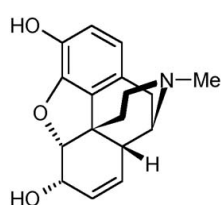
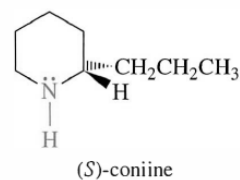


# Amines

เอกสารประกอบการสอน รายวิชา 01403224  
ดร.นงพงา จรัสโสภณ



*Morphine*

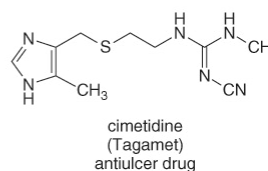
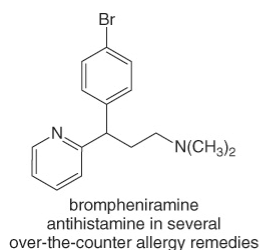
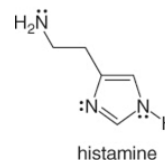


## Interesting and Useful Amines

- 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.

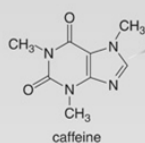
## Interesting and Useful Amines

- Histamine, a rather simple triamine that is present in many tissues, is responsible for a wide variety of physiological effects.
- Understanding the physiological properties of histamine has helped chemists design drugs to counteract some of its undesirable effects. Antihistamines bind to the same active site as histamine in the cell, but they evoke a different response. Examples are brompheniramine and cimetidine.

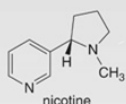


## Interesting and Useful Amines

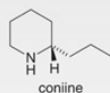
Figure 25.5 Three common alkaloids—Caffeine, nicotine, and coniine



- **Caffeine** is a bitter alkaloid found in coffee, tea, cola beverages, and chocolate. Caffeine is a mild stimulant, usually imparting a feeling of alertness after consumption. It also increases heart rate, dilates airways, and stimulates the secretion of stomach acid. Excessive use can result in insomnia.



- **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.

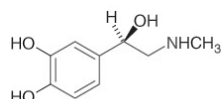


- **Coniine**, a poisonous alkaloid isolated from the seeds, leaves, and roots of hemlock (*Conium maculatum*), has been known since ancient times. Ingestion causes weakness, paralysis, and finally death. The Greek philosopher Socrates was executed by being forced to drink a potion prepared from hemlock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

5

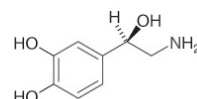
## Interesting and Useful Amines

- A large number of physiologically active compounds are derived from 2-phenethylamine ( $C_6H_5CH_2CH_2NH_2$ ). These compounds include adrenaline, noradrenaline, methamphetamine, and mescaline. Each contains a benzene ring bonded to a two-carbon unit with a nitrogen atom (shown in red).



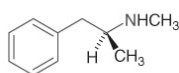
adrenaline  
(epinephrine)

a hormone secreted in response to stress  
(Chapter 7, introductory molecule)



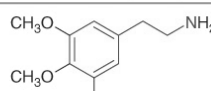
noradrenaline  
(norepinephrine)

a neurotransmitter that increases heart rate  
and dilates air passages



methamphetamine

an addictive stimulant sold as  
speed, meth, or crystal meth



mescaline

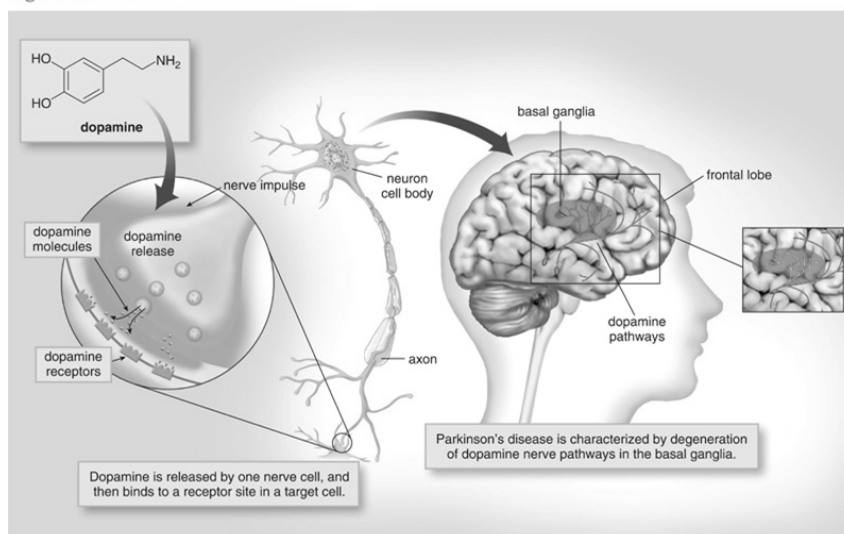
a hallucinogen isolated from peyote, a cactus native  
to the southwestern United States and Mexico

6

## Interesting and Useful Amines

- Another example is the neurotransmitter dopamine.

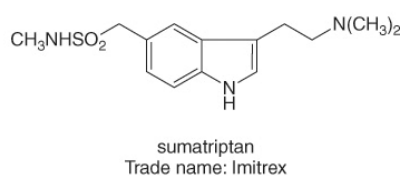
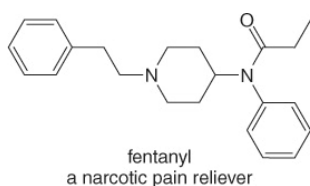
Figure 25.6 Dopamine—A neurotransmitter



7

## Interesting and Useful Amines

- Cocaine, amphetamines, and several other addicting drugs increase the level of dopamine in the brain, which results in a pleasurable "high." With time, the brain adapts to increased dopamine levels, so more drug is required to produce the same sensation.
- Understanding the neurochemistry of these compounds has led to the synthesis and availability of several useful drugs. Examples are fentanyl and sumatriptan.



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## Structure & Classification

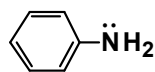
- Amines are categorized by the number of alkyl groups attached to nitrogen:

1° (primary amine)	$\text{RNH}_2$
2° (secondary amine)	$\text{R}_2\text{NH}$
3° (tertiary amine)	$\text{R}_3\text{N}$
4° (quaternary amine salt)	$\text{R}_4\text{N}^+$

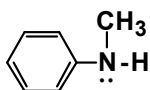
9

Amines are further divided into aliphatic, aromatic, and heterocyclic amines:

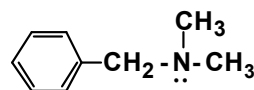
- Aliphatic amine: An amine in which nitrogen is bonded only to alkyl groups.
- Aromatic amine: An amine in which nitrogen is bonded to one or more aryl groups.



**Aniline**  
(a 1° aromatic amine)



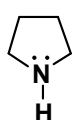
**N-Methylaniline**  
(a 2° aromatic amine)



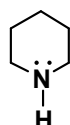
**Benzyltrimethylammonium**  
(a 3° aliphatic amine)

10

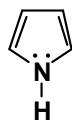
- Heterocyclic amine: An amine in which nitrogen is one of the atoms of a ring.



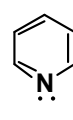
**Pyrrolidine**  
(heterocyclic aliphatic amines)



**Piperidine**



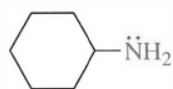
**Pyrrole**



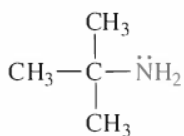
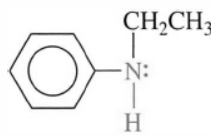
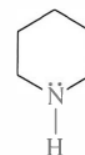
**Pyridine**

(heterocyclic aromatic amines)

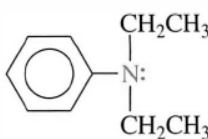
11

*Primary (1°) amines*

cyclohexylamine (1°)

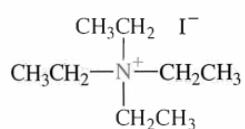
*tert*-butylamine (1°)*Secondary (2°) amines**N*-ethylaniline (2°)

piperidine (2°)

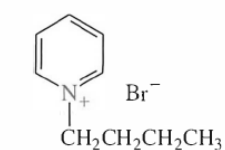
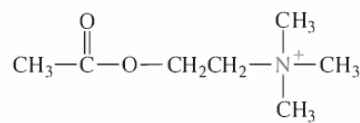
*Tertiary (3°) amines**N,N*-diethylaniline (3°)

quinuclidine (3°)

12



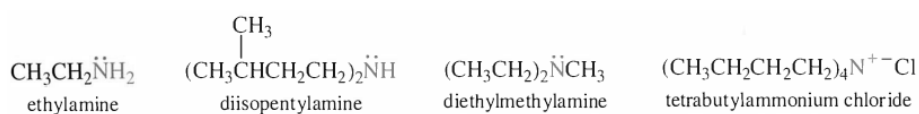
tetraethylammonium iodide

*N*-butylpyridinium bromide

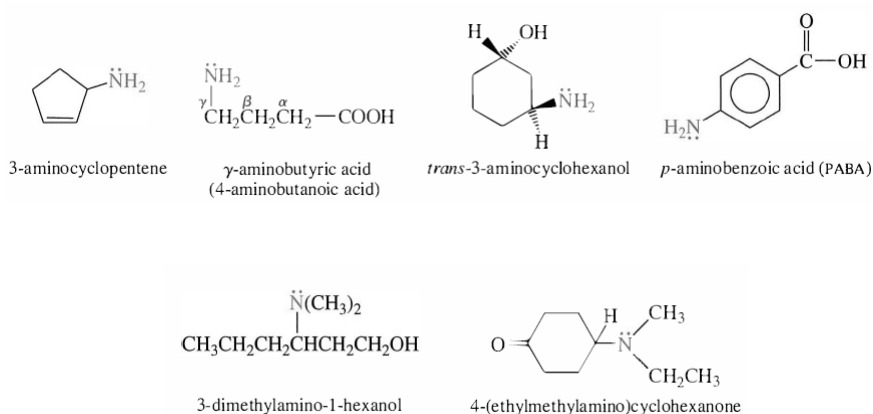
acetylcholine, a neurotransmitter

### Common Names

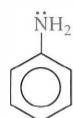
- 1<sup>o</sup> Amines are named using either systematic or common names.
- To assign a systematic name, find the longest continuous chain bonded to the amine nitrogen, and called "Alkyl" followed by amine.
- The prefixes di, tri, and tetra are used to describe two, three, or four substituents.



