Ministry of Education and Science of the Republic of Kazakhstan
Karaganda Buketov University

Conformational Analysis of Organic Compounds

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Type of lessons: lecture

Karaganda 2022

Course Topics

Topic 1. Cycloalkanes

Topic 2. Aromatic Hydrocarbons (Arenes)

Topic 3. Halogenated Aromatic Hydrocarbons

Topic 4. Aromatic Aromatic Sulfonic Acids

Topic 5. Aromatic Nitro Compounds

Topic 6. Aromatic Amines

Topic 7. Diazo and azo compounds

Topic 8. Phenols

Topic 9. Aromatic Aldehydes and Ketones

Topic 10. Aromatic Carboxylic Acids and Their Derivatives

Topic 11. Polynuclear Aromatic Compounds

Topic 12. Heterocycles

Cycloalkanes

Topic 1

Outline of the lecture

1. Cycloalkanes
2. Naming Cycloalkanes
3. Conformations of Cycloalkanes
4. Chemical Properties of Cycloalkanes

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1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
2. Chernykh, V.P. 2003. *Lectures on Organic Chemistry: Tutorial for students of Higher educational institutions.* Zolotye stranitsy: Kharkov
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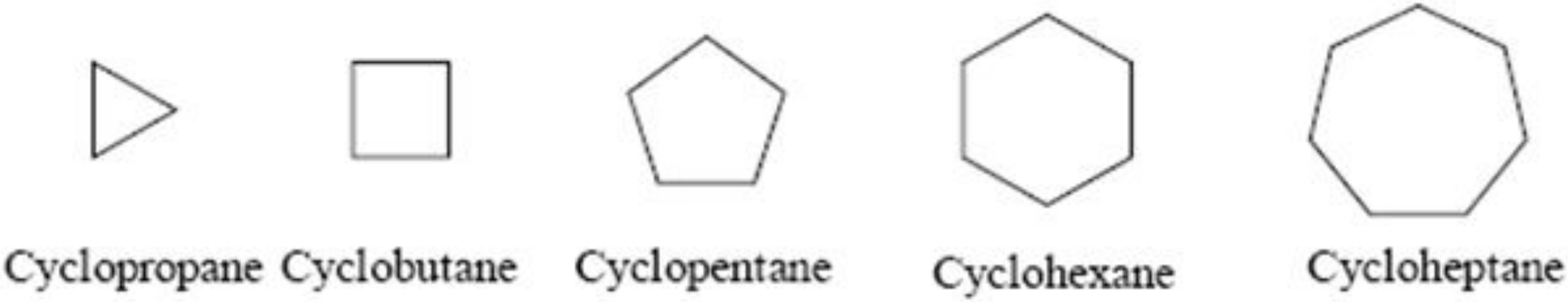
10. Kim, A.M. 2004. *Organic Chemistry*. Novosibirsk
11. https://www.masterorganicchemistry.com/2018/01/29/ortho-para-and-meta-directors-in-electrophilic-aromatic-substitution/

Cycloalkanes

- **Cycloalkanes** are hydrocarbons that have the general molecular formula C_nH_{2n} and in which some, or all, of the carbon atoms form a ring.



Cycloalkanes

Cycloalkanes are classified according to the cycle size, the number of cycles, and the way the cycles are connected in the molecule.

According to the cycle size there are distinguished:

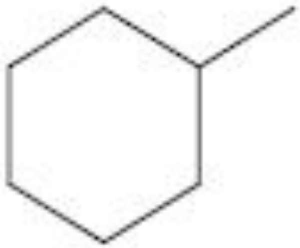
- cycloalkanes with small cycles (three- and four-membered);
- cycloalkanes with ordinary cycles (five-, six- and seven-membered);
- cycloalkanes with medium cycles (from eight to eleven members);
- macrocycles.

Depending on the number of cycles in the molecule, there are found:

- monocyclic
- bicyclic
- polycyclic cycloalkanes

Naming cycloalkanes

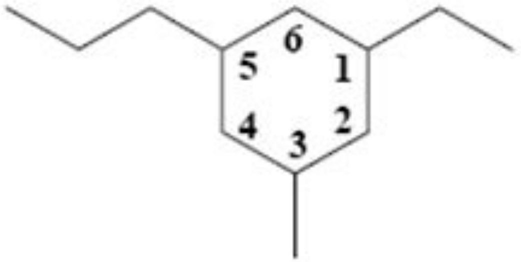
- In order to name cycloalkanes, determine the parent name of the compound by counting the number of carbons in the ring as for alkanes and add the prefix ***cyclo-*** to the parent name. Further determine the position of the alkyl group or groups on the ring and name them.



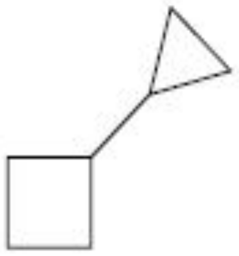
Methylcyclohexane

Naming cycloalkanes

- When a ring has more than one alkyl group attached, number the ring to give the lowest sum of numbers. If the sum of numbers is identical either direction around the ring, then count towards the second group alphabetically on the ring.

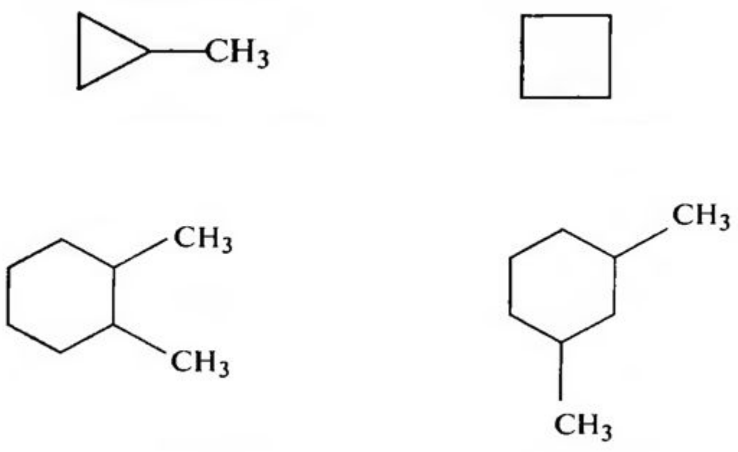


1-Ethyl-3-methyl-5-propylcyclohexane



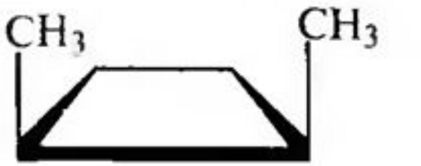
Cyclopropylcyclobutane

Structure and isomerism of cycloalkanes

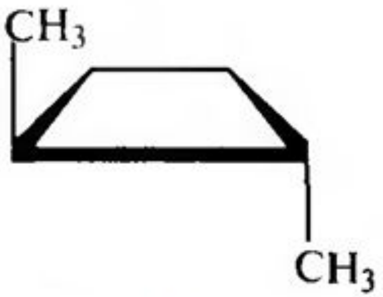


The structural isomerism of cycloalkanes is determined by the size of the cycle, the nature and mutual arrangement of substituents:

The geometric isomerism of cycloalkanes is due to the different arrangement of substituents relative to the ring plane.



cis-1,2-dimethylcyclobutane
(Z isomer)

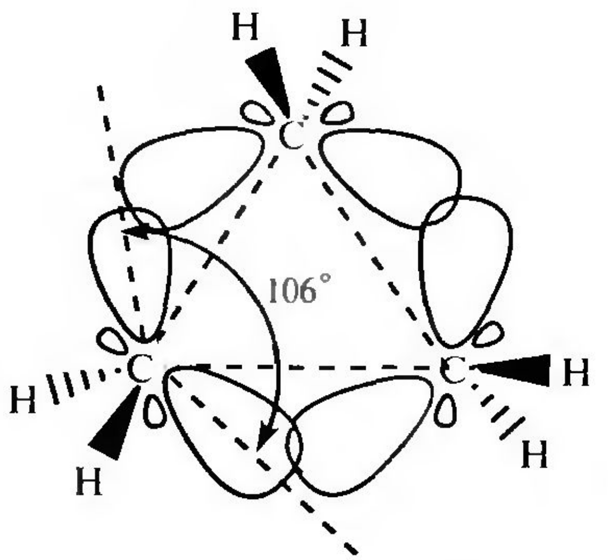


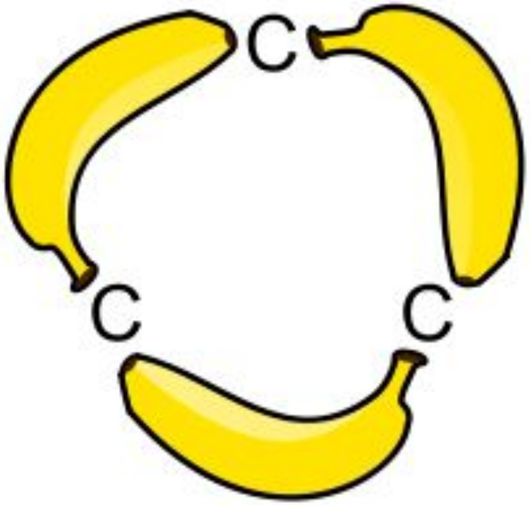
trans-1,2-dimethylcyclobutane
(E isomer)

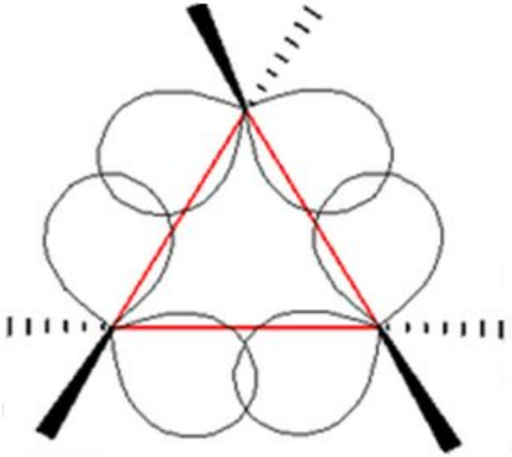
Conformations of cycloalkanes

- The molecule of any cycloalkane tends to occupy in space such a form (**conformation**) in which the sum of angle, torsional and van der Waals strains would be minimal.
- With the exception of cyclopropane, the rings of all cycloalkanes are nonplanar. Cyclopropane is planar and destabilized by *angle strain and torsional strain.* Other molecules of cycloalkanes adopt the shape that minimizes *the angle strain.*
- **Angle strain** is destabilization that results from distortion of bond angles from their normal values.
- **Torsional strain** is destabilization that results when bonds on adjacent atoms are not staggered.

Stereochemistry of Cycloalkanes

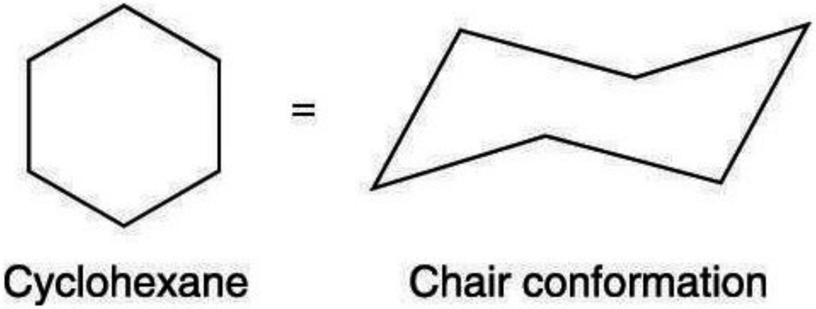


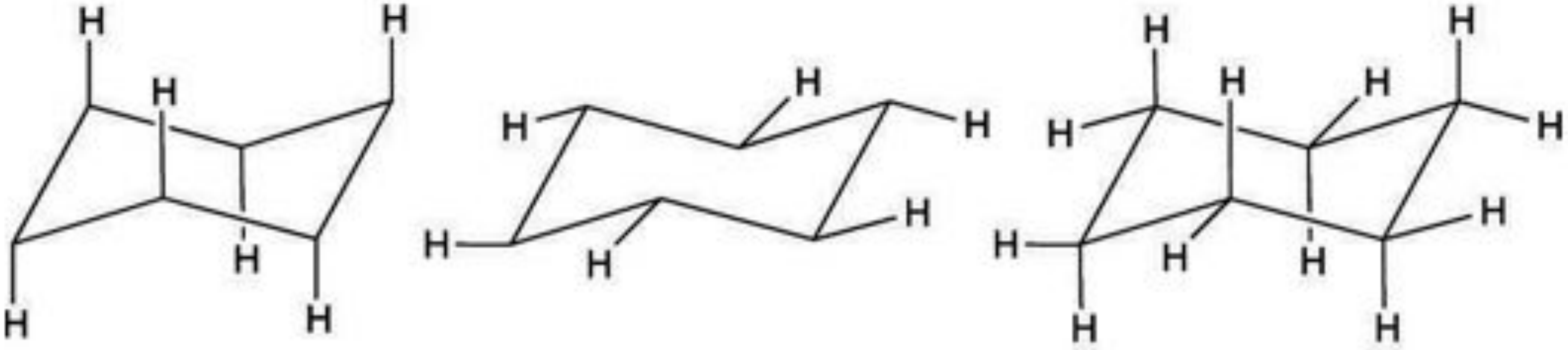




https://en.wikipedia.org/wiki/Bent_bond

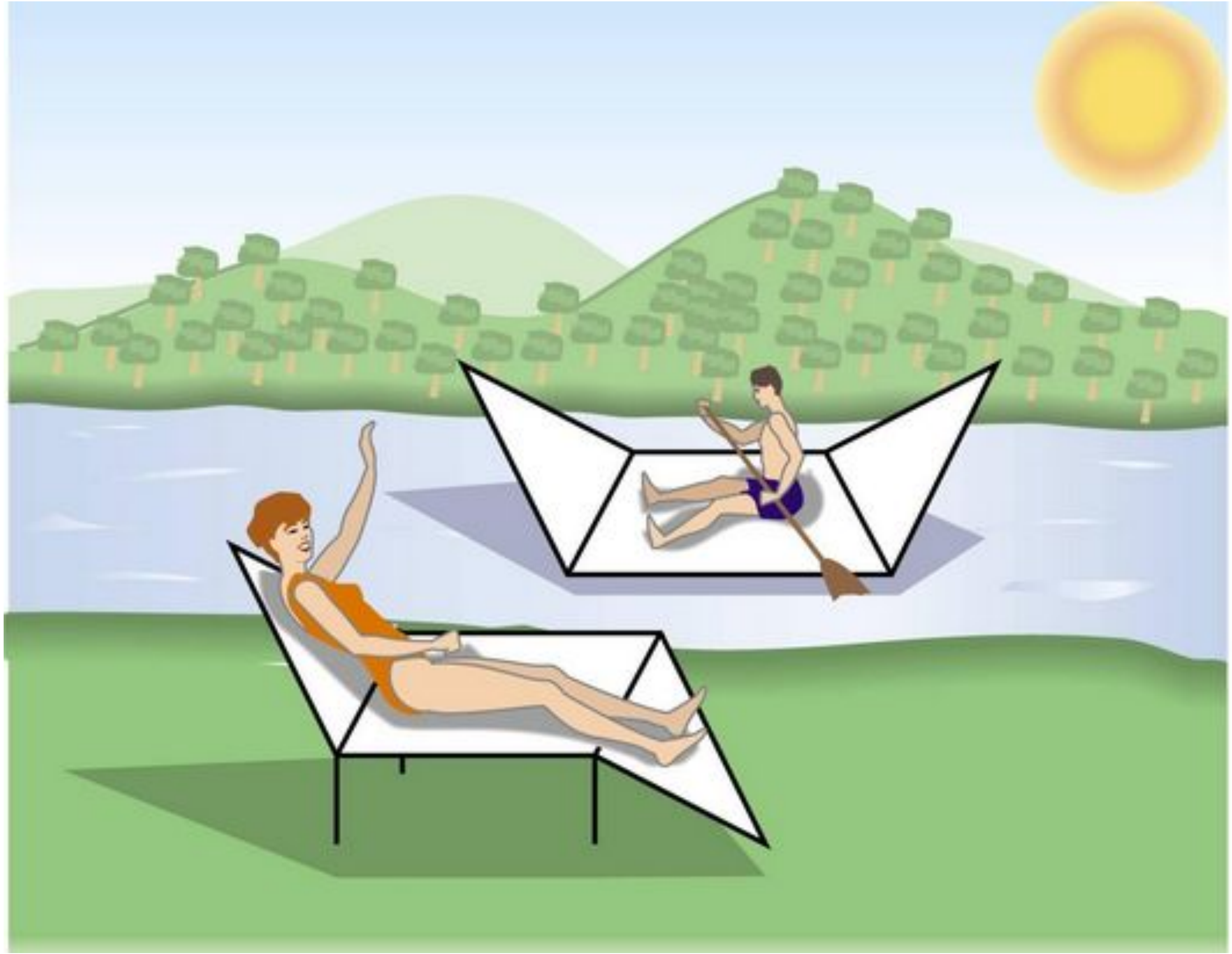
Stereochemistry of Cycloalkanes



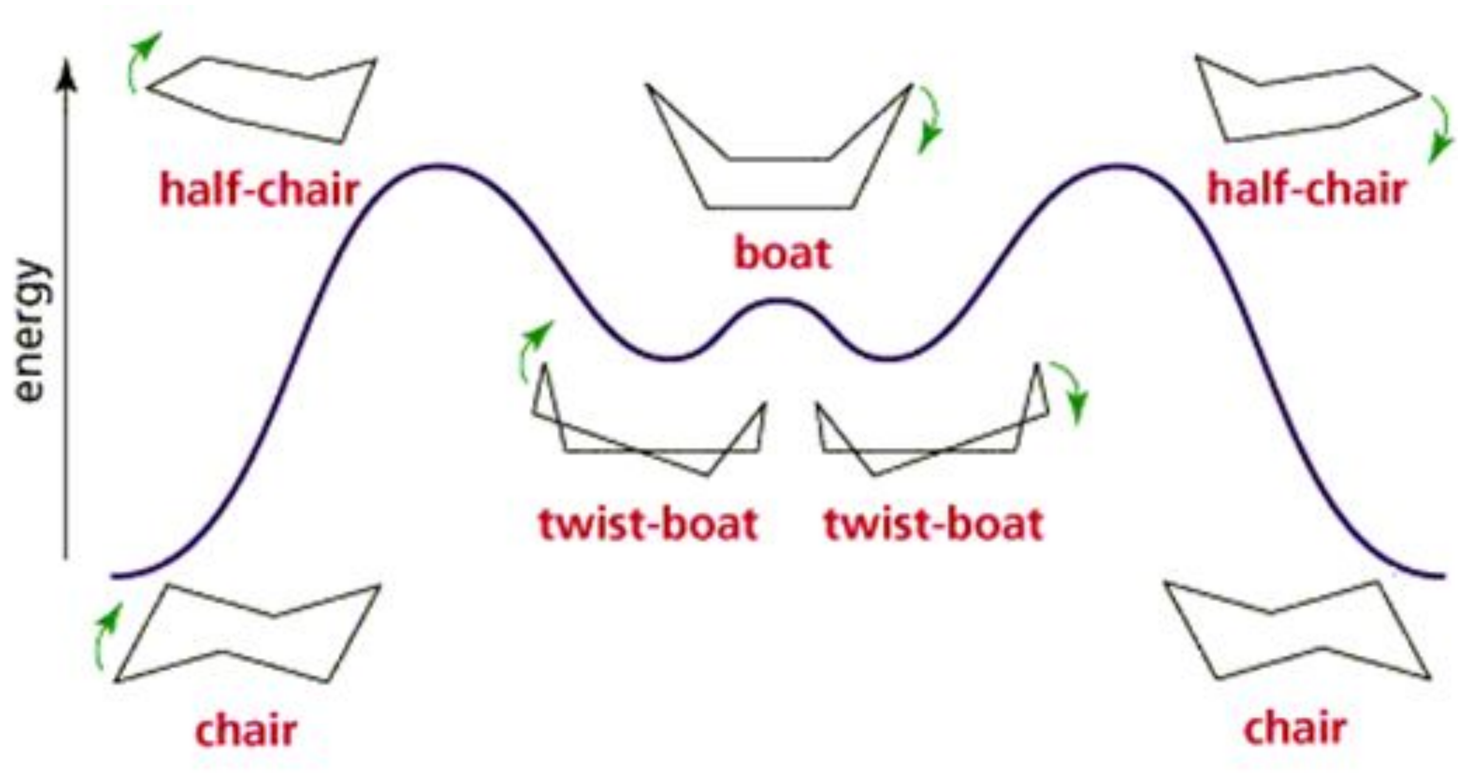


https://www.dummies.com/education/science/chemistry/how-to-draw-the-chair-conformation-of-cyclohexane/

Stereochemistry of Cycloalkanes

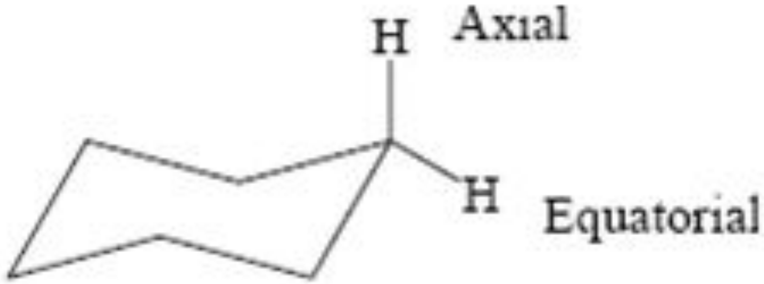


Conformations of cycloalkanes



Conformations of cycloalkanes

- The chair conformation of cyclohexane has two distinct types of carbon-hydrogen bonds, namely, **axial and equatorial ones**. Six of these bonds are axial and the other six are equatorial ones, with one axial and one equatorial bond on each carbon.

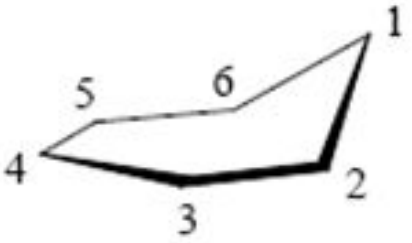


Conformations of cycloalkanes

- Through a process called *ring inversion*, or *chair-boat-chair interconversion,* one chair form of cyclohexane converts to another chair form of cyclohexane. In this process of *ring flipping,* the equatorial substituents become axial, and the axial substituents become equatorial.

Conformations of cycloalkanes

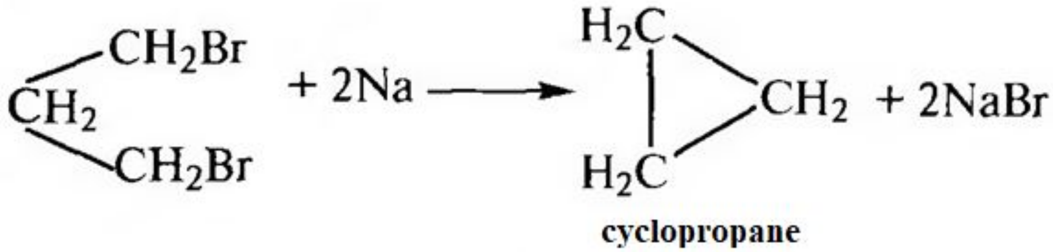
- The process of ring inversion takes cyclohexane through a conformation called the *half-chair conformation.*



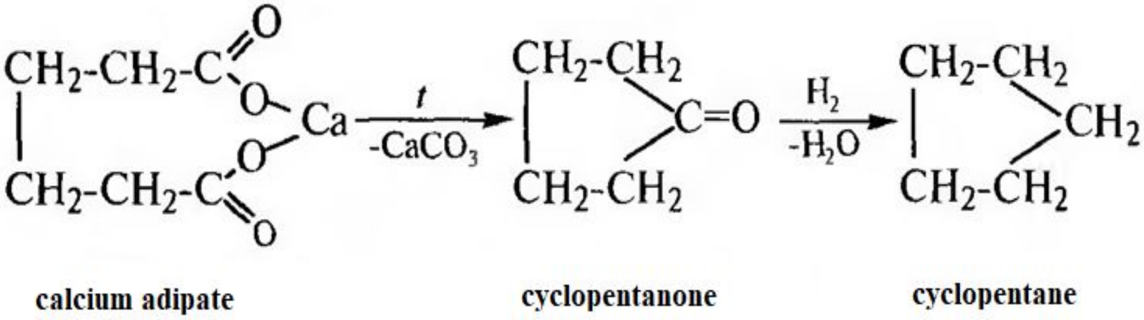
Half-chair conformation of cyclohexane

Methods for obtaining cycloalkanes

1. Interaction of ***α,ω***-dihaloalkanes with metallic sodium and zinc. This method is an intramolecular version of the Wurtz reaction, which makes it possible to obtain three-, four-, and five-membered cycloalkanes.

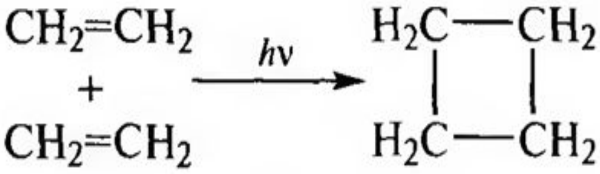


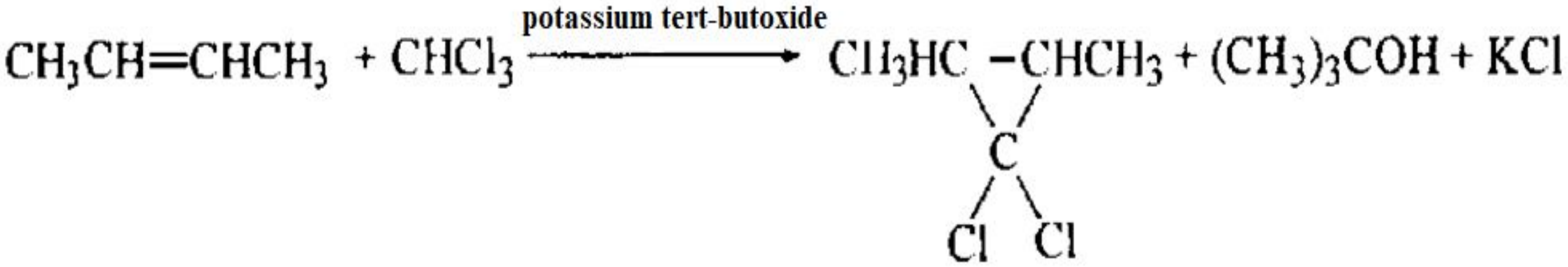
2. Pyrolysis of calcium, barium or thorium salts of dicarboxylic acids. During pyrolysis (dry distillation) of dicarboxylic acids salts, cyclic ketones are formed, which are then reduced to the corresponding cycloalkanes.

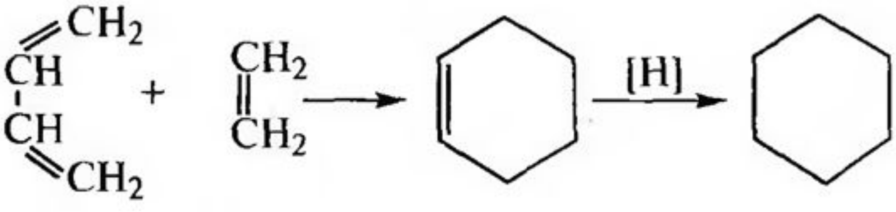


Methods for obtaining cycloalkanes

3. ***Cycloaddition.*** This is the process of combining two or more unsaturated molecules to form a product of a cyclic structure. For example, dimerization of alkenes ([2+2] cycloaddition) makes it possible to obtain cyclobutane and its homologues.

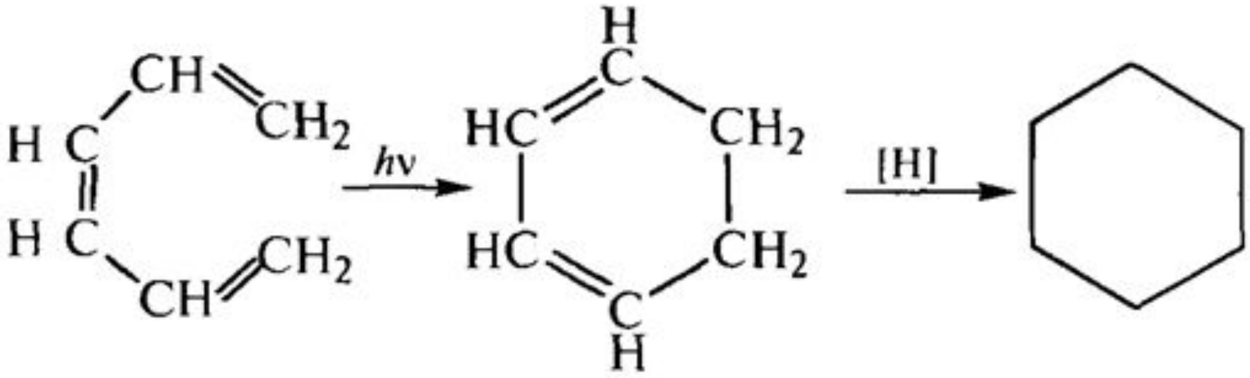






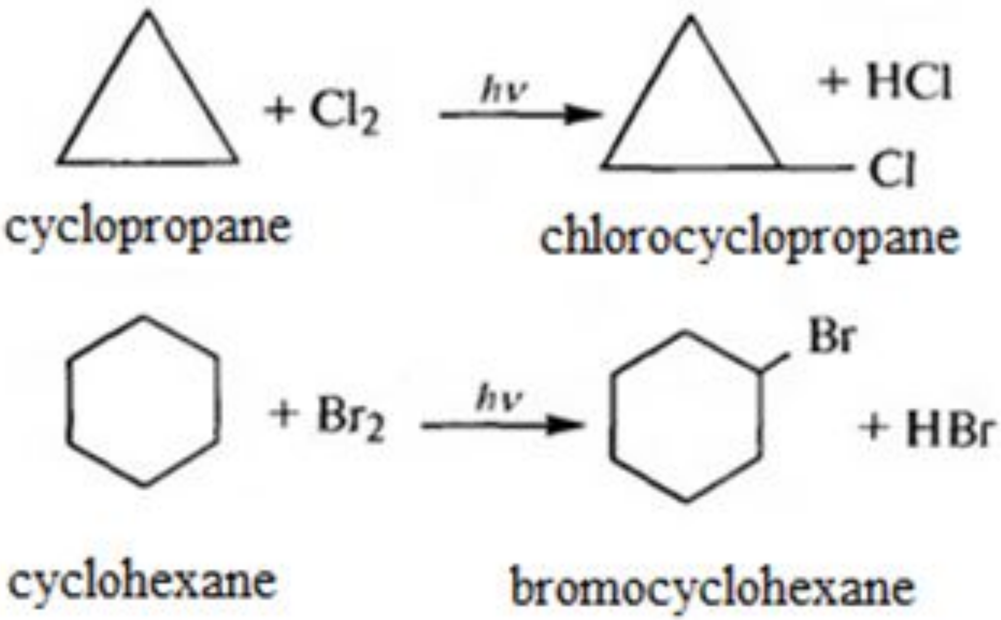
Methods for obtaining cycloalkanes

4. ***Electrocyclic reactions.*** An electrocyclic ring-closing reaction is a reaction in which a σ-bond is formed between the ends of the conjugated system of a molecule.



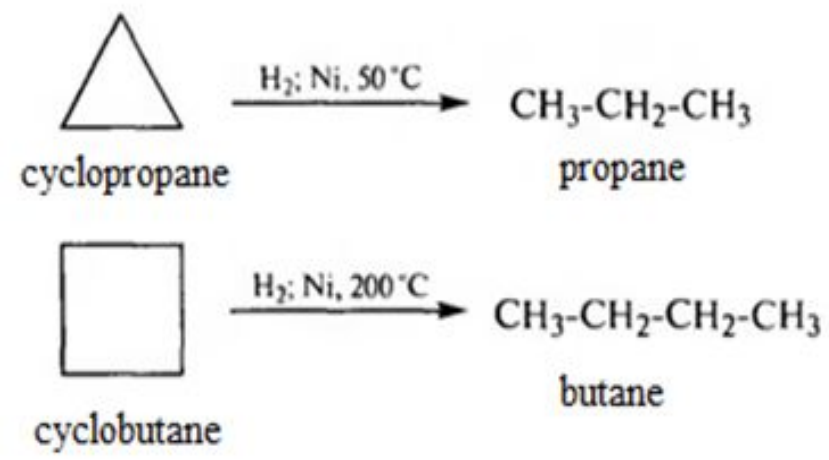
Chemical Properties of Cycloalkanes

- Free radical substitution reactions (S_R) are characteristic for cycloalkanes:



Chemical Properties of Cycloalkanes

Hydrogenation

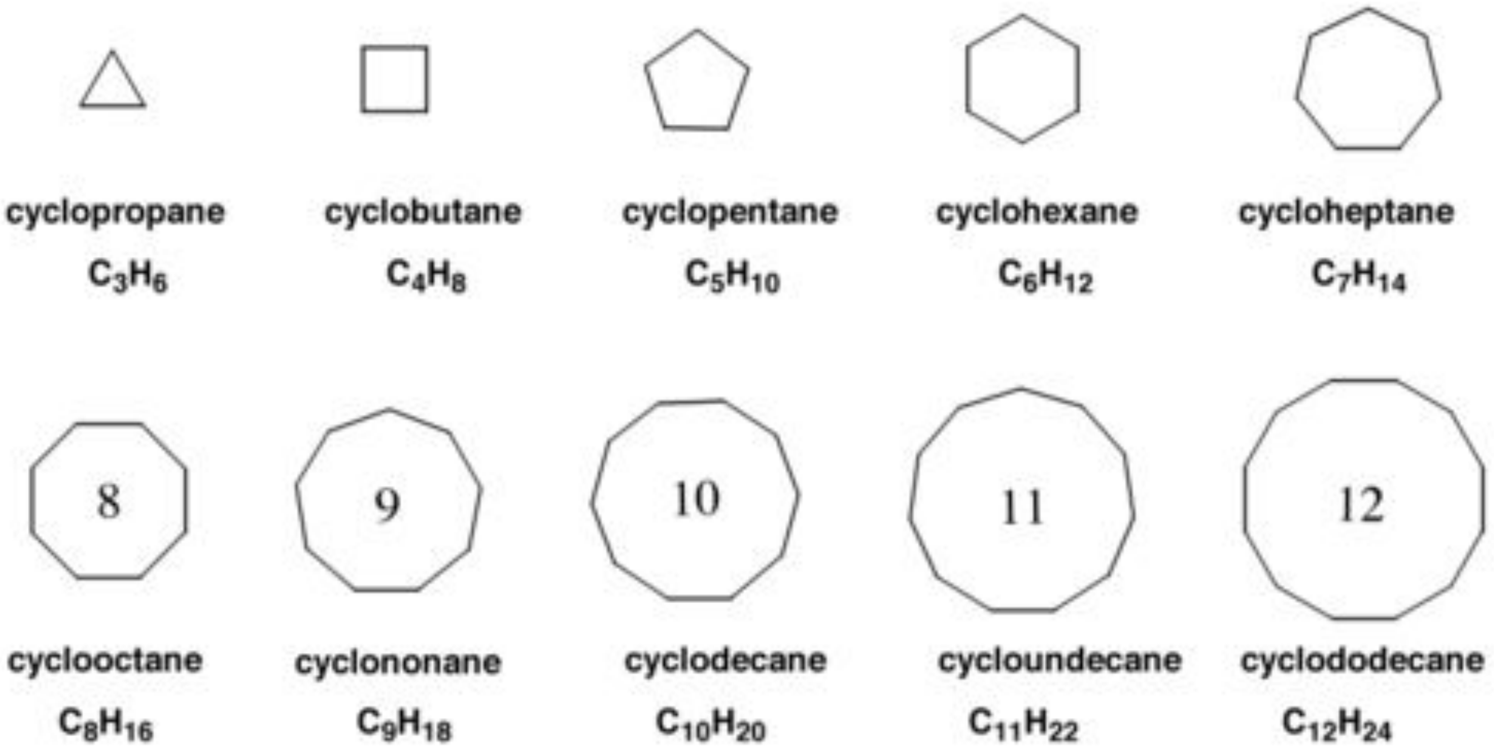


Halogenation

Hydrohalogenation

Summary

- This lecture considers cycloalkanes, conformations of cycloalkanes as well as their chemical properties.



Questions and Assignments

1. What are cycloalkanes? Give examples.
2. Name conformations of cycloalkanes.
3. What is ring inversion?
4. Discuss properties of cycloalkanes.
5. Compare halogenation of cyclopropane and cyclopentane.

Aromatic Hydrocarbons (Arenes)

Topic 2

Outline of the lecture

1. Aromaticity. Hückel's Rule
2. Benzene and its Derivatives
3. Nomenclature and isomerism of benzene derivatives
4. Chemical Properties of Benzene and its Derivatives

Bibliography:

1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
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11. https://www.masterorganicchemistry.com/2018/02/02/understanding-ortho-para-meta-directors/

Aromaticity. Hückel's Rule. Benzene and its Derivatives

Aromatic compounds are compounds, which contain cyclic conjugated π-electron systems, that meet the criteria of aromaticity. To be aromatic, a compound must be cyclic and the π electrons must be delocalized over the entire ring. The structure of the compound must be planar, or nearly planar.

Aromaticity. Hückel's Rule

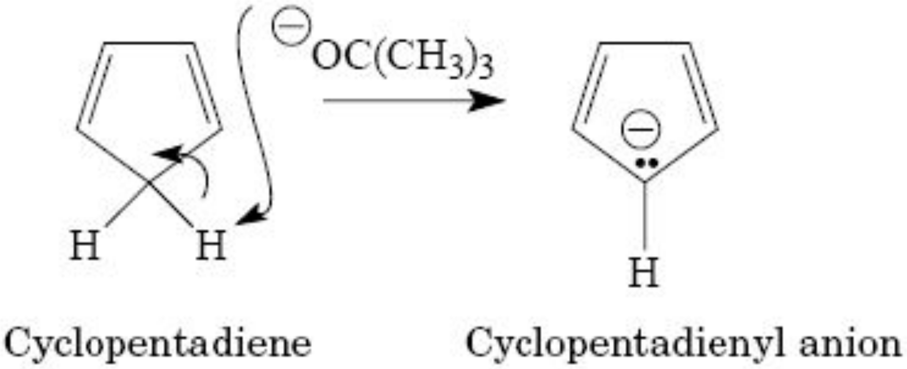
Hückel's rule

Hückel postulated that the number of delocalized π electrons contained in the molecule determined whether or not the molecule was aromatic. He suggested that the number of π electrons needed for aromaticity was $4N + 2$ electrons (*N is any integer value*. N=*0, 1, 2, …).*

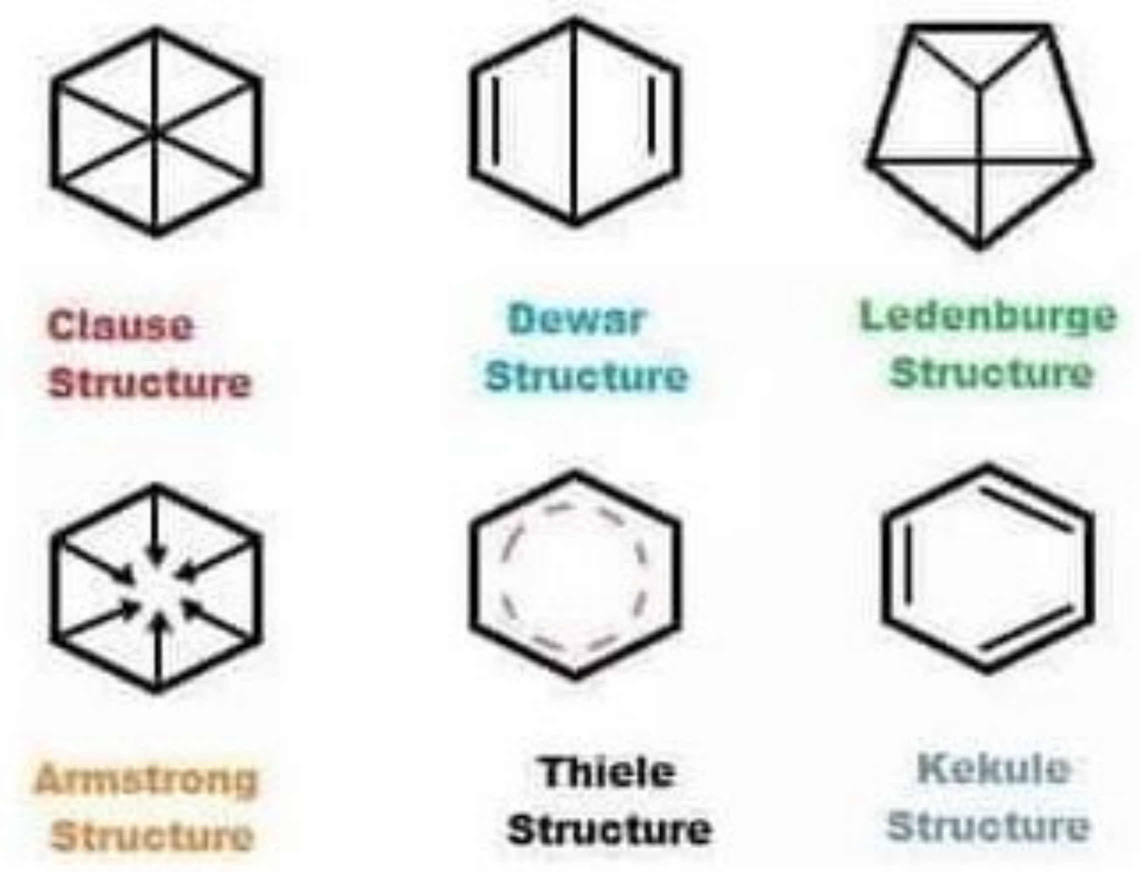
Aromatic ions

A number of cyclic species that bear a positive or negative charge exhibit unusual stability that suggests they are aromatic. These ions meet Hückel's rule, further indicating that they are aromatic.

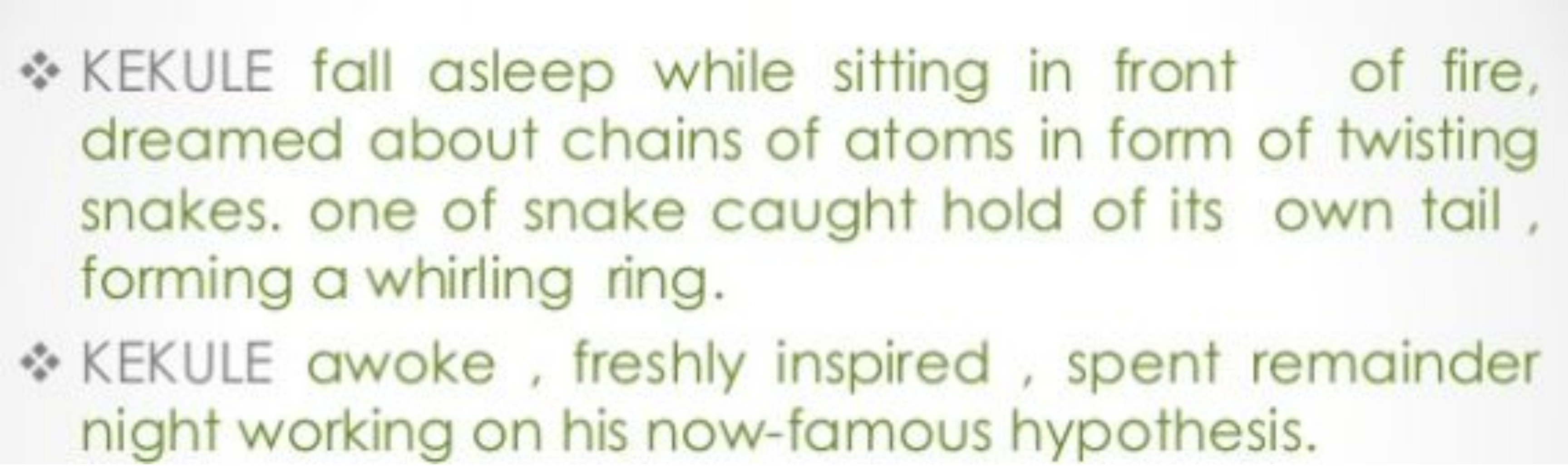
Because of the unusual stability of the cyclopentadienyl anion, and because these six π electrons meet the criteria for Hückel's rule, the cyclopentadienyl anion is considered to be an aromatic ion.



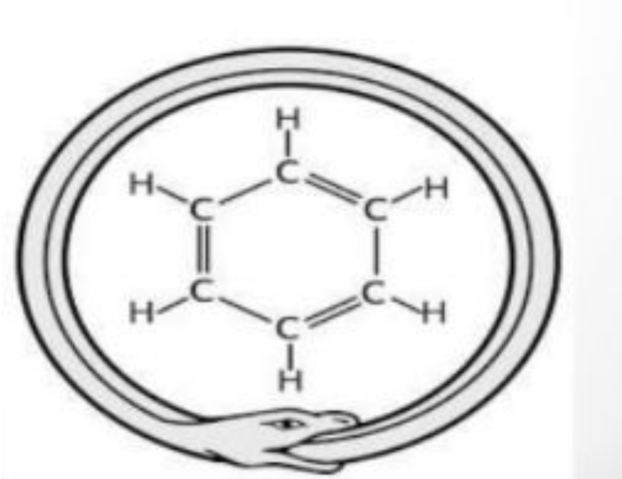
Benzene and its Derivatives



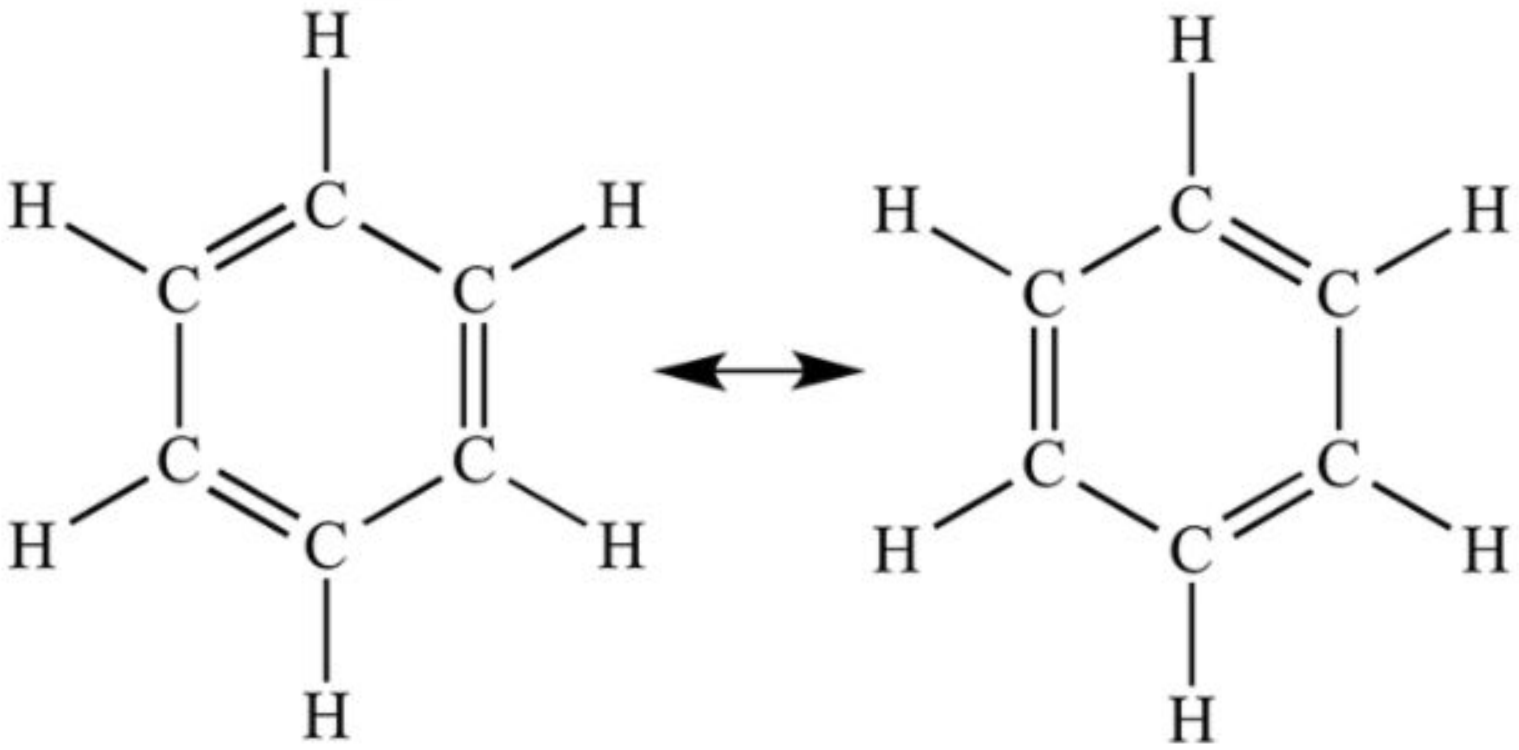
Benzene and its Derivatives



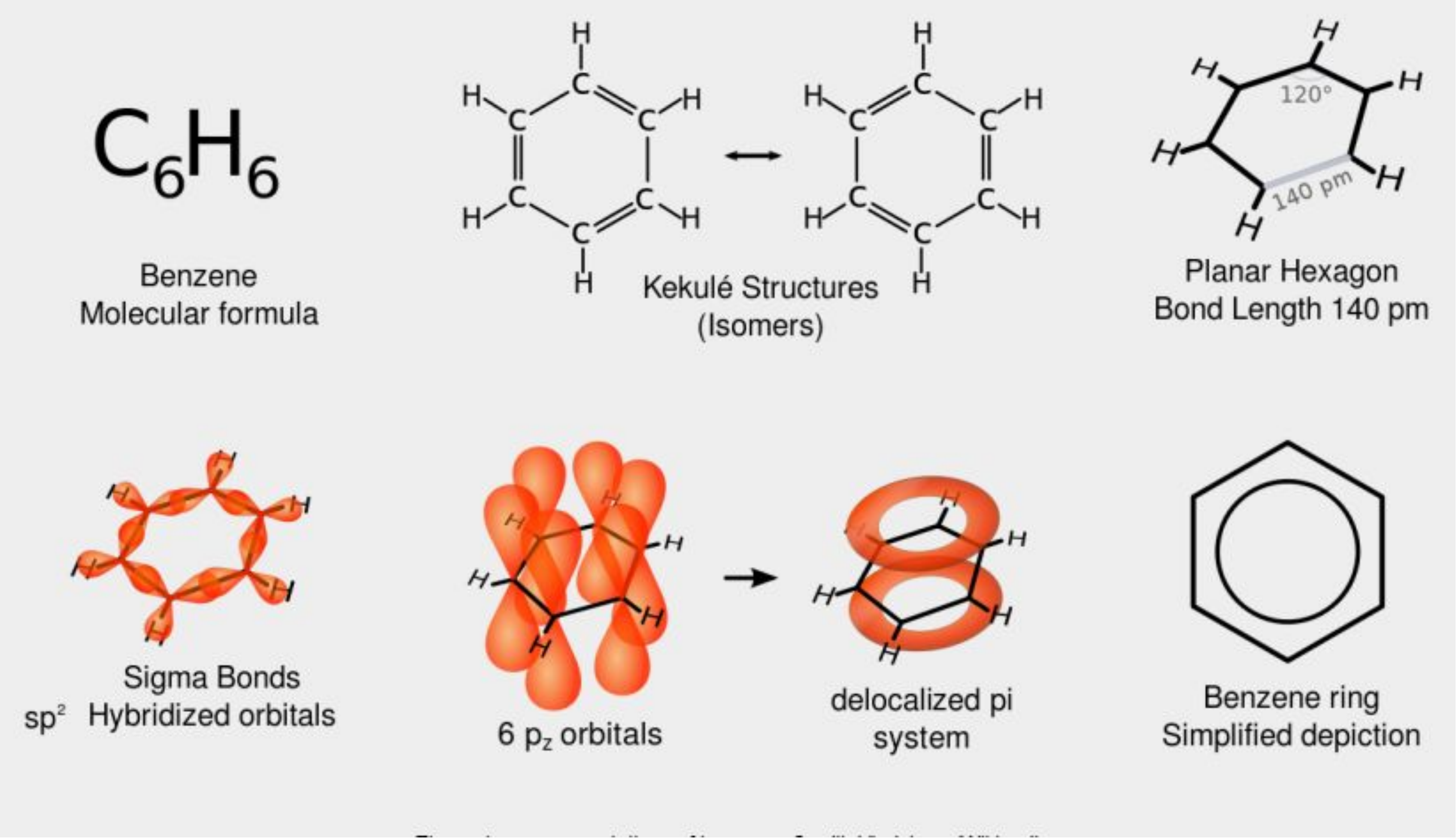
- KEKULE fall asleep while sitting in front of fire, dreamed about chains of atoms in form of twisting snakes. one of snake caught hold of its own tail , forming a whirling ring.
- KEKULE awoke , freshly inspired , spent remainder night working on his now-famous hypothesis.



