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Pharmacology Concepts
By Rajesh Choudhary
/pharmacologyconceptsbyrajeshchoudhary

BENZENE

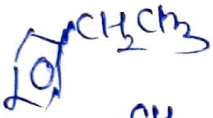
Benzene & its derivatives or homologues constitute the most imp. class of "Arenes" (aromatic hydrocarbons).

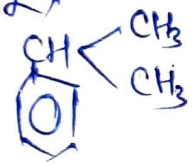
Nomenclature :-

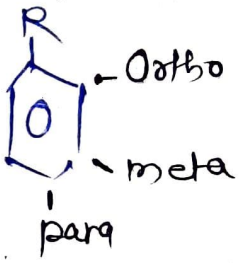
 Benzene - IUPAC Accepted
1,3,5-Cyclohexatriene

 Alkyl benzene

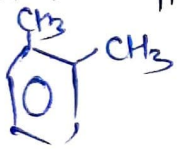
e.g.,-  - Methyl benzene (Toluene)

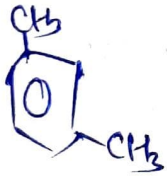
 Ethyl benzene

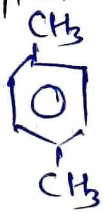
 Isopropyl benzene (Cumene)



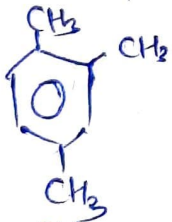
Dimethyl benzene → Xylene

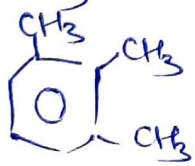
 O-xylene

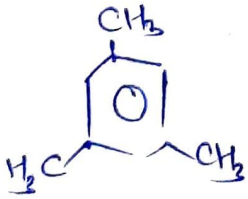
 m-Xylene

 p-xylene

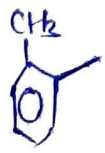
Trimethyl benzene

 1,2,4-Trimethyl benzene

 1,2,3,- " —

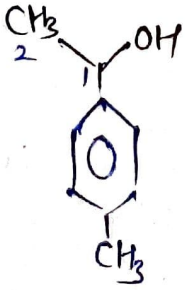
 1,3,5,- " —

Aryl group =  Phenyl

 o-tolyl

 meta-tolyl

 p-tolyl



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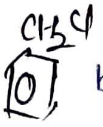
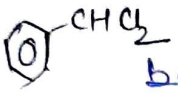
Aralkyl Group  Benzyl -  benzyl chloride

 Benzal  Benzo  benzochloride


benzal chloride

Structure of Benzene

1. Molecular Formula – C_6H_6 by elemental analysis & mole weight determination. : 78 amu or g/mol
   * Highly unsaturated as compared to C_6H_{14} (n-hexane)
2. Straight chain structure Not possible –

   proposed structure

   C_6H_6 = $HC \equiv C-CH_2-CH_2-C \equiv CH$

   1,5-hexadiyne

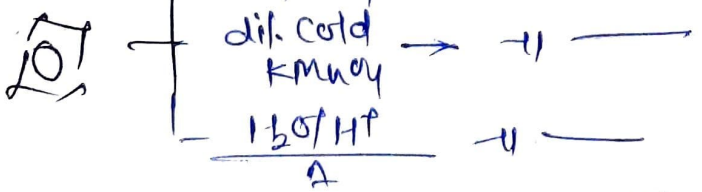
   C_6H_6 = $H_2C=CH-C \equiv C-CH=CH_2$

   1,5-hexadiene-3yne

   ↓

   They are decolourise bromine in CCl_4, or cold aqueous ~~pot. permanganate~~ $KMnO_4$ & Hydrolysis in presence of acid

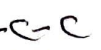
   But benzene did not react with them



And benzene did not behave like alkene & alkyne

∴ So benzene has not straight chain structure

* benzene donot give addit^n reaction with $KMnO_4$
* benzene donot follow general formula of alkane (C_nH_{2n+2}), alkene (C_nH_{2n}) & alkyne (C_nH_{2n-2})
* straight chain of C_6 produce 3 substitut^n while benzene produce only 1



3. Evidence of Cyclic Structure

1. Substitution of benzene – One monosubstitution reaction

$C_6H_6 + Br_2 \xrightarrow{FeBr_3} C_6H_5Br + HBr$

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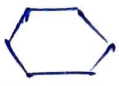
↳ Only one mono sub. reactn

↳ No isomeric product

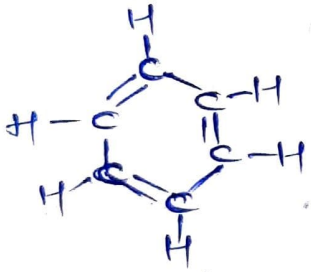
Concluded that all six hydrogen atoms in benzene were identical That could be possible when benzene had a cyclic structure of 6C & to each C was attached one hydrogen.

b. Addition of Hydrogen –

$C_6H_6 + 3H_2 \xrightarrow[150°, Atmp]{Ni}$  Cyclohexane C_6H_{12}

confirmed - cyclic structure & presence of 3 C=C

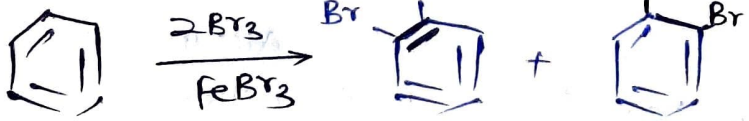
4. Kekule's Structure of Benzene – Proposed by "August Kekule"



 1,3,5-cyclohexatriene

These were two objection –

① If correct ~~there~~ should exist two orthoisomer of dibromobenzene



but only one ortho-dibromobenzene could be prepared.

- To overcome this objection, Kekule further suggest that benzene was a mixture of two forms

② Kekule's structure failed to explain why benzene with 3 C=C did not give add" reactn like other alkene.

 + HBr or Br_2/CH_4 —— No Reactn

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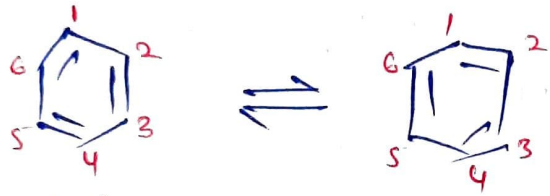
5. Resonance Description of Benzene

The phenomenon in which two or more structure can be written for a substance which involve identical positions of atoms is called Resonance.

