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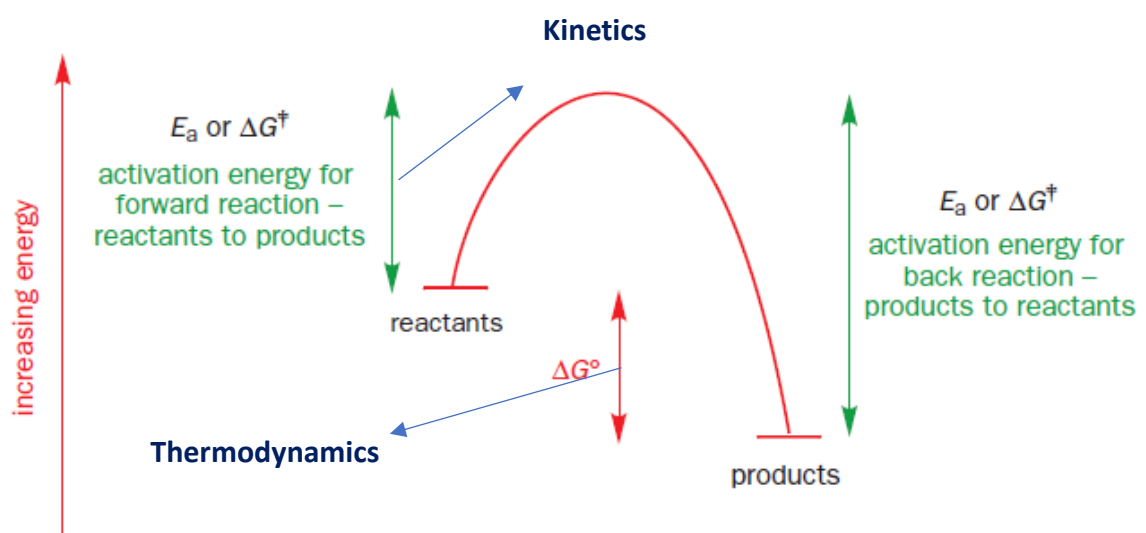
***CH1101***

***Class Notes 2: Nucleophilic  
Substitution Reactions***

Supratim Banerjee

## A general discussion on the kinetics and thermodynamic of a reaction:

Before moving to the main discussion on nucleophilic substitution reactions, it is important to understand certain aspects of a chemical reaction. As shown in fig. 1, in every reaction, the reactants have to go through an energy barrier before being converted to the products. The top of the barrier is called the transition state (TS) which represents the reorganizations in the bonds involved in the reaction. There are a couple of important parameters to understand here. The first one is the difference between the energy level of the reactants and the TS. This is called the activation energy ( $E_a$ ) of a chemical reaction. The rate of the reaction is critically dependent on this parameter. The lower the activation barrier, the faster the reaction. The rate of a reaction is related to its kinetics. In a bimolecular reaction, when two reactant molecules collide with proper orientation, the product will be formed only *if the collision energy is more than the activation energy ( $E_a$ )*. For those collisions whose energies are less than  $E_a$ , no reaction happens. The reactant molecules remain unchanged even after the collision.



**Fig. 1.** The energy vs. reaction coordinate diagram for a reaction.

The other parameter is the change in Gibbs free energy ( $\Delta G$ ) in going from the reactants to the products. This is related to the thermodynamics of a reaction. The higher the negative value of  $\Delta G$ , the more favorable is the reaction in a thermodynamic sense and a higher conversion of the reactants to products will occur. Remember the following equation which connects  $\Delta G$  to the equilibrium constant ( $K$ ) of a reaction.

### Equation 1:

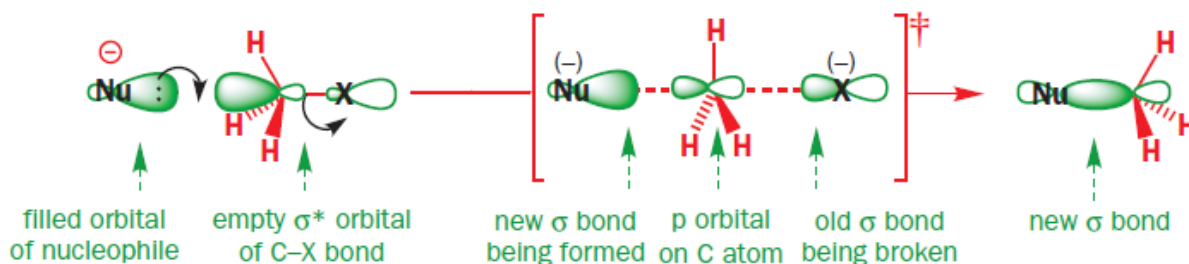
$$\Delta G^\circ = -RT \ln K$$

During the discussions on  $S_N$  reactions, we generally talk about the rate of a reaction and it is related to  $E_a$ . Remember a reaction may be thermodynamically favorable (large value of  $-\Delta G$ ) but kinetically slow (high  $E_a$ ). We term these instances as: thermodynamics and kinetics are not in parallel. There are many such examples in biology. For example, chymotrypsin is a digestive enzyme which helps in the hydrolysis of the peptide bonds in proteins. The hydrolysis reactions are actually thermodynamically favorable but kinetically very slow. Chymotrypsin lowers the activation energy of the TS and makes the reactions faster so that we can digest the taken food in a reasonable length of time.