Benzene and its Derivatives



Benzene and its Derivatives



Nomenclature and isomerism of benzene derivatives

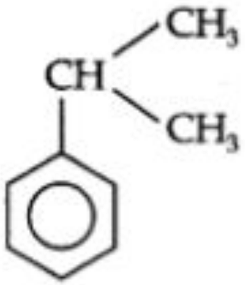
- According to the IUPAC nomenclature arenes are considered as derivatives of benzene.
- When two substituents are present in a benzene ring, three isomers are possible; they can be distinguished by numbering the atoms of the ring or using the *ortho (o), meta (m), and para (p)* system.
- When a benzene ring is the substituent, use the phenyl group name.

Nomenclature and isomerism of benzene derivatives

Benzene

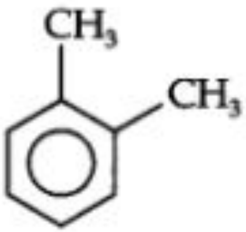
Toluene
(Methyl benzene)

Ethyl Benzene

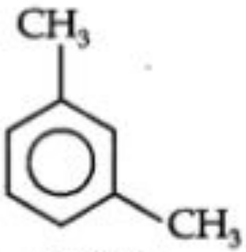


Cumene
(Isopropyl
benzene)

Dimethylbenzenes have the common name Xylenes. The three isomeric xylenes are



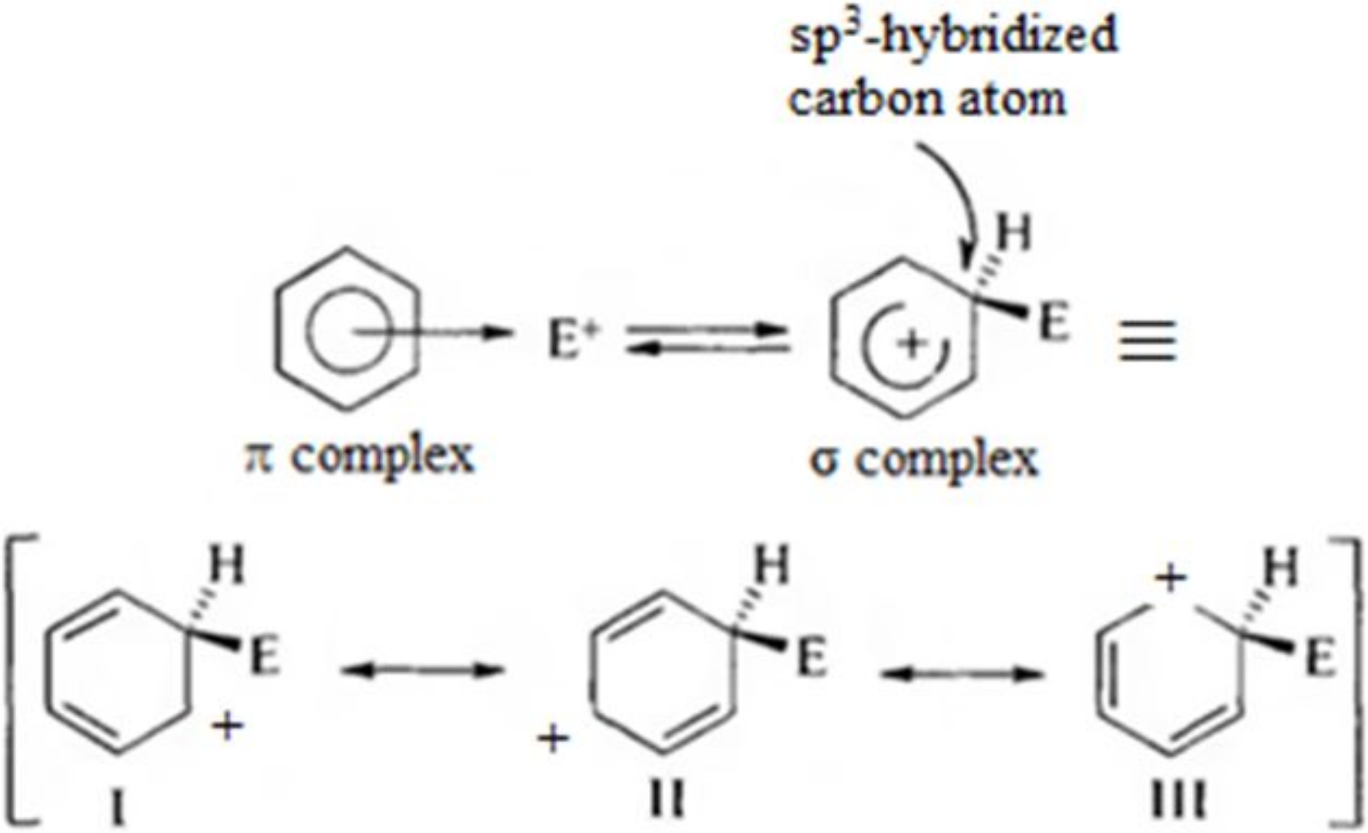
o – xylene



m – xylene

p – xylene

Chemical Properties of Benzene and its Derivatives



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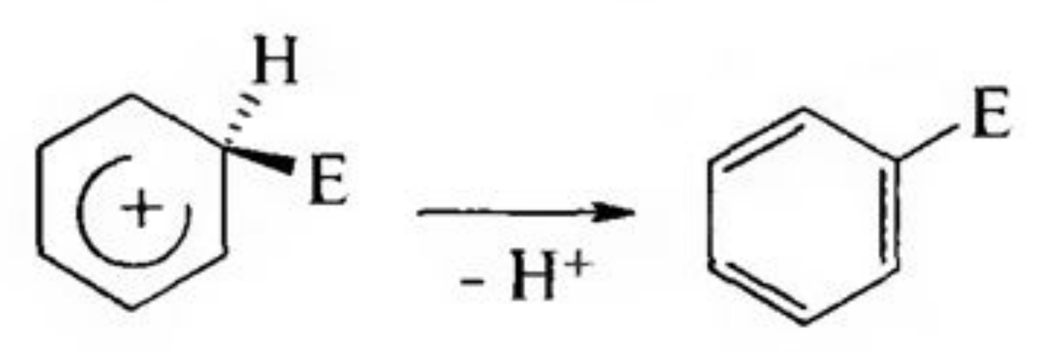
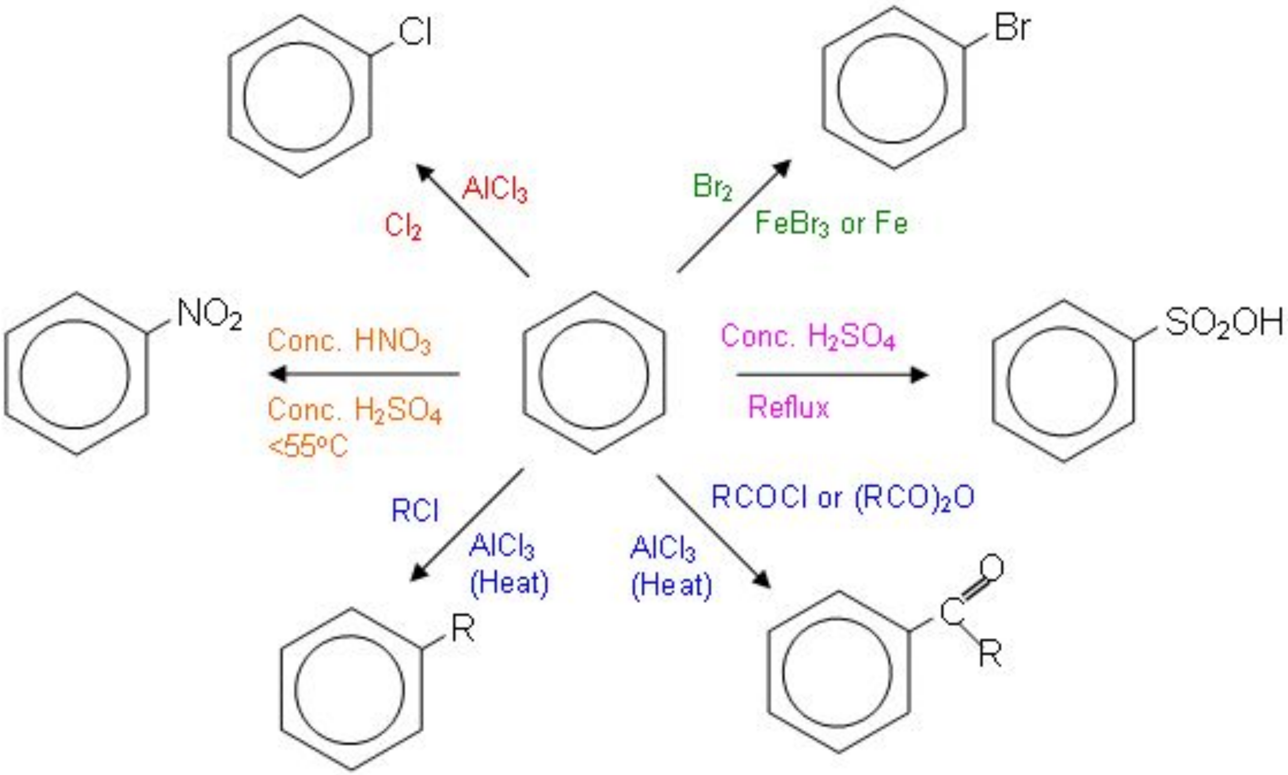


- *This reaction type is called an electrophilic aromatic substitution.* The most important S_EAr reactions are nitration, sulfonation, halogenation, alkylation, and acylation.

Chemical Properties of Benzene and its Derivatives

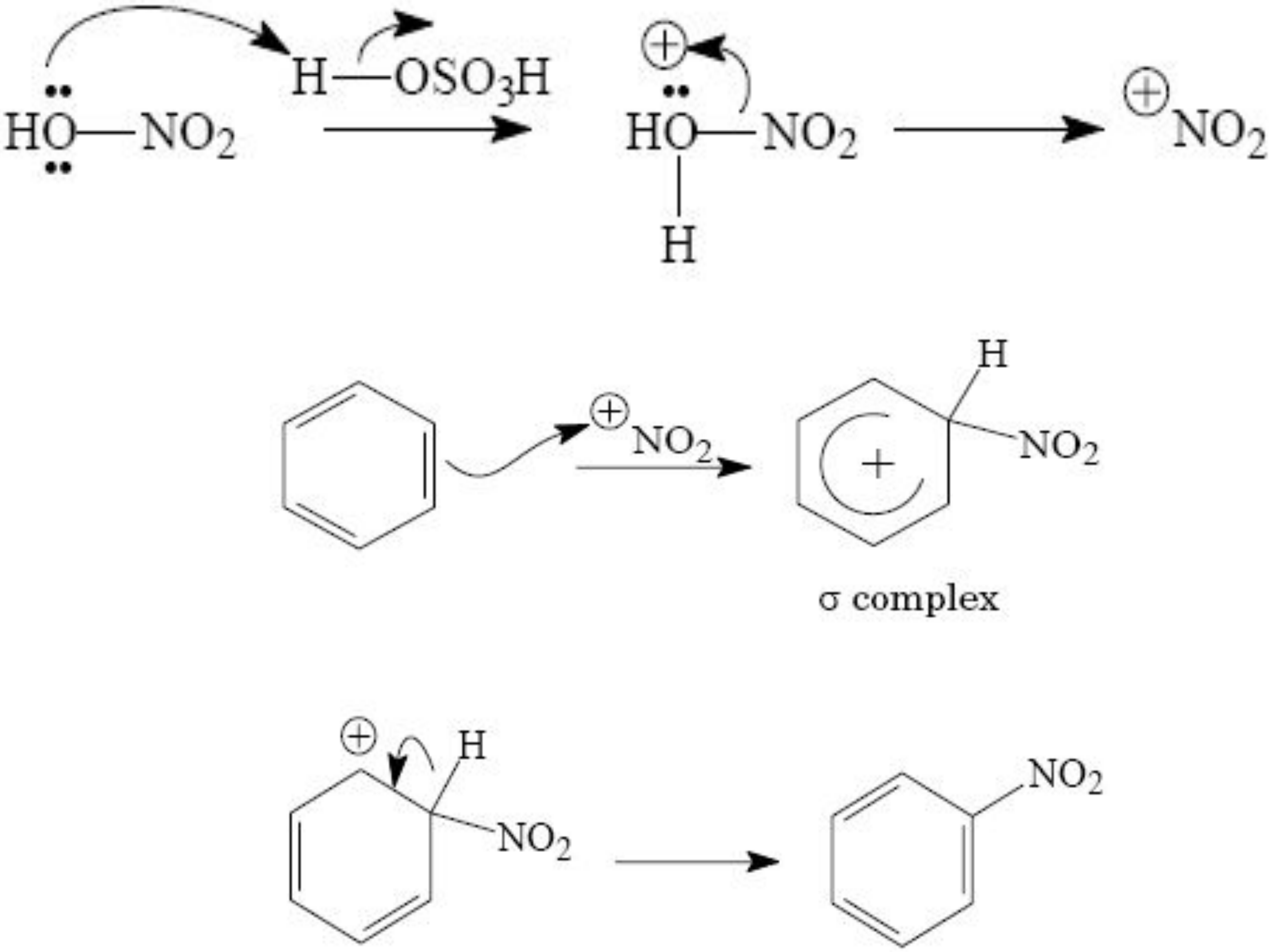


Chlorination
Bromination
Sulphonation
Friedel-Crafts (Alkylation)
Nitration

Nitration of benzene

- Concentrated nitric acid or a mixture of concentrated nitric and sulfuric acid (nitrating mixture) are often used as nitrating agents.
- An electrophilic particle in the nitration reaction is a nitronium ion NO_2^+, which is formed in the result of the acid-base interaction between nitric and sulfuric acid, where nitric acid is a base.

Nitration of benzene

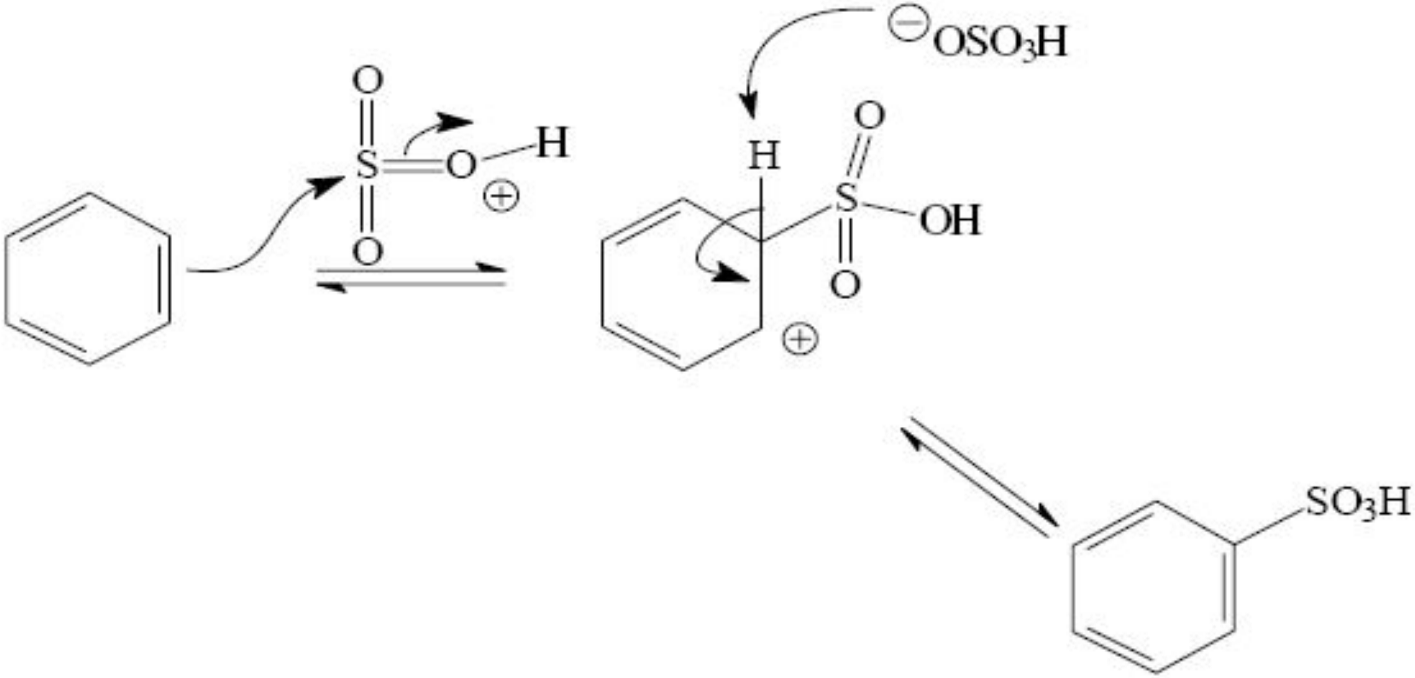


Sulfonation of benzene

- The sulfonation reaction is the reaction of replacing a hydrogen atom on the benzene ring by SO_3H. Concentrated sulfuric acid or oleum (sulfur trioxide in sulfuric acid solution) is used for the sulfonation of benzene and its homologues.
- The essential difference of the sulfonation reaction from other reactions of electrophilic substitution is its reversibility. Attacking electrophillic particle is sulfur trioxide, SO_3.

Sulfonation of benzene

$$SO_3 + H_2O \longrightarrow H_2SO_4$$



Halogenation of benzene

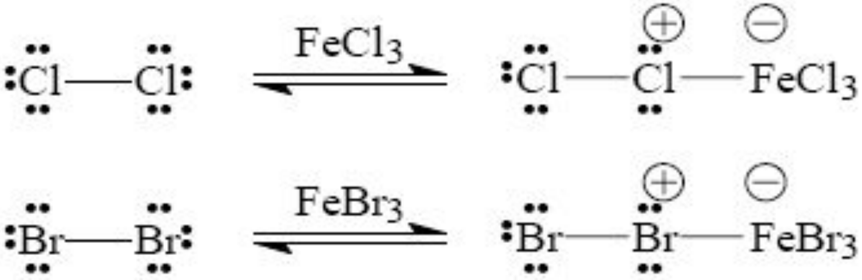
- Substitution of hydrogen atoms on the benzene ring by chlorine or bromine atoms is carried out in the presence of catalysts, which are Lewis acids ($AlCl_3$, $FeBr_3$, $ZnCl_2$ and others). The most common laboratory procedure involves adding the halogen to benzene in the presence of some metallic iron. The iron reacts with the halogen to form a small amount of iron(III) chloride or iron(III) bromide.

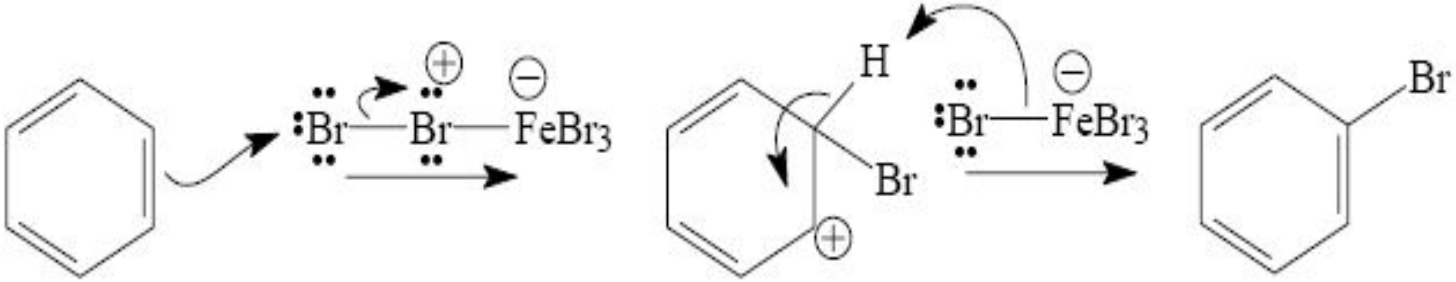
Halogenation of benzene

- The iron halides are Lewis acids and form complexes with the halogen atoms.
- The formation of the bromine-iron (III) bromide complex increases the electrophilicity of the bromine. It can attack the benzene ring and form a σ complex. The next step, in which the $FeBr_4^-$ ion removes the proton from the σ complex producing bromobenzene, HBr, and $FeBr_3$, is fast.

Halogenation of benzene

$$2Fe + 3Cl_2 \longrightarrow 2FeCl_3$$
$$2Fe + 3Br_2 \longrightarrow 2FeBr_3$$

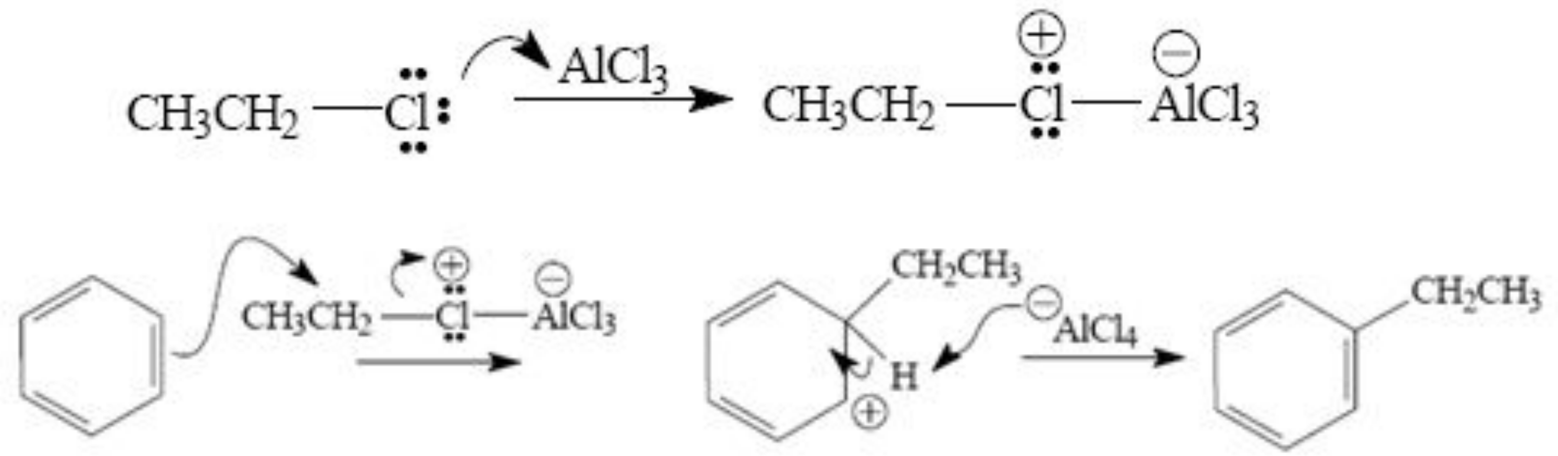


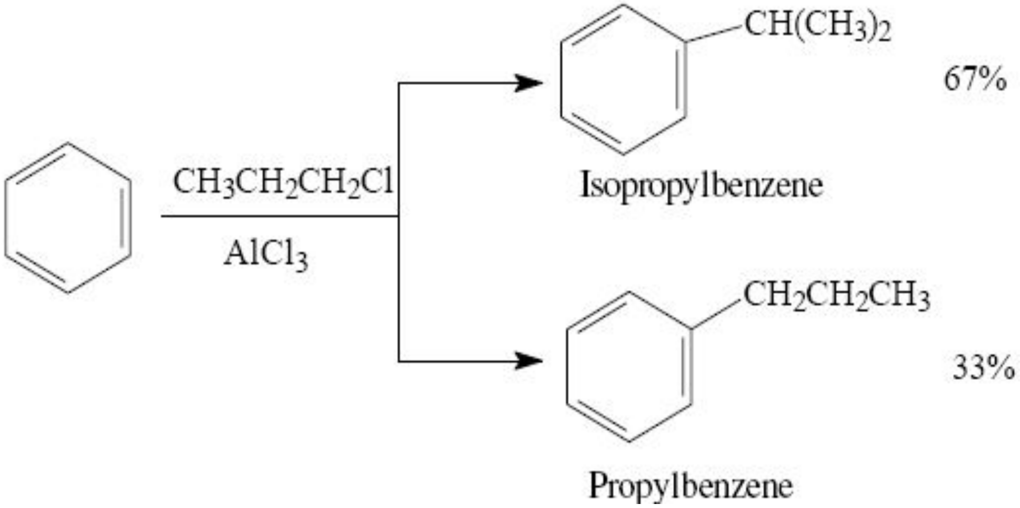


Friedel-Crafts alkylation

- The mechanism for an alkylation reaction begins as the Lewis acid, in this case $AlCl_3$, reacts with the alkyl halide to form a complex. This complex is the reacting species for a primary alkyl halide. The complex tends to dissociate forming a free carbocation for a tertiary alkyl halide. In addition, if a carbocation-like rearrangement of the alkyl group can occur, it will.
- The benzene ring then undergoes electrophilic attack by the complex to form a σ complex – completing the first step of the electrophilic aromatic substitution reaction. Immediately following the first step, the σ complex undergoes the second step and loses a proton to form the alkyl benzene.

Friedel-Crafts alkylation

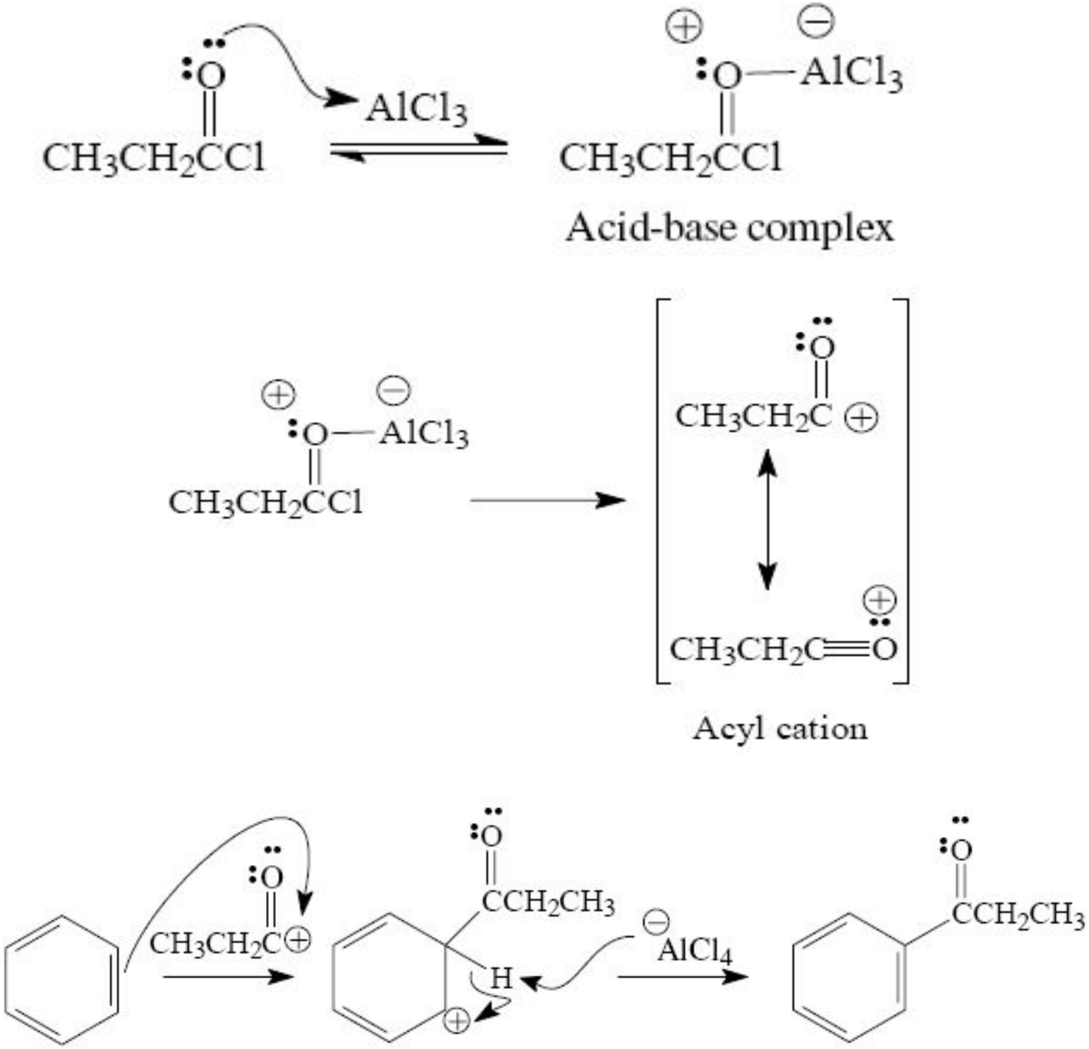




Friedel-Crafts acylation

- A variation of the Friedel-Crafts reaction is the acylation reaction. A Friedel-Crafts acylation reaction involves the reaction of an acyl halide or an acid anhydride and a Lewis acid with benzene to yield an acylbenzene. Acylation reactions need stoichiometric amount of aluminum chloride because the aluminum chloride first forms an acid/base complex with the carbonyl group of the acyl halide.

Friedel-Crafts acylation



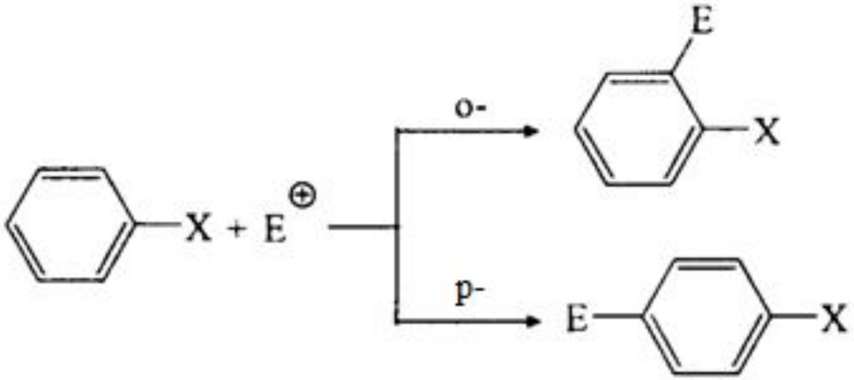
Effects of Monosubstituted Arenes on Substitution

- All benzene ring substituent groups are either ***ortho*, *para directors or meta directors***. Each group varies as how it affects the rate of the electrophilic substitution.
- In general, *ortho*, *para* directors activate the aromatic ring compared to benzene, and *meta* directors deactivate the ring.

Effects of Monosubstituted Arenes on Substitution

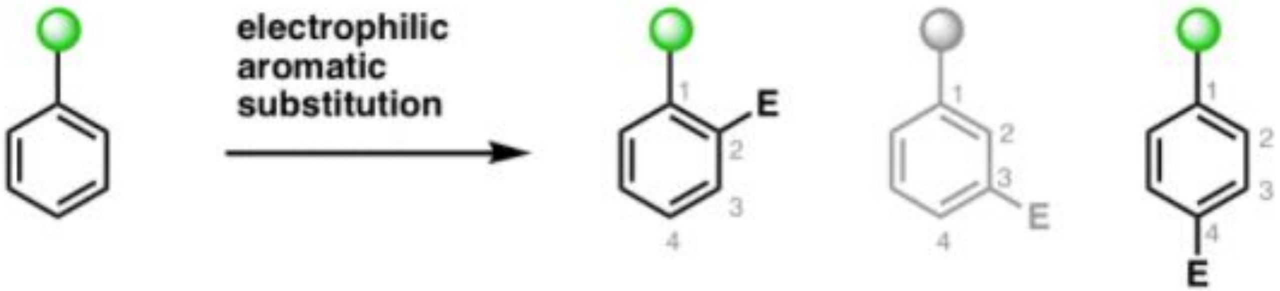
- The *ortho* and *para* directors are atoms and atomic groups with positive inductive (+*I*) or positive mesomeric (+*M*) effects (electron donors):

$-\ddot{N}R_2$, $-\ddot{N}HR$, $-NH_2$, $-\ddot{O}H$, $-\ddot{O}R$, $-NHCOR$, $-\ddot{O}COR$, $-\ddot{S}H$, -Alk, -Hal



Effects of Monosubstituted Arenes on Substitution

Pattern 1: *ortho-* and *para-* products are major; *meta* product is minor



1,2	1,3	1,4
[*ortho-*]	[*meta-*]	[*para-*]
Major	Minor	**Major**

🟢 a substituent referred to as an "*ortho-,para-* director"

Examples of *ortho-,para-* directors:

$-O^{\ominus}$

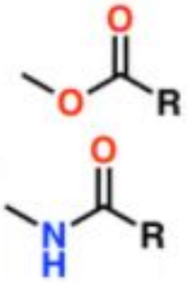
$-OH$

$-OR$

$-NH_2$

$-NHR$

$-NR_2$



$-CH_3$

alkyl groups (R)

$-SH$ $-SR$

$-F$

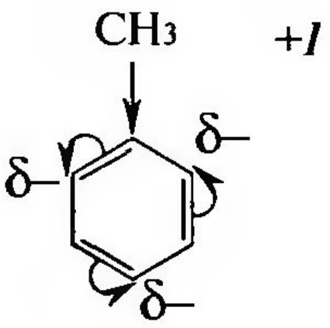
$-Cl$

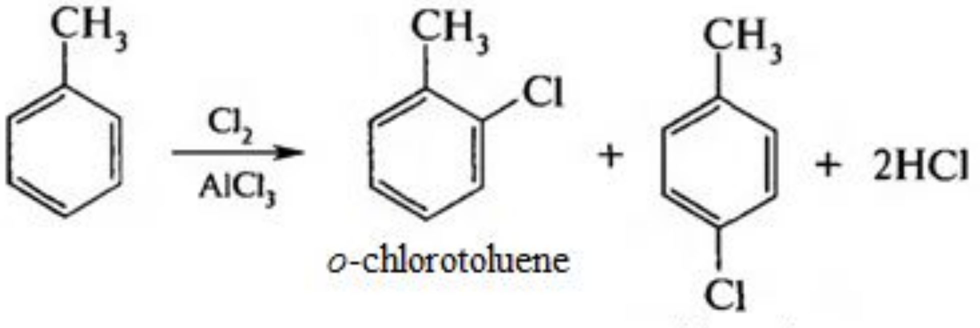
$-Br$

$-I$

Effects of Monosubstituted Arenes on Substitution

- A methyl group is an electron-donating group, and although it activates all three positions relative to benzene, it activates the *ortho* and *para* positions more than the *meta* positions. This increased reactivity at the *ortho* and *para* sites directs the incoming electrophiles primarily to those positions. All alkyl groups are electron-donating ones; thus, they are all *ortho* and *para* directing groups.



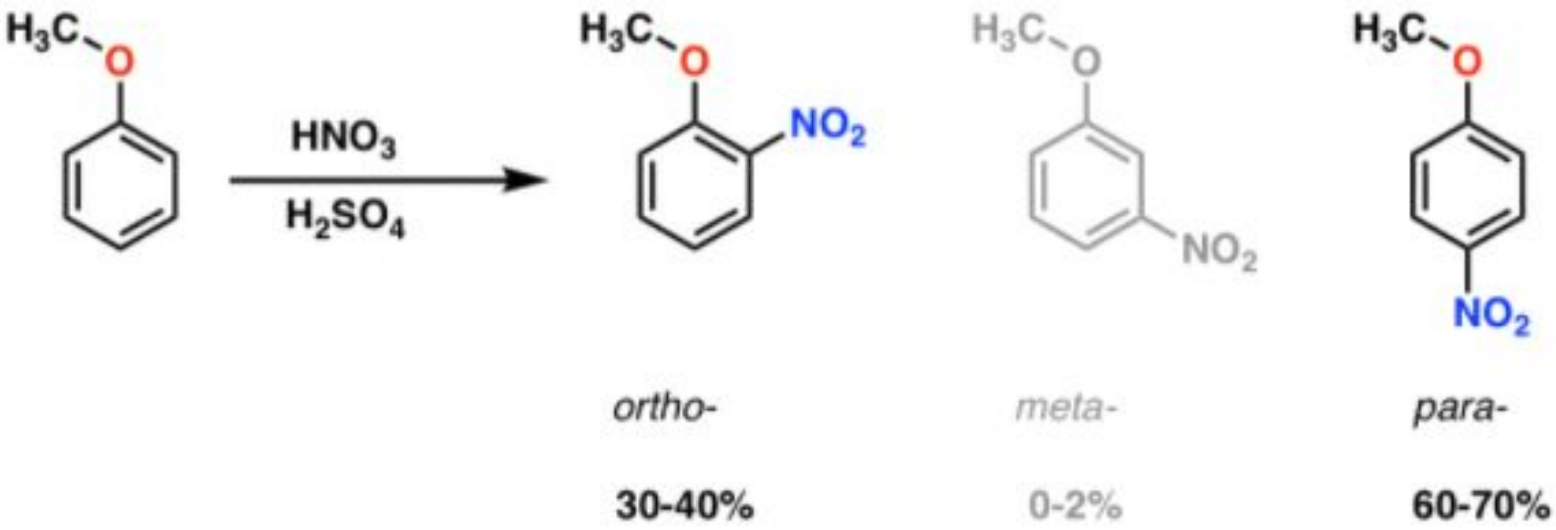


o-chlorotoluene

p-chlorotoluene

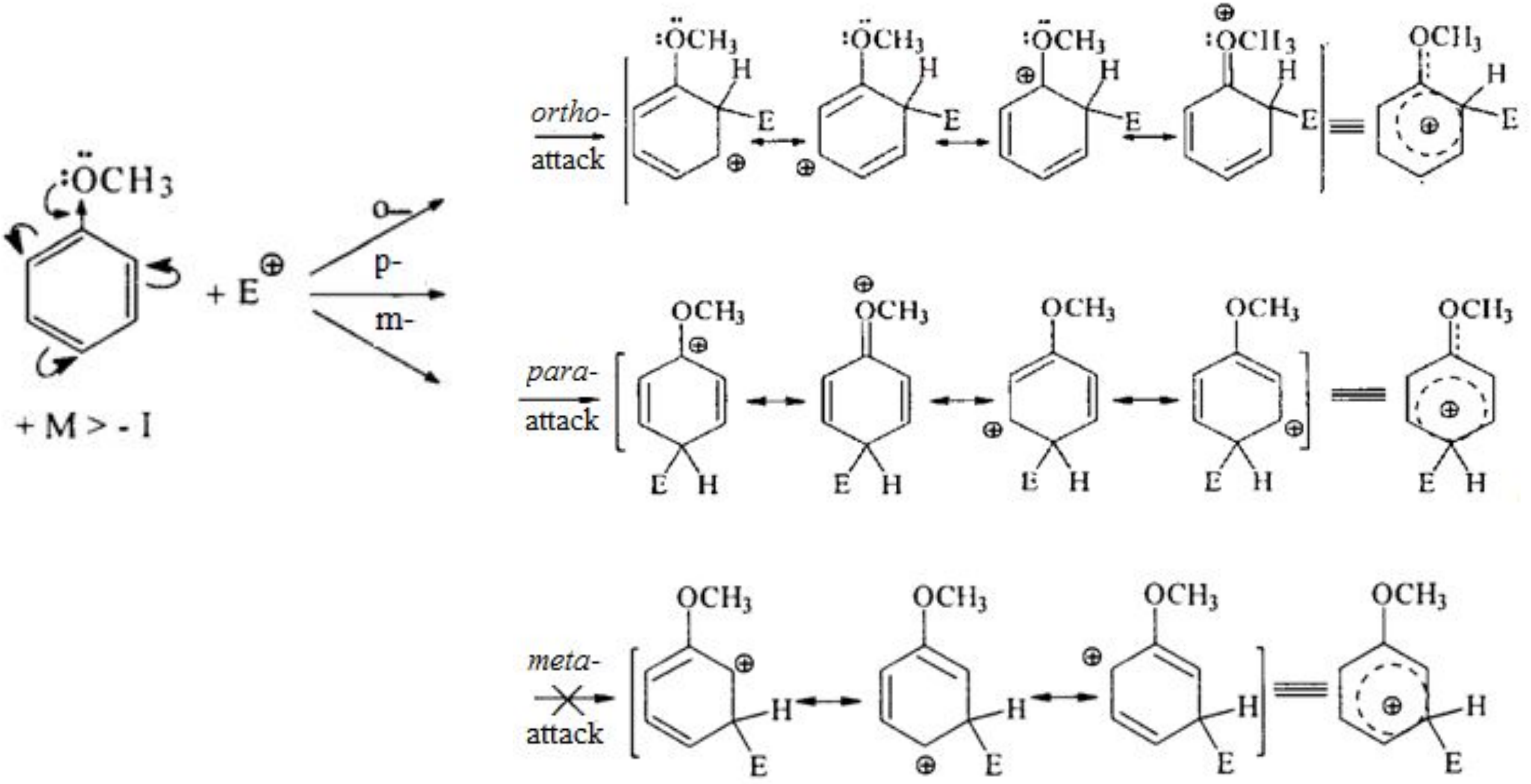
Effects of Monosubstituted Arenes on Substitution

Electrophilic aromatic substitution (e.g. nitration) of methoxybenzene gives mostly *ortho*- and *para*- products:

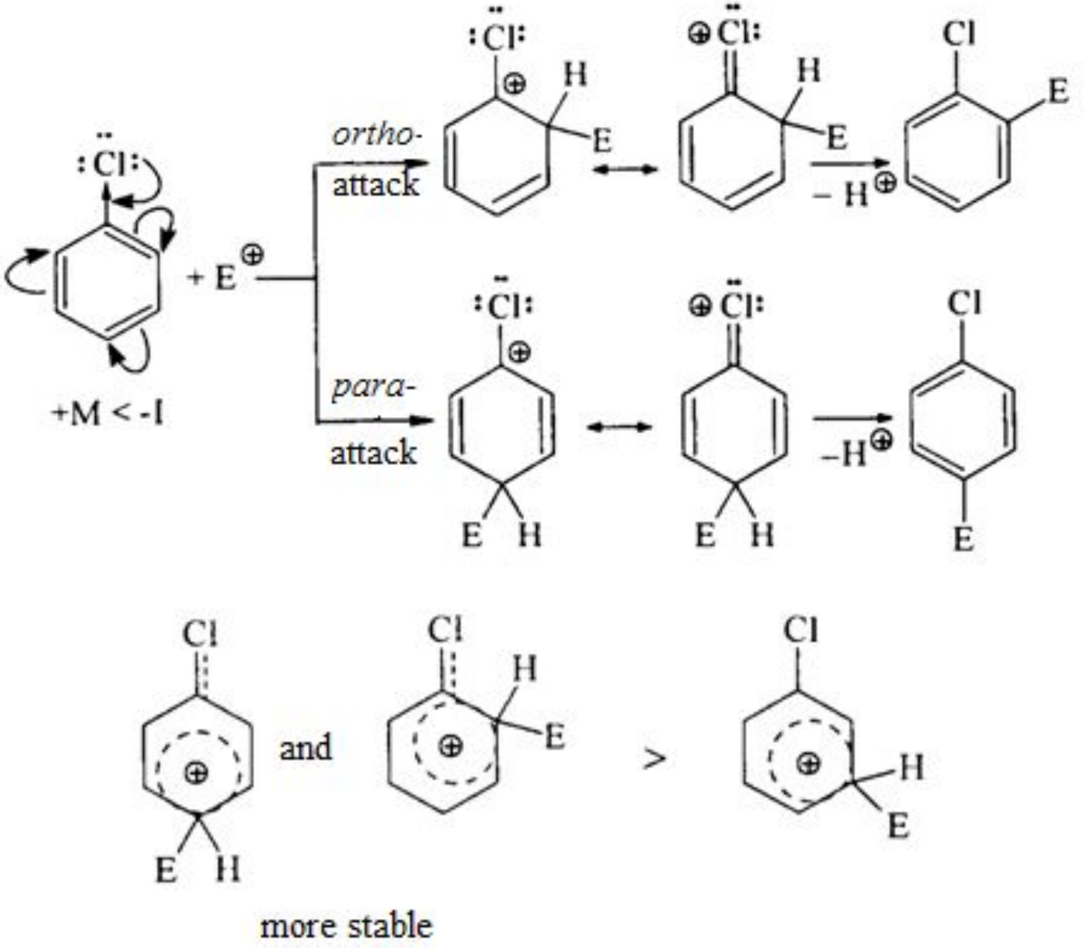


ortho- and *para*- products dominate, while *meta*– products comprise less than 3%.

