Organic Chemistry, *Fourth Edition*

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Chapter 25
Lecture Outline

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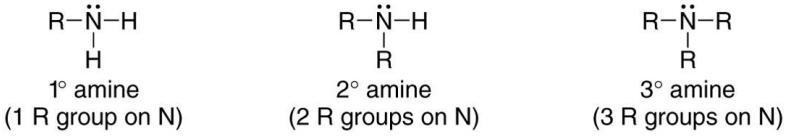
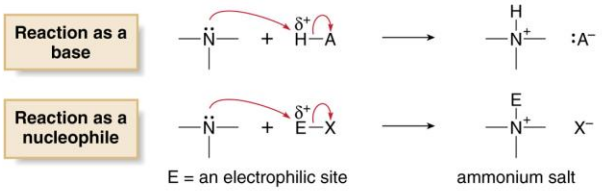
Amine Structure

- **Amines are organic nitrogen compounds, formed by replacing one or more hydrogen atoms of ammonia (NH_3) with alkyl or aryl groups.**
- **Amines are classified as 1°, 2°, or 3° based on the number of alkyl groups bonded to the nitrogen atom.**
- **Amines are stronger bases and better nucleophiles than other neutral organic compounds.**



General Amine Reactions

- **Like ammonia, the amine nitrogen atom has a nonbonded electron pair, making it both a base and a nucleophile.**
- **As a result, amines react with electrophiles to form quaternary ammonium salts—compounds with four bonds to nitrogen.**



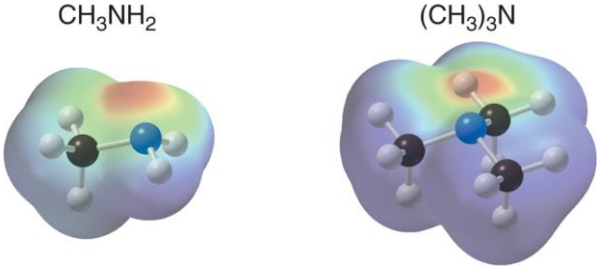
- The chemistry of amines is dominated by the nonbonded electron pair on the nitrogen atom.

3

Electrostatic Potential Map of Amines

- **Both methylamine and trimethylamine clearly show the electron-rich region at the N atom.**

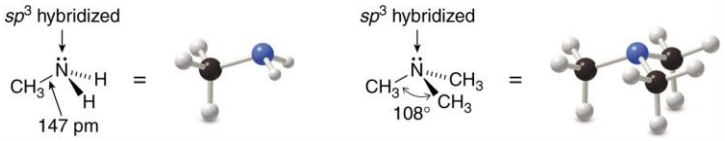
Figure 25.1



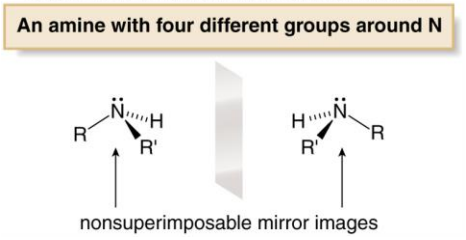
4

3D Structure of Amines

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



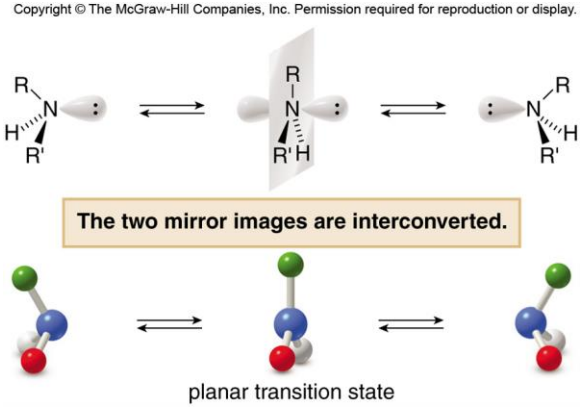
- **Since an amine nitrogen has four different groups around it, it is technically a stereogenic center.**



5

Chirality of Amines

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



6

Chirality of Ammonium Salts

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

Two enantiomers of an ammonium salt

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

7

Nomenclature of Amines

- **1° 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 change the *–e* ending of the parent alkane to the suffix *–amine*.**
- **Then use the usual rules of nomenclature to number the chain and name the substituents.**
- **To assign a common name, name the alkyl group bonded to the nitrogen atom and add the word amine, forming a single word.**

Examples

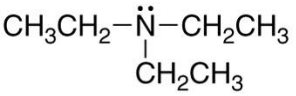
Systematic name: **methanamine**
Common name: **methylamine**

Systematic name: **cyclohexanamine**
Common name: **cyclohexylamine**

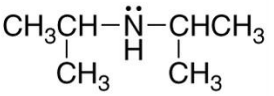
8

Naming 2° and 3° Amines

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



triethylamine



diisopropylamine

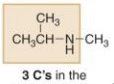
Nomenclature of 2° and 3° Amines

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

How To Name 2° and 3° Amines with Different Alkyl Groups

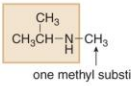
Example Name the following 2° amine: $(CH_3)_2CHNHCH_3$.

Step [1] Designate the longest alkyl chain (or largest ring) bonded to the N atom as the parent amine and assign a common or systematic name.



3 C's in the longest chain ⟶ isopropylamine (common name) or 2-propanamine (systematic name)

Step [2] Name the other groups on the N atom as alkyl groups, alphabetize the names, and put the prefix *N*- before the name.

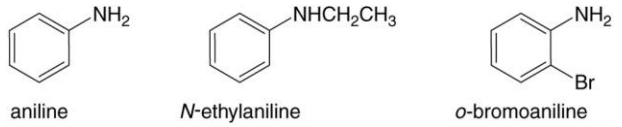


one methyl substituent

Answer: *N*-methylisopropylamine (common name) or *N*-methyl-2-propanamine (systematic name)

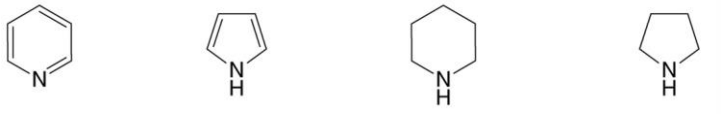
Aromatic and Heterocyclic Amines

- **Aromatic amines are named as derivatives of aniline.**



aniline *N*-ethylaniline *o*-bromoaniline

- **There are a variety of nitrogen heterocycles, each with a unique name.**
- **The N atom is considered to be at position "1" in each of these rings.**

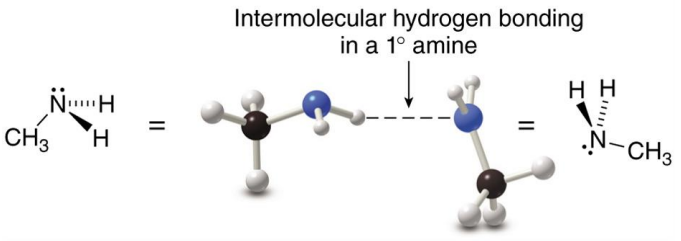


pyridine pyrrole piperidine pyrrolidine

11

Intermolecular Forces of Amines

- **Amines exhibit dipole-dipole interactions because of the polar C–N and N–H bonds.**
- **1° and 2° amines are capable of intermolecular hydrogen bonding because they contain N–H bonds.**
- **Since nitrogen is less electronegative than oxygen, these hydrogen bonds are weaker than those between O and H.**



12

Table 25.1 Physical Properties of Amines

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

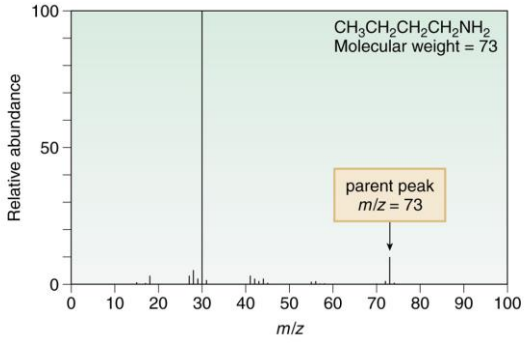
MW = molecular weight

13

Mass Spectra of Amines

- **Amines with an odd number of N atoms give an odd molecular ion in their mass spectra.**
- **Amines differ from compounds that contain only C, H, and O atoms, which always have a molecular ion with an even mass in their spectra.**

Figure 25.2
Mass spectrum of butylamine



14

IR Spectra of Amines

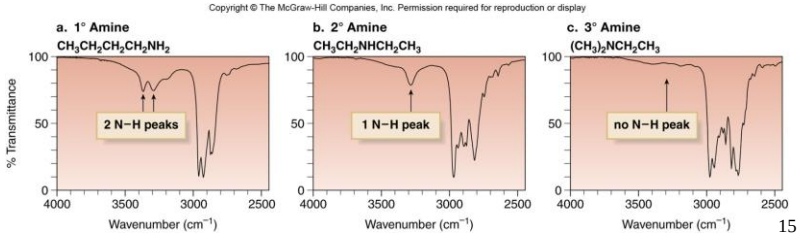
- **Amines with N–H bonds show characteristic absorptions in their IR spectra:**

[1] 1° Amines show two N–H absorptions at 3300–3500 cm^{-1}.