This actual structure of the molecule is said to be Resonance Hybrid of various possible alternative structure

The alternative structures are reffered to as the Resonance Structure or Contributing forms

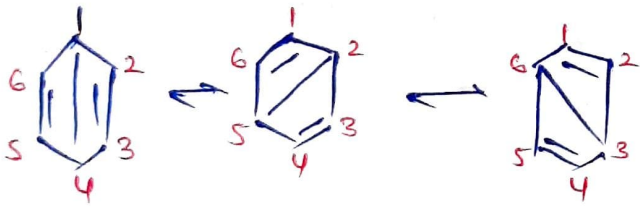
A. Kekule's Structure – 80% possibility



1-6
2-3
4-5

1-2
3-4
5-6

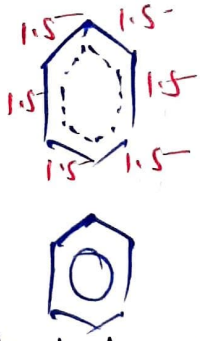
B. Dewar Structure – 20%



1-4 =
2-3
5-6

1-6
2-5 =
3-4

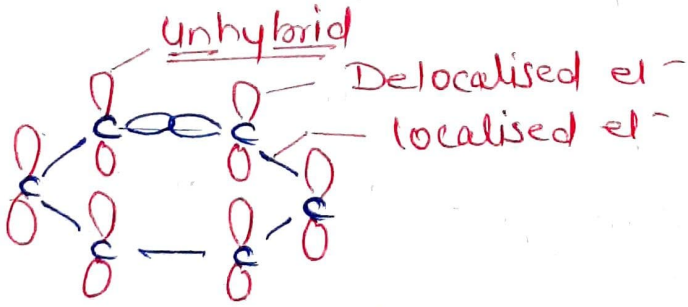
1-2
3-6 =
4-5



Short-hand Representation

- Single Bond length $-\overset{|}{C}-\overset{|}{C}-$ = 1.54 A° - Alkane
- Double Bond length $>C=C<$ = 1.34 A° Alkene
- Benzene  = 1.40 A° all are equal lengths

This value lies in between C-C & C=C

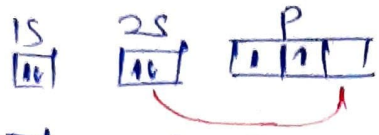


" It is probality of different pairing schemes between various el⁻ of an aton

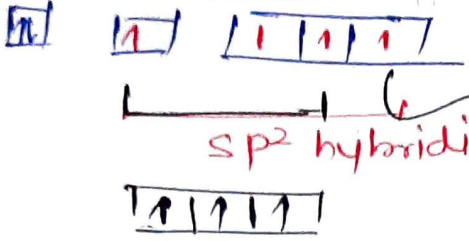
Resonance Energy ∝ Stability ∝ Resonance Structure

6. Molecular orbital Structure of Benzene

C_6^{12}



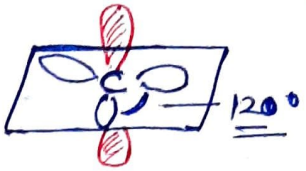
- ground state

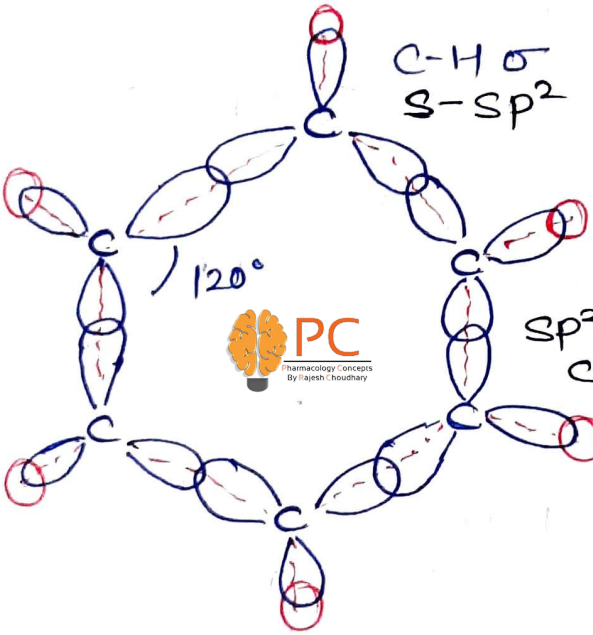


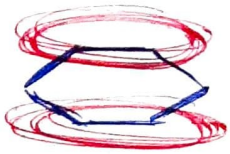
- Complete (100%) P-character

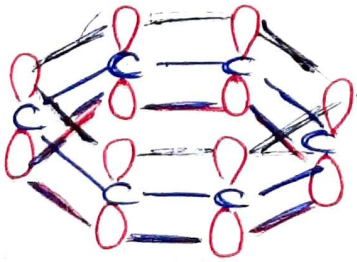
S: 33% character

P: 66% character









- unhybrid orbital

P-P overlap

Delocalised e⁻

↓

formed a stronger π bond & more stable

Energy - 36 kcal/mole

Right for Representation

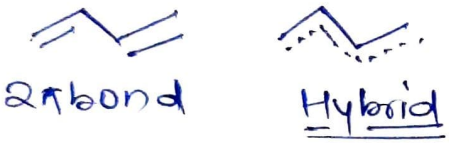
Resonance Energy of Benzene :-

Resonance energy (RE) is a difference between expected hypothetical or calculated energy and observed or real energy.

The energy is decreased from the expected hypothetical energy due to Resonance Stability.

RE ∝ Stability

ⓐ Butadiene



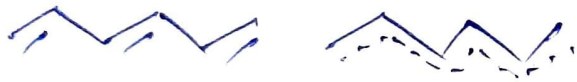
2π bond Hybrid

E ↑ Expected/calculated

= RE

observed/real energy

ⓑ



3π bond to resonate

E ↑ RE = observed − calculated

ⓒ  3π bond to resonate

Stability ~~of~~ ~~co~~ order = 1 quantity of (=) bond

C & B > a

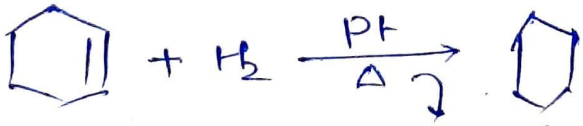
2. quality of resonance

C > B > A

BENZENE STABILITY

Benzene has special stability is due to the formation of the delocalised π ~~bond~~ molecular orbital. The magnitude of the extra stability can be estimated by measuring the changes in the heat of hydrogination that are associated with reaction.

① Cyclohexene



$+ H_2 \xrightarrow[\Delta]{Pt}$

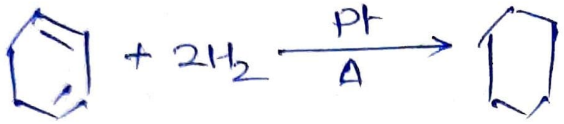
ΔH : Heat of hydrogination.

