

Take-home quiz and announcements

- Evaluate your strengths and weaknesses and develop a study plan for the remaining semester (Test 4 and Final); due 11/13/09 at the beginning of class
- I have placed a copy of the ACS Study Guide on reserve in the library
- Quiz next Wed on Chapter 20

Chapter 20

Amines

Amines are **organic bases**. They are found widely in nature. Trimethylamine occurs in animal tissue, and the distinctive odor of fish is due to amines. Amines isolated from plants are called alkaloids and many are pharmacologically important.

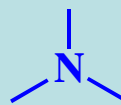
Nomenclature

Amines are classified according to the number of R groups on the nitrogen.	RNH_2 <i>primary</i> <i>(1^\circ) amine</i>	R_2NH <i>secondary</i> <i>(2^\circ) amine</i>	R_3N <i>tertiary</i> <i>(3^\circ) amine</i>
	The R groups may be alkyl or aryl.		

For the **common name** of simple aliphatic amines, name the alkyl group(s) on the nitrogen and attach "**amine.**" Use the prefixes "**di**" and "**tri**" as needed.



Ethylmethanamine
***N*-Methylethanamine**

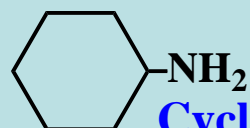


Trimethylamine
***N,N*-Dimethylmethanamine**

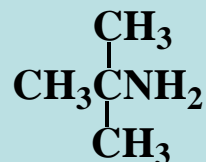
The **systematic name** is derived from the name of the longest alkane chain present by dropping the final "**e**" and adding the suffix "**amine.**" Then designate smaller alkyl groups as shown, using the italicized locant "**N.**"

Additional Examples

1° Amines

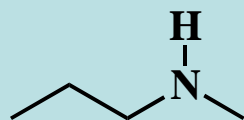


Cyclohexylamine
Cyclohexanamine

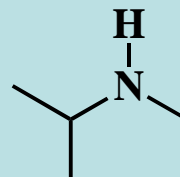


tert-Butylamine
2-Methyl-2-propanamine

2° Amines

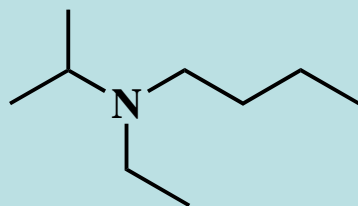


Methylpropylamine
N-Methylpropanamine

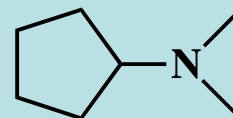


Isopropylmethylamine
N-Methyl-2-propanamine

3° Amines



Butylethylisopropylamine
N-Ethyl-N-(1-methylethyl)-butanamine



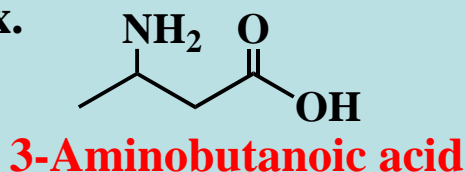
Cyclopentyl dimethylamine
N,N-Dimethylcyclopentanamine

Polyfunctional Amines When the amino function is not the **principal group**, it is designated by use of the prefix "**amino.**"

There is an established order of precedence of compound classes, which is used to determine which functional group is the principal one. A highly abbreviated list, in order of decreasing precedence, is:

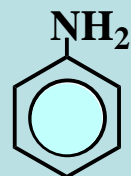
Acids, aldehydes, ketones, alcohols, amines.

So in most polyfunctional compounds, an amine function will be designated by use of the prefix.



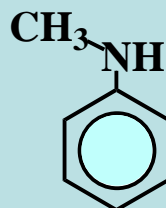
Arylamines

Aromatic amines are often named as derivatives of **aniline.**



Aniline

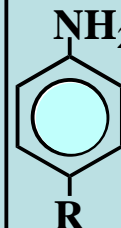
Benzenamine



N-Methylaniline

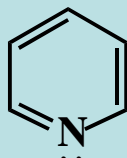
N-Methylbenzenamine

Additional unique common names:
When R = CH₃,
p-toluidine.
When R = OCH₃,
p-anisidine.