There are reactions in which the product is thermodynamically more stable than the reactants as well as is formed at a fast rate (low  $E_a$ ). In those reactions thermodynamics and kinetics are in parallel. It is interesting to note that among the number of chemical reactions which have been discovered so far, both instances are seen in almost 50:50 ratio. In the following few sections, we will rarely look at the stability of the products; *rather we are interested in the rate of the reactions i.e. the kinetics and hence the  $E_a$  associated with the rate determining step (the slowest step in a reaction)*.

### Nucleophilic Substitution Bimolecular ( $S_N2$ ):

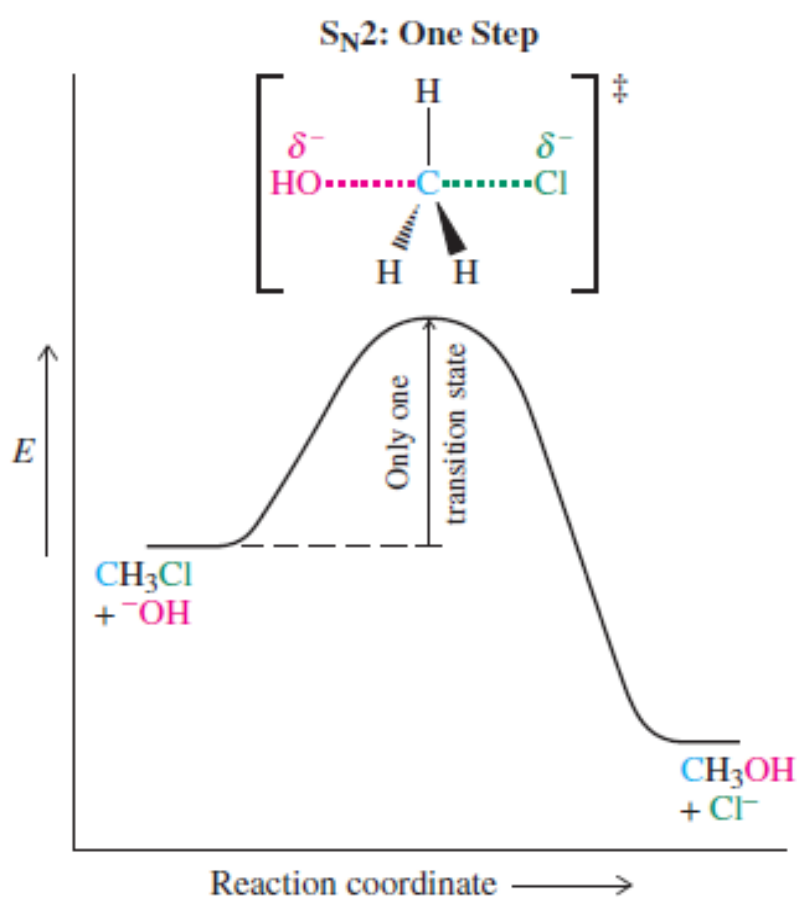
$S_N2$  reactions are bimolecular reactions and the rate law is first order with respect to both alkyl halide and nucleophile. The discussion will be focussed on alkyl halides as the electrophiles (saturated carbon in a tetrahedral geometry).  $S_N2$  reactions happen in a single step and there is no intermediate involved during the course of the reaction. So, the nucleophile approaches the tetrahedral carbon in a concerted step in which the leaving group also departs. In order to explain the approach of the nucleophile, we try to look at the orbitals involved in this reaction. As usual, we will consider the interaction of the HOMO of the nucleophile with the LUMO of the C-X bond in an alkyl halide. As shown in fig. 2, if the approach of the nucleophile is exactly opposite to the C-X bond



**Fig. 2.** HOMO-LUMO interactions govern the approach of a nucleophile to an alkyl halide in a  $S_N2$  reaction: orbital overlap is maximum if the HOMO (Nu) interacts with the LUMO (C-X) from the opposite direction in a linear fashion.

in a linear fashion, then the overlap of the HOMO of the Nu and the LUMO of the C-X bond will be maximum. This in fact is the observation from the experimental findings.

Now let's look at the energy vs. reaction co-ordinate diagram (fig. 3) for the  $S_N2$  reaction between  $\text{OH}^-$  and  $\text{CH}_3\text{Cl}$ . Note how the transition state structure is represented here. The C-Cl bond partially breaks and the C-O bond partially forms. The initial negative charge on  $\text{OH}^-$  is now dispersed and exists on both O and Cl atoms in the TS.



**Fig. 3.** Energy vs. reaction coordinate diagram in the  $S_N2$  reaction between  $\text{OH}^-$  and  $\text{CH}_3\text{Cl}$ .

There are four factors that affect the rate of  $S_N2$  reactions. They are a) the structure of the alkyl halide, b) the nature of the nucleophile; c) the nature of the leaving group and d) solvent. Factors a, c and d also influence  $S_N1$  reactions. We will now discuss the effect of the alkyl halide structure on the rates of the  $S_N2$  reactions. Other factors will be discussed later. We will try to use eq. 2 in most of the cases to analyse the factors influencing a reaction.

## Equation 2:

$$\Delta E \text{ (interaction energy)} : \Sigma \text{ sterics} - \Sigma \text{ orbital overlap} / (E_{\text{LUMO}} - E_{\text{HOMO}}) + \Sigma \text{ charge interaction}$$


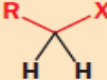
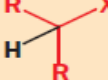
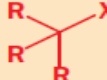
↓  
Reactivity

↓  
(Interaction between frontier molecular orbitals)

### Effect of the nature of alkyl halide in S<sub>N</sub>2 reactions:

The S<sub>N</sub>2 reaction rate depends critically on the nature of the alkyl halide. As can be seen from table 1 that in going from primary to tertiary, the rate of the reaction decreases dramatically. This can be explained from the steric environment around the electrophilic carbon. As evident from eq. 2, an increase in steric interaction reduces the reactivity drastically in t-alkyl halides. Methyl and primary alkyl halides are the best substrates among them.

