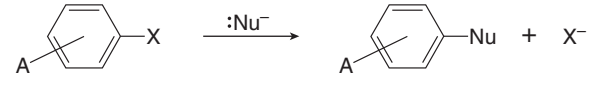
Supplementary Topic A

Nucleophilic Aromatic Substitution

Although most reactions of aromatic compounds occur by way of electrophilic aromatic substitution, aryl halides undergo a limited number of substitution reactions with strong nucleophiles.

General reaction



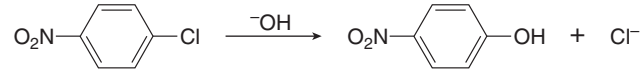
X = F, Cl, Br, I
A = H or electron-withdrawing group

- **Nucleophilic aromatic substitution results in the substitution of a halogen X on a benzene ring by a nucleophile (:Nu⁻).**

As we learned in Section 7.18, these reactions *cannot* occur by an S_N1 or S_N2 mechanism, which take place only at sp^3 hybridized carbons. Instead, two different mechanisms are proposed to explain the results: **addition–elimination** (Section A.1) and **elimination–addition** (Section A.2).

A.1 Nucleophilic Aromatic Substitution by Addition–Elimination

Aryl halides with strong electron-withdrawing groups (such as NO_2) 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.

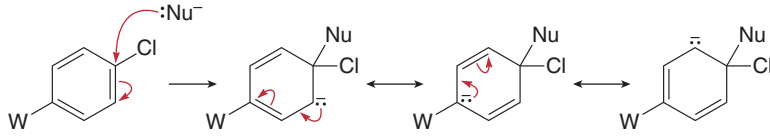


p-chloronitrobenzene *p*-nitrophenol

Nucleophilic aromatic substitution occurs with a variety of strong nucleophiles, including ^-OH, ^-OR, $^-NH_2$, ^-SR, and in some cases, neutral nucleophiles such as NH_3 and RNH_2. The mechanism of these reactions has two steps: **addition of the nucleophile** to form a resonance-stabilized carbanion, followed by **elimination of the halogen leaving group.** Mechanism A.1 is drawn with an aryl chloride containing a general electron-withdrawing group W.

Mechanism A.1 Nucleophilic Aromatic Substitution by Addition–Elimination

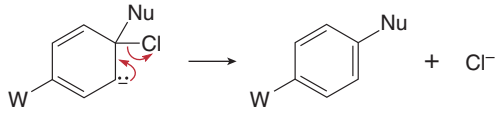
Step [1] Addition of the nucleophile (:Nu⁻) to form a carbanion



resonance-stabilized carbanion

- Addition of the nucleophile (: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 [2] Loss of the leaving group to re-form the aromatic ring



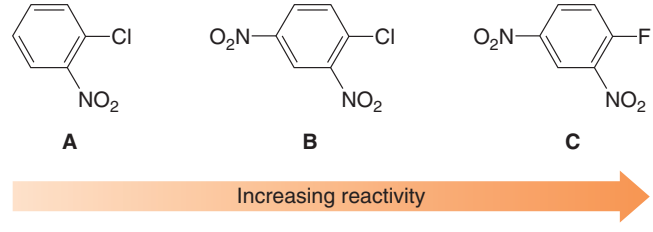
- In Step [2], loss of the leaving group re-forms the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.

In nucleophilic aromatic substitution, the following trends in reactivity are observed.

- **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.**

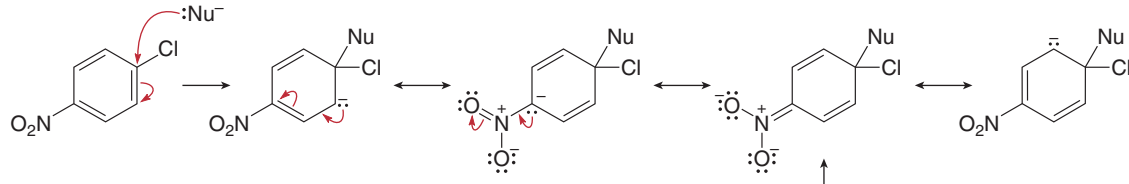
- **Increasing the electronegativity of the halogen increases the reactivity of the aryl halide. A more electronegative halogen stabilizes the intermediate carbanion by an inductive effect, making aryl fluorides (ArF) much *more* reactive than other aryl halides, which contain less electronegative halogens.**

Thus, aryl chloride **B** is more reactive than *o*-chloronitrobenzene (**A**) because it contains two electron-withdrawing NO_2 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_2 group, thus stabilizing it. With a meta NO_2 group, no such additional delocalization onto the NO_2 group occurs.

