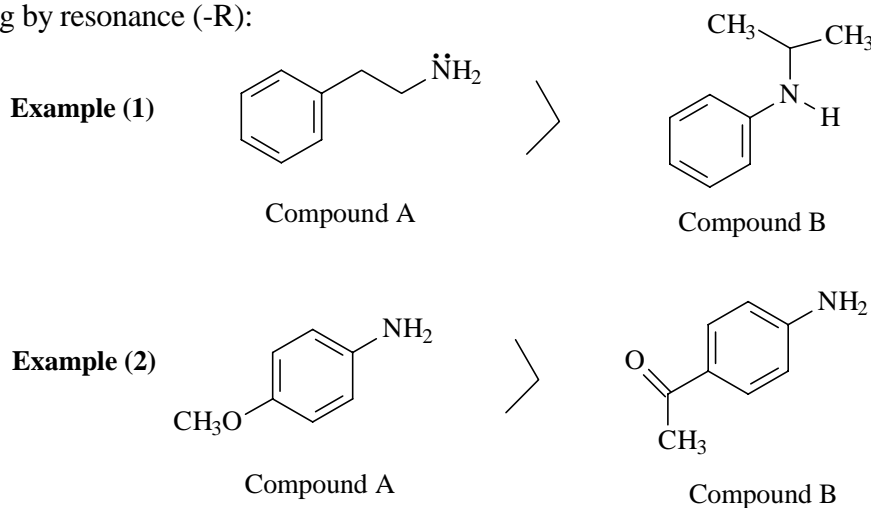


Thus while most strong bases are good nucleophiles, not all "good" nucleophiles are strong bases. As a result of their valence and bonding order, amines have a NBEs and thus can function as nucleophiles as well as bases. In the presence of electrophilic species, amines may react to form a substituted amine product; this reaction is referred to as a "nucleophilic substitution" or displacement reaction. For such a reaction to proceed the electrophile must have a "leaving group"; an electronegative functionality capable of displacement from the electrophile with the bonding electrons. Also, to form a neutral product, the amine nucleophile must have at least one hydrogen atom (a primary or secondary amine) to be lost as a proton. These principles are illustrated in the general example below:



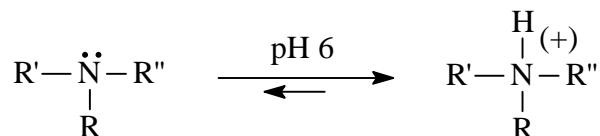
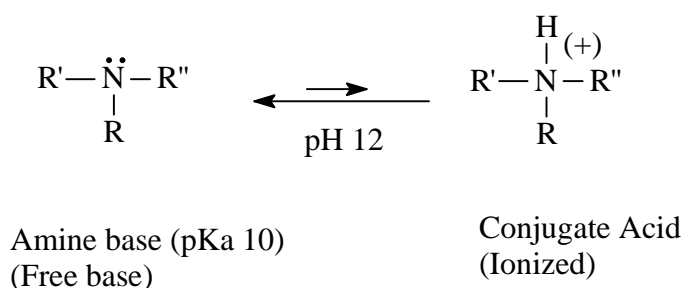
The reaction shown above is a classic "S_N2" reaction - a bimolecular nucleophilic substitution reaction, where the both reactants, the nucleophilic amine and electrophile are involved in the rate determining step. Amines may also function as nucleophiles in comparable "S_N1" reactions where the rate of the reaction is determined by ionization of the electrophile alone. Further discussion of different mechanistic classes of displacement reactions can be found in any organic chemistry textbook.

The ability of an amine to function as a nucleophile in such substitution reactions is dependent on the "availability" of the NBEs for attack at an electrophilic center. Thus same electronic and steric factors that influence the relative basicity of an amine will affect its nucleophilicity. These are discussed above in the "Amine Basicity" section. Generally, amines with strong electron withdrawing substituents will be weaker nucleophiles than amines with electron donating substituents. Also, sterically bulky amines will be weaker nucleophiles than less hindered amines. These principles are illustrated by the comparisons below: In the first example (1) compound A is a primary aliphatic amine and sterically unhindered. In compound B the amino group is sterically hindered AND the electrons on nitrogen are delocalized into the aromatic ring. In the second example (2) both compounds are anilines, but the methoxy group in compound A is electron donating by resonance (+R) and thereby enhances the nucleophilicity of the aniline nitrogen, while the ketone group of compound B is in conjugation with its aniline nitrogen and is electron withdrawing by resonance (-R):



V. Reactions of Amines:A. Basicity and Ionization

Amines are classified as "weak bases" since in water the base-conjugate acid equilibrium tends to favor the base. The degree of protonation and therefore ionization of a particular amine, however, is dependent upon its pKa and the pH of its environment. For example, an aliphatic amine with a pKa of 9 will be predominantly unprotonated and therefore non-ionized at pHs exceeding 10. At pH values several orders of magnitude below 9, however, the amine will be predominantly protonated and therefore ionized (and water soluble). Since the pH of many physiologic fluids is near 7, many biologic amines and amine drugs with pKas ≥ 9 will be predominantly ionized in these environments.



