Ministry of Higher Education
and Scientific Research
Southern Technical University
Medical Technical institute/ Basra
Pharmacy Techniques Department

Basics of Organic chemistry

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"Assistant Lecturer"

Department: Pharmacy Technique " First Class"

Second semester

Subject	Teaching Language	Year of the study	Weekly hours		
		First Year	Theory	Practice	Total
Basics Of Organic Chemistry	English	Course 2	2	3	5

Weeks	Theoretical Topics 2nd
1st	Organic halogen compound (Alky / halide) Structure; Nomenclature; physical & chemical properties.
2nd	Preparation & uses; reactions.(Nucleophilic substitution)
3rd	Alcohol; structure & nomenclature preparation; reaction; uses in pharmacy.
4th	Aldehydes & ketones ; structure nomenclature .
5th	Preparations method & reaction .
6th	Carboxylic acid &lts derivatives structure ; nomenclature preparation methods &lts reaction ; uses in pharmacy .
7th	Amine ; structure ; nomenclature physical properties ; Basicity of amine .
8th	Preparation & reaction of amine uses in pharmacy
9th	Aromatic Diazonium salt; structure nomenclature ; preparation & reactions, the uses .
10th	Ethers ; structure ; nomenclature Physical and chemical properties reactions .
11th	Ester ; structure ; nomenclature ; reaction
12th	Merercaptons ; thiols (sulfur organic compound)
13th	Structure ; reaction
14th	Hetero cyclic compounds structure ; nomenclature Physical and chemical properties.
15th	Hetero cyclic compounds five membered rings; six membered ring ; structure ; reaction

Week 1

- Topic Title: Organic Halogen Compounds
- Lecture Duration: 2 hours

➢ Lecture Objectives:

1. To define organic halogen compounds and identify the halogen elements (F, Cl, Br, I)
2. To recognize and classify the types of halogenated compounds based on their structure:
   – Primary halogen compounds
   – Secondary halogen compounds
   – Tertiary halogen compounds
3. To become familiar with **alkyl halides** and understand their basic structures.
4. To learn the **IUPAC** rules for naming halogenated organic compounds.
5. To explore the **physical and chemical properties** of organic halogen compounds.
6. To recognize the **medical applications** of halogen-containing compounds.

- Behavioral Objectives:

1. Cognitive Domain:

- The student will be able to define halogens accurately.
- The student will be able to differentiate between alkyl halides and other organic compounds.
- The student will be able to apply IUPAC nomenclature rules to name simple halogenated organic compounds.

2. Psychomotor Domain:

- The student will be able to draw the structural formula of a given halogenated compound.
- The student will be able to analyze chemical formulas to identify the type of halide present.

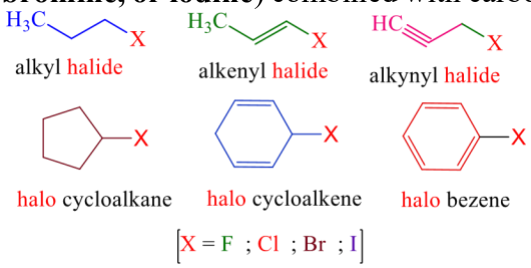
3. Affective Domain:

- The student will demonstrate interest in the industrial and medical relevance of halogenated compounds.

Week-1- [Theoretical]
Organic Halogen Compounds

1. **Definition**

   - Organic halogen compounds are a large class of natural and synthetic chemicals that contain one or more **halogens** (**fluorine, chlorine, bromine, or iodine**) combined with carbon and other elements.

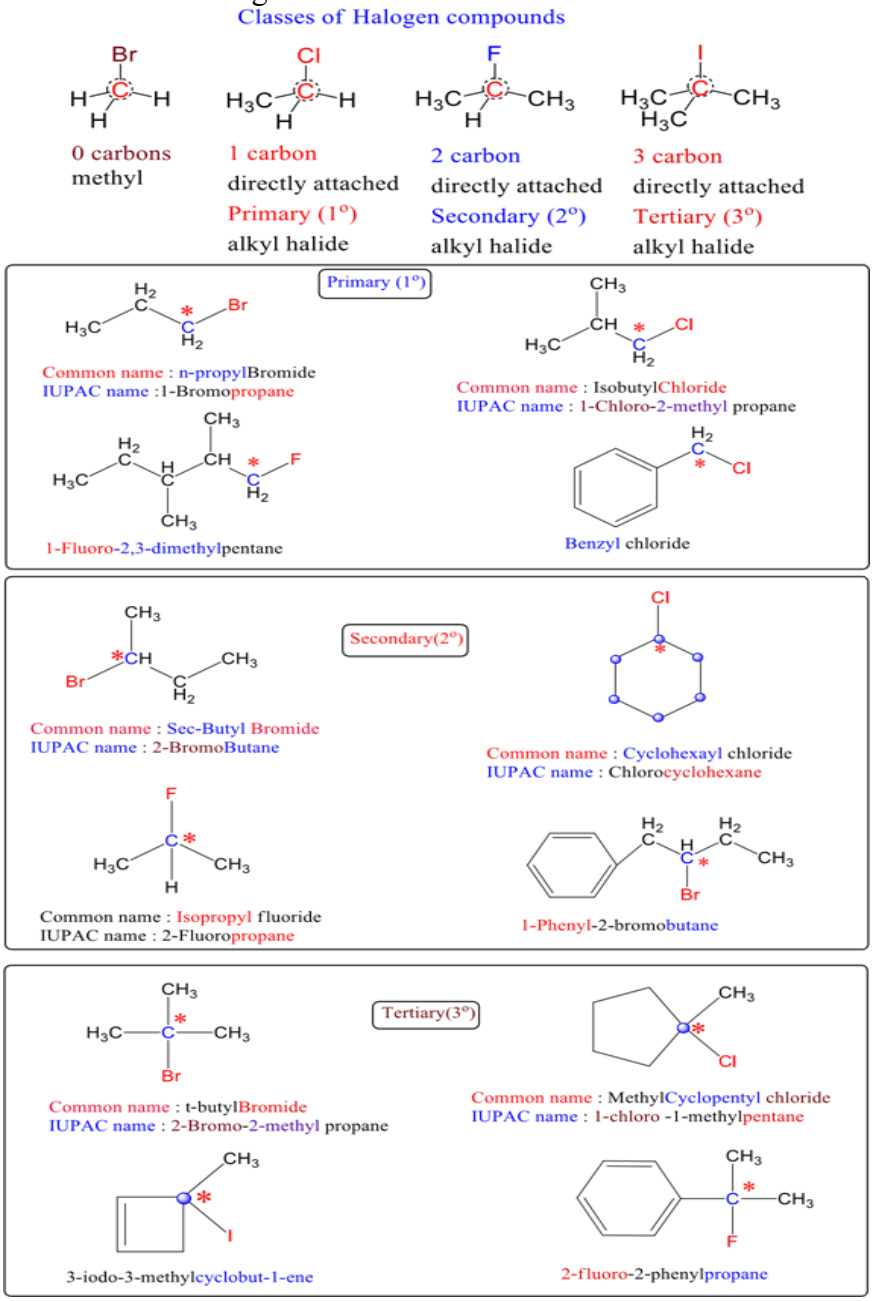


2. Classes of Halogen compounds:

   1) Alkyl Halides, R- X.

   Alkyl halides: Halogen, X, [X may be F, Cl, Br or I.] is directly bonded to sp^3 carbon.

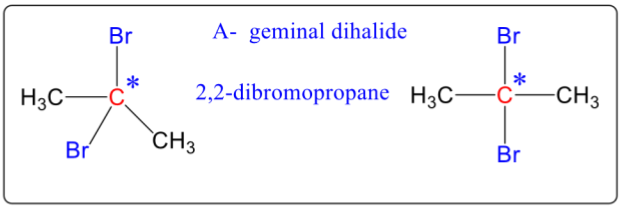
   Alkyl Halides are subdivided into **primary (1°), secondary (2°)** or **tertiary (3°),**depending on the **type of carbon** to which halogen attached.



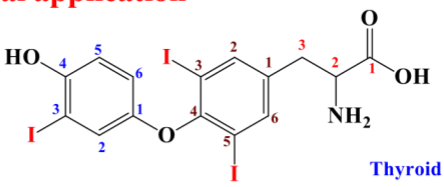
1. Types of Dihalides

A. **Geminal dihalide**: two halogen atoms are bonded to the same carbon.

B. **Vicinal dihalide**: two halogen atoms are bonded to adjacent carbons.



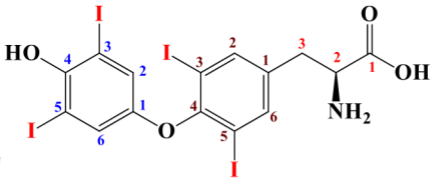
➲ Medical application



2-amino-3-(4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl)propanoic acid

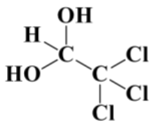
triiodothyroxine (T_3)

Thyroid hormone



(*S*)-2-amino-3-(4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)propanoic acid

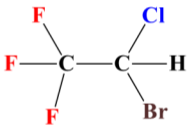
thyroxine (T_4)



2,2,2-trichloroethane-1,1-diol

chloral hydrate

sedative and hypnotic drug

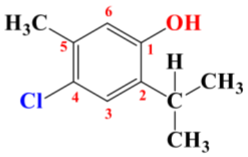


Common name :Halothane

(general anesthetic)

IUPAC name :

2-Bromo-2-chloro-1,1,1-trifluoroethane



4-chloro-2-isopropyl-5-methylphenol

chlorothymol

Treatment : cold sores , common cold, cough

Nomenclature of Organic Halides:

A. Haloalkane style: (IUPAC system)

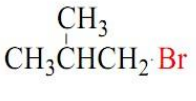
The IUPAC names of alkyl halides are obtained by using the following:

a) Select the longest carbon chain containing the halogen atom and name the alkyl halide.
b) Number the chain so as to give the carbon carrying the halogen atom the lowest possible number.
c) Indicate the position of the halogen atom by a number and by the fluoro-,chloro-, bromo-, or iodo-.
d) Name other substituents and indicate their positions by numbers.

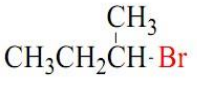
B. Alkyl halide style: (Common)

a) The alkyl group is attached to the halogen atom is named first.
b) Useful only for small alkyl groups.
c) The alkyl groups is a substituent on halide, then follow by an appropriate word fluoride, chloride, bromide, or iodide.

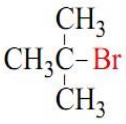
Examples



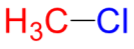
iso-butyl bromide



sec-butyl bromide

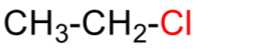


tert-butyl bromide

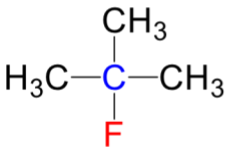


Common name : Methyl chloride
IUPAC name : Chloromethane

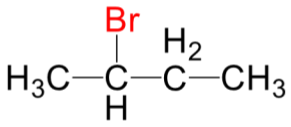
Common name : Methyl Bromide
IUPAC name : Bromomethane



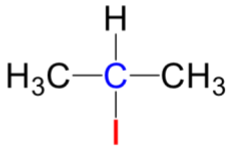
Common name : Ethyl chloride
IUPAC name : Chloroethane



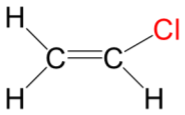
Common name : tert-butyl fluoride
IUPAC name :2- Bromo-2methylpropane



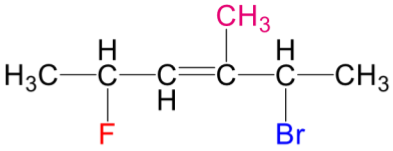
Common name : sec-butyl bromide
IUPAC name :2- Bromobutane



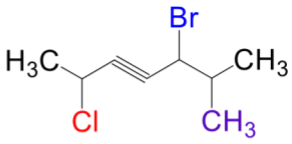
Common name : isopropyl iodide
IUPAC name :2- iodopropane



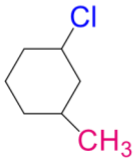
Common name :Vinyl chloride
IUPAC name : Chloroethene



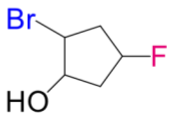
2-bromo-5-fluoro-3-methylhex-3-ene



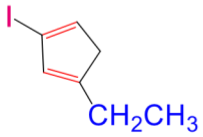
5-bromo-2-chloro-6-methylhept-3-yne



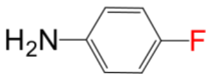
1-chloro-3-methylcyclohexane



2-bromo-4-fluorocyclopentanol



1-ethyl-3-iodocyclopent-1,3-diene

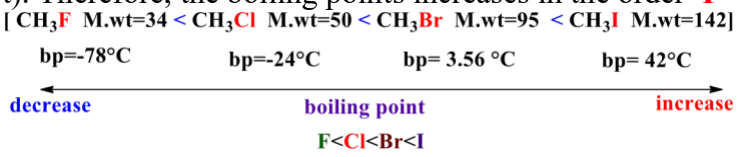


p-fluoroaniline

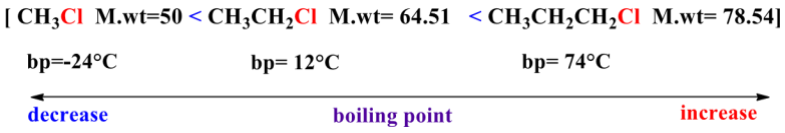
Physical Properties of Organic Halides

A. **Solubility** :- All organic halides are insoluble in water and soluble in common organic solvents (benzene, ethers, etc.).

B. **The boiling point** :- The boiling point of the organic **halide increase**, as the size of the halogen increase (molecular wt). Therefore, the boiling points increases in the order **F<Cl<Br<I**



C. Within a homologous serious the boiling point also increase regularly with molecular weight. For example,



D. Additionally, the boiling point also increases for isomeric haloalkanes. However, the boiling point decreases with the branching of the compound. This is because branching of haloalkanes results in the lesser surface area, thus decreasing the van der Waal's forces interaction.

E. Alkyl halides have higher melting points than alkanes, alkenes & alkynes because of: a. Polarity b. Molecular weight

F. **Density:**

1) Density is directly proportional to the mass of any compound. Therefore, as the mass increases down the homologous series, the density increases.
2) Thus, the derivatives of fluorine are less dense than derivatives of chlorine and derivatives of chlorine are less dense than derivatives of bromine.
3) Additionally, density increases with the increase in the number of carbon and halogen atoms. Furthermore, it depends upon the atomic mass of the halogen atom. For example, refer to the below diagram **n-C_3H_7Cl density 0.89g/ml < n-C_3H_7Br density 1.33 g/ml < n-C_3H_7I density 1.75 g/ml**
4) In the above example, the number of carbon atoms remains same but the mass of halogen atoms is different from one another. This, in turn, increases the density of the derivatives. Therefore, the arrangement of relative densities are **RI > RBr > RCl**

Practice

1. Draw the structure of the following:
    a) Chloroform
    b) Hexafluoroethane
    c) Vinylbromide
    d) Cis-2-Methylcyclohexyl bromide
    e) Triphenylmethyl chloride
    f) Nitrobenzylbromide
    g) 2-Chloro-3,3-dimethylpentane
    h) 1,1-Dichloro-4-isopropylcyclohexane
    i) 3-bromo-3-ethylhexane
    j) 5-ethyl-4-iodo-3methyl-octane

Week 2

- Lecture Title: Organic Halogen Compounds – Preparation, Uses, and Reactions (Nucleophilic Substitution)
- Duration: 2 hours

➢ Lecture Objectives:

1. To understand the general methods of preparing organic halogen compounds.
2. To explore the practical uses of halogenated organic compounds in various fields.
3. To identify and explain the mechanisms of nucleophilic substitution reactions (SN1 and SN2).

- Behavioral Objectives:

1- **Cognitive Domain**:

- The student will be able to describe the different methods used in the preparation of organic halogen compounds.
- The student will be able to identify examples of industrial and medical uses of halogenated compounds.

2- Psychomotor Domain:

- The student will be able to analyze reaction schemes and determine the likely mechanism involved.

3- **Affective Domain**:

- The student will show appreciation for the role of halogen compounds in drug design and chemical synthesis.

Week -2- [Theoretical]

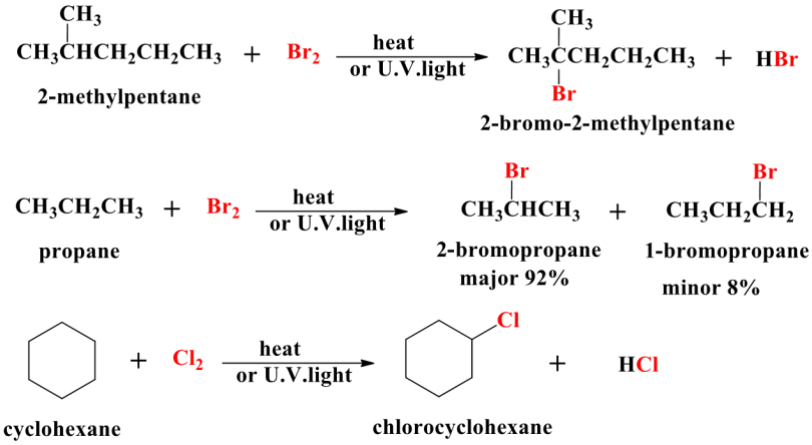
Organic Halogen Compounds

Preparation of Halogen Compounds

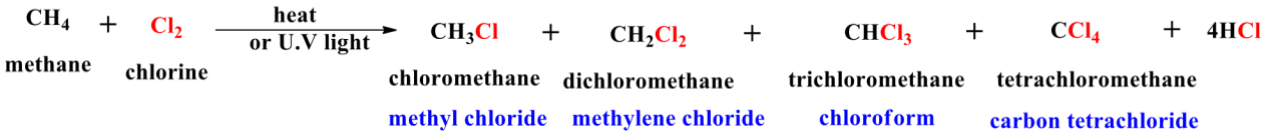
1. Direct halogenation of hydrocarbons

A. Halogenation of alkanes by heating or U.V light

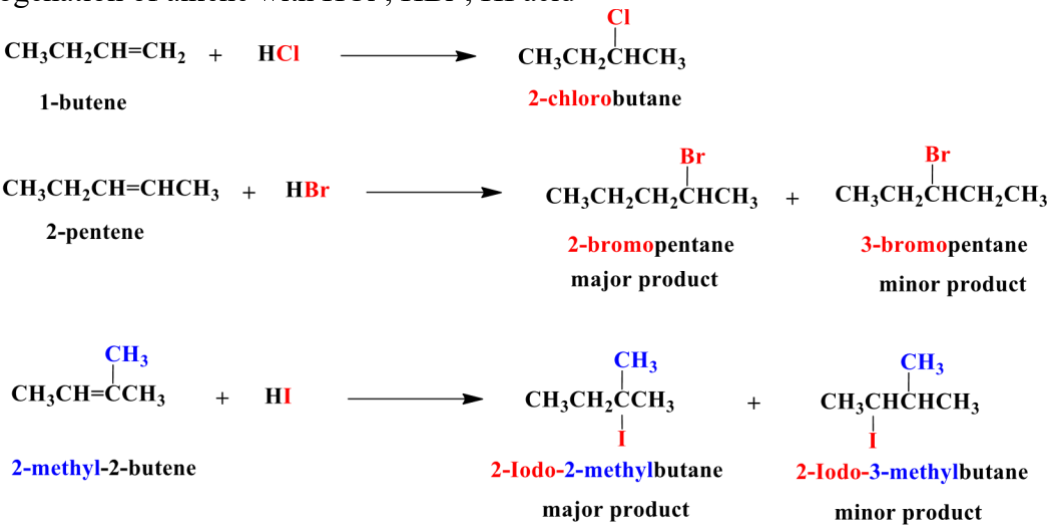
Halogenation of alkanes by heating or U.V light



Halogenation of Methane

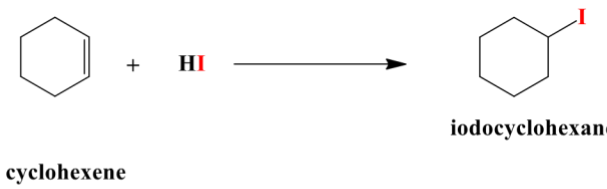


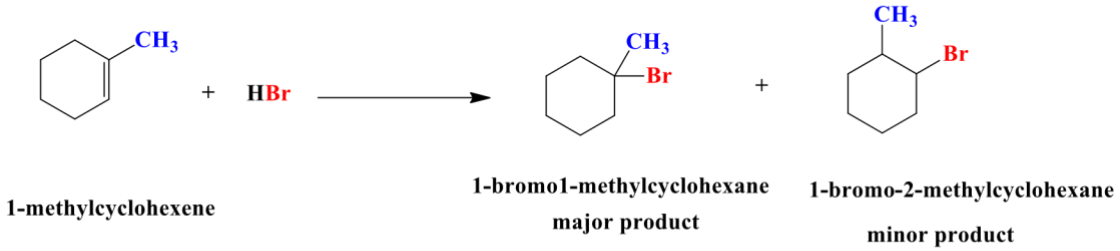
B. Halogenation of alkene with HCl ; HBr ; HI acid



⌘ Markownikkoff 's rule

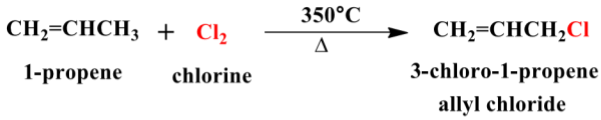
1. The addition of hydrogen halides (HX) to unsymmetrical alkenes or alkynes obeys the Markownikkoff's rule



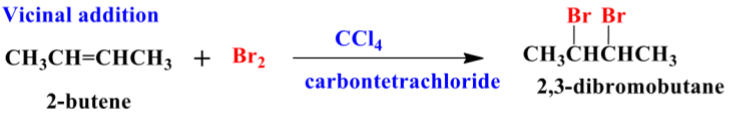


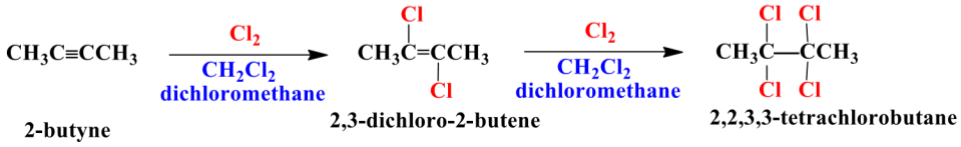
⌘ Addition reaction of Cl_2 ; Br_2 ; I_2

Addition reaction of Cl_2 ; Br_2 ; I_2 to alkene and alkyne



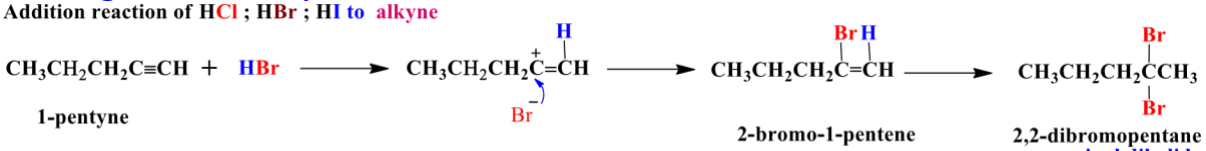
Vicinal addition





C. Halogenation of alkynes

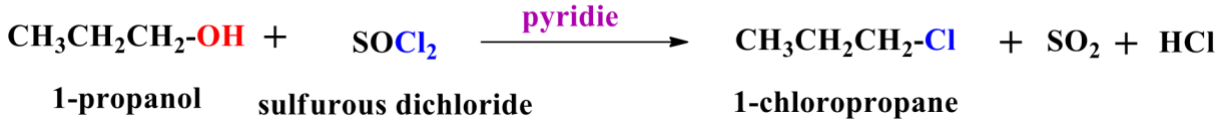
Addition reaction of HCl ; HBr ; HI to alkyne

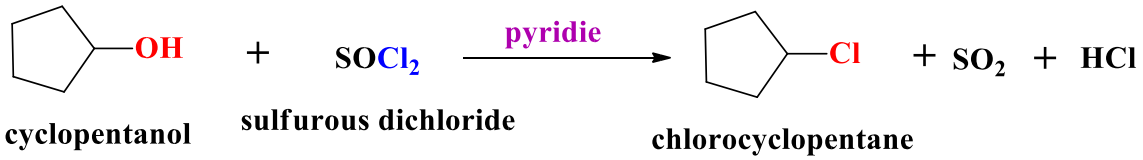


2. Conversion of alcohols: alkyl halides

1) Preparation using thionylchlorid; $SOCl_2$

Preparation alkyl halde using thionylchlorid; $SOCl_2$



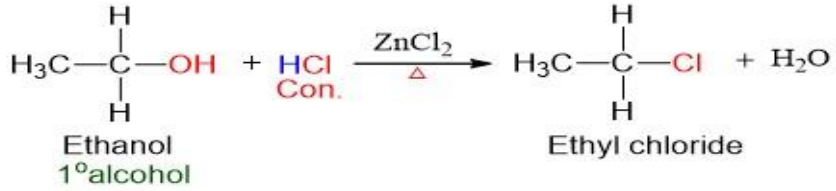


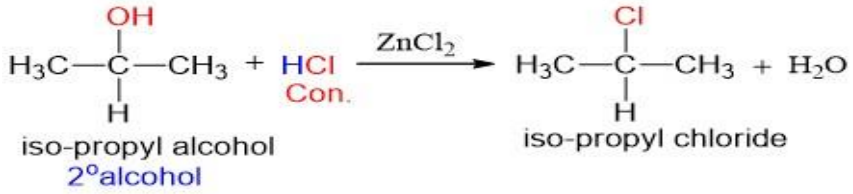
2) Preparation using concentrated halogen acid HX:

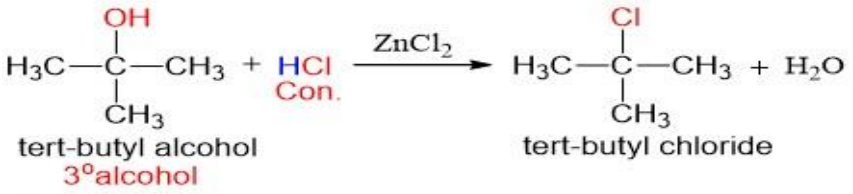
✞ **They react with HCl in presence of ($ZnCl_2$) zinc chloride catalyst.Lucas' reagent**

1. no visible reaction at room temperature and forming an oily layer only on heating: primary, such as 1-pentanol
2. solution forms oily layer in 3–5 minutes: secondary, such as 2-butanol
3. solution forms an oily layer immediately: tertiary, such as 2-methyl-2-propanol

Preparation alkyl halide using concentrated halogen acid HX



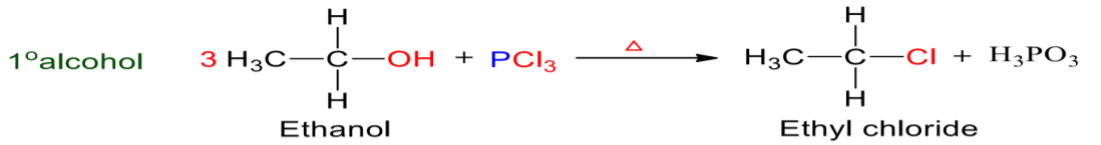


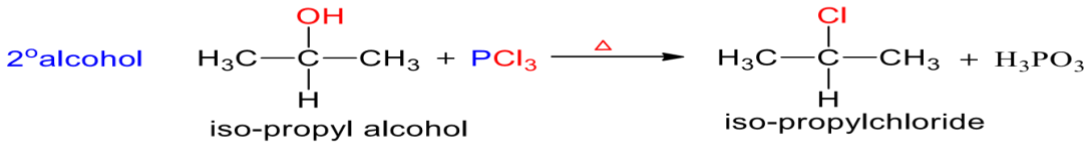


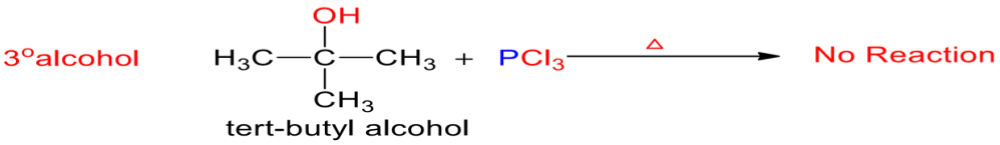
Tertiary alcohol > Secondary alcohol > primary alcohol

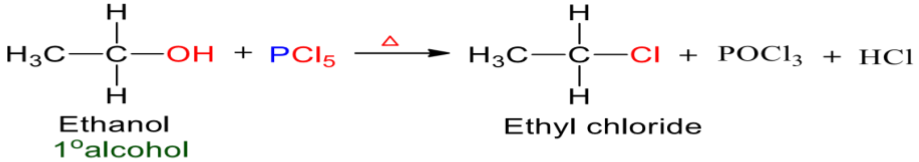
3)- Preparation using phosphorus halides; PX_3 or PX_5 dilute

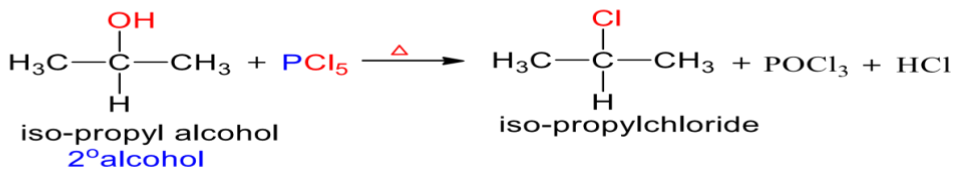
Preparation using phosphorus halides; PX3 or PX5 dilute











Alcohol react with phosphorus halides; PBr_3 or PI_3 dilute to give alkyl halide

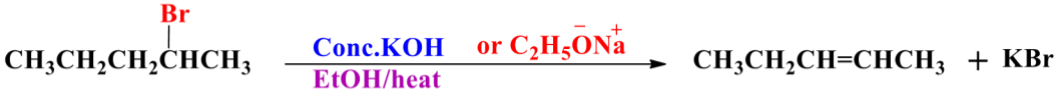
✞ Reactions of Organic Halides

1. Elimination Reactions

The most common bases used in elimination reactions are negatively charged oxygen compounds, such as HO^- and its alkyl derivatives, RO^-, called alkoxides.

Common base used in dehydrohalogenation	
$Na^+ -OH$	Sodium hydroxide
$K^+ -OH$	Potassium hydroxide
$Na^+ -OCH_3$	Sodium methoxide
$Na^+ -OCH_2CH_3$	Sodium ethoxide
$K^+ -OC(CH_3)_3$	Potassium tert-butoxide

Elimination Reactions (dehydrohalogenation)



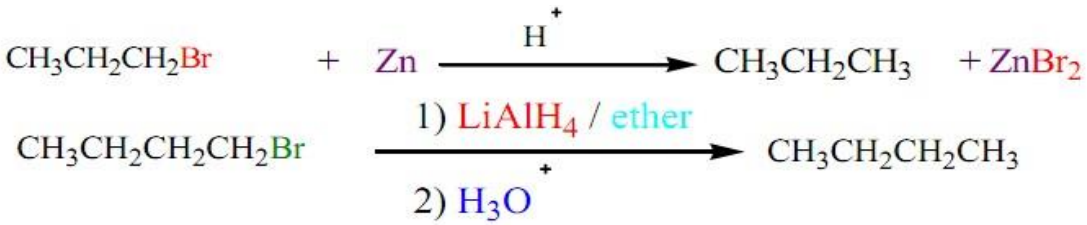
2-bromopentane — 2-pentene

2. Reactions of Organometalic Compounds (Reduction):

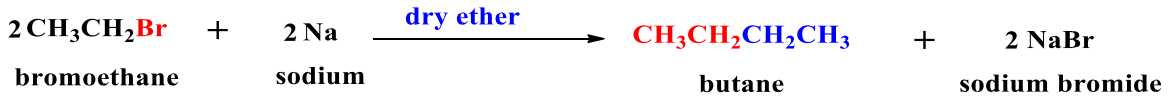
The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents

1) Reduction with alkali metals

a) Reduction by Zinc metal and acids or by metal hydrides



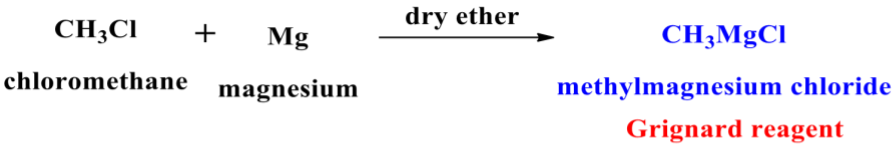
b) Reduction by sodium metal (coupling reaction)



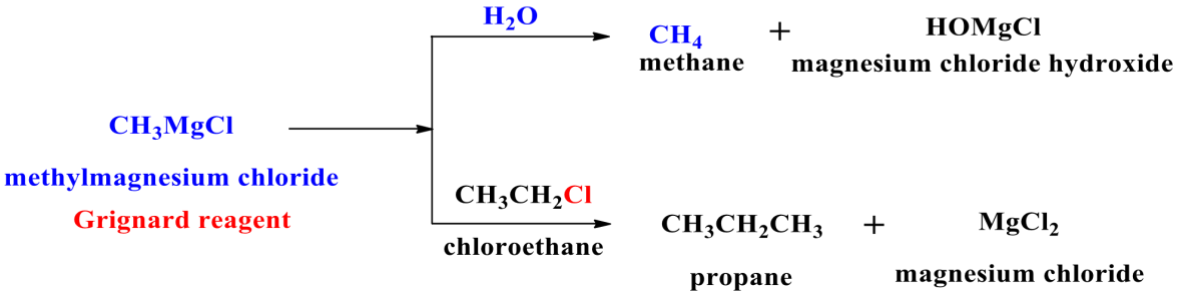
bromoethane — sodium — butane — sodium bromide

2) Reduction with alkaline earth metals

Formation of Grignard reagent (X= Cl ; Br ; I)



chloromethane — magnesium — methylmagnesium chloride (Grignard reagent)



Week 3

- **Lecture Title:** Alcohols
- **Duration:** 2 hours

Lecture Objectives:

1. To understand the chemical structure of alcohols.
2. To learn how to name alcohols using both IUPAC and common naming systems.
3. To study the chemical reactions of alcohols, including oxidation and dehydration.
4. To explore the different methods of preparing alcohols.
5. To identify the medical and pharmaceutical applications of alcohols.
6. To recognize the role of alcohols in formulation.

- **Behavioral Objectives:**

1- Cognitive Domain:

- The student will be able to identify the functional group of alcohols and determine their general formula.
- The student will be able to name alcohol compounds correctly using IUPAC and common nomenclature.
- The student will be able to describe and classify types of alcohols (primary, secondary, tertiary).
- The student will be able to explain key reactions of alcohols (e.g., oxidation, esterification, dehydration).
- The student will be able to discuss the pharmaceutical importance and uses of alcohols.

2- Psychomotor Domain:

- The student will be able to draw structures of alcohols and show their reaction mechanisms.
- The student will be able to write balanced chemical equations for alcohol reactions.

3- Affective Domain:

- The student will appreciate the role of alcohols in pharmacy and medicine.

Week-3-[Theoretical]

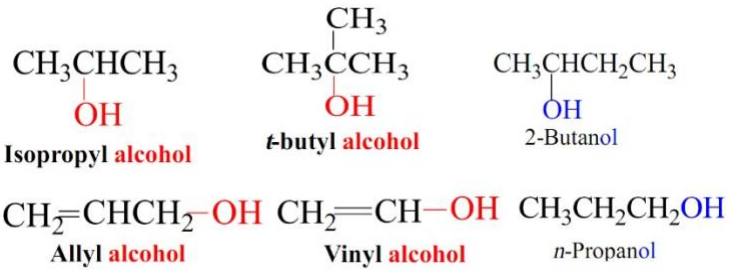
Alcohols

1. **Definition :** Alcohol is an organic compound in which a hydroxyl group is bound to a carbon atom
2. The hydroxyl group is one of the most important functional groups of naturally occurring organic molecules.
3. All **carbohydrates** and their derivatives, including **nucleic acids**, have **hydroxyl groups**.
4. Some **amino acids**, most **steroids**, many **terpenes**, and **plant pigments** have **hydroxyl groups**.
5. The general formula for the alcohols is $C_nH_{2n+1}OH$ and the naming indicated by the prefix' hydroxyl' or the **suffix' ol** ' in the systematic name:

✈ Hydroxyl (-OH) is the functional group.

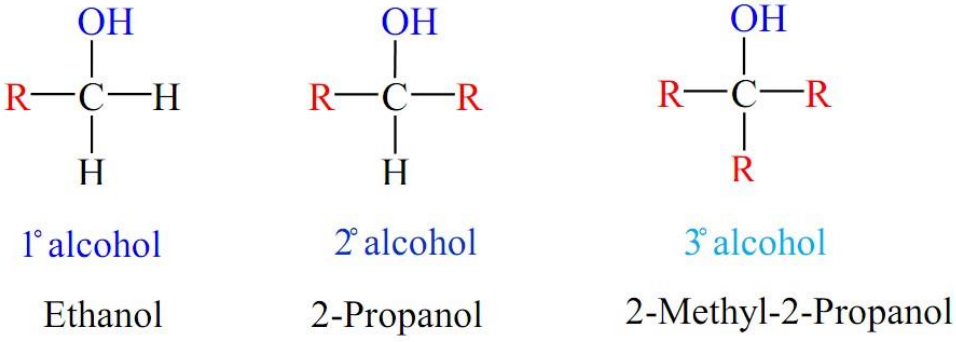
1. Alcohol has an -OH group attached to an aliphatic carbon. General formula is R-OH.
2. Phenol has an -OH group on a benzene ring.

Aliphatic Alcohols			
	Structural	Systematic name	Trivial name
1	CH_3OH	Methanol	Methyl alcohol
2	CH_3CH_2OH	Ethanol	Ethyl alcohol
3	$CH_3CH_2CH_2OH$	Propan-1-ol	n-Propyl alcohol
4	$CH_3CH(OH)CH_3$	Propan-2-o1	Isopropyl alcohol
5	$CH_3(CH_2)_2CH_2OH$	Butan-1-ol	n-Butyl alcohol
6	$CH_3CH_2CH(OH)CH_3$	Butan-2-ol	sec-Butyl alcohol
7	$(CH_3)_2CHCH_2OH$	2-Methylpropan-1-ol	Isobutyl alcohol
8	$(CH_3)_3COH$	2-Methylpropan-2-ol	t-Butyl alcohol



✈ Calcification of alcohols

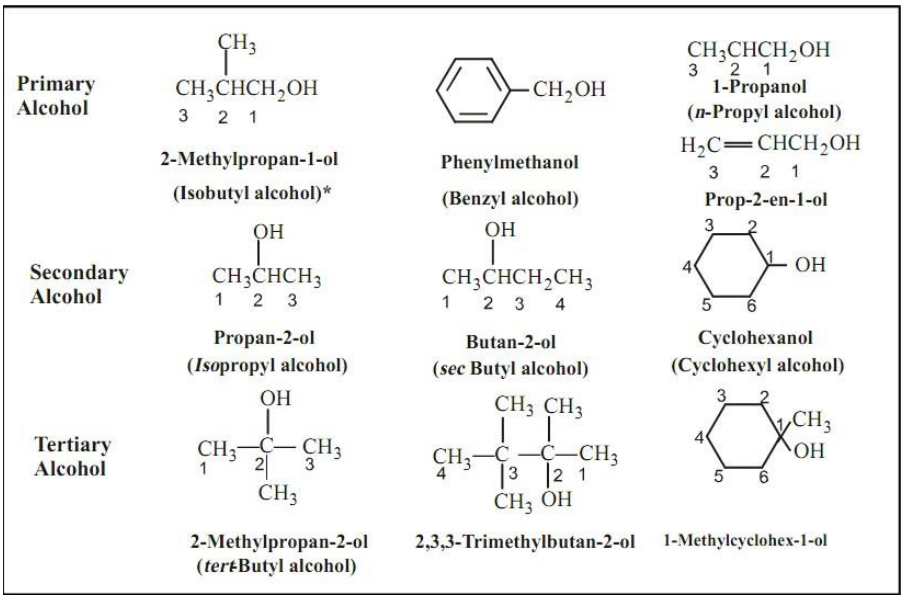
1) Primary alcohol
2) Secondary alcohol
3) Tertiary alcohol



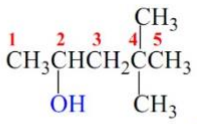
Naming of Alcohols:

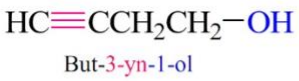
According to the IUPAC system of nomenclature, alcohols are called alkanols. They are named as the derivatives of the corresponding alkane in which the **-e** of the alkane is replaced by **-ol** .

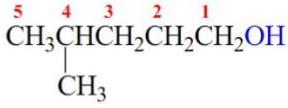
1. **Step 1:** Select the longest carbon chain which contains the carbon atom **bearing the –OH group**. Count the number of carbon atoms and identify the **corresponding alkane**. From the name of this alkane, drop the final e and **suffix -ol** in its place. This gives the root name or the parent name.
2. **Step 2:** Number the carbon chain starting from the end nearest to the hydroxy group. The number of the carbon atom bearing the hydroxy group is indicated before **-ol** in the name .
3. **Step 3:** Number the other substituents **according to their position** on the chain.
4. **Step 4:** Write the name of the alcohol by listing the substituents in the **alphabetical** order along with their position.




3-chloropropan-1-ol

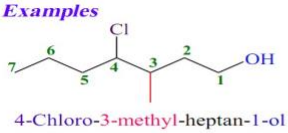

4,4-Dimethylpentan-2-ol

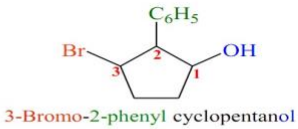

But-3-yn-1-ol

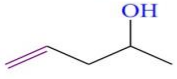

4-Methylpentan-1-ol

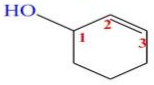
Not 2-Methylpentan-5-ol

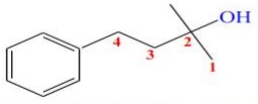
Examples

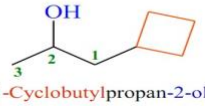

4-Chloro-3-methyl-heptan-1-ol


3-Bromo-2-phenyl cyclopentanol


Pent-4-ene-2-ol


Cyclohex-**2-en**ol


2-Methyl-4-phenyl butan-2-ol

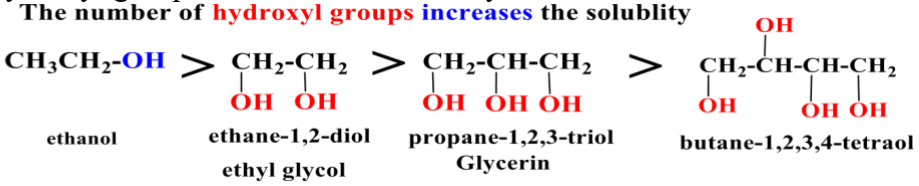

1-Cyclobutylpropan-2-ol

PHYSICAL PROPERTIES OF ALCOHOLS:

1. Hydrogen bonding

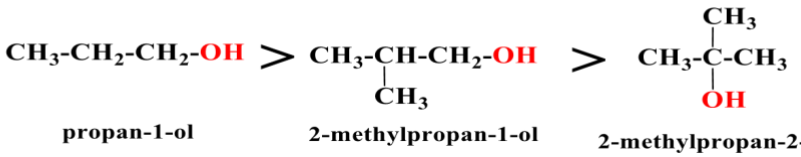
1) Alcohols are neutral product and are liquids or solids in physical state and less volatile,
2) All the lower alcohols are more or less poisonous, ethanol being exceptional in its low toxicity.
3) Alcohols are very much higher melting points, boiling points are than those of the parent alkanes .
4) The reason for these differences in physical properties is related to the high polarity of the hydroxyl group which, when substituted on a hydrocarbon chain, confers a measure of polar character to the molecule.
5) Alcohols greater water solubility than the corresponding hydrocarbons although the differences become progressively smaller as molecular weight increases.
6) Solubility :The lower ones are miscible with water or very soluble, but solubility **decreases** with **increasing size of the alkyl group.**
7) The higher members are almost insoluble in water but are soluble in organic solvents like benzene, ether etc ; and the **first three members** are completely **miscible with water**.
8) The solubility of lower alcohols is due to the existence of hydrogen bonds between water and polar -OH group of alcohol molecules.
9) The number of hydroxyl groups increases the solubility of alcohol

The number of hydroxyl groups increases the solublity



10) Also branching of chain increases in the solubility

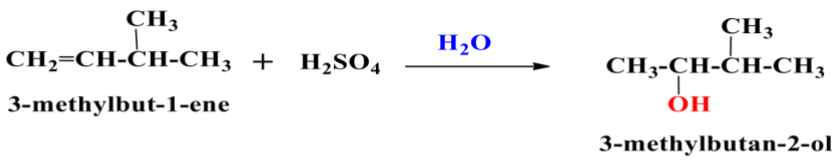
The solubility increases with increases branching chain

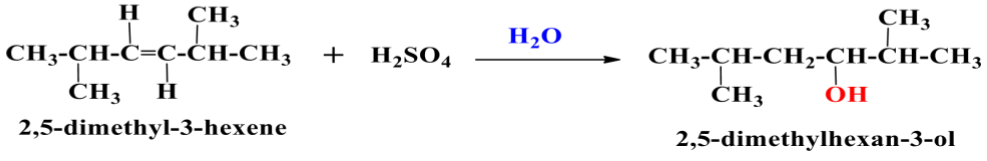


Physical properties of alcohols						
Name	Alcohol	M.Wt	B.P°C	M.P°C	density gm/ml (20 °C)	solubility in water
Methanol	CH_3OH	32	64.7	-97.6	0.79	miscible
Ethanol	CH_3CH_2OH	46	78	-114	0.789	miscible
Propanol	$CH_3CH_2CH_2OH$	60.10	97	-126	0.80	miscible
2-propanol	CH_3CH-$OHCH_3$	60.10	82	-89	0.786	miscible
Butanol	$CH_3CH_2CH_2CH_2OH$	74.12	118	-90	0.81	9.1%
2-butanol	CH_3CH-$OHCH_2CH_3$	74.12	100	-115	0.81	7.7%

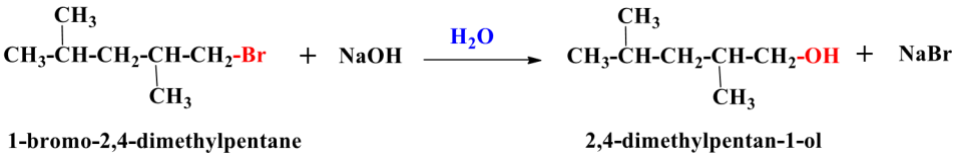
Preparation of alcohols.

