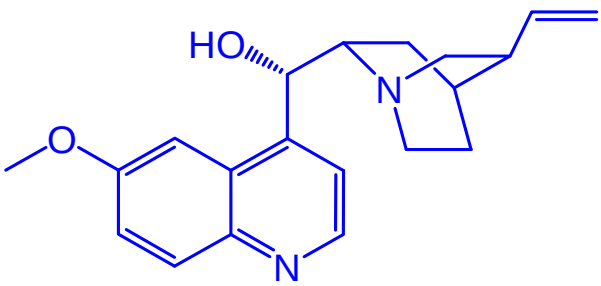
10. Amines (text 10.1 – 10.6)

A. Structure and Nomenclature

- Amines are derivatives of ammonia (NH_3), where one or more H atoms has been replaced by an alkyl or aryl group. They have the general formula R_3N (R = H, alkyl, aryl).
- If we compare the one-carbon alkane CH_4 to a one-carbon amine CH_3NH_2, we notice that each N atom in a molecular formula adds 1 H to the saturated formula. $C_nH_{2n+2+y}N_y$
- For unsaturation, subtract one H for each N in the molecule
    - C_3H_9N equivalent to C_3H_8 = saturated
    - $C_5H_{10}N_2$ equivalent to C_5H_8 = 2 units of unsaturation
- This and all the unsaturation calculations described in the previous chapters covers all the common heteroatoms. The rules can be combined and used in complicated formulas.
    - $C_{12}H_{17}N_2O_4Cl$ equiv. to $C_{12}H_{16}$ = 5 units unsat.
- Chemical tests (*e.g.* Br_2 and $KMnO_4$) can reveal how many alkene π bonds are present, so useful structural information can be obtained from tests and molecular formulas.

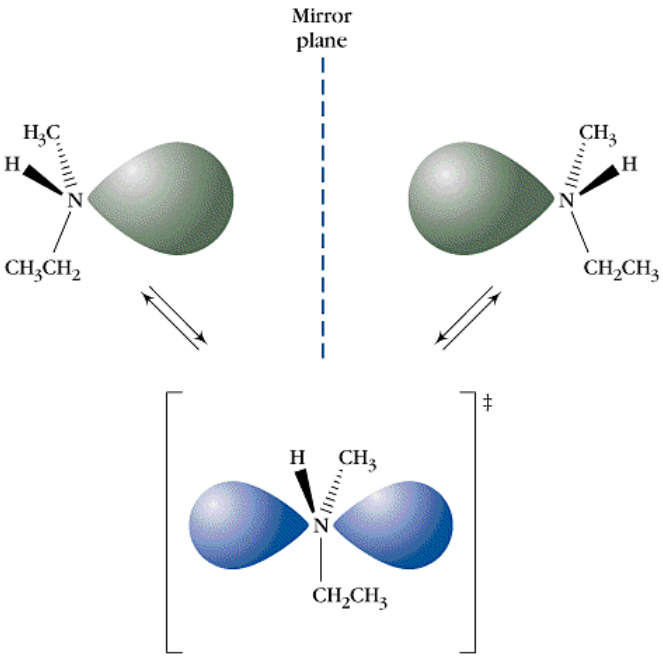
- For example, the anti-malarial drug quinine (extracted from a South American tree) has the formula $C_{20}H_{24}N_2O_2$ and therefore has 10 units of unsaturation.



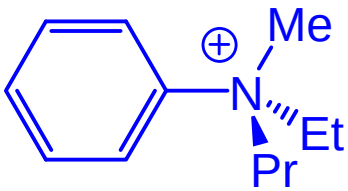
- Alkyl amines (N single bonded to alkyl C) are classified according to the number of C atoms bonded to the N.

Primary	1°	RNH_2	Secondary	2°	R_2NH
Tertiary	3°	R_3N	Quaternary	4°	R_4N^+

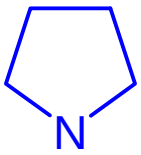
- Alkyl amines have N with a full octet, three σ bonds, *sp*^{3} hybridization, and one lone pair. (except 4°)
- N atoms don't act as stereocentres, since the lone pair rapidly interconverts from one enantiomer to the other and cannot be isolated.



