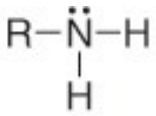
Amines

Chapter 24

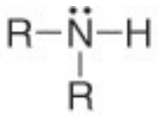
Organic Chemistry, *8th Edition*

John McMurry

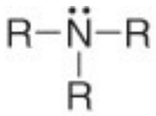
Introduction


$\mathrm{R-\underset{\underset{H}{|}}{\ddot{N}}-H}$

1° amine
(1 R group on N)

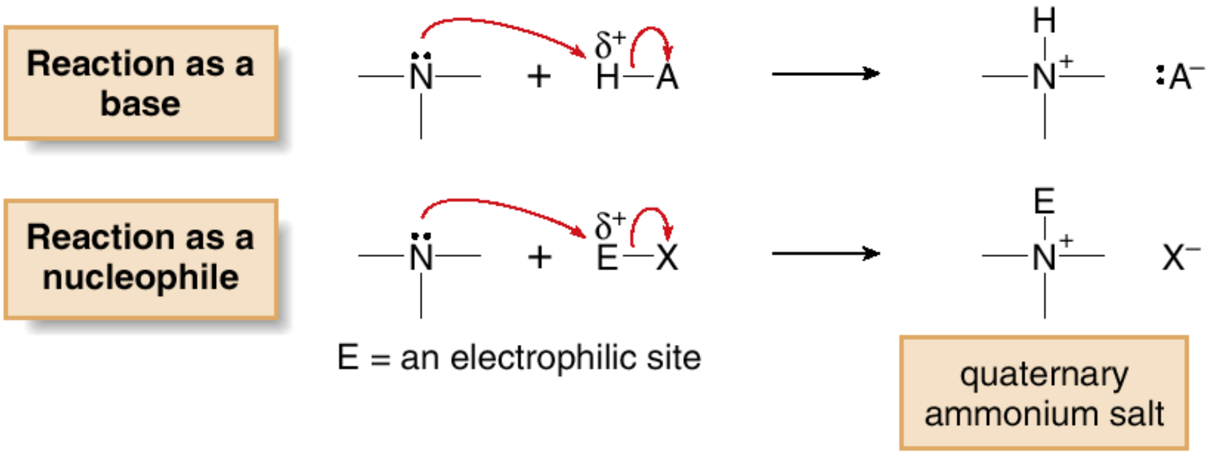

$\mathrm{R-\underset{\underset{R}{|}}{\ddot{N}}-H}$

2° amine
(2 R groups on N)


$\mathrm{R-\underset{\underset{R}{|}}{\ddot{N}}-R}$

3° amine
(3 R groups on N)

Amines are stronger bases and better nucleophiles than other neutral organic compounds.


Reaction as a base

Reaction as a nucleophile

E = an electrophilic site

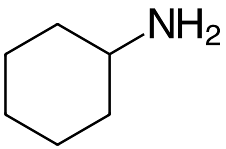
quaternary ammonium salt

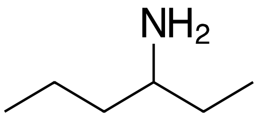
- **The chemistry of amines is dominated by the nonbonded electron pair on the nitrogen atom.**

Nomenclature

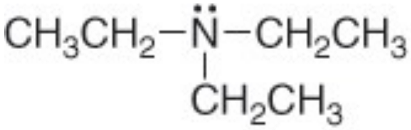
1ry Amines are named using either systematic or common names.

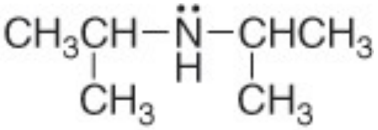
CH_3NH_2
methanamine
(methylamine)


cyclohexanamine
(cyclohexylamine)

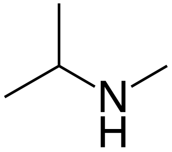

3-hexanamine

Secondary and tertiary amines having identical alkyl groups are named using the prefix di- or tri- with the name of the primary amine.


$CH_3CH_2-\ddot{N}(CH_2CH_3)-CH_2CH_3$
triethylamine

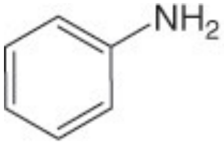

$CH_3CH(CH_3)-\ddot{N}H-CH(CH_3)CH_3$
diisopropylamine

Secondary and 3° amines having more than one kind of alkyl group are named as *N*-substituted primary amines:

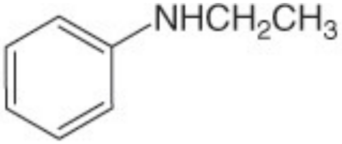

N-methyl-2-propanamine

Nomenclature

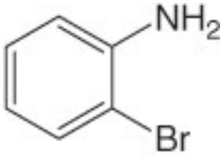
Aromatic amines are named as derivatives of aniline.



aniline

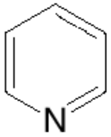


N-ethylaniline

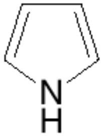


o-bromoaniline

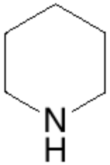
There are many different nitrogen heterocycles, each with a different name. The N atom is considered to be at position “1”.



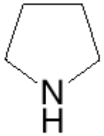
pyridine



pyrrole



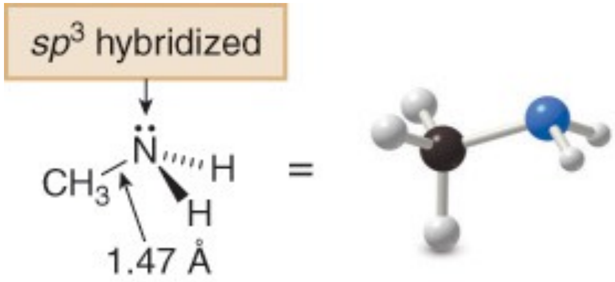
piperidine

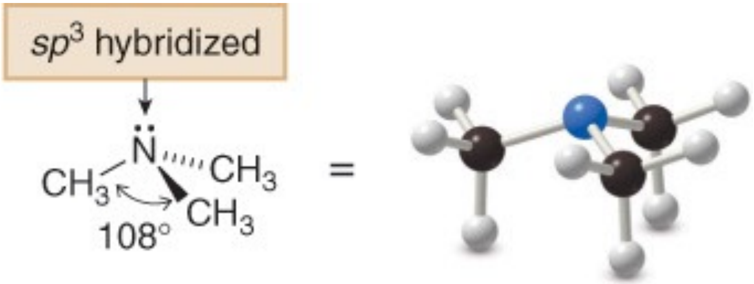


pyrrolidine

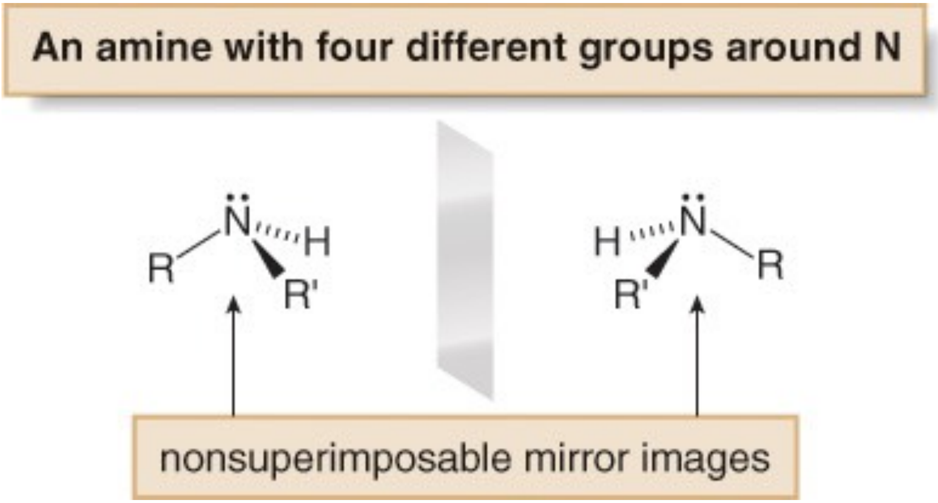
Structure and Bonding

An amine N atom is *sp*^{3} hybridized and trigonal pyramidal, with bond angles of approximately 109.5°.





Since an amine nitrogen has four different groups around it, it is technically a stereogenic center.