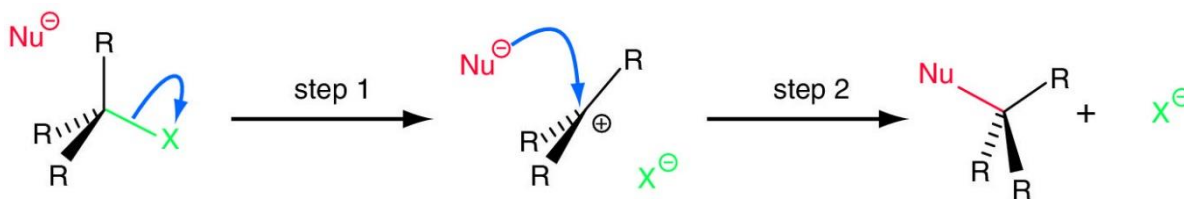
**Table 1.** The variation in the rates of S<sub>N</sub>2 reactions with the nature of alkyl halides

structure				
type	methyl	primary	secondary	tertiary
S <sub>N</sub> 2 reaction?	good	good	yes	no

### Nucleophilic Substitution Unimolecular (S<sub>N</sub>1):

S<sub>N</sub>1 reactions are not concerted like S<sub>N</sub>2 and typically multiple steps are involved. However, the rate determining step is the first step in which the leaving group departs as shown below (fig. 4) leading to the formation of a planar carbocation intermediate. Subsequently, the nucleophile attacks the planar carbocation in a kinetically faster step. S<sub>N</sub>1 reactions are very feasible with t-alkyl halides. As has been mentioned already, they are least reactive in S<sub>N</sub>2 reactions because of the higher steric crowding which makes it difficult for the nucleophiles to approach the tetrahedral carbon. However, in going from sp<sup>3</sup> to sp<sup>2</sup> geometry (in the carbocations), several parameters are now in favour of the nucleophiles. In a sp<sup>3</sup> geometry, the carbon atom is surrounded by four substituents which are, in angular terms, 109.5° apart from each other whereas in a sp<sup>2</sup> geometry,

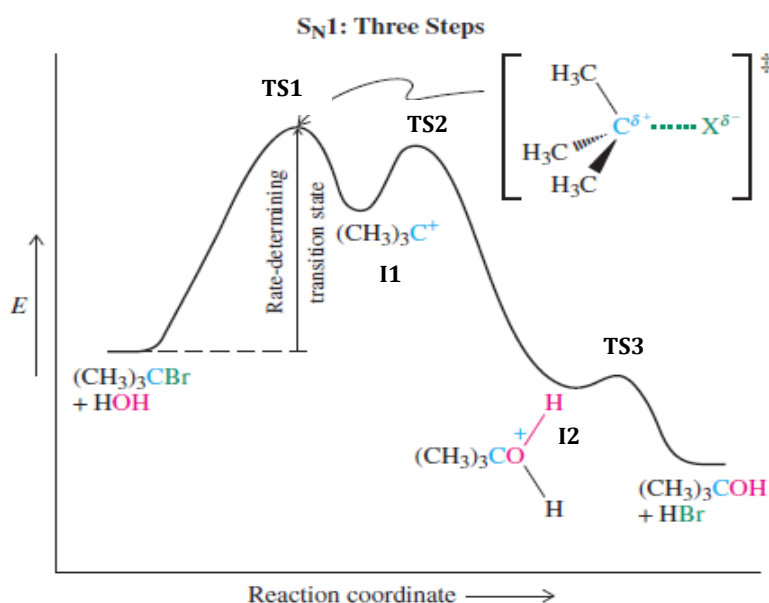
there are only three substituents around the carbon and they are 120° apart. This makes the attack of the nucleophile much more feasible compared to the tetrahedral carbon and hence this step is quite fast.



**Fig. 4.** The mechanistic steps involved in a  $S_N1$  reaction. Step 1 is the rate determining step.

Since the attack of the nucleophile does not affect the reaction kinetics,  $S_N1$  reactions also occur in the presence of weak nucleophiles such as  $H_2O$  and alcoholic solvents. Such reactions are called solvolysis reactions. The hydrolysis reaction of t-BuBr is shown in fig. 5. As can be seen, there are multiple steps involved with the formation of the t-butyl cation being the rate-determining step.

If you look carefully at fig. 5, you will find that there are two intermediates (**I1** and **I2**) and three TS (**TS1**, **TS2** and **TS3**) involved in the reaction. Remember that unlike TS, intermediates have real-life existence even if in many cases they are extremely short-lived. Another key thing is to note that the conversion of t-BuBr to t-Bu cation is actually an energy uphill process. This is not surprising since the carbocation has a carbon with only 6e and hence energetically higher



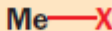
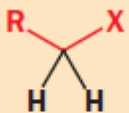
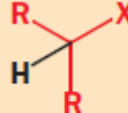

**Fig. 5.** The energy vs. reaction coordinate diagram for the hydrolysis of t-butyl bromide.

than the reactant alkyl halide. *In this context it is noteworthy to mention that all carbocations are unstable.* t-Bu cation is relatively more stable than primary and secondary carbocations, but nevertheless it is a reactive species. It is a common misconception that  $S_N1$  reactions are faster with t-butyl halides because of the higher stability of the corresponding tertiary carbocations. While it is indeed true that t-Bu cations are more stable than its methyl, primary and secondary

counterparts, the higher rate of  $S_N1$  reactions is in fact due to the lower  $E_a$  of formation of the *t*-butyl carbocations.