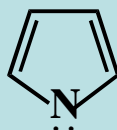


Heterocyclic Amines

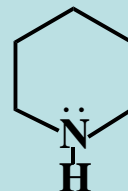
Examples



Pyridine



Pyrrole



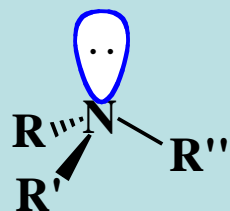
Piperidine



Pyrrolidine

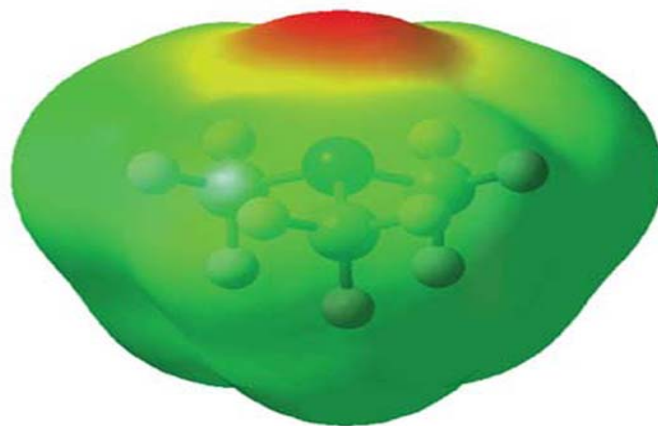
Structure of Amines

The nitrogen atom in most amines is similar to that in ammonia and can be considered to be sp^3 hybridized. The nonbonding electron pair is in an sp^3 orbital.



The geometry is described as **trigonal pyramidal**.

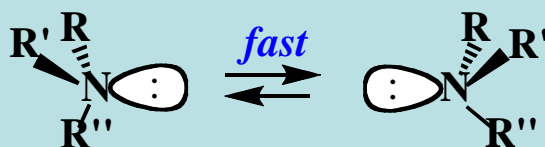
Bond angles are close to 109.5° .



A calculated structure for trimethylamine
The electrostatic potential map shows charge associated with the nitrogen unshared electron pair.

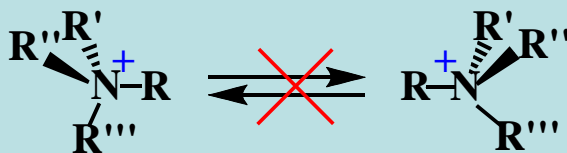
Stereochemical Features

When there are three (four, counting the unshared pair) different groups attached to the nitrogen, the structure is **chiral**. But because of very fast inversion at the stereocenter (the inversion rate in NH_3 is close to 10^{11} s^{-1}), **it is not possible to resolve a chiral amine**.



Interconversion of amine enantiomers by fast inversion at the nitrogen center

Quaternary ammonium salts (compounds of type $\text{R}_4\text{N}^+ \text{X}^-$) display stereochemical features similar to chiral tetravalent carbon. If they contain four different R groups, they are chiral and, being of stable, non-inverting form, can be resolved into their enantiomers.

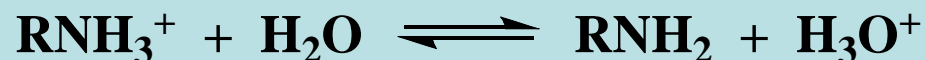


Chiral quaternary ammonium salts can be resolved.

Interconversion of enantiomers would require bond breaking.

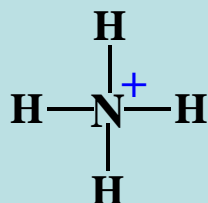
Basicity of Amines: Amine Salts

The greater the basicity of an amine, the weaker the acidity of its conjugate acid, the cation in its salts.

