Organic Chemistry II / CHEM 252
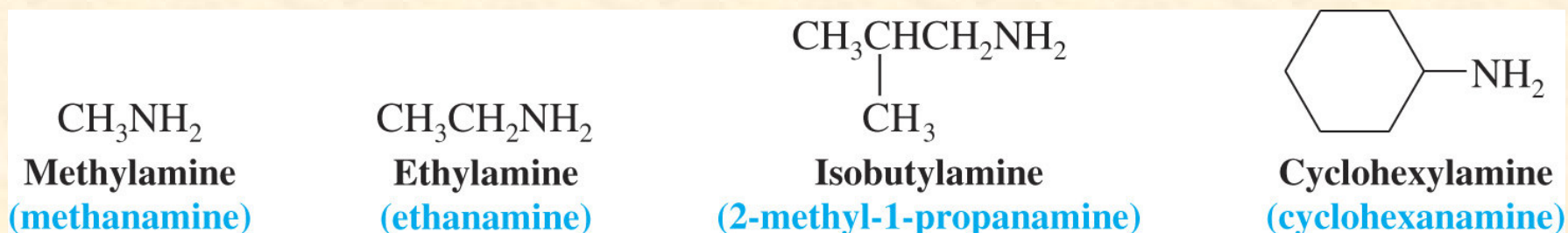
Chapter 20 – Amines

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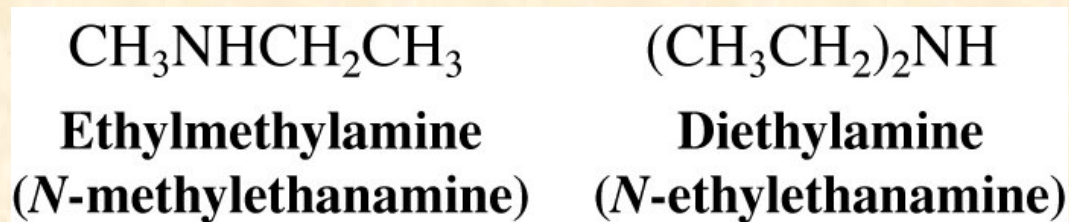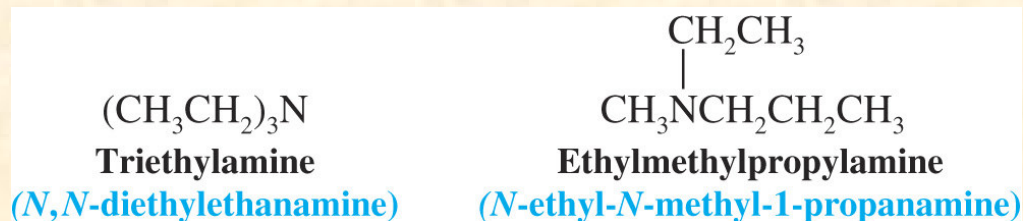
Boston, MA

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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

CH_3NH_2
Methylamine
(methanamine)

$CH_3CH_2NH_2$
Ethylamine
(ethanamine)

$CH_3CHCH_2NH_2$
|
CH_3
Isobutylamine
(2-methyl-1-propanamine)

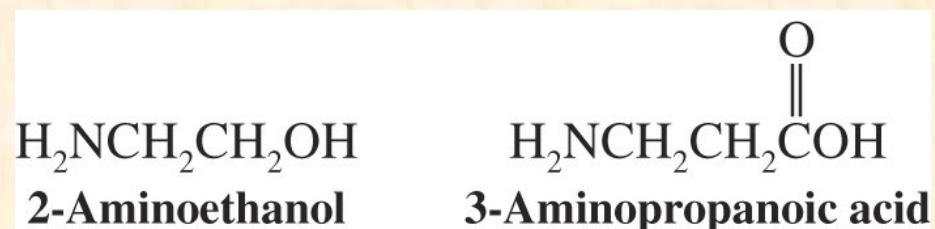—NH_2
Cyclohexylamine
(cyclohexanamine)

  - *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*
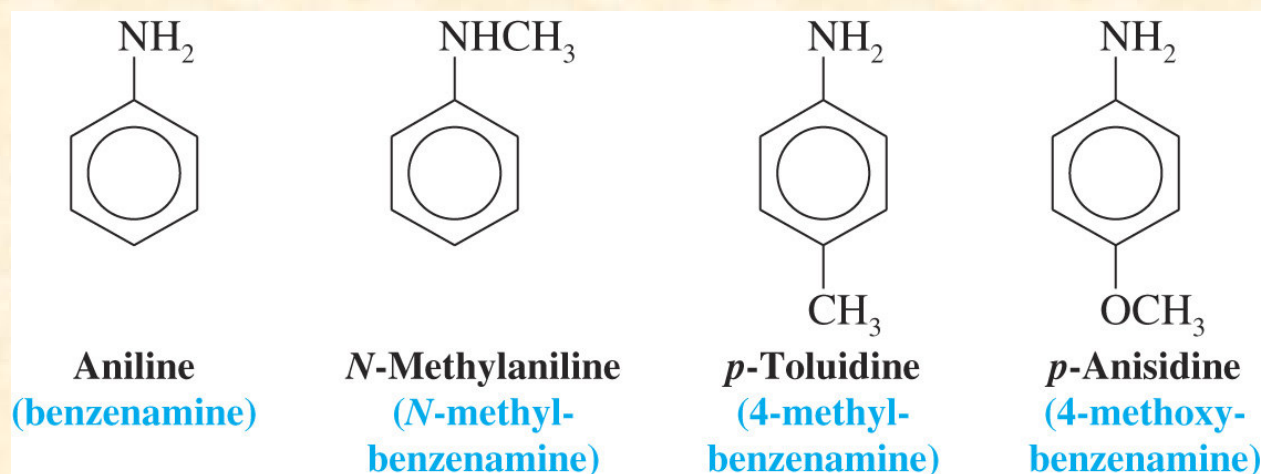
$CH_3NHCH_2CH_3$
Ethylmethylamine
(N-methylethanamine)

$(CH_3CH_2)_2NH$
Diethylamine
(N-ethylethanamine)

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Nomenclature

$(CH_3CH_2)_3N$
Triethylamine
(N,N-diethylethanamine)

$$CH_3NCH_2CH_2CH_3$$
with CH_2CH_3 substituent on N
Ethylmethylpropylamine
(N-ethyl-N-methyl-1-propanamine)

- In IUPAC nomenclature the substitutent -NH_2 is called the *amino* group

$H_2NCH_2CH_2OH$
2-Aminoethanol

$H_2NCH_2CH_2COH$ (with =O on the C)
3-Aminopropanoic acid

– Aryl Amines
  - The common arylamines have the following names:

NH_2
Aniline
(benzenamine)

$NHCH_3$
N-Methylaniline
(N-methyl-benzenamine)

NH_2 ... CH_3
p-Toluidine
(4-methyl-benzenamine)

NH_2 ... OCH_3
p-Anisidine
(4-methoxy-benzenamine)
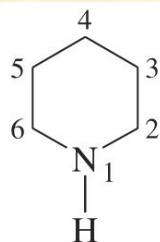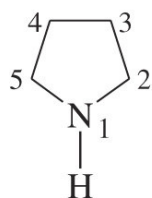
Nomenclature

– Heterocyclic Amines

- The important heterocylcic amines have common names

- In IUPAC nomenclature the prefixes *aza-*, *diaza-* and *triaza-* 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
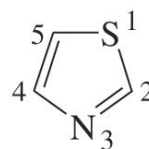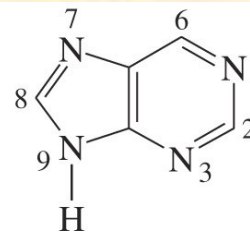
Pyrrole
(1-azacyclopenta-
2,4-diene)

Pyrazole
(1,2-diazacyclopenta-
2,4-diene)

Imidazole
(1,3-diazacyclopenta-
2,4-diene)

Indole
(1-azaindene)

Pyridine
(azabenzene)

Pyridazine
(1,2-diazabenzene)

Pyrimidine
(1,3-diazabenzene)

Quinoline
(1-azanaphthalene)

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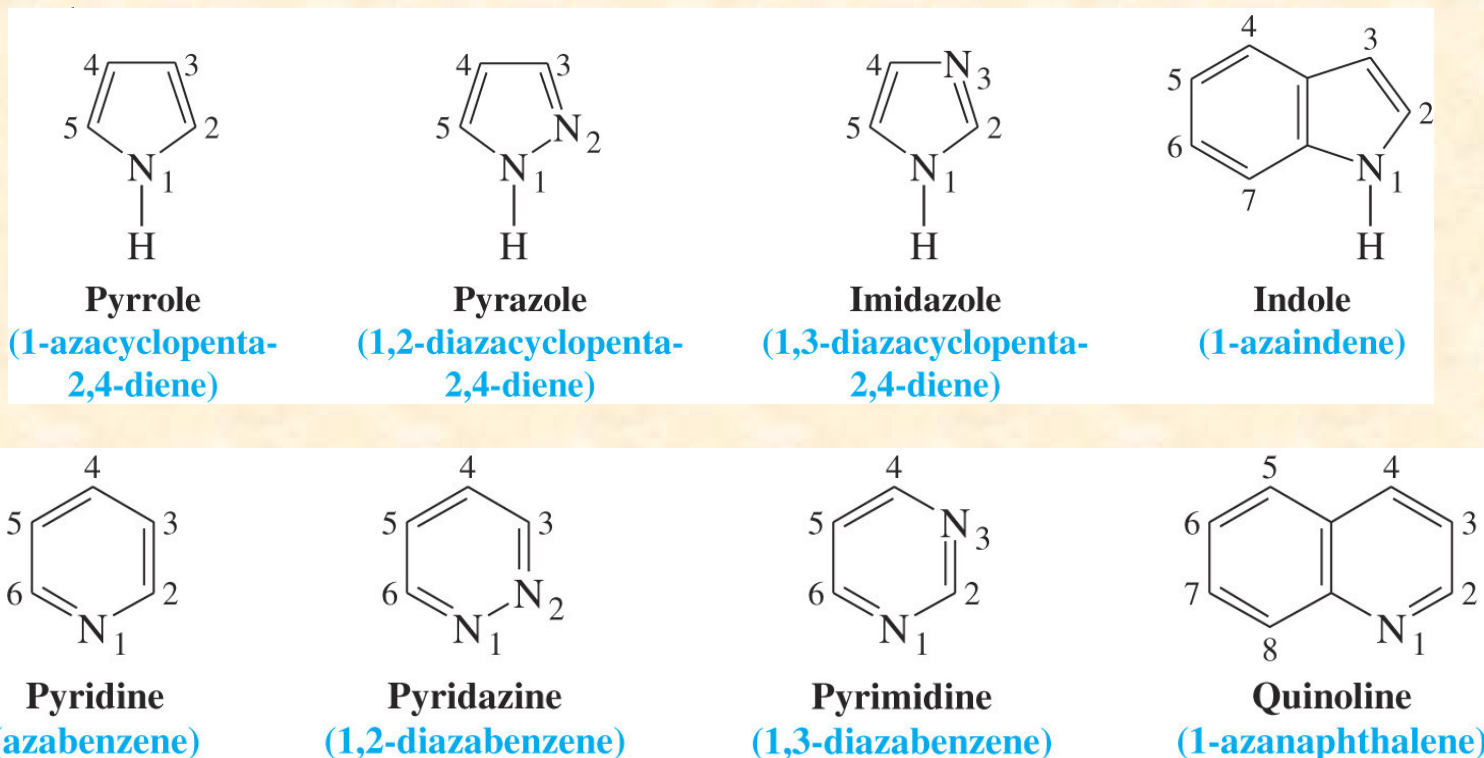
Nomenclature

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_3NH_2	−94	−6	Very soluble	10.64
Ethylamine	$CH_3CH_2NH_2$	−81	17	Very soluble	10.75
Propylamine	$CH_3CH_2CH_2NH_2$	−83	49	Very soluble	10.67
Isopropylamine	$(CH_3)_2CHNH_2$	−101	33	Very soluble	10.73
Butylamine	$CH_3(CH_2)_2CH_2NH_2$	−51	78	Very soluble	10.61
Isobutylamine	$(CH_3)_2CHCH_2NH_2$	−86	68	Very soluble	10.49
sec-Butylamine	$CH_3CH_2CH(CH_3)NH_2$	−104	63	Very soluble	10.56
tert-Butylamine	$(CH_3)_3CNH_2$	−68	45	Very soluble	10.45
Cyclohexylamine	$Cyclo\text{-}C_6H_{11}NH_2$	−18	134	Slightly soluble	10.64
Benzylamine	$C_6H_5CH_2NH_2$	10	185	Slightly soluble	9.30
Aniline	$C_6H_5NH_2$	−6	184	3.7	4.58
p-Toluidine	$p\text{-}CH_3C_6H_4NH_2$	44	200	Slightly soluble	5.08
p-Anisidine	$p\text{-}CH_3OC_6H_4NH_2$	57	244	Very slightly soluble	5.30
p-Chloroaniline	$p\text{-}ClC_6H_4NH_2$	73	232	Insoluble	4.00
p-Nitroaniline	$p\text{-}NO_2C_6H_4NH_2$	148	332	Insoluble	1.00
Secondary Amines					
Dimethylamine	$(CH_3)_2NH$	−92	7	Very soluble	10.72
Diethylamine	$(CH_3CH_2)_2NH$	−48	56	Very soluble	10.98
Dipropylamine	$(CH_3CH_2CH_2)_2NH$	−40	110	Very soluble	10.98
N-Methylaniline	$C_6H_5NHCH_3$	−57	196	Slightly soluble	4.70
Diphenylamine	$(C_6H_5)_2NH$	53	302	Insoluble	0.80
Tertiary Amines					
Trimethylamine	$(CH_3)_3N$	−117	2.9	Very soluble	9.70
Triethylamine	$(CH_3CH_2)_3N$	−115	90	14	10.76
Tripropylamine	$(CH_3CH_2CH_2)_3N$	−93	156	Slightly soluble	10.64
N,N-Dimethylaniline	$C_6H_5N(CH_3)_2$	3	194	Slightly soluble	5.06

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Structure

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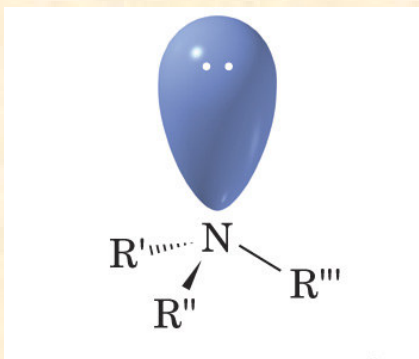

Structure of an amine

  - 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
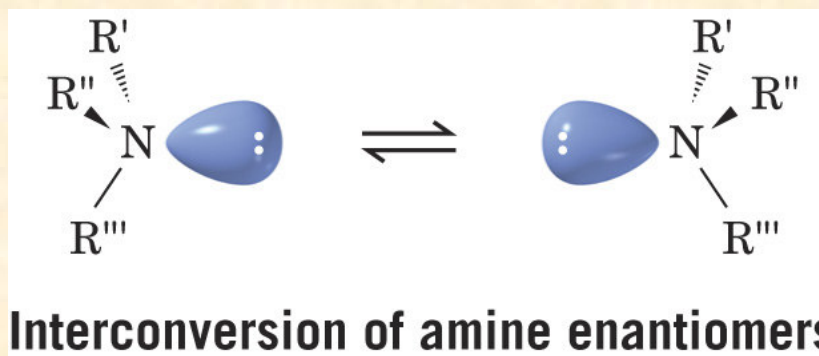

Interconversion of amine enantiomers

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
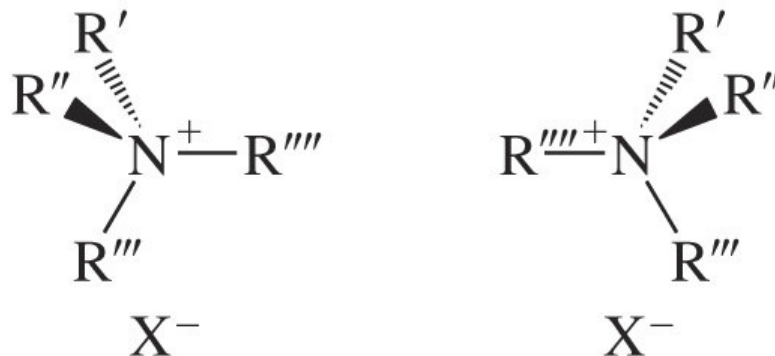
Quaternary ammonium salts such as these can be resolved.