The comparison of the reactivity of different alkyl halides towards  $S_N2$  and  $S_N1$  reactions (table 2) reveals that methyl halides are most reactive in  $S_N2$  reactions while  $S_N1$  reactions are fastest with *t*-alkyl halide. Secondary alkyl halides undergo both types of reactions.

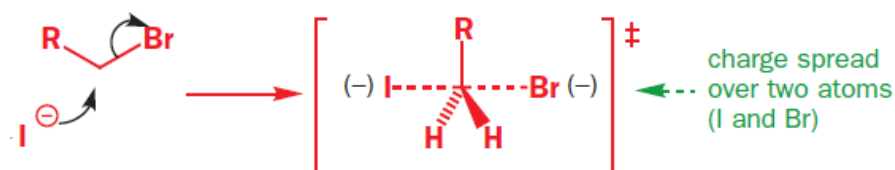
**Table 2.** The dependence of the rates of  $S_N2$  and  $S_N1$  reactions on the nature of alkyl halides

structure				
type	methyl	primary	secondary	tertiary
$S_N1$ reaction?	no	no	yes	good
$S_N2$ reaction?	good	good	yes	no

### Solvent effect in $S_N2$ reactions:

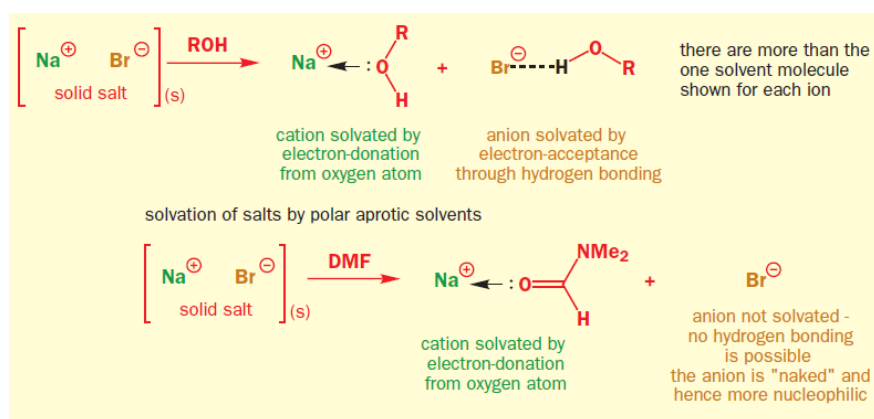
Typically, very highly polar solvents are not chosen for  $S_N2$  reactions. The chosen solvents are just polar enough to dissolve the reactants. It has to be kept in mind that in  $S_N2$  reactions, typically the nucleophiles are ionic salts and hence they can be dissolved in polar solvents. However, polar solvents tend to decrease the rate of the reaction by strongly solvating the nucleophiles. As can be seen from fig. 6 that the negative charge of the nucleophile gets dispersed in the transition state and in a more polar solvent, the nucleophile gets preferentially solvated compared to the TS and hence results in a higher  $E_a$ . In principle, in a non-polar solvent the rate should be high, but there are practical problems in dissolving the ionic salts. Therefore, a solvent is chosen which balances both these factors. To summarize:

- The most common  $S_N2$  reactions use an anion as the nucleophile and the transition state is less polar than the localized anion as the charge is spread between two atoms
- A polar solvent solvates the anionic nucleophile and slows the reaction down
- A nonpolar solvent destabilizes the starting materials more than it destabilizes the transition state and speeds up the reaction.



**Fig. 6.** The dispersion of the charge density in the transition state for a  $S_N2$  reaction between an alkyl bromide and iodide ion.

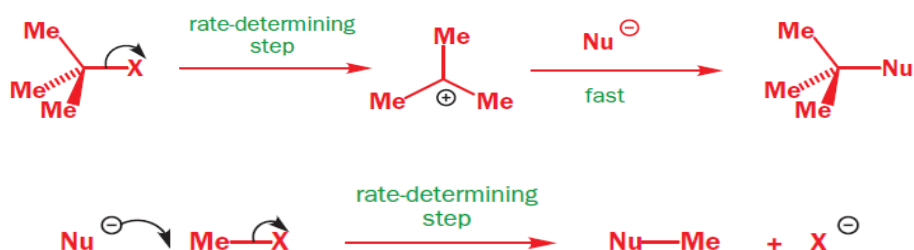
The best solvents for  $S_N2$  reactions, however, are polar aprotic solvents like DMF and DMSO. Both DMF and DMSO can act as only H-bond acceptors (scheme 1). On the other hand, polar protic solvents like alcohol and water are H-bond acceptors as well as H-bond donors. This means that for an ionic salt, polar protic solvents can solvate both the cation and anion. However, the anion is not solvated in solvents like DMF and DMSO and only the cation is solvated through the electron donation from the oxygen atom (scheme 1). The negligible solvation of the anions mean that they have high charge density and act as efficient nucleophiles.



