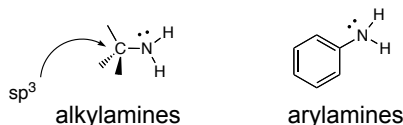
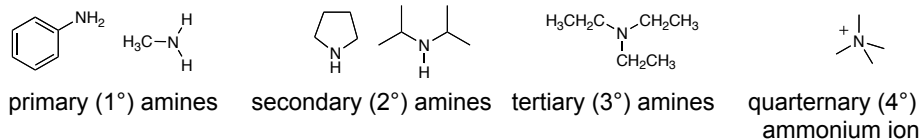


Chapter 21: Amines. Organic derivatives of ammonia, NH_3 . Nitrogen atoms have a lone pair of electrons, making the amine both basic and nucleophilic

21.1: Amines Nomenclature. (please read)



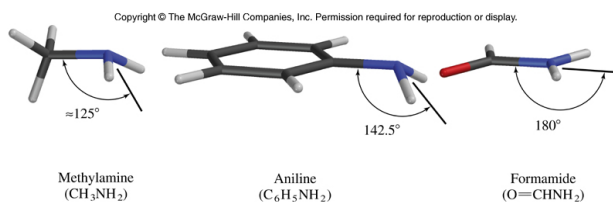
Amines are classified according to the degree of nitrogen substitution: 1° (RNH_2), 2° (R_2NH), 3° (R_3N) and 4° (R_4N^+)



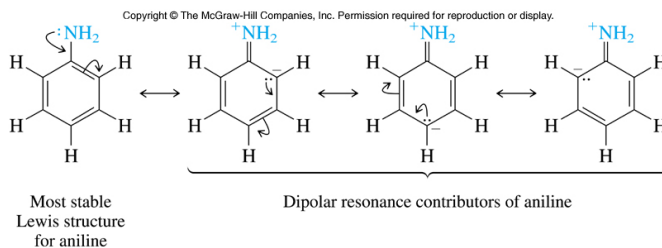
Note: Although the terminology is the same, the classification of amines is different from that of alcohols.

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21.2: Structure and bonding. The nitrogen of alkylamines is sp^3 hybridized and tetrahedral.

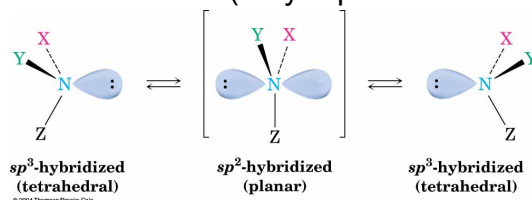


The nitrogen of arylamines (aniline) is slightly flattened, reflecting resonance interactions with the aromatic ring.



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In principle an amine with three different substituents on the nitrogen is chiral with the lone pair of electrons being the fourth substituent; however, for most amines the *pyramidal inversion* of nitrogen is a racemization mechanism. The barrier to nitrogen inversion is about 25 KJ/mol (very rapid at room temperature).



21.3: Physical Properties. (please read)

21.4: Basicity of Amines. The basicity is reflective of and is expressed as the pK_a of the conjugate acid.

The conjugate base of a weak acid is a strong base:

Higher pK_a = weaker acid = stronger conjugate base

The conjugate base of a strong acid is a weak base

Lower pK_a = stronger acid = weaker conjugate base

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Table 21.1 (p. 964): pK_a values of ammonium ions

Alkyl ammonium ions, $R_3NH^+ X^-$, have pK_a values in the range of 10-11 (ammonium ion, $H_4N^+ X^-$, has a $pK_a \sim 9.3$)

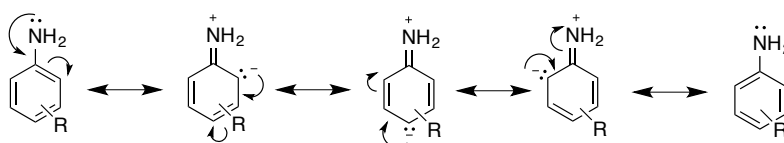
The ammonium ions of aryl amines and heterocyclic aromatic amines are considerably more acidic than alkyl amines ($pK_a < 5$). The nitrogen lone pair is less basic if it is in an sp^2 hybridized orbital (versus an sp^3)

