

Organic Chemistry II / CHEM 252

Chapter 20 – Amines

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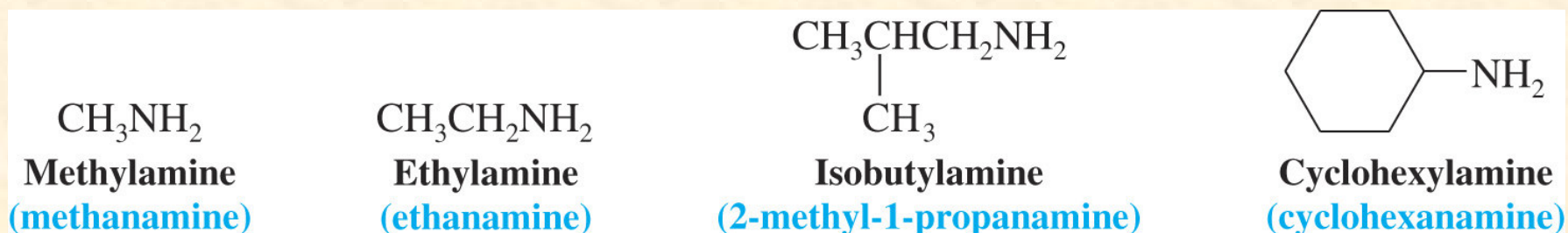
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Boston, MA

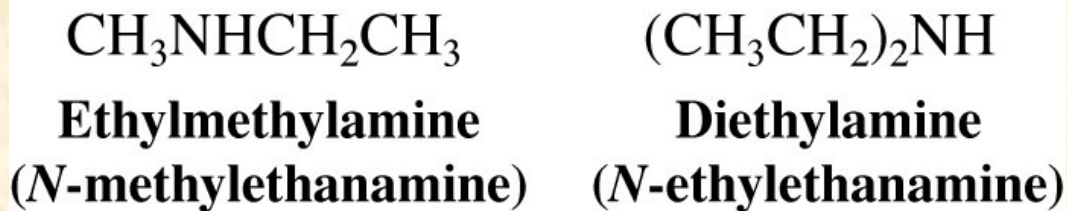
Nomenclature

- Nomenclature

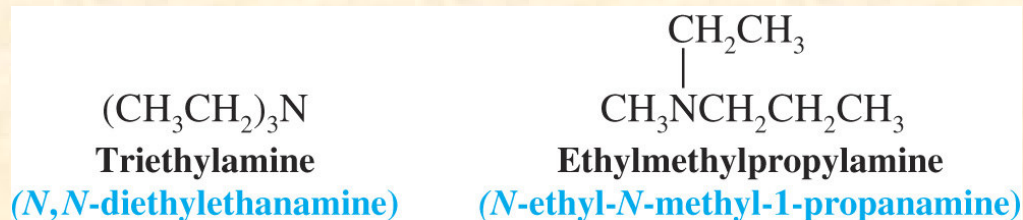
- Primary amines* are named in systematic (IUPAC) nomenclature by replacing the *-e* of the corresponding parent alkane with *-amine*
- In common nomenclature they are named as alkylamines



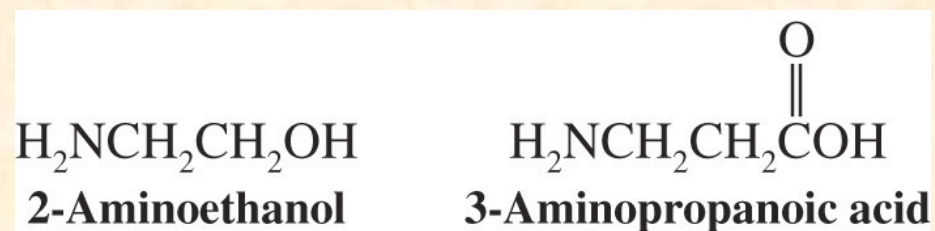
- Simple secondary and tertiary amines* are named in common nomenclature by designating the organic groups separately in front of the word *amine*
- In systematic nomenclature, the smaller groups on the amine nitrogen are designated as substituents and given the locant *N*



Nomenclature

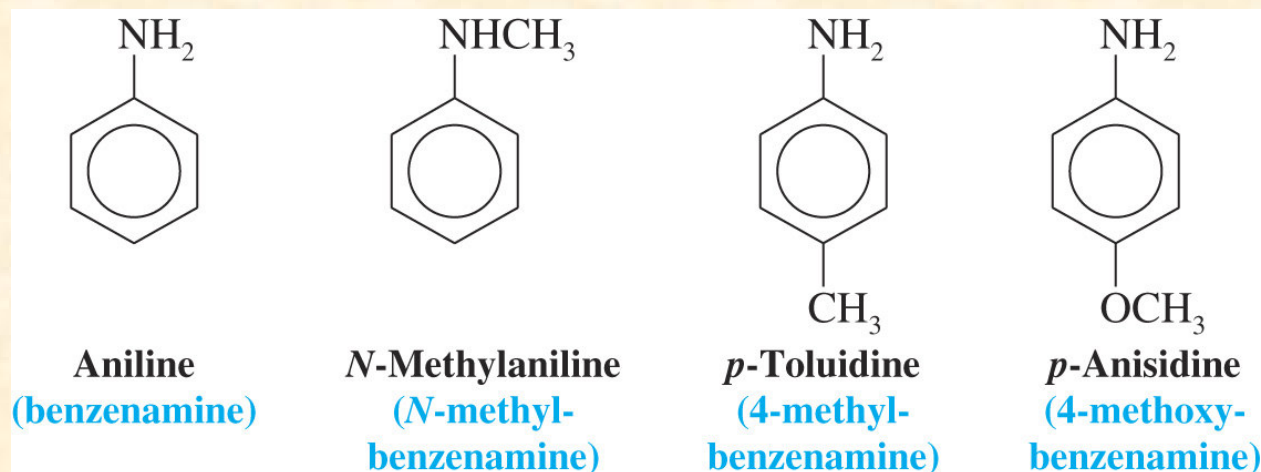


- In IUPAC nomenclature the substituent $-\text{NH}_2$ is called the *amino* group



– Aryl Amines

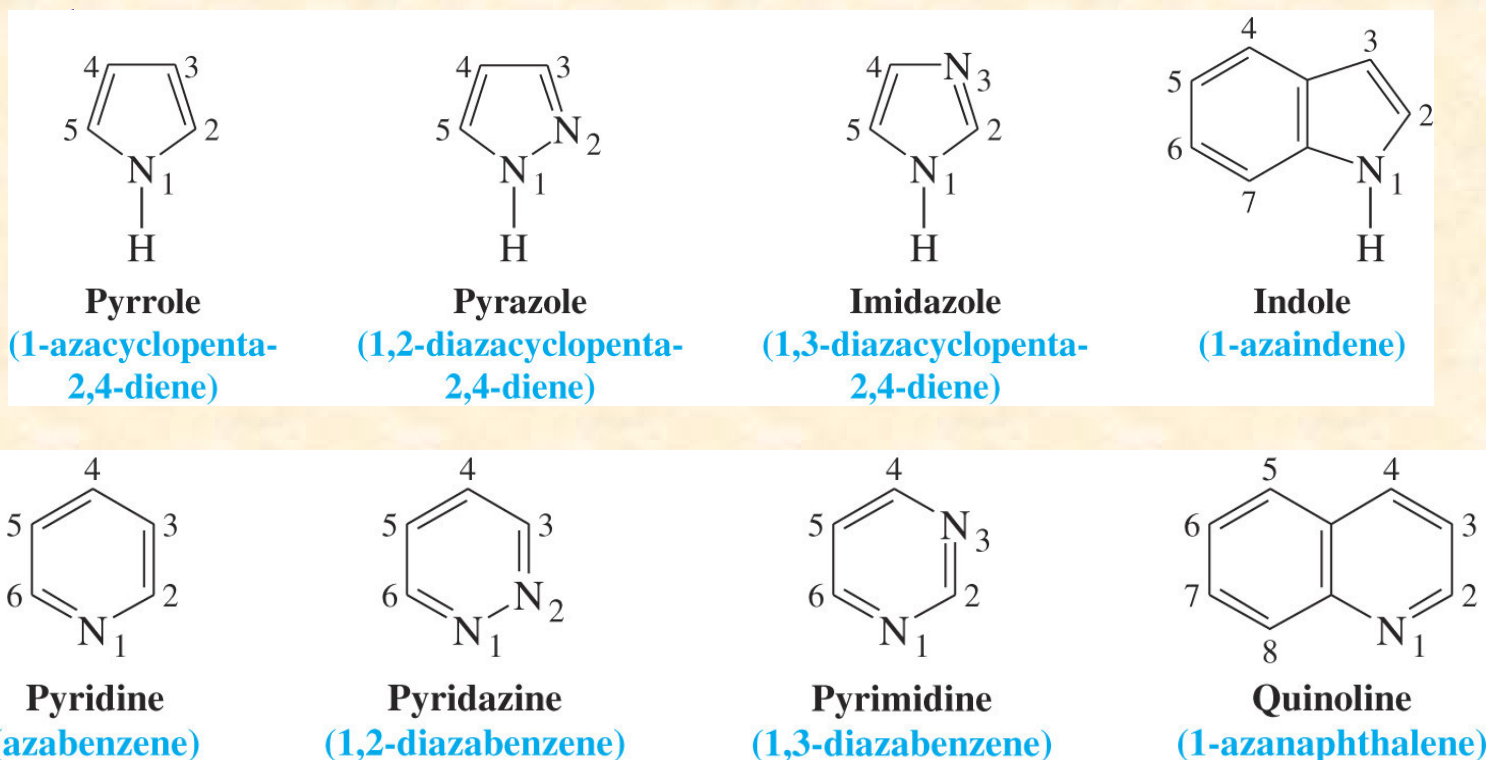
- The common arylamines have the following names:



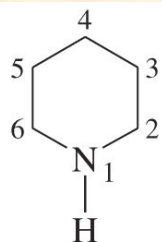
Nomenclature

– Heterocyclic Amines

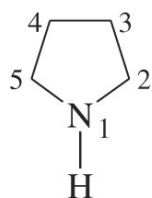
- The important heterocyclic amines have common names
- In IUPAC nomenclature the prefixes *aza-*, *diaza-* and *triaz-* are used to indicate that nitrogen has replaced carbon in the corresponding hydrocarbon
 - The nitrogen is assigned position 1 and the ring is numbered to give the lowest overall set of locants to the



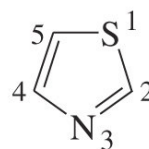
Nomenclature



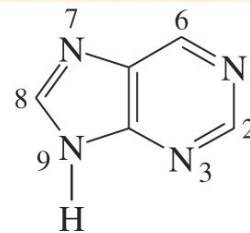
Piperidine
(azacyclohexane)



Pyrrolidine
(azacyclopentane)



Thiazole
(1-thia-3-
azacyclopenta-
2,4-diene)



Purine

Physical Properties



Physical Properties and Structure of Amines

- Primary and secondary amines can form hydrogen bonds to each other and water
- Tertiary amines cannot form hydrogen bonds to each other but can form hydrogen bonds to hydrogen bond donors such as water
- Tertiary amines have lower boiling points than primary or secondary amines of comparable molecular weights
- Low molecular weight amines tend to be water soluble whether they are primary, secondary or tertiary

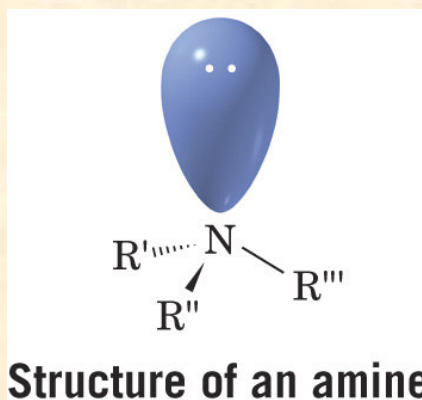
Physical Properties



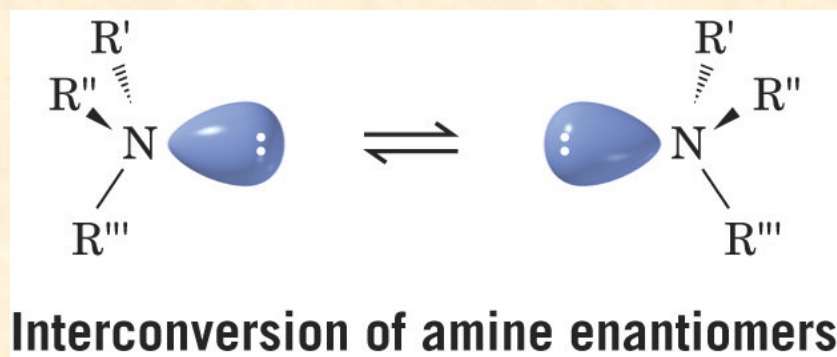
Name	Structure	mp (°C)	bp (°C)	Water Solubility (25°C) (g 100 mL ⁻¹)	pK _a (aminium ion)
Primary Amines					
Methylamine	CH ₃ NH ₂	-94	-6	Very soluble	10.64
Ethylamine	CH ₃ CH ₂ NH ₂	-81	17	Very soluble	10.75
Propylamine	CH ₃ CH ₂ CH ₂ NH ₂	-83	49	Very soluble	10.67
Isopropylamine	(CH ₃) ₂ CHNH ₂	-101	33	Very soluble	10.73
Butylamine	CH ₃ (CH ₂) ₂ CH ₂ NH ₂	-51	78	Very soluble	10.61
Isobutylamine	(CH ₃) ₂ CHCH ₂ NH ₂	-86	68	Very soluble	10.49
<i>sec</i> -Butylamine	CH ₃ CH ₂ CH(CH ₃)NH ₂	-104	63	Very soluble	10.56
<i>tert</i> -Butylamine	(CH ₃) ₃ CNH ₂	-68	45	Very soluble	10.45
Cyclohexylamine	Cyclo-C ₆ H ₁₁ NH ₂	-18	134	Slightly soluble	10.64
Benzylamine	C ₆ H ₅ CH ₂ NH ₂	10	185	Slightly soluble	9.30
Aniline	C ₆ H ₅ NH ₂	-6	184	3.7	4.58
<i>p</i> -Toluidine	<i>p</i> -CH ₃ C ₆ H ₄ NH ₂	44	200	Slightly soluble	5.08
<i>p</i> -Anisidine	<i>p</i> -CH ₃ OC ₆ H ₄ NH ₂	57	244	Very slightly soluble	5.30
<i>p</i> -Chloroaniline	<i>p</i> -ClC ₆ H ₄ NH ₂	73	232	Insoluble	4.00
<i>p</i> -Nitroaniline	<i>p</i> -NO ₂ C ₆ H ₄ NH ₂	148	332	Insoluble	1.00
Secondary Amines					
Dimethylamine	(CH ₃) ₂ NH	-92	7	Very soluble	10.72
Diethylamine	(CH ₃ CH ₂) ₂ NH	-48	56	Very soluble	10.98
Dipropylamine	(CH ₃ CH ₂ CH ₂) ₂ NH	-40	110	Very soluble	10.98
<i>N</i> -Methylaniline	C ₆ H ₅ NHCH ₃	-57	196	Slightly soluble	4.70
Diphenylamine	(C ₆ H ₅) ₂ NH	53	302	Insoluble	0.80
Tertiary Amines					
Trimethylamine	(CH ₃) ₃ N	-117	2.9	Very soluble	9.70
Triethylamine	(CH ₃ CH ₂) ₃ N	-115	90	14	10.76
Tripropylamine	(CH ₃ CH ₂ CH ₂) ₃ N	-93	156	Slightly soluble	10.64
<i>N,N</i> -Dimethylaniline	C ₆ H ₅ N(CH ₃) ₂	3	194	Slightly soluble	5.06