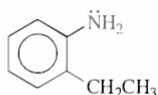
In naming amines with more complicated structures, the —NH<sub>2</sub> group is called the **amino** group. It is treated like any other substituent, with a number or other symbol indicating its position on the ring or carbon chain.



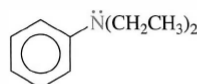
Aromatic and heterocyclic amines are generally known by historical names. Phenylamine is called *aniline*, for example, and its derivatives are named as derivatives of aniline.



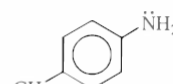
aniline



2-ethylaniline



N,N-diethylaniline

4-methylaniline  
or p-toluidine

### The Nitrogen heterocyclics



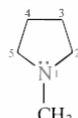
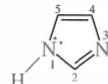
aziridine



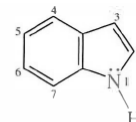
pyrrole



pyrrolidine

1-methylpyrrolidine  
(N-methylpyrrolidine)

imidazole

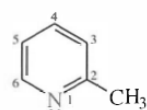


indole

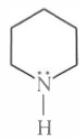
### The Nitrogen heterocyclics (continued)



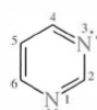
pyridine



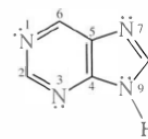
2-methylpyridine



piperidine



pyrimidine



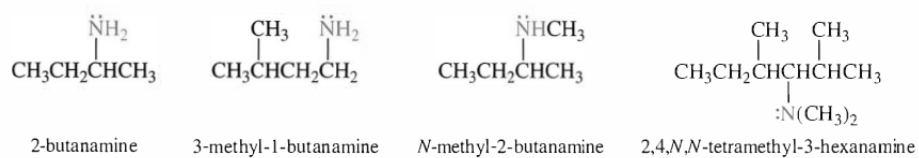
purine

### IUPAC Names

- The longest continuous chain of carbon atoms determines the root name
- The e-ending in the alkane name is changed to *-amine*, and a number shows the position of the amino group along the chain.
- Other substitutions on the carbon chain are given numbers and prefix N- is used for each substituent on nitrogen



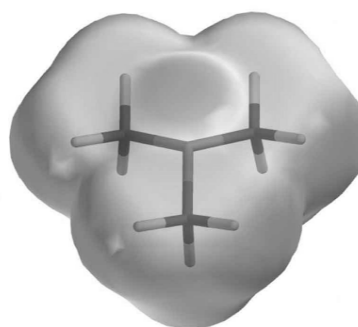
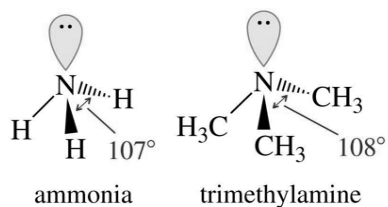
17



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### Structure of Amines

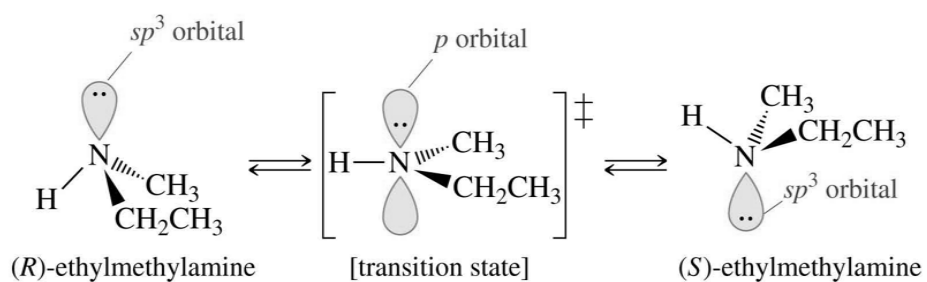
Nitrogen is  $sp^3$  hybridized with a lone pair of electrons in an  $sp^3$  orbital.



electrostatic potential map of trimethylamine

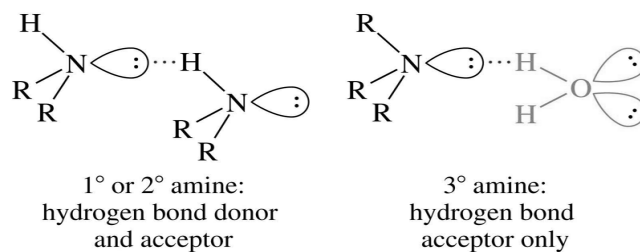
## Chirality of Amines

Nitrogen may have 3 different groups and a lone pair, but enantiomers cannot be isolated due to inversion around N.



## Boiling Points

- N-H less polar than O-H.
- Weaker hydrogen bonding.
- Tertiary amines cannot hydrogen bond.



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**TABLE 19-1** Comparison of the Boiling Points of an Ether, an Alcohol, and Amines of Similar Molecular Weights

Compound	bp (°C)	Type	Molecular Weight
$(\text{CH}_3)_3\text{N}$ :	3	tertiary amine	59
$\text{CH}_3-\text{O}-\text{CH}_2-\text{CH}_3$	8	ether	60
$\text{CH}_3-\text{NH}-\text{CH}_2-\text{CH}_3$	37	secondary amine	59
$\text{CH}_3\text{CH}_2\text{CH}_2-\text{NH}_2$	48	primary amine	59
$\text{CH}_3\text{CH}_2\text{CH}_2-\text{OH}$	97	alcohol	60

### Solubility and Odor

- Small amines (<6 C) soluble in water.
- All amines accept hydrogen bonds from water and alcohol.
- Branching increases solubility.
- Most amines smell like rotting fish.

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### Physical Properties

- Amines are polar compounds, and both 1° and 2° amines form intermolecular hydrogen bonds.
- ❖ N-H- -N hydrogen bonds are weaker than O-H- -O hydrogen bonds because the difference in electronegativity between N and H (3.0 - 2.1 = 0.9) is less than that between O and H (3.5 - 2.1 = 1.4).

Using bp as an indication of H bonding

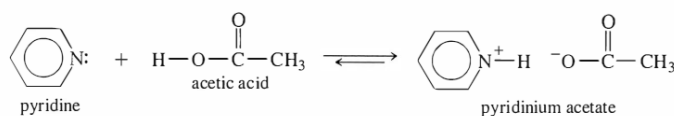
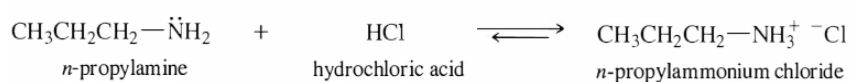
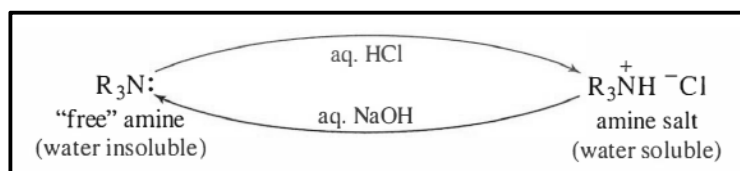
	$\text{CH}_3\text{CH}_3$	$\text{CH}_3\text{NH}_2$	$\text{CH}_3\text{OH}$
MW (g/mol)	30.1	31.1	32.0
bp (°C)	-88.6	-6.3	65.0