1. **Hydration of alkene in the presence of acid** .

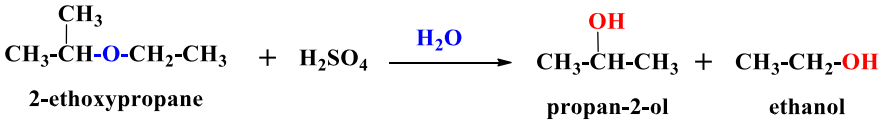




2. Hydrolysis of alkyl halides by water or alkali .

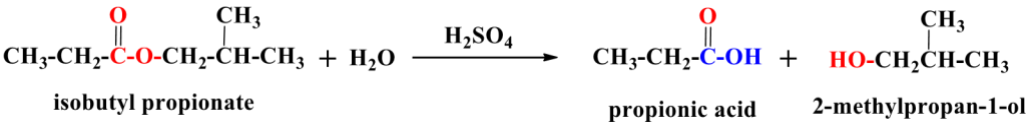


3. Hydrolysis of ethers under strongly acidic conditions .

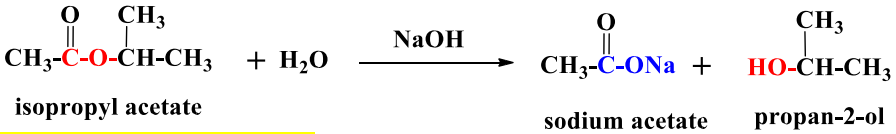


4. Hydrolysis of esters:

a) **Acid catalyzed hydrolysis**

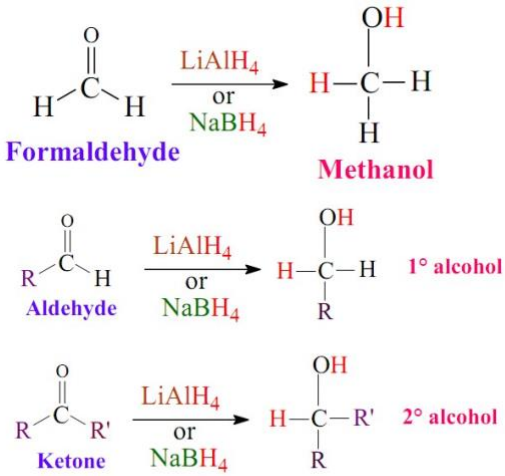


b) **Alkaline hydrolysis (' saponification)**



5. Reduction of Aldehydes and Ketones

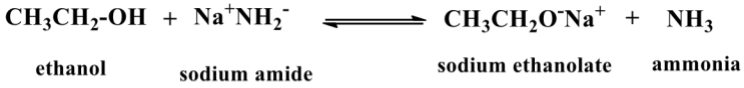
- **Aldehydes and ketones are most readily reduced with hydride reagents, LiAl H_4 or $NaBH_4$.**
- **The reducing agents $LiAlH_4$ and $NaBH_4$ act as a source of (hydride ion, H-),the hydride reacts with the carbonyl group, C=O, in aldehydes or ketones to give alcohols.**

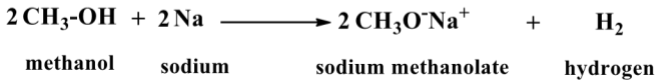


✈ Reaction of alcohol

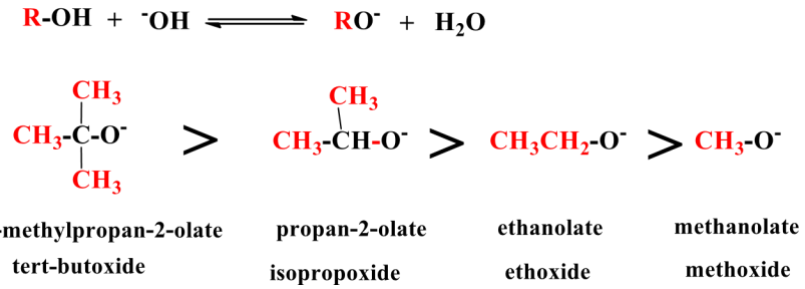
1. Acidic Properties

1) Several important reactions of alcohols involve only the oxygen-hydrogen bond and leave the carbonoxygen bond intact.
2) Alcohols, like water, are both weak bases and weak acids.



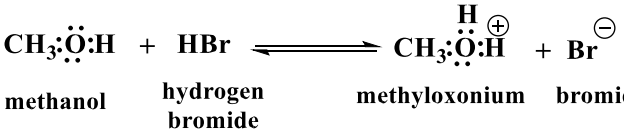


3) The order of acidity of various liquid alcohols **ROH** generally **is water > primary > secondary > tertiary .**
4) By this we mean that the equilibrium position for the proton-transfer reaction lies more on the side of **R-OH and H_2O** as **R** is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered **more** acidic than ethanol in the gas phase **[3°>2°>1°]**



2. Basic Properties

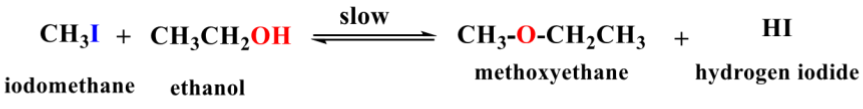
1) Alcohols are bases similar in strength to water and accept protons from strong acids.
2) An example is the reaction of methanol with hydrogen bromide to give methyl-oxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide :

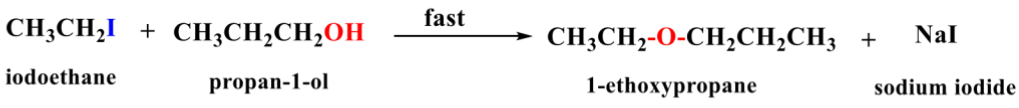


3) The basicity of **alkoxides** depends on the class of the parent alcohol, the tertiary alkoxides (e.g. **$(CH_3)_3CO^-$**) being the strongest bases, and **methoxide** the weakest, the **basicity** order is : **$R_3CO^- > R_2CHO^- > RCH_2O^- > CH_3O^-$** (**R = alkyl group**).

3. Nucleophilic Properties. Ether Formation

1) Thus ethanol reacts very slowly with methyl iodide to give methyl ethyl ether, but sodium ethoxide in ethanol solution reacts quite rapidly:

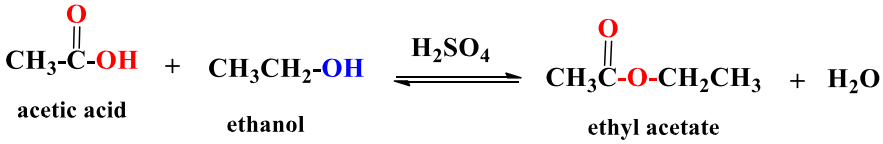




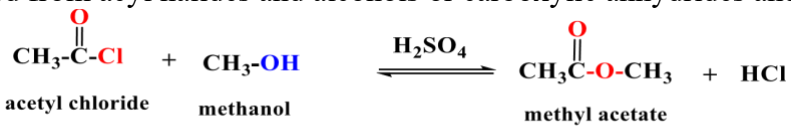
4. Nucleophilic Properties.

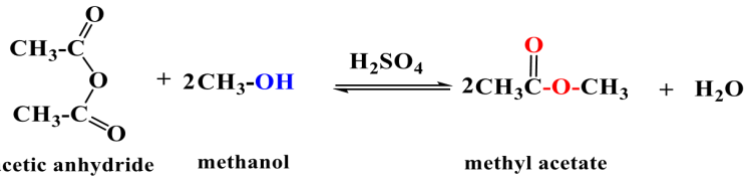
A. Ester Formation

a) An ester may be thought of as a carboxylic acid in which the acidic proton has been replaced by some organic group, R,
b) Esters can be prepared from carboxylic acids and alcohols provided an acidic catalyst is present,

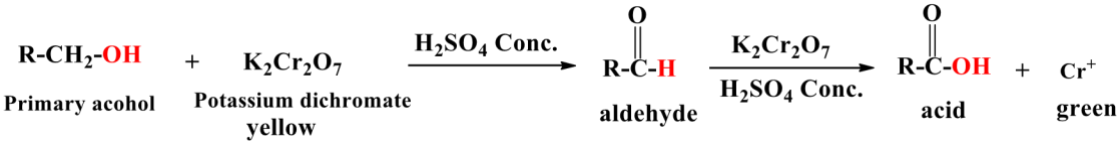


c) they can be prepared from acyl halides and alcohols or carboxylic anhydrides and alcohols:

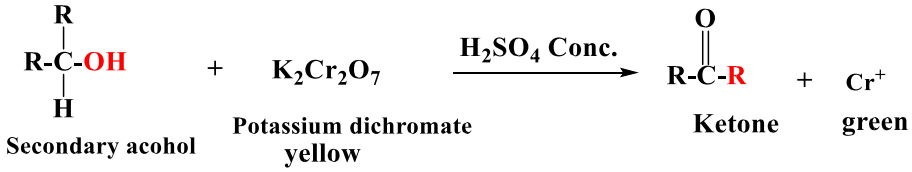




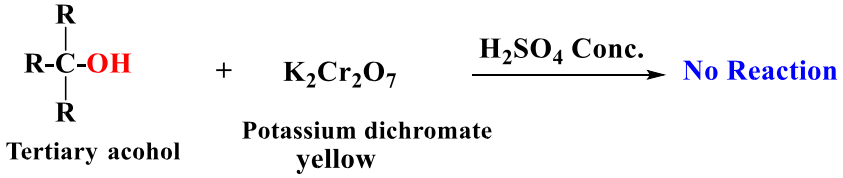
5. **Oxidation of alcohols** gives products which vary according to the class of alcohol.
   1) **Primary alcohols** can be oxidized to aldehydes, which can be further oxidized to carboxylic acids. Use of chromic acid ($K_2Cr_2O_7$ + H_2SO_4 ; or CrO_3) as the oxidant permits the isolation of some aldehyde, but further oxidation to carboxylic acid also occurs.



   2) **Primary alcohols** Powerful oxidizing agents such as **permanganates** or concentrated **nitric acid** give only **carboxylic acids.**
   3) **Secondary alcohols** are oxidized readily to **ketones**, with $K_2Cr_2O_7$ in H_2SO_4 conc the color changing from yellow to green .

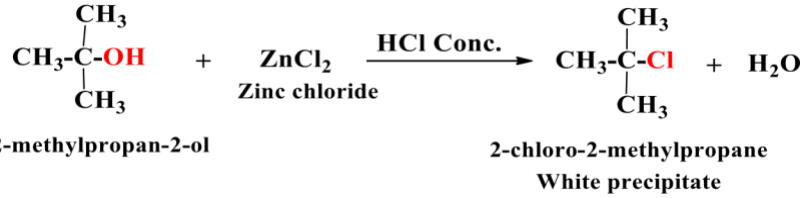


   4) **Tertiary alcohol** much more resistant to oxidation with $K_2Cr_2O_7$ in H_2SO_4 and No Reaction occur



6. **Conversion of alcohols: alkyl halides**

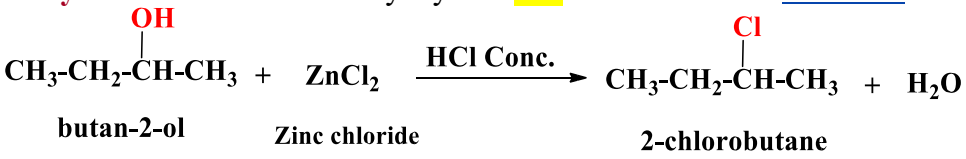
- Alcohols react with HCl ; HBr ; HI to give alkyl chloride alkyl bromide or alkyl iodide.
- They react with HCl in presence of ($ZnCl_2$) zinc chloride catalyst. White precipitate
  1. tertiary alcohol forms an white oily layer immediately:, such as 2-methyl-2-propanol



2-methylpropan-2-ol

2-chloro-2-methylpropane
White precipitate

2. **Secondary alcohol** forms white oily layer in 3–5 minutes such as 2-butanol

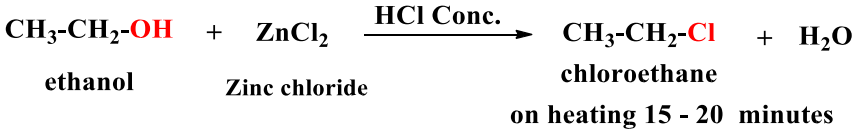


butan-2-ol

Zinc chloride

2-chlorobutane

3. **Primary alcohol** no visible reaction at room temperature and forming an white oily layer only on heating 15 – 20 minutes such as ethanol



ethanol

Zinc chloride

chloroethane

on heating 15 - 20 minutes

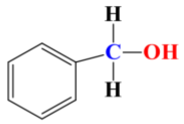
Aromatic Alcohol { Phenols }

Aromatic hydroxy-compounds in which the hydroxyl group is attached to an aromatic ring are called phenols, and the name 'phenol' is also applied to the simplest compound of the series, hydroxybenzene, C_6H_5OH. Typical examples of phenols are:

1. **Phenols differ from alcohols in that the -OH is directly attached to the aromatic ring.**
2. **Phenol form hydrogen bonds with water molecules**
3. **Phenols are sparingly soluble in water but readily soluble in organic solvents .**
4. **Phenols tend to have higher boiling points than alcohols of similar molecular weight because they have stronger intermolecular hydrogen bonding.**

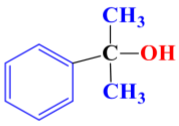
✈ Calcification of alcohols

1) Primary alcohol
2) Secondary alcohol
3) Tertiary alcohol



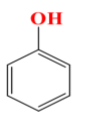
phenylmethanol
benzyl alcohol
primary aromatic alcohol

1-phenylethan-1-ol
secondary aromatic alcohol

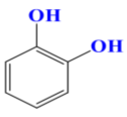


2-phenylpropan-2-ol
tertary aromatic alcohol

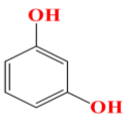
Naming of aromatic alcohol (phenols)



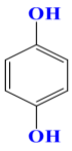
phenol
hydroxybenzene



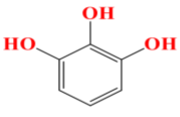
catechol
benzene-1,2-diol



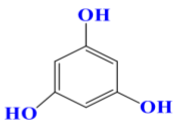
resorcinol
benzene-1,3-diol



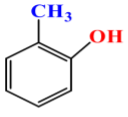
hydroquinone
benzene-1,4-diol



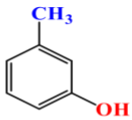
pyrogallol
benzene-1,2,3-triol



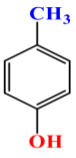
phloroglucinol
benzene-1,3,5-triol



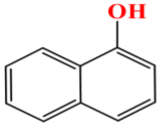
o-cresol
2-methylphenol



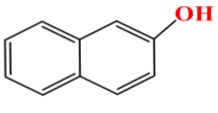
m-cresol
3-methylphenol



p-cresol
4-methylphenol



1-naphthol
naphthalen-1-ol



2-naphthol
naphthalen-2-ol

Week 4

• **Lecture Title:** Aldehydes and Ketones
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the chemical structure and functional groups of aldehydes and ketones.
2. To learn the IUPAC and common naming systems of aldehydes and ketones.
3. To describe the physical properties of these compounds (boiling point, solubility, polarity).
4. To differentiate between aldehydes and ketones based on structure and reactivity.
5. To explore the importance of carbonyl compounds in organic chemistry.

• Behavioral Objectives:

1- Cognitive Domain:

- The student will be able to define aldehydes and ketones and identify their functional groups.
- The student will be able to name aldehyde and ketone compounds using both IUPAC and common nomenclature.
- The student will be able to describe the physical properties of aldehydes and ketones and compare them.
- The student will be able to distinguish between aldehydes and ketones based on structure and reactivity.
- The student will be able to explain the importance of carbonyl groups in organic reactions.

2- Psychomotor Domain:

- The student will be able to draw the structural formulas of selected aldehydes and ketones.
- The student will be able to write and balance basic chemical equations involving aldehydes and ketones.

3- Affective Domain:

- The student will value the relevance of aldehydes and ketones in biological and pharmaceutical contexts.

Aldehyde and Ketone Compounds

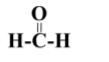
Second semester

Week-4- [Theoretical]

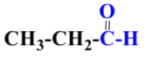
- **An aldehyde** is an organic compound in which the carbonyl group is attached to a carbon atom at the end of a carbon chain. R-CHO . General formula $C_nH_{2n}O$
- **A ketone** is an organic compound in which the carbonyl group is attached to a carbon atom within the carbon chain R-CO-R'. General formula $C_nH_{2n}O$
- The groups **R** and **Ŕ** may be **aliphatic** or **aromatic**, & in one aldehyde,(formaldehyde, **R=H**).
- **Nomenclature:Aliphatic aldehydes and ketones**
  - ✈ In the IUPAC system of nomenclature, aliphatic aldehydes are named as **alkanals**.
  - ✈ The **final -e** in the name of the corresponding alkane is substituted by **-al**. ✈ Some common examples of aldehydes and their names are given below :

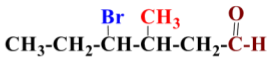
Aliphatic Aldehyde

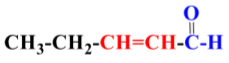

Aldehyde

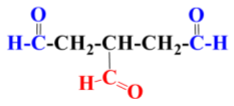

formaldehyde
Methanal

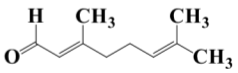

acetaldehyde
Eethanal


Propanal

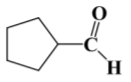

4-bromo-3-methylhexanal


Pent-2-enal

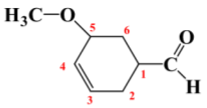

propane-1,2,3-tricarbaldehyde

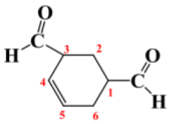

3,7-dimethylocta-2,6-dienal
citral) lemony odor
isolated from lemon grass

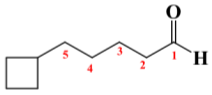
Cycloaldehyde

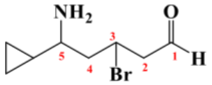

cyclopentanecarbaldehyde


4-methylcyclohexane-1-carbaldehyde

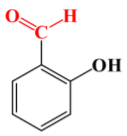

5-methoxycyclohex-3-ene-1-carbaldehyde

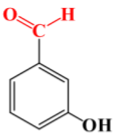

cyclohex-4-ene-1,3-dicarbaldehyde

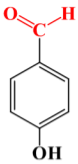

5-cyclobutylpentanal

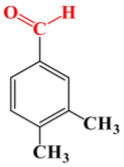

5-amino-3-bromo-5-cyclopropylpentanal

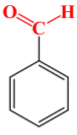
Aromatic aldehyde

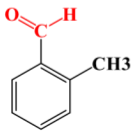

2-hydroxybenzaldehyde
o-Salicylaldehyde

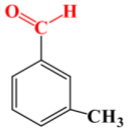

3-hydroxybenzaldehyde
m-Salicylaldehyde

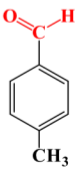

4-hydroxybenzaldehyde
p-Salicylaldehyde


3,4-dimethylbenzaldehyde


benzaldehyde


2-methylbenzaldehyde

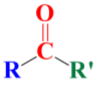

3-methylbenzaldehyde


4-methylbenzaldehyde

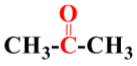

4-Hydroxy-3-methoxybenzaldehyde
vanillin


3-Phenylprop-2-enal
cinnamaldehyde

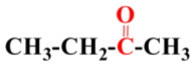
Aliphatic ketones



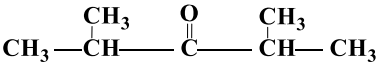
Ketone



propan-2-one
Acetone

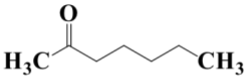


butan-2-one

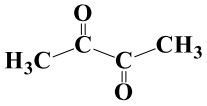


2,4-dimethyl-3-pentanone

4-hexen-2-one

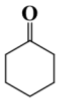


heptan-2-one
fruity odor like banana odor

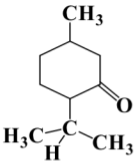


butanedione
biacetyl

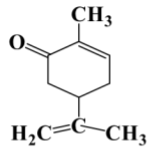
Cycloketones



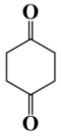
cyclohexanone



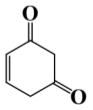
2-isopropyl-5-methylcyclohexan-1-one
menthone



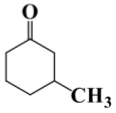
2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one
spearmint oil



cyclohexane-1,4-dione

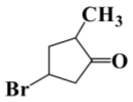


cyclohex-4-ene-1,3-dione



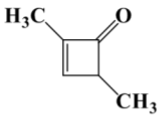
3-methylcyclohexan-1-one

cyclohex-2-en-1-one

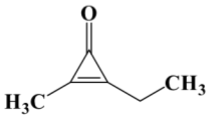


4-bromo-2-methylcyclopentan-1-one

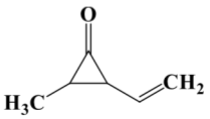
2-methylcyclopent-2-en-1-one



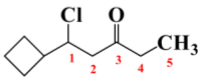
2,4-dimethylcyclobut-2-en-1-one



2-ethyl-3-methylcycloprop-2-en-1-one

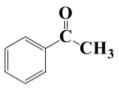


2-methyl-3-vinylcyclopropan-1-one

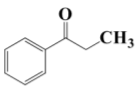


1-chloro-1-cyclobutylpentan-3-one

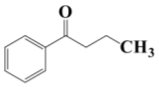
Aromatic Ketones



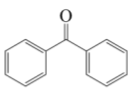
acetophenone
methyl phenyl ketone



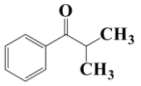
propiophenone
phenyl propyl ketone



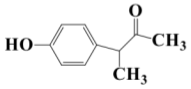
1-phenylbutan-1-one
butyl phenylketone



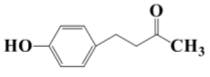
benzophenone
diphenyl ketone



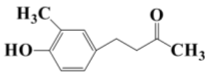
2-methyl-1-phenylpropan-1-one
isopropyl phenyl ketone



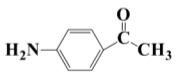
3-(4-hydroxyphenyl)butan-2-one
odor of ripe raspberries



4-(4-hydroxyphenyl)butan-2-one
odor of ripe raspberries



4-(4-hydroxy-3-methylphenyl)butan-2-one
The pungent , hot component of ginger
zingerone



1-(4-aminophenyl)ethan-1-one
4-amino actophnone

✈ PHYSICAL PROPERTIES OF ALDEHYDES AND KETONE

1. Physical state
    1) Lower members of aldehydes and ketones (upto C10) are colourless volatile liquids except formaldehyde which is gas at ordinary temperature
    2) Higher members of aldehyde and ketones are solids with fruity odour
    3) Lower aldehydes have unplesent odour but ketones posses pleasant smell
    4) Both aldehydes and ketones are **neutral compounds** that don't change the color of litmus paper.

2. Boiling point

1) Boiling point of aldehyde and ketones is slightly lower than corresponding alcohol due to lack of hydrogen bonding. However their boiling point is slightly higher than that of corresponding non-polar hydrocarbon or weakly polar ether. This may attributed to reason that aldehydes and ketones are polar compounds and thus possess intermolecular dipoledipole interaction
2) Among isomeric aldehydes and ketones, boiling point of ketones is slightly higher than that of aldehydes due to the presence of two electron donating alkyl groups making them more polar.

3. Solubility

1) Lower members of aldehydes and ketones (upto C4) are soluble in water due to Hbonding between polar carbonyl group and water.
2) However, solubility decreases with increase in molecular weight
3) Aromatic aldehydes and ketones are much less soluble than corresponding aliphatic aldehydes and ketones due to large benzene ring. However all carbonyl compounds are fairly soluble in organic solvents.

Week 5

- **Lecture Title:** Preparation Methods and Chemical Reactions of Aldehydes and Ketones
- **Duration:** 2 hours

Lecture Objectives:

1. To identify various methods for the laboratory and industrial preparation of aldehydes and ketones.
2. To understand the mechanisms of key chemical reactions involving carbonyl compounds.
3. To study oxidation and reduction reactions relevant to aldehydes and ketones.
4. To explore characteristic qualitative tests such as Tollens' and Fehling's tests.
5. To analyze the significance of these reactions in organic and pharmaceutical chemistry.

• Behavioral Objectives:

1- Cognitive Domain:

- The student will be able to describe multiple preparation methods for aldehydes (e.g., oxidation of primary alcohols) and ketones (e.g., oxidation of secondary alcohols).
- The student will be able to explain the mechanism of nucleophilic addition reactions to carbonyl groups.
- The student will be able to distinguish between oxidation and reduction reactions of aldehydes and ketones.
- The student will be able to interpret the outcomes of qualitative tests such as Tollens' and Fehling's.

2- Psychomotor Domain:

- The student will be able to write balanced chemical equations for different preparation methods.
- The student will be able to draw reaction mechanisms, including nucleophilic addition and oxidation pathways.

3- Affective Domain:

- The student will appreciate the role of aldehyde and ketone chemistry in pharmaceutical and analytical contexts.

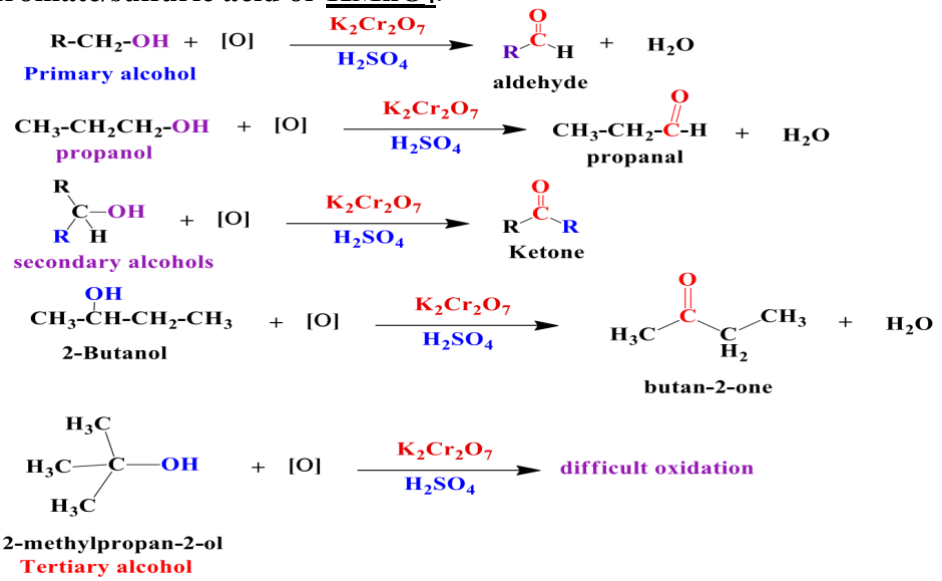
Preparation Methods and Chemical Reactions of Aldehydes and Ketones

Week-5- [Theoretical]

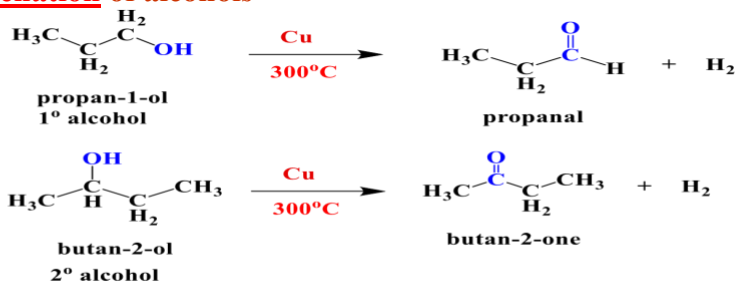
Preparation of aldehydes and ketones

1. Oxidation of Primary and Secondary Alcohols

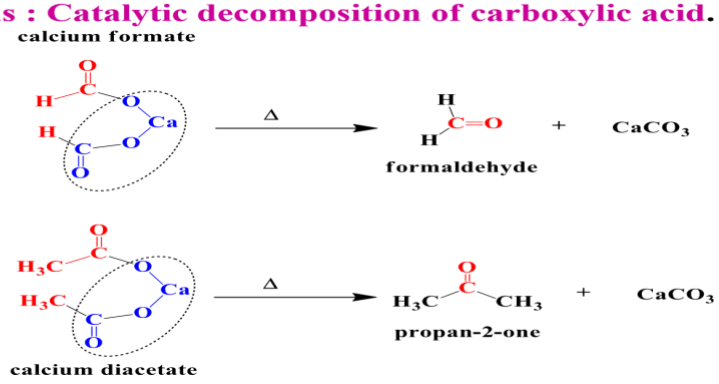
- The **oxidation** of **primary or secondary alcohols** is the classical method of preparation of aldehydes and ketones. Tertiary alcohol is difficult oxidation
- **Chromic acid** (acidified sodium dichromate) is frequently used in the laboratory, but industrially oxygen and catalysts are employed.
- When oxidizing primary alcohols, care must be taken that the aldehyde produced is not oxidized further to a carboxylic acid.
- Primary alcohols can be oxidized with **pyridinium chlorochromate**(PCC) to aldehydes. Ketones can be obtained from secondary alcohols by oxidation with sodium **dichromate/sulfuric acid or $KMnO_4$**.



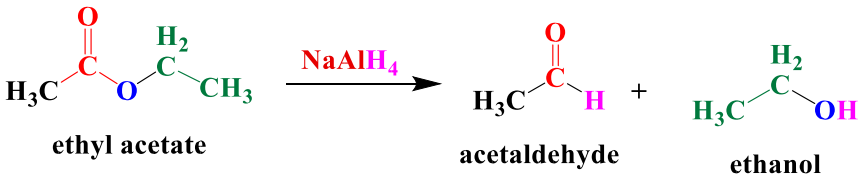
2. Catalytic dehydrogenation of alcohols



3. From carboxylic acids : Catalytic decomposition of carboxylic acid.

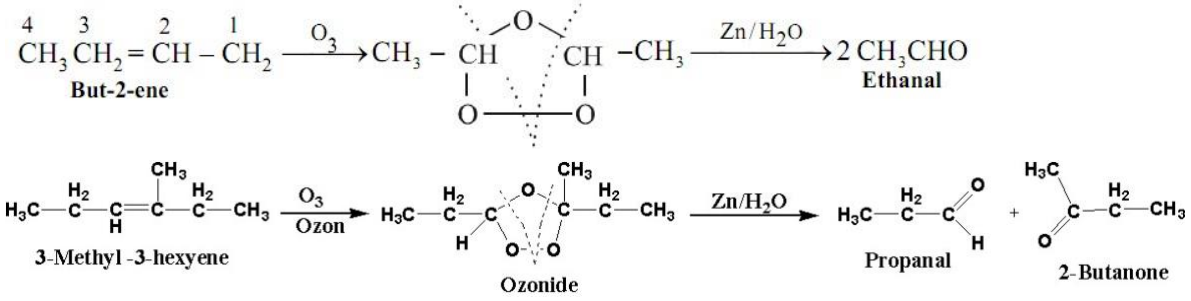


4. Reduction of esters by sodium aliminum hydride $NaAlH_4$:

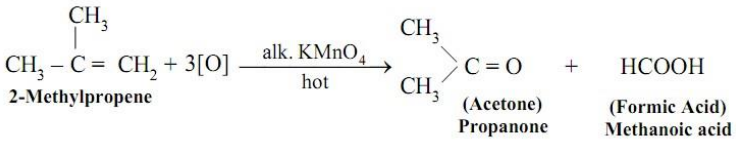


5. From alkenes Reduction

A- ozonolysis of alkenes: This process of addition of ozone in CCl_4 to an unsaturated hydrocarbon followed by hydrolysis is called ozonolysis.

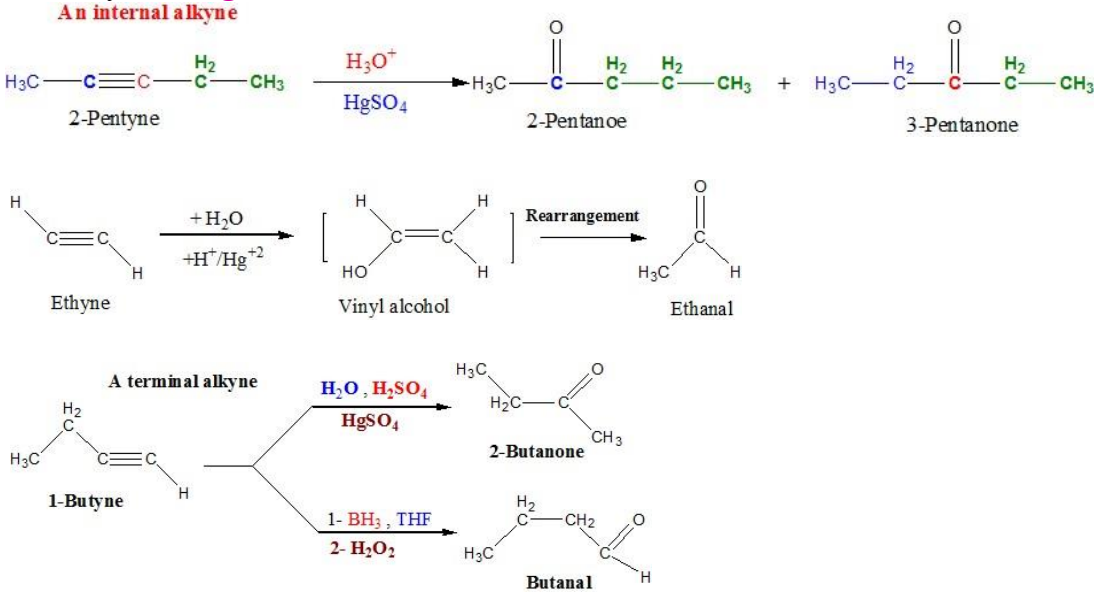


B- Oxidation of alkene with O_2 in hot alkaline $KMnO_4$



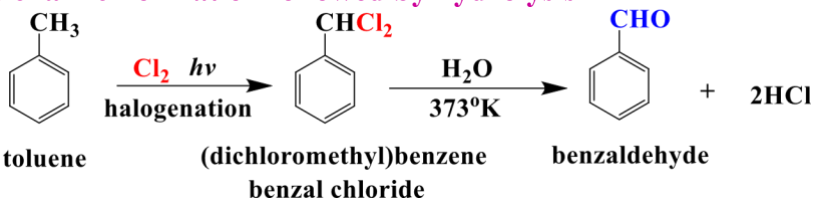
6. Hydration of Unsymmetrical Alkynes

One very important addition reaction is the hydration of the triple bond, catalyzed by acid and mercury salts $HgSO_4$ / H_2SO_4 are form **ketones**.



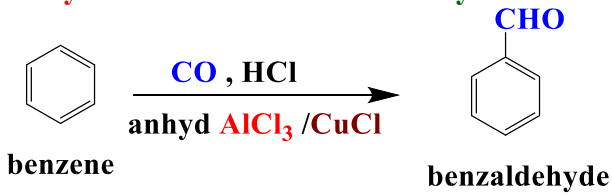
Preparation of aromatic carbonyl compounds.

1) By side chain chlorination followed by hydrolysis

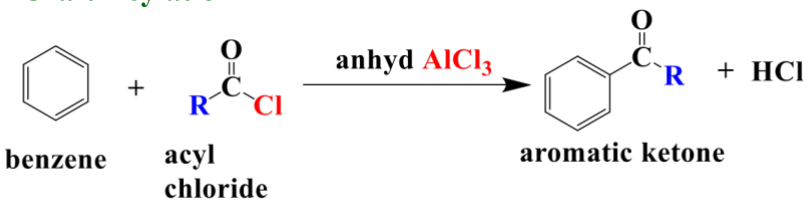


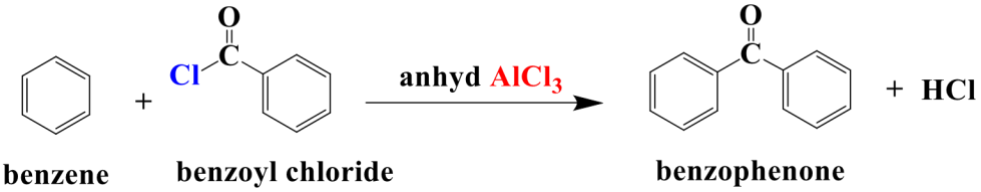
2) Gatterman – Koch reaction

When benzene or its derivative is treated with carbon monoxide CO and hydrochloric acid HCl in the presence of anhydrous aluminum chloride $AlCl_3$ or cuprous chloride CuCl , it gives benzaldehyde or substituted benzaldehyde



3) Friedel Craft Acylation



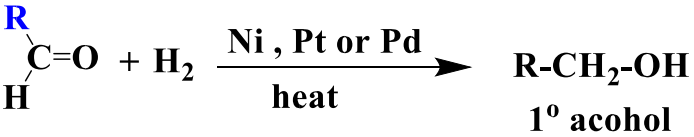


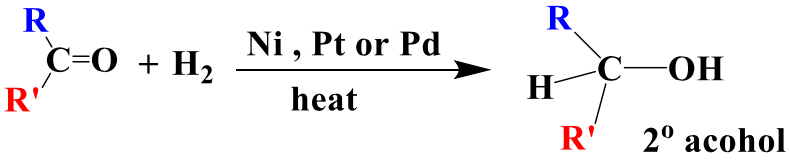
Reactions of aldehydes and ketones.

The reactions of aliphatic aldehydes and ketones can be divided into a number of sections, differing in the type of reaction and the group or atom initially involved. The sections which will be considered here are:

1. Reduction reactions

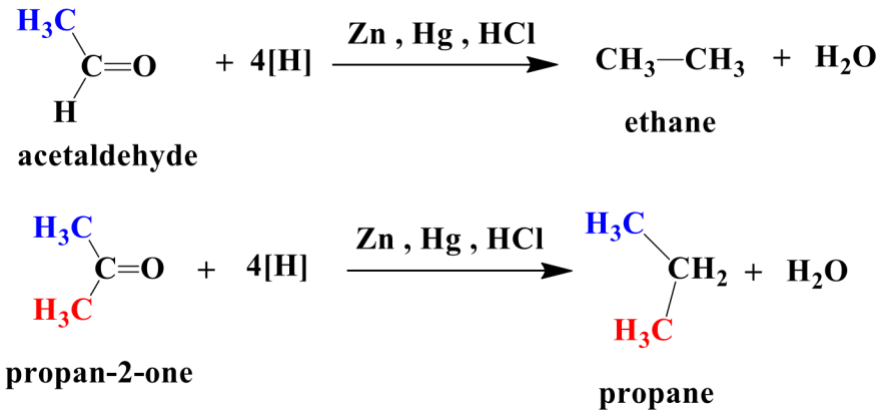
1) Catalytic reduction to alcohol



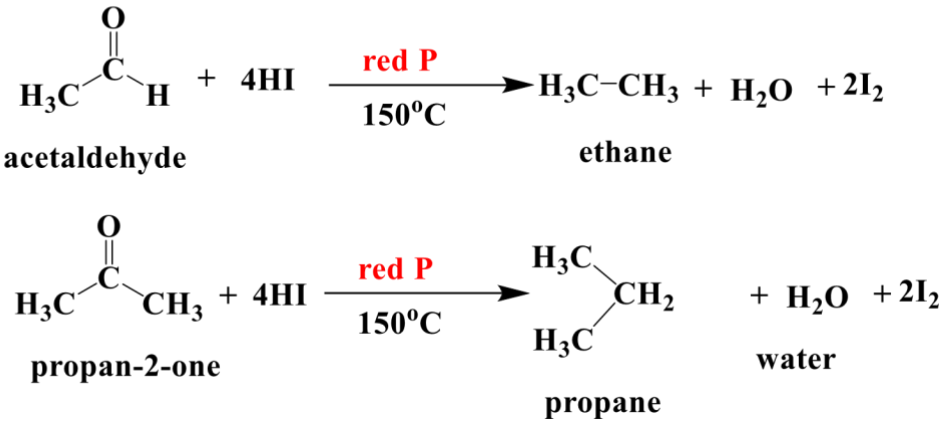


2) Clemmensen reduction

Clemmensen reduction is a chemical reaction described as a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and concentrated hydrochloric acid to formation alkane .This reaction is named after Erik Christian Clemmensen.

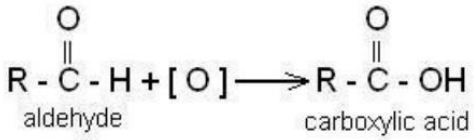


3) Reduction with HI + P (red)



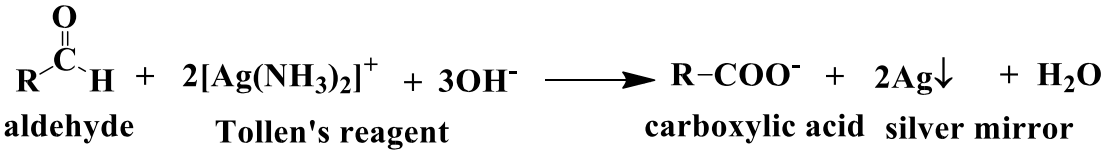
2. Oxidation reactions

1) Oxidation with mild oxidizing agents

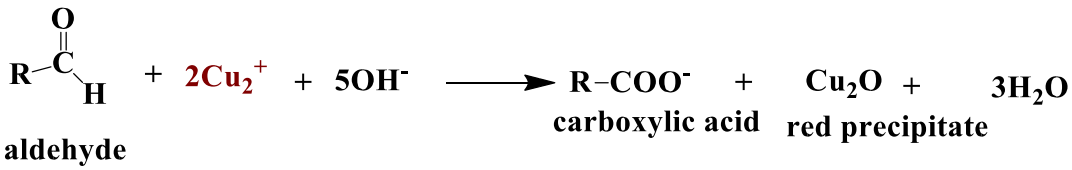


Ketones are not oxidized by mild oxidizing agents

A. Aldehydes reduces Tollen's reagent to metallic silver which appears as a silver mirror on wall of test tube. Thus the reaction is also known as silver mirror test.

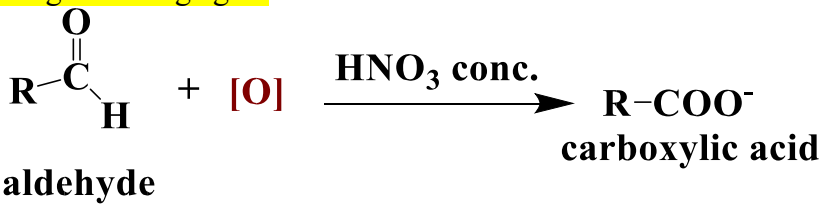


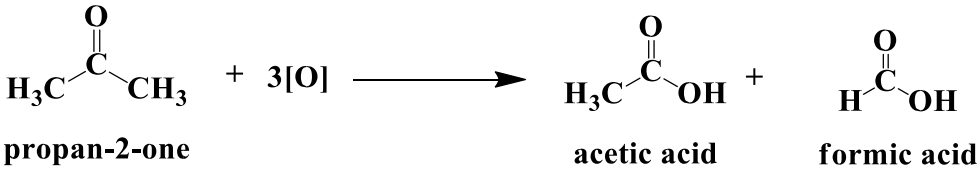
B. Reduction of Fehling's solution is an alkaline solution of $CuSO_4$ mixed with Rochelle slat i.e. Fehling's solution sodium potassium tartarate. Aldehydes reduces cupric ion (Cu^{2+}) of Fehling's solution to cuprous ions (Cu^{+}) to form red precipitate of cuprous oxide



Fehling's solution is reduced by aliphatic aldehydes only. Aromatic aldehydes and ketones so not give this reaction.

2) Oxidation with strong oxidizing agent





Week 6

• **Lecture Title:** Carboxylic Acids
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structure and functional groups of carboxylic acids and their derivatives (esters, amides, acid chlorides, anhydrides).
2. To learn systematic (IUPAC) and common naming rules for carboxylic acids and their derivatives.
3. To study laboratory and industrial preparation methods of carboxylic acids and their derivatives.
4. To examine major chemical reactions involving carboxylic acids and their derivatives (e.g., hydrolysis, esterification, amidation).
5. To explore the pharmacological and pharmaceutical uses of carboxylic acids and their derivatives.