Structure

- Structure of Amines
 - The nitrogen atom in an amine is sp^3 hybridized - *tetrahedral* geometry
 - only the groups - *trigonal pyramidal*

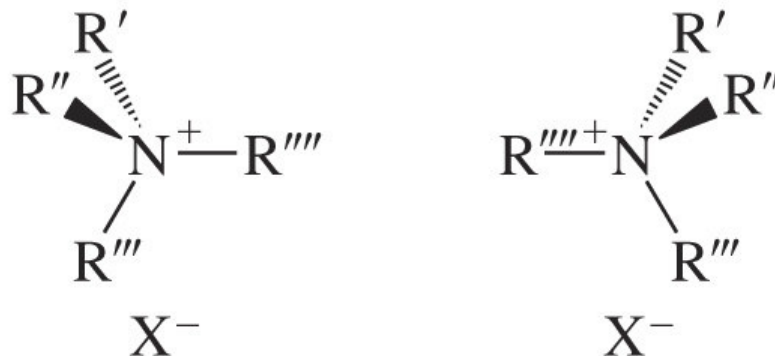


- It is usually impossible to resolve amine enantiomers that are chiral at nitrogen because they interconvert rapidly
 - The interconversion occurs through a *pyramidal* or *nitrogen inversion* involving the unshared electron pair



Structure

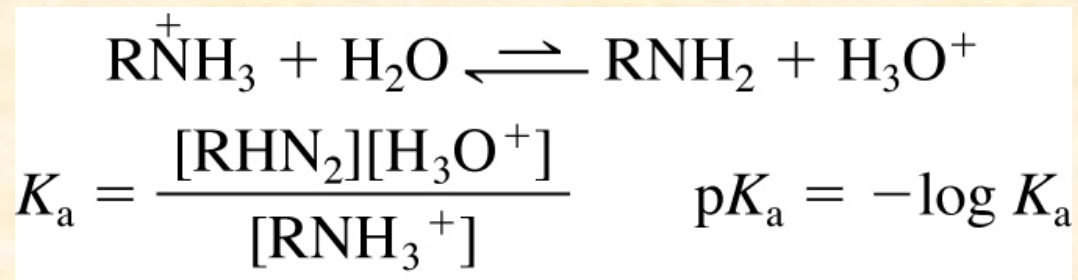
- Quaternary ammonium salts can be resolved into enantiomers
 - Chiral quaternary ammonium salts cannot undergo nitrogen inversion because they lack an unshared electron pair on the nitrogen atom



**Quaternary ammonium salts such as these
can be resolved.**

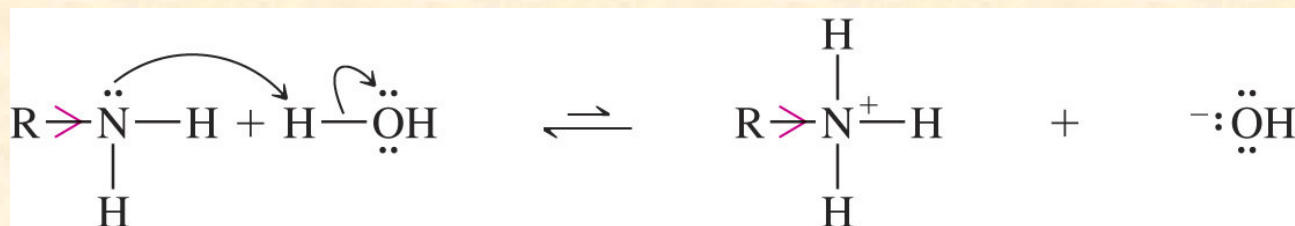
Basicity

- Amines are weak bases
- Relative basicity of amines can be compared in terms of pK_a values for their respective conjugate acids
 - The more basic the amine, the higher the pK_a of its conjugate acid will be



- Primary alkyl amines are more basic than ammonia
 - An alkyl group helps to stabilize the alkylaminium ion

	$\ddot{\text{N}}\text{H}_3$	$\text{CH}_3\ddot{\text{N}}\text{H}_2$	$\text{CH}_3\text{CH}_2\ddot{\text{N}}\text{H}_2$	$\text{CH}_3\text{CH}_2\text{CH}_2\ddot{\text{N}}\text{H}_2$
Conjugate acid pK_a	9.26	10.64	10.75	10.67



By releasing electrons, $\text{R} \rightarrow$ stabilizes the alkylaminium ion through dispersal of charge.

Basicity



- gas phase : basicity increases with increasing methyl substitution



- aqueous solution: trimethylamine is less basic than dimethyl- or methylamine
 - An alkylammonium ion in water is solvated and stabilized by hydrogen bonding of its hydrogens with water
 - The trimethylammonium ion has only one hydrogen with which to hydrogen bond to water
 - The trimethylammonium ion is solvated less well (and therefore stabilized less) than the dimethylammonium ion, which has two hydrogen atoms for hydrogen bonding

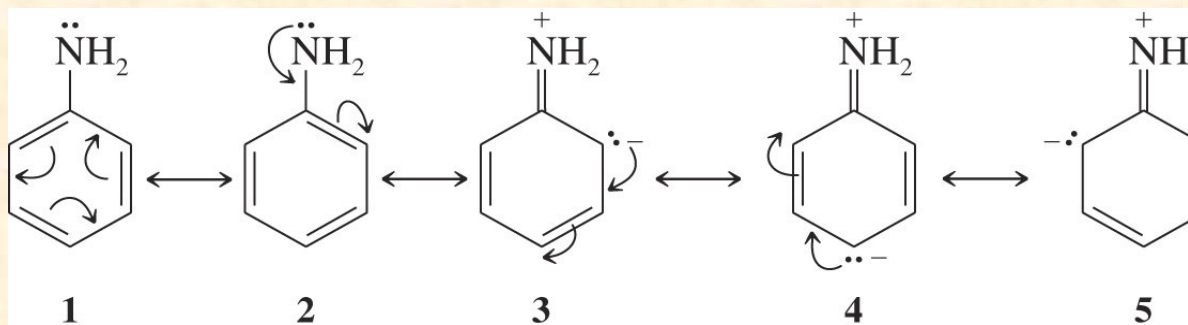


Basicity

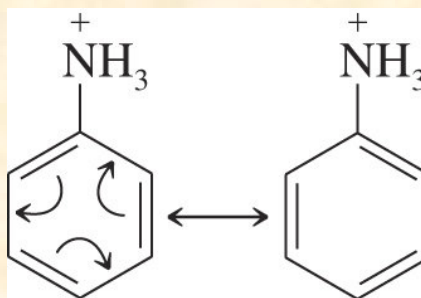
- Arylamines are weaker bases than nonaromatic cyclohexylamines

	Cyclo-C ₆ H ₁₁ NH ₂	C ₆ H ₅ NH ₂	<i>p</i> -CH ₃ C ₆ H ₄ NH ₂
Conjugate acid p <i>K</i> _a	10.64	4.58	5.08

- The unshared electron pair is *delocalized* to the ring
 - The lone pair is less available for protonation, *i.e.*, it is less basic



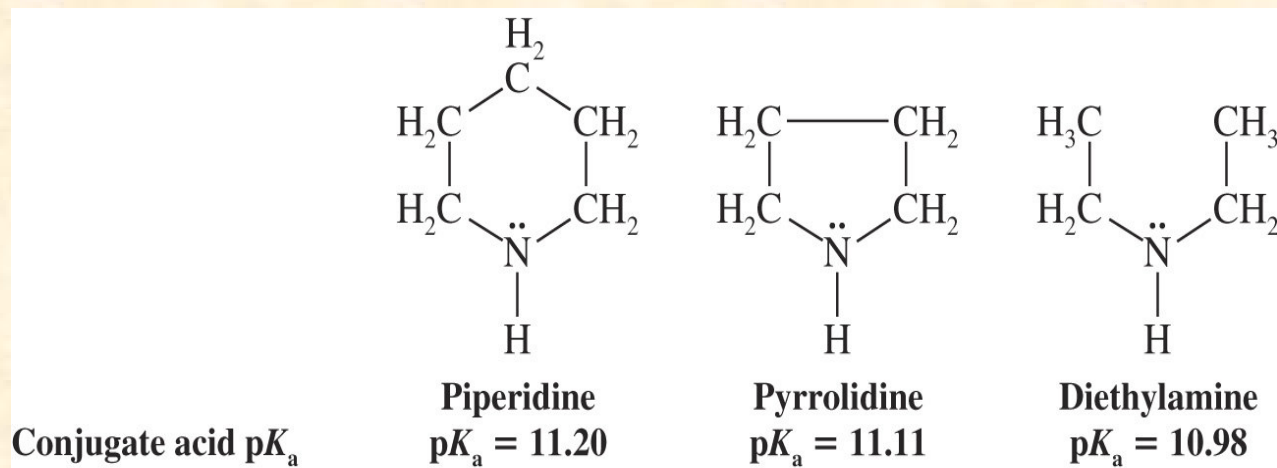
- Protonation of aniline is also disfavored because a protonated arylamine has only two resonance forms
 - Anilinium ion is not as well stabilized by resonance as aniline itself



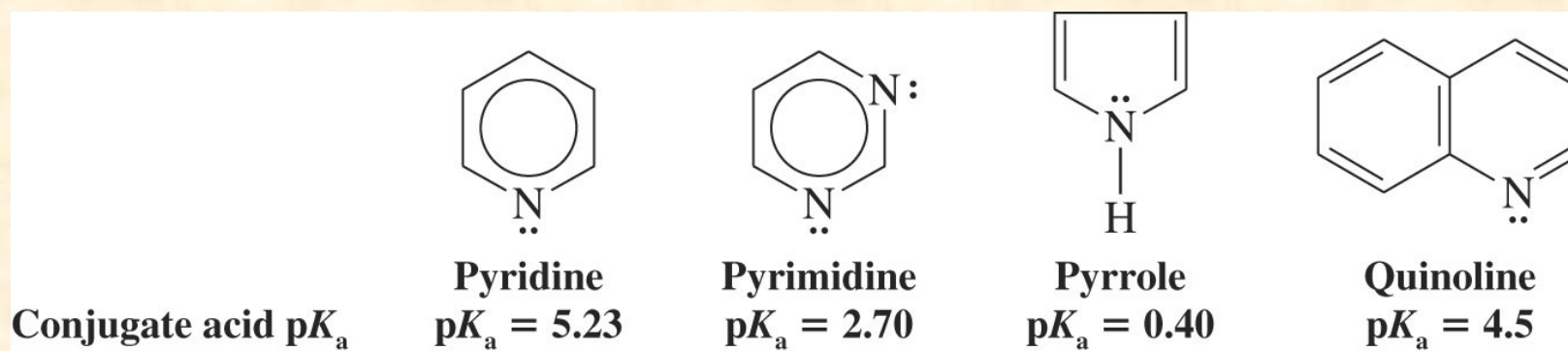
Basicity

– Basicity of Heterocyclic Amines

- Nonaromatic heterocyclic amines have approximately the same basicity as their acyclic counterparts



- Aromatic heterocyclic amines (in aqueous solution) are much weaker bases than nonaromatic amines

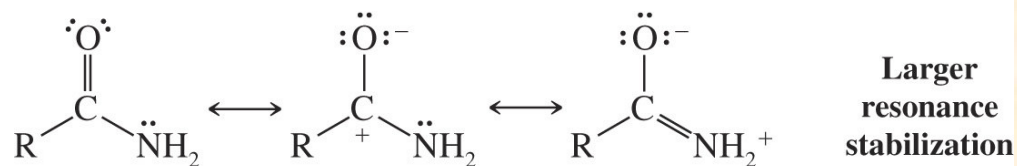


Basicity

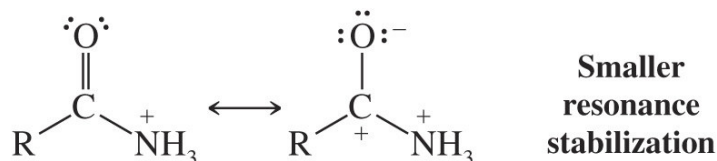
– Amines versus Amides

- Amides are much less basic than amines
 - The pK_a of a protonated amide is typically about zero
- One reason for this much lower basicity is that the amide is greatly stabilized by resonance but the protonated amide is not

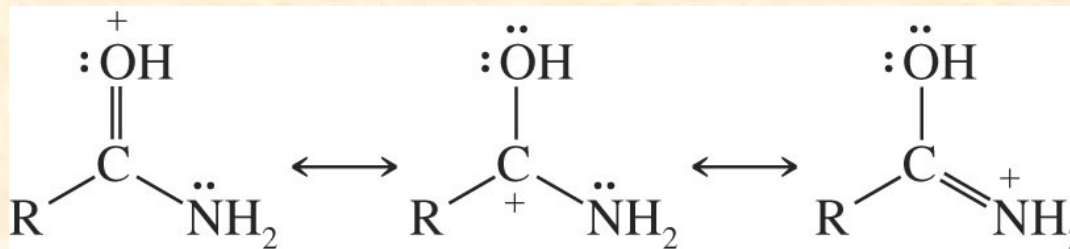
Amide



N-Protonated Amide



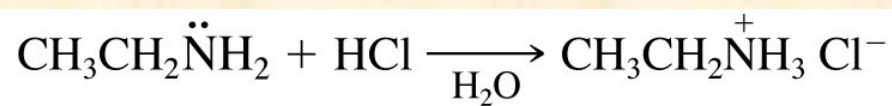
- A more important reason for the weaker basicity of amides is that the nitrogen lone pair is delocalized, amides are protonated at the oxygen
 - Protonation at the oxygen allows resonance stabilization of the positive charge