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

$$R\overset{+}{N}H_3 + H_2O \rightleftharpoons RNH_2 + H_3O^+$$

$$K_a = \frac{[RHN_2][H_3O^+]}{[RNH_3{}^+]} \qquad pK_a = -\log K_a$$
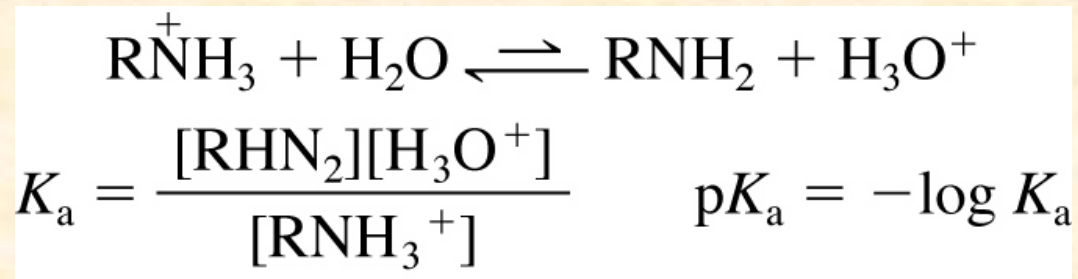
- Primary alkyl amines are more basic than ammonia
  - An alkyl group helps to stabilize the alkylaminium ion

	$\ddot{N}H_3$	$CH_3\ddot{N}H_2$	$CH_3CH_2\ddot{N}H_2$	$CH_3CH_2CH_2\ddot{N}H_2$
Conjugate acid pK_a	9.26	10.64	10.75	10.67
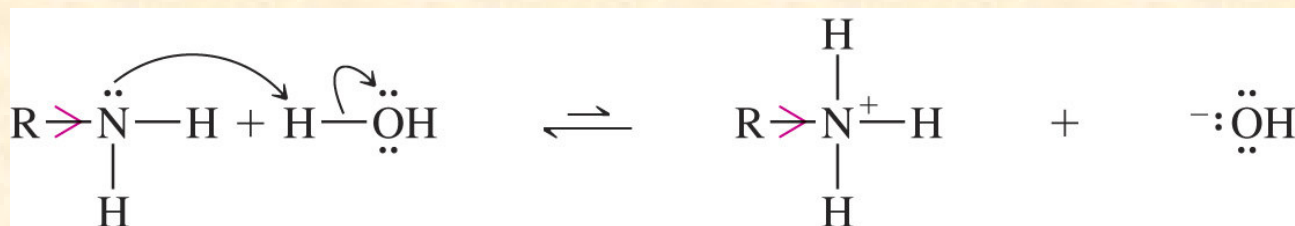
By releasing electrons, R→ stabilizes the alkylaminium ion through dispersal of charge.

Basicity

- gas phase : basicity increases with increasing methyl substitution

$$(CH_3)_3N > (CH_3)_2NH > CH_3NH_2 > NH_3$$

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

$$(CH_3)_2NH > CH_3NH_2 > (CH_3)_3N > NH_3$$

Basicity

- Arylamines are weaker bases than nonaromatic cyclohexylamines

	Cyclo-$C_6H_{11}NH_2$	$C_6H_5NH_2$	p-$CH_3C_6H_4NH_2$
Conjugate acid pK_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
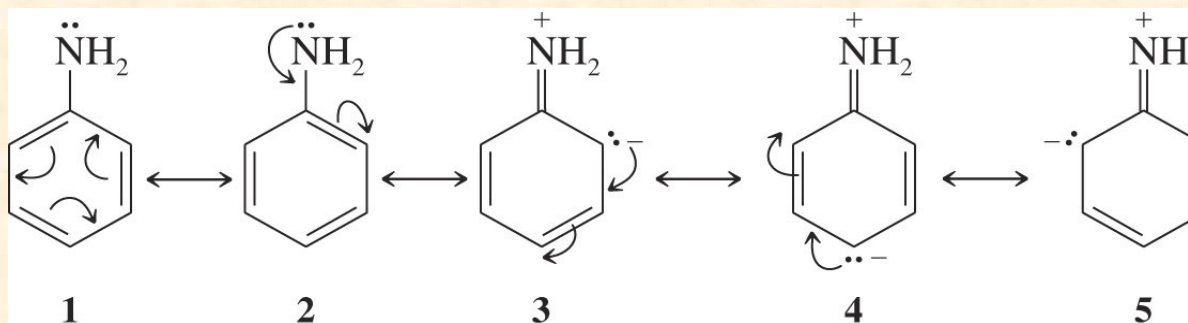
- Protonation of aniline is also disfavored because a protonated arylamine has only two resonance forms
  - Anilinium ion is not as well stabilized by resonance as aniline itself

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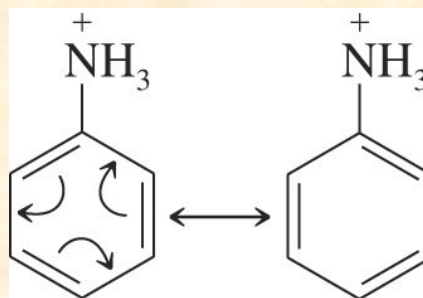
Basicity

– Basicity of Heterocyclic Amines

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

	Piperidine	**Pyrrolidine**	**Diethylamine**
Conjugate acid pK_a	$pK_a = 11.20$	$pK_a = 11.11$	$pK_a = 10.98$
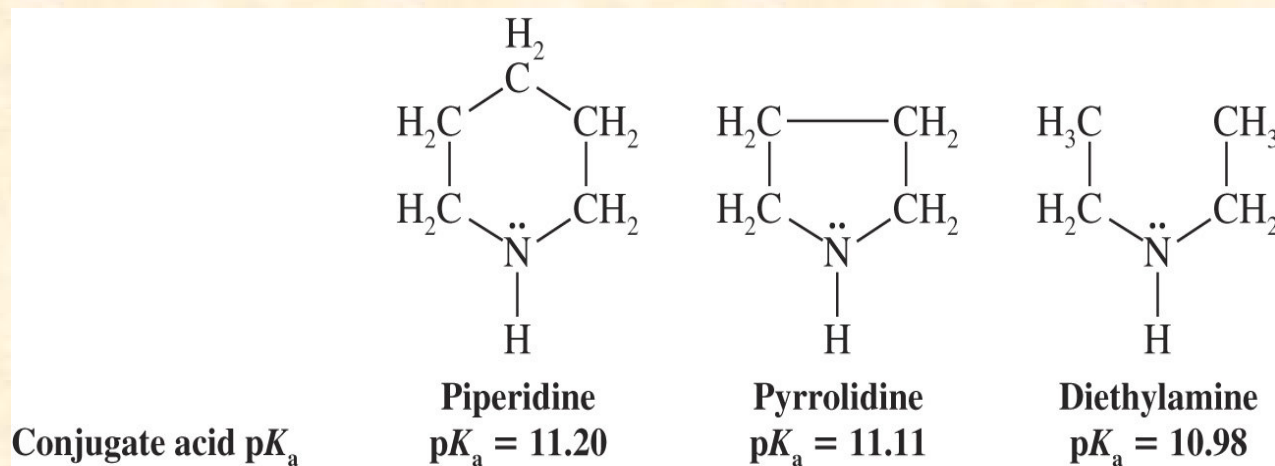
- Aromatic heterocyclic amines (in aqueous solution) are much weaker bases than nonaromatic amines

	Pyridine	**Pyrimidine**	**Pyrrole**	**Quinoline**
Conjugate acid pK_a	$pK_a = 5.23$	$pK_a = 2.70$	$pK_a = 0.40$	$pK_a = 4.5$

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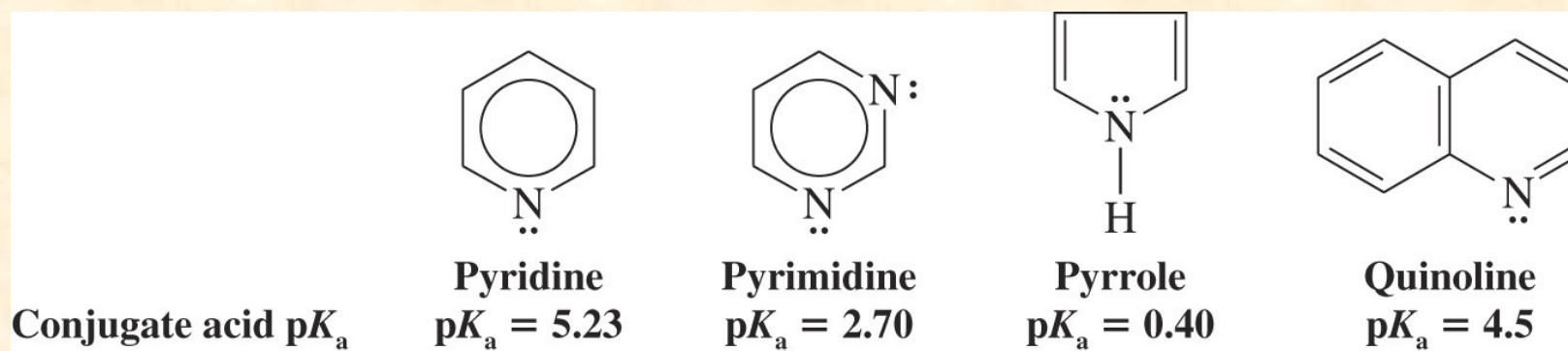
Basicity

– 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
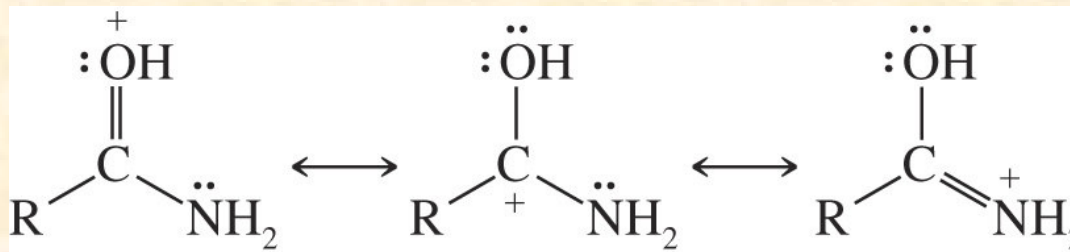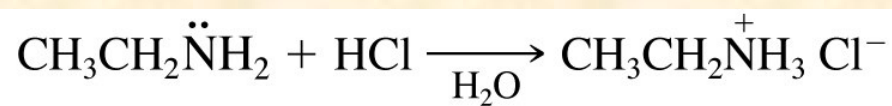

Amide
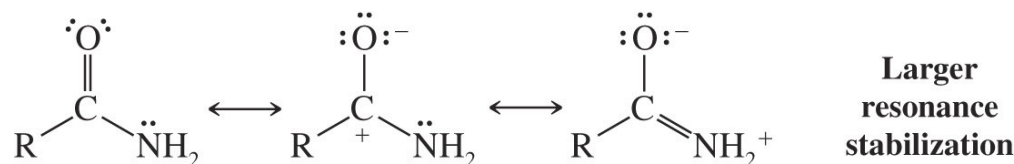
N-Protonated Amide
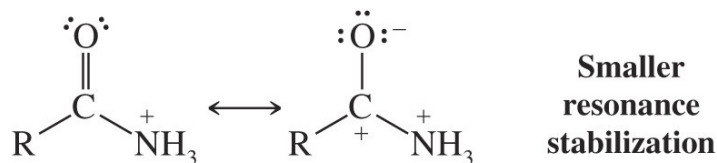
- A more important reason for the weaker basicity of amides is that the nitrogen lone pair is delocalized, amides are protonated at the oxygen
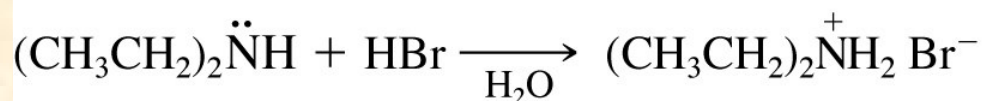 - Protonation at the oxygen allows resonance stabilization of the positive charge

Salts
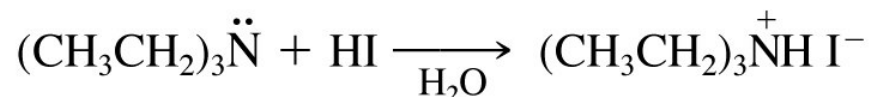
– Aminium Salts and Quaternary Ammonium Salts

• Protonation of amines with acids leads to formation of aminium salts

– Aminium salts are formed from 1º, 2º or 3º amines and the aminium ion bears at least one hydrogen

$$CH_3CH_2\ddot{N}H_2 + HCl \xrightarrow[H_2O]{} CH_3CH_2\overset{+}{N}H_3 \; Cl^-$$

Ethylaminium chloride
(an aminium salt)

$$(CH_3CH_2)_2\ddot{N}H + HBr \xrightarrow[H_2O]{} (CH_3CH_2)_2\overset{+}{N}H_2 \; Br^-$$