The extent of ionization of an amine of known pKa at a particular pH can be calculated using the Henderson-Hasselbalch equation covered in any organic or biochemistry textbook. This equation is derived from the equilibrium reaction as follows:

$$\begin{aligned}
 \text{RNH}_2 + \text{H}^+ &\rightleftharpoons \text{RNH}_3^+ \\
 \text{Ka} &= \frac{[\text{H}^+][\text{RNH}_2]}{[\text{RNH}_3^+]} \\
 [\text{H}^+] &= \text{Ka} \frac{[\text{RNH}_3^+]}{[\text{RNH}_2]} \\
 -\log [\text{H}^+] &= -\log \text{Ka} - \log \frac{[\text{RNH}_3^+]}{[\text{RNH}_2]} \\
 \boxed{\text{pH} = \text{pKa} + \log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]}}
 \end{aligned}$$

Consider An amine (RNH_2) with a pK_a of 9 at physiologic pH (assume pH of 7). Substituting these values, the log ratio of ionized to non-ionized acid is 1:2, for an actual ratio of ionized to non-ionized compound being 100:1. When expressed as a percent, this means that the amine is 99% ionized at this pH:

$$7 = 9 + \log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]}$$

$$\log \frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = -2$$

$$\frac{[\text{RNH}_2]}{[\text{RNH}_3^+]} = \frac{1}{100}$$

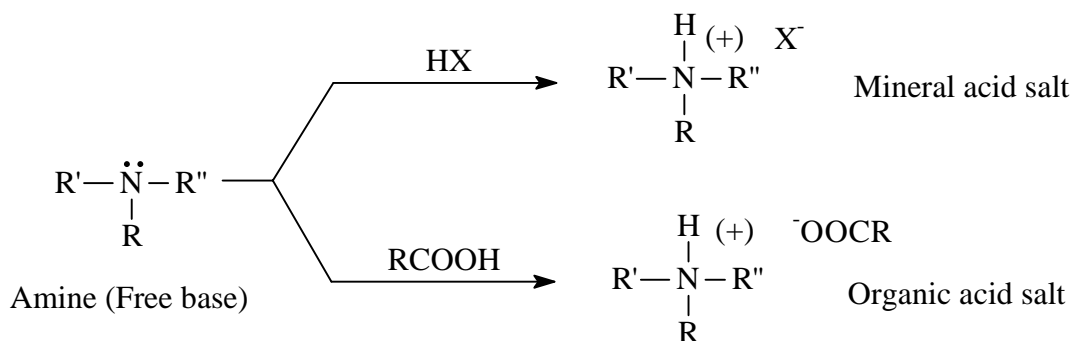
$$\text{Percent ionized } (\text{RNH}_3^+) = (100/101) \times 100 = 99\%$$

Also, based on the Henderson-Hasselbalch equation, the ratio of ionized and non-ionized amine is 1 when the pH equals the pK_a (50% ionized, 50% non-ionized). Also, each pH unit below the pK_a of an amine results in a 10-fold increase in the ratio of ionized to non-ionized compound. Thus at a pH value of 5, the ratio of ionized to non-ionized of this amine (pK_a 9) would be 10,000 to 1 (or 5 log units). Conversely each pH unit above the pK_a of an amine results in a 10-fold increase in the ratio of non-ionized to ionized compound!

B. Basicity and Salt Formation

Because of their basicity, amines react with acids to form salts. Many amine drugs are liquids at standard temperatures and are chemically unstable (oxidation and other processes). Salt forms of amines, however, typically are usually solids and chemically more stable than the parent (free) amines. Thus many amine drugs and converted to stable solid salt forms for pharmaceutical formulation.