NH_4^+	$pK_a = 9.3$		$pK_a = 4.6$
$(H_3CH_2C)NH_3^+$	10.8		5.2
$(H_3CH_2C)_2NH_2^+$	11.1		0.4
$(H_3CH_2C)_3NH^+$	10.8		6.9
			7.0
			- 1.0

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Arylamines are less basic than alkylamines. The lone pair of electrons on the nitrogen of aniline are conjugated to the π -electrons of the aromatic ring and are therefore less available for acid-base chemistry. Protonation disrupts the conjugation.

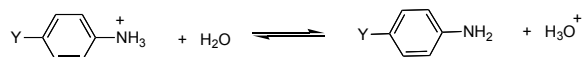
Substituents can greatly influence the basicity of the aniline. The effect is dependent upon the nature and position of the substituent.



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Electron-donating substituents (-CH₃, -OH, -OCH₃) make the substituted aniline more basic than aniline itself (the pK_a of the substituted anilinium ion is higher than 4.6)

Electron-withdrawing substituents (-Cl, -NO₂) make the substituted aniline less basic than aniline itself (the pK_a of the substituted anilinium ion is lower than 4.6)



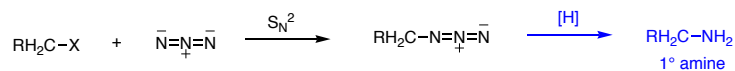
Y= -NH ₂	$pK_a = 6.2$	less acidic (more basic)
-OCH ₃	$pK_a = 5.3$	
-CH ₃	$pK_a = 5.1$	more acidic (less basic)
-H	$pK_a = 4.6$	
-Cl	$pK_a = 4.0$	
-CF ₃	$pK_a = 3.5$	
-CN	$pK_a = 1.7$	
-NO ₂	$pK_a = 1.0$	

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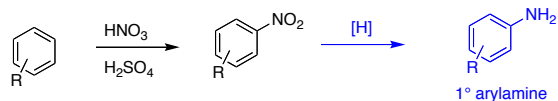
21.5: Tetraalkylammonium Salts as Phase-Transfer Catalysts
(please reads)

21.6: Reactions That Lead to Amines: A Review and Preview
Formation of C–N bonds (Table 21.3, p. 871):

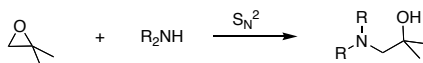
a. Nucleophilic substitution with azide ion (Ch. 8.1, 8.10)



b. Nitration of arenes (Ch. 12.3)

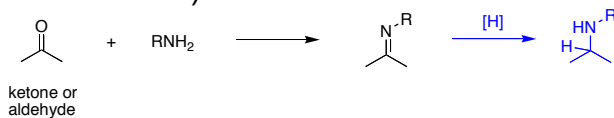


c. Nucleophilic ring opening of epoxides with NH₃ (Ch. 16.11)

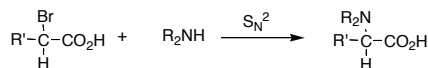


229

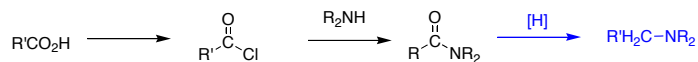
d. Reaction of amines with ketones and aldehydes
(Ch. 17.10 - 17.11)



d. Nucleophilic substitution of α-halo acids with NH₃ (Ch. 20.1)



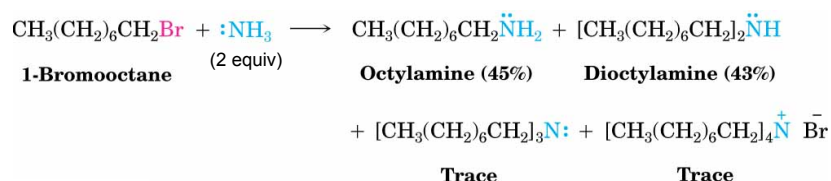
f. Nucleophilic acyl substitution (Ch. 19.4, 19.5, 19.10)



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21.7: Preparation of Amines by Alkylation of Ammonia

Ammonia and other alkylamines are good nucleophiles and react with 1° and 2° alkyl halides or tosylates via an S_N² reaction yielding alkyl amines.