[2] 2° Amines show one N–H absorption at 3300–3500 cm^{-1}.

- **Because 3° amines have no N–H bonds, they do not absorb in this region in their IR spectra.**

Figure 25.3 The single bond region of the IR spectra for a 1°, 2°, and 3° amine



15

NMR Spectra of Amines

- **Amines exhibit the following characteristic ^{1}H NMR and ^{13}C NMR absorptions:**

[1] The N–H signal appears between 0.5 and 5.0 ppm. The exact location depends on the degree of hydrogen bonding and the concentration of the sample.

[2] The protons on the carbon bonded to the amine nitrogen are deshielded and typically absorb at 2.3–3.0 ppm.

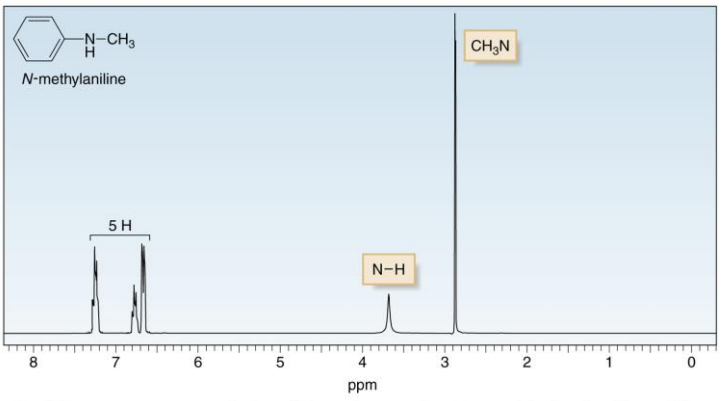
[3] In the ^{13}C NMR spectrum, the carbon bonded to the N atom is deshielded and typically absorbs at 30–50 ppm.

- **Like the OH absorption of an alcohol, NH absorption is not split by adjacent protons, nor does it cause splitting of adjacent C–H absorptions in a ^{1}H NMR spectrum.**

16

^{1}H NMR Spectrum of N-methylaniline

Figure 25.4



- The CH_3 group appears as a singlet at 2.7 ppm because there is no splitting by the adjacent NH proton.
- The NH proton appears as a broad singlet at 3.6 ppm.
- The five H atoms of the aromatic ring appear as a complex pattern at 6.6–7.2 ppm.

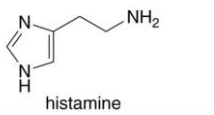
17

Interesting 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 also products of decay with putrid odors.**

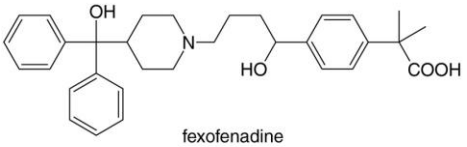
18

Histamine and Antihistamines

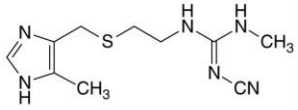


histamine

- **Histamine, a rather simple triamine that is present in many tissues, is responsible for a wide variety of physiological effects.**
- **It is a vasodilator and is also responsible for symptoms of allergies.**
- **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.**



fexofenadine
antihistamine

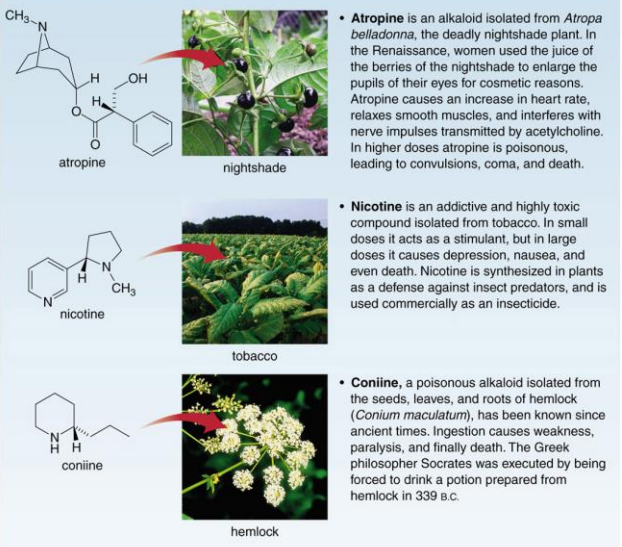


cimetidine
(Tagamet)
antiulcer drug

19

Common Alkaloids

Figure 25.5

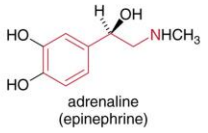


(nightshade): © Werner Arnold;
(tobacco): © Creatas Images RF;
(hemlock): © Steven P. Lynch;

20

Derivatives of 2-Phenylethylamine

- **A large number of physiologically active compounds are derived from 2-phenylethylamine ($C_6H_5CH_2CH_2NH_2$).**
- **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).**

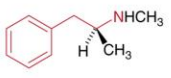


adrenaline
(epinephrine)

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

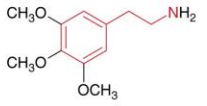
noradrenaline
(norepinephrine)

a neurotransmitter that increases heart rate
and dilates air passages



methamphetamine

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

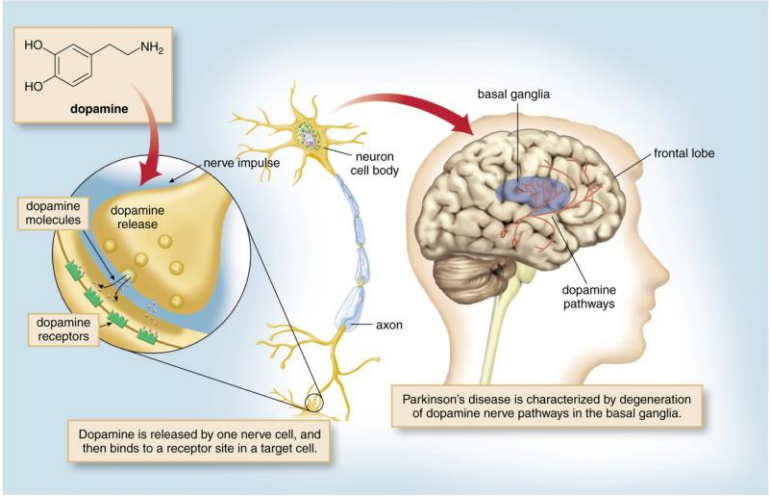


mescaline

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

Dopamine—A Neurotransmitter

Figure 25.6



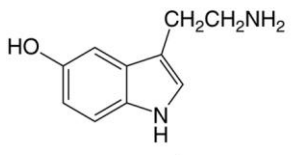
Dopamine Affecting Drugs

- **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.**

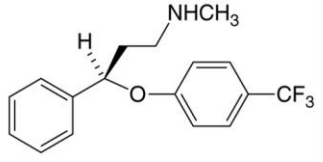
23

AntiDepressants

- **Serotonin is a neurotransmitter that plays an important role in mood, sleep, perception, and temperature regulation.**
- **A deficiency of serotonin causes depression.**
- **The most widely used antidepressants are selective serotonin reuptake inhibitors (SSRIs).**
- **These drugs act by inhibiting the reuptake of serotonin by the neurons that produce it, increasing its available concentration.**
- **Fluoxetine (trade name Prozac) works in this way.**



serotonin

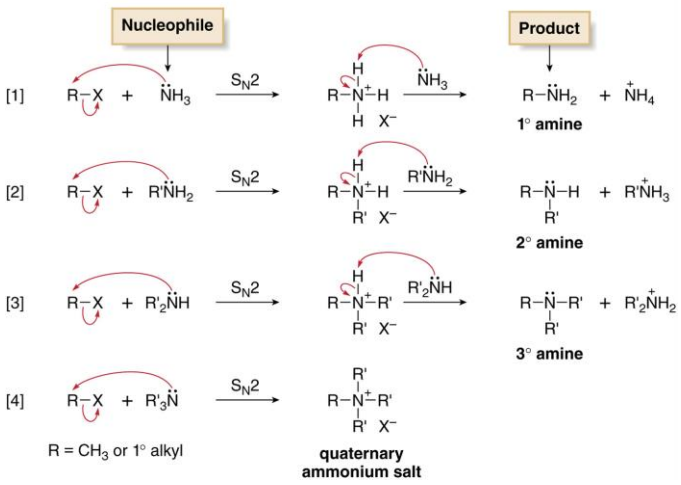


fluoxetine

24

Preparation of Amines

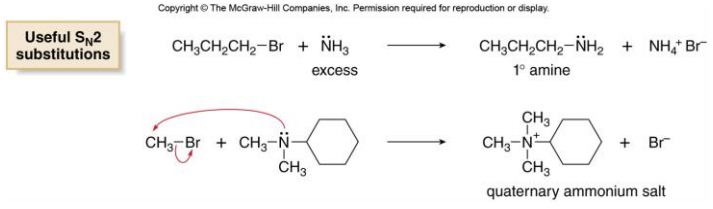
- **Amines can be prepared by direct nucleophilic substitution.**



