

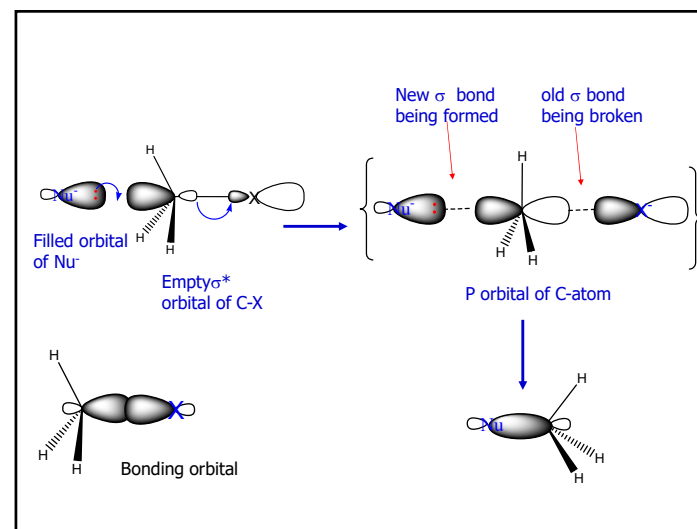
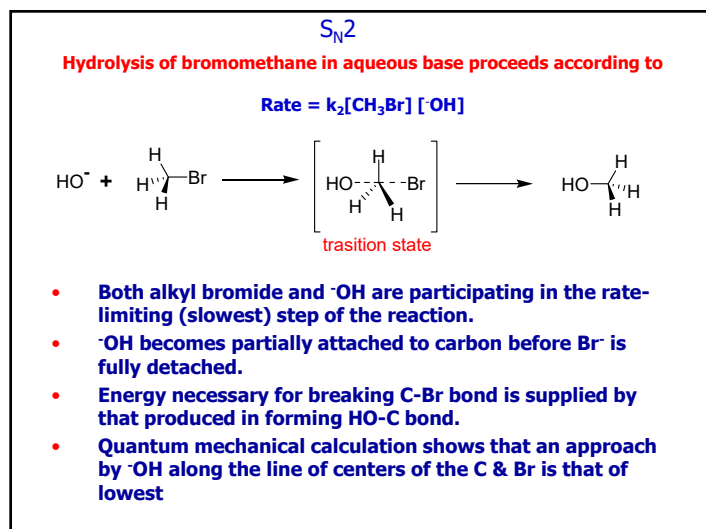
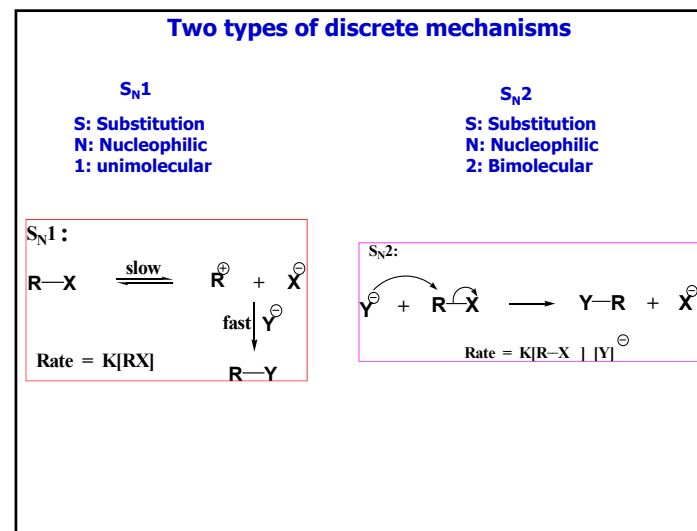
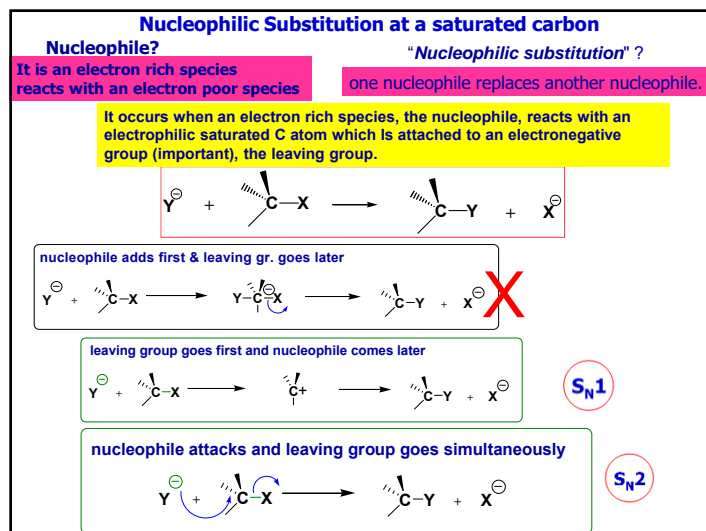
Nucleophilic Substitutions & Eliminations