Effects of Monosubstituted Arenes on Substitution



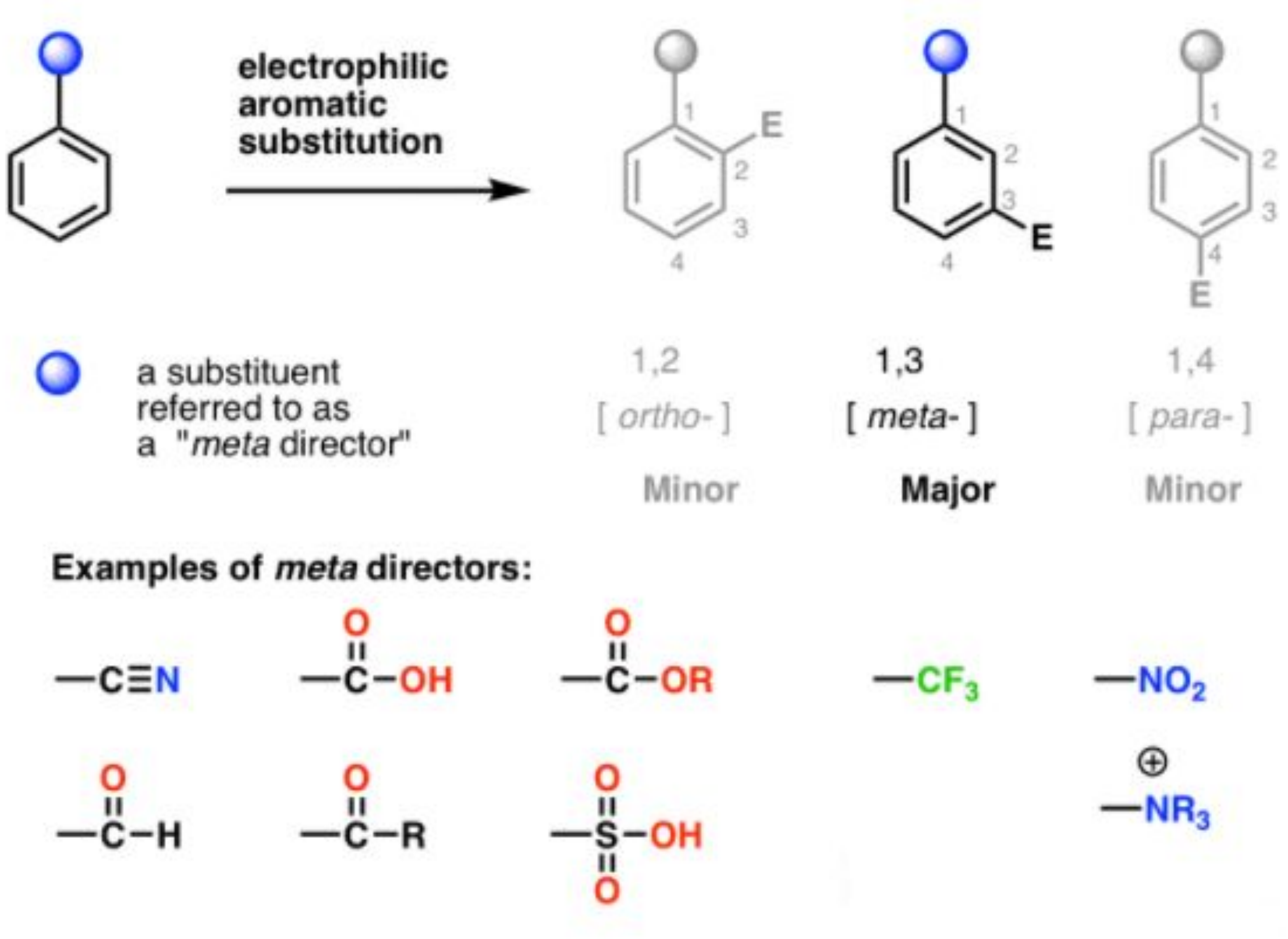
Effects of Monosubstituted Arenes on Substitution



Effects of Monosubstituted Arenes on Substitution

- ***Ortho and para-directors*** stabilize the σ complex by their electron-donating properties, and activate a benzene ring in S_EAr reactions.
- ***The electrophilic substitution of the corresponding benzene derivatives is faster compared to benzene.***
- Halogens are *ortho, para*-directors, but they deactivate the electrophilic substitution reactions, since the following ratio of inductive and mesomeric effects are typical for them: -I > + M.

Effects of Monosubstituted Arenes on Substitution



Effects of Monosubstituted Arenes on Substitution

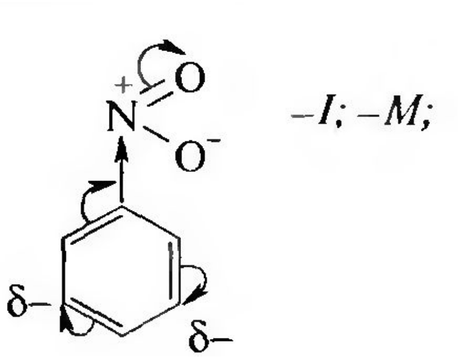
- The *meta*-directors are atoms or atomic groups with negative inductive (-*I*) or negative mesomeric effects (-*M*) (electron-acceptors):

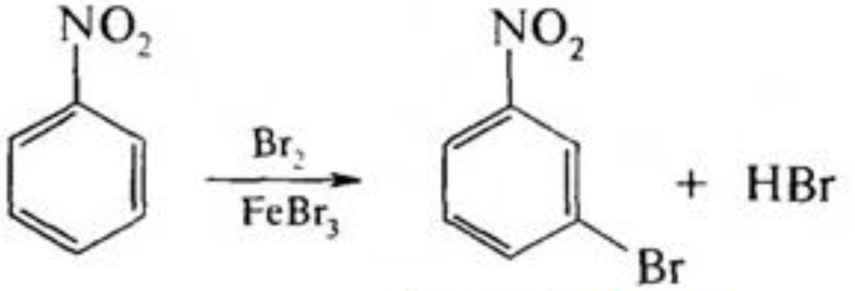
$-\overset{+}{N}R_3$, $-NO_2$, $-SO_3H$, $-CN$, $-CHO$, $-COR$, $-COOH$, $-COOR$, $-CCl_3$

X – *meta*-director

Effects of Monosubstituted Arenes on Substitution

- Meta-directors decrease an electronic density in the benzene ring and lower the rate of S_EAr reactions compared to a non-substituted benzene:

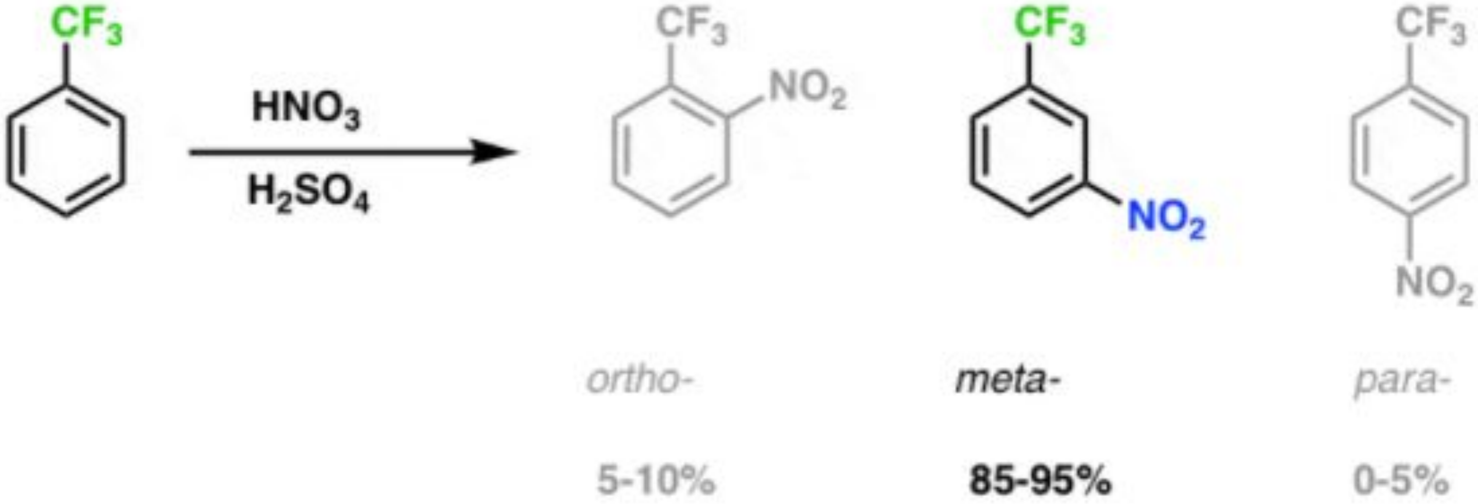




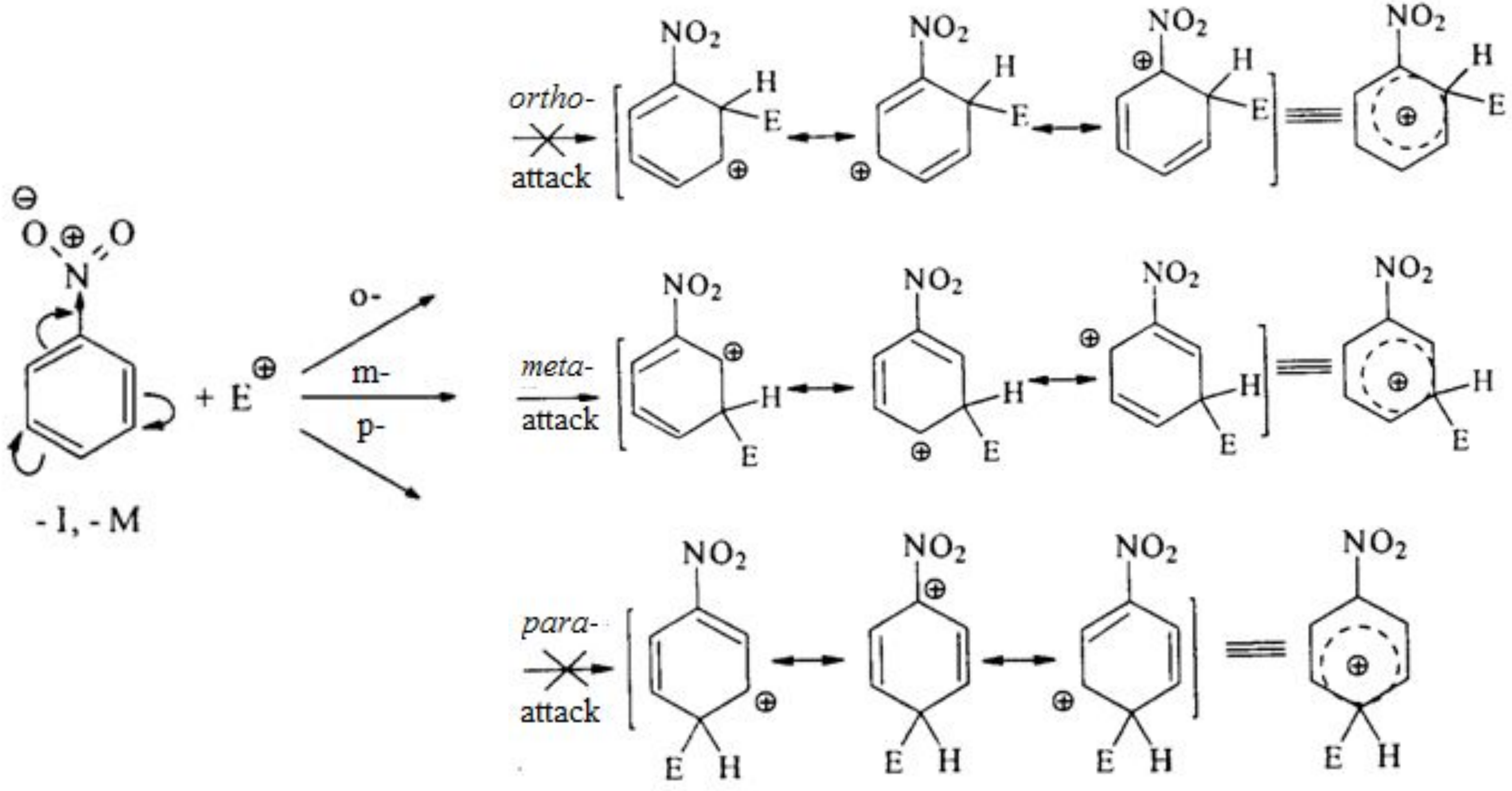
m-bromonitrobenzene

Effects of Monosubstituted Arenes on Substitution

Electrophilic aromatic substitution (e.g. nitration) of trifluoromethylbenzene gives mostly *meta*- products



Effects of Monosubstituted Arenes on Substitution



Multiple substituent effects

When a benzene ring has two or more substituents, all the substituents exert their combined effects on the reactivity of the ring and in the placement of any incoming electrophiles. In most cases, multiple substituents affect an electrophilic aromatic substitution reaction in one of the following four ways.

- All available sites are equivalent. This means that a substitution at any one of these sites gives the same product.
- All sites have comparable reactivity, but one site is more sterically hindered than the other. The reaction then takes place at the less sterically hindered site.

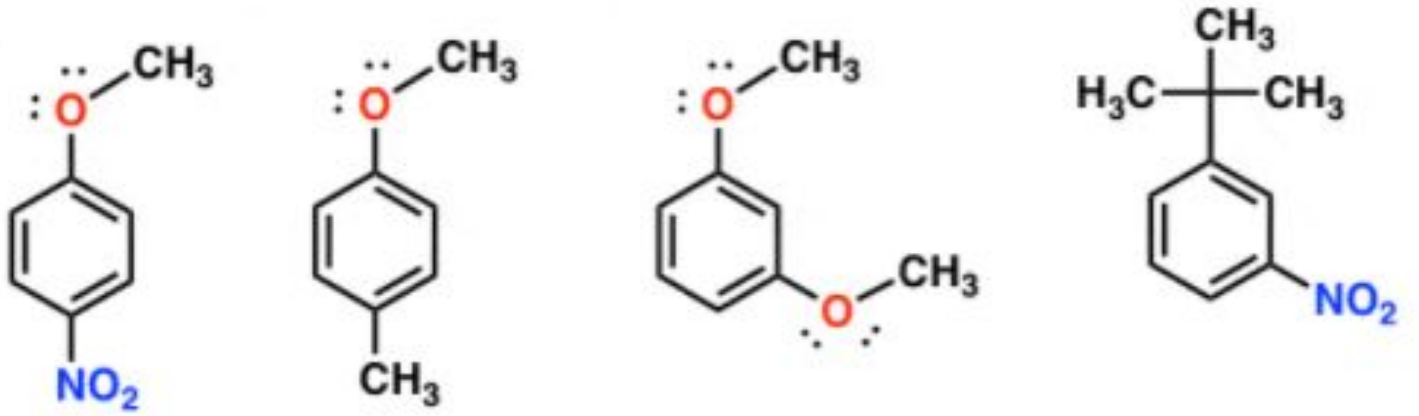
Multiple substituent effects

- The directing effects of the groups reinforce one another. For example, in *p*-nitrotoluene the nitro group is a *meta* directing group, the methyl group is an *ortho*, *para* directing group, and the two groups are *para* to each other. Thus, both groups direct to the same pair of carbon atoms as the preferred site of reaction.
- The substituents have directing influences that oppose one another. When this occurs, the substituent with the greatest influence controls the outcome of the reaction.

Multiple substituent effects

Which directing group “wins?”.

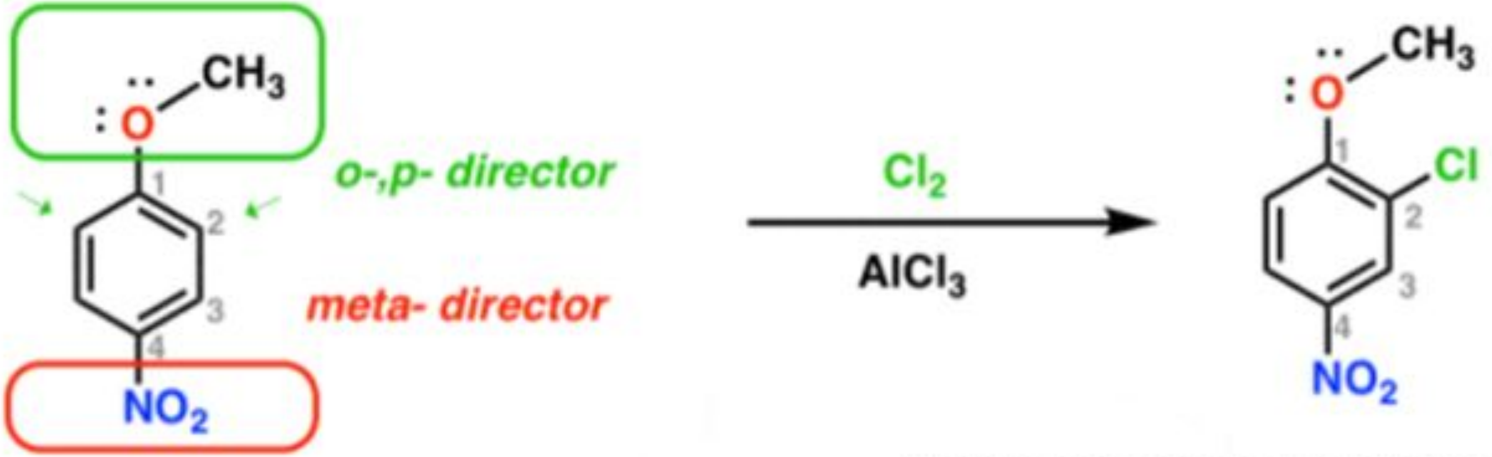
When a benzene ring has *two* substituents, how can we predict the products of electrophilic aromatic substitution?



https://www.masterorganicchemistry.com/2018/03/19/eas-disubstituted-benzenes/

Multiple substituent effects

Analyze the effect of each substituent in turn:

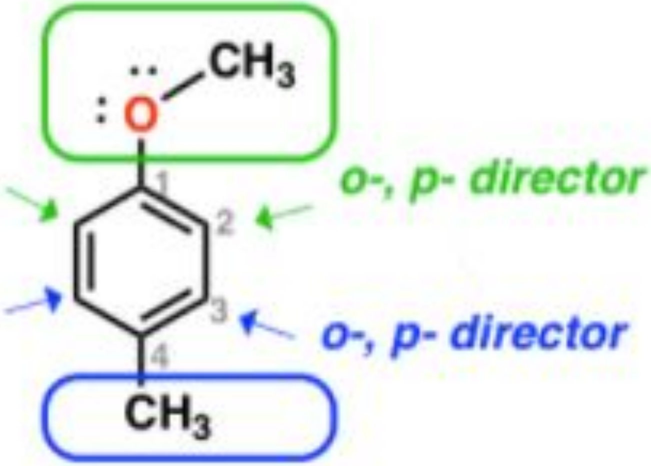


Both substituents
direct to the same position!
(C-2)

2-chloro-1-methoxy-4-nitrobenzene
(only product)

Multiple substituent effects

What about *p*-methylanisole ?



Each substituent directs to
a *different* position (C–2 or C–3)

Which directing group "wins" ?

Multiple substituent effects

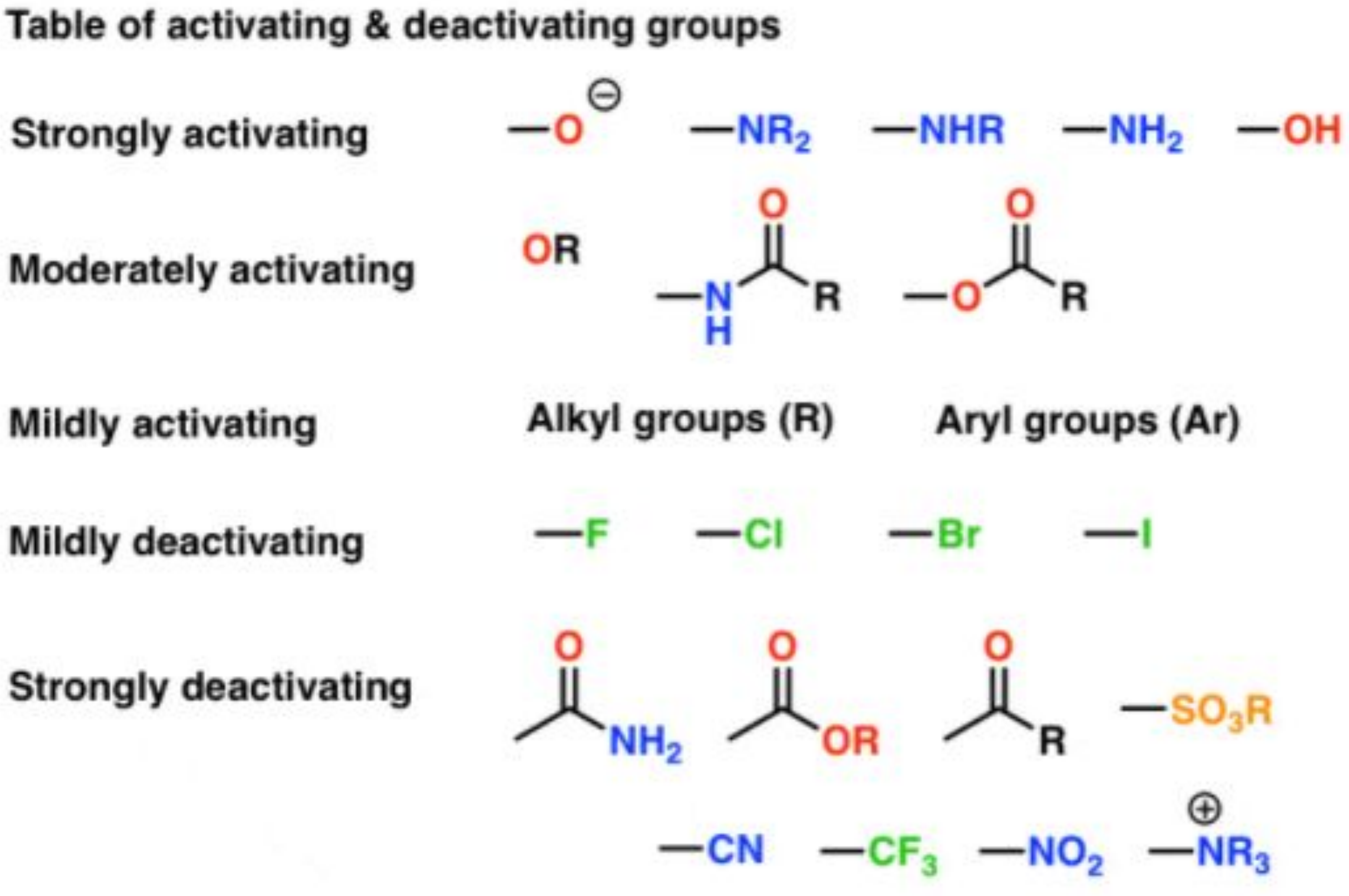


Table of activating & deactivating groups

Strongly activating	$-O^{\ominus}$	$-NR_2$	$-NHR$	$-NH_2$	$-OH$
Moderately activating	OR	$-NH-\overset{O}{\overset{\|}{C}}-R$	$-O-\overset{O}{\overset{\|}{C}}-R$		
Mildly activating	Alkyl groups (R)	Aryl groups (Ar)			
Mildly deactivating	$-F$	$-Cl$	$-Br$	$-I$	
Strongly deactivating	$-\overset{O}{\overset{\|}{C}}-NH_2$	$-\overset{O}{\overset{\|}{C}}-OR$	$-\overset{O}{\overset{\|}{C}}-R$	$-SO_3R$	
	$-CN$	$-CF_3$	$-NO_2$	$-NR_3^{\oplus}$	

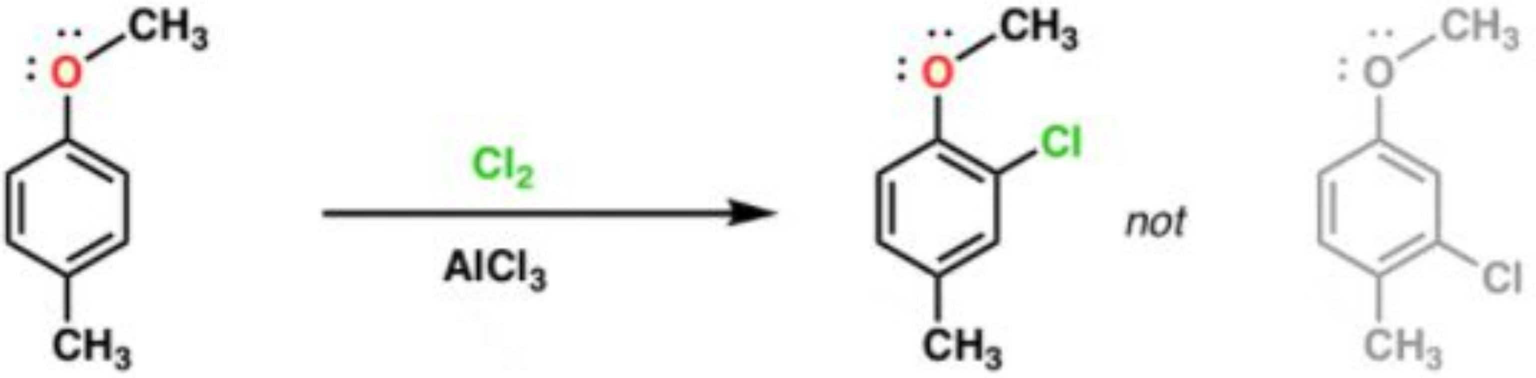
Multiple substituent effects

The most activating group "wins"

- when multiple products are possible, the fastest reaction will be the one with the lowest-energy transition state for the rate limiting step

- the rate-limiting step is formation of the electron-poor carbocation intermediate

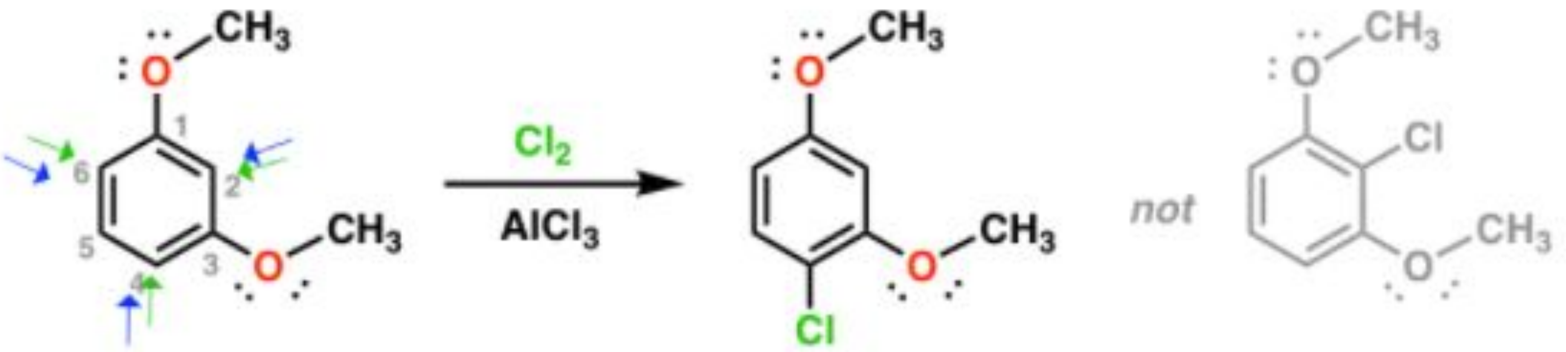
- OCH_3 is more strongly activating (i.e. a better electron donor) than CH_3
- therefore OCH_3 will "win"



Multiple substituent effects

When electronic effects are equal, choose the less sterically hindered site

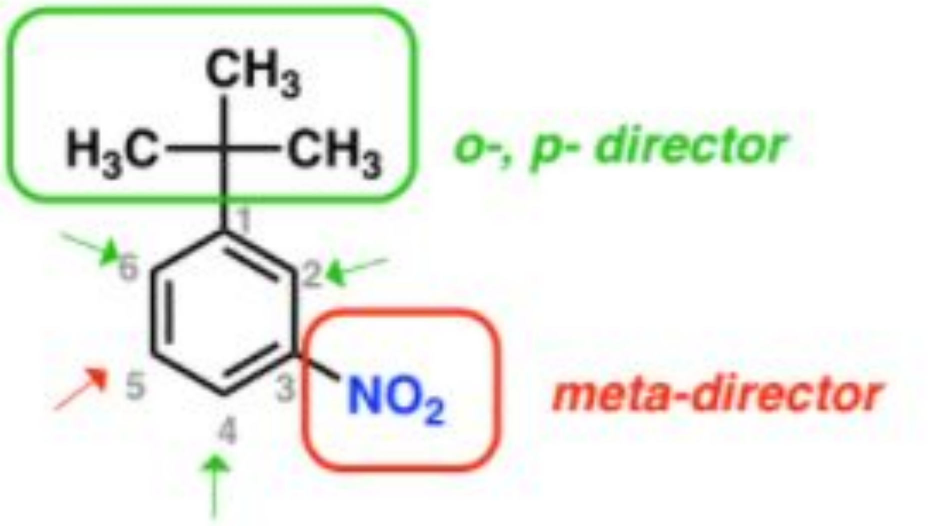
C-2, C-4 and C-6 are equally "electron-rich". But C-2 is flanked by two substituents and C-4/C-6 are each flanked by one substituent.



Therefore the major product will be 1-chloro-2,4-dimethoxybenzene, not 2-chloro-1,3-dimethoxybenzene.

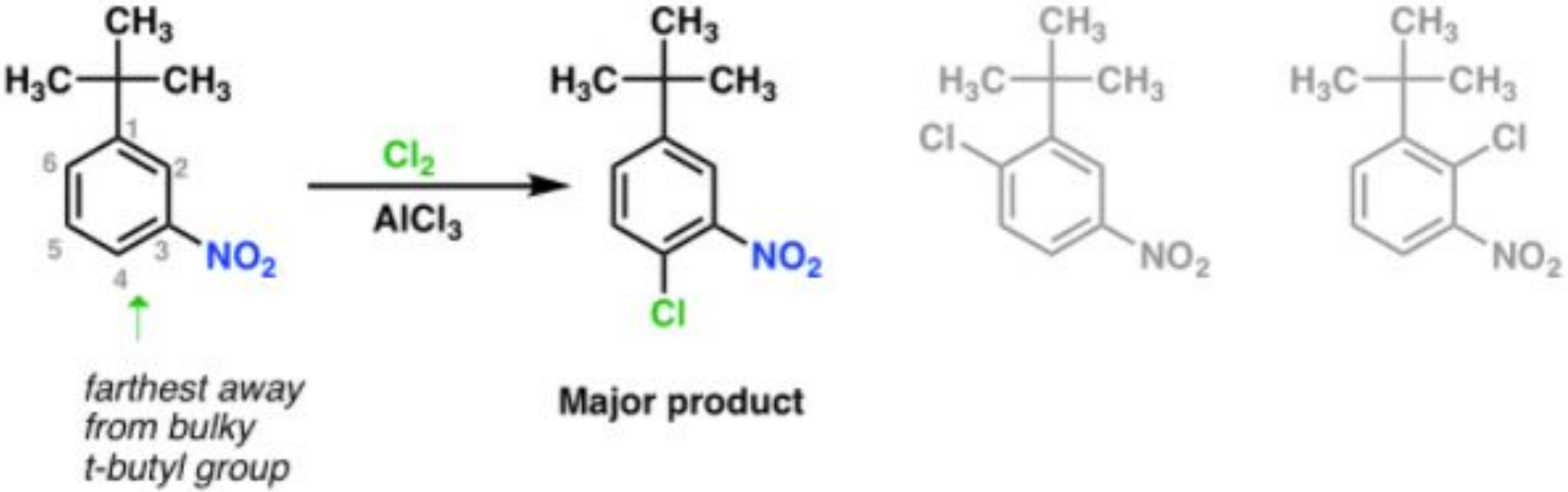
Multiple substituent effects

1-*t*-butyl-3-nitrobenzene



Multiple substituent effects

Since *t*-butyl is much bulkier than NO_2, electrophilic substitution of 1-*t*-butyl 3-nitrobenzene is expected to give only one major product

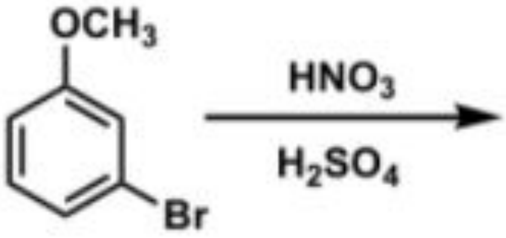


farthest away from bulky t-butyl group

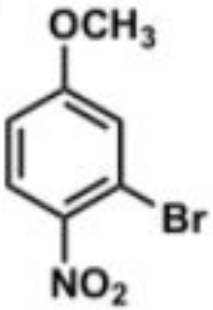
Major product

Quiz Yourself!

Choose the major product(s).



A



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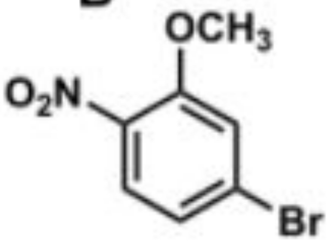

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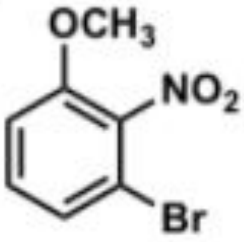
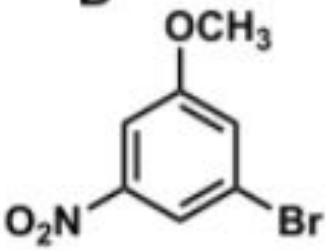


D



Summary

- Benzene is very important for the synthesis of dyes, pharmaceuticals and perfumes etc.
- Electrophilic substitution reactions provide us with ways of introducing different groups into the benzene ring.
- These groups can be modified further and more complex molecules can be synthesized.

Questions and Assignments

1. What are the aromatic hydrocarbons?
2. Explain the contemporary understanding of the structure of a benzene molecule.
3. What are the methods of obtaining aromatic hydrocarbons? Specify the reactions.
4. Explain the mechanism of aromatic electrophilic substitution.
5. Write the equations for the reactions of nitration of chlorobenzene, ethylbenzene, and benzenesulfonic acid.
6. Write the equations of sulfonation reactions of toluene, nitrobenzene, and bromobenzene.

Halogenated Aromatic Hydrocarbons

Topic 3

Outline of the lecture

1. Aryl Halides
2. Nucleophilic Substitution on an Aromatic Ring

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1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
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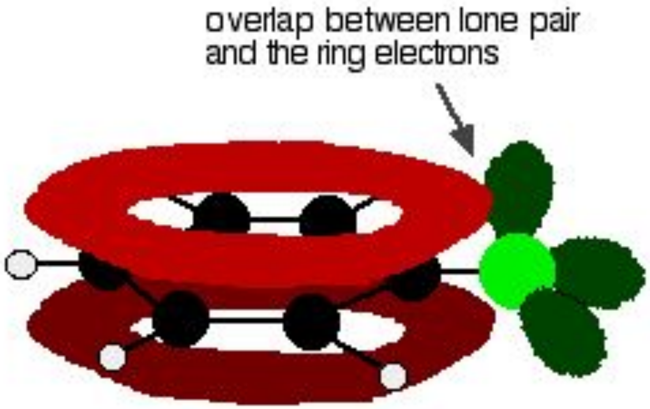
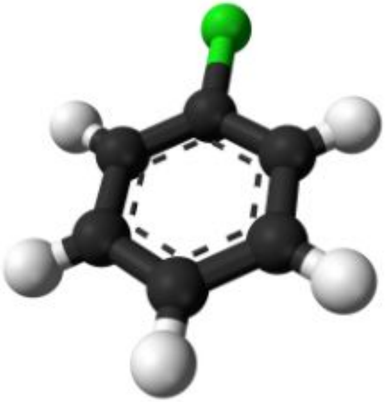
10. Kim, A.M. 2004. *Organic Chemistry*. Novosibirsk

Aryl Halides

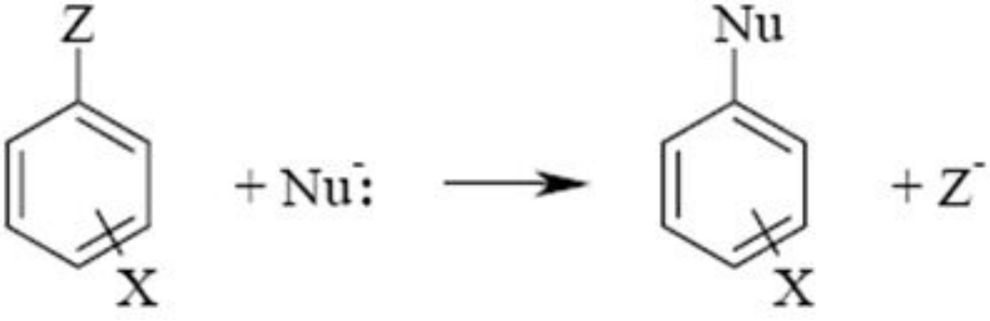
- **An aryl halide** is an aromatic compound containing a halogen atom bonded to a benzene ring or other aromatic group.





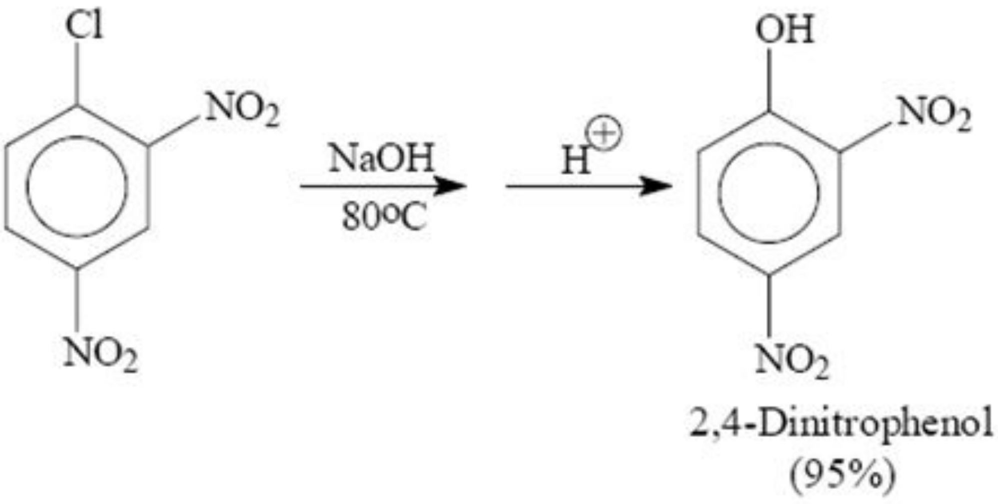
Nucleophilic Substitution on an Aromatic Ring

- Nucleophilic aromatic substitution mechanisms are very diverse, and the type of the mechanism depends on the nature of the aromatic substrate. The most common mechanisms are an addition-elimination mechanism (S_NAr) for activated substrates and elimination-addition one for non-activated substrates. Activated substrates contain the strongly electron-withdrawing groups in the *ortho* or *para* positions to the halide and non-activated substrates are aryl halides without electron-withdrawing substituents.

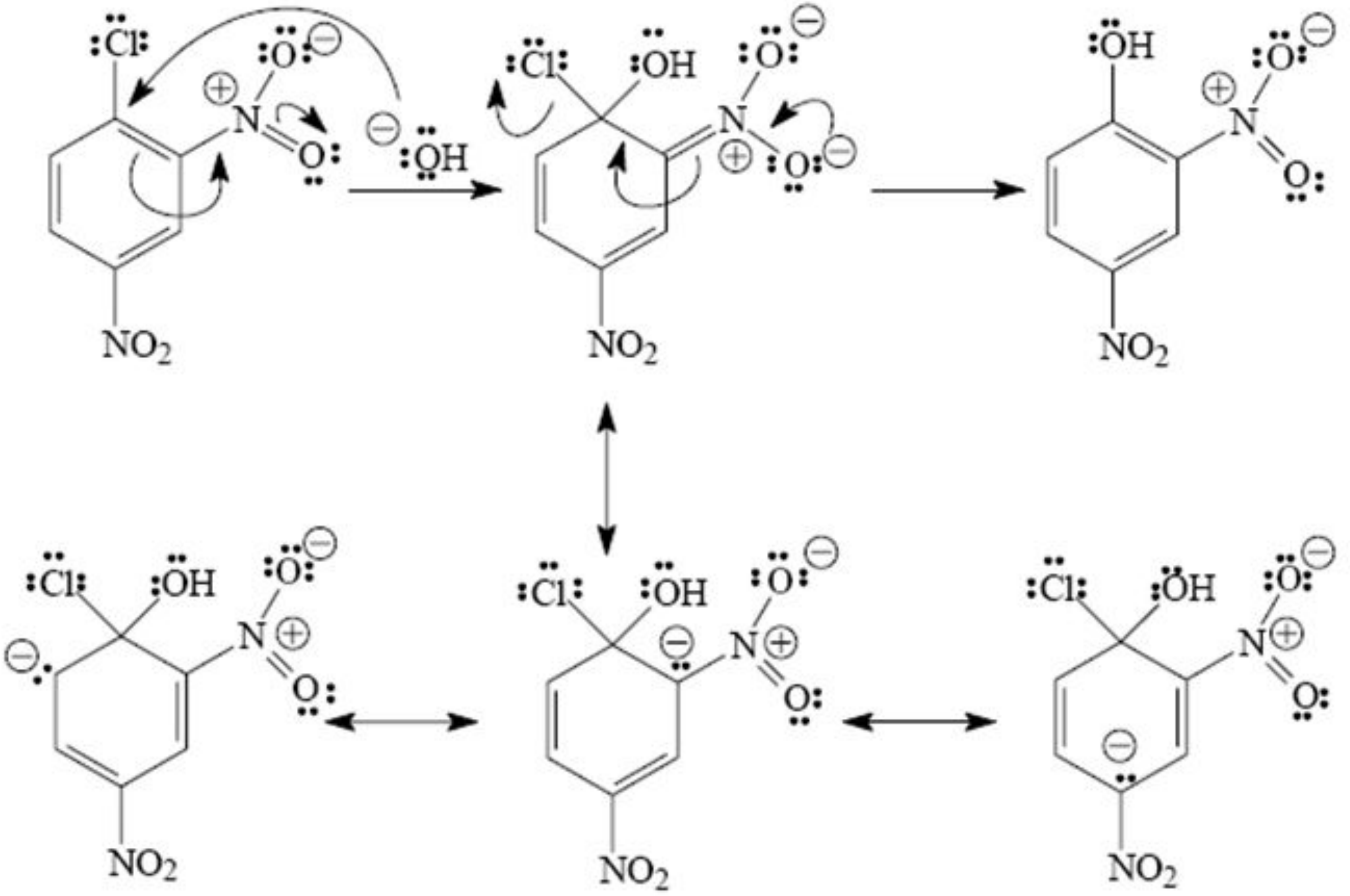


The mechanism of addition-elimination (S_NAr)

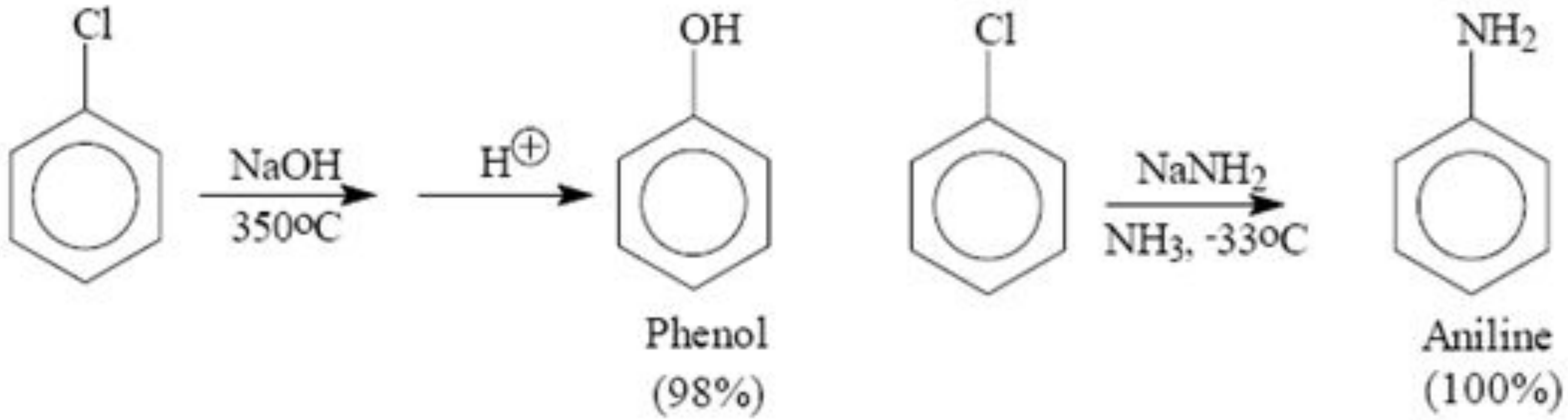
- Aryl halides that bear one or more strongly electron-withdrawing groups in the *ortho* or *para* positions to the halide readily undergo nucleophilic substitution reactions. These electron-withdrawing groups must be groups that withdraw the electron density due to resonance rather than inductively.



The mechanism of addition-elimination (S_NAr)



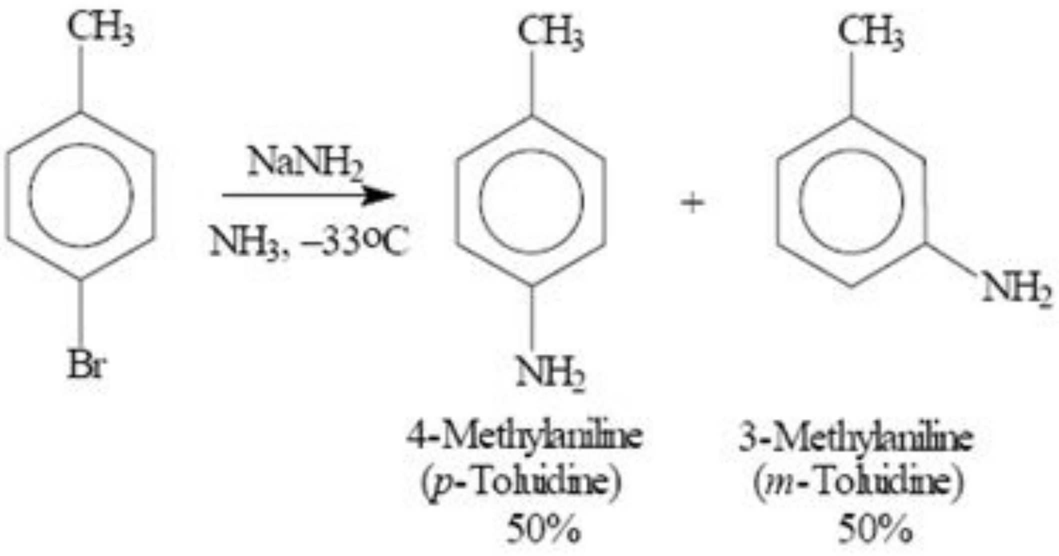
Benzyne

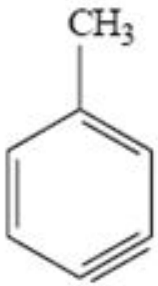


- Aryl halides without electron-withdrawing substituents require extreme conditions or very strong bases for nucleophilic substitution reactions to proceed. For example, under high temperature and pressure, chlorobenzene can be converted into sodium phenoxide when reacted with sodium hydroxide.

Benzyne

- The elimination-addition mechanism proceeds via **a *benzyne* intermediate**. In this case the substitution takes place not only at the carbon bearing the halide but also at the carbon adjacent to the halide bearing carbon. For example, a 50:50 mixture of 3-methylaniline and 4-methylaniline is formed in the reaction of 4-bromotoluene with sodium amide.

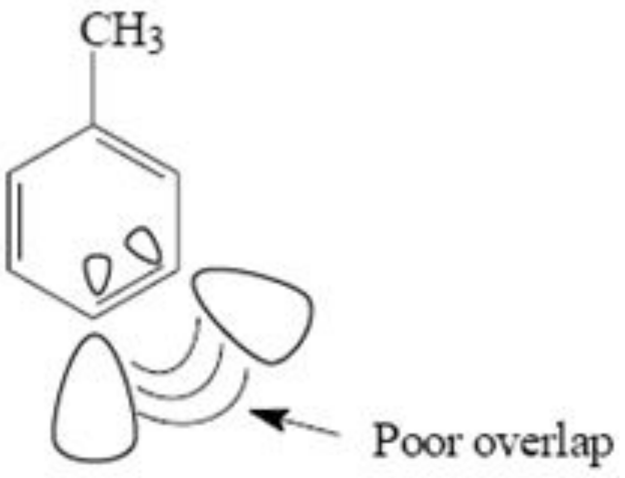




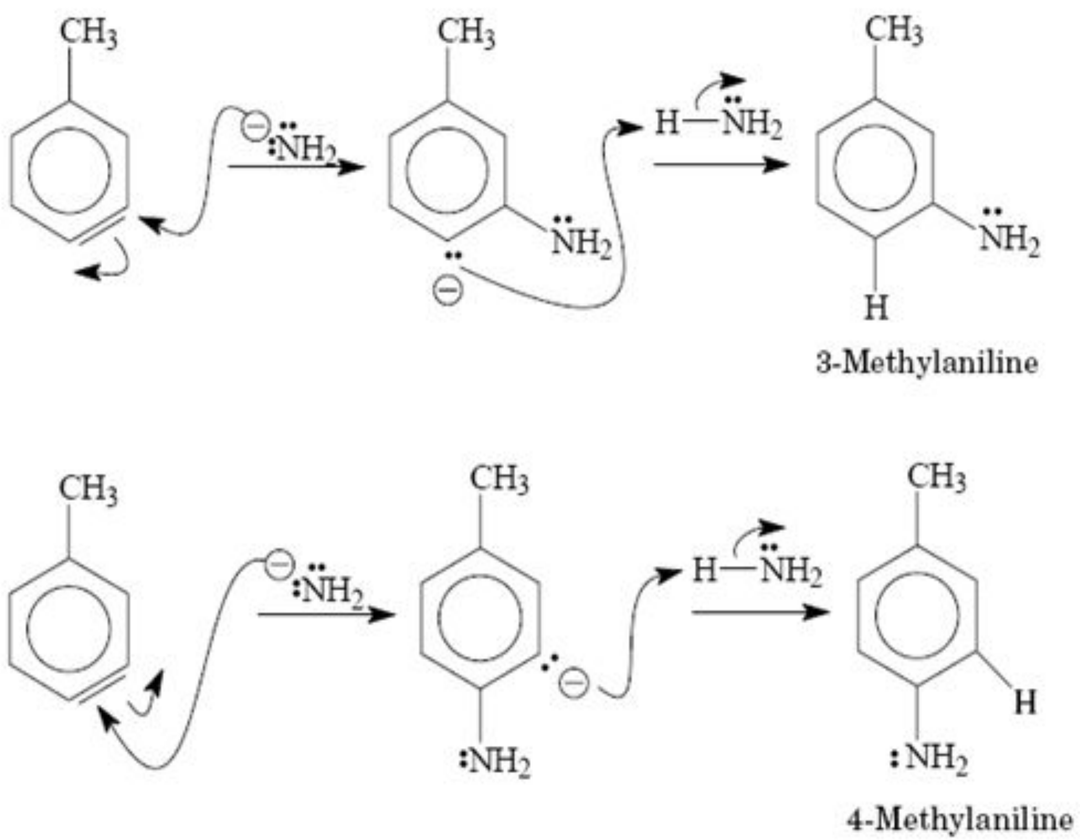
a Benzyne

Benzyne

The extra bond in benzyne results from the overlap of sp^2 orbitals on adjacent carbon atoms of the ring. The overlap of their bonding orbitals is ineffective. The additional bond is weak and the **benzyne** is highly unstable and highly reactive.



