

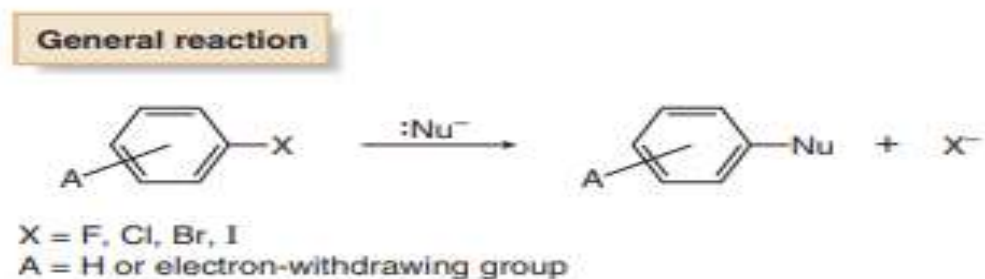
# NUCLEOPHILIC AROMATIC SUBSTITUTION



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Nucleophilic aromatic substitution results in the substitution of a halogen X on a benzene ring by a nucleophile ( $:\text{Nu}^-$ ).

Aryl halides undergo a limited number of substitution reactions with strong nucleophiles.

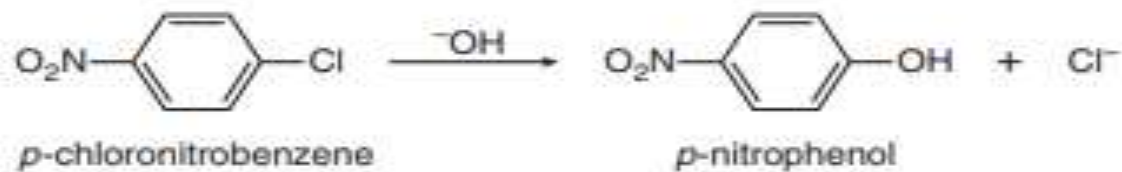


NAS occurs by two mechanisms

- i) Bimolecular displacement (Addition –Elimination)
- ii) Benzyne Formation( Elimination –Addition)

# Bimolecular displacement (Addition – Elimination)

- Aryl halides with strong electron-withdrawing groups (such as NO<sub>2</sub>) on the ortho or para positions react with nucleophiles to afford substitution products.
- For example, treatment of *p*-chloronitrobenzene with hydroxide (–OH) affords *p*-nitrophenol by replacement of Cl by OH.
- Nucleophilic aromatic substitution occurs with a variety of strong nucleophiles, including –OH, –OR, –NH<sub>2</sub>, –SR, and in some cases, neutral nucleophiles such as NH<sub>3</sub> and RNH<sub>2</sub>

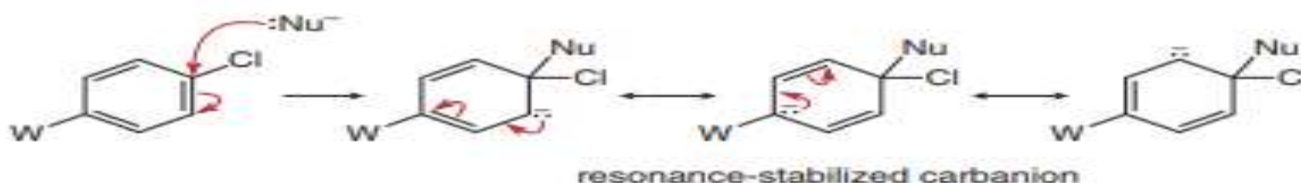


# Mechanism.....

The mechanism of these reactions has two steps:

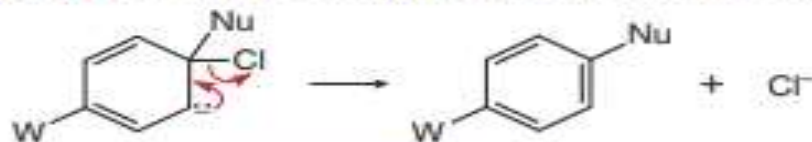
- Step i) Addition of the nucleophile ( $:\text{Nu}^-$ ) forms a resonance-stabilized carbanion with a new C – Nu bond—three resonance structures can be drawn. • Step [1] is rate-determining since the aromaticity of the benzene ring is lost.

**Step [1]** Addition of the nucleophile ( $:\text{Nu}^-$ ) to form a carbanion



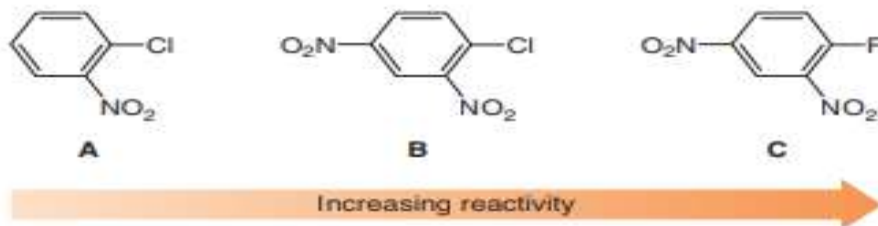
- In Step ii) loss of the leaving group re-forms the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.

