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PHARMACEUTICAL ORGANIC CHEMISTRY-2

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MODULE-1

UNIT I 10 Hours
Benzene and its derivatives

- A. Analytical, synthetic and other evidences in the derivation of structure of benzene, Orbital picture, resonance in benzene, aromatic characters, Huckel's rule
- B. Reactions of benzene - nitration, sulphonation, halogenation-reactivity, Friedelcrafts alkylation- reactivity, limitations, Friedelcrafts acylation.
- C. Substituents, effect of substituents on reactivity and orientation of mono substituted benzene compounds towards electrophilic substitution reaction
- D. Structure and uses of DDT, Saccharin, BHC and Chloramine

Derivation of structure of benzene

- https://www.slideshare.net/slideshow/unit-1structure-of-benzeneanalytical-synthetic-evidence/241190600
- Analytical evidence strongly suggests benzene has a cyclic, planar structure with all carbon-carbon bonds being equivalent, rather than alternating single and double bonds as initially proposed. This is supported by molecular weight determination, X-ray diffraction, IR and UV spectroscopy, and chemical reactions.

Derivation of structure of benzene

1. Molecular Formula and Weight:

- Benzene's molecular formula, C6H6, indicates a high degree of unsaturation. However, its molecular weight (78) and mass spectrometry data further define its structure.

2. X-ray Diffraction:

- X-ray diffraction studies of benzene crystals reveal all carbon-carbon bond lengths are identical (1.39 Å), which is intermediate between a single and double bond. This contradicts the idea of alternating single and double bonds as proposed by Kekulé.

3. Spectroscopic Evidence:

- **IR and UV Spectroscopy:** IR and UV spectra indicate that all six carbon-carbon bonds in benzene are equivalent and the molecule is planar.
- **NMR Spectroscopy:** NMR spectra show that all hydrogen atoms are equivalent.

Derivation of structure of benzene

4. Chemical Reactions:

- **Substitution Reactions:** Benzene readily undergoes electrophilic substitution reactions (like bromination) rather than addition reactions.
- **Hydrogenation:** Benzene reacts with hydrogen to form cyclohexane, but the enthalpy change is less than what would be expected for three double bonds, indicating a more stable structure.

5. Ozonolysis:

- Ozonolysis of benzene under strong conditions yields glyoxal (CHO-CHO), indicating the presence of three CH=CH units.

6. Planar Structure:

- The planar hexagonal structure is further supported by various physical and chemical properties.

7. Resonance:

- The evidence points towards benzene being a resonance hybrid of multiple contributing structures, rather than a single structure with alternating single and double bonds.

ORBITAL PICTURE OF BENZENE

Benzene's orbital picture involves sp^2 hybridization of each carbon atom, resulting in a planar hexagonal ring. Each carbon atom has a p orbital that is not involved in the sigma bonds and these p orbitals overlap to form two pi molecular orbitals, one above and one below the plane of the ring. This delocalization of pi electrons contributes to benzene's stability.

Video

https://www.google.com/search?q=analytical+evidence+in+the+derivation+of+structure+of+benzene&sca_esv=08bd8e8cec846723&sxsrf=AE3TifM2Ryu4zbD7VN08jor97AXsVBH74g%3A1755005658959&ei=2kKbaJ-rOs6q4-EP_ZWXyAc&oq=evidence+in+the+derivation+of+structure+of+benzene+&gs_lp=Egxnd3Mtd2l6LXNlcnAiM2V2aWRlbmNlIGluIHRoZSBkZXJpdmF0aW9uIG9mIHN0cnVjdHVyZSBvZiBiZW56ZW5lICoCCAIyChAjGIAEGCcYigUyBhAAGBYYHjIGEAAYFhgeMgYQABgWGB4yBhAAGBYYHjIGEAAYFhgeMgYQABgWGB4yBhAAGBYYHjIGEAAYFhgeMgYQABgWGB5ItjhQwQdYsApwAXgAkAEAmAGCAqAB2waqAQUwLjEuM7gBAcgBAPgBAZgCAqAC0wHCAgoQABiwAxjWBBhHmAMAiAYBkAYIkgcDMS4xoAe-IrIHAzAuMbgHuwHCBwUzLTEuMcgHHw&sclient=gws-wiz-serp#fpstate=ive&vld=cid:5ec10d73,vid:uMz2peE9J38,st:0

