

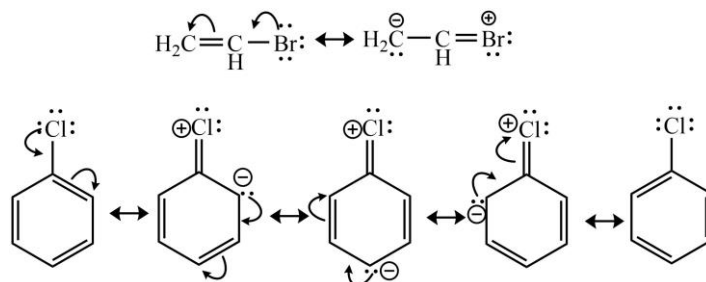
## ❖ Reactivity – Effects of Substrate Structure, Attacking Nucleophile, Leaving Group and Reaction Medium

The reactivity of aliphatic nucleophilic substitution reactions is affected by many factors which can be better understood via experimental data and theoretical treatment combined. In this section, we will discuss some major factors that greatly influence the nucleophilic substitution's rate in aliphatic compounds like substrate structure, attacking nucleophile, leaving group, and reaction medium.

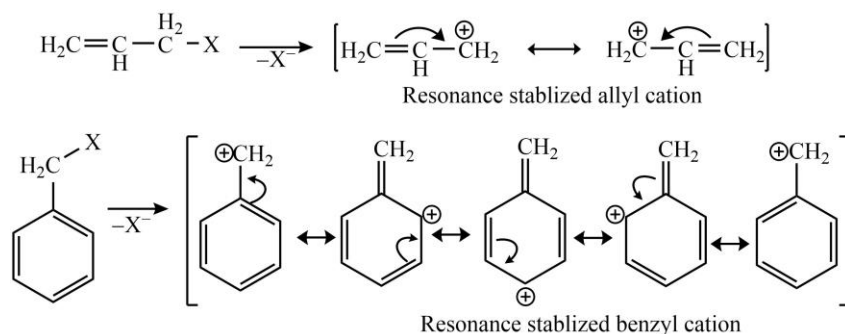
### ➤ Effect of Substrate Structure on the Reactivity of Aliphatic Nucleophilic Substitution

Since the rates in  $S_N1$  and  $S_N1'$  reactions are determined by the 1st step (formation of carbocation), the more stable the carbocation is, readily it will be formed, and the faster the rate will be. Also, the neighboring group participation takes place via first-order kinetics; therefore, the enhanced rate (anchimeric assistance) must be analyzed with special reference to the substrate. The effect of substrate structure on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

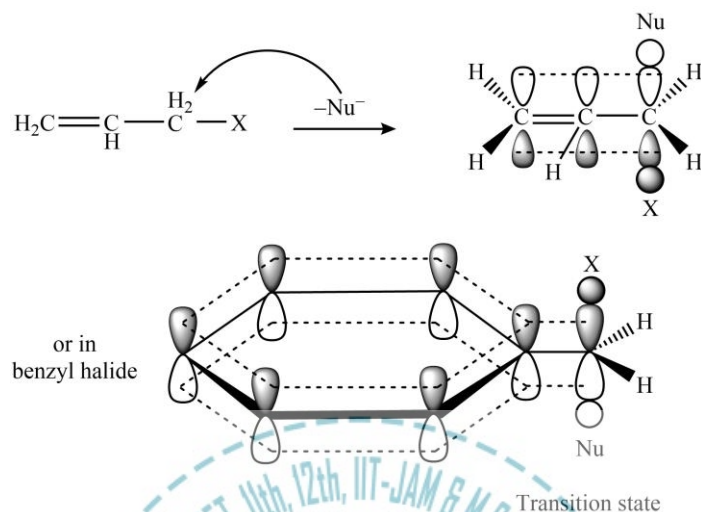
**1. Unsaturation at  $\alpha$ -carbon:** It is quite a well-known fact that aryl halide, vinyl halide, and acetylenic halides show very small reactivity towards nucleophilic substitution reactions because the carbon-halogen bond gains some double bond nature due to resonance. All this makes the breaking of C–X bond more difficult resulting in a lower tendency to undergo nucleophilic substitution.



**2. Unsaturation at  $\beta$ -carbon:** Unlike the unsaturation at  $\alpha$ -carbon, the presence of multiple bonds at  $\beta$ -carbon enhances the favourability of nucleophilic substitution because of the generation of resonance stabilized benzyl or allyl carbocation. This is true for  $S_N1$  as well as for  $S_N2$  pathways. For instance, consider the unimolecular nucleophilic substitution in allyl- and benzyl halides.

