

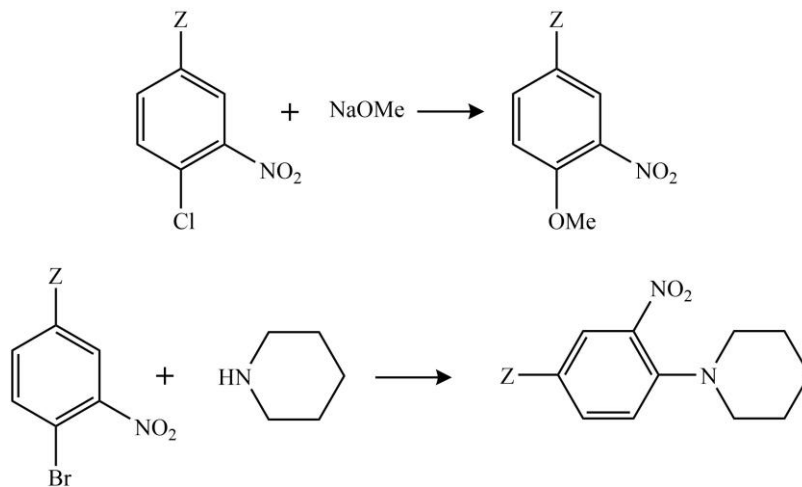
❖ Reactivity – Effect of Substrate Structure, Leaving Group and Attacking Nucleophile

In this section, we will discuss the effect of substrate structure, leaving group and attacking nucleophiles on the reactivity of nucleophilic substitution in aromatic compounds.

➤ Effect of Substrate Structure on the Reactivity of Aromatic Electrophilic Substitution

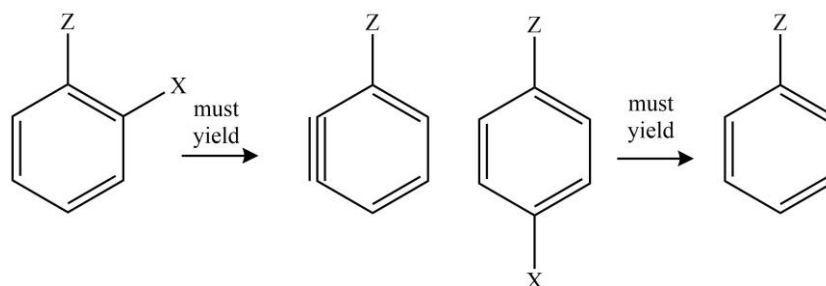
Just like the case of aromatic electrophilic substitution, substrate structure also affects the reactivity of aromatic nucleophilic substitution w.r.t orientation as well as ring-activation. However, orientation-effect was of more importance in the electrophilic case four or five hydrogens were able that act as leaving groups in comparison to the nucleophilic-case where the typical number of leaving group one. Consequently, substrate reactivity is primarily studied w.r.t other molecules rather than the same species.

Aromatic nucleophilic substitution reactions are typically opposed by electron attracting groups but enhanced by electron-withdrawing groups mainly at ortho and para positions to the leaving group, which is just the reverse order for electrophilic substitutions. Therefore, all the groups can be arranged in ascending or descending order of their activating (or deactivating) abilities.



Groups with nitrogen atoms activating in nature w.r.t to *o*- and *p*-position with N_2^+ as the strongest activator. Also, $-NO_2$ is the most common activating group; whereas 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides are considered as the most common substrates. Furthermore, substrates without activating groups are largely useless to serve in $ArSN_{1,2}$ pathways, which can be attributed to the presence of 2 antibonding electrons in the ring. If attached groups are electron-withdrawing, they can activate the reaction by withdrawing electron density, and therefore, will stabilize the transition states (or intermediate). Aromatic electrophilic substitutions of type $ArSN_{1,2}$ are also supported if a transition metal is connected to the aromatic ring. Finally, the Hammett equation can also be modified for aromatic electrophilic substitution with the difference of σ^- instead of σ^+ .

