

Nucleophilic substitution is the reaction of an electron pair donor (the nucleophile, Nu) with an electron pair acceptor (the electrophile). A  $sp^3$ -hybridized electrophile must have a leaving group (X) in order for the reaction to take place.

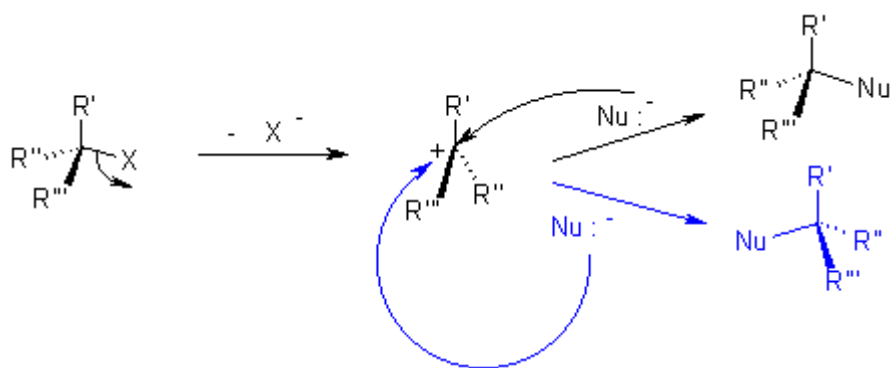
### Mechanism of Nucleophilic Substitution

The term  $S_N2$  means that two molecules are involved in the actual transition state:



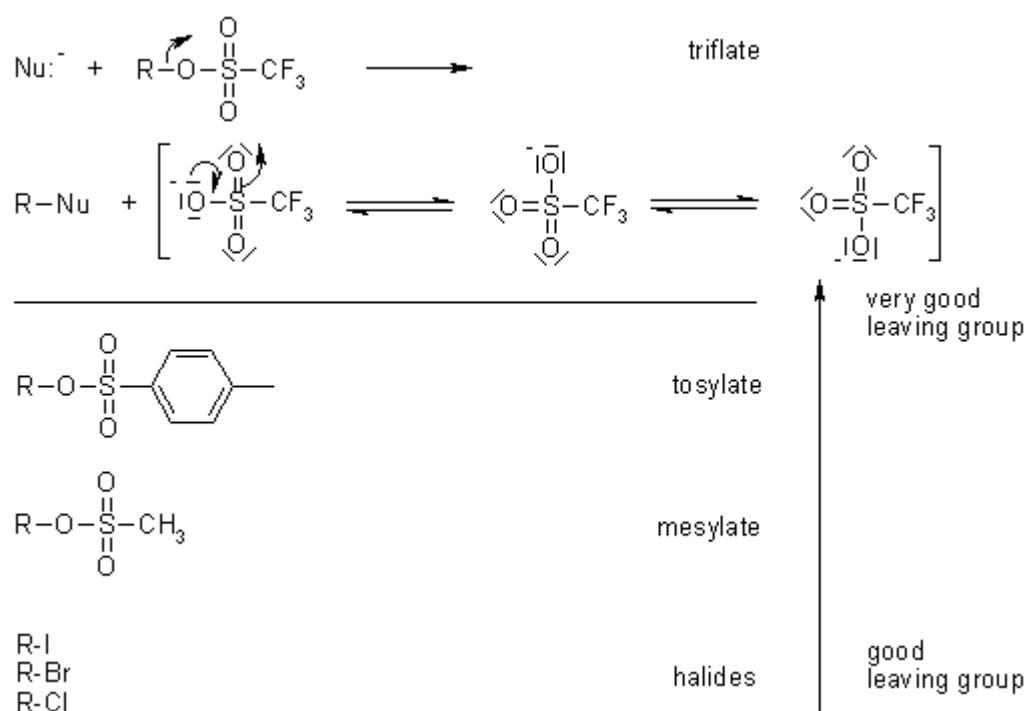
The departure of the leaving group occurs simultaneously with the backside attack by the nucleophile. The  $S_N2$  reaction thus leads to a predictable configuration of the stereocenter - it proceeds with inversion (reversal of the configuration).

In the  $S_N1$  reaction, a planar carbenium ion is formed first, which then reacts further with the nucleophile. Since the nucleophile is free to attack from either side, this reaction is associated with racemization.