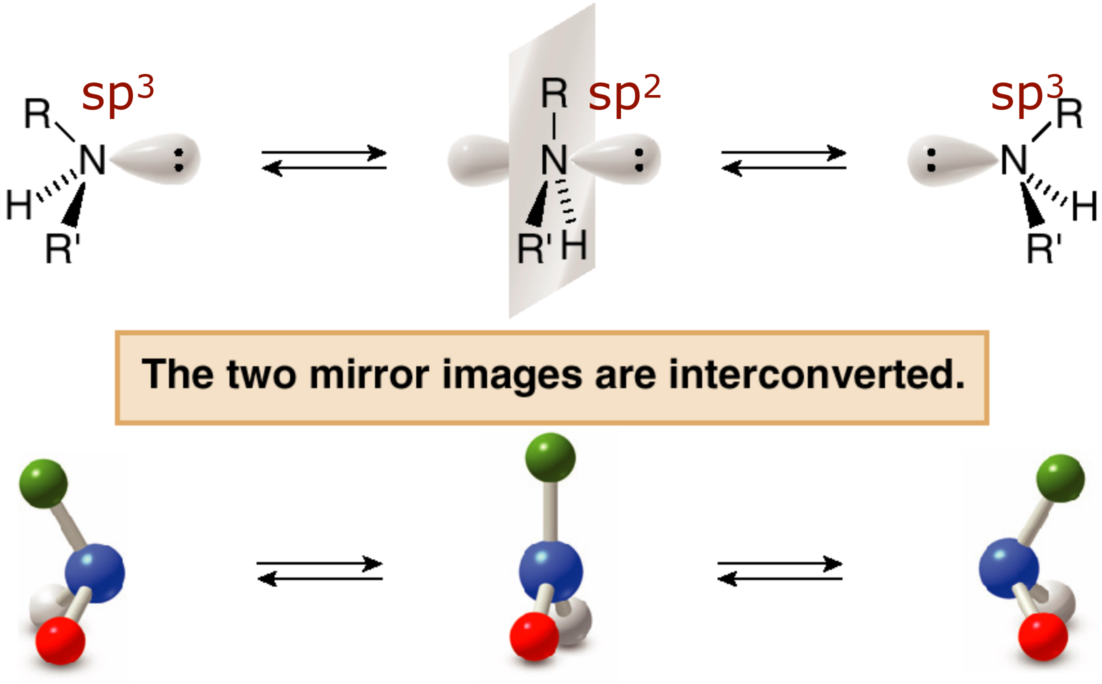


An amine with four different groups around N

nonsuperimposable mirror images

Structure and Bonding

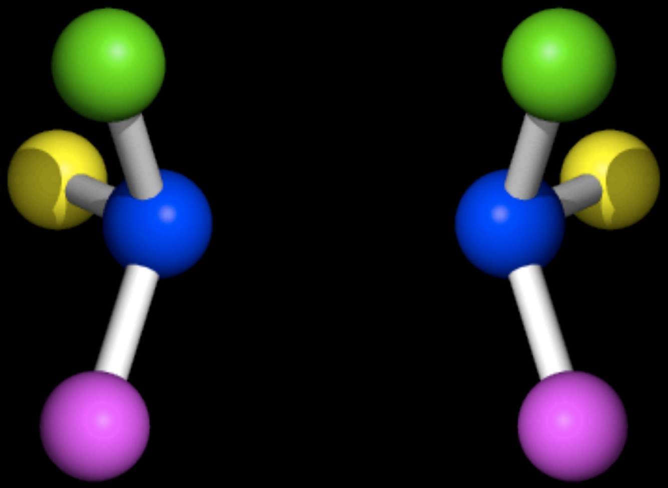
However, the chirality of the amine nitrogen can be ignored because the two enantiomers interconvert by passing through a trigonal planar (achiral) transition state.



The two mirror images are interconverted.

planar transition state

Inversion of Configuration in Amines



Structure and Bonding

In contrast, the chirality of a quaternary ammonium salt with four different groups cannot be ignored. Because there is no nonbonded electron pair on the nitrogen atom, interconversion cannot occur, and the N atom is just like a carbon atom with four different groups around it.

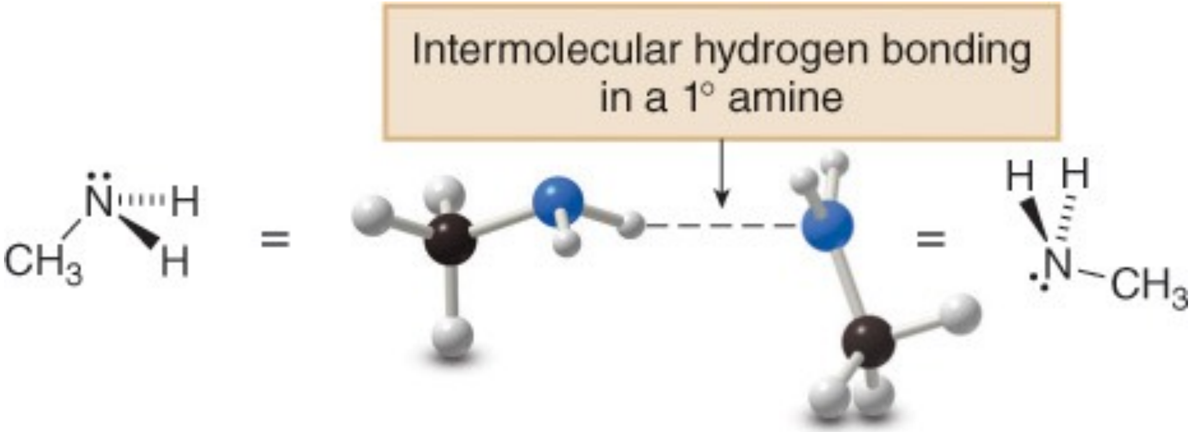
Two enantiomers of a quaternary ammonium salt

- The N atom of a quaternary ammonium salt is a stereogenic center when N is surrounded by four different groups.

Physical Properties

- Amines exhibit dipole-dipole interactions because of the polar C—N and N—H bonds.

- Primary and 2° amines are capable of intermolecular hydrogen bonding because they contain N—H bonds.



Physical Properties

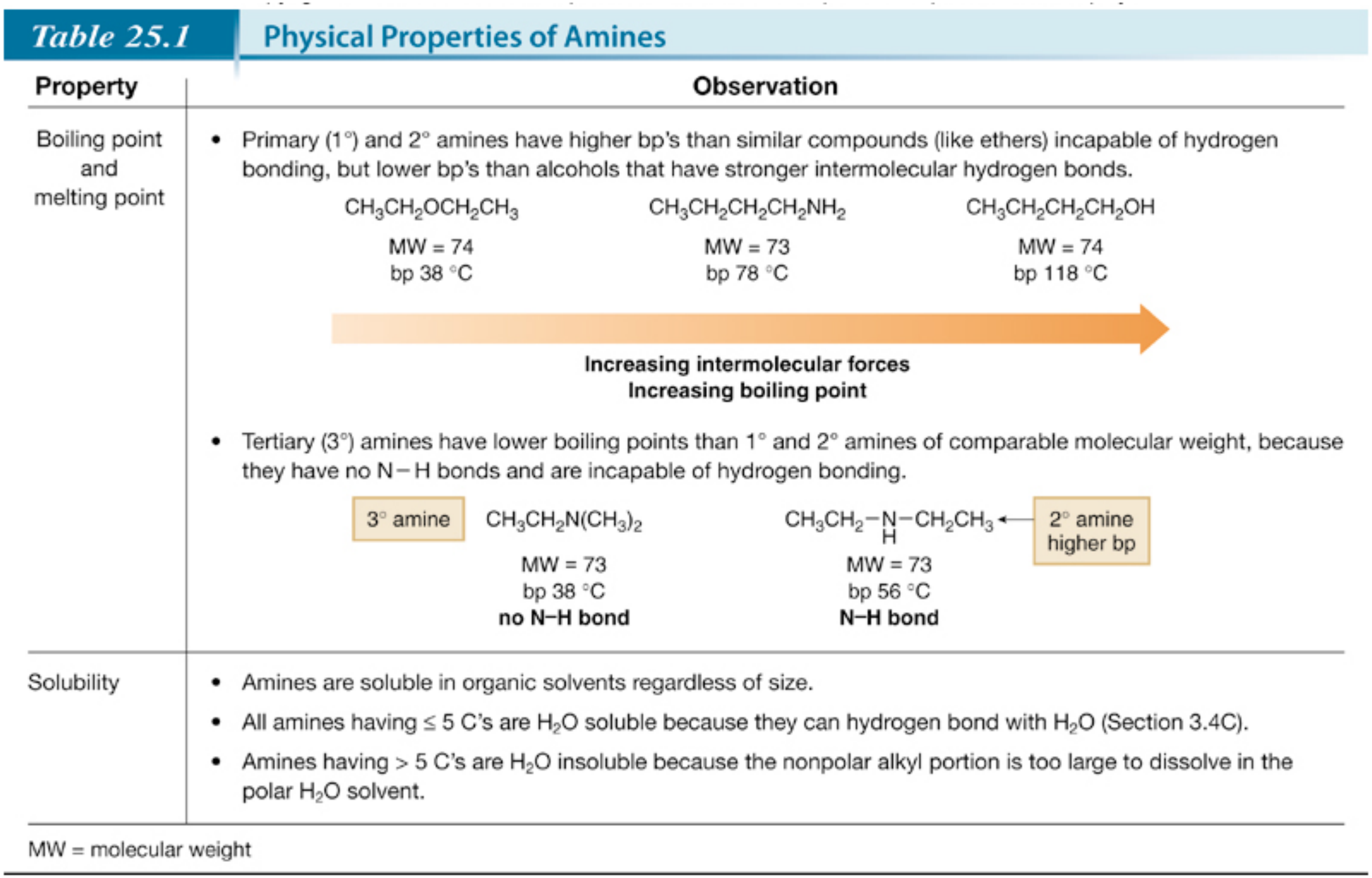


Table 25.1 Physical Properties of Amines

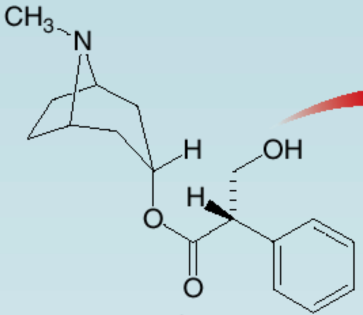
Property	Observation
Boiling point and melting point	• Primary (1°) and 2° amines have higher bp's than similar compounds (like ethers) incapable of hydrogen bonding, but lower bp's than alcohols that have stronger intermolecular hydrogen bonds. $CH_3CH_2OCH_2CH_3$ MW = 74 bp 38 °C $CH_3CH_2CH_2CH_2NH_2$ MW = 73 bp 78 °C $CH_3CH_2CH_2CH_2OH$ MW = 74 bp 118 °C **Increasing intermolecular forces** **Increasing boiling point** • Tertiary (3°) amines have lower boiling points than 1° and 2° amines of comparable molecular weight, because they have no N–H bonds and are incapable of hydrogen bonding. 3° amine $CH_3CH_2N(CH_3)_2$ MW = 73 bp 38 °C **no N–H bond** $CH_3CH_2-\underset{H}{N}-CH_2CH_3$ ← 2° amine higher bp MW = 73 bp 56 °C **N–H bond**
Solubility	• Amines are soluble in organic solvents regardless of size. • All amines having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • Amines having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

MW = molecular weight

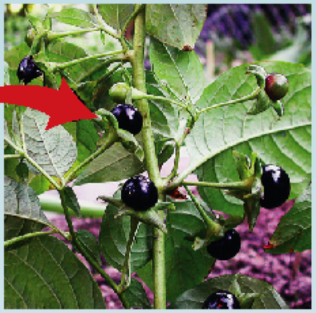
Interesting and Useful Amines

- Many low molecular weight amines have foul odors.
- Trimethylamine [$(CH_3)_3N$], formed when enzymes break down certain fish proteins, has the characteristic odor of rotting fish.
- Putrescine ($NH_2CH_2CH_2CH_2CH_2NH_2$) and cadaverine ($NH_2CH_2CH_2CH_2CH_2CH_2NH_2$) are both poisonous diamines with putrid odors. They too are present in rotting fish, and are partly responsible for the odors of semen, urine, and bad breath.
- Naturally occurring amines derived from plant sources are called alkaloids.