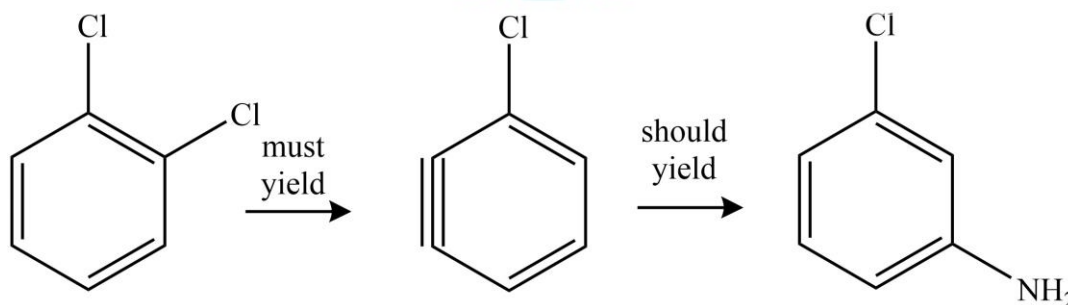
As far as the benzyne pathway is concerned, the reactivity w.r.t to the substrate can be factored in categories; one is the direction the aryne forms in, and the second is the presence of groups at ortho or para positions to the leaving group.



However, if the aryne substrate is *m*-substituted, the nucleophilic substitution can occur via two different routes as shown below.



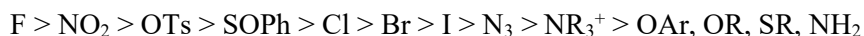
These types of attacks occur via the removal of more acidic hydrogen; and because the acidity is correlated to the magnitude of field effect of the $-Z$ group, we can conclude that Z with more electron-attracting character will support the removal of the *o*-hydrogen whereas the Z with electron-donating character will elimination of the *p*-hydrogen atom. On the other hand, the other route says that though the aryne attacked at two sites, the favored site for the nucleophile to attack will be the one that gives rise to a stabler carbanion (which is also a function of Z 's field effect).



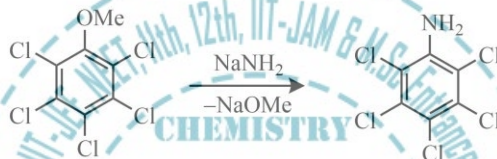
In other words, we may conclude that the carbanion with the negative charge closer to Z will be more stable than others.

➤ **Effect of Leaving Group on the Reactivity of Aromatic Electrophilic Substitution**

Typical leaving groups for nucleophilic substitutions in aromatic compounds are X^- (halides), sulfonate, sulfate, NR_3^+ , etc., which also act as a leaving-group for nucleophilic substitution in aliphatic compounds. Nevertheless, some groups are common; for instance, OAr, SO_2R , NO_2 , OR, and SR, which do not act as leaving-group in aliphatic compounds but exclusively in aromatic systems. The typical order of leaving group power in aromatic nucleophilic substitution is given below.



It is obvious from the order given above that F and NO_2 are exceptionally good leaving groups in the aromatic nucleophilic substitution. Nonetheless, it should also be kept in mind that a better leaving group doesn't always lead to the preferred product because the nature of attacking nucleophile also decide the final departed result. For example, Cl is better a better leaving group than OR but the attack of NH_2^- on $C_6Cl_5OCH_3$ always results in $C_6Cl_5NH_2$ which is contrary to expectations.



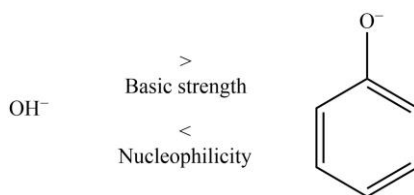
Routinely, the formation of an inorganic ester can also make OH act like a leaving group. It can also be seen that leaving group order give here different than aliphatic nucleophilic substitution because the first step (rate-determining) in the present case is assisted by prevalent $-I$ effects.

➤ **Effect of Attacking Nucleophile on the Reactivity of Aromatic Electrophilic Substitution**

Just like the order of leaving groups, the manifestation of a universal nucleophilicity order is very hard; though an approximation can still be made.



The nucleophilic strength also depends upon the base strength and shows an increase we select the attacking atom more down the group. Nevertheless, like other physical concepts, some exceptions are always present like a stronger basic character of OH than ArO but weaker nucleophilicity.



It is also worthy to remember that even though the nucleophilicity order is not invariant, it still finds application in a wide range of synthetic and practical applications including the assignment of electrophilicity parameters in the case of electron-short heteroarenes.

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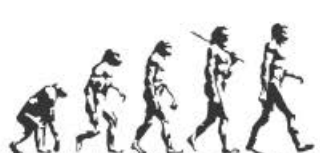
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Volume I

MANDEEP DALAL



First Edition

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