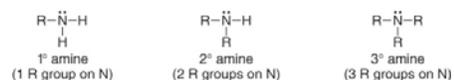


Chapter 20 Amines

Amines

Classification of amines

- Amines are organic nitrogen compounds, formed by replacing one or more hydrogen atoms of ammonia (NH₃) with alkyl groups.
- Amines are classified as 1°, 2°, or 3° based on the number of alkyl groups bonded to the nitrogen atom.

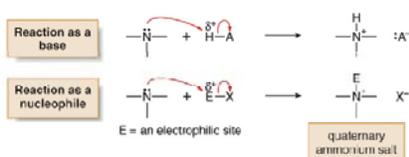


2

Amines

Introduction

- 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.



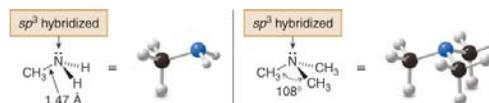
♦ The chemistry of amines is dominated by the nonbonded electron pair on the nitrogen atom.

3

Amines

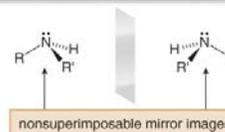
Structure and Bonding

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



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

An amine with four different groups around N

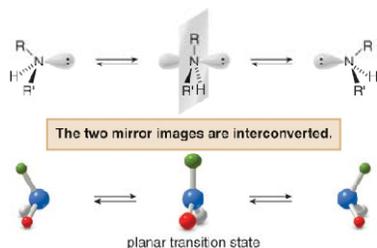


4

Amines

Structure and Bonding

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

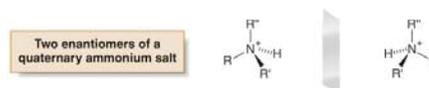


5

Amines

Structure and Bonding

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



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

6

Amines

Nomenclature

- 1^o 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

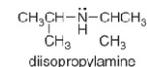
7

Amines

Nomenclature

- Secondary and 3^o Amines having identical alkyl groups are named using the prefix di- or tri- with the name of the primary amine.

Secondary Amines



Tertiary Amines

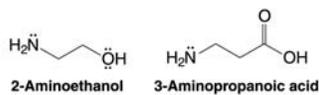


- Secondary and 3^o Amines having more than one kind of alkyl group are named as **N-substituted primary amines** by listing all the constituents' in an alphabetic order and putting prefix *N* before them.

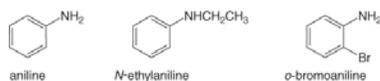
Amines

Nomenclature

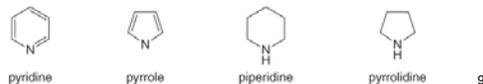
- The substituent NH_2 in the IUPAC system is called **amino group**.



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



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



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Amines

Interesting and Useful Amines

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

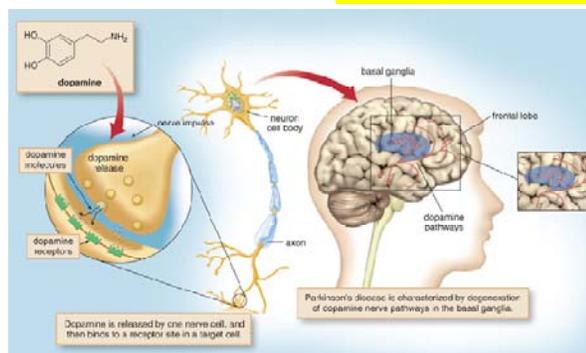
- Caffeine** is a bitter alkaloid found in coffee, tea, cola beverages, and chocolate. Caffeine is a mild stimulant, usually imparting a feeling of alertness after consumption. It also increases heart rate, dilates airways, and stimulates the secretion of stomach acid. Excessive use can result in insomnia.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

Amines

Interesting and Useful Amines

The neurotransmitter dopamine.

Cocaine, amphetamines, and several other addicting drugs (based on amines) 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:

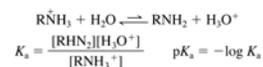


◆ Basicity of Amines: Amine Salts

→ Amines are weak bases

→ Relative basicity of amines can be compared in terms of $\text{p}K_a$ values for their respective conjugate acids

↗ The more basic the amine, the higher the $\text{p}K_a$ of its conjugate acid will be



→ Primary alkyl amines are more basic than ammonia

↗ An alkyl group helps to stabilize the alkylammonium ion resulting from protonation of the amine



By releasing electrons, R^- stabilizes the alkylammonium ion through dispersal of charge.