Diethylaminium bromide

$$(CH_3CH_2)_3\ddot{N} + HI \xrightarrow[H_2O]{} (CH_3CH_2)_3\overset{+}{N}H \; I^-$$

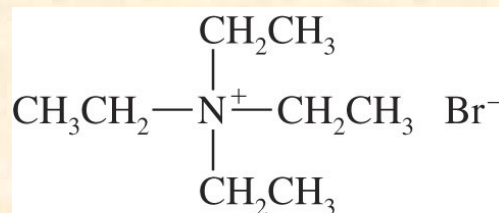**Triethylaminium iodide**

• Quaternary ammonium salts have four groups on the nitrogen

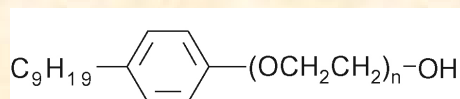– The nitrogen atom is positively charged *but does not bear a hydrogen atom*

$$CH_3CH_2 - \overset{\overset{\displaystyle CH_2CH_3}{|}}{\underset{\underset{\displaystyle CH_2CH_3}{|}}{N^+}} - CH_2CH_3 \quad Br^-$$

Tetraethylammonium bromide
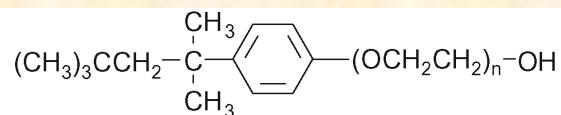**(a quaternary ammonium salt)**

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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
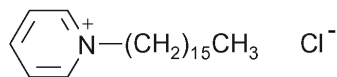
$$(CH_3)_4\overset{+}{N}\ OH^- + HCl \longrightarrow (CH_3)_4\overset{+}{N}\ Cl^- + H_2O$$

$(CH_3CH_2)_4N\ Br^-$
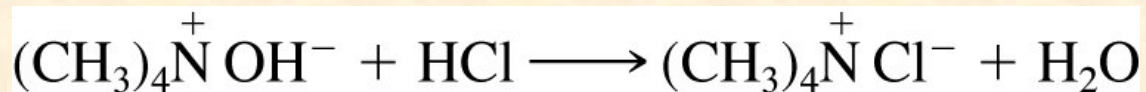
Tetraethylammonium bromide
(does not undergo reaction with acid)

C_9H_{19}—⟨benzene⟩—$(OCH_2CH_2)_n$—OH

Nonoxynol-9 (spermaticide)

$(CH_3)_3CCH_2$—C(CH_3)_2—⟨benzene⟩—$(OCH_2CH_2)_n$—OH

Octoxynol-9 (spermaticide)

⟨pyridinium⟩$\overset{+}{N}$—$(CH_2)_{15}CH_3$ Cl⁻

Cetylpyridinium chloride
(disinfectant)

$\left[\text{⟨benzene⟩—CH}_2\text{—}\overset{CH_3}{\underset{CH_3}{N}}\text{—R} \right]^+$ Cl⁻
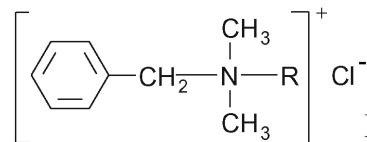
Benzalkonium chloride
(antiseptic)

Solute with strong hydrophilic affinity

Non-polar solute

Solute with weak hydrophilic affinity

(a)   (b)
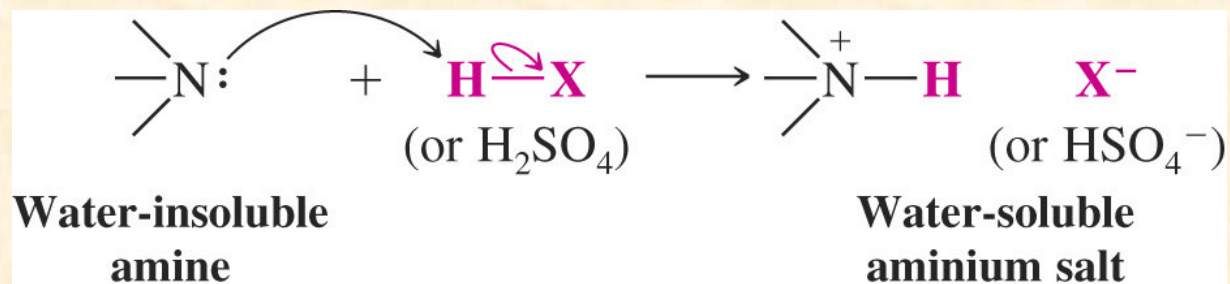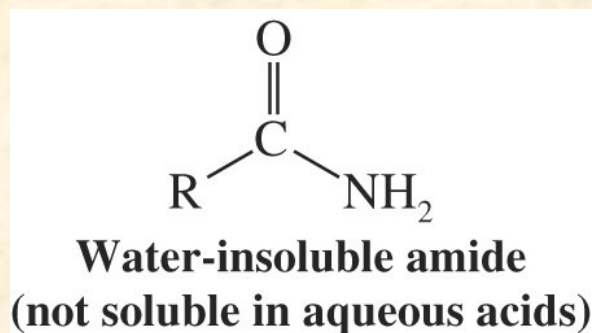
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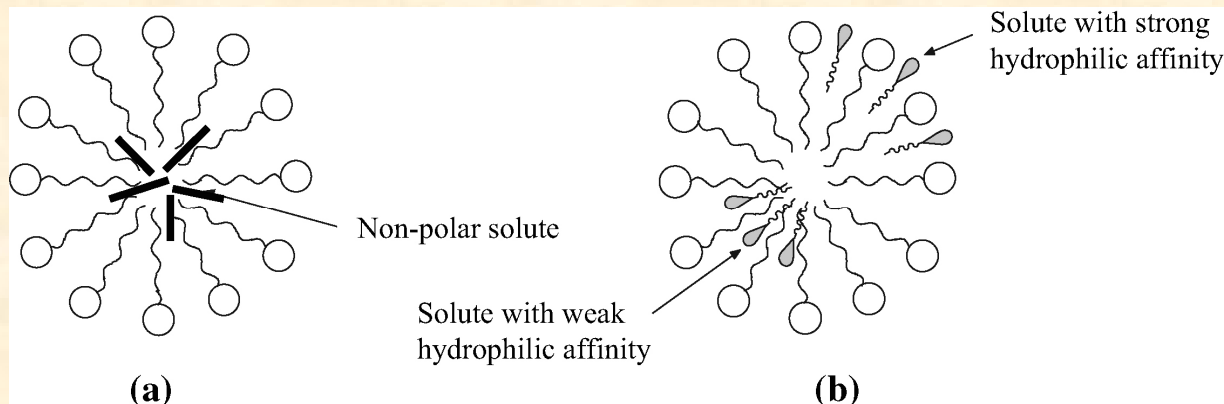
Basicity

– 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

Water-insoluble amide
(not soluble in aqueous acids)

Resolving Agents

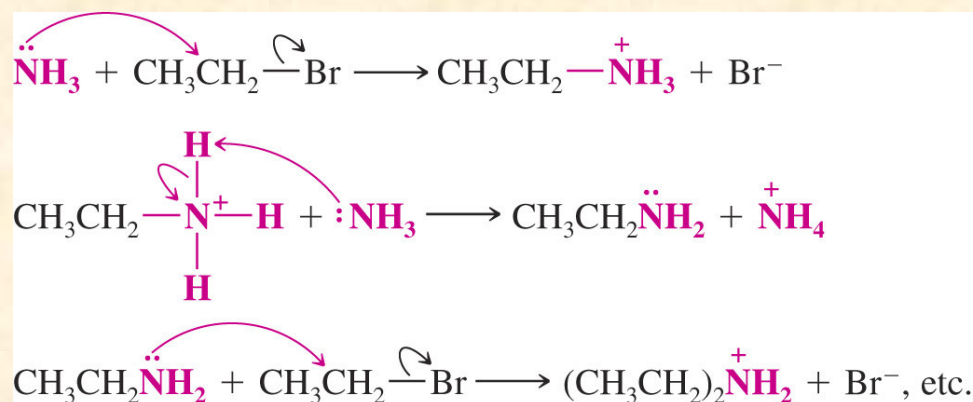– Amines as Resolving Agents

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


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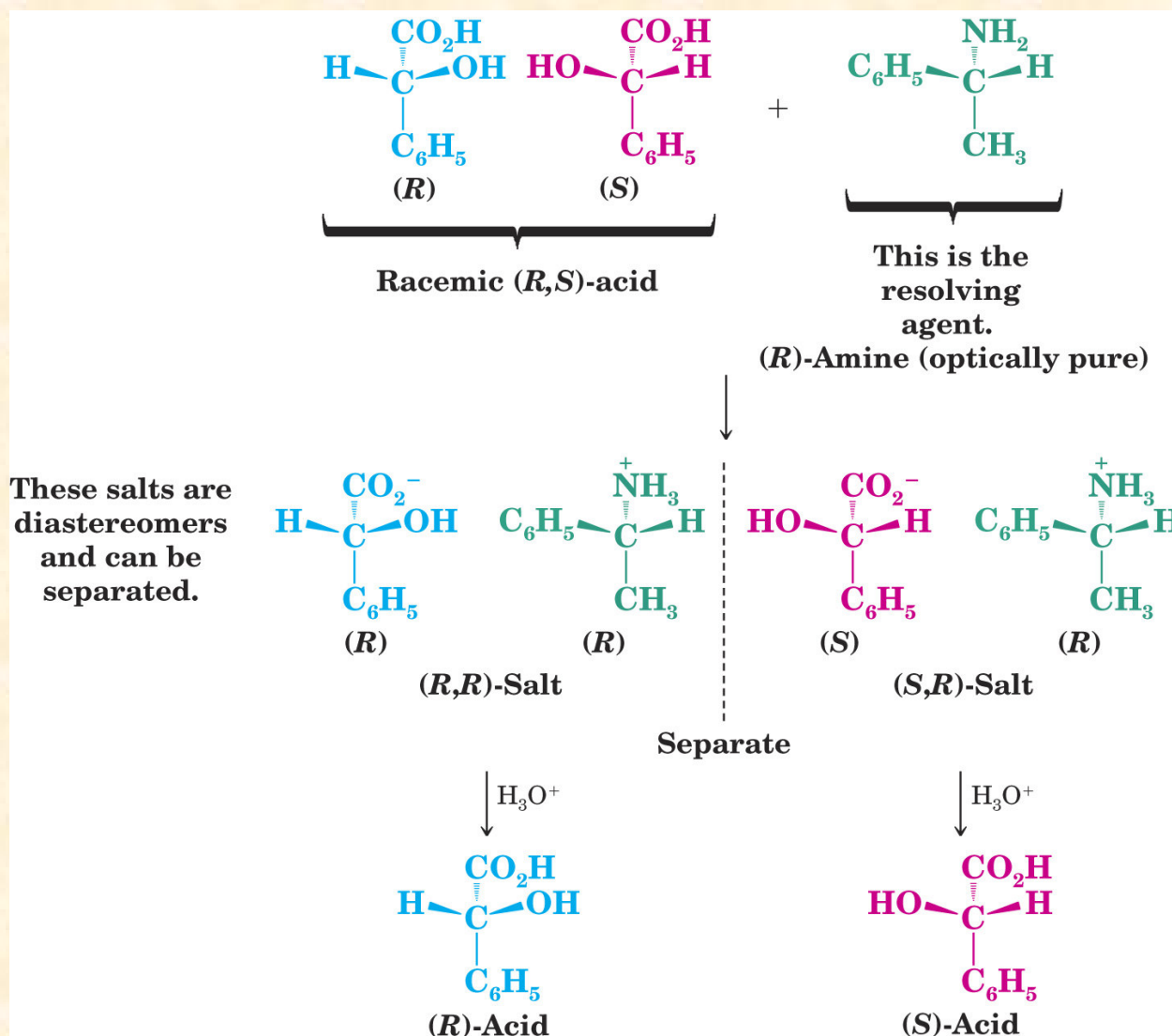
Synthesis of Amines

By Nucleophilic Substitution Reactions

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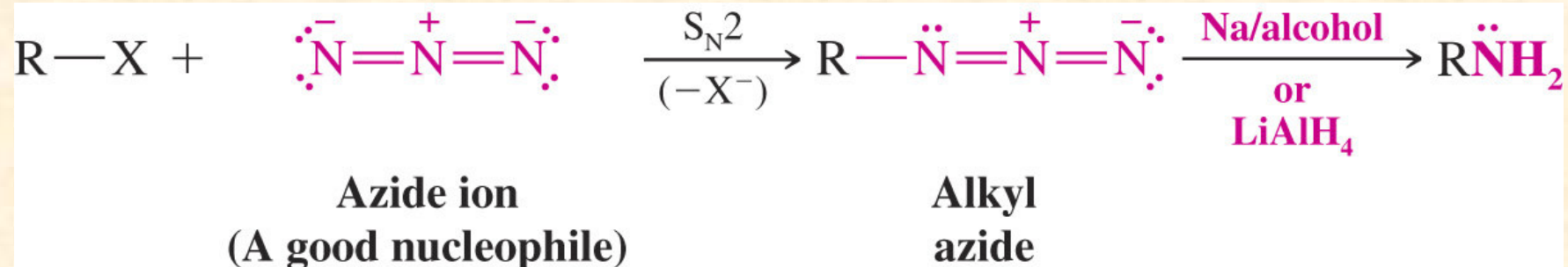 - Reaction of ammonia with an alkyl halide

$$\ddot{N}H_3 + R{-}X \longrightarrow R{-}\overset{+}{N}H_3 \ X^- \xrightarrow{OH^-} R\,NH_2$$

$$\ddot{N}H_3 + CH_3CH_2{-}Br \longrightarrow CH_3CH_2{-}\overset{+}{N}H_3 + Br^-$$

$$CH_3CH_2{-}\overset{+}{\underset{H}{\overset{H}{N}}}{-}H + :NH_3 \longrightarrow CH_3CH_2\ddot{N}H_2 + \overset{+}{N}H_4$$

$$CH_3CH_2\ddot{N}H_2 + CH_3CH_2{-}Br \longrightarrow (CH_3CH_2)_2\overset{+}{N}H_2 + Br^-, \text{etc.}$$

  - Using an excess of ammonia helps to minimize multiple alkylations

$$CH_3\underset{Br}{CH}CO_2H + NH_3 \longrightarrow CH_3\underset{NH_2}{CH}CO_2^- \ NH_4^+$$

(1 mol)   (70 mol)   Alanine
(65–70%)
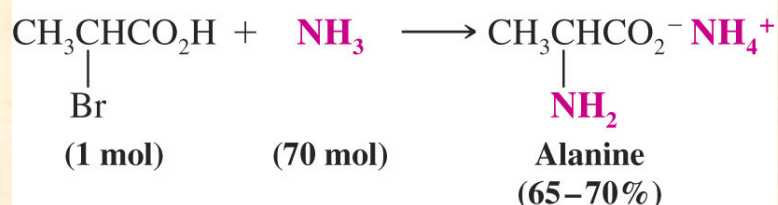
Synthesis of Amines