Interesting and Useful Amines

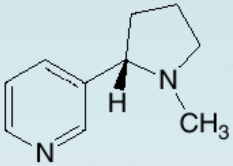


atropine



nightshade

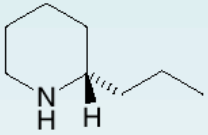
- **Atropine** is an alkaloid isolated from *Atropa belladonna*, the deadly nightshade plant. In the Renaissance, women used the juice of the berries of the nightshade to enlarge the pupils of their eyes for cosmetic reasons. Atropine causes an increase in heart rate, relaxes smooth muscles, and interferes with nerve impulses transmitted by acetylcholine. In higher doses atropine is poisonous, leading to convulsions, coma, and death.



nicotine

tobacco

- **Nicotine** is an addictive and highly toxic compound isolated from tobacco. In small doses it acts as a stimulant, but in large doses it causes depression, nausea, and even death. Nicotine is synthesized in plants as a defense against insect predators, and is used commercially as an insecticide.

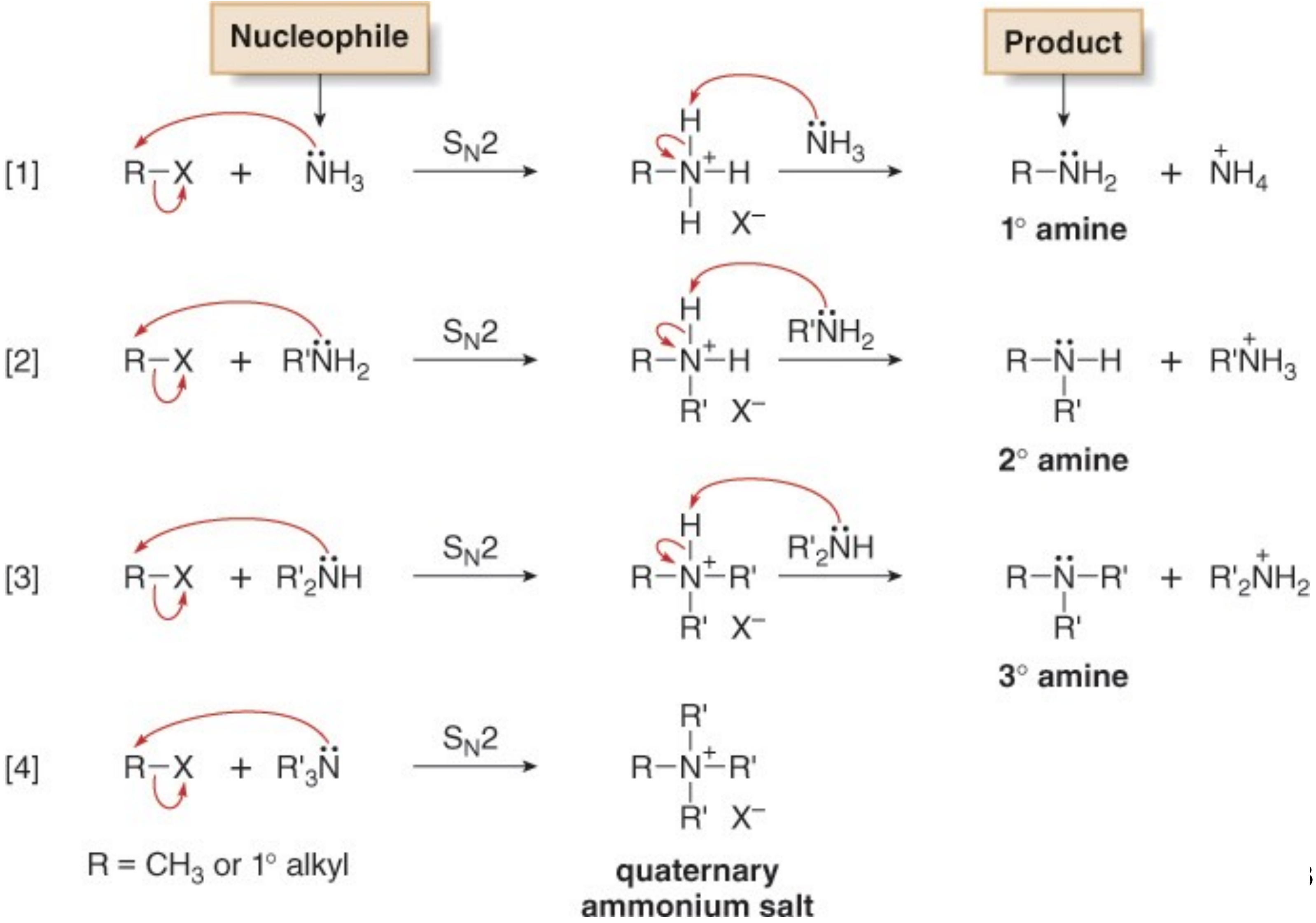


coniine

hemlock

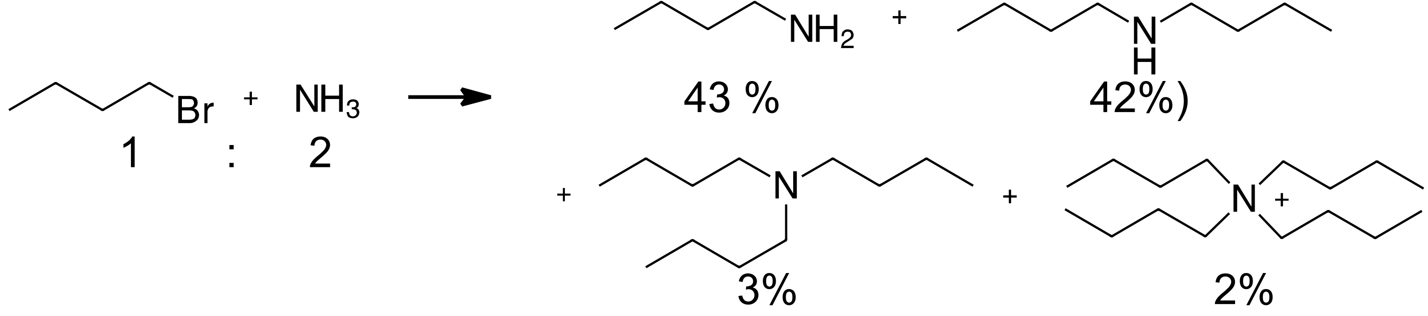
- **Coniine**, a poisonous alkaloid isolated from the seeds, leaves, and roots of hemlock (*Conium maculatum*), has been known since ancient times. Ingestion causes weakness, paralysis, and finally death. The Greek philosopher Socrates was executed by being forced to drink a potion prepared from hemlock in 339 B.C.

Preparation of Amines—Direct Nucleophilic Substitution



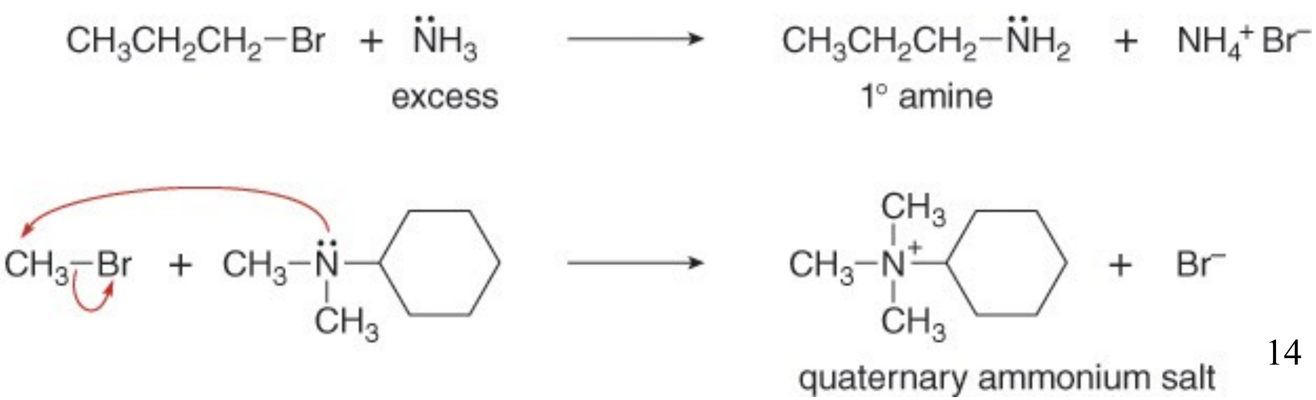
Preparation of Amines—Direct Nucleophilic Substitution

Although the process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness.



Consequently, the reaction is most useful in preparing 1^{ry} amines by using a large excess of NH_3, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.