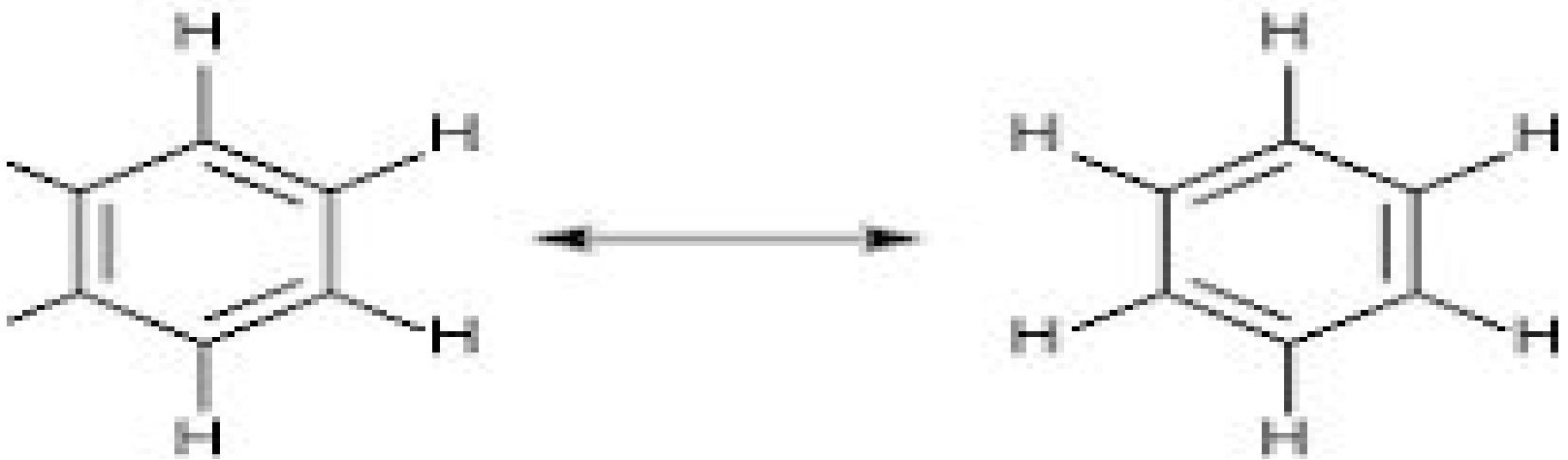
ORBITAL PICTURE OF BENZENE

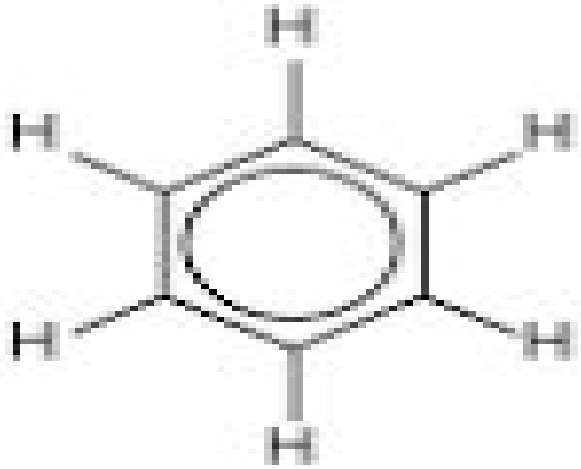
•**sp² Hybridization:**
Each carbon atom in benzene is sp^2 hybridized, meaning it forms three sigma bonds: two with neighboring carbon atoms and one with a hydrogen atom.
•**Unpaired p Orbitals:**
Each carbon atom also has a single, unhybridized p orbital that is perpendicular to the plane of the ring.
•**Pi Molecular Orbitals:**
These six p orbitals can overlap with each other in two ways: either above or below the plane of the ring. This overlap forms two pi molecular orbitals that encompass the entire benzene ring.
•**Delocalization:**
The six pi electrons are not localized in individual double bonds but are delocalized across the entire ring, forming a continuous pi electron cloud above and below the plane.
•**Stability:**
This delocalization of pi electrons is a major contributor to benzene's stability, making it less reactive than other molecules with similar