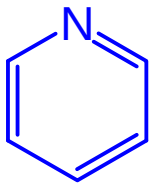
- However, quaternary ammonium salts can be chiral and have two non-interconverting enantiomers.



- N is often found as part of a ring in natural products, such as in quinine. It can be a simple heterocyclic amine or an aromatic heterocyclic amine (quinine has one of both).

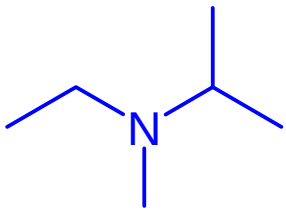


heterocyclic amine



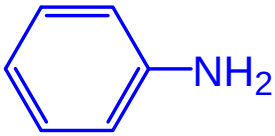
heterocyclic aromatic amine

- Simple amines are named by placing the names of the alkyl substituents in alphabetical order before the word *amine*

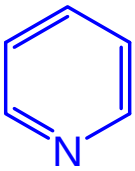


ethyl isopropyl methyl amine

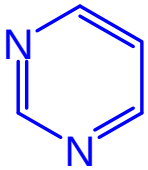
- You should also know aniline and pyridine. Biochemists, biologists, and medical scientists should also recognize pyridmidines and purines (part of DNA baes).



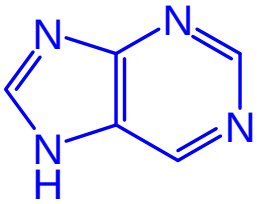
aniline



pyridine

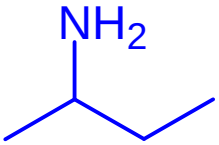


pyrimidine



purine

- The NH_2 substituent is called an amino group in IUPAC nomenclature.



2-aminobutane

- Many early folk medicines are compound compounds that contained N and were weak bases. They became known as alkaloids and comprise a large group of compounds, including morphine, caffeine, amphetamine, and cocaine. (textbook page 278 – 279).

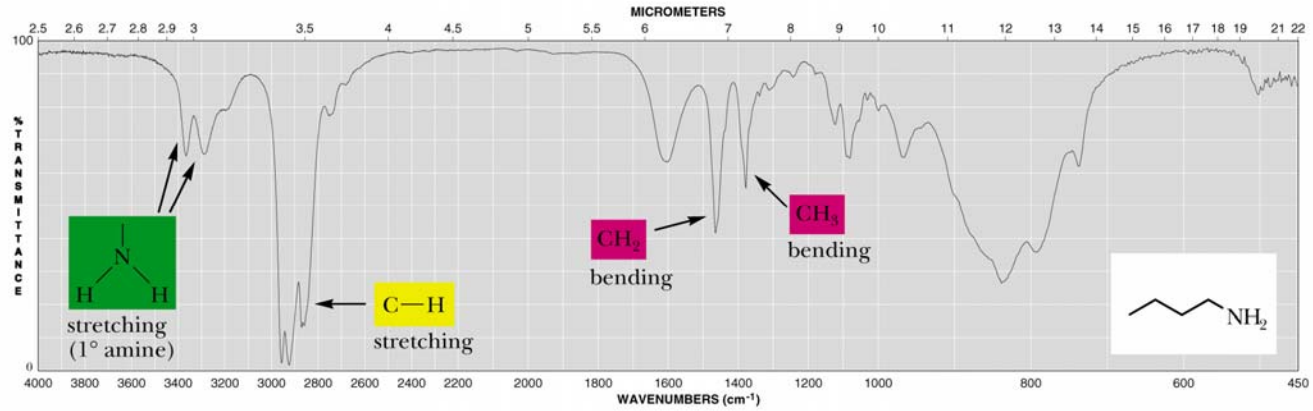
- The N–H bond in amines is polar, so 1° and 2° amines have intermolecular bonding. *i.e.* higher boiling points than alkanes, but lower than the corresponding alcohols.

C_5H_{12} = 36° $C_4H_{11}N$ = 78° C_4H_9OH = 118°

B. Spectroscopy of Amines

- In IR spectroscopy, amines have strong N–H stretching peaks in the 3100-3500 cm^{-1} region. Primary amines have two peaks, while secondary amines have one. Tertiary and quaternary have none (they have no NH bonds).