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→ In the gas phase, basicity in the family of methylamines increases with increasing methyl substitution

‡ More alkyl substitution results in more stabilization of the alkylammonium ion



→ In aqueous solution, trimethylamine is less basic than dimethyl- or methylamine

‡ An alkylammonium ion in water is solvated and stabilized by hydrogen bonding of its hydrogens with water

‡ The trimethylammonium ion has only one hydrogen with which to hydrogen bond to water

‡ The trimethylammonium ion is solvated less well (and therefore stabilized less) than the dimethylammonium ion, which has two hydrogen atoms for hydrogen bonding



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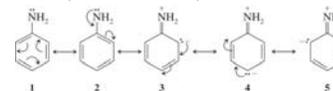
• Basicity of Arylamines

→ Arylamines are weaker bases than the corresponding nonaromatic cyclohexylamines. Why?

Conjugate acid pK_a	Cyclo- $\text{C}_6\text{H}_{11}\text{NH}_2$	$\text{C}_6\text{H}_5\text{NH}_2$	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$
	10.64	4.58	5.08

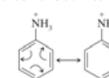
→ The unshared electron pair on nitrogen of an arylamine is **delocalized to the ortho and para positions of the ring**

‡ The lone pair is less available for protonation, i.e., it is less basic



→ Protonation of aniline is also disfavored because a protonated arylamine has only two resonance forms

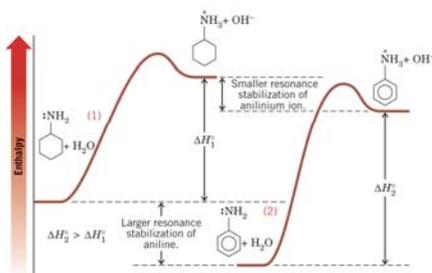
‡ Anilinium ion is not as well stabilized by resonance as aniline itself



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→ ΔH° for protonation of aniline is larger than ΔH° for protonation of cyclohexylamine

‡ Greater resonance stabilization of aniline relative to anilinium ion accounts for the larger ΔH° for protonation, as compared with ΔH° for protonation of an amine that is not aromatic



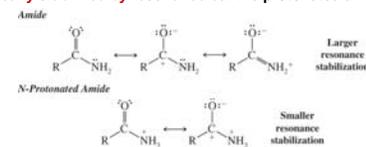
15

• Amines versus Amides

→ Amides are much less basic than amines

‡ The pK_a of a protonated amide is typically about zero

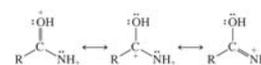
→ One reason for this much lower basicity is that the **amide is greatly stabilized by resonance** but the protonated amide is not



→ A more important reason for the weaker basicity of amides is that the **nitrogen lone pair is delocalized to the carbonyl oxygen**

‡ Amides are actually protonated at the oxygen atom

‡ Protonation at the oxygen allows resonance stabilization of the positive charge



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Amines

Amines as Bases

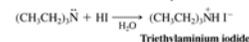
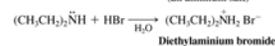
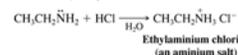
TABLE 25.3 Table of pK_a Values of Some Representative Organic Nitrogen Compounds

Compound	pK_a of the conjugate acid	Comment	
Ammonia	NH_3	9.3	
Alkylamines		11.1	
	$(CH_3CH_2)_2NH$	11.1	Alkylamines have pK_a values of ~10–11.
	$(CH_3CH_2)_3N$	11.0	
	$CH_3CH_2NH_2$	10.8	
Arylamines	$p\text{-}CH_3C_6H_4NH_2$	5.3	
$\beta\text{-}CH_3C_6H_4NH_2$	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	$RC(=O)NH_2$	-1	

• Aminium Salts and Quaternary Ammonium Salts

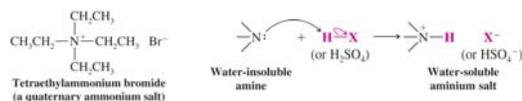
→ Protonation of amines with acids leads to formation of aminium salts

• Aminium salts are formed from 1°, 2° or 3° amines with acids. Note that aminium ion bears at least one hydrogen



→ Quaternary ammonium salts have four groups on the nitrogen

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



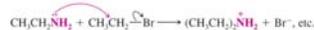
Aminium and Quaternary ammonium halides are not basic because they do not have an unshared electron pair on nitrogen
However, Quaternary ammonium hydroxide salts act as strong bases
Many aminium chlorides, bromides, iodides and sulfates are water soluble