Calculated ΔH = −119.5 kJ/mol

Observed ΔH = −119.5 kJ/mol

RE = 0

2. 1,3-Cyclohexadiene

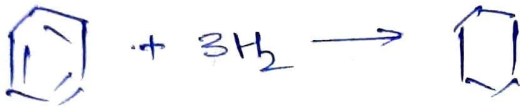


$\Delta H_{cal} = -239$ kJ/mol

$\Delta H_{ob} = -231$ kJ/mol

RE = 7.5 kJ/mol

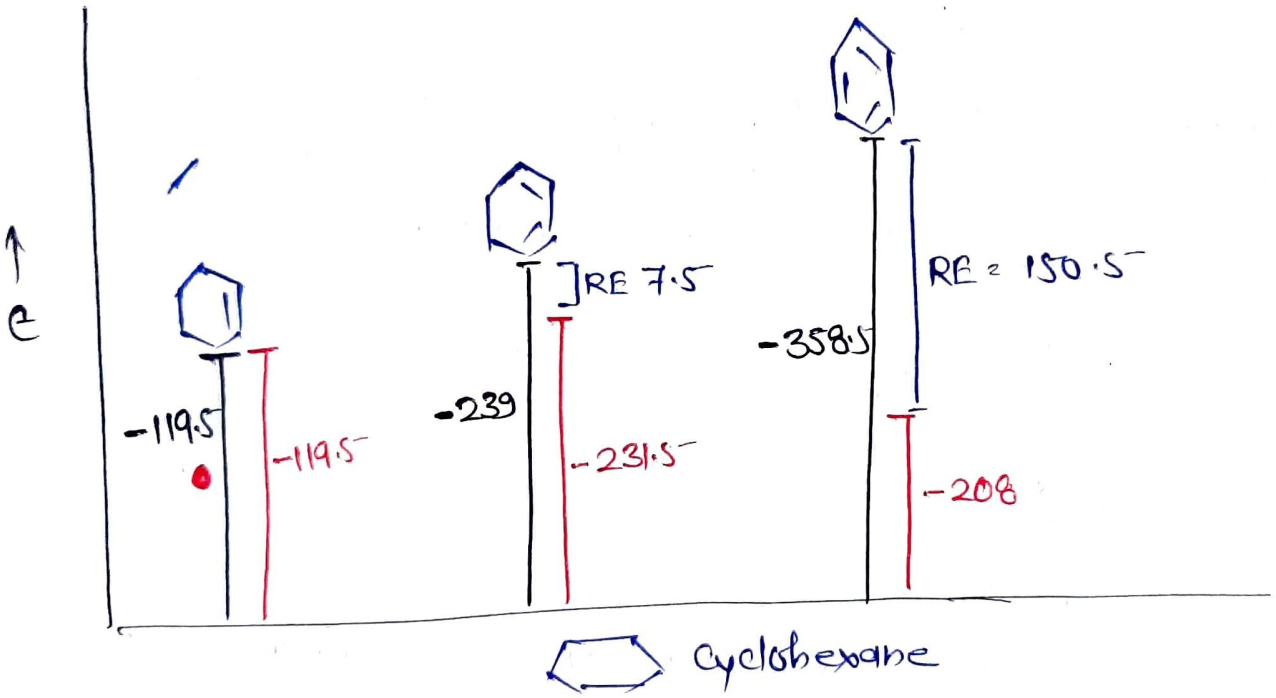
3. 1,3,5-Cyclohexatriene



$\Delta H_{cal} = -358.5$ kJ/mol

$\Delta H_{ob} = -208$ kJ/mol

RE = 150.5 kJ/mol



Stability order = cyclohexane > Benzene > cyclohexadiene > cyclohexene

"Resonance energy is a measure of how much more stable a resonance hybrid structure is than its extreme resonance structure"

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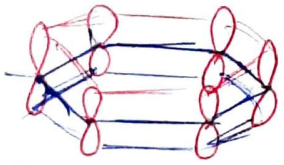
AROMATICITY (HUCKEL RULE)

- The aromatic compound -
  - ↳ contain alternate double (=) and single (–) bonds in cyclic compound/ structure
  - ↳ Resemble benzene in chemical behaviour
  - ↳ They undergo substitution reaction rather than addition reaction
- These characteristic behaviour is called Aromatic character or Aromaticity.

" Aromaticity is, infact a property of the sp^2 hybridized planner rings in which the p-orbital (one on each atom) allow cyclic delocalization of π electron "



- Criteria for Aromaticity

on the basis of ~~criteri~~ the above consideration -

Rule 1 - An aromatic compound is cyclic & planner

Rule 2. Each atom in an aromatic ring has a p-orbital These p-orbital must be parallel so that a continuous overlap is possible around the ring.

Rule 3. The cyclic π molecular orbital (el cloud) formed by overlap of p-orbitals must contain $(4n+2)$ electrons, where n = integer 0, 1, 2, 3 ...etc. This is know as Huckel Rule

Apply these rule to following examples -

Benzene

- has 3 (=)
  6 π el$^-$

Acc to Hukkel Rule

$4n+2 = 6$

$4n = 4$

$n = 1$

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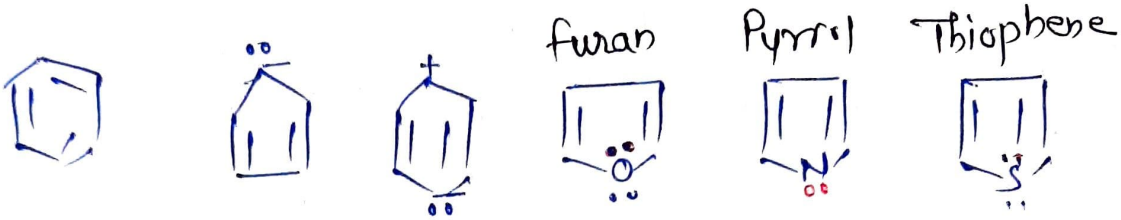
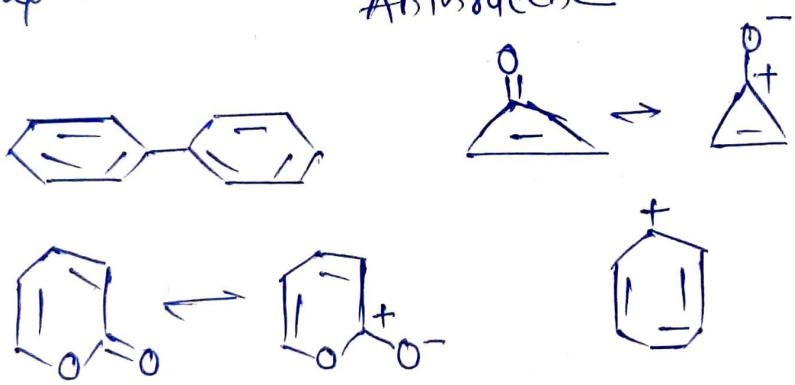
4. Criteria:- should be satisfied for Aromatic compound

