Amines

Part A

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

At the end of this lesson, students will be able to describe

Amines

- **Nomenclature of Amines**
- **Properties and structure of Amines**
- **Basicity of Amines**
- **Effect of substituents on Basicity of Amines**

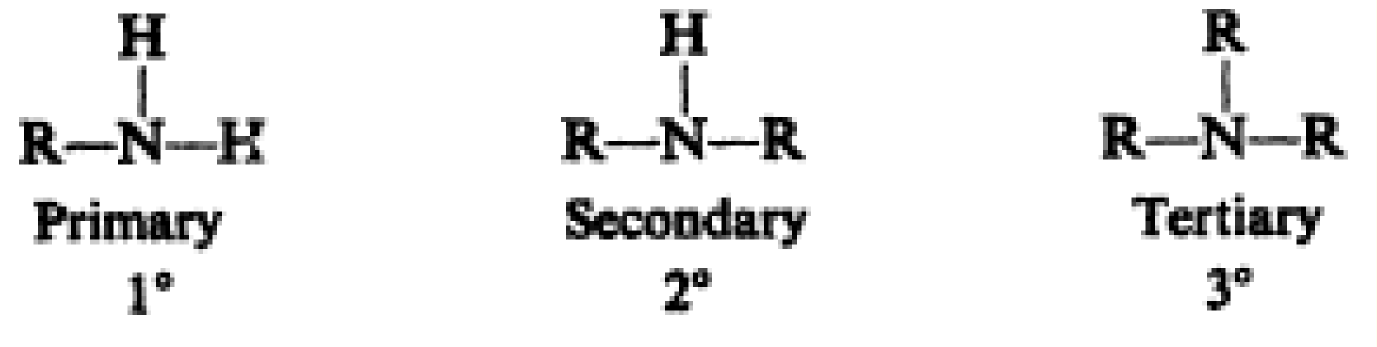
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

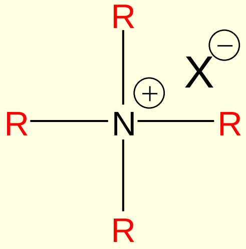
Amines

Amines are organic derivatives of ammonia, NH_3.

- 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 wherein R is any alkyl or aryl group.

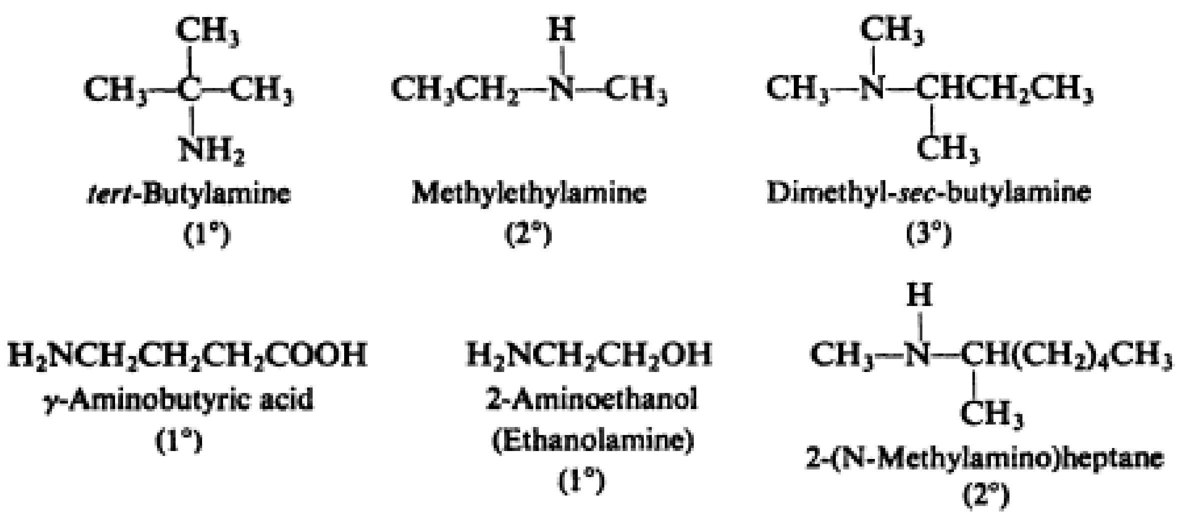


Quaternary ammonium salt



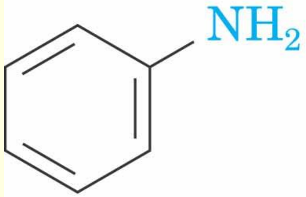
Amines: Nomenclature

- 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.