Nucleophilic Substitution on an Aromatic Ring



After benzyne forms, the amide ion can attack it on either end of its weak, reactive triple bond. This part of the reaction produces a benzene anion. The benzene anion then removes a proton from an ammonia molecule giving the final products, 3-methylaniline and 4-methylaniline.

Summary

- In this lecture structure and chemical properties of aryl halides are considered. Mechanisms of nucleophilic substitution on an aromatic ring are discussed.

Questions and Assignments

1. Discuss structure and reactivity of aryl halides.
2. What are chemical properties of aryl halides?
3. Specify mechanisms of aromatic nucleophilic substitution.
4. Specify the structure of benzyne.

Aromatic Sulfonic Acids

Topic 4

Outline of the lecture

1. Aromatic sulfonic acids
2. Mechanism of the sulfonation reaction
3. Isolation and identification of sulfonic acids
4. Sulfonation of benzene, its homologues and derivatives
5. Chemical properties of sulfonic acids

Bibliography:

1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
2. Chernykh, V.P. 2003. *Lectures on Organic Chemistry: Tutorial for students of Higher educational institutions.* Zolotye stranitsy: Kharkov
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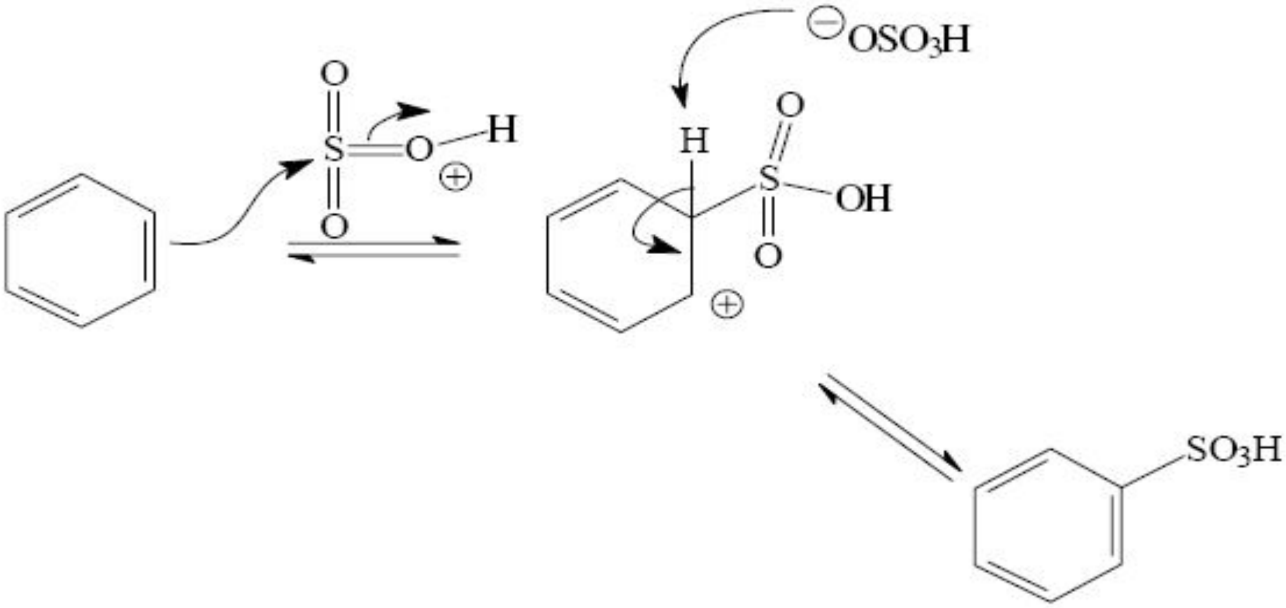
Aromatic sulfonic acids

- ***Aromatic sulfonic acids*** are derivatives of arenes containing the **SO_3H sulfo group**. Aromatic sulfonic acids and their derivatives are used as intermediates for the synthesis of dyes, drugs, detergents, and other practically useful compounds. Nitro, halo, hydroxy and amino compounds can be obtained by substituting the sulfo group.
- ***Aromatic sulfonic acids*** are obtained by direct sulfonation of hydrocarbons or their derivatives. The most common sulfonating agents are concentrated sulfuric acid and oleum.

Mechanism of the sulfonation reaction

- *The essential difference of the sulfonation reaction from other reactions of electrophilic substitution is its reversibility.* Attacking electrophillic particle is sulfur trioxide, SO_3:

$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^{\oplus} + HSO_4^{\ominus}$$



Mechanism of the sulfonation reaction

- Sulfuric acid with various concentrations, vitriol oil containing ~93% H_2SO_4, or monohydrate (100% H_2SO_4) are used as a sulfonating agent. Sulfonation is often carried out with oleum (solution of SO_3 in 100% H_2SO_4).
- Chlorosulfonic acid (sulfuric acid monochloride - $ClSO_3H$), sulfuric anhydride, complexed sulfuric anhydride (pyridine sulfotrioxide, dioxane sulfotrioxide) are also used as sulfonating agents.

Mechanism of the sulfonation reaction

- As mentioned above, ***sulfonation*** with sulfuric acid is ***a reversible process***: the water released dilutes the sulfuric acid and causes a desulfonation reaction.
- The equilibrium can be shifted towards the formation of sulfonation products by increasing the amount and concentration of sulfuric acid or by removing water from the reaction medium.

Isolation and identification of sulfonic acids

- The isolation of sulfonic acids from the reaction mass containing a large amount of spent sulfuric acid presents significant difficulties.
- Most often, sulfonic acids are isolated from the reaction medium in the form of their salts. Soda ash, sodium sulfite, chalk and lime are used as neutralizing agents. Salts of sulfonic acids can be isolated from the solution by evaporation. Salting out with common salt and sodium sulfate is used to isolate salts of sulfonic acids.

Isolation and identification of sulfonic acids

- The isolation process of sulfonic acids can be simplified ***if chlorosulfonic acid is used as a sulfonating agent***. In this case, sulfochlorides, are obtained, which are slowly hydrolyzed. Pure sulphonic acid can be obtained by hydrolysis of sulfochlorides. In many cases, sulfochlorides are even more convenient than sulfonic acids or their salts, so ***it is often preferred to use sulfochlorination instead of sulfonation***.

Derivatives of sulfonic acids

- ***Sulfonic acids are compounds difficult to characterize***, often do not have certain constants (melting point, boiling point) due to decomposition.
- Derivatives of sulfonic acids, namely salts, acid chlorides (***sulfochlorides***), amides (***sulfamides***), esters, which have clear melting or boiling points, are used to identify sulfonic acids.
- Sulfochlorides are of greatest interest. They are stable compounds, many of which, unlike sulfonic acids, can be distilled.

Derivatives of sulfonic acids

- ***Sulfochlorides*** can be converted to easily purified amides and other derivatives:

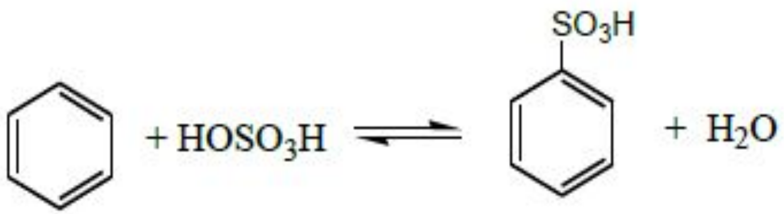
$$ArSO_2Cl + NH_3 \rightarrow ArSO_2NH_2 + HCl$$

- They are of great independent importance in the production of dyes and in medicine (sulfa drugs, chloramines "B", "T") along with the use for identification purposes.
- Esters of sulfonic acids, which are used as alkylating agents, are obtained by acting alcohols or sodium alcoholates on sulfochlorides:

$$ArSO_2Cl + HOC_2H_5 \rightarrow ArSO_2OC_2H_5 + HCl$$

Sulfonation of benzene, its homologues and derivatives

- Sulfonation of benzene is carried out with a 2.5-3-fold excess of concentrated sulfuric acid at 80-100^{0}C:

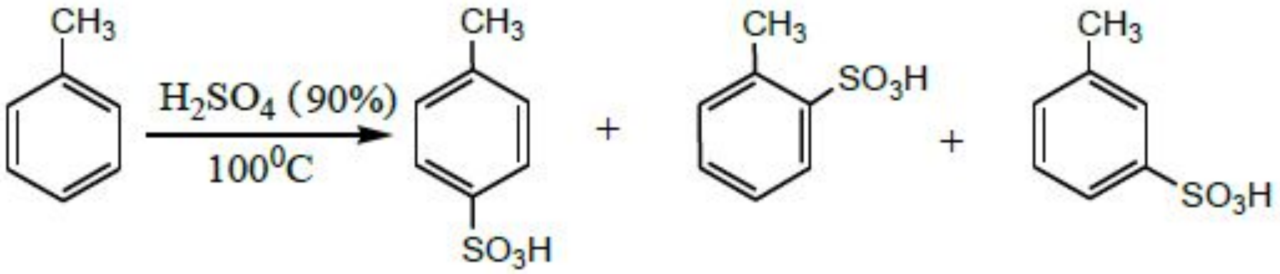


benzenesulfonic acid

Alkyl substituents facilitate the reaction somewhat. Toluene, for example, is sulfonated with vitriol oil at 100°C, forming mainly *p*-toluenesulfonic acid with an admixture of *ortho* and *meta* isomers.

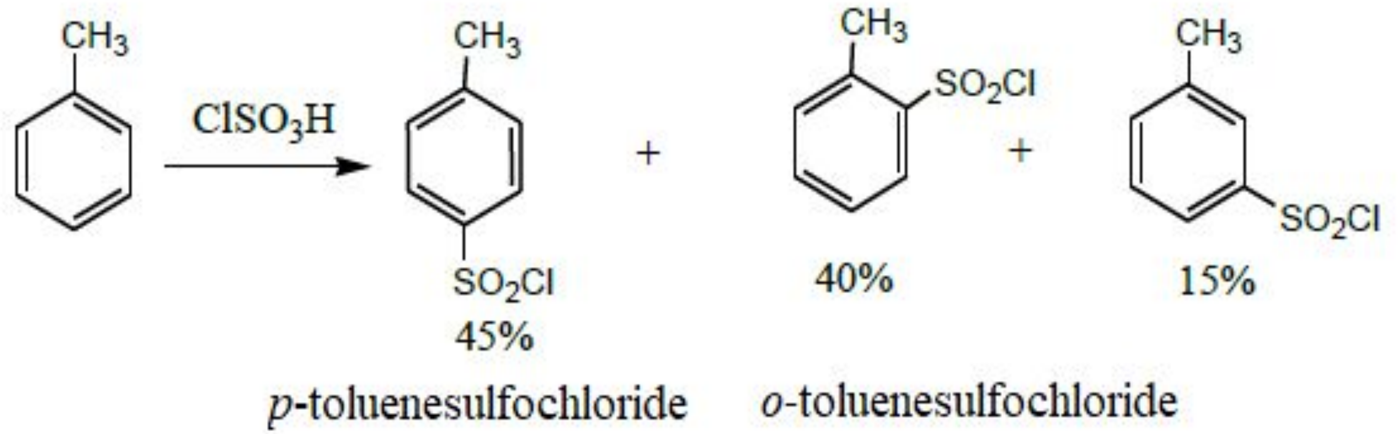
Sulfonation of benzene, its homologues and derivatives

- The proportion of the *para*-isomer increases with an increase in the volume of the alkyl radical in the benzene cycle, and sulfonation of *tert.*-butylbenzene occurs mainly in the *para*-position.



Sulfonation of benzene, its homologues and derivatives

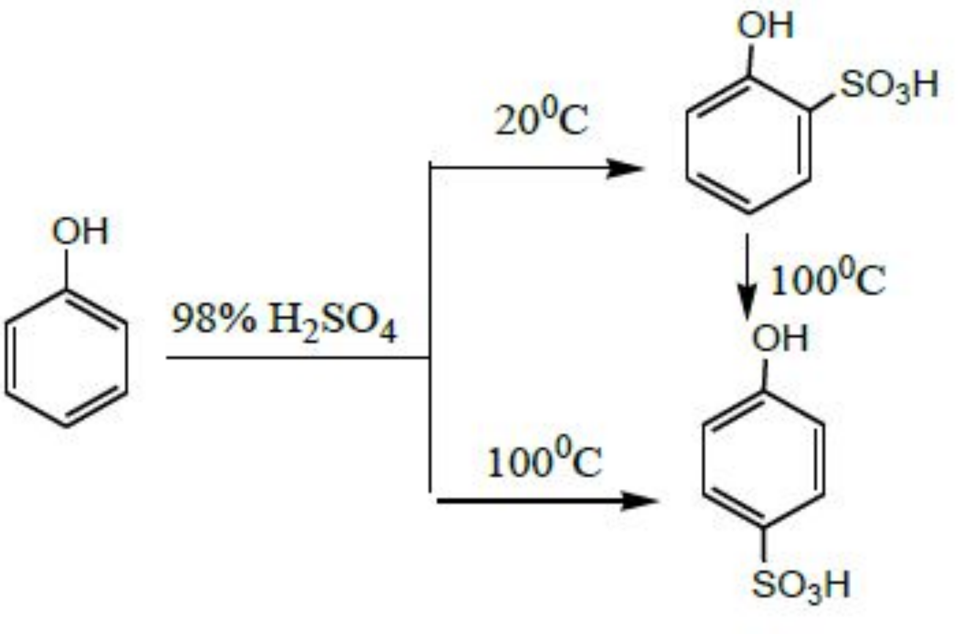
- Sulfochlorination of benzene and its homologues with chlorosulfonic acid proceeds under milder conditions than direct sulfonation and is less regioselective.



p-toluenesulfochloride *o*-toluenesulfochloride

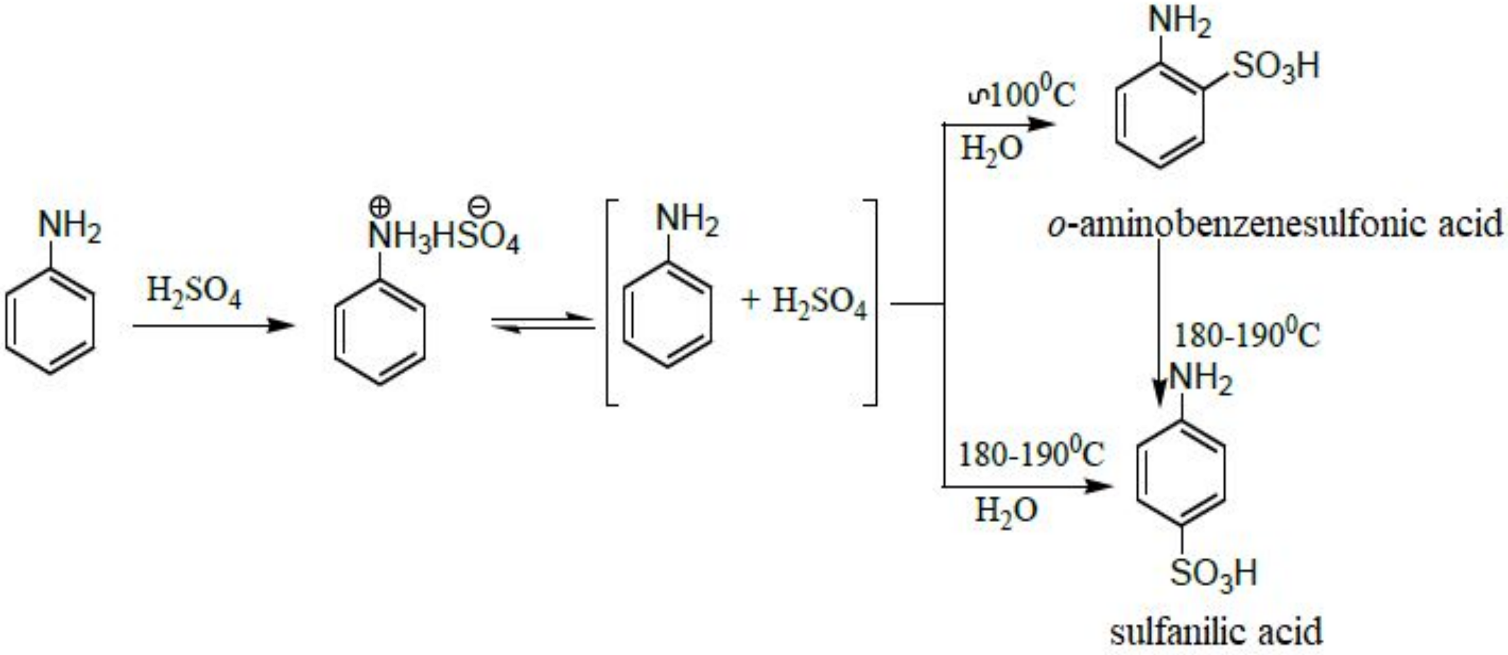
Sulfonation of benzene, its homologues and derivatives

- Sulfonation of phenol with sulfuric acid proceeds with the formation of a mixture *ortho*- and *para*-hydroxybenzenesulfonic acids and it is an example of the temperature influence on the direction of the process. *Ortho*-hydroxybenzenesulfonic acid forms at 20^{0}C, *para*-hydroxybenzenesulfonic acid forms at 100^{0}C, which is due to the reaction reversibility.



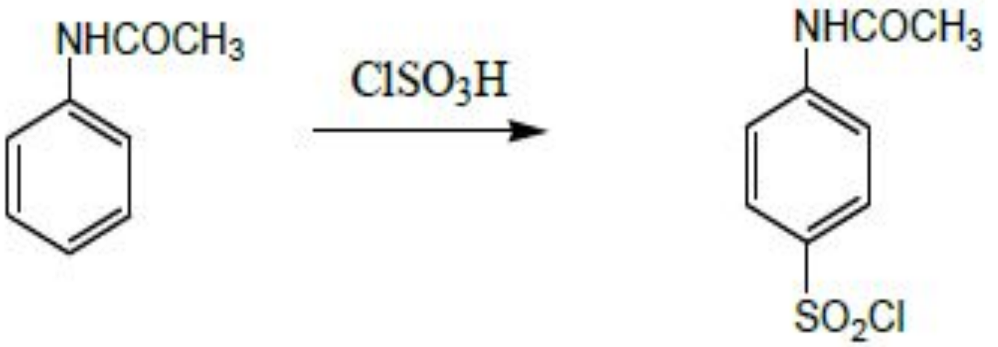
Sulfonation of benzene, its homologues and derivatives

- The amino group is one of the strongest electron-donating ortho- and para- directors; however, it is protonated in 90-100% sulfuric acid or oleum, while the equilibrium shifts towards the protonated form.



Sulfonation of benzene, its homologues and derivatives

- ***Sulfanilic acid*** is used in the production of dyes and drugs. The product of sulfochlorination of acetanilide with chlorosulfonic acid (*para*-acetaminobenzenesulfonic acid chloride) is used in the synthesis of sulfanilamide preparations, diuretics, and antidiabetic agents.



p-acetaminobenzenesulfochloride

Chemical properties of sulfonic acids

- Reactions of the sulfo group.
- Substitution reactions of the sulfo group.
- Reactions of the benzene ring.

Chemical properties of sulfonic acids

Reactions of the sulfo group

Arenesulfonic acids are strong acids and are often compared in strength to sulfuric acid. They are fully ionized in aqueous solutions.

They are characterized by the following reactions:

a) Formation of stable salts:

$ArSO_3H + NaOH \rightarrow ArSO_3Na + H_2O$

$ArSO_3H + NaCl \rightarrow ArSO_3Na + HCl$

b) Formation of acid chlorides (sulfonyl chlorides):

$ArSO_3Na + PCl_5 \rightarrow ArSO_2Cl + POCl_3 + NaCl$

Chemical properties of sulfonic acids

c) Formation of esters that have electrophilic properties and are good alkylating agents:

$ArSO_2Cl + C_2H_5ONa \rightarrow ArSO_2O\ C_2H_5 + NaCl$

d) Formation of amides (sulfonamides):

$ArSO_2Cl + 2NH_3 \rightarrow ArSO_2\ NH_2 + NH_4Cl$

Sulfonamides, being weak NH-acids, react with alkalis:

$ArSO_2\ NH_2 + NaOH \rightarrow ArSO_2\ N^-HNa^+ + H_2O$

Chemical properties of sulfonic acids

- ***Sulfo group substitution reactions***

a) hydrolysis of sulfonic acids when heated with dilute sulfuric acid:

$$ArSO_3H + H_2O \xrightleftharpoons{H^+} Ar{-}H + H_2SO_4$$

b) substitution of the sulfo group with a hydroxyl group when fused with alkali - an industrial method for producing phenols:

$$C_6H_5SO_3Na + 2NaOH \rightarrow C_6H_5ONa + Na_2SO_3 + H_2O$$

$$2C_6H_5ONa + H_2SO_4 \rightarrow C_6H_5OH + Na_2SO_4$$

Chemical properties of sulfonic acids

c) when salts of sulfonic acids are fused with cyanides, nitriles of carboxylic acids are formed:

$$C_6H_5SO_3Na + NaCN \rightarrow C_6H_5CN + Na_2SO_3$$

Reactions of the benzene ring

Sulfo group, being an electron-withdrawing substituent (it *has -I* and *-M* effects), deactivates electrophilic substitution and directs the incoming substituent to the *meta* position.

Summary

- In this lecture chemical properties of aromatic sulfonic acids are considered. Derivatives of aromatic sulfonic acids are discussed.

Questions and Assignments

1. What are aromatic sulfonic acids?
2. Discuss mechanism of the sulfonation reaction.
3. Explain how isolation and identification of sulfonic acids is carried out.
4. Discuss sulfonation of benzene, its homologues and derivatives.
5. Sum up chemical properties of sulfonic acids and their derivatives.

Aromatic Nitro Compounds

Topic 5

Outline of the lecture

1. General Information
2. Nitro Compounds
3. Reactions of Nitro Compounds
4. Reduction in Neutral Medium
5. Reduction in Basic Medium
6. Electrophilic Substitution
7. Nucleophilic Substitution

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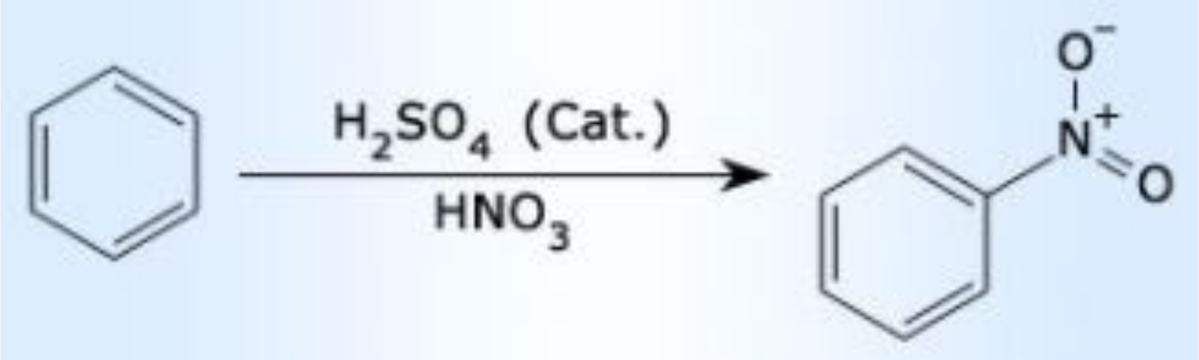
General Information

- Nitro compounds are obtained by replacing the H–atom of an hydrocarbon with the –NO_2 functional group.
- The compounds containing more than one nitro group are often highly explosive and impure. Nitro compounds may be liquids or solids. They are not usually found in nature. They are prepared commercially by nitration of organic compounds.

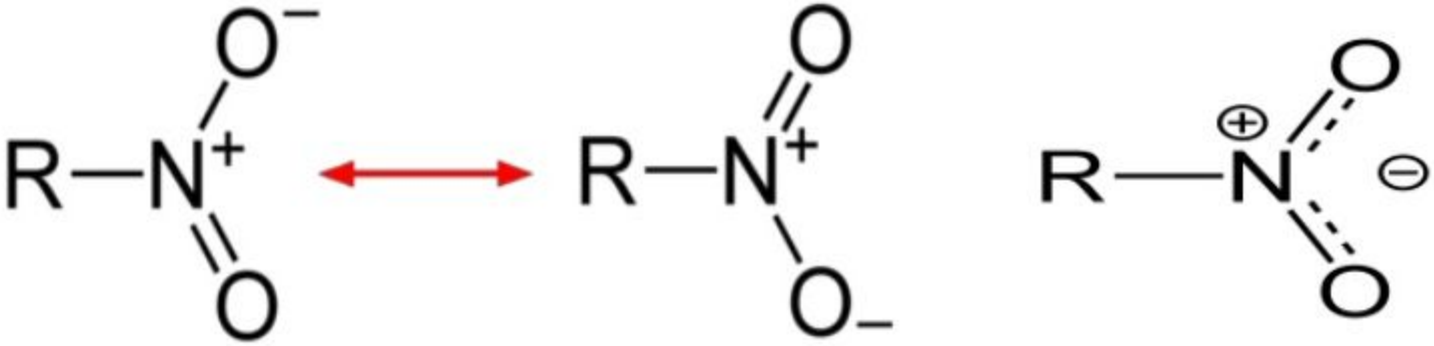


Nitro Compounds

- Nitro compounds are present in the following forms in the nature:
  3–Nitropropionic acid found in fungi and plants (Indigofera). Nitropentadecene is a defense compound found in termites.
  Chloramphenicol is a rare example of a naturally occurring nitro compound.
  2–Nitrophenol is an aggregation pheromone of ticks.

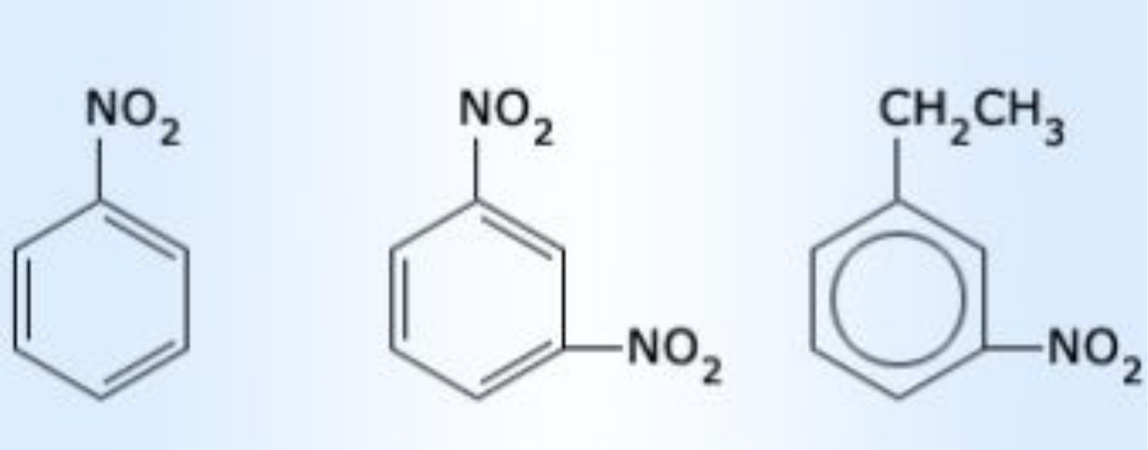
Nitro Compounds

It is electron withdrawing group due to its **-Inductive effect** as well as **-Resonance effect**.



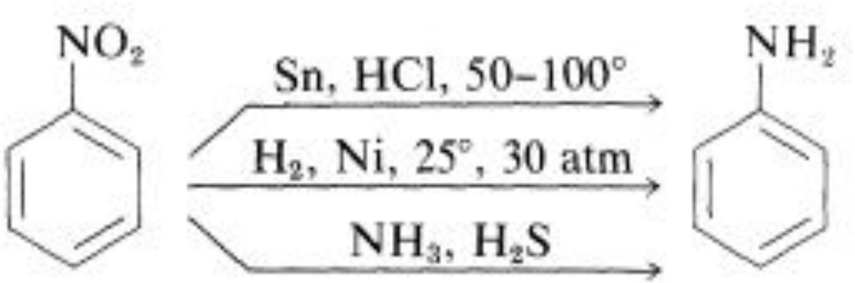
Nitro Compounds

- Aromatic nitro compounds are called nitroarenes. The position of nitro group and other substituents if any are indicated by Arabic numerals.



Reactions of Nitro Compounds

- ***Reduction of nitro compounds*** occurs readily with a variety of reducing agents and such reductions afford a particularly useful synthesis of aromatic amines.



The reduction of a nitro compound to an amine requires six equivalents of reducing agent:

$$R{-}NO_2 + 6H^{\oplus} + 6e^{\ominus} \rightarrow RNH_2 + 2H_2O$$

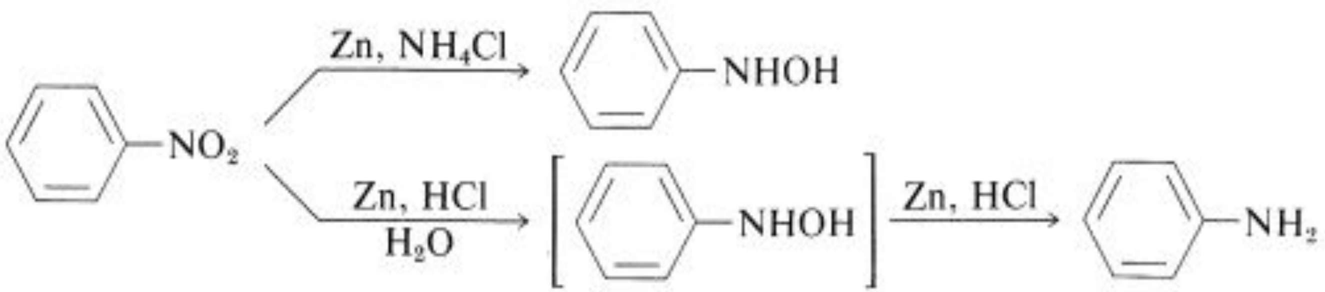
Reactions of Nitro Compounds

- One would not expect such a reduction to occur in a single step. Indeed, reduction is stepwise and proceeds through a string of intermediates, which, with strong reducing agents in acid solution, have at most a transient existence. The intermediates formed successively from RNO_2 by increments of two equivalents of reducing agent are nitroso compounds, R−N=O, and N-substituted azanols (hydroxylamines), RNHOH:

$$RNO_2 \xrightarrow[-H_2O]{2[H]} RN{=}O \xrightarrow{2[H]} RNHOH \xrightarrow[-H_2O]{2[H]} RNH_2$$

Reactions of Nitro Compounds

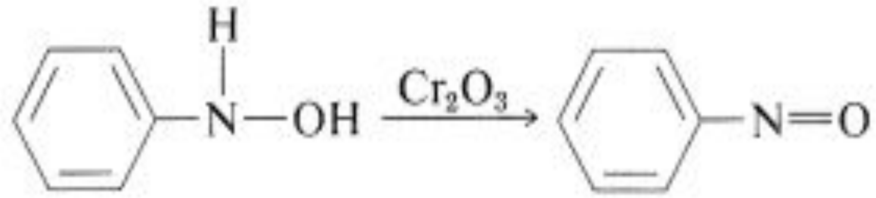
- Thus N-aryl-substituted azanols can be obtained directly from the corresponding nitro compounds with zinc and ammonium chloride solution. However, zinc and hydrochloric acid gives the amine:



The difference between these reactions is in the reduction rates associated with the *acidity* of the solution. Ammonium chloride is a much weaker acid than HCl; the pH of ammonium chloride solutions is around 6.

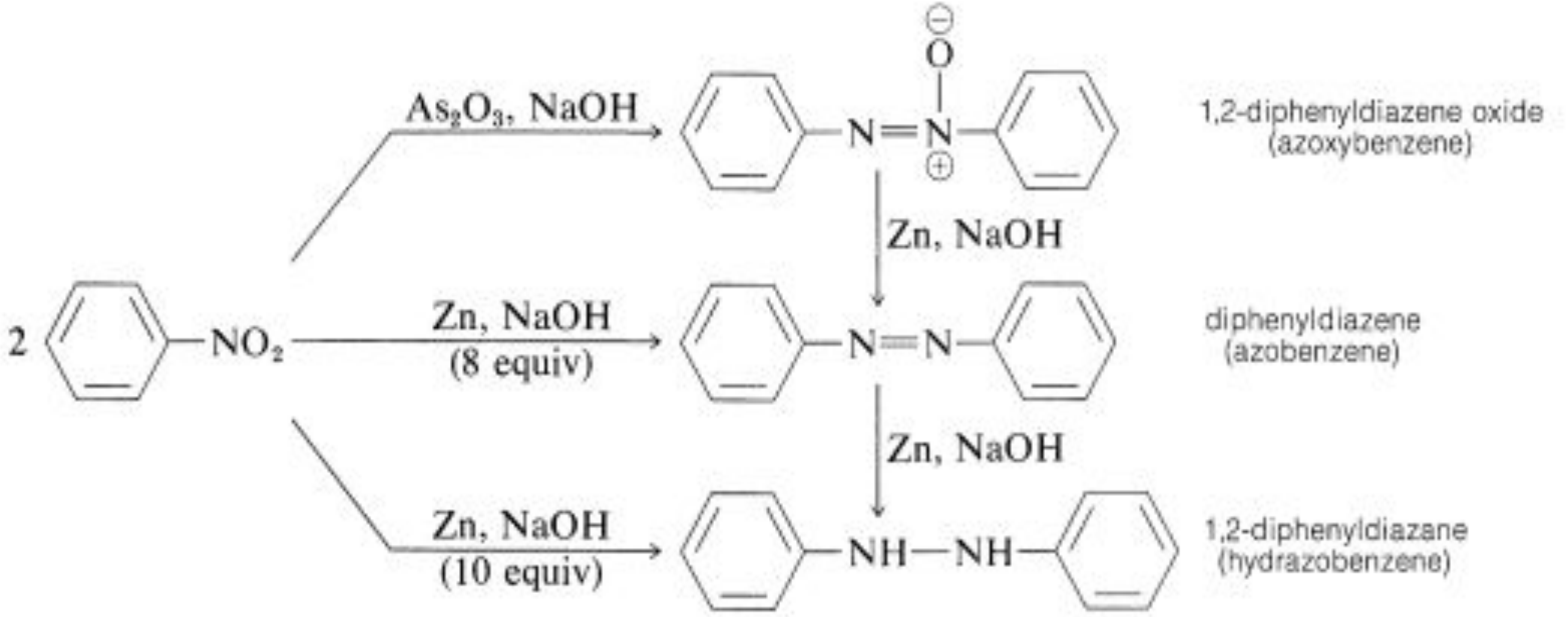
Reactions of Nitro Compounds

- *Oxidation* of the N-arylazanols under controlled conditions yields nitroso compounds. This reaction is not unlike the oxidation of alcohols to ketones.



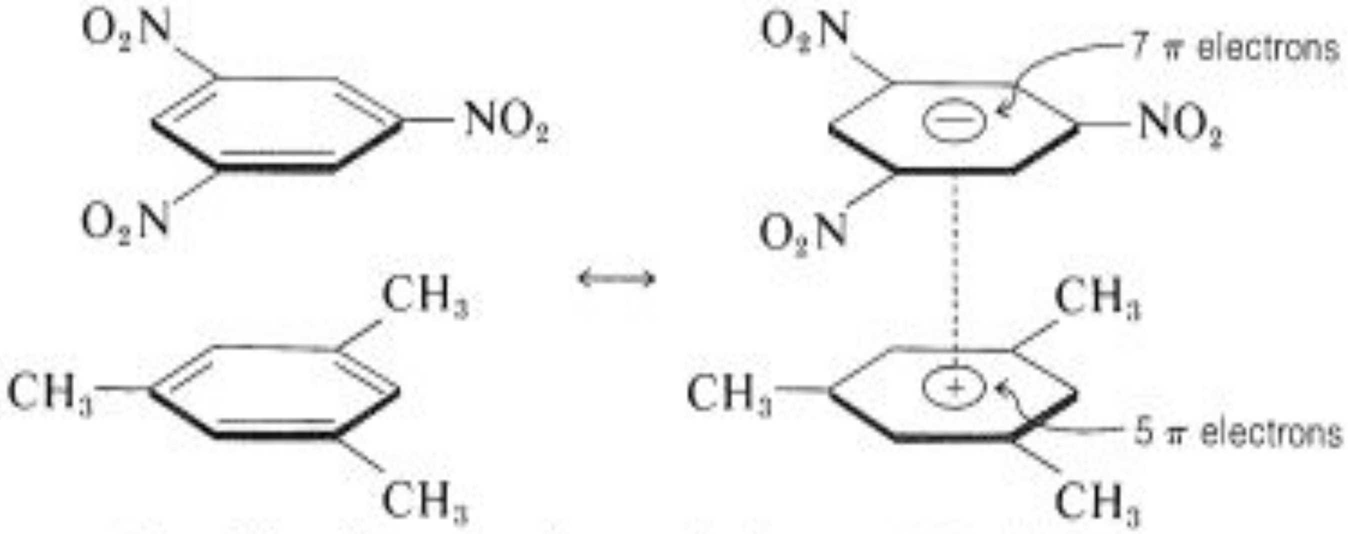
Reactions of Nitro Compounds

- Reduction of aryl nitro compounds with less-powerful reducing agents, especially in alkaline media, gives what may appear to be a mysterious conglomerate of bimolecular reduction products. All of these substances can be reduced to benzeneamine with tin and hydrochloric acid.



Reactions of Nitro Compounds

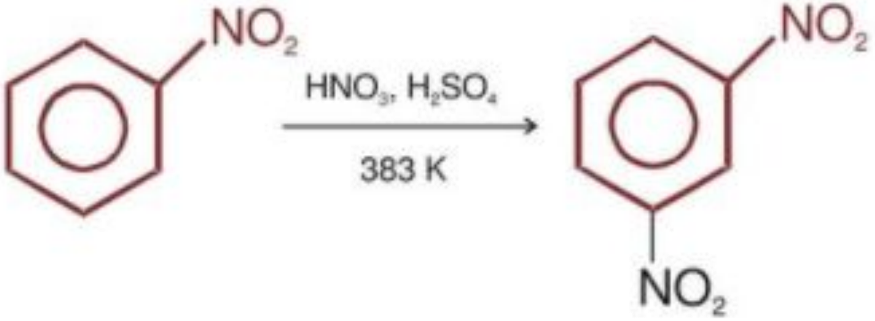
- An important characteristic of aromatic polynitro compounds is their ability to form “charge-transfer” complexes with aromatic hydrocarbons, especially those that are substituted with alkyl groups.



formulation of charge-transfer complex between 1,3,5-trinitrobenzene (acceptor) and 1,3,5-trimethylbenzene (donor)

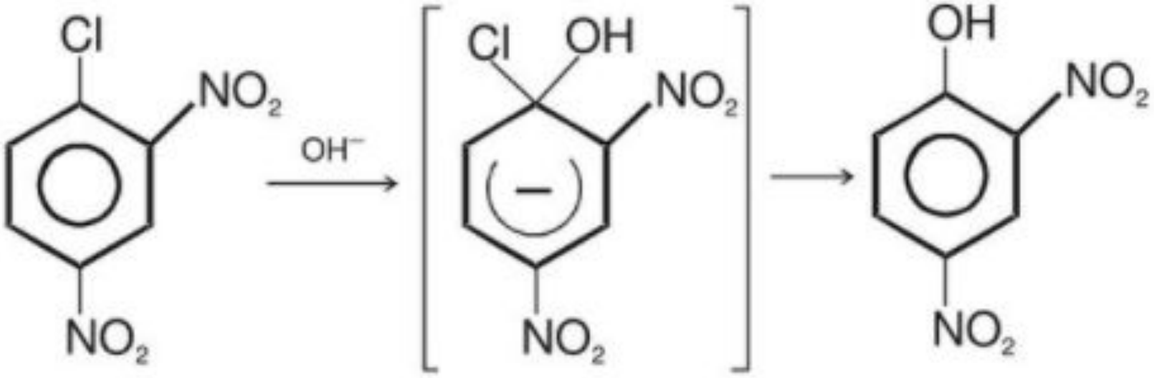
Electrophilic Substitution

- The nitro group strongly deactivates the benzene ring towards electrophilic substitution.
- Required strong conditions.



Nucleophilic Substitution

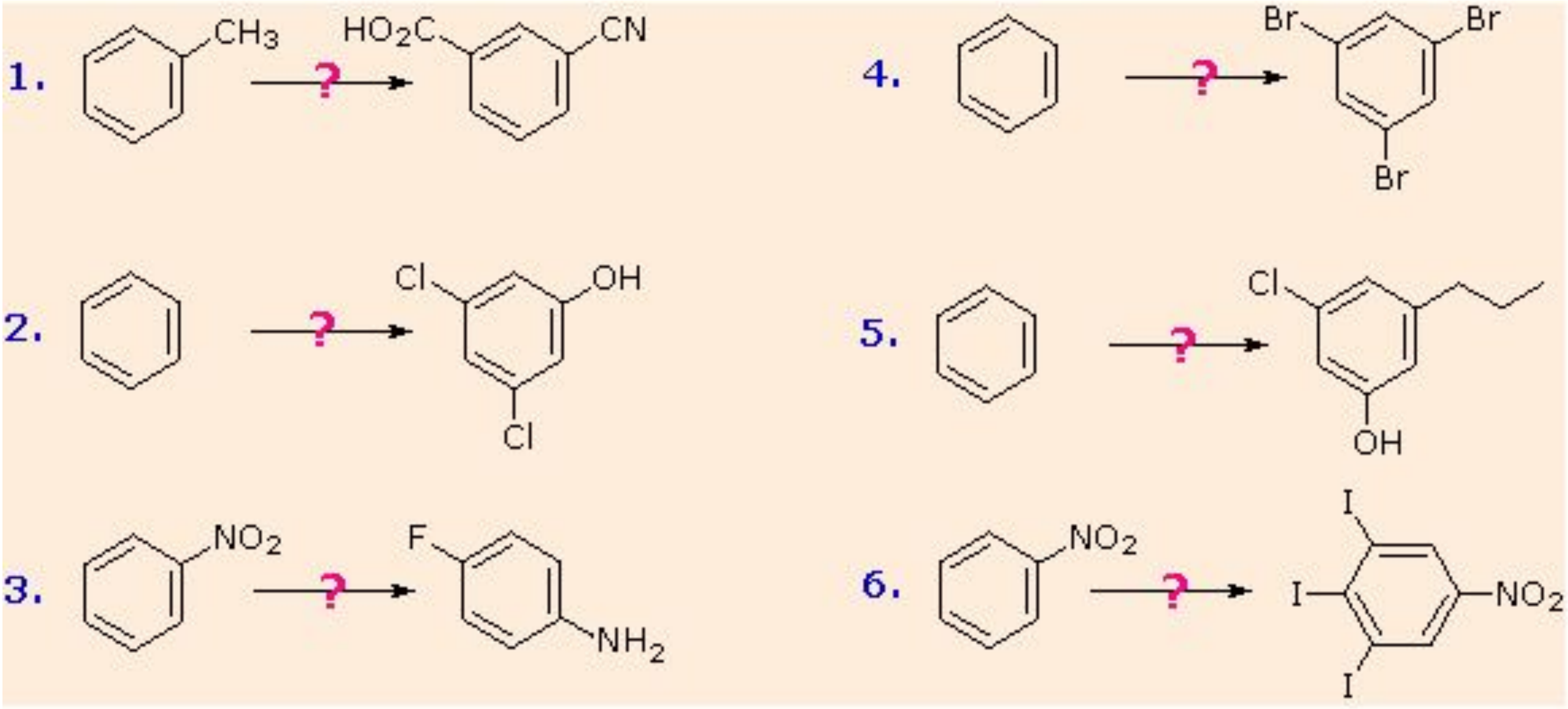
- Nitro group facilitates the nucleophilic substitution by stabilising the intermediate carbanion as depicted below.



Summary

In this lecture chemical properties of aromatic nitro compounds are considered. Reduction reactions are discussed in detail.

Questions and Assignments



Aromatic Amines

Topic 6

Outline of the lecture

1. Aromatic Amines
2. Naming Aromatic Amines
3. Basicity of Aromatic Amines
4. Reactions of Aromatic Amines
5. Amide Formation
6. Ring Halogenation of Phenylamine
7. Protection of NH2- Group by Acylation
8. Synthesis of Dyes
9. Application of Azo Dyes

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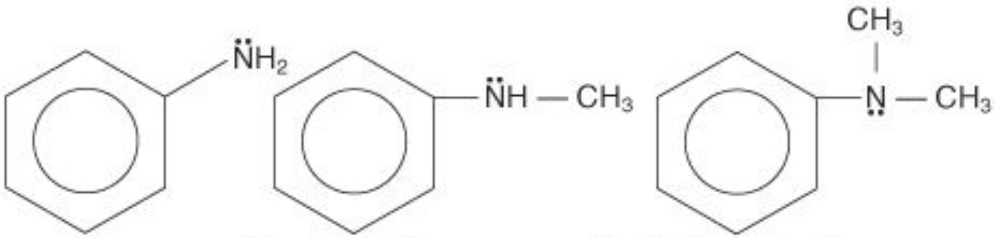
Aromatic Amines

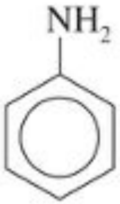
- Aryl-substituted amines are called arylamines. Amines are classified as primary, secondary, and tertiary depending on the degree of substitution at the nitrogen atom.



aniline
(parent)

N-methylaniline
(N-substituted)

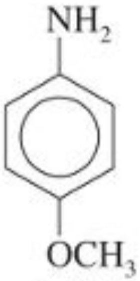
N, N-dimethylaniline
(N, N-disubstituted)



Aniline
(benzenamine)

***N*-Methylaniline**
(*N*-methyl-benzenamine)

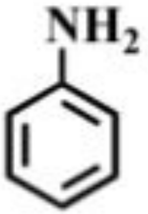
***p*-Toluidine**
(4-methyl-benzenamine)



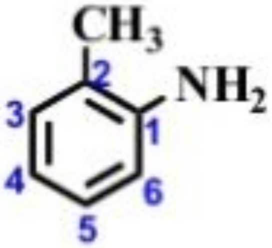
***p*-Anisidine**
(4-methoxy-benzenamine)

Naming Aromatic Amines

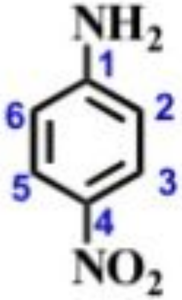
- Aromatic amines have an amine group (-NH_2) attached directly to the aromatic ring.
- Aromatic amines known as arylamines.
- Examples,



phenylamine
(aniline)



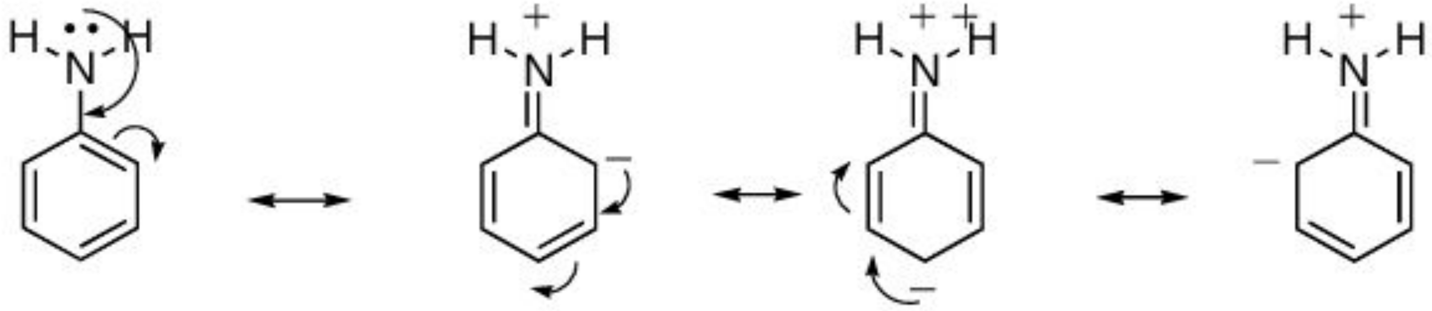
2-methylphenylamine
(2-methylaniline)



4-nitrophenylamine
(4-nitroaniline)

Basicity of Aromatic Amines

- Aromatic amines have the basic character. However, they are weaker than alkyl amines and ammonia. This is mainly due to the conjugation of a lone pair of electrons of a nitrogen atom with π-electron system of the aromatic ring. This makes the lone pair less available for bonding with H^+. When aniline is protonated, the resonance stabilization is lost. The difference in energy for the arylamine and its protonated form is higher than that for alkylamines. Being weak bases, arylamines form salts with mineral acids only.