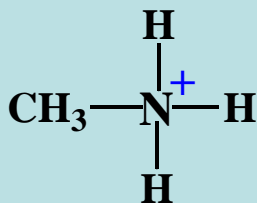


$$K_a = \frac{[\text{RNH}_2][\text{H}_3\text{O}^+]}{[\text{RNH}_3^+]} \quad \text{p}K_a = -\log K_a$$

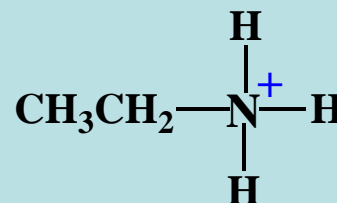
Influence of alkylation on the acidity of aminium ions:



pK_a **9.26**



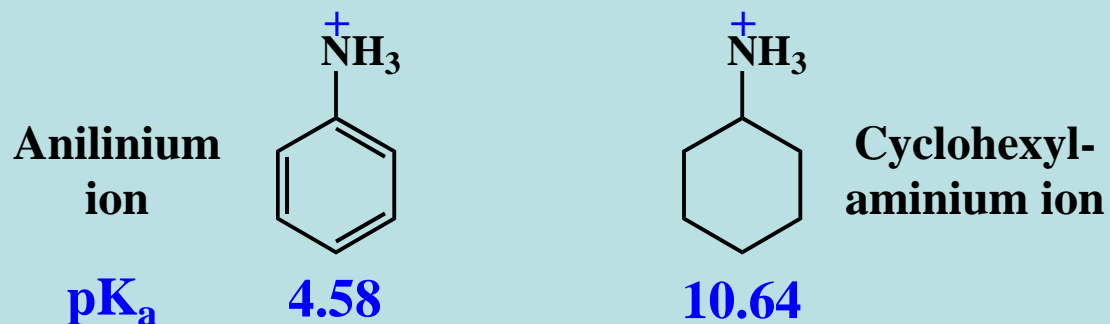
10.64



10.75

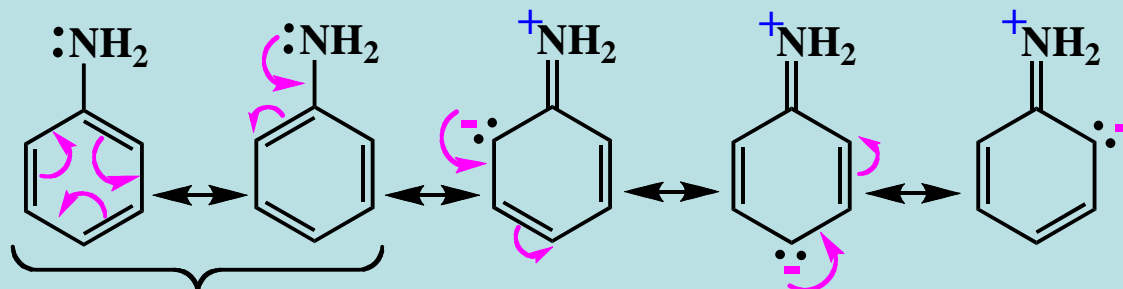
These experimentally determined pK_a values show that alkylation decreases the acidity of these conjugate acids, **which means that their parent amines became more basic on alkylation.**

Basicity of Arylamines

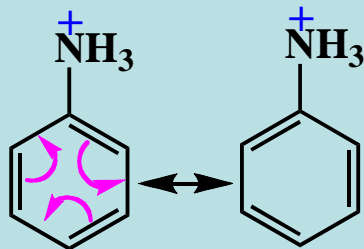


The greater acidity of the anilinium ion means that aniline is a markedly weaker base than is cyclohexylamine, a typical 1° alkylamine.