- The spectrum of butanamine is illustrative…



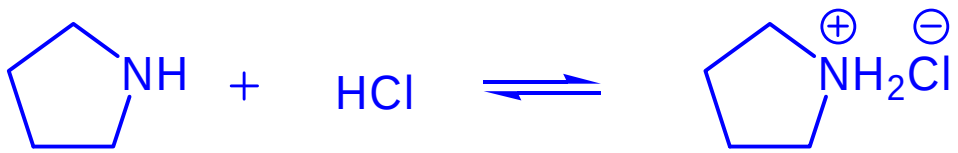
C. Basicity of Amines

- All amines except quaternary contain a lone pair that can accept a proton, so these amines can act as bases.

base — conjugate acid

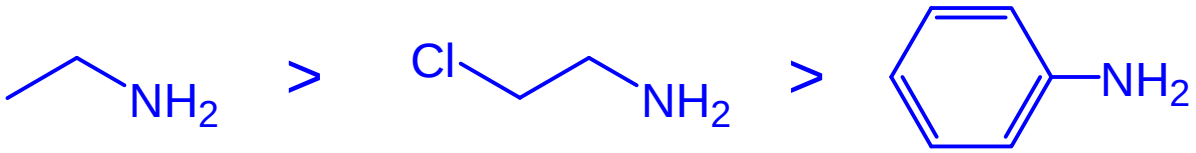
$$R_3N: + H^{\oplus} \rightleftharpoons R_3\overset{\oplus}{N}H$$

amine — ammonium ion



- Formation of a salt by reaction of an amine with an acid is a useful way of separating amines from reaction mixtures (Expt 2).

- Base strengths can be predicted as per Chapter 2, based on structural differences.



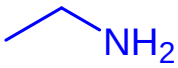
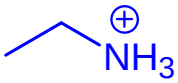
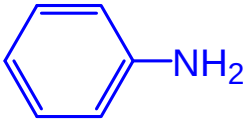
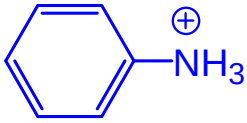
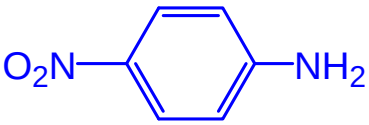
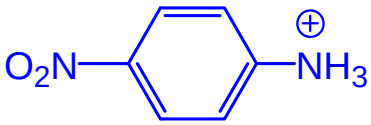
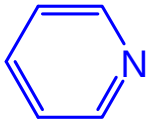
- Note that a protonated amine is a conjugate acid

$$R_3N: \quad + \quad H^{\oplus} \quad \rightleftharpoons \quad R_3\overset{\oplus}{N}H$$

- Because amines are weak bases, their conjugate acids can be relatively strong. Recall the relationship between a base (or acid) and its conjugate acid (or conjugate base):

$$pK_b \text{ (base)} + pK_a \text{ (conjugate acid)} = 14$$

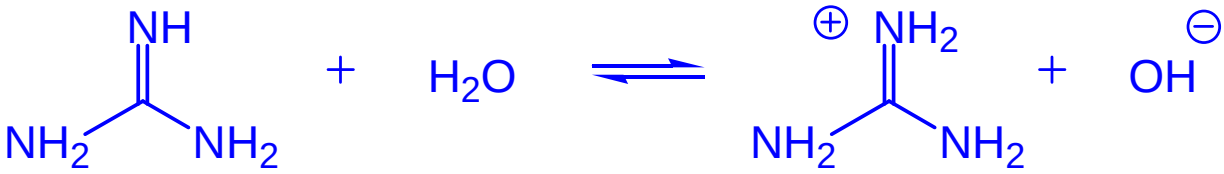
- Note: the weaker the base, the stronger the conjugate acid.