1°, 2°, and 3° amines all have similar reactivity; the initially formed monoalkylation product can undergo further reaction to yield a mixture of alkylated products.

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21.8: The Gabriel Synthesis of Primary Alkylamines.

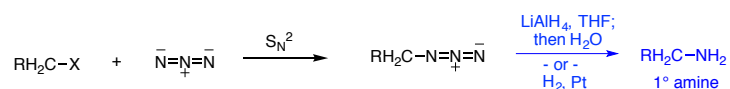
Reaction of potassium phthalimide with alkyl halides or tosylates via an S_N² reaction. The resulting *N*-substituted phthalimide can be hydrolyzed with acid or base to a 1° amine.

The Gabriel amine synthesis is a general method for the preparation of 1° alkylamines (but not anilines)

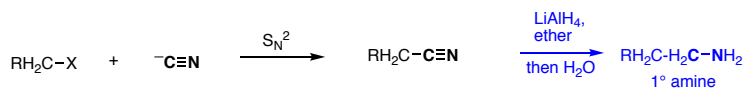
232

21.9: Preparation of Amines by Reduction. Alkyl azides, nitriles, amides, and nitroarene can be reduced to the corresponding amines.

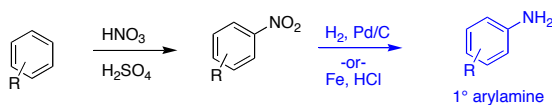
LiAlH₄ reduces alkyl azides to 1° amines



LiAlH₄ reduces nitriles to 1° amines

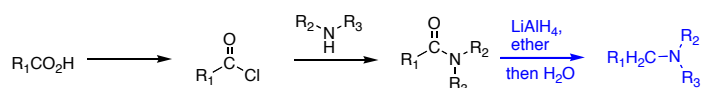


Nitroarenes are reduced to anilines

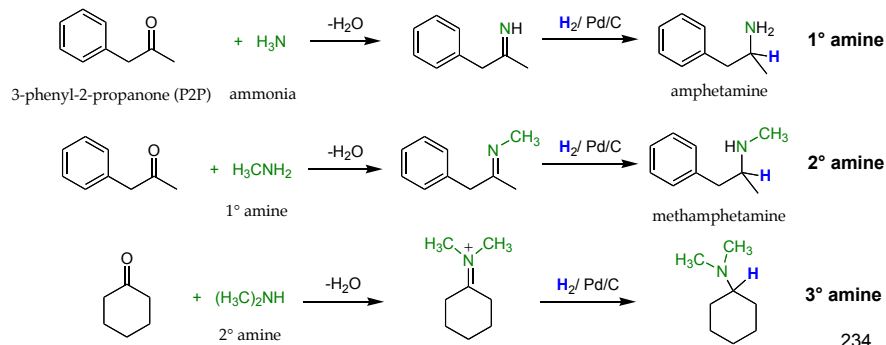


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LiAlH₄ reduces amides to 1°, 2° or 3° amines (mechanism 21.1, p. 877)



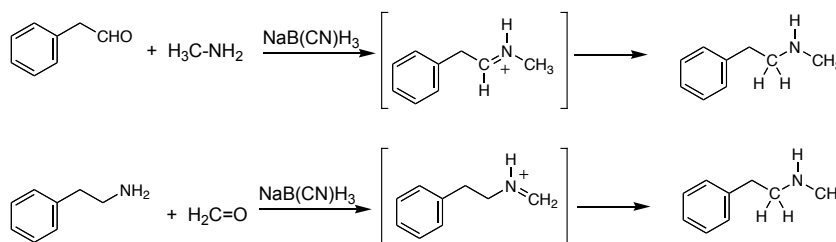
21.10: Reductive Amination. Imines and iminium ions are easily reduced to amines.