**Step [2]** Loss of the leaving group to re-form the aromatic ring



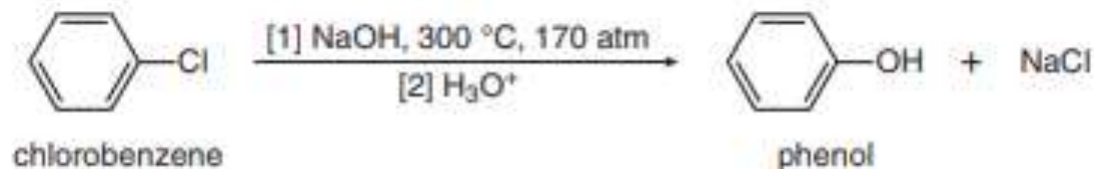
# Factors affecting Bimolecular displacement

- Increasing the number of electron-withdrawing groups increases the reactivity of the aryl halide. Electron-withdrawing groups stabilize the intermediate carbanion, and by the Hammond postulate, lower the energy of the transition state that forms it.
- Increasing the electronegativity of the halogen increases the reactivity of the aryl halide. A more electronegative halogen stabilizes the intermediate carbanion by an inductive effect, making aryl fluorides (ArF) much more reactive than other aryl halides, which contain less electronegative halogens.
- Thus, aryl chloride B is more reactive than o-chloronitrobenzene (A) because it contains two electron-withdrawing NO<sub>2</sub> groups. Aryl fluoride C is more reactive than B because C contains the more electronegative halogen, fluorine.
- Note, too, that the location of the electron-withdrawing group greatly affects the rate of nucleophilic aromatic substitution. When a nitro group is located ortho or para to the halogen, the negative charge of the intermediate carbanion can be delocalized onto the NO<sub>2</sub> group, thus stabilizing it. With a meta NO<sub>2</sub> group, no such additional delocalization onto the NO<sub>2</sub> group occurs.



## Benzyne formation ( Elimination-Addition)

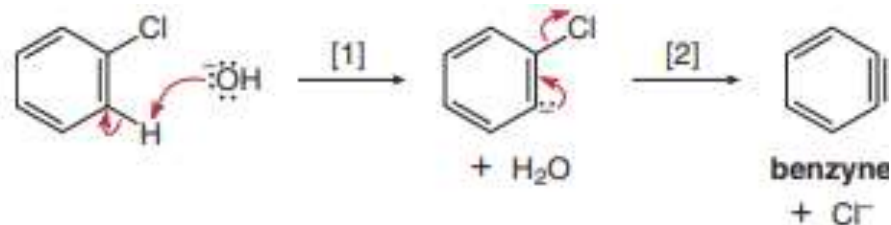
- Aryl halides that do not contain an electron-withdrawing group generally do not react with nucleophiles. Under extreme reaction conditions, however, nucleophilic aromatic substitution can occur with aryl halides.
- For example, heating chlorobenzene with NaOH above 300 °C and 170 atmospheres of pressure affords phenol.
- The mechanism proposed to explain this result involves formation of a benzyne intermediate (C<sub>6</sub>H<sub>4</sub>) by elimination–addition. As shown in Mechanism A.2, benzyne is a highly reactive, unstable intermediate formed by elimination of HX from an aryl halide.



# Mechanism.....

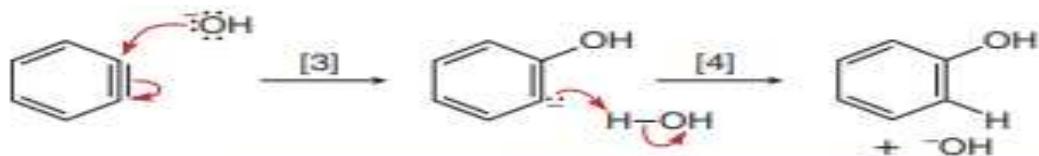
- Part [1] Elimination of HX to form benzyne

Elimination of H and X from two adjacent carbons forms a reactive benzyne intermediate.



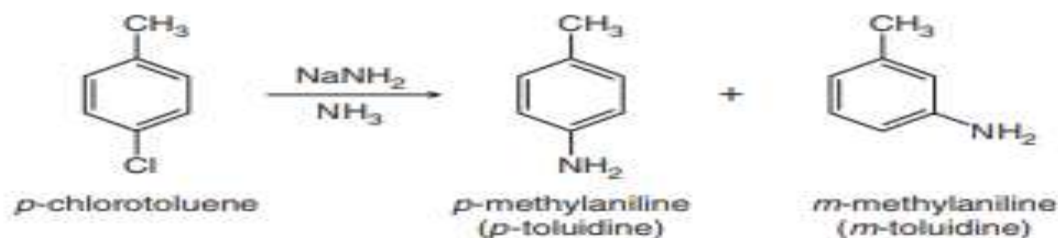
- Part [2] Nucleophilic addition to form the substitution product

Addition of the nucleophile ( $\text{-OH}$  in this case) and protonation form the substitution product (Steps [3] and [4]).



## Note:-

- Formation of a benzyne intermediate explains why substituted aryl halides form mixtures of products. Nucleophilic aromatic substitution by an elimination–addition mechanism affords substitution on the carbon directly bonded to the leaving group and the carbon adjacent to it. As an example, treatment of *p*-chlorotoluene with  $\text{NaNH}_2$  forms para- and meta-substitution products.





Thank  
you!