Resonance in benzene

- Benzene exhibits resonance, a phenomenon where electrons are delocalized over multiple atoms, rather than being confined to specific bonds.
- This delocalization leads to increased stability and unique properties for benzene, represented by a resonance hybrid with a circle inside the HEXAGON
- The resonance hybrid represents the actual molecule as the "average" of the contributing structures, with bond lengths and partial charges taking on intermediate values compared to those expected for the individual Lewis structures of the contributors, were they to exist as "real" chemical entities.

Resonance in benzene





Huckel’s rule of AROMATICITY

Hückel's rule of aromaticity states that a cyclic, planar molecule is aromatic if it contains 4n + 2 π electrons, where 'n' is any non-negative integer (0, 1, 2, 3, etc.). This rule helps determine if a molecule will exhibit the unique stability and properties associated with aromatic compounds

- **Cyclic and planar:** The molecule must be a closed ring and flat.
- **Fully conjugated:** All atoms in the ring must have a p-orbital, allowing for continuous overlap of these orbitals (creating a π electron cloud).
- **4n + 2 π electrons:** The molecule must have a specific number of π electrons (electrons in p-orbitals involved in double bonds or lone pairs) following the 4n + 2 rule.

Huckel's rule of AROMATICITY-Examples

- **Benzene (C6H6):**

Has 6 π electrons (3 double bonds), and with n=1 in the formula (4n+2), it satisfies the rule (4(1)+2 = 6).

- **Cyclopentadienyl anion:**

Has 6 π electrons (5 from the carbons and 1 from the negative charge) and is also aromatic.

- **Cyclooctatetraene (C8H8):**

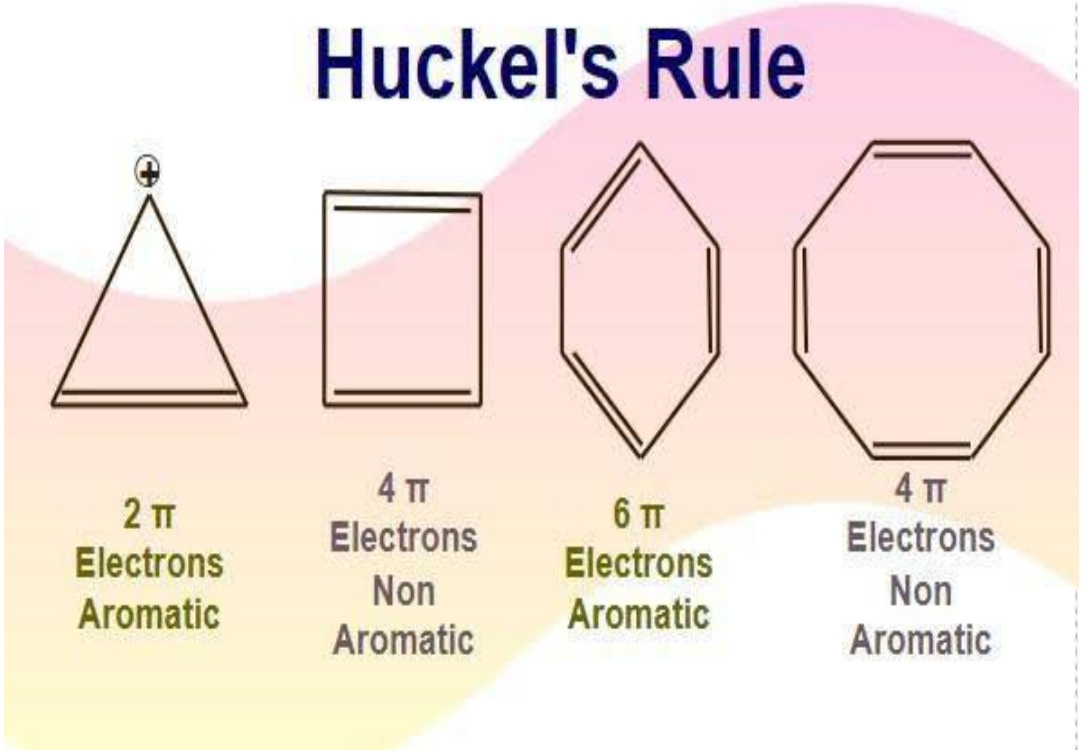
Has 8 π electrons, which does not fit the 4n+2 rule (no integer n will make 4n+2 equal to 8).