• Behavioral Objectives:

1- Cognitive Domain:

- The student will be able to identify and differentiate the structures of carboxylic acids and their derivatives.
- The student will be able to apply IUPAC rules to name carboxylic acids, esters, amides, acid chlorides, and anhydrides.
- The student will be able to describe common methods of synthesizing carboxylic acids (e.g., oxidation of primary alcohols, hydrolysis of nitriles).
- The student will be able to explain the mechanisms of key reactions such as esterification, hydrolysis, and nucleophilic acyl substitution.
- The student will be able to discuss the importance and applications of carboxylic acid derivatives in drug design and formulation.

2- Psychomotor Domain:

- The student will be able to draw the structural formulas of carboxylic acids and their derivatives.
- The student will be able to write balanced chemical equations and reaction mechanisms.

3- Affective Domain:

- The student will appreciate the critical role of carboxylic acids and their derivatives in pharmaceutical chemistry and therapeutics.

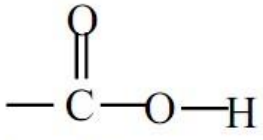
Second semester

Week-6- [Theoretical PHT116]

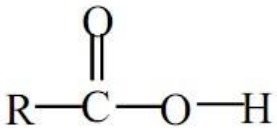
Carboxylic acid

⌘ Introduction

- ☒ The combination of a **carbonyl group** and a **hydroxyl** on the same carbon atom is called a **carboxyl group**.
- ☒ Compounds containing the **carboxyl group** are distinctly acidic and are called **carboxylic acids**.
- ☒ The carboxyl group is one of the most **widely occurring functional groups** in **chemistry and biochemistry**. Not only are **carboxylic acids** themselves **important**, but the **carboxyl group** is the parent group of a **large family of related compounds called carboxylic acid derivatives.**



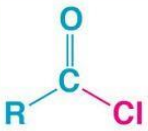
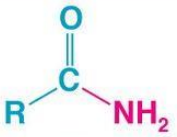
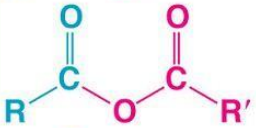
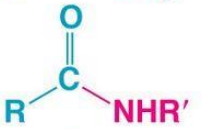
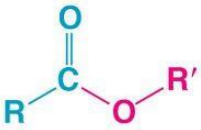
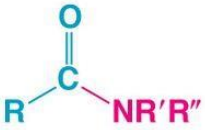
carboxyl group



carboxylic acid

condensed structure

The carboxyl group **(-COOH)** is the parent group of a family of compounds called **acyl** compounds or **carboxylic acid derivatives**

Structure	Name	Structure	Name
	Acyl (or acid) chloride		Amide
	Acid anhydride		
	Ester		
	Nitrile		

⌘ Classification of carboxylic acids.

Carboxylic acids are classified according to the substituent bonded to the carboxyl group.

1. **An aliphatic acid** has an alkyl group bonded to the carboxyl group.
2. **Dicarboxylic acids** are named by adding the suffix -dioic, followed by the word acid, to the name of the carbon chain that contains both carboxyl groups.
3. **A cycloalkane carboxylic acid** containing a carboxyl group bonded to a cycloalkane ring is named by giving the name of the ring and adding the suffix -carboxylic acid. The atoms of the ring are numbered beginning with the carbon bearing the ─COOH group:

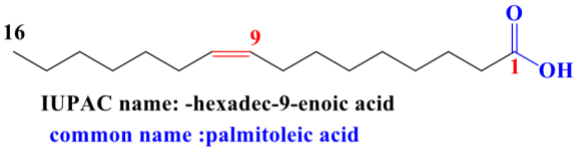
4. **Aromatic acid** has an aryl group.
5. **Fatty acids** are long-chain aliphatic acids derived from the hydrolysis of fats and oils.

⌘ Nomenclature of carboxylic acids.

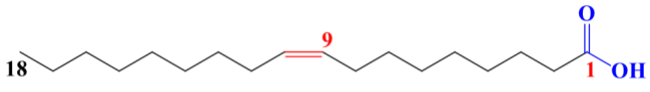
Saturated carboxylic acid

Carbon Atom	Structure	IUPAC Name	Common Name
1	$HCOOH$	methanoic acid	Formic acid
2	CH_3COOH	ethanoic acid	Acetic acid
3	CH_3CH_2COOH	Propionic acid	Propionic acid
4	$CH_3CH_2CH_2COOH$	butanoic acid	Butyric acid
5	$CH_3(CH_2)_3COOH$	pentanoic acid	Valeric acid
6	$CH_3(CH_2)_4COOH$	Hexanoic acid	caproic acid,
8	$CH_3(CH_2)_6COOH$	octanoic acid	Caprylic acid
9	$CH_3(CH_2)_7COOH$	Nonanoic acid	pelargonic acid
10	$CH_3(CH_2)_8COOH$	Decanoic acid	capric acid
12	$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid
14	$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid
16	$CH_3(CH_2)_{14}COOH$	hexadecanoic acid	Palmitic acid
18	$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid
20	$CH_3(CH_2)_{18}COOH$	Icosanoic acid	Arachidic acid

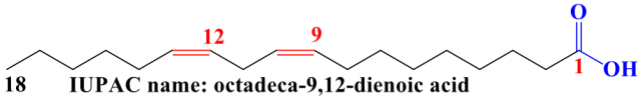
Usaturated alphatic acid (oil)



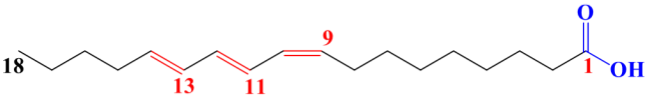
IUPAC name: -hexadec-9-enoic acid
common name :palmitoleic acid



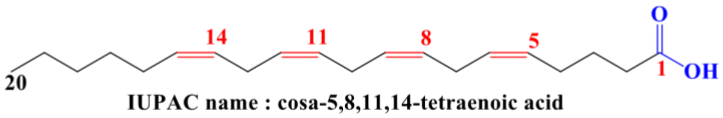
IUPAC name : octadec-9-enoic acid
common name: oleic acid



IUPAC name: octadeca-9,12-dienoic acid
common name: linoleic acid



IUPAC name :octadeca-9,11,13-trienoic acid
common name: eleostearic acid

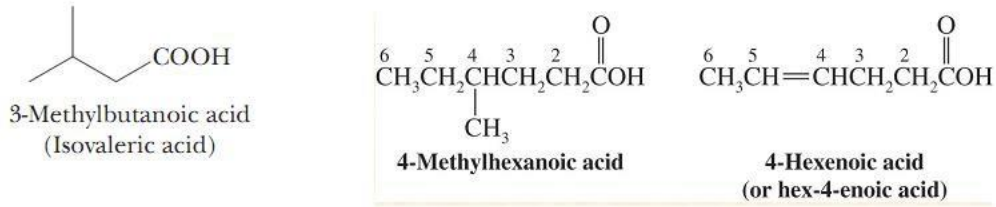


IUPAC name : cosa-5,8,11,14-tetraenoic acid
common name : arachidonic acid

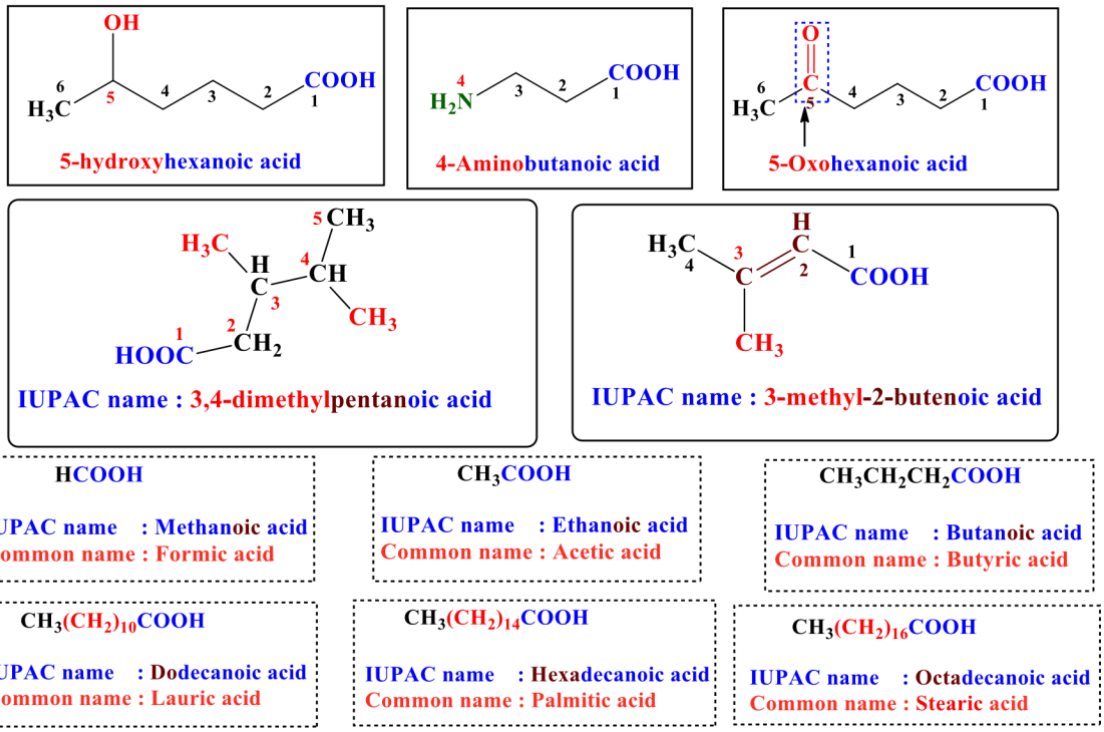
A. IUPAC Names:

Aliphatic carboxylic acids

1) We derive the IUPAC name of a **carboxylic acid** from that of the longest carbon chain that contains the carboxyl group by dropping the final -e from the name of the parent alkane and adding the **suffix -oic**, followed by the **word acid** .
2) We **number** the chain **beginning** with the carbon of the **carboxyl group**. Because the **carboxyl carbon** is understood to be **carbon 1**, there is no need to give it a number.
3) If the **carboxylic acid** contains a **carbon–carbon double bond**, we change the infix from **-an-** to **-en-** to indicate the presence of the **double bond**, and we show the location of the **double bond** by a **number**.



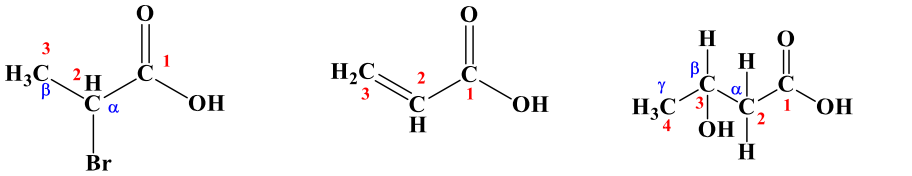
4) **In the IUPAC system**, a carboxyl group takes precedence over most other **functional groups** ; including hydroxyl and **amino groups**, as well as the **carbonyl groups** of **aldehydes** and **ketones**. As illustrated in the following examples, an **–OH** group of an **alcohol** is indicated by the **prefix hydroxy-**, an **–NH_2 group** of an **amine** by **amino-,** and an **C=O group** of an **aldehyde** or **ketone** by **oxo-:** Carboxylic acids contain the functional group:



Substituted acids are named in two ways :

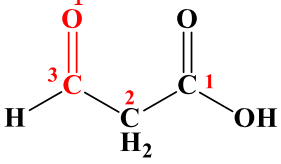
IUPAC system : the chain is numbered beginning with the carboxyl carbon atom , and substituents are located in the usual way .

Common name : substituents are located with Greek letters , beginning with the **α**-carbon atom .

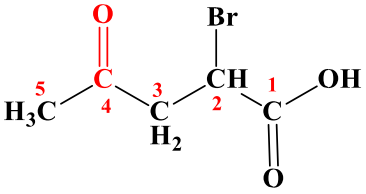


The carboxyl group has priority over alcohol , aldehyde , or ketone functionality in naming .

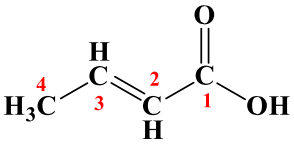
The prefix oxo- is used to locate the carbonyl group of the aldehyde or ketone.



3-oxopropanoic acid

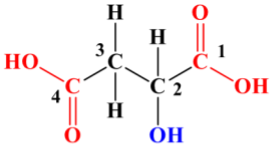


2-bromo-4-oxopentanoic acid

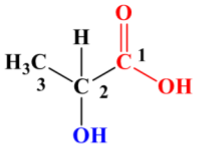


but-2-enoic acid
(2-butenoic acid)

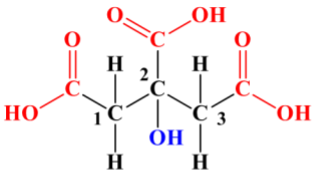
5) **Dicarboxylic acids** are named by adding the **suffix -dioic**, followed by the word **acid**, to the name of the carbon chain that contains both carboxyl groups. Because the two carboxyl groups can be only at the ends of the parent chain, there is no need to number them. Following are IUPAC names and common names for several important aliphatic dicarboxylic acids:



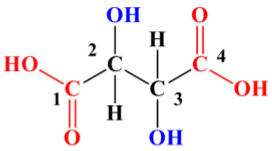
Malic acid
2-hydroxybutanedioic acid
2-Hydroxysuccinic acid
Apple acid



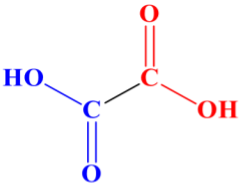
Lactic acid
2-hydroxypropanoic acid
Lactic acid is found primarily in sour milk products, such as koumiss, laban, yogurt, kefir, and some cottage cheeses.



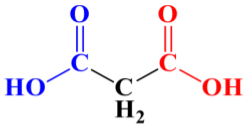
Citric acid
2-hydroxypropane-1,2,3-tricarboxylic acid
It occurs naturally in citrus fruits



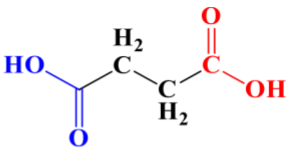
Tartaric acid
2,3-Dihydroxybutanedioic acid
2,3-Dihydroxysuccinic acid
many fruits, most notably in grapes, but also in bananas, tamarinds, and citrus



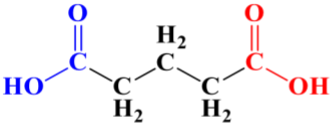
Ethanedioic acid
(Oxalic acid)
isolated oxalic acid from flowering plants of the genus Oxalis .Members of the spinach family and the brassicas (cabbage, broccoli, brussels sprouts) are high in oxalates.



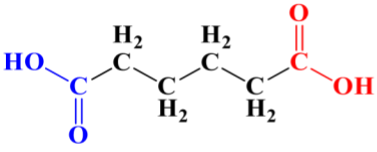
Propanedioic acid
(Malonic acid)
Malonic acid is a naturally occurring substance found in some fruits like citrus, fruits .The name originates from the Greek word (malon) meaning 'apple'.



Butanedioic acid
(Succinic acid)
occurs naturally in plant broccoli, rhubarb, sugar beets,and animal tissues fresh meat extracts,



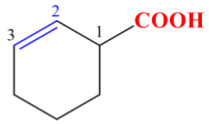
Pentanedioic acid
(Glutaric acid)



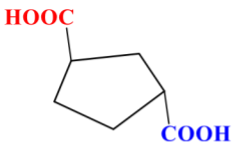
Hexanedioic acid
Hexane-1,6-dioic acid
(Adipic acid)

6) **Cycloalkane carboxylic acid**

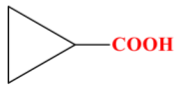
A carboxylic acid containing a carboxyl group bonded to a **cycloalkane ring** is named by giving the name of the ring and adding the suffix **-carboxylic acid**. The atoms of the ring are **numbered beginning** with the **carbon bearing the –COOH group:**



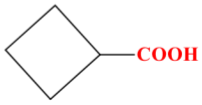
2-Cyclohexenecarboxylic acid



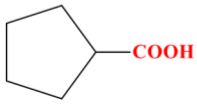
trans-1,3-Cyclopentane-dicarboxylic acid



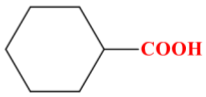
Cyclopropane carboxylic acid



Cyclobutane carboxylic acid

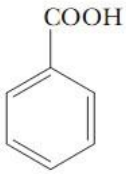


Cyclopentane carboxylic acid

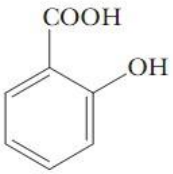


Cyclohexane carboxylic acid

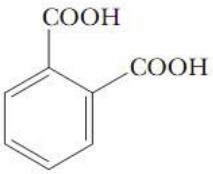
7) **Aromatic dicarboxylic acids** are named by adding the words **dicarboxylic acid** to **benzene**. Examples are 1,2-benzenedicarboxylic acid and 1,4benzenedicarboxylic acid. Each is more usually known by its common name: **phthalic acid** and **terephthalic acid**, respectively.



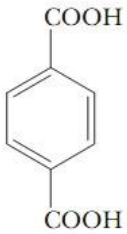
Benzoic acid



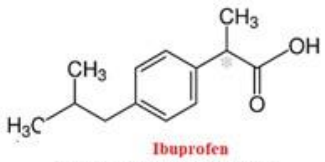
2-Hydroxybenzoic acid
(Salicylic acid)



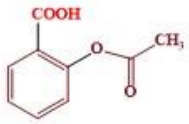
1,2-Benzenedicarboxylic acid
(Phthalic acid)



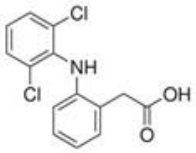
1,4-Benzenedicarboxylic acid
(Terephthalic acid)



Ibuprofen
2-(4-(2-methylpropyl)phenyl)
propanoic acid

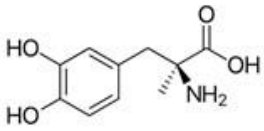


acetyl salicylic acid
Aspirin

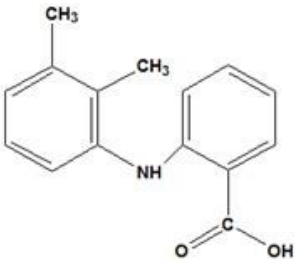


Diclofenac, Voltaren
[2-(2,6-Dichloroanilino)phenyl]acetic acid

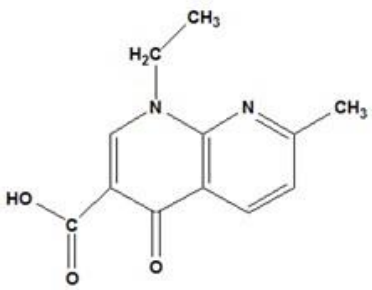
2-hydroxybenzoicacid
salicylic acid



(methyldopa)
L-α-Methyl-3,4-dihydroxyphenylalanine or
(2S)-2-amino-3-(3,4-dihydroxyphenyl)
-2-methylpropanoic acid



Mefenamic acid
dimethylphenylaminobenzoic acid
used to tretment migrain headaci..

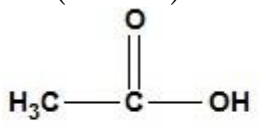


Nalidixic acid
antibiotics

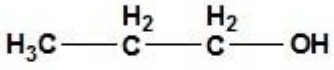
⌘ Physical Properties of Carboxylic Acids

1. Boiling Points

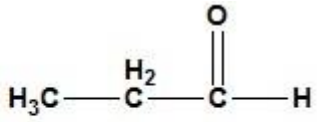
Carboxylic acids boil at considerably higher temperatures than do alcohols, ketones, or aldehydes of similar molecular weights. For example, acetic acid (MW 60) boils at 118°C, 1-propanol (MW 60) boils at 97°C, and propionaldehyde (MW 58) boils at 49°C.



acetic acid , bp 118°C

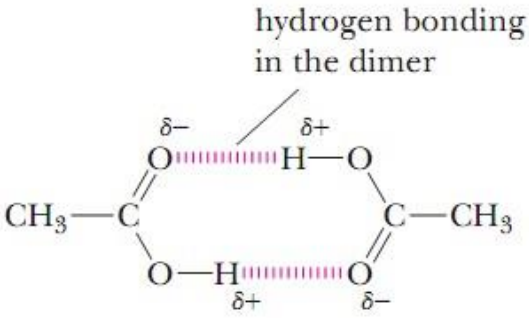


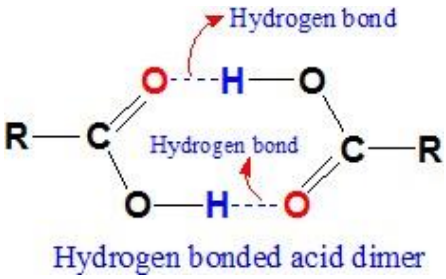
1-Propanol , bp 97°C



Propanal , bp 49°C

The high boiling points of carboxylic acids result from formation of a stable, hydrogenbonded dimer contains an eight –membered ring joined by two hydrogen bonds, effectively doubling the molecular weight of the molecules leaving the liquid phase.

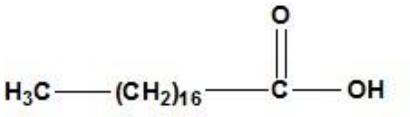




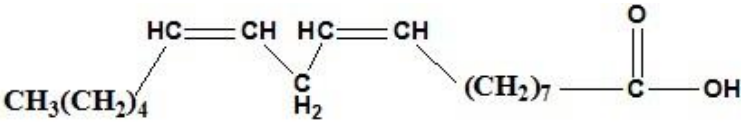
Hydrogen bonded acid dimer

2. Melting Points

1) Acids containing more than eight carbon atoms are generally solids, unless they contain **double bonds**. The presence of double bonds (especially cis double bonds)in a long chain impedes formation of a stable crystal lattice, resulting in a **lower melting** point. For example, both stearic acid (octadecanoic acid) and linoleic acid (cis-9,12- octadecadienoic acid) have 18 carbon atoms, but stearic acid melts at 70°C and linoleic acid melts at -5°C.



Steric acid , mp 70°C
$C_{18}H_{36}O_2$ Solid



Linoleic acid , mp -5°C
$C_{18}H_{32}O_2$ Liquid

3. Solubilities

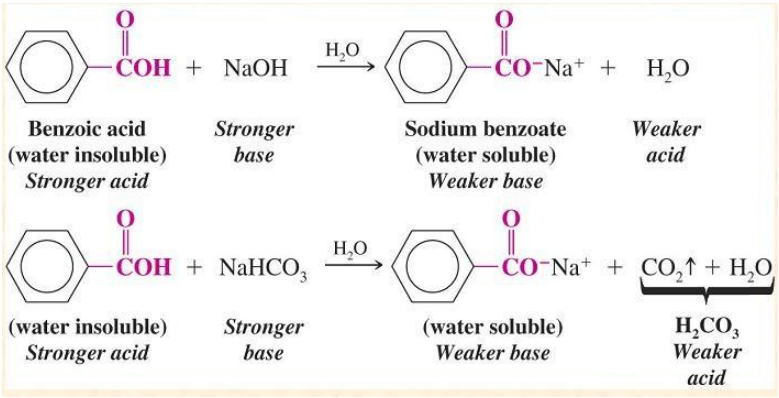
1) Carboxylic acids form hydrogen bonds with water, and the lower molecular-weight carboxylic acids (up **through four carbon atoms)** are miscible with water. As the length of the hydrocarbon chain increases, water solubility decreases until acids with more than 10 carbon atoms are essentially insoluble in water.
2) Carboxylic acids are very soluble in alcohols because acids form hydrogen bonds with alcohols. Also, alcohols are not as polar as water, so the longer-chain acids are more

soluble in alcohols than they are in water. Most carboxylic acids are quite soluble in relatively nonpolar solvents such as chloroform , hexane , benzene, carbon tetrachloride.

3) **The solubility of a carboxylic acid** in water **decreases as its molecular weight increases.** We account for this trend in the following way:
   a) A carboxylic acid consists of two regions of different polarity a **polar hydrophilic** carboxyl group and, except for formic acid, the hydrophilic carboxyl group increases water solubility
   b) **nonpolar hydrophobic** hydrocarbon chain ; the hydrophobic hydrocarbon chain decreases water solubility.

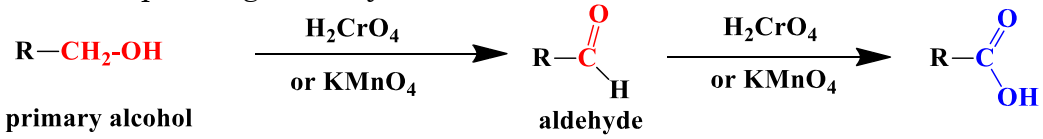
Boiling point and solubilities in water of carboxylic acid				
Structure	Name	M.Wt.	Boiling point (°C)	Solubility g/100ml H_2O
HCOOH	Formic acid			infinite
CH_3COOH	Acetic acid	60.1	118	infinite
$CH_3(CH_2)_2COOH$	Butanoic acid	88.1	163	infinite
$CH_3(CH_2)_5COOH$	Hexanoic acid	116.2	205	1.0

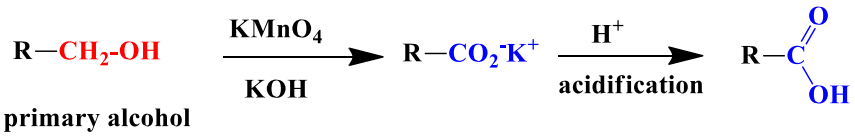
⌘ The carboxyl proton of most carboxylic acids has a pKa = 4 - 5
– Carboxylic acids are deprotonated by NaOH or $NaHCO_3$
– Carboxylate salts are more water soluble than the acid



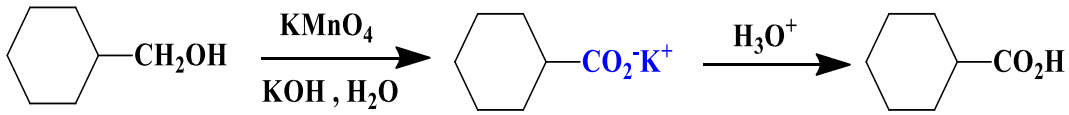
Preparation of carboxylic acids #$!

1. **Oxidation** : Carboxylic acids may be prepared by the oxidation of primary alcohols and aldehydes or by the more difficult oxidation of ketones . Other reagents such as $KMnO_4$, HNO_3 ; $K_2Cr_2O_7$ etc… will also oxidize a 1° alcohol to the corresponding carboxylic acid.





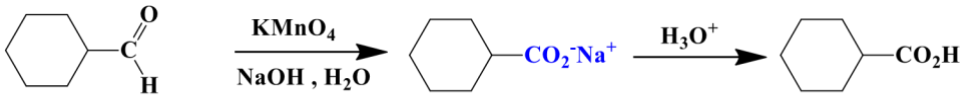
primary alcohol



cyclohexylmethanol

cyclohexanecarboxylic acid

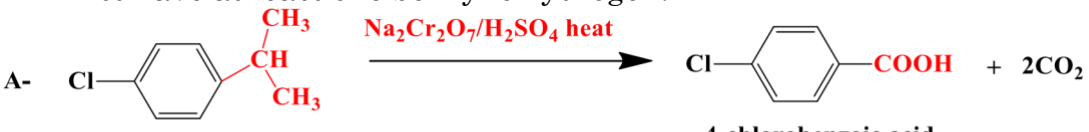
2. **Oxidations of aldehydes with $KMnO_4$ in basic media** yields a carboxylate salt that must be acidified to provide the free carboxylic acid.



cyclohexanecarbaldehyde

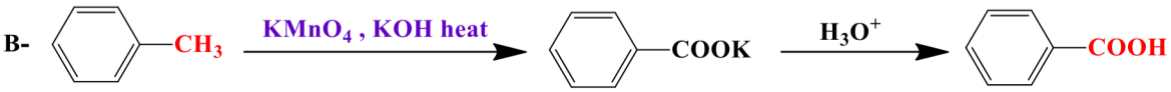
cyclohexanecarboxylic acid

3. **Oxidation of alkyl benzene :** Also provides carboxylic acids as the product. Must have at least one benzylic hydrogen.



1-chloro-4-isopropylbenzene

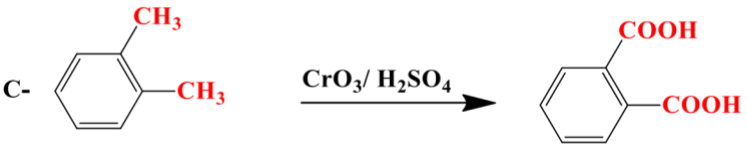
4-chlorobenzoic acid



toluene

potassium benzoate

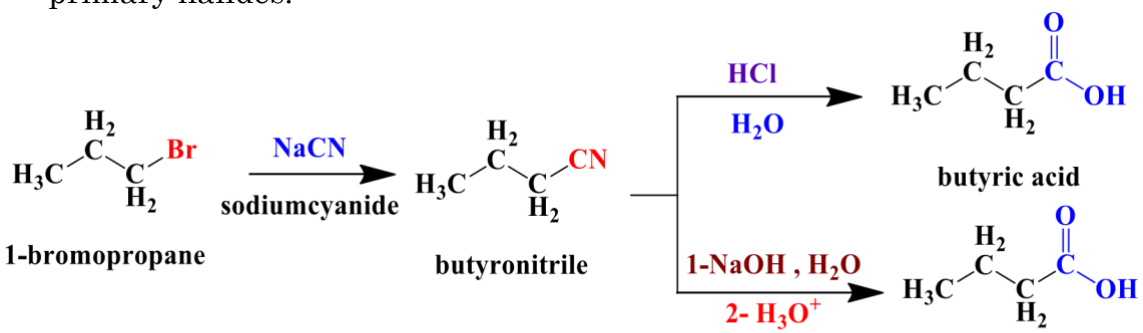
benzoic acid



o-xylene

phthalic acid

4. **Hydrolysis of Nitriles** : Nitriles can be hydrolyzed to the corresponding carboxylic acid, either under acidic or basic conditions. (mechanisms will be discussed in we have seen that they can easily formed by SN_2 reactions with primary halides.



1-bromopropane

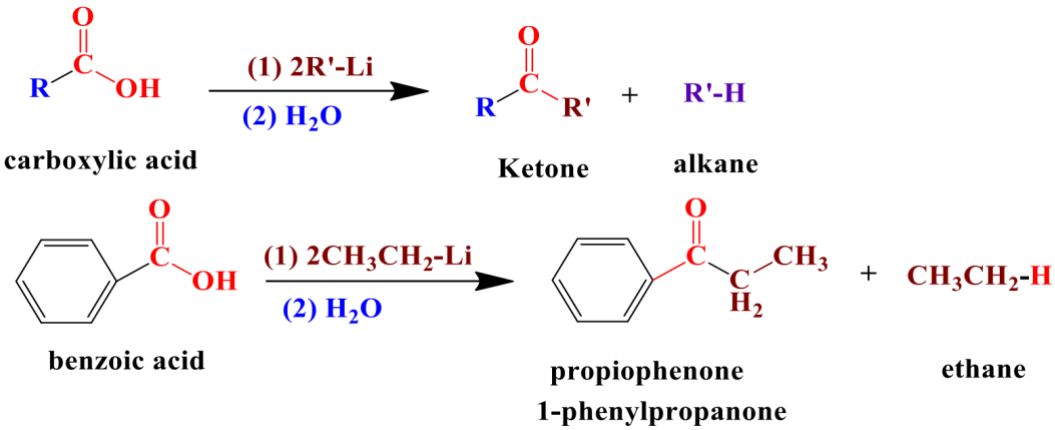
butyronitrile

butyric acid

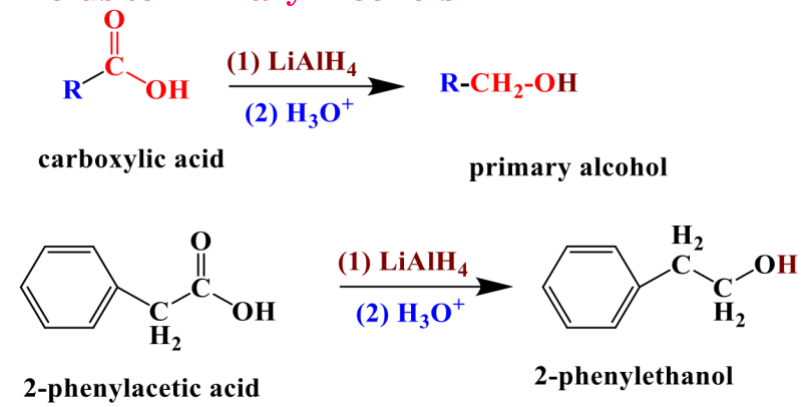
butyric acid

Reactions of carboxylic acids

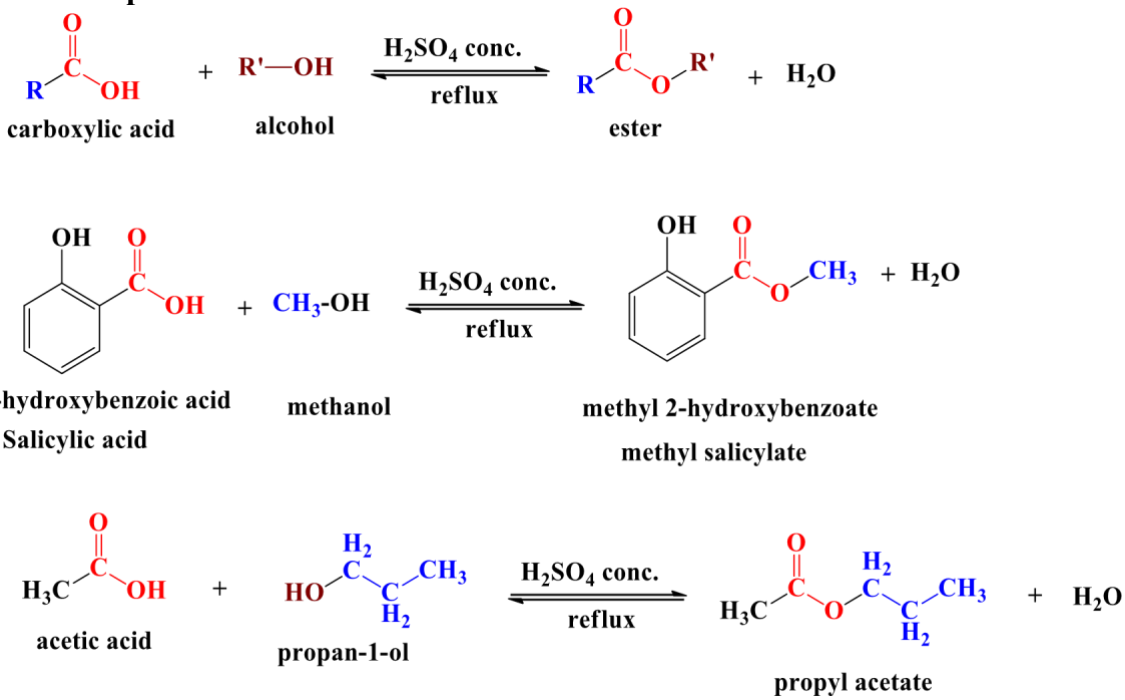
1. Alkylation of Acids to form Ketones



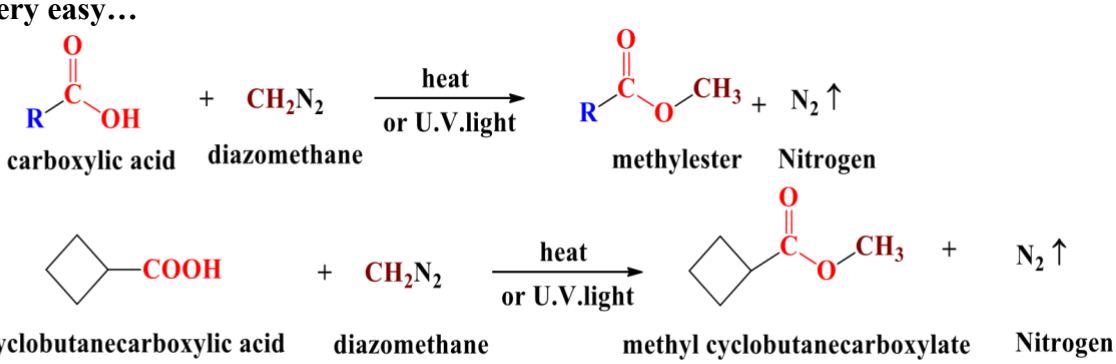
2. Reduction of Acids to Primary Alcohols



3. The Fisher Esterification : Reaction of a carboxylic acid with an alcohol under acidic conditions produces an ester.



4. **Esterification Using Diazomethane :One of the best way to make methyl ester is to react the corresponding carboxylic acid with Diazomethane. The reaction is quantitative and very easy…**



⌘ Uses of carboxylic acid:

1. Manufacturing of soaps need higher fatty acid. Soaps are generally sodium or potassium salts of higher fatty acids such as stearic acid.
2. Food industry uses many organic acids for the production of soft drinks, food products etc. for example, acetic acid is used in making vinegar . Sodium salts of organic acids find application in preservatives.
3. In pharmaceutical industry organic acids are used in many drugs such aspirin , phenacetin etc.
4. Acetic acids are often used as a coagulant in the manufacturing of rubber.
5. Organic acids find huge application in making dye stuff, perfumes and rayon.

Week 7

• **Lecture Title:** Amines
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structure and classification of amines (primary, secondary, tertiary, aromatic).
2. To learn the systematic (IUPAC) and common naming conventions of amines.
3. To study the physical properties of amines including boiling point, solubility, and odor.
4. To examine the concept of basicity in amines and factors affecting their basic strength.
5. To explore important reactions involving amines and their applications in industry and pharmaceuticals.

• **Behavioral Objectives:**

1- **Cognitive Domain:**

• The student will be able to identify and classify different types of amines based on their structure.
• The student will be able to apply IUPAC nomenclature rules to name amines systematically.
• The student will be able to describe physical properties of amines and explain the reasons behind these properties.
• The student will be able to explain the concept of amine basicity, including resonance and inductive effects.
• The student will be able to discuss the applications of amines in chemical synthesis and drug development.

2- **Psychomotor Domain:**

• The student will be able to draw structural formulas of various amines.
• The student will be able to write chemical equations illustrating reactions involving amines.

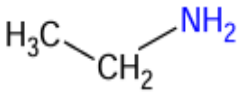
3- **Affective Domain:**

• The student will appreciate the significance of amines in organic chemistry and their role in pharmaceuticals and industry.

Amine

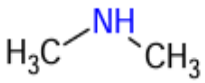
⌘ Amines are organic compounds containing a nitrogen functionality. Depending upon the number of alkyl or aryl, groups attached to nitrogen. determines its classification, or order.

The order also affects the number of hydrogens attached to nitrogen, (and charge with a quaternary nitrogen).



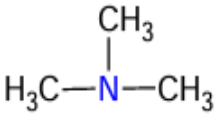
ethanamine

Primary



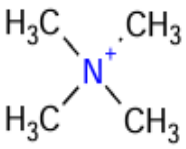
N-methylmethanamine

Secondary



N,*N*-dimethylmethanamine

tertiary

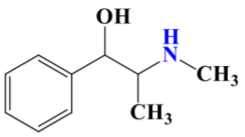


N,*N*,*N*-trimethylmethanaminium

qurternary

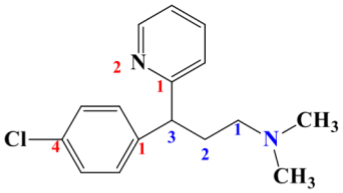
⌘ Application

Alkaloids refer to amines that are produced by plants. They are often used for medicinal or physiological purposes, (the plant makes them to cause an effect when an animal eats them for protection).



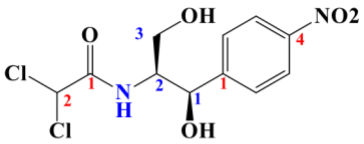
2-(methylamino)-1-phenylpropan-1-ol

ephedrine : central nervous system (CNS) stimulant that is often used to prevent low blood pressure during anesthesia



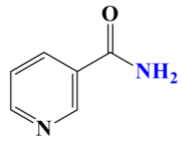
3-(4-chlorophenyl)-*N*,*N*-dimethyl -3-(pyridin-2-yl)propan-1-amine

chlorpheniramine :Antihistamines drug



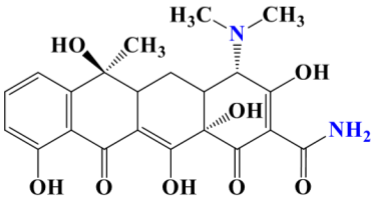
2,2-dichloro-*N*-(1,3-dihydroxy -1-(4-nitrophenyl)-2-propyl)acetamide

Chloramphenicol : antibiotic



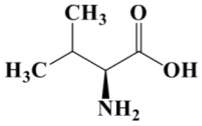
Nicotinamide

vitamin B3



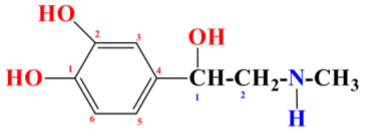
Tetracycline

antibiotic



valine

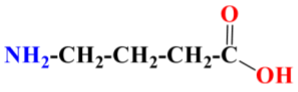
amino acid



4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol

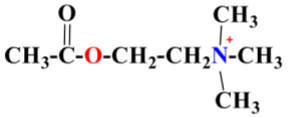
Epinephrine (Adrenalin)

Adrenaline is normally produced by the adrenal glands and by a small number of neurons in the medulla oblongata. It plays an essential role in the fight-or-flight response by increasing blood flow to muscles, heart output by acting on the SA node,pupil dilation response, and blood sugar level.



gamma-aminobutanoic acid

GABA is an inhibitory transmitter in the mature brain; its actions were thought to be primarily excitatory in the developing brain.



2-acetoxy-*N*,*N*,*N*-trimethylethan-1-aminium

Acetycholine

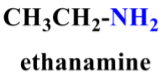
acetylcholine, an ester of choline and acetic acid that serves as a transmitter substance of nerve impulses within the central and peripheral nervous systems. Acetylcholine is the chief neurotransmitter of the parasympathetic nervous system, the part of the autonomic nervous system (a branch of the peripheral nervous system) that contracts smooth muscles, dilates blood vessels, increases bodily secretions, and slows heart rate. Acetylcholine can stimulate a response or block a response and thus can have excitatory or inhibitory effects.

➢ AMINE NOMENCLATURE

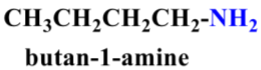
- **Aliphatic Amine**

1. The groups attached to nitrogen may be any combination of alkyl or aryl groups. Amines are named in two main ways, in the IUPAC system: either as alkylamines or as alkanamines. When primary amines are named as alkylamines, the ending -amine is added to the name of the alkyl group that bears the nitrogen. When named as alkanamines, the alkyl group is named as an alkane and the -e ending replaced by -amine.

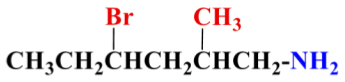
Primary amine [1°]



ethanamine
ethylamine



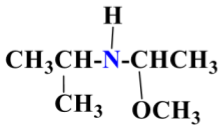
butan-1-amine
butyl amine



4-bromo-2-methylhexan-1-amine

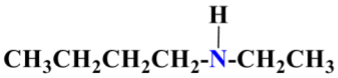
4-chloro-2-ethyl-6-methoxyheptan-1-amine

Secondary amine [2°]

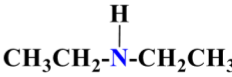


N-(1-methoxyethyl)propan-2-amine
N-(1-methoxyethyl)isopropylamine

1-chloro-*N*-methylethan-1-amine

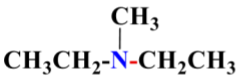


N-ethylbutan-1-amine
ethylbutylamine

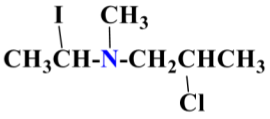


diethylamine

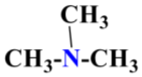
tertiary amine [3°]



N-ethyl-*N*-methylethanamine

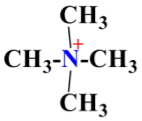


2-chloro-*N*-(1-iodoethyl)-*N*-methylpropan-1-amine

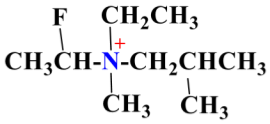


trimethylamine

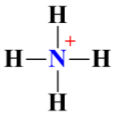
quaternary amine [4°]



tetramethylammonium
N,*N*,*N*-trimethylmethanamine

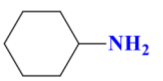


N-ethyl-*N*-(1-fluoroethyl)-*N*,2-dimethylpropan-1-aminium

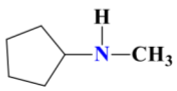


ammonium

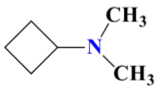
Cyclo-amine



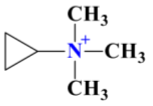
cyclohexanamine
primary amine



N-methylcyclopentanamine
Scondary amine



N,*N*-dimethylcyclobutanamine
tertiary amine

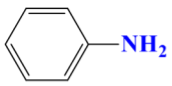


N,*N*,*N*-trimethylcyclopropanaminium
quaternary amine

Aromatic amine

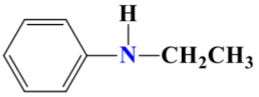
Aniline is the parent IUPAC name for amino-substituted derivatives of benzene. Substituted derivatives of aniline are numbered beginning at the carbon that bears the amino group. Substituents

are listed in alphabetical order, and the direction of numbering is governed by the usual "first point of difference" rule.



