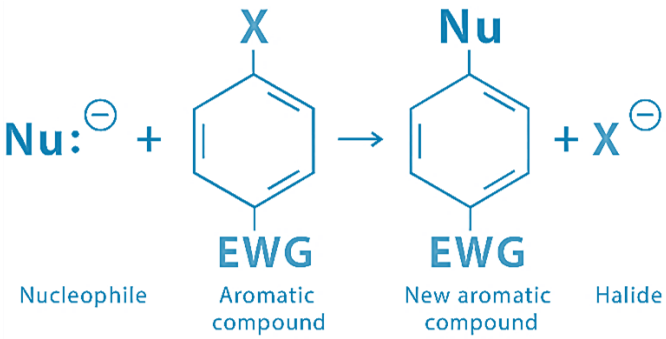
Nucleophilic Aromatic Substitution

Nucleophilic Aromatic Substitution (NAS)

Definition:

- Nucleophilic Aromatic Substitution (NAS) refers to a class of organic reactions in which a nucleophile replaces a leaving group (usually a halide) on an aromatic ring.
- This is unlike electrophilic aromatic substitution (EAS), where an electrophile attacks the aromatic ring.
- In NAS, the ring acts as an electrophilic site, especially when electron-withdrawing groups (EWGs) activate the ring toward nucleophilic attack.



Why Is It Challenging on Aromatic Rings?

- Unlike aliphatic compounds, aromatic rings are electron-rich and relatively stable due to delocalized π electrons.
- Thus, they do not easily undergo attack by nucleophiles unless:
  - The ring is activated by strong electron-withdrawing groups.
  - A good leaving group is present, usually at the ortho or para position to the EWG.

Typical Structure Required:

- **Aromatic halide** (Ar–X) with X = Cl, Br, or F.
- **Electron-withdrawing groups** (like $–NO_2$, –CN, –COOR) at ortho and/or para positions.

Example:

Reactants:

- 1-chloro-4-nitrobenzene: $Cl–C_6H_4–NO_2$
- Sodium methoxide: CH_3ONa

Products:

- 1-methoxy-4-nitrobenzene: $CH_3O–C_6H_4–NO_2$
- Sodium chloride: NaCl

Balanced Reaction:

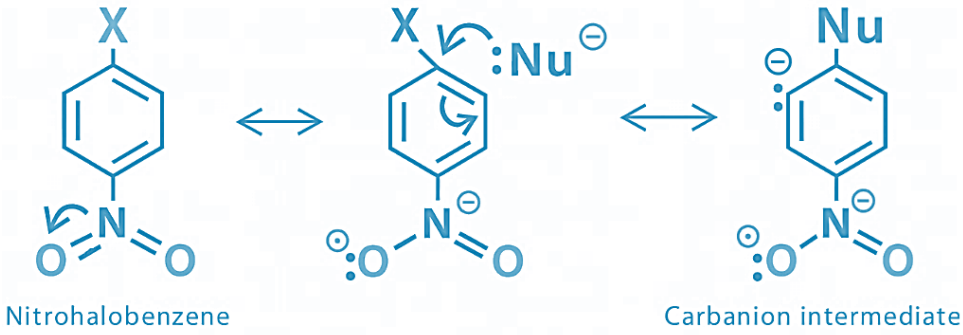
$Cl–C_6H_4–NO_2 + CH_3ONa \rightarrow CH_3O–C_6H_4–NO_2 + NaCl$

Types of NAS Mechanisms:

A. Reactants and Symbols

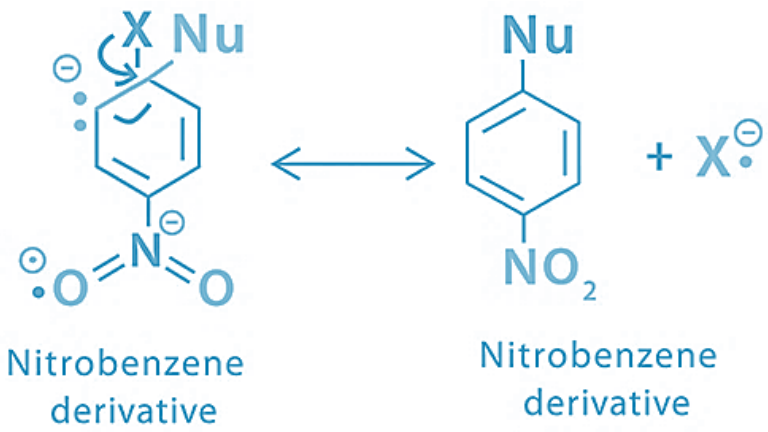
- X = Halogen (usually Cl, Br, or F)
- Nu^- = Nucleophile (e.g., CH_3O^-, OH^-)
- NO_2 = Electron-withdrawing nitro group, activating the ring