**Scheme 1.** The comparative solvation of an ionic salt in alcohol and DMF.

### The effect of leaving group:

The departure of the leaving group from alkyl halides is important in both  $S_N1$  and  $S_N2$  reactions as illustrated in fig. 7.



**Fig. 7.** The departure of leaving group is involved in the rate determining steps in both  $S_N1$  and  $S_N2$  reactions.

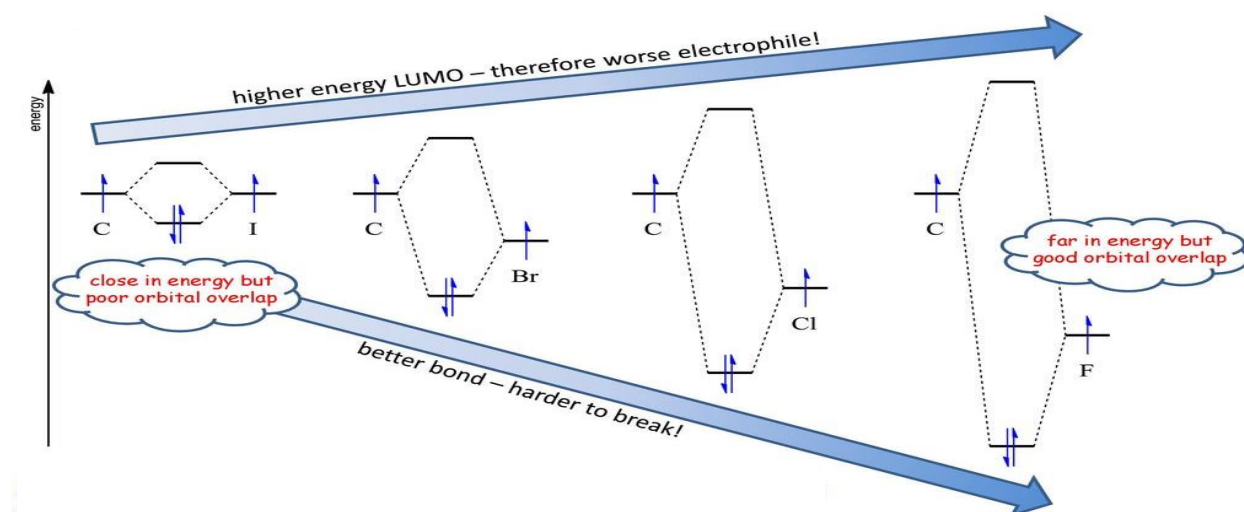


We will first concentrate on the  $S_N2$  reactions between alkyl halides ( $\text{CH}_3\text{X}$ ) and  $\text{OH}^-$ . Different data sets are shown below in table 3. It is apparent that iodide is the best leaving group among all the halide ions. This can be correlated to its lowest bond strength as shown in table 3. One standard comparison is to look at the  $\text{p}K_a$  of the conjugate acids  $\text{HX}$ . This comparison is typically done to correlate the basicity and the leaving group ability. As can be seen, iodide is the weakest base among the halides and the best leaving group.

**Table 3** Halide leaving groups in the  $S_N2$  reaction

Halide X in $\text{MeX}$	$\text{p}K_a$ of conjugate acid $\text{HX}$	Rate of reaction with $\text{NaOH}$	Halide (X)	Strength of C-X bond, $\text{kJ mol}^{-1}$
F	+3	very slow indeed	fluorine	118
Cl	-7	moderate	chlorine	81
Br	-9	fast	bromine	67
I	-10	very fast	iodine	54

A better and clearer picture, however, will be obtained from the MO energy diagrams of the C-X bond in different alkyl halides (fig. 8). The C-F bond is the strongest while the C-I bond is the weakest. Hence, the  $\sigma$  bonding orbital of the C-F bond is energetically most stabilized and the corresponding  $\sigma^*$  is equally the most destabilized. The energy of the  $\sigma^*$  orbital gradually decreases in going from the C-F to C-Cl and C-Br bonds and eventually becomes lowest in the C-I bond. This compels the  $\sigma^*$  of the C-I bond most reactive towards receiving a pair of electrons from nucleophiles and this in turn makes iodide the best leaving group among the halide ions.



**Fig. 8.** Comparative energy level diagram showing  $\sigma$  and  $\sigma^*$  MOs of C-X bond in different alkyl halides.

## Nucleophilicity and Basicity

This is a topic of great interest in organic chemistry. However, it is also a topic which often creates confusions. It is generally expected that nucleophilicity can be correlated to basicity since both involve the availability of electron pairs and the ease with which they are donated. However, basicity involves electron pair donation to hydrogen (Bronsted sense) whereas nucleophilicity involves electron pair donation to another atom usually carbon. We typically associate basicity with equilibrium (thermodynamics) whereas the nucleophilicity is considered in connection to the kinetics of a reaction. Basicity is likely to be little affected by steric influences, whereas nucleophilicity may be significantly affected. This is because hydrogen is a small atom with only one substituent whereas carbon has four substituents.

Depending on the donor atom, the bases are roughly divided into two categories: a) hard base: high electronegativity and low polarizability of the donor atom ( $\text{OH}^-$ ,  $\text{OR}^-$ ,  $\text{NR}_3$ , etc) and b) soft base: low electronegativity and high polarizability of the donor atom:  $\text{RS}^-$ ,  $\text{I}^-$ ,  $\text{SCN}^-$ . In  $\text{S}_{\text{N}}2$  reactions, typically the soft bases react as better nucleophiles. But this statement is mainly based on the fact that we are talking about alkyl halides as the electrophiles. One has to be slightly careful in talking about the comparative basicity and nucleophilicity. To illustrate this point, let's look at the datasets provided in table 4 and 5.