→  
Increasing strength

23

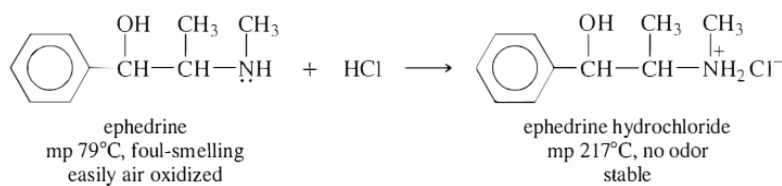
## Amine Salts

- Ionic solids with high melting points
- Soluble in water
- No fishy odor

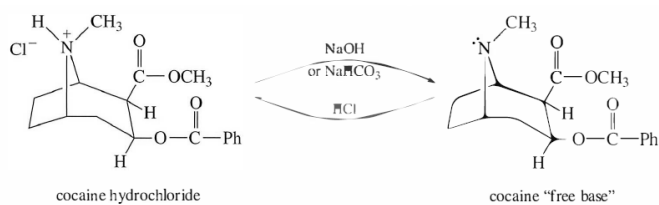


24

## Ephedrin drug



## Cocaine

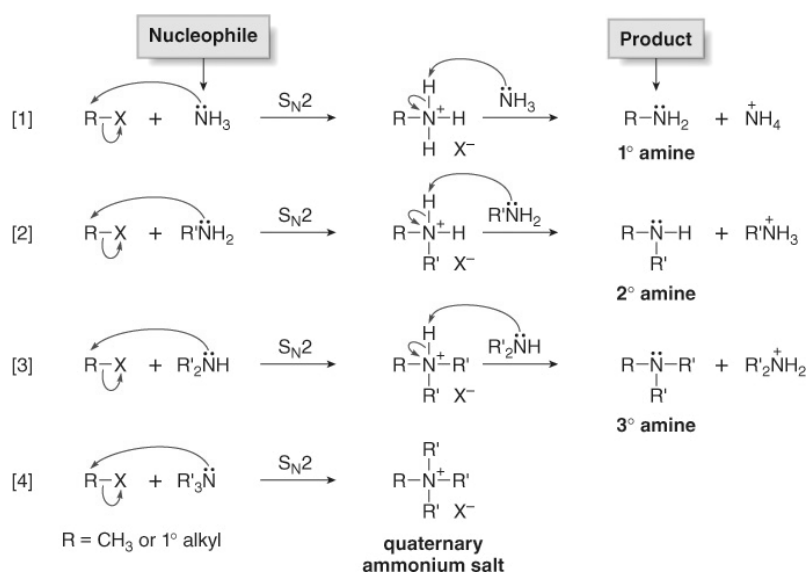


25

# Preparation of Amines

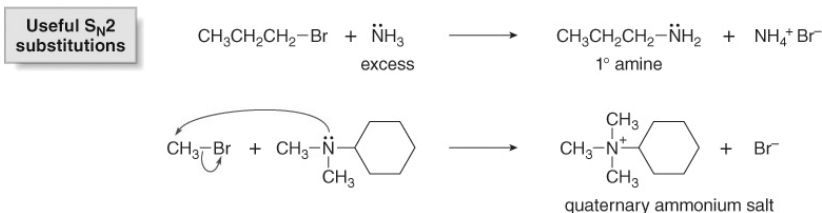
26

## Preparation of Amines—Direct Nucleophilic Substitution



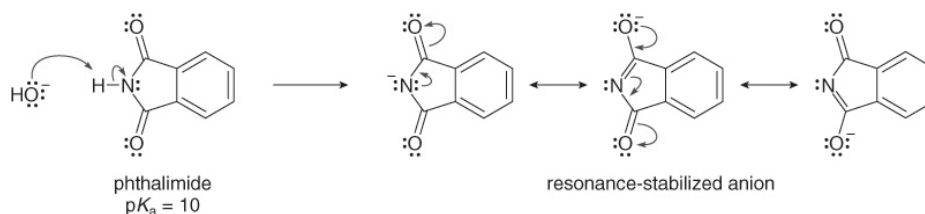
## 1. Direct Nucleophilic Substitution

- Although the process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness.
- Any amine formed by nucleophilic substitution still has a nonbonded electron pair, making it a nucleophile as well. It will react with remaining alkyl halide to form a more substituted amine, resulting in a mixture of 1<sup>o</sup>, 2<sup>o</sup>, and 3<sup>o</sup> amine products.
- Consequently, the reaction is most useful in preparing 1<sup>o</sup> amines by using a large excess of NH<sub>3</sub>, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.



## 2. Gabriel Synthesis of 1<sup>o</sup> Amines

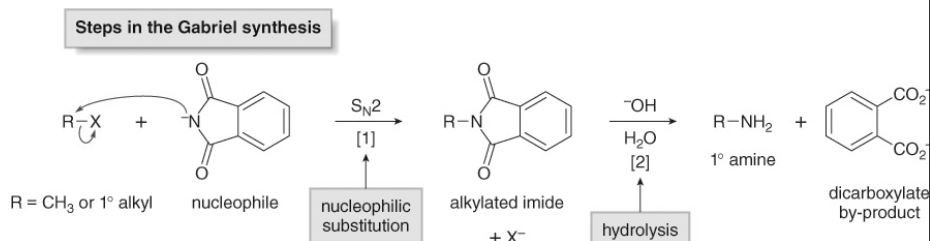
- The **Gabriel synthesis** consists of two steps and uses a nucleophile derived from phthalimide to synthesize 1<sup>o</sup> amines via **nucleophilic substitution**.
- The N—H bond of a phthalimide is especially acidic because the resulting anion is resonance stabilized by the two flanking carbonyl groups.



- An acid-base reaction forms a nucleophilic anion that can react with an unhindered alkyl halide in an S<sub>N</sub>2 reaction to form a substituted product.

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- The alkylated imide is then hydrolyzed with aqueous base to give a 1° amine and a dicarboxylate.



- The Gabriel synthesis converts an alkyl halide into a 1° amine by a two-step process: nucleophilic substitution followed by hydrolysis.

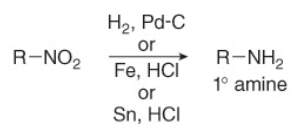
30

### 3. Reduction of N-Containing Functional Groups

- Recall that amines can be prepared by reduction of nitro compounds, nitriles and amides.

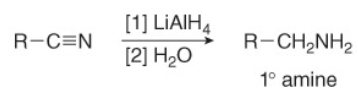
#### [1] From nitro compounds

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



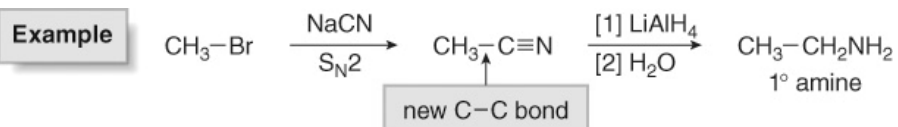
#### [2] From nitriles

Nitriles are reduced to 1° amines with  $\text{LiAlH}_4$ .



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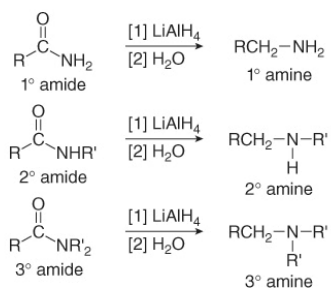
- Because the cyano group is readily introduced by  $S_N2$  substitution of alkyl halides with  $^-CN$ , this provides a two-step method to convert an alkyl halide to a  $1^\circ$  amine with one more carbon atom.



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[3] From amides

$1^\circ$ ,  $2^\circ$ , and  $3^\circ$  amides are reduced to  $1^\circ$ ,  $2^\circ$ , and  $3^\circ$  amines, respectively, by using  $LiAlH_4$ .



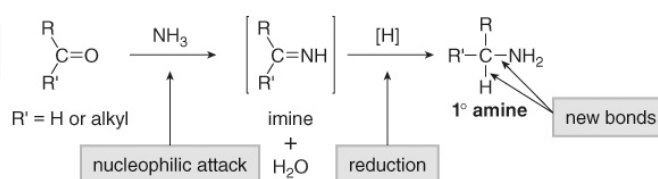


## 4. Reductive Amination

- Reductive amination is a two-step method that converts aldehydes and ketones into 1<sup>o</sup>, 2<sup>o</sup>, and 3<sup>o</sup> amines.
- Consider the reductive amination of an aldehyde or ketone using NH<sub>3</sub>.  
There are two distinct parts to this reaction.

- [1] Nucleophilic attack of NH<sub>3</sub> on the carbonyl group forms an imine.
- [2] Reduction of the imine forms an amine.

Reductive amination—  
A two-step process

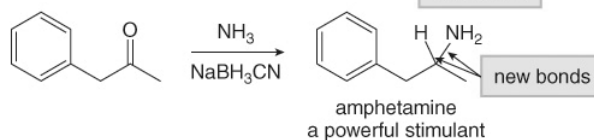
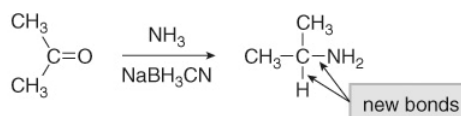


◆ Reductive amination replaces a C=O by a C-H and C-N bond.

- The most effective reducing agent for this reaction is sodium cyanoborohydride (NaBH<sub>3</sub>CN).

NaBH<sub>3</sub>CN  
sodium cyanoborohydride

Examples



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

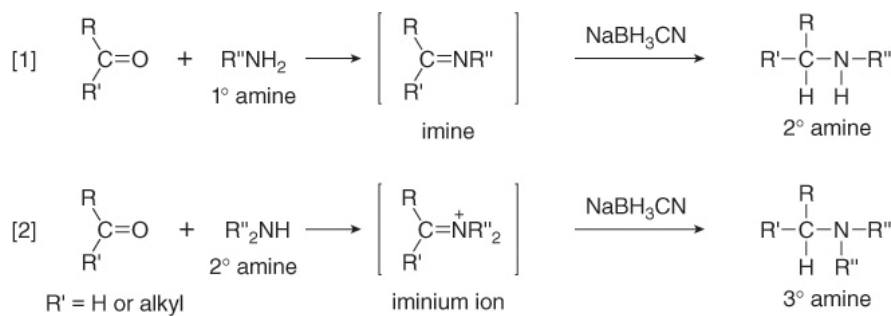
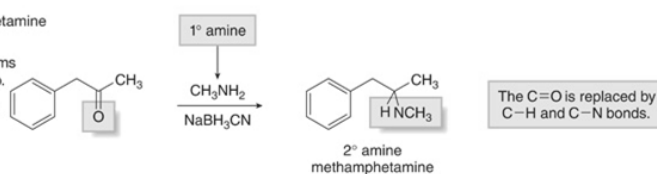


Figure 25.7 Synthesis of methamphetamine by reductive amination

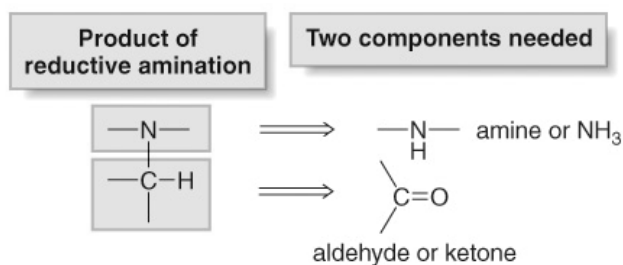
- In reductive amination, one of the H atoms bonded to N is replaced by an alkyl group. As a result, a 1° amine is converted to a 2° amine and a 2° amine is converted to a 3° amine. In this reaction,  $\text{CH}_3\text{NH}_2$  (a 1° amine) is converted to methamphetamine (a 2° amine).