Topics

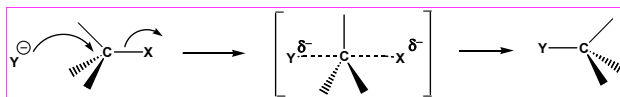
S_N1 & S_N2 :
Mechanisms, Reaction profiles

Various Effects on S_N1 and S_N2 reactions
Substrate, Solvent, Nucleophile, Leaving groups

Stereo chemical implications in substitutions and elimination reactions



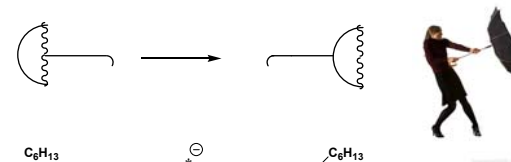
T.S. for S_N2



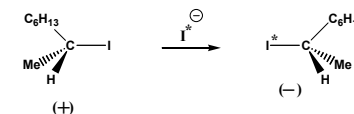
Inversion of configuration (Walden inversion)

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.

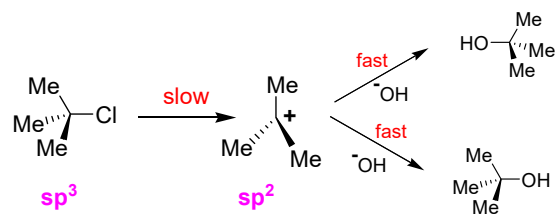


Q.



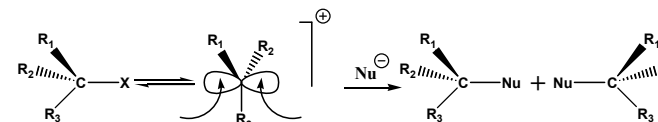
Rate of racemization = twice the rate of inversion or incorporations

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 S_N1 :

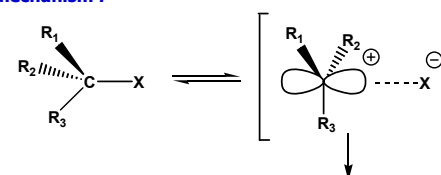


Racemization is expected

Extent of inversion = extent of retention

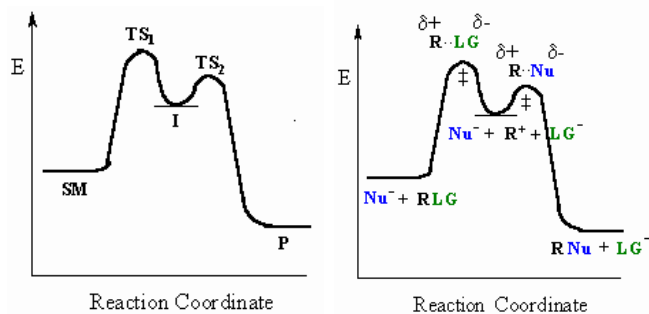
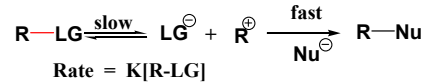
However, due to ion pair formation, more inversion than retention.

Ion pair mechanism :



More inversion than retention.

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

ready hydrolysis

H₃C-Br H₃CH₂C-Br Me₂HC-Br Me₃C-Br

more resistant

$\text{R-X} \xrightarrow{\text{Y}^-} \text{RY} + \text{X}^-$

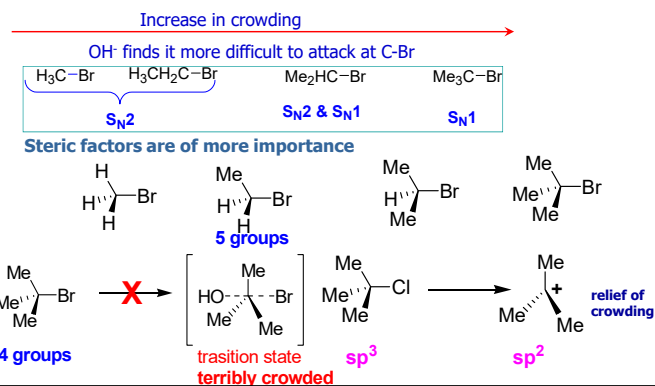
Substituent	Compound	Relative Rate, k ₂ (S _N 2)	Relative Rate, k ₁ (S _N 1)
Methyl	H ₃ C-X	6x10 ³	0.002
1°	H ₃ CH ₂ C-X	30	0.004
2°	(H ₃ C) ₂ HC-X	1	1
3°	(H ₃ C) ₃ C-X	0.00005	4x10 ⁶