The decreased basicity of aniline is primarily due to the delocalization of the unshared pair on nitrogen by the benzene ring:

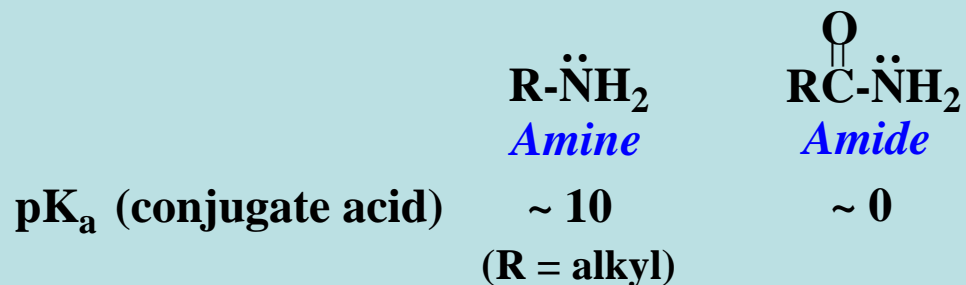


These two general types of benzene resonance forms are the only ones available to stabilize the anilinium ion:



Amines versus Amides

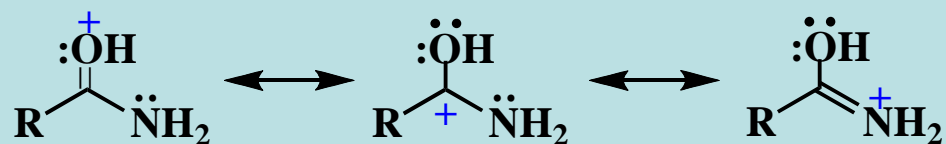
Amides are much less basic than amines even though their structural formulas both show an unshared pair of electrons on the nitrogen.



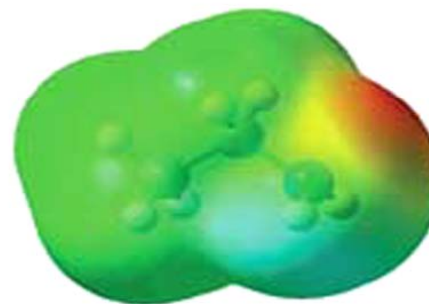
The decreased base strength of amides is **explained by both resonance and inductive influences**, as with aryl amines.

Under sufficiently acidic conditions, amides do become protonated but on the oxygen atom, not the nitrogen.

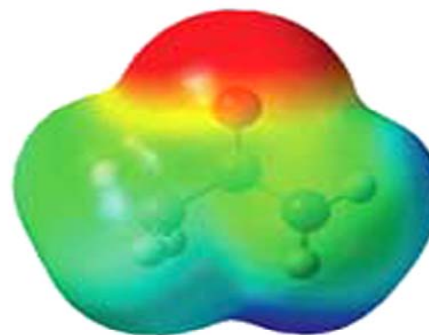
Protonation occurs on the carbonyl oxygen because that adduct is resonance stabilized:



This outcome can be further explained by comparing the electrostatic potential maps for ethylamine and acetamide, which show a shift of the high electron density from nitrogen in the amine to oxygen in the amide.



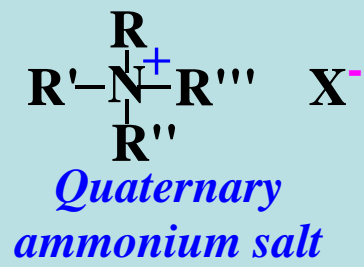
Ethylamine



Acetamide

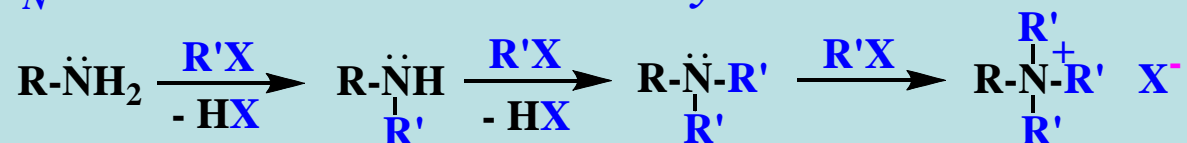
Quaternary Ammonium Salts

When there are four R groups (alkyl or aryl) attached to the nitrogen, the function is called a quaternary ammonium ion.