25

Limitations of Direct Substitution

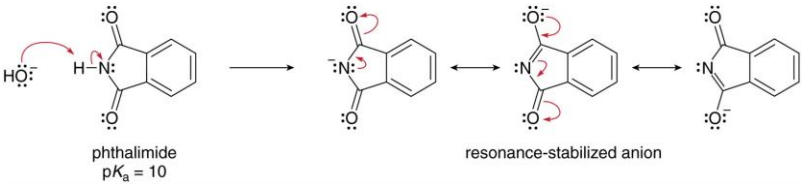
- **Although the process seems straightforward, polyalkylation of the nitrogen nucleophile limits its usefulness.**
- **Any amine formed by nucleophilic substitution still has a nonbonded electron pair, making it a nucleophile as well.**
- **It will react with remaining alkyl halide to form a more substituted amine, resulting in a mixture of 1°, 2°, and 3° amine products.**
- **Consequently, the reaction is most useful in preparing 1° amines by using a large excess of NH_3, and for preparing quaternary ammonium salts by alkylating any nitrogen nucleophile with one or more equivalents of alkyl halide.**



26

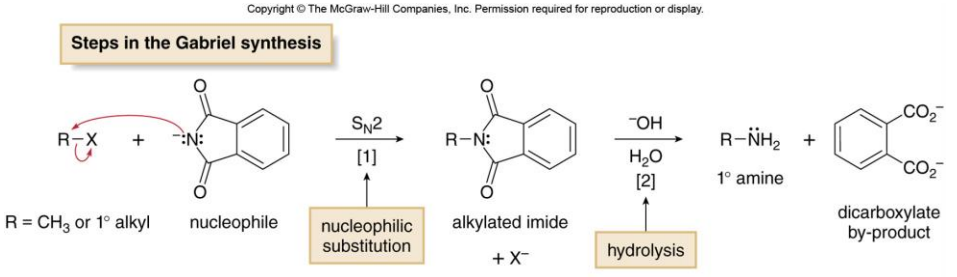
Gabriel Synthesis of 1° Amines

- **The Gabriel synthesis is comprised of two steps and uses a nucleophile derived from pthalimide to synthesize 1° amines via nucleophilic substitution.**
- **The N–H bond of a pthalimide 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_N2 reaction to form a substituted product.**

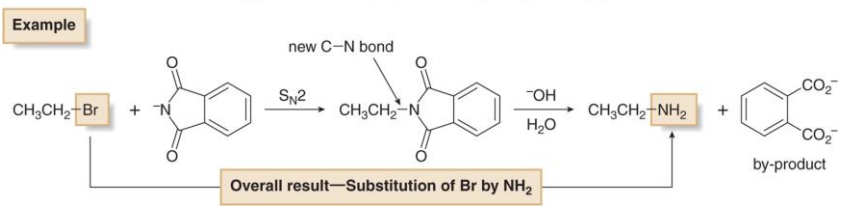
Steps in the Gabriel Synthesis



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

Example of the Gabriel Synthesis

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



29

Reduction of Nitro and Nitrile Groups

- **Amines can be prepared by reduction of nitro compounds, nitriles, and amides.**

[1] From nitro compounds (Section 18.15C)

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

$$R{-}NO_2 \xrightarrow[\text{or Fe, HCl or Sn, HCl}]{H_2,\ \text{Pd-C}} R{-}NH_2 \quad (1°\ \text{amine})$$

[2] From nitriles (Section 22.18B)

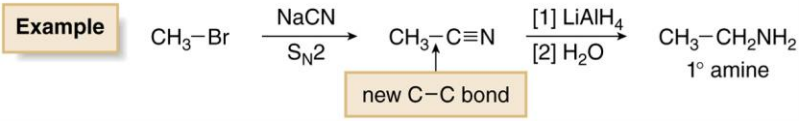
Nitriles are reduced to 1° amines with $LiAlH_4$.

$$R{-}C{\equiv}N \xrightarrow[[2]\ H_2O]{[1]\ LiAlH_4} R{-}CH_2NH_2 \quad (1°\ \text{amine})$$

30

Two-Step Synthesis of Amines Using Nitriles

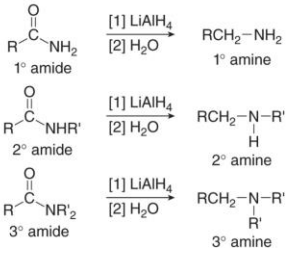
- **Because the cyano group is readily introduced by S_N2 substitution of alkyl halides with ^-CN, this provides a two-step method to convert an alkyl halide to a 1° amine with one more carbon atom.**



Reduction of Amides

[3] From amides (Section 20.7B)

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

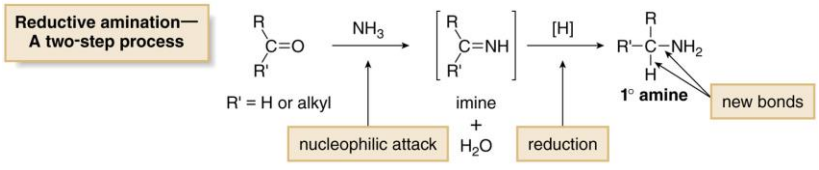


Reductive Amination

- **Reductive amination is a two-step method that converts aldehydes and ketones into 1°, 2°, and 3° amines.**
- **There are two distinct steps to this reaction.**

[1] Nucleophilic attack of NH_3 on the carbonyl group forms an imine.

[2] Reduction of the imine forms an amine.



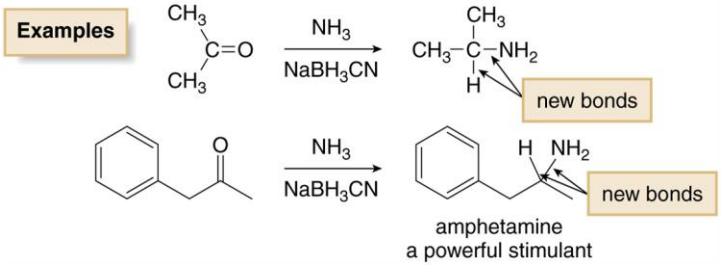
- Reductive amination replaces a C=O by a C–H and C–N bond.

33

Reductive Amination

- **The most effective reducing agent for this reaction is sodium cyanoborohydride ($NaBH_3CN$).**

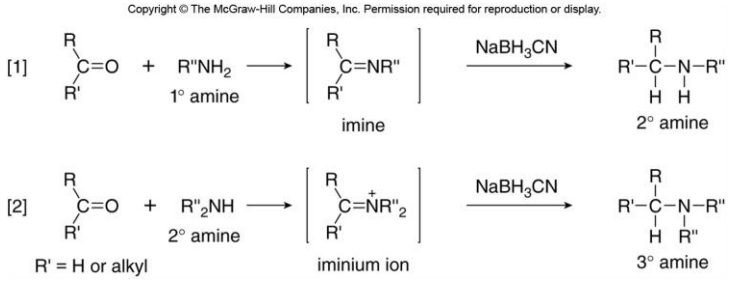
$NaBH_3CN$
sodium cyanoborohydride



34

2° and 3° Amines Via Reductive Amination

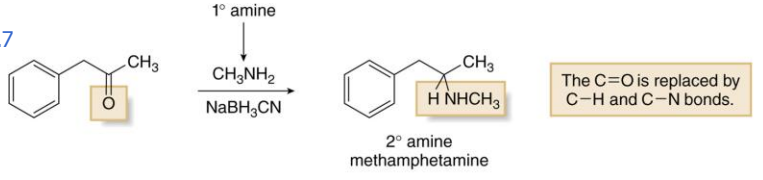
- **With a 1° or 2° amine as starting material, reductive amination is used to prepare 2° and 3° amines, respectively.**



Synthesis of Methamphetamine by Reductive Amination

- **In reductive amination process, one of the H atoms bonded to N is replaced by an alkyl group.**
- **Thus, methylamine (a 1° amine) reacts with phenylacetone by reductive amination to produce methamphetamine (a 2° amine).**

Figure 25.7

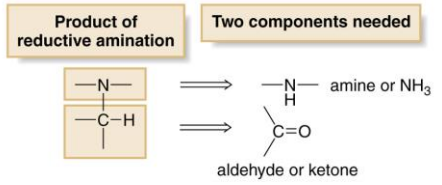


- In reductive amination, one of the H atoms bonded to N is replaced by an alkyl group. As a result, a 1° amine is converted to a 2° amine and a 2° amine is converted to a 3° amine. In this reaction, CH_3NH_2 (a 1° amine) is converted to methamphetamine (a 2° amine).