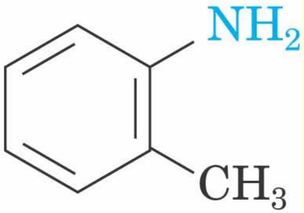


Amines: Nomenclature

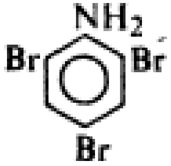
- ✓ Aromatic amines those in which nitrogen is attached directly to an aromatic ring are generally named as derivatives of the simplest aromatic amine (**aniline**).



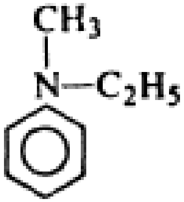
Aniline



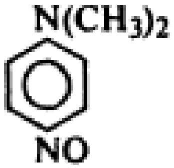
***o*-Toluidine**



2,4,6-Tribromoaniline
(1°)

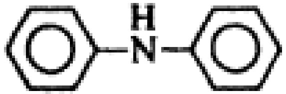


N-Methyl-N-ethylaniline
(3°)

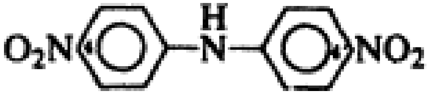


p-Nitroso-N,N-dimethylaniline
(3°)

p-Toluidine
(1°)



Diphenylamine
(2°)



4,4′-Dinitrodiphenylamine
(2°)

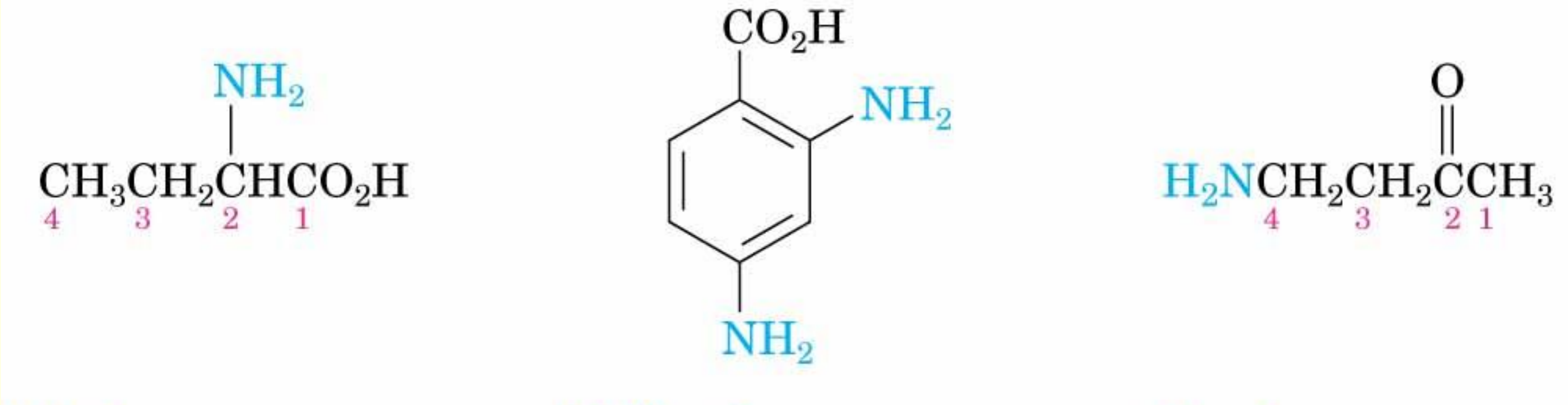
Amines: Nomenclature

- 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.).

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

Amines: Nomenclature

Amines with more than one functional group: Consider the -NH_2 as an amino substituent on the parent molecule.