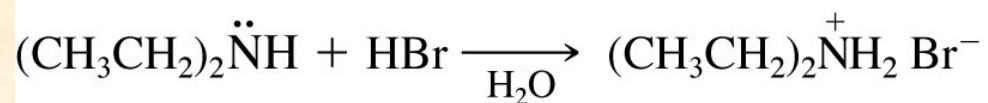
Salts

– Aminium Salts and Quaternary Ammonium Salts

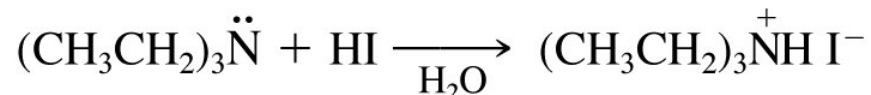
- Protonation of amines with acids leads to formation of aminium salts
 - Aminium salts are formed from 1°, 2° or 3° amines and the aminium ion bears at least one hydrogen



Ethylaminium chloride
(an aminium salt)

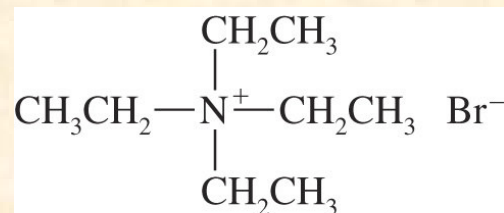


Diethylaminium bromide



Triethylaminium iodide

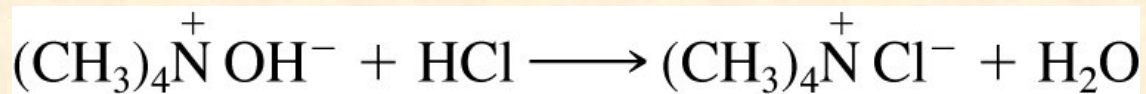
- Quaternary ammonium salts have four groups on the nitrogen
 - The nitrogen atom is positively charged *but does not bear a hydrogen atom*



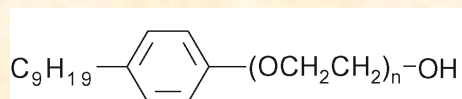
Tetraethylammonium bromide
(a quaternary ammonium salt)

Salts

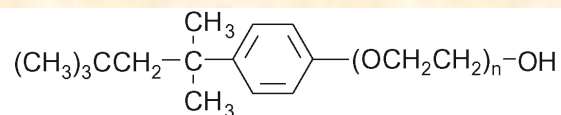
- Quaternary ammonium halides are not basic because they do not have an unshared electron pair on nitrogen
- Quaternary ammonium hydroxides are very basic because they contain the very strong base hydroxide



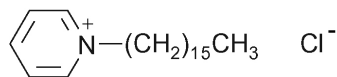
$(\text{CH}_3\text{CH}_2)_4\text{N}^+\text{Br}^-$
Tetraethylammonium bromide
 (does not undergo reaction with acid)



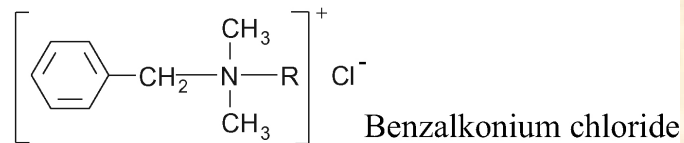
Nonoxynol-9 (spermaticide)



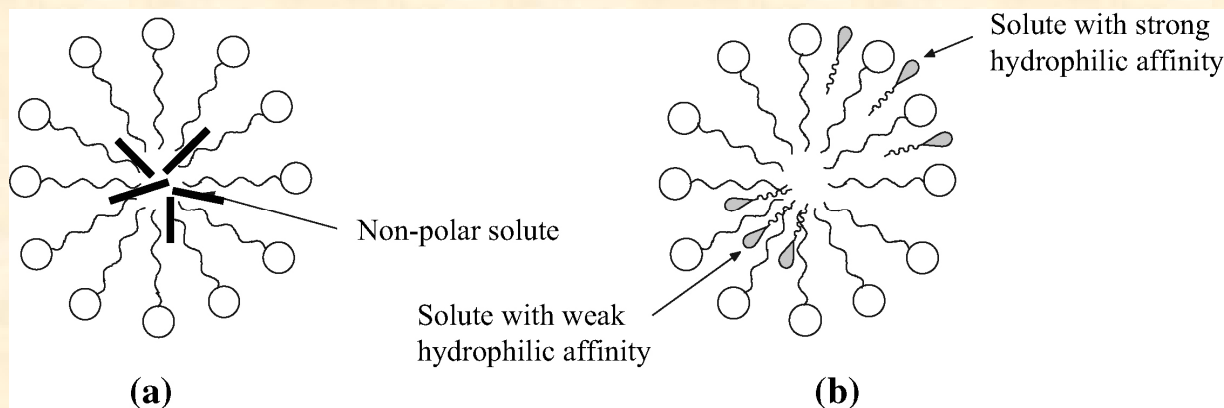
Octoxynol-9 (spermaticide)



Cetylpyridinium chloride
(disinfectant)



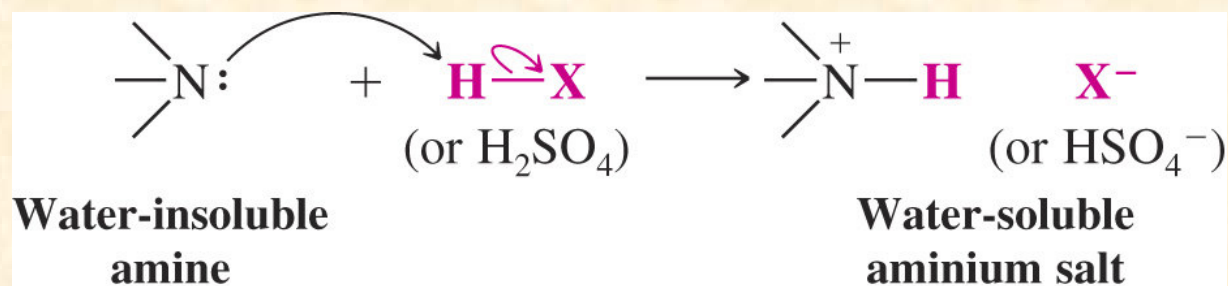
Benzalkonium chloride
(antiseptic)



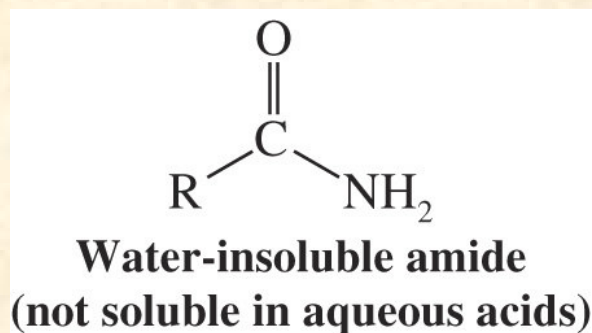
Basicity

– Solubility of Amines in Aqueous Acid

- Many aminium chlorides, bromides, iodides and sulfates are water soluble



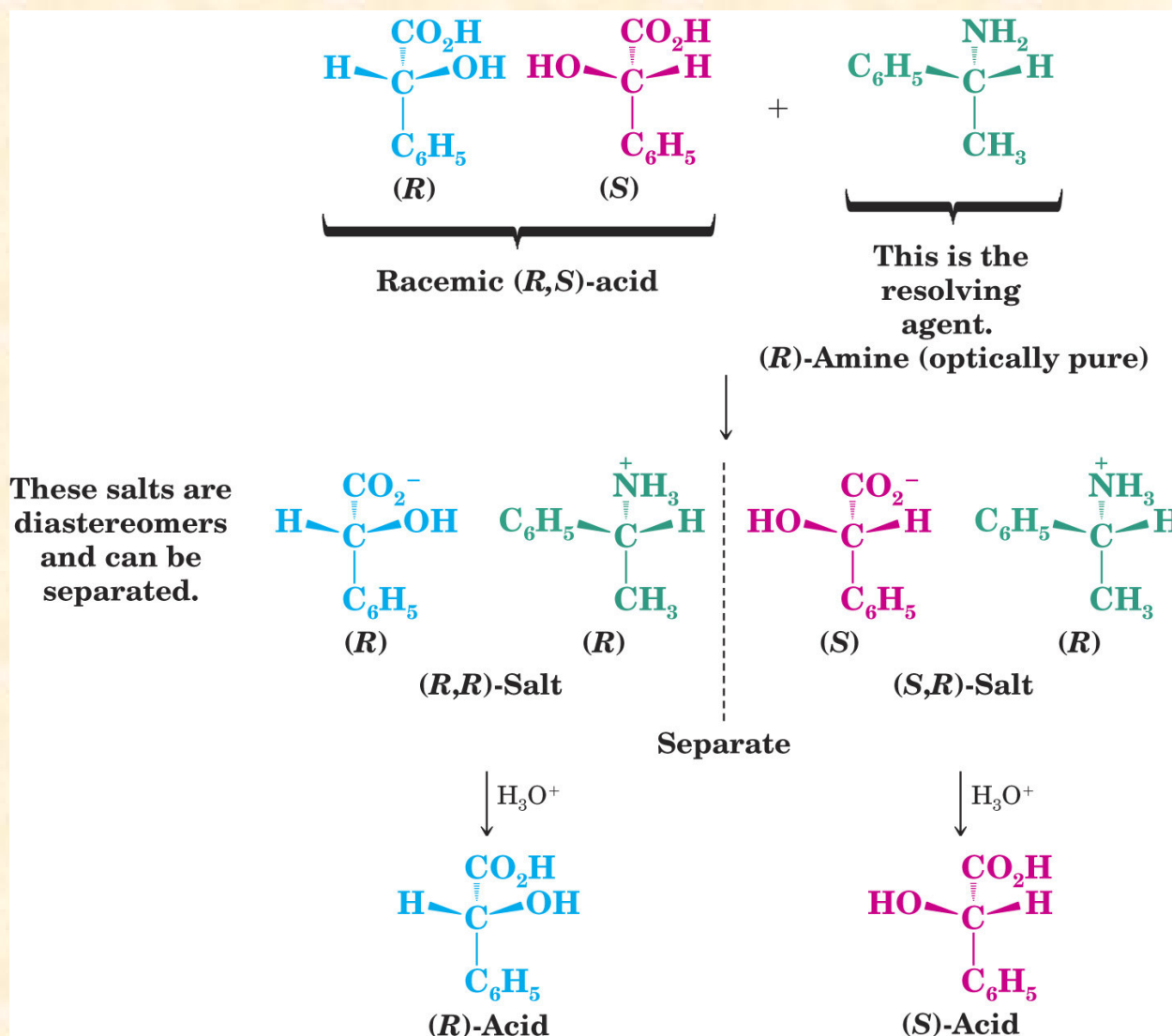
- Solubility of amines in dilute acid can be used as a chemical test
- Amides are not basic and are not soluble in aqueous acids



Resolving Agents

– Amines as Resolving Agents

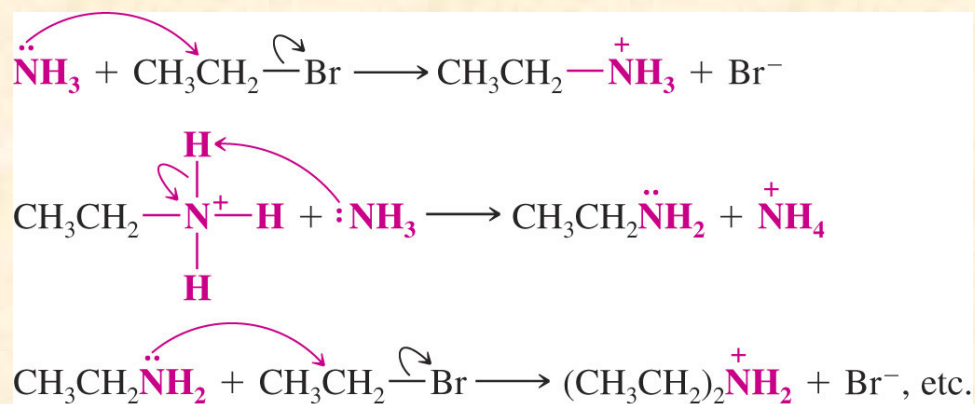
- A chiral amine can be used to resolve a racemic mixture of carboxylic acids by formation of diastereomeric salts