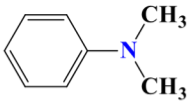
aniline

primary amine



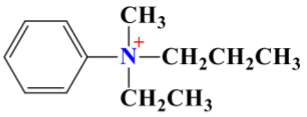
N-ethylaniline

Scondary amine



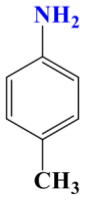
N,*N*-dimethylaniline

tertiary amine



N-ethyl-*N*-methyl-*N*-propylbenzenaminium

quaternary amine

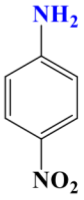


p-toluidine

4-methylaniline

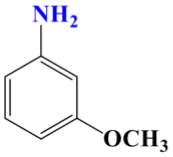
2-bromoaniline

o-bromoaniline



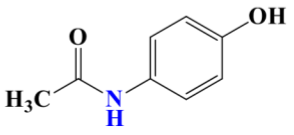
4-nitroaniline

p-nitroaniline



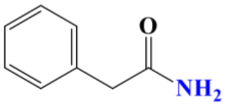
3-methoxyaniline

m-anisidine



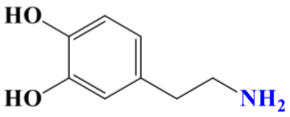
N-(4-hydroxyphenyl)acetamide

paracetamol



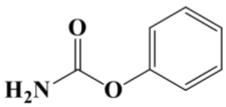
2-phenylacetamide

phenylAcetamide



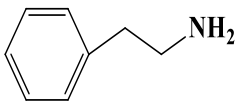
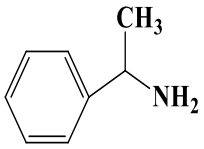
4-(2-aminoethyl)benzene-1,2-diol

Dopamine



phenyl carbamate

✡ PROBLEM [1] :Give an acceptable alkylamine or alkanamine name for each of the following amines:

a)  b)  c) CH_2=$CHCH_2$-NH_2

SAMPLE SOLUTION

(a) The amino substituent is bonded to an ethyl group that bears a phenyl substituent at C-2. The compound C_6H_5-$CH_2CH_2NH_2$ may be named as either 2-phenylethylamine or 2phenylethanamine.

(b) The amino substituent is bonded ethyl group that bears a phenyl substituent at C-1. The compound C_6H_5-$CHNH_2CH_3$ may be named as either 1-phenylethylamine

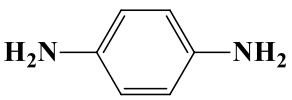
(c) 2-Propen-1-amine (Allylamine)

Diamine

Compounds with two amino groups are named by adding the suffix -diamine to the name of the corresponding alkane or arene. The final of the parent hydrocarbon is retained.

propane-1,2-diamine

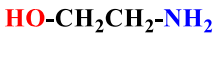
hexane-1,6-diamine



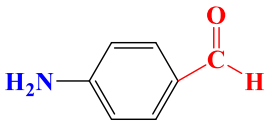
benzene-1,4-diamine

Amine with another functional groups

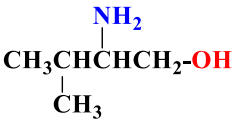
1. Amino groups rank rather low in seniority when the parent compound is identified for naming purposes. Hydroxyl groups and carbonyl groups outrank amino groups. In these cases, the amino group is named as a substituent.



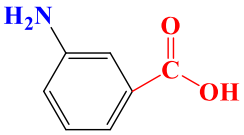
2-aminoethan-1-ol



4-aminobenzaldehyde

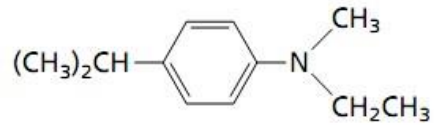


2-amino-3-methylbutan-1-ol



3-aminobenzoic acid

- PROBLEM [2] : Assign alkanamine names to N-methylethylamine and to N,Ndimethylcycloheptylamine.
  SAMPLE SOLUTION: N-Methylethylamine (given as $CH_3NHCH_2CH_3$ in the pre-ceding example) is an N-substituted derivative of ethanamine; it is N-methylethanamine.
- PROBLEM [3] : Classify the following amine as primary, secondary, or tertiary, and give it an acceptable IUPAC name.



PHYSICAL PROPERTIES

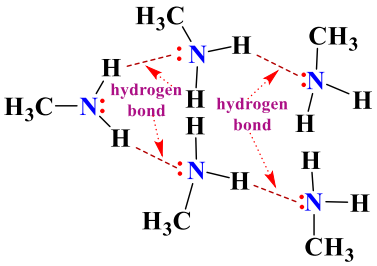
1. We have often seen that the polar nature of a substance can affect physical properties such as boiling point. This is true for amines, which are more polar than alkanes but less polar than alcohols. For similarly constituted compounds, alkylamines have boiling points higher than those of alkanes but lower than those of alcohols.

$CH_3CH_2CH_3$	CH_3CH_2-NH_2	CH_3CH_2OH
propane	**ethanamine**	**ethanol**
bp -42°C	**bp 17°C**	**bp 78°C**

2. Dipole–dipole interactions, especially hydrogen bonding, are present in amines but absent in alkanes. The less polar nature of amines as compared with alcohols, however, makes these intermolecular forces weaker in amines than in alcohols. Among isomeric amines, primary amines have the highest boiling points, and tertiary amines the lowest.

$CH_3CH_2CH_2NH_2$	CH_3CH_2-NH-CH_3	CH_3-N(CH_3)-CH_3
propan-1-amine	***N*-methylethanamine**	**trimethylamine**
bp 50°C	**bp 34°C**	**bp 3°C**
primary amine	**secodary amine**	**tertiary amine**

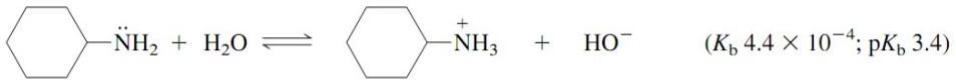
3. Primary and secondary amines can participate in intermolecular hydrogen bonding, but tertiary amines cannot.
   1) Primary and secondary amines can form hydrogen bonds to each other and water
   2) Tertiary amines cannot form hydrogen bonds to each other but can form hydrogen bonds to hydrogen bond donors such as water.



4. Amines that have fewer than six or seven carbon atoms are soluble in water. All amines, even tertiary amines, can act as proton acceptors in hydrogen bonding to water molecules.
5. The simplest arylamine, aniline, is a liquid at room temperature and has a boiling point of 184°C. Almost all other arylamines have higher boiling points. Aniline is only slightly soluble in water (3 g/100 mL). Substituted derivatives of aniline tend to be even less water-soluble.
6. Low molecular weight amines tend to be water soluble whether they are primary, secondary or tertiary

BASICITY OF AMINES

1. Amines are weak bases, but as a class, amines are the strongest bases of all neutral molecules. lists basicity data for a number of amines.
   1) Alkylamines are slightly stronger bases than ammonia.
   2) Alkylamines differ very little among themselves in basicity. Their basicities over a range of less than 10 in equilibrium constant (1 pK unit).
   3) Arylamines are much weaker bases than ammonia and alkylamines. Their basicity constants are on the order of 106 smaller than those of alkylamines (6 pK units).
2. The differences in basicity between ammonia, and primary, secondary, and tertiary alkylamines result from the interplay between steric and electronic effects on the molecules themselves and on the solvation of their conjugate acids. In total, the effects are small, and most alkylamines are very similar in basicity.

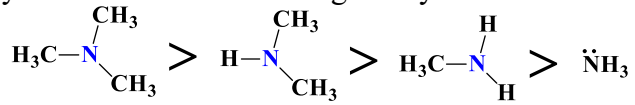


Cyclohexylamine Water Cyclohexylammonium ion Hydroxide ion

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

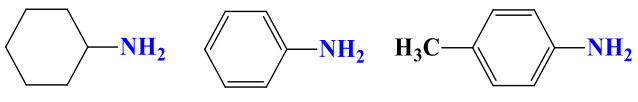
	$\ddot{N}H_3$	$CH_3\ddot{N}H_2$	$CH_3CH_2\ddot{N}H_2$	$CH_3CH_2CH_2\ddot{N}H_2$
	ammonia	methanamine	ethanamine	propan-1-amine
conjugate acid pKa	9.26	10.64	10.75	10.67

4. gas phase : basicity increases with increasing methyl substitution



trimethylamine > dimethylamine > methanamine > ammonia

5. Arylamines are weaker bases than nonaromatic cyclohexylamines



	cyclohexanamine	aniline	*p*-toluidine
conjugate acid pKa	10.64	4.58	5.08

Week 8

• **Lecture Title:** Preparation of Amines, Reactions of Amines, and Their Uses in Pharmacy
• **Duration:** 2 hours

Lecture Objectives:

1. To understand various methods for the preparation of amines (e.g., amination, reduction of nitriles, reaction of alkyl halides with ammonia).
2. To study the principal chemical reactions involving amines (such as acid-base reactions, alkylation, acylation, and amide formation).
3. To explore the pharmaceutical applications of amines, including their roles in drug synthesis and as active pharmaceutical ingredients.

• **Behavioral Objectives:**
1- **Cognitive Domain:**
• The student will be able to explain different synthetic routes for preparing amines, providing relevant examples.
• The student will be able to describe key chemical reactions undergone by amines.
• The student will be able to discuss the pharmaceutical significance of amines and their impact on drug development.

2- **Psychomotor Domain:**
• The student will be able to write balanced chemical equations for the preparation and reactions of amines.
• The student will be able to draw structural formulas of amines and their reaction products.

3- **Affective Domain:**
• The student will appreciate the critical role of amines in pharmaceutical development and their therapeutic importance.

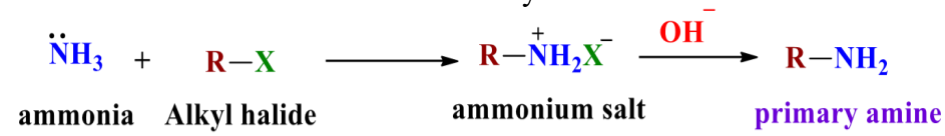
Preparation, Reactions, and Their Uses in Pharmacy of Amines

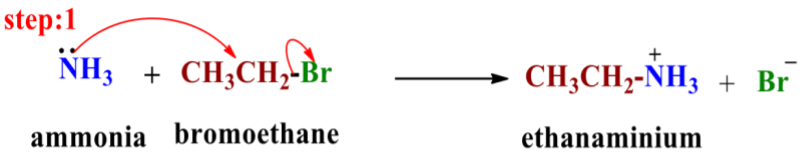
Week -8 -Theoretical

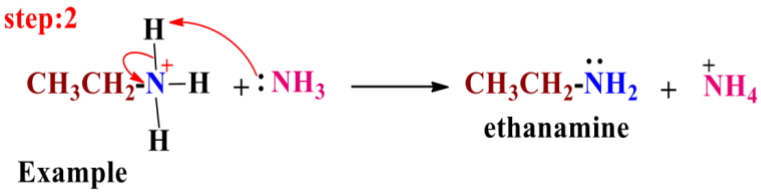
Preparation of Amines

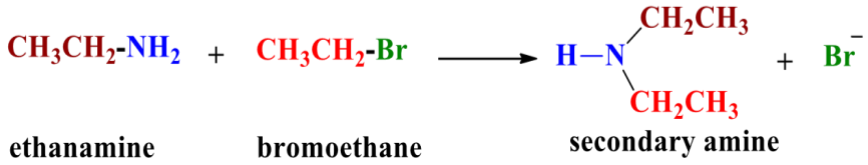
1) By Nucleophilic Substitution Reactions

✞ Alkylation of Ammonia : Reaction of ammonia with an alkyl halide









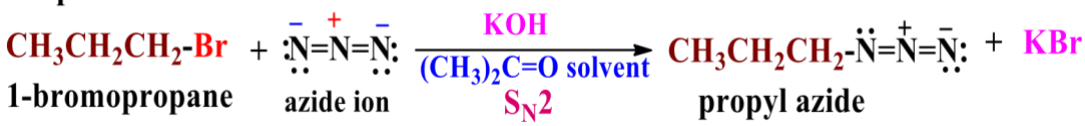
✞ **Alkylation of Azide Ion followed by Reduction step**

Azide ion is an excellent nucleophile (far better than amines) and will readily participate in S_N2 reaction with alkyl halide and sulfonates in alkali medium KOH or NaOH ; usually carried out in polar aprotic solvent (e.g. **DMSO** $(CH_3)_2S=O$. or **acetonitrile** CH_3CN

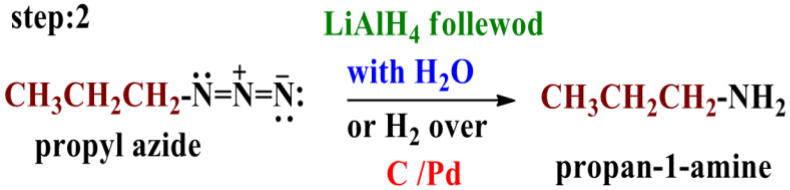
✞ Reduction of azide to primary amine with either **lithium aluminum hydride ($LiAlH_4$)** or through catalytic **hydrogen with H_2 over Pd/C**

- **The azide N_3^- is an excellent nucleophile**

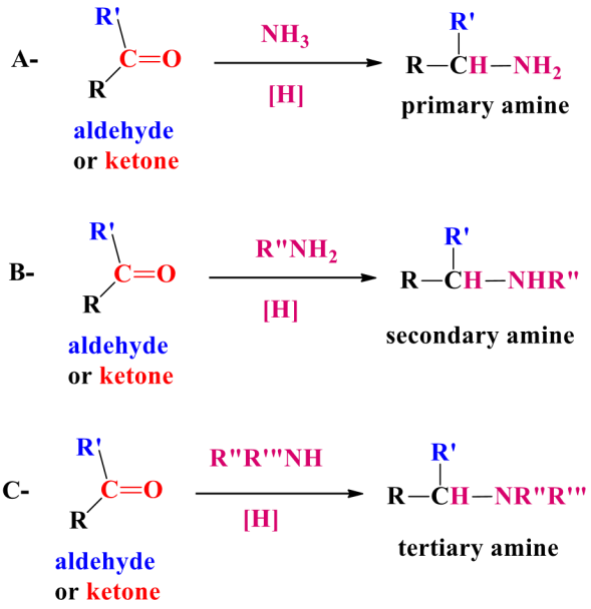
step:1



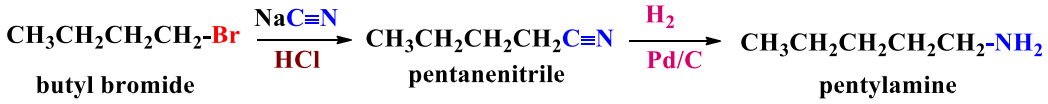
step:2



2) Preparation of Primary, Secondary and Tertiary Amines through Reductive Amination

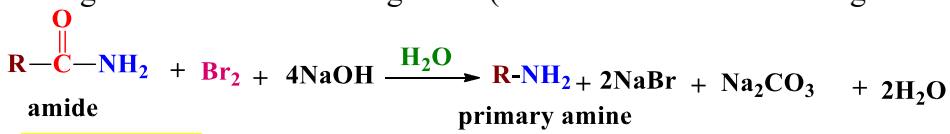


3) **Preparation of Primary, Secondary, or Tertiary Amines through Reduction of Nitriles, Oximes, and Amides**



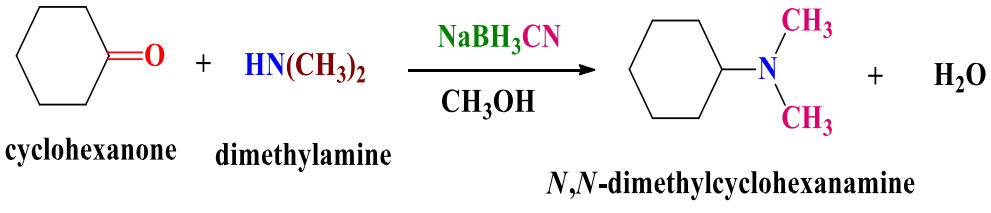
4) Preparation of Primary Amines by the Hofmann and Curtius Rearrangements

- 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)

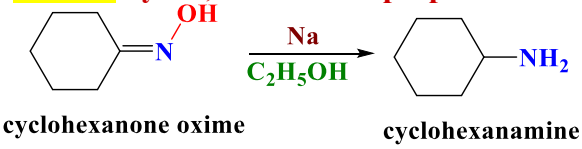


5) **Preparation of cyclic amines**:

- Reduction cyclic ketones by using catalytic hydrogenation or a hydride reducing reagent $NaBH_3CN$ are especially effective in reductive aminations

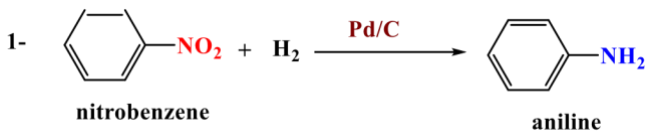


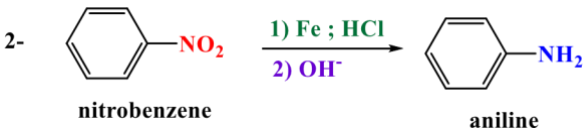
- **Reduction of Oximes by Na, C_2H_5OH to prepare Primary**



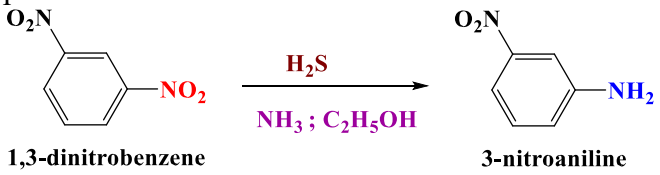
6) Preparation of Aromatic Amines by Reduction of Nitro Compounds

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

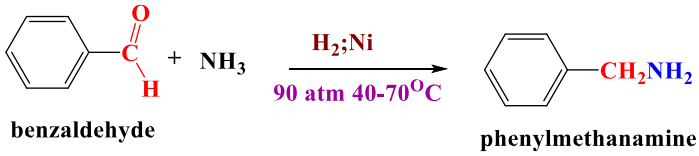


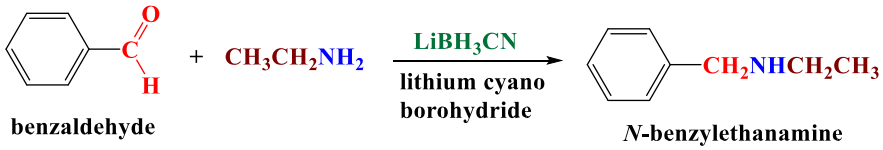


- One molar equivalent of hydrogen sulfide in alcoholic ammonia can be used to reduce one nitro group in the presence of another

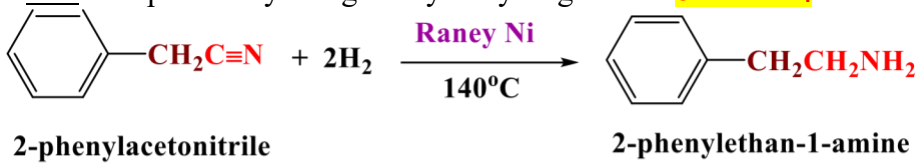


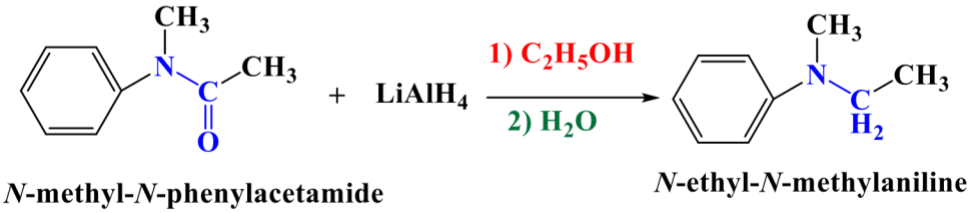
- The reduction can be accomplished using catalytic hydrogenation or a hydride reducing reagent sodium cynoborohydrideNaBH$_3$CN and lithium cynoborohydrideLiBH$_3$CN are especially effective in reductive aminations





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

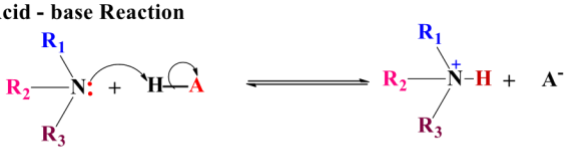




Reactions of Amines

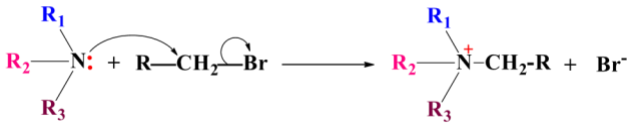
1. **The lone pair** of the nitrogen atom accounts for most chemistry of amines. The unshared electron pair can act as a base or as a nucleophile

Acid - base Reaction



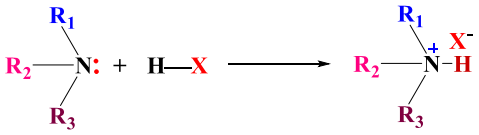
$R_1;R_2;R_3 = H$ $R_1 = CH_3;R_2;R_3 = H$ $R_1;R_2 = CH_3;R_3 = H$

$R_1;R_2 = H;R_3 = Ar$ $R_1;R_2;R_3 = CH_3$



amine acting as a nucleophile in an alkylation reaction

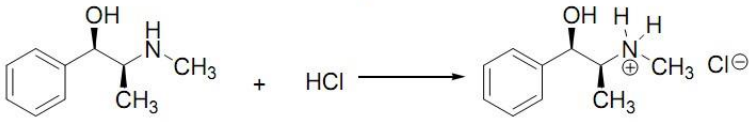
2. Salt Formation



amine strong acid ammonium salts

Amines react with strong mineral acids such as **HCl**, **H_2SO_4** and **H_3PO_4** to form ammonium salts. Since free amines are easily oxidised, sometimes by just being exposed to the air, their conversion to ammonium salts serves to stabilize them.

Example



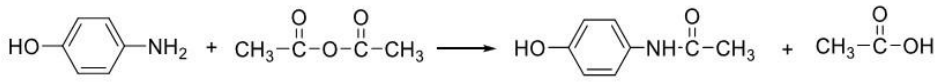
Ephedrine Ephedrine hydrochloride

Ephedrine was used as a decongestant in the treatment of Asthma. It was sold & administered as the hydrochloride salt.

3. Reaction of Amines with Acid Anhydrides

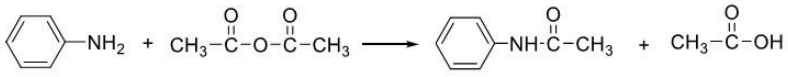
Amines react with acid anhydrides (by nucleophilic acyl substitution) to provide amides.

Example



p-Aminophenol Acetic anhydride *p*-Acetamidophenol Paracetamidophenol Paracetamol

Paracetamol is a pain reliever found in medicines such as Panadol and Tylenol.

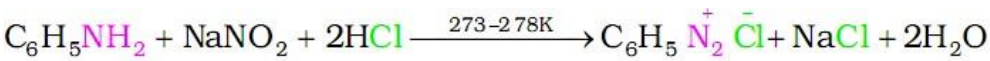


1° Aniline Acetic anhydride Acetanilide N-Phenylacetamide

Diazonium salts Formation

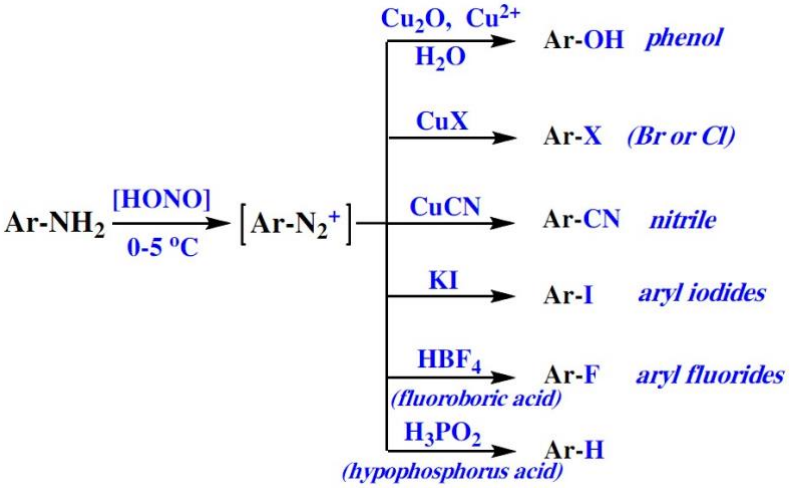
The diazonium salts have the general formula $RN_2^+X^-$ where R stands for an aryl group and X^- ion may be Cl^- ,Br- , HSO^-_4 , BF_4^- , etc. They are named by suffixing diazonium to the name of the parent hydrocarbon from which they are formed, followed by the name of anion such as chloride, hydrogensulphate, etc. The **N_2^+** group is called diazonium **$C_6H_5N_2^+CL^-$** group. For example, is

named as benzenediazoniumchloride and $C_6H_5N_2^+HSO^-_4$ is known as benzenediazonium hydrogensulphate



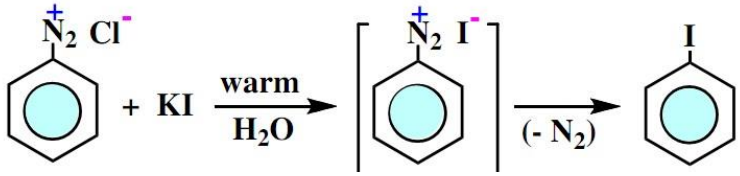
➔ **Replacement Reactions of Aryl Diazonium Salts**

Reaction of aryl diazonium salts with various reagents results in replacement of the diazonium group by other groups.

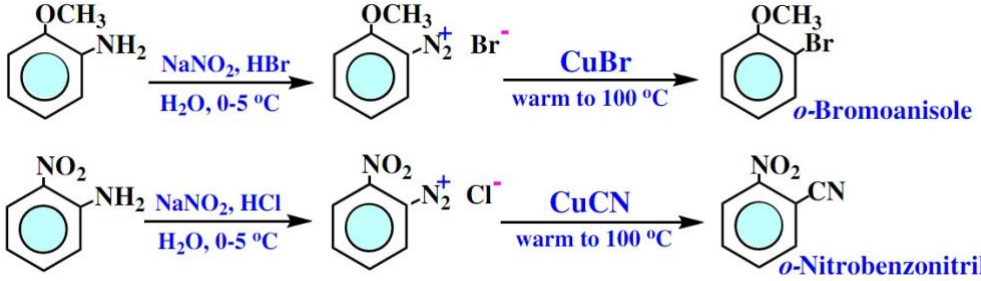


➔ **The Sandmeyer Reaction**

When an aqueous solution of benzenediazonium chloride and KI is allowed to warm to room temperature, the benzenediazonium iodide produced decomposes with liberation of N2 to give a good yield of iodobenzene.

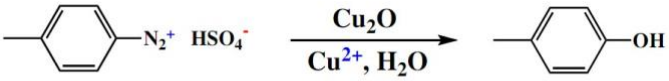


A similar reaction does not occur with the aryldiazonium chlorides and bromides. But in 1884, the Swiss chemist Traugott Sandmeyer discovered that replacement reactions are catalyzed by cuprous salts. With CuCl , CuBr, or CuCN added, replacement reactions occur as the diazonium salt is allowed to warm to room temperature.



➔ **Phenols via Aryldiazonium Salts**

The diazonium group can be replaced with a hydroxyl group by adding cuprous oxide to a dilute solution of the diazonium salt that contains a large excess of cupric nitrate:

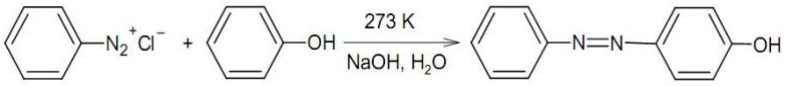


p-Toluenediazonium hydrogen sulfate

p-Cresol

➔ **Conversion to Azo Dyes: Coupling Reactions**

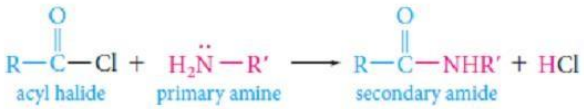
Arenediazonium salts are weak electrophiles and attack aromatic ring of highly activated compounds such as amines and phenols to yield azo compounds. This electrophilic aromatic substitution reaction is called diazo coupling and is shown below:

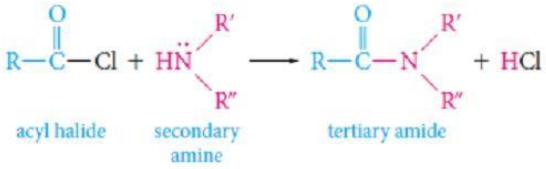


benezenediazonium chloride | benzenol (phenol) | 4-hydroxyazobenzene (orange)

➔ **Acylation of Amines: Amides Formation**

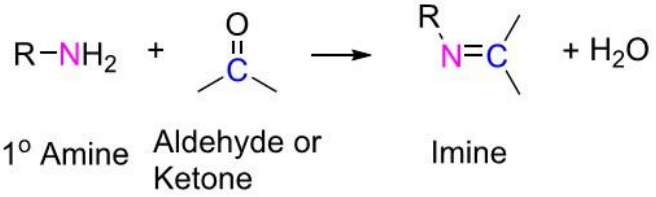
Primary and secondary amines react with acyl halides to form amides.

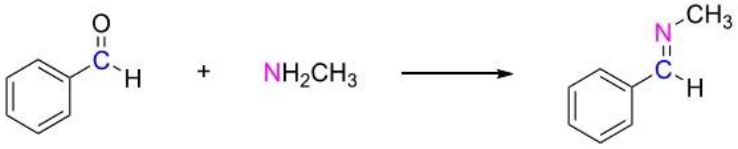


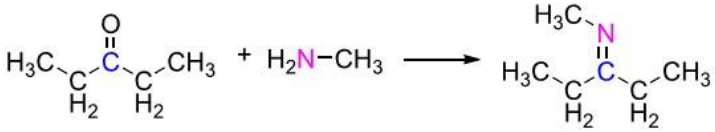


➔ **Imines Formation**

Primary amines, R-NH_2 or $ArNH_2$, undergo nucleophilic addition with aldehydes or ketones in an **acidic buffer** to give substituted imines.







Week 9

• **Lecture Title:** Aromatic Diazonium Salts
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the structure and bonding of aromatic diazonium salts.
2. To learn the nomenclature rules for naming aromatic diazonium salts systematically.
3. To study the common methods for preparing aromatic diazonium salts.
4. To examine the key chemical reactions involving aromatic diazonium salts (e.g., coupling reactions, Sandmeyer reactions, azo dye formation).
5. To explore the practical uses of aromatic diazonium salts in industry and research.

• **Behavioral Objectives:**

1- **Cognitive Domain:**

• The student will be able to describe the structure and electronic configuration of aromatic diazonium salts.
• The student will be able to apply nomenclature rules to name aromatic diazonium compounds correctly.
• The student will be able to explain the preparation methods of aromatic diazonium salts, including the diazotization reaction.
• The student will be able to outline major reactions involving diazonium salts and their mechanisms.
• The student will be able to discuss the applications of diazonium salts in dye synthesis and other industrial processes.

2- **Psychomotor Domain:**

• The student will be able to draw structural formulas of aromatic diazonium salts and reaction intermediates.
• The student will be able to write balanced chemical equations for preparation and reactions involving diazonium salts.

3- **Affective Domain:**

• The student will appreciate the significance of aromatic diazonium salts in organic synthesis and their contribution to industrial chemistry

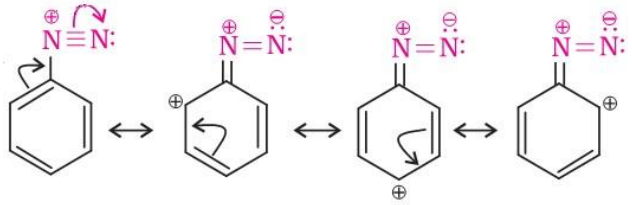
Week-9- : Theoretical

Aromatic Diazonium Slats

DIAZONIUM SALTS

☒ The diazonium salts have the general formula $RN_2^+X^-$ where R stands for an aryl group and X^- ion may be Cl^- ,Br- , HSO^-_4 , BF_4^- , etc. They are named by suffixing diazonium to the name of the parent hydrocarbon from which they are formed, followed by the name of anion such as chloride, hydrogensulphate, etc. The N_2^+ group is called diazonium $C_6H_5N_2^+CL^-$ group. For example, is named as benzenediazoniumchloride and $C_6H_5N_2^+HSO^-_4$ is known as benzenediazonium hydrogensulphate.

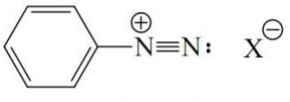
☒ Primary aliphatic amines form highly unstable alkyldiazonium salts (refer to Section 13.6). Primary aromatic amines form arenediazonium salts which are stable for a short time in solution at low temperatures (273-278 K). The stability of arenediazonium ion is explained on the basis of resonance.



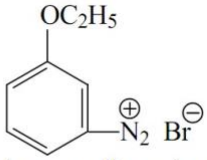
☒ **Benzenediazonium chloride** is prepared by the reaction of aniline with nitrous acid at 273-278K. Nitrous acid is produced in the reaction mixture by the reaction of sodium nitrite with hydrochloric acid. The conversion of primary aromatic amines into diazonium salts is known as diazotisation. Due to its instability, the diazonium salt is not generally stored and is used immediately after its preparation.

$$C_6H_5NH_2 + NaNO_2 + 2HCl \xrightarrow{273\text{-}278K} C_6H_5\overset{+}{N_2}\,\bar{Cl} + NaCl + 2H_2O$$

⌘ **Aromatic Diazonium Salts Named** by adding -diazonium to the name of the aromatic compound from which they are derived, followed by the anion name.



a diazonium salt

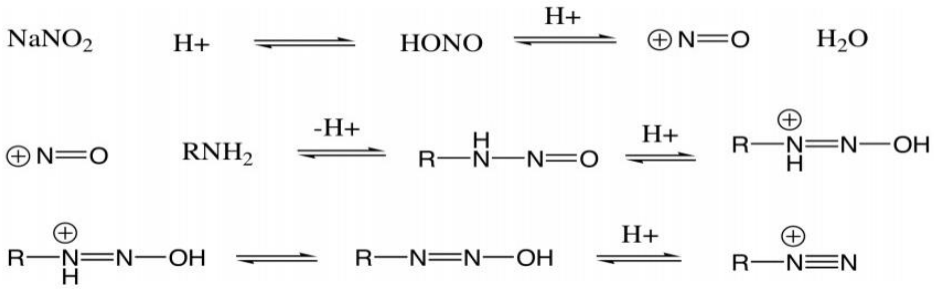


m-ethoxybenzenediazonium bromide

⌘ **Physical properties** :- Crystalline solids, soluble in water, explosive in solid state.

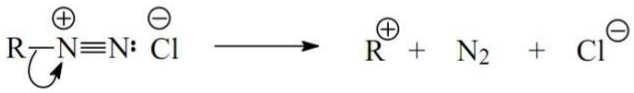
Preparation of Diazonium Salts

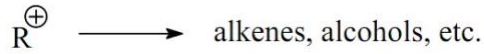
1) **Primary amines** will react with nitrous acid to form diazonium salts



The key step is that the nitrogen will leave to generate a carbocation!

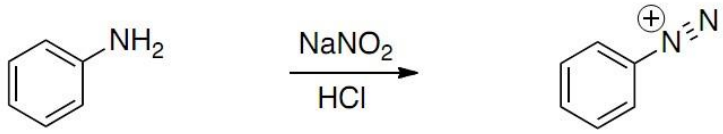
Primary aliphatic amines give diazonium salts but these compounds are unstable and decompose.



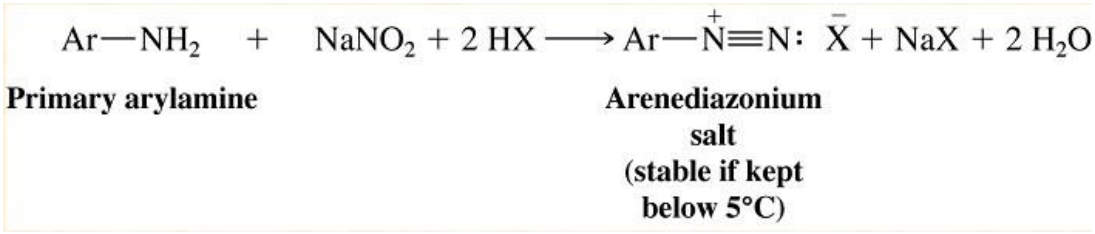


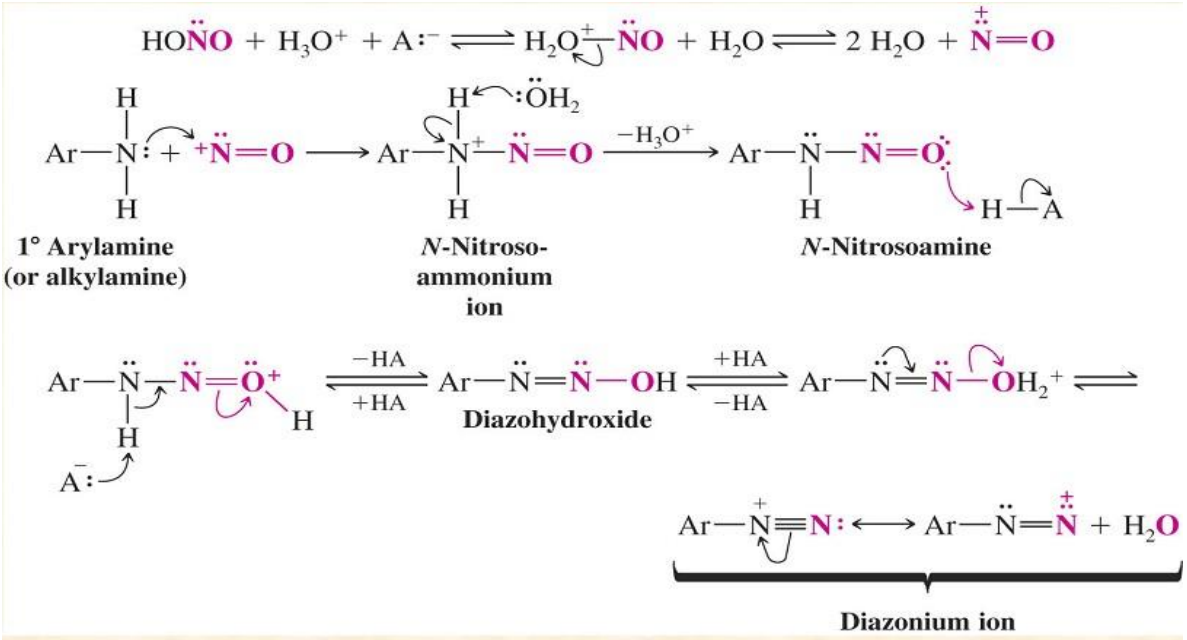
2) Arenediazonium Salts

While the generation of alkyl carbocations with this method is unnecessary ;(there are many other more efficient ways to generate alkyl carbocations), it is a unique method to generate aryl substituted products . First the arenediazonium salt is generated from an aniline derivative!



Primary aromatic amines give diazonium salts —





Reaction of Diazonium Salts

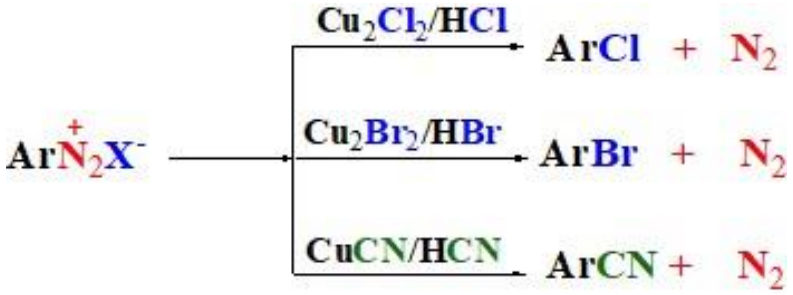
☒ Benzene diazonium chloride is a colorless crystalline solid. It is readily soluble in water and is stable in cold but reacts with water when warmed. It decomposes easily in the dry state.

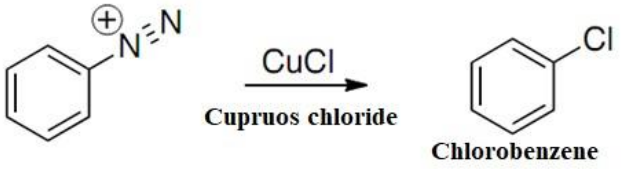
☒ Benzene diazonium fluoroborate is water insoluble and stable at room temperature. The reactions of diazonium salts can be broadly divided into two categories, namely (A) reactions involving displacement of **nitrogen** and (B) reactions involving retention of **diazo group**.

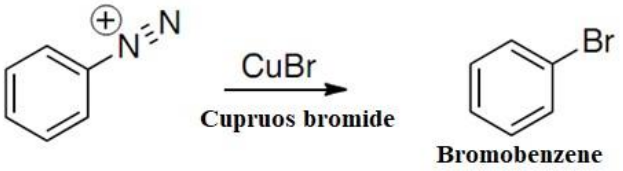
A. Reactions involving displacement of nitrogen

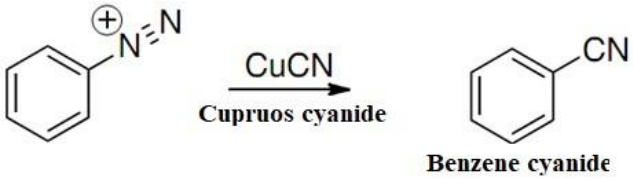
Diazonium group being a very good leaving group, is substituted by other groups such as Cl^- , Br^- , I^- , CN^- and OH^- which displace nitrogen from the aromatic ring. The nitrogen formed escapes from the reaction mixture as a gas.

1) **Replacement by halide or cyanide ion**: The Cl^-, $Br^-$and CN^- nucleophiles can easily be introduced in the benzene ring in the presence of Cu(I) ion. This reaction is called **Sandmeyer** reaction.

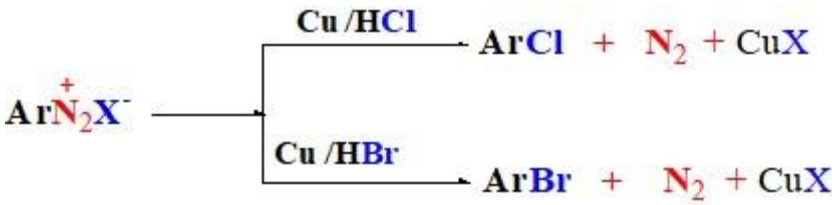








Alternatively, chlorine or bromine can also be introduced in thebenzene ring by treating the diazonium salt solution with corresponding halogen acid in the presence of copper powder. This is referred as **Gatterman** reaction.



2) **Replacement by iodide ion**: Iodine is not easily introduced into the benzene ring directly, but, when the diazonium salt solution is treated with potassium iodide, iodobenzene is formed.

3) **Replacement by fluoride ion**: When arenediazonium chloride is treated with fluoroboric acid, arene diazonium fluoroborate is precipitated which on heating decomposes to yield aryl fluoride.

$$ArN_2^+Cl^- + HBF_4 \longrightarrow Ar-N_2^+BF_4^- \xrightarrow{\Delta} Ar-F + BF_3 + N_2$$

4) **Replacement by H**: Certain mild reducing agents like hypophosphorous acid (phosphinic acid) or ethanol reduce diazonium salts to arenes and themselves get oxidised to phosphorous acid and ethanal, respectively.

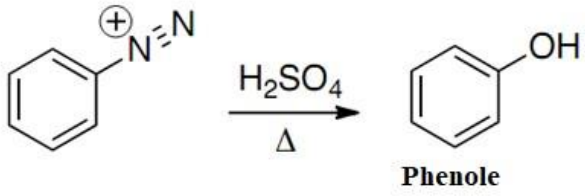
$$ArN_2^+Cl^- + H_3PO_2 + H_2O \longrightarrow ArH + N_2 + H_3PO_3 + HCl$$

$$ArN_2^+Cl^- + CH_3CH_2OH \longrightarrow ArH + N_2 + CH_3CHO + HCl$$

5) **Replacement by hydroxyl group**: If the temperature of the diazonium salt solution is allowed to rise up to 283 K, the salt gets hydrolysed to phenol.

$$ArN_2^+Cl^- + H_2O \longrightarrow ArOH + N_2 + HCl$$

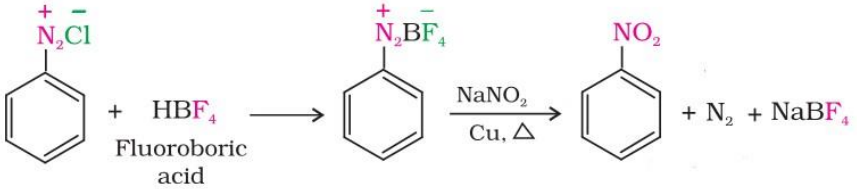
The nitrogen leaving group (N_2) can then be replaced in a second step. Example of unique potential products:



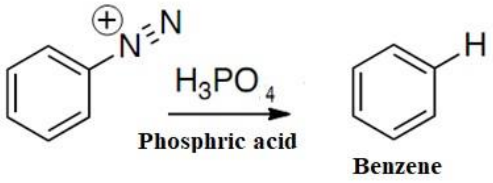
Phenole

Convenient method to generate phenol derivatives , (other method is usually a nucleophilic aromatic substitution) . It is difficult to generate an oxygen electrophile to perform a typical electrophilic aromatic substitution!

6) **Replacement by –NO2 group**: When diazonium fluoroborate is heated with aqueous sodium nitrite solution in the presence of copper, the diazonium group is replaced by $–NO_2$ group.