$CH_3CH_2CH(NH_2)CO_2H$

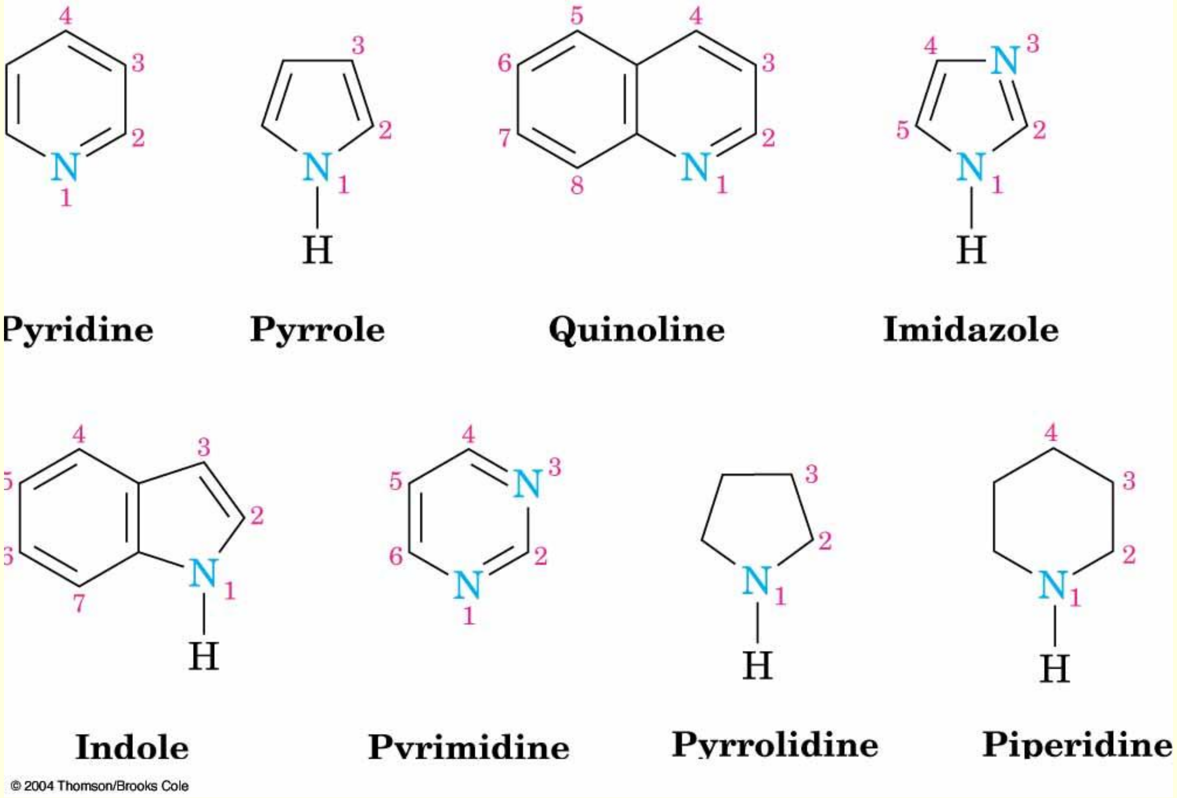
$C_6H_3(CO_2H)(NH_2)_2$

$H_2NCH_2CH_2C(=O)CH_3$

2-Aminobutanoic acid **2,4-Diamino**benzoic acid **4-Amino**-2-butanone

Common names of heterocyclic amines

- ✓ If the nitrogen atom occurs as part of a ring, the compound is designated as being heterocyclic.
- ✓ Each ring system has its own parent name.

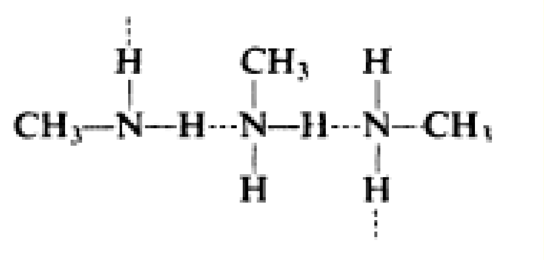


Amines: Physical Properties

- 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.
- 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 being reached at about six carbon atoms.
- Amines are soluble in less polar solvents like ether, alcohol, benzene, etc.

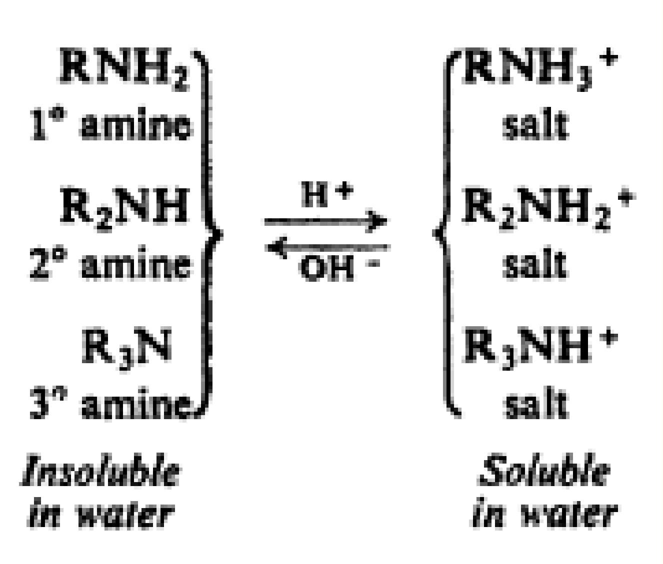
Amines: Physical Properties

The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly “fishy” odors.



- ❖ Aromatic amines are generally very toxic since they can readily absorbed through the skin.
- ❖ Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.
- ❖ Aliphatic amines are about as basic as ammonia; aromatic amines are considerably less basic.