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## Retrosynthesis of amine

- ◆ One alkyl group on N comes from the carbonyl compound.
- ◆ The remainder of the molecule comes from  $\text{NH}_3$  or an amine.

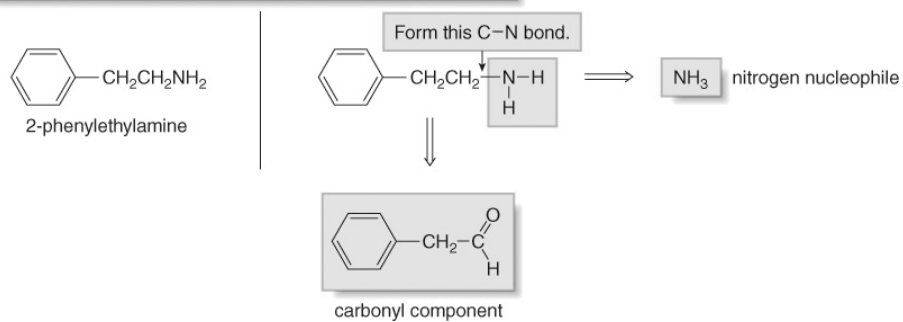


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## Preparation of Amines—Reductive Amination

- For a 1<sup>o</sup> amine, the nitrogen component must be NH<sub>3</sub>.

Retrosynthetic analysis for preparing 2-phenylethylamine:

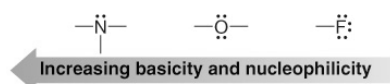


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## Reaction of Amines

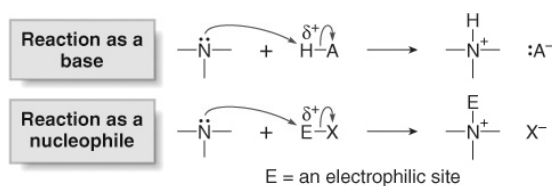
## Reactions of Amines—General Features

- The chemistry of amines is dominated by the lone electron pair 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.

## Reactions of Amines—General Features

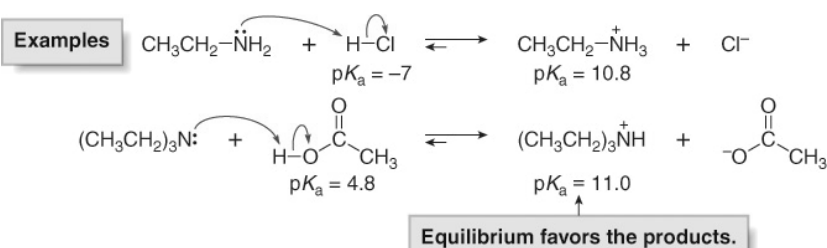
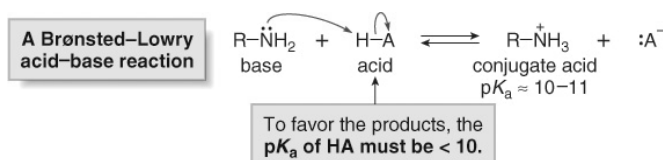


- ◆ Amines react as bases with compounds that contain acidic protons.
- ◆ Amines react as nucleophiles with compounds that contain electrophilic carbons.

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## Amines as Bases

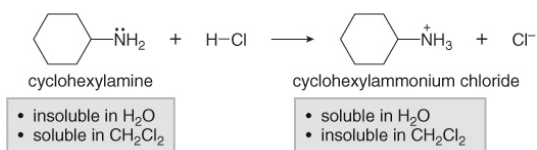
- Recall that amines react as bases with a variety of organic and inorganic acids.



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## Amines as Bases

- Because amines are protonated by aqueous acid, they can be separated from other organic compounds by extraction using a separatory funnel.
- When an amine is protonated by aqueous acid, its solubility properties change.



- When cyclohexylamine is treated with aqueous HCl, it is protonated, forming an ammonium salt. Since this salt is ionic, it is water soluble, but insoluble in organic solvents. A similar acid-base reaction does not occur with other organic compounds like alcohols, which are much less basic.
- This difference in acid-base chemistry can be used to separate cyclohexylamine and cyclohexanol by a stepwise extraction procedure.

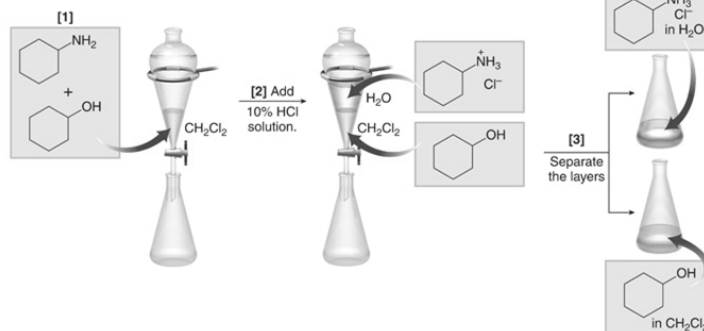
## Amines as Bases

Figure 25.8 Separation of cyclohexylamine and cyclohexanol by an extraction procedure

**Step [1]** Dissolve cyclohexylamine and cyclohexanol in  $\text{CH}_2\text{Cl}_2$ .

**Step [2]** Add 10% HCl solution to form two layers.

**Step [3]** Separate the layers.



- Both compounds dissolve in the organic solvent  $\text{CH}_2\text{Cl}_2$ .

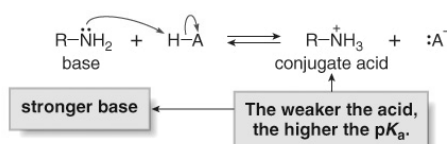
- Adding 10% aqueous HCl solution forms two layers. When the two layers are mixed, the HCl protonates the amine ( $\text{RNH}_2$ ) to form  $\text{RNH}_3^+\text{Cl}^-$ , which dissolves in the aqueous layer.
- The cyclohexanol remains in the  $\text{CH}_2\text{Cl}_2$  layer.

- Draining the lower layer out the bottom stopcock separates the two layers, and the separation process is complete.
- Cyclohexanol (dissolved in  $\text{CH}_2\text{Cl}_2$ ) is in one flask. The ammonium salt,  $\text{RNH}_3^+\text{Cl}^-$  (dissolved in water), is in another flask.

## Amines as Bases

- The relative acidity of different compounds can be compared using their  $\text{p}K_a$  values. The relative basicity of different compounds (such as amines) can be compared using the  $\text{p}K_a$  values of their conjugate acids.

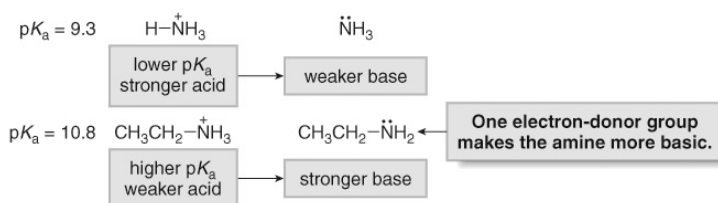
◆ The weaker the conjugate acid, the higher its  $\text{p}K_a$  and the stronger the base.



- To compare the basicity of two compounds, keep in mind that (1) any factor that increases the electron density on the N atom increases the amines basicity; (2) any factor that decreases the electron density on N decreases an amines basicity.

### Amines as Bases

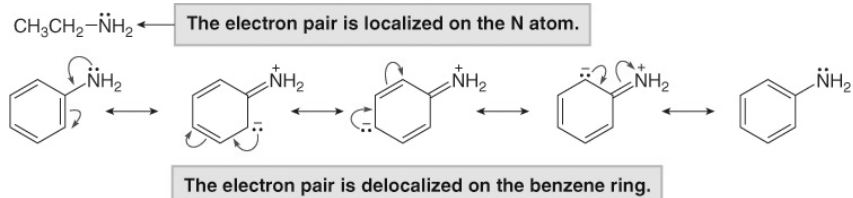
- Because alkyl groups are electron-donating, they increase the electron density on nitrogen, which makes an amine like  $\text{CH}_3\text{CH}_2\text{NH}_2$  more basic than  $\text{NH}_3$ .
- Thus, the  $\text{p}K_a$  of  $\text{CH}_3\text{CH}_2\text{NH}_3^+$  is higher than the  $\text{p}K_a$  of  $\text{NH}_4^+$ , so  $\text{CH}_3\text{CH}_2\text{NH}_2$  is a stronger base than  $\text{NH}_3$ .



- ◆ Primary ( $1^\circ$ ),  $2^\circ$ , and  $3^\circ$  alkylamines are more basic than  $\text{NH}_3$  because of the electron-donating inductive effect of the R groups.

### Amines as Bases

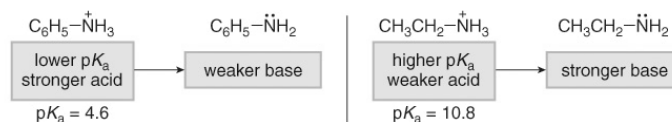
- To compare an alkylamine and an arylamine, we must look at the availability of the nonbonded electron pair on N.
- With  $\text{CH}_3\text{CH}_2\text{NH}_2$  for example, the electron pair is localized on the N atom. With an arylamine, the electron pair is delocalized on the benzene ring. This decreases the electron density on N, and makes an amine like  $\text{C}_6\text{H}_5\text{NH}_2$  less basic than  $\text{CH}_3\text{CH}_2\text{NH}_2$ .