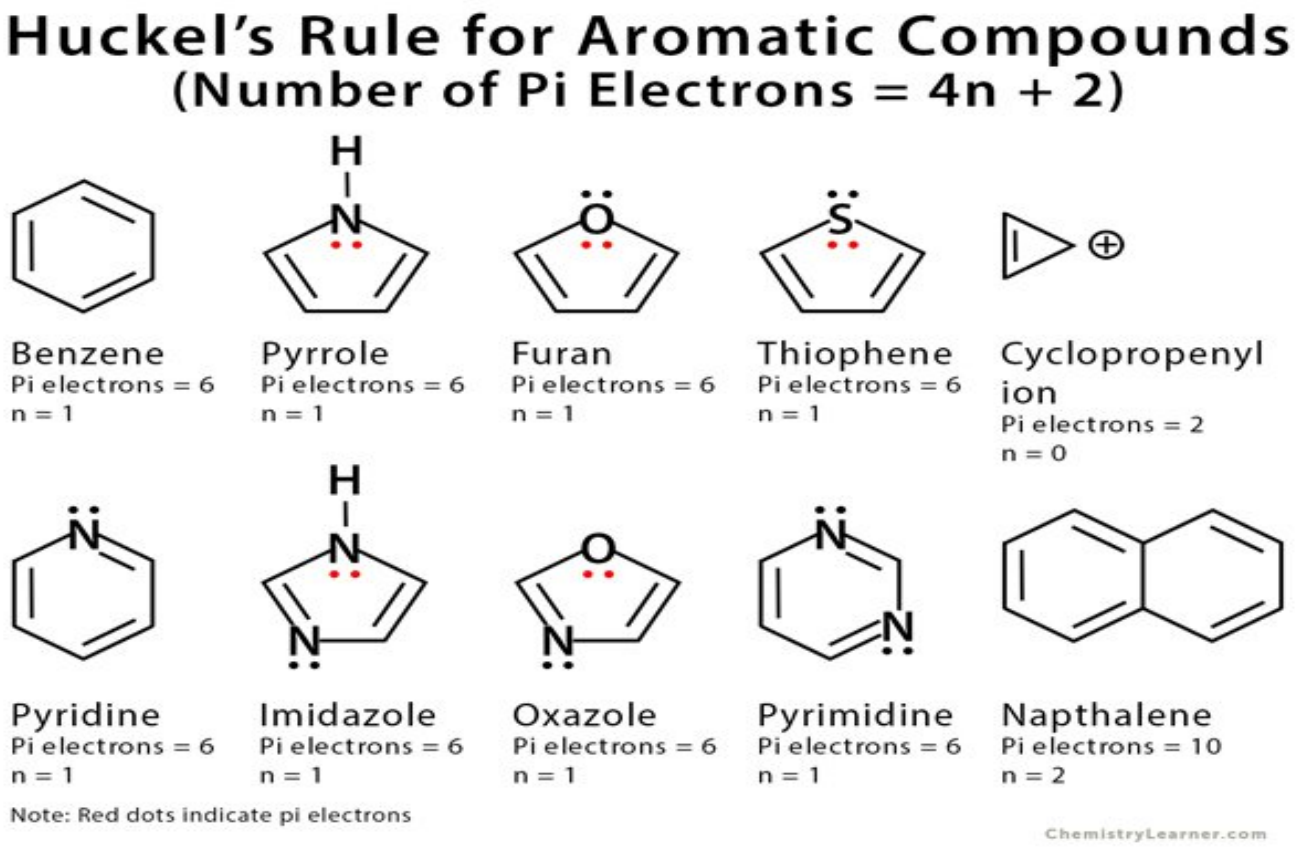
Video

https://www.youtube.com/watch?v=ab4WFo0Eq-k

Significance of Huckel's rule

- Hückel's rule is a powerful tool for predicting the aromaticity of molecules, which is a key factor in determining their stability and reactivity. Aromatic compounds are exceptionally stable and exhibit unique chemical behavior, such as resistance to addition reactions and preference for substitution