Amines: Salts

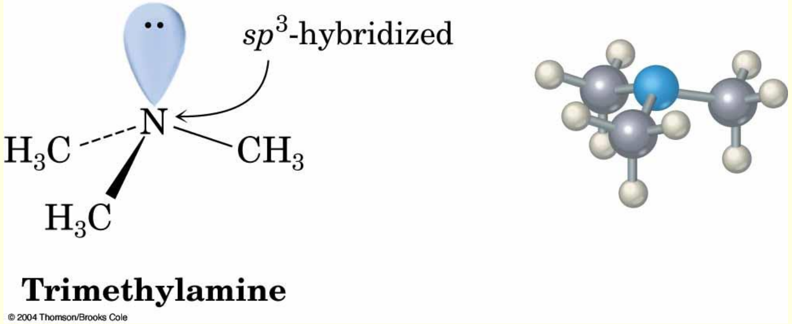


- The halides, nitrates, and sulfates are soluble in water but are insoluble in non-polar solvents.
- The difference in solubility behavior between amines and their salts can be used to detect amines and to separate them from non-basic compounds.

Amines: Structure and Bonding

Bonding of ‘Nitrogen’ is similar to that in ammonia

N is sp^3-hybridized C–N–C bond angles are close to 109° tetrahedral value.



Trimethylamine

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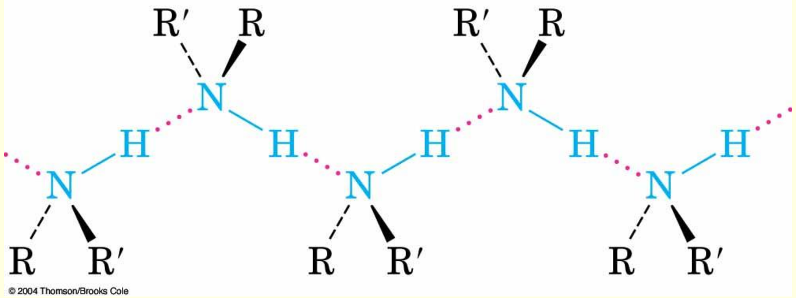
Primary and secondary amines form hydrogen bonds, increasing their boiling points



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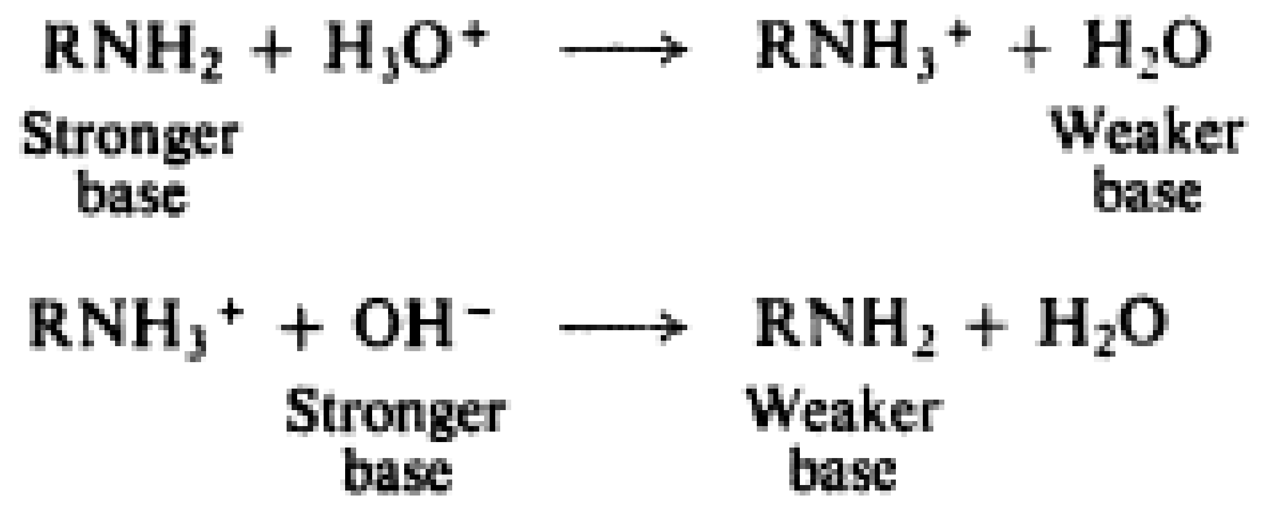
Basicity of Amines

Like ammonia, amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides.