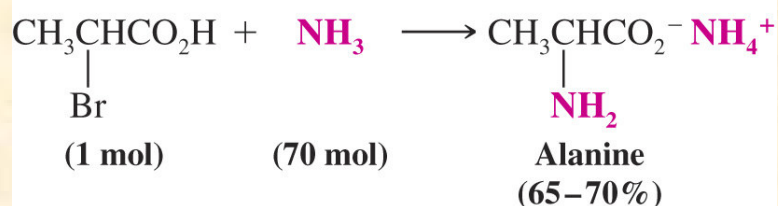
Synthesis of Amines

By Nucleophilic Substitution Reactions

- Alkylation of Ammonia
 - Reaction of ammonia with an alkyl halide

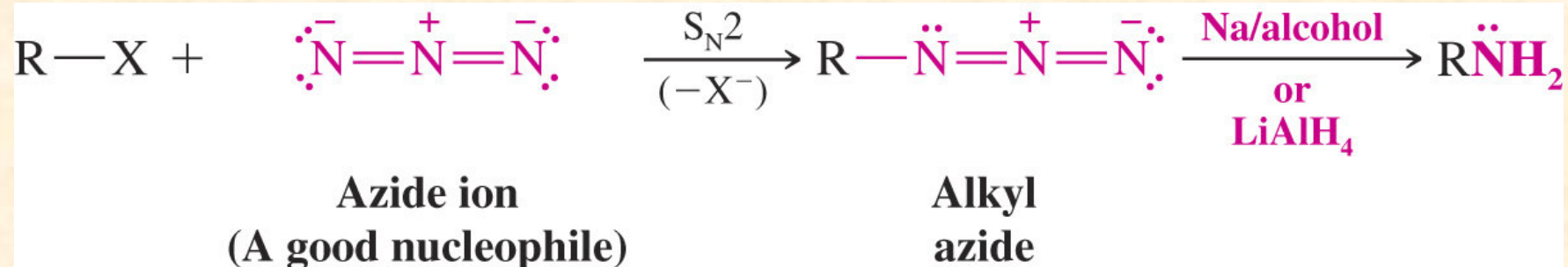


- Using an excess of ammonia helps to minimize multiple alkylations

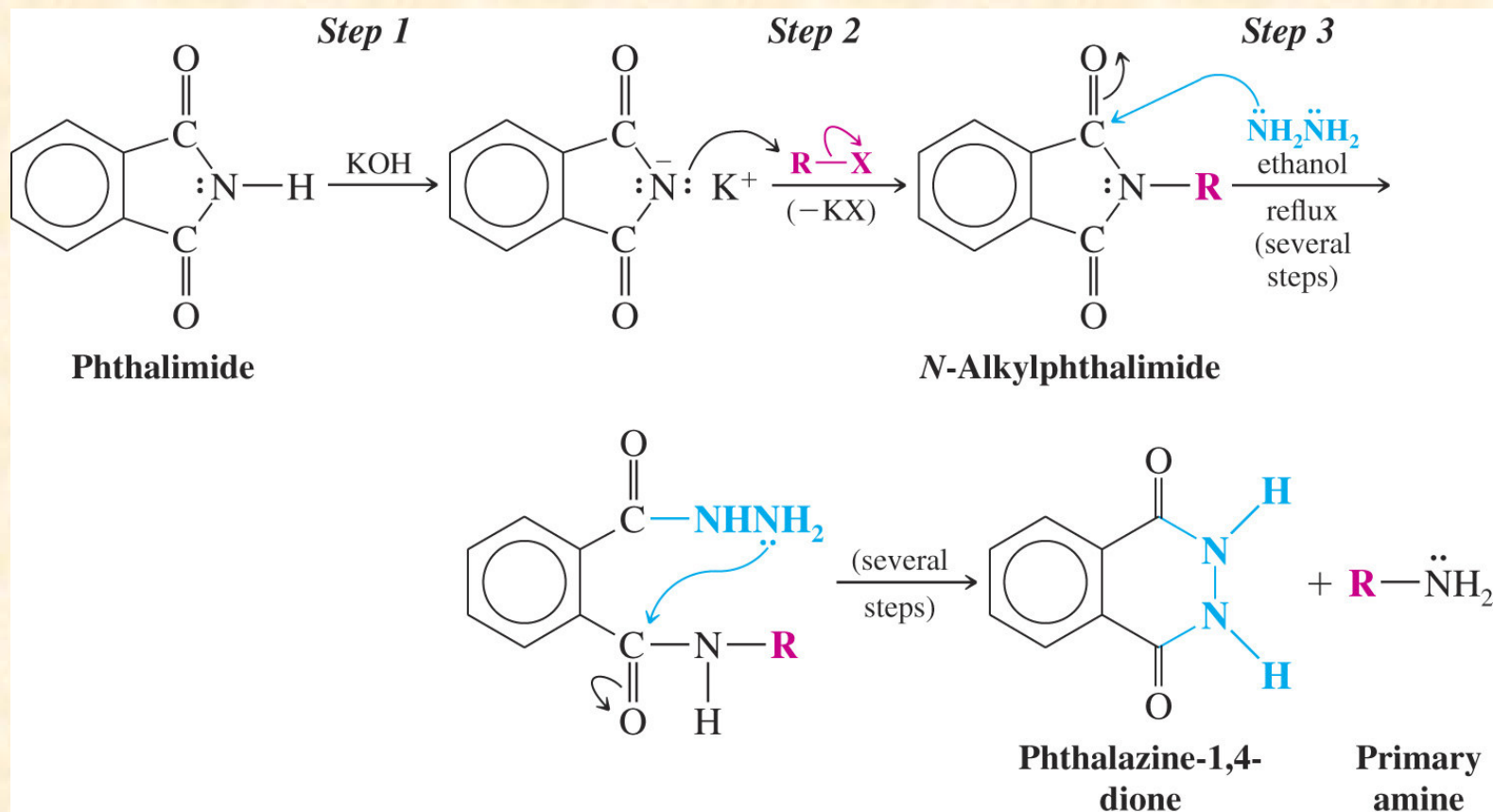


Synthesis of Amines

- Alkylation of Azide Ion followed by Reduction

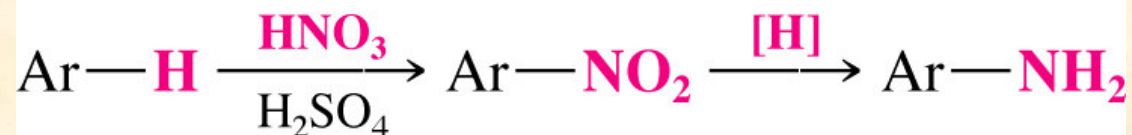


- The Gabriel Synthesis for primary amines

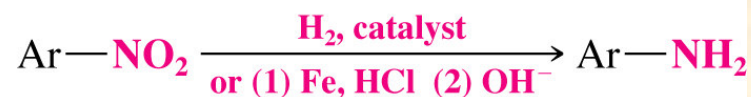


Synthesis of Amines

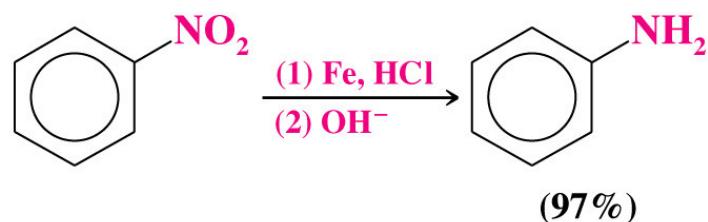
- Preparation of Aromatic Amines by Reduction of Nitro Compounds
 - Aromatic amines can be synthesized by reduction of the corresponding nitro compound



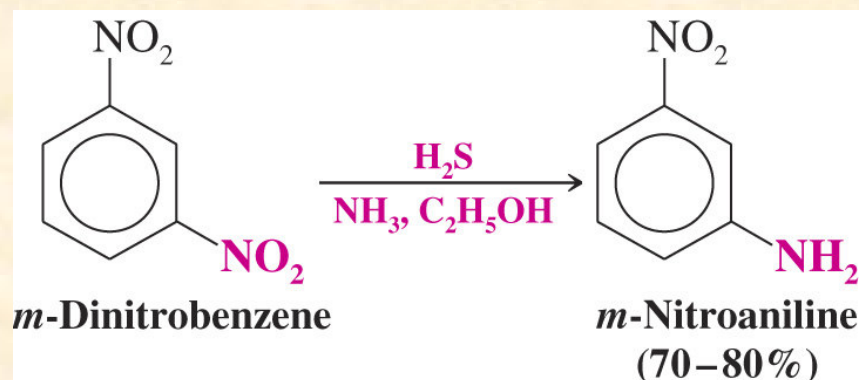
General Reaction



Specific Example

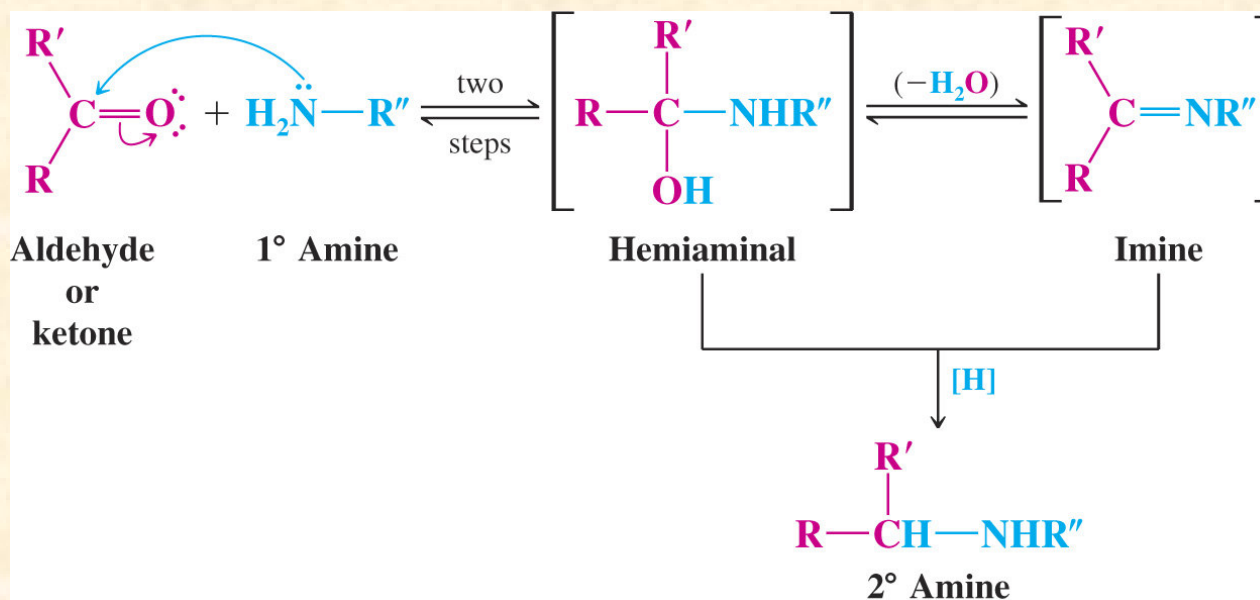
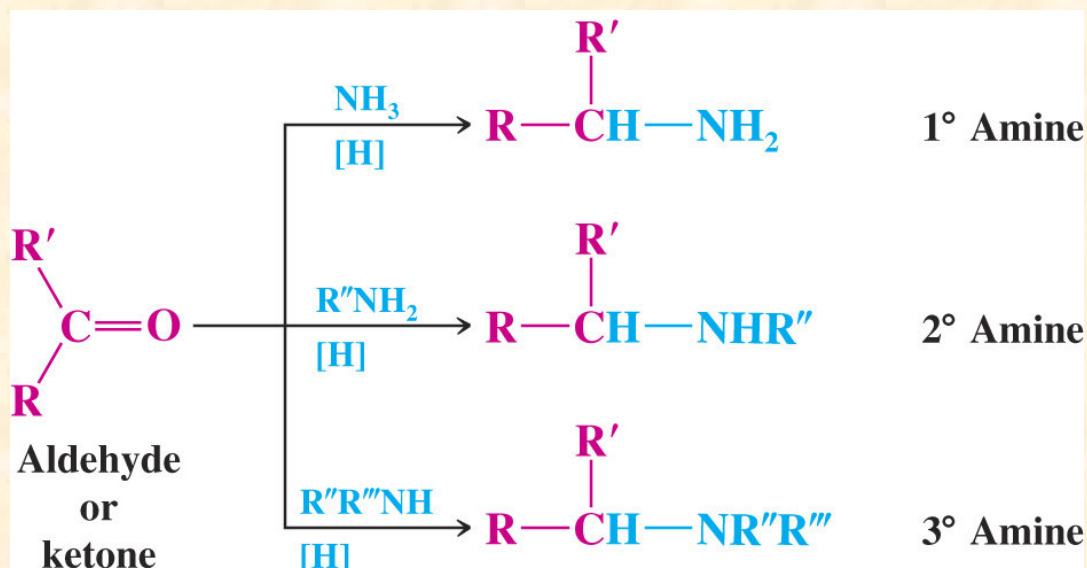


- One molar equivalent of hydrogen sulfide in alcoholic ammonia can be used to reduce one nitro group in the presence of another



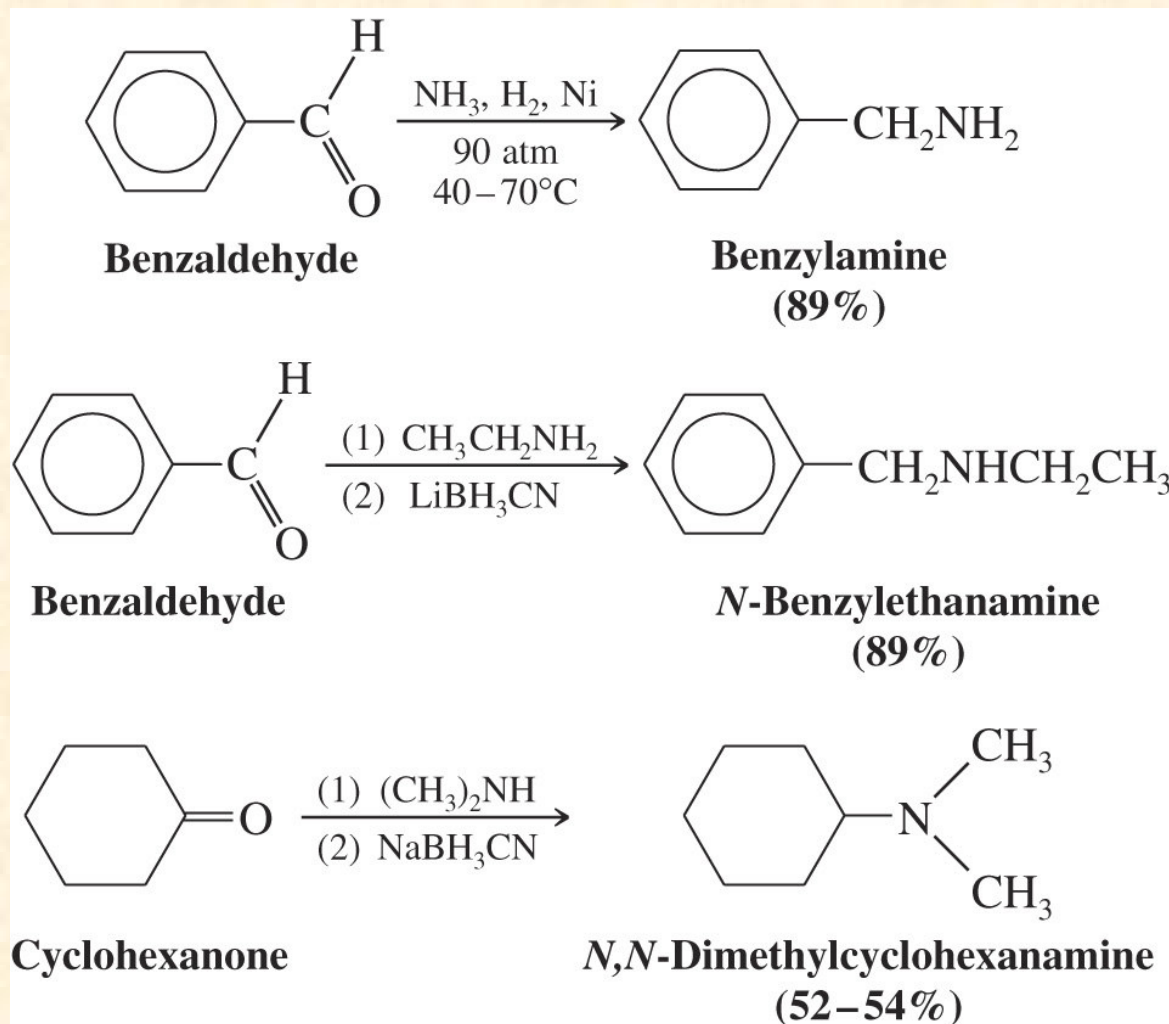
Synthesis of Amines

- Preparation of Primary, Secondary and Tertiary Amines through Reductive Amination