Quaternary ammonium salts are prepared by exhaustive N-alkylation of amines:

S_N2 reactions: "exhaustive" N-alkylation

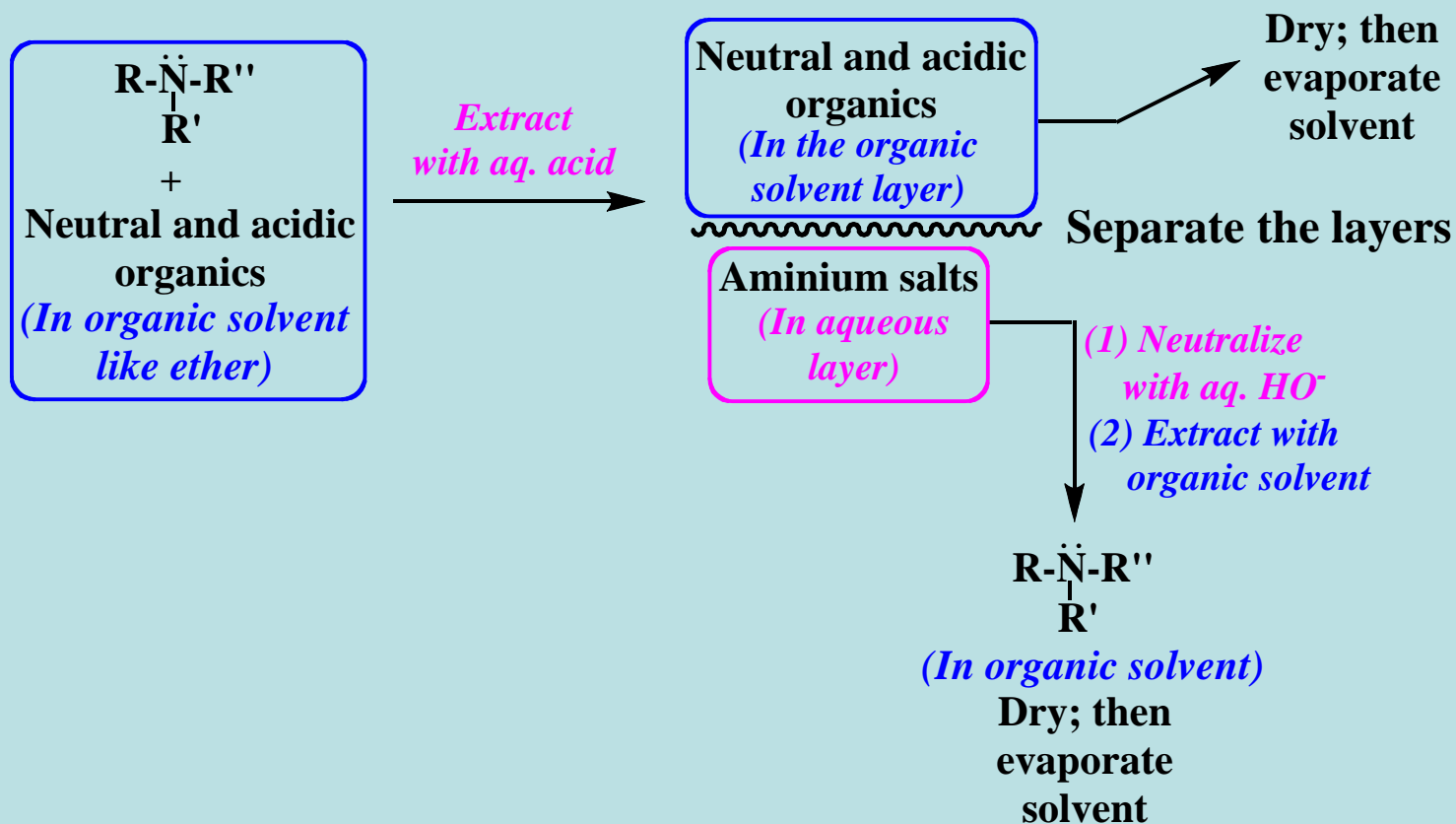


Quaternary ammonium halides, having no unshared pair on nitrogen, cannot act as bases. If, however, the halide ion is replaced with a hydroxide ion they are fully ionic, strong bases like NaOH or KOH.