Reductive Amination in Synthesis

- **To use reductive amination in synthesis, you must be able to determine what aldehyde or ketone and nitrogen compound are needed to prepare a given amine—that is, you must work backwards in the retrosynthetic direction.**
- **Keep in mind the following two points:**

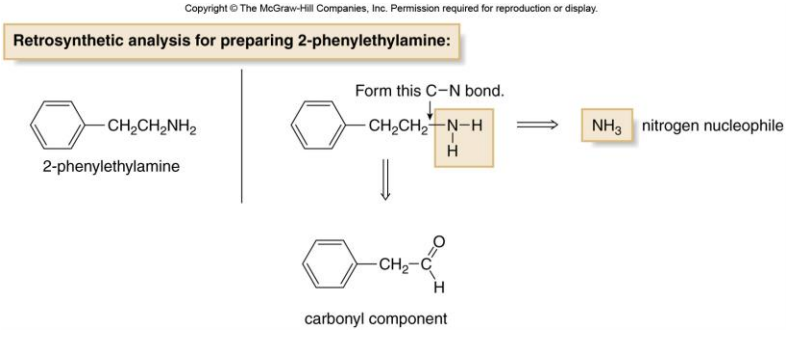
- One alkyl group on N comes from the carbonyl compound.
- The remainder of the molecule comes from NH_3 or an amine.



37

Synthesis of a 1° Amine

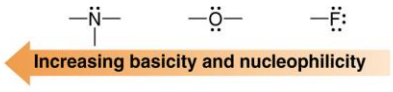
- **For a 1° amine, the nitrogen component must be NH_3.**



38

General Reactivity of Amines

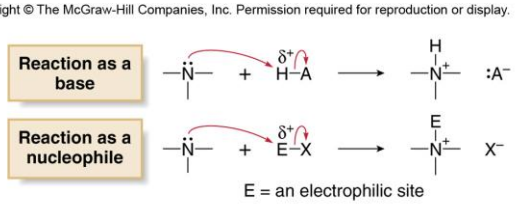
- **The chemistry of amines is dominated by the lone pair of electrons on nitrogen.**
- **Only three elements in the second row of the periodic table have nonbonded electron pairs in neutral organic compounds: nitrogen, oxygen, and fluorine.**
- **Because basicity and nucleophilicity decrease across a row, nitrogen is the most basic and the most nucleophilic.**



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

39

Amines React as Bases or Nucleophiles

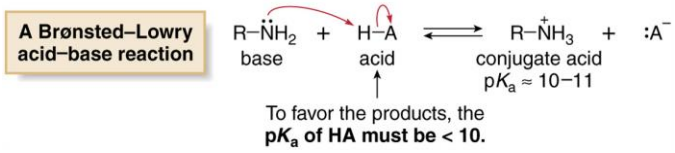


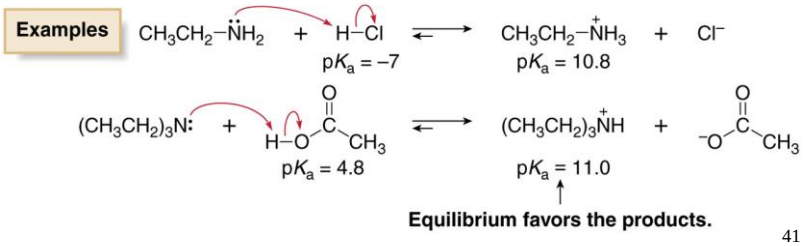
- Amines react as bases with compounds that contain acidic protons.
- Amines react as nucleophiles with compounds that contain electrophilic carbons.

40

Amines as Bases

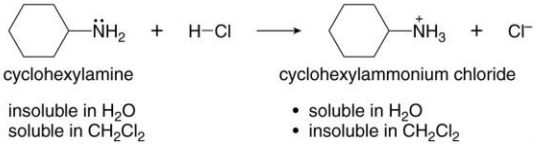
- **Amines react as bases with a variety of organic and inorganic acids.**





Extraction of Amines

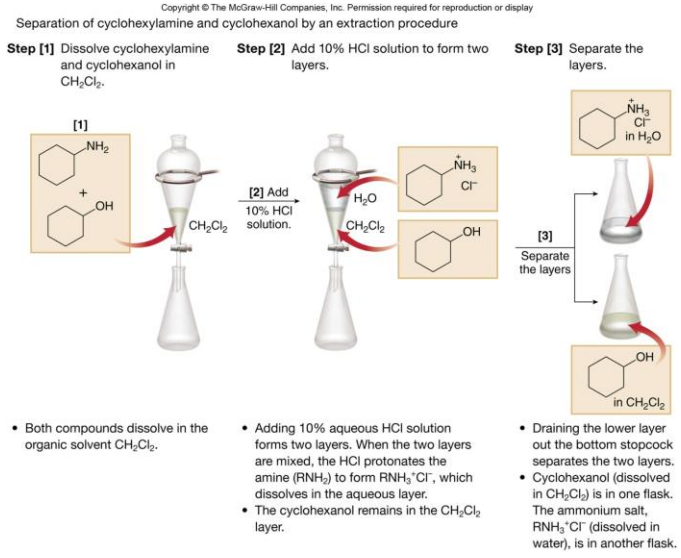
- **Because amines are protonated by aqueous acid, they can be separated from other organic compounds by extraction using a separatory funnel.**
- **When an amine is protonated by aqueous acid, it forms an ammonium salt.**



- **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.**

Separation of Amines and Alcohols

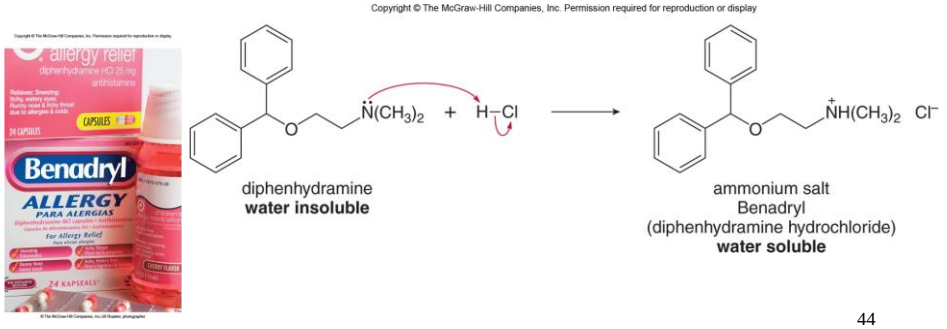
Figure 25.8



43

Water Soluble Ammonium Salts

- **Many water-insoluble amines with useful medicinal properties are sold as their ammonium salts.**
- **These are more easily transported through the body in the aqueous medium of the blood.**
- **Benadryl is an over-the-counter antihistamine that is used to relieve the itch and irritation of skin rashes and hives.**

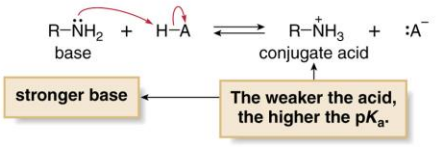


44

Basicity of Amines

- **The relative acidity of different compounds can be compared using their pK_a values.**
- **The relative basicity of different compounds (such as amines) can be compared using the pK_a values of their conjugate acids.**

- The weaker the conjugate acid, the higher its pK_a and the stronger the base.



45

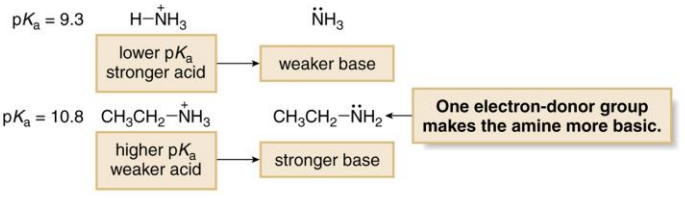
Comparing Basicity of Amines

- **Any factor that increases the electron density on the N atom increases the amine's basicity.**
- **Any factor that decreases the electron density on N decreases an amine's basicity.**
- **Because alkyl groups are electron-donating, they increase the electron density on nitrogen, which makes an amine like $CH_3CH_2NH_2$ more basic than NH_3.**

46

Comparing Basicity of Amines, *continued*

- **Thus, the pK_a of $CH_3CH_2NH_3^+$ is higher than the pK_a of NH_4^+, so $CH_3CH_2NH_2$ is a stronger base than NH_3.**

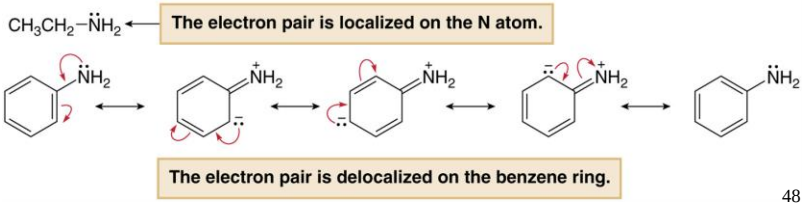


- Primary (1°), 2°, and 3° alkylamines are more basic than NH_3 because of the electron-donating inductive effect of the R groups.