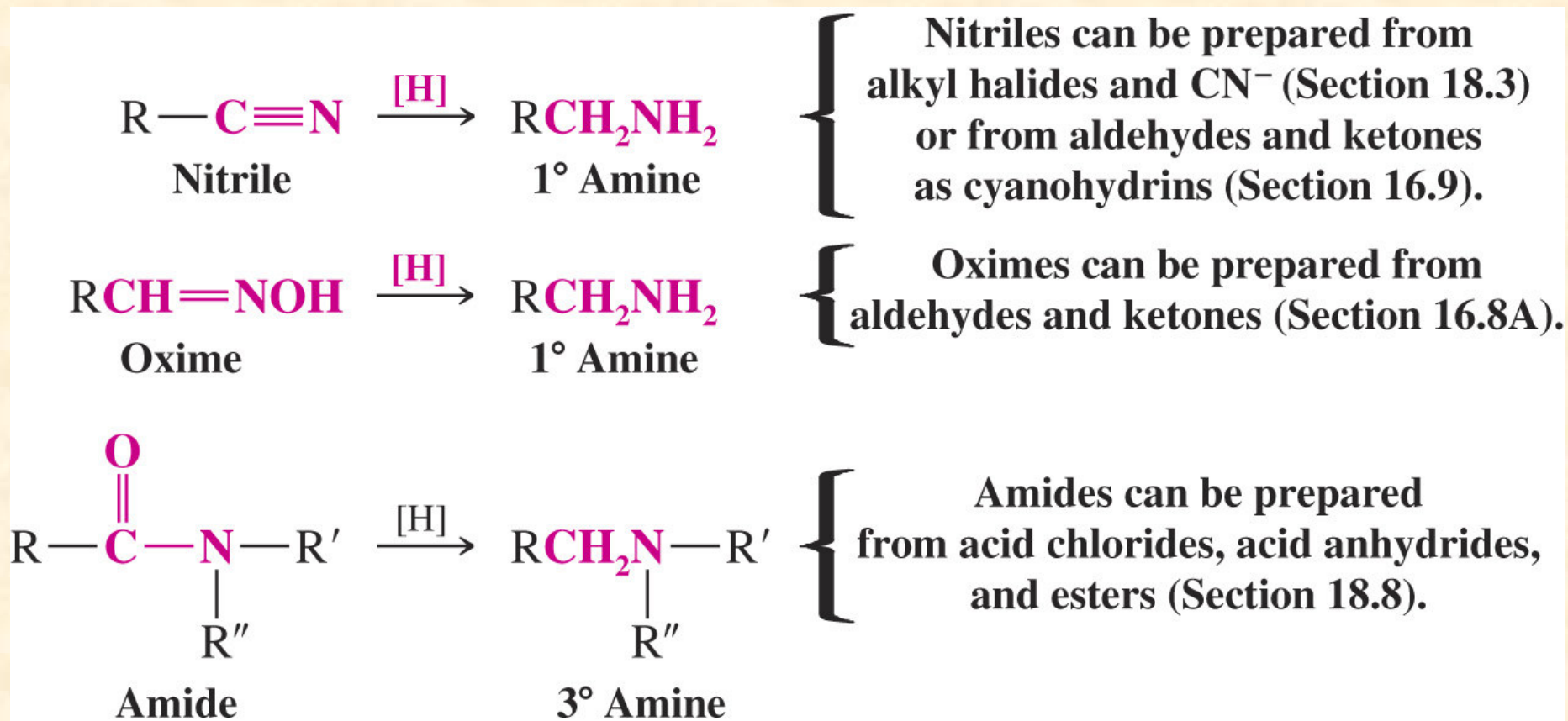
Synthesis of Amines

- The reduction can be accomplished using catalytic hydrogenation or a hydride reducing reagent
 - NaBH_3CN and LiBH_3CN are especially effective in reductive aminations



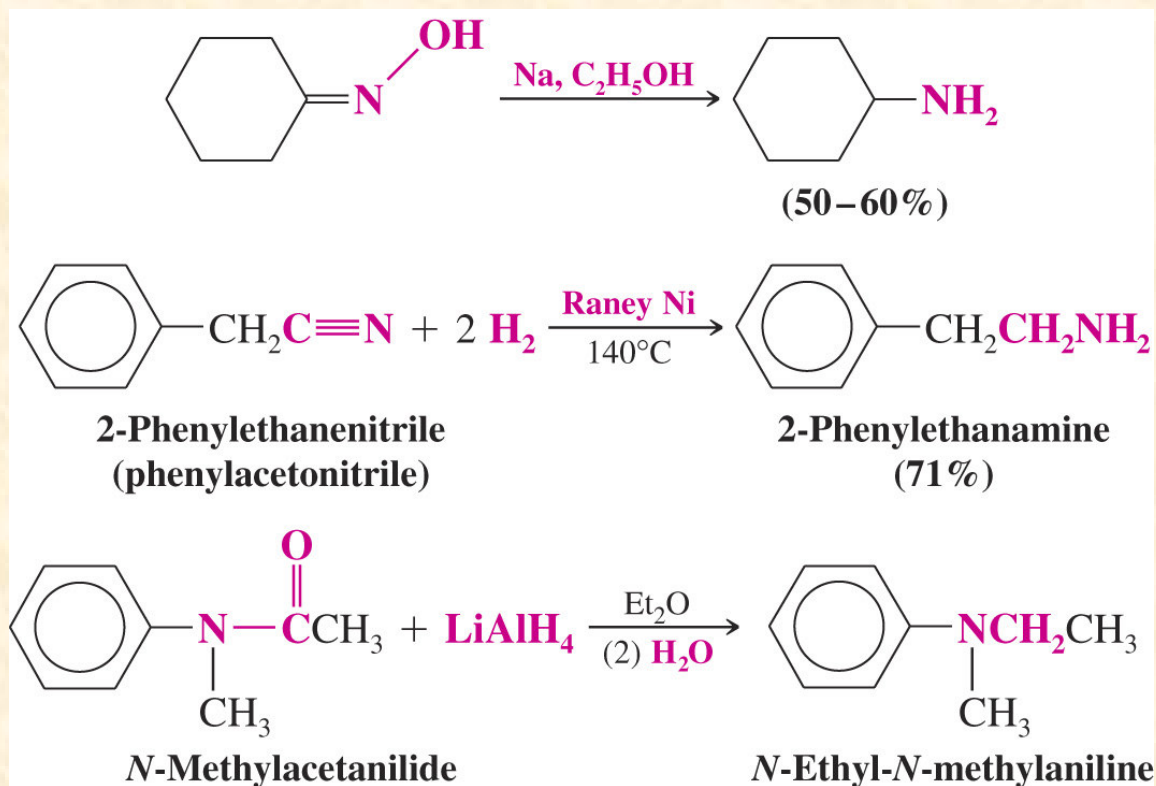
Synthesis of Amines

- Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

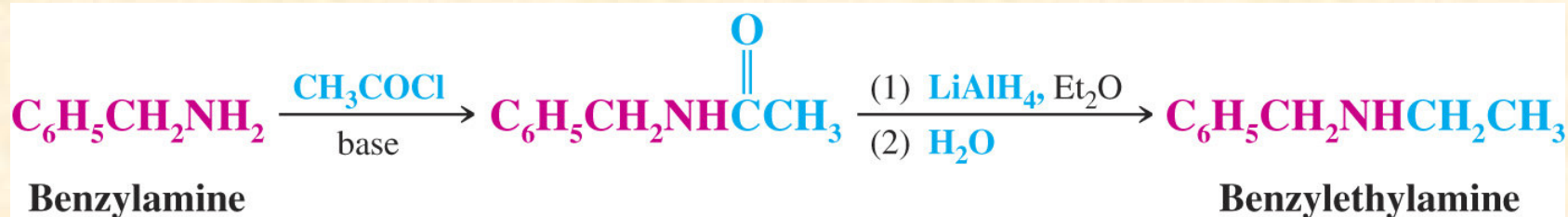


Synthesis of Amines

- Reduction can be accomplished by using catalytic hydrogenation or LiAlH_4



- Monoalkylation of an amine can be achieved by acylation of the amine and then reduction of the resulting amide

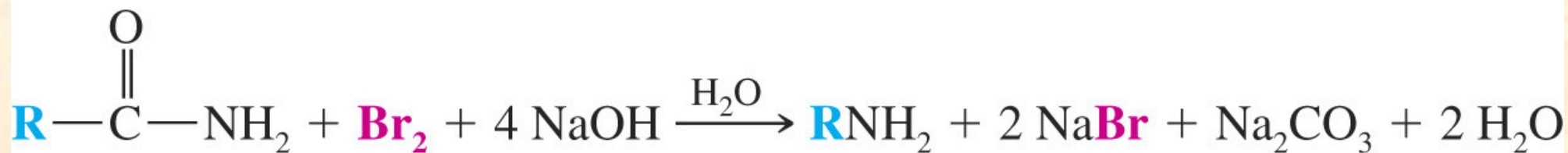


Synthesis of Amines



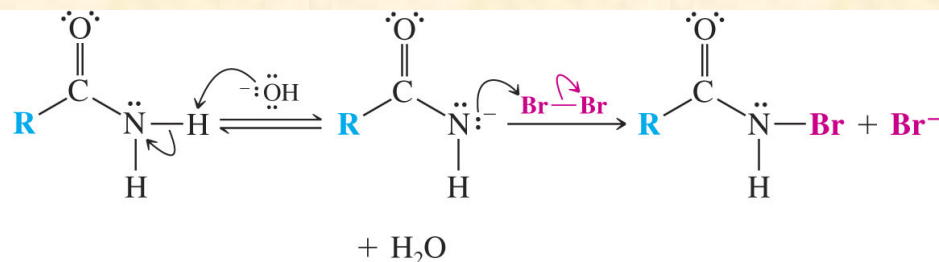
– Preparation of Primary Amines by the Hofmann and Curtius Rearrangements

- An unsubstituted amide can be converted to a primary amine by formal loss of the amide carbonyl through the *Hofmann rearrangement* (also called the *Hofmann degradation*)

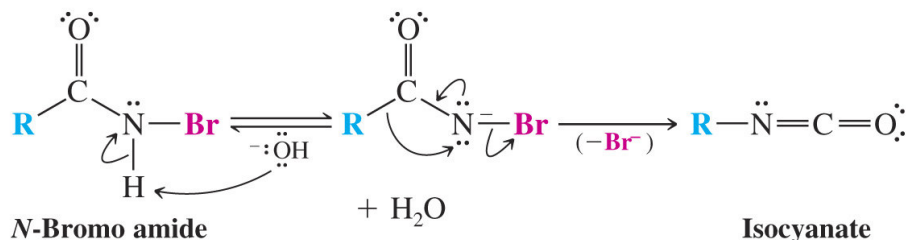


- The first two steps of the mechanism result in *N*-bromination of the amide
 - The *N*-bromoamide is deprotonated and rearranges to an isocyanate
 - The isocyanate is hydrolyzed to a carbamate which decarboxylates to the amine

Synthesis of Amines

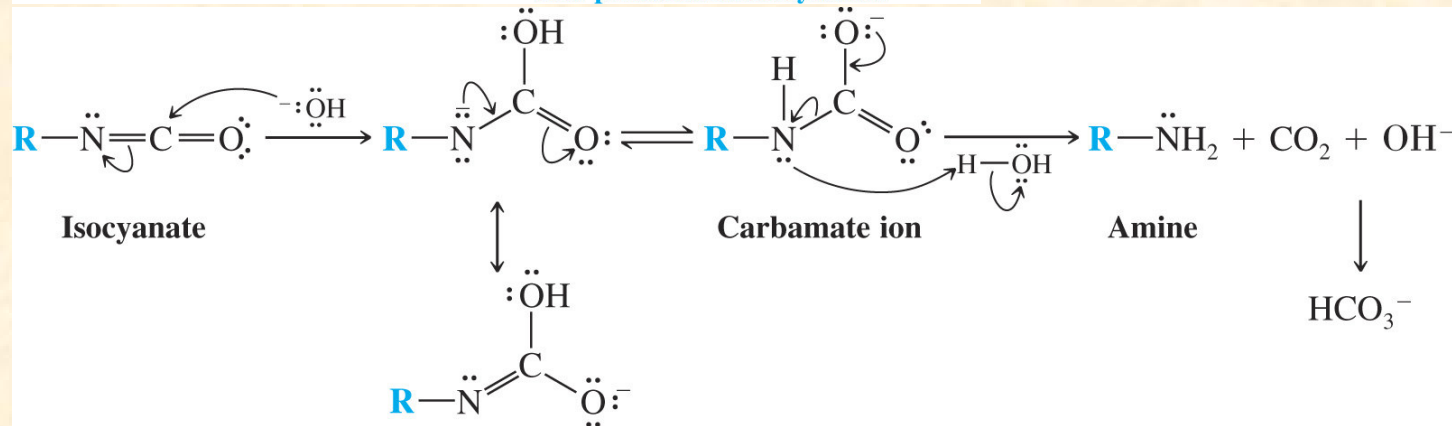


Base-promoted *N*-bromination of the amide occurs.



Base removes a proton from the nitrogen to give a bromo amide anion.