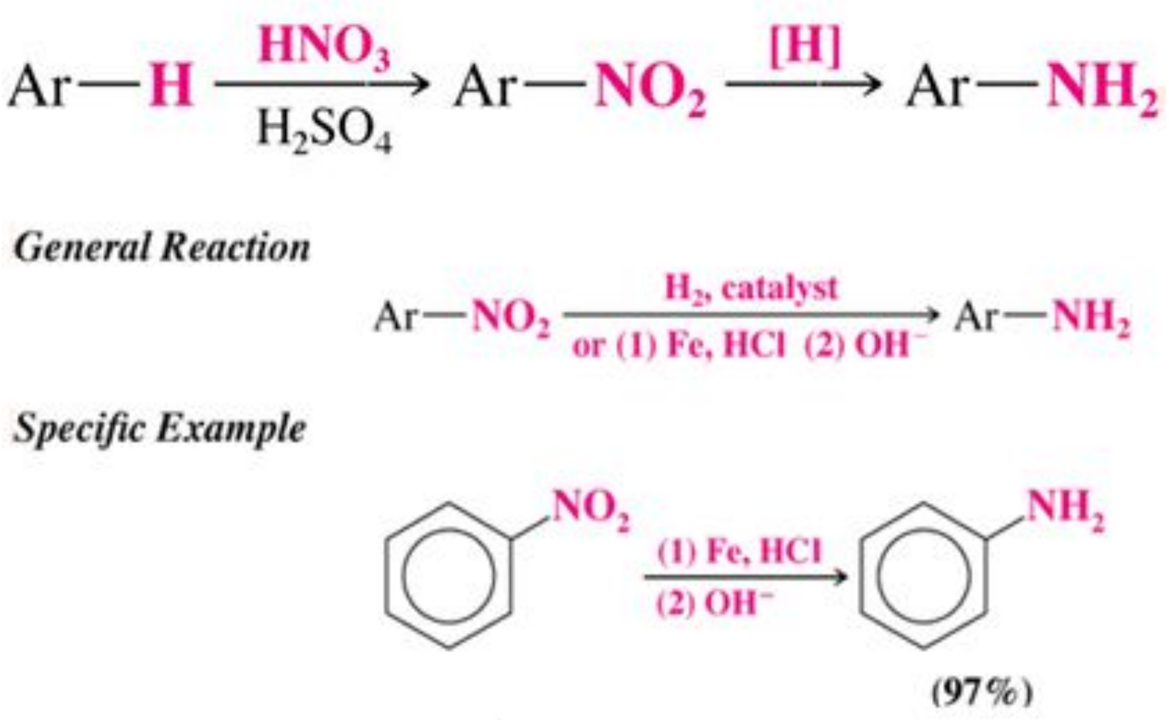


Basicity of Aromatic Amines

- Substituted anilines have different basicities depending on the electronic nature of the substituent. Electron donating groups at the para position increase the basicity of aniline. The stronger the electron donor on the ring is, the higher the basicity of the aniline. Similarly, electron-withdrawing groups at the para position decreases the basicity of anilines. Substituents at the meta and ortho positions also exert their influence on the basicity of anilines.

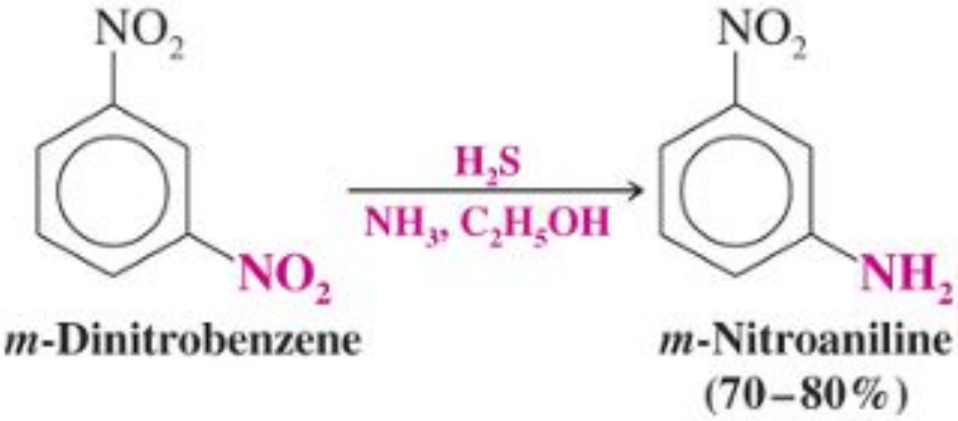
Preparation of Aromatic Amines

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



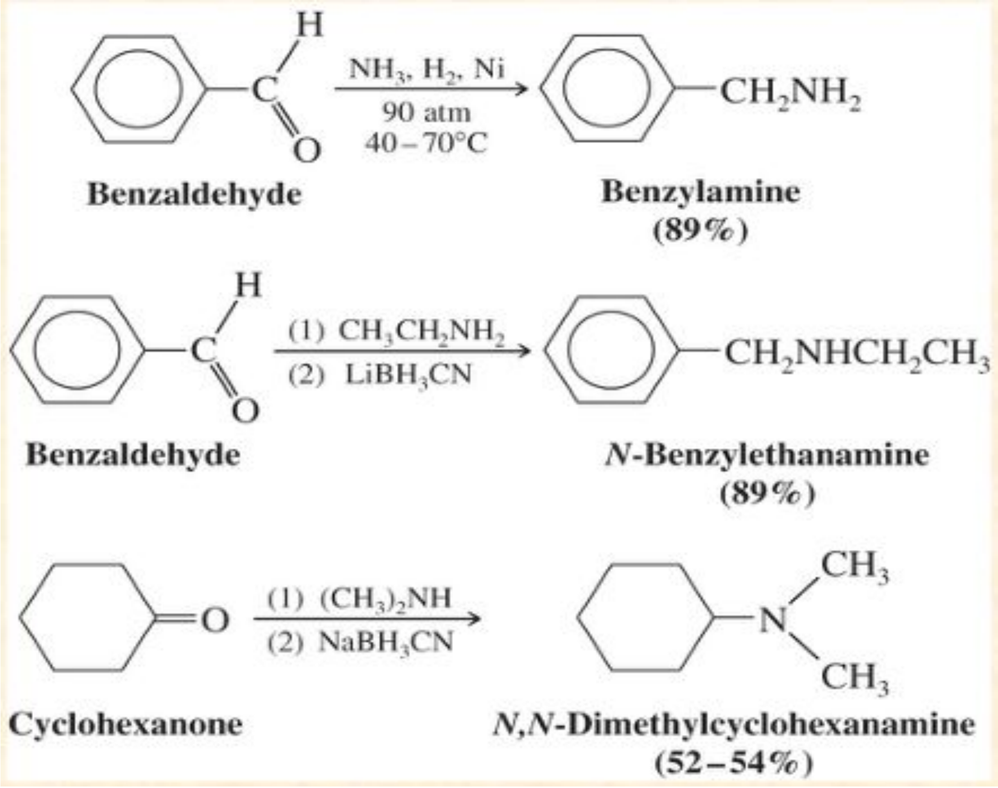
Preparation of Aromatic Amines

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



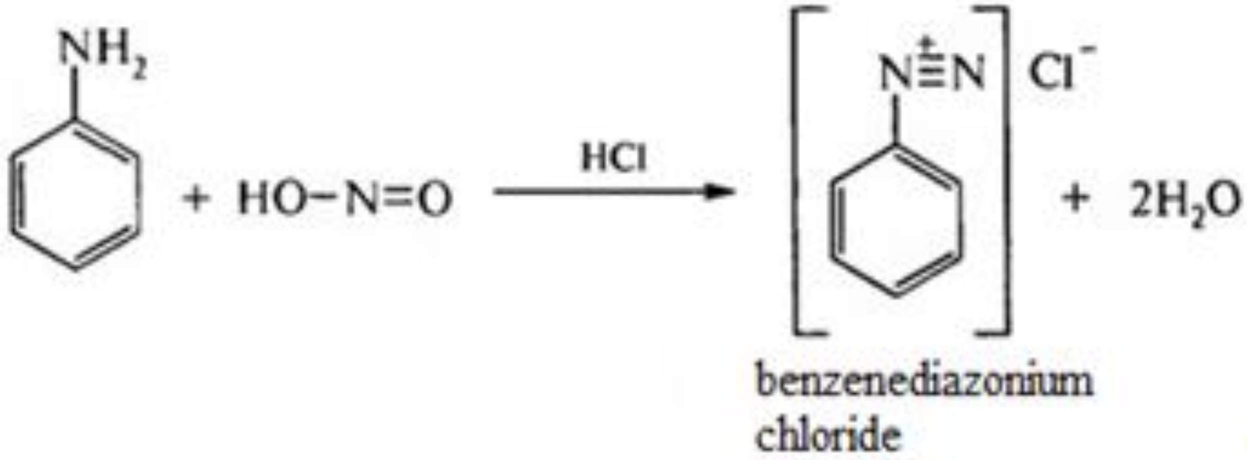
Preparation of Aromatic Amines

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



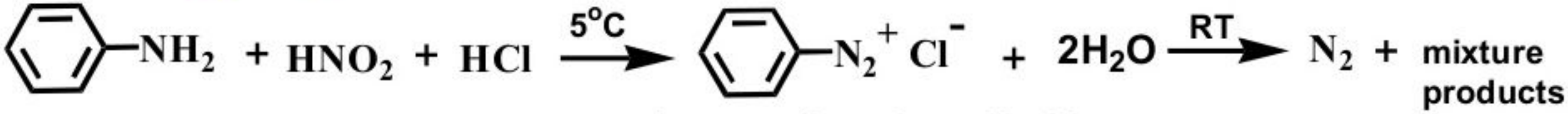
Reactions of Arylamines

- This reaction is called ***diazotization.***



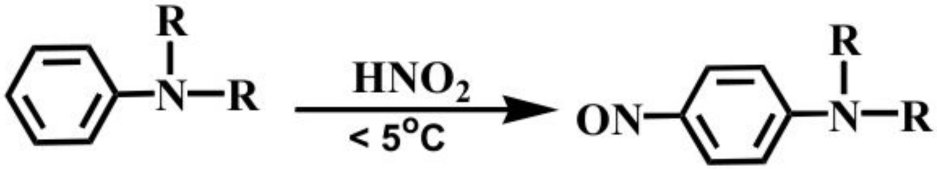
Reactions of Aromatic Amines

- A primary aromatic amines react with cold HNO_2 and dissolved in dilute HCl at 0-5°C will produced diazonium salt. When this cold salts heated at room temperature, nitrogen gas will evolved.



benzenediazonium chloride

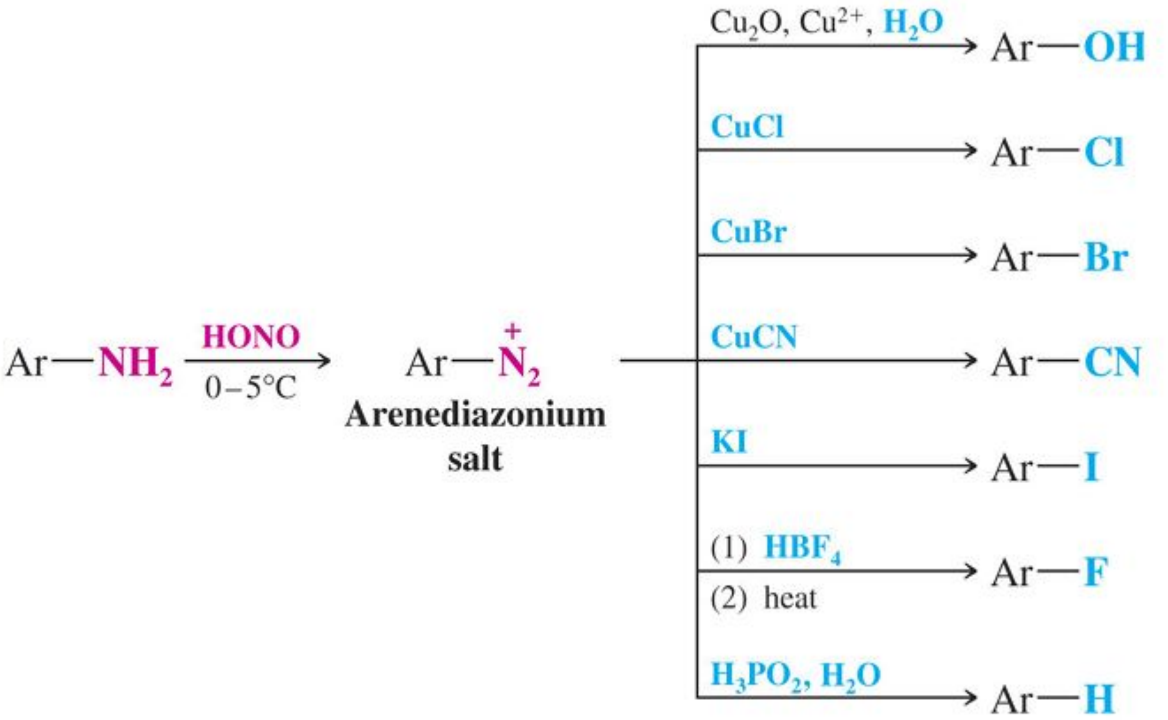
- Tertiary aromatic amines reacts with nitrous acid by undergoing substitution at the *para* position of the benzene ring to form nitrosoaniline which is a yellow precipitate.



a nitosoamiline compound (yellow precipitate)

Reactions of Arylamines

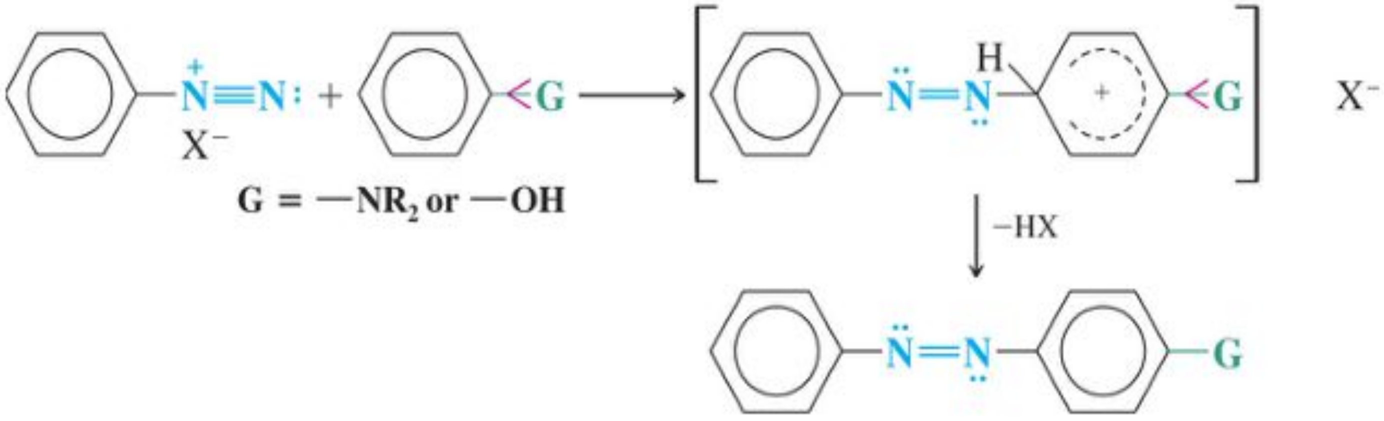
- ***Replacement Reactions of Arenediazonium Salts - Sandmeyer Reactions***
- Aryldiazonium salts react readily with various nucleophilic reagents to give a wide variety of aromatic compounds



Reactions of Arylamines

- ***Coupling Reactions of Arenediazonium Salts***
- Arenediazonium ions react as electrophiles with highly reactive aromatic compounds such as phenol and aromatic tertiary amines. The reaction is called ***a diazo coupling reaction*****.**

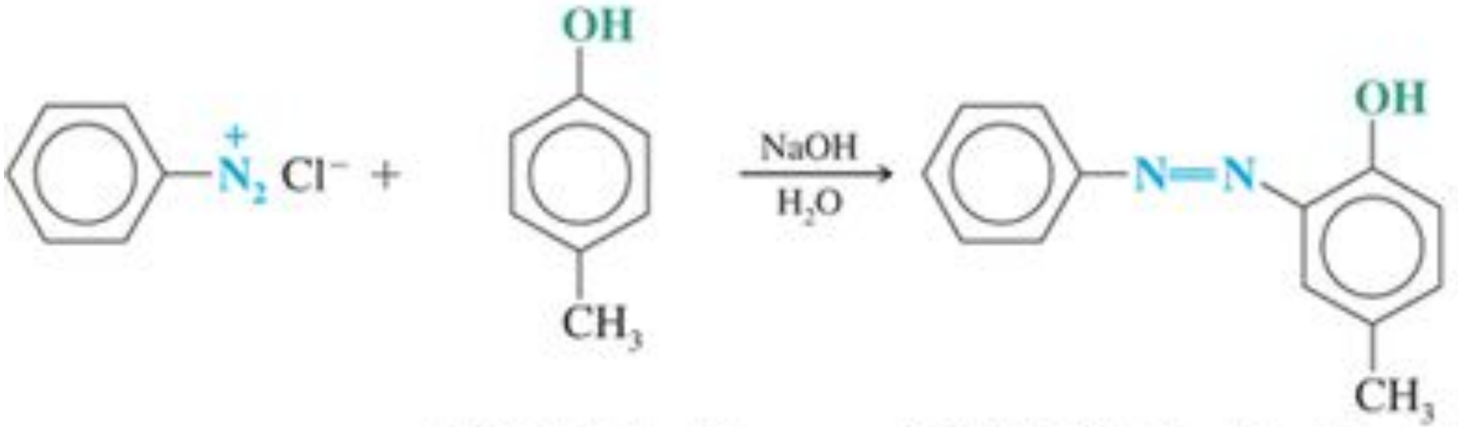
General Reaction



An azo compound

Reactions of Arylamines

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



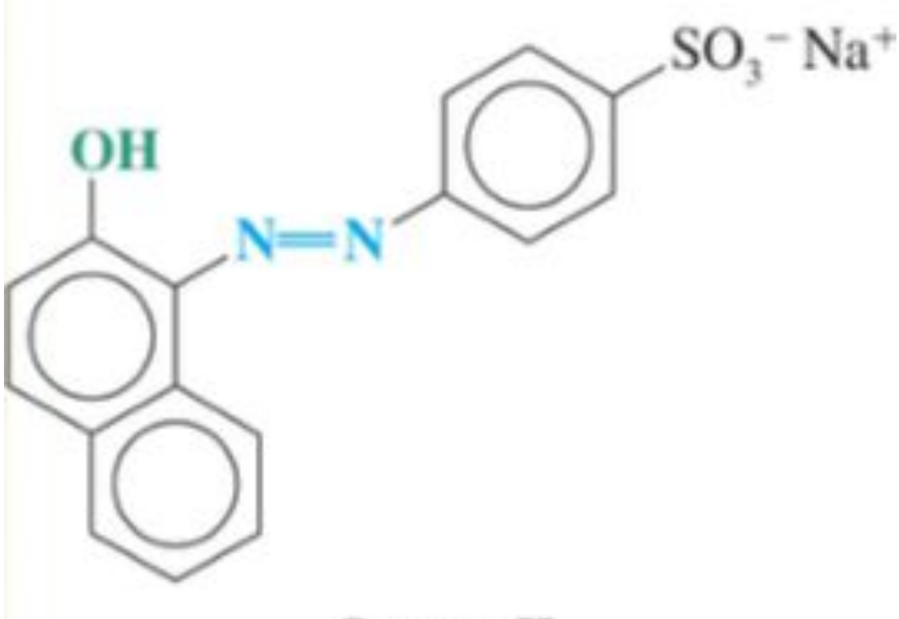
4-Methylphenol
(*p*-cresol)

4-Methyl-2-(phenylazo)phenol

Reactions of Arylamines

- Phenol and aniline derivatives undergo coupling almost exclusively at the para position unless this position is blocked.
- Azocompounds are commonly used as dyes. The azo coupling results in compounds which are highly conjugated. The $-SO_3^-Na^+$ group is added to the molecule for solubility and to link the dye to the polar fibers of wool, cotton etc.–Orange II is made from 2-naphthol.

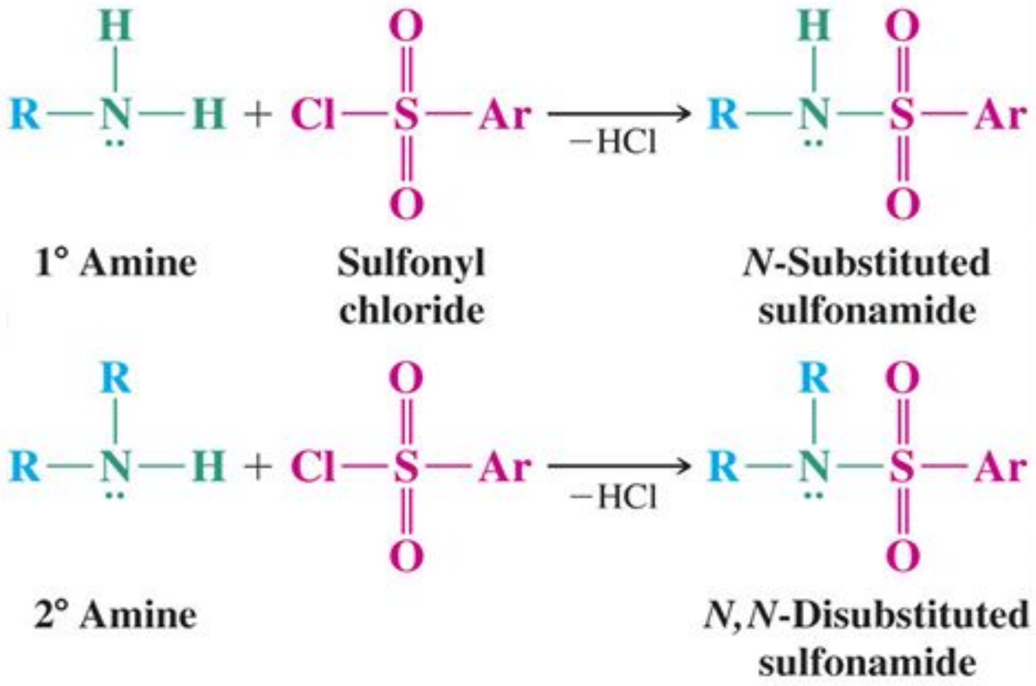
Reactions of Arylamines



Orange II

Reactions of Arylamines

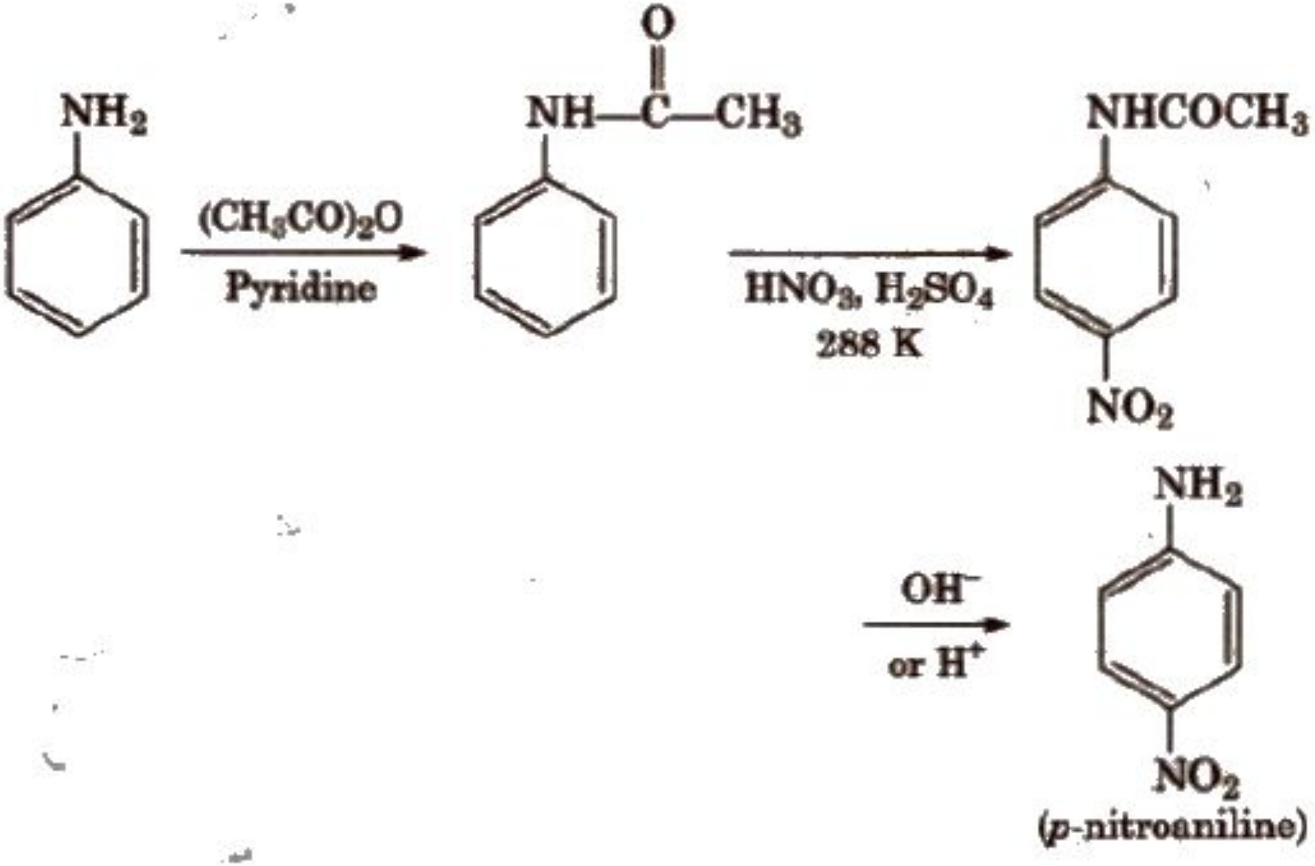
- ***Reactions of Amines with Sulfonyl Chlorides***
- Primary and secondary amines react with sulfonyl chlorides to produce ***sulfonamides***. A sulfonamide can be hydrolyzed to an amine by heating with aqueous acid.



Reactions of Arylamines

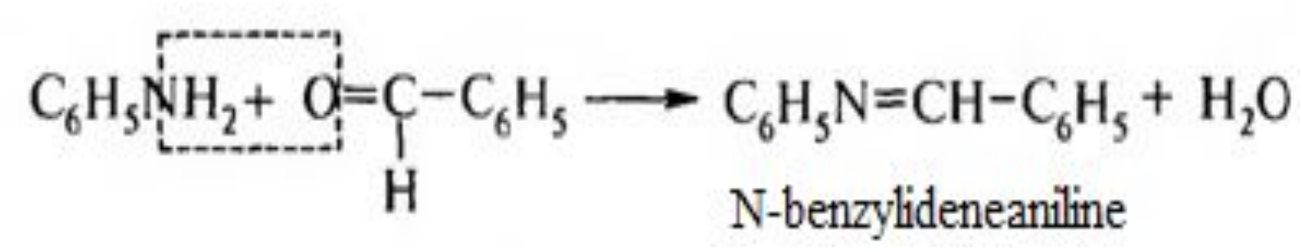
- ***The alkylation reaction.*** Primary and secondary arylamines react with haloalkanes forming N-alkyl and N, N-dialkylarylamines. The reaction proceeds more difficult due to reduced nucleophilic properties of the nitrogen atom.
- ***The acylation reaction.*** N-acyl derivatives of aniline and its homologues are called anilides. Amides of carboxylic acids are readily hydrolyzed under acidic or alkaline conditions to form the starting amine and carboxylic acid.
- The ability of acyl derivatives to undergo hydrolysis allows applying this reaction in organic synthesis for the temporary protection of the amino group from oxidation and undesirable reactions.

Protection of NH2- Group by Acylation



Reactions of Arylamines

- ***Reaction with aromatic aldehydes***



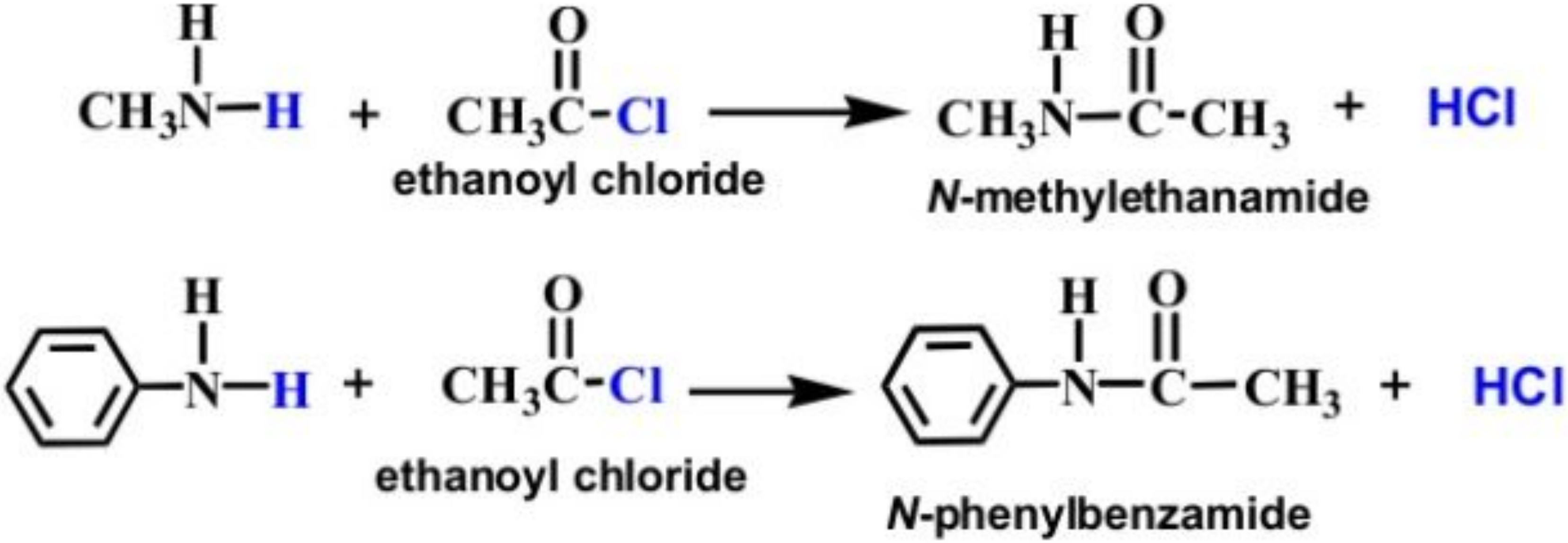
$$C_6H_5N\boxed{H_2 + O}{=}\underset{\substack{|\\ H}}{C}{-}C_6H_5 \longrightarrow C_6H_5N{=}CH{-}C_6H_5 + H_2O$$

N-benzylideneaniline

Reactions involving the aromatic ring

Reactions of aromatic electrophilic substitution are typical for arylamines. The amino group exhibits + *M* effect and acts as a strong electron donor in relation to the benzene ring, thereby activating it in electrophilic substitution reactions. For example, the aniline reacts with bromine water in the absence of a catalyst to form 2,4,6-tribromoaniline immediately.

Amide Formation

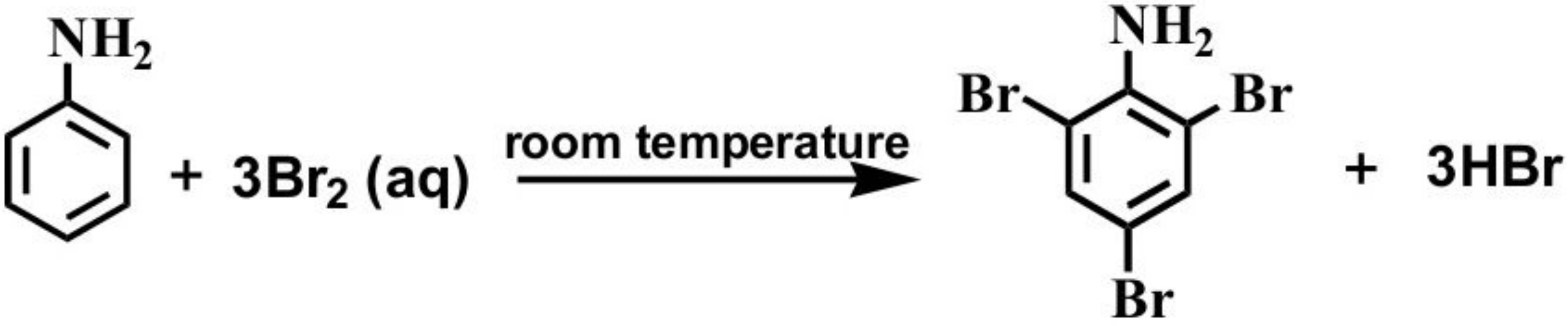


$$CH_3\overset{H}{\overset{|}{N}}-H + CH_3\overset{O}{\overset{\|}{C}}-Cl \longrightarrow CH_3\overset{H}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-CH_3 + HCl$$

Ring Halogenation of Phenylamine

When bromine water is added to phenylamine (aniline) at room temperature, decolorisation of the bromine water occurs and a white precipitate of 2,4-6-tribromoaniline ($C_6H_4Br_3N$) is obtained.

This reaction is used as a test for aniline.

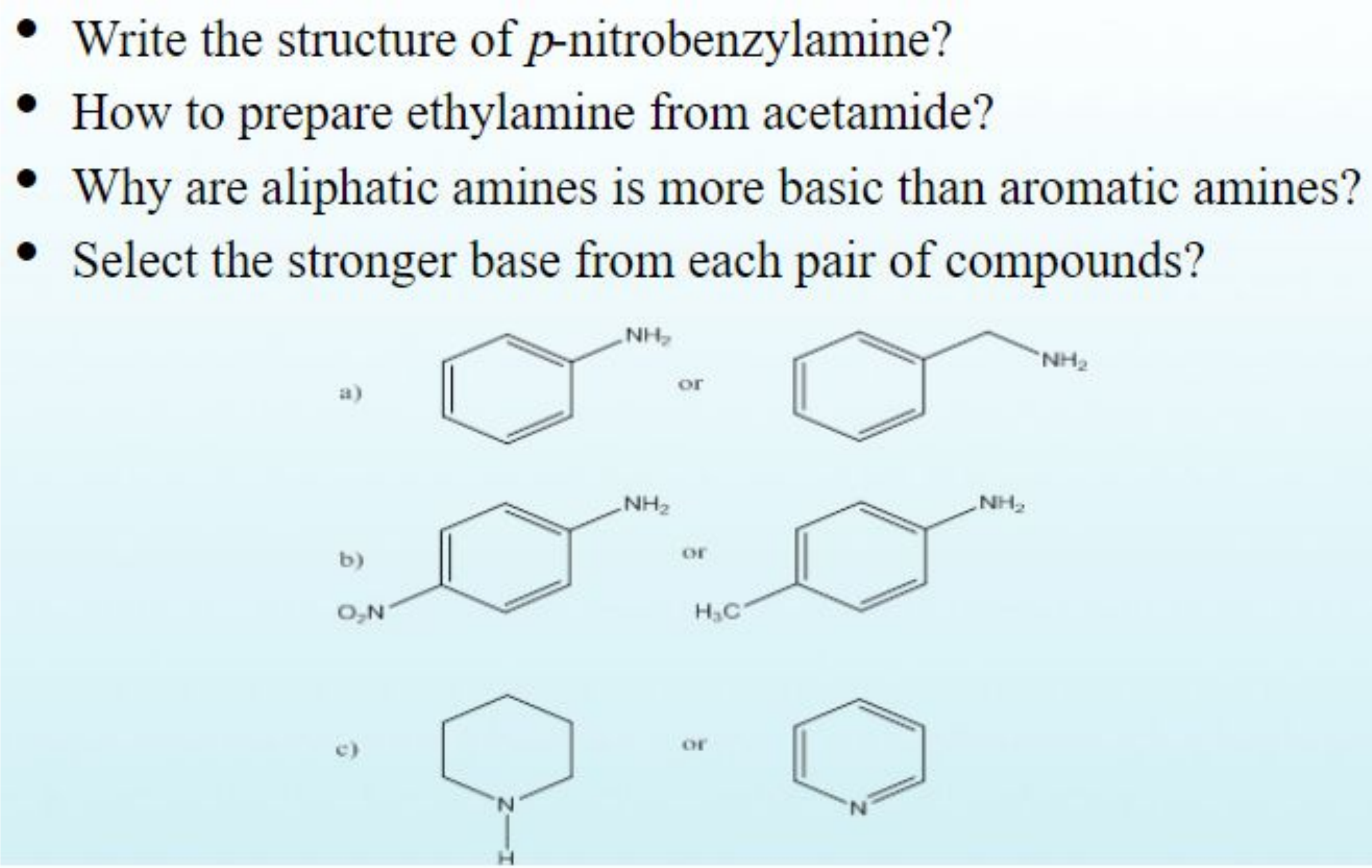


2,4,6-tribromoaniline
(white precipitate)

Summary

In this lecture nomenclature, methods of synthesis as well as chemical properties of aromatic nitro compounds are considered. coupling reactions of arenediazonium salts are discussed.

Questions and Assignments



- Write the structure of *p*-nitrobenzylamine?
- How to prepare ethylamine from acetamide?
- Why are aliphatic amines is more basic than aromatic amines?
- Select the stronger base from each pair of compounds?

Diazo and azo compounds

Topic 7

Outline of the lecture

1. Diazonium salts
2. Preparation of Diazonium Salts
3. Chemical Properties of Diazonium Salts

Bibliography:

1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
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10. Kim, A.M. 2004. *Organic Chemistry*. Novosibirsk

Diazonium Salts

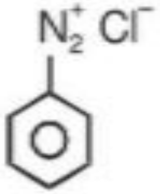
- The diazonium salts are represented by general formula $ArN_2^+X^-$, where Ar stands for the aryl group and X may be any anion such as

$Cl^-, Br^-, HSO_4^-, BF_4^-$ etc.

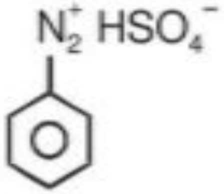
Nomenclature

- obtained by adding the suffix diazonium to the parent compound and is further followed by the name of the anion, e.g.

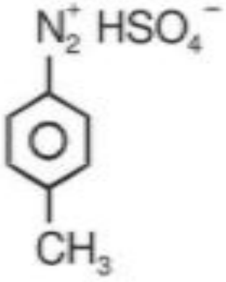
Diazonium Salts



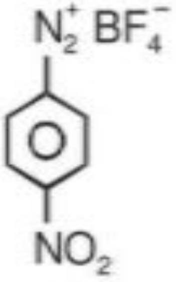
Benzene
diazonium
chloride



Benzene
diazonium
hydrogen sulphate



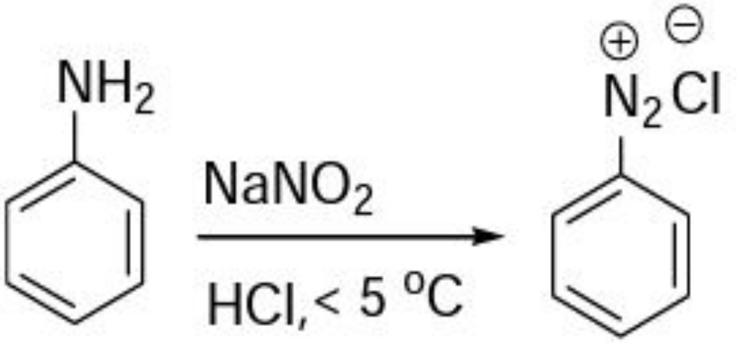
p - toluene
diazonium
hydrogen sulphate



p -nitrobenzene
diazonium
fluoroborate

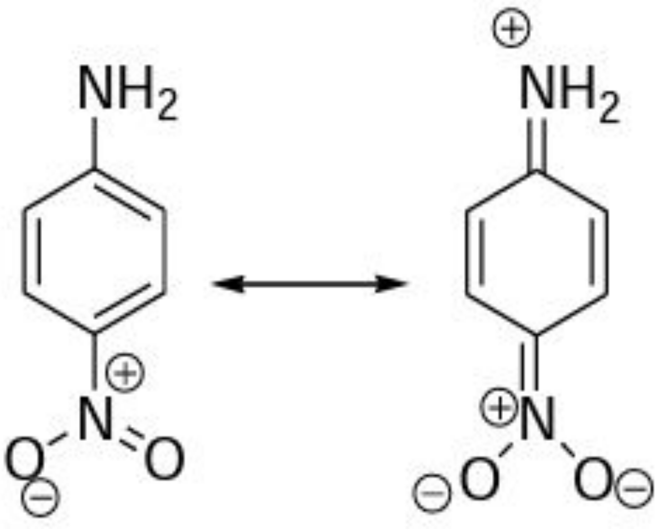
Preparation of Diazonium Salts

- Addition of aqueous solution of $NaNO_2$ to a solution of amine hydrochloride in presence of excess of HCl which is cooled by an ice-bath such that the temperature of the reaction remains below 5^0C diazotization of primary aromatic amine occurs.



Preparation of Diazonium Salts

- If electron withdrawing groups are attached to aromatic nucleus then the aromatic amines are difficult to diazotize because the nucleophilicity of the amino-nitrogen is reduced by the partial withdrawal of the unshared electron pair into the nucleus.

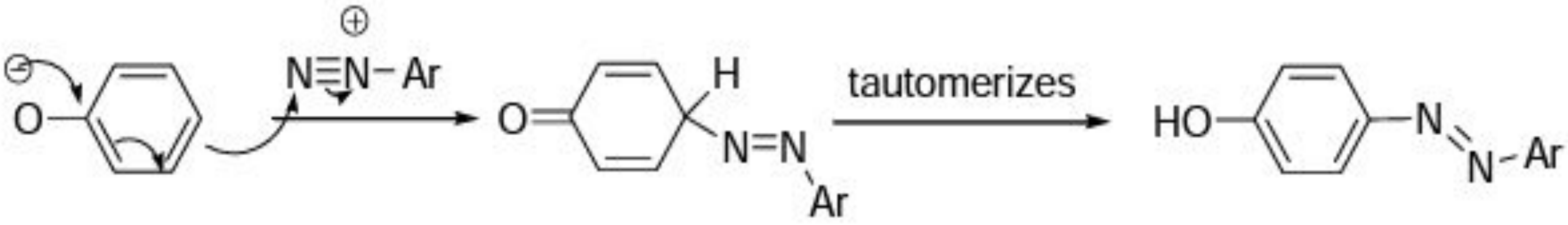


Reactions of Diazonium Salts

- ***The Reaction of Diazonium Salts***

Reactions of nucleophiles at nitrogen

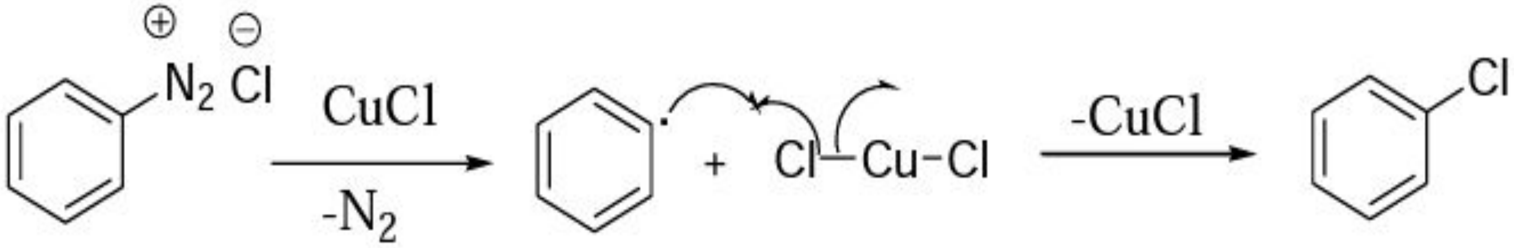
Nucleophiles react with diazonium ions to give covalent diazo-compounds. For example, phenol via phenoxide ion couples with diazonium salt at pH 9-10 to afford *para*-azophenols in good yield.



Reactions of Diazonium Salts

- ***One Electron Reductions***

Diazonium ions could be reduced by single electron transfer to give an aryl radical and nitrogen. Copper (I) is frequently used for this purpose and the aryl radical is highly reactive capable of abstracting a ligand from the transition metal ion or a hydrogen atom from a covalent bond.

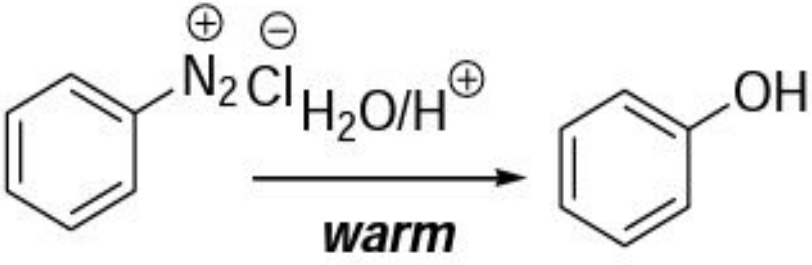


Reactions of Diazonium Salts

- ***Reactions in which Nitrogen Eliminated***

Replacement by Hydroxyl

Diazonium salt on warming in water gives phenol via S_N1 mechanism. The reaction is generally performed in acidic solution to preserve phenol in its unionized form.

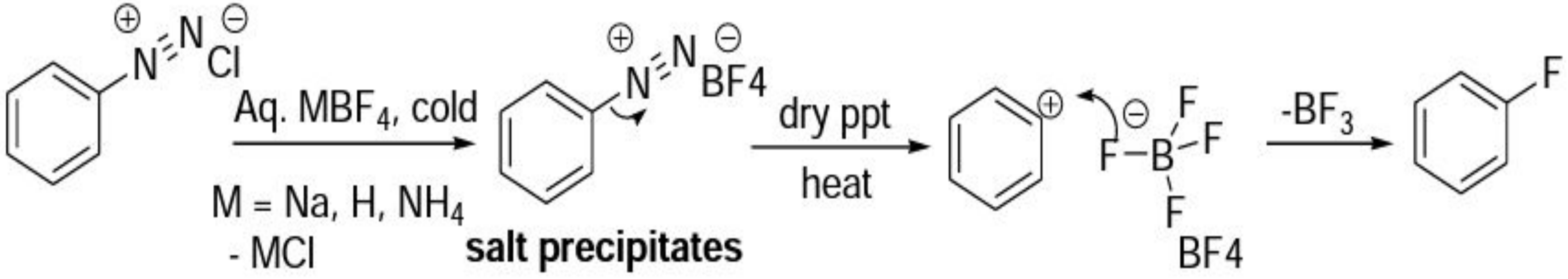


Reactions of Diazonium Salts

- ***Replacement by Halogen***

Schiemann Reaction

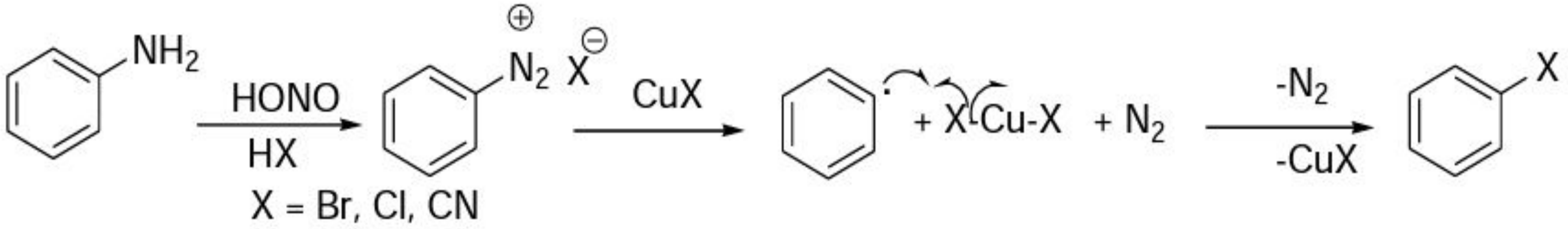
Treatment of an aqueous solution of diazonium salt with fluoroboric acid under cold conditions gives diazonium fluoroborate as precipitate, which could be dried and gently heated to afford the flurobenzene by decomposition. The reaction involves S_N1 mechanism.



Reactions of Diazonium Salts

- ***Sandmeyer Reaction***

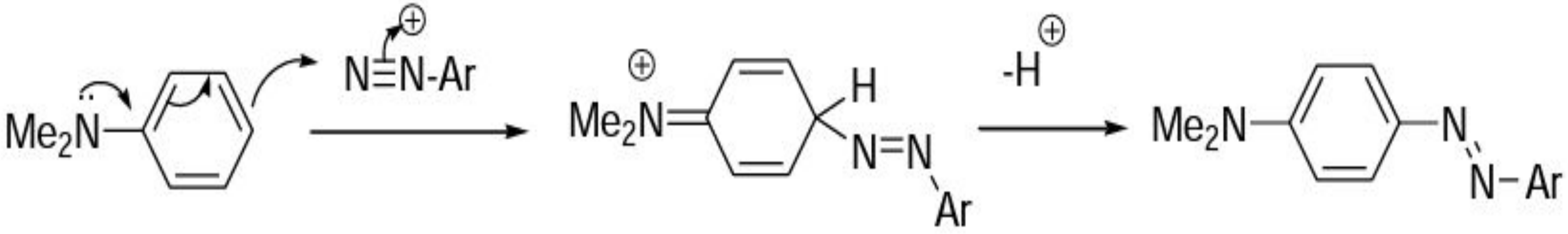
This method provides an effective route for the preparation of aromatic bromides and chlorides. Addition of cold aqueous solution of Diazonium chloride to a solution of CuCl in HCl medium gives a sparingly soluble complex which is separated and heated to give aryl chloride or bromide by decomposition.