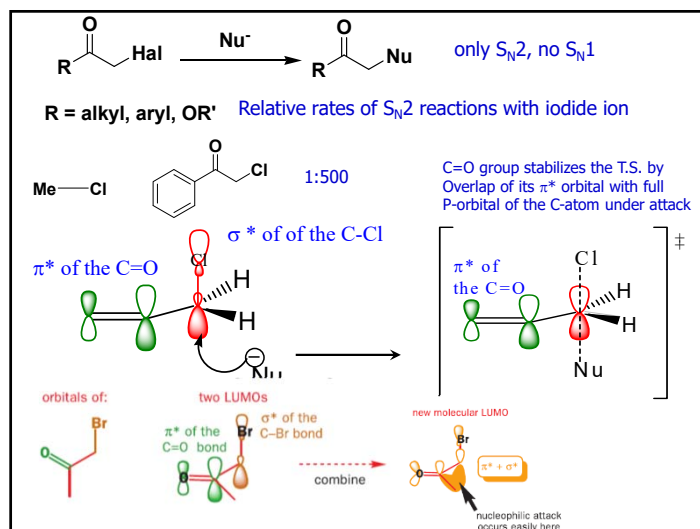
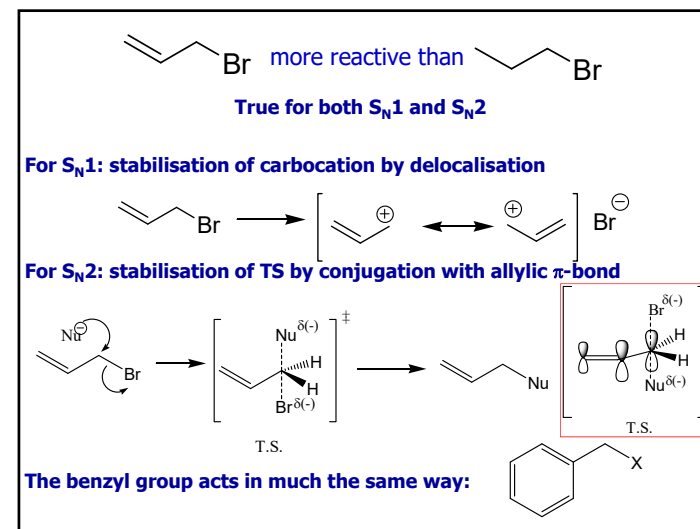
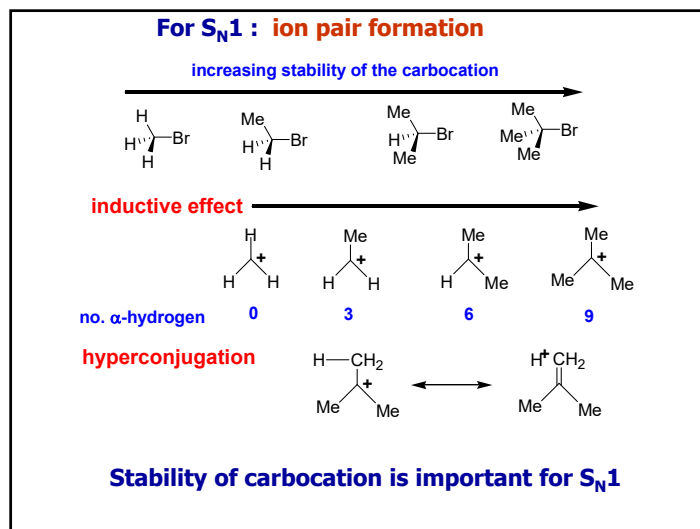
For S_N2 methyl > primary > secondary >> tertiary (unreactive)
For S_N1 tertiary >> secondary > primary > methyl

To explain we should consider:

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

Increase in Me groups: •Inductive effect increases





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

Alkyl chloride	relative rate
<chem>Me-Cl</chem>	200
<chem>CH3CH(Cl)CH3</chem>	0.02
<chem>CH2=CHCH2Cl</chem>	79
<chem>c1ccccc1CH2Cl</chem>	200
<chem>MeOCH2Cl</chem>	920
<chem>c1ccccc1C(=O)CH2Cl</chem>	1,00,000

The rates are given with respect to n-BuCl

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

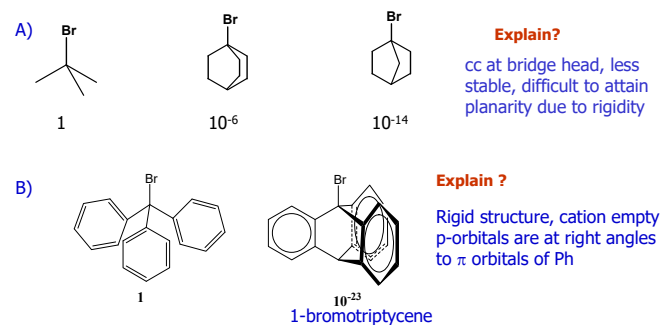
Alkyl group	Relative Rate
Isopropyl	1.0
Cyclopropyl	no reaction detected
Cyclobutyl	0.008
Cyclopentyl	1.6
Cyclohexyl	0.01
Cycloheptyl	1.0

Problems :

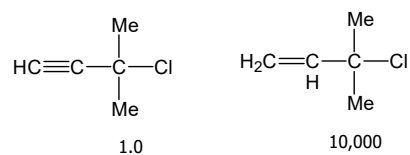
1) S_N2 reaction by EtO⁻ in EtOH:

	CH ₃ CH ₂ -Br	CH ₃ CH ₂ CH ₂ -Br	Me ₂ HCCH ₂ -Br	Me ₃ CCH ₂ -Br	Explain ?
relative rate	1	2.8X10 ⁻¹	3.0X10 ⁻²	24.2X10 ⁻⁶	

2) Rate of solvolysis in EtOH :



Q. Relative rate of solvolysis under S_N1 condition



Explain?

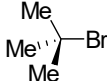
Q. Compare the relative rates of solvolysis of



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

$$\text{R}-\text{Hal} \longrightarrow \left[\text{R}^{\delta+} \cdots \text{Hal}^{\delta-} \right] \longrightarrow \text{R}^+ \text{Hal}^-$$

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

$$\text{Nu}^- + \text{R}-\text{Hal} \longrightarrow \left[\text{Nu}^{\delta-} \cdots \text{R} \cdots \text{Hal}^{\delta-} \right] \longrightarrow \text{R}-\text{Nu}$$

- 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.

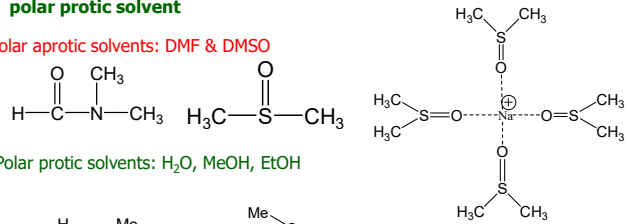
$$\text{Me}-\text{I} + \text{N}_3^-\text{Na}^+ \xrightarrow{\text{solvent}} \text{Me}-\text{N}_3 + \text{NaI}$$

Rate in MeOH (ε = 33)	1	
DMF (ε = 37)	4.5X10⁴	DMF: HCONMe ₂
DMSO (ε = 46)	1X10⁹	DMSO: Me ₂ SO

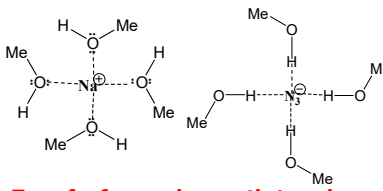
- In MeOH both Na⁺ and N₃⁻ are solvated.
- In DMF only Na⁺ is solvated, but not N₃⁻.
- So, unsolvated N₃⁻ is a much more powerful nucleophile

- 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: H₂O, MeOH, EtOH



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

Transfer from polar, protic to polar, aprotic solvents can change the reaction mode from S_N1 → S_N2

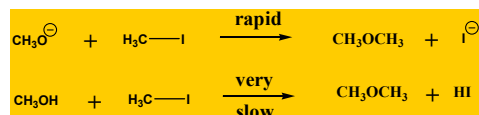
Q. Which reaction will take place more rapidly?