♦ Preparation of Amines

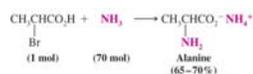
• By Nucleophilic Substitution Reactions

→ Alkylation of Ammonia

- Reaction of ammonia with an alkyl halide leads to an aminium salt
- The salt is treated with base to give the primary amine
- The method is limited because multiple alkylations usually occur



• Using an excess of ammonia helps to minimize multiple alkylations



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→ Alkylation of Azide Ion followed by Reduction

• A primary amine is prepared more efficiently by reaction of azide anion with an alkyl halide and subsequent reduction of the alkylazide to the amine



→ The Gabriel Synthesis

- Primary amines can also be made cleanly by the Gabriel Synthesis
- The first step in the Gabriel synthesis is alkylation of potassium phthalimide
- Reaction of the N-alkylphthalimide with hydrazine in boiling ethanol gives the primary amine



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Preparation of Aromatic Amines by Reduction of Nitro Compounds

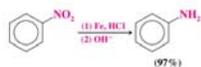
→ Aromatic amines can be synthesized by reduction of the corresponding nitro compound



General Reaction



Specific Example

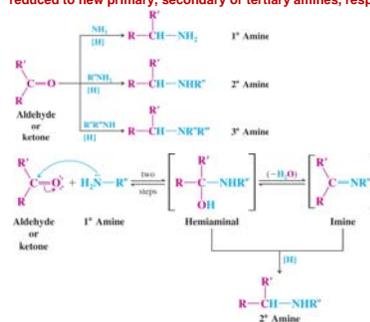


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Preparation of Primary, Secondary and Tertiary Amines through Reductive Amination

→ Aldehydes and ketones react with ammonia, primary or secondary amines to yield imines or iminium ions

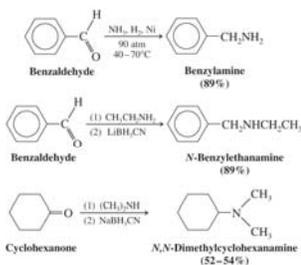
↳ The imines and iminium ions having C=N double bond can then be reduced to new primary, secondary or tertiary amines, respectively



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→ The reduction can be accomplished using catalytic hydrogenation or a hydride reducing reagent

↳ NaBH_4/CN and LiBH_4/CN are especially effective in reductive aminations

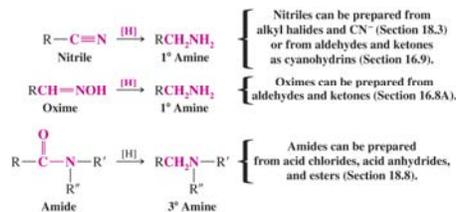


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Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides

→ Reduction of nitriles or oximes yield primary amines

→ Reduction of amides can yield primary, secondary or tertiary amines



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→ Reduction can be accomplished by using catalytic hydrogenation or LiAlH_4



→ **INTERESTING:** Monoalkylation of an amine can be achieved by acylation of the amine and then reduction of the resulting amide



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◆ Reactions of Amines (Reminder)

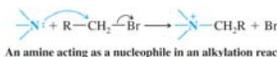
→ The lone pair of the amine nitrogen atom accounts for most chemistry of amines

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

Acid-Base Reactions

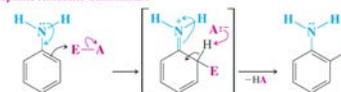


Alkylation



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

Electrophilic Aromatic Substitution

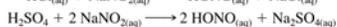


The amino group acting as an activating group and as an ortho-para director in electrophilic aromatic substitution

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◆ Reactions of Amines with Nitrous Acid

→ Nitrous acid (HONO) is a weak acid and is prepared *in situ* by reaction of sodium nitrite with a strong aqueous acid



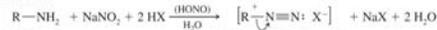
● Reaction of Primary Aliphatic Amines with Nitrous Acid

→ Primary amines undergo *diazotization* with nitrous acid

⚡ The unstable *diazonium salts* decompose to form carbocations

⚡ The carbocations react further to give alkenes, alcohols and alkyl halides

General Reaction



1° Aliphatic amine

Aliphatic diazonium salt (highly unstable)