Strong base ion exchange resins are of this hydroxide type, with the quaternary ammonium ion covalently bonded to the polymer matrix.

Solubility Properties and Separation Procedures

Because most aminium salts are soluble in water, it is possible to separate amines (whether they are water-soluble or water-insoluble) from other organic materials by extraction into an aqueous acid like dilute HCl.

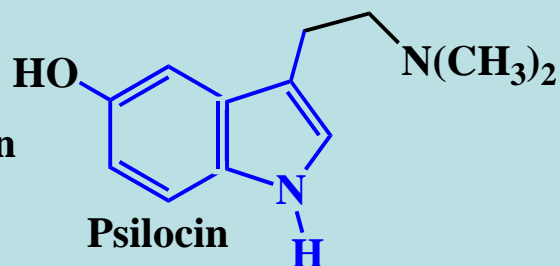
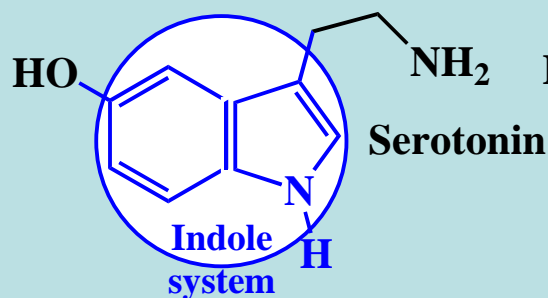


Structure-Reactivity Relationships

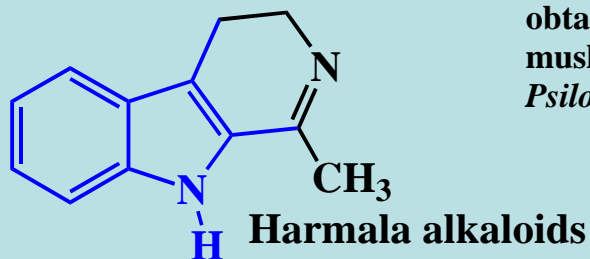
Medicinal chemists have long used structural features as a key to drug design. The structural similarity between the amphetamines and the natural brain hormones (like adrenaline, noradrenaline, and dopamine) is an example.

Serotonin Mimics

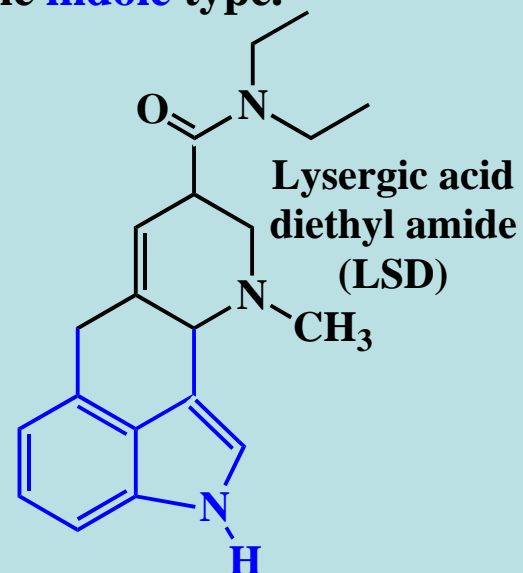
Another example of structure-reactivity relationships appears to be the hallucinogenic effect of a number of compounds of the **indole** type.



A hallucinogenic alkaloid obtained from the "sacred" mushrooms of Central America, *Psilocybe mexicana*.



Found in plants in Peru, Ecuador, Columbia and Brazil. Used as a hallucinogen by native indians.



First synthesized by Albert Hofmann in 1938 at Sandoz Pharmaceutical Co. while working on derivatives of the hallucinogenic ergot alkaloids .