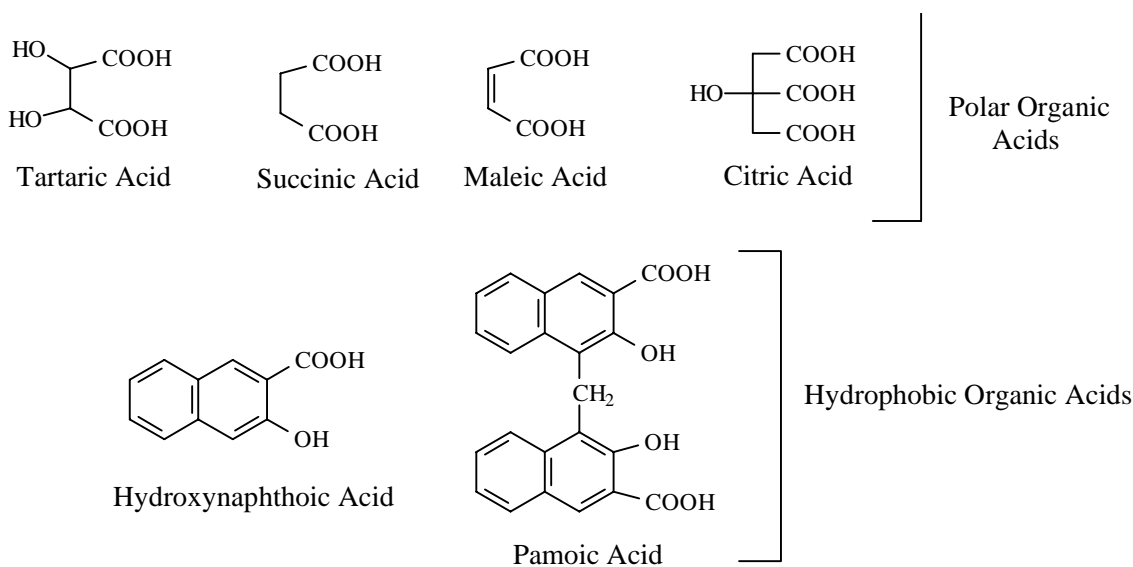
Both mineral acids (HX such as HCl , H_2SO_4 , H_3PO_4) and organic acids (RCOOH and see below) are commonly used to form amine salts of drug molecules. The general salt formation reaction for mineral and organic acids is shown below:



Note that HCl is a monoacid and therefore reacts with one molecule of amine. Sulfuric acid and the most of the organic acids shown below are diacids and can react with two molecules of amine. Phosphoric acid and citric acid are triacids and can react with three molecules of amine.

Salts formed from mineral acids and polar organic acids are water soluble. Salt formation results in formation of a cationic nitrogen center that can participate in ion-dipole bonding interactions with water and thereby enhanced water solubility compared to the parent free base.

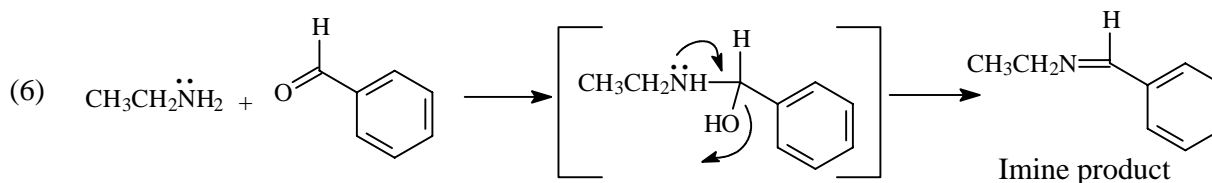
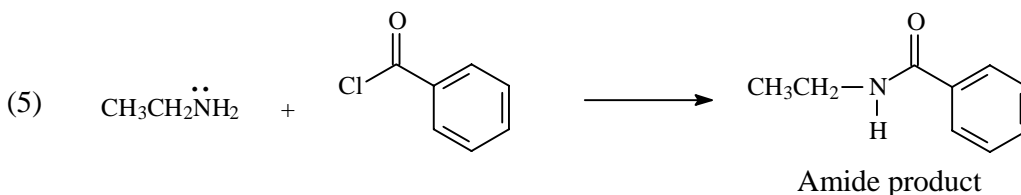
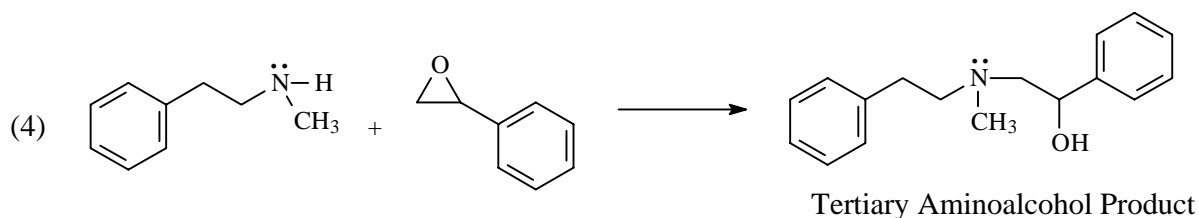
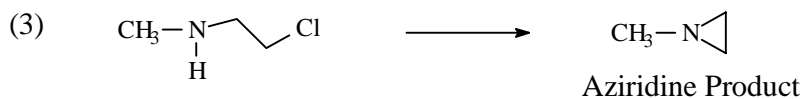
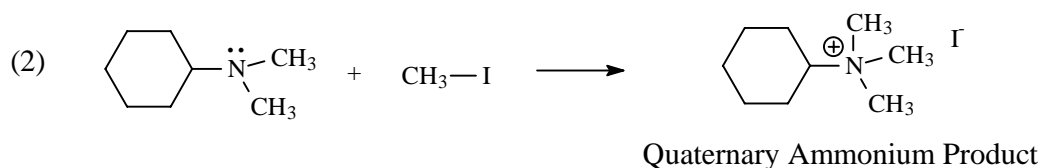
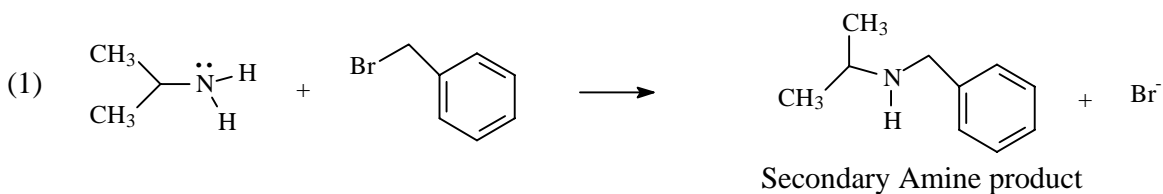
The effect on pH of dissolving an amine salt in water is dependent on the acid used in forming the salt. The salt of an amine (weak base) + a weak organic acid (COOH acid) gives a neutral or nearly neutral solution in water. The salt of amine (weak base) + a strong acid (mineral acid) yields an acidic solution when dissolved in water. The use of a hydrophobic acid in forming an amine salt will result in water de-solubilization. Drug salts of this type have utility in cases where one wishes to limit amine dissolution.