B. Step 1: Addition (Formation of the Meisenheimer Complex)



- The nucleophile (Nu^-) attacks the carbon bearing the halogen (X) on the aromatic ring.
- This attack occurs ortho or para to the electron-withdrawing nitro group (NO_2).
- The result is a non-aromatic, negatively charged intermediate known as the Meisenheimer complex.
- This intermediate is stabilized by resonance, especially due to the electron-withdrawing nature of the nitro group.
- **Key Characteristics:**
  - Aromaticity is lost temporarily.
  - The negative charge is delocalized across the ring and the NO_2 group.

C. Step 2: Elimination (Restoration of Aromaticity)



- The halide ion (X^-) is expelled from the intermediate.
- Aromaticity of the ring is restored.

- The final product is a substituted nitrobenzene, where the nucleophile has replaced the halogen.
- Products:
  - Nitrobenzene derivative ($Nu–C_6H_4–NO_2$)
  - Halide ion (X^-)

D. Overall Transformation

$$Ar–X \text{ (with } –NO_2 \text{ group)} + Nu^- \rightarrow Ar–Nu \text{ (with } –NO_2 \text{ group)} + X^-$$

- This reaction only proceeds efficiently if:
  - The halogen is ortho or para to an electron-withdrawing group like NO_2.
  - The nucleophile is sufficiently reactive (e.g., CH_3O^-, OH^-, NH_2^-).

Bimolecular Displacement Mechanisms in NAS

Key Features of Biomolecular displacement Mechanism

1. Substrate Requirement:

- The substrate is typically an aryl halide (Ar–X), such as chlorobenzene, where X = Cl, Br, or F.



- The aromatic ring must carry at least one strong electron-withdrawing group (e.g., $–NO_2$) positioned ortho or para to the leaving group.

2. Nucleophile:

- A strong nucleophile is required (e.g., CH_3O^-, OH^-, NH_2^-), capable of attacking the electron-deficient carbon.

3. Reaction Conditions:

- Often carried out under basic conditions or in polar aprotic solvents to stabilize intermediates.

Mechanism Overview:

- The most common mechanism of nucleophilic aromatic substitution is the addition-elimination mechanism, often called the SNAr (Substitution Nucleophilic Aromatic) mechanism.
- It involves two key steps:

- Addition of the nucleophile to the aromatic ring, forming a negatively charged intermediate.
- Elimination of the leaving group, restoring aromaticity.

- This is different from aliphatic SN2 or SN1 mechanisms.
- Here, the reaction is not concerted and involves a resonance-stabilized intermediate.

Step-by-Step Mechanism:

Step 1: Nucleophilic Attack (Addition)

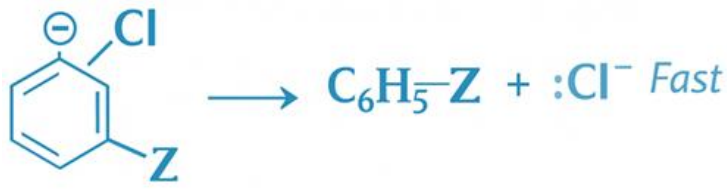
- The hydroxide ion attacks the carbon atom that holds the chlorine atom.
- This breaks the aromaticity of the benzene ring.
- A Meisenheimer complex (a non-aromatic intermediate) is formed where the negative charge is delocalized onto the ring and particularly stabilized by the nitro group at the para position.



- Intermediate Structure:
  - The negative charge is delocalized over the ring.
  - The presence of the nitro group helps stabilize this negative charge by resonance.

Step 2: Elimination of Leaving Group

- The chloride ion (Cl^-) is expelled.



- Aromaticity is restored to the ring.
- Final Product:
  - The aromatic compound now has an –OH group in place of the –Cl.

Energetics of SNAr:

- The rate-determining step is the formation of the Meisenheimer complex (i.e., the nucleophilic attack).
- Elimination is usually fast because it restores aromaticity.
- Electron-withdrawing groups accelerate the reaction by stabilizing the intermediate.

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