**Table 4** Relative rates (water = 1) of reaction with MeBr in EtOH

Nucleophile X	$\text{p}K_{\text{a}}$ of HX	Relative rate
$\text{HO}^-$	15.7	$1.2 \times 10^4$
$\text{PhO}^-$	10.0	$2.0 \times 10^3$
$\text{AcO}^-$	4.8	$9 \times 10^2$
$\text{H}_2\text{O}$	-1.7	1.0
$\text{ClO}_4^-$	-10	0

**Table 5** Relative rates (water = 1) of reaction with MeBr in EtOH

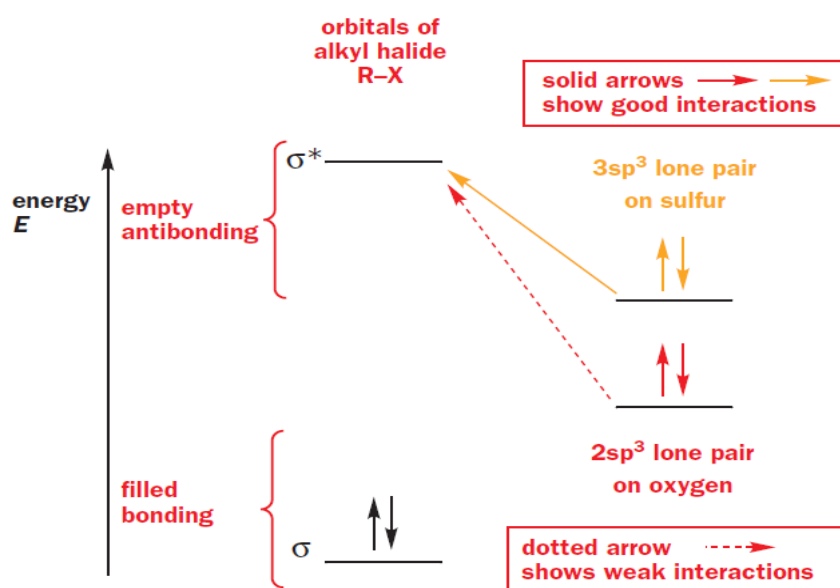
Nucleophile X	$\text{p}K_{\text{a}}$ of HX	Relative rate
$\text{PhS}^-$	6.4	$5.0 \times 10^7$
$\text{PhO}^-$	10.0	$2.0 \times 10^3$

In both cases, the alkyl halide and the solvent are same. In table 4, we see that in going from  $\text{OH}^-$  to  $\text{ClO}_4^-$ , a decrease in basicity occurs. Interestingly, the same trend is also observed in the nucleophilicity. So,  $\text{OH}^-$  is the strongest base as well as the best nucleophile here. But it has to be kept in mind that here we are comparing nucleophiles in which all of them have the same donor

atom O and in this series, nucleophilicity parallels basicity. The trend, however, is quite different in table 5. Here, the more basic  $\text{PhO}^-$  is actually a poorer nucleophile than  $\text{PhS}^-$ . The donor atoms are different here. One is oxygen (hard) and the other is sulphur (soft).

The trends shown in table 4 and 5 clearly point out that we have to be slightly careful in correlating nucleophilicity and basicity. In order to find a more consistent explanation about the nucleophilicity, we will take the help of MO arguments. For example, in table 4, in going from  $\text{OH}^-$  to  $\text{ClO}_4^-$  as the charge on the oxygen atom is getting more and more dispersed, there is a decrease in the HOMO energy level and this means that the energy gap between the HOMO and LUMO is smallest in case of  $\text{OH}^-$ . The LUMO energy level ( $\sigma^*$ , C-Br) is same for all the reactions. This can explain a higher rate for  $\text{OH}^-$  compared to others in accordance with eq. 2.

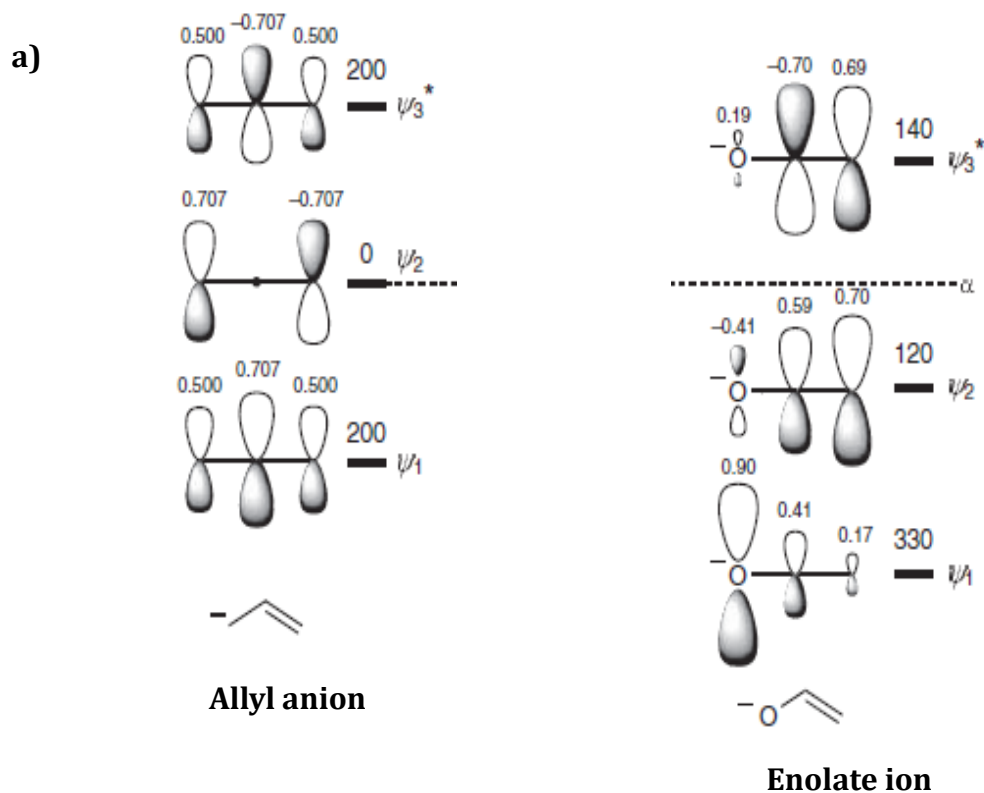
Similarly, for table 2, the higher rate for the S nucleophile can be explained from its higher energy HOMO as shown in fig. 9. So, the aforementioned discussions suggest that, with alkyl halides as the electrophiles, orbital interactions provide us a reasonable explanation behind the observed rates for different nucleophiles.