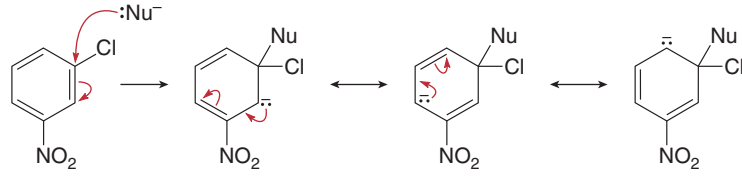
Para NO_2 group



additional resonance stabilization

The negative charge is delocalized on the O atom of the NO_2 group.

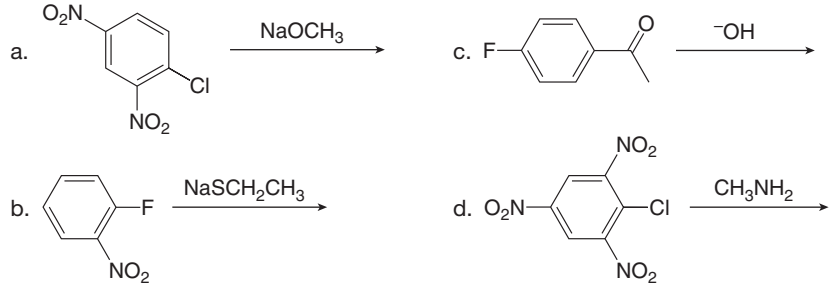
Meta NO_2 group



The negative charge is never delocalized on the NO_2 group.

Thus, nucleophilic aromatic substitution by an addition–elimination mechanism occurs only with aryl halides that contain electron-withdrawing substituents at the ortho or para position.

Problem A.1 Draw the products of each reaction.

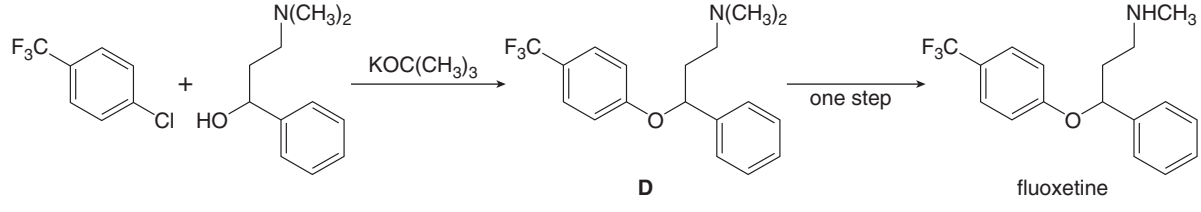


Problem A.2 Rank the aryl halides in each group in order of increasing reactivity in nucleophilic aromatic substitution by an addition–elimination mechanism.

a. chlorobenzene, *p*-fluoronitrobenzene, *m*-fluoronitrobenzene
b. 1-fluoro-2,4-dinitrobenzene, 1-fluoro-3,5-dinitrobenzene, 1-fluoro-3,4-dinitrobenzene
c. 1-fluoro-2,4-dinitrobenzene, 4-chloro-3-nitrotoluene, 4-fluoro-3-nitrotoluene

Problem A.3 Explain why a methoxy group (CH_3O) increases the rate of electrophilic aromatic substitution, but decreases the rate of nucleophilic aromatic substitution.

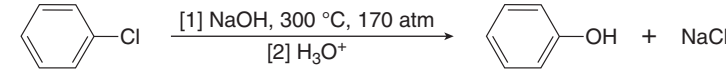
Problem A.4 Draw a stepwise mechanism for the following reaction that forms ether **D. D** can be converted to the antidepressant fluoxetine (trade name Prozac) in a single step.



D fluoxetine

A.2 Nucleophilic Aromatic Substitution by Elimination–Addition: Benzyne

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.

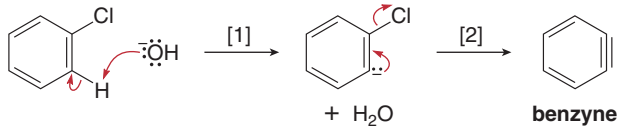


chlorobenzene phenol

The mechanism proposed to explain this result involves formation of a **benzyne** intermediate (C_6H_4) 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.

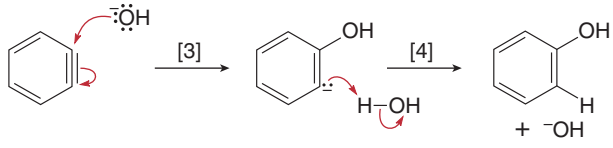
Mechanism A.2 Nucleophilic Aromatic Substitution by Elimination–Addition: Benzyne

Part [1] Elimination of HX to form benzyne



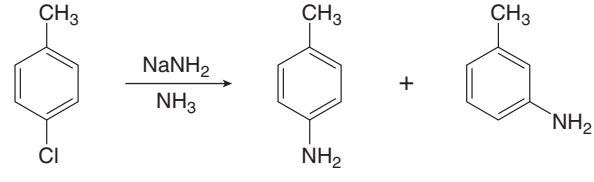
- Elimination of H and X from two adjacent carbons forms a reactive benzyne intermediate (Steps [1] and [2]).