Alkenes, alcohols, alkyl halides

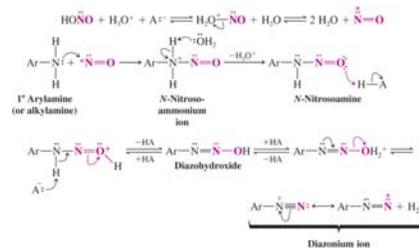
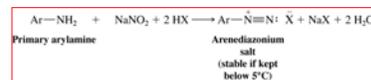
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● Reaction of Primary Arylamines with Nitrous Acid

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

⚡ This reaction occurs through the intermediacy of an *N*-nitrosoamine

⚡ The *N*-nitrosoamine is converted to a diazonium ion in a series of steps

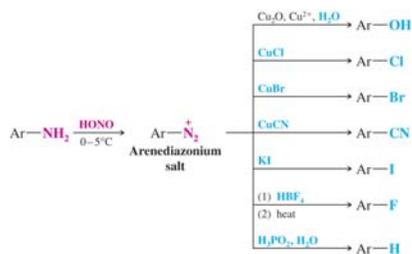


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◆ Replacement Reactions of Arenediazonium Salts

→ Aryldiazonium salts react readily with various nucleophilic reagents to give a wide variety of aromatic compounds

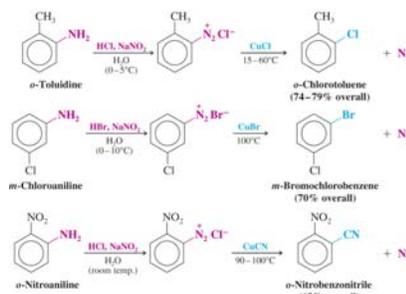
- ⚡ The aryldiazonium salt is made from the corresponding arylamine
- ⚡ The arylamine can be made by reduction of a nitroaromatic compound



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● The Sandmeyer Reaction: Replacement of the Diazonium Group by -Cl, -Br or -CN

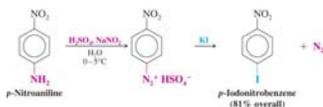
→ The mechanism of the Sandmeyer reaction is not well-understood but is thought to occur via radicals



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● Replacement by -I

→ Reaction of arenediazonium salts with potassium iodide gives the aryl iodide



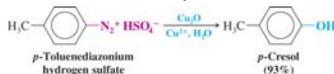
● Replacement by -F

→ A diazonium fluoroborate is isolated, dried and heated until it decomposes to the fluoroaromatic product



● Replacement by -OH

→ An aryl diazonium salt is placed in aqueous solution with a large excess of cupric nitrate and then treated with cuprous oxide



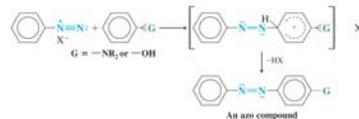
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◆ Coupling Reactions of Arenediazonium Salts

→ Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines

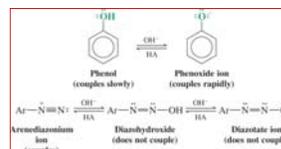
- ⚡ The reaction is called a *dialzo coupling reaction*

General Reaction



→ Coupling with phenol occurs best in slightly alkaline solution

- ⚡ The alkaline solution produces a phenoxide ion that couples more rapidly
- ⚡ If the solution is too alkaline, a nonreactive diazohydroxide is produced

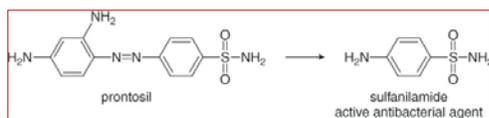


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Amines

Sulfa Drugs

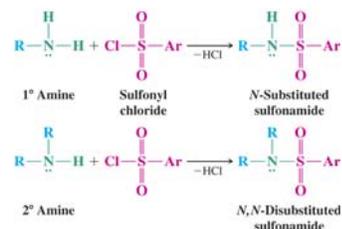
- In 1935, Gerhard Domagk first used a synthetic dye, prontosil, to kill bacteria.
- Prontosil and other sulfur containing antibiotics are collectively known as sulfa drugs.
- Prontosil is not the active ingredient itself—In cells, it is metabolized to sulfanilamide, the active drug.