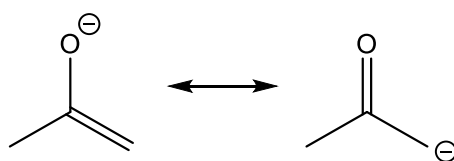
**Fig. 9.** Energy level diagram showing  $\sigma^*$  MO of a C-X bond and the HOMO MOs from oxygen and sulphur nucleophiles.

**EXTRA READING MATERIAL (NOT PART OF THE EXAM)**

**A.  $\pi$ -Molecular orbitals of an enolate ion:**



b)



**Figure 10:** A) A comparison between the energy levels of the  $\pi$ -molecular orbitals of an allyl anion and an enolate ion (both are 4- $\pi$  electron systems) and B) the canonical forms of enolate ion.

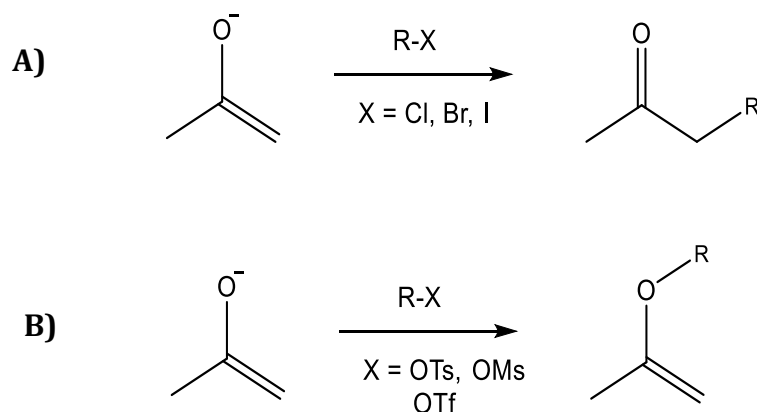
The  $\pi$ -molecular orbitals of an enolate ion are shown in fig. 10a and are compared with that of an allyl anion. One can easily note that the molecular orbitals of the enolate ion are lower in energy than those of the allyl anion. This is simply a consequence of the higher electronegativity of oxygen compared to carbon. The electron density in the bonding MOs of the enolate ion is obtained by calculating the term  $2[\Psi_1^2 + \Psi_2^2]$ . We know from the resonance theory that enolate exists in two canonical forms (fig. 10B). The canonical form with the negative charge on oxygen is more stable

and contributes more to the resonance hybrid. In other words, if we calculate the electron density, the oxygen atom will have a higher share of it. Indeed, the same conclusion is arrived in a more quantitative manner from MOs. The calculation shows that out of the four electrons in the enolate ion, practically 2 electrons reside on oxygen, one on carbonyl carbon and the other one on the  $\alpha$ -carbon. Thus, the MO calculation correlates nicely with our classical understanding of the charge distribution in the enolate ion.

### ***Ambident nucleophilic character of enolates:***

Enolates fall in the category of ambident nucleophiles, capable of reacting with electrophiles through two or more non-identical centres. For example, the reaction of enolates with electrophiles such as alkyl halides produces mainly C-alkylated products (fig. 11A). On the other hand, with electrophiles such as alkyl tosylates, mesylates and triflates, the products are enol ethers and the alkylation takes place at the oxygen (fig. 11B). How do we explain these observations based on the molecular orbital theory?