47

Basicity of Aryl and Alkyl Amines

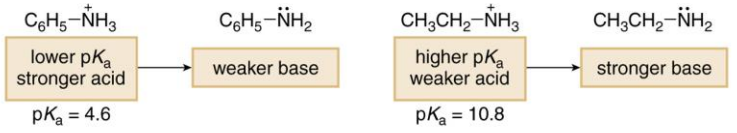
- **To compare an alkylamine and an arylamine, we must look at the availability of the nonbonded electron pair on N.**
- **With $CH_3CH_2NH_2$ for example, the electron pair is localized on the N atom.**
- **With an arylamine, the electron pair is delocalized on the benzene ring via resonance.**
- **This decreases the electron density on N, and makes an amine like $C_6H_5NH_2$ less basic than $CH_3CH_2NH_2$.**



48

Basicity of Aryl and Alkyl Amines

- **pK_a Values support this reasoning.**
- **Since the pK_a of $CH_3CH_2NH_3^+$ is higher than the pK_a of $C_6H_5NH_3^+$, $CH_3CH_2NH_2$ is a stronger base than $C_6H_5NH_2$.**



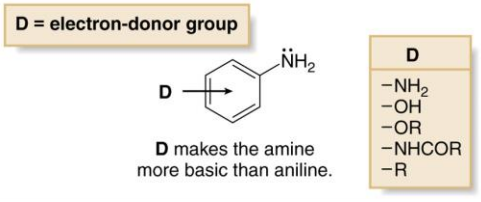
- Arylamines are less basic than alkylamines because the electron pair on N is delocalized.

49

Basicity of Substituted Aryl Amines

- **Substituted anilines are more basic 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.



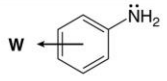
50

Basicity of Substituted Aryl Amines

- **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.

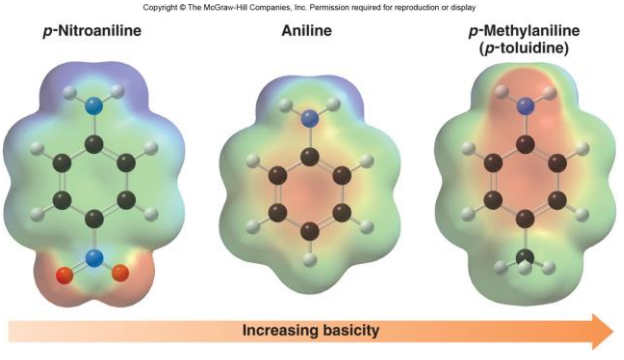
W	
−X	−CN
−CHO	$-SO_3H$
−COR	$-NO_2$
−COOR	$-NR_3^+$
−COOH	

51

Electrostatic Potential Plot of Anilines

- **The amine group gets more electron rich as the para substituent changes from nitro to hydrogen to methyl.**

Figure 25.9



52

Weaker Basicity of Amides

- **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_2, 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, accounting for its much lower basicity than an alkylamine.**

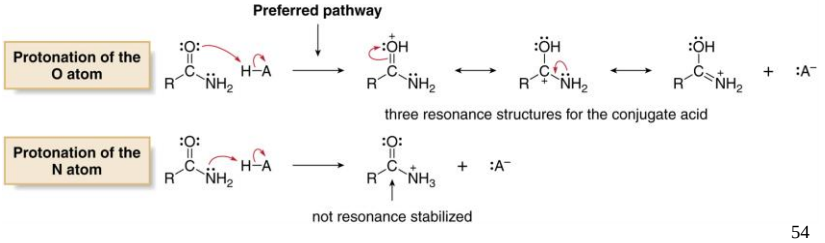
The electron pair on N is delocalized on O by resonance.

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

53

Amide Basicity Resembles Other Carbonyl Compounds

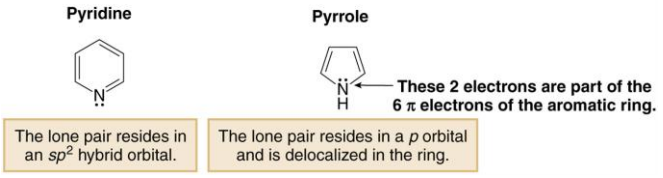
- **When an amide is treated with acid, protonation occurs at the carbonyl oxygen, not the nitrogen, because the resulting cation is resonance stabilized.**
- **The product of protonation on the NH_2 group cannot be resonance stabilized.**
- **Thus, protonation on oxygen is the preferred pathway.**



54

Basicity of Heterocyclic Amines

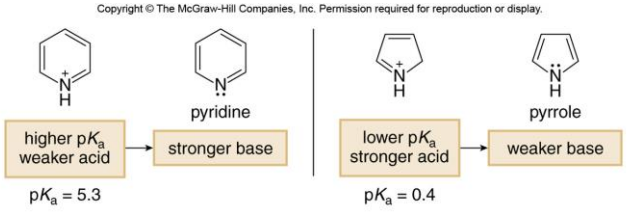
- **To determine the relative basicity of nitrogen heterocycles that are also aromatic, you must know whether the nitrogen lone pair is part of the aromatic π system.**
- **Both pyridine and pyrrole are aromatic, but the nonbonded electron pair on the N atom in these compounds is located in different orbitals.**
- **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 delocalized aromatic system.**
- **Thus, pyrrole is a much weaker base than pyridine.**



55

Basicity of Heterocyclic Amines

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

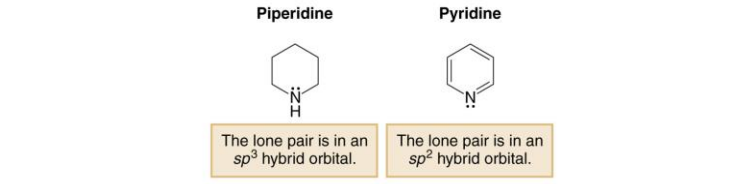


- Pyrrole is much less basic than pyridine because its lone pair of electrons is part of the aromatic π system.

56

Basicity of Heterocyclic Amines—Hybridization

- **The hybridization of the orbital that contains an amine's lone pair also affects its basicity.**
- **The lone pair on pyridine is not part of the delocalized π system, but occupies an sp^2 orbital.**
- **These electrons are held more tightly than the sp^3 piperidine electrons.**
- **Therefore, pyridine is a weaker base than piperidine.**

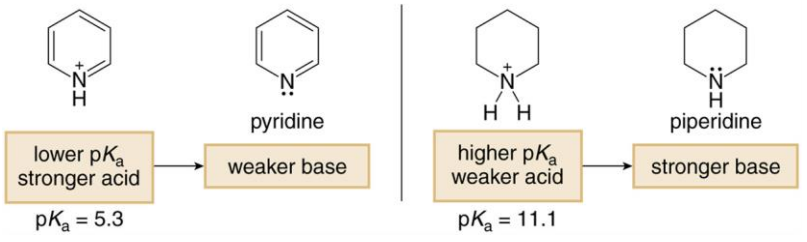


- The higher the percent *s*-character of the orbital containing the lone pair, the more tightly the lone pair is held, and the weaker the base.

57

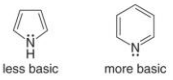
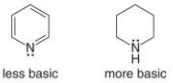
Basicity of Heterocyclic Amines—Hybridization

- **The lower basicity of pyridine is reflected in the pK_a value of its conjugate acid which is much lower than that for the conjugate acid of piperidine.**



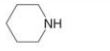
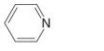
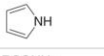
58

Table 25.2 Factors That Determine Amine Basicity

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

59

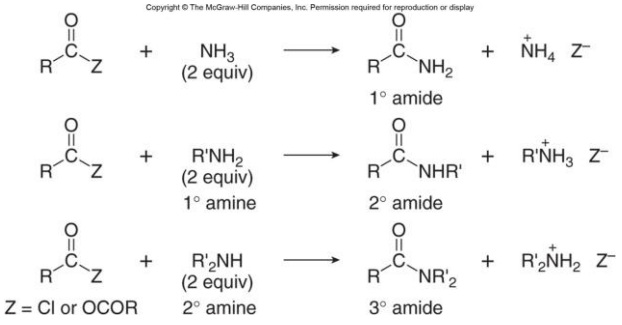
Table 25.3 Table of pK_a Values of Some Representative Organic Nitrogen Compounds