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Sodium cyanoborohydride, $\text{Na}^+ \text{N}\equiv\text{C}-\text{BH}_3^-$: the cyano ligand makes cyanoborohydride a weak hydride source and it will react with only the most easily reduced functional groups, such as an iminium ion. $\text{NaB}(\text{CN})\text{H}_3$ reduces ketones and aldehydes slowly.

Reductive amination with $\text{NaB}(\text{CN})\text{H}_3$ is a one-pot reaction

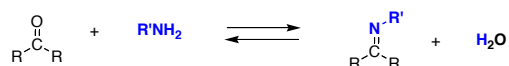


235

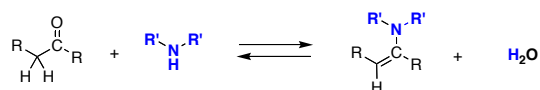
21.11: Reactions of Amines: A Review and a Preview.

Table 21.4, p. 880

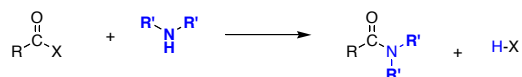
Reaction of ammonia and 1° amines with aldehyde and ketones to afford imines (w/ loss of H_2O) (Ch. 17.10)



Reaction of 2° amines with aldehyde and ketones (w/ an α -proton) to afford an enamine (w/ loss of H_2O) (Ch. 17.11)



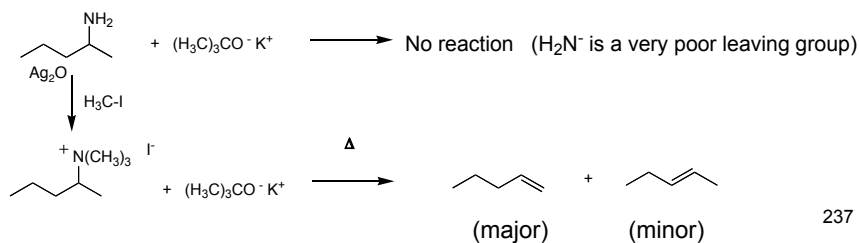
Reaction of ammonia, 1° , and 2° amines with acid chloride, Anhydrides, and esters to afford amides. (Ch. 19.4)



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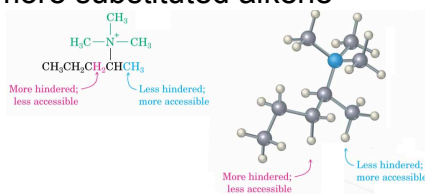
21.12: Reaction of Amines with Alkyl Halides. Amines react with alkyl halides and tosylates by nucleophilic substitution (S_N2). Products from multiple alkylation often results.

21.13: The Hoffmann Elimination. 1° amine react with excess methyl iodide yielding quaternary (4°) ammonium salts. E2 elimination of the resulting trimethyl ammonium group gives an alkene.



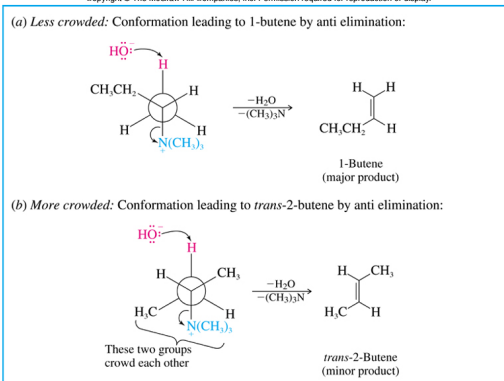
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Hofmann elimination gives the less substituted alkene, where E2 elimination of an alkyl halide or tosylate will follow Zaitsev rule to give the more substituted alkene



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Fig 21.5,
p. 883

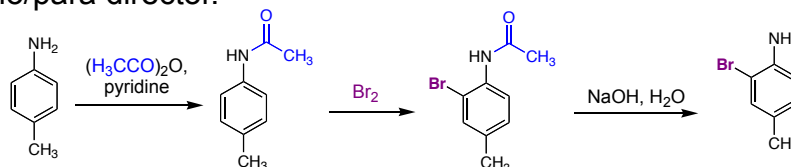


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21.14: Electrophilic Aromatic Substitution in Arylamines.