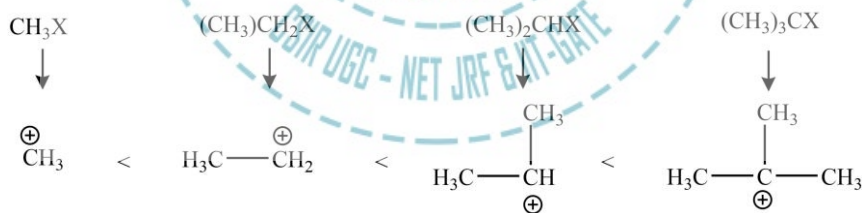


Similarly, the transition state formed during the course of the bimolecular nucleophilic substitution is also stabilized by the phenomenon of resonance.



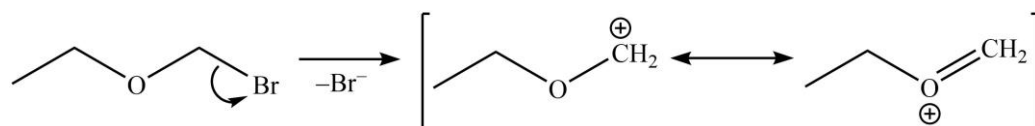
Therefore, we can conclude that allyl and benzyl halides are more reactive than alkyl halides in  $S_N1$  as well in  $S_N2$  pathways.

**3. Steric effects:** Since the alkyl carbocations are primarily obtained from alkyl halides with tetrahedral geometry, a link between the steric relief and carbocation formed can be established. During the formation of carbocations in such cases, the carbon-carbon bond angles change from  $109^\circ 28'$  to  $120^\circ$ . Therefore, the carbon with bulky groups around is expected to get more relief from this carbocationic conversion. The stability order of alkyl carbocations on the basis of steric effect is given below.

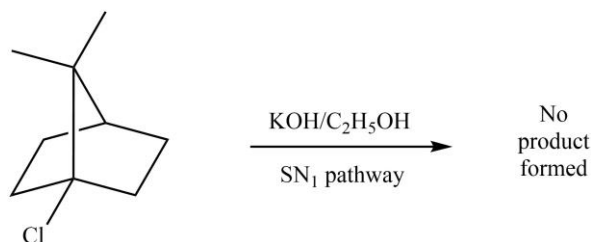


Furthermore, the steric bulk around or near the central carbon also affects the rate of bimolecular nucleophilic substitution ( $S_N2$ ) but in a negative way. This is because the bulky groups disfavor the formation of transition state resulting in a slower reaction rate.

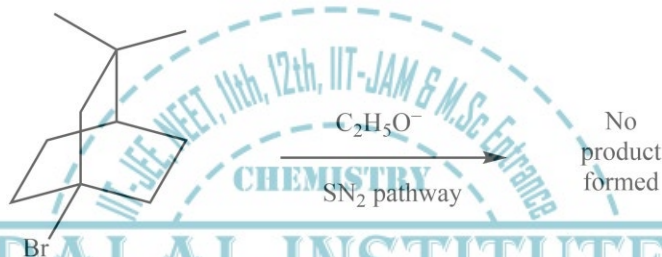
**4. Presence of heteroatom at  $\alpha$ -carbon:** The rate of  $S_N1$  reactions is greatly enhanced by the presence of heteroatom at  $\alpha$ -carbon because it stabilizes the carbocation formed during the first step.



**5. Substitution at bridgehead carbon:** The nucleophilic substitution at bridgehead carbons is extremely disfavoured both in  $S_N1$  as well as in  $S_N2$  pathways. The reason for low reactivity at bridgehead carbon in the  $S_N1$  pathway is the 'non-planar' structure of carbocation involved.



However, the low reactivity at bridgehead carbon in the  $S_N2$  pathway is due to different reasons i.e. disfavorability of backside attack of nucleophile which an essential request of the same.



**6. Carbonyl groups at  $\alpha$ -carbon in alkyl halides:** The rate of  $S_N2$  reactions is greatly enhanced if some carbonyl group is situated at the  $\alpha$ -carbon in alkyl halides. This is because the electron-withdrawing effect raises the stability of the transition state.



However, a reverse effect will be observed for  $S_N1$  pathway which is obviously due to the destabilization of carbocation formed.