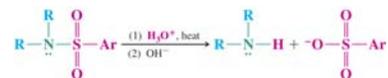
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♦ Reactions of Amines with Sulfonyl Chlorides

→ Primary and secondary amines react with sulfonyl chlorides to produce *sulfonamides*



→ A sulfonamide can be hydrolyzed to an amine by heating with aqueous acid

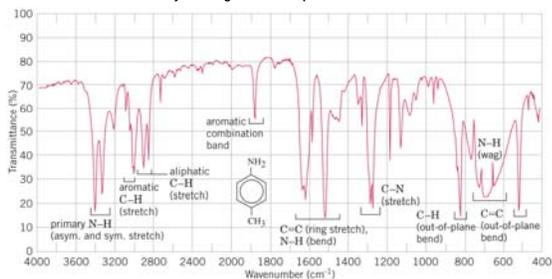


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• Spectroscopic Analysis

→ Infrared Spectra

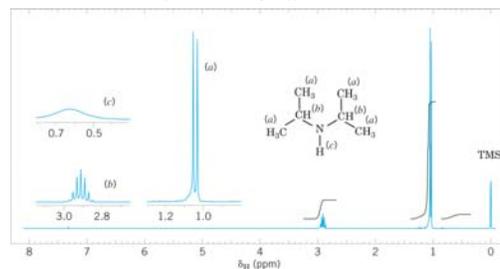
- Primary and secondary amines are characterized by N-H stretching vibrations in the 3300-3555 cm^{-1} region
- Primary amines give 2 absorptions (from symmetric and asymmetric stretching); secondary amines give one absorption



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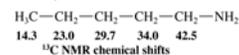
→ ^1H NMR Spectra

- Primary and secondary amines have broad, uncoupled N-H peaks at δ 0.5-5
- N-H protons will exchange with D_2O and disappear from the ^1H spectrum
- Protons on carbons adjacent to the nitrogen appear at δ 2.2-2.9



→ ^{13}C NMR Spectra

- Carbons bonded to nitrogen exhibit ^{13}C signals not as far downfield (δ 20-70) as carbons bonded to oxygen (δ 40-80) due to the lesser electronegativity of nitrogen as compared to oxygen
- The deshielding effect of the nitrogen atom decreases with distance

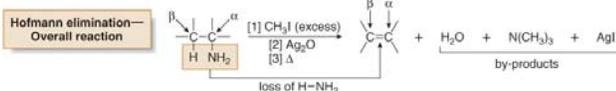


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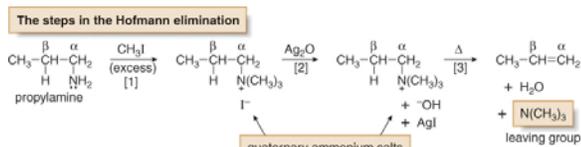
Amines

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.



Chapter 20

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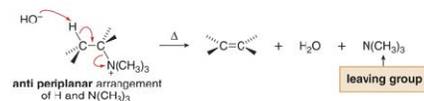
Amines

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

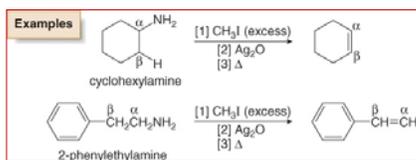


MECHANISM 25.1

The E2 Mechanism for the Hofmann Elimination



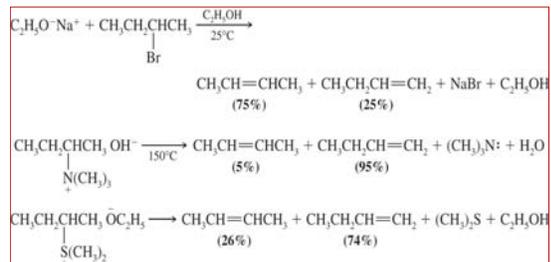
All Hofmann elimination reactions result in the formation of a new π bond between the α and β carbon atoms, as shown for cyclohexylamine and 2-phenylethylamine



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→ However, Hofmann elimination and other elimination reactions of charged substrates proceed to give the **least substituted double bond**:

- This is called the **Hofmann rule**, and the **least substituted alkene product is called the Hofmann product**
- Recall here: Zaitzev Rule for the Elimination reaction of alkyl halides

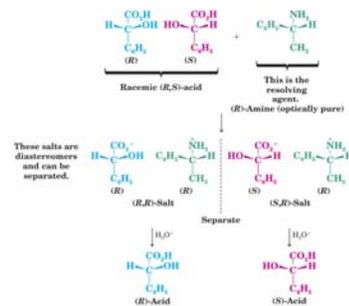


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Amines as Resolving Agents

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

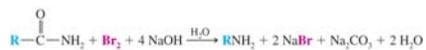
- Diastereomers can be separated on the basis of differences in physical properties
- Acidification of the separated diastereomeric salts gives the resolved carboxylic acids