Like ammonia, amines are more basic than water and less basic than hydroxide ion:-



$$\underset{\text{Stronger base}}{RNH_2} + H_3O^+ \longrightarrow RNH_3^+ + \underset{\text{Weaker base}}{H_2O}$$

$$RNH_3^+ + \underset{\text{Stronger base}}{OH^-} \longrightarrow \underset{\text{Weaker base}}{RNH_2} + H_2O$$

Basicity of Amines

It is convenient to compare basicity of amines by measuring the extent to which they accept hydrogen ion from water; the equilibrium constant for this reaction is called a basicity constant, K_b.

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

$$K_b = \frac{[\mathrm{RNH_3^+}][\mathrm{OH^-}]}{[\mathrm{RNH_2}]}$$

(As in the analogous expression for an acidity constant, the concentration of the solvent, water, is omitted) Each amine has its characteristic K_b; the larger the K_b, the stronger the base.

Basicity of Amines

The principal base in an aqueous solution of an amine (or of ammonia, for that matter) is the amine itself, not hydroxide ion.

Measurement of $[OH^-]$ is simply a convenient way to compare basicity.

Aliphatic amines of all three classes have K_b's of about 10^{-3} to 10^{-4} (0.001 to 0.0001); they are thus somewhat stronger bases than ammonia ($K_b = 1.8 \times 10^{-5}$).

Basicity of Amines

Aromatic amines, on the other hand, are considerably weaker bases than ammonia, having K_b's of 10^{-9} or less.

Substituents on the ring have a marked effect on the basicity of aromatic amines, *p*-nitroaniline, for example, being only 1/4000 as basic as aniline.

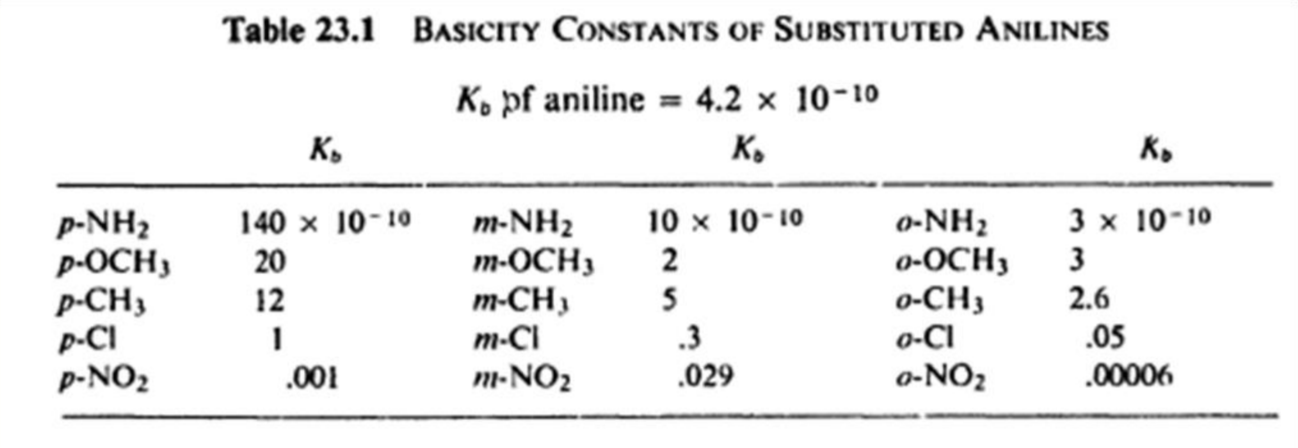


Table 23.1 BASICITY CONSTANTS OF SUBSTITUTED ANILINES

K_b of aniline = 4.2×10^{-10}

	K_b		K_b		K_b
p-NH_2	140×10^{-10}	*m*-NH_2	10×10^{-10}	*o*-NH_2	3×10^{-10}
p-OCH_3	20	*m*-OCH_3	2	*o*-OCH_3	3
p-CH_3	12	*m*-CH_3	5	*o*-CH_3	2.6
p-Cl	1	*m*-Cl	.3	*o*-Cl	.05
p-NO_2	.001	*m*-NO_2	.029	*o*-NO_2	.00006

Structure and Basicity

We shall compare the stabilities of amines with the stabilities of their ions; the more stable the ion relative to the amine from which it is formed, the more basic the amine.

First of all, amines are more basic than alcohols, ethers, esters, for the same reason that ammonia is more basic than water: nitrogen is less electronegative than oxygen, and can better accommodate the positive charge of the ion.

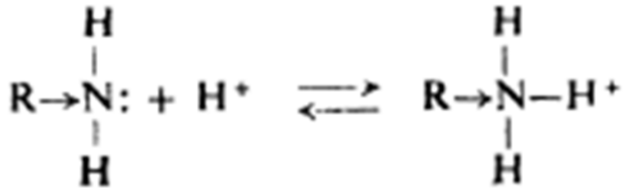
An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion.