- Alkylation of Azide Ion followed by Reduction

$$R-X + \quad :\overset{-}{\ddot{N}}=\overset{+}{\ddot{N}}=\overset{-}{\ddot{N}}: \quad \xrightarrow[(-X^-)]{S_N2} \quad R-\overset{..}{\ddot{N}}=\overset{+}{\ddot{N}}=\overset{-}{\ddot{N}}: \quad \xrightarrow[\substack{\text{or}\\ \text{LiAlH}_4}]{\text{Na/alcohol}} \quad R\overset{..}{\ddot{N}}H_2$$

Azide ion
(A good nucleophile)

Alkyl azide

- The Gabriel Synthesis for primary amines

Step 1 ... KOH ... *Step 2* ... R—X (−KX) ... *Step 3* ... $\ddot{N}H_2\ddot{N}H_2$ ethanol reflux (several steps)

Phthalimide

N-Alkylphthalimide

C—NHNH₂

$\xrightarrow[\text{steps}]{\text{(several}}$

C—N—R
O H

Phthalazine-1,4-dione

+ R—$\ddot{N}$H₂
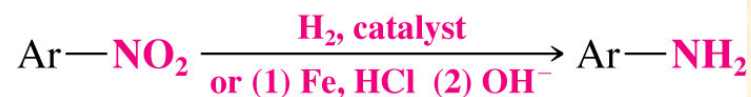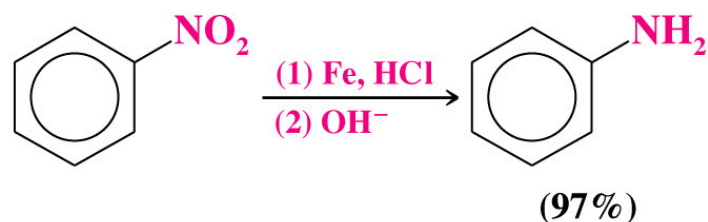
Primary amine
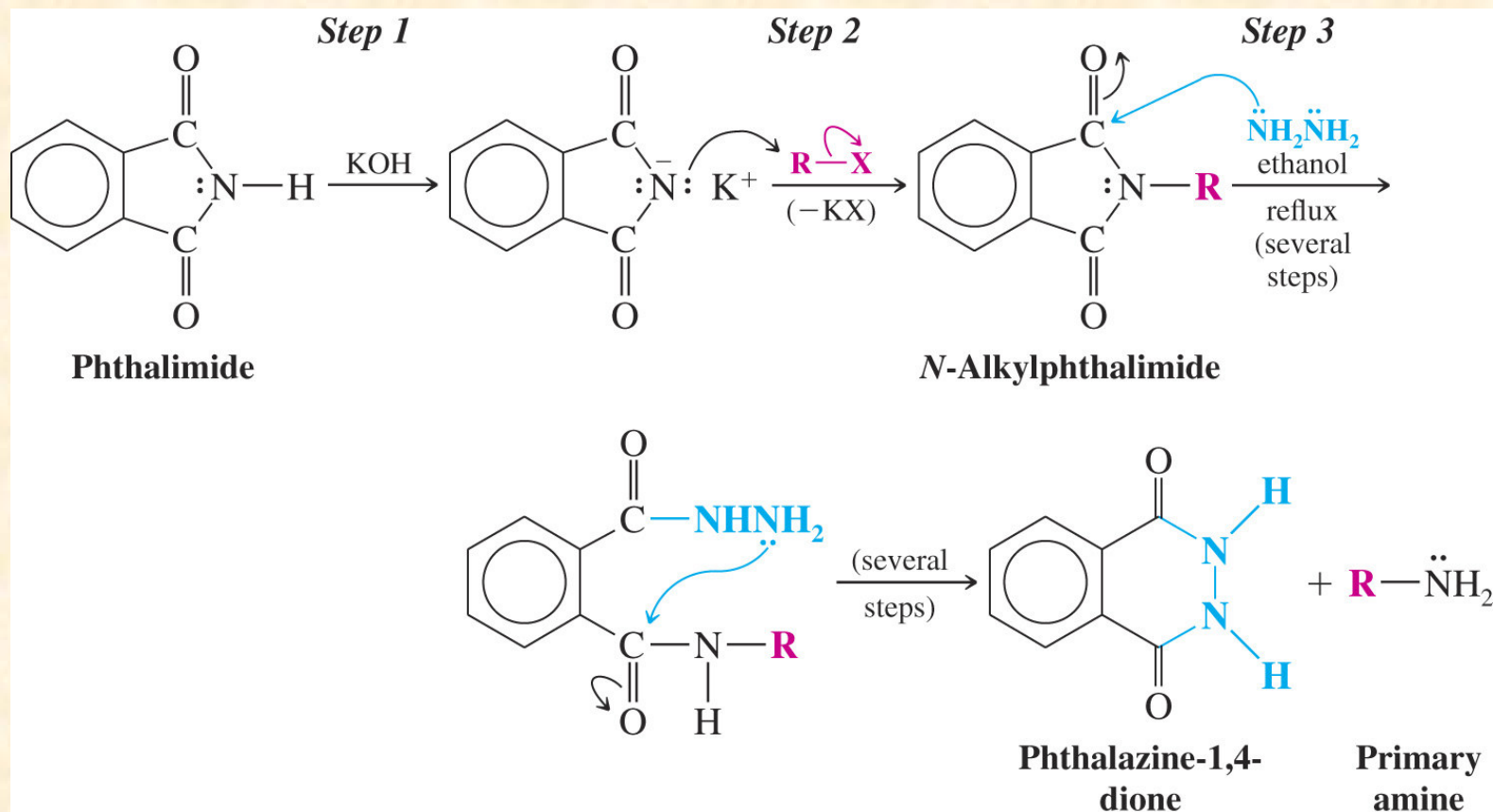
Synthesis of Amines

– Preparation of Aromatic Amines by Reduction of Nitro Compounds

- Aromatic amines can be synthesized by reduction of the corresponding nitro compound

$$Ar-H \xrightarrow[H_2SO_4]{HNO_3} Ar-NO_2 \xrightarrow{[H]} Ar-NH_2$$

General Reaction

$$Ar-NO_2 \xrightarrow[\text{or (1) Fe, HCl (2) OH}^-]{H_2, \text{catalyst}} Ar-NH_2$$

Specific Example

(1) Fe, HCl
(2) OH⁻

(97%)

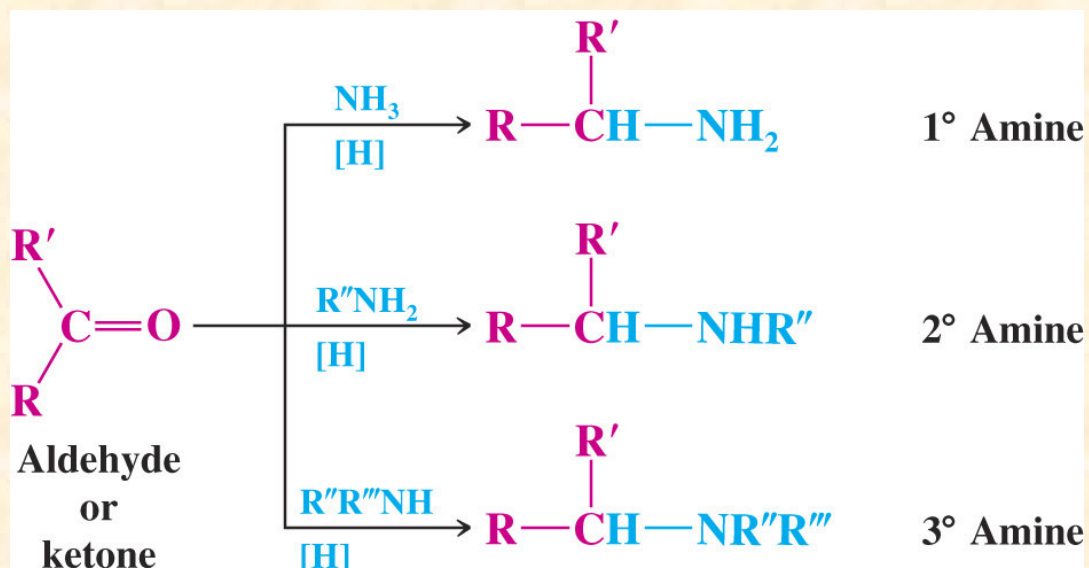- One molar equivalent of hydrogen sulfide in alcoholic ammonia can be used to reduce one nitro group in the presence of another

H₂S
NH₃, C₂H₅OH

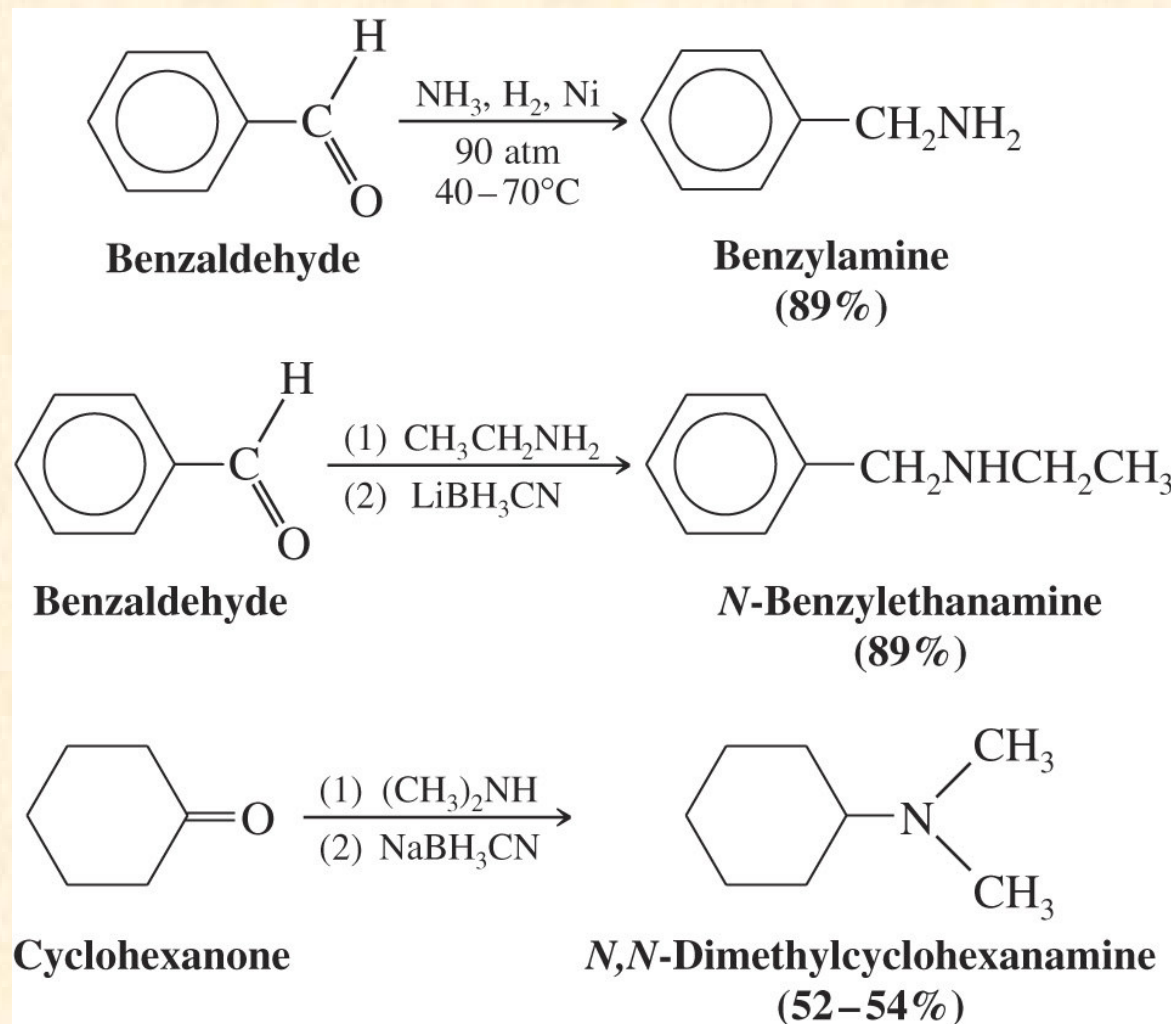*m*-Dinitrobenzene *m*-Nitroaniline
(70–80%)

21
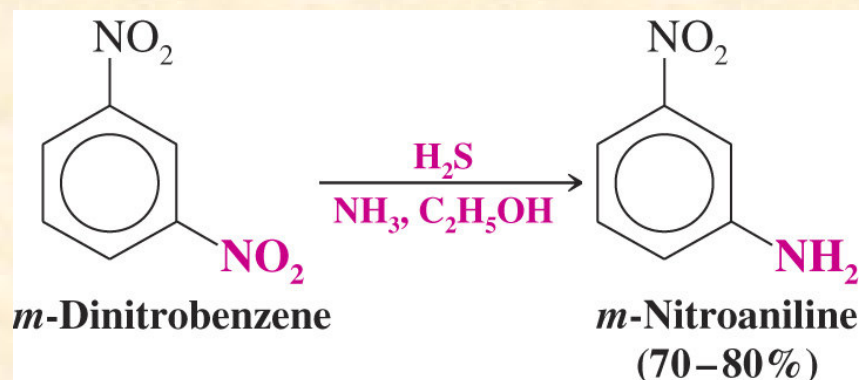
Synthesis of Amines

– Preparation of Primary, Secondary and Tertiary Amines through Reductive Amination
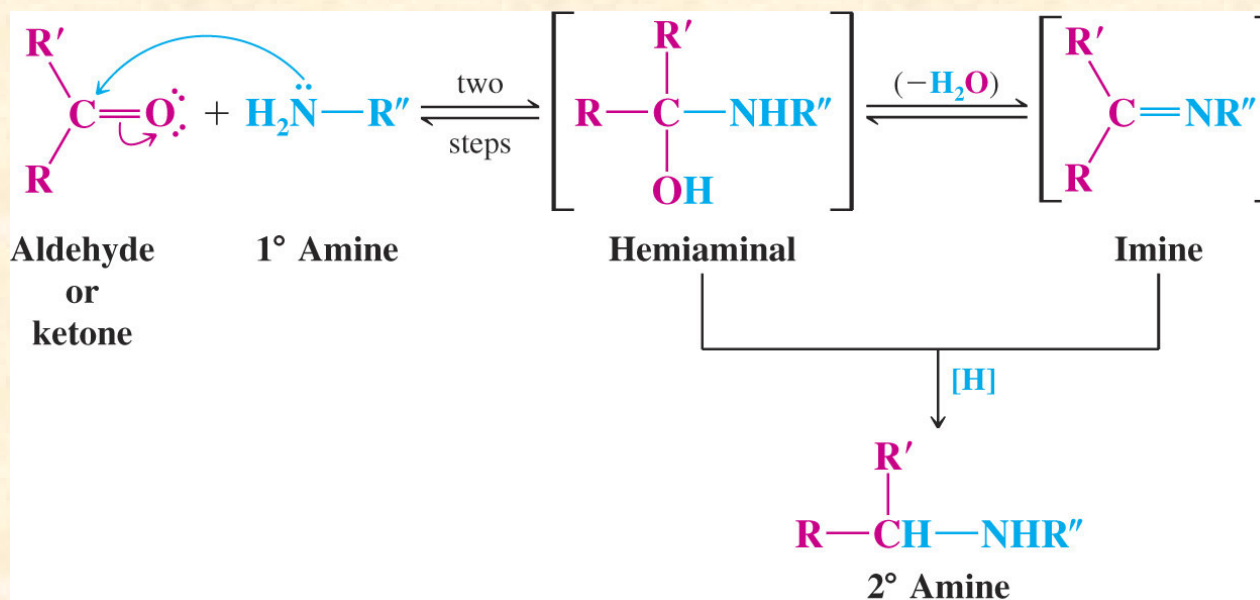
Synthesis of Amines