Reactions of Diazonium Salts

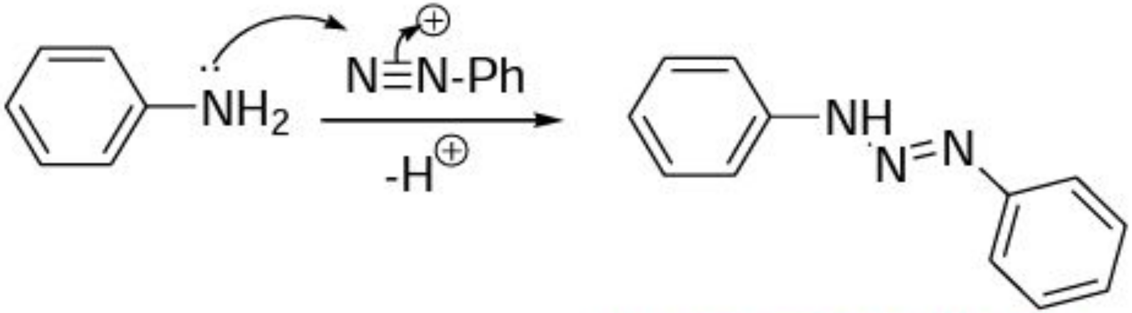
- *Coupling Reactions*

Diazonium ions are weak electrophiles, however, they undergo coupling with activated aromatic nuclei such as aryl amines, phenols and aromatic heterocyclic compounds. For example, N,N-dimethylaniline reacts with diazonium ion almost at the *para*-position. However, the careful control of the pH of the reaction medium is necessary for the success of the process.



Reactions of Diazonium Salts

- In case of primary and secondary aromatic amines, the reaction preferentially takes place at the nitrogen atoms of the diazonium ions. For example, aniline adds to the aromatic diazonium salt to give ***diazoaminobenzene***.



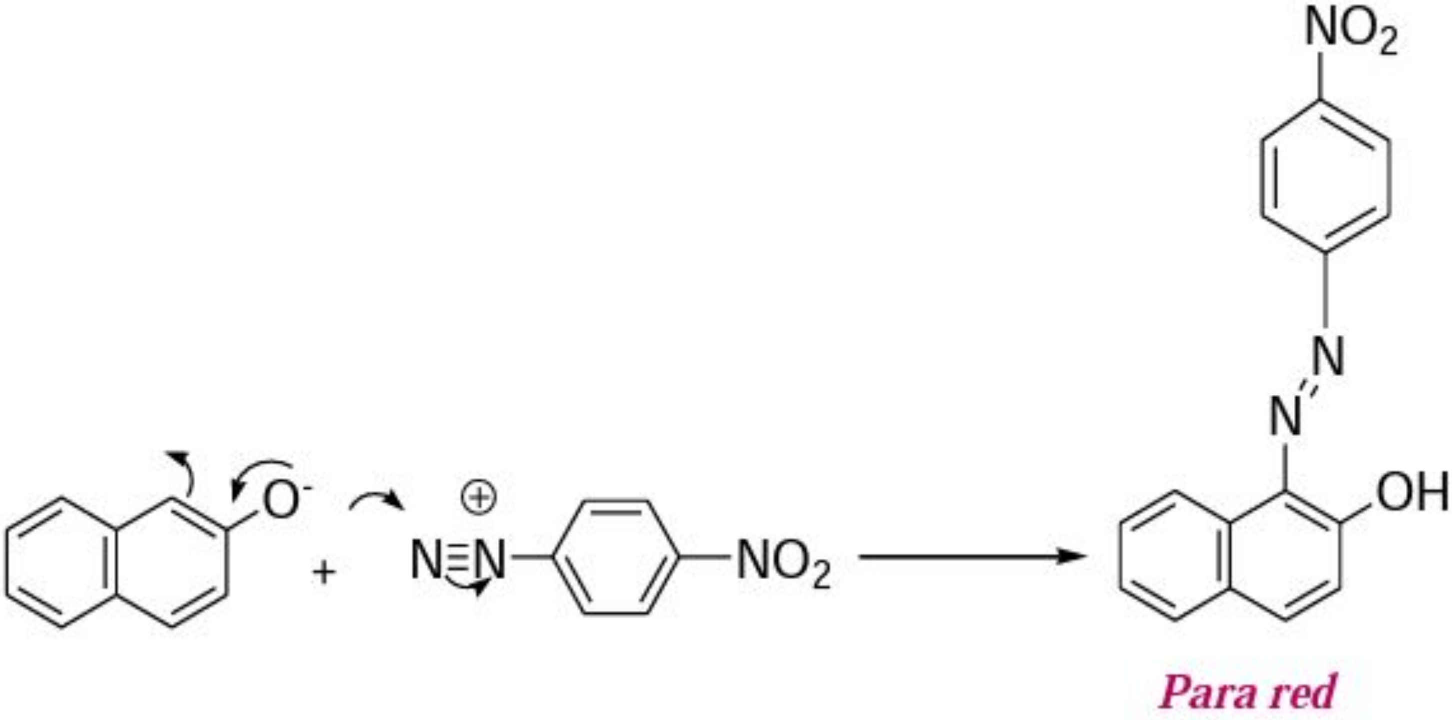
Diazoaminobenzene

The Synthetic Value of Diazo-Coupling

- ***Dye-stuffs***

Aromatic azo-compounds are coloured. Several of those compounds synthesized by the diazo-coupling are employed as ***dye-stuffs***. These compounds can be classified into three groups. First group of azo-compounds are neutral which are used *as azoic combination* (or ingrain) dyes. An example is *para* red which is prepared by coupling of 2-napthol with *p*-nitrobenzenediazonium salt.

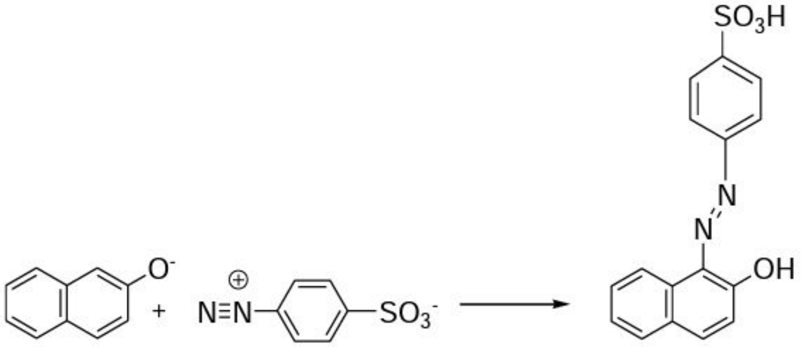
The Synthetic Value of Diazo-Coupling



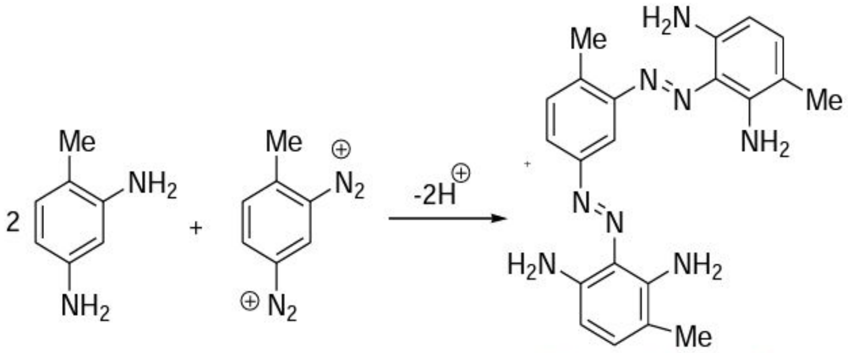
The Synthetic Value of Diazo-Coupling

- The second group of azo-compounds posses either a sulfonic acid group or an amino group which are generally adsorbed directly on the fiber from aqueous solution. Examples are orange II (an acidic dye) and Bismarck brown R (a basic dye).

The Synthetic Value of Diazo-Coupling



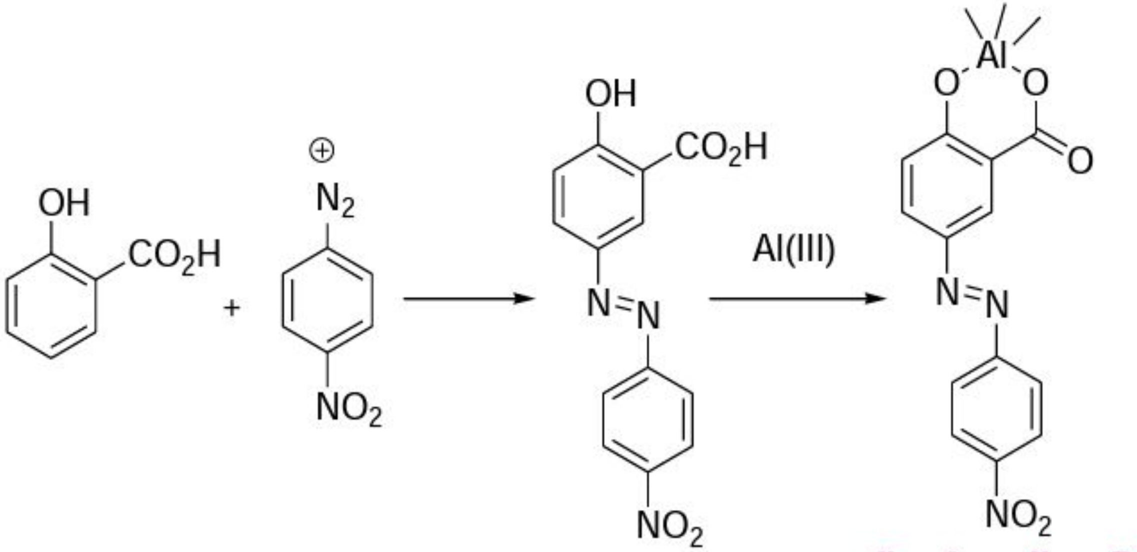
orange II (acidic dye)



Bismarck brown R

The Synthetic Value of Diazo-Coupling

- Azo-compounds that contain chelating groups to bind with a metal ions such as Al(III) are used a mordant dyes. An example is alizarin yellow R, which contains phenolic and carboxyl chelating groups.



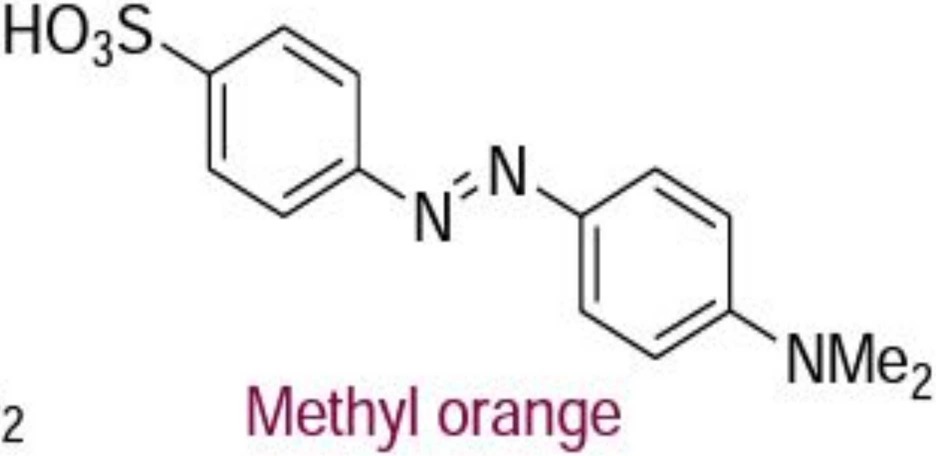
alizarin yellow R

Indicators

- Azo-compounds that contain both an acidic and a basic group can be utilized as indicators since the colours of the conjugate acid and the conjugate base are different. Examples are methyl orange and methyl red which are prepared by coupling of dimethylaniline with diazotized sulfanilic acid and diazotized anthranilic acid, respectively.

Indicators

Methyl red

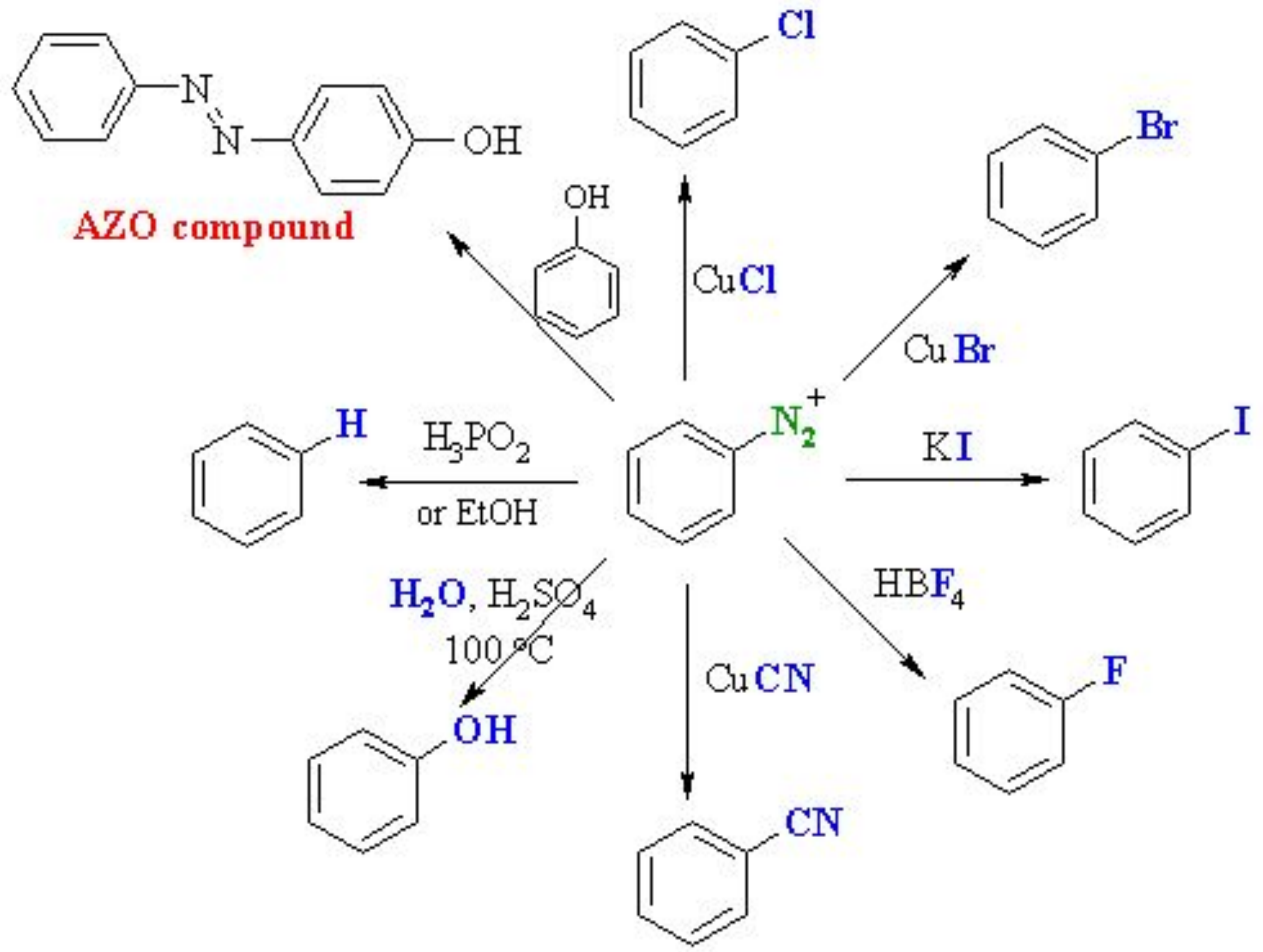


Methyl orange

Application of Azo Dyes

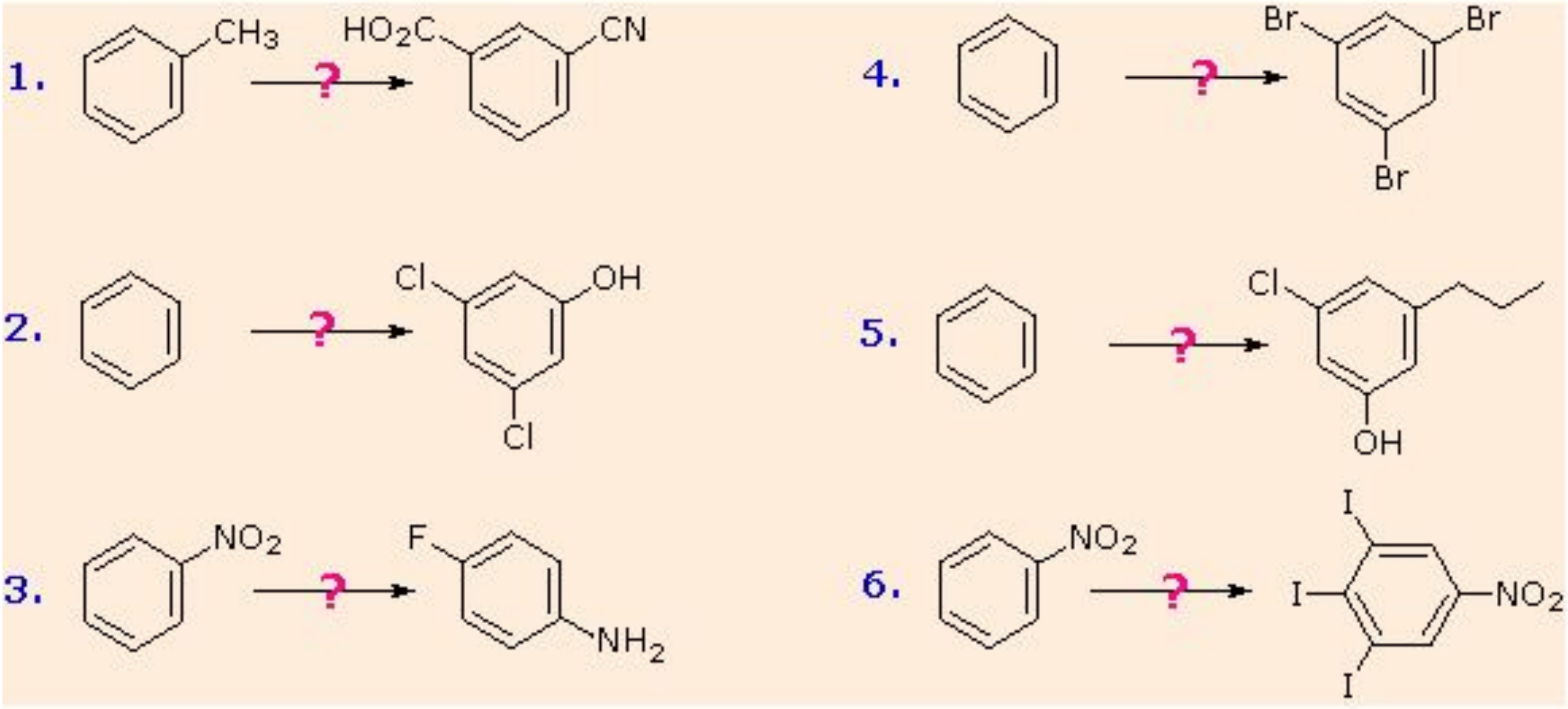
- Methyl orange - used as acid-base indicators due to the different colors of their acid and salt forms
- Artist’s paints – clays, yellow to red range
- Dye in food and textiles

Summary



AZO compound
OH
Cl
CuCl
Br
CuBr
N_2^+
H
H_3PO_2
or EtOH
KI
I
H_2O, H_2SO_4
100 °C
OH
CuCN
CN
HBF_4
F

Questions and Assignments



Phenols

Topic 8

Outline of the lecture

1. Phenols
2. Naming Phenols
3. Chemical Properties of Phenols. Acidity
4. Ester Formation
5. Ether Formation
6. Halogenation
7. Nitration
8. Sulfonation
9. Kolbe Reactions

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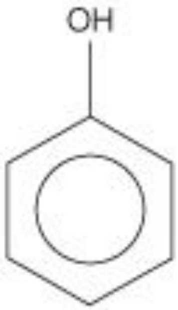
10. Kim, A.M. 2004. *Organic Chemistry*. Novosibirsk

Phenols

- Phenol is a compound that has a hydroxyl group bonded to one carbon atom in a benzene ring. Each carbon atom in a benzene ring is sp^2 hybridized. Although phenol is an alcohol, its properties are quite different from “normal” alcohols. **Phenol and similar ring compounds are called *aromatic* or *aryl* alcohols.**

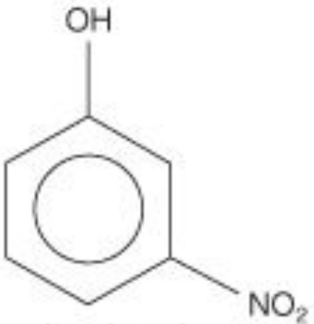
Naming Phenols

Phenol nomenclature is complicated. Many phenols have common names that are more widely used than the IUPAC names. For example, 2-methylphenol is known as *o*-cresol, 3-methylphenol is known as *m*-cresol and 4-methylphenol is known as *p*-cresol.

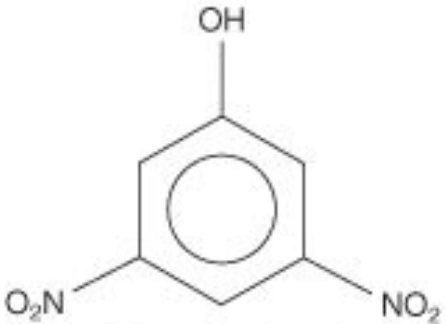


phenol
benzenol

p-chlorophenol
4-chlorobenzenol



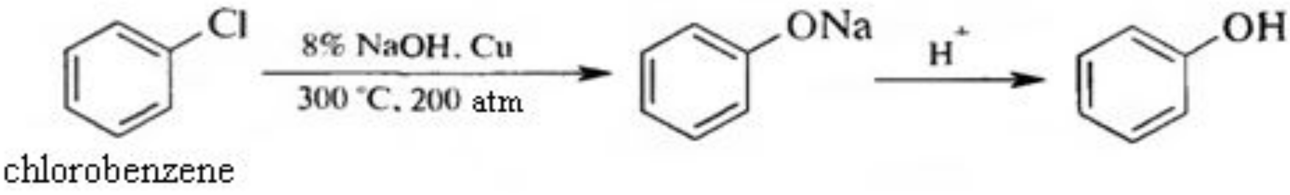
m-nitrophenol
3- nitrobenzenol



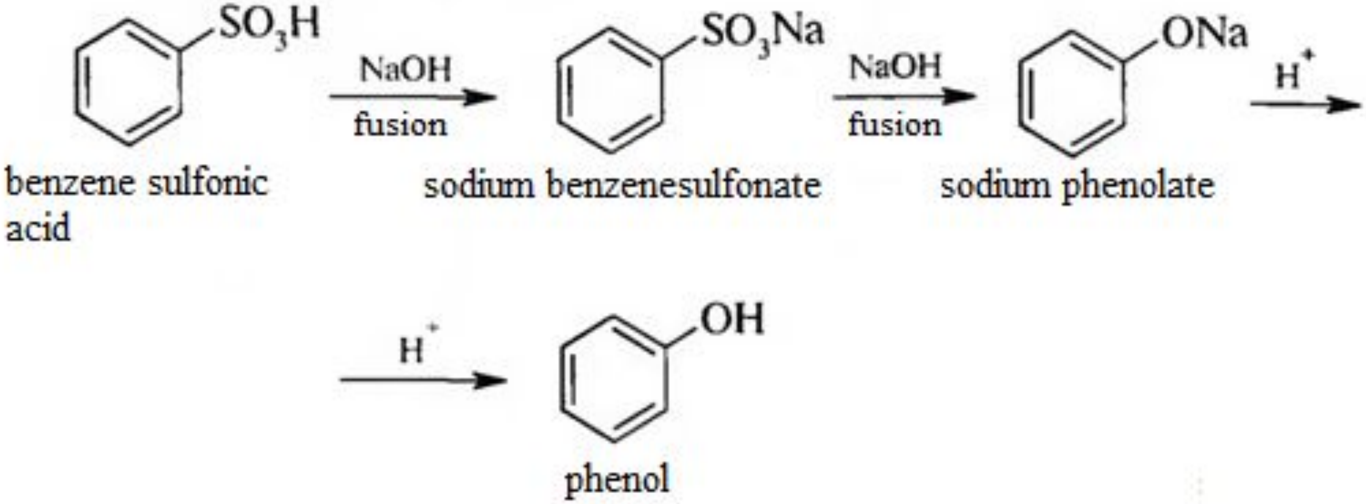
3,5-dinitrophenol
3,5-dinitrobenzenol

Methods of obtaining phenols

Heating of halogenated benzene with an alkali in the presence of a catalyst

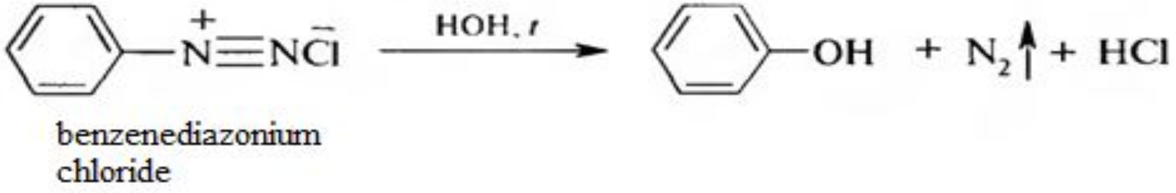


The fusion of sodium salts of sulfonic acids with an alkali

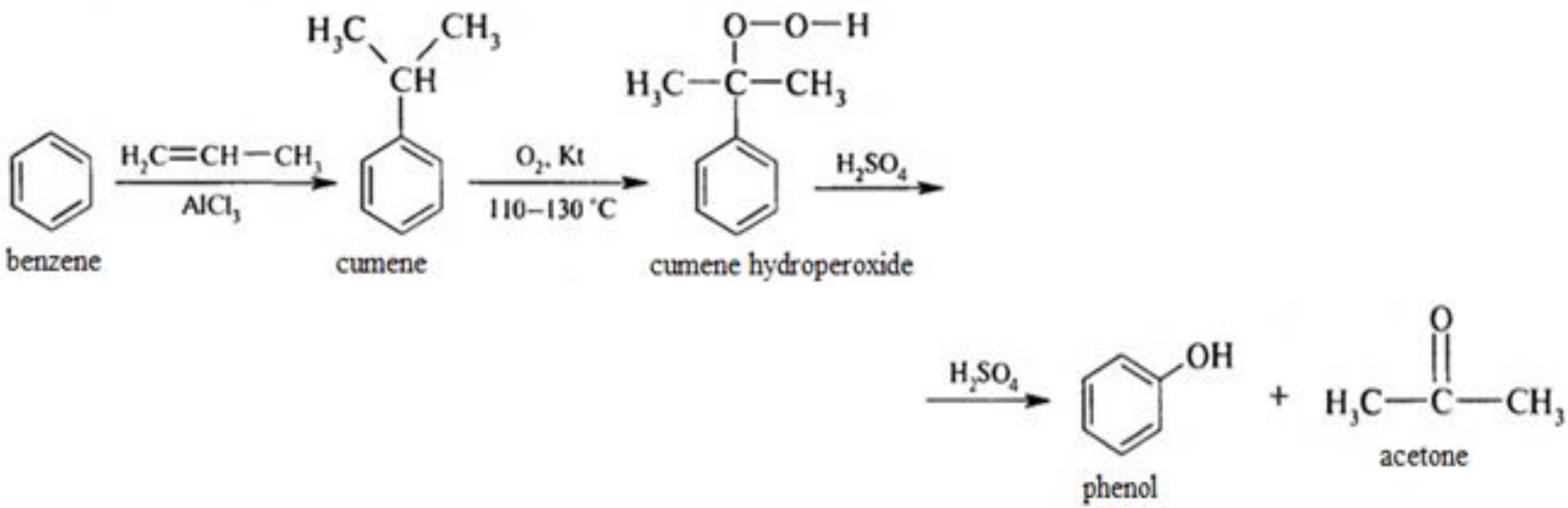


Methods of obtaining phenols

The decomposition of the diazonium salt

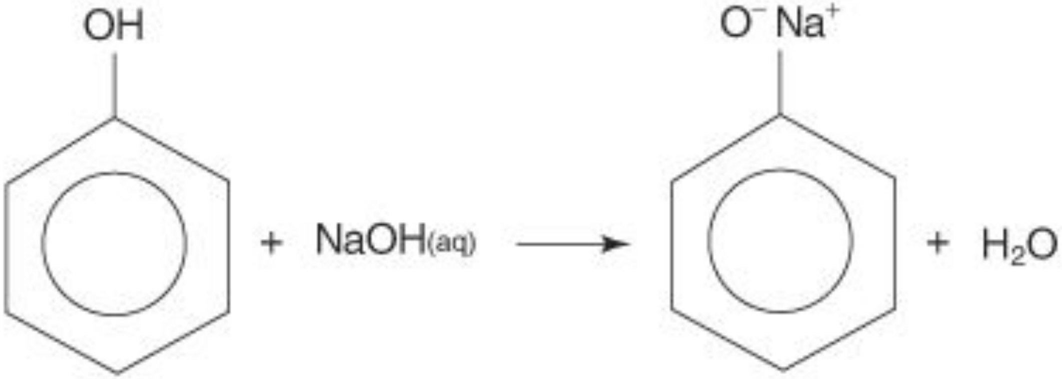


Oxidation of cumene (the cumene method)



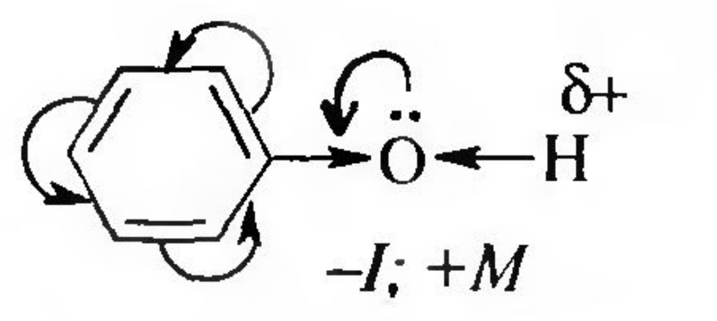
Chemical Properties of Phenols. Acidity

- Phenols show appreciable acidity (pK_a = 8 $^{-10}$). For example, phenol reacts with aqueous NaOH as follows.

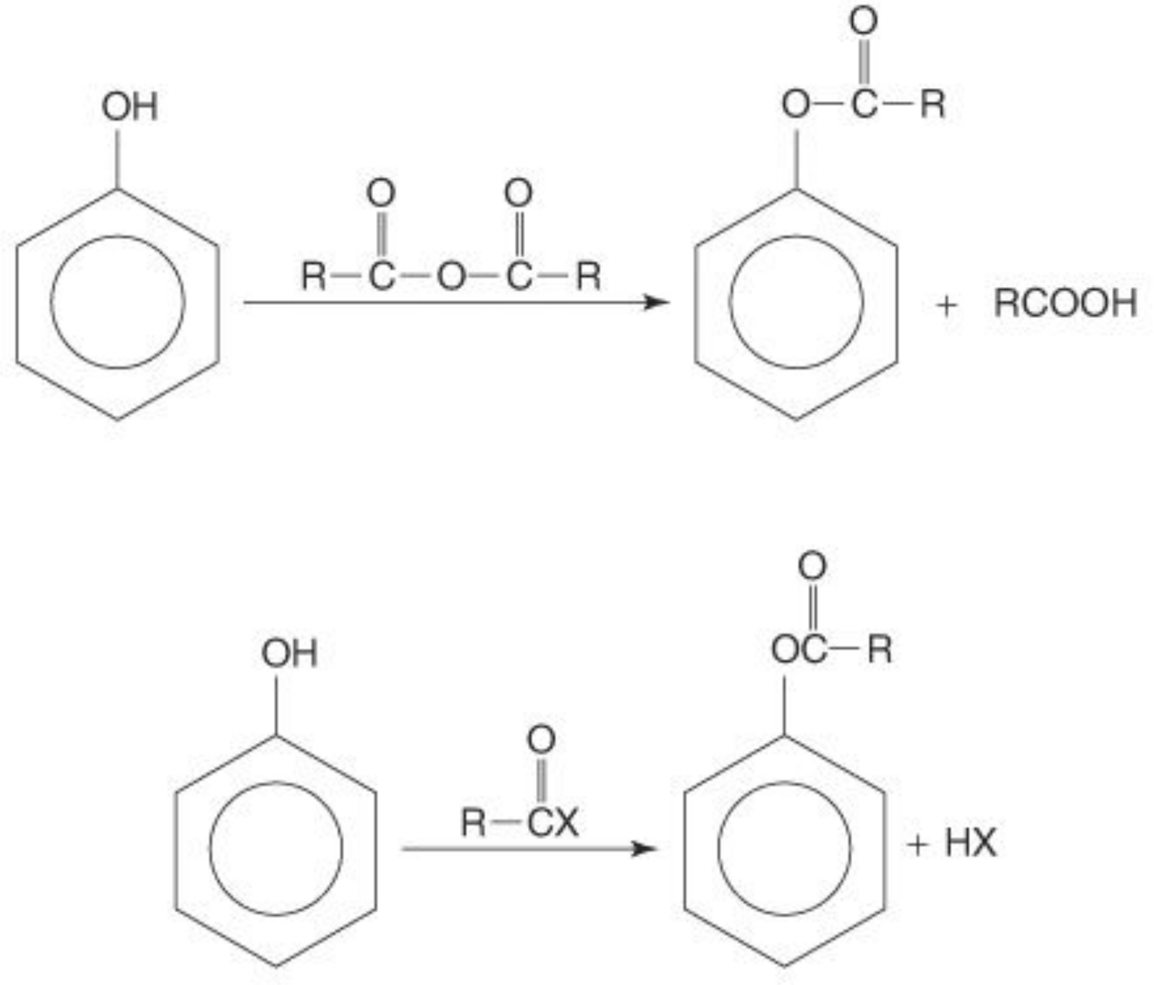


Chemical properties of phenols

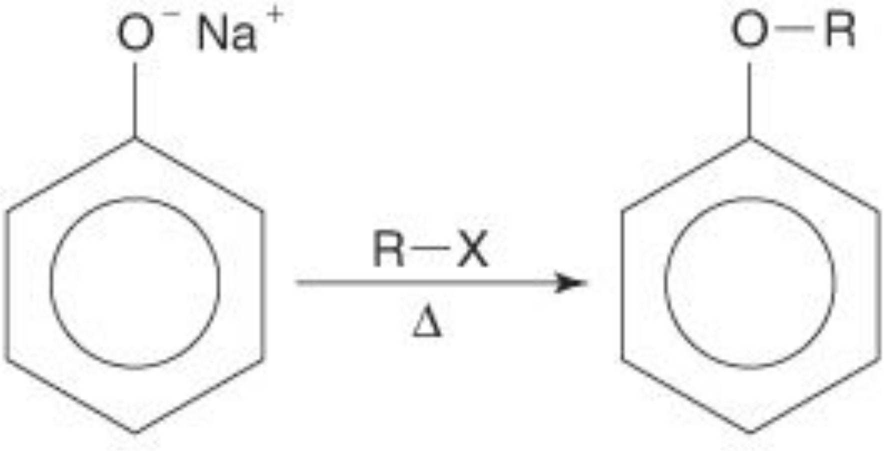
- Reactions involving the hydroxyl group and the aromatic ring are characteristic for phenols.



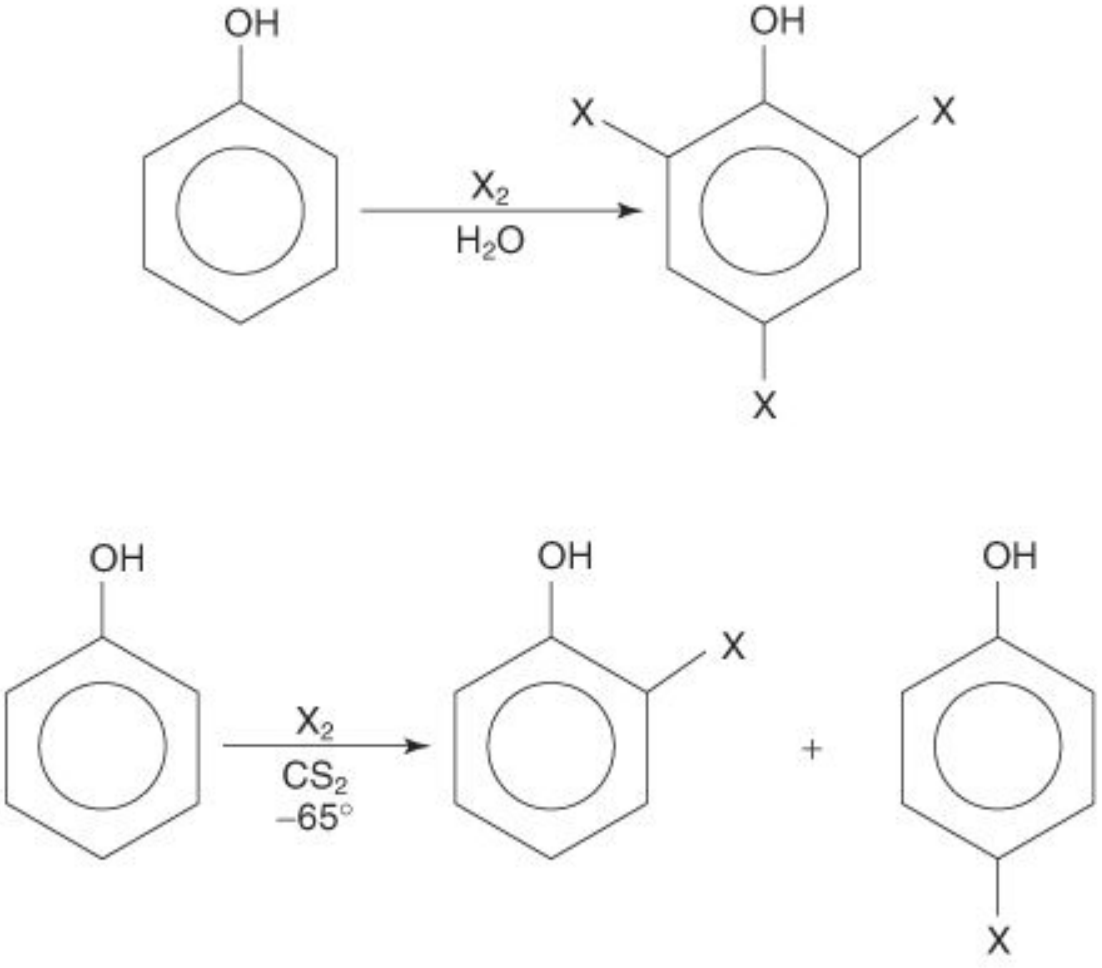
Ester Formation



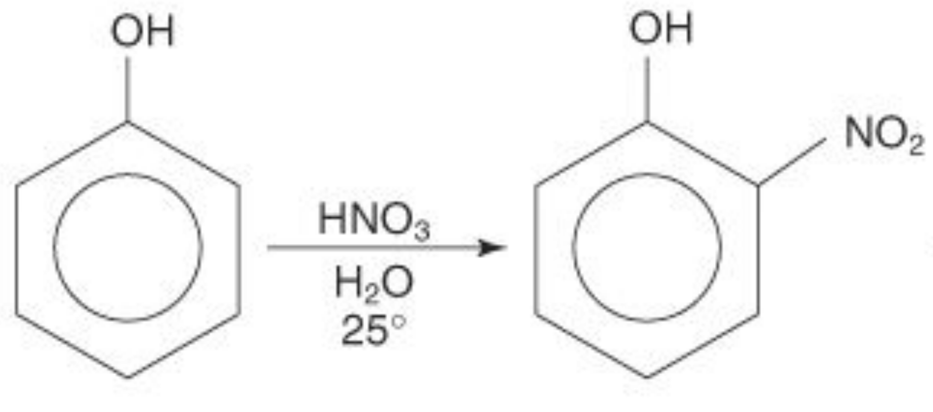
Ether Formation



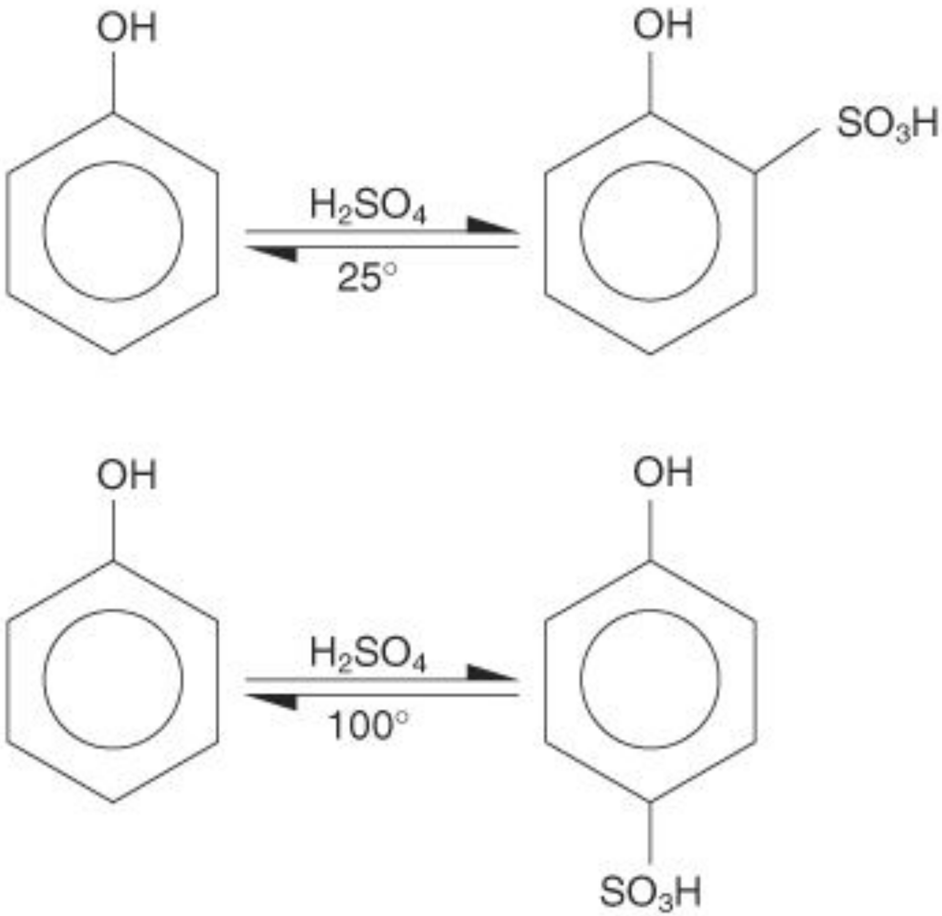
Halogenation



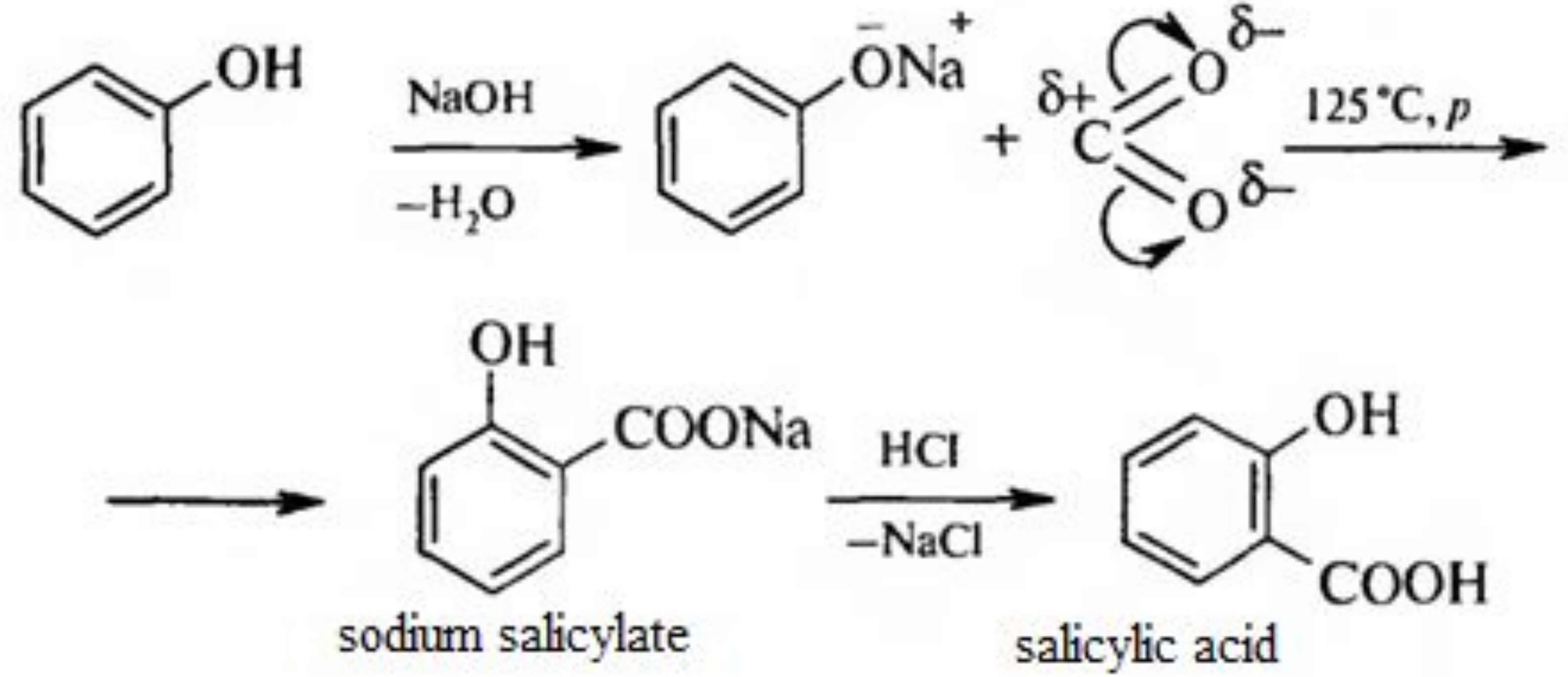
Nitration



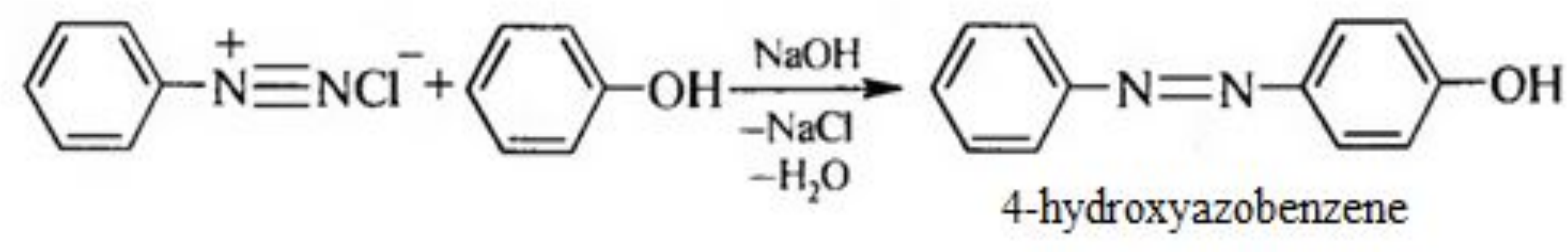
Sulfonation



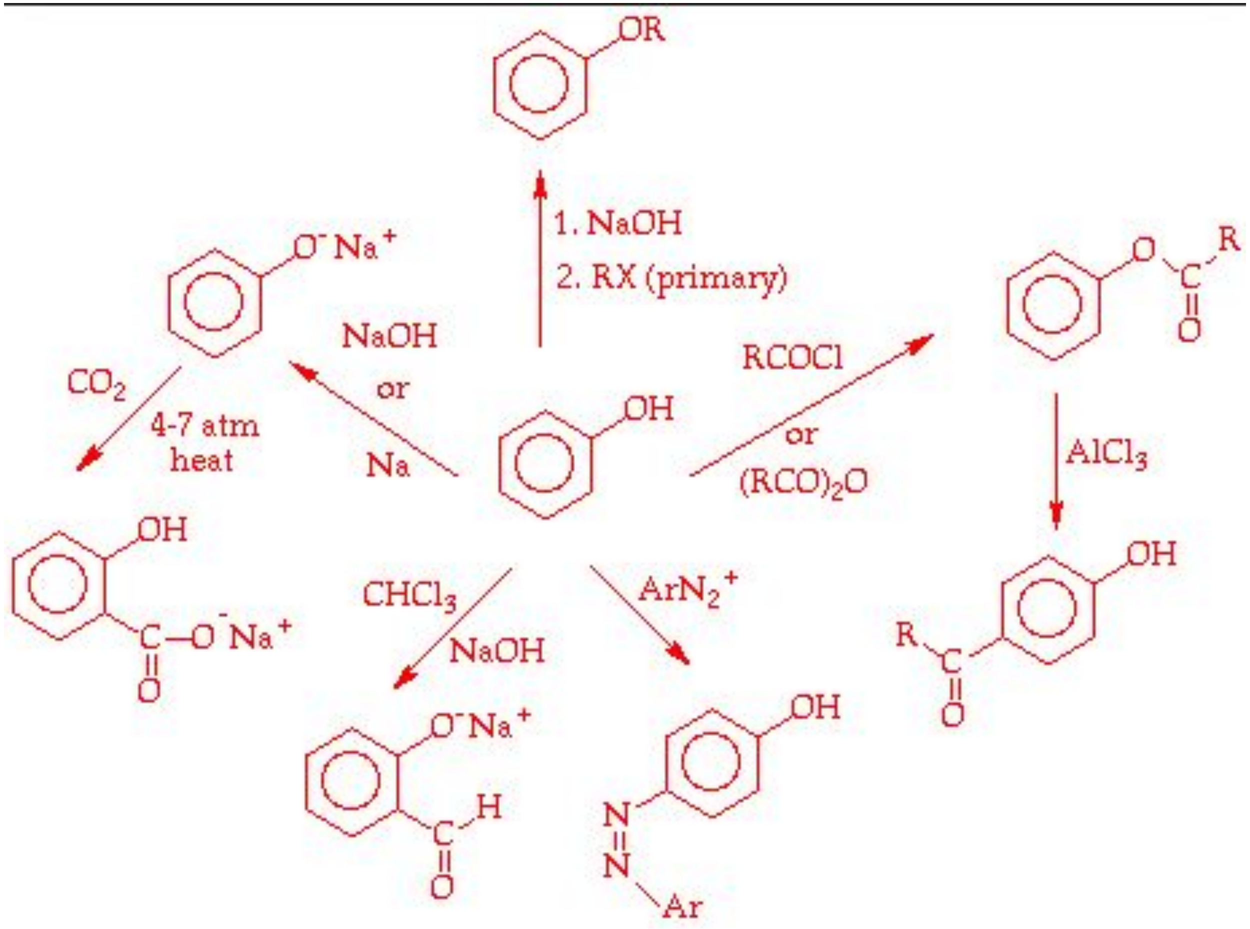
Kolbe Reaction



Azo coupling

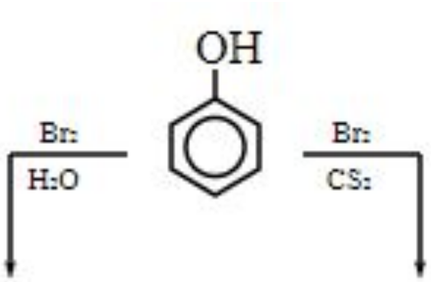


Summary


OR
1. NaOH
2. RX (primary)
O⁻ Na⁺
NaOH
or
Na
OH
RCOCl
or
$(RCO)_2O$
O
C
R
O
$AlCl_3$
OH
R
C
O
CO_2
4-7 atm
heat
OH
C—O⁻ Na⁺
O
$CHCl_3$
NaOH
ArN_2^+
O⁻ Na⁺
H
C
O
OH
N
N
Ar