Structure and Basicity

Thus an ammonium ion is stabilized by electron release in the same way as a carbonium ion.

From another point of view, we can consider that an alkyl group pushes electrons toward nitrogen, and thus makes the fourth pair more available for sharing with an acid.

The differences in basicity among primary, secondary, and tertiary aliphatic amines are due to a combination of solvation and electronic factors.



$$R\rightarrow\overset{\displaystyle H}{\underset{\displaystyle H}{N}}: + H^{+} \rightleftharpoons R\rightarrow\overset{\displaystyle H}{\underset{\displaystyle H}{N}}-H^{+}$$

R *releases electrons: makes unshared pair more available*

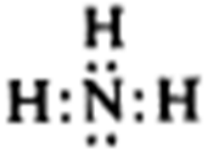
R *releases electrons stabilizes ion, increases basicity*

Structure and Basicity

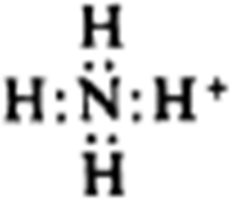
How can we account for the fact that aromatic amines are weaker bases than ammonia?

Let us compare the structures of **aniline** and the **anilinium ion** with the structures of ammonia and the ammonium ion.

We see that ammonia and the ammonium ion are each represented satisfactorily by a single structure:-



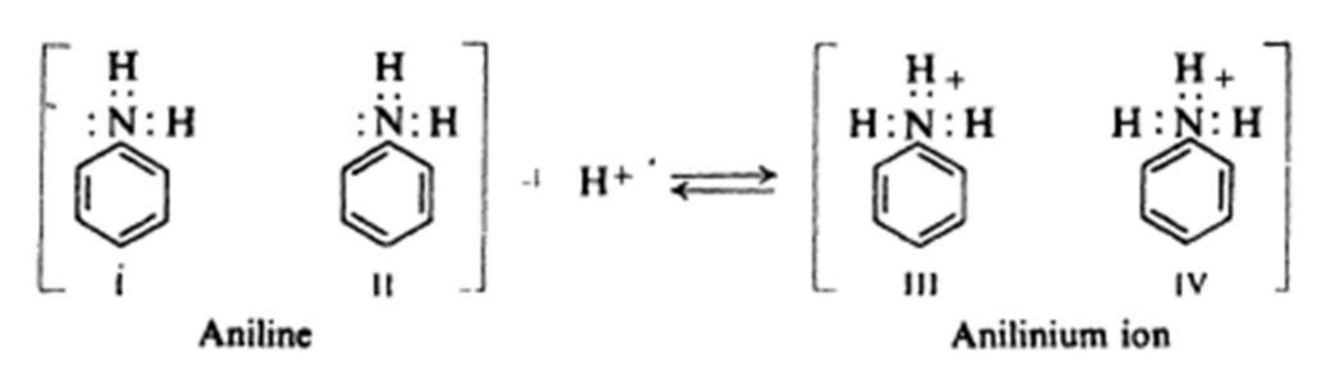
Ammonia



Ammonium ion

Structure and Basicity

- ☐ Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the Kekule structures I and II, and III and IV.
- ☐ This resonance presumably stabilizes both amine and ion to the same extent.
- ☐ It lowers the energy content of each by the same number of kcal/mole, and hence does not affect difference in their energy contents.
- ☐ If there were no other factors involved, then, we might expect the basicity of aniline to be about the same as the basicity of ammonia.



Structure and Basicity

- However, there are additional structures to be considered.
- To account for the powerful activating effect of the $-NH_2$ group on electrophilic aromatic substitution, we considered that the intermediate carbonium ion is stabilized by structures in which there is a double bond between nitrogen and the ring; contribution from these structures is simply a way of indicating the tendency for nitrogen to share its fourth pair of electrons and to accept a positive charge.
- It is generally believed that the $-NH_2$ group tends to share electrons with the ring, not only in the carbonium ion which is the intermediate in electrophilic aromatic substitution, but also in the aniline molecule itself.