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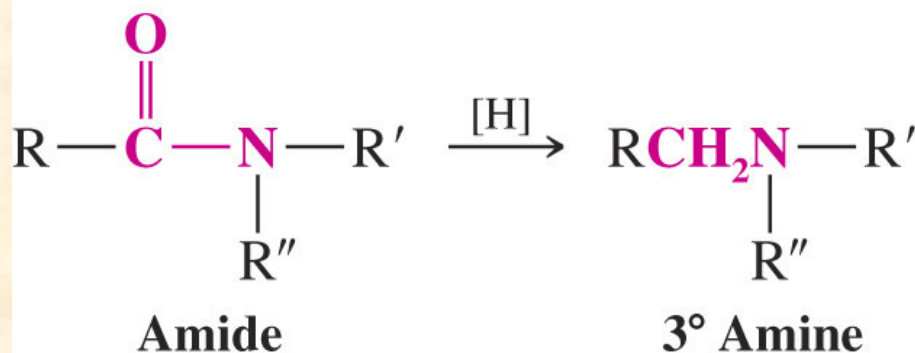 - $NaBH_3CN$ and $LiBH_3CN$ are especially effective in reductive aminations

Benzaldehyde → Benzylamine (89%)
Reagents: NH_3, H_2, Ni, 90 atm, 40–70°C

Benzaldehyde → N-Benzylethanamine (89%)
Reagents: (1) $CH_3CH_2NH_2$ (2) $LiBH_3CN$

Cyclohexanone → N,N-Dimethylcyclohexanamine (52–54%)
Reagents: (1) $(CH_3)_2NH$ (2) $NaBH_3CN$

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Synthesis of Amines

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

$$R-C\equiv N \xrightarrow{[H]} RCH_2NH_2$$

Nitrile → 1° Amine
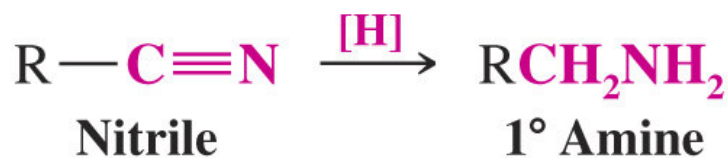
Nitriles can be prepared from alkyl halides and CN^- (Section 18.3) or from aldehydes and ketones as cyanohydrins (Section 16.9).
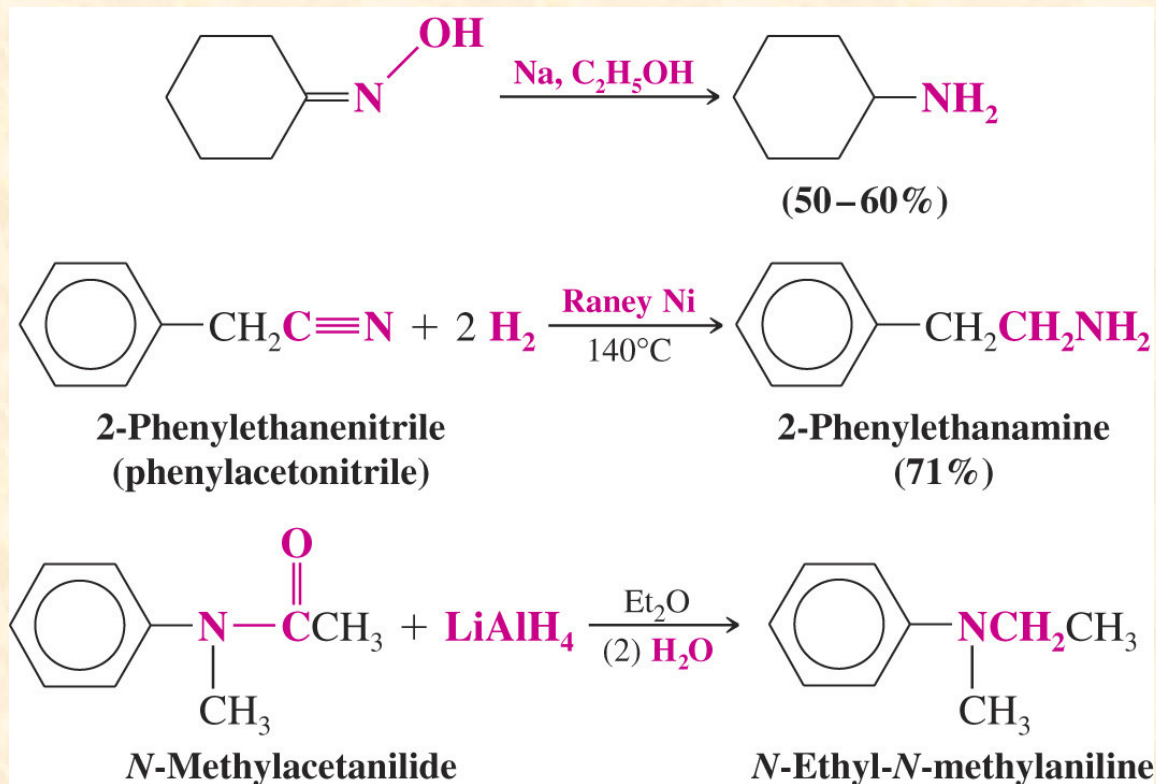
$$RCH=NOH \xrightarrow{[H]} RCH_2NH_2$$

Oxime → 1° Amine

Oximes can be prepared from aldehydes and ketones (Section 16.8A).

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle R''}{|}}{N}-R' \xrightarrow{[H]} RCH_2\underset{\underset{\displaystyle R''}{|}}{N}-R'$$

Amide → 3° Amine

Amides can be prepared from acid chlorides, acid anhydrides, and esters (Section 18.8).

Synthesis of Amines

- Reduction can be accomplished by using catalytic hydrogenation or LiAlH$_4$

2-Phenylethanenitrile
(phenylacetonitrile)

2-Phenylethanamine
(71%)

N-Methylacetanilide

N-Ethyl-*N*-methylaniline

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

Benzylamine

Benzylethylamine

25
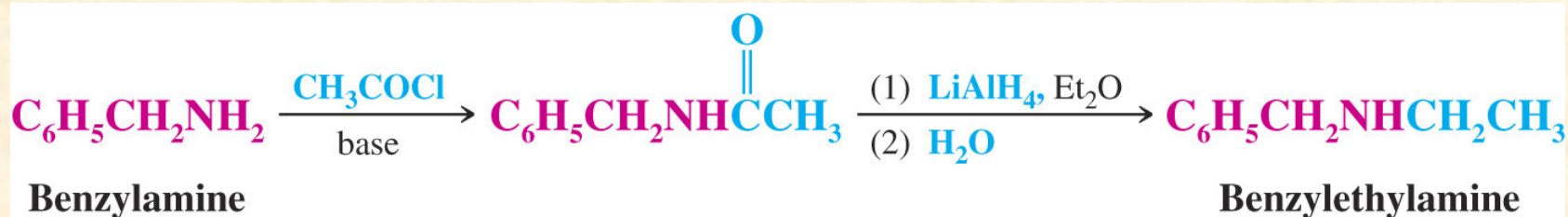
Synthesis of Amines

– 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)*

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 + Br_2 + 4\,NaOH \xrightarrow{H_2O} RNH_2 + 2\,NaBr + Na_2CO_3 + 2\,H_2O$$
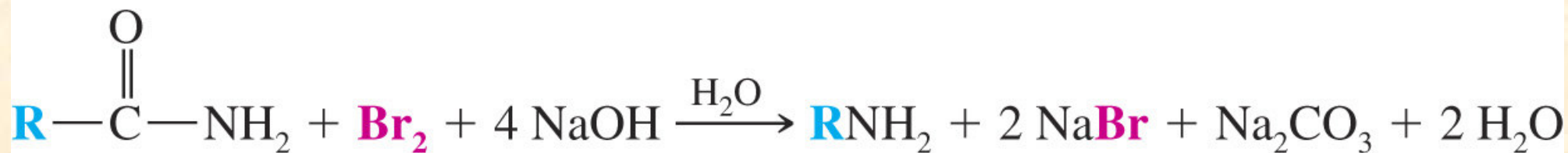
  - The first two steps of the mechanism result in *N*-bromination of the amide
    – The *N*-bromoamide is deprotonated and rearranges to an isocyanate
    – The isocyanate is hydrolyzed to a carbamate which decarboxylates to the amine
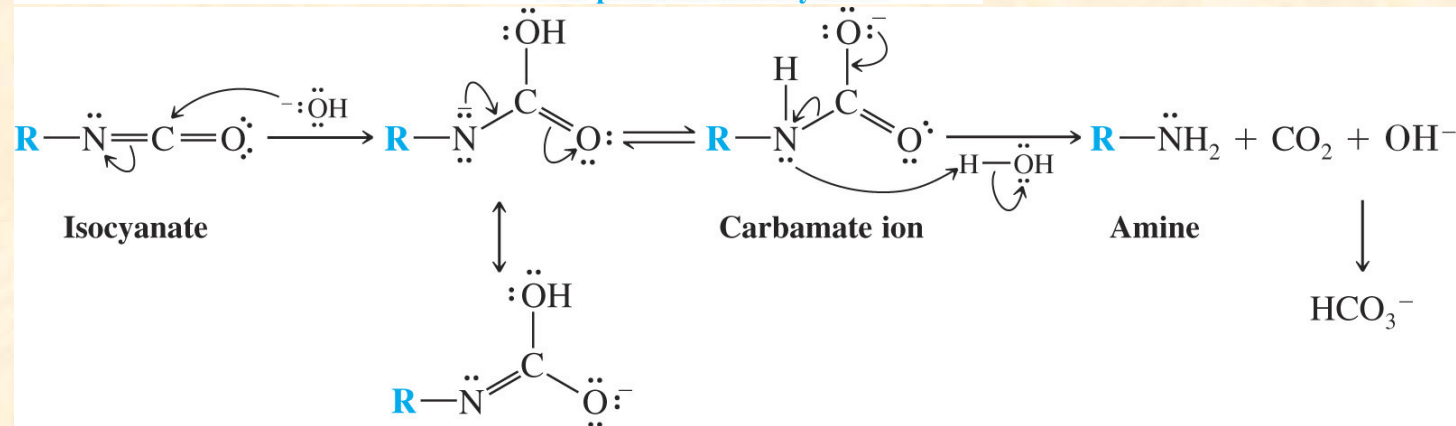
26

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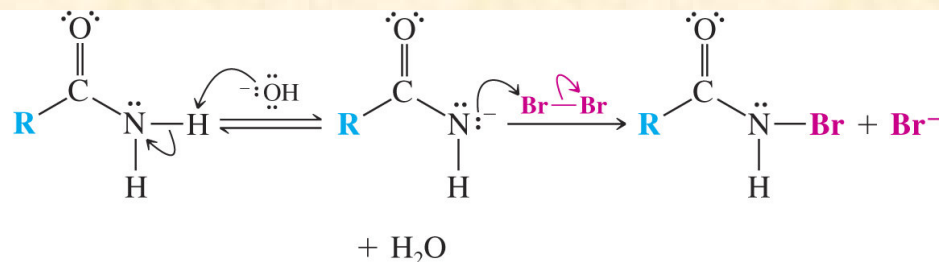
Base-promoted *N*-bromination of the amide occurs.

Amide → *N*-Bromo amide

N-Bromo amide + H₂O → Isocyanate
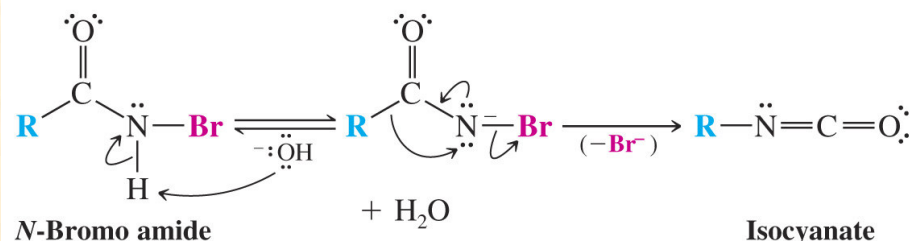
Base removes a proton from the nitrogen to give a bromo amide anion.

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

Isocyanate → Carbamate ion → Amine

The isocyanate undergoes hydrolysis and decarboxylation to produce the amine.