C. Nucleophilic Displacement Reactions

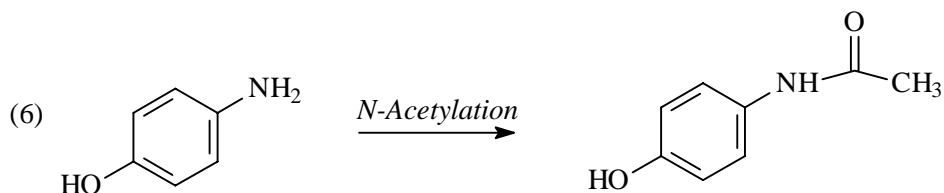
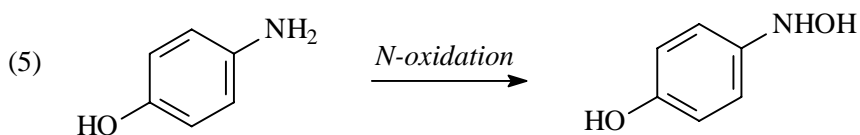
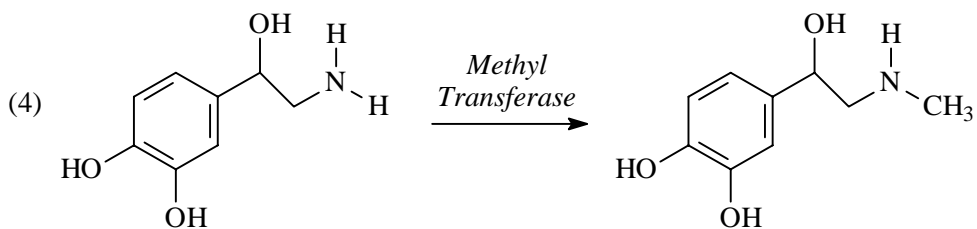
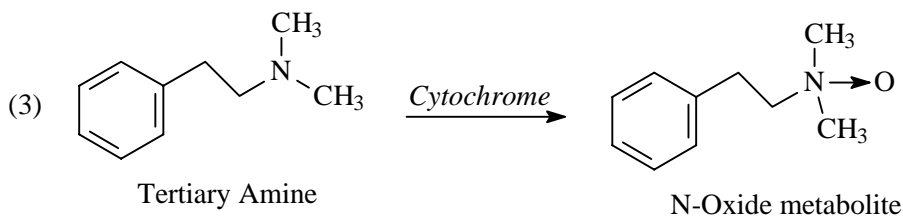
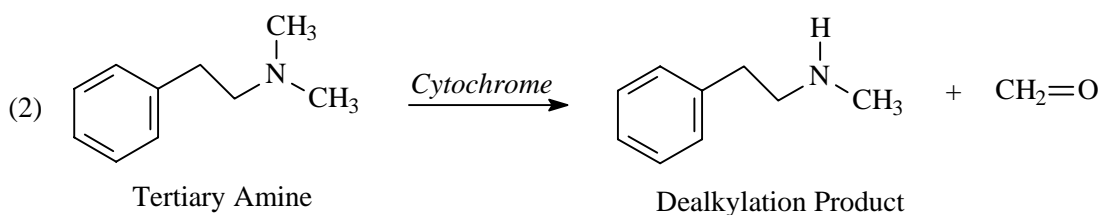
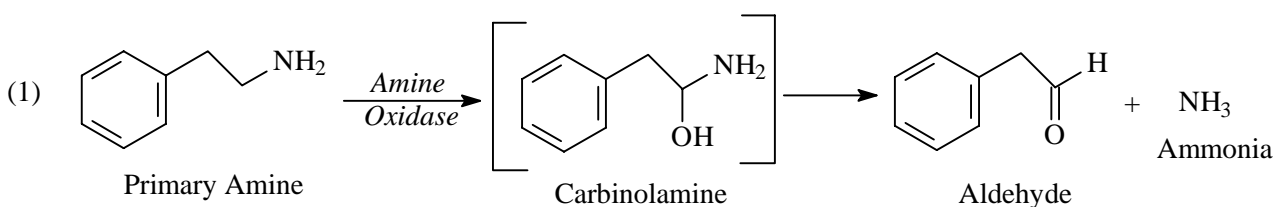
The types of products formed from amine displacement reactions is determined by the structure of the amine nucleophile and electrophile as illustrated by the examples below. In example (1) the intermolecular reaction of a primary amine with an alkyl halide yields a secondary amine; the electrophile becomes the second alkyl substituent. In example (2) the intermolecular reaction of a tertiary amine with methyl iodide yields a quaternary amine. In this case the starting amine does not have a proton to lose in the reaction and thus the addition of a fourth alkyl substituent to nitrogen results in a permanent cationic center on nitrogen. Quaternary amines are discussed in greater detail later in this tutorial. Example (3) shows an intramolecular reaction of a beta-haloethylamine to form an aziridine. This reaction is important for some cancer chemotherapeutic agents as well as other drugs designed to alkylate neurotransmitter receptors. In example (4) the reaction of a secondary amine with an oxirane (epoxide) yields a tertiary amino alcohol product. Note that the oxygen "leaving group" in this reaction was displaced from the electrophilic carbon, but remains within the structure since it was attached to