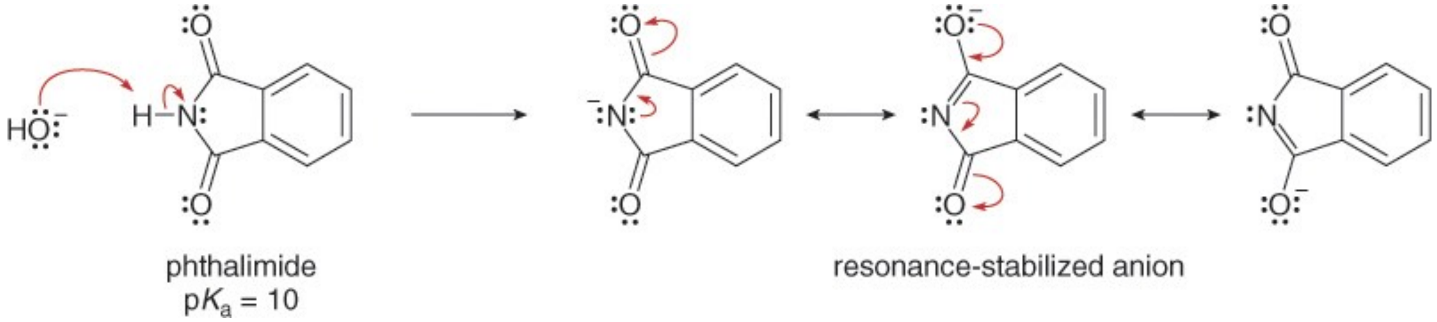
Useful S_N2 substitutions

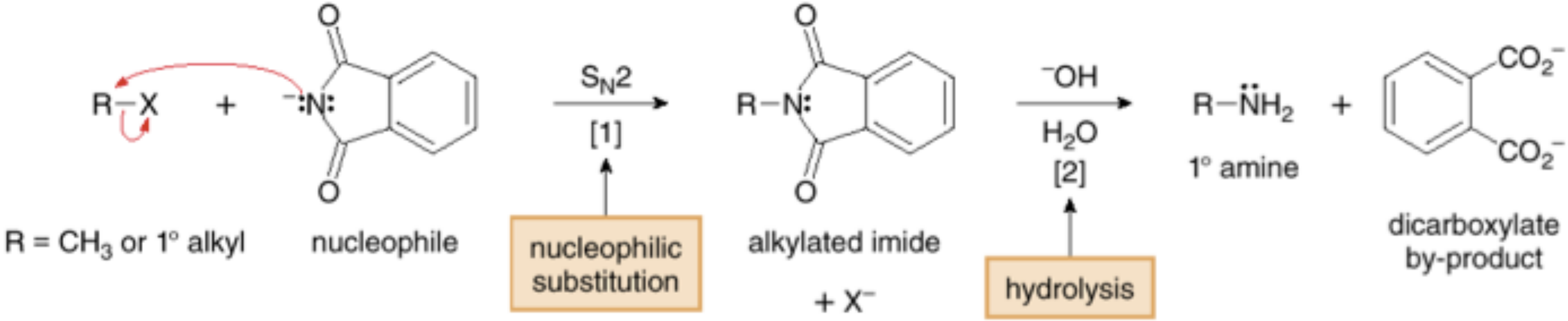


$$\mathrm{CH_3CH_2CH_2{-}Br} + \underset{\text{excess}}{\mathrm{\ddot{N}H_3}} \longrightarrow \underset{1^\circ\text{ amine}}{\mathrm{CH_3CH_2CH_2{-}\ddot{N}H_2}} + \mathrm{NH_4^+\,Br^-}$$

Preparation of Amines—Gabriel Synthesis of 1^{ry} Amines

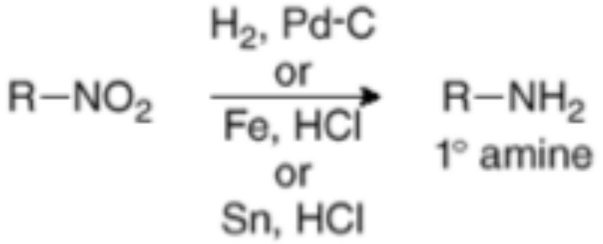
The Gabriel synthesis is comprised of two steps and uses a nucleophile derived from phthalimide to synthesize 1^{ry} amines via nucleophilic substitution.





Preparation of Amines—Reduction of N-Containing Functional Groups

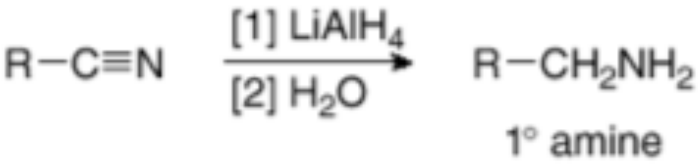
Nitro groups are reduced to 1° amines using a variety of reducing agents.



$$R{-}NO_2 \xrightarrow[\text{Fe, HCl or Sn, HCl}]{H_2\text{, Pd-C or}} R{-}NH_2$$

1° amine

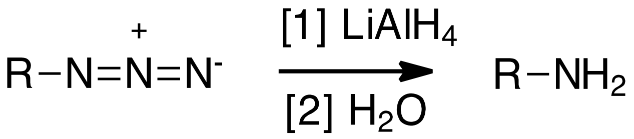
Nitriles are reduced to 1° amines with $LiAlH_4$.



$$R{-}C{\equiv}N \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} R{-}CH_2NH_2$$

1° amine

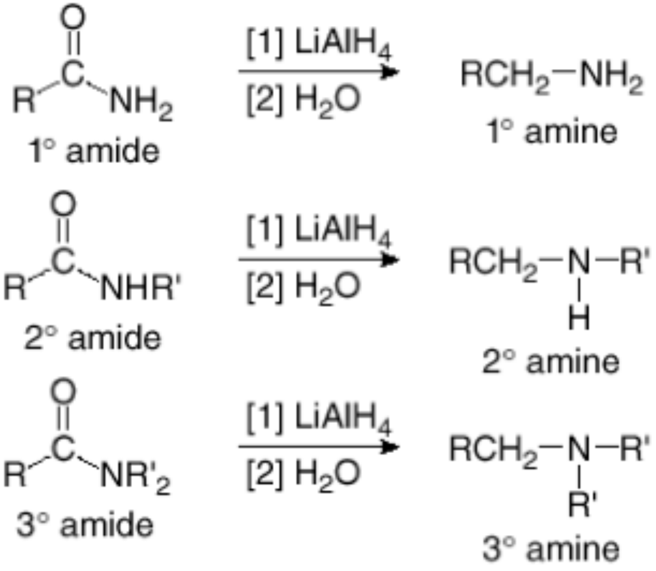
Azides are reduced to 1° amines with $LiAlH_4$



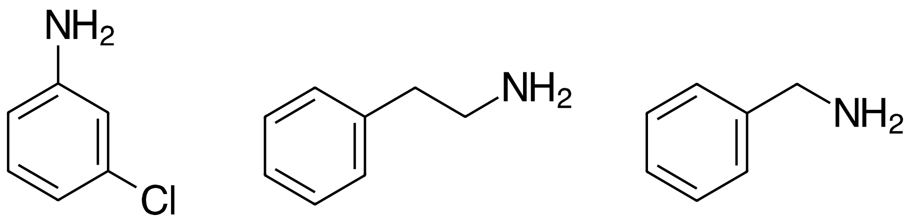
$$R{-}N{=}\overset{+}{N}{=}N^{-} \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} R{-}NH_2$$

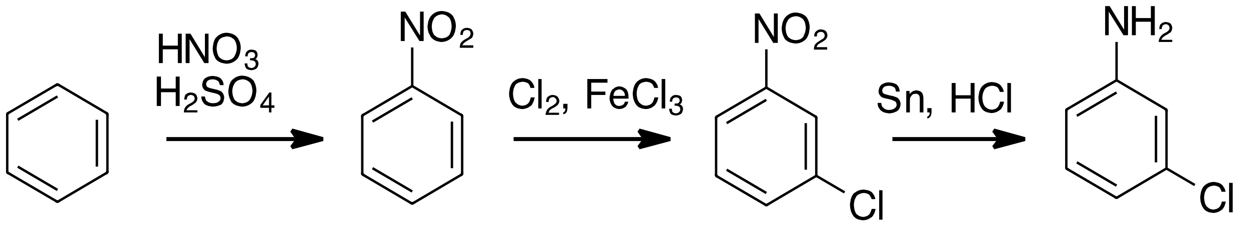
Preparation of Amines—Reduction of N-Containing Functional Groups

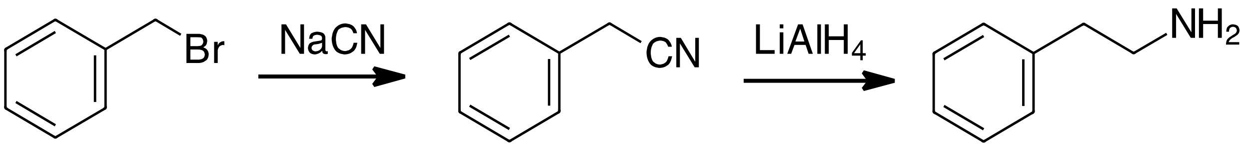
Primary (1°), 2°, and 3° amides are reduced to 1°, 2°, and 3° amines, respectively, by using $LiAlH_4$.