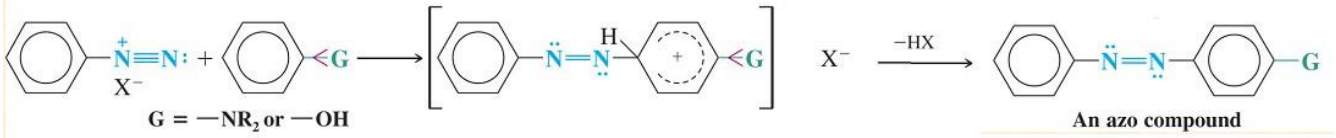
7) Replacing Diazonium group with Hydrogen

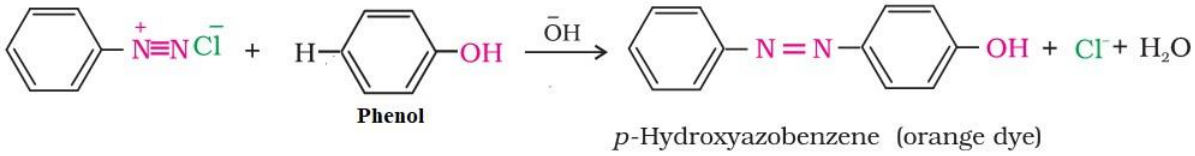


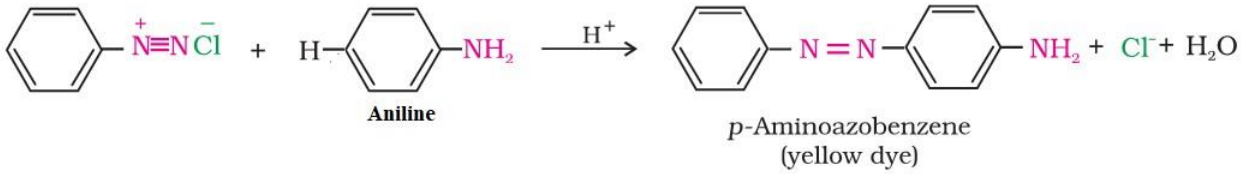
B. Reactions involving retention of diazo group coupling reactions @@@

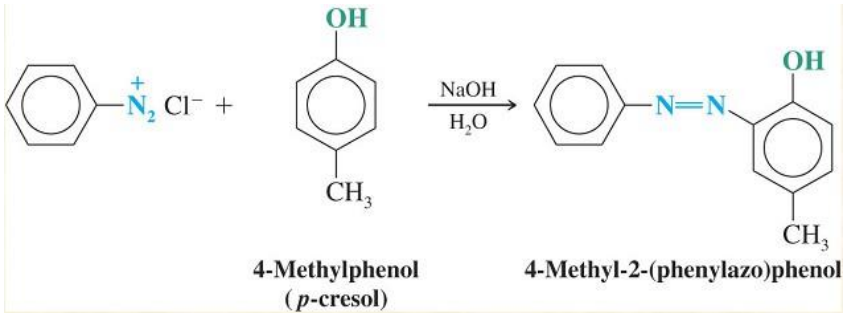
- The azo products obtained have an extended conjugate system having both the aromatic rings joined through the –N=N– bond. These compounds are often coloured and are used as dyes.
- Benzene diazonium chloride reacts with phenol in which the phenol molecule at its para position is coupled with the diazonium salt to formp-hydroxyazobenzene.
- This type of reaction is known as coupling reaction. Similarly the reaction of diazonium salt with aniline yields p-aminoazobenzene. This is an example of electrophilic substitution reaction.

General Reaction









Week 10

• **Lecture Title:** Ethers
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structure and classification of ethers (simple vs. mixed; symmetrical vs. asymmetrical).
2. To learn the IUPAC and common naming rules for ethers.
3. To study the physical properties of ethers, such as boiling point, solubility, and polarity.
4. To examine the chemical reactivity of ethers, including cleavage by strong acids and oxidation reactions.
5. To explore the laboratory and industrial significance of ethers, including their use as solvents and anesthetics.

• **Behavioral Objectives:**

1- **Cognitive Domain:**

• The student will be able to describe the molecular structure and classification of ethers.
• The student will be able to name ethers using both IUPAC and common nomenclature.
• The student will be able to explain the physical properties of ethers and the factors that influence them.
• The student will be able to outline and explain the main chemical reactions of ethers.
• The student will be able to discuss the practical applications of ethers in pharmaceutical and chemical industries.

2- **Psychomotor Domain:**

• The student will be able to draw structural formulas of various ethers.
• The student will be able to write balanced chemical equations involving reactions of ethers.

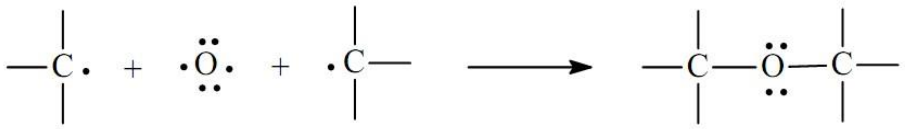
3- **Affective Domain:**

• The student will appreciate the importance of ethers in both academic chemistry and real-world applications.

Week-10- Theoretical

Ethers

- Ethers are hydrocarbon derivatives containing a carbon-oxygen-carbon (C-O-C) fragment. Recall that carbon has a valence of four and thus requires four electrons or bonds to achieve an octet in its neutral state. Oxygen has a valence of six and thus requires two electrons or bonds to achieve an octet in its neutral state. In ethers there is a single oxygen atom bound to two carbons; in this bonding arrangement oxygen maintains two pairs of non-bonded electrons (NBEs) as is typical for oxygen in the neutral (uncharged) state:



- Ethers are organic compounds in which an oxygen atom is bonded to two alkyl groups or aryl groups. Thus, ethers can be represented as R O R' where R and R' may be alkyl or aryl groups. When the two substituent groups (R and R') are identical, then the ether is called a symmetrical ether, otherwise if these two groups are different, then the ether is known as an unsymmetrical ether.

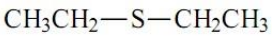
A symmetricalether **An unsymmetrical ether**

- The oxygen atom of the ether can also be part of a ring, in which case the ether is known as a cyclic ether. Tetrahydrofuran is one such cyclic ether which is used as a solvent.

Tetrahydrofuran (THF)

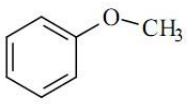
- Ethers are commonly used as solvents for organic reactions. The symmetrical ether shown above is diethyl ether and is commonly also referred to simply as ether because of its wide use as a solvent for reactions and extraction of organic compounds. It was also used as an anaesthetic for over hundred years.
- **Ethers can be classified** as aliphatic saturated or unsaturated, cycloaliphatic, aromatic, etc. as shown below. Thioethers are simple ether derivatives where the oxygen replaced by sulfur (note sulfur is in the same atomic "family" as oxygen). Thioethers display reactivity profiles similar to ethers, but generally are more reactive due to the presence of a less electronegative and "larger" (more polarizable) sulfur atom.

Saturated Aliphatic **Unsaturated Aliphatic**



Saturated Aliphatic Thioether

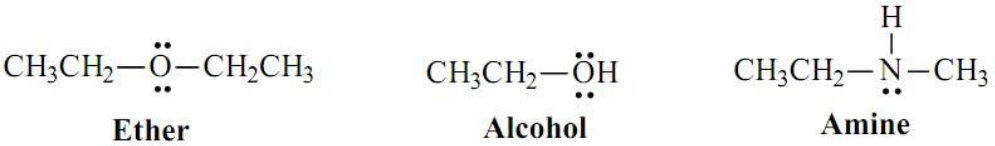
Cycloaliphatic



Aromatic

- Ethers can be considered to structural analogues of alcohol in which the hydroxyl hydrogen has been replaced with a second hydrocarbon substituent. This structural difference results in significantly different properties. Ethers also are structurally related to amines which are

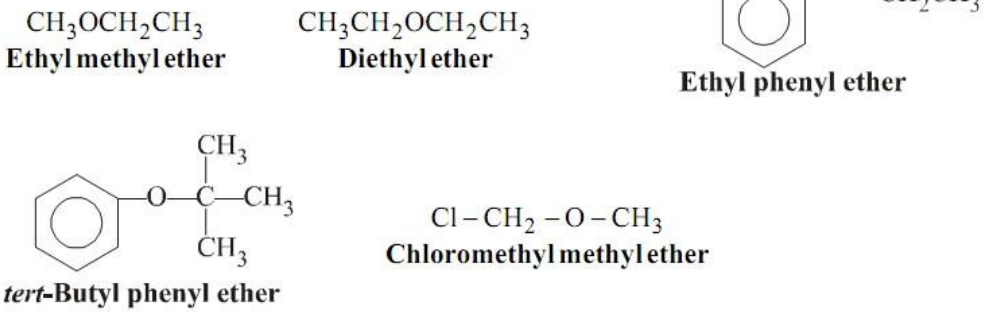
hydrocarbons containing at least one C-N. However, because of the electronegativity difference between oxygen and nitrogen, ethers and amines have very different physicochemical properties and reactivity profiles, as discussed below.



Ether **Alcohol** **Amine**

Nomenclature of Ethers

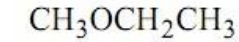
A. Common names of ethers are arrived by alphabetically naming the two groups attached to the oxygen followed by the word ether. The common names for some ethers are given below :



Ethyl methyl ether **Diethyl ether** **Ethyl phenyl ether**

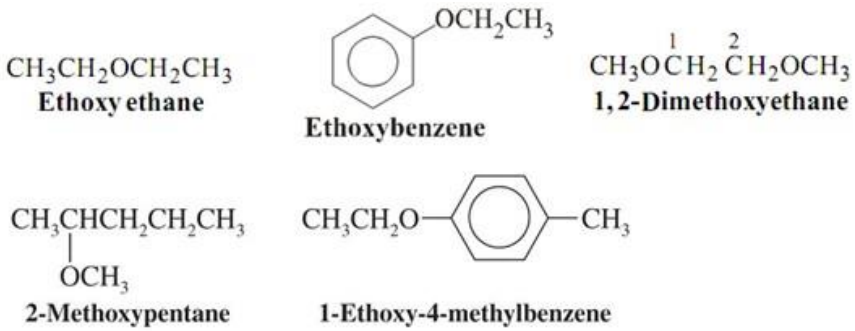
***tert*-Butyl phenyl ether** **Chloromethyl methyl ether**

B. In IUPAC nomenclature, the larger alkyl (or aryl) group is used as the root name as the alkane and the smaller alkyl group is treated as an alkoxysubstituent on this alkane. For example, in ethyl methyl ether having ethyl and methyl groups, the ethyl group is larger than methyl group and hence this ether is treated as the ethane derivative.



Ethyl methyl ether

C. The remaining portion , i.e, OCH_3 part in this case, is called the methoxy substituent. Hence, the above ether is called methoxyethane. Some more examples of IUPAC names of ethers are given below :



Ethoxy ethane **Ethoxybenzene** **1,2-Dimethoxyethane**

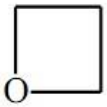
2-Methoxypentane **1-Ethoxy-4-methylbenzene**

D. Cyclic ether

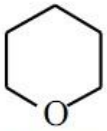
1) Cyclic ethers can be named using the prefix oxa- 2) Three-membered ring ethers can be called oxiranes.

3) Four-membered ring ethers can be called oxetanes

Oxacyclopropane or oxirane (ethylene oxide)

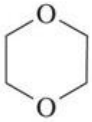


Oxacyclobutane or oxetane



tetrahydropyran
oxane

Oxacyclopentane (tetrahydrofuran)
oxolane



1,4-Dioxacyclohexane (1,4-dioxane)

Physical Properties

1) The C-O bonds in ethers are polar and thus, ethers have a net dipole moment. The weak polarity of ethers do not appreciably affect their boiling points which are comparable to those of the alkanes of comparable molecular masses but are much lower than the boiling points of alcohols as shown in the following cases:

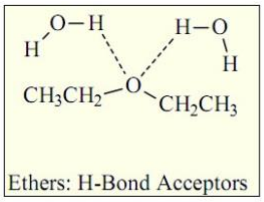
2)

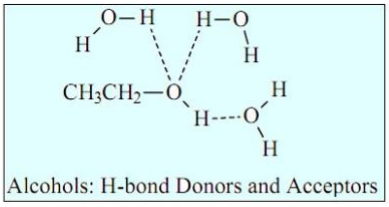
Formula	$CH_3(CH_2)_3CH_3$ n-Pentane	C_2H_5-O-C_2H_5 Ethoxyethane	$CH_3(CH_2)_3$-OH Butan-1-ol
b.p./K	309.1	307.6	390

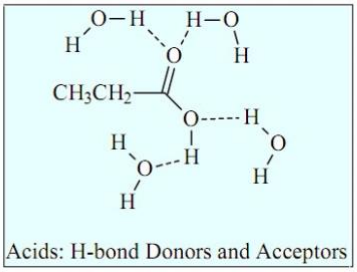
3) The large difference in boiling points of alcohols and ethers is due to the presence of hydrogen bonding in alcohols.

4) The miscibility of ethers with water resembles those of alcohols of the same molecular mass. Both ethoxyethane and butan-1-ol are miscible to almost the same extent i.e., 7.5 and 9 g per 100 mL water, respectively while pentane is essentially immiscible with water. Can you explain this observation ?

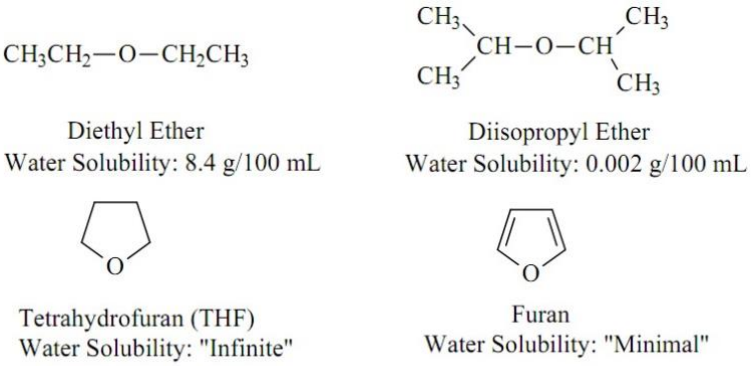
5) Ethers are less water soluble than corresponding alcohols, acids or like compounds. Alcohols and acids can both donate and accept hydrogen bonds from water, and may form more hydrogen bonds with water due to the presence of both C-O and O-H dipoles. Ethers contain on C-O dipoles and thus can only accept hydrogen bonds from water and not donate hydrogen bonds. For these reasons ethers are less water soluble than alcohols and other organic compound containing more polar functionality:



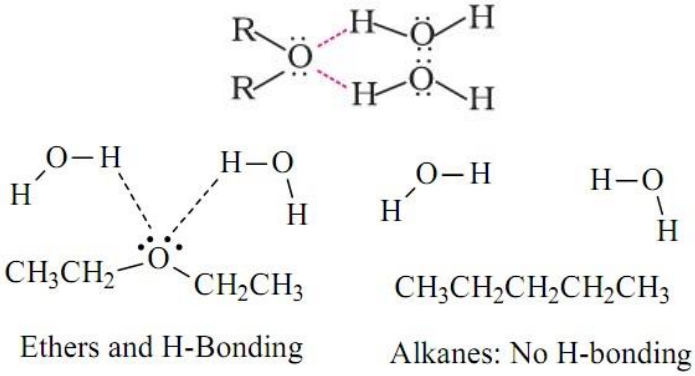




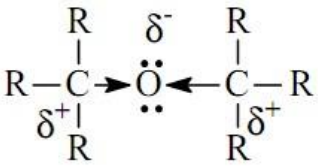
6) solubility rapidly decreases as the total hydrocarbon content of ethers increase. This is illustrated by comparison of the water solubilities of diethyl ether to diisopropyl ether:



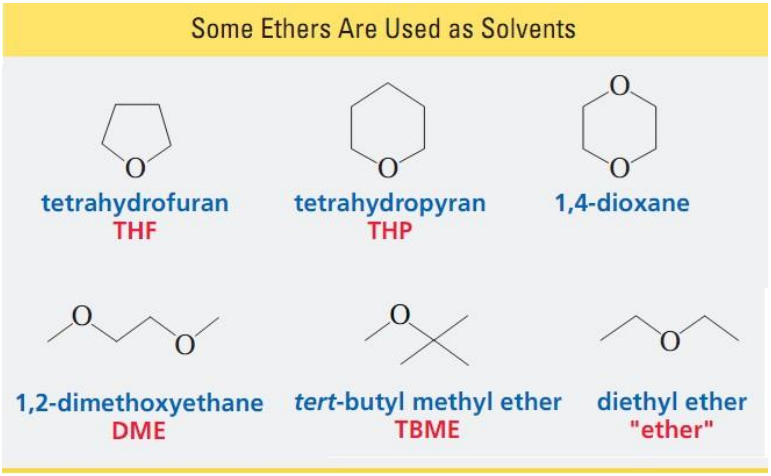
7) Because of the presence of this dipole, ethers have the ability to act as hydrogen bond acceptors and thus they display higher solubility in polar solvents such as water than corresponding hydrocarbons.



8) Since oxygen is significantly more electronegative than carbon, ether linkages are dipolar – a negative oxygen dipole linked to two positive carbon dipoles:



9) Because hydrogen halides are the only reagents that react with ethers, ethers are frequently used as solvents. Some common ether solvents are shown in Table .



Preparation of Ethers:

1. General Methods of Preparation

You have already studied under the reactions of alcohols that ethers can be obtained by the dehydration of alcohols. Ethers can also be prepared by Williamson synthesis which is explained below :

Williamson Synthesis : It involves the reaction of a metal alkoxide with a primary alkyl halide. The metal alkoxide is prepared by adding sodium or potassium metal or sodium hydride (NaH) to the alcohol. Williamson synthesis involves the displacement of the halide ion by the alkoxide ion.

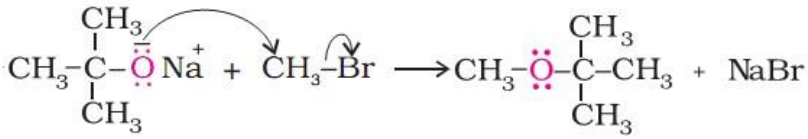
General reaction

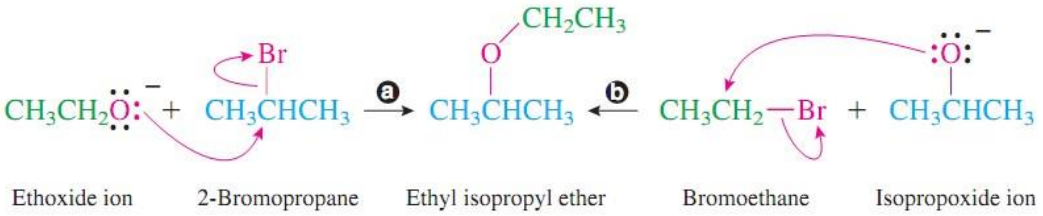
$$ROH + Na \longrightarrow \underset{\text{Metal alkoxide}}{RO^-Na^+} + \frac{1}{2}H_2$$

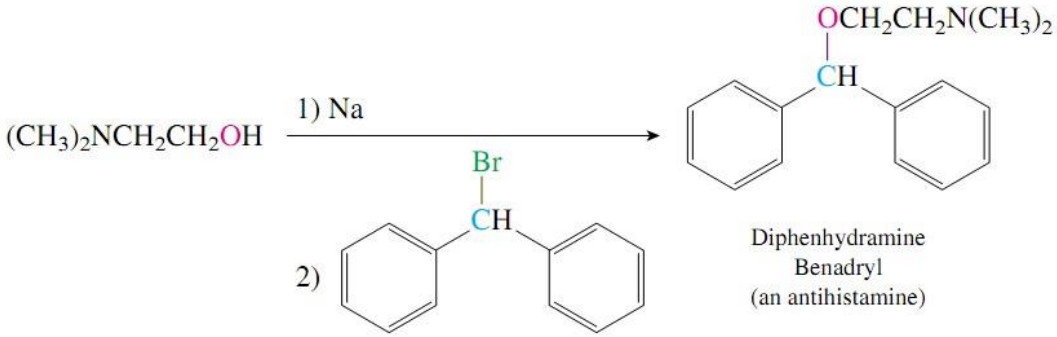
$$ROH + NaH \longrightarrow \underset{\text{Metal alkoxide}}{RO^-Na^+} + H_2$$

$$\underset{\text{Metal alkoxide}}{RO^-Na^+} + \underset{\text{Alkyl halide}}{R'-X} \longrightarrow \underset{\text{Ether}}{R-O-R'} + NaX$$

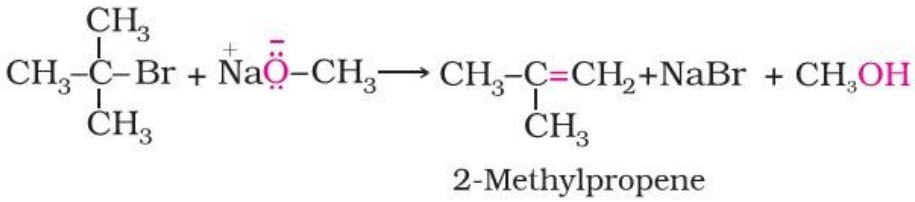
$$\underset{\text{propan-1-ol}}{CH_3CH_2CH_2OH} + NaH \longrightarrow \underset{\text{Sodium propoxide}}{CH_3CH_2CH_2ONa} \xrightarrow{CH_3CH_2I} \underset{\text{1-Ethoxypropane (Ethyl propyl ether)}}{CH_3CH_2CH_2OCH_2CH_3} + NaI$$







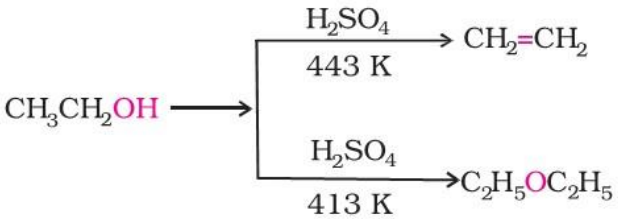
☒ **secondary and tertiary alkyl halides** gives an alkene is the only reaction product and no ether is formed.



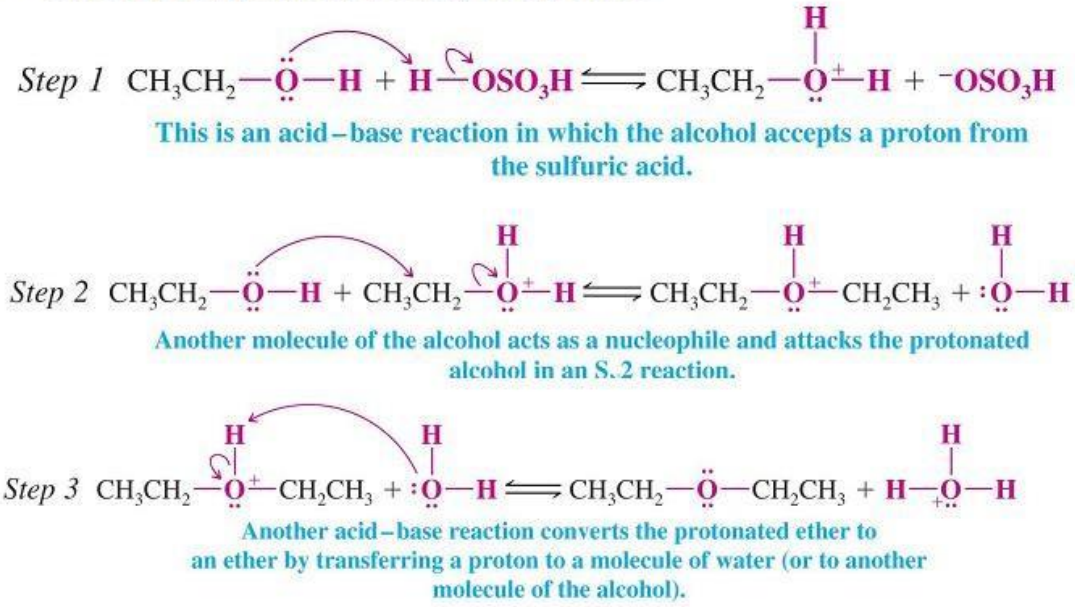
2. By dehydration of alcohols

Alcohols undergo dehydration in the presence of protic acids (H_2SO_4, H_3PO_4). The formation of the reaction product, alkene or ether depends on the reaction conditions. For example, ethanol dehydrated to ethene in the presence of sulphuric acid at 443 K [170°C]. At 413 K [140°C], ethoxyethane is the main product.

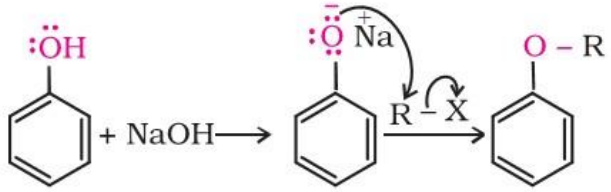
1. Primary alcohols can dehydrate to ethers this reaction occurs at lower temperature
2. This method generally does not work with 2° or 3° alcohols because elimination competes strongly



▪ **The mechanism is an S_N2 reaction**



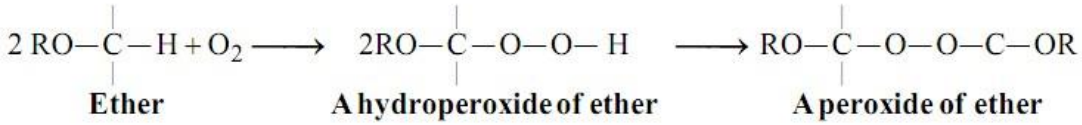
3. **Phenols are also converted to ethers** by this method. In this, phenol is used as the phenoxide moiety.



Reactions of Ethers

Ethers are normally unreactive in nature. Their unreactivity makes them good solvents.However, they show some reactions which are discussed below :

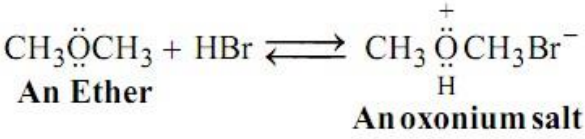
1. Reaction with Oxygen : Ethers slowly react with oxygen to form hydroperoxides and peroxides.



Peroxides have a tendency to explode. Therefore, one should be very careful in handling ethers which may have been stored for sometime because they may contain some peroxide.

2. Reaction with Acids

Since the oxygen atom of ethers contains lone pairs of electrons, they can accept a proton from the acids. Thus, ethers are basic in nature.

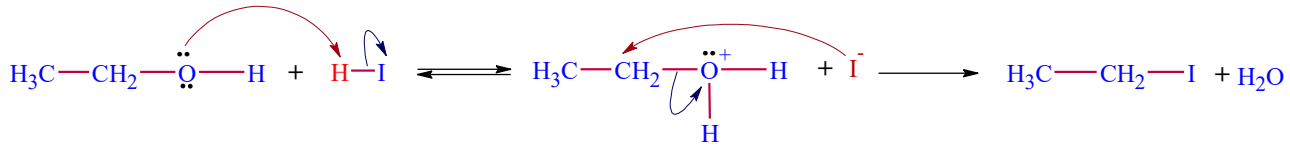


3. Acidic Cleavage

1) Heating dialkyl ethers with strong acids such as HI, HBr or H_2SO_4 leads to their cleavage.

$$CH_3CH_2OCH_2CH_3 + HBr \longrightarrow CH_3CH_2Br + CH_3CH_2OH$$

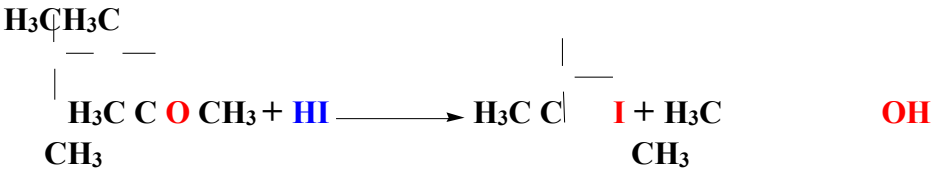
Ethoxyethane **Bromoethane** **Ethanol**



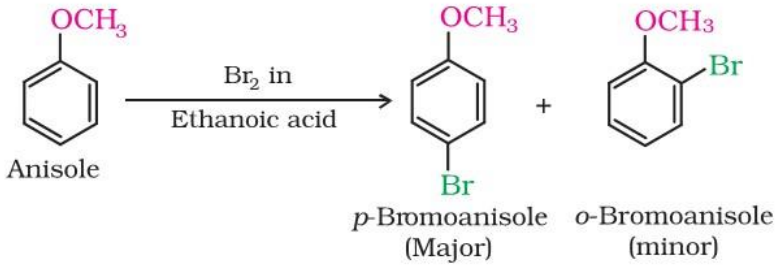
The alcohol formed further reacts with additional HBr to give bromoethane. Hence,

$$CH_3CH_2OCH_2CH_3 + 2HBr \longrightarrow 2CH_3CH_2Br + H_2O$$

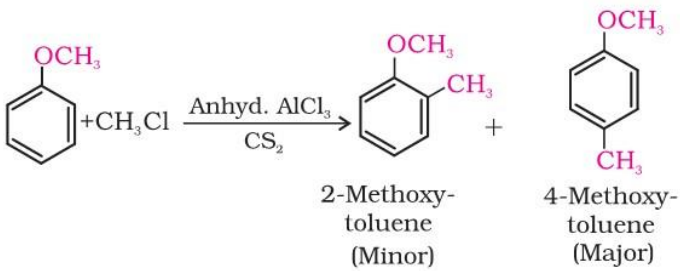
2) In case of ethers having primary or secondary alkyl groups, the nucleophile (Br^- or I^-)
3) However, when one of the alkyl group is a tertiary group, the halide formed is a tertiary halide.

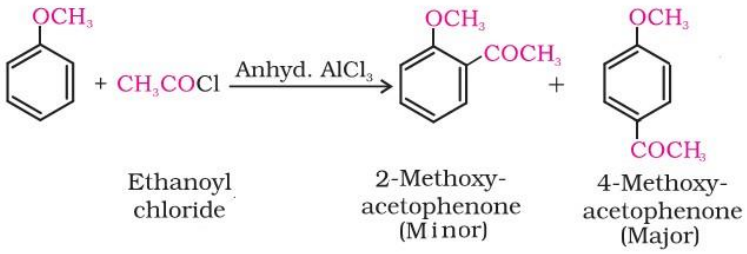


4. **Halogenation**: Phenylalkyl ethers undergo usual halogenation in the benzene ring, e.g., anisole undergoes bromination with bromine in ethanoic acid even in the absence of iron (III) bromide catalyst. It is due to the activation of benzene ring by the methoxy group. Para isomer is obtained in 90% yield.

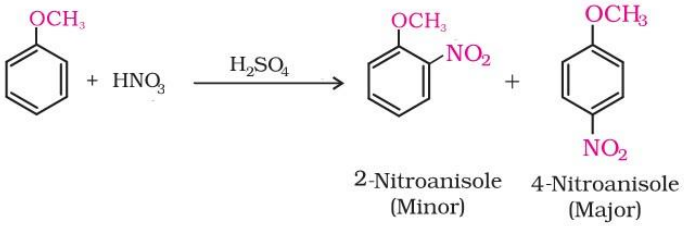


5. Friedel -Crafts reaction: Anisole undergoes Friedel-Crafts reaction, i.e., the alkyl and acyl groups are introduced at ortho and para positions by reaction with alkyl halide and acyl halide in the presence of anhydrous aluminium chloride (a Lewis acid) as catalyst.



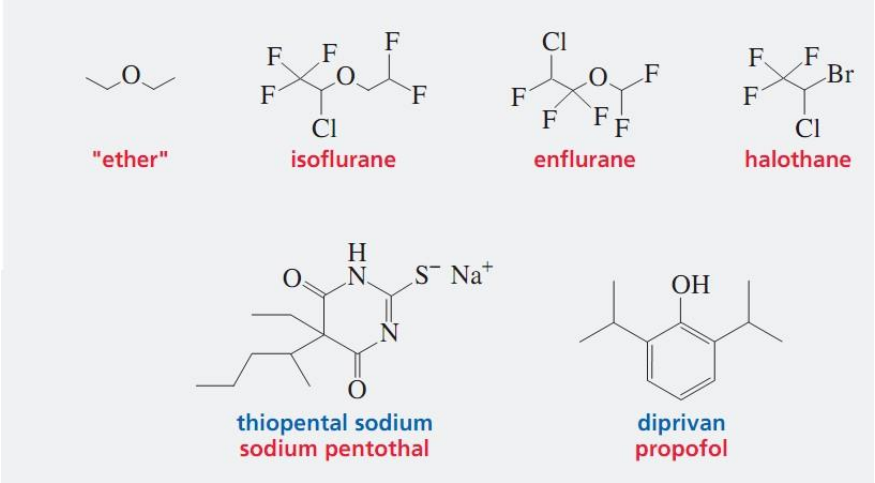


6. **Nitration:** Anisole reacts with a mixture of concentrated sulphuric and nitric acids to yield a mixture of ortho and para nitroanisole.



Anesthetics

1. Because **diethyl ether** (commonly known as ether) is a short-lived muscle relaxant, it was at one time widely used as an inhalation anesthetic.
2. However, it takes effect slowly and has a slow and unpleasant recovery period so, over time, other anesthetics, such as **isoflurane**, **enflurane**, and **halothane,** replaced it. Even so, **diethyl ether** is still used where trained anesthesiologists are **scarce** because it is the safest anesthetic for an untrained person to administer.
3. Anesthetics interact with the **nonpolar molecules** of cell membranes, causing the membranes to swell, which interferes with their permeability.
4. **Sodium pentothal** (also called thiopental sodium) is an intravenous anesthetic. The onset of anesthesia and the loss of consciousness occur within seconds of its administration. Care must be taken when administering sodium pentothal because the dose for effective anesthesia is 75% of the lethal dose.
5. Because of this **high level of toxicity**, it cannot be used as the sole anesthetic but, instead, is generally used to **induce anesthesia** before an inhalation anesthetic is administered.
6. **Propofol,** in contrast, has all the properties of the "**perfect anesthetic":** it can be administered as the sole anesthetic by **intravenous drip**, it has a rapid and pleasant induction period, and it has a **wide margin** of safety in trained hands. Recovery from the drug is also rapid and pleasant.



Week 11

• **Lecture Title:** Esters
• **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structure and classification of esters.
2. To learn systematic (IUPAC) and common naming rules for esters.
3. To study the major reactions involving esters (e.g., hydrolysis, esterification, transesterification, reduction).
4. To explore the role of esters in biological systems, pharmaceuticals, and industry.

• Behavioral Objectives:

1- **Cognitive Domain:**
• The student will be able to describe the molecular structure and functional group of esters.
• The student will be able to apply IUPAC rules to name esters correctly.
• The student will be able to explain the mechanisms of esterification and hydrolysis reactions.
• The student will be able to discuss the importance of esters in both natural and synthetic compounds.

2- **Psychomotor Domain:**
• The student will be able to draw the structural formulas of esters and related reactants/products.
• The student will be able to write balanced equations for key ester reactions.

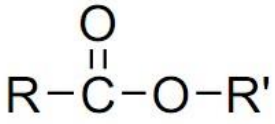
3- **Affective Domain:**
• The student will appreciate the significance of esters in organic chemistry and their applications in pharmaceuticals and flavor industries.

Week-11- Theoretical

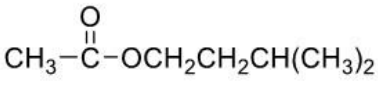
Esters

Introduction

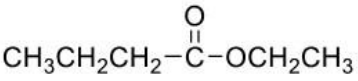
Structurally, an ester is a compound attached to the **carbonyl group**.



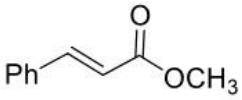
R may be **H**, **alkyl** or **aryl**, while **R'** may be **alkyl** or **aryl** only. Esters are widespread in nature. Many of the **fragrances** of **flowers** and **fruits** are due to the esters present. Ethyl butanoate is the chief component that accounts for the pineapple-like aroma and flavour of pineapples.



Isopentyl ethanoate
(Banana aroma)

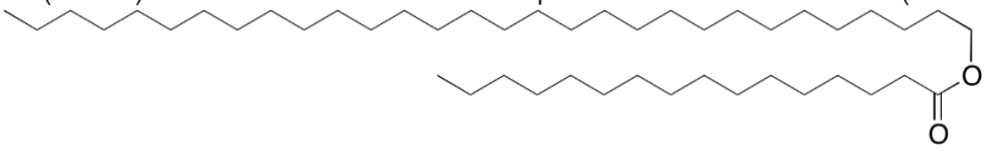


Ethyl butanoate
(Pineapple aroma)

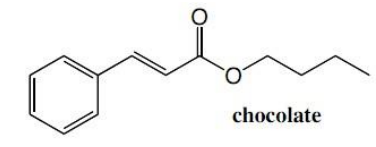


Methyl *trans*-cinnamate
(Strawberry aroma)

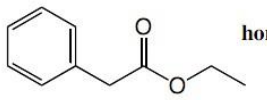
1. **Esters are the products** of the combination of carboxylic acids with alcohols, Esters are widely spread in nature, They are present in all **plant** and animal organisms, Most of the esters are characterized by a pleasant smell which is responsible for the **odour** and **flavour** of fruits and flowers.
2. **Many organic esters** have been prepared for the commercial production of **perfumes** and **flavours,** They are used either alone or mixed with natural compounds, The **odour** of the **ester decreases** by the **increase of the molecular** weight of the **alcohol** and acid used for their formation.
3. **The nature of the ester** changes from a **liquid with a pleasant odour** to a **waxy solid which is nearly odourless**, waxes such as **bees wax** are high molecular weight esters, Fats and oils are esters derived from glycerol which is trihydric **alcohol** and high fatty acids .
4. **Bees wax** An approximate chemical formula for beeswax is $C_{15}H_{31}COOC_{30}H_{61}$. beeswax has a relatively low melting point range of 62 to 64 °C (144 to 147 °F). If beeswax is heated above 85 °C (185 °F) discoloration occurs. The flash point of beeswax is 204.4 °C (400 °F)



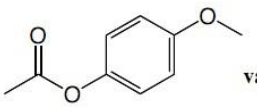
5. Many of the compounds that contribute to the **flavors** and aromas in **fruits** and **flowers are esters**. Natural flavors and aromas result from complex mixtures of many compounds, esters being a large component.
6. The **natural orange aroma** consists of 30 different esters, **10 carboxylic acids**, **34 alcohols**, **34 aldehydes** and **ketones,** and **36 hydrocarbons**.



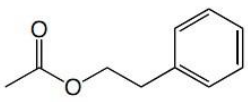
chocolate



honey



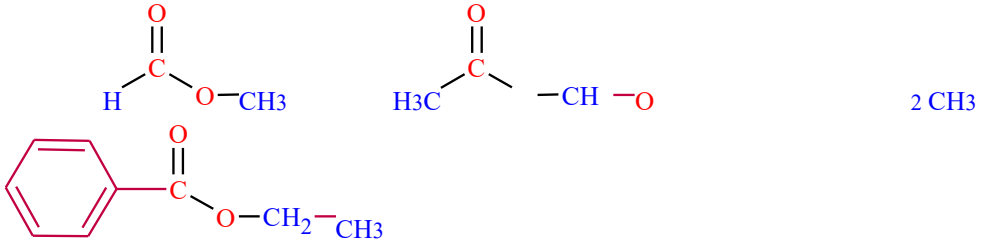
vanilla



caramel

Nomenclature of Esters

1. The name of an ester is derived from the name of the acid radical and the name of the **alkyl group** of the **alcohol** such as

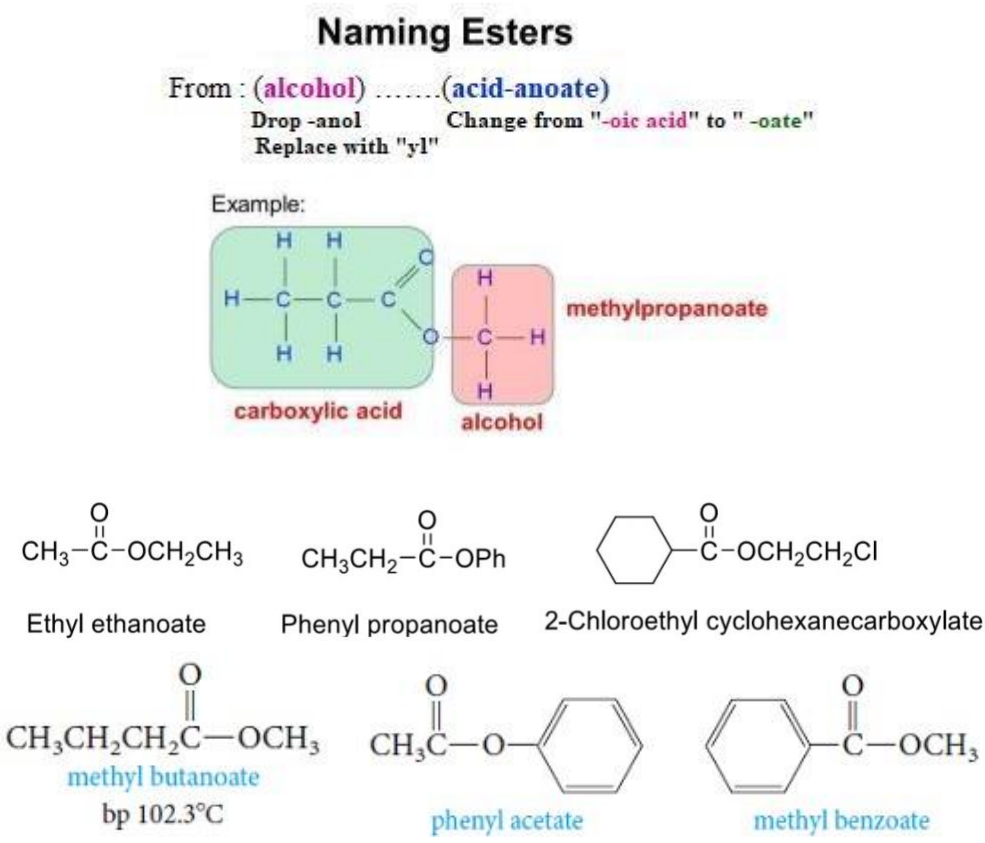


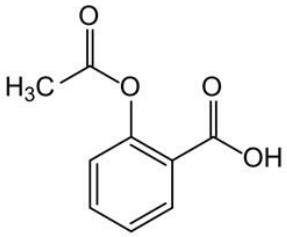
Methyl Formate | Ethyl Acetate | Ethyl Benzoate

Methyl formate $HCOOCH_3$ | Ethyl acetate $CH_3COOCH_2CH_3$ | Ethyl benzoate $C_6H_5COOC_2H_5$.

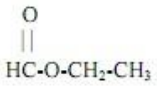
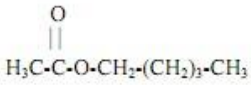
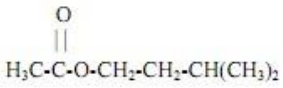
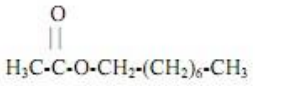
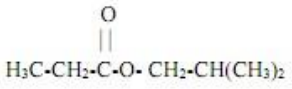
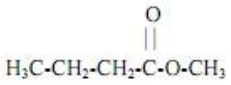
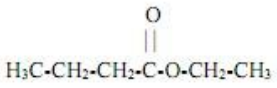
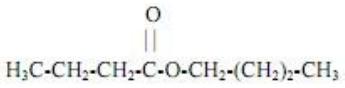
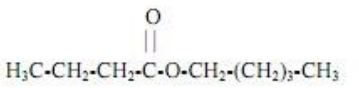
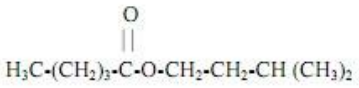
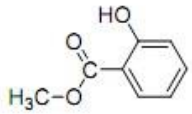
2. The **first word** is derived from the **alkyl group** of the **alcohol component**, and the **second word** from the **carboxylate group** of the the **ester**.

1. The name of the carboxylate portion is derived by substituting the **-ic acid suffix** of the parent carboxylic acid with the **–ate suffix**.
2. The **alkyl group is cited first** followed by the **carboxylate group separated by a space**. An ester is thus named as an **alkyl alkanoate**.





Acetylsalicylic acid
2-acetoxybenzoic acid
Aspirin

Formula	Common name	IUPAC name	Flavor/odor
	ethyl formate	ethyl methanoate	rum
	n-amyl acetate	pentyl ethanoate	pears, bananas
	isoamyl acetate	3-methylbutyl ethanoate	pears, bananas
	n-octyl acetate	octyl ethanoate	oranges
	isobutyl propionate	2-methylpropyl propanoate	rum
	methyl butyrate	methyl butanoate	apples
	ethyl butyrate	ethyl butanoate	pineapples
	n-butyl butyrate	butyl butanoate	pineapples
	n-amyl butyrate	pentyl butanoate	apricots
	isoamyl valerate	3-methylbutyl butanoate	apples
	methyl salicylate	methyl 2-hydroxybenzoate	oil of wintergreen

Physical properties

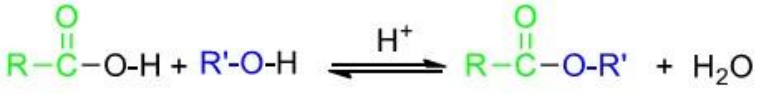
1. Most of the **esters are liquids** with **much lower boiling point** than those of the **acids or** alcohols of nearly **equal weight**, this is due to the absence of the **polar hydroxyl group** which found
in **alcohols** and **acids** and leads to the association of the alcohol and carboxylic acid molecules with **hydrogen bonds**, Esters have a **neutral effect on litmus.**

2. The **boiling point of the ester** is **less than the boiling point** of the **acid and alcohol** forming it due to the absence of **polar hydroxyl group (presents in alcohols and acids)** which has the ability to form **hydrogen bonds** between molecules and water.
3. The **solubility degree** of ester in water is **less than that of the corresponding acid** due to the absence of **polar hydroxyl group** (presents in alcohols and acids) which has the ability to **form hydrogen bonds** between molecules and water.