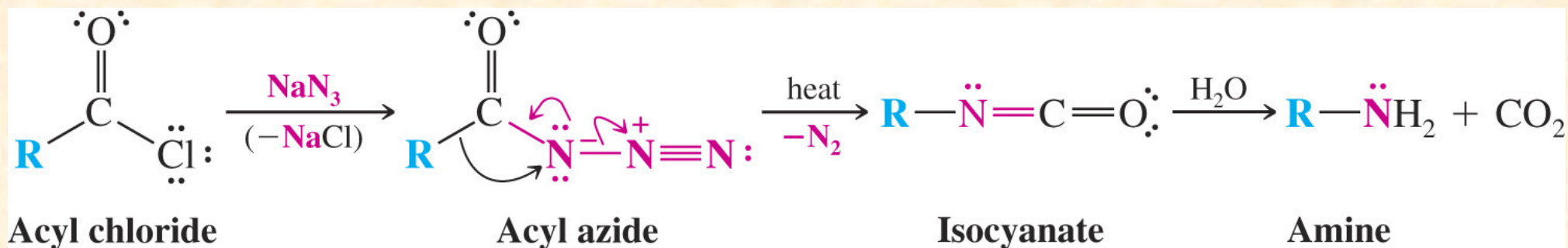
The R— group migrates to the nitrogen as a bromide ion departs. This produces an isocyanate.



The isocyanate undergoes hydrolysis and decarboxylation to produce the amine.

Synthesis of Amines

- The *Curtius rearrangement* occurs through the intermediacy of an acyl azide
 - The acyl azide is obtained from an acid chloride
 - Rearrangement of the acyl azide occurs with loss of N_2 , a very stable leaving group
 - In the last step, the isocyanate is hydrolyzed by adding water

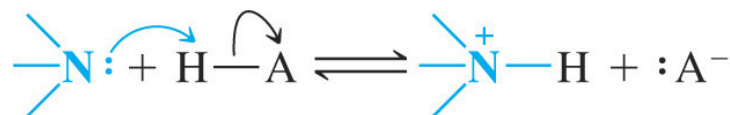


Reactions of Amines

The lone pair of the nitrogen atom accounts for most chemistry of amines

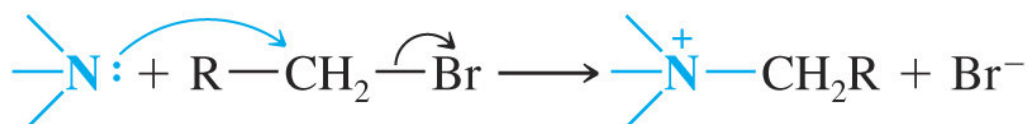
- The unshared electron pair can act as a base or as a nucleophile

Acid-Base Reactions



An amine acting as a base

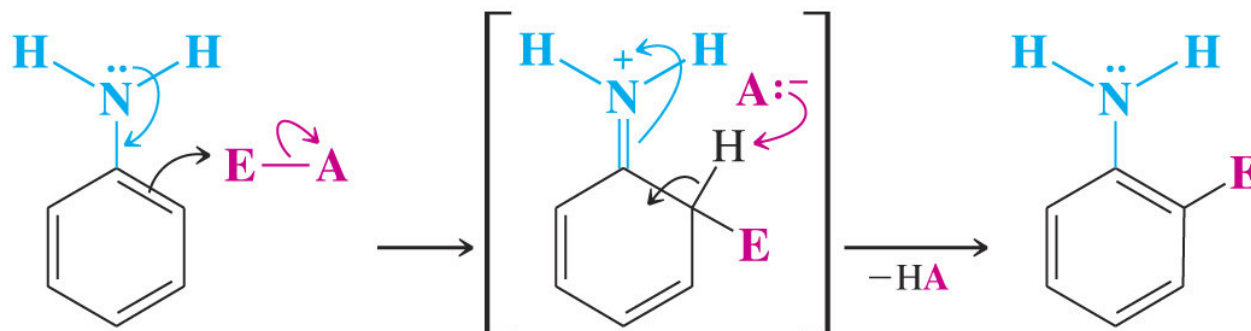
Alkylation



An amine acting as a nucleophile in an alkylation reaction

- The nitrogen lone pair can also make a carbon nucleophilic by resonance

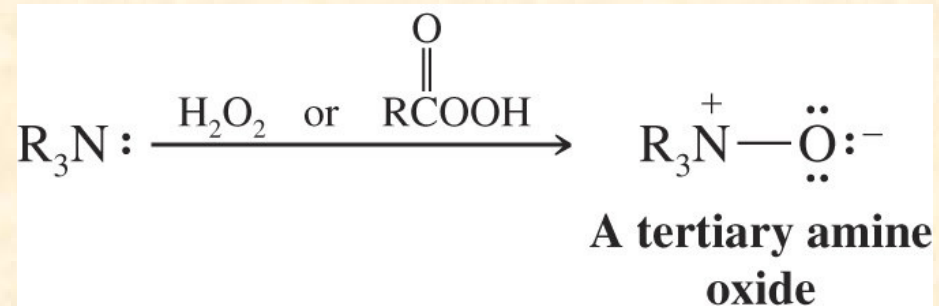
Electrophilic Aromatic Substitution



Reactions of Amines

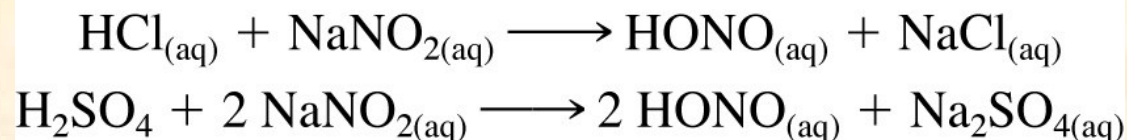
Oxidation of Amines

- Primary and secondary amines undergo *N*-oxidation, but useful products are not obtained because of side-reactions
- Tertiary amines undergo clean *N*-oxidation



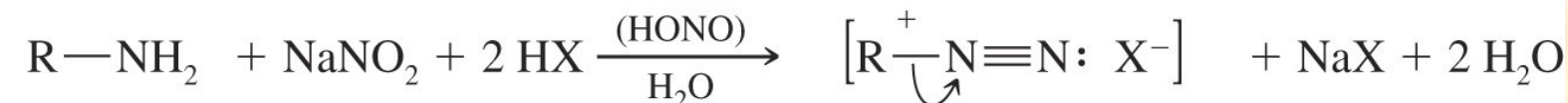
Reactions of Amines

- Reactions of Amines with Nitrous Acid
 - Nitrous acid (HONO) is prepared *in situ* by reaction of sodium nitrite with a strong aqueous acid



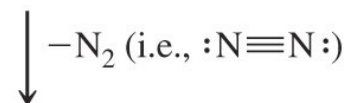
- Primary amines undergo *diazotization* with nitrous acid
 - The unstable *diazonium salts* decompose to form carbocations

General Reaction



1° Aliphatic
amine

Aliphatic diazonium salt
(highly unstable)

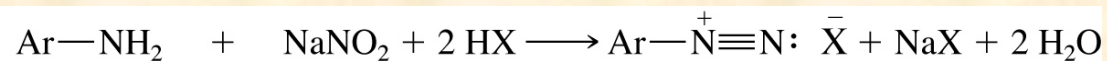


Alkenes, alcohols, alkyl halides

Reactions of Amines

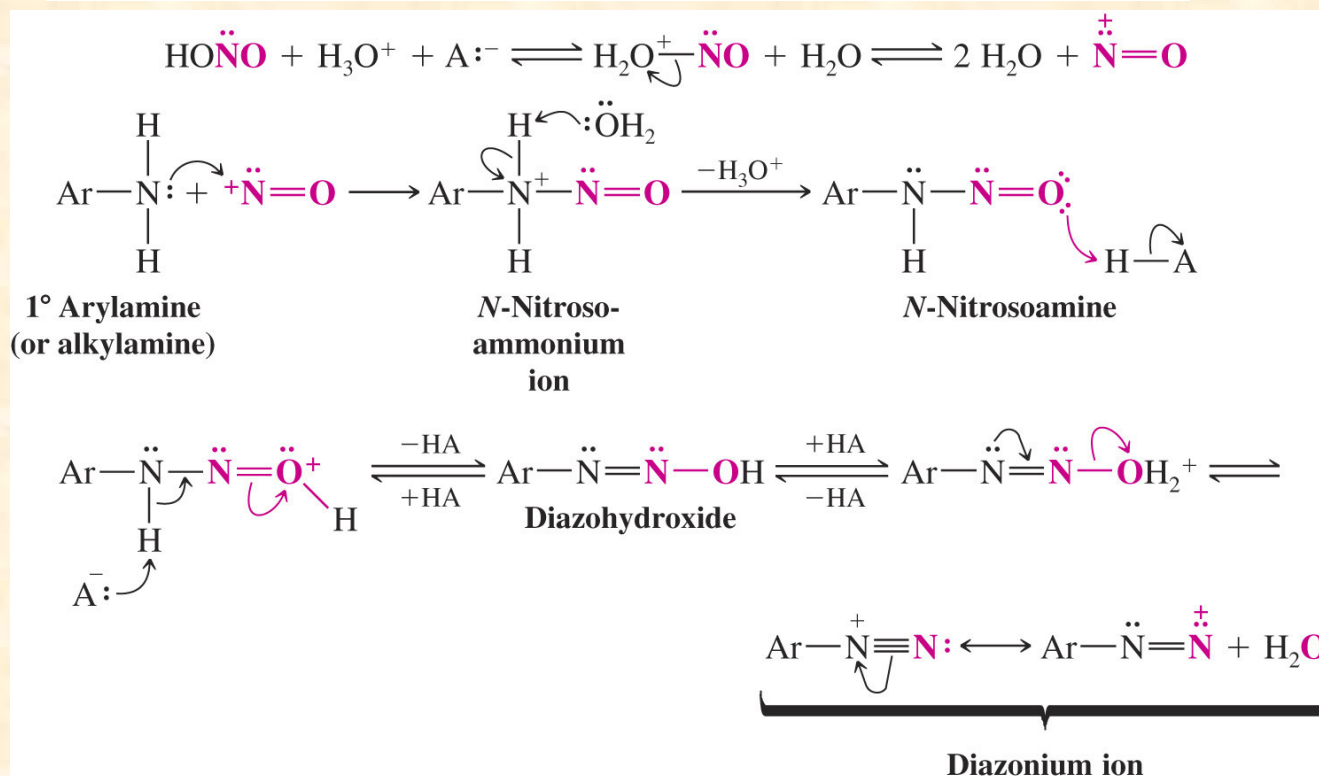
Reaction of primary arylamines with nitrous acid results in the formation of relatively stable arenediazonium salts

- This reaction occurs through the intermediacy of an *N*-nitrosoamine
- The *N*-nitrosoamine is converted to a diazonium ion



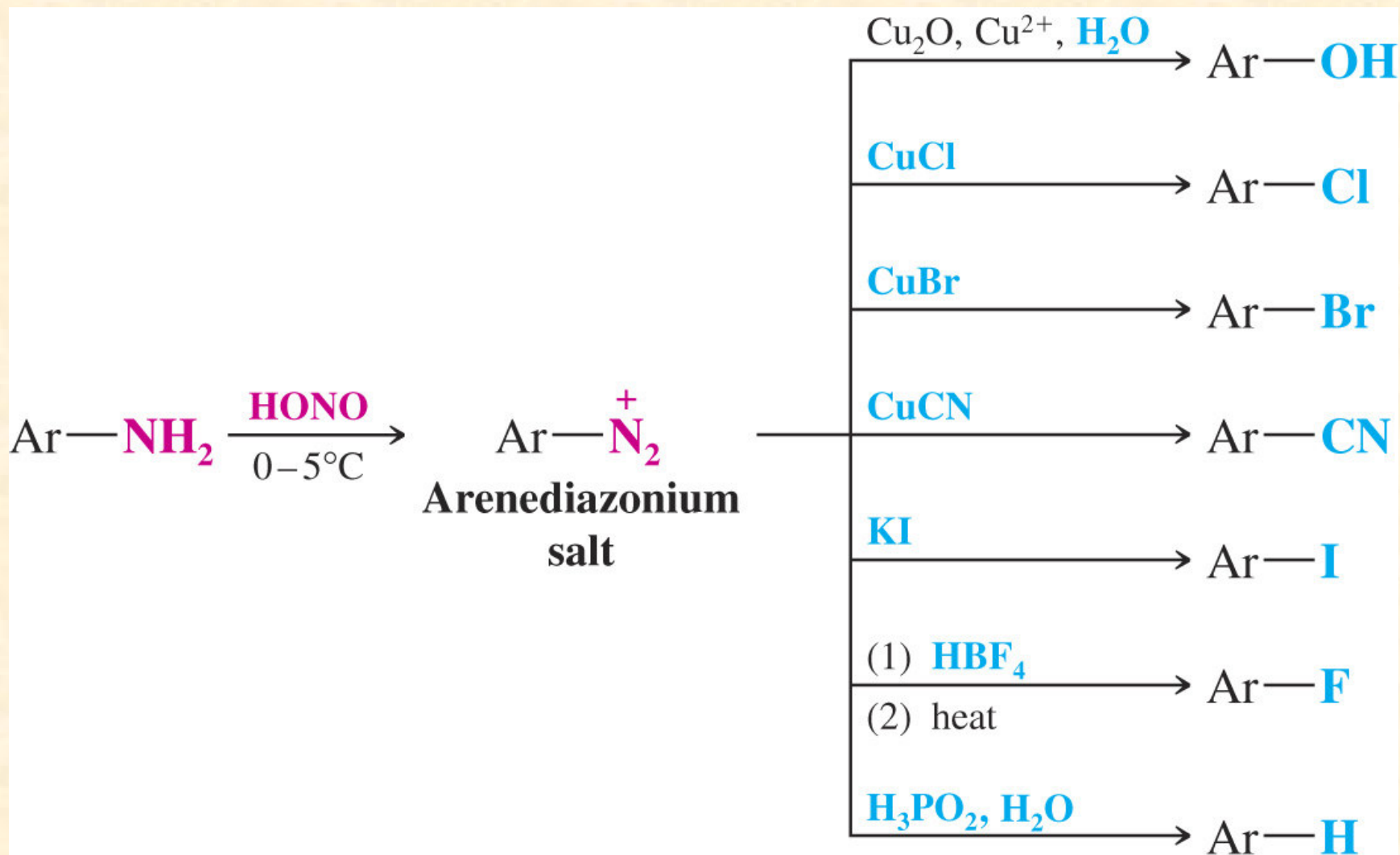
Primary arylamine

Arenediazonium salt
(stable if kept below 5°C)