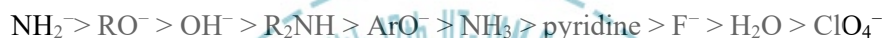
	$\text{H}_3\text{C}-\text{X}$	$\text{H}_3\text{C}-\text{O}-\text{CH}_2\text{X}$	$\text{C}_6\text{H}_5-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\text{X}$
Reactivity of substrate in $S_N2$ pathway	202	920	100000

➤ **Effect of Nucleophile on the Reactivity of Aliphatic Nucleophilic Substitution**

Since the rate in  $\text{SN}_1$  reactions is determined by the 1st step (formation of carbocation), and the nucleophile attacks in the second step; the rate of  $\text{SN}_1$  reactions is pretty much independent of nucleophilic strength. However, the rate of  $\text{SN}_2$  and  $\text{SN}_2'$  depends upon the strength of the attacking nucleophile due to second-order kinetics. The effect of the nucleophile on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

**1. Formal charge:** The nucleophiles with higher negative charge have more strength than corresponding conjugate acids. In other words, if the conjugate acid of a nucleophile is also a nucleophile, it will be of less strength always. For instance, the amide is a stronger nucleophile than ammonia; and  $\text{OH}^-$  is stronger than water.

**2. Basic character:** The strength of different nucleophiles follows the same order as basicity if the attacking atom comes from the same period. For instance, consider the following order.



Furthermore, it is also worthy to recall that nucleophilicity is kinetically controlled but basicity is thermodynamically controlled.

**3. Solvation level:** The strength of different nucleophiles increases as the attacking comes from more down the group. Now, although the basic character of such nucleophiles decreases down the group, the increasing nucleophilicity can be rationalized in terms of higher solvation of smaller anions making them less suitable for attack. For instance, consider the following order.



The effect is more prominent in polar protic solvents where smaller nucleophiles are more solvated than usual. Furthermore, it is also worthy to note that this effect becomes inefficient for neutral nucleophile because they don't get much solvated. However, they also show an increase in nucleophilic strength down the group which can be explained in terms of the hard-soft acid-base principle. In other words, the reason for the increasing strength of neutral nucleophiles is that a softer nucleophile prefers an alkyl carbocation (soft acid) over the proton (soft acid).

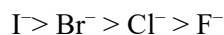
**4. Attacking liberty:** As the nucleophile becomes more free to attack, the rate of reaction increases. For instance, consider the case of  $(\text{EtOOC})_2\text{CBu}^- \text{Na}^+$  in  $\text{C}_6\text{H}_6$ , where the addition of  $\text{Na}^+$ -solvating compound makes the  $(\text{EtOOC})_2\text{CBu}^-$  ion free to attack, and increasing rate consequently.

Nevertheless, it must be kept in mind that these rules do not hold at all conditions always because there are many factors like steric influences. For instance, the tert-butoxide ion ( $\text{Me}_3\text{CO}^-$ ) much weaker nucleophile though it is an even stronger base than  $\text{OH}^-$  or  $\text{OEt}^-$ ; which can be attributed to the fact that its huge bulk hinders it from approaching a substrate more closely. Finally, we may conclude that only rough estimates can be made about the order of nucleophilic strengths and there is no absolute order of either leaving group and nucleophilicity.

➤ **Effect of Leaving Group on the Reactivity of Aliphatic Nucleophilic Substitution**

A good leaving group is that becomes stable after the detachment from substrate. The effect of leaving group on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

**1. Basic character:** The betterment of the leaving-group is inversely proportional to the strength of its basic character. In other words, weak bases are good leaving and vice-versa. For instance, consider the order of goodness for halides as leaving group.

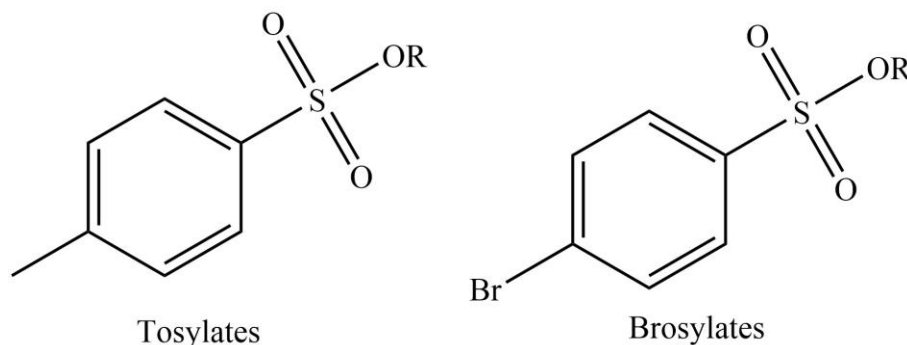


This is just the opposite trend of acidic character order of corresponding their hydro acids i.e.,  $HI > HBr > HCl > HF$ .

**2. Ester conversion:** The power of a leaving group can be improved by converting it into its ester, which is why brosylates or tosylates (sulphonic esters) are more popular as leaving group than halides.