Let us first look at the nature of the electrophiles. Alkyl halides are typically soft in nature due to their lower energy LUMO (C-X bond). On the other hand, the LUMO of the C-O bond in the sulphonates has much higher energy. When enolates react with these two different kinds of electrophiles, it essentially depends on whether the reaction is dominated by charge or by molecular orbital interactions. It is clear from the coefficients of the HOMO of the enolate ion that the electron density is higher on the  $C_\alpha$  than the other two atoms. So, if the HOMO of the enolate attacks the LUMO of an electrophile, it would be through  $C_\alpha$ . This explains the C-alkylation reactions of enolates with alkyl halides (fig. 11A). But how to explain the O-alkylation reactions? Surely, it can't be explained solely based on the MOs of the enolate ion. The reaction of enolates with hard



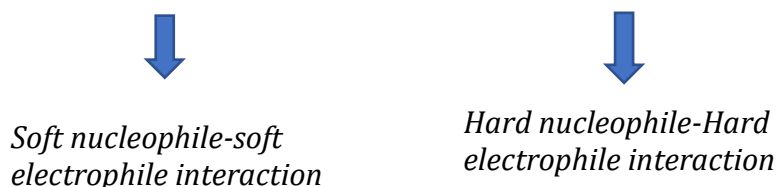
**Figure 11:** C-alkylation and O-alkylation reactions of enolates

electrophiles such as sulphonates (fig 11B) are actually dominated by charge interactions; MOs play a much lesser role. This is in fact true for many other reactions. As shown earlier in eq. 2, the reactivity of a reaction is dependent on three factors: steric, MOs and charge interactions.

Based on the aforementioned discussion, we can now write another form (**eq. 3**) of the earlier discussed eq. 2.

### Equation 3:

**Interaction energy:**  $\Sigma \text{sterics} - \Sigma \text{orbital overlap} / (E_{\text{LUMO}} - E_{\text{HOMO}}) + \Sigma \text{charge interaction}$

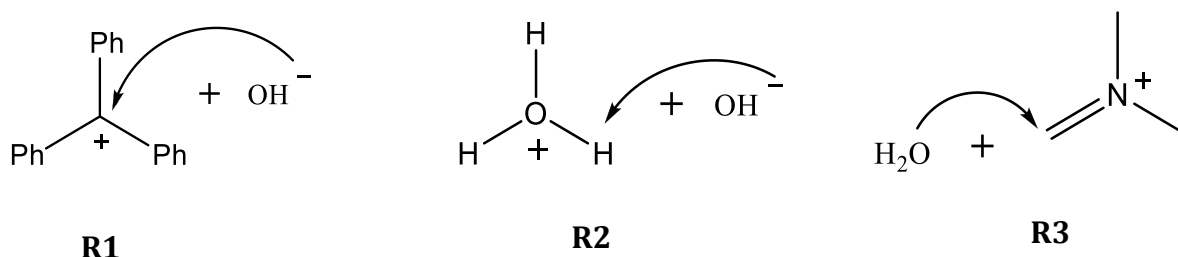


*In summary:*

1. A **hard nucleophile** (negative charge localized and low-energy HOMO) would tend to react with a **hard electrophile** (positive charge localized and high-energy LUMO), leading to a great stabilization by the *electrostatic term*.
2. A **soft nucleophile** (high-energy HOMO) would react with a **soft electrophile** (low-energy LUMO), stabilized by the *orbital term*, because  $E_{\text{HOMO}}(\text{Nu}) - E_{\text{LUMO}}(\text{E})$  is small.

### B. Formal charges in Lewis dot structures and actual charge density in molecules:

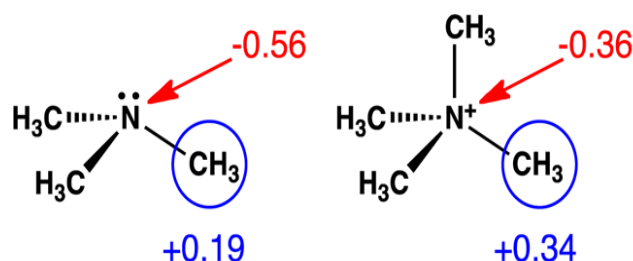
In organic chemistry while drawing mechanisms, very regularly we use the curly arrows to show the movement of electrons from an environment of high negative charge density to one of lower negative charge density. But sometimes if we follow only the interaction between the



**Figure 12:** Reactions involving charged reactants

charges, we would land into problems. Let's look at the three reactions (R1, R2 and R3) shown in fig. 12. In case of R1, there is no ambiguity. A hydroxide ion indeed attacks the central carbon atom of the trityl cation. Hence, in this example the reaction outcome can be predicted by moving the negative charge from hydroxide to the carbon atom possessing a formal positive charge. However, the outcome of the reactions R2 and R3 can't be predicted based on arrow pushing involving only charges. The hydroxide ion never attacks the oxygen atom in hydronium atom which apparently has a positive formal charge of +1. Similarly, water will never attack the nitrogen in the iminium ion in R3. Therefore, the reactions R2 and R3 suggest that there is a problem in following formal charges as often shown in Lewis structures. Of course, you all know now that such outcomes can be explained based on the MO interactions.

Now let's have a look at the calculated charge distributions in trimethylamine and tetramethyl ammonium cation (fig. 13). There is nothing unusual about the charge distribution in trimethylamine. Nitrogen being the more electronegative element, contains a partial negative charge of -0.56 which is cancelled by the fractional +0.19 charge on each of the three methyl groups thus making the molecule on a whole neutral. But if we look at the calculated charge density in tetramethylammonium cation, we find something very interesting. According to the formal charge in Lewis dot structure, we expect a unit positive charge on nitrogen. However, the results show that the situation is quite different. Even in this positively charged ammonium cation, the more electronegative nitrogen still holds a partial negative charge of -0.36 while each of the three methyl groups carries a partial positive charge of +0.34. Logically speaking, it is not surprising at all. Nitrogen being more electronegative than carbon, will always have a negative charge on it, irrespective of the net charge on the molecule.



**Figure 13:** Calculated charge distribution in trimethylamine and tetramethylammonium salt (ref: D. A. Dougherty, *Acc. Chem. Res.* **2013**, 46, 885).