$$\text{CH}_3\text{Br} + \text{NH}_3 \xrightarrow{\text{Et}_2\text{O}} \text{CH}_3\text{NH}_3^+ + \text{Br}^-$$

$$\text{CH}_3\text{Br} + \text{NH}_3 \xrightarrow{\text{EtOH}} \text{CH}_3\text{NH}_3^+ + \text{Br}^-$$

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

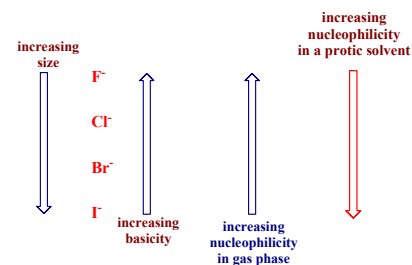


Nucleophilicity of $\text{CH}_3\text{O}^- > \text{CH}_3\text{OH}$ A negatively charged nucleophile is always stronger than its conjugate acid.

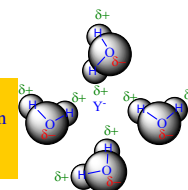
Stronger base better nucleophile		weaker base poorer nucleophile
HO^-	$>$	H_2O
CH_3O^-	$>$	CH_3OH
H_2N^-	$>$	NH_3

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

Halide ions nucleophilicity

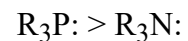
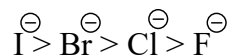


- Ion-dipole interactions
- In order to undergo $\text{S}_\text{N}2$ these interactions should be broken
- Weak bases interact weakly with polar solvents
- Strong bases interact strongly with polar solvents



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^-	15.7	1.2×10^4
PhO^-	10.0	2.0×10^3
AcO^-	4.8	19.0×10^2
H_2O	-1.7	1.0

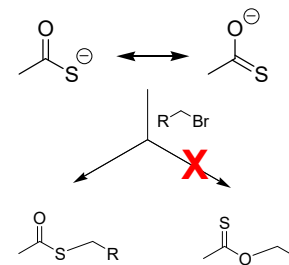
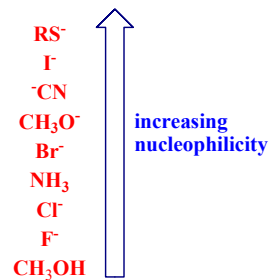
The anions of the weakest acids are the best nucleophiles

Relative rates of reaction with MeBr in EtOH

Nucleophile	pKa of HX	Relat. rates
PhS^-	6.4	5.0×10^7
PhO^-	10.0	2.0×10^3

PhO^- (RO^-) is more basic than PhS^- (RS^-)

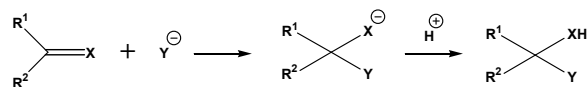
Relative nucleophilicity toward CH_3I in MeOH



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

There are two main factors controlling bimolecular reaction:

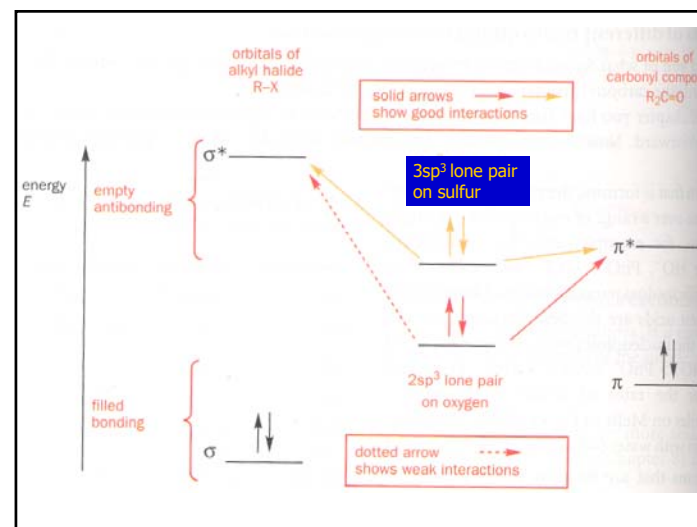
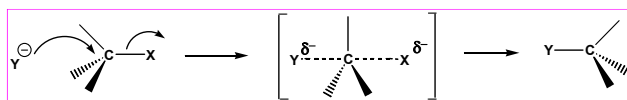
- Electrostatic attraction (simple attraction of opposite charges)
- Productive interaction between the HOMO of the nucleophile and the LUMO of the electrophile



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

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

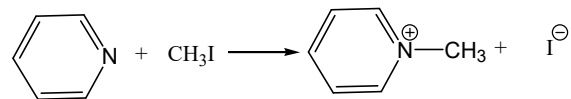
Electrostatic attraction is unimportant in $\text{S}_{\text{N}}2$ reactions, only HOMO-LUMO interaction matters



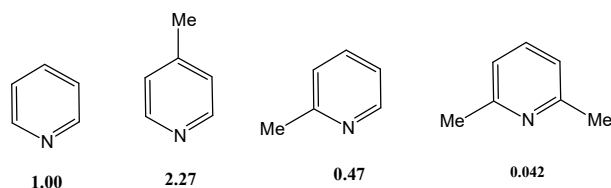
Hard nucleophiles and Soft nucleophiles

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 ₃ P, RSH
Reactions are controlled by Electrostatic interactions	Reactions are controlled by HOMO-LUMO interactions

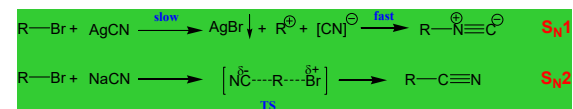
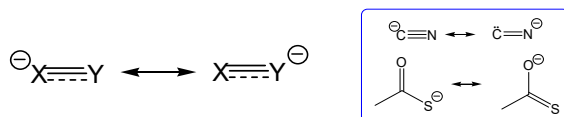
Broder line: N_3^{\ominus} , CN^{\ominus} , Br^{\ominus} , RNH_2



Explain the relative rate

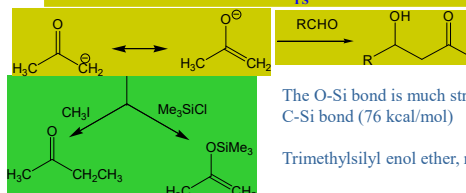
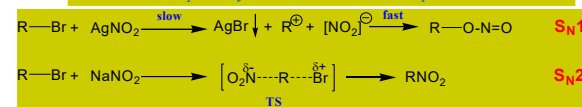


Ambident nucleophile: Nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate.



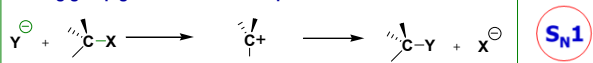
Ag⁺ promotes the formation of R⁺ by the formation of AgX ppt.
Nu attacks from the side that has more electro negative atom.

Na⁺ doesn't show such promotion for the formation of R⁺.
Nu attack takes place by the end which has more polarisable atom.

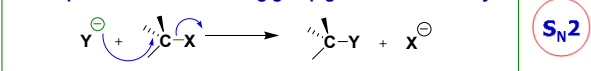


Effect of leaving Group

leaving group goes first and nucleophile comes later

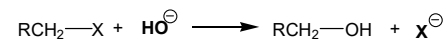


nucleophile attacks and leaving group goes simultaneously



There is an effect of leaving group!!!!

The leaving group:



X:	I	Br	Cl	F
Relative rate	30,000	10,000	2,00	1
Strength of C-X bond (kJ mol ⁻¹)				
Halide (X)				pk _a of HX
Fluorine		118		+3
Chlorine		81		-7
Bromine		67		-9
Iodine		54		-10

Low C-X energy, ionizes easily

I⁻ is weaker base

The weaker the basicity of a group, the better is the leaving ability.

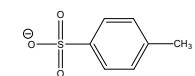
Size is more important than the electronegativity

Influencing Factors of Leaving groups

- The strength of R-X bond
- The polarisability of the bond
- The stability of X⁽⁻⁾
- The degree of stabilisation through solvation of X⁽⁻⁾

For halides (a) & (b) are more important

(c) & (d) becomes more important for following groups

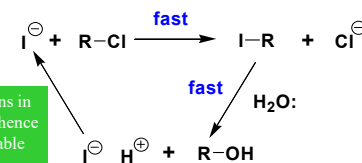
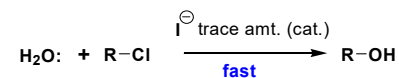
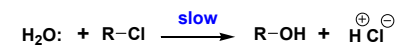


p-toluenesulfonate ion
(Tosylate)



triflate ion
(a "super" leaving group)

Nucleophilic catalysis



Outer shell electrons in I⁻ are loosely held hence it is highly polarisable

It is a good leaving and good entering group.