**3. Ring strain:** The leaving-group power can also be increased via ring strain. For instance, simple ethers do not undergo breaking while protonated ethers show cleavage conditions are strenuous; however, epoxides undergo bond cleavage effortlessly whereas protonated epoxides show even more tendency.

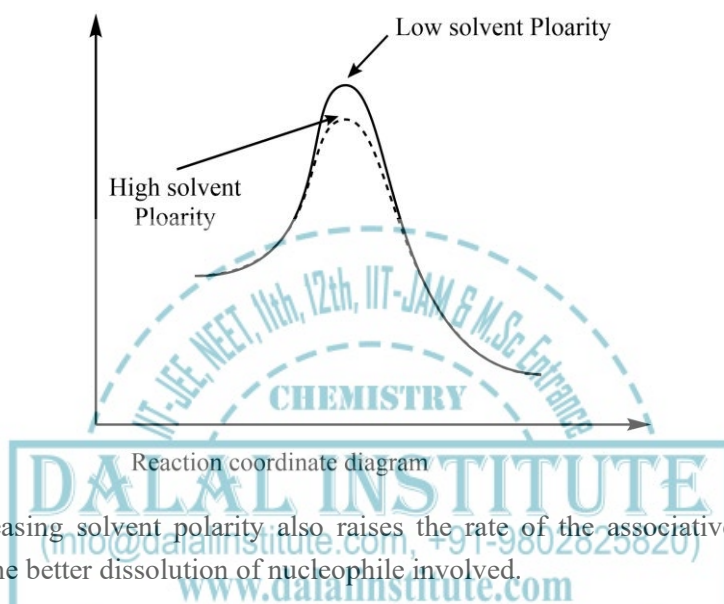


Furthermore, it is also worthy to note that the nature of leaving the group not only affects the reaction speed but can also change the mechanism of the same from associative to dissociative and vice-versa.

➤ **Effect of Reaction Medium on the Reactivity of Aliphatic Nucleophilic Substitution**

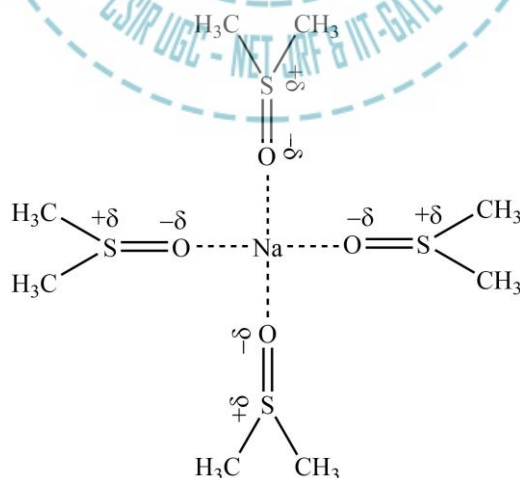
The effect of the reaction medium on the reactivity of aliphatic nucleophilic substitution reactions can be divided into the following categories.

**1. Solvent polarity:** The rate of reaction in  $S_N1$  transformations increases with the increase in solvent polarity and vice-versa. This is because the polar solvent stabilizes carbocation intermediate greatly, which in turn decreases the activation energy required for the change.



Furthermore, the increasing solvent polarity also raises the rate of the associative pathway ( $S_N2$ ) which obviously because of the better dissolution of nucleophile involved.

**2. Protic-aprotic type:** It has been observed that polar protic solvents decrease the nucleophilic strength and enhances the stability of the anionic leaving group; consequently, supporting the dissociative pathway ( $S_N1$ ).



On the other hand, protic solvents slow down the rate of  $S_N2$  reaction by solvating the nucleophile involved; whereas, aprotic solvents enhance the rate by freeing the nucleophile via the binding cation mechanism.

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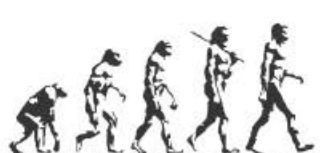
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*Mandeep Dalal*

*(M.Sc, Ph.D, CSIR UGC – NET JRF, IIT-GATE)*

*Founder & Educator, Dalal Institute*

*E-Mail: dr.mandeep.dalal@gmail.com*

*www.mandeepdalal.com*

Mandeep Dalal is an Indian research scholar who is primarily working in the field of Science and Philosophy. He received his Ph.D in Chemistry from Maharshi Dayanand University, Rohtak, in 2018. He is also the Founder of "Dalal Institute" (India's best coaching centre for academic and competitive chemistry exams), the organization that is committed to revolutionize the field of school-level and higher education in Chemistry across the globe. He has published more than 40 research papers in various international scientific journals, including mostly from Elsevier (USA), IOP (UK), and Springer (Netherlands).

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