1. Cyclic
2. Complete conjugation π o π, π o lonepair e^-, π o (+)/p
3. Planner - sp^2 or Sp hybridization
4. $(4n+2)\ \pi e^-$: $n = 0, 1, 2, 3, 4, \cdots$

$= 2, 6, 10, 14, 18\ e^-. \cdots$

ex. :





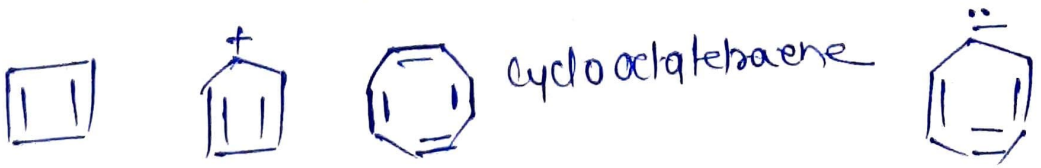
Anti-Aromatic Comp :- Highly unstable

1. Cyclic
2. Complete Conjugated
3. planar
4. $4n\ \pi e^-$: $n = 1, 2, 3, 4, \cdots$

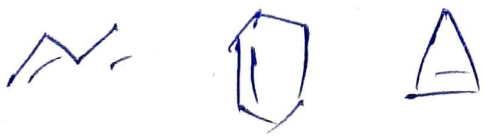
$= 4, 8, 12, 16\ e^-$

* Stability

Aromatic > Non Aromatic > Antiaromatic



Non-Aromatic :- neither aromatic nor Antiaromatic



PREPARATION OF BENZENE (C_6H_6)

A. Large Scale production

1. from Petroleum :- We already know that the aromatisation or platforming of $C_6 - C_8$ fraction naphtha yields a mixture of benzene, toluene, & xylene

↳ n-Hexane $CH_3-(CH_2)_4-CH_3$ $\xrightarrow[500°C,\ 15\ atm]{Pt/Al_2O_3}$ benzene $+ 4H_2$

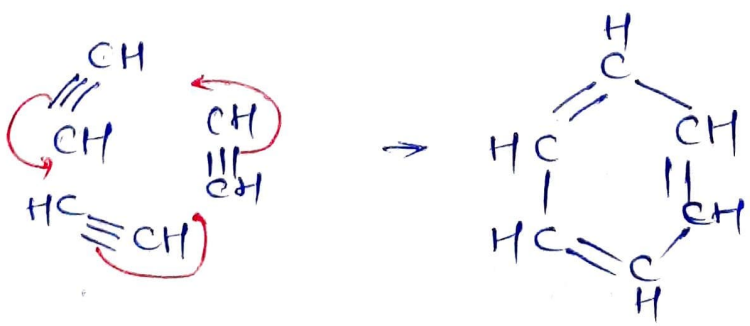
↳ $CH_3(CH_2)_5CH_3$ n-heptane $\xrightarrow[500°C,\ 15\ atm]{Pt/Al_2O_3}$ Toluene $+ 4H_2$

↳ $CH_3(CH_2)_6CH_3$ n-Octane $\xrightarrow[500°C,\ 15\ atm]{Pt/Al_2O_3}$ xylene

↳ Benzene is recovered from the mixture by solvent extraction & fractional distillation

B. Small Scale production :-

(1) $3\ CH{\equiv}CH$ Acetylene $\xrightarrow[500°C]{\text{Red hot tube}}$ benzene



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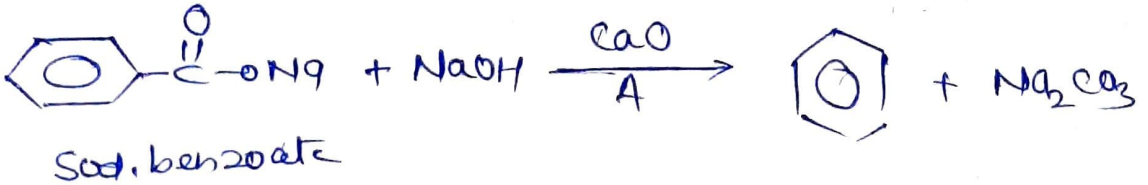
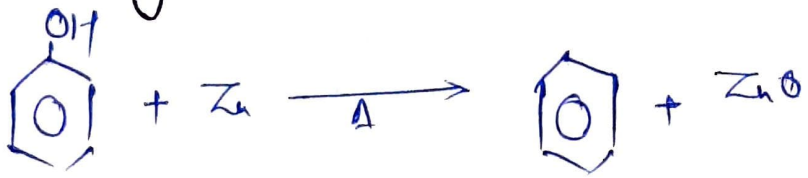
2. By benzoic acid sod. salt with Soda lime

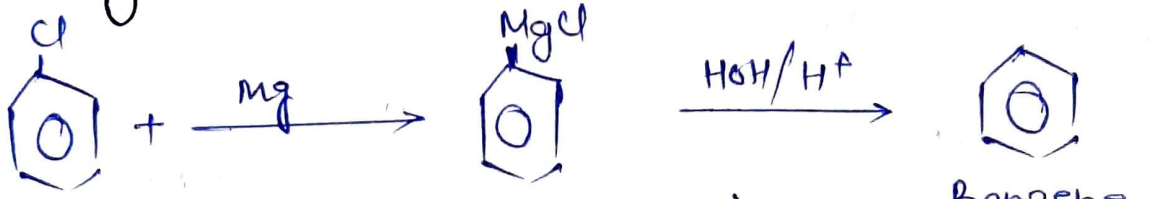


Sod. benzoate

3. By Heating phenol with Zinc dust



4. By heating chlorobenzene with magnesium followed by dil HY



chlorobenzene — Phenyl magnesium chloride — Benzene

PHYSICAL PROPERTIES OF BENZENE

1. Colourless liquid, BP - 80.1°C, MP 5.5°C
2. Solubility – insoluble with water – forming upper layer
   soluble in org. solvents – alcohol, ether, $CHCl_3$
3. Good Solvents – for fats, Resin, sulphur & iodine
4. Vapours are highly toxic, inhalation may produce loss of consciousness. Benzene poisoning may cause fetal, destroying the RBC & WBC
5. Burns with a luminous flam.
6. IR-Spectra – * two bands near 1600 cm^{-1} & 1500 cm^{-1}, that corresponds with stretching of C-C bonds of aromatic compound
   * sharp band – 3030 cm^{-1} — by Aromatic C-H ~~band~~ bond

Alkane

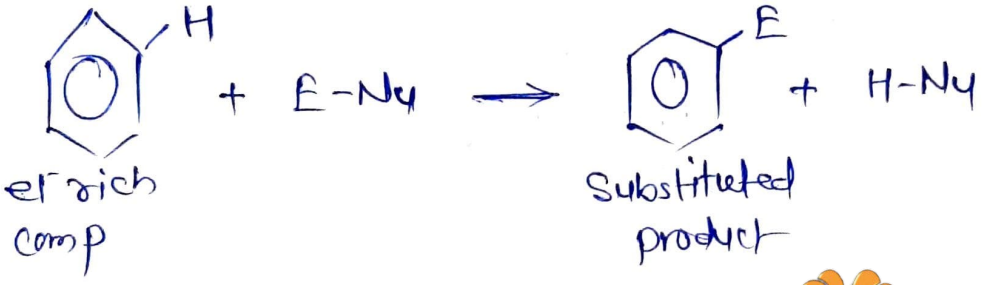
CHEMICAL REACTION OF BENZENE

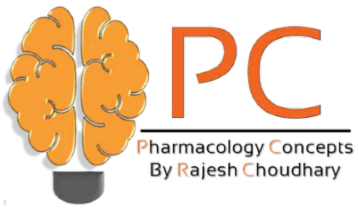
The principal type of Reaction of Benzene -

A. Electrophilic Substitution Reaction
B. Addition Reaction
C. Oxidation Reaction

A. Electrophilic Substitution Reaction

Electrophile = E^+ = Electron loving
Nucleophile - Nu^- = proton loving



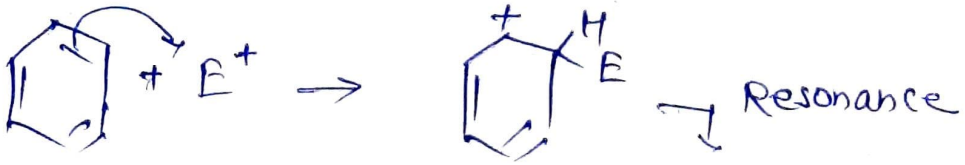


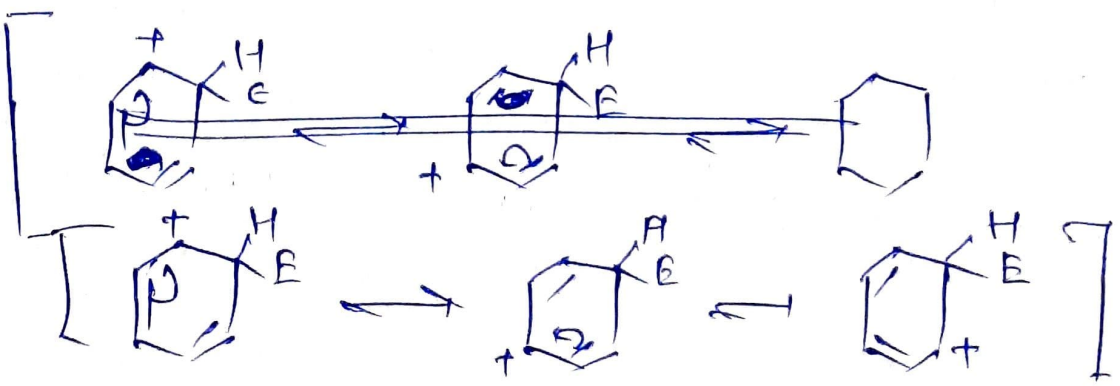
General Mechanism

① Formation of Electrophile

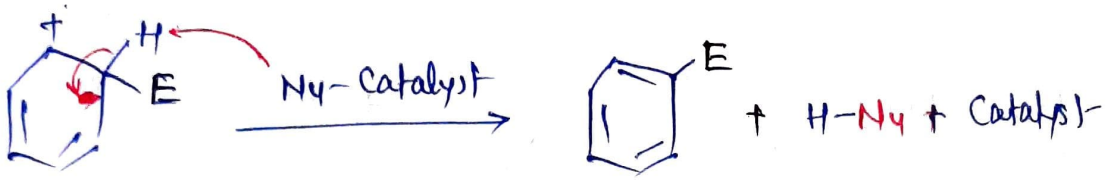
$$E\text{-}Nu \xrightarrow{\text{Catalyst}} E^+ + Nu\text{-catalyst}$$

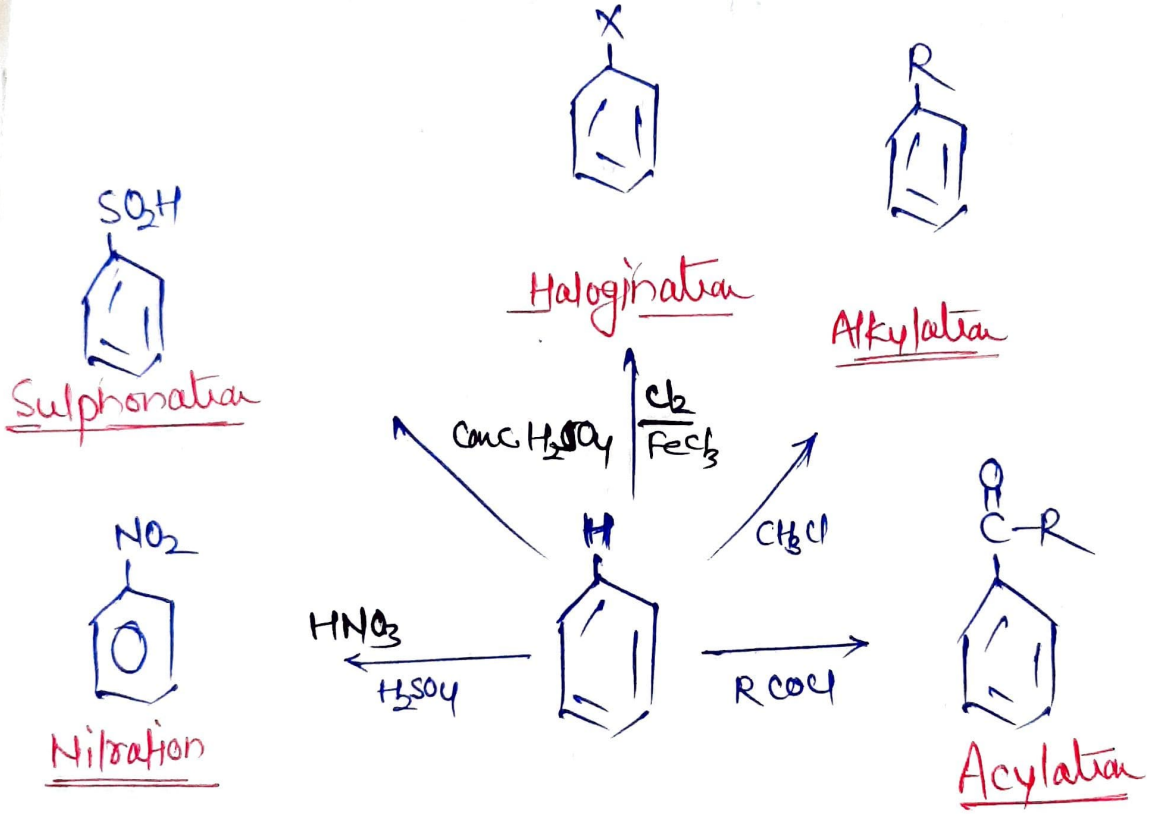
② Attack of electrophile to aromatic ring to form a carbonium ion





3. loss of proton & gives the Substitution Reaction





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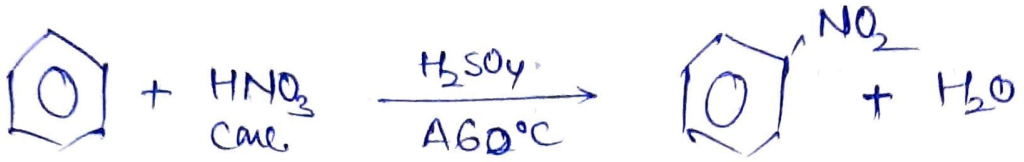
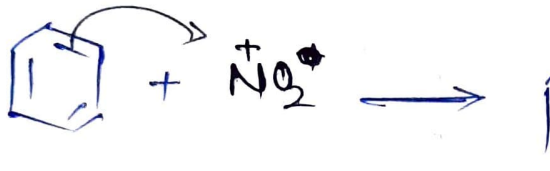
1. Nitration :-



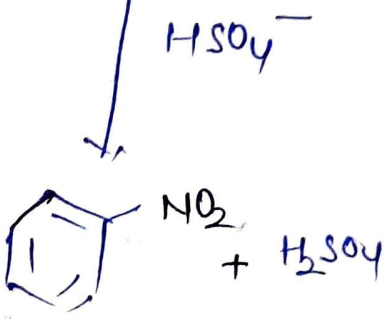
Nitro benzene

Steps

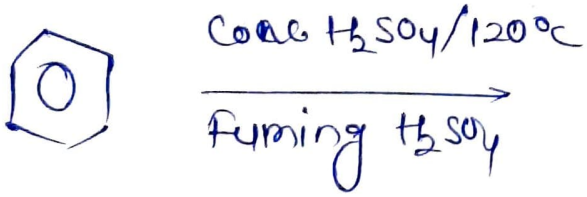
1. $HNO_3 + 2H_2SO_4 \longrightarrow \overset{+}{N}O_2^{\bullet} + 2HSO_4^- + H_3O^+$

2. 

(3) loss of proton

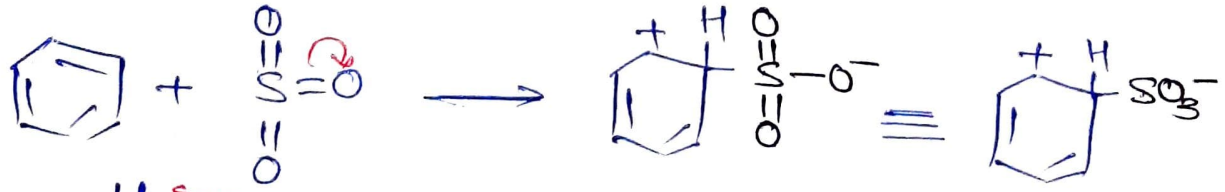


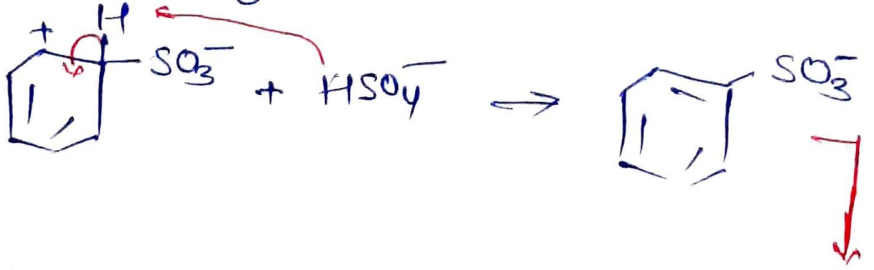
2. Sulphonation



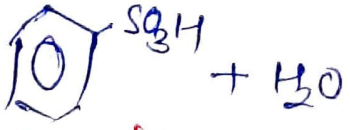
Benzene sulphonic acid

1. $2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$

2. 

3. 

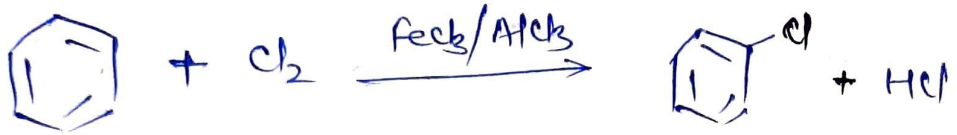
(4)