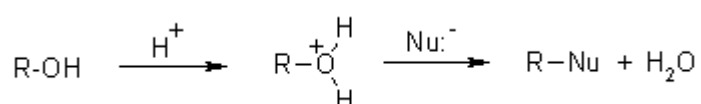


In both reactions, the nucleophile competes with the leaving group. Because of this, one must realize what properties a leaving group should have, and what constitutes a good nucleophile. For this reason, it is worthwhile to know which factors will determine whether a reaction follows an  $S_N1$  or  $S_N2$  pathway.

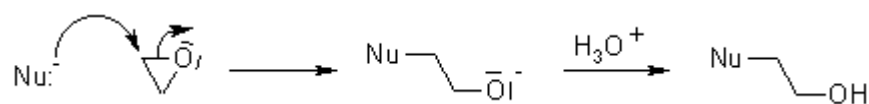
Very good leaving groups, such as triflate, tosylate and mesylate, stabilize an incipient negative charge. The delocalization of this charge is reflected in the fact that these ions are not considered to be nucleophilic.



Hydroxide and alkoxide ions are not good leaving groups; however, they can be activated by means of Lewis or Brønsted acids.

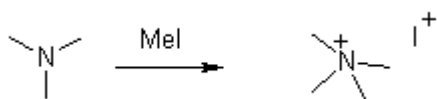


Epoxides are an exception, since they relieve their ring strain when they undergo nucleophilic substitution, with activation by acid being optional:

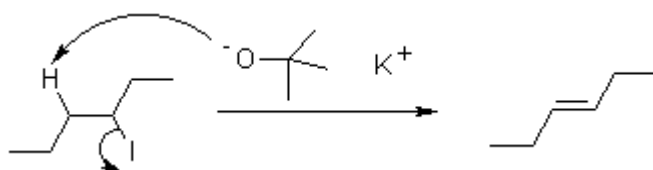


Triflate, tosylate and mesylate are the anions of strong acids. The weak conjugate bases are poor nucleophiles. Nucleophilicity increases in parallel with the base strength. Thus, amines, alcohols and alkoxides are very good nucleophiles. Base strength is a rough measure of how reactive the nonbonding electron pair is; thus, it is not necessary for a nucleophile to be anionic.

Under substitution conditions, amines proceed all the way to form quaternary salts, which makes it difficult to control the extent of the reaction.

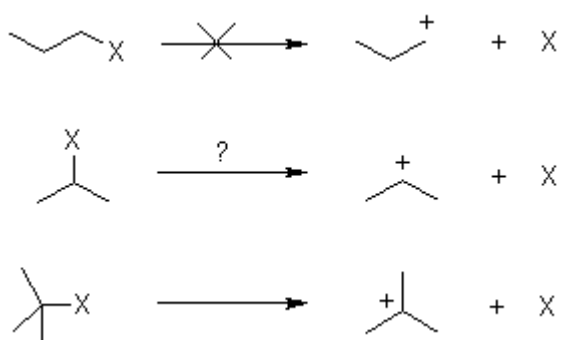


However, as a nucleophile's base strength and steric hindrance increase, its basicity tends to be accentuated. If there are abstractable protons at the  $\beta$ -position of the electrophile, an elimination pathway can compete with the nucleophilic substitution.



An additional factor that plays a role is the character of the solvent. Increasing stabilization of the nucleophile by the solvent results in decreasing reactivity. Thus, polar protic solvents will stabilize the chloride and bromide ions through the formation of hydrogen bonds to these smaller anions. Iodide is a comparatively better nucleophile in these solvents. The reverse behavior predominates in aprotic polar media.

The solvent also plays an important role in determining which pathway the reaction will take,  $\text{S}_{\text{N}}1$  versus  $\text{S}_{\text{N}}2$ . It may safely be assumed that a primary-substituted leaving group will follow an  $\text{S}_{\text{N}}2$  pathway in any case, since the formation of the corresponding unstable primary carbenium ion is disfavored. Reaction by the  $\text{S}_{\text{N}}1$  pathway is highly probable for compounds with tertiary substitution, since the corresponding tertiary carbenium ion is stabilized through hyperconjugation:



The better the solvent stabilizes the ions, the more probable that the reaction will follow an  $S_N1$  pathway (e.g., in polar protic solvents such as water/acetone). The more highly substituted is the incipient carbenium ion, the more probable that the reaction will follow an  $S_N1$  pathway. The more unreactive the nucleophile, the more probable it becomes that a reaction with secondary and tertiary electrophiles will follow an  $S_N1$  pathway. A weaker nucleophile is not as effective in the backside attack, since this location is sterically shielded, especially in the case of tertiary substrates. Carbenium ions are planar and therefore less sterically hindered, and are naturally more reactive as electrophiles than the uncharged parent compound.