- 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

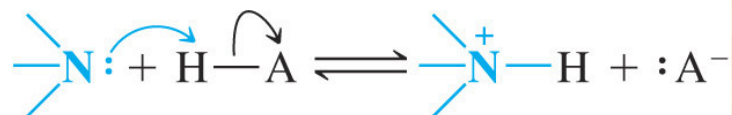Acyl chloride   Acyl azide   Isocyanate   Amine
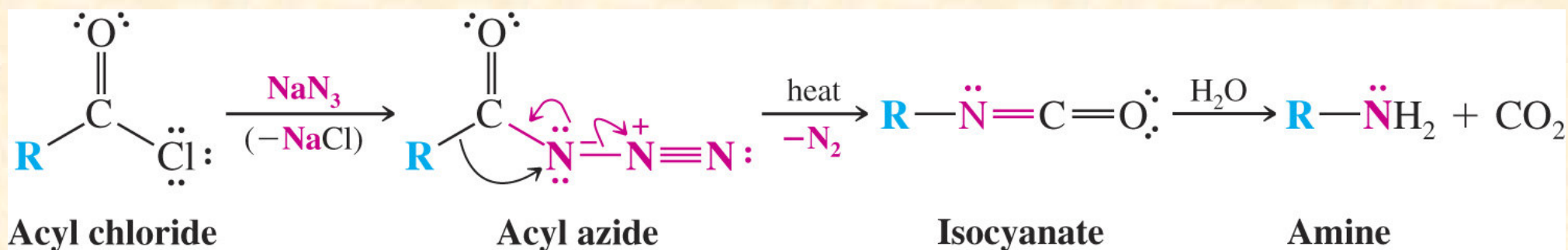
Reactions of Amines

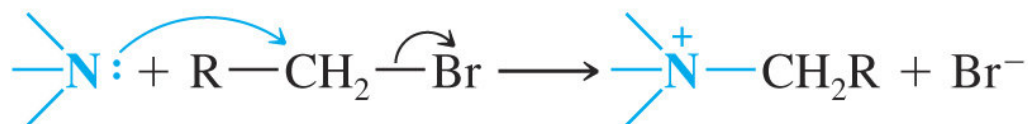The lone pair of the nitrogen atom accounts for most chemistry of amines

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

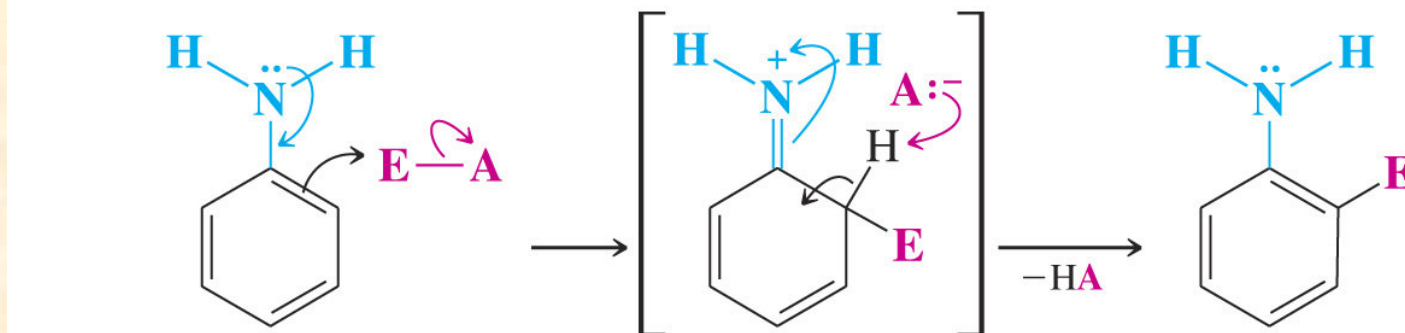*Acid–Base Reactions*

An amine acting as a base

Alkylation

An amine acting as a nucleophile in an alkylation reaction

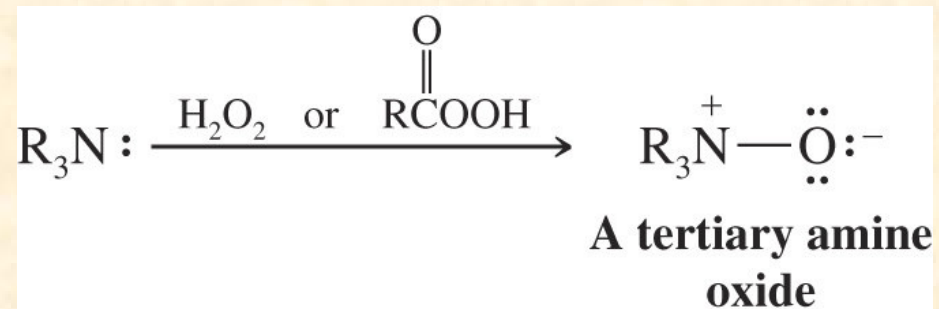- The nitrogen lone pair can also make a carbon nucleophilic by resonance

Electrophilic Aromatic Substitution
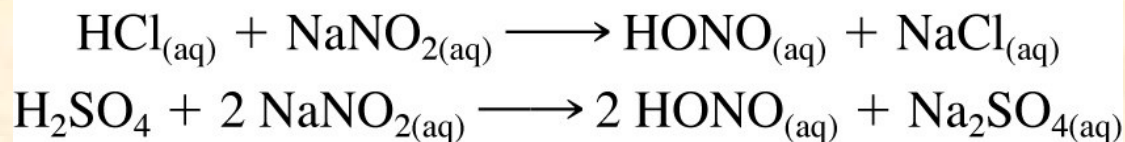
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Reactions of Amines

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


A tertiary amine oxide

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

$$HCl_{(aq)} + NaNO_{2(aq)} \longrightarrow HONO_{(aq)} + NaCl_{(aq)}$$

$$H_2SO_4 + 2\,NaNO_{2(aq)} \longrightarrow 2\,HONO_{(aq)} + Na_2SO_{4(aq)}$$

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

General Reaction

$$R-NH_2 + NaNO_2 + 2\,HX \xrightarrow[H_2O]{(HONO)} \left[R{\overset{+}{-}}N{\equiv}N\!: \ X^- \right] + NaX + 2\,H_2O$$
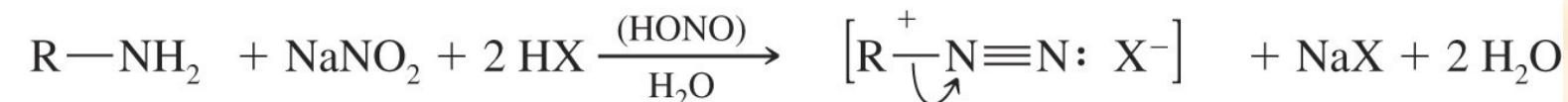
1° Aliphatic amine

Aliphatic diazonium salt (highly unstable)

$$\downarrow -N_2 \ (i.e., :N{\equiv}N:)$$

$$R^+ + X^-$$

$$\downarrow$$
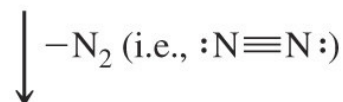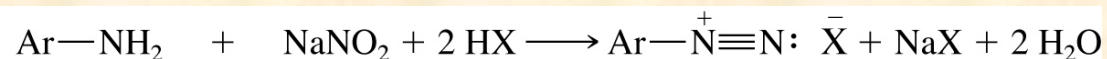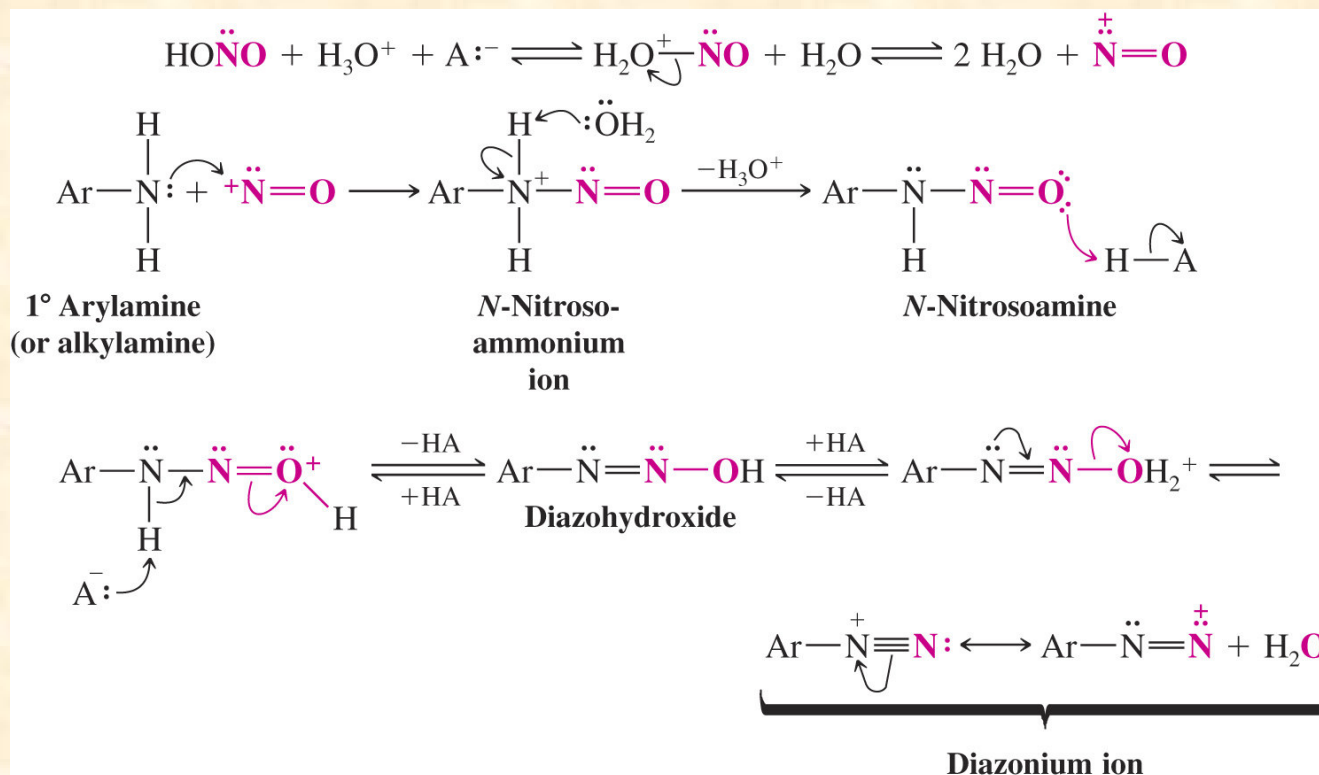
Alkenes, alcohols, alkyl halides

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
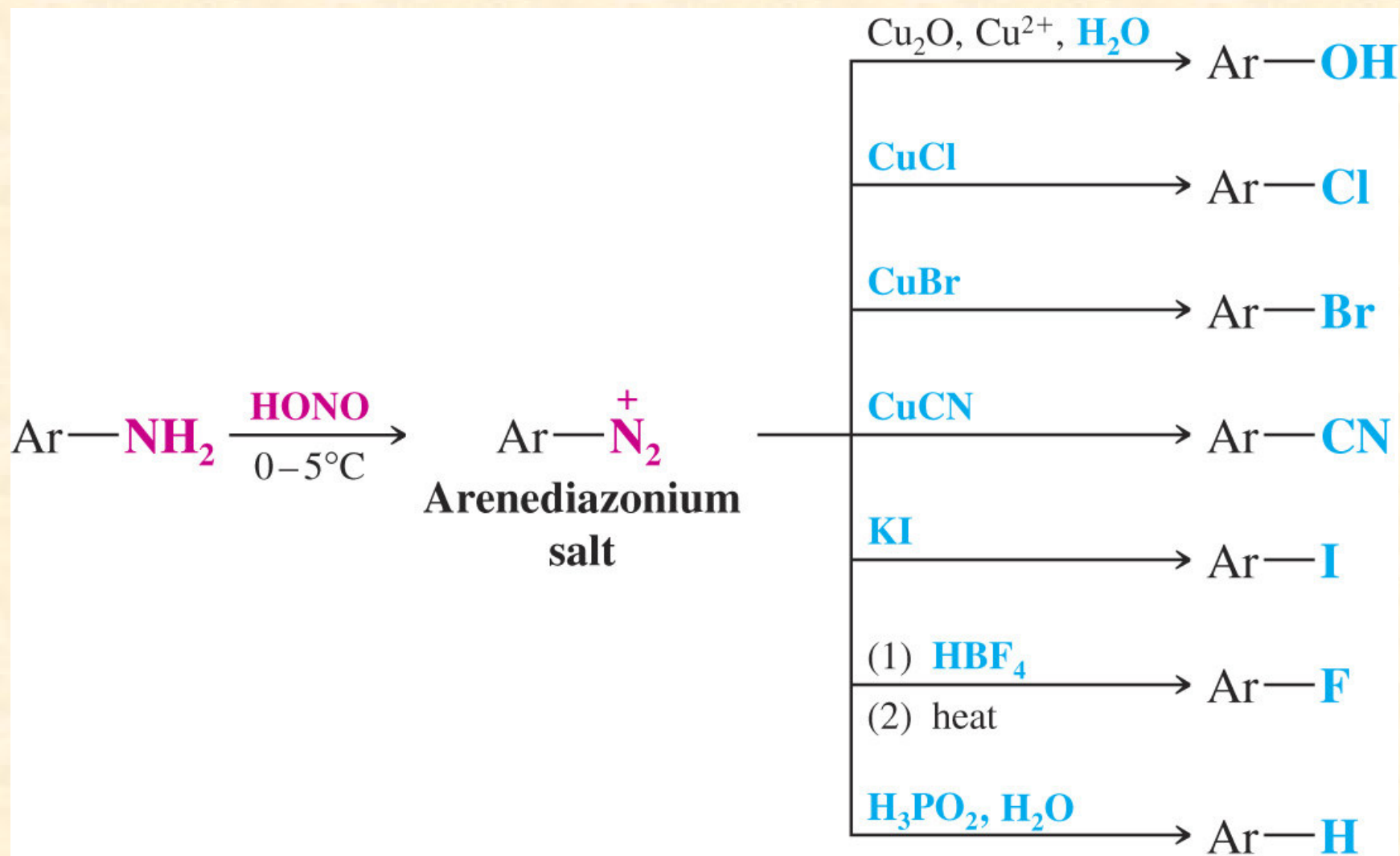- The *N*-nitrosoamine is converted to a diazonium ion

$$Ar-NH_2 \quad + \quad NaNO_2 + 2\ HX \longrightarrow Ar-\overset{+}{N}\equiv N\colon\ \overset{-}{X} + NaX + 2\ H_2O$$

Primary arylamine

Arenediazonium salt (stable if kept below 5°C)

$$HO\ddot{N}O + H_3O^+ + A\colon^- \rightleftharpoons H_2\overset{+}{O}-\ddot{N}O + H_2O \rightleftharpoons 2\ H_2O + \overset{\pm}{N}{=}O$$