a second carbon in the oxirane electrophile. The fifth example (5) illustrates the reaction between a primary amine and an acid chloride to form an amide. Acid chlorides are good electrophiles because they have a very electrophilic carbon due to the presence of a carbonyl dipole that is also linked to an electronegative Cl, and the Cl is a good leaving group. The sixth example (6) shows the formation of an imine in a reaction between a primary amine and an aldehyde. Primary and secondary amines can react with the electrophilic carbonyl carbon atoms of aldehydes or ketones to form carbinolamine intermediates that are unstable and eliminate oxygen as water to yield the imine product. Imine formation reactions are somewhat different than the reactions illustrated by the other examples because the reaction occurs at an sp^2 hybridized center to give an intermediate that can either revert to starting materials, or eliminate water to yield a C=N structural pattern. Imine formation is an important biochemical reaction as discussed in other drug tutorials.



F. Amines and Metabolism

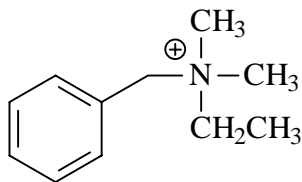
Amine compounds and drugs undergo a variety of metabolic transformations depending on the structural features of the amine and the enzymes capable of binding and metabolizing them. For example, example (1) shows a common metabolic reaction that occurs with sterically unhindered primary amines (usually linked to an aromatic ring). These compounds are bound by "amine oxidase" enzymes that catalyze oxidation of the carbon adjacent to nitrogen to yield a carbinolamine intermediate which spontaneously decomposes to yield the "deamination



products" the aldehyde and ammonia. Aliphatic amines (Example 2) with small (methyl) alkyl substituents typically undergo oxidation by cytochrome enzymes to ultimately yield deamination or dealkylation products. Aliphatic amines may also undergo N-oxidation to yield N-oxides (example 3) or conjugation by methyltransferases to give N-methyl metabolites (Example 4). Aromatic amines cannot undergo the deamination reaction of the type shown in example 1, but are subject to N-oxidation reactions (Example 5) or conjugation by acetylation (Example 6) All of the metabolic transformations of amines are covered in more detail in the *Metabolism Chapter*.

VI. Quaternary Ammonium Salts (QAS) Quaternary Ammonium Salts (QAS)

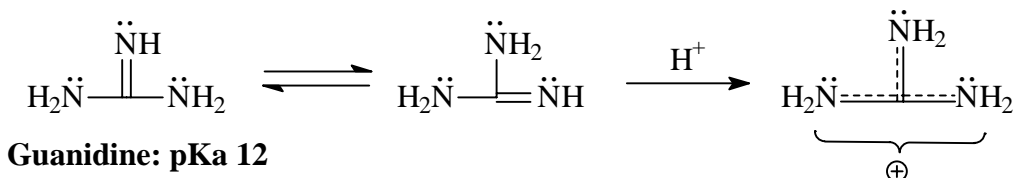
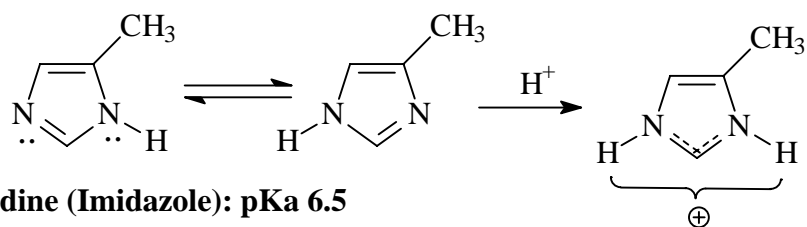
Amine compounds in which the nitrogen is bound to four carbon atoms through covalent bonds are known as quaternary ammonium salts (QASs). QASs are stable compounds that are **not** converted to amines by treatment with base and generally show good H₂O solubility because of their ionic structure. Since the reactivity of amines that was discussed above (reaction as nucleophiles, basicity, imine formation) depends upon the presence of a free electron pair on nitrogen, QASs do not undergo these reactions. In fact, QASs are relatively unreactive. Also, because they exist as permanent cations, they do not diffuse readily across biological membranes.