Reactions of benzene - Nitration

https://www.chemistrysteps.com/nitration-of-benzene/

- Nitration of benzene is a chemical reaction where a nitro group (-NO2) is introduced into the benzene ring, forming nitrobenzene.
- This reaction is an example of electrophilic aromatic substitution, requiring a mixture of concentrated nitric acid and concentrated sulfuric acid at a controlled temperature (typically not exceeding 50°C).
- The concentrated sulfuric acid acts as a catalyst, facilitating the formation of the nitronium ion (NO2+), which is the electrophile that attacks the benzene ring.

- SOURCE:

- https://www.google.com/search?q=nitration+of+benzene&oq=Nitration+of+benzene&gs_lcrp=EgZjaHJvbWUqBwgAEAAYgAQyBwgAEAAYgAQyBwgBEAAYgAQyBwgCEAAYgAQyBwgDEAAYgAQyBwgEEAAYgAQyBwgFEAAYgAQyBwgGEAAYgAQyBwgHEAAYgAQyBwgIEAAYgAQyBwgJEAAYgATSAQkxMDkwN2owajeoAgiwAgHxBWf0XqnBEkB-8QVn9F6pwRJAfg&sourceid=chrome&ie=UTF-8#vhid=dSC0NCoRsTFbNM&vssid=_XzelaOWCI-W4seMPz7rSqQY_31

Mechanism: **Electrophile Generation**:

Concentrated nitric acid reacts with concentrated sulfuric acid, with the sulfuric acid donating a proton to the nitric acid. This protonation leads to the formation of the nitronium ion (NO_2^+) and water.

Electrophilic Attack:

The positively charged nitronium ion acts as an electrophile and attacks the benzene ring, forming a carbocation intermediate (arenium ion) stabilized by resonance.

Deprotonation:

The arenium ion loses a proton (H^+) to a base (often a conjugate base from the acid), resulting in the formation of nitrobenzene and regenerating the catalyst (sulfuric acid).

- The reaction is carried out at temperatures not exceeding 50°C to prevent further nitration of the benzene ring (i.e., adding more nitro groups). Nitrobenzene is a yellow oily liquid and is a crucial intermediate in the synthesis of various other organic compounds, particularly in the production of dyes, pharmaceuticals, and explosives.**The sulfuric acid acts as a catalyst and is not consumed in the overall reaction**. The reaction is highly exothermic, and the temperature needs to be carefully controlled.

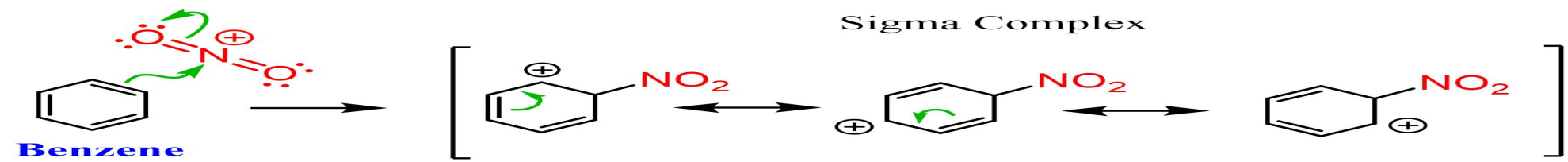
The Benzene Nitration Mechanism

Part 1. Formation of Nitronium Ion

The stronger sulfuric acid protonates the nitric acid to form $^{+}NO_2$ electrophile.