1° Arylamine (or alkylamine) — **N-Nitroso-ammonium ion** — **N-Nitrosoamine**

Diazohydroxide

$$Ar-\overset{+}{N}\equiv N\colon \longleftrightarrow Ar-\ddot{N}{=}\overset{\pm}{N} + H_2O$$
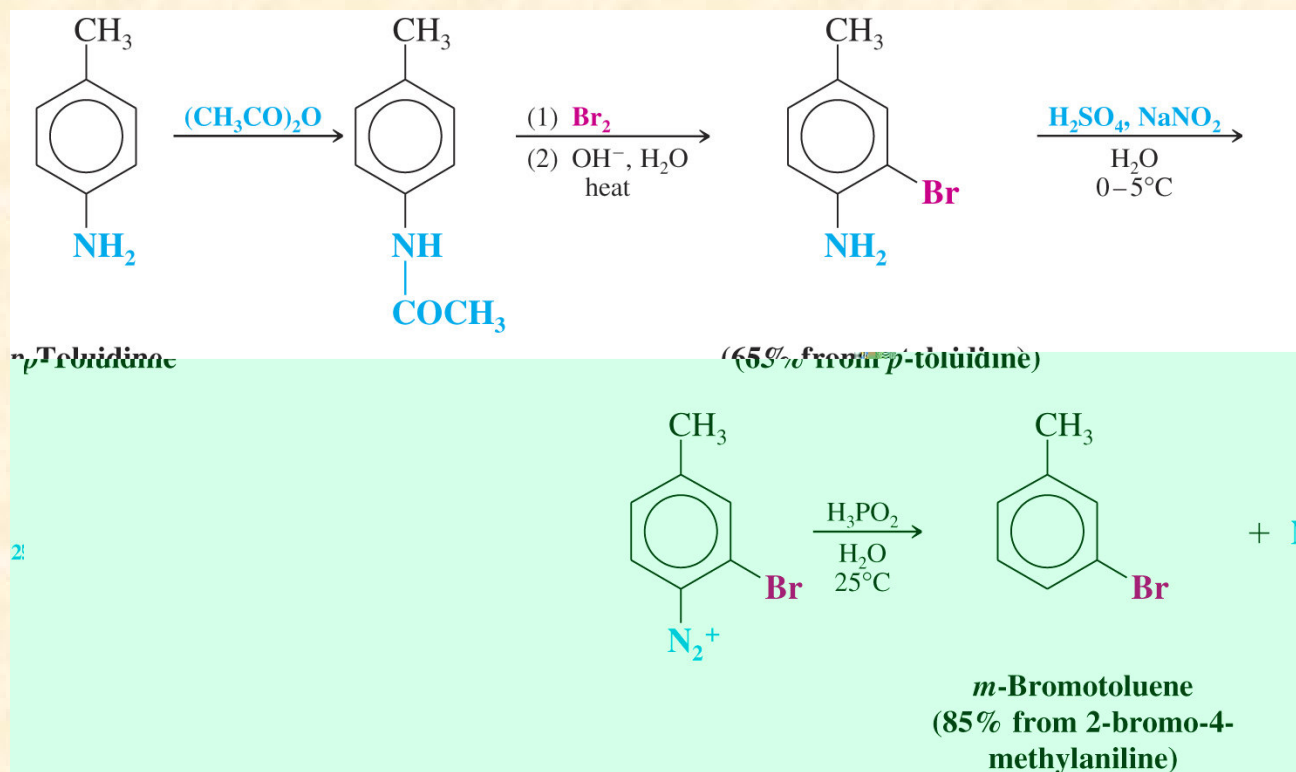
Diazonium ion

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Reactions of Amines

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

$$Ar-NH_2 \xrightarrow[0-5°C]{HONO} Ar-\overset{+}{N_2}$$

Arenediazonium salt

- $\xrightarrow{Cu_2O,\ Cu^{2+},\ H_2O}$ Ar—**OH**
- $\xrightarrow{CuCl}$ Ar—**Cl**
- $\xrightarrow{CuBr}$ Ar—**Br**
- $\xrightarrow{CuCN}$ Ar—**CN**
- $\xrightarrow{KI}$ Ar—**I**
- $\xrightarrow[(2)\ heat]{(1)\ HBF_4}$ Ar—**F**
- $\xrightarrow{H_3PO_2,\ H_2O}$ Ar—**H**

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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


p-Toluidine

(55% from *p*-toluidine)

m-Bromotoluene
(85% from 2-bromo-4-methylaniline)

- 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*

General Reaction

$G = -NR_2$ or $-OH$

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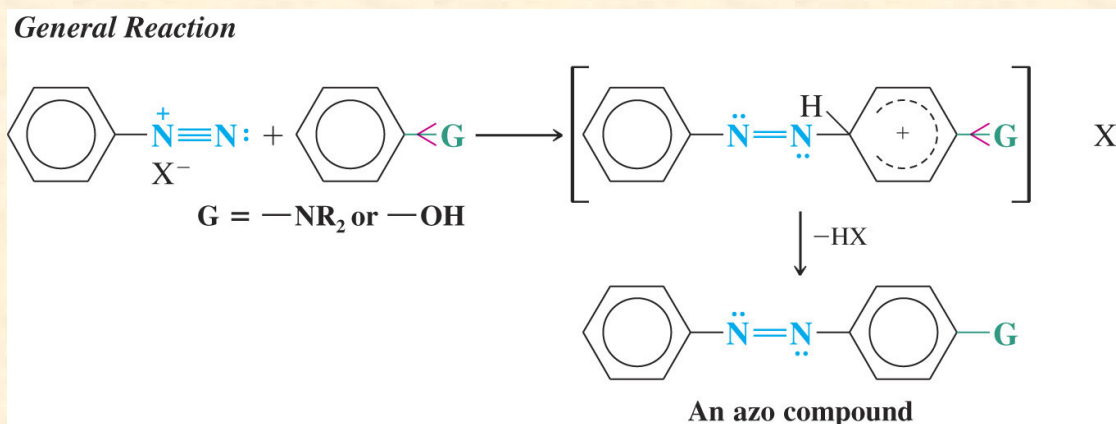
    - Coupling with phenol occurs best in slightly alkaline solution
        – The alkaline solution produces a phenoxide ion that couples more rapidly, if the solution is too alkaline, a nonreactive diazohydroxide is produced
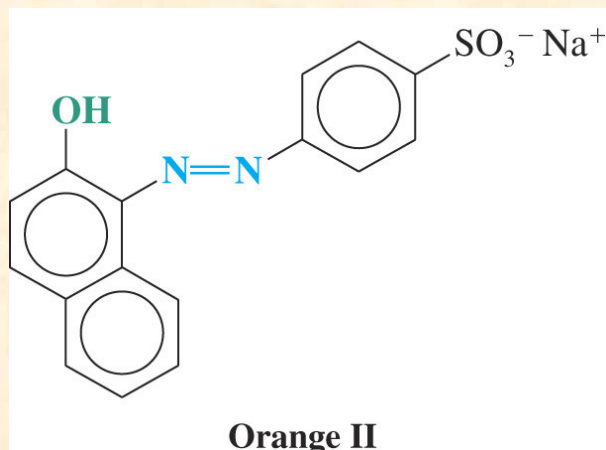

4-Methylphenol
(*p*-cresol)
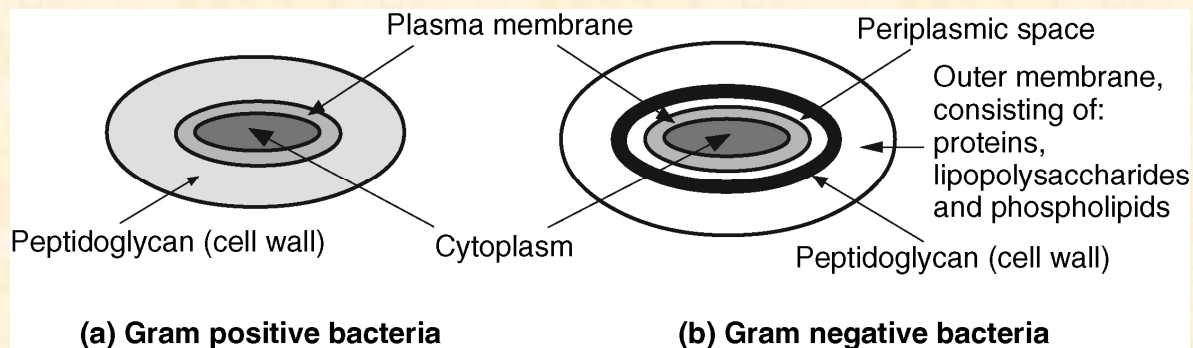
4-Methyl-2-(phenylazo)phenol

35
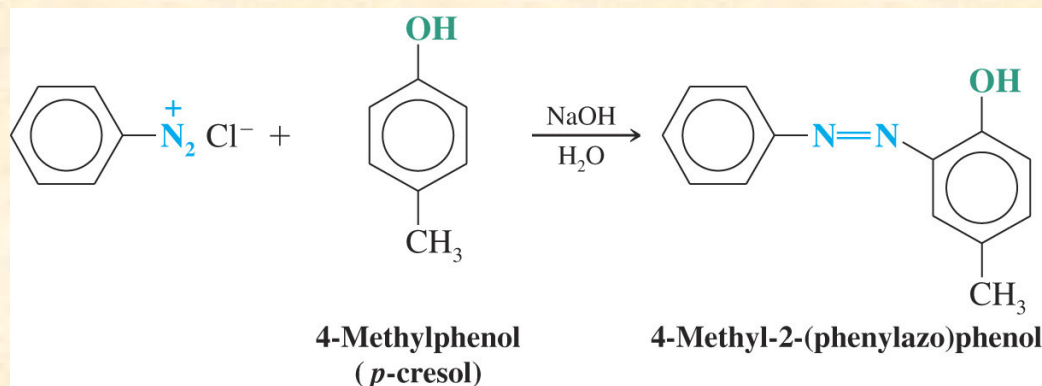
- Phenol and aniline derivatives undergo coupling almost exclusively at the para position unless this position is blocked

4-Methylphenol
(*p*-cresol)   4-Methyl-2-(phenylazo)phenol
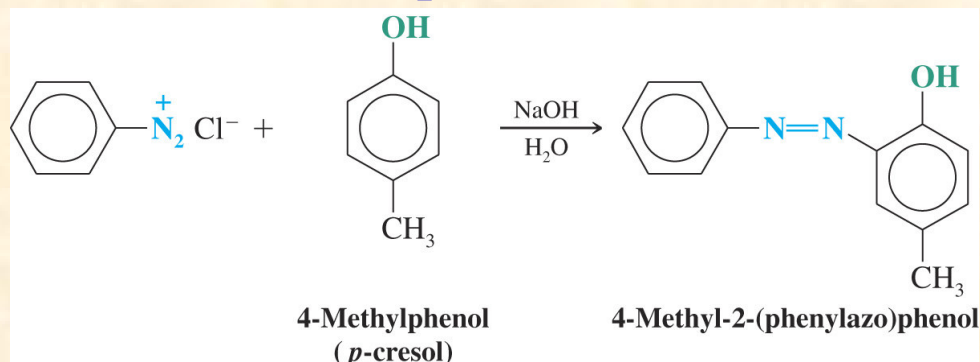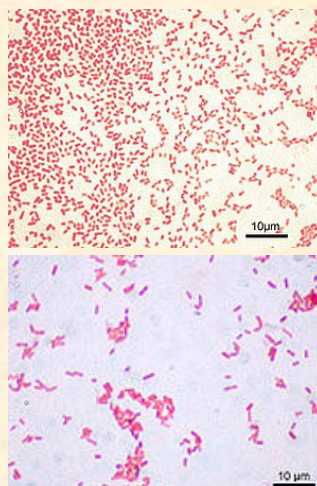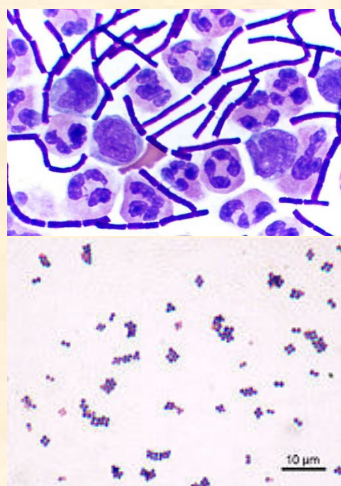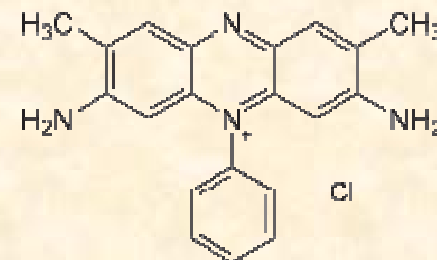
- Azo compounds are commonly used as dyes
    - The azo coupling results in compounds which are highly conjugated
    - The -$SO_3^-Na^+$ group is added to the molecule for solubility and to link the dye to the polar fibers of wool, cotton *etc.*
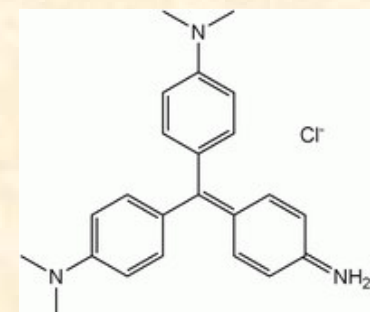   - Orange II is made from 2-naphthol

Orange II

Reactions of Amines

Plasma membrane   Periplasmic space

Outer membrane, consisting of: proteins, lipopolysaccharides and phospholipids

Peptidoglycan (cell wall)   Cytoplasm   Peptidoglycan (cell wall)

(a) Gram positive bacteria   **(b) Gram negative bacteria**

Safranin

Crystal violet

1935

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

Prontosil Red   →metabolism→   Sulfanilamide
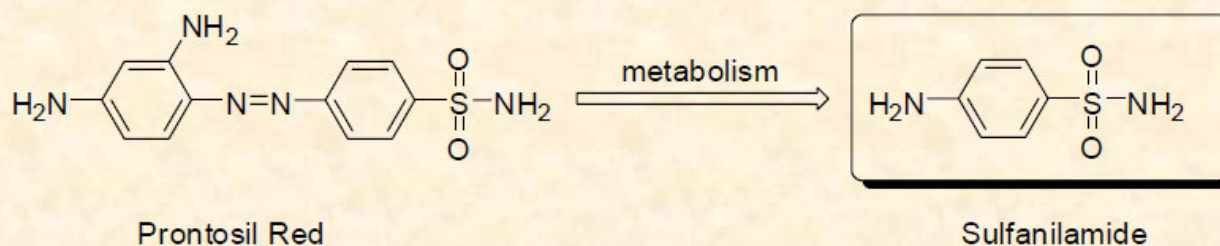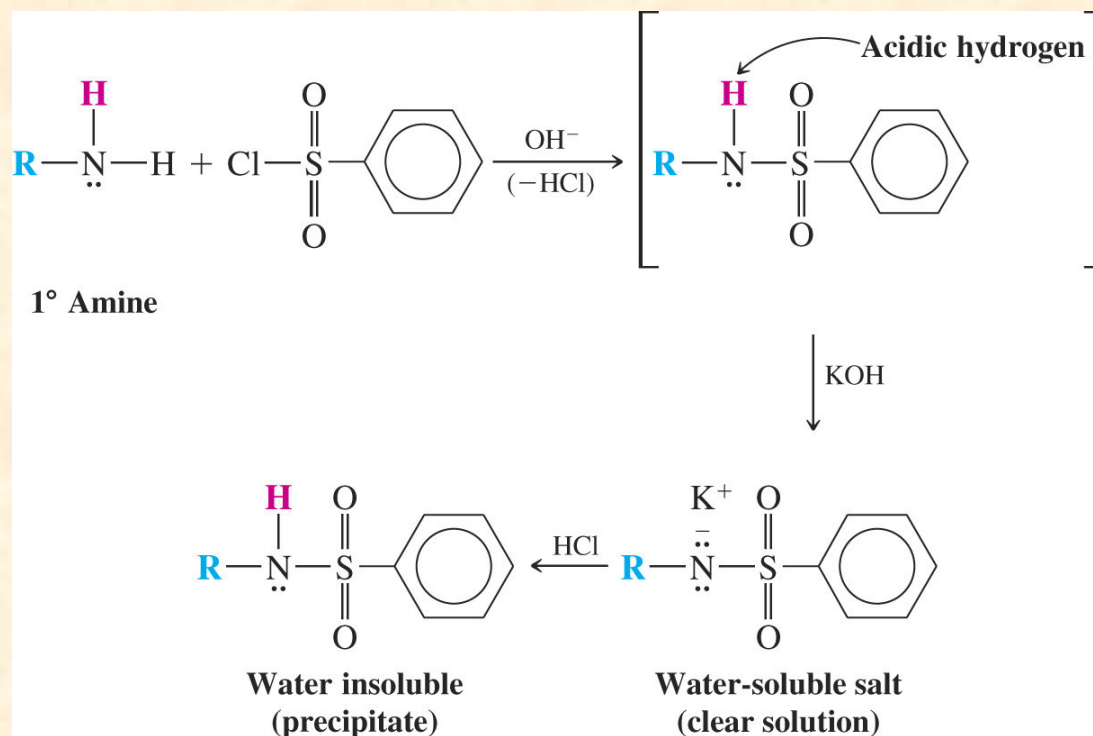
Reactions of Amines