Quaternary ammonium compound

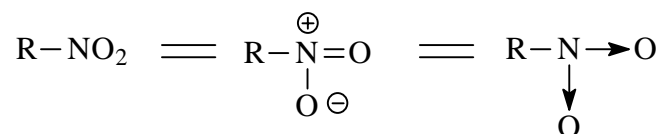
VII. Amidines, Guanidines and Similar Systems

As noted in the section on "*Amine Basicity*" above, nitrogen basicity is reduced significantly if it is in a conjugated bonding arrangement with an electron withdrawing functionality as in an amide group. The electron withdrawal created by such a conjugated system limits the ability of nitrogen's NBEs to coordinate with a proton (act as a base) and renders amides essentially "non-basic". However, it is important to understand that resonance delocalization alone does not necessarily render a nitrogen-containing system non-basic. Consider the examples of the amidine (imidazole) and guanidine groups shown below. In these cases one nitrogen atom is in conjugation with at least one other nitrogen atom and delocalization of the NBEs of one nitrogen can be viewed to "enhance the electron density" of another nitrogen atom. Thus these systems retain significant basicity as indicated by the pK_a values for the system:



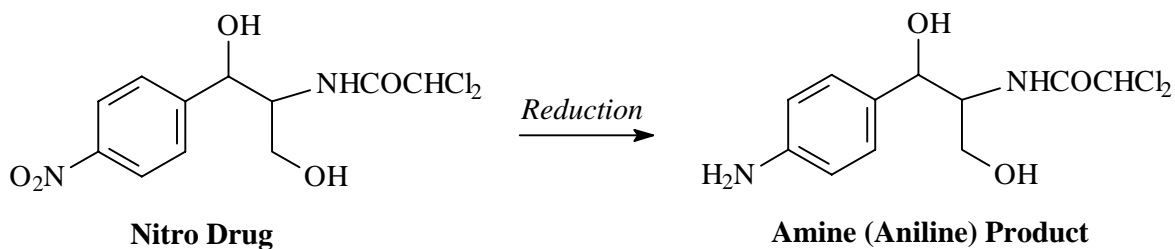
VIII. The Nitro Group

The nitro group is composed of a nitrogen atom bound to two oxygen atoms and a carbon atom. This functional group can be illustrated a number of ways as shown below:



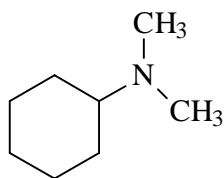
Nitro compounds are very different from amines in their physico-chemical properties because the nitrogen atom of the nitro group is not basic or nucleophilic. However, because of the electronic nature of the atoms its composite atoms, the nitro group is relatively polar group.

The most significant reaction of nitro groups both chemically and metabolically is reduction. Typically nitro groups are readily reduced to the corresponding amines as illustrated in the example below:

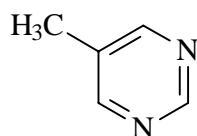


IX. Problems

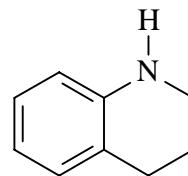
1. Classify each amine below as aliphatic, aniline or heterocyclic. Also categorize each amine as primary, secondary or quaternary.



A

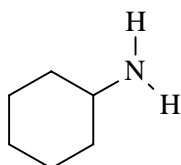


B

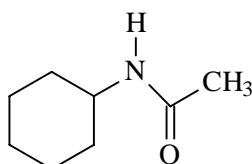


C

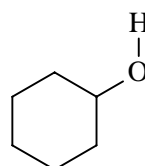
2. Which compound below would be most soluble in water of pH 4?