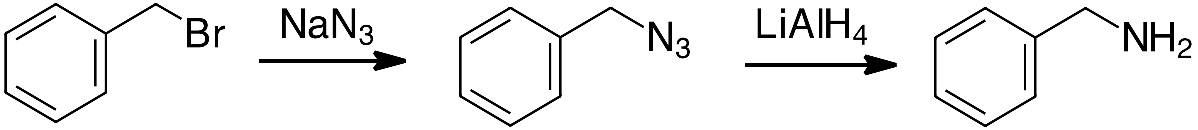


Preparation of Amines—Reduction of N-Containing Functional Groups



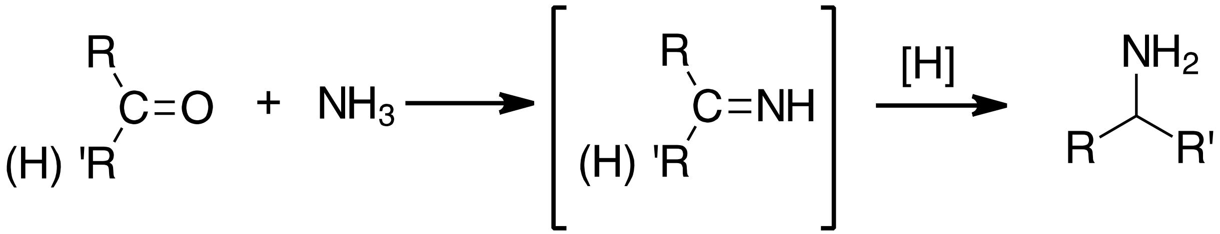


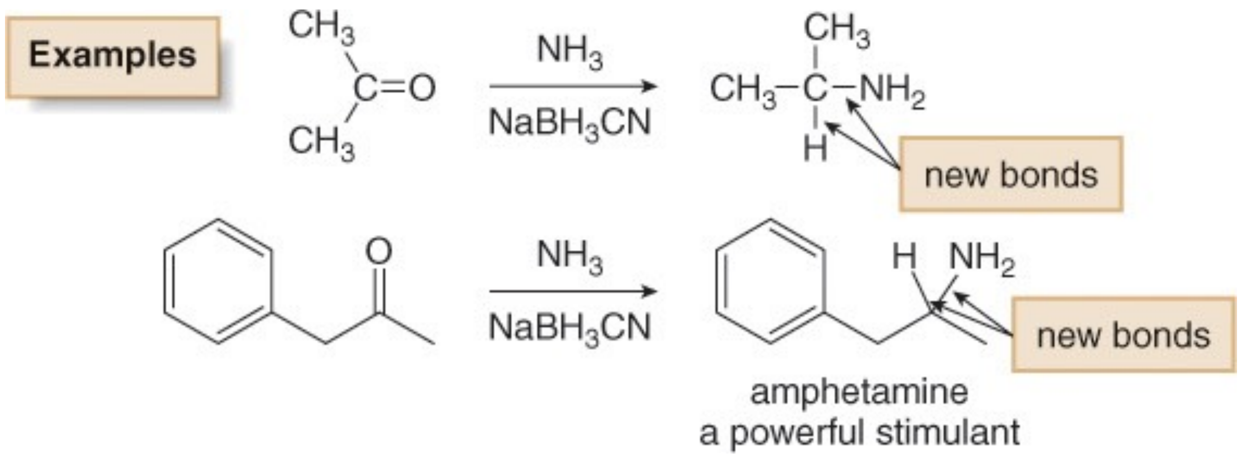




Preparation of Amines—Reductive Amination

Reductive amination is a two-step method that converts aldehydes and ketones into 1ry, 2ry, and 3ry amines.

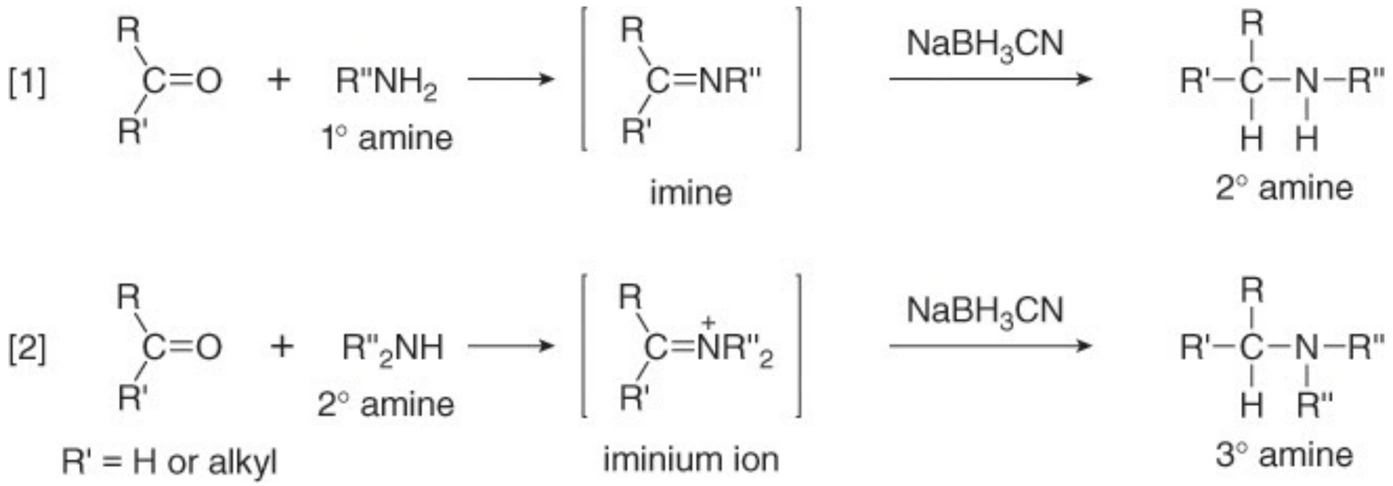




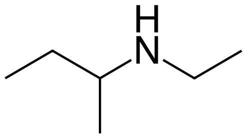
amphetamine
a powerful stimulant

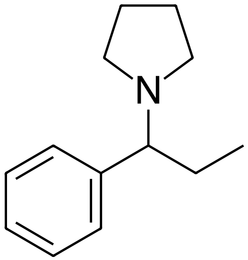
Preparation of Amines—Reductive Amination

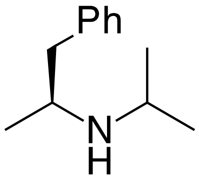
With a 1ry or 2ry amine as starting material, reductive amination is used to prepare 2ry and 3ry amines respectively.



Preparation of Amines—Reductive Amination



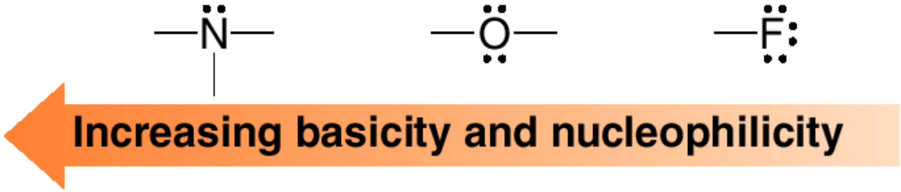




Reactions of Amines—General Features

- The chemistry of amines is dominated by the lone pair of electrons on nitrogen.

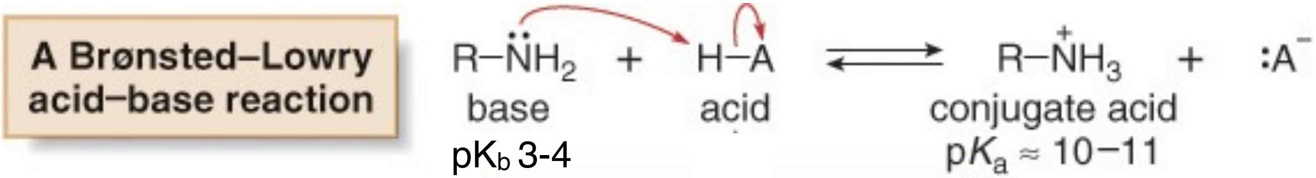
- Only three elements in the second row of the periodic table have nonbonded electron pairs in neutral organic compounds: nitrogen, oxygen and fluorine. Because basicity and nucleophilicity decrease across a row, nitrogen is the most basic and the most nucleophilic.

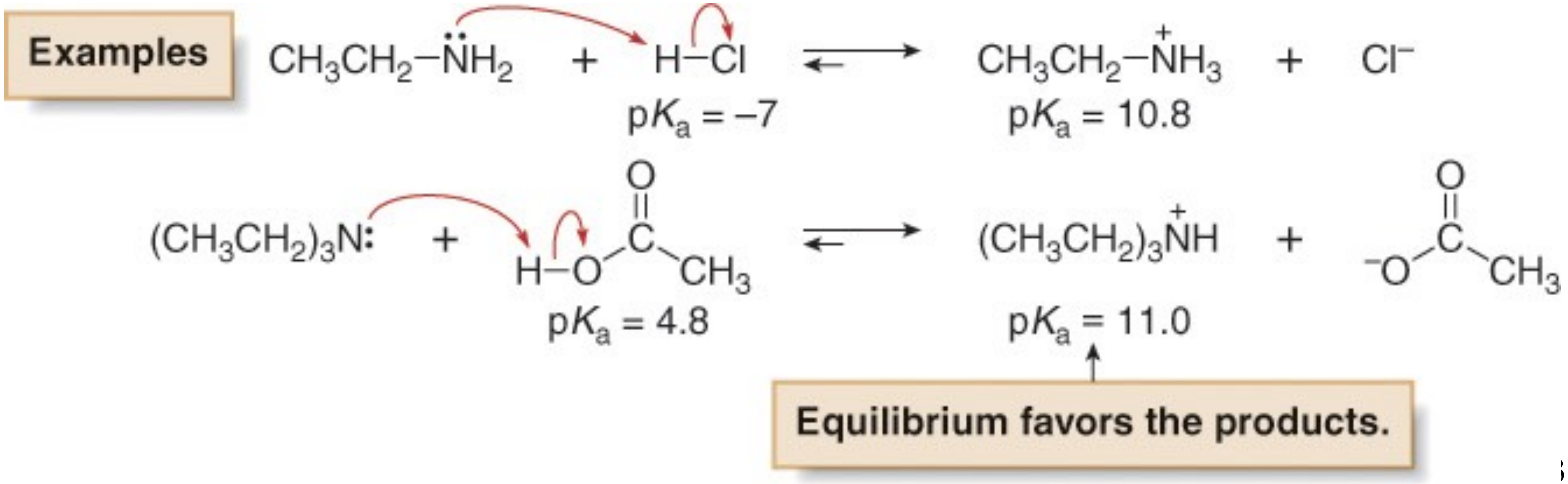


- Amines are stronger bases and nucleophiles than other neutral organic compounds.