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

60

Reaction of Amines with Aldehydes and Ketones

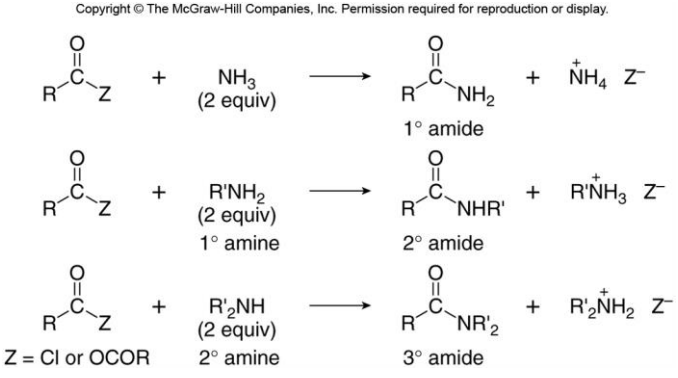
- **Reaction of 1º and 2º amines with aldehydes and ketones (Sections 21.11-21.12).**
- **Aldehydes and ketones react with 1º amines to form imines.**
- **They react with 2º amines to form enamines.**
- **Both reactions involve nucleophilic addition of the amine to the carbonyl group to form a carbinolamine, which then loses water to form the final product.**



61

Reaction of Amines with Acid Derivatives

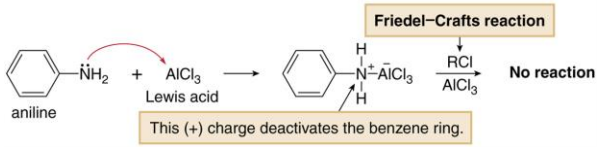
- **Reaction of NH_3 and 1º and 2º amines with acid chlorides and anhydrides (Sections 22.8-22.9).**
- **NH_3, 1º and 2º amines react with acid chlorides and anhydrides to form 1º, 2º and 3º amides, respectively.**



62

Synthesis of Substituted Anilines

- **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 ($AlCl_3$) to form a deactivated complex that does not undergo further reaction.**

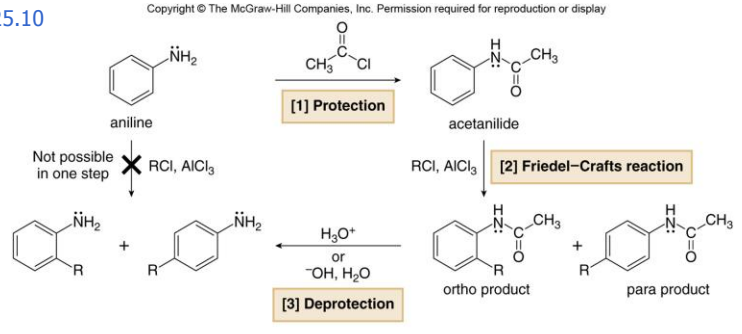


- **The N atom of an amide, however, is much less basic than in an amine, so it does not undergo a similar Lewis acid–base reaction with $AlCl_3$.**

Amides as Protecting Groups

- **Thus, a three-step reaction sequence involving an intermediate amide can be used to form the products of the Friedel–Crafts reaction.**

Figure 25.10



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

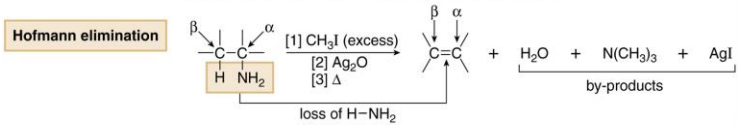
[1] Treatment of aniline with acetyl chloride (CH_3COCl) forms an amide (acetanilide).

[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.

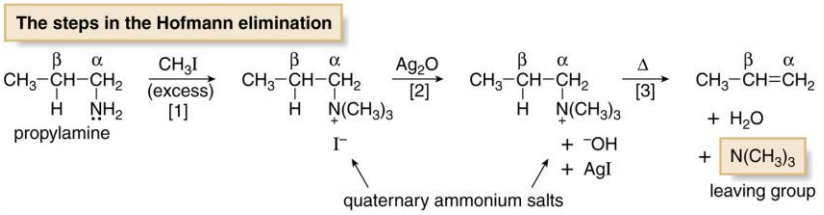
[3] Hydrolysis of the amide forms the Friedel–Crafts substitution products.

Hofmann Elimination

- **The Hofmann elimination converts an amine into an alkene.**



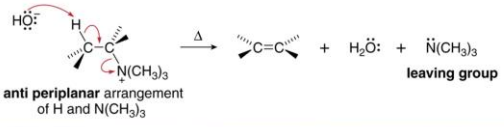
- **The Hofmann elimination consists of three steps, as shown for the conversion of propylamine to propene.**



65

Hofmann Elimination

Mechanism 25.1 The E2 Mechanism for the Hofmann Elimination

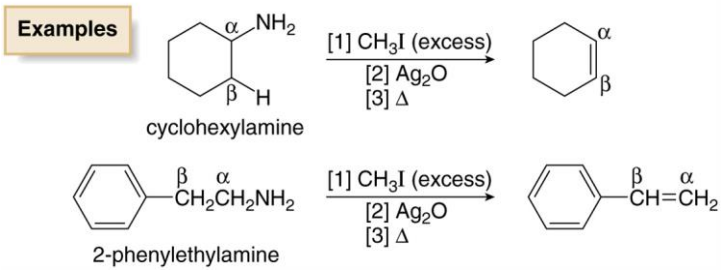


- **To help remember the reagents needed for the steps of the Hofmann elimination, keep in mind what happens in each step.**
  - **Step [1] makes a good leaving group by forming a quaternary ammonium salt.**
  - **Step [2] provides the strong base, $^-$OH, needed for elimination.**
  - **Step [3] is the E2 elimination that forms the new π bond.**

66

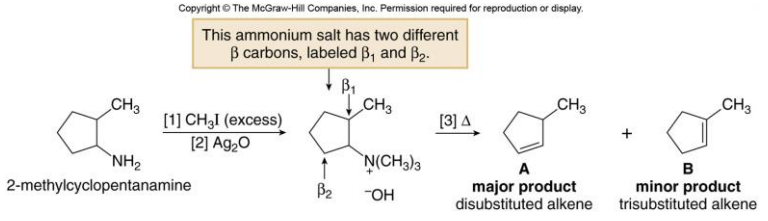
Hofmann Elimination

- **All Hofmann elimination reactions result in the formation of a new π bond between the α and β carbon atoms, as shown for cyclohexylamine and 2-phenylethylamine.**



Hofmann Elimination vs. Other E2 Eliminations

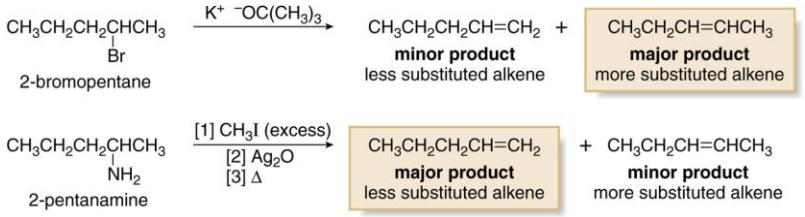
- **One major difference between the Hofmann elimination and other E2 eliminations: when constitutional isomers are possible, the major alkene has the less-substituted double bond.**



- **This result is explained by the size of the leaving group.**
- **The base removes a proton from the less substituted, more accessible β carbon atom, because of the size of the bulky leaving group on the nearby α carbon.**

Comparison of E2 Elimination Reactions

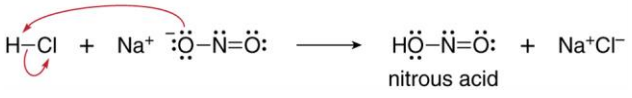
Figure 25.11



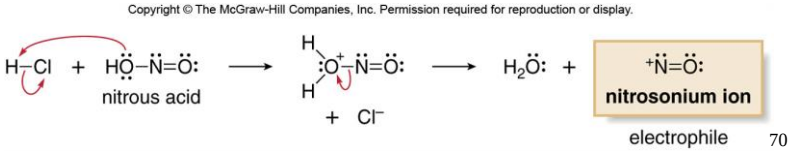
69

Reaction of Amines with Nitrous Acid

- **Nitrous acid, HNO_2, is a weak unstable acid formed from $NaNO_2$ and a strong acid like HCl.**



- **In the presence of acid, nitrous acid decomposes to ^{+}NO, the nitrosonium ion.**
- **This electrophile then goes on to react with the nucleophilic nitrogen atom of amines to form diazonium salts ($RN_2^{+}Cl^{-}$) from 1° amines and N-nitrosamines ($R_2NN{=}O$) from 2° amines.**

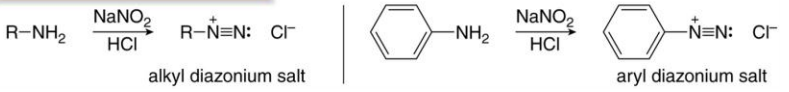


70

Diazotization

- **Nitrous acid reacts with 1° alkylamines and arylamines to form diazonium salts.**
- **This reaction is called diazotization.**

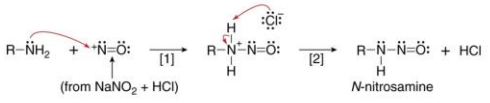
Preparation of diazonium salts



- **The mechanism for this reaction begins with nucleophilic attack by the amine on the nitrosonium ion.**
- **It can conceptually be divided into two parts: formation of an N-nitrosamine, followed by loss of H_2O.**

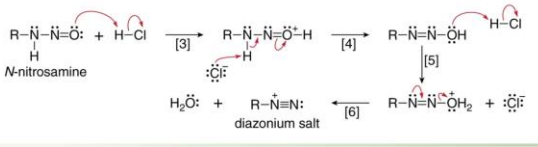
Mechanism 25.2 Formation of a Diazonium Salt from a 1° Amine

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 ^+NO, followed by loss of a proton.