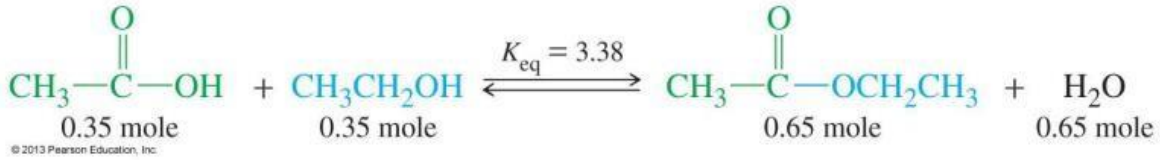
Ester name	B.P/°C	Ester name	B.P/°C	Ester name	B.P/°C
Methyl butyrate	102	n-butyl butyrate	156.9	Methyl benzoate	199
Ethyl butyrate	121.9	n-amyl butyrate	179	Methyl salicylate	223
n-amyl acetate	142	n-octyl acetate	199	Ethyl benzoate	213
Methyl propanoate	80	Methyl butanoate	102	Methyl pentanoate	126
Methyl hexanoate	151	Ethyl methanoate	54	Ethyl ethanoate	77

Preparation of ester

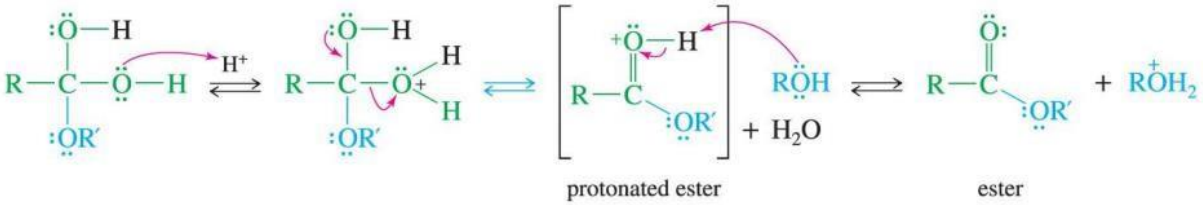
1. **Esterification** an **alcohol** with a **carboxylic acid** will produce no **ester**. A strong-acid catalyst such as sulfuric acid is required. Even then the reaction is an equilibrium and so does not go to completion. The overall transformation is that the -OH of an acid is replaced by the -OR' of an alcohol.

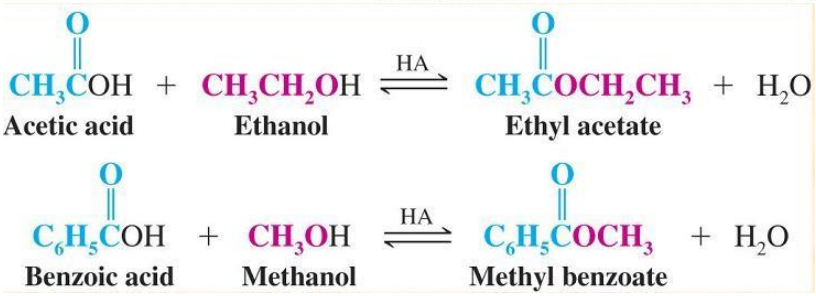


Esterification reactions such as this one are equilibrium reactions, and the equilibrium normally will lie to the left.



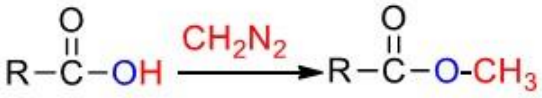
The ester is produced via acid catalyzed dehydration of the ester hydrate. As usual, the hydroxyl oxygen is protonated, thus creating a good leaving group.



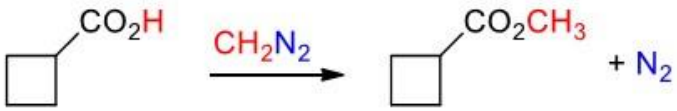


2. Esterification using Diazomethane

The addition of an ethereal solution of diazomethane smoothly converts carboxylic acids to their methyl esters.

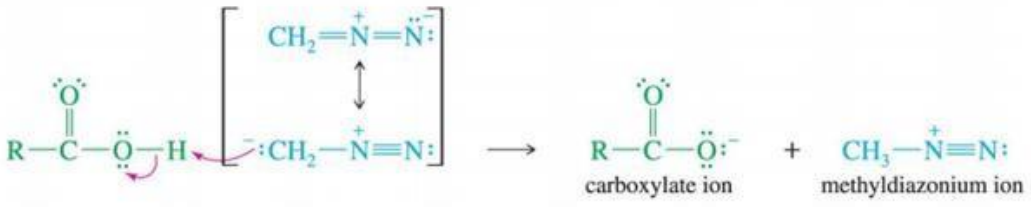


The only by-product is nitrogen gas.



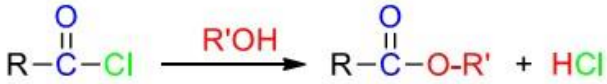
Diazomethane is a toxic, explosive yellow gas that dissolves in ether, and requires special glassware .

Step 1: Proton transfer, forming a carboxylate ion and a methyldiazonium ion.

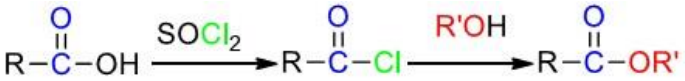


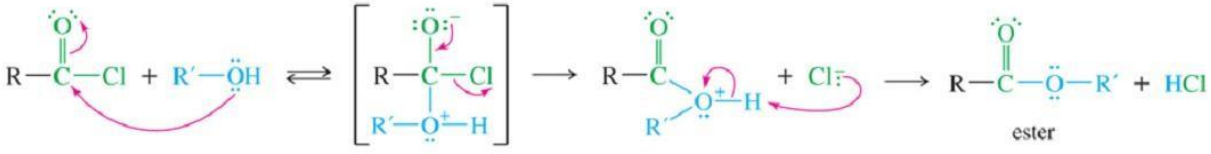
Step 2: Nucleophilic attack on the methyl group displaces nitrogen.

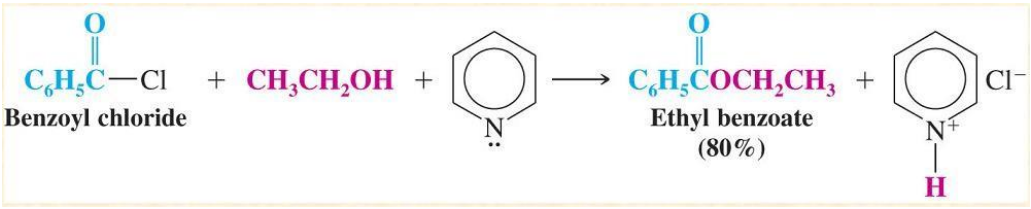
3. **Esterification using Acid chlorides** : Acid chlorides react with alcohols to give esters through a nucleophilic acyl substitution by the addition elimination mechanism.

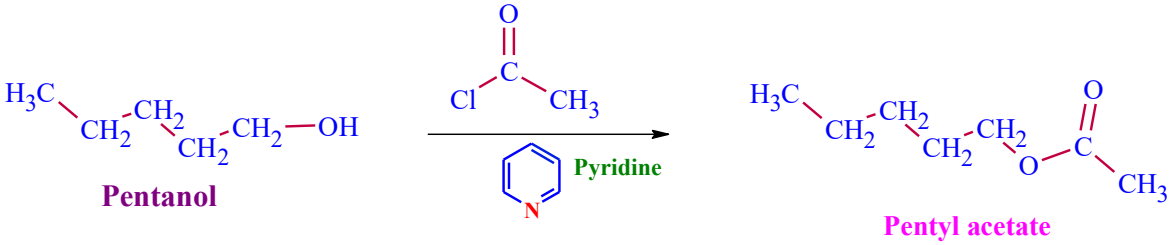


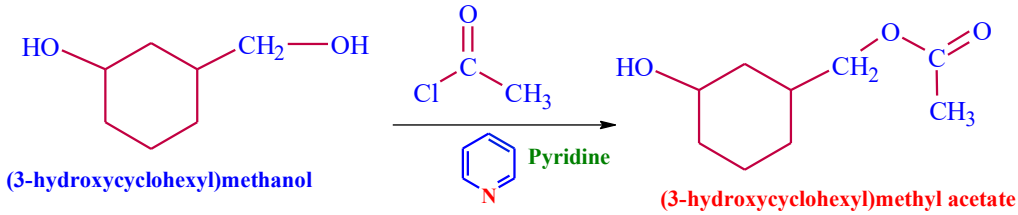
The overall transformation of this two step scheme is a carboxylic acid is converted into an acid chloride, then into an ester.

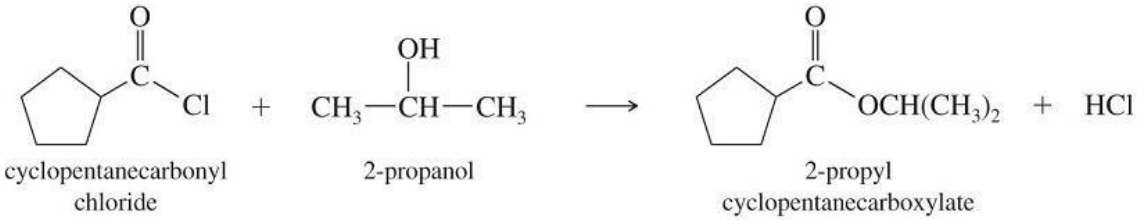




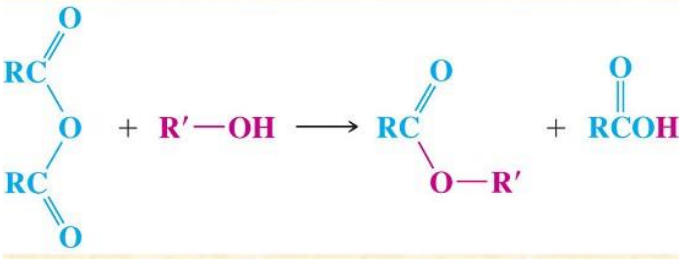


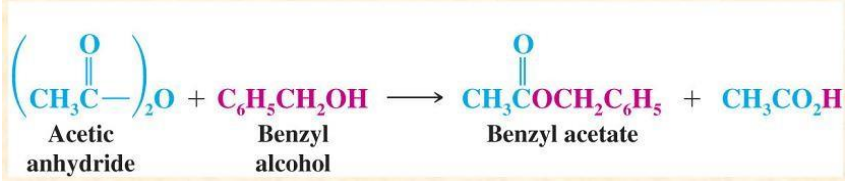


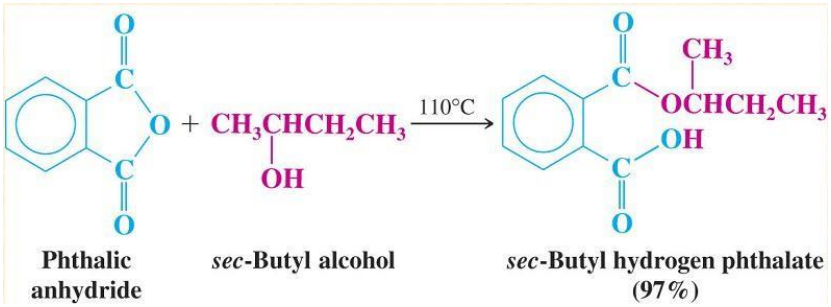




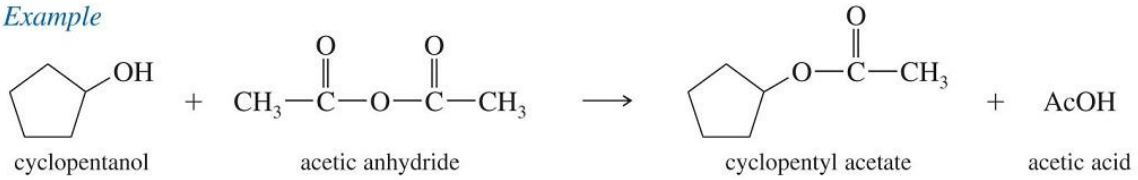
4. Esters from Carboxylic Acid Anhydrides : Alcohols react readily with anhydrides to form esters







Example

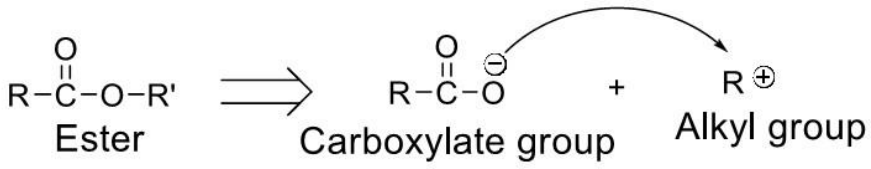


cyclopentanol | acetic anhydride | cyclopentyl acetate | acetic acid

Chemical properties

1. Hydrolysis of esters: Alcohol and acid are produced from the hydrolysis of ester, this reaction reverse to ester formation, Hydrolysis may take place by the use of dilute mineral acids as a catalyst and is called acid hydrolysis, Dilute mineral acid (H+) is used to prevent the reversible reaction**.**

$$CH_3COOC_2H_5 + H_2O \rightarrow CH_3COOH + C_2H_5OH$$



1) Hydrolysis of esters may also be carried out by heating with aqueous alkalies, to produce the **alcohol** and the salt of the acid, this is **called alkaline-hydrolysis or saponification**, (since soap is the sodium salt of high **carboxylic acids),** NaOH is added to react with the produced acid converting it to salt and prevent the reversible reaction.

$$CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH$$
$$C_6H_5COOC_2H_5 + NaOH \rightarrow C_6H_5COONa + C_2H_5OH$$

2) Hydrolysis of esters is the reaction of the ester with **water** (in an acidic medium) to form acid and **alcohol, saponification is the heating of ester with aqueous alkalis** to produce the **alcohol** and the salt of the acid, Soap is the sodium salt of high fatty carboxylic acids.

3) The hydrolysis product of **ester depends on the reaction medium** because in acidic medium, acid and alcohol are formed while in alkali medium, salt of organic acid and **alcohol** are formed, Ammonolysis is the reaction of esters with ammonia to produce acid amide and the **alcohol.**

$$CH_3COOC_2H_5 + NH_3 \rightarrow CH_3CONH_2 + C_2H_5OH$$
$$C_6H_5COOC_2H_5 + NH_3 \rightarrow C_6H_5CONH_2 + C_2H_5OH$$

4) The **esterification** reaction is not a **neutralization reaction** as it is a reversible reaction "incomplete", It needs a dehydrating agent, It is a slow reaction because it takes place between molecules, water is formed due to the combination of molecules, H from **alcohol** and OH from acid.

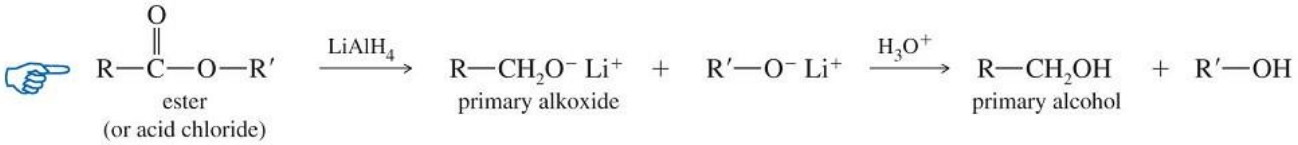
$$Acid + alcohol \leftrightarrow ester + H_2O$$

5) The neutralization reaction is **irreversible reaction** "complete", It is a fast reaction because it takes place between ions, water is formed due to the combination of ions H^+ from acid and OH^- from alkali.

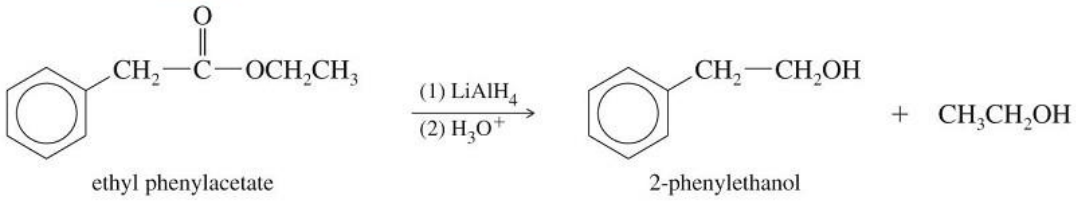
$$Acid + base \rightarrow salt + H_2O$$

2. Reduction of ester

Like other compounds bearing C=O functions, acid derivatives can be reduced easily using reagents such as ($LiAlH_4$). The majority of the reductions of acid derivatives give the corresponding primary alcohols. Aldehydes and amines can also be generated.

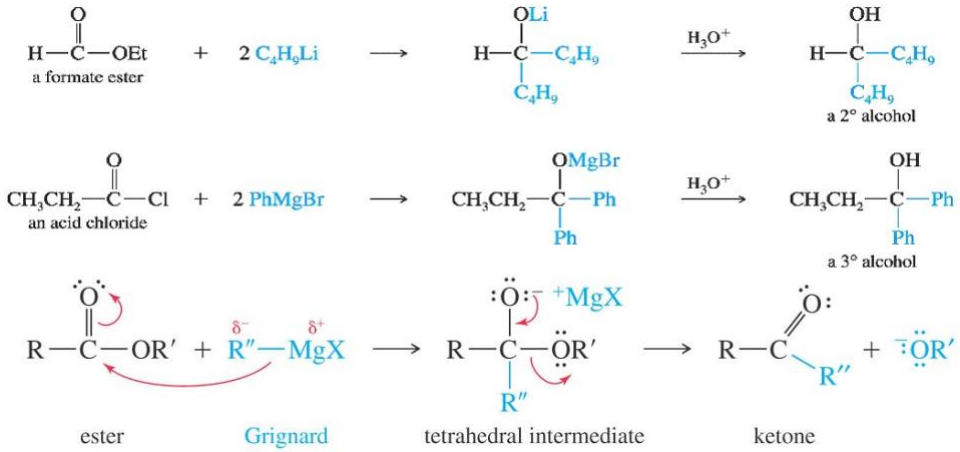


Example



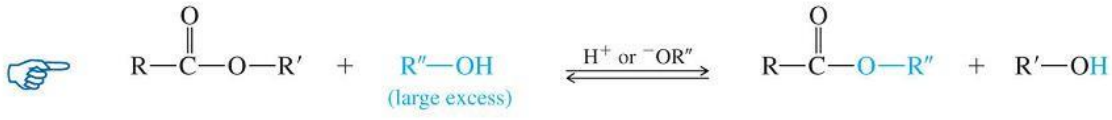
3. Reactions of Acids Derivatives with Grignards

We have seen that esters and acid chlorides add two equivalents of Grignard reagent to give tertiary alcohols

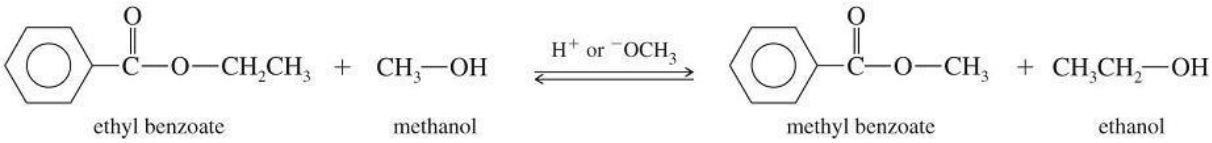


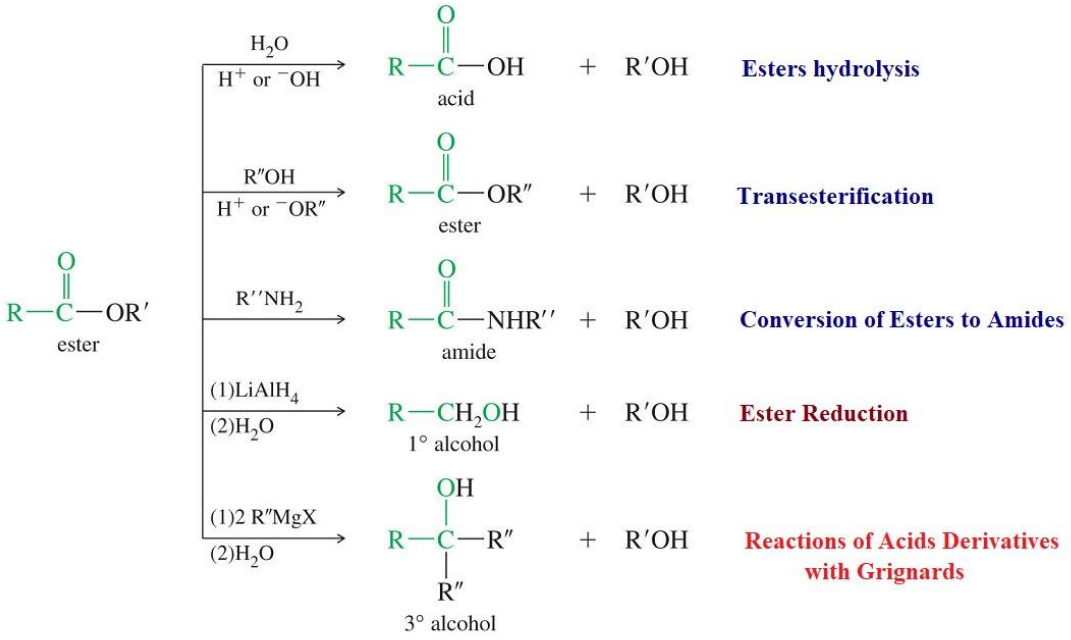
4. Transesterification

This reaction is very similar to the hydrolysis reaction . The only difference is that an alcohol is used in large excess instead of water. This results in the formation of a new ester, one that has the structure of the alcohol that was used in excess. The reaction can be performed under basic or acidic conditions, the latter being more common.

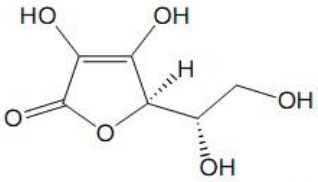


Example

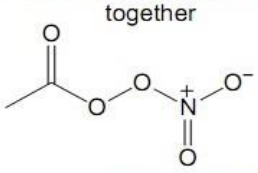




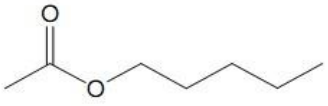
Important Esters



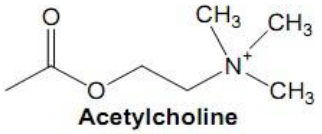
Vitamin C (ascorbic acid)
A water-soluble vitamin found in citrus fruits; prevents scurvy; essential for healthy blood vessels, bones, and teeth; helps form collagen, a protein that holds tissues together



Peroxyacetyl nitrate (PAN)
Produced by the action of sunlight on fragments of unburnt hydrocarbon fuel, oxygen, and nitrogen dioxide; one of the irritants (lachrymator) found in photochemical smog



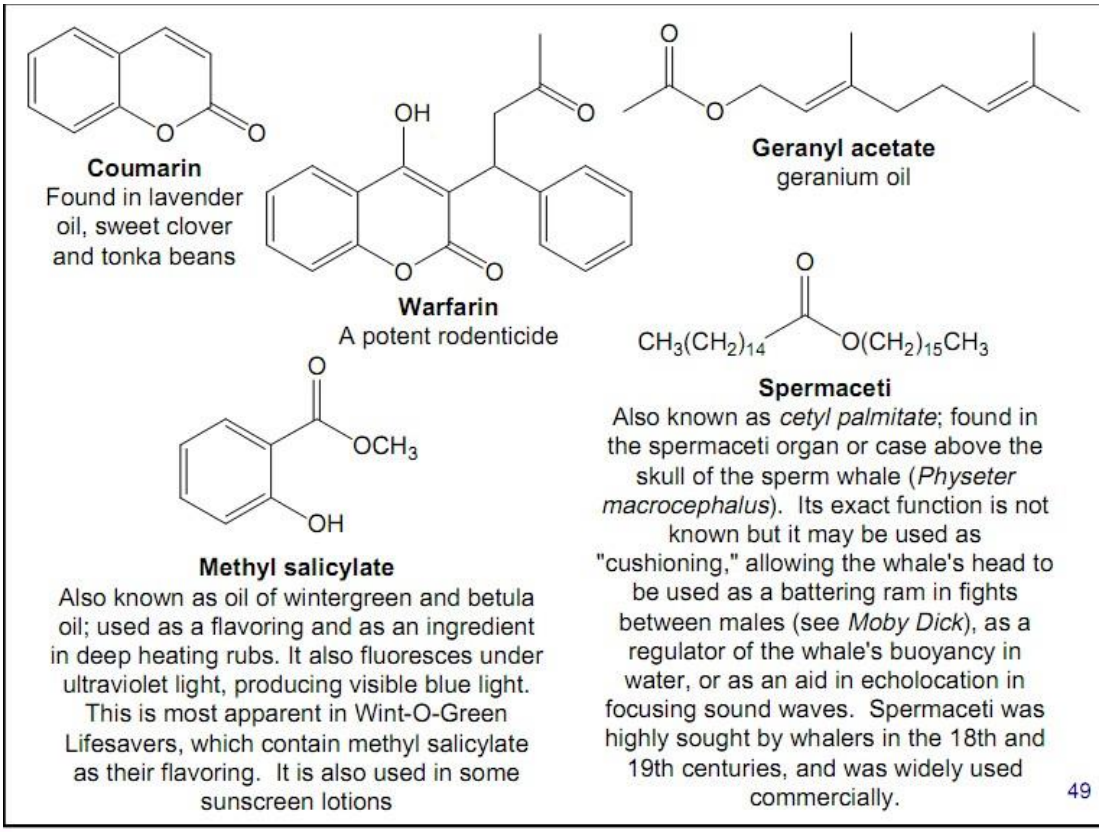
Amyl acetate
Also known as banana oil and pear oil; the commercially available compound is a mixture of amyl (pentyl) isomers



Acetylcholine
an important neurotransmitter

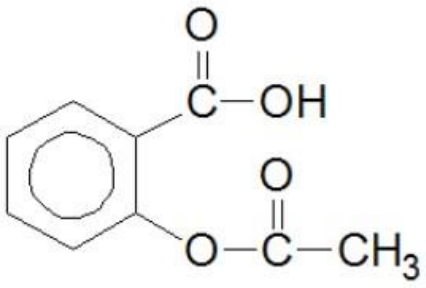
Benzyl acetate
oil of jasmine

48



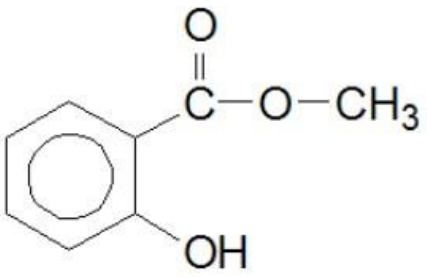
Aspirin

- is used to relieve pain and reduce inflammation.
- is an ester of salicylic acid and acetic acid.



Oil of wintergreen

- is used to soothe sore muscles.
- is an ester of salicylic acid and methanol.



Week 12

- **Lecture Title:** Mercaptans / Thiols
- **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structure and functional group of thiols (–SH group).
2. To learn the IUPAC and common naming rules for thiols (mercaptans).
3. To study the physical and chemical properties of thiols.
4. To examine important reactions involving thiols, such as oxidation and disulfide bond formation.
5. To explore the biological and pharmaceutical relevance of thiols.

• Behavioral Objectives:

1- **Cognitive Domain:**
• The student will be able to identify and describe the structure of thiol compounds.
• The student will be able to name thiols using IUPAC and common nomenclature.
• The student will be able to explain the unique physical properties of thiols, such as odor and polarity.
• The student will be able to describe key reactions such as oxidation to disulfides and nucleophilic substitution.

2- **Psychomotor Domain:**
• The student will be able to draw structural formulas of thiols and their reaction products.
• The student will be able to write balanced chemical equations for thiol reactions.

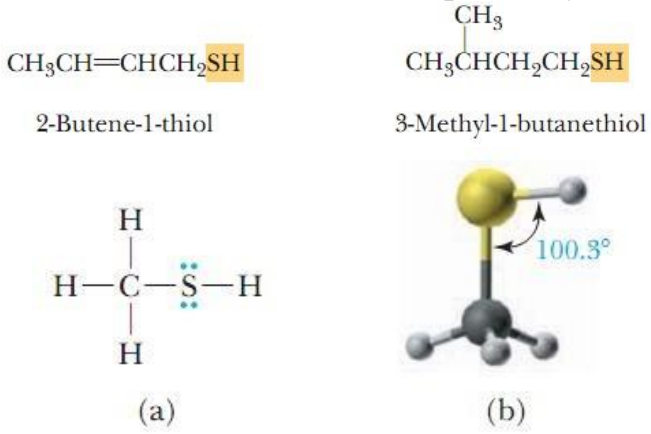
3- **Affective Domain:**
• The student will appreciate the importance of thiols in biochemical processes and drug development.

Second semester

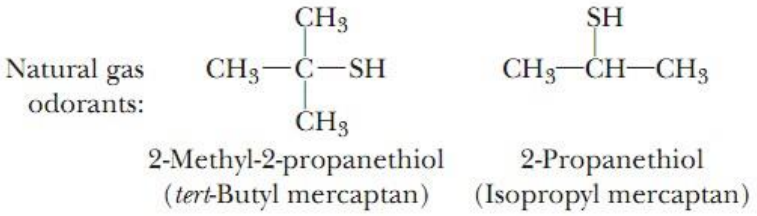
Week-12- Theoretical

Mercaptans [Sulfur compound]

1. The functional group of a thiol is an ─SH (**sulfhydryl**) group. Lewis structure and a balland-stick model of methanethiol, **CH_3SH**, the simplest thiol.
2. The most outstanding property of **low-molecular-weight thiols** is their stench.
3. They are responsible for the **unpleasant odors** such as those from **skunks**, **rotten eggs**, and sewage. The scent of skunks is due primarily to two thiols:

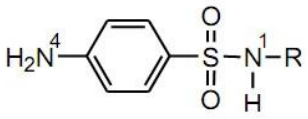


4. **Methanethiol.** The electronegativities of carbon and sulfur are virtually identical (2.5 each), while sulfur is slightly more electronegative than hydrogen (2.5 versus 2.1). The electron density model shows some slight partial positive charge on hydrogen of the S─H group and some slight partial negative charge on sulfur.
5. A blend of **low-molecular-weight** thiols is added to **natural gas** as an **odorant**. The most common of these **odorants** is **2-methyl-2-propanethiol** (**tert-butyl mercaptan**), because it is the most **resistant to oxidation** and has the greatest soil penetration.
6. 2-Propanethiol is also used for this purpose, usually as a blend with tert-butyl mercaptan.

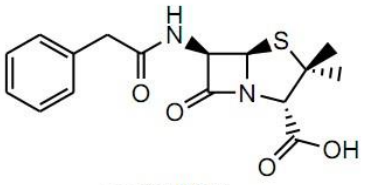


7. Methanethiol (also known as methyl mercaptan) is an organosulfur compound with the chemical formula CH_4S. It is a colorless gas with a distinctive putrid smell. It is a natural substance found in the blood and brain of humans and animals, as well as in plant tissues. It is disposed of through animal feces. It also occurs naturally in certain foods, such as some **nuts** and **cheese**. It is one of the main compounds responsible for bad breath and the smell of flatus.

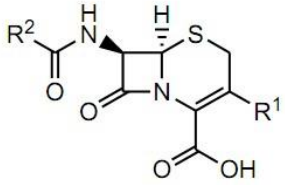
Methanethiol is classified as a thiol and is sometimes abbreviated as MeSH. It is very flammable.



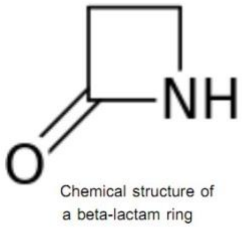
Chemical structure of sulfonamides

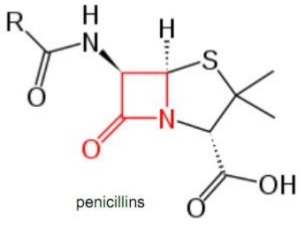


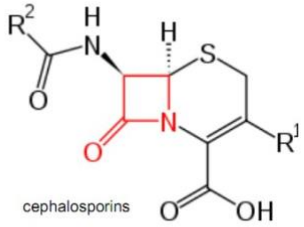
penicillins



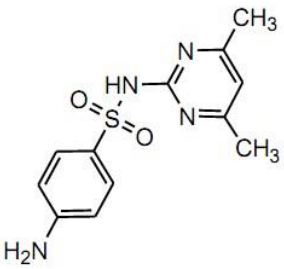
cephalosporins



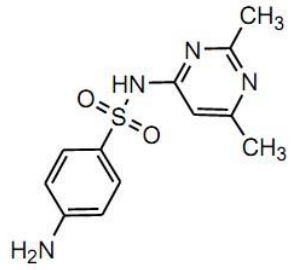




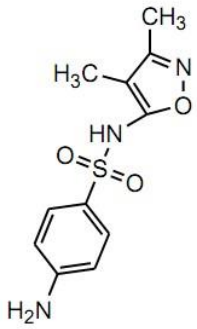
Chemical structure of beta- lactam structure. Core structure



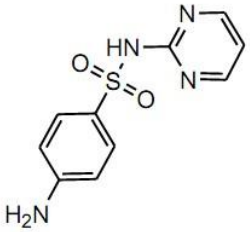
Sulfamethazine



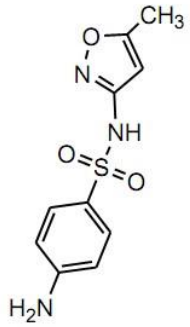
Sulfaisodimidine



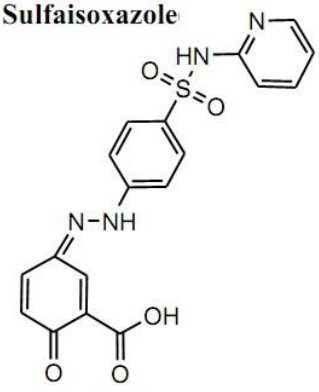
Sulfaisoxazole



Sulfadiazine



Sulfamethoxazole

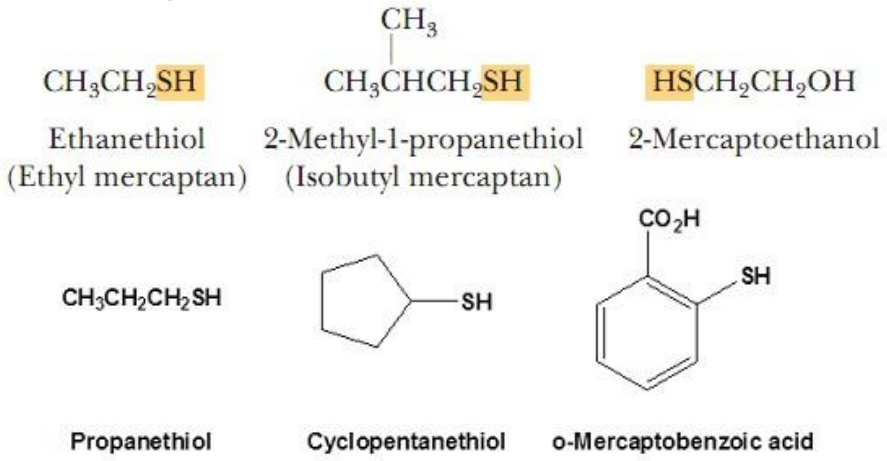


Sulfasalazine

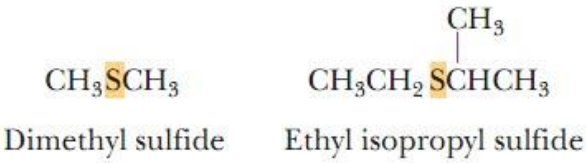
Some important sulfonamides as antibacterial

Nomenclature

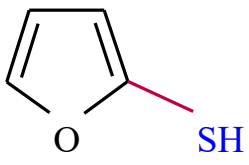
1. The sulfur analog of an alcohol is called a **thiol** (**thi- from the Greek: theion, sulfur**) or, in the older literature, a **mercaptan**, which literally means "mercury capturing." 2. **Thiols** react with Hg^{+2} in aqueous solution to give sulfide salts as insoluble precipitates.
3. **Thiophenol**, C_6H_5SH, for example, gives $(C_6H_5S)_2Hg$.
4. **Mercaptan** A common name for any molecule containing an ─SH group.
5. **In the IUPAC** system, **thiols** are named by selecting as the parent alkane the longest chain of carbon atoms that contains the **─SH** group. To show that the compound is a **thiol**, we add **-thiol** to the name of the parent **alkane** and number the parent chain in the direction that gives the ─SH group the lower number.
6. Common names for simple thiols are derived by naming the alkyl group bonded to ─SH and adding the word mercaptan. In compounds containing other functional groups, the presence of an ─SH group is indicated by the prefix mercapto-.
7. According to the IUPAC system, **─OH** takes precedence over **─SH** in both numbering and naming:



8. **Sulfur** analogs of ethers (**thioethers**) are named by using the word **sulfide** to show the presence of the **─S─** group. Following are common names of two sulfides:



⌘ Mushrooms, onions, garlic, and coffee all contain sulfur compounds. One of these present in coffee is

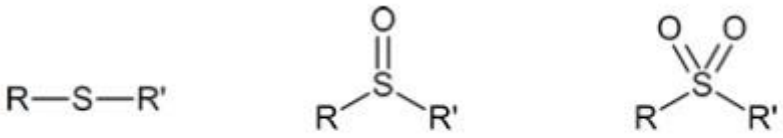


furan-2-thiol

Key Terms

All of these terms are defined in the "Study Notes," below.

1. Disulfide
2. mercapto group(organic) sulfide
3. sulfone
4. sulfoxide
5. thiol
6. thiolate anion
7. trialkylsulfonium ion (trialkylsulfonium salt)



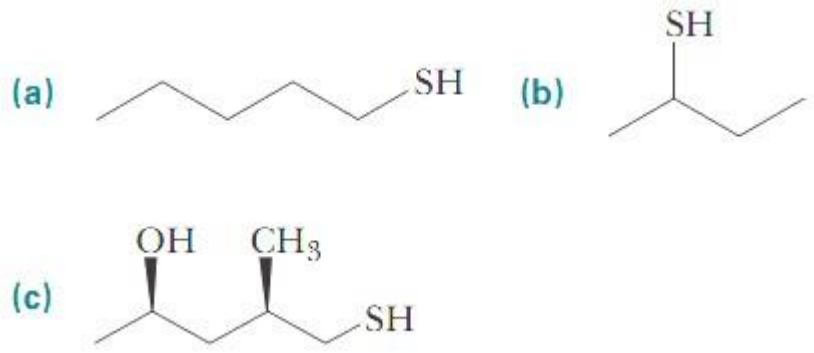
sulfide sulfoxide sulfone

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(⊕)–R R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S(=O)–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R–O–S(=O)–O–R sulfite esters	SO_3 R–O–S(=O)(=O)–O–R sulfate esters

⌘ **EXAMPLE**

⌘ Write the IUPAC name for each compound



⌘ STRATEGY

Identify the root name of the compound. If the compound only contains an ─SH group, name it as an **alkanethiol**. If the compound contains both an ─OH group

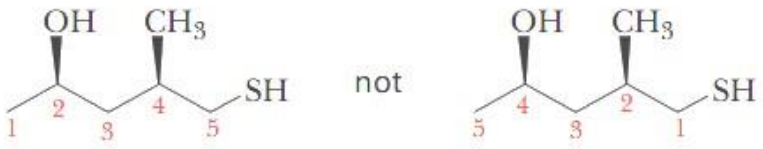
and an ─SH group, name the compound as an alcohol with a mercapto substituent. Remember that priority for numbering is given to the ─OH group.

⌘ **SOLUTION**

a) The parent alkane is pentane. We show the presence of the ─SH group by adding thiol to the name of the parent alkane. The IUPAC name of this thiol is **1-pentane-thiol**. Its common name is **pentyl mercaptan**.

b) The parent alkane is butane. The IUPAC name of this thiol is **2-butanethiol**. Its common name is **sec-butyl mercaptan**. It is a chiral molecule due to the **stereocenter** at C-2. However, the stereochemical configuration was not indicated here.

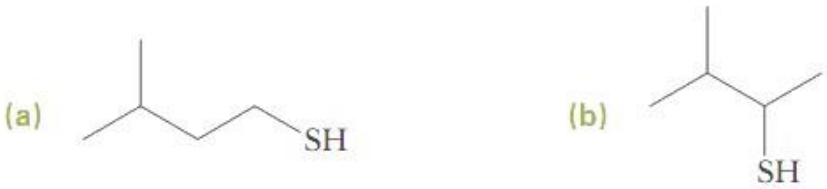
c) The parent alkane is pentane. Because **─OH** receives priority over **─SH**, the compound is named as an alcohol, with the **─OH** group receiving priority for numbering as well.



(2*R*,4*R*)-5-Mercapto-4-methylpentan-2-ol

⌘ **PROBLEM**

Write the IUPAC name for each thiol:



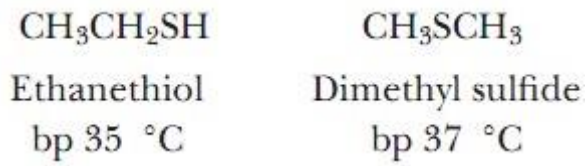
Physical Properties

1) Because of the **small difference in electronegativity between** sulfur and hydrogen (2.5
2.1 - 0.4), we classify the S─H bond as nonpolar covalent.
2) Because of this **lack of polarity**, thiols show little association by **hydrogen bonding**.
3) Consequently, they have **lower boiling points** and are less **soluble in water** and **other polar solvents** than are **alcohols** of similar **molecular weight**.
4) Table gives the boiling points of three low-molecular-weight thiols. For comparison, the table also gives the boiling points of alcohols with the same number of carbon atoms.Earlier, we illustrated the importance of hydrogen bonding in alcohols by comparing the boiling points of ethanol (78 °C) and its constitutional isomer dimethyl ether (24 °C).

TABLE 8.4 Boiling Points of Three Thiols and Three Alcohols with the Same Number of Carbon Atoms

Thiol	Boiling Point (°C)	Alcohol	Boiling Point (°C)
methanethiol	6	methanol	65
ethanethiol	35	ethanol	78
1-butanethiol	98	1-butanol	117

5) By comparison, the boiling point of ethanethiol is 35 °C, and that of its constitutional isomer dimethyl sulfide is 37 °C:



6) The fact that the boiling points of these constitutional isomers are almost identical indicates that little or no association by hydrogen bonding occurs between thiol molecules.
7) Many thiols have strong odors resembling that of garlic. The odors of thiols, particularly those of low molecular weight, are often strong and repulsive

Week 13

- **Lecture Title:** Thiols (Mercaptans): Structure and Reactions
- **Duration:** 2 hours

Lecture Objectives:

1. To understand the general structural features of thiols (mercaptans) and compare them with alcohols.
2. To learn the systematic (IUPAC) and common naming rules for thiols.
3. To examine the physical and chemical properties of thiols.
4. To study laboratory and industrial methods for the preparation of thiols.
5. To analyze major chemical reactions involving thiols, such as oxidation, disulfide bond formation, and coupling reactions.

• Behavioral Objectives:

1- Cognitive Domain:
• The student will be able to identify the general structure of thiols and distinguish them from alcohols.
• The student will be able to apply IUPAC nomenclature rules to name thiols and their derivatives.
• The student will be able to explain the chemical properties of thiols, such as relative acidity and susceptibility to oxidation.
• The student will be able to describe common methods of thiol synthesis, including nucleophilic substitution reactions with alkyl halides and thiourea.
• The student will be able to discuss the role of thiol reactions, such as disulfide bond formation, in biological systems (e.g., protein structure and function).

2- Psychomotor Domain:
• The student will be able to draw structural formulas of thiols and their key derivatives.
• The student will be able to write balanced chemical equations for thiol reactions, including oxidation and disulfide formation.
• The student will be able to illustrate reaction mechanisms involving thiols, particularly those relevant to redox chemistry.

3- Affective Domain:
• The student will appreciate the vital importance of thiols in biochemical systems, particularly in protein folding and enzymatic activity.
• The student will express an awareness of the pharmaceutical relevance of thiols in drug design and antioxidant therapy.