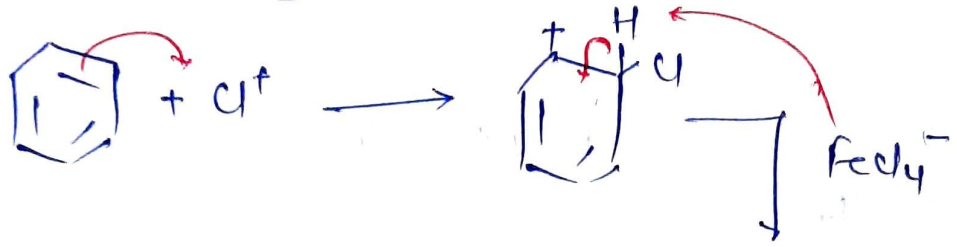
Benzene Sulfonic acid

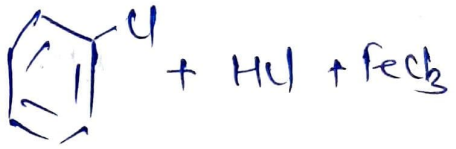
3. Halogination

order = F > Cl > Br > I

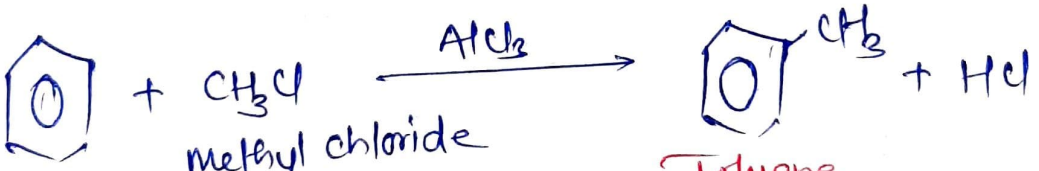


1. $Cl-Cl + FeCl_3 \longrightarrow Cl^+ + FeCl_4^-$

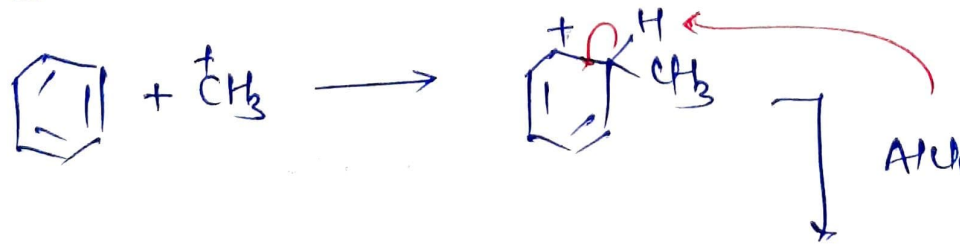
2. 

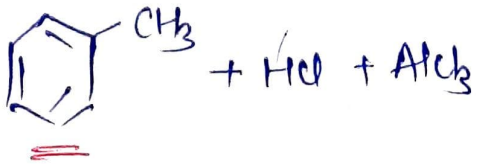
3. 

4. Friedal-Craft Alkylation : by Alkyl chloride / $AlCl_3$



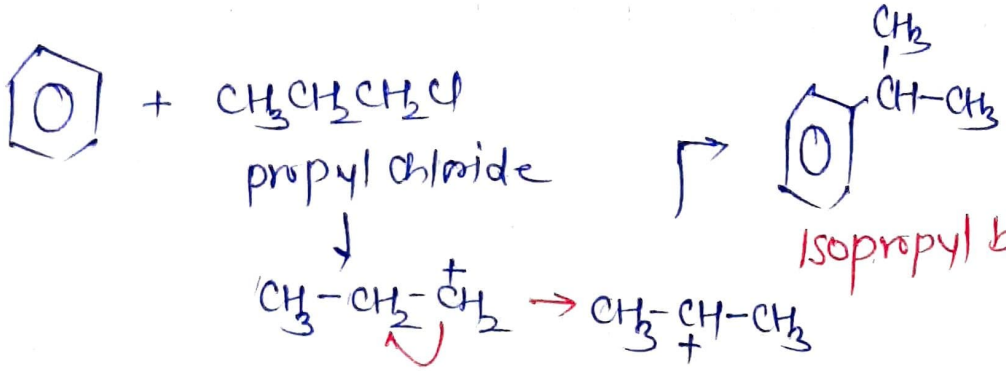
① $CH_3-Cl + AlCl_3 \longrightarrow \overset{+}{C}H_3 + AlCl_4^-$

② 



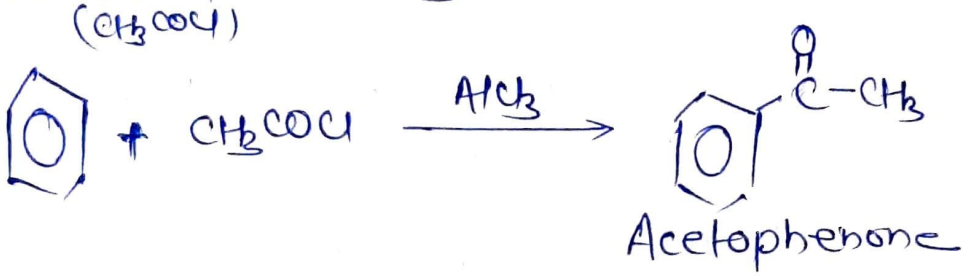
Limitation / Drawbacks –

1. difficult to stop the reaction when one alkyl group has entered the ring. – Di / Tri-alkyl benzene are also formed.
2. Alkyl group often tends to rearrange for stability. (3° / 2° are more stable)



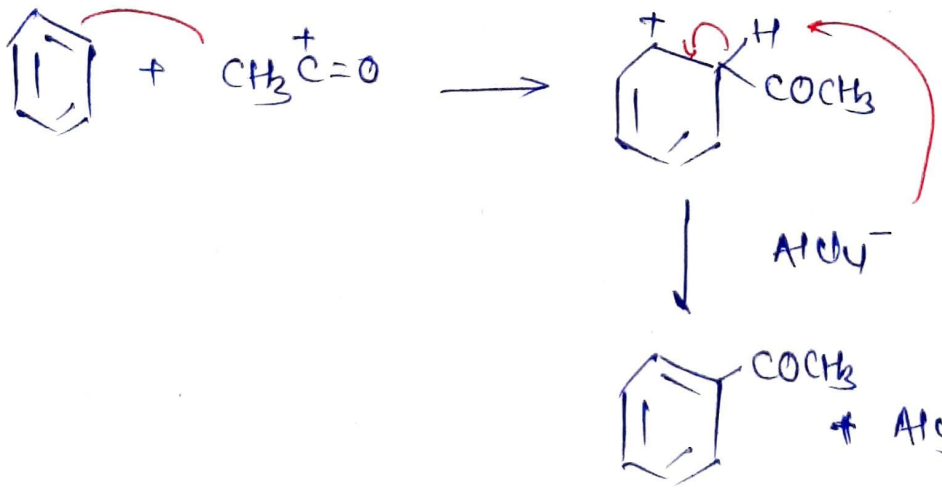
5. Friedal Crafts Acylation - anhydrous acetyl chloride

~~RO~~ RCOCl with $AlCl_3$.
(CH_3COCl)