Part [2] Nucleophilic addition to form the substitution product



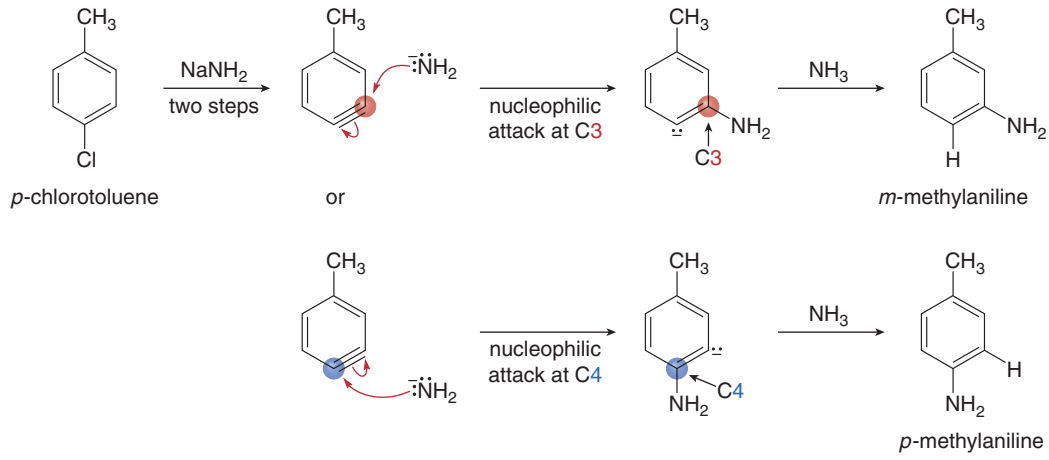
- Addition of the nucleophile ($^-$OH in this case) and protonation form the substitution product (Steps [3] and [4]).

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 $NaNH_2$ forms para- and meta-substitution products.



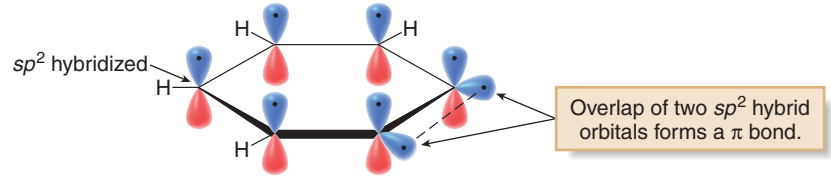
p-chlorotoluene *p*-methylaniline (*p*-toluidine) *m*-methylaniline (*m*-toluidine)

This result is explained by the fact that nucleophilic attack on the benzyne intermediate may occur at either C3 to form *m*-methylaniline, or C4 to form *p*-methylaniline.



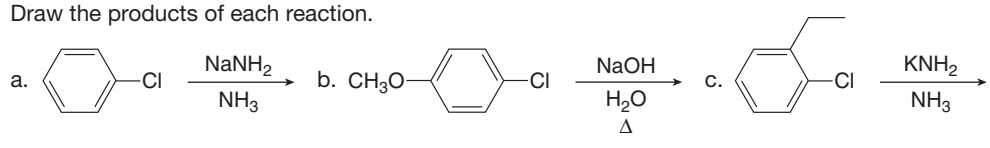
As you might expect, the triple bond in benzyne is unusual. Each carbon of the six-membered ring is sp^2 hybridized, and as a result, the σ bond and two π bonds of the triple bond are formed with the following orbitals.

- **The σ bond is formed by overlap of two sp^2 hybrid orbitals.**
- **One π bond is formed by overlap of two *p* orbitals perpendicular to the plane of the molecule.**
- **The second π bond is formed by overlap of two sp^2 hybrid orbitals.**



Thus, the second π bond of benzyne differs from all other π bonds seen thus far, because **it is formed by the side-by-side overlap of *sp^2 hybrid orbitals,* not *p* orbitals.** This π bond, located in the plane of the molecule, is extremely weak.

Problem A.5 Draw the products of each reaction.



Problem A.6 Draw all products formed when *m*-chlorotoluene is treated with KNH_2 in NH_3.

Problem A.7 Explain why 2-chloro-1,3-dimethylbenzene is inert to nucleophilic aromatic substitution by way of an elimination–addition mechanism.

Problem A.8 Draw a stepwise mechanism for the following reaction.