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PHARMACEUTICAL ORGANIC CHEMISTRY - II

UNIT 1

TOPIC :

- Substituents, effect of substituents on reactivity and orientation of mono substituted benzene compounds towards electrophilic substitution reaction

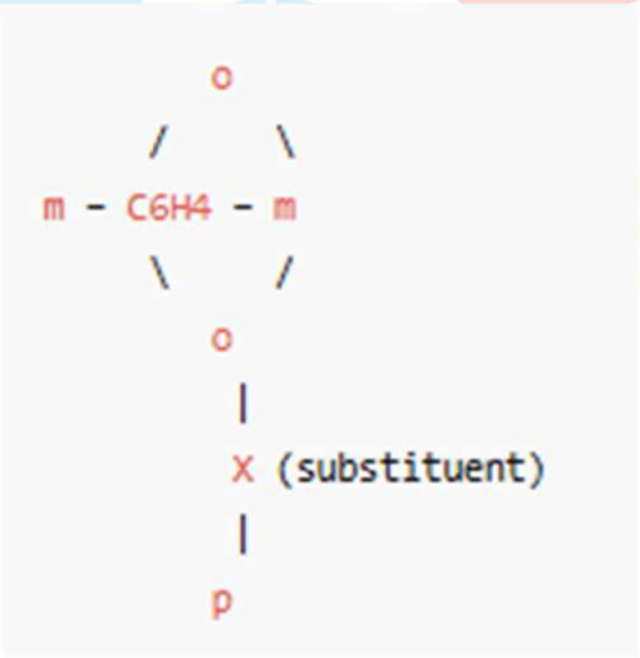
EFFECT OF SUBSTITUENTS ON BENZENE RING

- Benzene contains 6 hydrogen atoms, and all are identical.
- When 1 hydrogen is replaced by a group (called a substituent), it becomes mono-substituted benzene.

Once a group (say X) is attached to the benzene ring, the remaining 5 positions are no longer equal.
The positions are classified as:

1. Ortho (o-) → Adjacent to X
2. Meta (m-) → One carbon away from X
3. Para (p-) → Opposite to X

Structure Example:



The nature of the substituent (X) determines:

- Reactivity: How fast benzene reacts with electrophiles.
- Orientation: Where the incoming group (electrophile) attaches on the ring.

Types of Substituents

1. Ring Activating Groups (RAGs)
2. Ring Deactivating Groups (RDGs)

Ring Activating Groups

→ Groups that increase the reactivity of benzene towards Electrophilic Substitution Reactions are called Ring Activating Groups.
→ These groups increase the electron density on the benzene ring by donating electrons either through +I (inductive effect) or +M (mesomeric effect).
→ Due to their electron-donating nature, they are also known as Ortho-Para Directing Groups.

Types of Activating Groups

Activating groups are classified into three categories based on the strength of their electron-donating ability:

1. Strongly Activating Groups:

- Strongly increase electron density.
- Donate electrons via lone pair conjugation (+M effect).
- **Examples:** $-NH_2$ (amino), –NHR, $-NR_2$ (dialkylamino), –OH (hydroxy)

2. Moderately Activating Groups:

- Moderate electron donors through resonance and induction.
- **Examples:** –NHCOR (amide), –OCOR (ester), –OR (alkoxy)

3. Weakly Activating Groups:

- Slightly increase electron density via inductive effect (+I).

- **Examples:** $-CH_3$ (methyl), $-C_2H_5$ (ethyl), other alkyl groups

Effect on Reactivity

→ These groups increase the electron density on the benzene ring, especially at the ortho and para positions, making the ring more reactive toward electrophilic attack.

Effect on Orientation

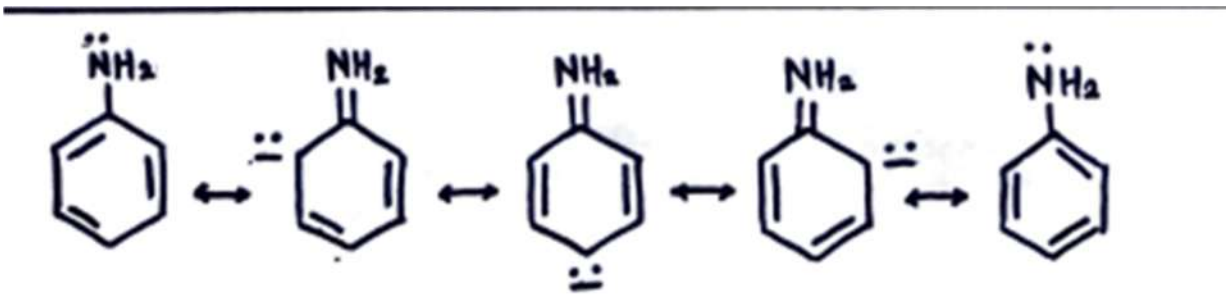
Ring Activating Groups direct incoming electrophiles to the ortho and para positions of the ring during substitution reactions.

This happens because:

- The ortho and para positions have higher electron density due to resonance.
- This makes them favorable sites for electrophilic attack.

Mechanism of Ortho & Para Directing (Example: $-NH_2$ group)

The $-NH_2$ group donates a lone pair into the ring via resonance, resulting in structures like:



Ring Deactivating Groups

- Groups that decrease the reactivity of benzene toward Electrophilic Substitution Reactions are called Ring Deactivating Groups.
- These groups withdraw electron density from the benzene ring through –I (inductive effect) or –M (mesomeric effect).
- Due to their electron-withdrawing nature, they are known as Meta Directing Groups.

Types of Deactivating Groups

Deactivating groups are classified into three categories based on their electron-withdrawing strength:

1. Strongly Deactivating Groups:

- Powerful electron-withdrawing groups
- Decrease electron density sharply
- **Examples:**
  –NO_2 (nitro), –C≡N (cyano), –SO_3H (sulfonic acid)

2. Moderately Deactivating Groups:

- Moderate electron withdrawal, mostly by resonance and induction
- **Examples:**
  –COOH (carboxylic acid), –$COCH_3$ (acetyl), –CHO (aldehyde), –COOR (ester), –$CONH_2$ (amide)

3. Weakly Deactivating Groups:

- Slightly withdraw electrons via inductive effect
- **Examples:**
  Halogens (–F, –Cl, –Br, –I)

Effect on Reactivity:

- ❖ These groups decrease electron density on the benzene ring, especially at ortho and para positions, making the ring less reactive towards electrophilic substitution.

Effect on Orientation:

Deactivating groups direct incoming electrophiles to the meta position during substitution.

Reason:

- Ortho and para positions are electron-deficient due to –M/–I effects.
- Meta position has relatively higher electron density compared to ortho/para.

Mechanism of Meta Directing (Example: $-NO_2$ group)

The $-NO_2$ group withdraws electrons through resonance, delocalizing the positive charge to ortho and para positions:

Resonance structures of nitrobenzene: