

Nucleophilic Substitution

Topics

General Reactions

Representing mechanisms through curly arrows

S_N1 & S_N2 :

Mechanisms, Reaction profiles

Various Effects on S_N1 and S_N2 reactions

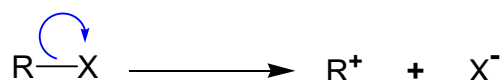
Substrate, Solvent, Nucleophile, Leaving groups

Stereo chemical implications

Reactions

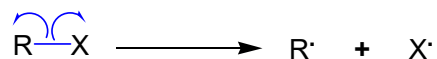
Ionic reactions:

Bond breaking and bond making take place in a **heterolytic fashion**



Radical reactions:

Bond breaking and bond making take place in a **homolytic fashion**



Ionic Reactions :

1) Nucleophilic substitution :



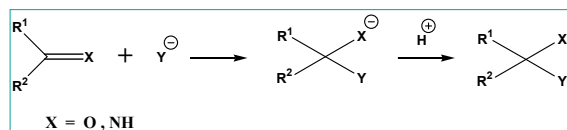
R = aliphatic as well as aromatic

2) Electrophilic substitution :

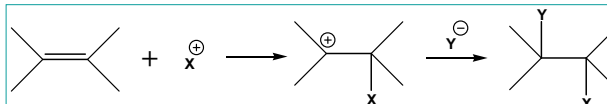


R = aromatic

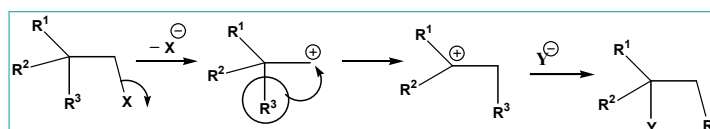
3) Nucleophilic addition :



4) Electrophilic addition :



5) Rearrangements :



Nucleophilic Substitution at a saturated carbon

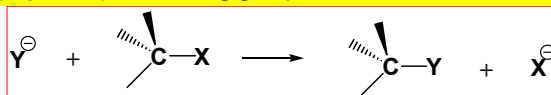
Nucleophile?

It is an electron rich species
reacts with an electron poor species

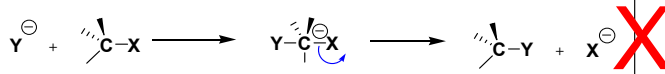
"Nucleophilic substitution" ?

one nucleophile replaces another nucleophile.

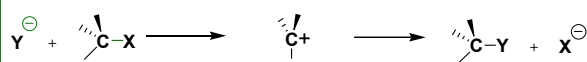
It occurs when an electron rich species, the nucleophile, reacts with an electrophilic saturated C atom which is attached to an electronegative group (important), the leaving group.



nucleophile adds first & leaving gr. goes later

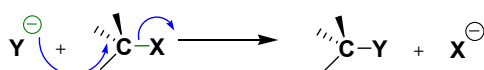


leaving group goes first and nucleophile comes later



S_N1

nucleophile attacks and leaving group goes simultaneously



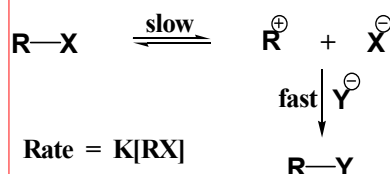
S_N2

Two types of mechanisms

S_N1

S: Substitution
N: Nucleophilic
1: unimolecular

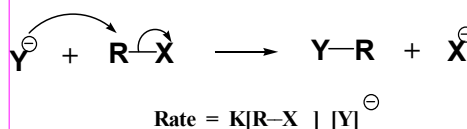
S_N1 :



S_N2

S: Substitution
N: Nucleophilic
2: Bimolecular

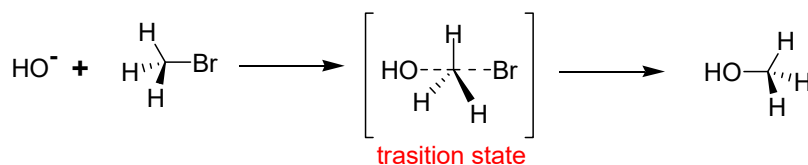
S_N2 :



S_N2

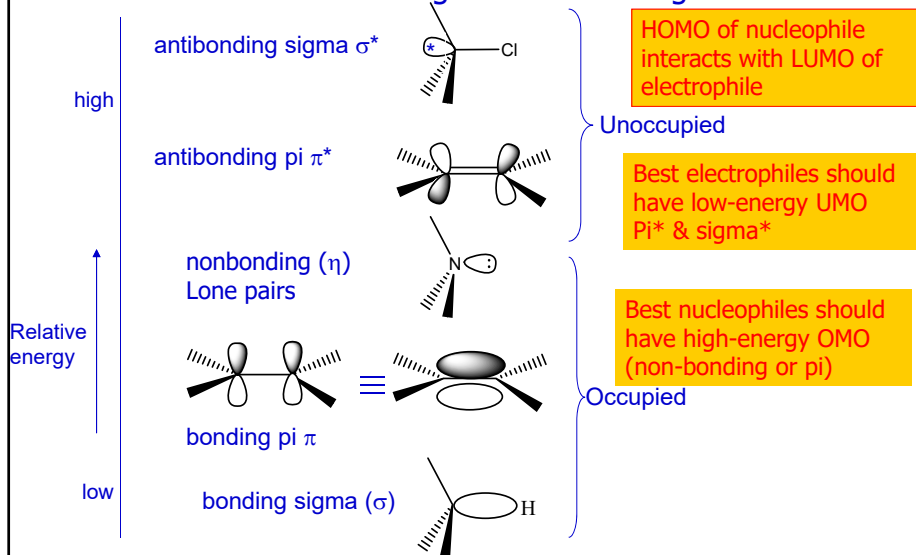
Hydrolysis of bromomethane in aqueous base proceeds according to

$$\text{Rate} = k_2[\text{CH}_3\text{Br}][^-\text{OH}]$$

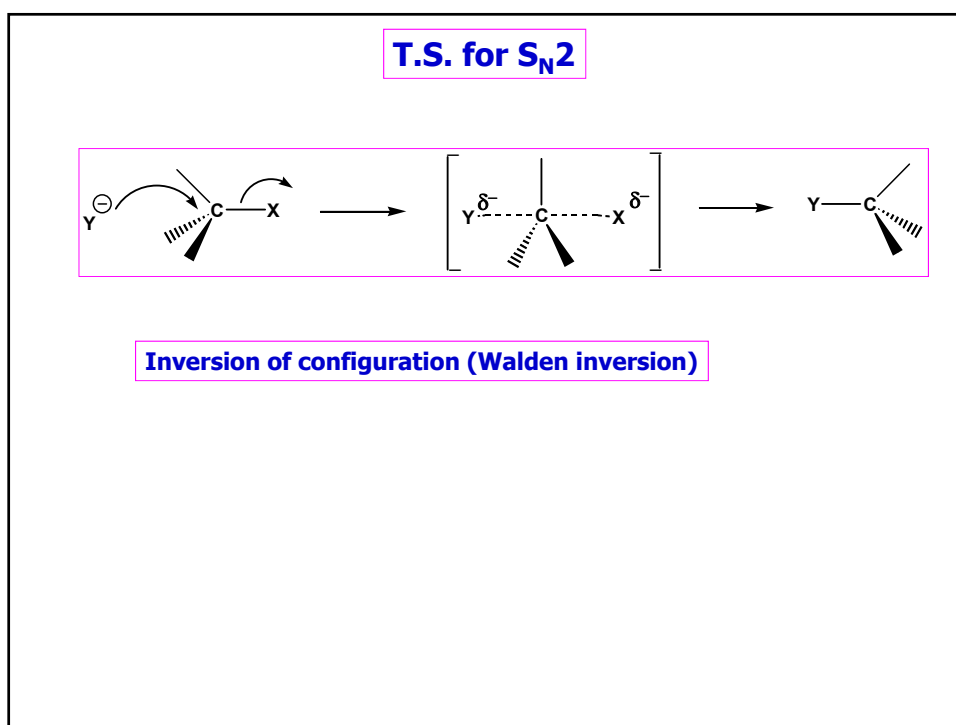
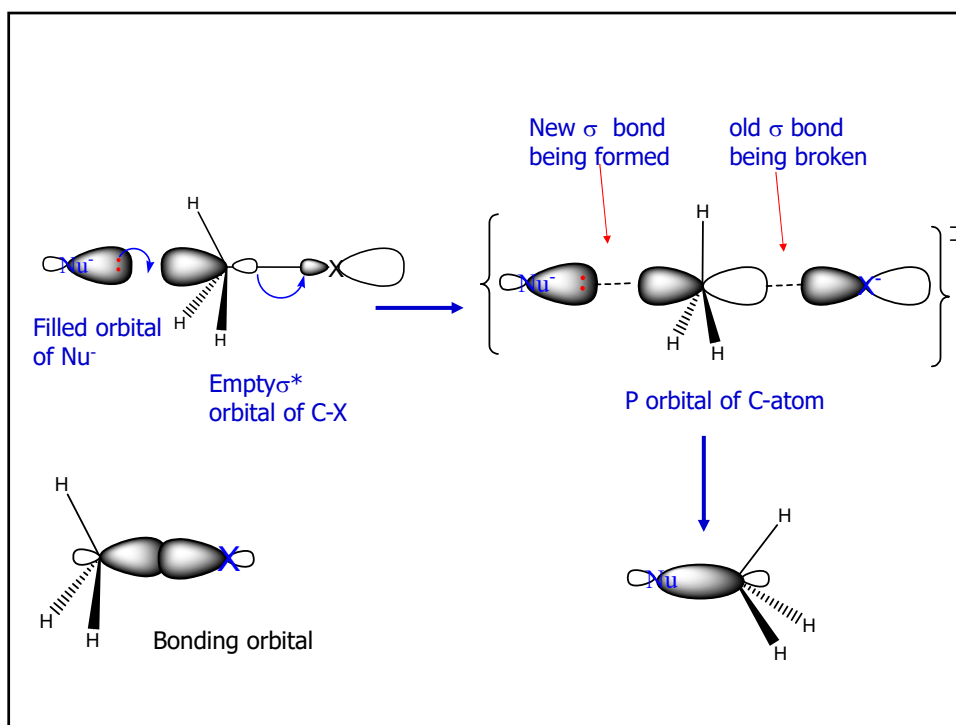


- Both alkyl bromide and ⁻OH are participating in the rate-limiting (slowest) step of the reaction.
- ⁻OH becomes partially attached to carbon before Br⁻ is fully detached.
- Energy necessary for breaking C-Br bond is supplied by that produced in forming HO-C bond.
- Quantum mechanical calculation shows that an approach by ⁻OH along the line of centers of the C & Br is that of lowest

Pictures of bonding and antibonding Orbitals

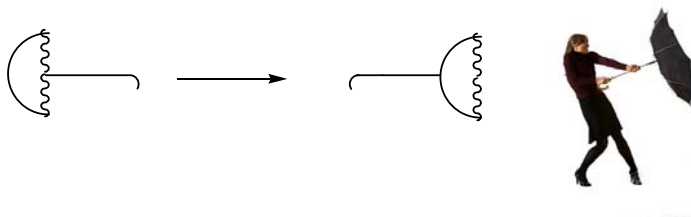


LUMO: lowest unoccupied molecular orbital
HOMO: highest occupied molecular orbital

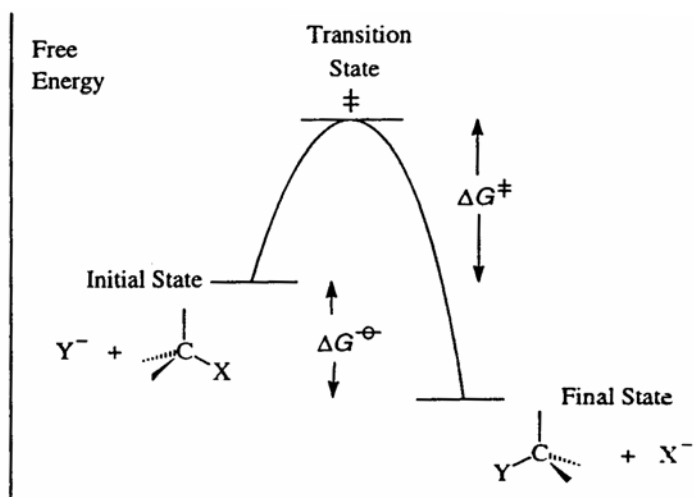


Important Point to Remember :

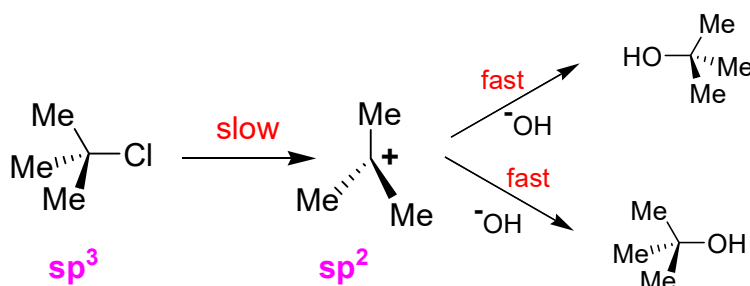
Inversion of configuration does not mean R going to S or vice versa. It means that bond formation takes place opposite to that of bond breaking.....which leads to the inversion. it is like inversion of umbrella in a storm.



Reaction profile for S_N2 reaction:

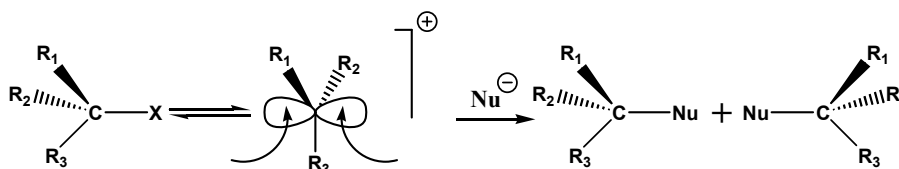


S_N1: Hydrolysis of *t*-butyl chloride by base proceeds according to
Rate = $k_1[t\text{-BuCl}]$ or independent of $[\text{OH}^-]$



1. Halide undergoes slow ionization to yield the ion pair R^+ and Cl^- followed by first attack by OH^- or solvent or nucleophile.
2. The energy necessary to effect the initial ionization is largely recovered from the energy evolved through solvation of the resultant ion-pair.

For $\text{S}_{\text{N}}1$:

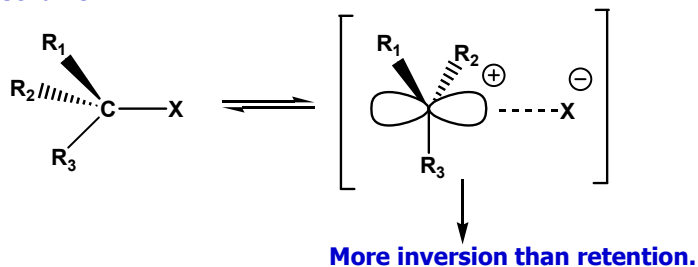


Racemization is expected

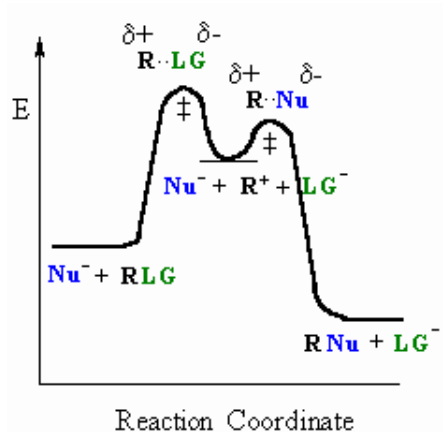
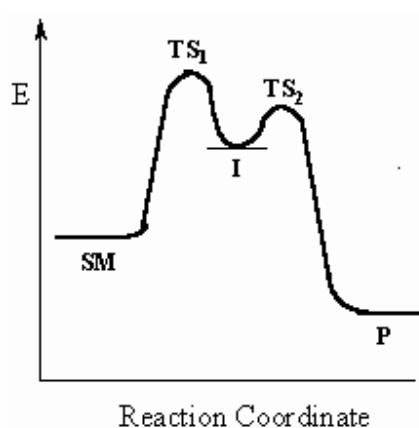
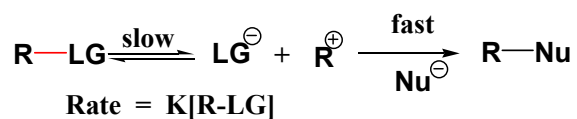
Extent of inversion = extent of retention

However, due to ion pair formation, more inversion than retention.

Ion pair mechanism :



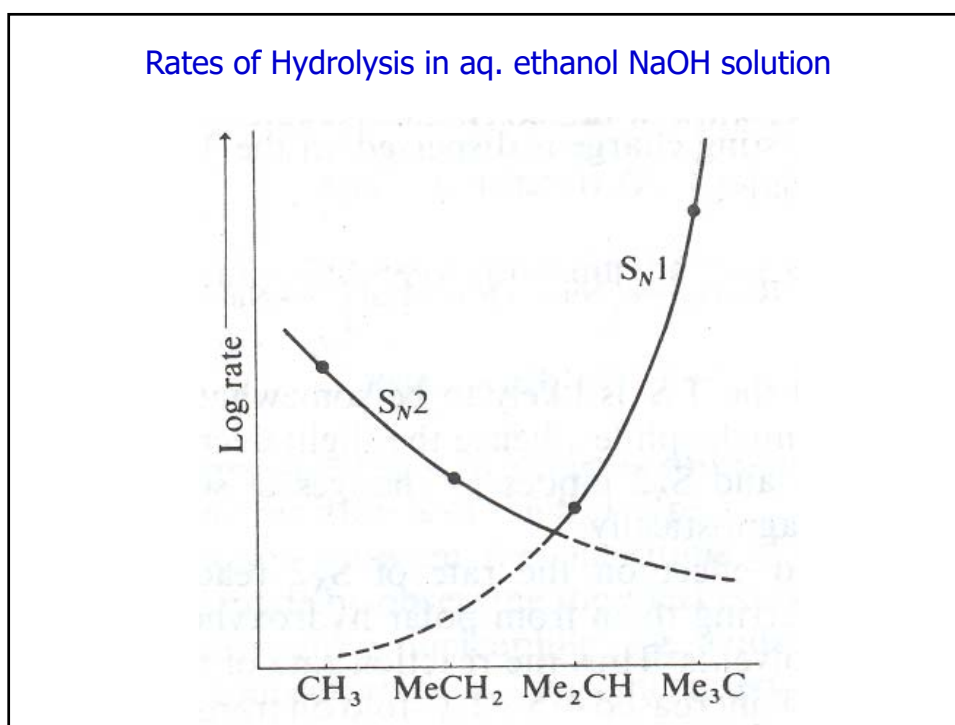
Reaction profile for S_N1 reaction



Factors Affecting the Rates of S_N1 and S_N2 reactions :

- 1) The structure of the substrate
- 2) Concentration and Reactivity of Nucleophile
(for bimolecular reactions only)
- 3) The effect of solvent.
- 4) The nature of leaving group (nucleofuge)
- 5) Stereochemical implications of mechanism

Effect of substrate structure			
<div> <div>ready hydrolysis</div> <div> $\text{H}_3\text{C}-\text{Br}$ $\text{H}_3\text{CH}_2\text{C}-\text{Br}$ $\text{Me}_2\text{HC}-\text{Br}$ $\text{Me}_3\text{C}-\text{Br}$ </div> <div>more resistant</div> </div>			
$\text{R}-\text{X} \xrightarrow{\text{Y}^\ominus} \text{RY} + \text{X}^\ominus$			
Substituent	Compound	$\text{S}_\text{N}2$ Relative Rate, k_2	$\text{S}_\text{N}1$ Relative Rate, k_1
Methyl	$\text{H}_3\text{C}-\text{X}$	6×10^3	0.002
1°	$\text{H}_3\text{CH}_2\text{C}-\text{X}$	30	0.004
2°	$(\text{H}_3\text{C})_2\text{HC}-\text{X}$	1	1
3°	$(\text{H}_3\text{C})_3\text{C}-\text{X}$	0.00005	4×10^6
<p>For $\text{S}_\text{N}2$ methyl > primary > secondary >> tertiary (unreactive)</p> <p>For $\text{S}_\text{N}1$ tertiary >> secondary > primary > methyl</p>			



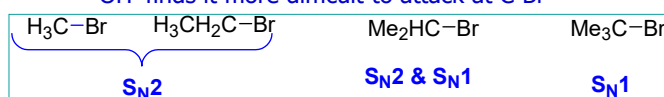
To explain we should consider:

The effect of both **electronic** and **steric** factors on T.S.

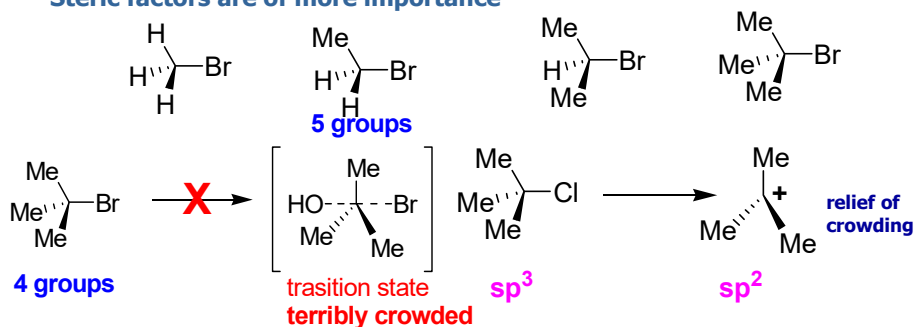
Increase in Me groups: •Inductive effect increases

→ Increase in crowding

OH⁻ finds it more difficult to attack at C-Br

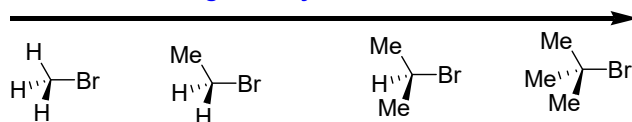


Steric factors are of more importance

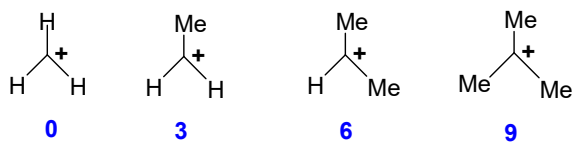


For S_N1 : ion pair formation

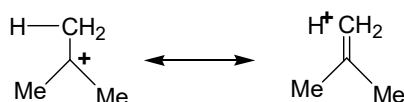
→ increasing stability of the carbocation



inductive effect →



hyperconjugation

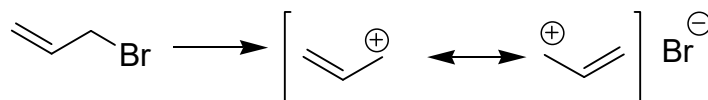


Stability of carbocation is important for S_N1

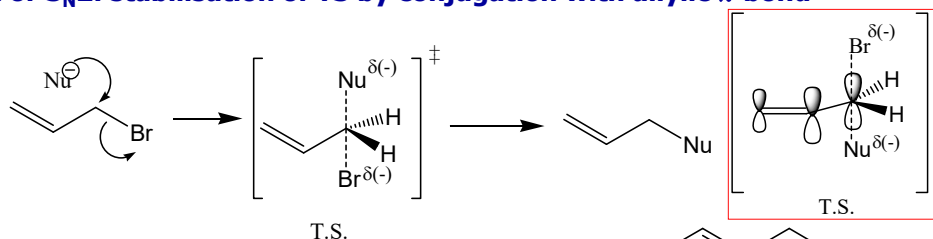


True for both S_N1 and S_N2

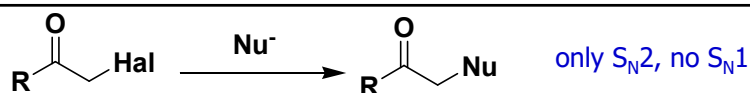
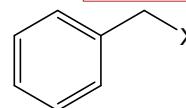
For S_N1 : stabilisation of carbocation by delocalisation



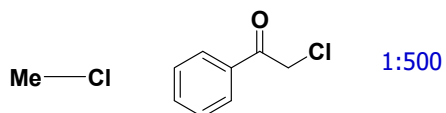
For S_N2 : stabilisation of TS by conjugation with allylic π -bond



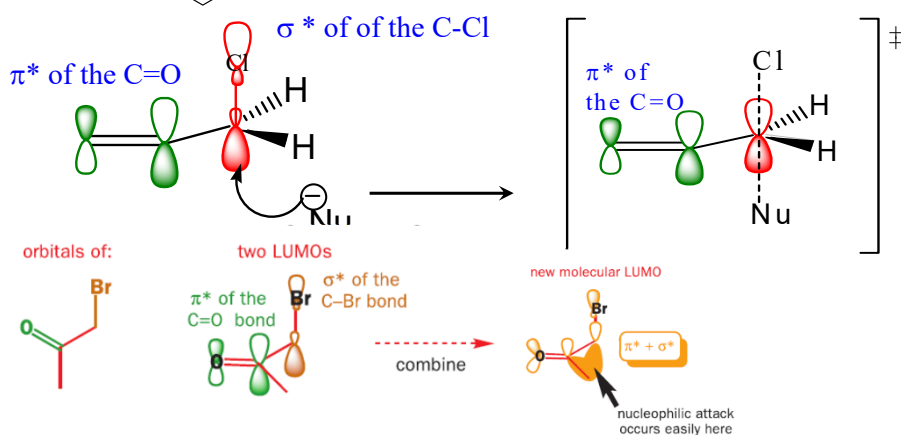
The benzyl group acts in much the same way:



R = alkyl, aryl, OR' Relative rates of S_N2 reactions with iodide ion



C=O group stabilizes the T.S. by Overlap of its π^* orbital with full P-orbital of the C-atom under attack



Relative rates of S_N2 reactions of alkyl chlorides with the iodide ion

Alkyl chloride

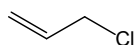
relative rate



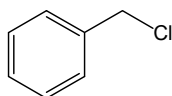
200



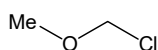
0.02



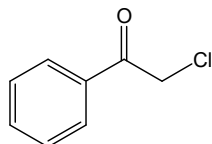
79



200



920



1,00,000

The rates are given with respect to n-BuCl

Relative Rates of Reaction of Alkyl Bromides with Lithium Iodide in Acetone

Alkyl group

Relative Rate

Isopropyl

1.0

Cyclopropyl

no reaction detected

Cyclobutyl

0.008

Cyclopentyl

1.6

Cyclohexyl

0.01

Cycloheptyl

1.0

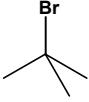
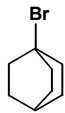
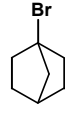
Problems :

1) S_N2 reaction by EtO^- in EtOH :

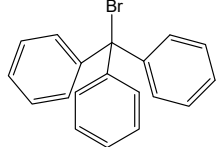
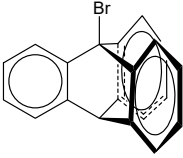
	$\text{CH}_3\text{CH}_2-\text{Br}$	$\text{CH}_3\text{CH}_2\text{CH}_2-\text{Br}$	$\text{Me}_2\text{HCCH}_2-\text{Br}$	$\text{Me}_3\text{CCH}_2-\text{Br}$	
relative rate	1	2.8×10^{-1}	3.0×10^{-2}	24.2×10^{-6}	Explain ?

2) Rate of solvolysis in EtOH :

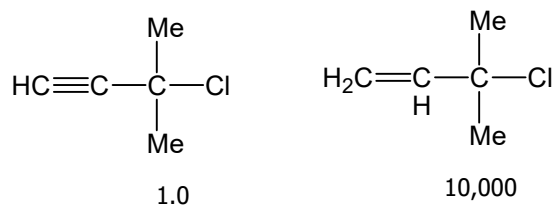
A)

			
1	10^{-6}	10^{-14}	Explain? cc at bridge head, less stable, difficult to attain planarity due to rigidity

B)

		
1	10^{-23} 1-bromotriptycene	Explain ? Rigid structure, cation empty p-orbitals are at right angles to π orbitals of Ph

Q. Relative rate of solvolysis under S_N1 condition



Explain?

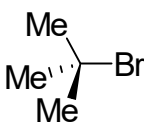
Q. Compare the relative rates of solvolysis of



Which reaction is faster?

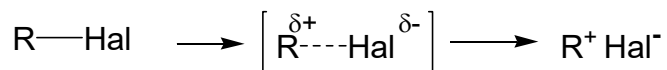
600 times faster
Steric
acceleration

Solvent effect

Solvolysis rate of  in EtOH **1**
in EtOH-H₂O (1:1) **3X10⁴**

Dielectric constant (ϵ , at 25 C): H₂O **79**
EtOH **25**

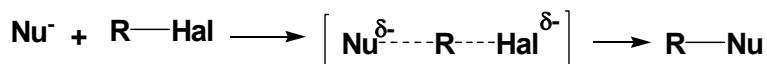
Increase in dielectric constant and/or ion-solvating ability result in a marked increase in reaction rate



The energy required for this process decreases as dielectric constant increases

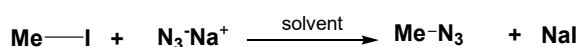
The process is facilitated by increasing solvation and consequent stabilization of the ion-pair

For S_N2 : Increasing dielectric constant has much less effect.
Results in slight decrease in rate



- New charge is not developed.
- Existing charge is dispersed in the T.S. compared with the starting material

Marked effect on the rate of S_N2 reaction, when that transferred from polar protic solvent to polar aprotic solvent.



Rate in MeOH ($\epsilon = 33$) 1

DMF ($\epsilon = 37$) 4.5×10^4

DMSO ($\epsilon = 46$) 1×10^9

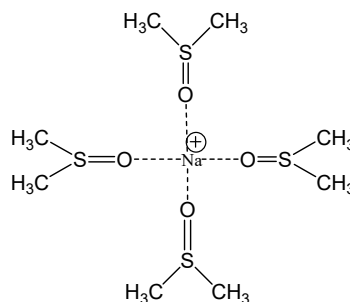
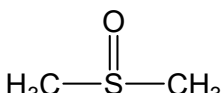
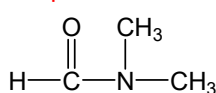
DMF: HCONMe_2

DMSO: Me_2SO

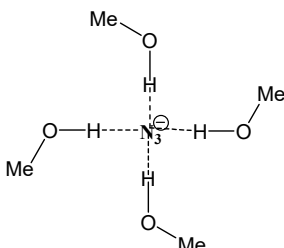
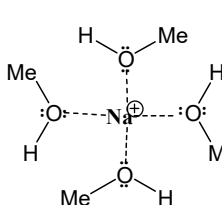
- In MeOH both Na^+ and N_3^- are solvated.
- In DMF only Na^+ is solvated, but not N_3^- .
- So, unsolvated N_3^- is a much more powerful nucleophile

- When RX is capable of undergoing both S_N1 and S_N2 reactions:
- S_N2 reaction will be favored by a high concentration of a good (negatively charged) nucleophile in a polar aprotic solvent,
- S_N1 reaction will be favored by a poor (neutral) nucleophile in a polar protic solvent

Polar aprotic solvents: DMF & DMSO



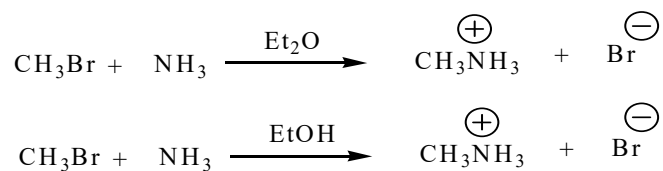
Polar protic solvents: H_2O , MeOH, EtOH



Increase in solvent polarity & ion-solvating ability may change the reaction mode from $S_N2 \rightarrow S_N1$

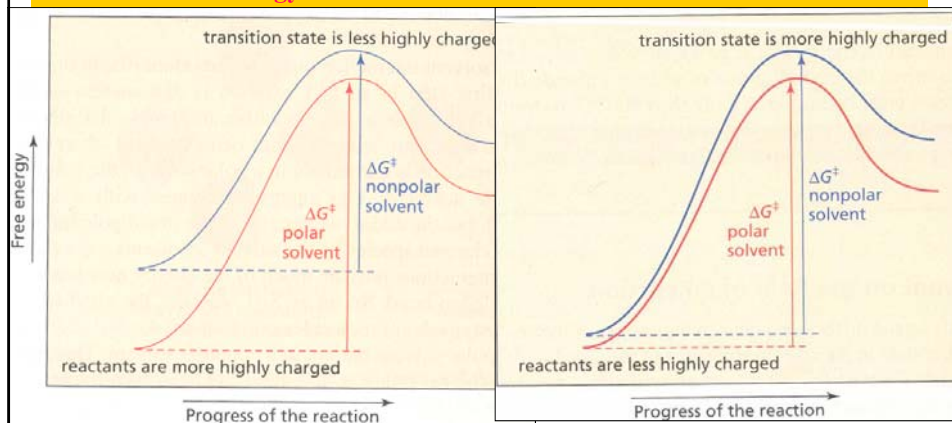
Transfer from polar, protic to polar, aprotic solvents can change the reaction mode from $S_N1 \rightarrow S_N2$

Q. Which reaction will take place more rapidly?



Solvent effects

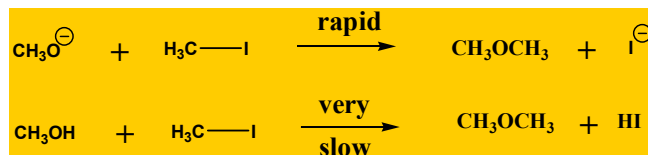
Rate of a reaction depends on the difference between the energy of the reactants & the energy of the TS in the r.d.s. of reaction



- Increasing the polarity of the solvent decreases the rate of the reaction if the reactants in RDS are charged
- Increasing polarity of the solvent increases the rate of the reaction if none of the reactants in RDS are charged

Effect of Nucleophile :

The nucleophilicity may be correlated to its basicity as both involve the availability of the electron pairs and the ease with which it is donated



Nucleophilicity of

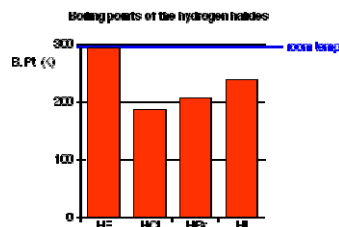
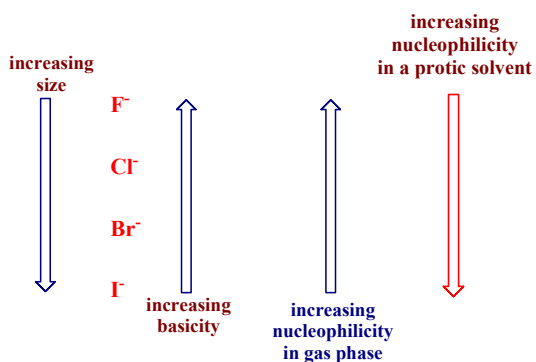


A negatively charged nucleophile is always stronger than its conjugate acid.

Stronger base better nucleophile		weaker base poorer nucleophile
HO^\ominus	$>$	H_2O
$\text{CH}_3\text{O}^\ominus$	$>$	CH_3OH
$\text{H}_2\text{N}^\ominus$	$>$	NH_3

The direct relationship between basicity and nucleophilicity is maintained if the reaction occurs in the gas phase

Halide ions nucleophilicity



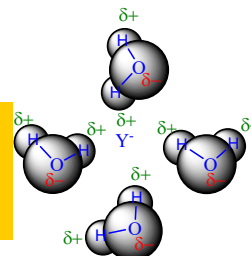
pKa (aq)

3.17

-7

-9

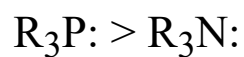
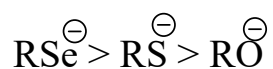
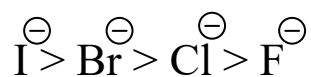
-10



- Ion-dipole interactions
- In order to undergo NS these interactions should be broken
- Weak bases interact weakly with polar solvents
- Strong bases interact strongly with polar solvents

Nucleophilic power towards saturated carbon

In a particular group, nucleophilicity increases as we go down the group



Effectiveness of different nucleophiles in $\text{S}_{\text{N}}2$ reaction

Relative rates of reaction with MeBr in EtOH

Nucleophile	pKa of HX	Relat. rates
HO^{\ominus}	15.7	1.2×10^4
PhO^{\ominus}	10.0	2.0×10^3
AcO^{\ominus}	4.8	19.0×10^2
H_2O	-1.7	1.0

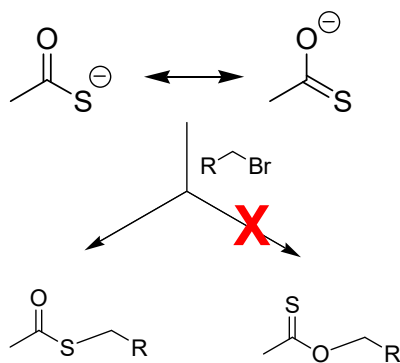
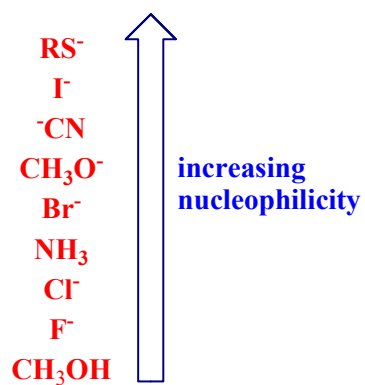
The anions of the weakest acids are the best nucleophiles

Relative rates of reaction with MeBr in EtOH

Nucleophile	pKa of HX	Relat. rates
PhS^{\ominus}	6.4	5.0×10^7
PhO^{\ominus}	10.0	2.0×10^3

PhO^{\ominus} (RO^{\ominus}) is more basic than PhS^{\ominus} (RS^{\ominus})

Relative nucleophilicity toward CH_3I in MeOH

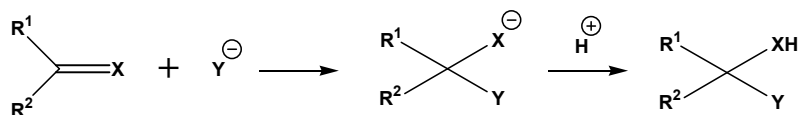


So, sulfur is a better nucleophile than oxygen for saturated carbon. Why should this be ?

There are two main factors controlling bimolecular reaction:

i) Electrostatic attraction (simple attraction of opposite charges)

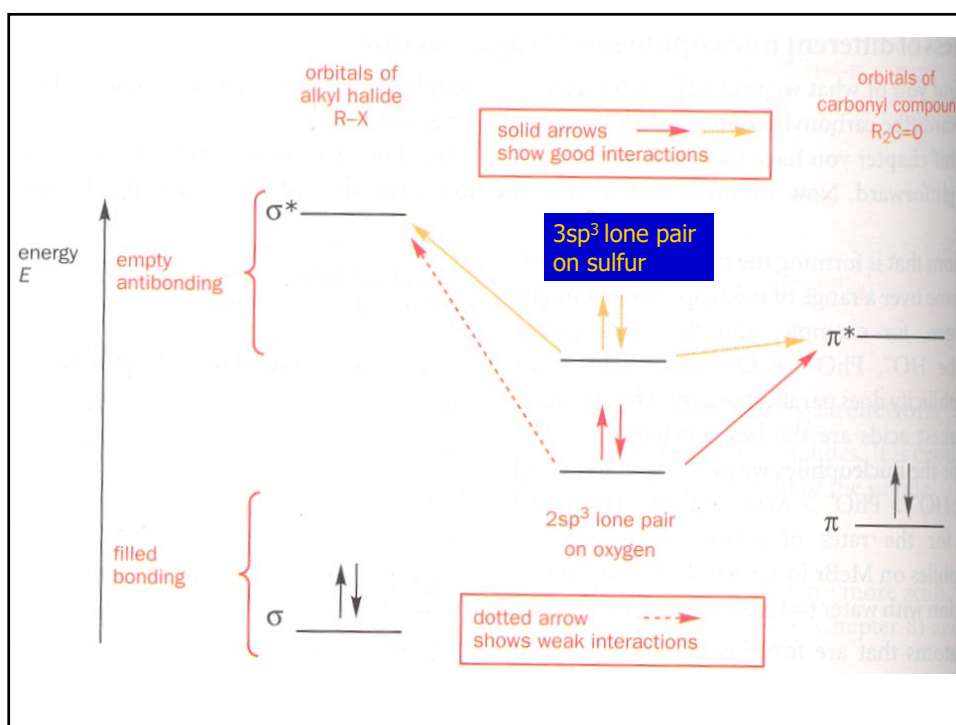
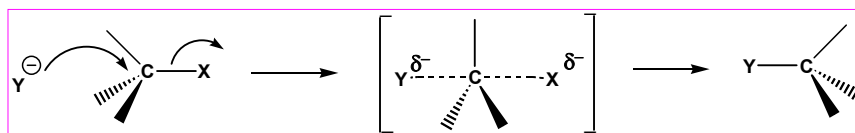
ii) Productive interaction between the HOMO of the nucleophile and the LUMO of the electrophile



$\text{X} = \text{O}, \text{NH}$

Heavily influenced by electrostatic attraction
(as well as by HOMO-LUMO interaction).

**Electrostatic attraction is unimportant in $\text{S}_{\text{N}}2$ reactions,
only HOMO-LUMO interaction matters**



Hard nucleophiles and Soft nucleophiles

Small with closely held electrons with high charge density	Large & Flabby with diffuse high energy electrons
Only charged	Can be neutral
Basic (HX weak acid)	Not basic (HY strong acid)
Low energy HOMO	High energy HOMO
Like to attack at C=O	Like to attack at saturated carbon
RO^- , NH_2^- , R^- , F^- , Cl^-	RS^- , I^- , R_3P , RSH
Reactions are controlled by Electrostatic interactions	Reactions are controlled by HOMO-LUMO interactions

Broder line: N_3^- , CN^- , Br^- , RNH_2