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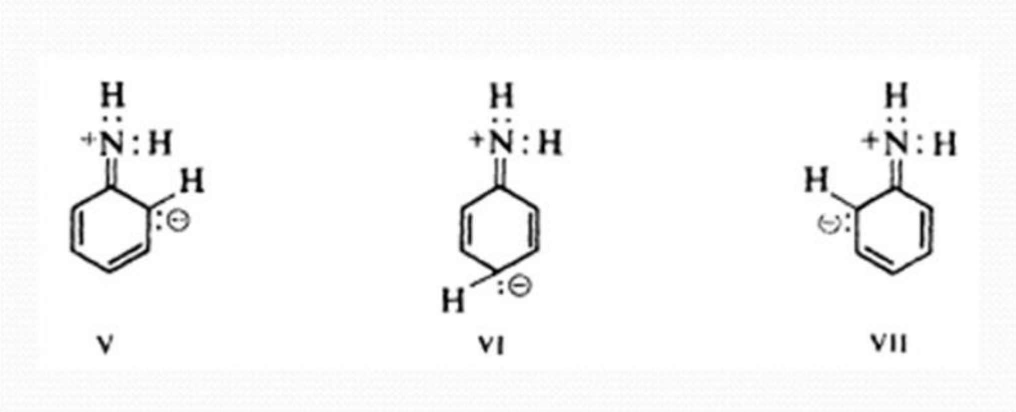
Structure and Basicity

Thus, aniline is a hybrid not only of structures **I** and **II** but also of structures V, VI, and VII.



Contribution from the three structures V, VI, and VII stabilizes the amine in a way that is not possible for the ammonium ion; resonance thus lowers the energy content of aniline more than it lowers the energy content of the anilinium ion.

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Structure and Basicity

- The net effect is to shift the equilibrium in the direction of less ionization, that is, to make K_b smaller.
- The low basicity of aromatic amines is thus due to the fact that the amine is stabilized by resonance to a greater extent than is the ion.
- From another point of view, we can say that aniline is a weaker base than ammonia because the fourth pair of electrons is partly shared with the ring and is thus less available for sharing with a hydrogen ion.
- The tendency (through resonance) for the NH_2 group to release electrons to the aromatic ring makes the ring more reactive toward electrophilic attack; at the same time this tendency necessarily makes the amine less basic. Similar considerations apply to other aromatic amines.