Questions and assignments

1. What are phenols? Give examples.
2. What are chemical properties of phenols?
3. Complete the reactions:



Aromatic Aldehydes and Ketones

Topic 9

Outline of the lecture

1. Aromatic Aldehydes and Ketones
2. Friedel-Crafts Acylation
3. Chemical Properties of Aromatic Aldehydes and Ketones
4. Addition of Hydrogen Cyanide
5. The Cannizzaro-Tishchenko reaction
6. The Benzoin Condensation

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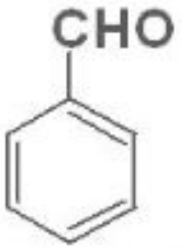
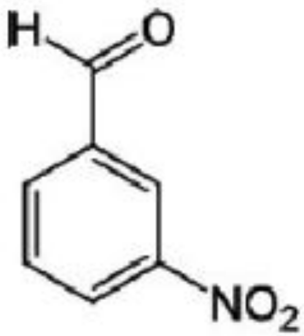
Aromatic Aldehydes and Ketones

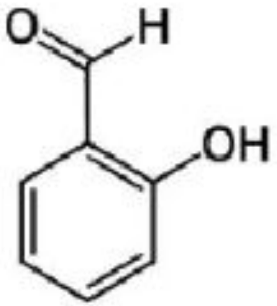
Benzaldehyde



Benzaldehyde



m-Nitrobenzaldehyde
3-Nitrobenzaldehyde



Salicylaldehyde
(*o*-Hydroxybenzaldehyde)
2-Hydroxybenzaldehyde

Friedel-Crafts Acylation

- Friedel–Crafts acylation of an aromatic ring with an acid chloride in the presence of $AlCl_3$ catalyst

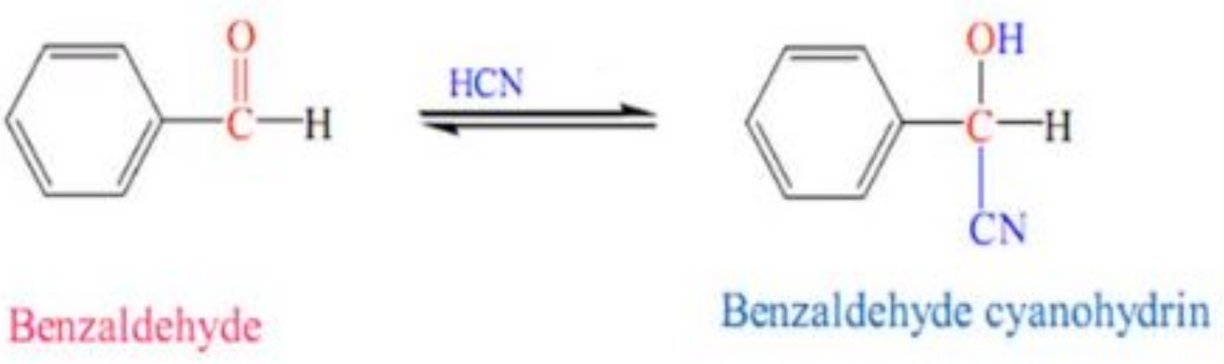
$$CH_3\overset{O}{\overset{\|}{C}}Cl \xrightarrow[\text{Heat}]{AlCl_3}$$

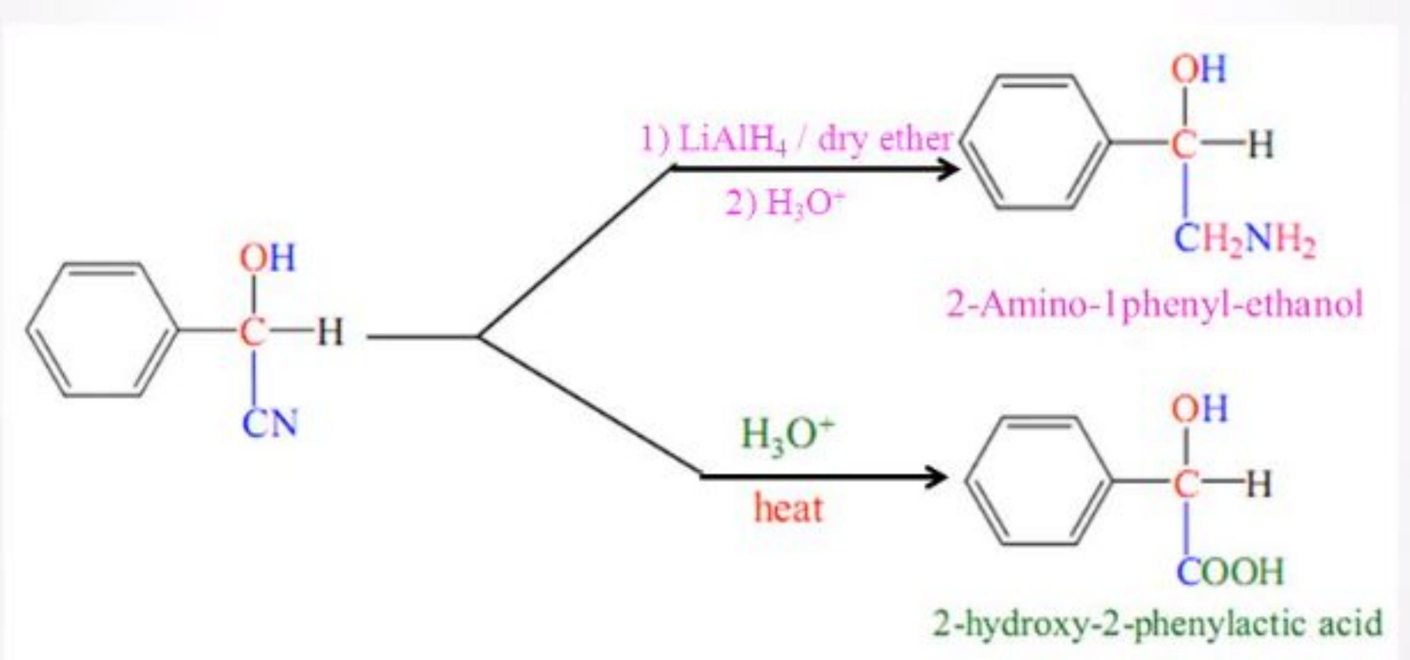
Benzene **Acetyl chloride** **Acetophenone (95%)**

Chemical Properties of Aromatic Aldehydes and Ketones

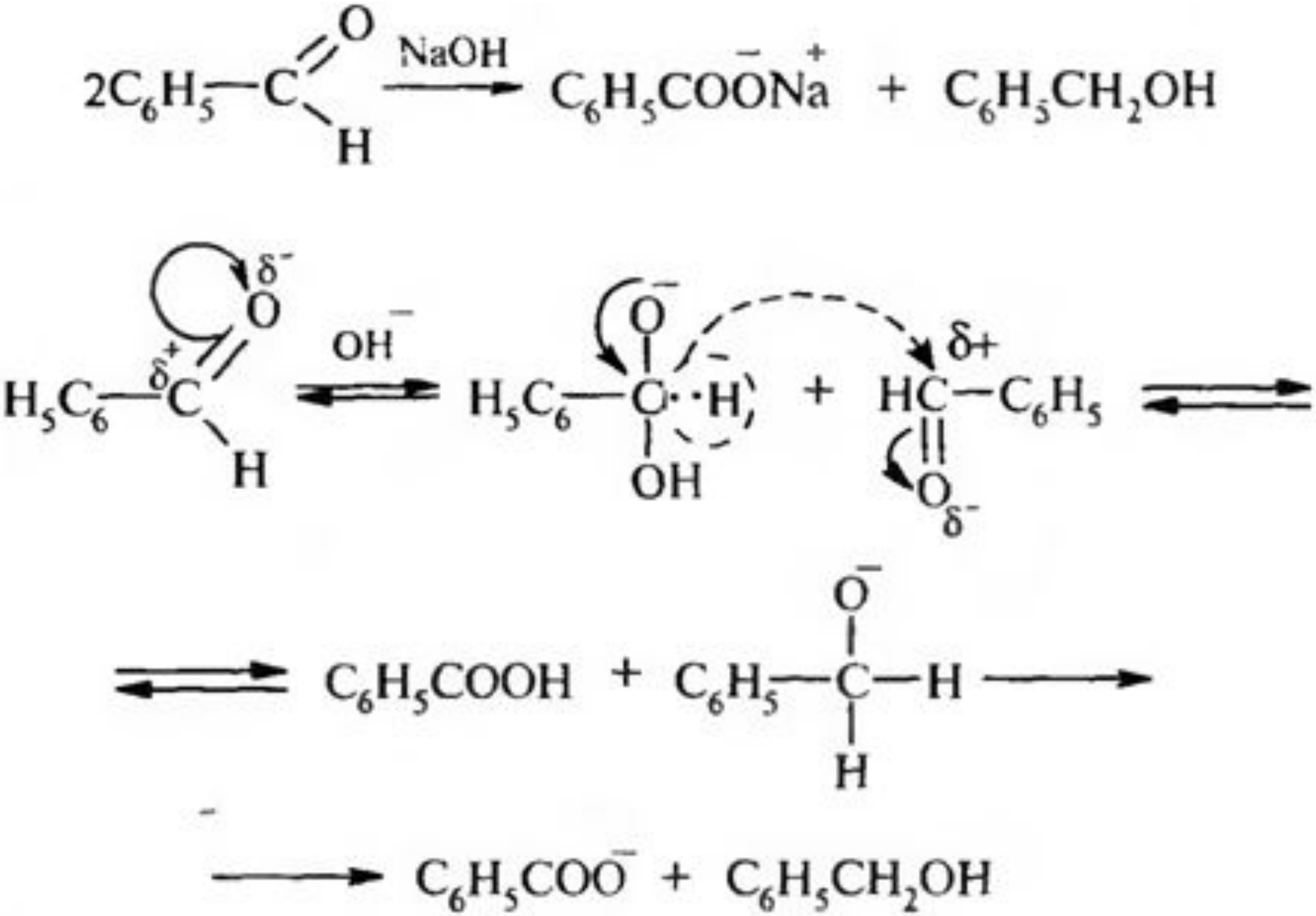
- Aromatic aldehydes mostly have the same properties as aliphatic aldehydes. However, aromatic aldehydes exhibit a number of specific characteristics.
- *Aromatic aldehydes do not undergo the aldol condensation.*

Addition of Hydrogen Cyanide



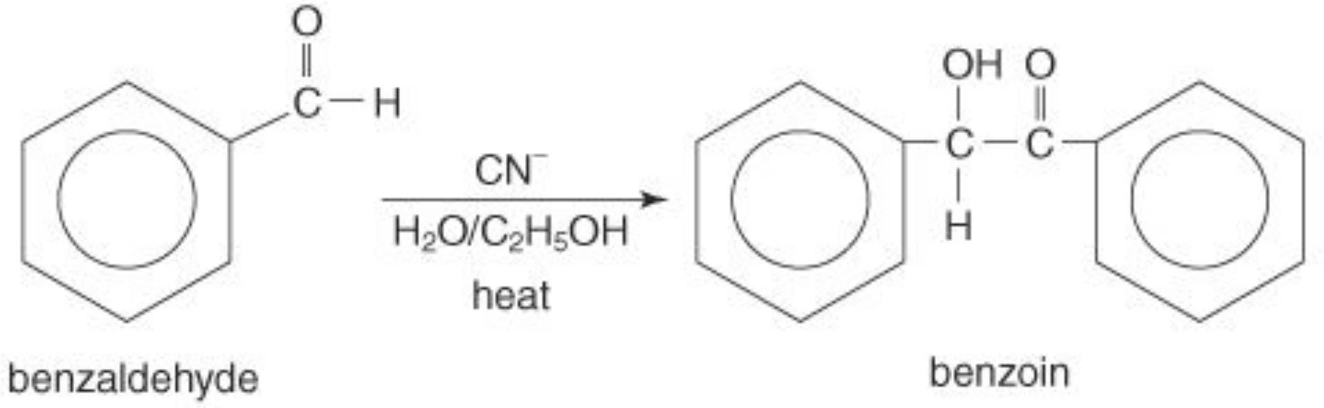


The Cannizzaro-Tishchenko reaction



The Benzoin Condensation

- Aromatic aldehydes form a condensation product when heated with a cyanide ion dissolved in an alcohol-water solution. This condensation leads to the formation of α hydroxy ketones.



Summary

- Most common general reaction type for aldehydes and ketones is nucleophilic addition reaction
- Addition of HCN to aldehydes and ketones yields cyanohydrins
- Primary amines add to carbonyl compounds yielding imines, or Schiff bases, and secondary amines yield enamines
- Wolff-Kishner reaction is the reaction of an aldehyde or a ketone with hydrazine and base to give an alkane

Questions and Assignments

- **In which following reactions aromatic aldehyde is treated with acid anhydride in presence of corresponding salt of the acid to give unsaturated aromatic acid**
- **Options**
- (a) Wurtz’s reaction
  (b) Perkin’s reaction
  (c) Friedel-Craft’s reaction
  (d) none of these

Aromatic Carboxylic Acids and Their Derivatives

Topic 10

Outline of the lecture

1. Aromatic Carboxylic acids
2. Side Chain Oxidation of Alkylbenzenes
3. Synthesis of Amides
4. Reduction Reactions of Aromatic Carboxylic Acids
5. Synthesis of Acids Chlorides

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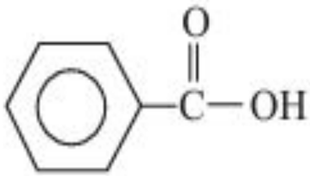
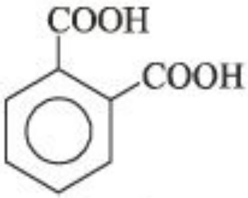
Aromatic Carboxylic Acids

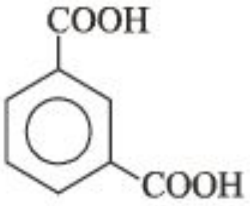
Aromatic carboxylic acids are compounds, in which a carboxyl group is bonded to a benzene ring. Chemical properties of aromatic carboxylic acids are due to the presence of the carboxyl group and the benzene ring.



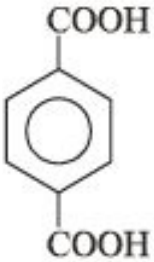
Phenylmethanoic acid
(Benzoic acid)



***o*-Phthalic acid**
(Phthalic acid)

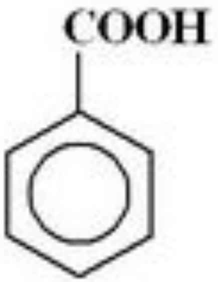


***m*-Phthalic acid**
(Isophthalic acid)

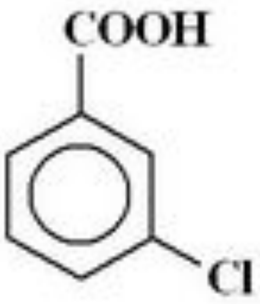


***p*-Phthalic acid**
(Terephthalic acid)

Aromatic Carboxylic Acids



Benzoic acid

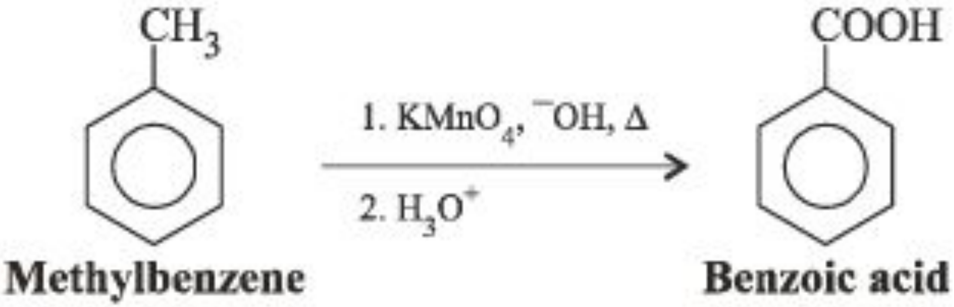


3-Chlorobenzoic acid
m-Chlorozenoic acid

4-Aminobenzoic acid
p-Aminobenzoic acid

Methods of synthesis

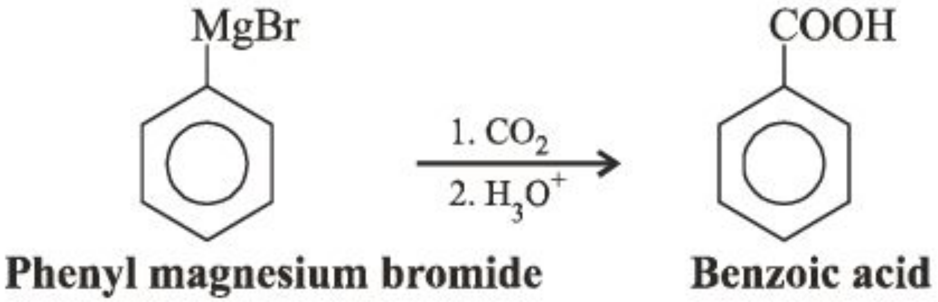
- ***Oxidation of Alkylbenzenes***
- Primary and secondary alkyl groups attached to the benzene ring can be oxidised, using alkaline $KMnO_4$, to the carboxyl group.



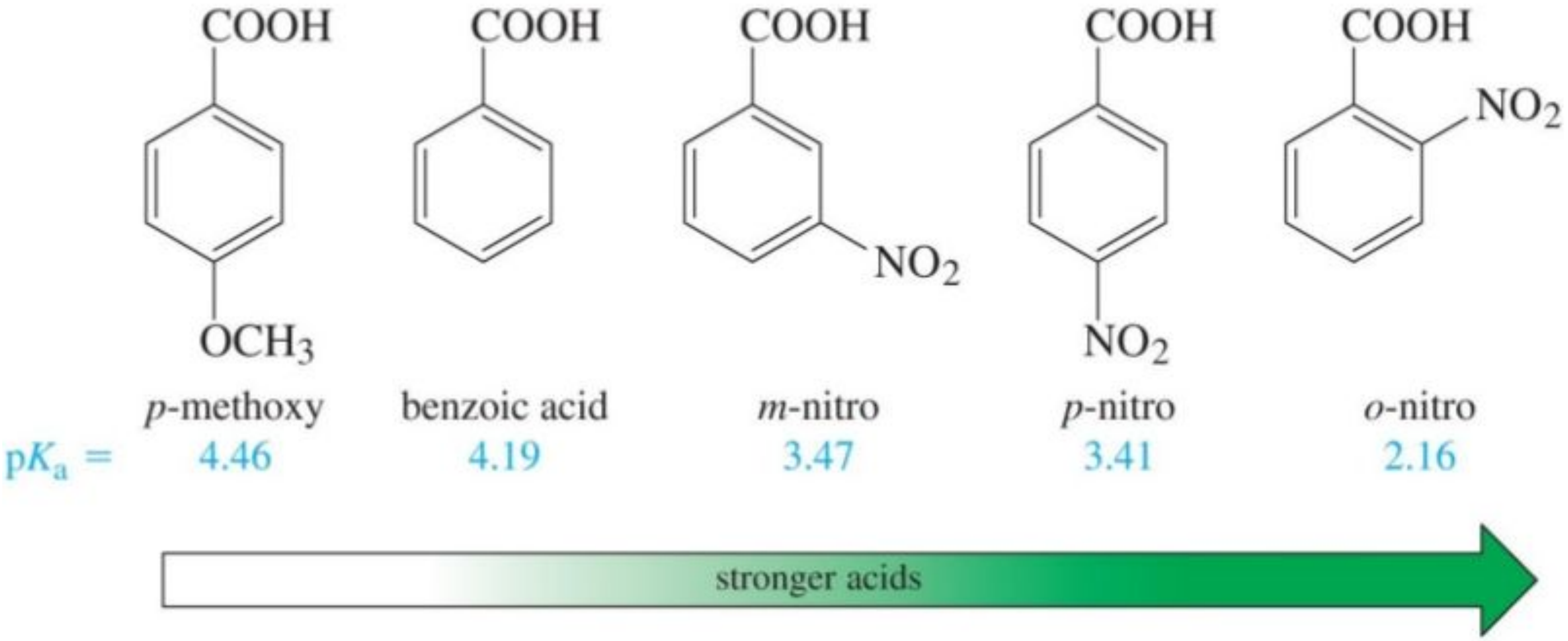
Methods of synthesis

- ***Carbonation of Grignard Reagents***

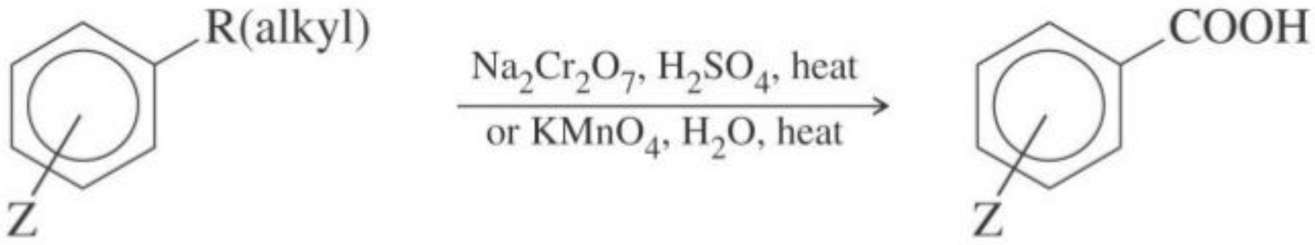
Grignard reagents (RMgX) react with carbon dioxide to give magnesium carboxylates which on acidification yield carboxylic acids.



Aromatic Carboxylic Acids



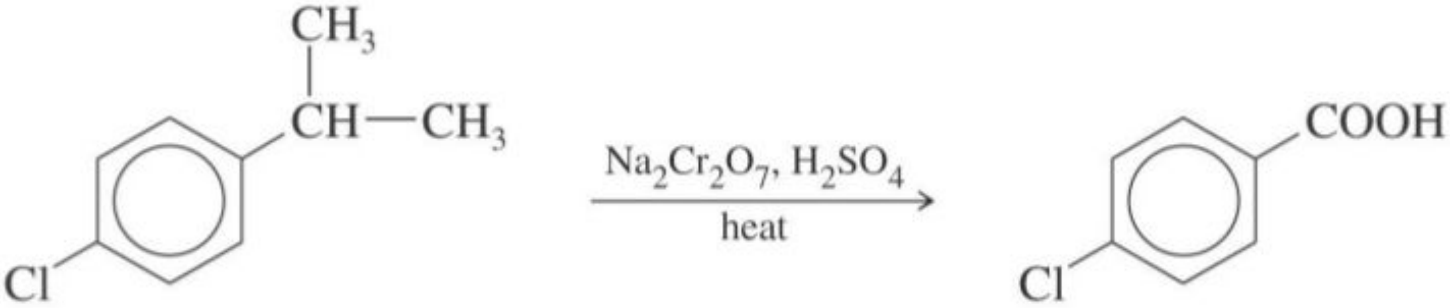
Side Chain Oxidation of Alkylbenzenes



an alkylbenzene
(Z must be oxidation-resistant)

a benzoic acid

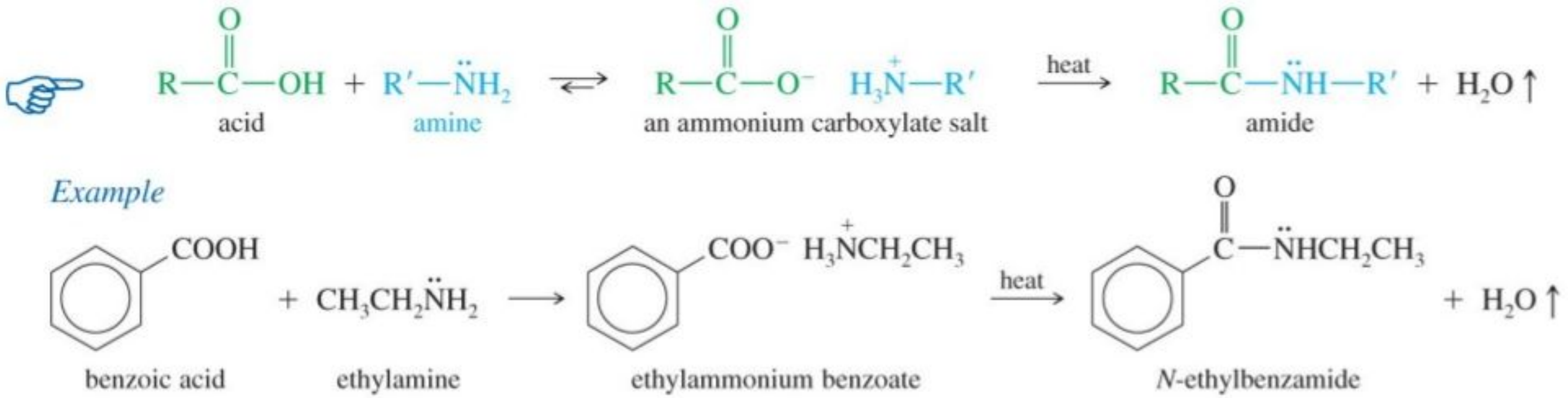
Example



p-chloroisopropylbenzene

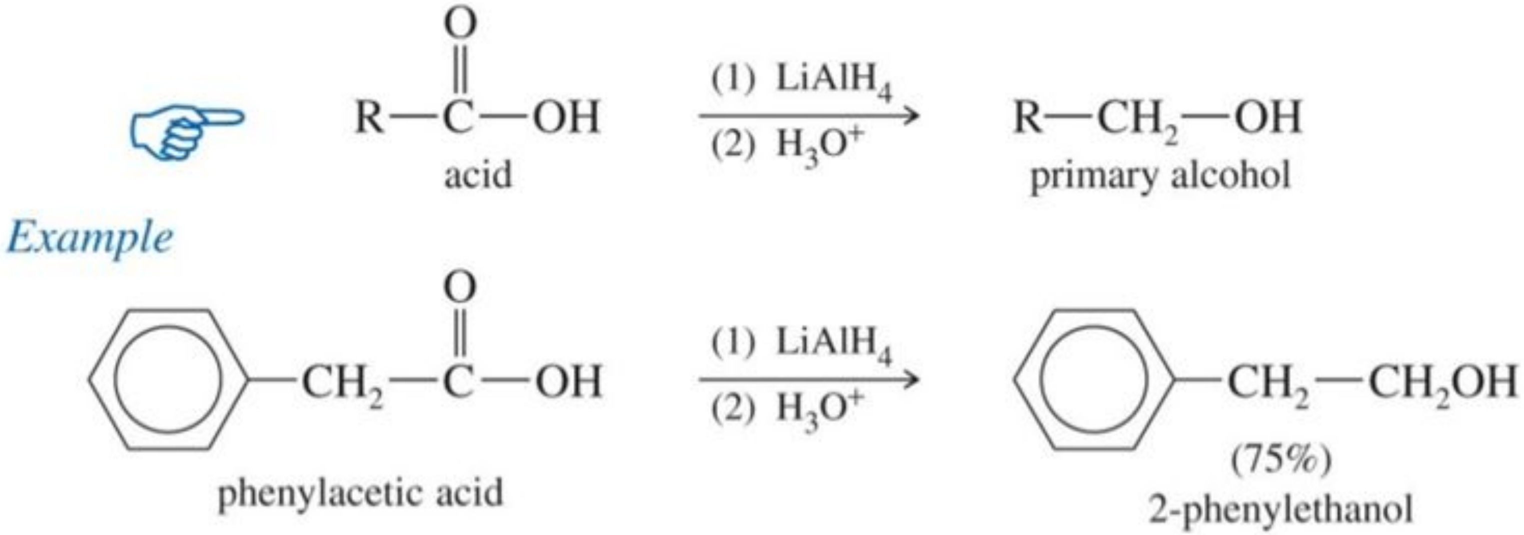
p-chlorobenzoic acid

Synthesis of Amides



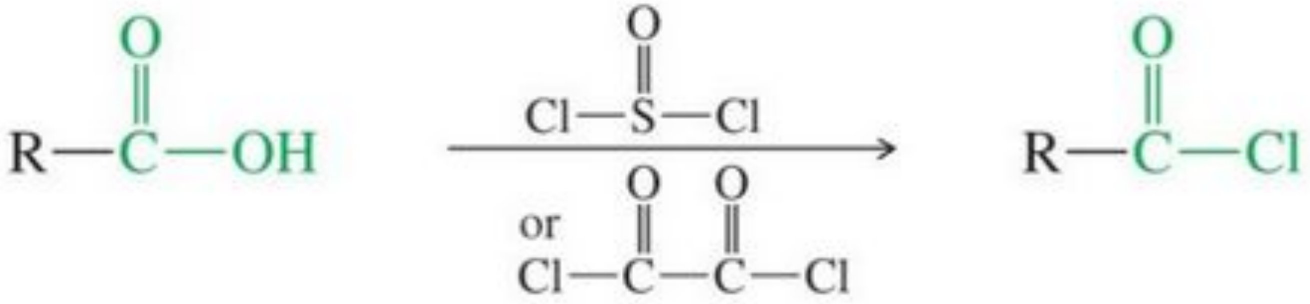
- The initial reaction of a carboxylic acid with an amine gives an ammonium carboxylate salt.
- Heating this salt to well above 100° C drives off steam and forms an amide.

Reduction Reactions of Aromatic Carboxylic Acids



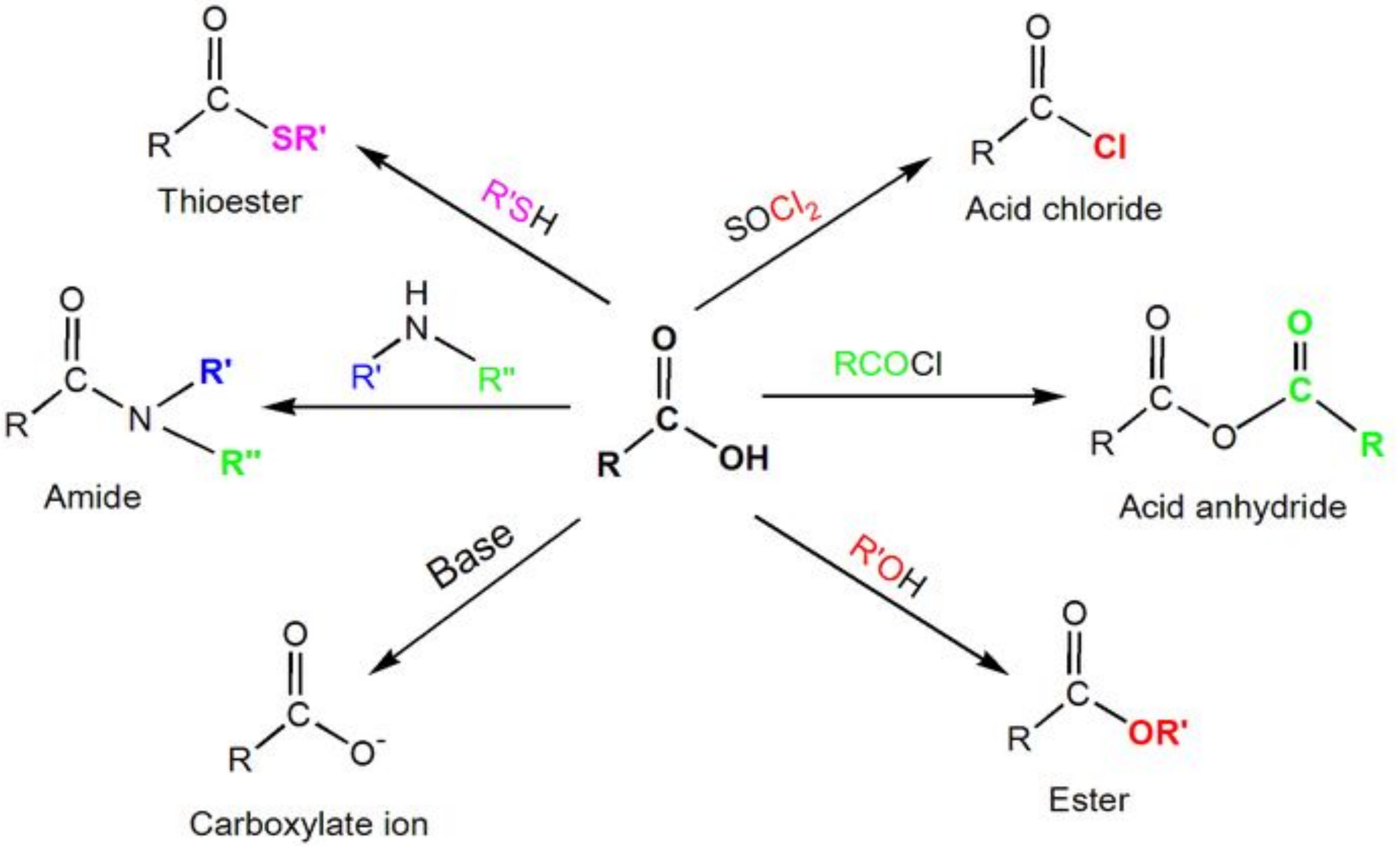
- $LiAlH_4$ reduces carboxylic acids to primary alcohols.
- The intermediate aldehyde reacts faster with the reducing agent than the carboxylic acid.
- BH_3•THF (or B_2H_6) can also reduce the carboxylic acid to the alcohol

Synthesis of Acids Chlorides



- The best reagent for converting carboxylic acids to acid chlorides are thionyl chloride ($SOCl_2$) and oxalyl chloride ($COCl_2$) because they form gaseous by-products that do not contaminate the product.
- Thionyl chloride reaction produces SO_2 while the oxalyl chloride reaction produces HCl, CO, and CO_2 (all gaseous).

Summary


R'SH
Thioester
SOCl2
Acid chloride
Amide
RCOCl
Acid anhydride
Base
Carboxylate ion
R'OH
Ester

Questions and Assignments

1. What are carboxylic acids? Give examples.
2. Draw a structure of *p*-aminobenzoic acid.
3. What are functional derivatives of carboxylic acids? Give examples.
4. What are chemical properties of carboxylic acids? Give examples of reactions.
5. What is application of aromatic carboxylic acids?

Polynuclear Aromatic Compounds

Topic 11

Outline of the lecture

1. Polynuclear Aromatic Compounds
2. SStructure and Structure and CStructure and Chemical Structure and Chemical PStructure and Chemical Properties of Structure and Chemical Properties of NStructure and Chemical Properties of Naphthalene
3. Reactions of electrophilic substitution

Bibliography:

1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
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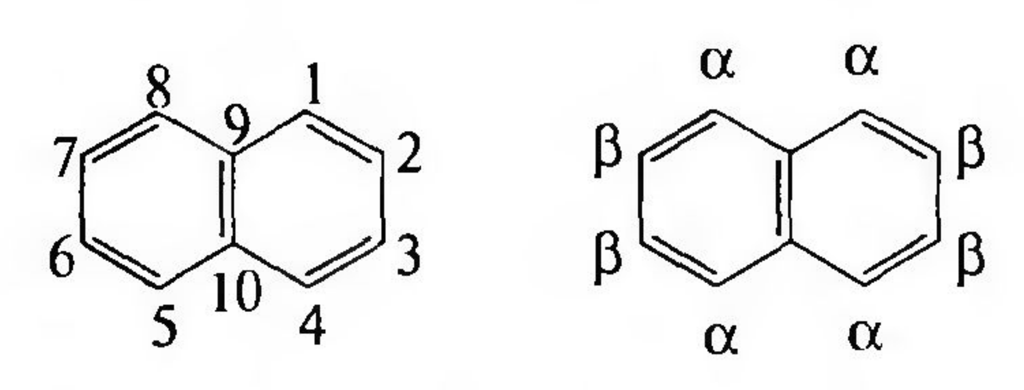
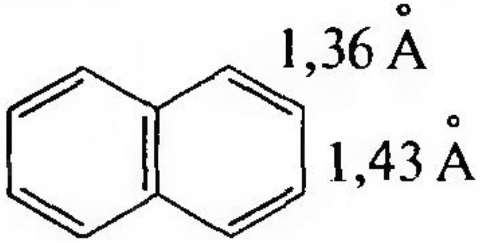
Polynuclear Aromatic Compounds

- The class of aromatic compounds includes not only benzene and its derivatives, but also other substances of a diverse structure. The derivatives of naphthalene are of great importance among these compounds.
- Naphthalene consists of two condensed benzene rings. Two carbon atoms (9 and 10) are common for two rings.



Structure and Chemical Properties of Naphthalene

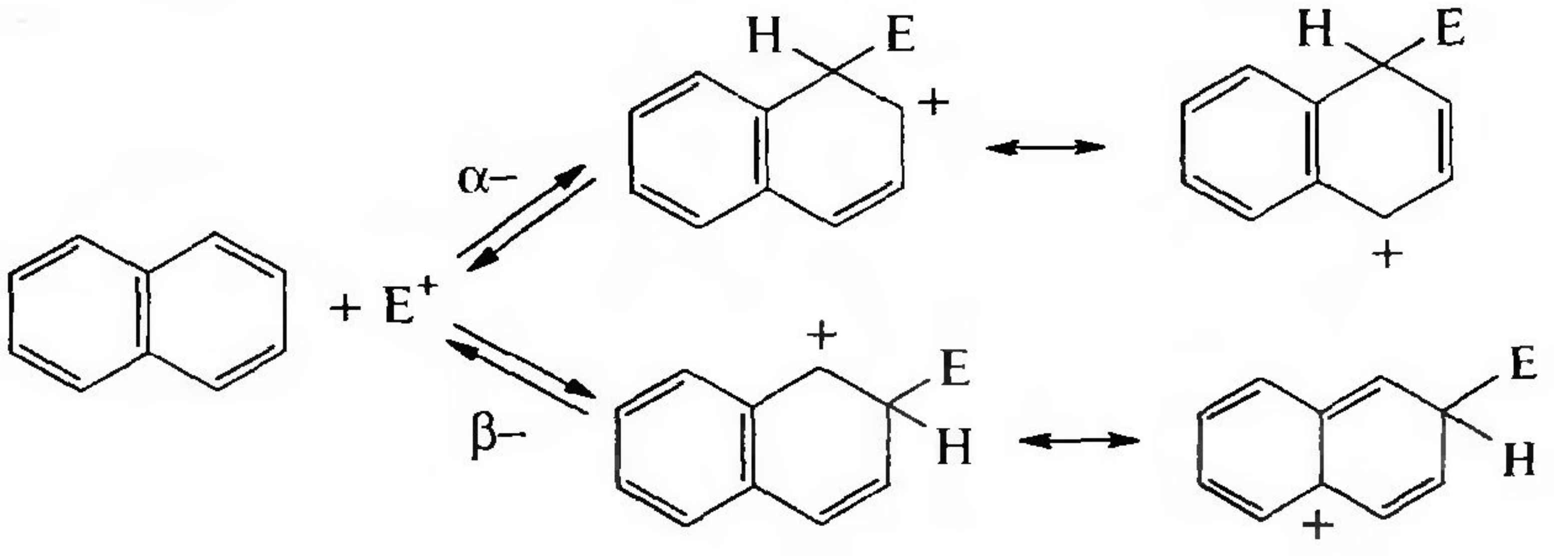
- The electronic structure of naphthalene is similar to that of benzene. The naphthalene molecule is flat. The dipole moment is zero, but the electron density is not distributed as uniformly as in the benzene molecule. A higher electron density of the α-positions of naphthalene makes them more reactive than the β-positions. The length of bonds in the molecule of naphthalene is different. Naphthalene, like benzene, exhibits the properties of aromatic compounds. It is characterized by reactions of electrophilic substitution, addition, and oxidation reactions.



Reactions of Electrophilic Substitution

- Naphthalene is more reactive than benzene in the reactions of electrophilic substitution (nitration, sulfonation, halogenation). α-Substitution products are mainly formed. This is due to the fact that the electron density is higher in the α-position of the naphthalene molecule. When attacking the α-position, σ-complex formed is more stable than σ-complex formed at the attack of the β-position.

Reactions of Electrophilic Substitution



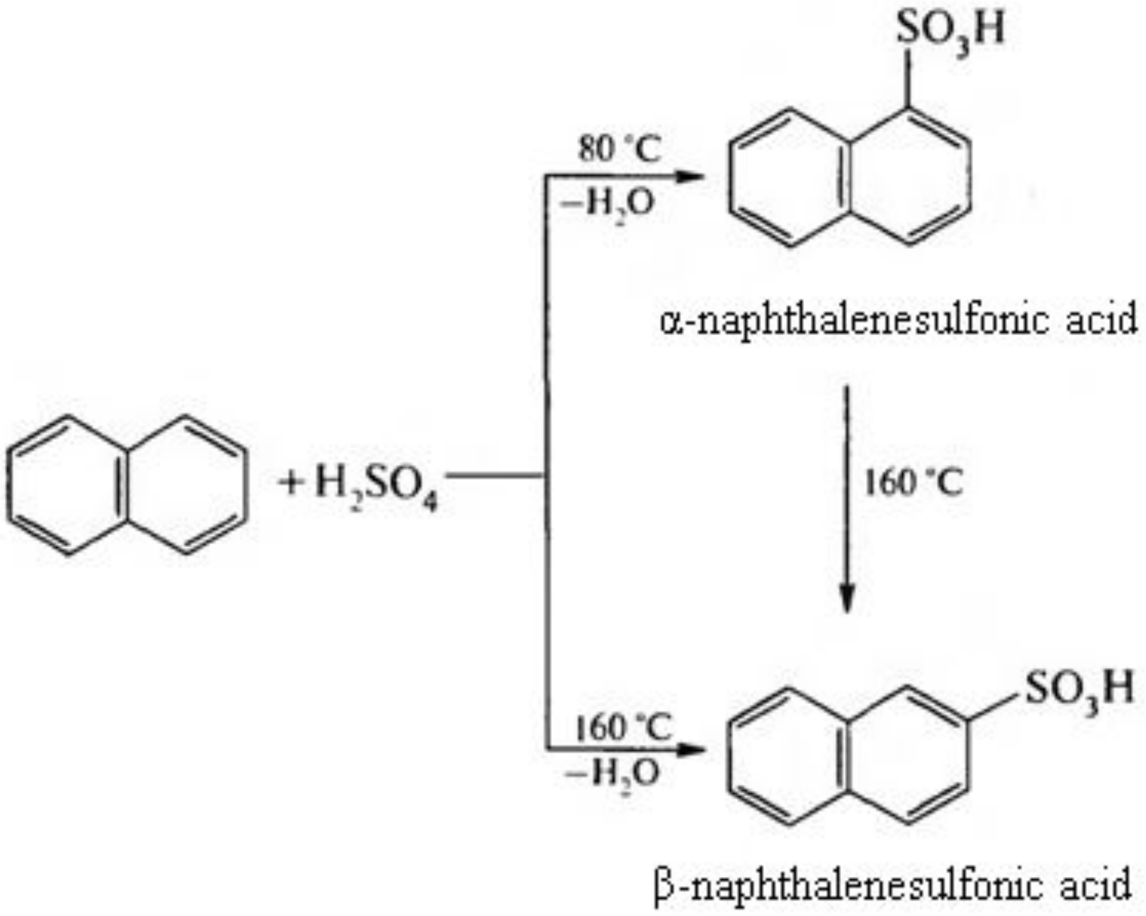
Reactions of Electrophilic Substitution

- When attacking α-positions, the delocalization of the positive charge in the σ-complex occurs with the preservation of the aromaticity of one of the benzene rings in possible resonance structures. In the case of the β-position attack, it is possible to preserve the aromaticity of the benzene ring in one case. Consequently, the α-position substitution is more energetically profitable.

Reactions of Electrophilic Substitution

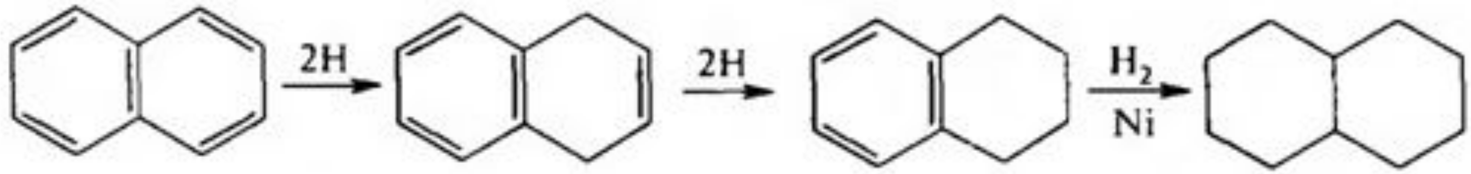
- ***Sulfonation.*** Concentrated sulfuric acid is used for sulfonation of naphthalene. Depending on the reaction temperature, α - and β-substitution products are obtained. α-Naphthalenesulfonic acid is formed at 80°C and β-naphthalene sulfonic acid is formed at 160°C.
- β-Isomer is converted to α-isomer when heated to a temperature of 160°C.

Reactions of Electrophilic Substitution



Reactions of Electrophilic Substitution

- *Oxidation reactions.* Unlike benzene, the naphthalene nucleus is easily oxidized. The nucleus is also oxidized during the oxidation of the naphthalene homologues.
- *Reduction reaction*. The addition of hydrogen occurs to form 1,4-dihydronaphthalene. Then 1,2,3,4-tetrahydronaphthalene is formed. The latter is further hydrogenated at 200°C to form decahydronaphthalene – decalin:



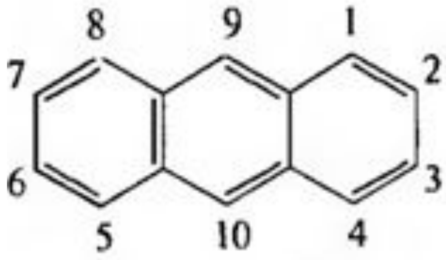
1,4-dihydronaphthalene

1,2,3,4-tetrahydro-naphthalene,
tetralin

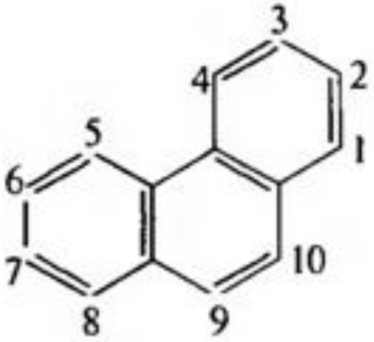
decahydro-naphthalene,
decalin

Polynuclear Aromatic Compounds

- More complex condensed systems are also known. They are anthracene and phenanthrene. The properties of anthracene and phenanthrene are similar to naphthalene. Naphthalene and anthracene derivatives are of great practical importance in the production of dyes. The phenanthrene nucleus underlies a number of natural substances related to hormones that are regulators of important life processes.