A



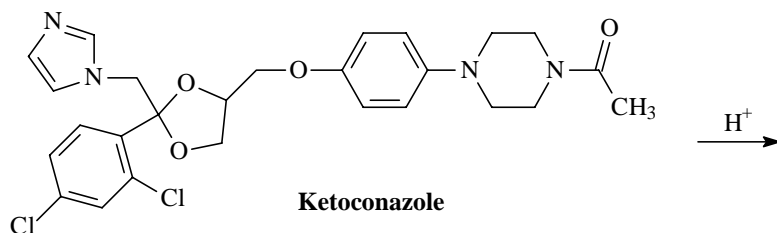
B



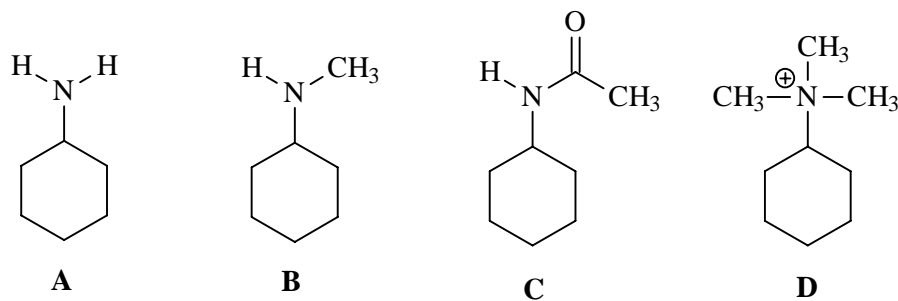
C

3. Calculate the percent ionized form an amine with a pKa of 9.6 in an aqueous solution of pH 8.

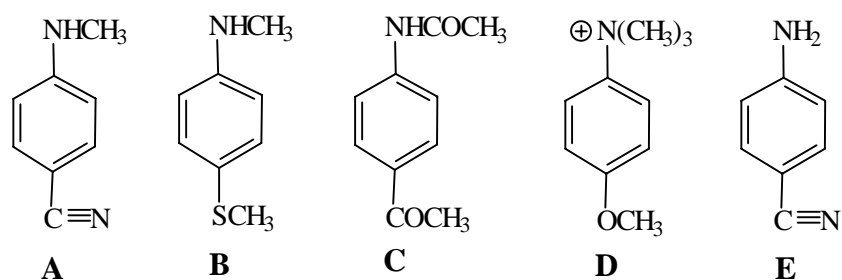
4. The systemic antifungal agent ketoconazole is administered orally as the free base. The oral bioavailability of this drug is dependent upon solubility in the gastric contents and solubility is promoted by the acidic pH of the GI tract. Using structures, show how acidity enhances ketoconazole solubility.



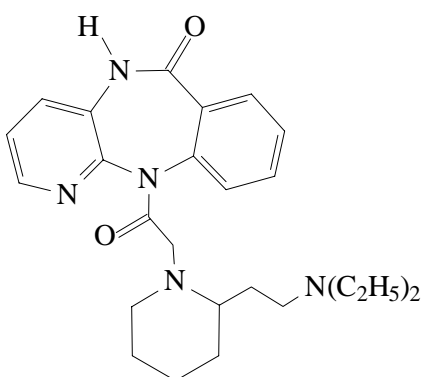
5. Rank the following set of compounds in terms of relative BASICITY (1 = most, 5 = least):



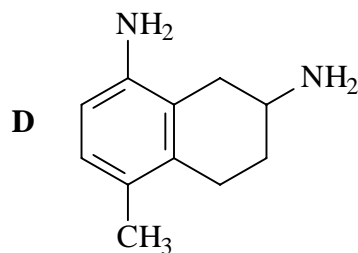
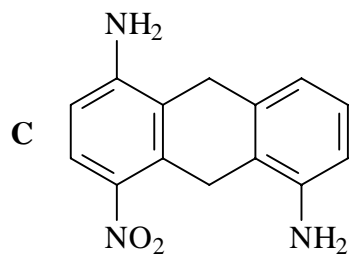
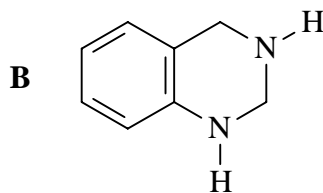
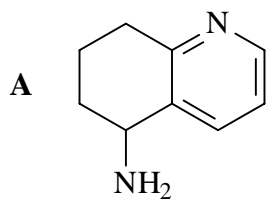
6. Rank the following set of compounds in terms of relative BASICITY (1 = most, 5 = least):



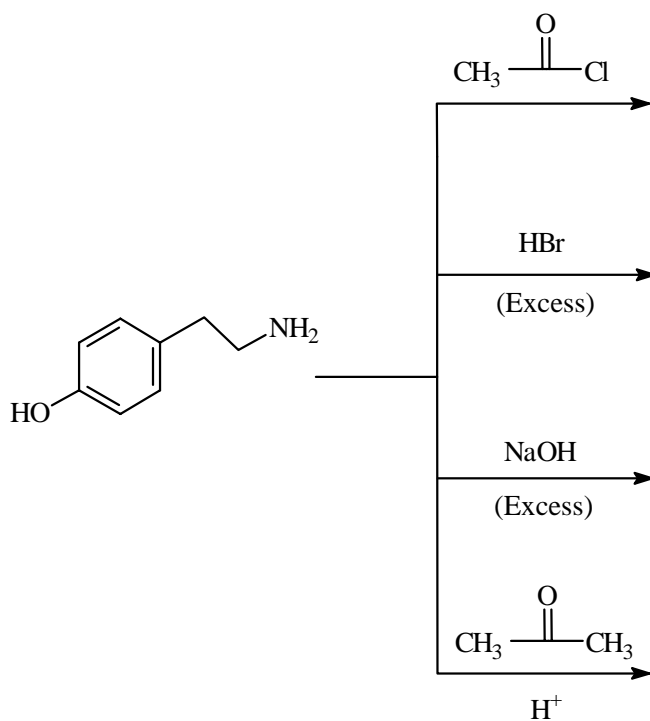
7. Show the structure of the predominate form of the following molecules at physiological pH 7.4.