Amines as Bases

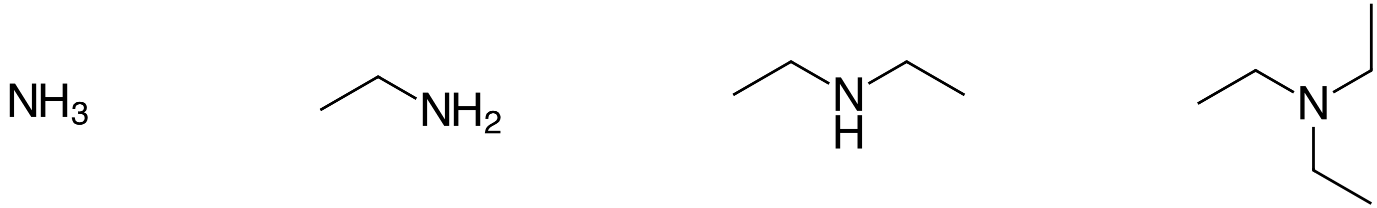
Amines react with a variety of organic and inorganic acids.





Structural Effects on Amine Basicity
1. Inductive Effects

1°, 2°, and 3° alkylamines are more basic than NH_3 because of the electron-donating inductive effect of the R groups.



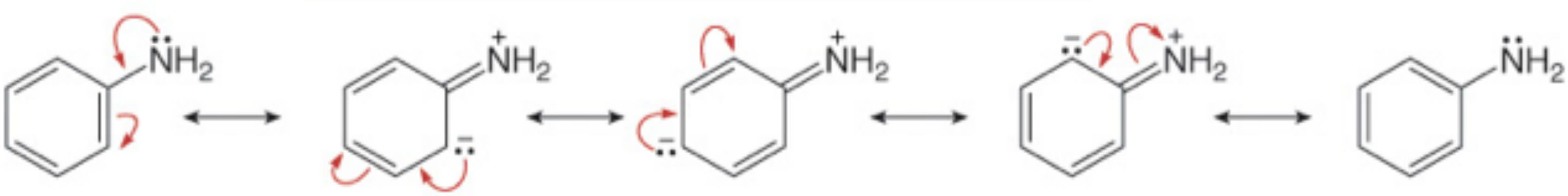
pKa (conjugate acid)	9.3	10.8	11.1	11.0

Amines as Bases

Arylamines are less basic than alkylamines because the electron pair on N is delocalized.

The electron pair is localized on the N atom.

$CH_3CH_2NH_3^+$: pK_a 10.8

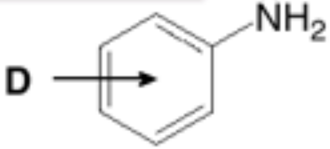


The electron pair is delocalized on the benzene ring.

$C_6H_5NH_3^+$: pK_a 4.6

Substituted Anilines

D = electron-donor group

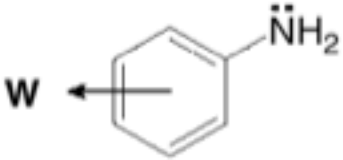


D makes the amine more basic than aniline.

D

- $-NH_2$
- $-OH$
- $-OR$
- $-NHCOR$
- $-R$

W = electron-withdrawing group



W makes the amine less basic than aniline.

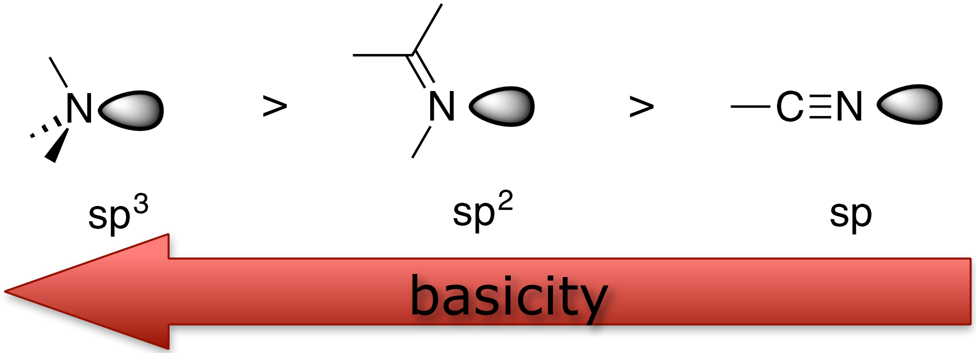
W

- $-X$
- $-CHO$
- $-COR$
- $-COOR$
- $-COOH$
- $-CN$
- $-SO_3H$
- $-NO_2$
- $-NR_3^+$

Amides, Imines, Nitriles

Amides are much less basic than amines because the election pair o
N is delocalised

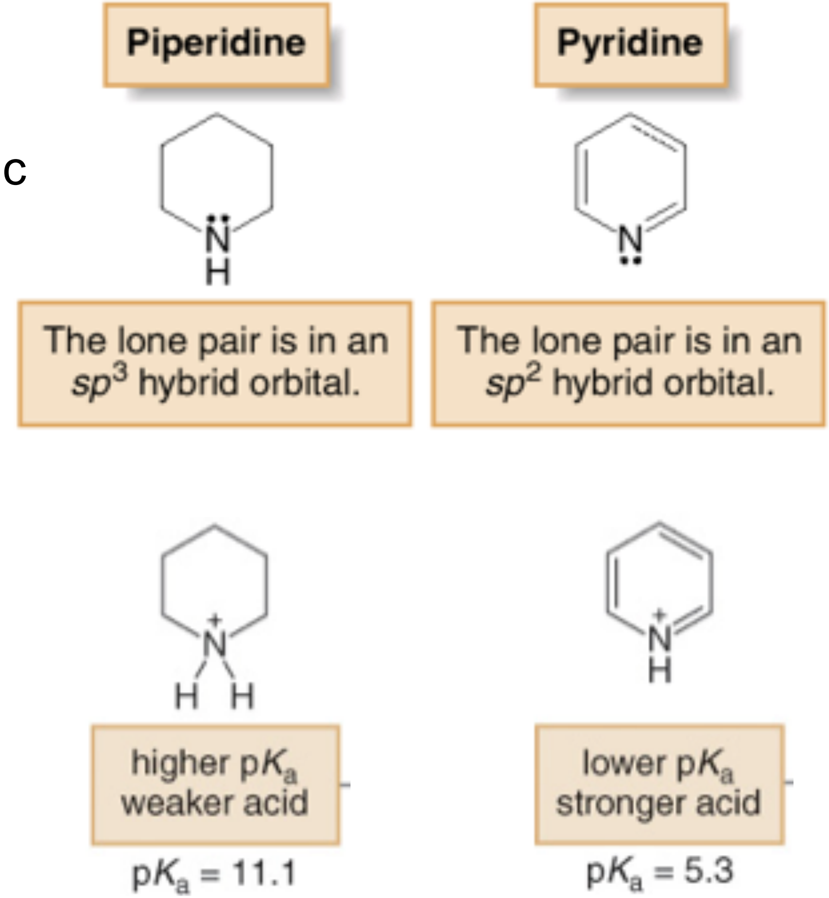
Imines and nitriles are less basic than amines because the election pair on N is in an sp² and sp orbital, respectively.



sp^3 orbitals are farther from the nucleus and therefore more available; sp orbitals are nearer to the nucleus and therefore less available.

Heterocyclic Amines

1. Hybridization



more basic

Piperidine

The lone pair is in an sp^3 hybrid orbital.

higher pK_a
weaker acid

$pK_a = 11.1$

less basic

Pyridine

The lone pair is in an sp^2 hybrid orbital.

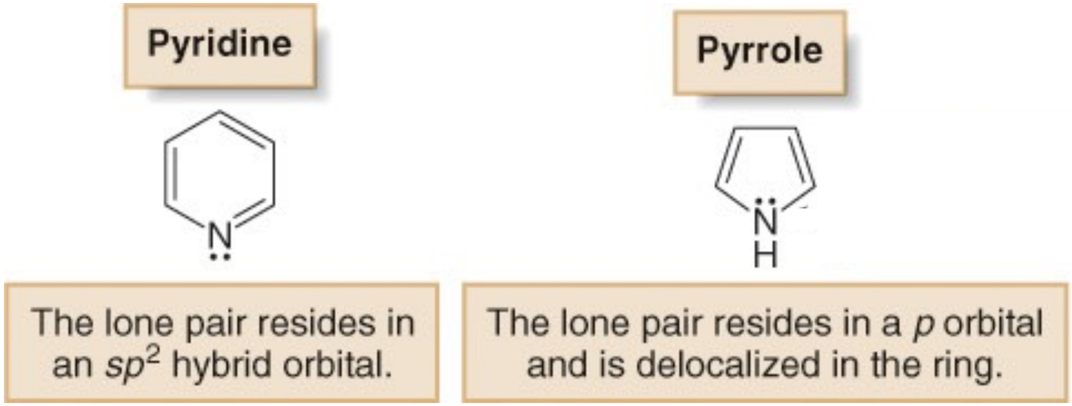
lower pK_a
stronger acid

$pK_a = 5.3$

- **The higher the percent *s*-character of the orbital containing the lone pair, the more tightly the lone pair is held, and the weaker the base.**

Heterocyclic Amines

2. Aromaticity

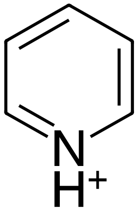


Pyridine

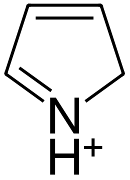
The lone pair resides in an sp^2 hybrid orbital.