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## Amines as Bases

- $pK_a$  Values support this reasoning. Since the  $pK_a$  of  $\text{CH}_3\text{CH}_2\text{NH}_3^+$  is higher than the  $pK_a$  of  $\text{C}_6\text{H}_5\text{NH}_3^+$ ,  $\text{CH}_3\text{CH}_2\text{NH}_2$  is a stronger base than  $\text{C}_6\text{H}_5\text{NH}_2$ .



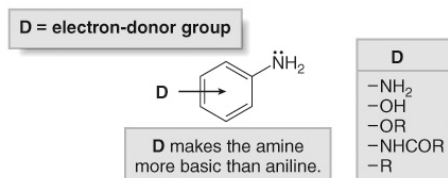
- ◆ Arylamines are less basic than alkylamines because the electron pair on N is delocalized.

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## Amines as Bases

- Substituted anilines are more or less basic than aniline depending on the nature of the substituent.

- ◆ Electron-donor groups add electron density to the benzene ring, making the arylamine more basic than aniline.



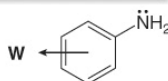


## Amines as Bases

- Recall that whether a substituent donates or withdraws electron density depends on the balance of its inductive and resonance effects.

◆ Electron-withdrawing groups remove electron density from the benzene ring, making the arylamine less basic than aniline.

W = electron-withdrawing group



W makes the amine less basic than aniline.

W

-X	-CN
-CHO	-SO <sub>3</sub> H
-COR	-NO <sub>2</sub>
-COOR	-NR <sub>3</sub> <sup>+</sup>
-COOH	

## Amines as Bases

- To compare the basicity of an alkylamine and an amide, we must once again compare the availability of the nonbonded electron pair on nitrogen.
- With RNH<sub>2</sub>, the electron pair is localized on the N atom. With an amide, however, the electron pair is delocalized on the carbonyl oxygen by resonance. This decreases the electron density on N, making an amide much less basic than an alkylamine.



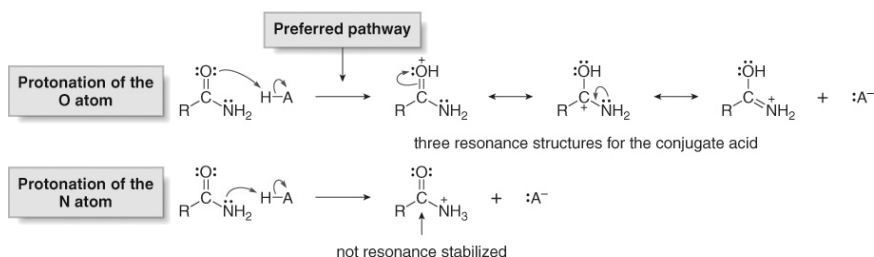
The electron pair on N is delocalized on O by resonance.

◆ Amides are much less basic than amines because the electron pair on N is delocalized.

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## Amines as Bases

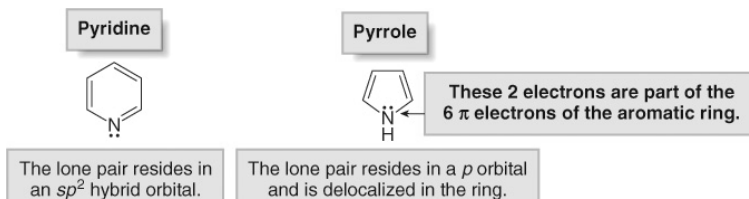
- Amides are not much more basic than any carbonyl compound.
- When an amide is treated with acid, protonation occurs at the carbonyl oxygen, not the nitrogen, because the resulting cation is resonance stabilized. The product of protonation on the  $\text{NH}_2$  group cannot be resonance stabilized. Thus, protonation on oxygen is the preferred pathway.



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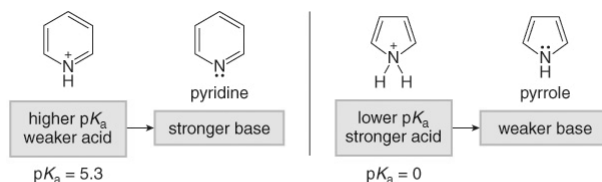
## Amines as Bases

- To determine the relative basicity of nitrogen heterocycles that are also aromatic, you must know whether the nitrogen lone pair is part of the aromatic  $\pi$  system.
- Consider pyridine and pyrrole. Both are aromatic, but the nonbonded electron pair on the N atom in these compounds is located in different orbitals.
- Recall that the lone pair in pyridine occupies an  $sp^2$  hybridized orbital, whereas that of pyrrole resides in a  $p$  orbital, making it part of the aromatic system. Thus, pyrrole is a much weaker base than pyridine.



## Amines as Bases

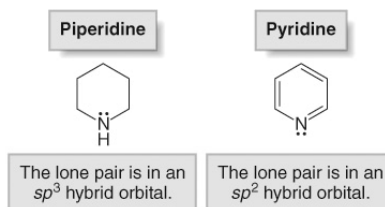
- As a result, the  $pK_a$  of the conjugate acid of pyrrole is much less than that for the conjugate acid of pyridine.



- ◆ Pyrrole is much less basic than pyridine because its lone pair of electrons is part of the aromatic  $\pi$  system.

## Amines as Bases

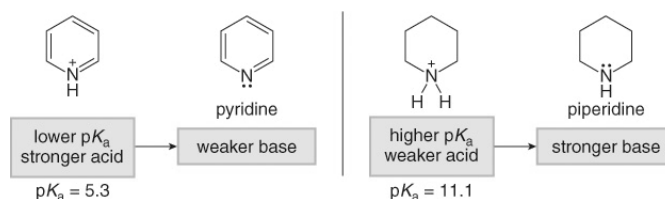
- The hybridization of the orbital that contains an amine's lone pair also affects its basicity. This is illustrated by comparing the basicity of piperidine and pyridine, two nitrogen heterocycles.



- ◆ 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.





## Amines as Bases

- Pyridine is a weaker base than piperidine because its nonbonded electron pair resides in an  $sp^2$  hybrid orbital. Although pyridine is an aromatic amine, its lone pair is not part of the delocalized  $\pi$  system, so its basicity is determined by the hybridization of its N atom.
- As a result, the  $pK_a$  value for the conjugate acid of pyridine is much lower than that for the conjugate acid of piperidine, making pyridine the weaker base.






## Amines as Bases

**TABLE 25.2 Factors that Determine Amine Basicity**

Factor	Example
[1] <b>Inductive effects:</b> Electron-donating groups bonded to N increase basicity.	<ul style="list-style-type: none"> <li><math>RNH_2</math>, <math>F_2NH</math>, and <math>R_3N</math> are more basic than <math>NH_3</math>.</li> </ul>
[2] <b>Resonance effects:</b> Delocalizing the lone pair on N decreases basicity.	<ul style="list-style-type: none"> <li>Arylamines (<math>C_6H_5NH_2</math>) are less basic than alkylamines (<math>RNH_2</math>).</li> <li>Amides (<math>RCONH_2</math>) are much less basic than amines (<math>RNH_2</math>).</li> </ul>
[3] <b>Aromaticity:</b> Having the lone pair on N as part of the aromatic $\pi$ system decreases basicity.	<ul style="list-style-type: none"> <li>Pyrrole is less basic than pyridine.</li> </ul> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  less basic         </div> <div style="text-align: center;">  more basic         </div> </div>
[4] <b>Hybridization effects:</b> Increasing the percent $s$ -character in the orbital with the lone pair decreases basicity.	<ul style="list-style-type: none"> <li>Pyridine is less basic than piperidine.</li> </ul> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  less basic         </div> <div style="text-align: center;">  more basic         </div> </div>

## Amines as Bases

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

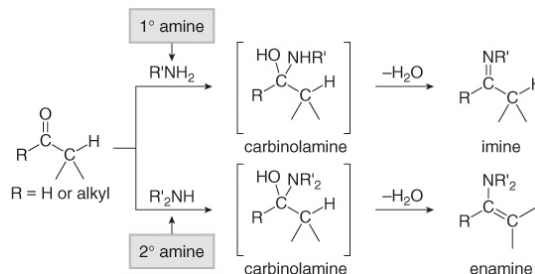
Compound	Chemical Structure	$pK_a$ of the conjugate acid	Comment
Ammonia	$NH_3$	9.3	
Alkylamines		11.1	Alkylamines have $pK_a$ values of ~10–11.
	$(CH_3CH_2)_2NH$	11.1	
	$(CH_3CH_2)_3N$	11.0	
	$CH_3CH_2NH_2$	10.8	
Arylamines	$p\text{-}CH_3OC_6H_4NH_2$	5.3	The $pK_a$ decreases as the electron density of the benzene ring decreases.
	$p\text{-}CH_3C_6H_4NH_2$	5.1	
	$C_6H_5NH_2$	4.6	
	$p\text{-}NO_2C_6H_4NH_2$	1.0	
Heterocyclic aromatic amines		5.3	The $pK_a$ depends on whether the lone pair on N is localized or delocalized.
		0	
Amides	$RCONH_2$	-1	

## Amines Nucleophiles

Recall that:

## [1] Reaction of 1° and 2° amines with aldehydes and ketones (Sections 21.11–21.12)

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.