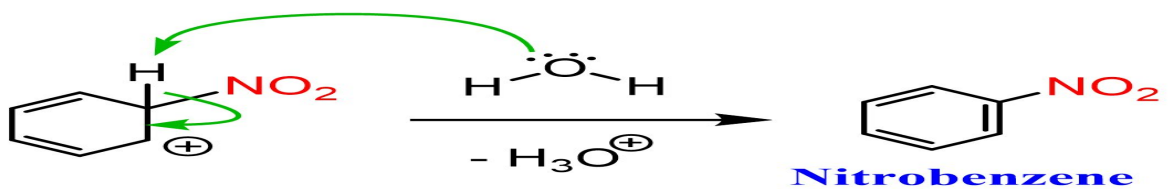
Nitronium ion

Part 2. Electrophilic Aromatic Substitution



Addition of the electrophile

Loss of a proton – restoring the aromaticity



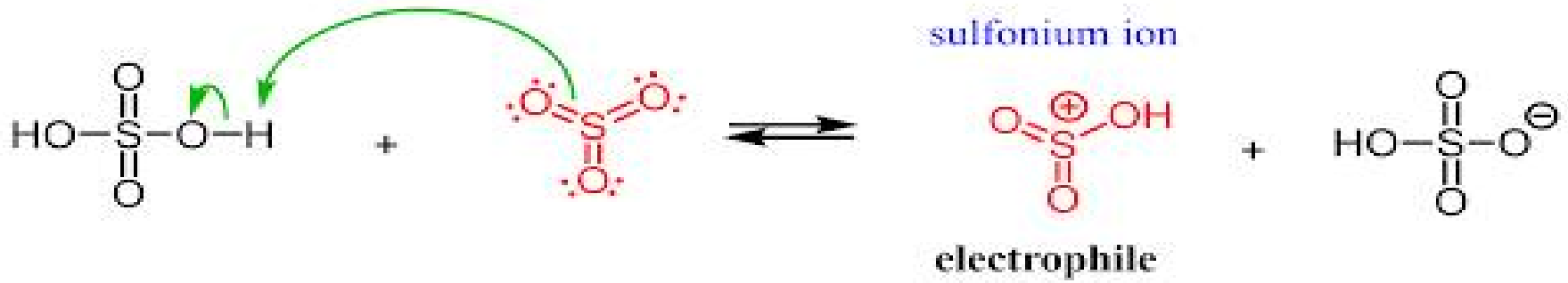
Nitrobenzene

ChemiStrysteps.com

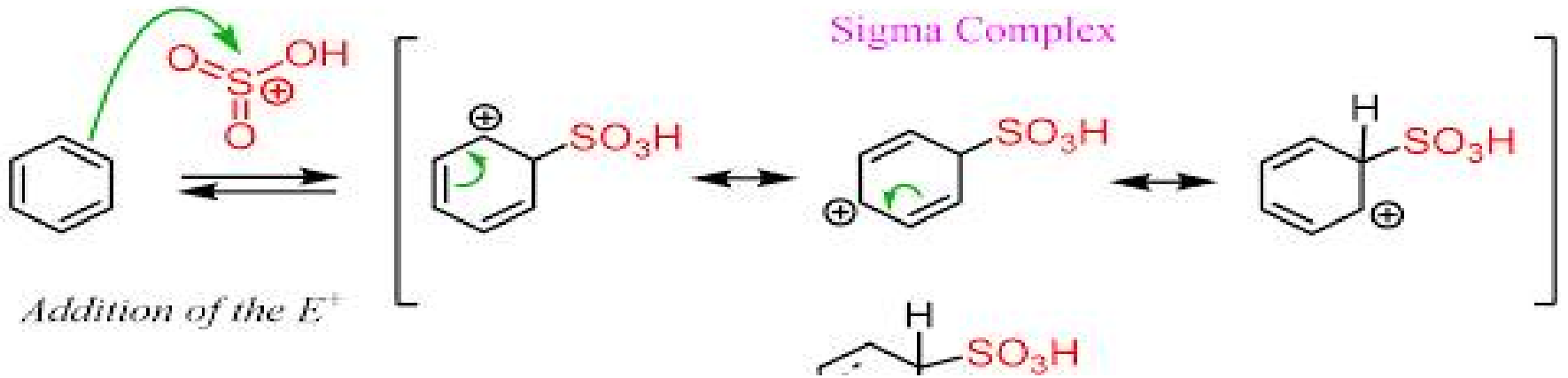
Reactions of benzene - sulphonation

https://www.chemistrysteps.com/sulfonation-of-benzene/

- Sulphonation of benzene is an electrophilic aromatic substitution reaction where a sulfonic acid group (SO3H) is attached to the benzene ring
- This is typically achieved by reacting benzene with fuming sulfuric acid (H2SO4 + SO3) or sulfur trioxide (SO3).
- The reaction is reversible, and the product is benzenesulfonic acid



Part 2. Electrophilic Aromatic Substitution



Electrophile Generation:

The key step is the generation of the electrophile, which is sulfur trioxide (SO_3). In fuming sulfuric acid, the sulfur trioxide acts as the electrophile.

Attack on Benzene:

The SO_3 attacks the benzene ring, forming a sigma complex (a carbocation intermediate).

Proton Abstraction:

A proton is removed from the carbon that was attacked by the SO_3, and the electrons from that bond re-establish the aromaticity of the ring.

Product Formation: This results in the formation of benzenesulfonic acid.

Reversible Reaction:

The sulphonation of benzene is a reversible reaction. Benzenesulfonic acid can be converted back to benzene under specific conditions (e.g., heating with dilute sulfuric acid).