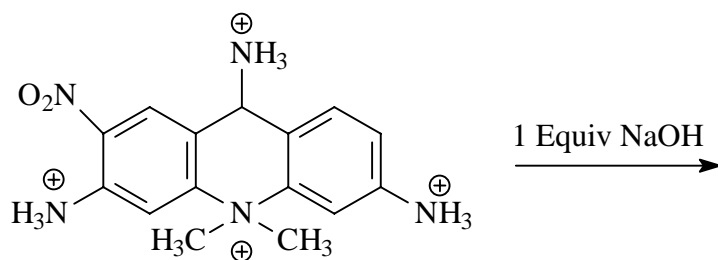
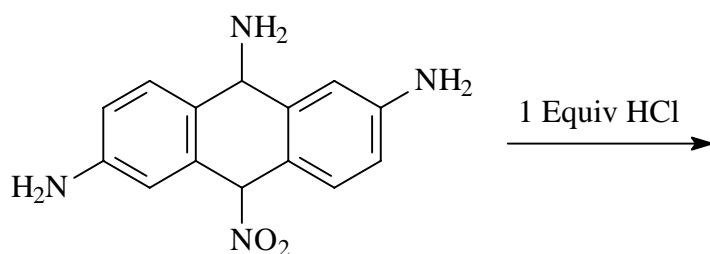
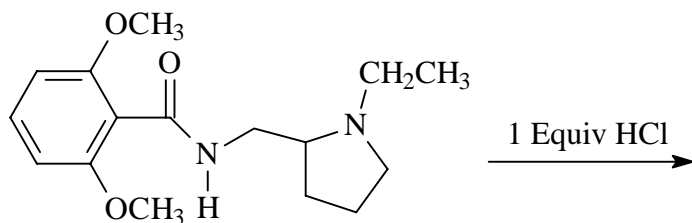
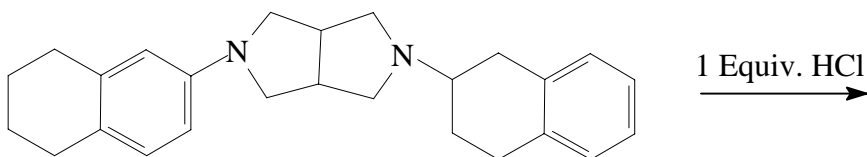
8. Circle the most basic nitrogen in the following compounds:



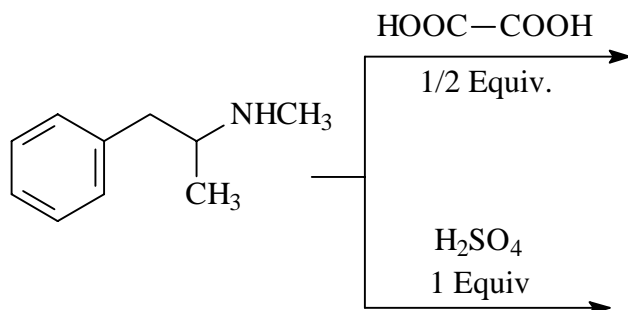
9. Provide the products that would form in the following reactions. In some cases more than one product may form. If no reaction will occur write "NR".



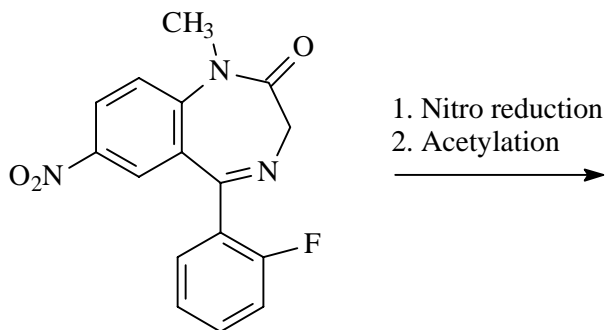
10. Show the products of the following acid/base reactions.



11. Show the products of the following acid/base reactions.



12. Show the end product of metabolism resulting from nitro group reduction followed by conjugation of the intermediate aniline derivative by acetylation.



13. Show the end product of metabolism resulting from oxidative deamination followed by oxidation of the intermediate aldehyde