- 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

1° Amine   Sulfonyl chloride   *N*-Substituted sulfonamide

2° Amine   *N,N*-Disubstituted sulfonamide
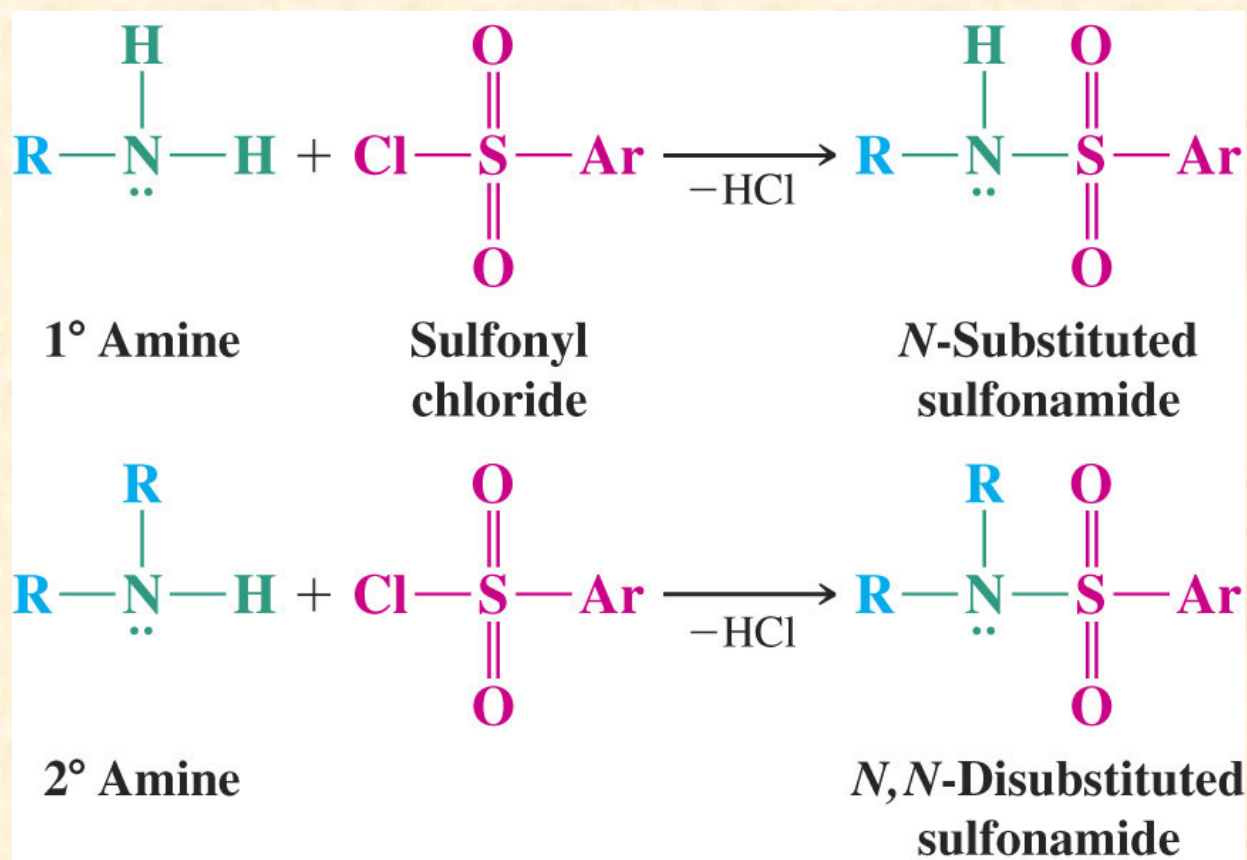
– The Hinsberg Test

- 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

1° Amine

Water insoluble
(precipitate)

Water-soluble salt
(clear solution)

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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
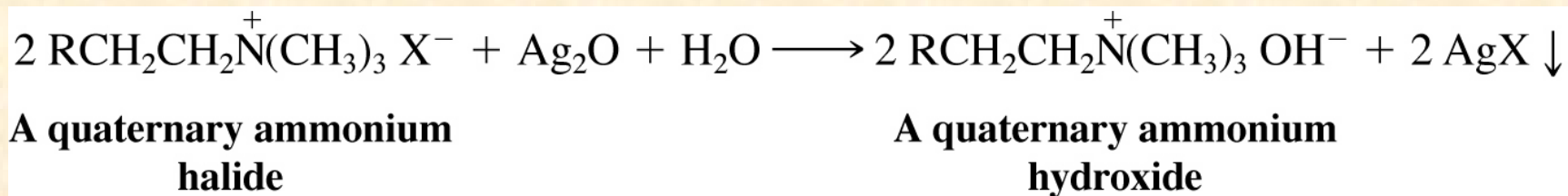

Water insoluble
(precipitate)
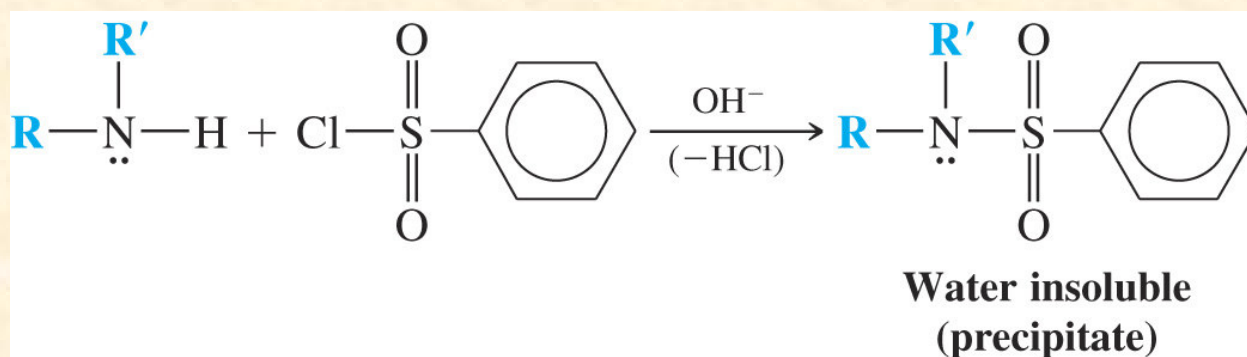
- A tertiary amine will not react to form a sulfonamide, but will dissolve upon acidification
    - Acidification converts the amine to a water soluble iminium salt

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   an alkene   a tertiary amine
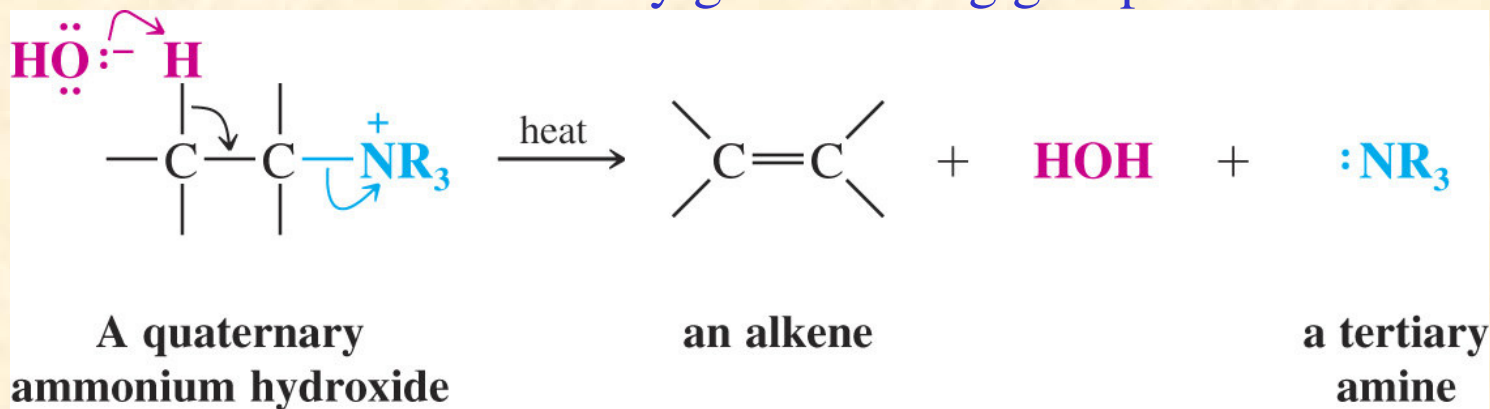
  - A quaternary ammonium hydroxide can be made from a quaternary ammonium halide using silver oxide

$$2\ RCH_2CH_2\overset{+}{N}(CH_3)_3\ X^- + Ag_2O + H_2O \longrightarrow 2\ RCH_2CH_2\overset{+}{N}(CH_3)_3\ OH^- + 2\ AgX\downarrow$$

A quaternary ammonium halide   A quaternary ammonium hydroxide

- 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

$$C_2H_5O^-Na^+ + CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3 \xrightarrow[25°C]{C_2H_5OH}$$

$$CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2 + NaBr + C_2H_5OH$$
$$(75\%) \qquad\qquad (25\%)$$

$$CH_3CH_2\underset{\underset{+}{\underset{N(CH_3)_3}{|}}}{C}HCH_3\ OH^- \xrightarrow{150°C} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2 + (CH_3)_3N{:} + H_2O$$
$$(5\%) \qquad\qquad (95\%)$$

$$CH_3CH_2\underset{\underset{+}{\underset{S(CH_3)_2}{|}}}{C}HCH_3\ \bar{O}C_2H_5 \longrightarrow CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2 + (CH_3)_2S + C_2H_5OH$$
$$(26\%) \qquad\qquad (74\%)$$

42
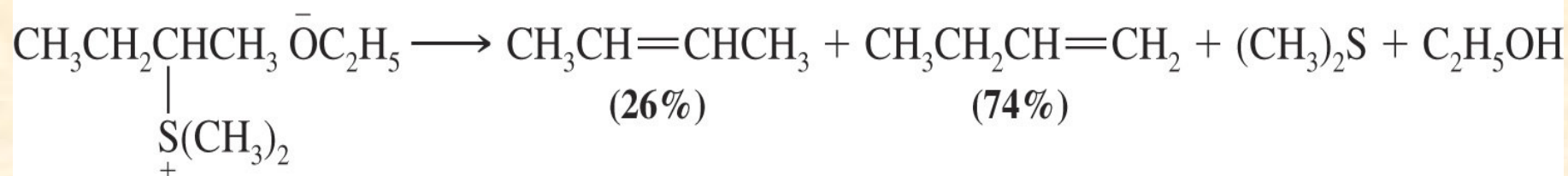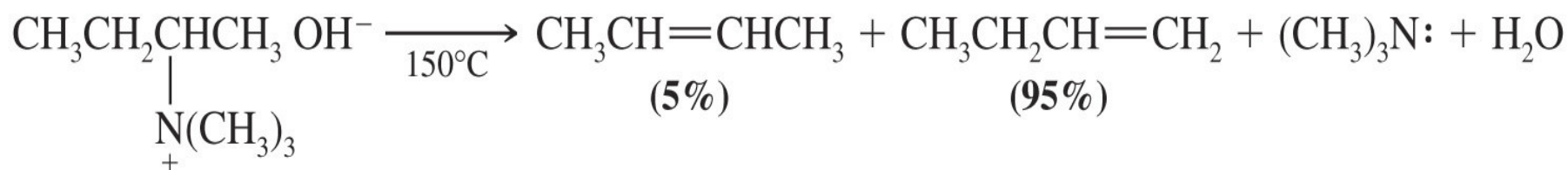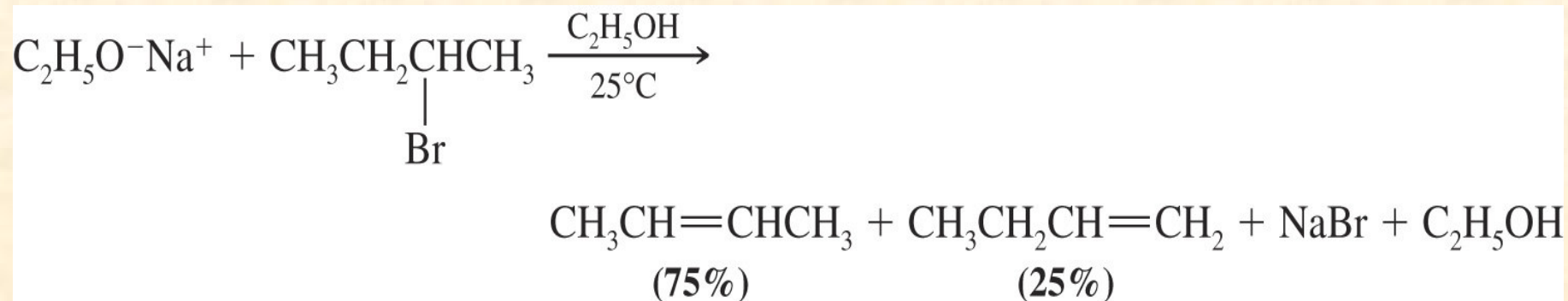
Reactions of Amines

- 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

A tertiary amine oxide → An alkene + N,N-Dimethylhydroxylamine

(98%)