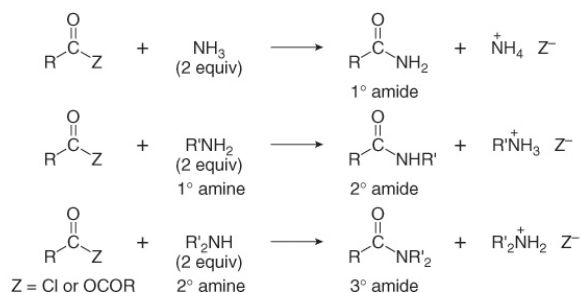


## Amines Nucleophiles

Recall that:

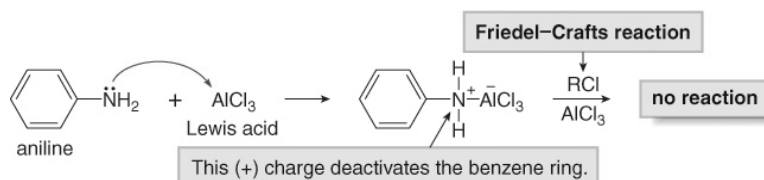
[2] **Reaction of  $\text{NH}_3$  and 1° and 2° amines with acid chlorides and anhydrides (Sections 22.8–22.9)**

Acid chlorides and anhydrides react with  $\text{NH}_3$ , 1° amines, and 2° amines to form 1°, 2°, and 3° amides, respectively. Both reactions involve attack of the nitrogen nucleophile on the carbonyl group followed by elimination of a leaving group ( $\text{Cl}^-$  or  $\text{RCOO}^-$ ). The overall result of this reaction is substitution of the leaving group by the nitrogen nucleophile.



## Amines Nucleophiles

- The conversion of amines to amides is useful in the synthesis of substituted anilines.
- Aniline itself does not undergo Friedel-Crafts reactions because the lone pair on N reacts with the Lewis acid ( $\text{AlCl}_3$ ) to form a deactivated complex that does not undergo further reaction.

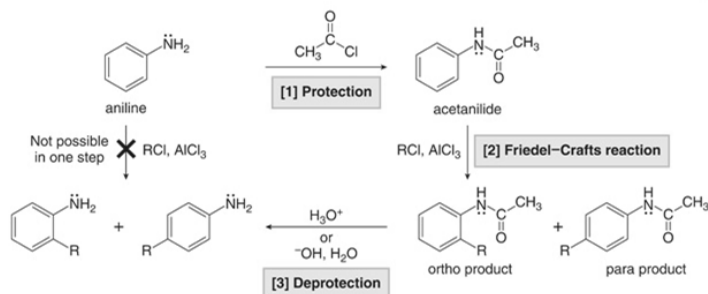


- The N atom of an amide, however, is much less basic than the N atom of an amine, so it does not undergo a similar Lewis acid-base reaction with  $\text{AlCl}_3$ . Thus, a three-step reaction sequence involving an intermediate amide can be used to form the products of the Friedel-Crafts reaction.

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## Amines Nucleophiles

Figure 25.10 An amide as a protecting group for an amine



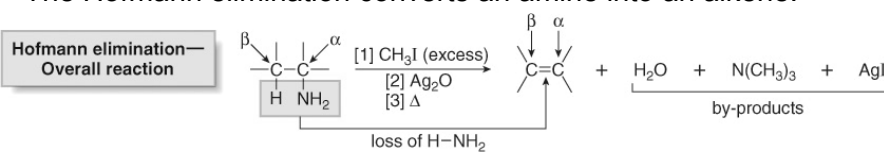
A three-step sequence uses an amide as a protecting group.

- [1] Treatment of aniline with acetyl chloride ( $\text{CH}_3\text{COCl}$ ) forms an amide (acetanilide).
- [2] Acetanilide, having a much less basic N atom compared to aniline, undergoes electrophilic aromatic substitution under Friedel-Crafts conditions, forming a mixture of ortho and para products.
- [3] Hydrolysis of the amide forms the Friedel-Crafts substitution products.

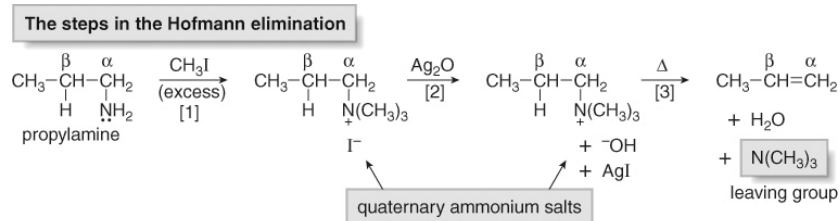
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## Hofmann Elimination

- The Hofmann elimination converts an amine into an alkene.



- The Hofmann elimination consists of three steps, as shown for the conversion of propylamine to propene.



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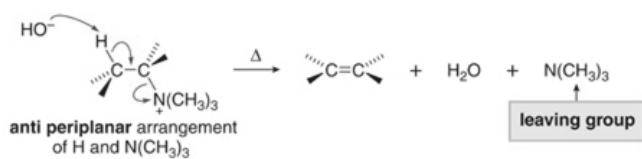
## Hofmann Elimination

The general E2 mechanism for the Hofmann elimination is shown below.



### MECHANISM 25.1

#### The E2 Mechanism for the Hofmann Elimination

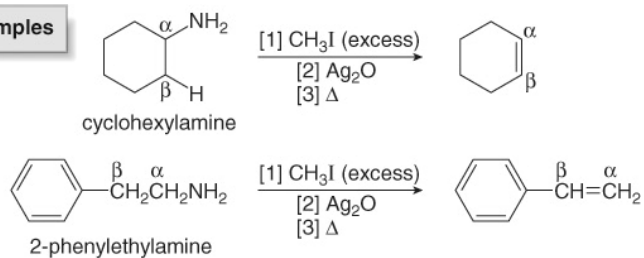


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## Hofmann Elimination

All Hofmann elimination reactions result in the formation of a new  $\pi$  bond between the  $\alpha$  and  $\beta$  carbon atoms, as shown for cyclohexylamine and 2-phenylethylamine.

### Examples

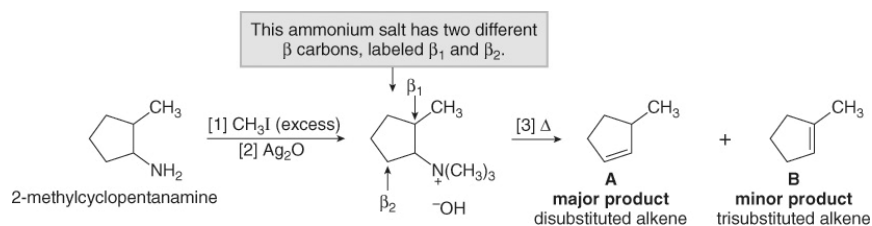




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## Hofmann Elimination

There is one major difference between the Hofmann elimination and other E2 eliminations: when constitutional isomers are possible, the major alkene has the less substituted double bond.

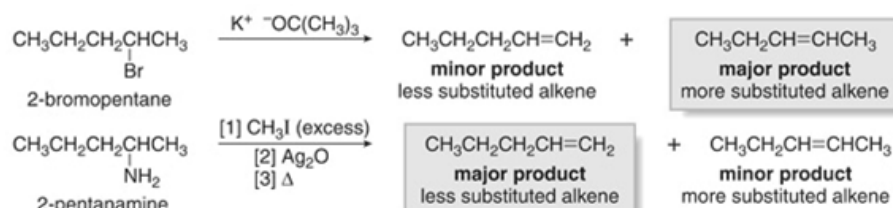


This result is explained by the size of the leaving group—The base removes a proton from the less substituted, more accessible  $\beta$  carbon atom, because of the size of the bulky leaving group on the nearby  $\alpha$  carbon.

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## Hofmann Elimination

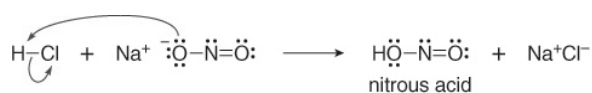
Figure 25.11 A  
comparison of E2 elimination  
reactions using alkyl halides and  
amines



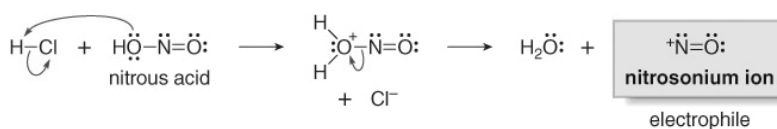
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## Reaction of Amines with Nitrous Acid

Nitrous acid,  $\text{HNO}_2$ , is a weak unstable acid formed from  $\text{NaNO}_2$  and a strong acid like  $\text{HCl}$ .



In the presence of acid, nitrous acid decomposes to  $^+\text{NO}$ , the nitrosonium ion. This electrophile then goes on to react with the nucleophilic nitrogen atom of amines to form diazonium salts ( $\text{RN}_2^+\text{Cl}^-$ ) from  $1^\circ$  amines and *N*-nitrosamines ( $\text{R}_2\text{NN}=\text{O}$ ) from  $2^\circ$  amines.



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## Reaction of Amines with Nitrous Acid

Nitrous acid reacts with  $1^\circ$  alkylamines and arylamines to form diazonium salts. This reaction is called diazotization.

### Preparation of diazonium salts

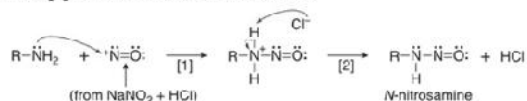


The mechanism for this reaction consists of many steps. It begins with nucleophilic attack of the amine on the nitrosonium ion, and it can conceptually be divided into two parts: formation of an *N*-nitrosamine, followed by loss of  $\text{H}_2\text{O}$ .

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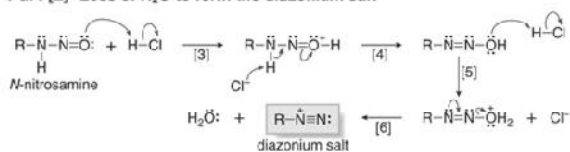
## Reaction of Amines with Nitrous Acid

### Part [1] Formation of an *N*-nitrosamine



◆ In Part [1], the amine is converted to an ***N*-nitrosamine** by nucleophilic attack of the amino group on  $\text{NO}$ , followed by loss of a proton.

### Part [2] Loss of $\text{H}_2\text{O}$ to form the diazonium salt

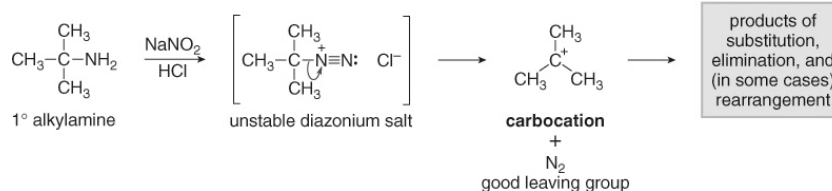


◆ In Part [2], three proton transfer reactions lead to loss of  $\text{H}_2\text{O}$  in Step [6] and formation of the diazonium ion.

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## Reaction of Amines with Nitrous Acid

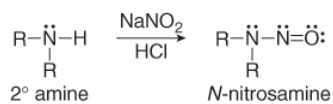
- Alkyl diazonium salts are generally not useful compounds.
- They readily decompose below room temperature and form carbocations with loss of  $\text{N}_2$ , a very good leaving group.
- These carbocations usually form a complex mixture of substitution, elimination and rearrangement products.



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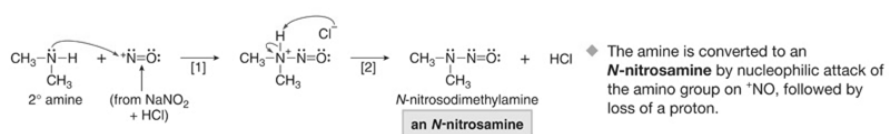
## Reaction of Amines with Nitrous Acid

2° Alkylamines and aryl amines react with nitrous acid to form *N*-nitrosamines.



### MECHANISM

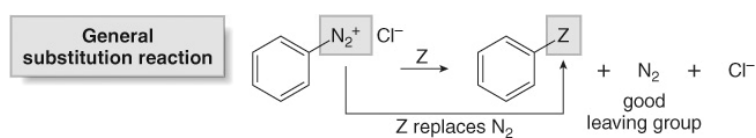
Formation of an *N*-Nitrosamine from a 2° Amine



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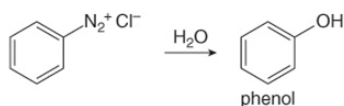
## Substitution Reactions of Aryl Diazonium Salts

- Aryl diazonium salts react with a variety of reagents to form products in which Z (an atom or group of atoms) replaces  $\text{N}_2$ , a very good leaving group.
- The mechanism of these reactions varies with the identity of Z.



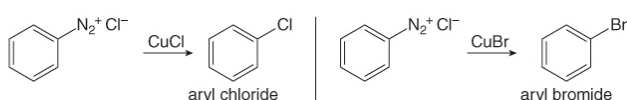
## Substitution Reactions of Aryl Diazonium Salts

### [1] Substitution by OH—Synthesis of phenols



A diazonium salt reacts with water to form a phenol.

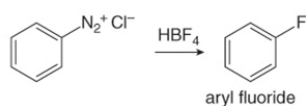
### [2] Substitution by Cl or Br—Synthesis of aryl chlorides and bromides



A diazonium salt reacts with copper(I) chloride or copper(I) bromide to form an aryl chloride or aryl bromide. This is called the Sandmeyer reaction. It provides an alternative to direct chlorination and bromination of the aromatic ring using  $\text{Cl}_2$  or  $\text{Br}_2$  and a Lewis acid catalyst.

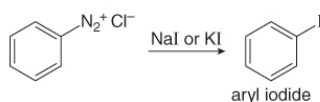
## Substitution Reactions of Aryl Diazonium Salts

### [3] Substitution by F—Synthesis of aryl fluorides



A diazonium salt reacts with fluoroboric acid to form an aryl fluoride. This is a useful reaction because aryl fluorides cannot be produced by direct fluorination with  $\text{F}_2$  and a Lewis acid catalyst.

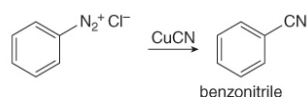
### [4] Substitution by I—Synthesis of aryl iodides



A diazonium salt reacts with sodium or potassium iodide to form an aryl iodide. This is a useful reaction because aryl iodides cannot be produced by direct iodination with  $\text{I}_2$  and a Lewis acid catalyst.

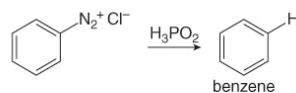
## Substitution Reactions of Aryl Diazonium Salts

### [5] Substitution by CN—Synthesis of benzonitriles



A diazonium salt reacts with copper(I) cyanide to form benzonitrile. Since the cyano group can be converted into a variety of other functional groups, this reaction provides easy access to a wide variety of benzene derivatives.

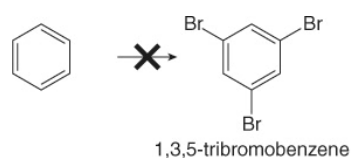
### [6] Substitution by H—Synthesis of benzene



A diazonium salt reacts with hypophosphorus acid to form benzene. This reaction is useful in synthesizing compounds that have substitution patterns that are not available by other means.

## Substitution Reactions of Aryl Diazonium Salts

- Regarding the reaction of an aryl diazonium salt with hypophosphorus acid to form benzene, consider the synthesis of 1,3,5-tribromobenzene.
- It is not possible to synthesize 1,3,5-tribromobenzene from benzene by direct bromination—Because Br is an o,p director, bromination with  $\text{Br}_2$  and  $\text{FeBr}_3$  will not add Br substituents meta to each other on the ring.

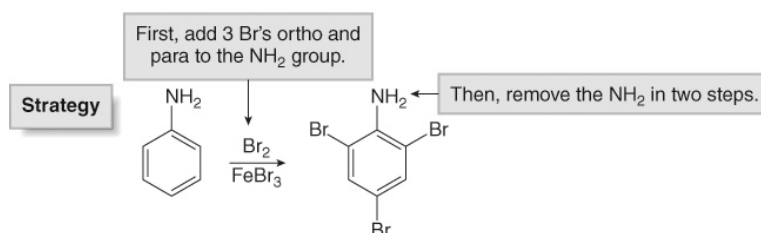


The Br atoms are ortho, para directors located meta to each other.

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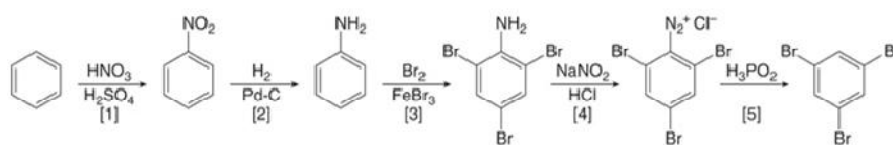
## Substitution Reactions of Aryl Diazonium Salts

- It is possible, however, to add three Br atoms meta to each other when aniline is the starting material.
- Because an  $\text{NH}_2$  group is a very powerful o,p director, three Br atoms are introduced in a single step on halogenation. Then, the  $\text{NH}_2$  group can be removed by diazotization and reaction with  $\text{H}_3\text{PO}_2$ .



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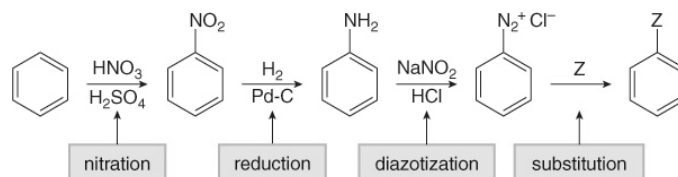
## Substitution Reactions of Aryl Diazonium Salts



- Nitration followed by reduction forms aniline ( $\text{C}_6\text{H}_5\text{NH}_2$ ) from benzene (Steps [1] and [2]).
- Bromination of aniline yields the tribromo derivative in Step [3].
- The  $\text{NH}_2$  group is removed by a two-step process: diazotization with  $\text{NaNO}_2$  and  $\text{HCl}$  (Step [4]), followed by substitution of the diazonium ion by H with  $\text{H}_3\text{PO}_2$ .

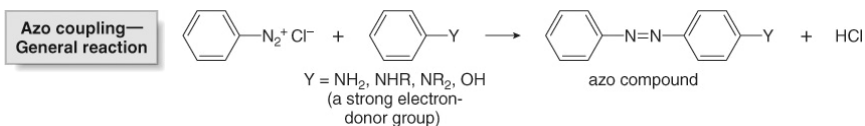
## Substitution Reactions of Aryl Diazonium Salts

- Diazonium salts provide easy access to many different benzene derivatives. Keep in mind the following four-step sequence, because it will be used to synthesize many substituted benzenes.

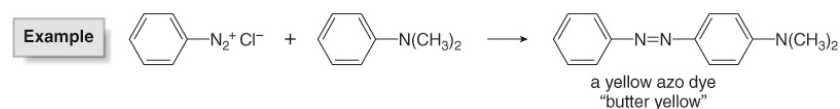


## Coupling Reactions of Aryl Diazonium Salts

- When a diazonium salt is treated with an aromatic compound that contains a strong electron-donor group, the two rings join together to form an azo compound, a compound with a nitrogen—nitrogen double bond.