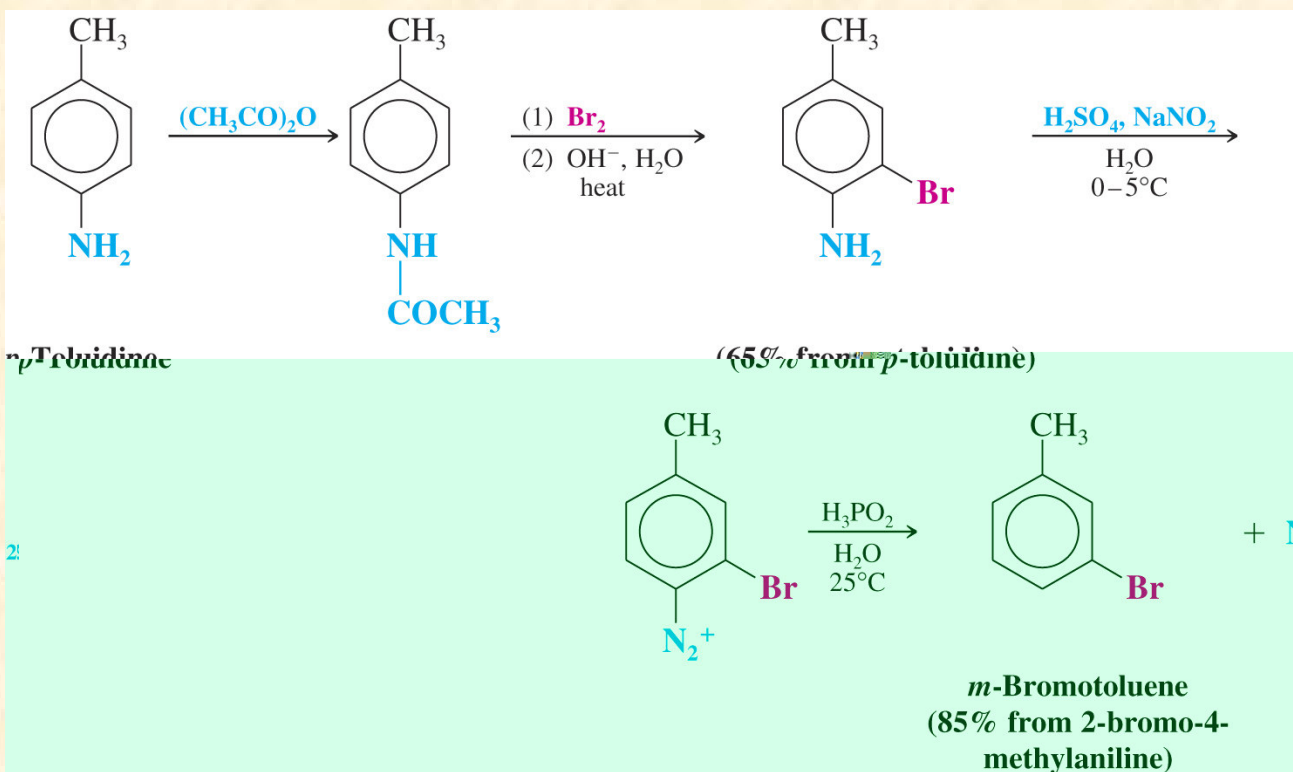
Reactions of Amines

- Replacement Reactions of Arenediazonium Salts - Sandmeyer Reactions
 - Aryldiazonium salts react readily with various nucleophilic reagents to give a wide variety of aromatic compounds



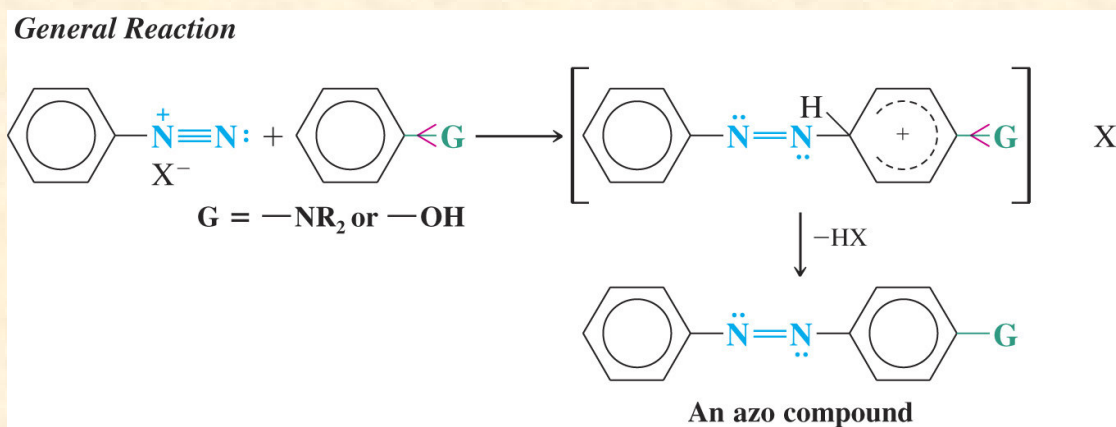
Reactions of Amines

- Practical Application of replacement with H
 - Example: *m*-Bromotoluene cannot be made directly from either toluene or bromobenzene
 - *N*-acetylation is used to reduce the activating effect of the amine

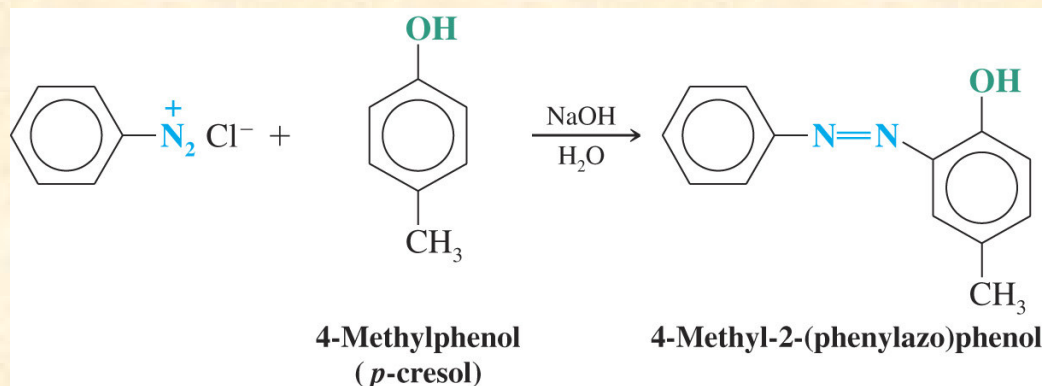


Reactions of Amines

- Coupling Reactions of Arenediazonium Salts
 - Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines
 - The reaction is called a *diazo coupling reaction*

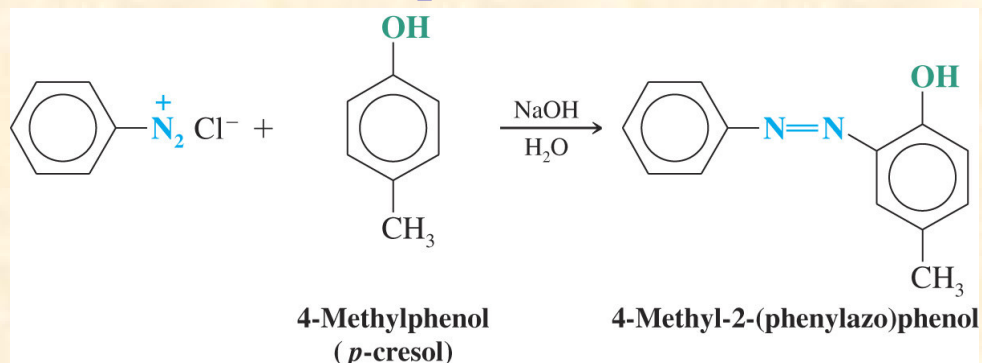


- Coupling with phenol occurs best in slightly alkaline solution
 - The alkaline solution produces a phenoxide ion that couples more rapidly, if the solution is too alkaline, a nonreactive diazohydroxide is produced

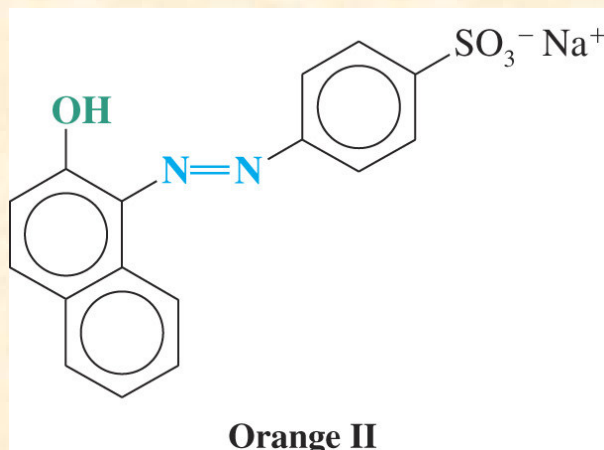


Reactions of Amines

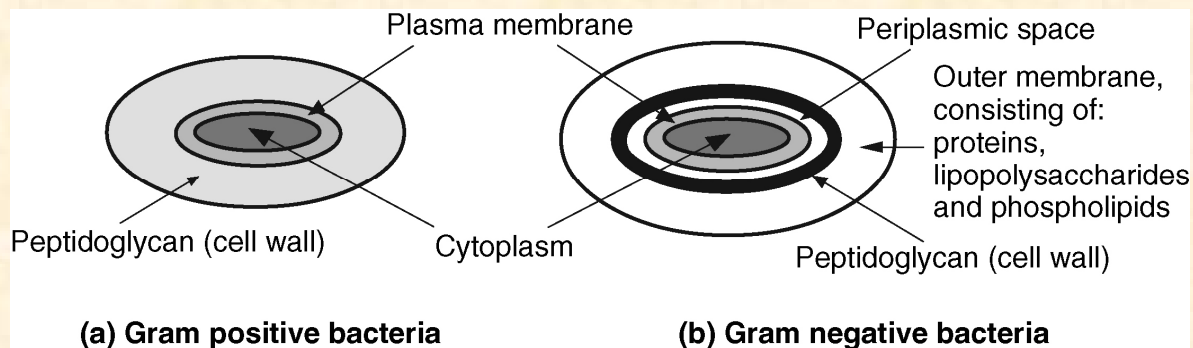
- Phenol and aniline derivatives undergo coupling almost exclusively at the para position unless this position is blocked



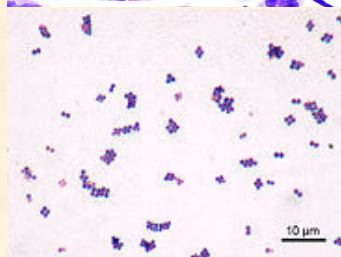
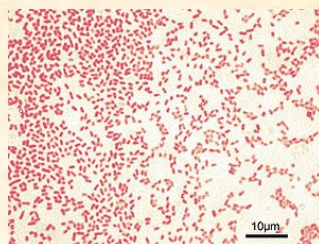
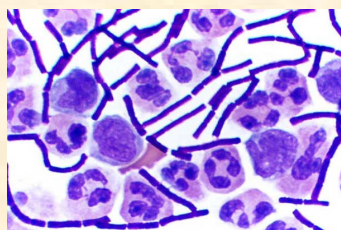
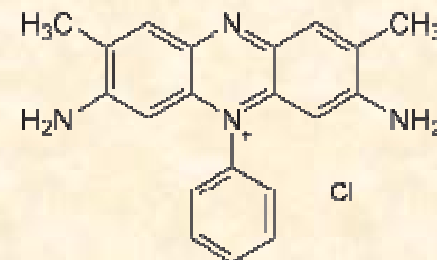
- Azo compounds are commonly used as dyes
 - The azo coupling results in compounds which are highly conjugated
 - The $-\text{SO}_3^-\text{Na}^+$ group is added to the molecule for solubility and to link the dye to the polar fibers of wool, cotton *etc.*
 - Orange II is made from 2-naphthol



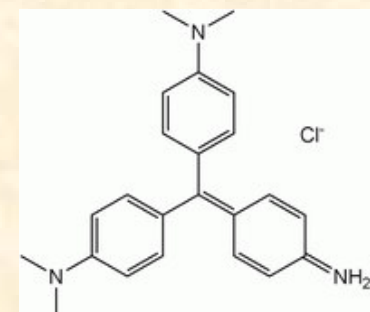
Reactions of Amines



Safranin



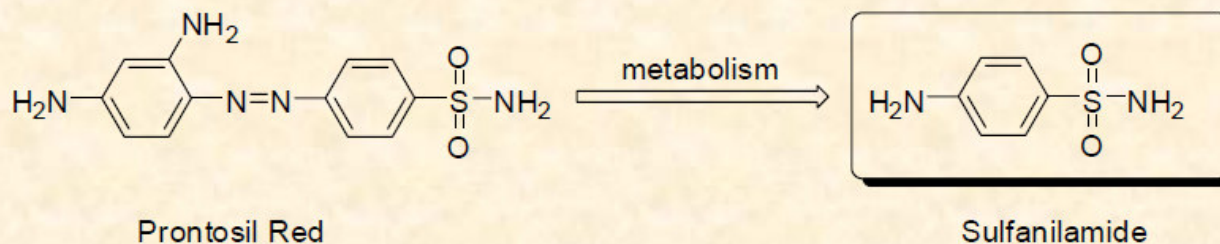
Crystal violet



- Half serendipity-half systematic
Dyes to Sulfa Drugs (IG Farben, Dogmak 1930s)