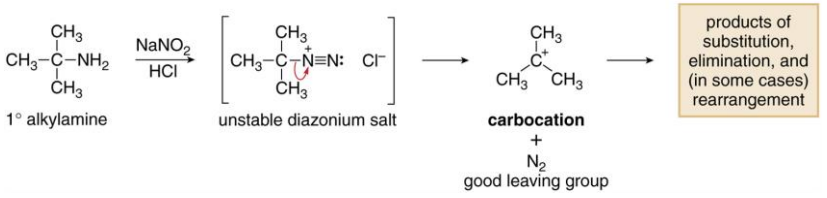
Part [2] Loss of H_2O to form the diazonium salt



- In Part [2], three proton transfer reactions lead to loss of H_2O in Step [6] and formation of the diazonium ion.

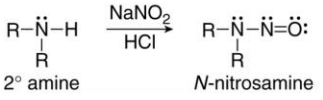
Alkyl Diazonium Salts

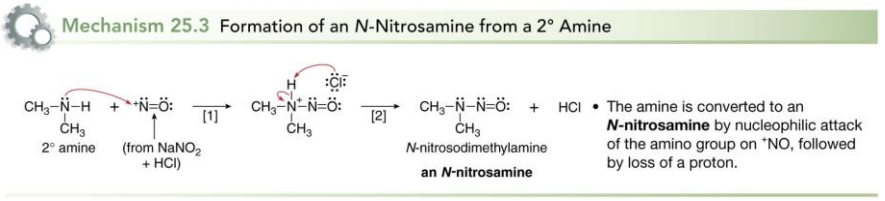
- **Alkyl diazonium salts are generally not useful compounds.**
- **They readily decompose below room temperature and form carbocations with loss of N_2, a very good leaving group.**
- **These carbocations usually form a complex mixture of substitution, elimination and rearrangement products.**



Formation of *N*-Nitrosamines

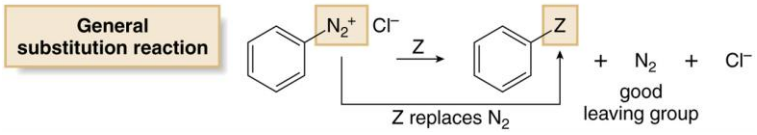
- **2° Alkylamines and aryl amines react with nitrous acid to form *N*-nitrosamines.**



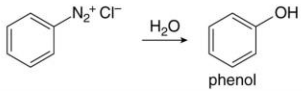


Substitution Reactions of Aryl Diazonium Salts

- **Aryl diazonium salts react with a variety of reagents to form products in which Z (an atom or group of atoms) replaces N_2, a very good leaving group.**
- **The mechanism of these reactions varies with the identity of Z.**



[1] Substitution by OH—Synthesis of phenols



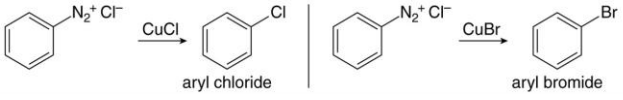
- **A diazonium salt reacts with water to form a phenol.**

75

Sandmeyer Reactions of Diazonium Salts

- **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 Cl_2 or Br_2 and a Lewis acid catalyst.**

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

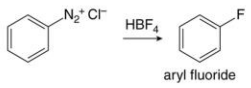


76

Synthesis of Aryl Fluorides and Iodides

- **A diazonium salt reacts with fluoroboric acid to form an aryl fluoride.**

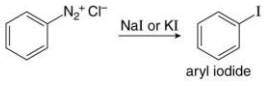
[3] Substitution by F—Synthesis of aryl fluorides



aryl fluoride

- **A diazonium salt reacts with sodium or potassium iodide to form an aryl iodide.**

[4] Substitution by I—Synthesis of aryl iodides



aryl iodide

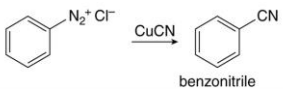
- **These are useful reactions because aryl fluorides and iodides cannot be produced by direct halogenation with F_2 or I_2 and a Lewis acid catalyst.**

77

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.**

[5] Substitution by CN—Synthesis of benzonitriles



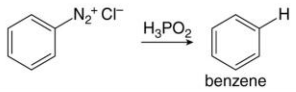
benzonitrile

78

Substitution by Hydrogen

- **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.**

[6] Substitution by H—Synthesis of benzene

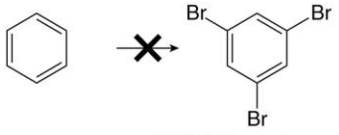


benzene

79

Practical Use of Substitution with Hydrogen

- **The synthesis of 1,3,5-tribromobenzene is an example of the usefulness of hydrogen substitution.**
- **Br is an ortho, para director, bromination with Br_2 and $FeBr_3$ will not add Br substituents meta to each other on the ring.**
- **It is not possible to synthesize 1,3,5-tribromobenzene from benzene by direct bromination.**



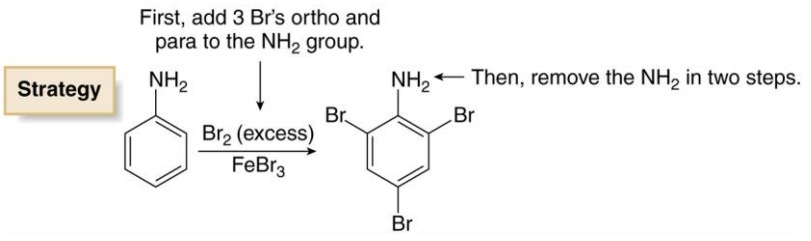
1,3,5-tribromobenzene

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

80

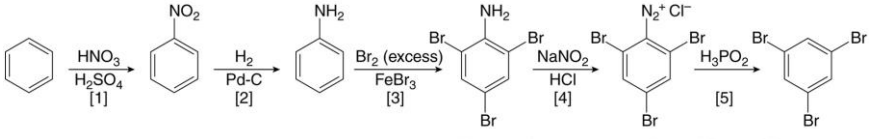
Synthesis of 1,3,5-Tribromobenzene

- **It is possible, however, to add three Br atoms meta to each other when aniline is the starting material.**
- **Because an NH_2 group is a very powerful o,p director, three Br atoms are introduced in a single step on halogenation.**
- **Then, the NH_2 group can be removed by diazotization and reaction with H_3PO_2.**



Synthesis of 1,3,5-Tribromobenzene

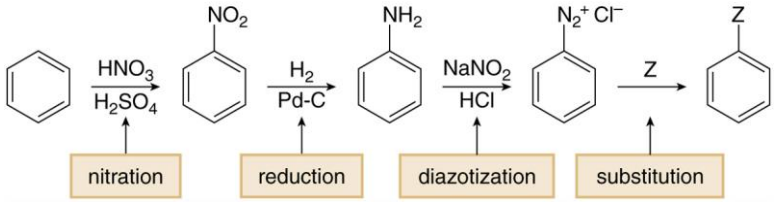
Figure 25.12



- Nitration followed by reduction forms aniline ($C_6H_5NH_2$) from benzene (Steps [1] and [2]).
- Bromination of aniline yields the tribromo derivative in Step [3].
- The NH_2 group is removed by a two-step process: diazotization with $NaNO_2$ and HCl (Step [4]), followed by substitution of the diazonium ion by H with H_3PO_2.