Fuming Sulfuric Acid:

Fuming sulfuric acid (also known as oleum) is a solution of SO_3 in concentrated sulfuric acid, and it's the common reagent for sulfonation.

Sulfur Trioxide:

SO_3 itself can also be used as the electrophile in this reaction.

Halogenation

https://www.google.com/search?q=halogenation+of+benzene+mechanism&sca_esv=f4a507d3545d66d8&sxsrf=AE3TifMKnhecfM41j4fc9kg9IHmDi3zrgw%3A1755660149768&ei=dT-laOHdLuOMnesPn-um4AI&oq=Halogenation++of+benzene&gs_lp=Egxnd3Mtd2l6LXNlcnAiGEhhbG9nZW5hdGlvbiAgb2YgYmVuemVuZSoCCAEyCxAAGIAEGJECGIoFMgsQABiABBiRAhiKBTIGEAAYBxgeMgUQABiABDIFEAAYgAQyBRAAGIAEMgUQABiABDIFEAAYgAQyBhAAGAcYHjIFEAAYgARIqX1QhQtYn2ZwAXgBkAEAmAHjAqABsCuqAQgwLjguMTQuM7gBAcgBAPgBAZgCD6AChjCAgoQABiwAxjWBBhHwgINEAAYgAQYsAMYQxiKBcICBxAAGIAEGA2YAwCIBgGQBgqSBwcxLjUuNy4yoAfV3AGyBwcwLjUuNy4yuAfrGMIHBTItOS42yAd1&sclient=gws-wiz-serp

- The halogenation of benzene, a type of electrophilic aromatic substitution

Involves three key steps:

- generation of a halogen electrophile
- electrophilic attack on the benzene ring
- subsequent restoration of aromaticity.
- This process typically requires a Lewis acid catalyst, such as AlCl3 or FeCl3, to activate the halogen.

1. Electrophile Formation:

A Lewis acid catalyst (like AlCl3) reacts with the halogen molecule (e.g., Cl2 or Br2) to form a highly electrophilic halogen ion (e.g., Cl+ or Br+).This electrophile is crucial for initiating the reaction with the benzene ring.