Base		*Conjugate Acid*	
	$pK_b = 3.19$		$pK_a = 10.81$
	$pK_b = 9.37$		$pK_a = 4.63$
	$pK_b = 13.0$		$pK_a = 1.0$
	$pK_b = 8.75$		$pK_a = 5.25$

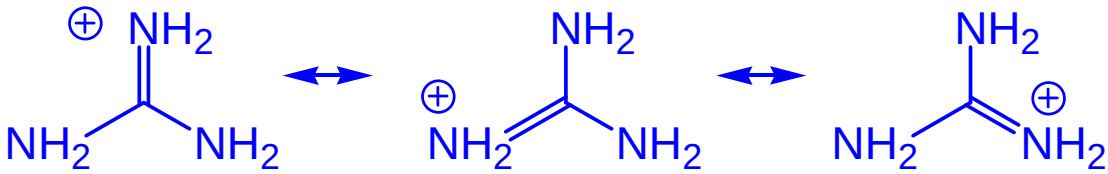
- In the above, the relative basicities are predictable using the same criteria examined in Chapter 2:

- o Aniline is less basic than ethyl amine because of resonance stabilization of the N non-bonding pair
- o *p*-nitroaniline is much less basic than aniline because of the added inductive effect of the nitro group
- o pyridine is less basic than ethyl amine because the N atom is sp^2-hybridized

- One naturally occurring base, guanidine, is very strong because the conjugate acid is resonance-stabilized.



guanidine guanidinium ion



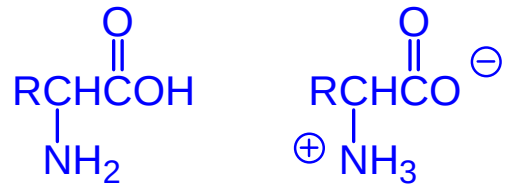
three equivalent contributing structures

- Guanidine is one that you cannot predict based on the rules learned in Chapter 2. The base strength is not predicted by looking at the stability of the N non-bonding pair on the neutral base itself, but rather on the stability of the conjugate acid. This shows that the rules learned in Chapter 2 are only guidelines and don't always work!

- The guanidinium group is found in the amino acid arginine.

- Acid-base chemistry is important in the monomeric units of α-amino acids, which form polymeric peptides and proteins through amide (peptide) linkages. Amino acids have both carboxylic acid and amine groups (covered in Chem 2223b and Biochem 2280a).

- Amino acids exist as ionic salts, so they are crystalline solids with high melting points.



neutral form ionic form

D. Substitution Reactions of Amines

- With a lone pair, amines can act as adequate nucleophiles. They are better bases/nucleophiles than alcohols.

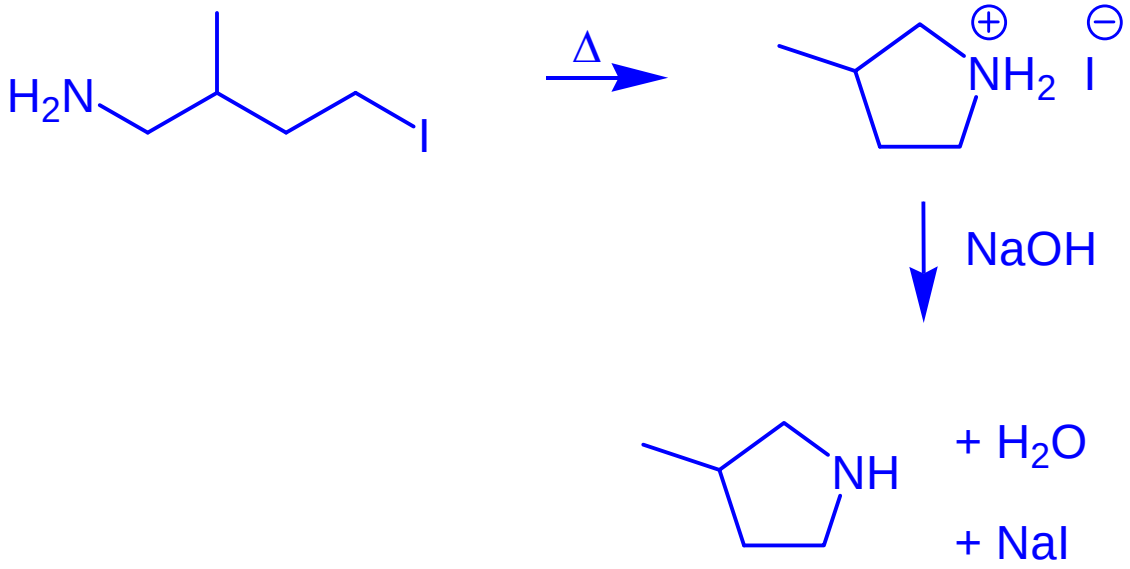
$$R{-}LG + R'{-}NH_2 \longrightarrow R{-}NH{-}R' + H{-}LG$$

$$CH_3CH_2{-}I + 2\ CH_3{-}NH_2 \longrightarrow CH_3CH_2NHCH_3 + CH_3\overset{\oplus}{N}H_3\overset{\ominus}{I}$$

- This is the normal method of synthesizing amines.