Pyrrole

The lone pair resides in a *p* orbital and is delocalized in the ring.



pK_a 5.3



pK_a 0.4

- Pyrrole is much less basic than pyridine because its lone pair of electrons is part of the aromatic π system.

Amines as Bases

Table 25.2 Factors That Determine Amine Basicity

	Factor	Example
[1]	**Inductive effects:** Electron-donating groups bonded to N increase basicity.	• RNH_2, R_2NH, and R_3N are more basic than NH_3.
[2]	**Resonance effects:** Delocalizing the lone pair on N decreases basicity.	• Arylamines ($C_6H_5NH_2$) are less basic than alkylamines (RNH_2). • Amides ($RCONH_2$) are much less basic than amines (RNH_2).
[3]	**Aromaticity:** Having the lone pair on N as part of the aromatic π system decreases basicity.	• Pyrrole is less basic than pyridine. 
[4]	**Hybridization effects:** Increasing the percent *s*-character in the orbital with the lone pair decreases basicity.	• Pyridine is less basic than piperidine. 

Amines as Bases

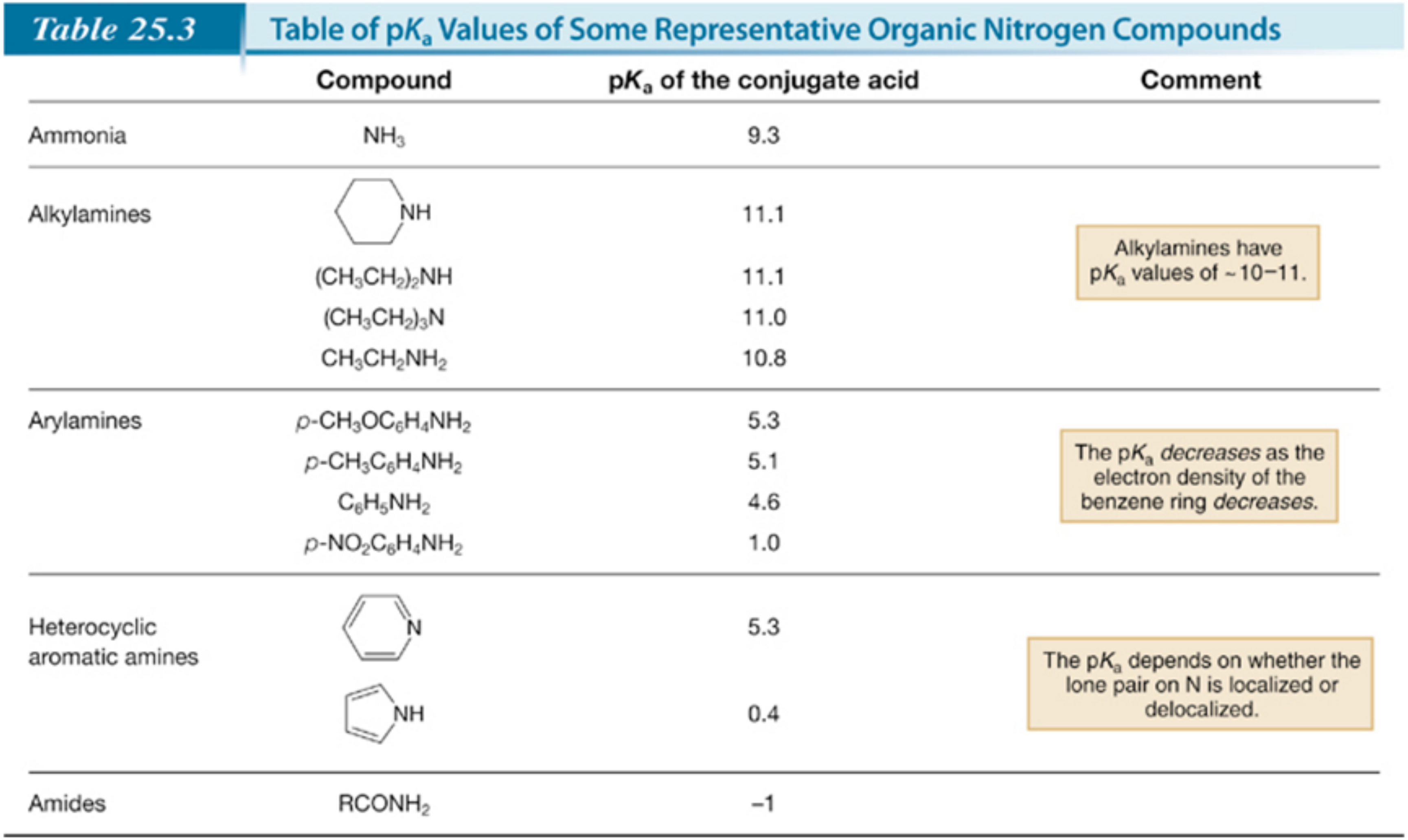
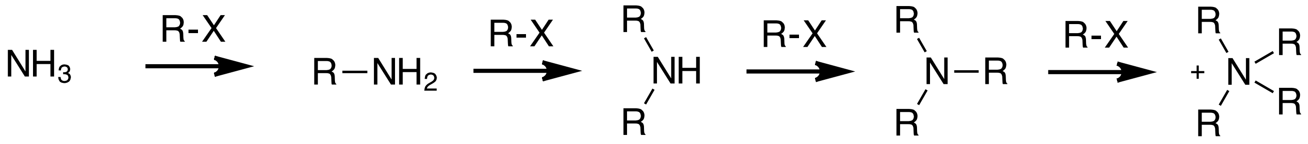


Table 25.3 Table of pK_a Values of Some Representative Organic Nitrogen Compounds

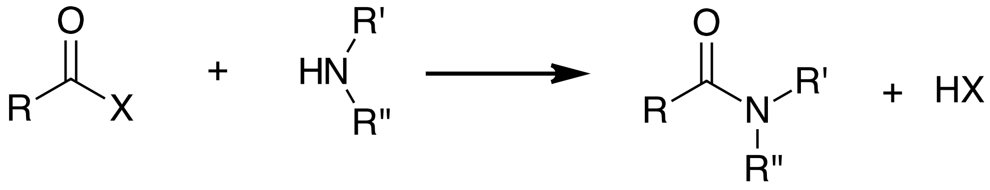
	Compound	pK_a of the conjugate acid	Comment
Ammonia	NH_3	9.3	
Alkylamines		11.1	Alkylamines have pK_a values of ~10–11.
	$(CH_3CH_2)_2NH$	11.1	
	$(CH_3CH_2)_3N$	11.0	
	$CH_3CH_2NH_2$	10.8	
Arylamines	*p*-$CH_3OC_6H_4NH_2$	5.3	The pK_a *decreases* as the electron density of the benzene ring *decreases.*
	p-$CH_3C_6H_4NH_2$	5.1	
	$C_6H_5NH_2$	4.6	
	p-$NO_2C_6H_4NH_2$	1.0	
Heterocyclic aromatic amines		5.3	The pK_a depends on whether the lone pair on N is localized or delocalized.
		0.4	
Amides	$RCONH_2$	–1	

Amines as Nucleophiles

alkylation (any amine):



acylation:



X = Cl, OCOR, NH$_3$, 1^{ry}, 2^{ry} 1^{ry}, 2^{ry}, 3^{ry}

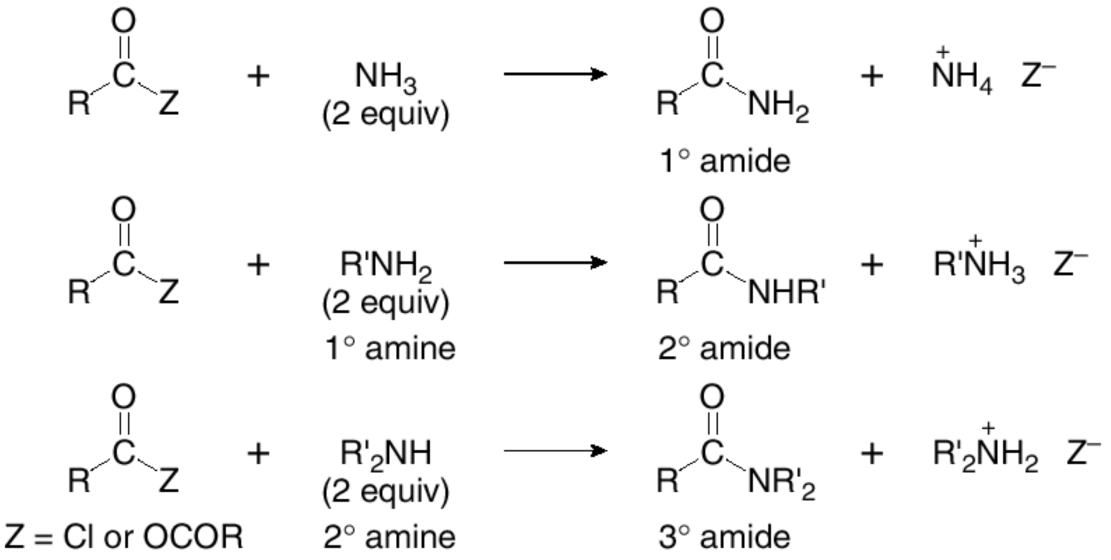
OR′, OH

condensation with aldehydes and ketones:

NH$_3$, 1^{ry} 2^{ry}

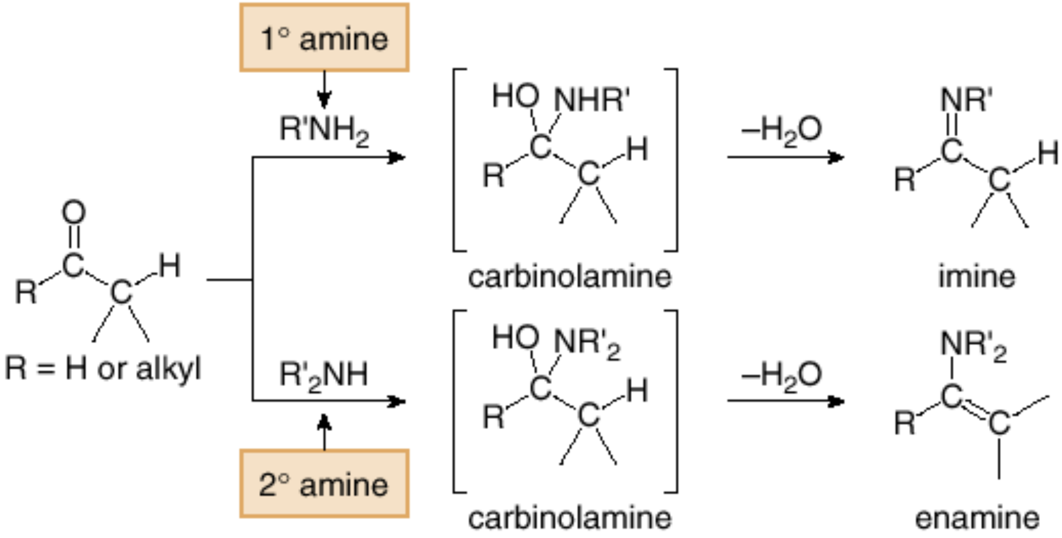
Amines as Nucleophiles. Acylation

Acid chlorides and anhydrides react with NH_3, 1° amines, and 2° amines to form **1°, 2°, and 3° amides,** respectively. These reactions involve attack of the nitrogen nucleophile on the carbonyl group followed by elimination of a leaving group (Cl^- or $RCOO^-$). The overall result of this reaction is substitution of the leaving group by the nitrogen nucleophile.



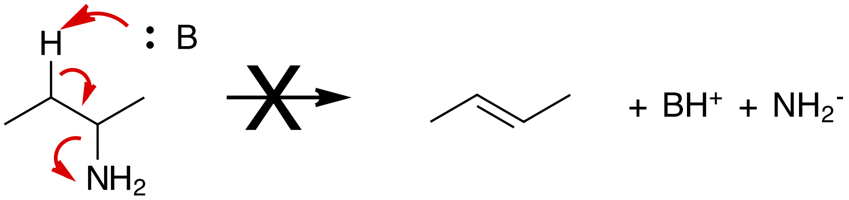
Amines as Nucleophiles. Reaction with Aldehydes and Ketones

Aldehydes and ketones react with 1° amines to form **imines** and with 2° amines to form **enamines.** Both reactions involve nucleophilic addition of the amine to the carbonyl group to form a carbinolamine, which then loses water to form the final product.

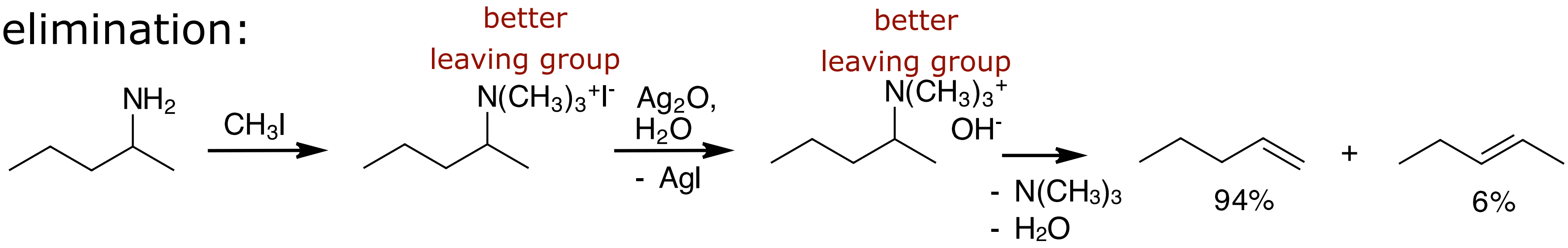


Amine as Leaving Group

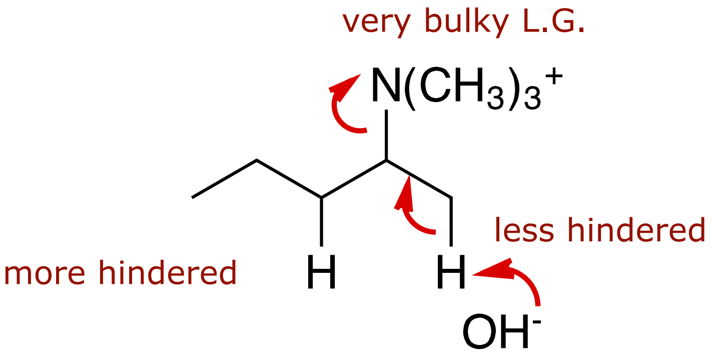
NH_2^- is not a good leaving group



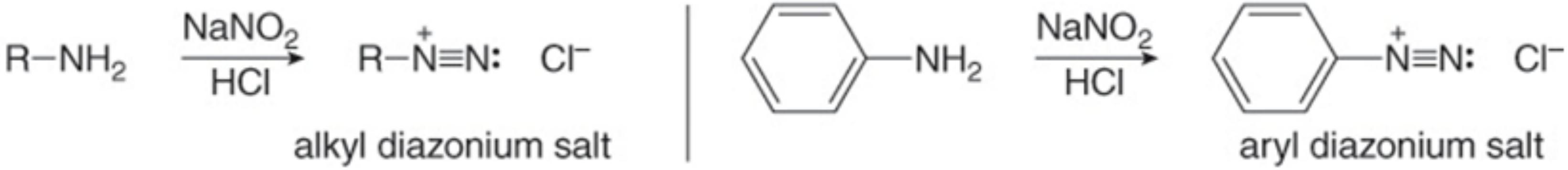
Hoffman elimination:



E2 mechanism:

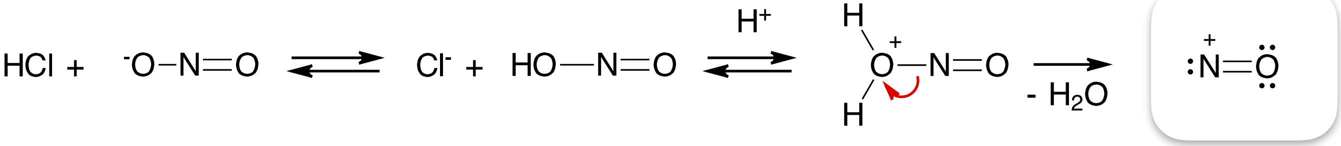


Reaction of Amines with Nitrous Acid



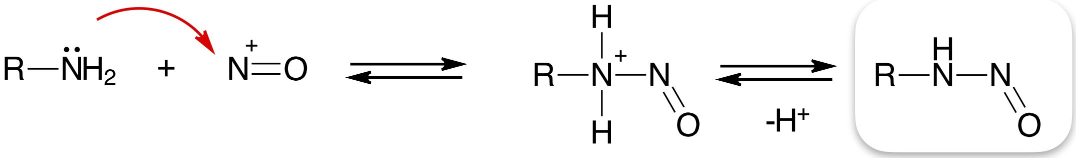
Reaction of Amines with Nitrous Acid

1. generation of the electrophile



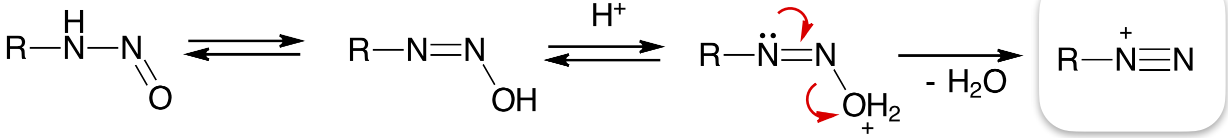
nitrosonium ion

2. nitrosation



N-nitrosamine

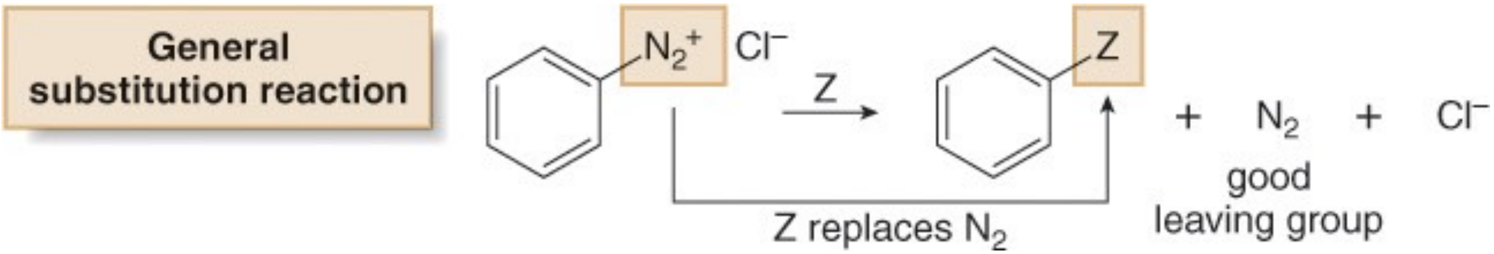
3. acid-catalysed elimination



diazonium ion

Substitution Reactions of Aryl Diazonium Salts

- Aryl diazonium salts react with a variety of reagents to form products in which a nucleophile Z replaces N_2, a very good leaving group.
- The mechanism of these reactions varies with the identity of Z.



Substitution Reactions of Aryl Diazonium Salts

Reactions often take place in the presence of Cu(I) salts (Sandmayer reaction)