2. **Electrophilic Attack:**

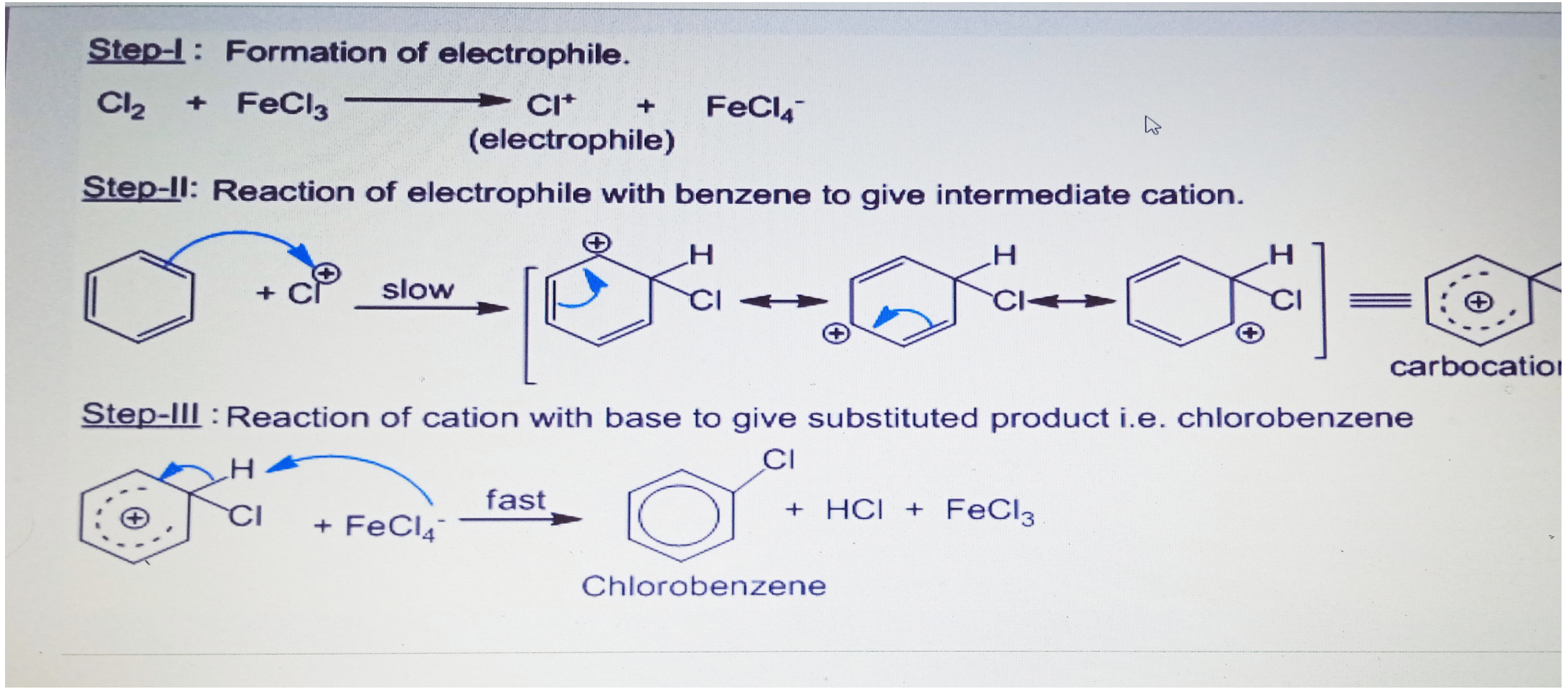
The benzene ring, with its pi electron cloud, acts as a nucleophile and attacks the electrophilic halogen ion.This attack results in the formation of a carbocation intermediate (also known as a sigma complex), where one carbon atom is sp3 hybridized and bonded to the halogen.The carbocation is resonance-stabilized but temporarily disrupts the aromaticity of the benzene ring.

3. Restoration of Aromaticity:

A base (often the counter-ion from the Lewis acid catalyst, e.g., AlCl4-) abstracts a proton from the carbon bonded to the halogen. This deprotonation regenerates the aromatic ring and releases the protonated catalyst (e.g., HCl). The final product is a halobenzene, and the catalyst is regenerated, making it a catalyst. In essence, the halogenation of benzene involves a substitution of a hydrogen atom on the benzene ring with a halogen atom, facilitated by an electrophilic attack and subsequent

Halogenation

https://chemicalnote.com/electrophilic-substitution-reactions-of-benzene-with-mechanism



Reactions of benzene - Friedelcrafts alkylation- reactivity, limitations

Reactions of benzene reactivity, limitations of Friedelcrafts acylation.