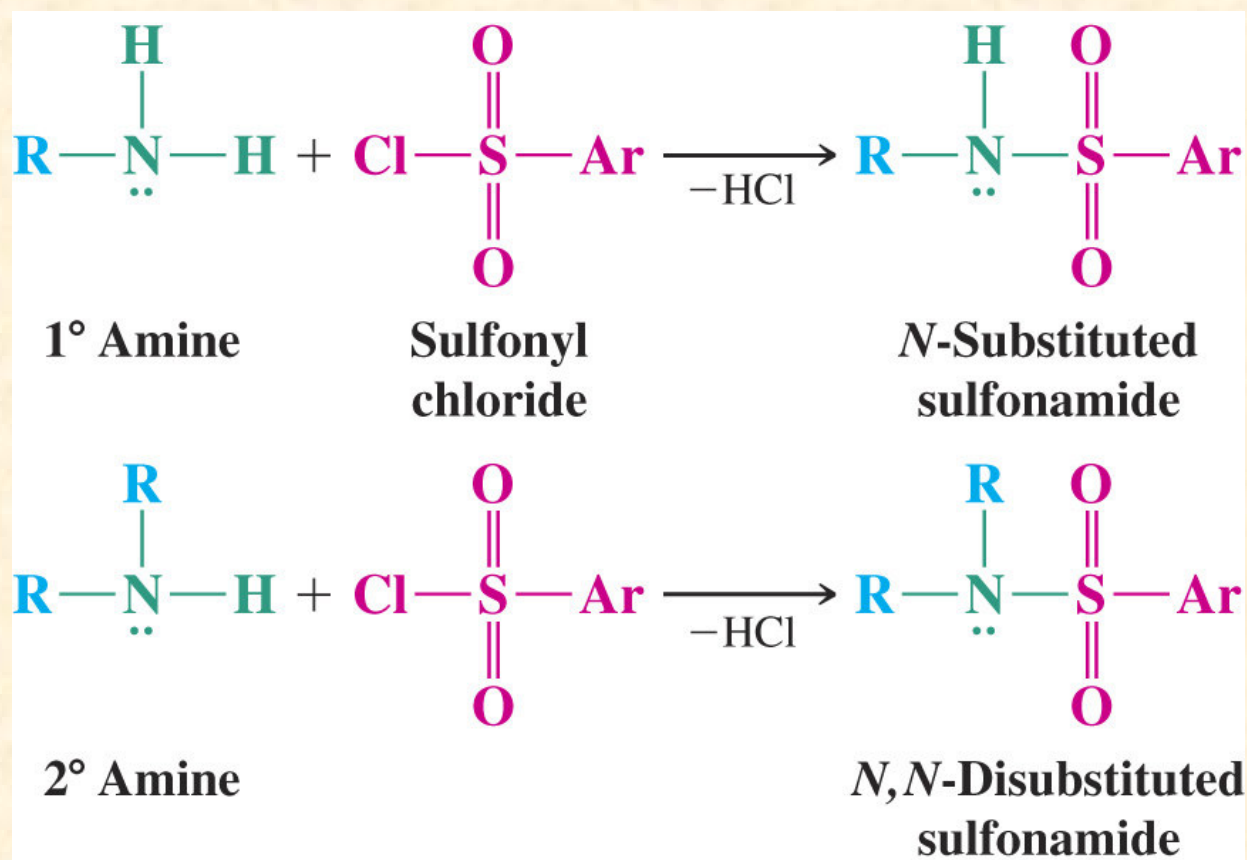


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Reactions of Amines

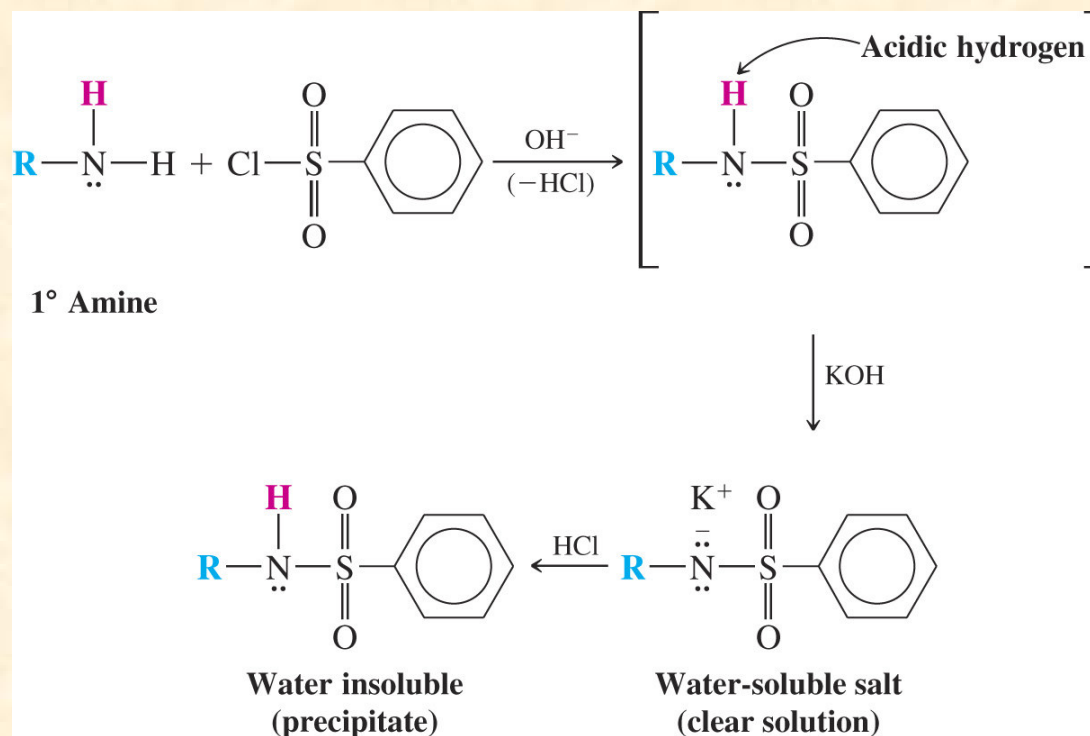
- Reactions of Amines with Sulfonyl Chlorides
 - Primary and secondary amines react with sulfonyl chlorides to produce *sulfonamides*
 - A sulfonamide can be hydrolyzed to an amine by heating with aqueous acid



Reactions of Amines

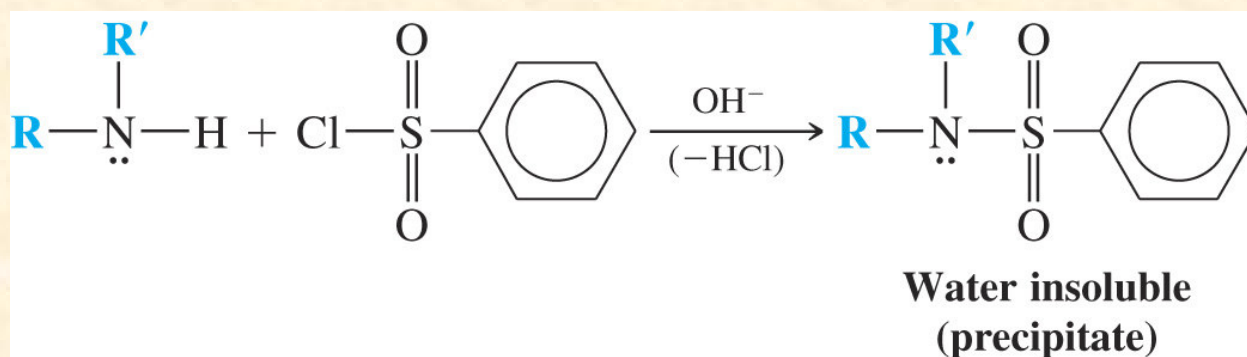
– The Hinsberg Test

- This test can distinguish between 1°, 2° and 3° amines
- An amine and benzenesulfonyl chloride are mixed with aqueous potassium hydroxide; the reaction is acidified in a second step
 - The results are different depending on the class of amine
- A benzenesulfonamide from a primary amine is soluble in basic solution, but precipitates upon acidification



Reactions of Amines

- A secondary amine forms a precipitate directly because an *N,N*-disubstituted sulfonamide remains insoluble in basic solution
- There is no acidic hydrogen in an *N,N*-disubstituted sulfonamide

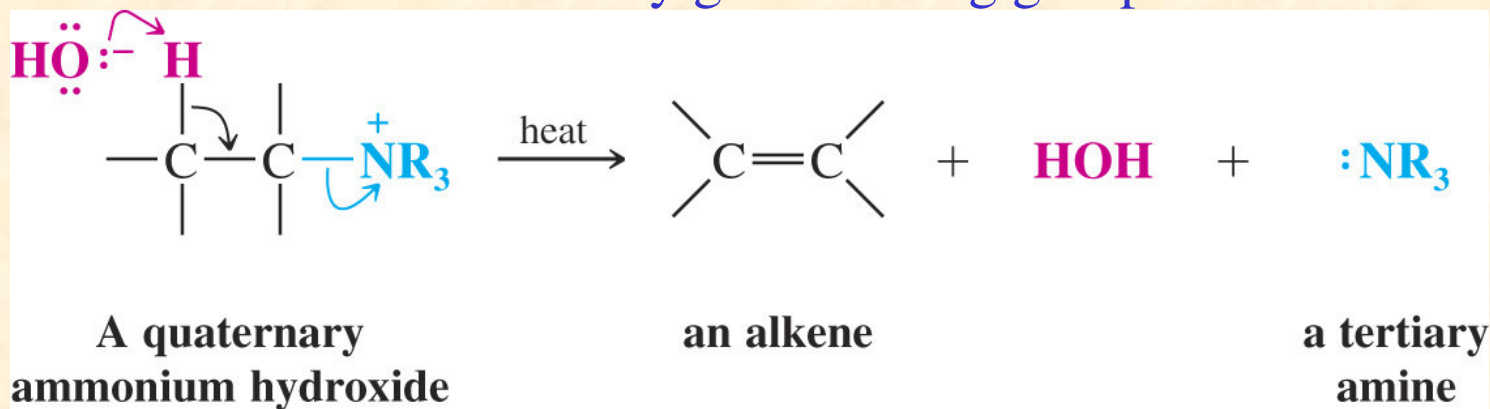


- A tertiary amine will not react to form a sulfonamide, but will dissolve upon acidification
 - Acidification converts the amine to a water soluble iminium salt

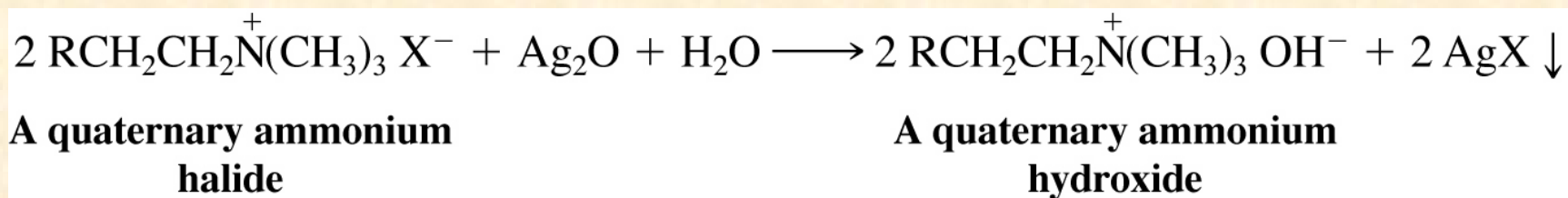
Reactions of Amines

- Eliminations Involving Ammonium Compounds
 - The Hofmann Elimination
 - An E2-type reaction occurs when a quaternary ammonium hydroxide is heated

– An amine is a relatively good leaving group

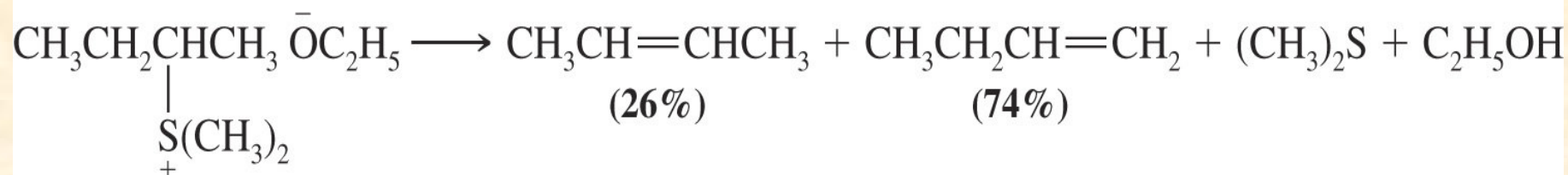
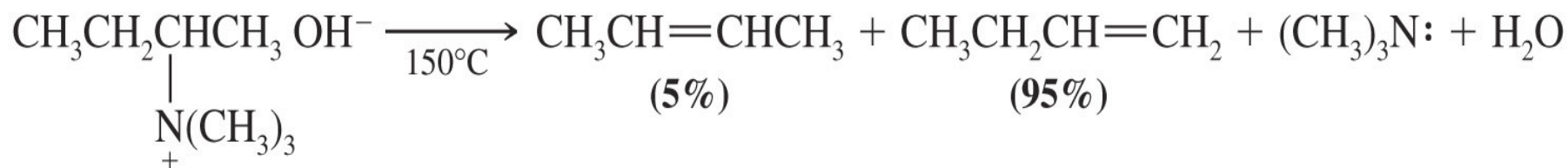
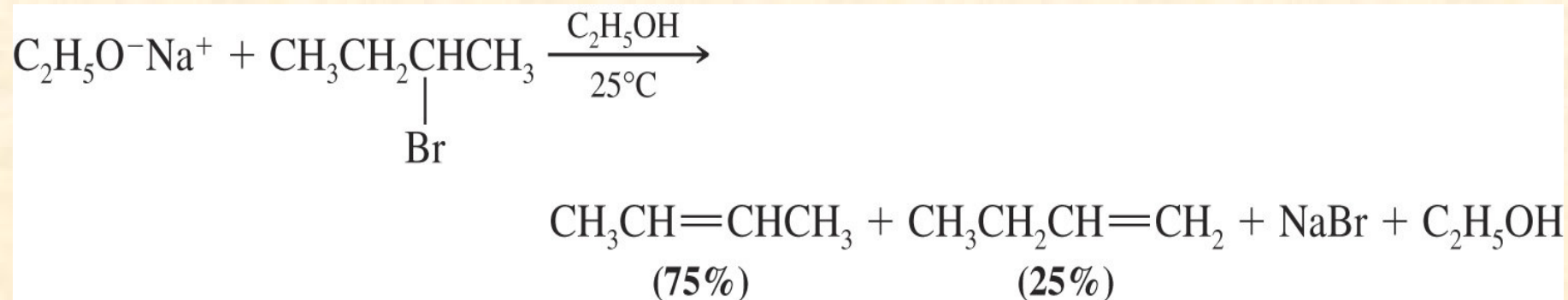


- A quaternary ammonium hydroxide can be made from a quaternary ammonium halide using silver oxide



Reactions of Amines

- Hofmann elimination and other elimination reactions of charged substrates proceed to give the least substituted double bond
 - This is called the Hofmann rule, and the least substituted alkene product is called the Hofmann product



Reactions of Amines

– The Cope Elimination

- A tertiary amine oxide will undergo elimination when heated
- Tertiary amine oxides can be made from tertiary amines by reaction with hydrogen peroxide

– the elimination is syn and proceeds via a cyclic transition state