- Azo compounds are highly conjugated, rendering them colored. Many of these compounds are synthetic dyes. Butter yellow was once used to color margarine.



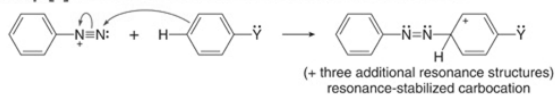


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## Coupling Reactions of Aryl Diazonium Salts

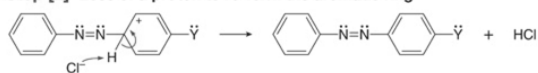
- This reaction is another example of electrophilic aromatic substitution, with the

### Step [1] Addition of the diazonium ion to form a carbocation



◆ **Step [1]** The electrophilic diazonium ion reacts with the electron-rich benzene ring to form a resonance-stabilized carbocation. (Only one resonance structure is drawn.)

### Step [2] Loss of a proton to re-form the aromatic ring



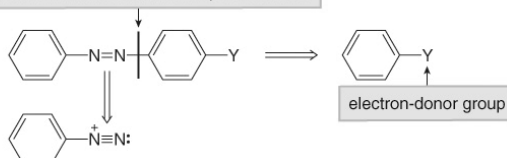
◆ **Step [2]** Loss of a proton regenerates the aromatic ring.

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## Coupling Reactions of Aryl Diazonium Salts

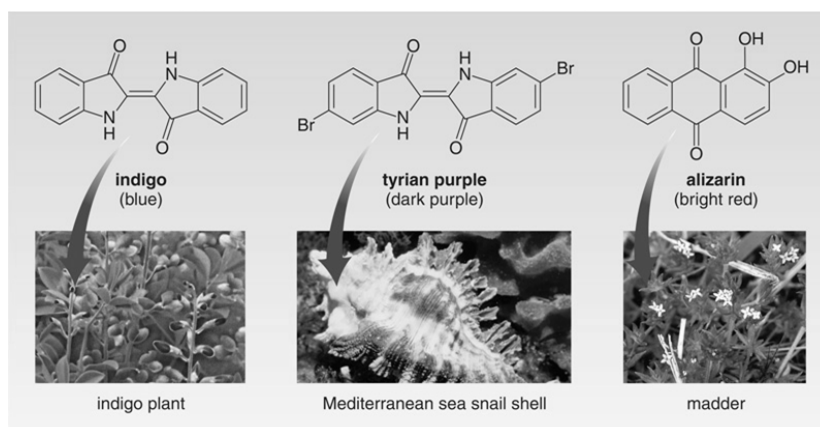
- Because a diazonium salt is only weakly electrophilic, the reaction only occurs when the benzene ring has a strong electron donor group, such as  $\text{NH}_2$ ,  $\text{NHR}$ ,  $\text{NR}_2$ , or  $\text{OH}$ .
- Although these groups activate both the ortho and para positions, substitution occurs unless the para position already has another substituent.
- To determine what starting materials are needed to synthesize a particular azo compound, always divide the molecule into two components: one has a benzene ring with a diazonium ion, and one has a benzene ring with a very strong electron donor group.

Break the molecule into two components here.



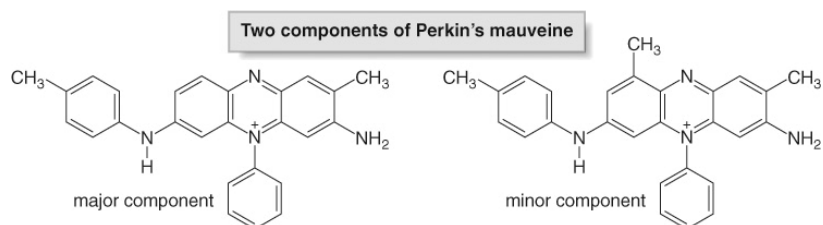
## Natural and Synthetic Dyes

- Three natural dyes known for centuries are indigo, tyrian purple, and alizarin.



## Natural and Synthetic Dyes

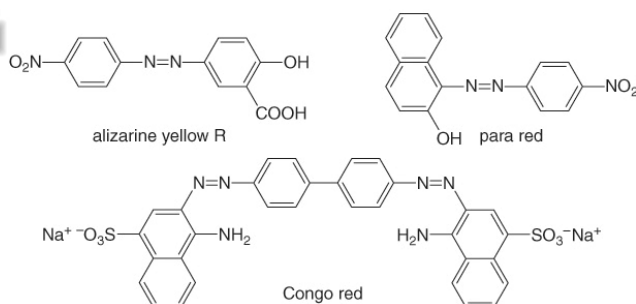
- In 1856 William Henry Perkin synthesized mauveine, a mixture of two compounds that differ only in the presence of one methyl group on one of the aromatic rings.



## Natural and Synthetic Dyes

- Many common synthetic dyes such as alizarine yellow R, para red, and Congo red, are azo compounds.

Three azo dyes



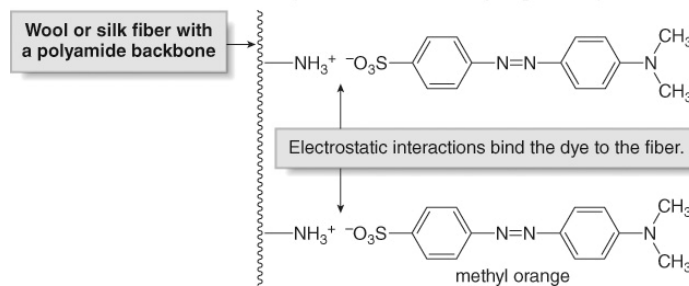
## Natural and Synthetic Dyes

- To be classified as a dye, a compound must be colored and it must bind fabric.
- Compounds that bind to fabric by some type of attractive force are called direct dyes.
- The attractive forces may be electrostatic interactions, van der Waals forces, hydrogen bonding, and sometimes even covalent bonding—The type of interaction depends on the structure of the dye and the fiber.
- A compound that may be good for dyeing wool or silk, both polyamides, may be poor for dyeing cotton, a carbohydrate.

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## Natural and Synthetic Dyes

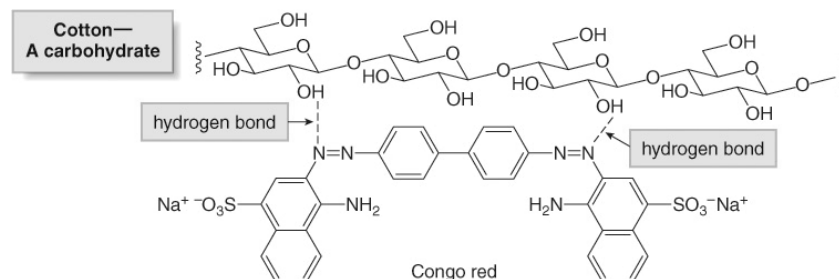
- Wool and silk contain charged functional groups, such as  $\text{NH}_3^+$  and  $\text{COO}^-$ . Thus, they bind to ionic dyes by electrostatic interactions.
- Positively charged  $\text{NH}_3^+$  groups bonded to the protein backbone are electrostatically attracted to anionic groups in a dye like methyl orange.



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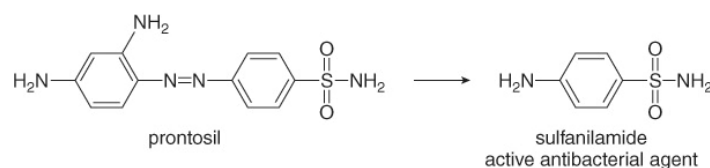
## Natural and Synthetic Dyes

- Cotton, on the other hand, binds dyes by hydrogen bonding interactions with its many OH groups. Thus, Congo red is bound to the cellulose backbone by hydrogen bonds.



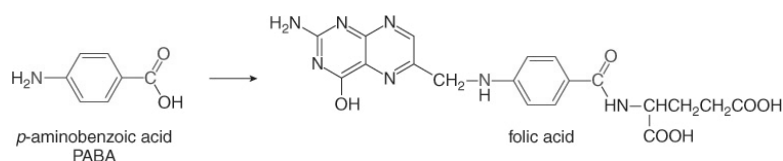
## Sulfa Drugs

- In 1935, Gerhard Domagk first used a synthetic dye, prontosil, to kill bacteria.
- Prontosil and other sulfur containing antibiotics are collectively known as sulfa drugs.
- Prontosil is not the active ingredient itself—In cells, it is metabolized to sulfanilamide, the active drug.

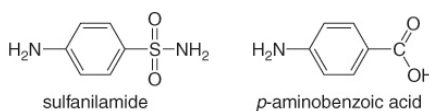


## Sulfa Drugs

- To understand how sulfanilamide functions as an antibacterial agent, we must examine folic acid, which microorganisms synthesize from *p*-aminobenzoic acid.



- Sulfanilamide and *p*-aminobenzoic acid are similar in size and shape and have related functional groups.

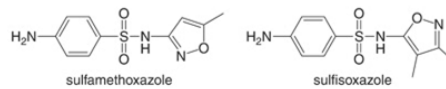


These compounds are similar in size and shape.

## Sulfa Drugs

- When sulfanilamide is administered, bacteria attempt to use it in place of *p*-aminobenzoic acid to synthesize folic acid. Derailing folic acid synthesis means that the bacteria cannot grow and reproduce. Sulfanilamide only affects bacterial cells, because humans do not synthesize folic acid, and must obtain it from their diets.

Figure 25.13 Two common sulfa drugs



- Sulfamethoxazole is the sulfa drug in Bactrim, and sulfisoxazole is sold as Gantrisin. Both drugs are commonly used in the treatment of ear and urinary tract infections.