Thiols (Mercaptans): Structure, Reactions and Preparation

Preparation

1. **In industry,** methanethiol is prepared by the reaction of hydrogen sulfide with methanol. This method is employed for the industrial synthesis of methanethiol:

$$CH_3OH + H_2S \rightarrow CH_3SH + H_2O$$

Such reactions are conducted in the presence of **acidic catalysts**. The other principal route to thiols involves the addition of hydrogen sulfide to alkenes. Such reactions are usually conducted in the presence of an acid catalyst or **UV light**. Halide displacement, using the suitable organic halide and sodium hydrogen sulfide has also been utilized. Another method entails the alkylation of sodium hydrosulfide.

$$RX + NaSH \rightarrow RSH + NaX \qquad (X = Cl, Br, I)$$

The molecule is tetrahedral at carbon, like methanol. It is a weak acid, with a pKa of ~10.4, but is about a million times more acidic than methanol. The colorless salt can be obtained in this way:

$$CH_3SH + CH_3ONa \rightarrow CH_3SNa + CH_3OH$$

The resulting thiolate anion is a strong nucleophile. It can be oxidized to dimethyl disulfide:

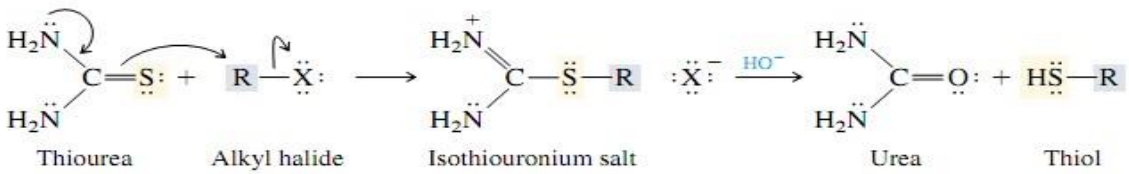
$$2CH_3SH + [O] \rightarrow CH_3S{-}SCH_3 + H_2O$$

2. Laboratory methods

This method is used for the production of thioglycolic acid from chloroacetic acid.

In general, on the typical laboratory scale, the direct reaction of a halogenoalkane with sodium hydrosulfide is inefficient owing to the competing formation of thioethers Instead, alkyl halides are converted to thiols via an S-alkylation of thiourea. This multistep, one-pot process proceeds via the intermediacy of the isothiouronium salt, which is hydrolyzed in a separate step:

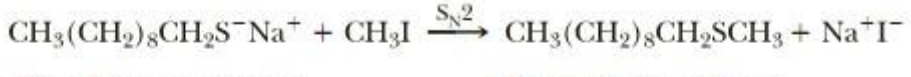
$$CH_3CH_2Br + SC(NH_2)_2 \rightarrow [CH_3CH_2SC(NH_2)_2]Br$$
$$[CH_3CH_2SC(NH_2)_2]Br + NaOH \rightarrow CH_3CH_2SH + OC(NH_2)_2 + NaBr$$



$$CH_3(CH_2)_4CH_2Br \xrightarrow[2.\ NaOH]{1.\ (H_2N)_2C{=}S} CH_3(CH_2)_4CH_2SH$$

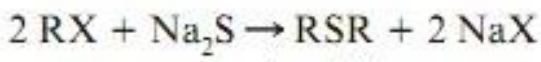
1-Bromohexane — 1-Hexanethiol (84%)

3. **Unsymmetrical sulfides, RSR'**, are prepared by converting a thiol to a sodium salt with either sodium hydroxide or sodium ethoxide and then allowing the salt to react with a haloalkane.



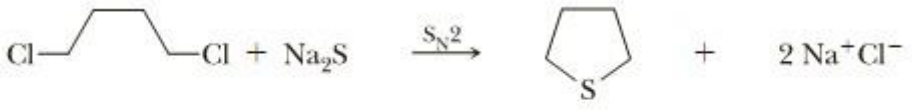
Sodium 1-decanethiolate — 1-Methylsulfanyldecane (Decyl methyl sulfide)

4. **Symmetrical sulfides**, R—S—R (also called symmetrical thioethers), are prepared by treating one mole of Na_2S (where S^{+2} is the nucleophile) with two moles of haloalkane.

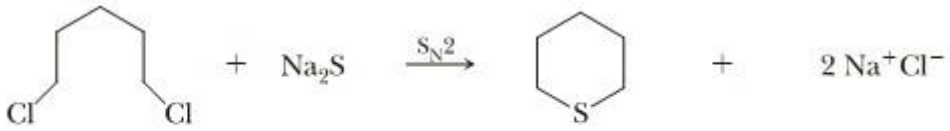


A sulfide

5. This same reaction can also be used to prepare **five- and six-membered cyclic sulfides**.Treating a 1,4-dihaloalkane with Na_2S gives a five-membered cyclic sulfide; treating a1,5-dihaloalkane with Na_2S gives a six-membered ring.

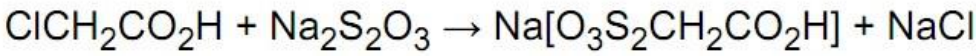


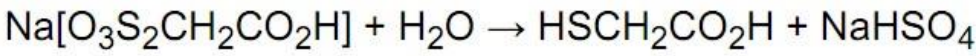
1,4-Dichlorobutane — Thiolane (Tetrahydrothiophene)



1,5-Dichloropentane — Thiane (Tetrahydrothiopyran)

6. **The thiourea** route works well with primary halides, especially activated ones. Secondary and tertiary thiols are less easily prepared. Secondary thiols can be prepared from the ketone via the corresponding dithioketals. A related two-step process involves alkylation of thiosulfate to give the thiosulfonate ("Bunte salt"), followed by hydrolysis. The method is illustrated by one synthesis of thioglycolic acid:





7. Organolithium compounds and Grignard reagents react with sulfur to give the thiolates, which are readily hydrolyzed:

8. Thiols are easily oxidized to disulfides, and the disulfides are easily reduced back to thiols.

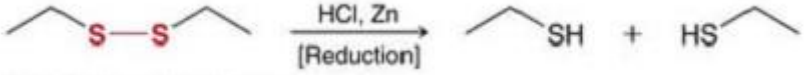
$$CH_3CH_2SH \underset{NaBH_4}{\overset{I_2}{\rightleftharpoons}} CH_3CH_2S\text{-}SCH_2CH_3$$

disulfide

9. Sulfides undergo a number of reactions:

A. Sulfides can also be oxidized. Thiols and Sulfides

B. Disulfides can be reduced by the reverse reaction.Thiols and Sulfides



Reactions of Thiols

In this section, we discuss the acidity of thiols and their reaction with strong bases, such sodium hydroxide, and with molecular oxygen.

A. Acidity

1) Hydrogen sulfide is a stronger acid than water:

$$H_2O + H_2O \rightleftharpoons HO^- + H_3O^+ \qquad pK_a = 15.7$$

$$H_2S + H_2O \rightleftharpoons HS^- + H_3O^+ \qquad pK_a = 7.0$$

2) Similarly, thiols are stronger acids than alcohols. Compare, for example, the pK_a's of ethanol and ethanethiol in dilute aqueous solution:

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \qquad pK_a = 15.9$$

$$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+ \qquad pK_a = 8.5$$

3) **thiols are more acidic** than **alcohols** because sulfides are more stable conjugate bases than are alkoxides. There is more area to delocalize the valence electrons about the negative sulfur atom because sulfur is larger than oxygen.

4) **Thiols** are sufficiently strong acids that, when dissolved in aqueous sodium hydroxide, they are converted completely to alkyl sulfide salts:

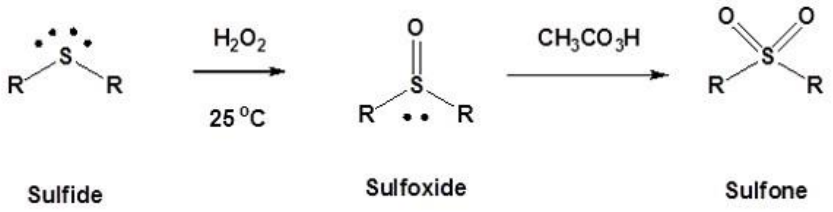
$$CH_3CH_2SH + Na^+OH^- \longrightarrow CH_3CH_2S^-\,Na^+ + H_2O$$

pK_a 8.5			pK_a15.7
Stronger acid	Stronger base	Weaker base	Weaker acid

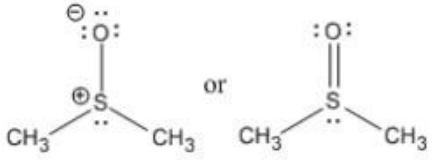
5) **To name salts of thiols**, give the name of the cation first, followed by the name of the alkyl group to which the suffix -sulfide is added. For example, the sodium salt derived from ethanethiol is named sodium ethylsulfide.

6) Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2 , as room termpeature produces a sulfoxide (R_2SO). The

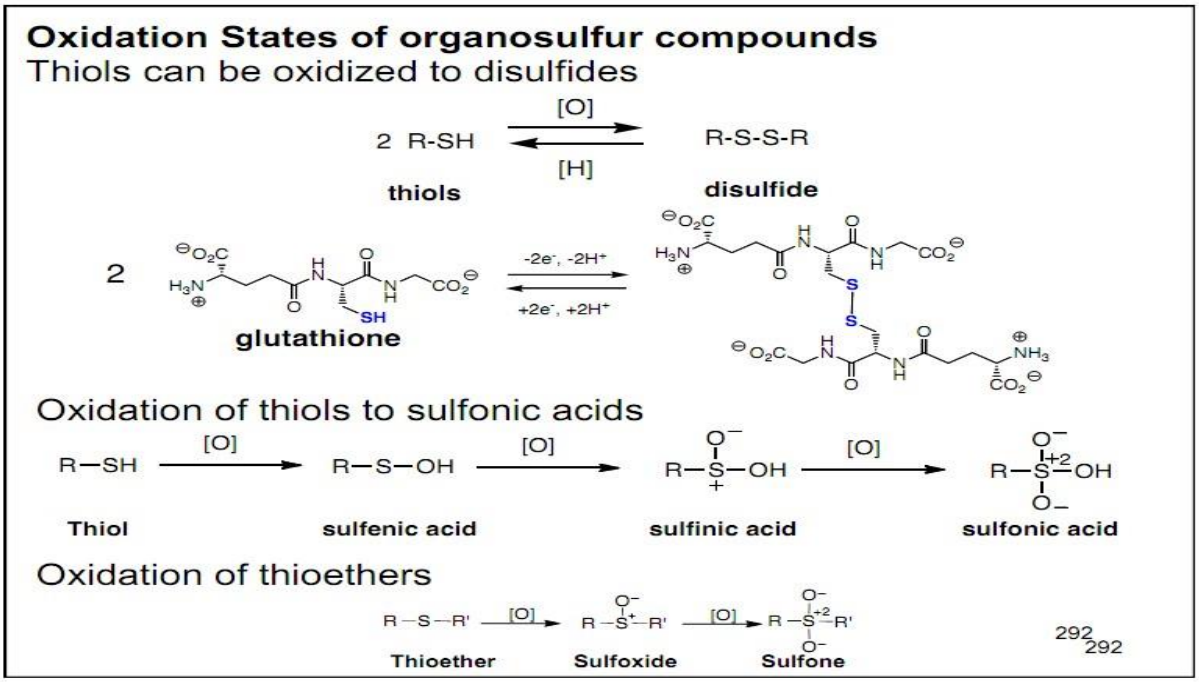
oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO) is polar aprotic solvent.



DMSO is a very polar, aprotic solvent.



Week 14

- **Lecture Title:** Heterocyclic Compounds
- **Duration:** 2 hours

Lecture Objectives:

1. To understand the general classification and structural features of heterocyclic compounds (aromatic and non-aromatic).
2. To become familiar with the systematic (IUPAC) and common nomenclature of five- and six-membered heterocycles.
3. To study the electronic structure and aromaticity of key heterocycles such as pyrrole, furan, thiophene, pyridine, and imidazole.
4. To examine the physical properties of heterocyclic compounds (e.g., boiling point, solubility, polarity).
5. To analyze the chemical reactivity of heterocycles, including electrophilic and nucleophilic substitution, oxidation, and reduction.
6. To explore the relevance of heterocyclic compounds in pharmaceuticals and natural products.

• Behavioral Objectives:

1- Cognitive Domain:
• The student will be able to classify heterocyclic compounds based on ring size, saturation, and aromaticity.
• The student will be able to apply IUPAC and common naming conventions to name simple and fused-ring heterocycles.
• The student will be able to explain aromaticity and electron delocalization in key heterocycles.
• The student will be able to describe and predict physical properties based on structure.
• The student will be able to discuss the significance of heterocycles in drug molecules and natural products.

2- Psychomotor Domain:
• The student will be able to draw the structures and resonance forms of heterocyclic compounds.
• The student will be able to write balanced chemical equations for characteristic heterocyclic reactions.
• The student will be able to sketch mechanisms for key electrophilic and nucleophilic substitution reactions.

3- Affective Domain:
• The student will develop an appreciation for the diversity and complexity of heterocyclic chemistry.
• The student will express interest in the wide-ranging applications of heterocycles in medicinal chemistry and materials science.

Second semester

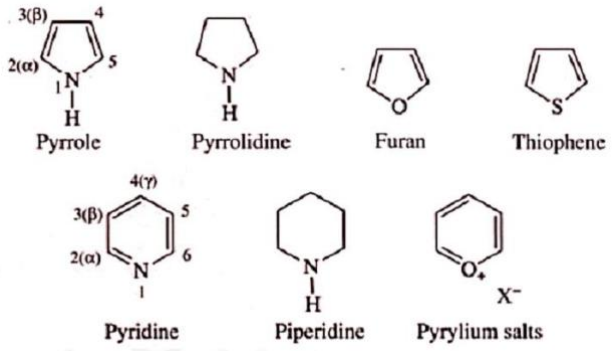
Week-14- Theoretical

Hetero cyclic compounds

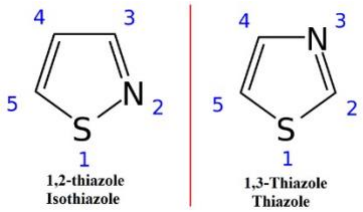
Definition Of Heterocyclic Compounds: Heterocyclic compounds are cyclic compounds which contains one/more atoms of other elements along with carbon atoms.

Definition Of Heteroatom: Hetero atoms are those which contains an atom other than carbon such as nitrogen, Sulphur, phosphorus etc. Introduction

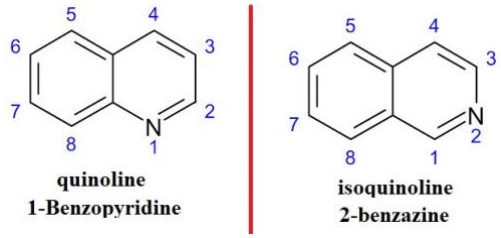
1. Students will be familiar with carbocyclic compounds, such as cyclohexane and benzene, that are built from rings of carbon atoms. If one or more of the carbon atoms is replaced by another element, the product is a heterocycle.
2. Multiple replacements are commonplace, and the elements involved need not be the same. The most common are oxygen, sulfur or nitrogen, but many other elements can function in this way, including boron, silicon and phosphorus.
3. Chemists have been working with heterocycles for more than two centuries, and trivial names were often applied long before the structures of the compounds were known. As a result, many heterocycles retain these names; a selection of common five- and six-membered heterocycles that contain one oxygen, nitrogen or sulfur atom are included in Box 1.1. The ring atoms are normally numbered such that the heteroatom carries the lowest number.

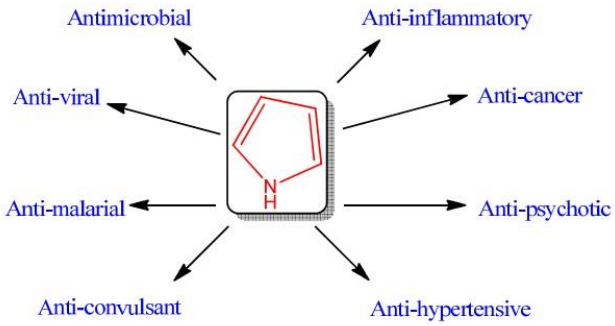


4. Cyclic compounds having as ring members atoms of at least two different elements, e.g.1,2-thiazole.

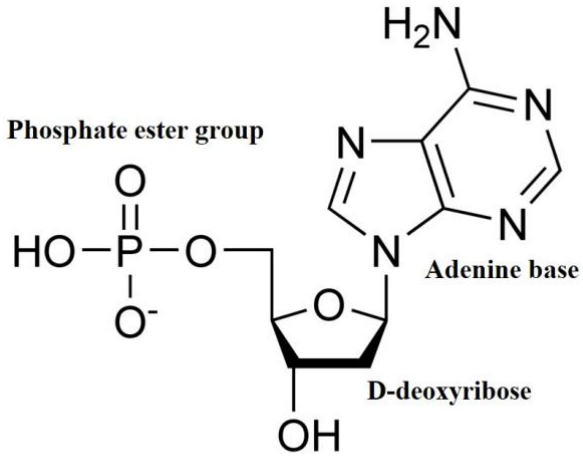


5. Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur.





6. Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together (DNA is composed of heterocyclic basespyrimidines and purines). Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds.

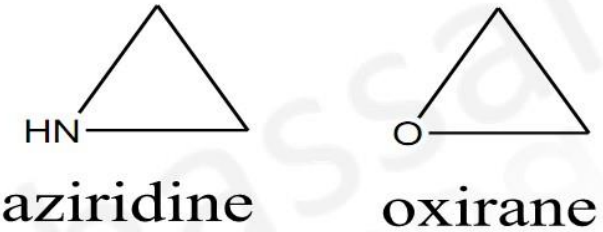


Deoxyadenosine monophosphate (dAMP)

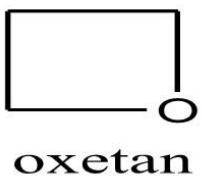
7. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Several heterocyclic compounds have applications in agriculture as insecticides, fungicides, herbicides, pesticides etc. They also find applications as sensitizers, developers, antioxidants, copolymers etc. They are used as vehicles in the synthesis of other organic compounds. Chlorophyll-photosynthesizing and hemoglobin-oxygen transporting pigments are also heterocyclic compounds.

CLASSIFICATION:

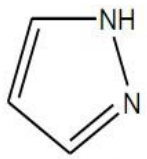
Depending upon the size of heterocyclic ring, they are classified into different types. 1- Three membered heterocyclic compounds:



2- Four membered heterocyclic compounds:

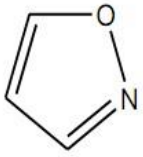


3- Five membered heterocyclic compounds:



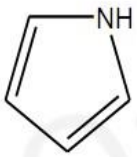
pyrazole

thiazole

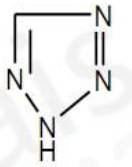


isooxazole

furan



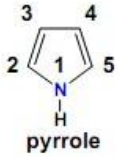
pyrrole



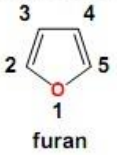
tetrazole

Isoelectronic carbocycle

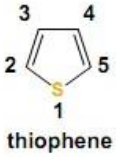
Heterocycles



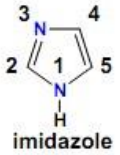
pyrrole



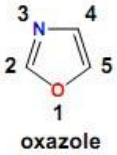
furan



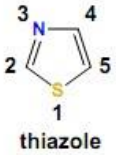
thiophene



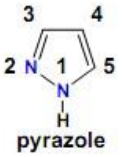
imidazole



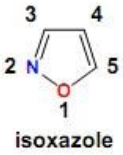
oxazole



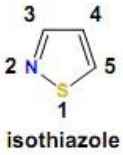
thiazole



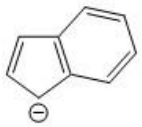
pyrazole

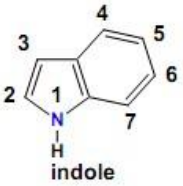


isoxazole



isothiazole

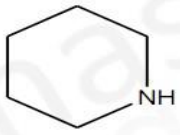




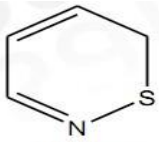
indole

4- Six membered heterocyclic compounds:

Pyridine



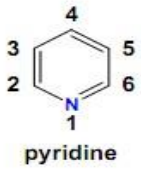
piperidine



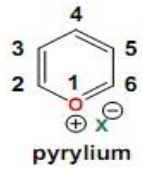
thiazine

Isoelectronic carbocycle

Heterocycles

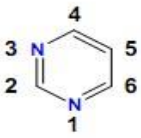


pyridine

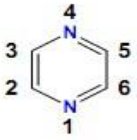


pyrylium

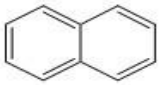
pyridazine

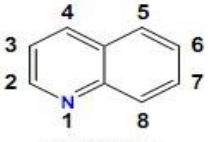


pyrimidine

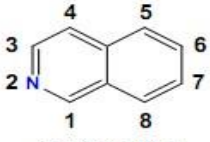


pyrazine



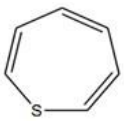


quinoline



isoquinoline

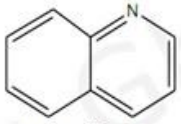
5- Seven and Eight membered heterocyclic compounds:



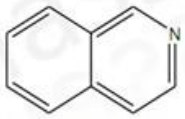
thiepine
Seven membered ring

azocine
Eight membered ring

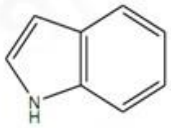
6- Fused heterocyclic compounds and Condensed ring systems:



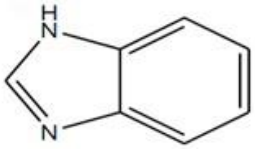
quinoline



isoquinoline



indole



benzimidazole

NOMENCLATURE

A. Systematic nomenclature system is used for naming 3-10 membered monocyclic heterocyclic of various degree of the unsaturation containing one/more heteroatoms. It specifies the following characters such as:
   1) the ring size
   2) the nature
   3) he type of heteroatom
   4) the position of heteroatom etc.

B. These hetrocompounds are also comply with the general rule that is proposed by the "Huckel Rule " "Huckel rule" states that aromaticity is obtained in the cyclic conjugated and planer system containing (4n+2) π electrons.

C. The heterocyclic compounds are named by fusing the following rules: 1) Combination of prefixes with stem 2) The prefixes for different heteroatoms.
   3) stem may be divided into two subdivided:
      a) Basic term represent of ring size.
      b) Suffixes represent of the end term.

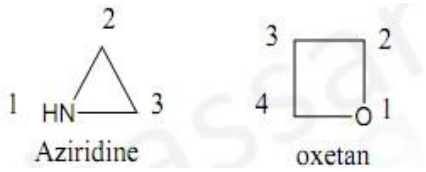
Prefixes for different Heteroatoms

S.No:	Heteroatom	Symbol	Valence	Prefix
1	Oxygen	o	2	oxa
2	Sulphur	s	2	Thia
3	Nitrogen	N	3	Aza
6	Phosphorus	P	3	Phospha
7	Arsenic	As	3	Arsa
8	Antimony	Sb	3	Siba
9	Bismuth	Bi	3	Bisma
10	Silicon	Si	4	Silica
11	Geranium	Ge	4	Germa
12	Tin	Sn	4	Stanna
13	Lead	Pb	4	Plumba
14	Boran	B	3	Bora
15	Mercury	Hg	2	Mercura

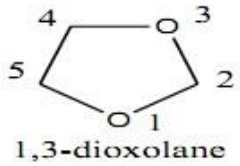
Rules that have to be considered while giving names to the heterocyclic compounds:

1. The names of the monocyclic compounds are derived by a prefix indicating the nature of

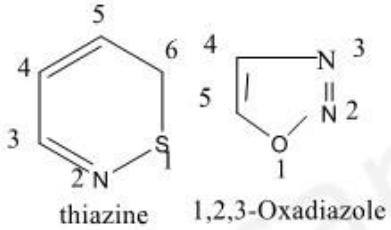
heteroatoms present and introducing or omitting the “a” where necessary.



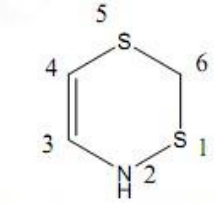
2. When two are more of the same heteroatoms are present, the prefixes “di,tri”etc. are used.



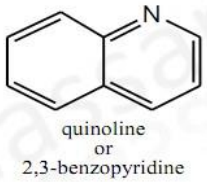
3. If the heteroatoms are different they are named in the order of “O, S, N, P, Si”etc. by combining the prefixes with the ending in the order of preference.



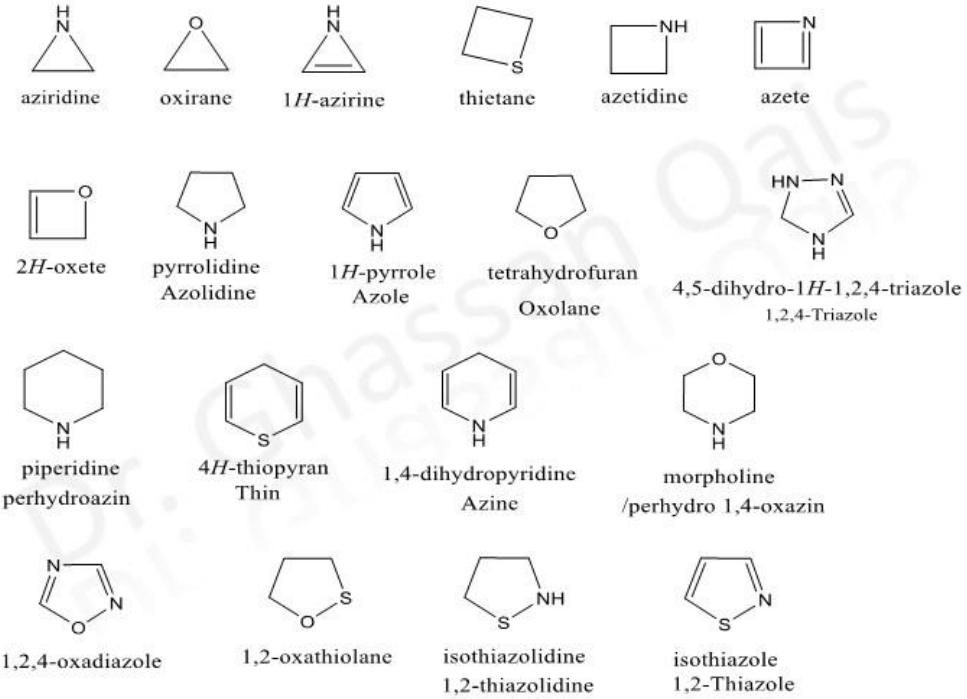
4. The state of hydrogenation is indicated in the suffix or by the prefixes dihydro, tetrahydro etc or by prefixing the name of the parent unsaturated compound with the symbol ”H” preceded by a number indicating the position of saturation.



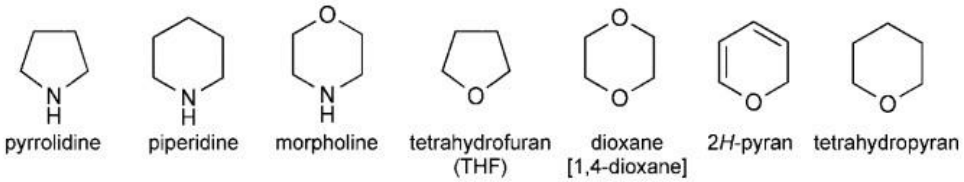
5. In a monocyclic compound containing only one heteroatom numbering starts at this atom. The ring is numbered to give the substituents or other heteroatoms the lowest number possible.



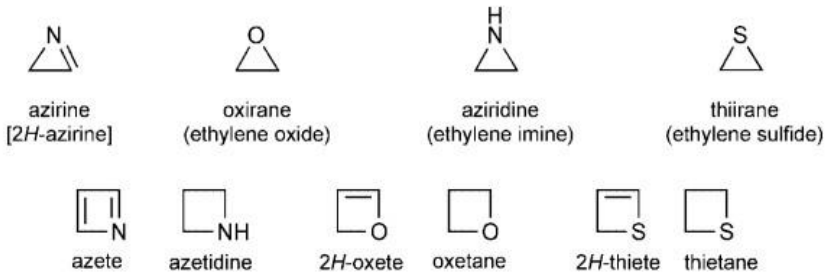
Other some example:



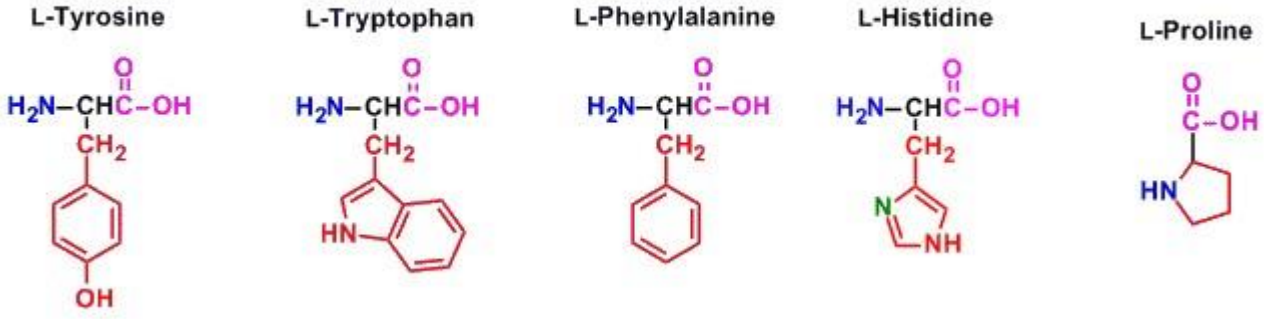
Non-aromatic heterocycles



Small-ring heterocycles

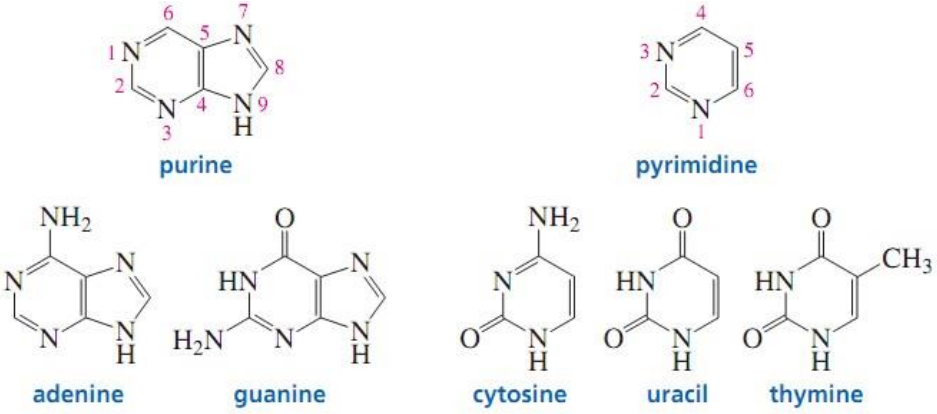


Amino Acids - Names & Structures



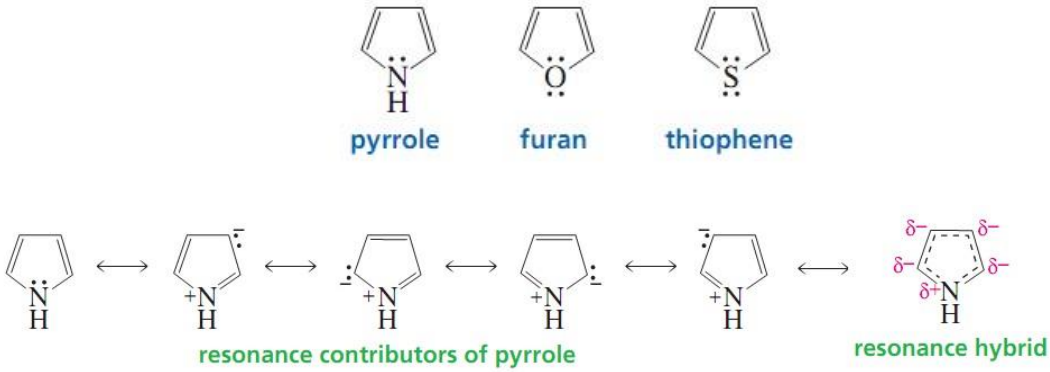
Nitrogen Base

Purine and Pyrimidine Nucleic acids (DNA and RNA) contain substituted purines and substituted pyrimidines (Section 27.1); DNA contains A, G, C, and T, and RNA contains A, G, C, and U. (Why DNA contains T instead of U is explained in Section 27.14.) Unsubstituted purine and pyrimidine are not found in nature. Notice that hydroxypurines and hydroxypyrimidines are more stable in the keto form. We will see that the preference for the keto form is crucial for proper base pairing in DNA .

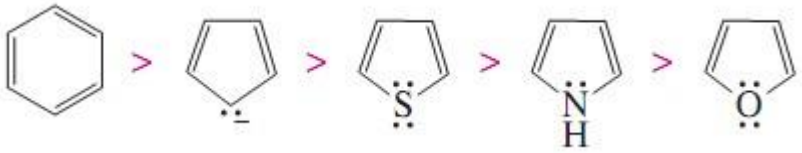


Resonance

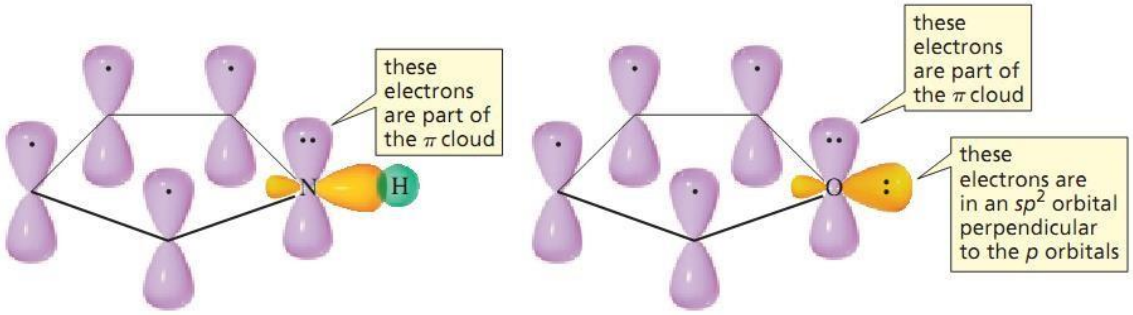
1. **Five-membered ring** :The resonance contributors of **pyrrole** show that nitrogen donates the electrons depicted as a lone pair



Relative resonance energies of some aromatic compounds



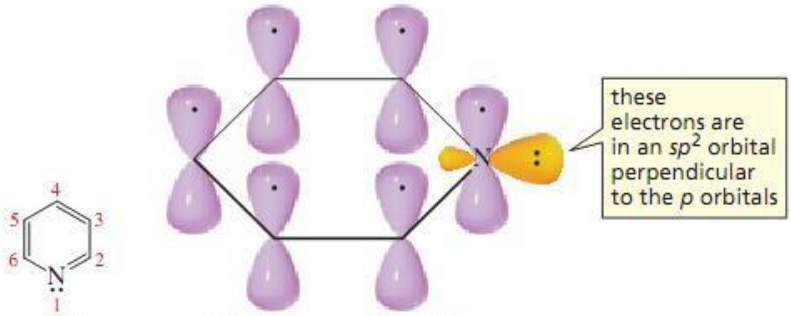
Structure of five membered ring



orbital structure of pyrrole orbital structure of furan

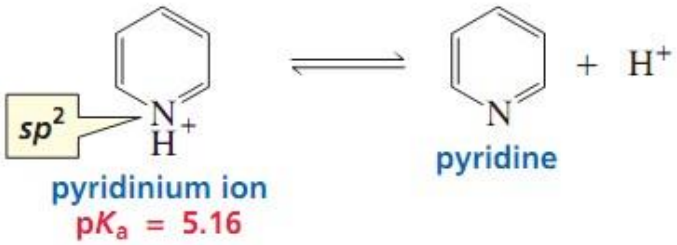
2. Aromatic Six-Membered-Ring Heterocycles

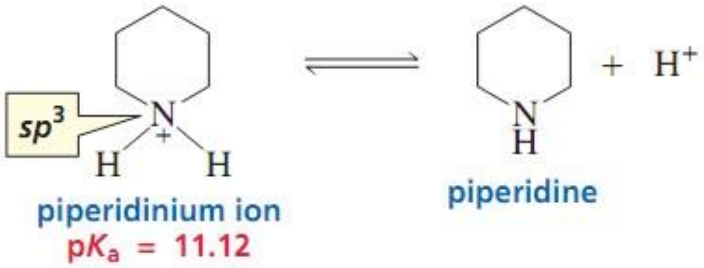
Pyridine :When one of the carbons of a benzene ring is replaced by a nitrogen, the resulting compound is called pyridine.



pyridine orbital structure of pyridine

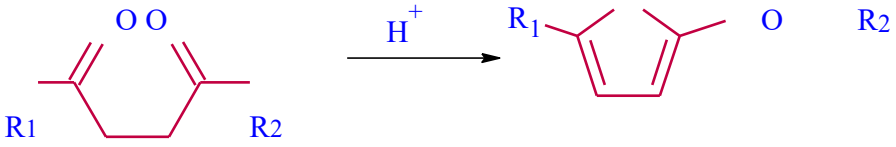
The pyridinium ion is a stronger acid than a typical ammonium ion because the acidic hydrogen of a pyridinium ion is attached to an **sp²** hybridized nitrogen, which is more electronegative than an **sp³** hybridized nitrogen .





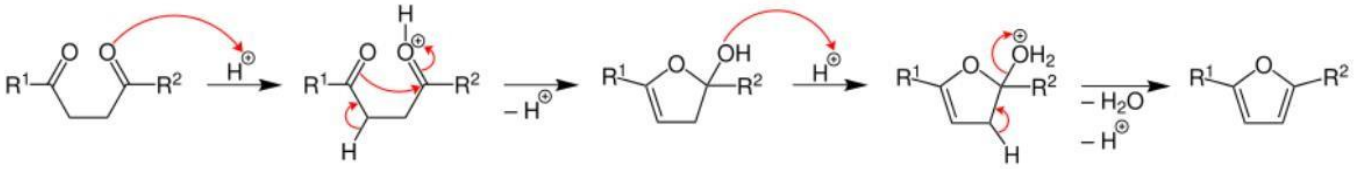
Synthesis of Heterocyclic compounds

1. **Synthesis furans, pyrroles, or thiophenes from 1,4-diketones**. The Synthesis in organic chemistry is a reaction that generates either furans, pyrroles, or thiophenes from 1,4-diketones. It is a synthetically valuable method for obtaining substituted furans and pyrroles, common structural components of many natural products. The furan synthesis requires an acid catalyst

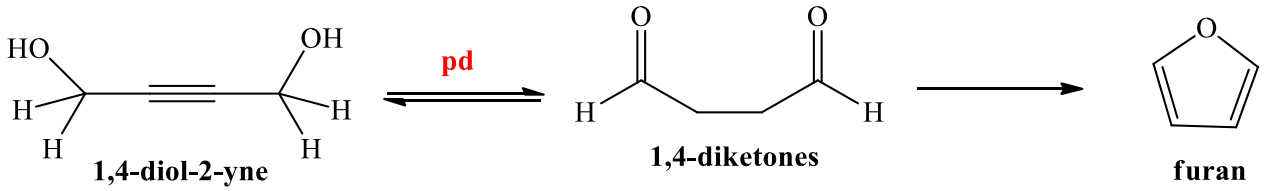


1,4-diketone **furan**

✞ Mechanism of Furan synthesis : The acid catalyzed furan synthesis proceeds by protonation of one carbonyl which is attacked by the forming enol of the other carbonyl. Dehydration of the hemiacetal gives the resultant furan.

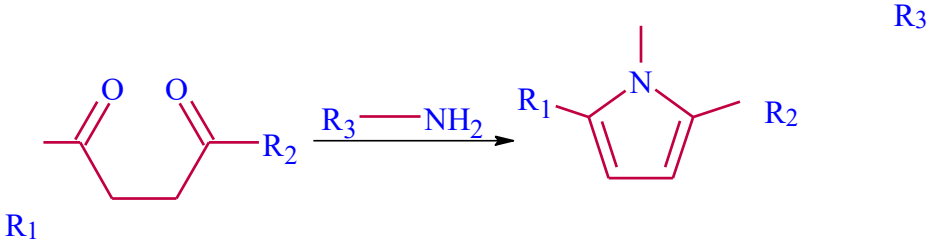


⌘ Synthesis furans from 1,4-Diol-2-ynes: Using palladium, a 1,4-diol-2-yne can be isomerized to the corresponding 1,4-diketone in situ and then dehydrated to the corresponding furan using a dehydration agent.



1,4-diol-2-yne **1,4-diketones** **furan**

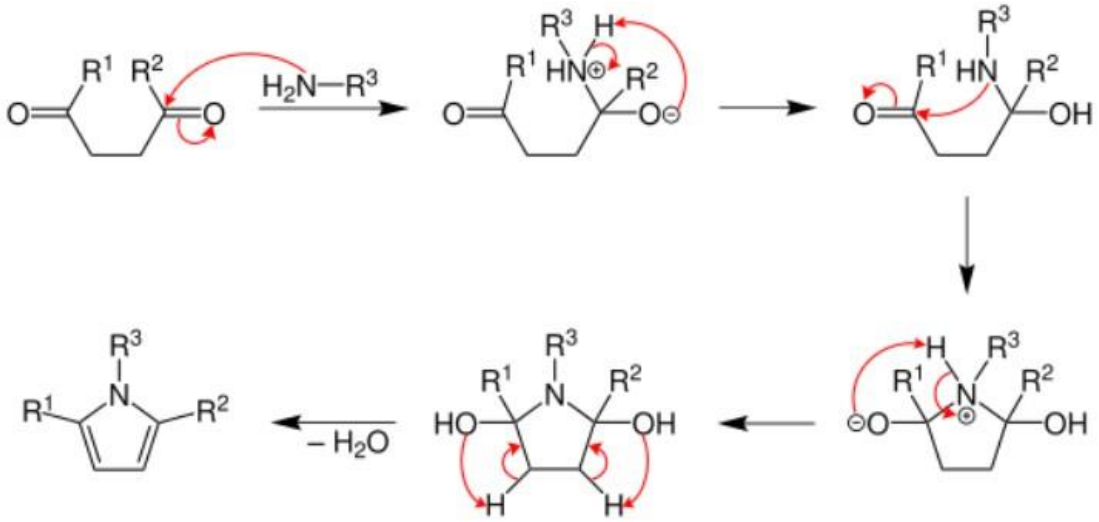
2. **Synthesis pyrrole from primary amine and 1,4-diketones** :



1,4-diketone **pyrrole**

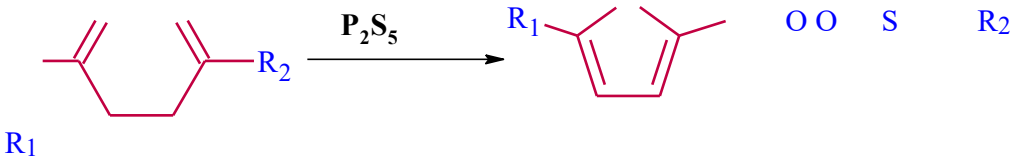
⌘ Mechanism Pyrrole synthesis

The mechanism for the synthesis of the pyrrole was suggests that the protonated carbonyl is attacked by the amine to form the hemiaminal. The amine attacks the other carbonyl to form a 2,5-dihydroxytetrahydropyrrole derivative which undergoes dehydration to give the corresponding substituted pyrrole.



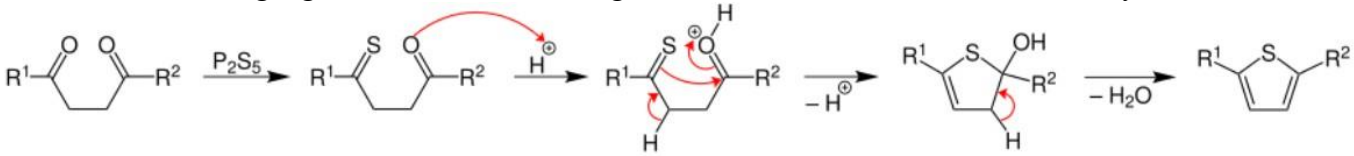
The reaction is typically run under protic or Lewis acidic conditions, with a primary amine. Use of ammonium hydroxide or ammonium acetate to gives the N-unsubstituted pyrrole

3. **Thiophene synthesis** :Thiophene for instance the compound phosphorus pentasulfide

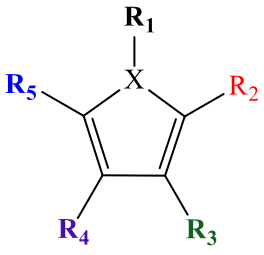


1,4-diketone **thiophene**

Mechanism of Thiophene synthesis : Thiophene synthesis is achieved via a mechanism very similar to the furan synthesis. The initial diketone is converted to a thioketone with a sulfurizing agent, which then undergoes the same mechanism as the furan synthesis.

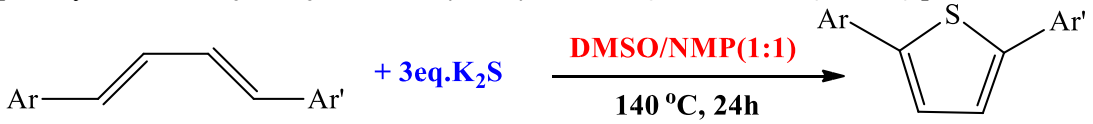


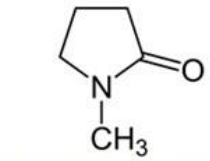
⌘ In all syntheses almost all dicarbonyls can be converted to their corresponding heterocycle. R_2 and R_5 can be H, aryl or alkyl. R_3 and R_4 can be H, aryl, alkyl, or an ester. In the pyrrole synthesis (X = N), R_1 can be H, aryl, alkyl, amino, or hydroxyl.



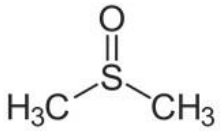
⌘ Synthesis of thiophenes via cleavage of multiple C-H bonds : The reaction of substituted buta-1,3-dienes with potassium sulfide enables an atom economical, and transition-metal-free synthesis of thiophenes via cleavage of multiple C-H bonds. Moreover, the strategy can also be used for the synthesis of thiophenes from 1,4-diaryl-1,3-dienes.