Synthesis Using the Four-Step Diazo Sequence

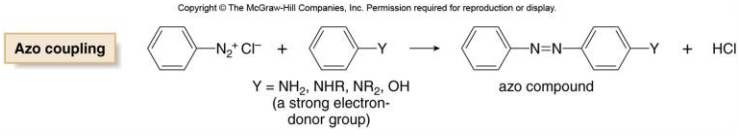
- **Diazonium salts provide easy access to many different benzene derivatives.**
- **Keep in mind the following four-step sequence, because it will be used to synthesize many substituted benzenes.**



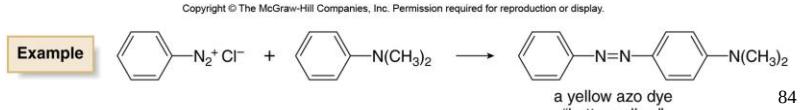
83

Coupling Reactions of Aryl Diazonium Salts

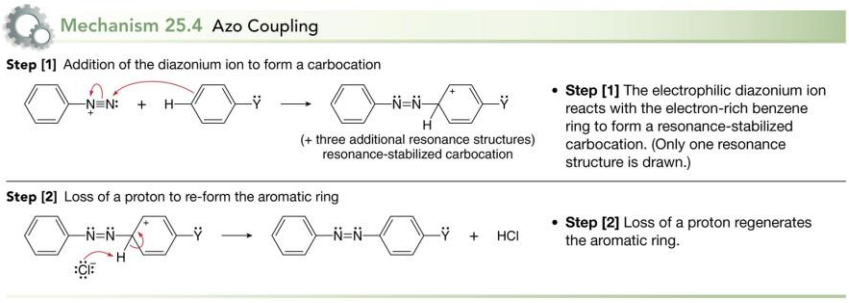
- **When a diazonium salt is treated with an aromatic compound that contains a strong electron-donor group, the two rings join together to form an azo compound, a compound with a nitrogen–nitrogen double bond.**



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



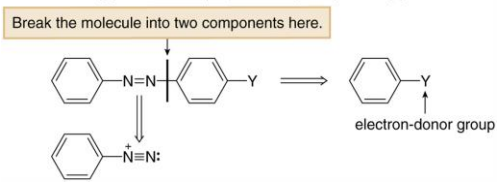
84



85

Synthesis of Azo Compounds

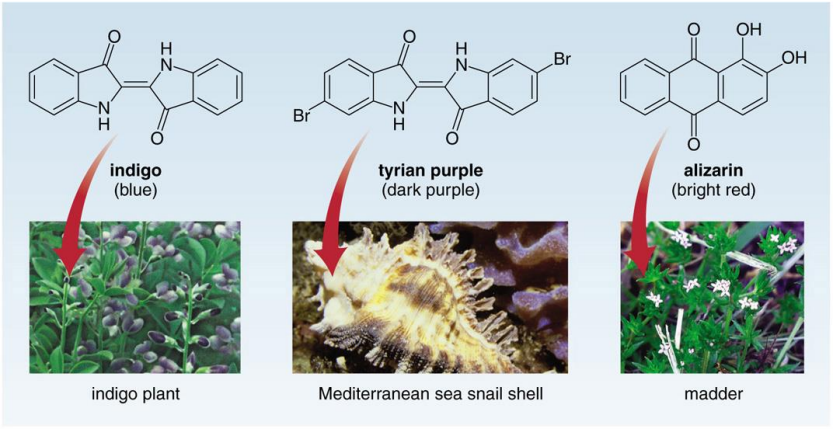
- **Because a diazonium salt is only weakly electrophilic, the reaction only occurs when the benzene ring has a strong electron donor group, such as NH_2, NHR, NR_2, or OH.**
- **Although these groups activate both the ortho and para positions, para substitution occurs unless that position already has 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.**



86

Natural and Synthetic Dyes

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

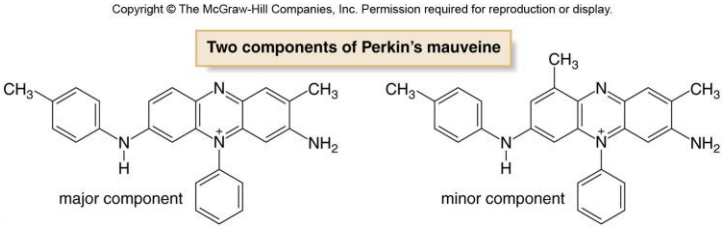


87

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.**

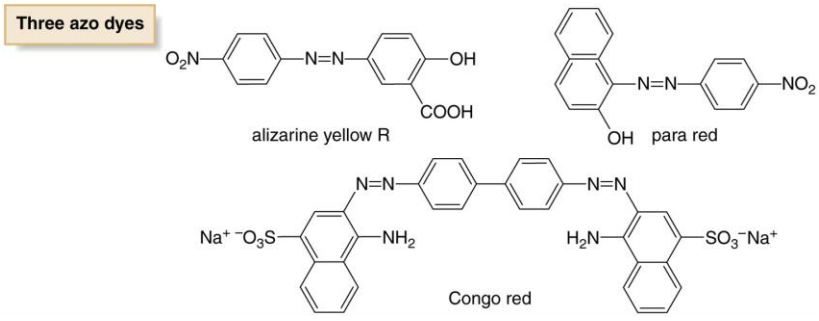
A purple shawl dyed with Perkin's mauveine



88

Synthetic Azo Dyes

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



89

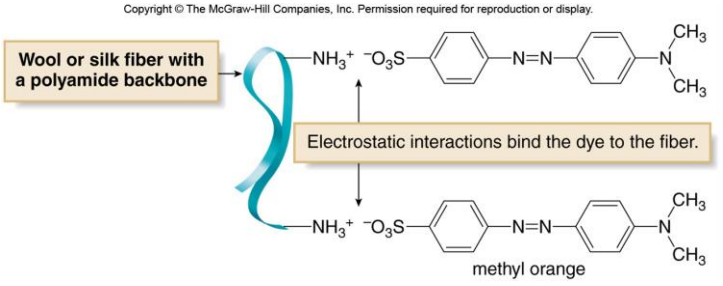
Natural and Synthetic Dyes

- **To be classified as a dye, a compound must be colored and it must bind to 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 dying wool or silk, both polyamides, may be poor for dying cotton, a carbohydrate.**

90

Dyes for Wool and Silk

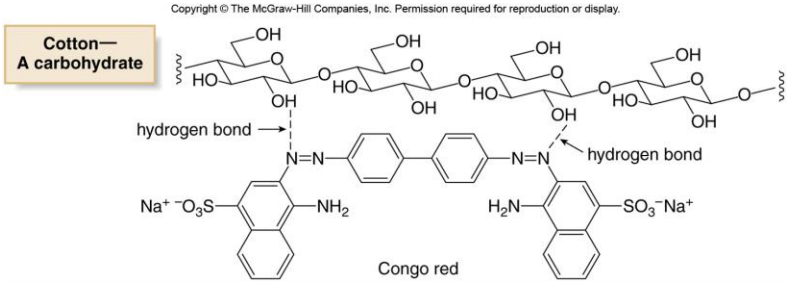
- **Wool and silk contain charged functional groups, such as NH_3^+ and COO^-.**
- **Thus, they bind to ionic dyes by electrostatic interactions.**
- **Positively charged NH_3^+ groups bonded to the protein backbone are electrostatically attracted to anionic groups in a dye like methyl orange.**



91

Dyes for Cotton—Congo Red

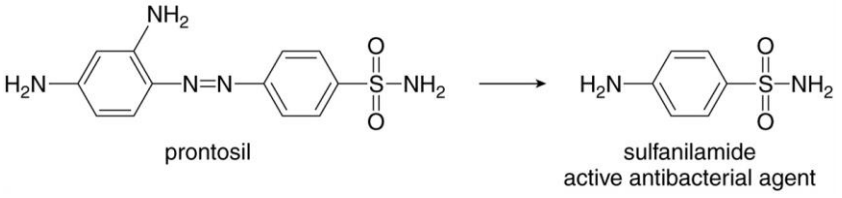
- **Cotton, on the other hand, binds dyes by hydrogen bonding interactions with its many OH groups.**
- **Thus, Congo red is bound to the cellulose backbone by hydrogen bonds.**



92

Sulfa Drugs

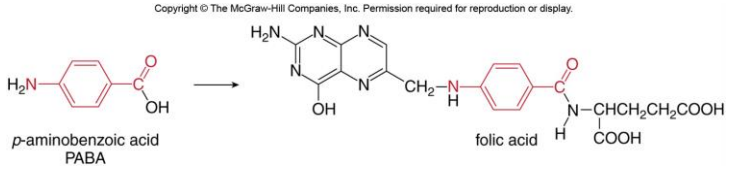
- **In 1935, Gerhard Domagk first used a synthetic dye, prontosil, to kill bacteria.**
- **Prontosil and other sulfur containing antibiotics are collectively known as sulfa drugs.**
- **Prontosil is not the active ingredient itself—in cells, it is metabolized to sulfanilamide, the active drug.**



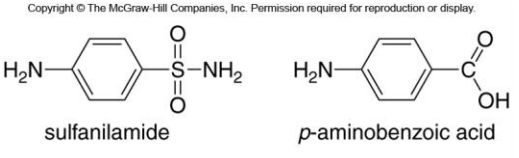
93

Sulfanilamide as an Antimicrobial Agent

- **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.**



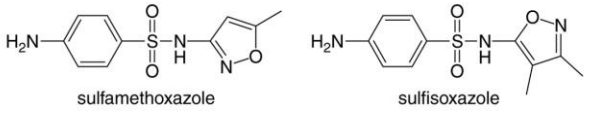
These compounds are similar in size and shape.

94

Sulfanilamide

- **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 sulfisoxazole

- 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.