Structure and Basicity

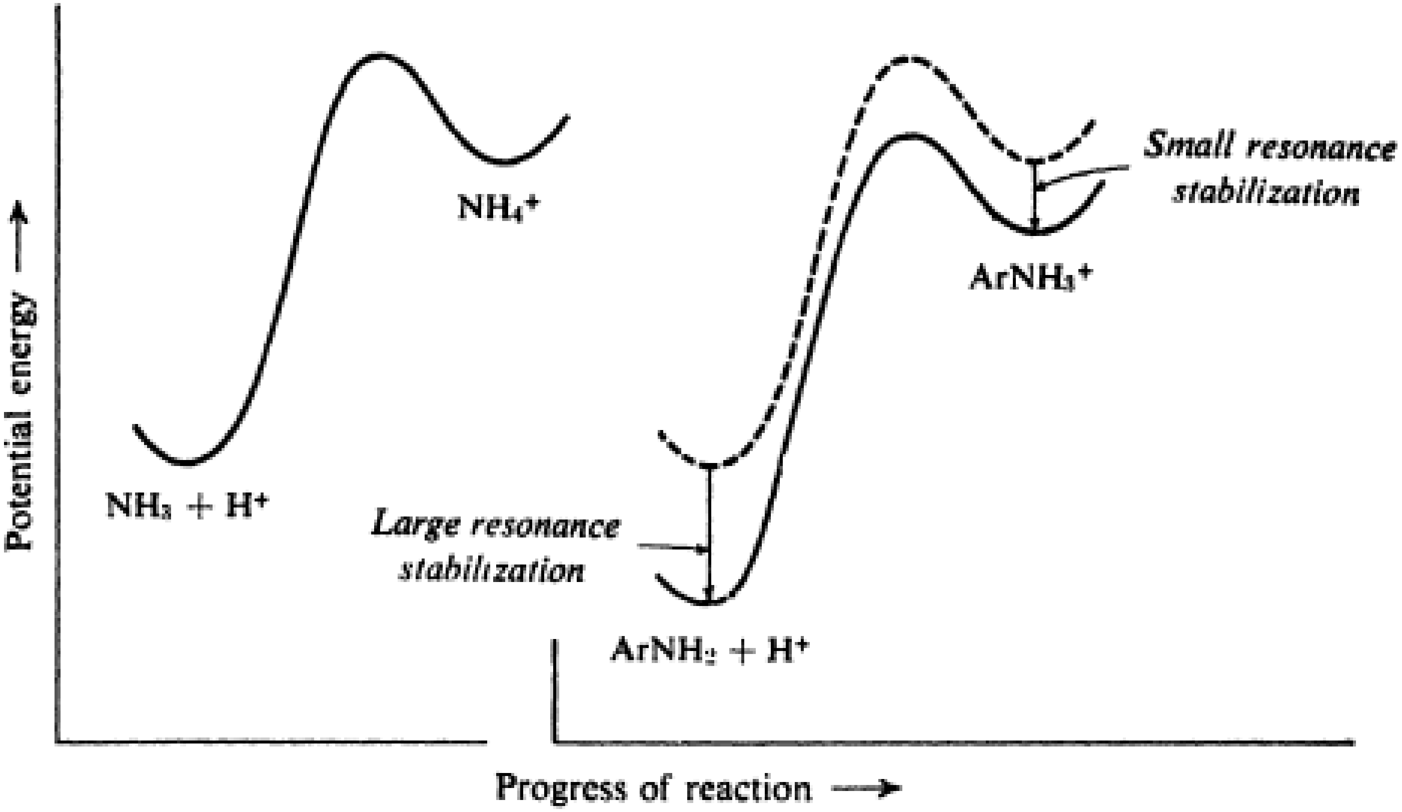
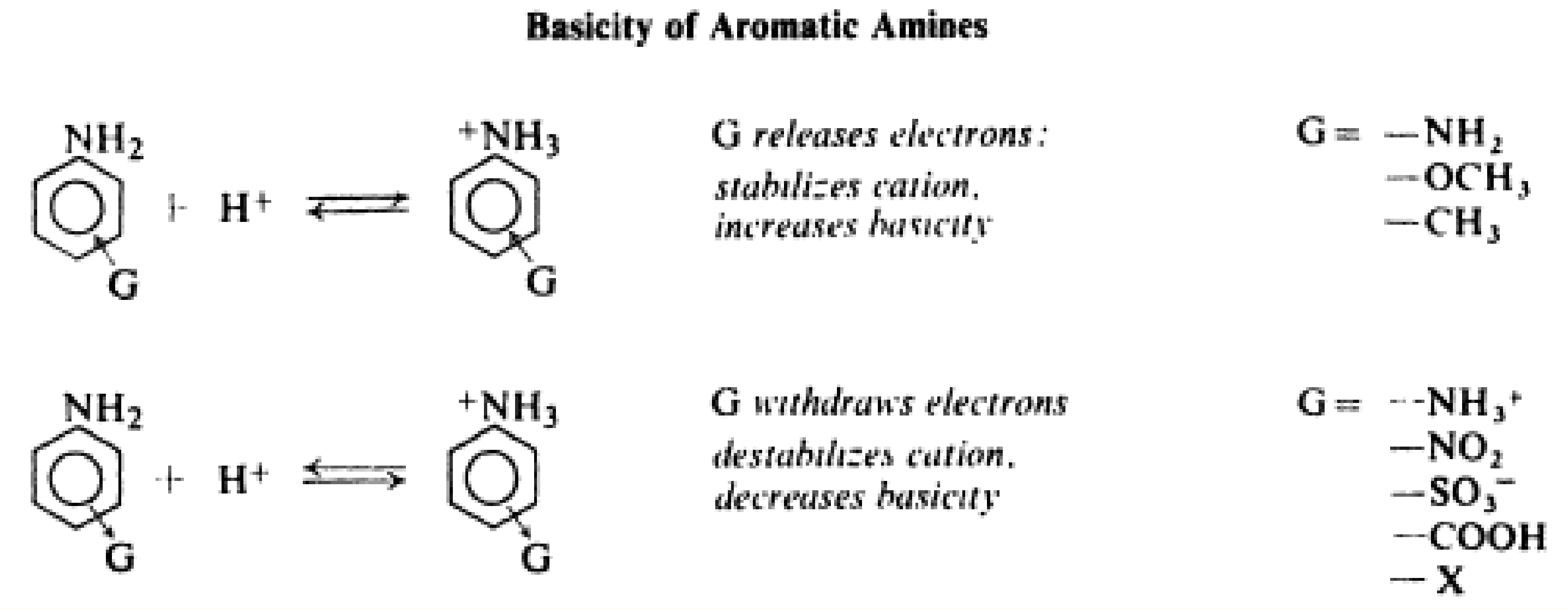


Figure 23.1. Molecular structure and position of equilibrium. Resonance-stabilized aromatic amine is weaker base than ammonia. (Plots aligned with each other for easy comparison.)

Effect of Substituents on Basicity of aromatic amines

- ✓ An electron-releasing substituent like CH_3 increases the basicity of aniline, and an electron-withdrawing substituent like -X or –NO_2 decreases the basicity.
- ✓ Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine.
- ✓ Electron withdrawal tends to intensify the positive charge of the, anilinium ion, and thus destabilizes the ion relative to the amine.

Effect of Substituents on Basicity of aromatic amines



Basicity of Aromatic Amines

G releases electrons:
stabilizes cation,
increases basicity

G = —NH_2
—OCH_3
—CH_3

G withdraws electrons
destabilizes cation,
decreases basicity

G = —NH_3^+
—NO_2
—SO_3^-
—COOH
—X

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