[Catalyst: N-Methyl-2-pyrrolidone (**NMP**) ; **Dimethyl sulfoxide** (**DMSO**)]



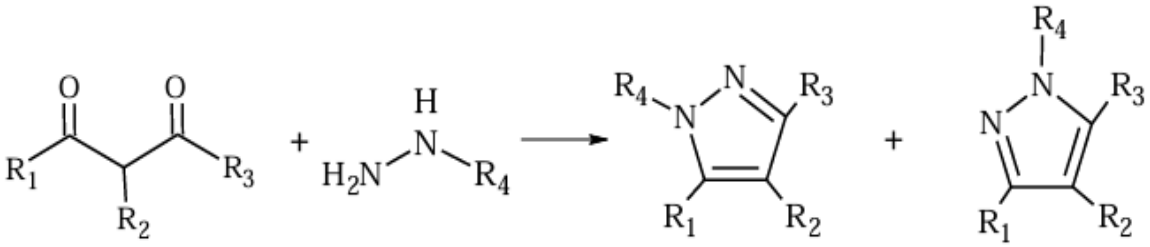


N-Methyl-2-pyrrolidone (NMP)



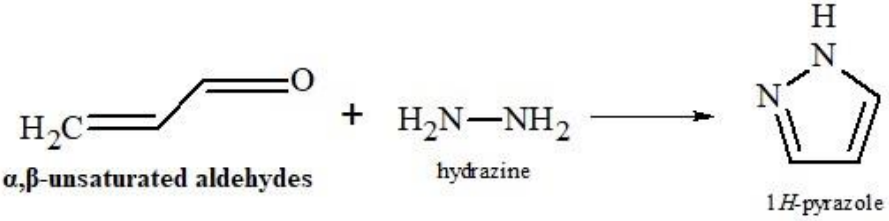
Dimethyl sulfoxide

4. **synthesis of pyrazoles** : Synthesis of pyrazoles from 1,3-dicarbonyls and hydrazines, hydrazides, or semibicarbazides. This synthesis occurs via a condensation mechanism similar to the Paal-Knorr, however if a substituted hydrazine is used, it results in a mixture of regio-isomers where the substituted heteroatom is either next to the R_1 substituent or the R_3 substituent.



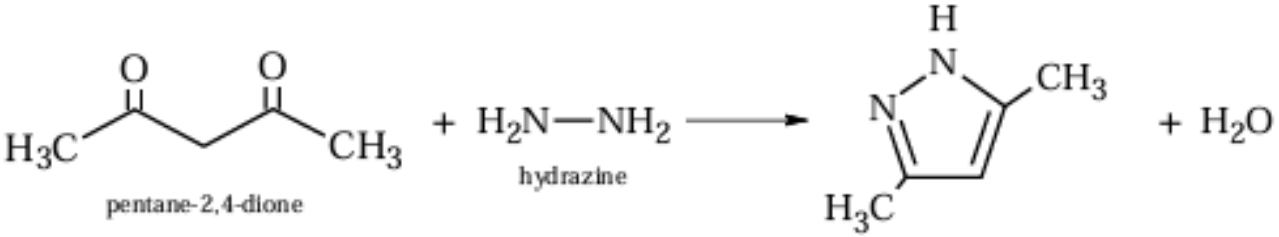
1,3-dicarbonyls **Hydrazines**

⌘ Pyrazoles are synthesized by the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation



α,β-unsaturated aldehydes hydrazine 1*H*-pyrazole

⌘ Substituted pyrazoles are prepared by condensation of 1,3-diketones with hydrazine . For example, acetylacetone and hydrazine gives 3,5-dimethylpyrazole:

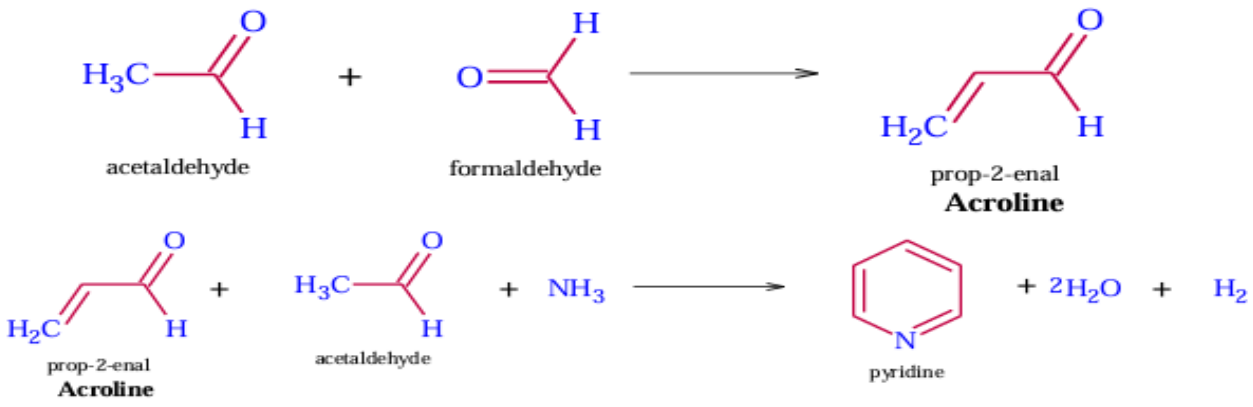


pentane-2,4-dione hydrazine 3,5-dimethyl-1*H*-pyrazole

acetylacetone

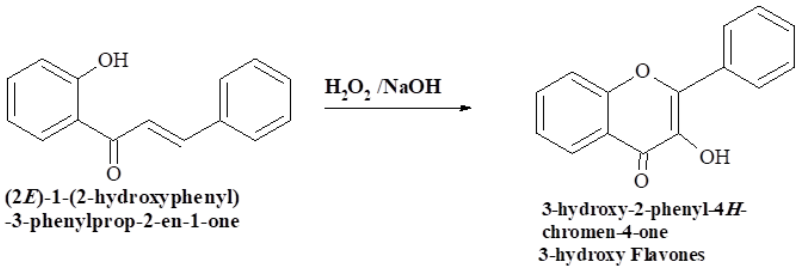
5. Synthesis pyridine

1. In its general form, the reaction can be described as a condensation reaction of aldehydes, ketones, α,β unsaturated carbonyl compounds, or any combination of the above, in ammonia or ammonia derivatives.
2. In particular, unsubstituted pyridine is produced from formaldehyde and acetaldehyde,
3. First, acrolein is formed in a Knoevenagel condensation from the acetaldehyde and formaldehyde. The acrolein is then condensed with acetaldehyde and ammonia to give dihydropyridine, which is oxidized with a solid-state catalyst to pyridine.
4. This process is carried out in a gas phase at 400–450 °C. The product consists of a mixture of pyridine, simple methylated pyridines (picolines and lutidines); its composition depends on the catalyst used and can be adapted to the needs of the manufacturer.
5. The catalyst is usually a transition metal salt such as cadmium(II) fluoride or manganese(II) fluoride, but cobalt and thallium compounds can also be used. The recovered pyridine is separated from by products in a multistage process.



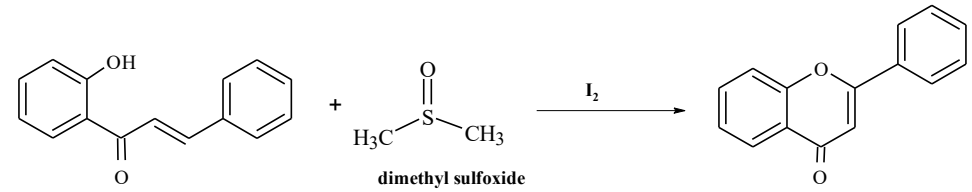
6. Synthesize of Flavones

1) In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed.
2) Chalcones are unsaturated ketone containing the reactive keto-ethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes.
3) Different methods are available for the preparation of chalcones.The most convenient method is the Claisen-Schmidt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic akali.
4) Chalcones are used to synthesize several derivatives like **Flavones**, pyrazolines, 3-chlrochromones, 1,5-benzothiazepines and having different heterocyclic ring systems



(2*E*)-1-(2-hydroxyphenyl) -3-phenylprop-2-en-1-one

3-hydroxy-2-phenyl-4*H*-chromen-4-one
3-hydroxy Flavones



(2E)-1-(2-hydroxyphenyl) -3-phenylprop-2-en-1-one

dimethyl sulfoxide

2-phenyl-4H-chromen-4-one
Flavones

Week 15

- **Lecture Title:** Heterocyclic Compounds: Five- and Six-Membered Rings – Structure and Reactions
- **Duration:** 2 hours

Lecture Objectives:

1. To examine the structure and bonding in common five- and six-membered heterocyclic compounds.
2. To compare aromatic and non-aromatic heterocycles in terms of electron distribution and stability.
3. To study the reactivity of six-membered heterocycles, especially pyridine and its derivatives.
4. To understand the influence of heteroatoms (e.g., nitrogen, oxygen, sulfur) on the chemical behavior of heterocyclic systems.
5. To explore examples of five- and six-membered heterocycles in pharmaceuticals and bioactive compounds.

• Behavioral Objectives:

1- Cognitive Domain:
• The student will be able to describe and compare the structures of common five- and six-membered heterocycles.
• The student will be able to distinguish between aromatic and non-aromatic heterocycles based on Hückel's rule.
• The student will be able to explain the chemical reactivity patterns of five-membered aromatic heterocycles in electrophilic substitution reactions.
• The student will be able to describe the nucleophilic substitution behavior of six-membered nitrogen-containing heterocycles.
• The student will be able to relate structural features to the biological activity of selected heterocyclic compounds.

2- Psychomotor Domain:
• The student will be able to draw the structural and resonance forms of five- and six-membered heterocycles.
• The student will be able to outline mechanisms of representative heterocyclic reactions.

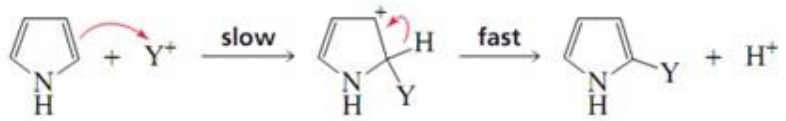
3- Affective Domain:
• The student will recognize the relevance of heterocyclic chemistry in the design of drugs and biologically active molecules.
• The student will express interest in the reactivity and versatility of heterocyclic compounds in both synthetic and medicinal chemistry.

Heterocyclic Compounds: Five- and Six-Membered Rings – Structure and Reactions

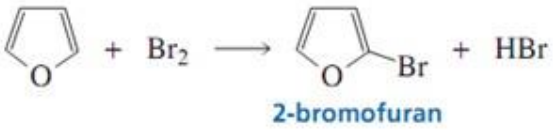
Week-15- Theoretical

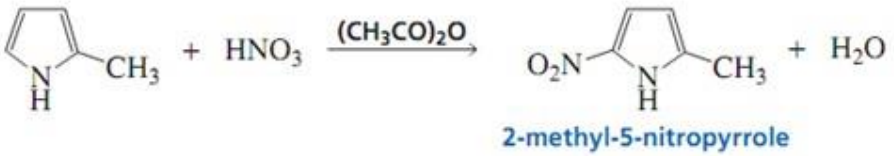
⌘ Reaction of Heterocyclic compounds :

1. Mechanism for electrophilic aromatic substitution five membered ring

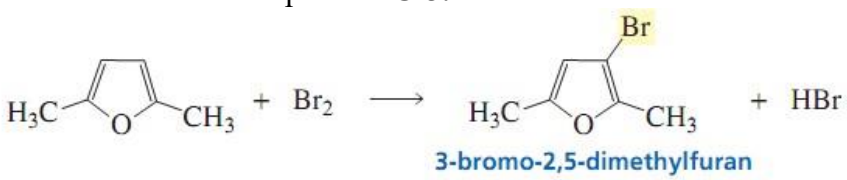


Example

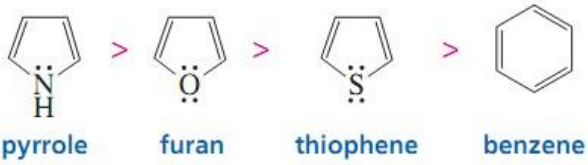




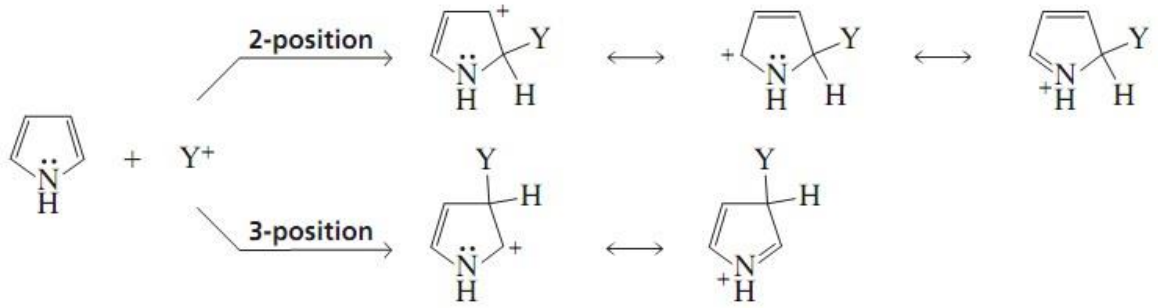
⌘ Substitution occurs preferentially at **C-2** because the intermediate obtained by attaching a substituent at this position is more stable than the intermediate obtained by attaching a substituent at **C-3**.. The intermediate resulting from **C-2** substitution of pyrrole has two additional resonance contributors, each with a positive charge on a secondary allylic carbon. The intermediate resulting from **C-3** substitution, however, has only one additional resonance contributor, which has a positive charge on a secondary carbon. If both positions adjacent to the heteroatom are occupied, electrophilic substitution will take place at **C-3.**



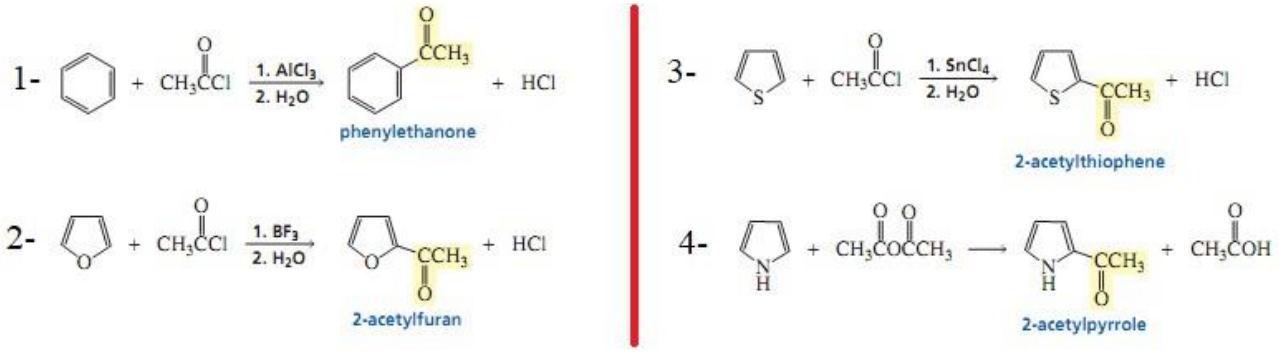
relative reactivity toward electrophilic aromatic substitution



⌘ Furan is not as reactive as pyrrole in electrophilic aromatic substitution reactions. The oxygen of furan is more electronegative than the nitrogen of pyrrole, so the oxygen is not as effective as nitrogen in stabilizing the carbocation. Thiophene is less reactive than furan toward electrophilic substitution because sulfur's π electrons are in a 3*p* orbital, which overlaps less effectively than the 2*p* orbital of nitrogen or oxygen with the 2*p* orbital of carbon.

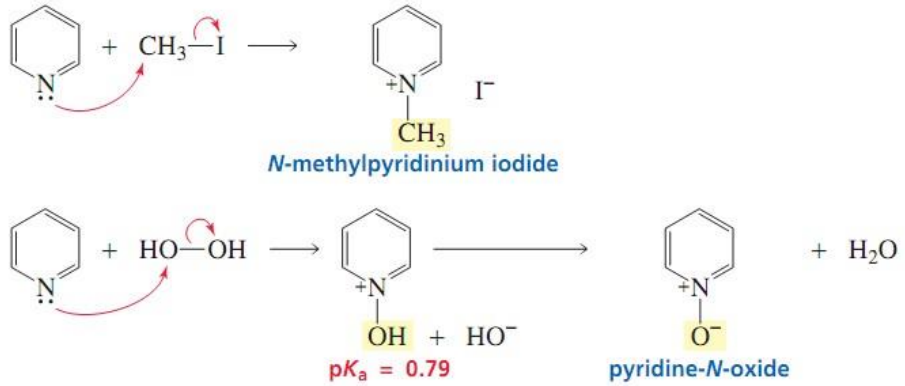


⌘ The relative reactivities of the five-membered-ring heterocycles are reflected in the Lewis acid required to catalyze a **Friedel–Crafts acylation reaction** . Benzene requires $AlCl_3$, a relatively strong Lewis acid. Thiophene is more reactive than benzene, so it can undergo a Friedel–Crafts reaction using $SnCl_4$,a weaker Lewis acid. An even weaker Lewis acid, BF_3 , can be used when the substrate is furan. Pyrrole is so reactive that an anhydride is used instead of a more reactive acyl chloride, and no catalyst is necessary.

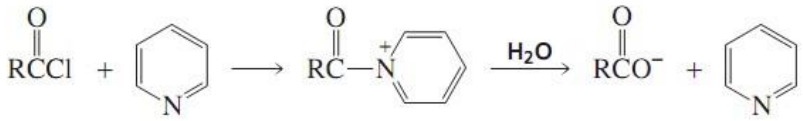


2. Mechanism for electrophilic aromatic substitution six membered ring

A. Pyridine is a tertiary amine, so it undergoes reactions characteristic of tertiary amines. For example, pyridine undergoesS_N2 reactions with alkyl halides, and it reacts with hydrogen peroxide to form an N-oxide .

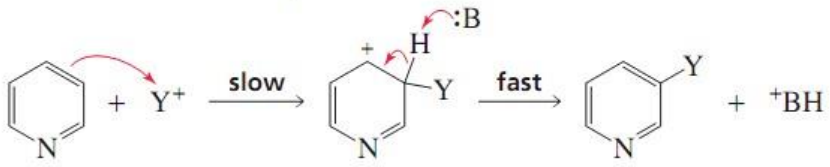


- PROBLEM : Will an amide be formed from the reaction of an acyl chloride with an aqueous solution of pyridine? Explain your answer.
- SOLUTION : An amide will not be formed because the positively charged nitrogen causes pyridine to be an excellent leaving group. Therefore, the final product of the reaction will be a carboxylic acid. (If the final pH of the solution is greater than the pKa of the carboxylic acid, the carboxylic acid will be predominantly in its basic form.)

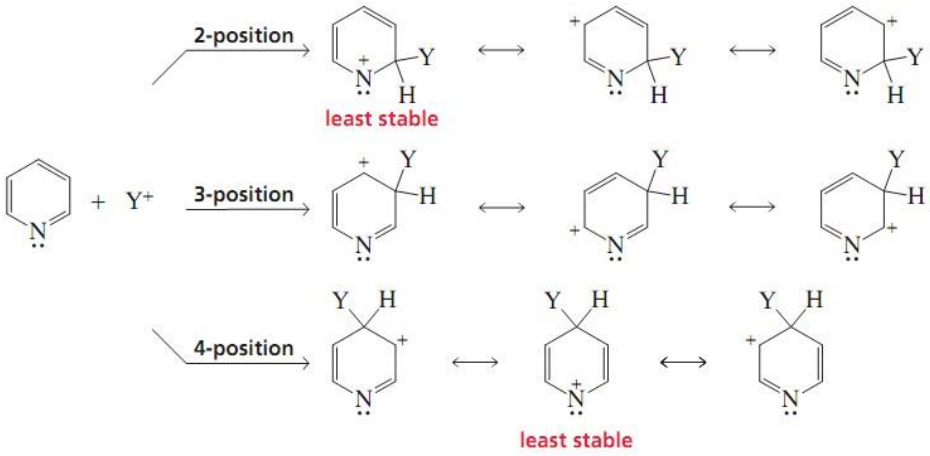


Because it is aromatic, pyridine (like benzene) undergoes electrophilic aromatic substitution reactions (:B is any base in the solution).

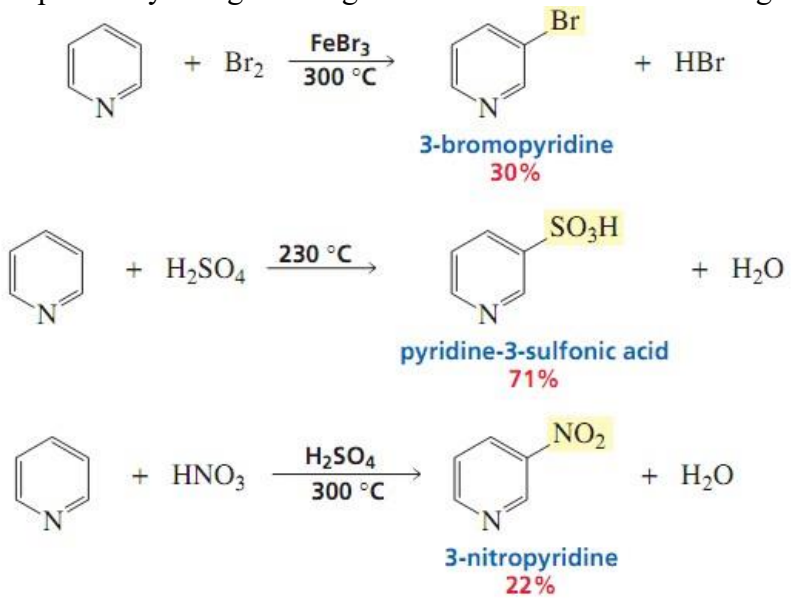
mechanism for electrophilic aromatic substitution



Structures of the intermediates that can be formed from the reaction of an electrophile with pyridine.

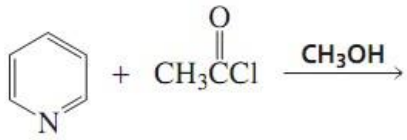


Pyridine, therefore, undergoes electrophilic aromatic substitution reactions only under vigorous conditions, and the yields of these reactions are often quite low. If the nitrogen becomes protonated under the reaction conditions, the reactivity is further decreased because a positively charged nitrogen is more electron withdrawing than a neutral nitrogen.



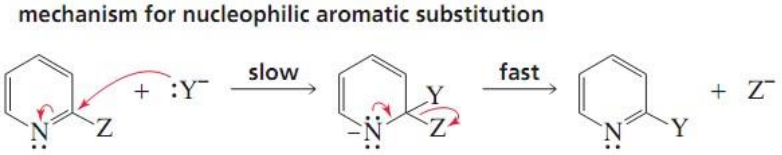
We have seen that highly deactivated benzene rings do not undergo Friedel–Crafts alkylation or acylation reactions. Therefore, pyridine, whose reactivity is similar to that of a highly deactivated benzene, does not undergo these reactions either.

☒ **PROBLEM** : Give the product of the following reaction:

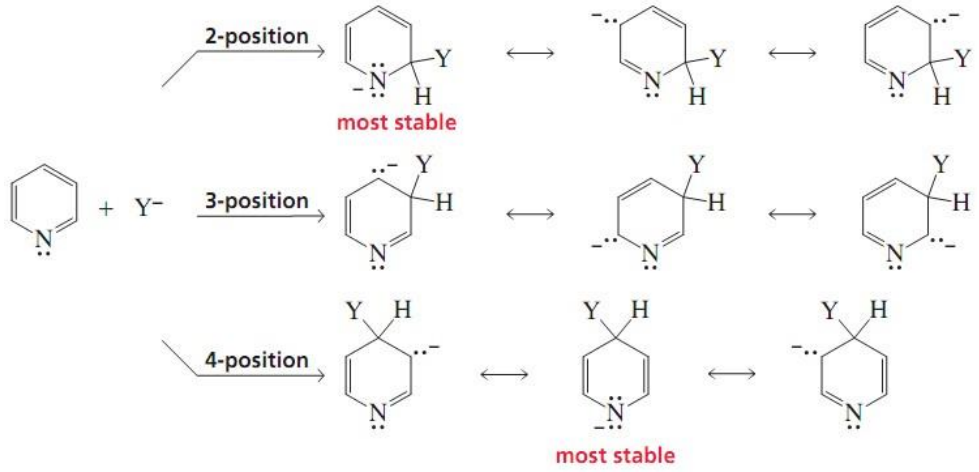


☒ Since pyridine is less reactive than benzene toward electrophilic aromatic substitution, it is not surprising that pyridine is more reactive than benzene toward nucleophilic aromatic substitution. The electron-withdrawing nitrogen atom that destabilizes the intermediate in electrophilic aromatic substitution stabilizes it in nucleophilic aromatic substitution.

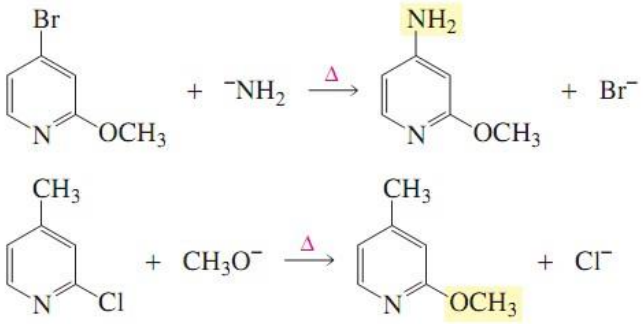
Nucleophilic aromatic substitution of pyridine

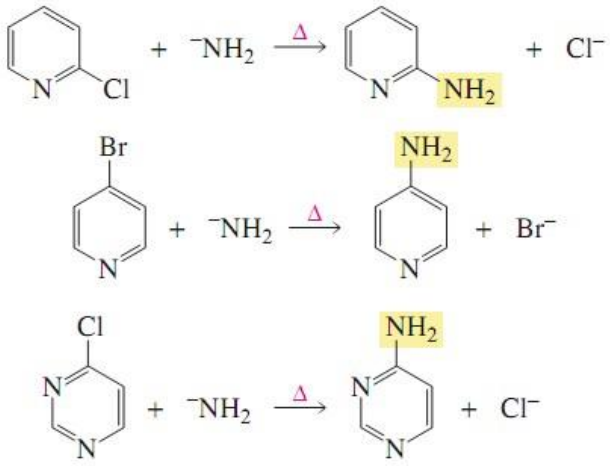


Nucleophilic aromatic substitution of pyridine takes place at C-2 and C-4, because attack at these positions leads to the most stable intermediate. Only when nucleophilic attack occurs at these positions is a resonance contributor obtained that has the greatest electron density on nitrogen, the most electronegative of the ring atoms .



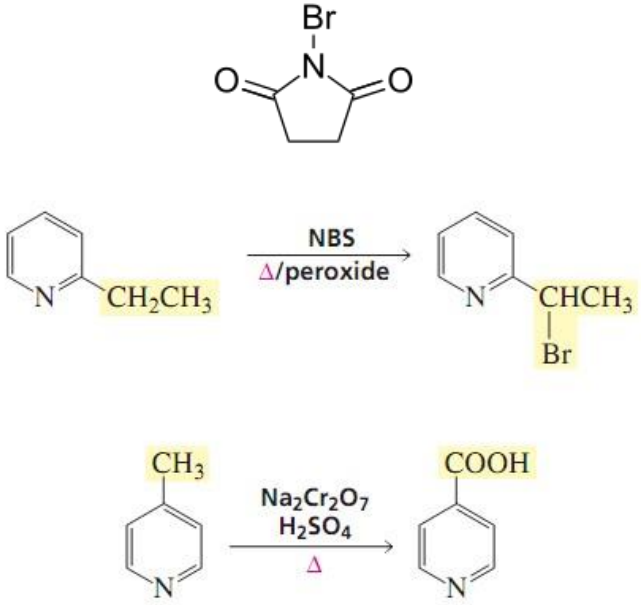
If the leaving groups at C-2 and C-4 are different, the incoming nucleophile will preferentially substitute for the weaker base (the better leaving group).



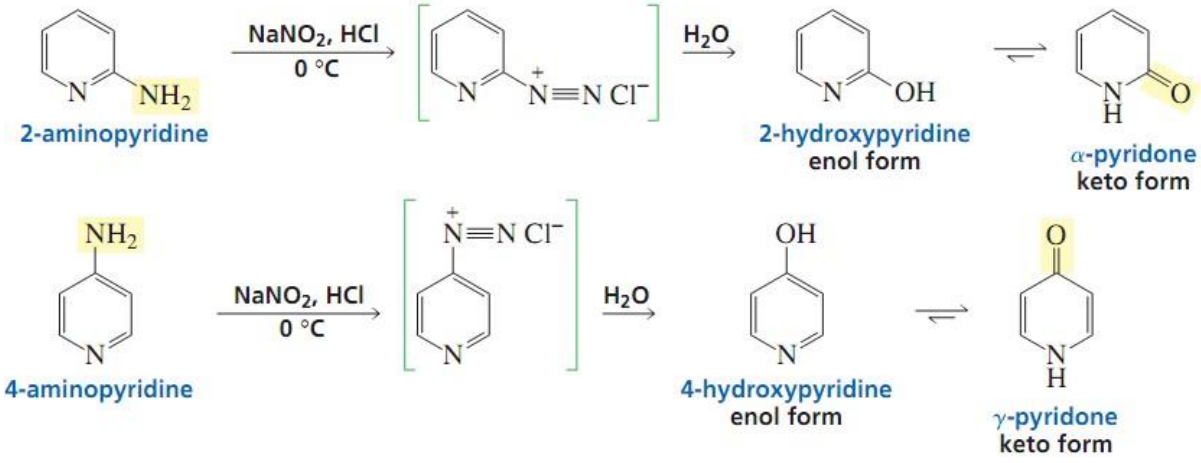


Substituted pyridines undergo many of the side-chain reactions that substituted benzenes undergo, such as bromination and oxidation. **N-bromosuccinamide**

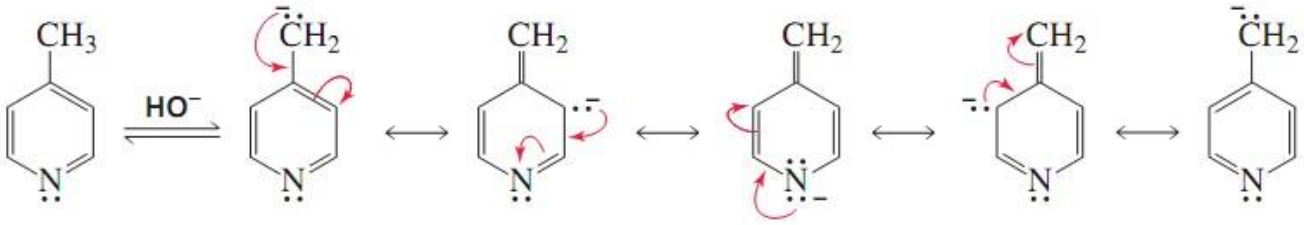
***N*-Bromosuccinimide** or **NBS** is a chemical reagent used in radical substitution, electrophilic addition, and electrophilic substitution reactions in organic chemistry. NBS can be a convenient source of Br•, the bromine radical.



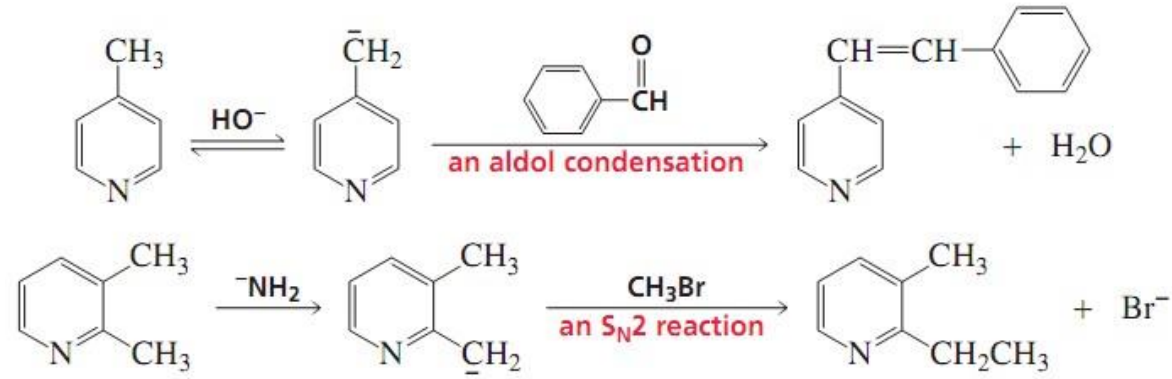
When 2- or 4-aminopyridine is diazotized, α-pyridone or γ-pyridone is formed. Apparently, the diazonium salt reacts immediately with water to form a hydroxypyridine. The product of the reaction is a pyridone because the keto form of a hydroxypyridine is more stable than the enol form. (The mechanism for the conversion of a primary amino group into a diazonium group .



The electron-withdrawing nitrogen causes the α-hydrogens of alkyl groups attached to the 2- and 4-positions of the pyridine ring to have about the same acidity as the α-hydrogens of ketones.

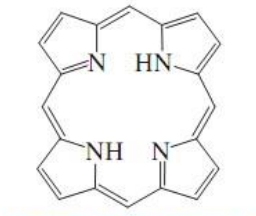


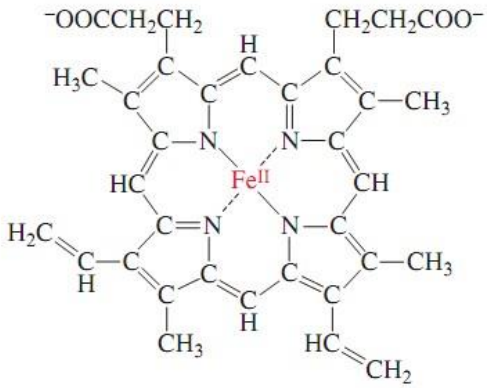
Consequently, the α-hydrogens of alkyl substituents can be removed by base, and the resulting carbanions can react as nucleophiles.



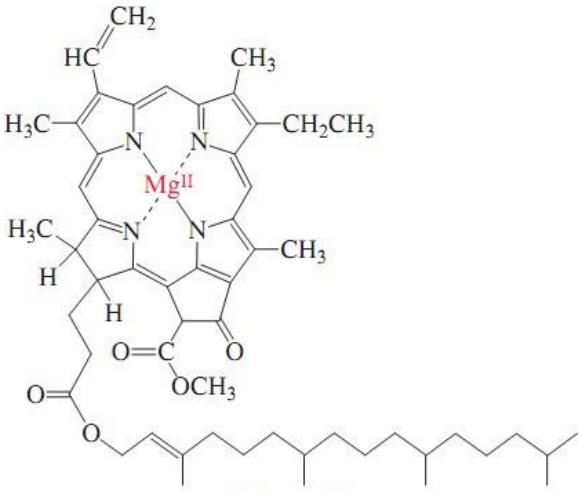
Importance to Life and Industry:

1) Many heterocyclic compounds are biosynthesized by plants and animals and are biologically active.
2) Over millions of years these organisms have been under intense evolutionary pressure, and their metabolites may be used to advantage; for example, as toxins to ward off predators, or as colouring agents to attract mates or pollinating insects.
3) Porphyrin :Substituted porphyrins are important naturally occurring heterocyclic compounds. A porphyrin ring system consists of four **pyrrole rings** joined by one-carbon bridges. **Heme**, which is found in **hemoglobin** and **myoglobin**, contains an iron ion Fe^{+2} ligated by the four nitrogen's of a porphyrin ring system. Ligation is the sharing of nonbonding electrons with a metal ion. The porphyrin ring system of heme is known as protoporphyrin IX; the ring system plus the iron atom is called iron protoporphyrin IX.

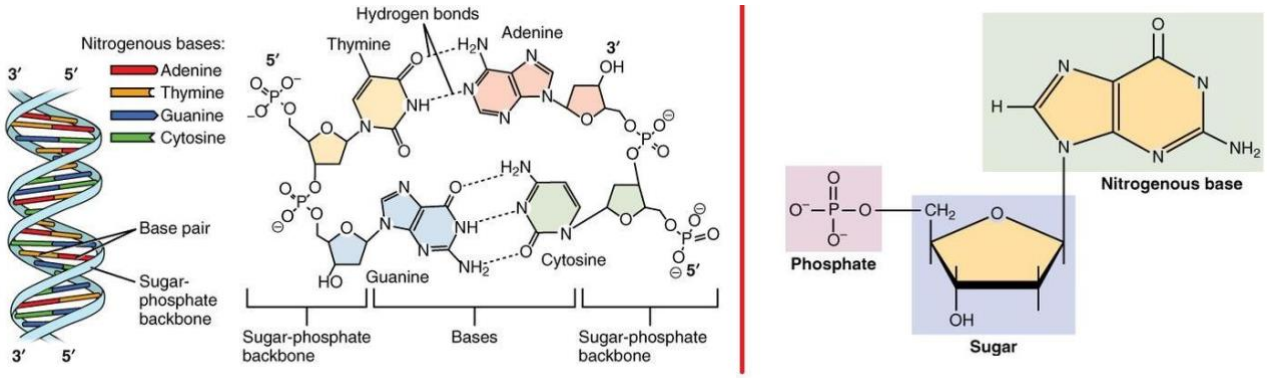

a porphyrin ring system


iron protoporphyrin IX
heme

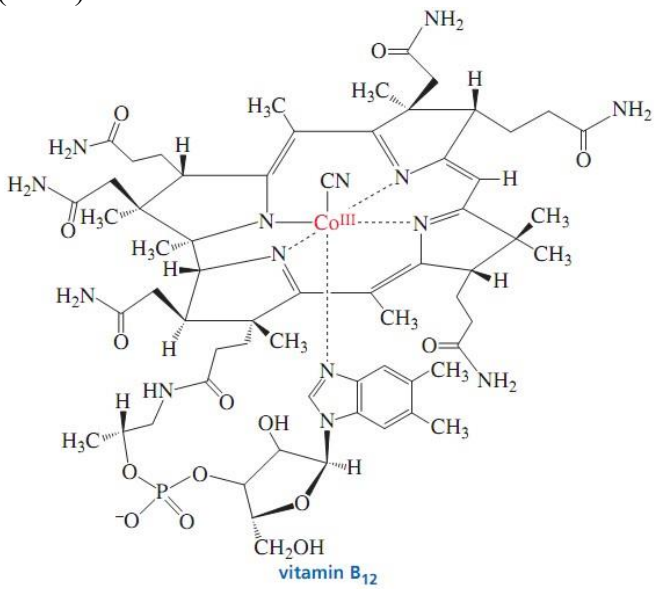
4) The ring system in chlorophyll a, the substance responsible for the green color of plants, is similar to porphyrin but contains a cyclopentanone ring, and one of its pyrrole rings is partially reduced. The metal atom in chlorophyll a is magnesium (Mg^{+2})



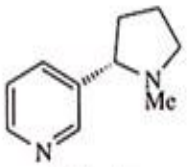
5) Similarly, the paired bases found in RNA and DNA are heterocycles, as are the sugars that in combination with phosphates provide the backbones and determine the topology of these nucleic acids.



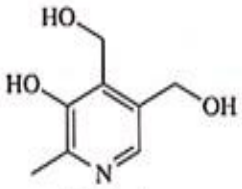
6) Vitamin B_{12} also has a ring system similar to porphyrin, but one of the methine bridges is missing. The ring system of vitamin B_{12} is known as a corrin ring system. The metal atom in vitamin B_{12} is cobalt (Co^{+3}).



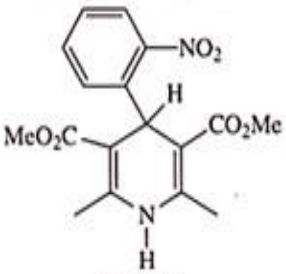
7) The biological properties of heterocycles in general make them one of the prime interests of the pharmaceutical and biotechnology industries. A selection of just six biologically active pyridine or piperidine derivatives . It includes four natural products (nicotine, pyridoxine, cocaine and morphine) and two synthetic compounds (nifedipine and paraquat).



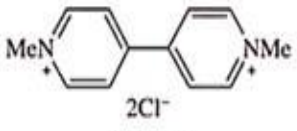
Nicotine
(addictive drug and an insecticide)



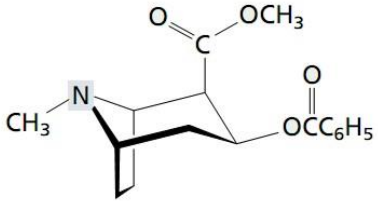
Pyridoxine
(vitamin B_6)



Nifedipine
(cardiovascular drug)

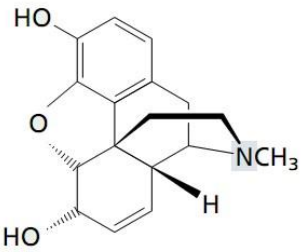


Paraquat
(herbicide, interfering with photosynthesis)



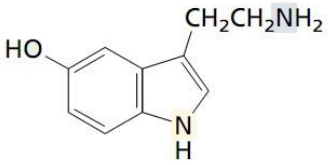
Cocaine

(A central nervous system stimulant obtained from the leaves of the coca plant.)



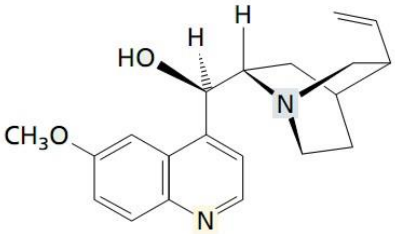
Morphine

(An opium alkaloid. Although it is an excellent analgesic, its use is restricted because of the potential for addiction. Heroin is the diacetate ester of morphine.)



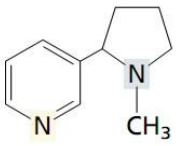
Serotonin

(A hormone synthesized in the pineal gland. Certain mental disorders are believed to be related to serotonin levels in the brain.)



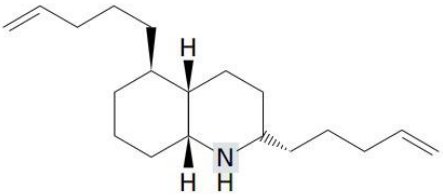
Quinine

(Alkaloid of cinchona bark used to treat malaria)



Nicotine

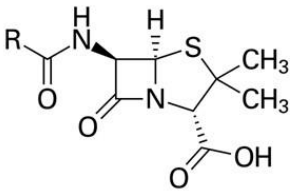
(An alkaloid present in tobacco; a very toxic compound sometimes used as an insecticide)



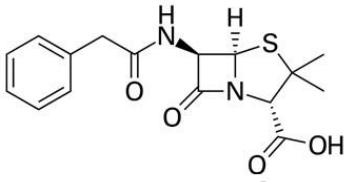
Dendrobine

(Isolated from frogs of the Dendrobatidae family. Related compounds have also been isolated from certain ants.)

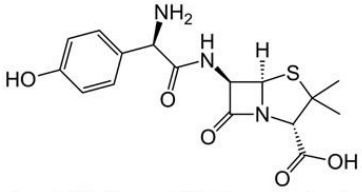
Antibiotic



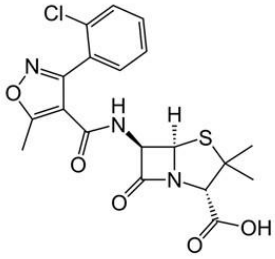
Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci. They are still widely used today, though many types of bacteria have developed resistance following extensive use.



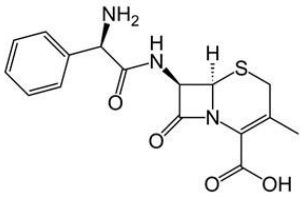
Benzylpenicillin, also known as penicillin G, is an antibiotic used to treat a number of bacterial infections.This includes pneumonia, strep throat, syphilis, necrotizing enterocolitis, diphtheria, gas gangrene, leptospirosis, cellulitis, and tetanus.It is not a first-line agent for pneumococcal meningitis.



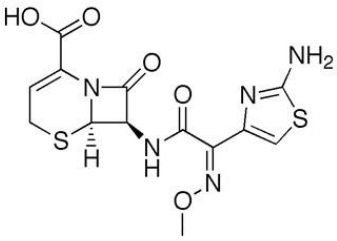
Amoxicillin is an antibiotic used to treat a number of bacterial infections.These include middle ear infection, strep throat,pneumonia, skin infections, and urinary tract infections among others. It is taken by mouth, or less commonly by injection.



Cloxacillin is an antibiotic useful for the treatment of a number of bacterial infections.This includes impetigo, cellulitis, pneumonia, septic arthritis, and otitis externa.It is not effective for methicillin-resistant Staphylococcus aureus (MRSA). It is used by mouth and by injection.



Cefalexin, also spelled cephalexin, is an antibiotic that can treat a number of bacterial infections. It kills gram-positive and some gram-negative bacteria by disrupting the growth of the bacterial cell wall. Cefalexin is a beta-lactam antibiotic within the class of first-generation cephalosporins. It works similarly to other agents within this class, including intravenous cefazolin, but can be taken by mouth.



Cefixime is an antibiotic useful to treat a number of bacterial infections. This includes otitis media, strep throat, pneumonia, urinary tract infections, gonorrhea, and Lyme disease.For gonorrhea typically only one dose is required.In the United States it is a second line treatment to ceftriaxone for gonorrhea.It is taken by mouth.

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