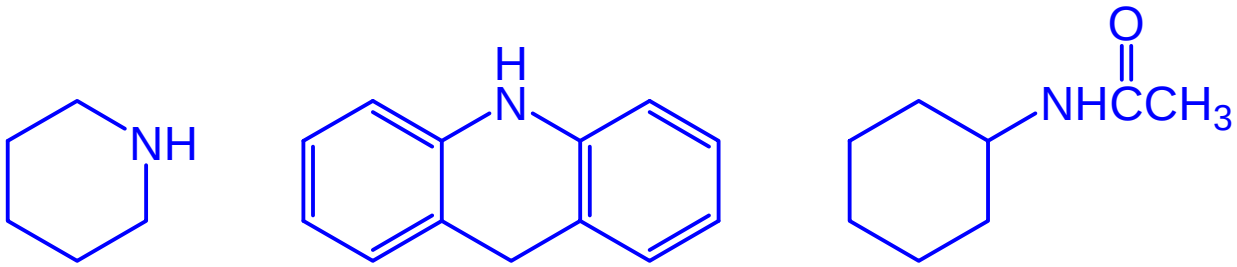
- Two moles of base are needed because 1 mole reacts as the Nu to give the product, while the 2nd mole reacts with the co-product HI (neutralization) to form the ammonium salt. This salt often precipitates out as it's formed, causing the reaction to proceed to completion.

- We can also make cyclic amines using the same reaction.



- Pages covered: Chapter 10, p. 277 - 291
- Problems: 9, 12, 15, 20, 27, 28, 30, 42, 45, and 11.14
- 2005: 32, 33; 2006: 30, 31; 2007: 29, 31; 2008: 30, 31

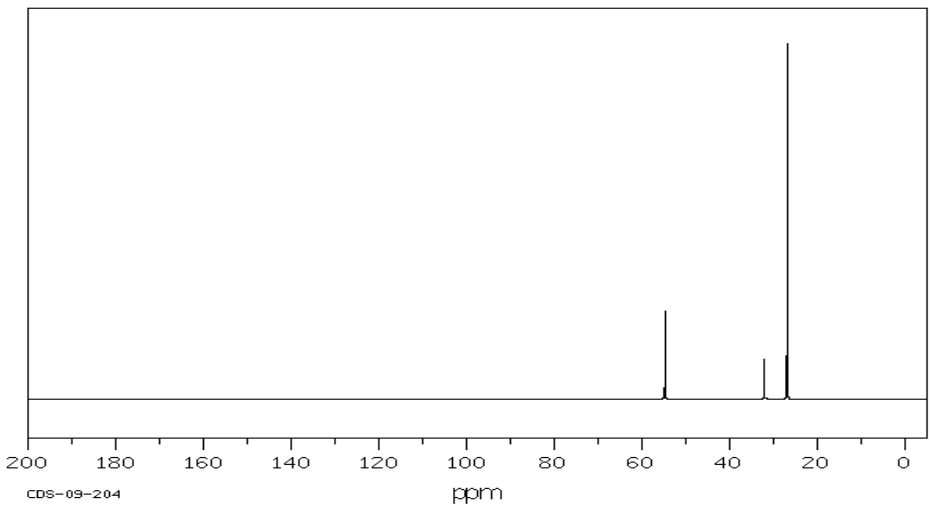
- Past test questions: Arrange the following in the order of base strength, from the strongest base to the weakest base.