The amino group is a strongly activating, ortho/para director; however, it is largely incompatible with Friedel-Crafts reactions.

Electrophilic aromatic substitution of phenyl acetamides (amides of aniline): The acetamide group is still activating and an ortho/para director.



The acetamide acts as a protecting group for the arylamine.

Anilines are so activated that multiple substitution reactions can be a problem. The reactivity of the acetamide is attenuated so that mono-substitution is achieved.

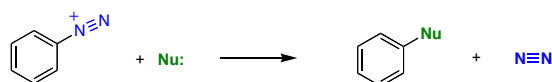
The acetamide group is compatible with Friedel-Crafts reactions.

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21.15: Nitrosation of Alkylamines. (please read)

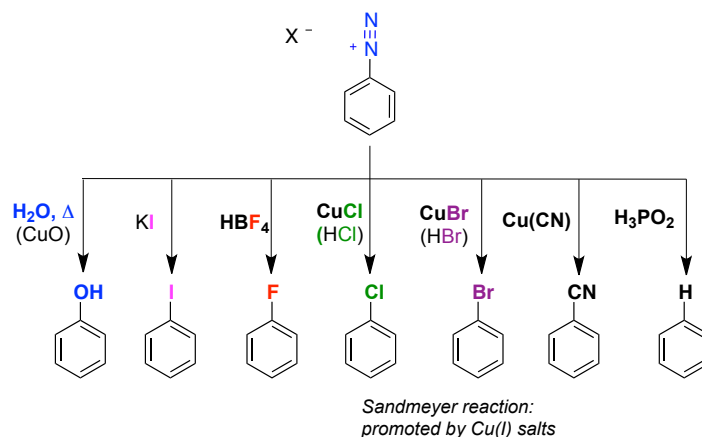
22.16: Nitrosation of Arylamines. Reaction of aniline with *nitrous acid* ($\text{NaNO}_2 + \text{H}^+ \rightarrow \text{HONO}$) leads to an aryl diazonium cation, which are valuable precursors to other functional groups.

Aryl diazonium salts react with nucleophiles in a substitution reaction. N_2 is one of the best leaving groups.



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21.17: Synthetic Transformations of Aryl Diazonium Salts.
(Fig. 21.6, p. 888)

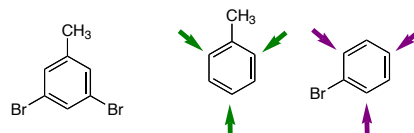


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Advantages of the aryl diazonium salt intermediate:

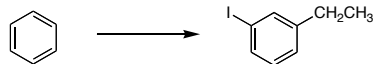
- 1) Introduces aryl substituents that are not otherwise accessible, such as $-\text{OH}$, $-\text{F}$, $-\text{I}$, and $-\text{CN}$.
- 2) Allows preparation of substituted arenes with substitution patterns that can not be prepared by other means.

Synthesis 3,5-dibromotoluene



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Synthesize 2-iodoethylbenzene from benzene:

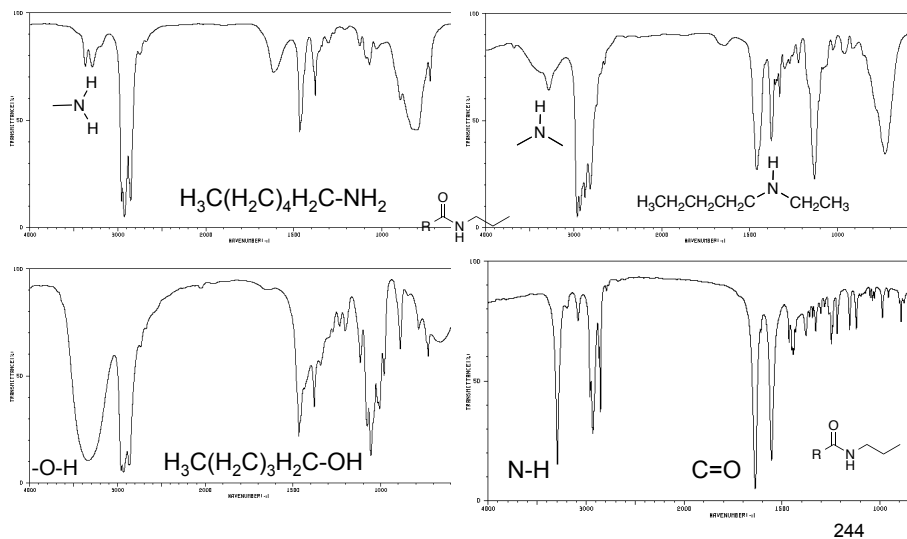


21.18: Azo Coupling. (please read)

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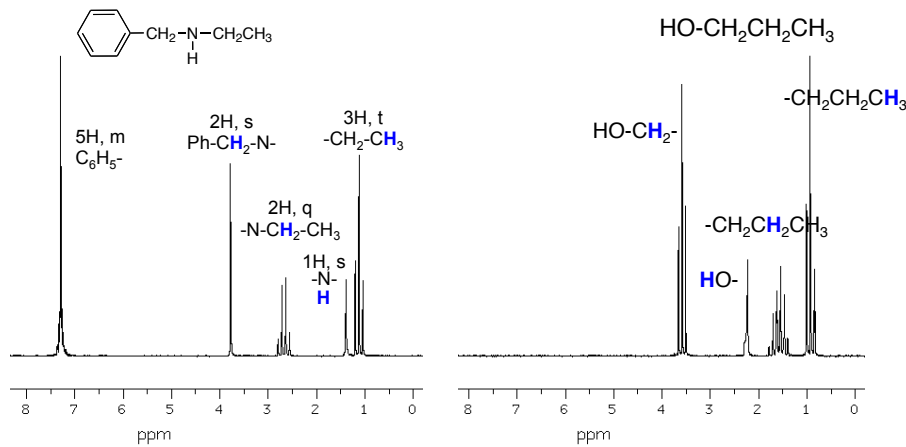
21.19: Spectroscopic Analysis of Amines.

IR: N-H stretches in the range of 3300 - 3500 cm^{-1} ; this is the same range as an O-H stretch, but N-H stretches are less intense.



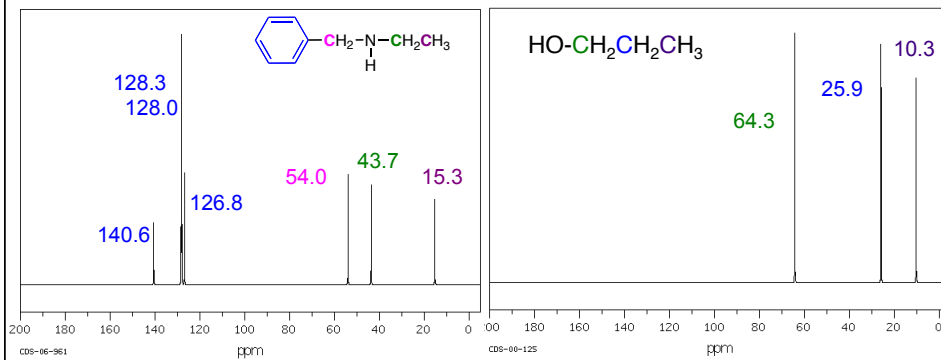
244

^1H NMR: Nitrogen is less deshielding than oxygen. Hydrogens on the carbon attached to the amino nitrogen have a typical chemical shift of δ 2.2 - 3.0



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^{13}C NMR: The resonances of carbon attached to a nitrogen of an amine are deshielded about 20 ppm downfield from those of an alkane.



Mass Spectrum: Nitrogen rule: small organic compounds with an odd number of nitrogen atoms have an odd mass; compounds with an even number of nitrogen atoms have an even mass

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