① $CH_3COCl + AlCl_3 \longrightarrow CH_3-\overset{+}{C}O + AlCl_4^-$

②



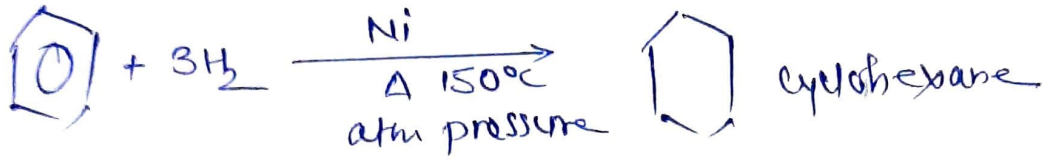
Acetophenone

* For preparation of propyl, butyl-benzene we can use
Friedal Crafts - acylation + Clemmensen Reduction

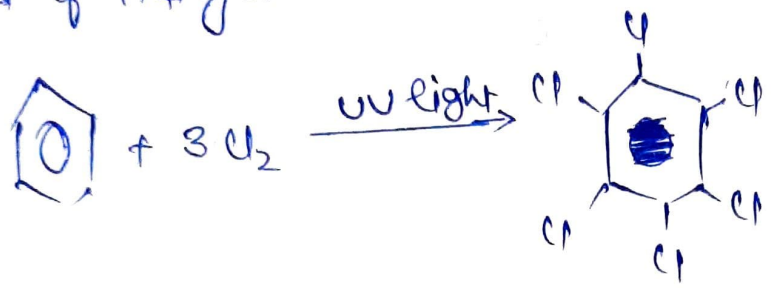
n-propyl benzene

2. ADDITION REACTION OF BENZENE

① Addⁿ of Hydrogen -



② Addⁿ of Halogen



$C_6H_6Cl_6$

benzene hexa chloride

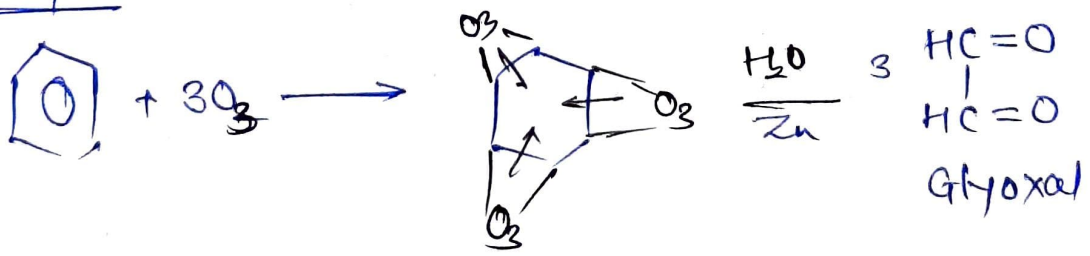
(BHC) 1,2,3,4,5,6 - hexachloro cyclohexane

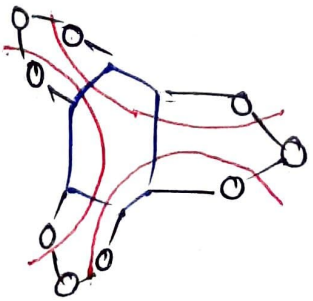
~~BHC~~ BHC — Insecticide

" Gammexane or Lindane"

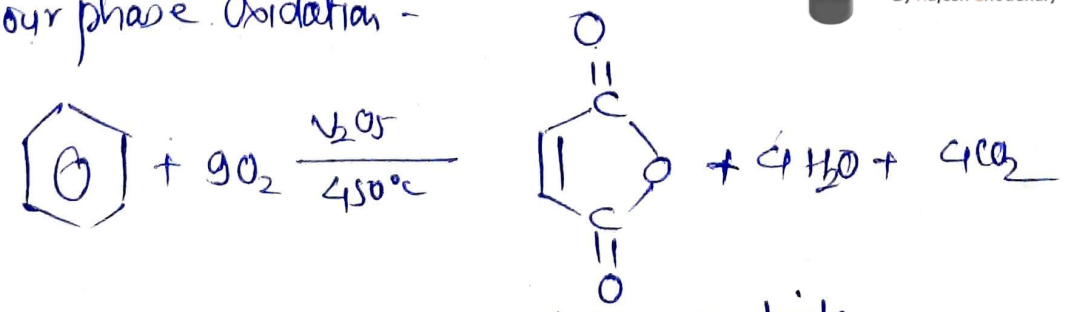
c. Oxidation Reaction of Benzene

① Ozonolysis





② Vapour phase Oxidation -



Maleic anhydride

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STRUCTURE & USES OF VARIOUS COMPOUNDS

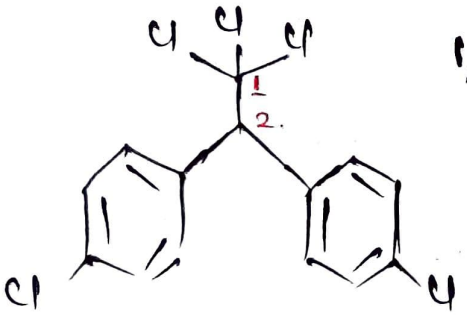
1. DDT

DDT :- Dichloro, Diphenyl, Trichloro

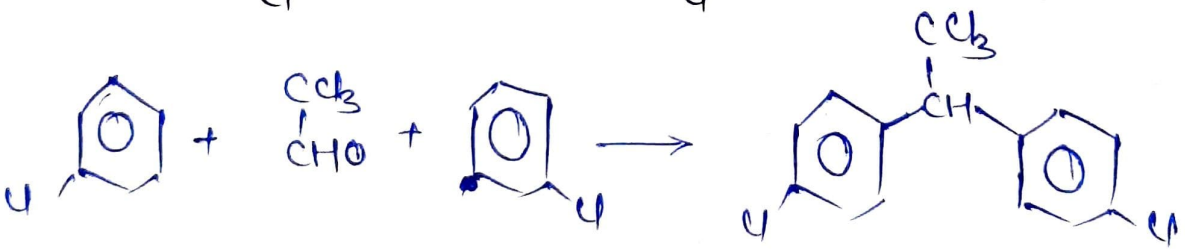
↳ It is an organo chlorine insecticide that kills by acting as a nerve poison

General formula - $C_{14}H_9Cl_5$, M Mass - 355 amu

Structure :-



1,1,1,-Trichloro-2,2-bis(4-chloro phenyl)-ethane



Physical Property :-

↳ colourless, tasteless & odourless crystalline comp.

↳ BP = 260°C & MP - 108.5°C

↳ ~~Iso~~ Insoluble in water & soluble in fats

↳ Density - 990 kg/m³

USES :-

↳ As insecticide

↳ Used with great effects to combat malaria, typhus, & other insect burn human disease

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