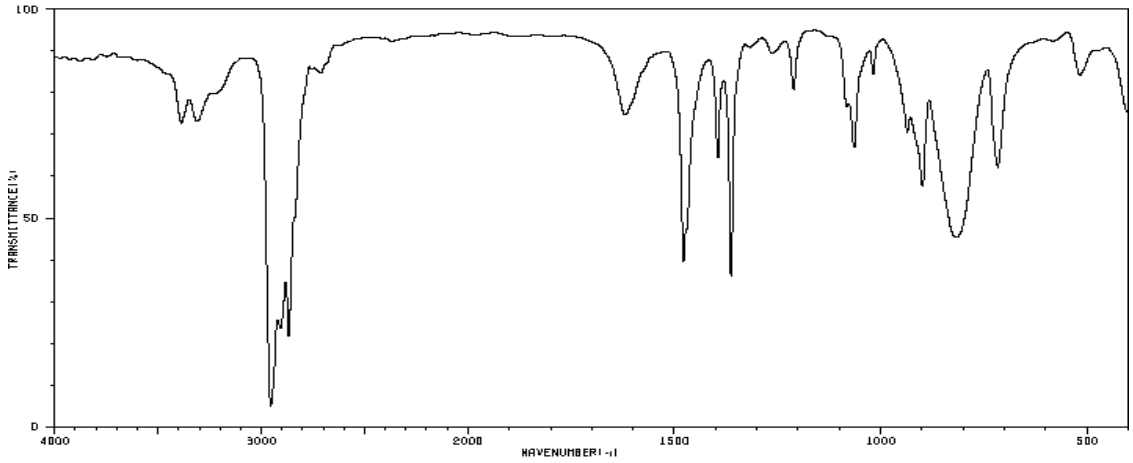


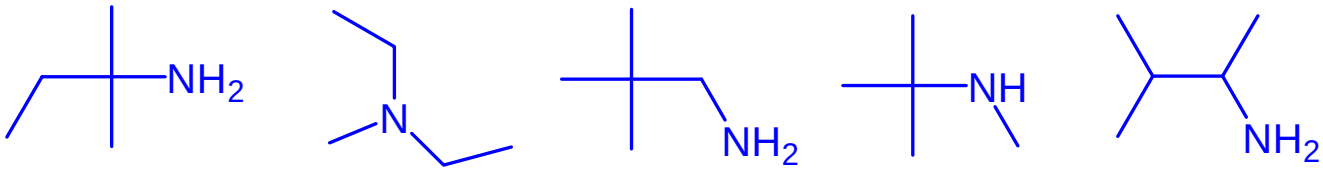
- Which one of the following compounds contains neither rings nor π-bonds?

  $C_{10}H_{20}O_2$ $C_{12}H_{14}N_2$ $C_6H_{11}NBr_2$ $C_7H_{17}NO_2$ $C_5H_8Cl_2$

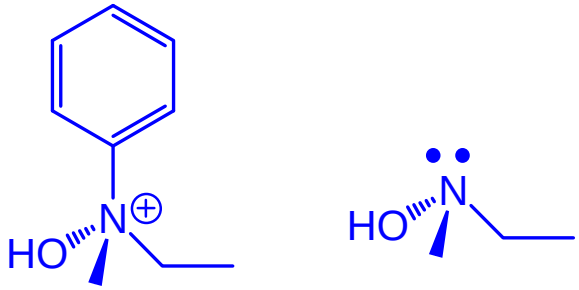
- A compound with formula $C_5H_{13}N$ has IR and ^{13}C-NMR shown. What is its structure?





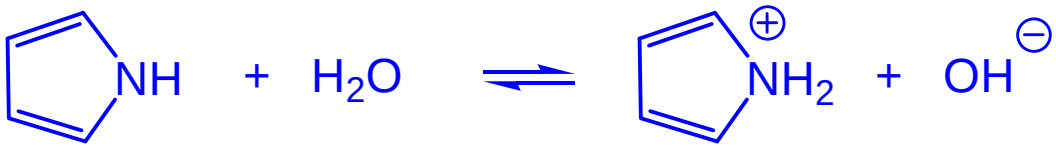


- MCAT: The amine on the left is chiral, while the amine on the right is not. What is the best explanation for this observation?



  - o The amine on the left has a phenyl group and the amine on the right does not
  - o The nitrogen on the left has resonance structures
  - o The amine on the right has a lone pair of electrons so nitrogen inversion is not possible
  - o The amine on the left does not have a pair of electrons so nitrogen inversion is not possible

- MCAT: At equilibrium the reaction below lies to the left (the reactants predominate). What is the best explanation for the energy relationship between reactants and products?



  - o Secondary amines are more basic than primary amines
  - o Primary amines are more basic than secondary amines
  - o The product is stabilized by aromaticity
  - o The reactant is stabilized by aromaticity