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● Preparation of Primary Amines by the Hofmann and Curtius Rearrangements

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



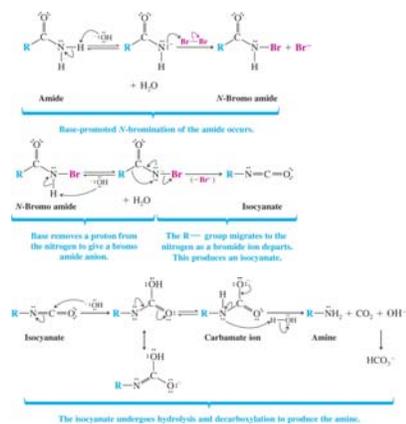
→ The first two steps of the mechanism result in *N*-bromination of the amide

- ⚡ The *N*-bromoamide is deprotonated and rearranges to an isocyanate
- ⚡ The isocyanate is hydrolyzed to a carbamate which decarboxylates to the amine

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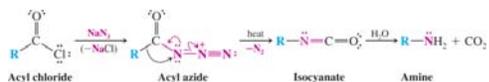
Hofmann rearrangement- mechanism



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→ The *Curtius rearrangement* occurs through the intermediacy of an acyl azide

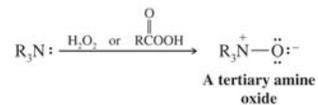
- ⚡ The acyl azide is obtained from an acid chloride
- ⚡ Rearrangement of the acyl azide occurs with loss of N₂, a very stable leaving group
- ⚡ In the last step, the isocyanate is hydrolyzed by adding water



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● Oxidation of Amines

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



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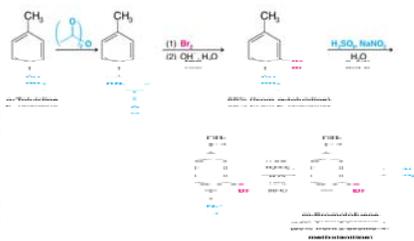
- **Replacement by Hydrogen: Deamination by Diazotization**

→ An arenediazonium salt can react with hypophosphorous acid (H_3PO_2) to replace the diazonium group with a hydrogen atom

↳ This reaction can be used to remove an amino group that was important early in a synthesis as an ortho, para director

→ Example: *m*-Bromotoluene cannot be made directly from either toluene or bromobenzene

↳ *N*-acetylation is used to reduce the activating effect of the amine



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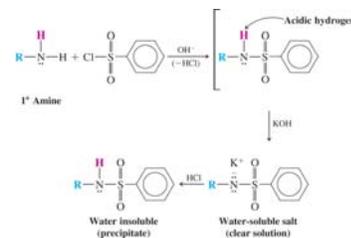
- **The Hinsberg Test**

→ This test can distinguish between 1°, 2° and 3° amines

→ An amine and benzenesulfonyl chloride are mixed with aqueous potassium hydroxide; the reaction is acidified in a second step

↳ The results are different depending on the class of amine

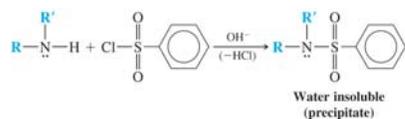
→ A benzenesulfonamide from a primary amine is soluble in basic solution, but precipitates upon acidification



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→ A secondary amine forms a precipitate directly because an *N,N*-disubstituted sulfonamide remains insoluble in basic solution

↳ There is no acidic hydrogen in an *N,N*-disubstituted sulfonamide



→ A tertiary amine will not react to form a sulfonamide, but will dissolve upon acidification

↳ Acidification converts the amine to a water soluble iminium salt

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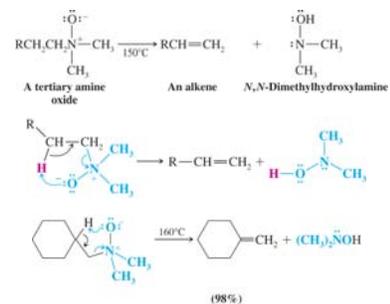
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- **The Cope Elimination**

→ A tertiary amine oxide will undergo elimination to the alkene when heated

→ Tertiary amine oxides can be made from tertiary amines by reaction with hydrogen peroxide

↳ Amine oxide elimination is syn and proceeds via a cyclic transition state



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