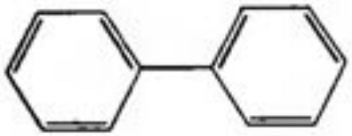
anthracene



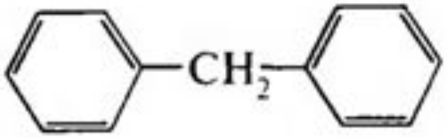
phenanthrene

Polynuclear Aromatic Compounds

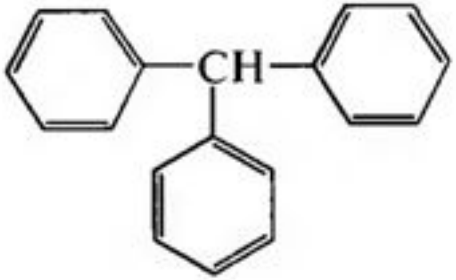
- Benzene rings can be combined with each other in different ways forming other groups of aromatic hydrocarbons.
- Derivatives of biphenyl and triphenylmethane are of great importance in the synthesis of dyes.



biphenyl



diphenylmethane



triphenylmethane

Questions and Assignments

1. What are polynuclear aromatic compounds called?
2. What are examples of polynuclear aromatic compounds?
3. What are chemical properties of polynuclear aromatic compounds?
4. Draw a Venn diagram, describing properties of benzene and naphthalene.
5. Solve problems on polynuclear aromatic compounds.
6. Review chemical properties of aromatic hydrocarbons. Fill in the Concept map.

Heterocycles

Topic 12

Outline of the lecture

1. Heterocyclic compounds
2. Classification of Heterocycles
3. Pyrrole
4. Synthesis of Heterocycles
5. Chemical Properties of Heterocycles

Bibliography:

1. Daley, R., Daley, S. 2012. *Organic Chemistry*. [online]. [Accessed 7 May 2012]. Available from World Wide Web: www.ochem4free.com
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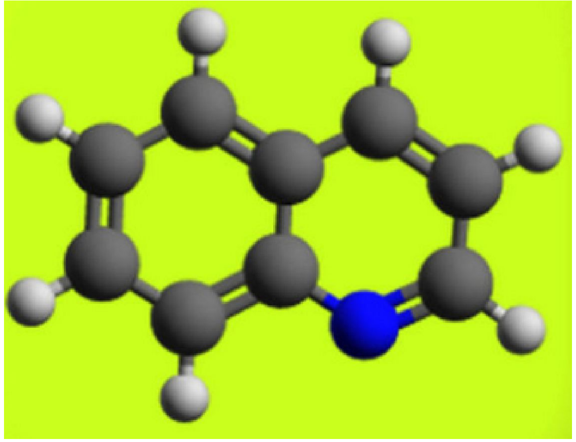
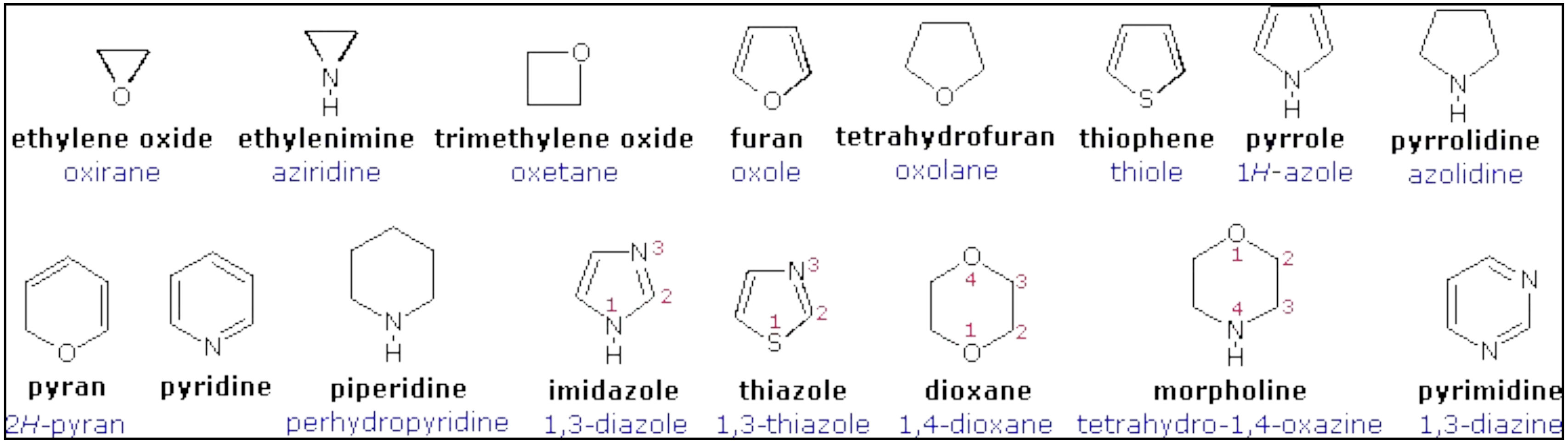
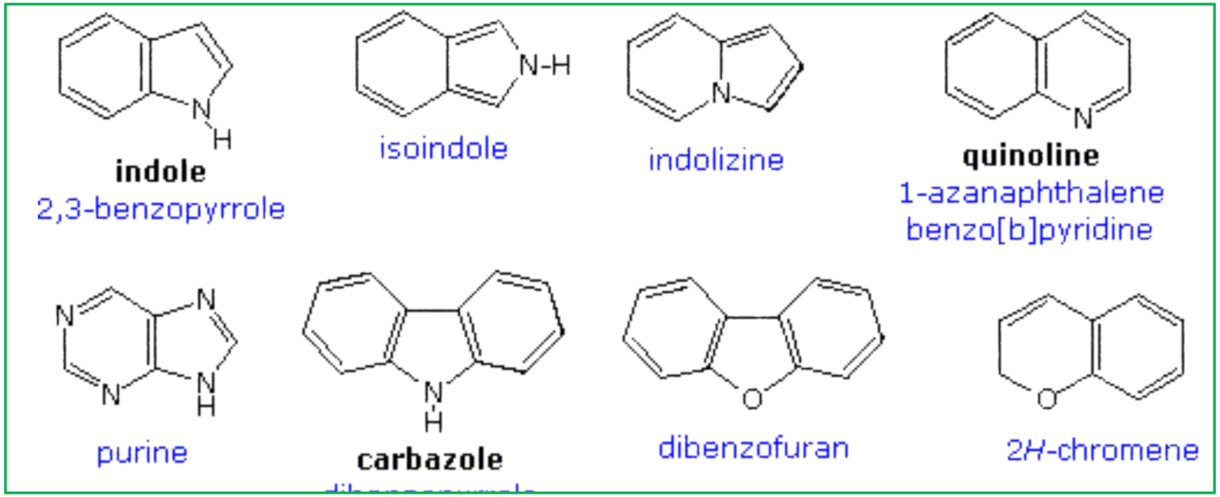
Heterocyclic compounds

- Heterocyclic compounds are cyclic compounds which contains one/more atoms of other elements along with carbon atoms.
- Hetero atoms are those which contains an atom other than carbon such as **nitrogen, sulphur, phosphorus etc.**

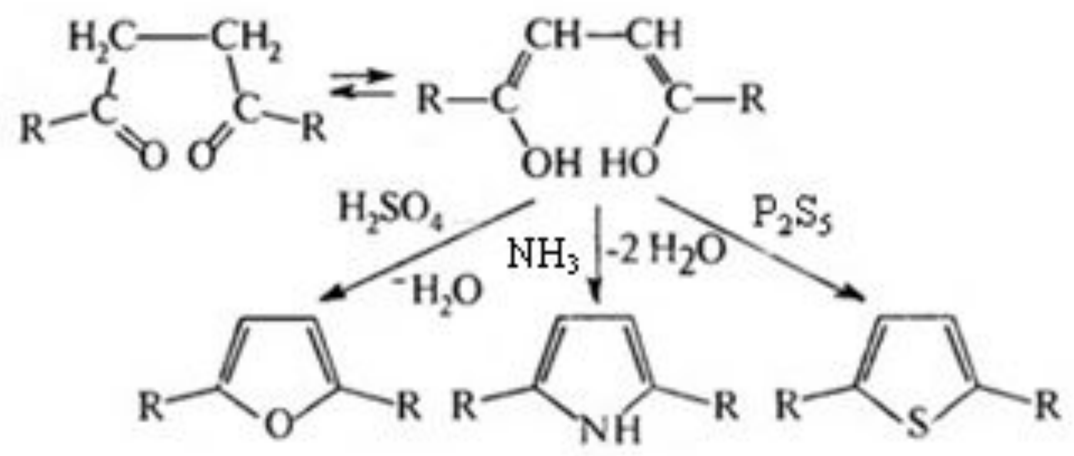


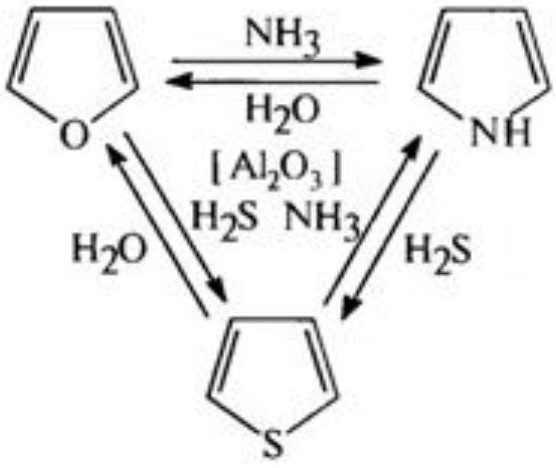
Classification of Heterocycles





Synthesis of Heterocycles





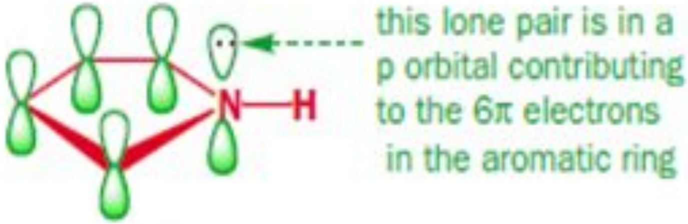
Pyrrole

The delocalization of the lone pair of Pyrrole pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron-rich and become more nucleophile.

Thus, decreased basicity of the nitrogen atom and increased acidity of the NH group as a whole

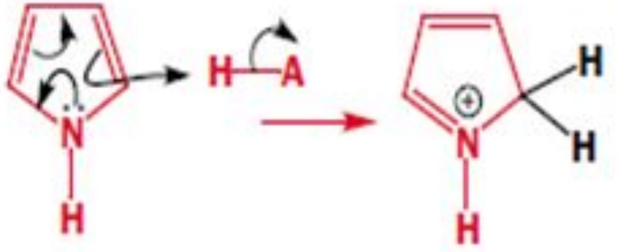
pyrrole

pK_{aH} ca. –4



this lone pair is in a p orbital contributing to the 6π electrons in the aromatic ring

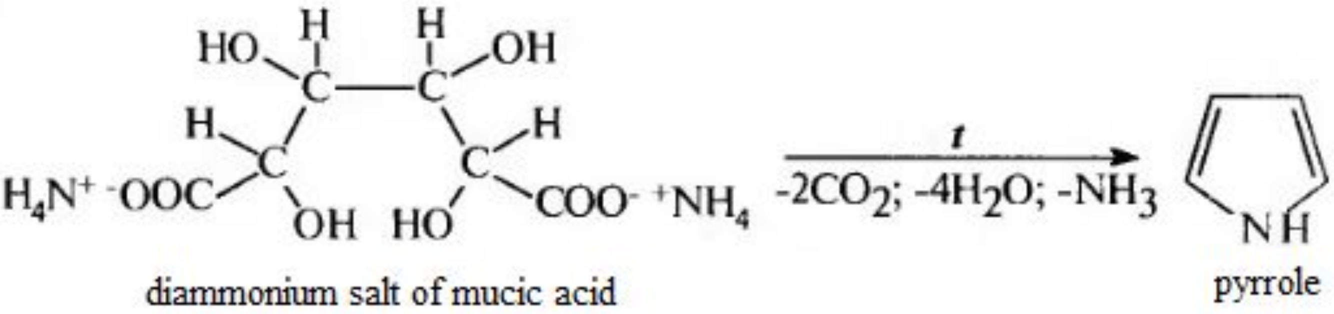
the aromaticity of pyrrole

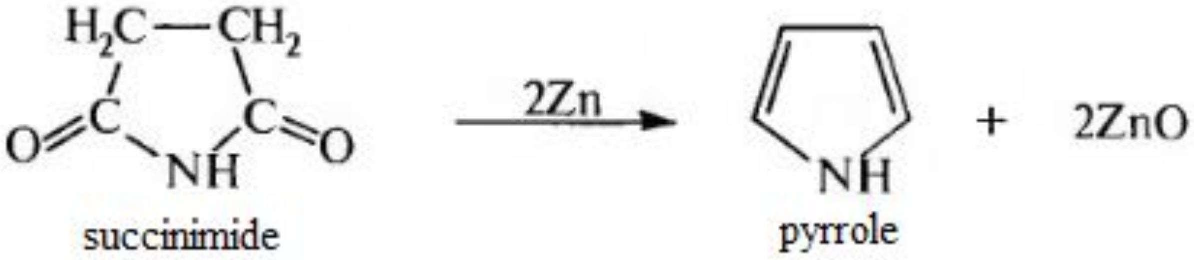


aromatic pyrrole

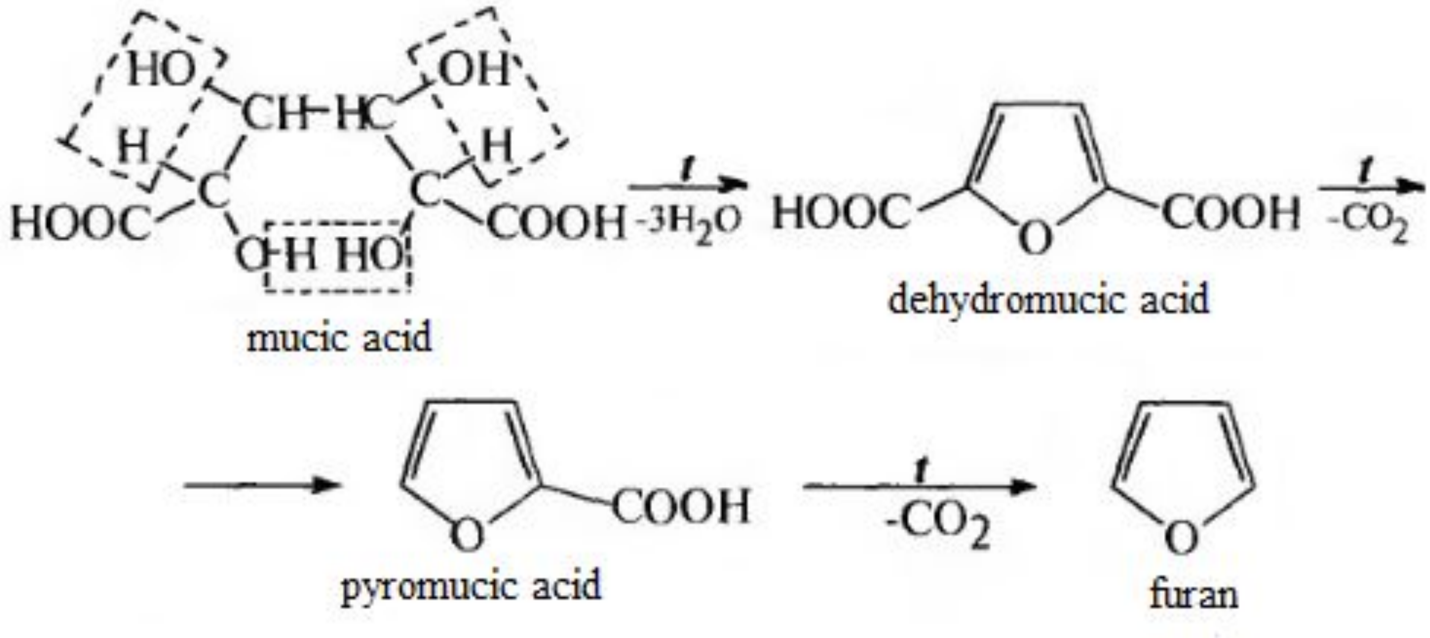
nonaromatic cation

Pyrrole

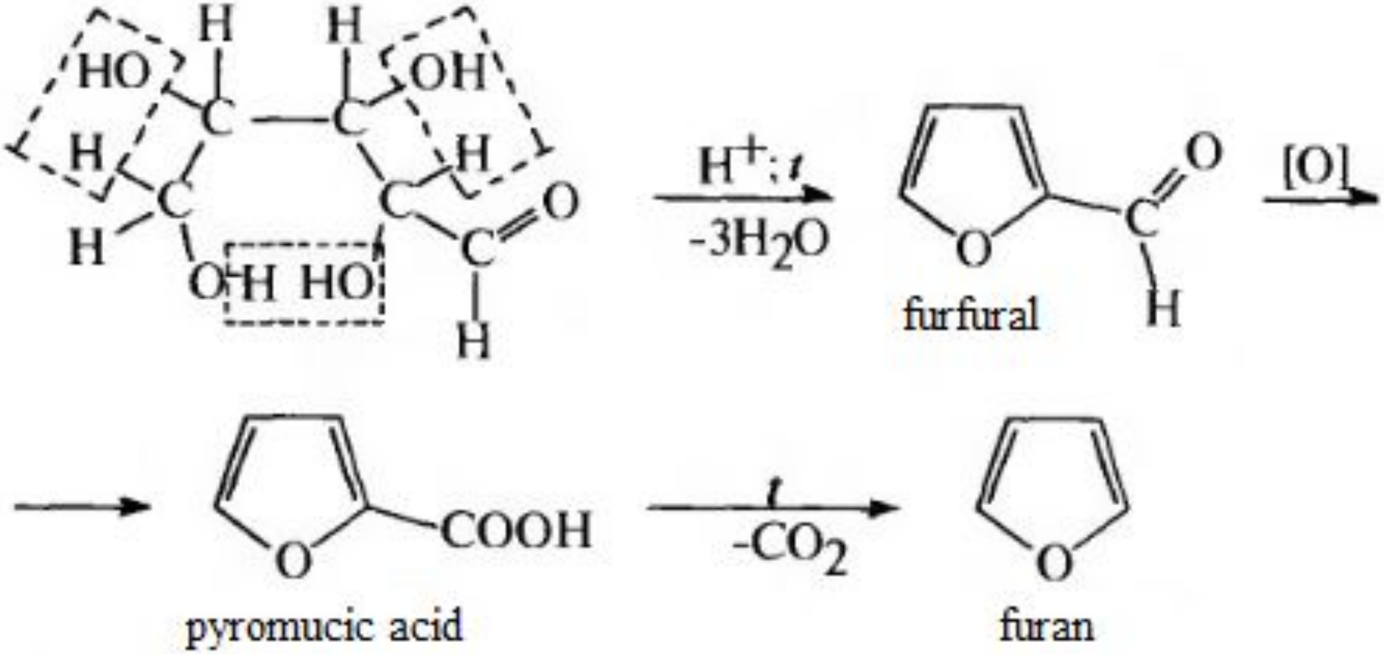

diammonium salt of mucic acid
t
-2CO2; -4H2O; -NH3
pyrrole


succinimide
2Zn
pyrrole
+ 2ZnO

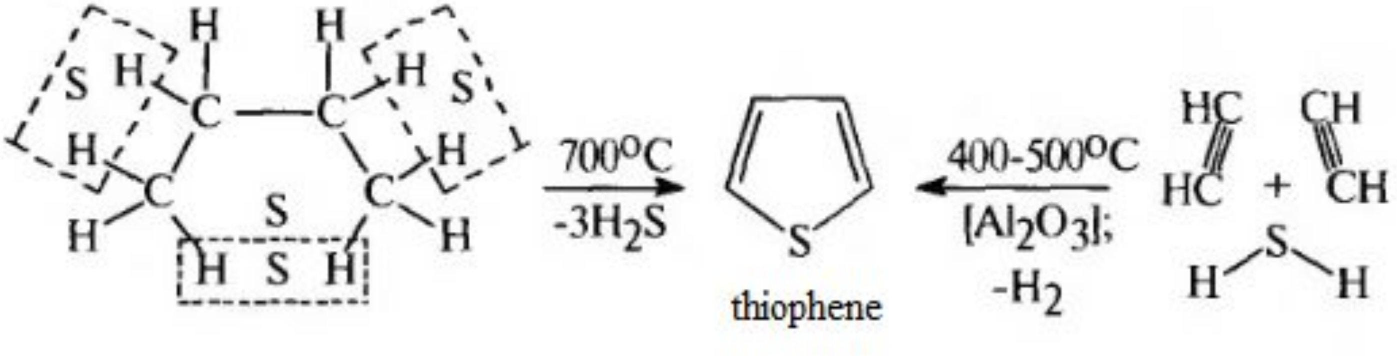
Furan


HO
OH
CH
HC
H
H
C
C
HOOC
COOH
OH
HO
mucic acid
t
-3H2O
HOOC
COOH
O
dehydromucic acid
t
-CO2
COOH
O
pyromucic acid
t
-CO2
O
furan

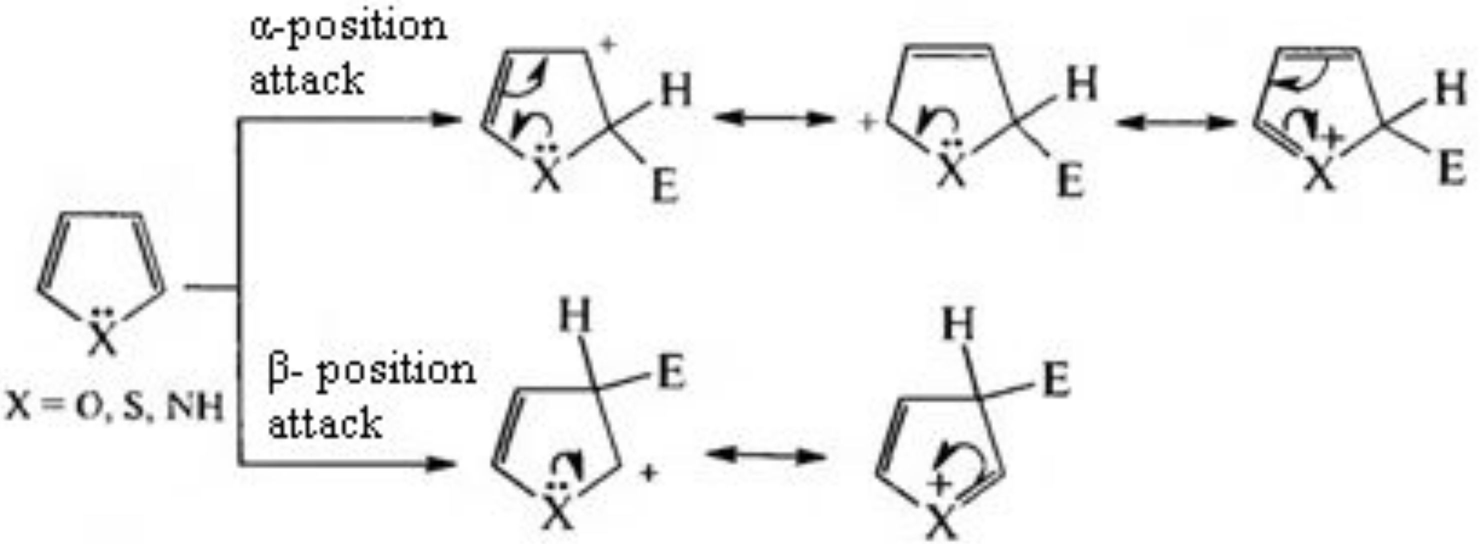
Furan


H
H
HO
OH
C
C
H
H
C
C
H
O
OH HO
C
O
H
H⁺; t
-3H₂O
O
C
O
furfural
H
[O]
O
COOH
pyromucic acid
t
-CO₂
O
furan

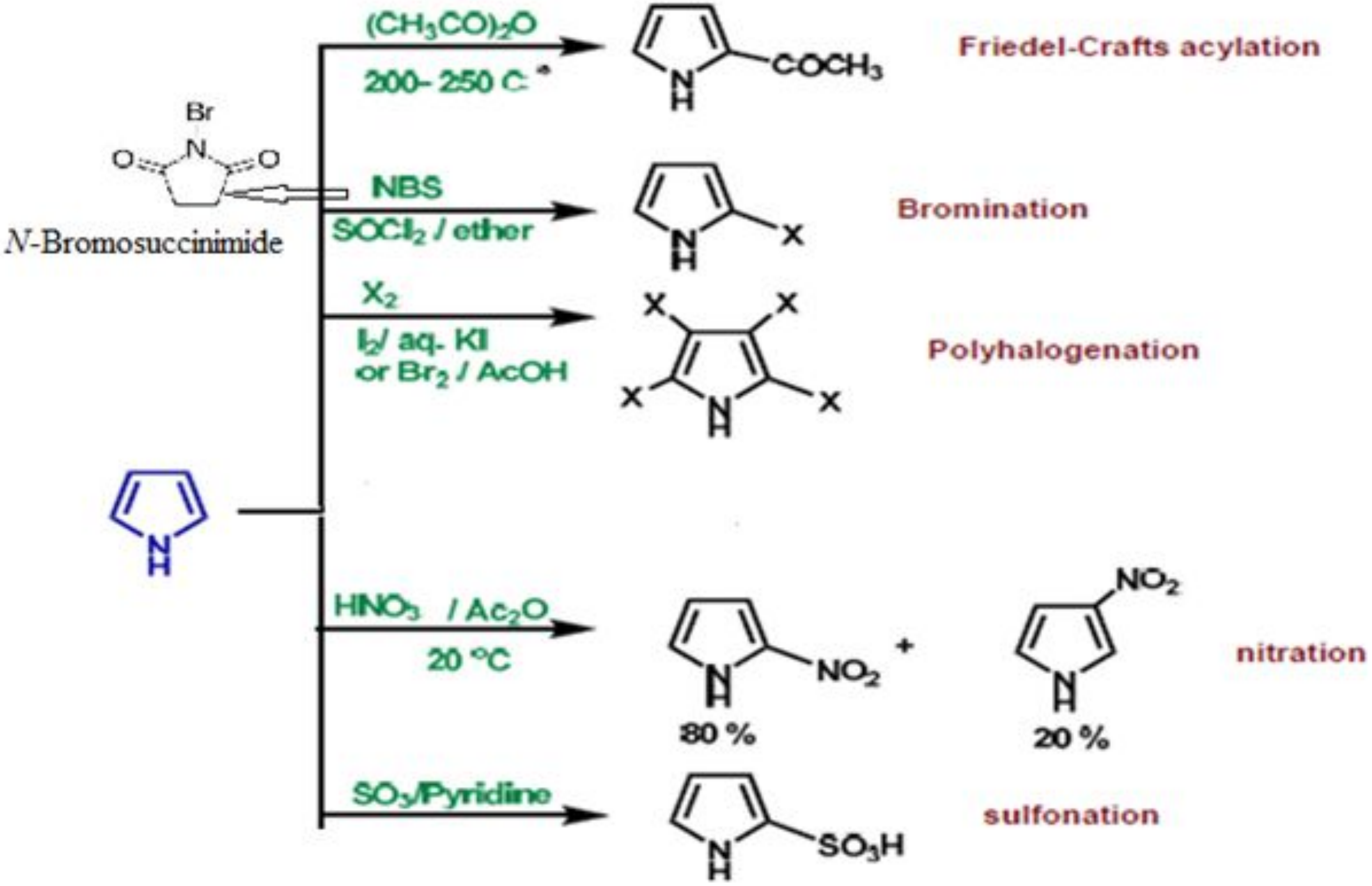
Thiophene



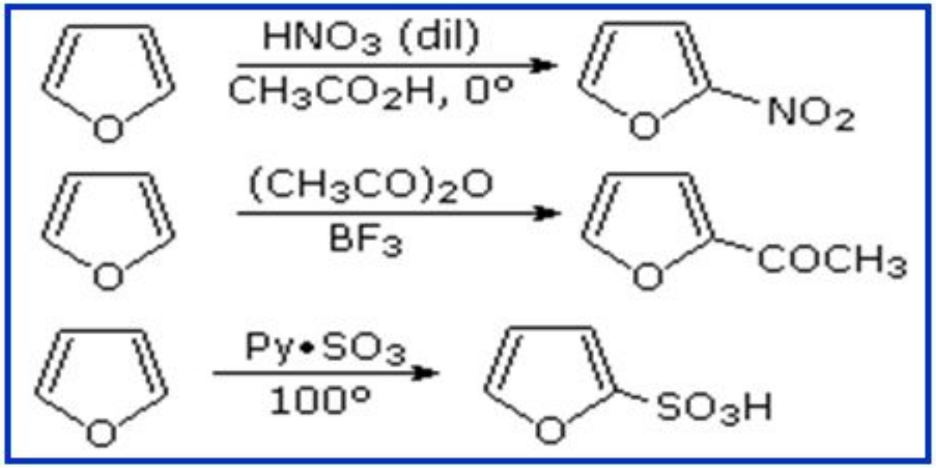
Chemical Properties of Heterocycles

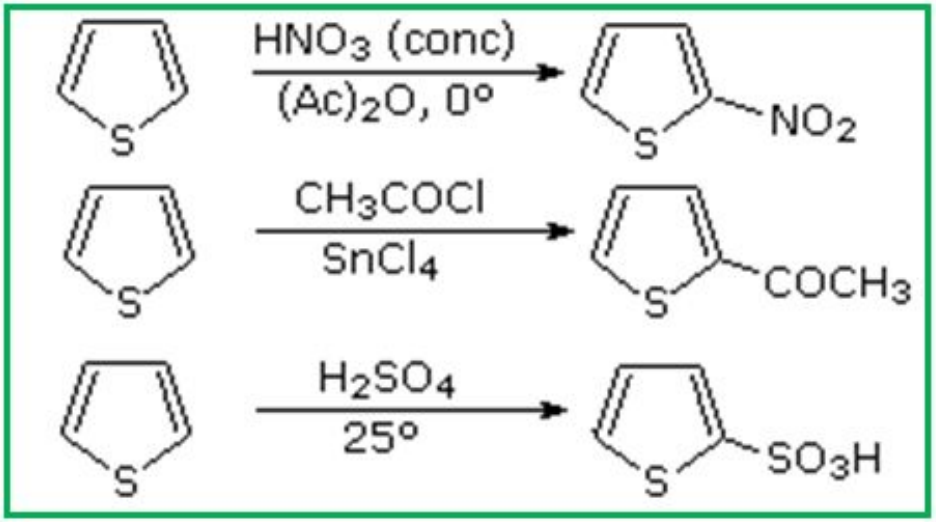


Chemical Properties of Heterocycles

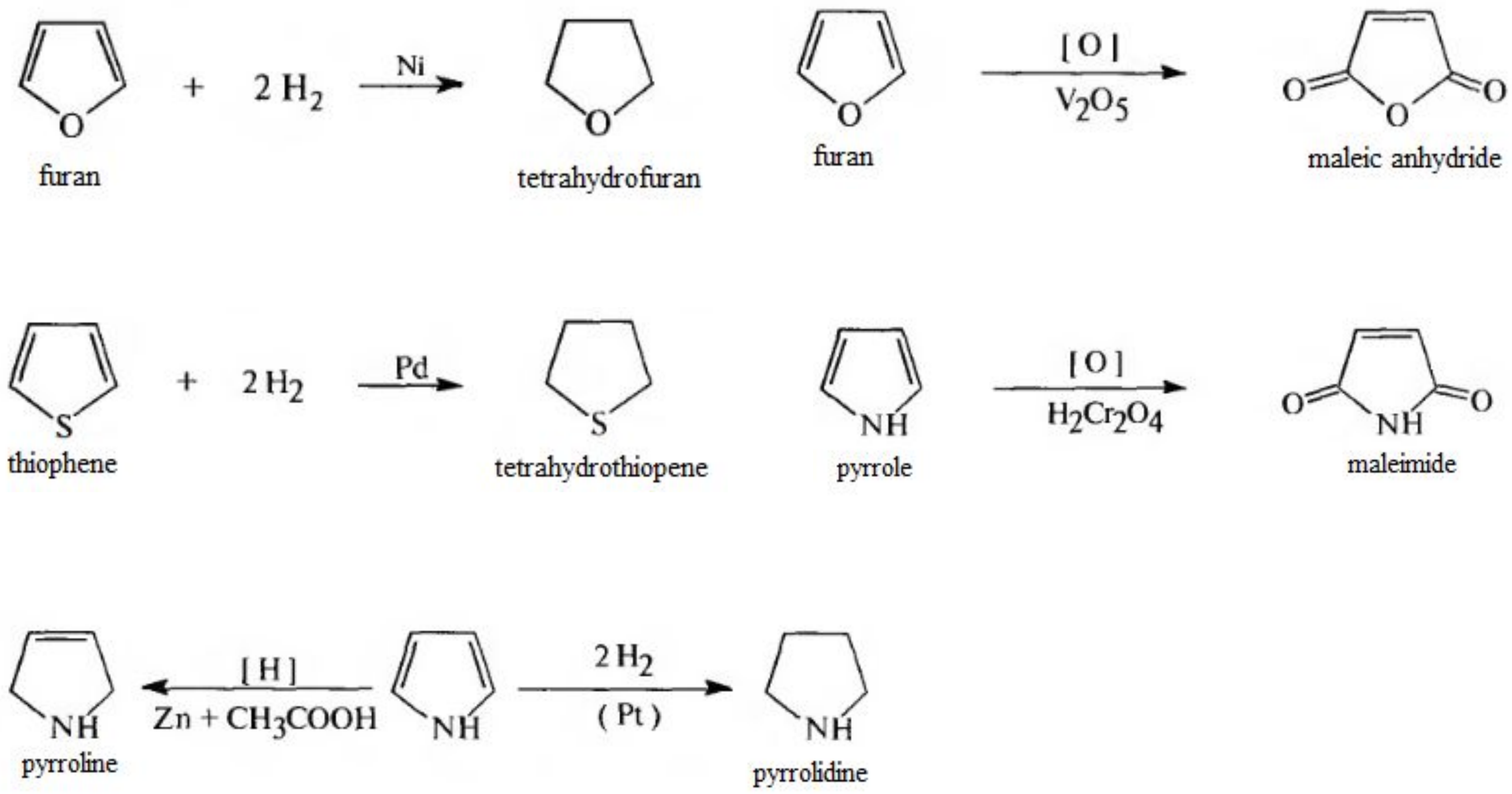


Chemical Properties of Heterocycles

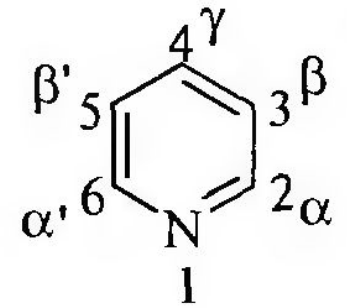


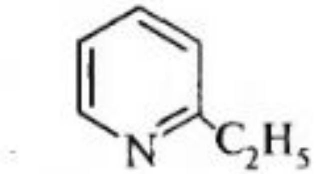


Reduction and Oxidation Reactions

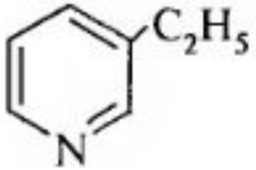


Six-membered Heterocycles with One Heteroatom

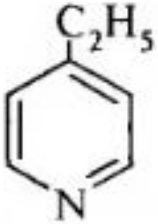




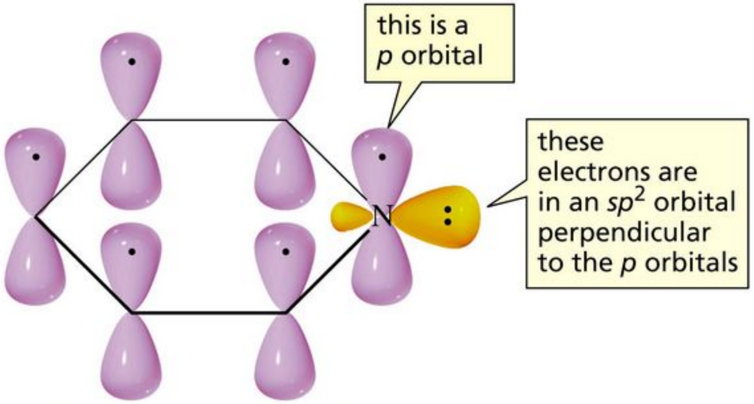
α-ethylpyridine
2-ethylpyridine



β-ethylpyridine
3-ethylpyridine



γ-ethylpyridine
4-ethylpyridine

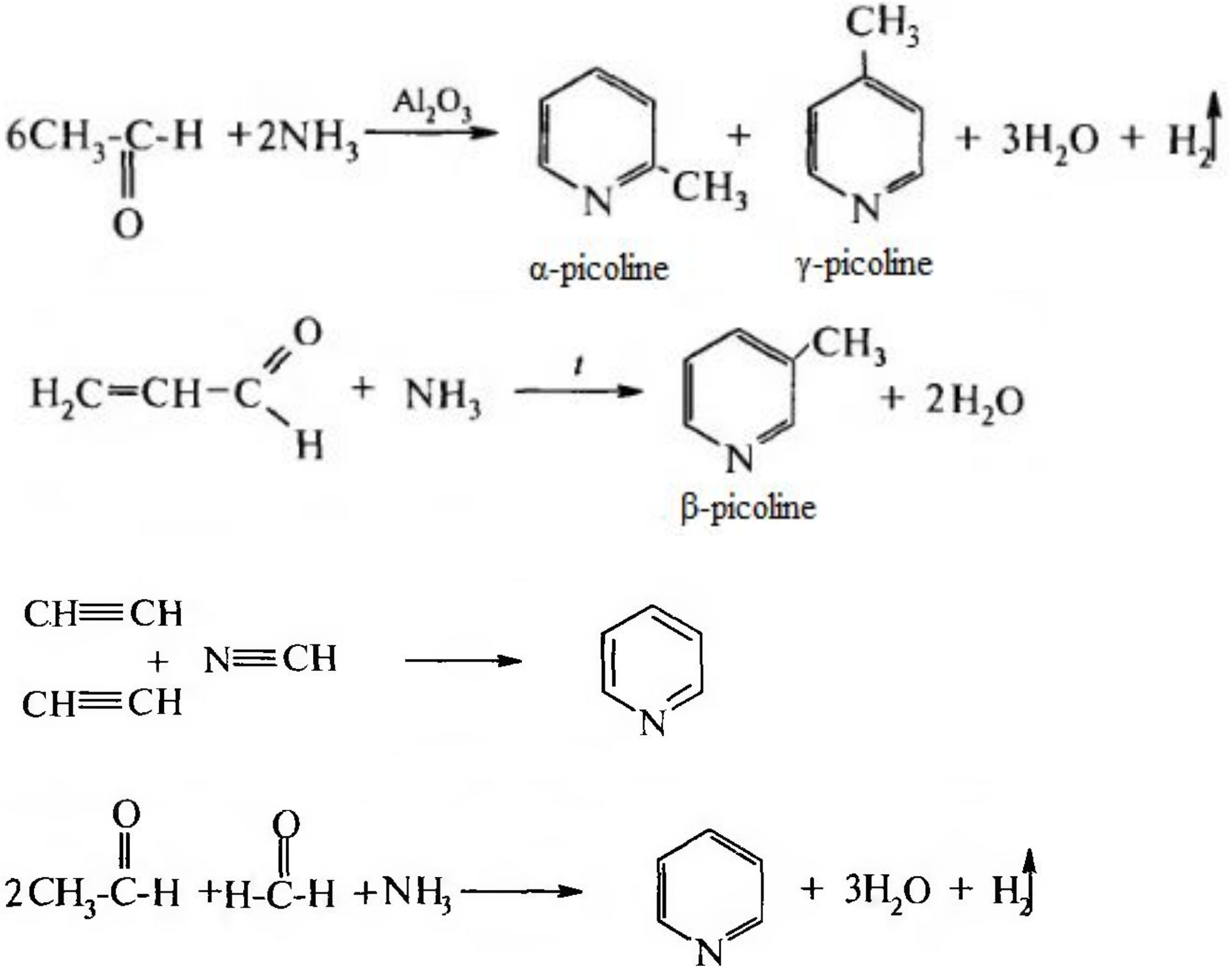


this is a *p* orbital

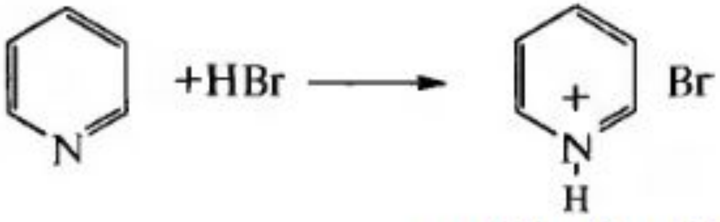
these electrons are in an *sp*^{2} orbital perpendicular to the *p* orbitals

orbital structure of pyridine

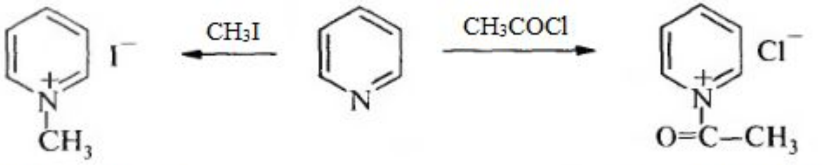
Methods for obtaining pyridine and its derivatives



Chemical Properties

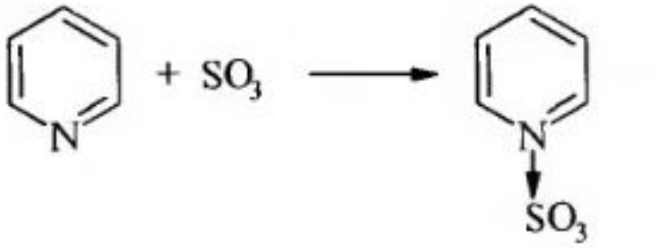


pyridinium bromide



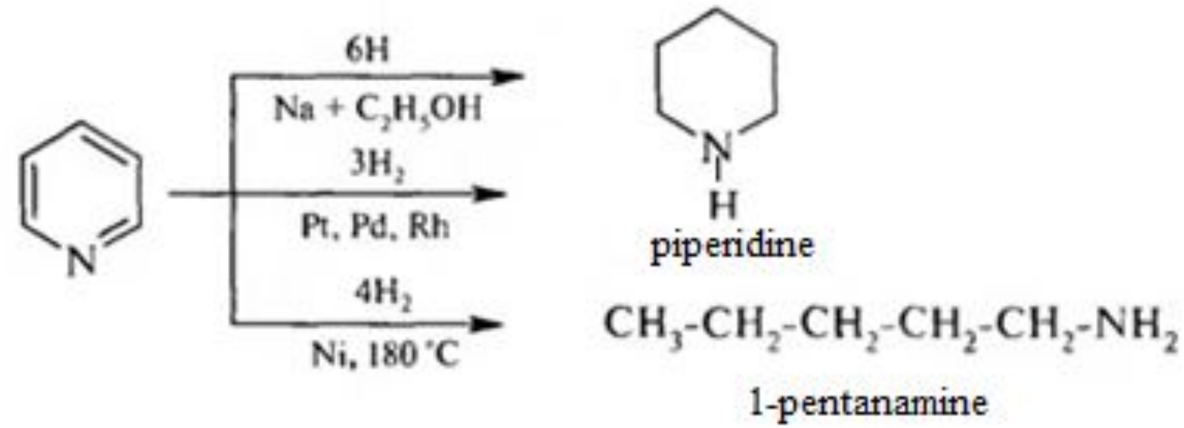
N-methylpyridinium iodide

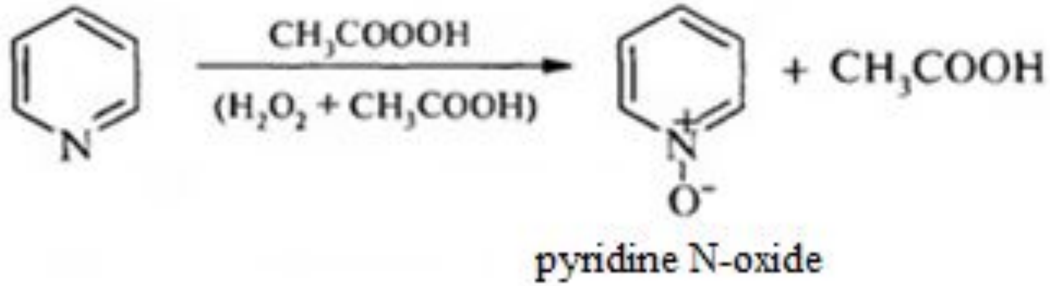
N-acetylpyridinium chloride



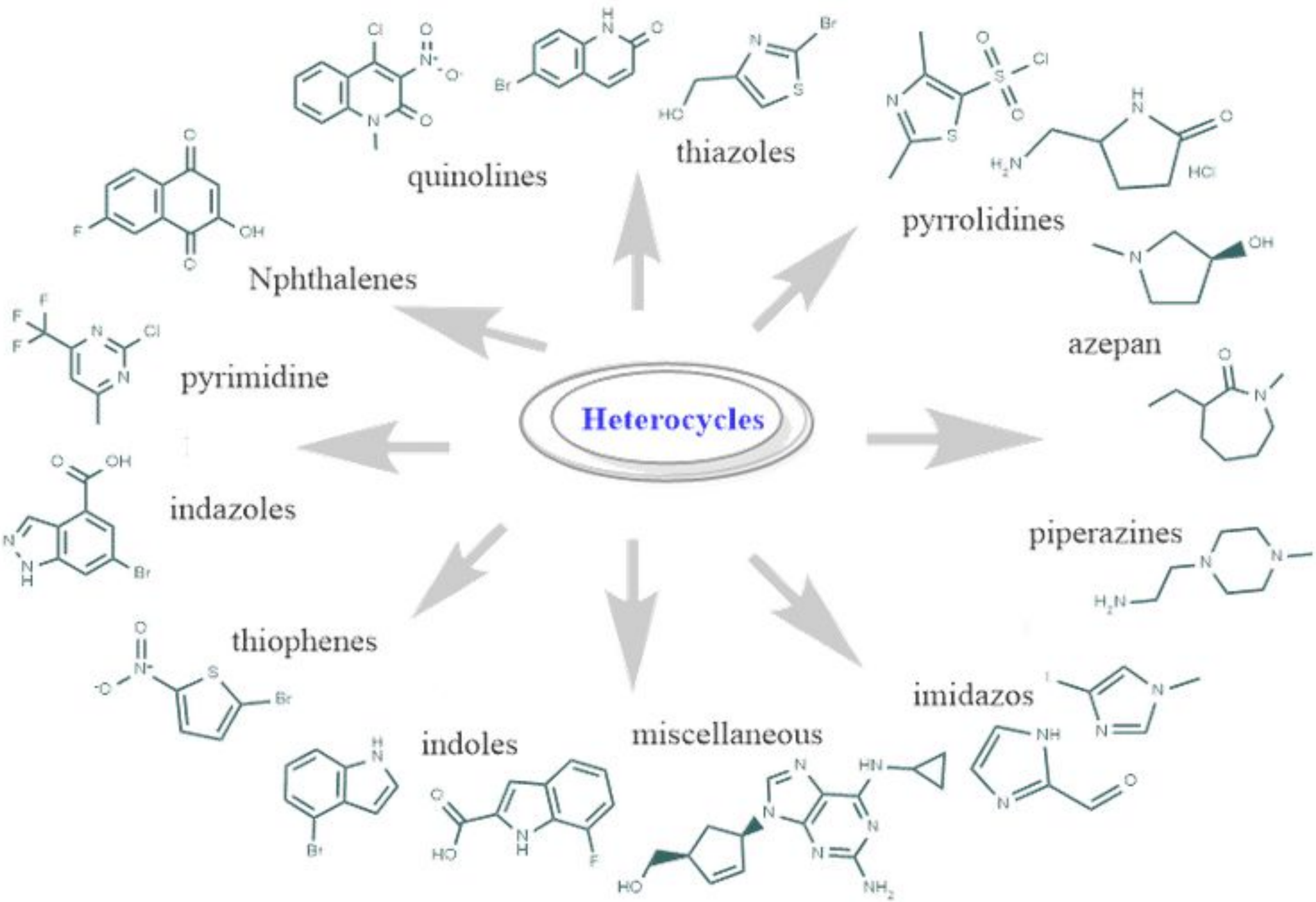
pyridine sulfur trioxide

Chemical Properties





Summary


Heterocycles
quinolines
thiazoles
pyrrolidines
azepan
piperazines
imidazos
miscellaneous
indoles
thiophenes
indazoles
pyrimidine
Nphthalenes

Questions and Assignments

1. What are heterocycles? Give examples.
2. What are fused heterocycles? Give examples.
3. Draw structures of five- and six-membered heterocycles.
4. What are common and specific properties of furan, pyrrole and thiophene?
5. Characterize chemical properties of pyridine.