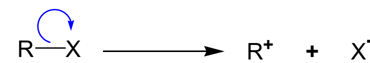
Nucleophilic Substitution

Reactions

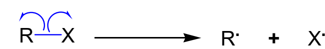
Ionic reactions:

Bond breaking and bond making take place in a heterolytic fashion



Radical reactions:

Bond breaking and bond making take place in a homolytic fashion



Topics

General Reactions

Representing mechanisms through curly arrows

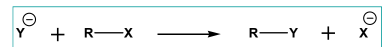
S_N1 & S_N2:
Mecahanisms, Reaction profiles

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

Stereo chemical implications

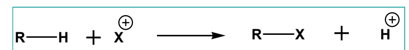
Ionic Reactions :

1) Nucleophilic substitution :



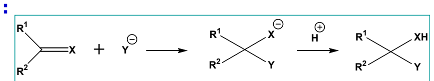
R = aliphatic as well as aromatic

2) Eletrophilic substitution :



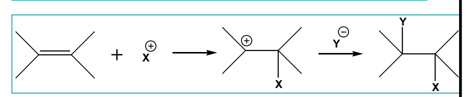
R = aromatic

3) Nucleophilic addition :

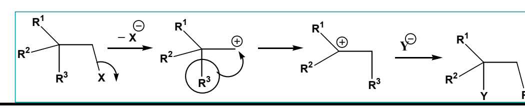


X = O , NH

4) Eletrophilic addition :



5) Rearrangements :



Nucleophilic Substitution at a saturated carbon

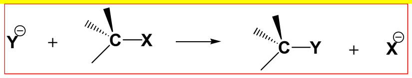
Nucleophile?

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

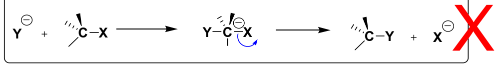
"*Nucleophilic substitution*" ?

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.



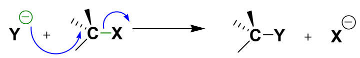
nucleophile adds first & leaving gr. goes later



leaving group goes first and nucleophile comes later

S_N1

nucleophile attacks and leaving group goes simultaneously

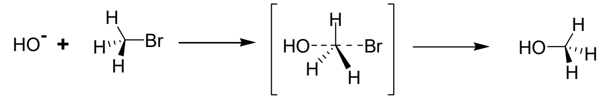


S_N2

S_N2

Hydrolysis of bromomethane in aqueous base proceeds according to

Rate = $k_2[CH_3Br]\,[^-OH]$



trasition state

- **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**

Two types of mechanisms

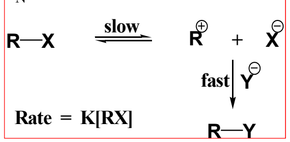
S_N1

S: Substitution
N: Nucleophilic
1: unimolecular

S_N2

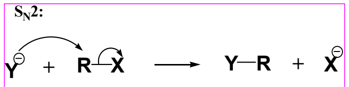
S: Substitution
N: Nucleophilic
2: Bimolecular

S_N1 :



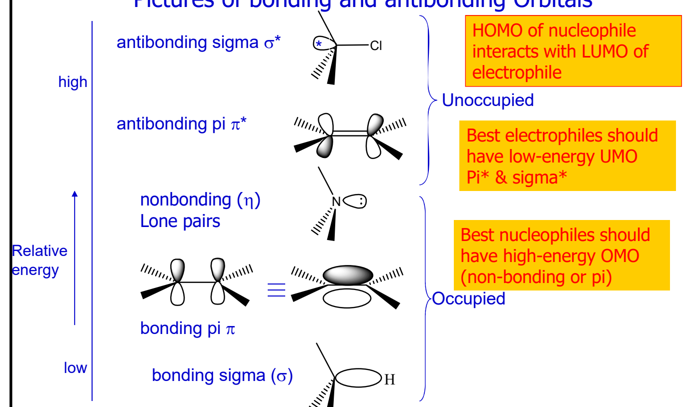
Rate = K[RX]

S_N2:

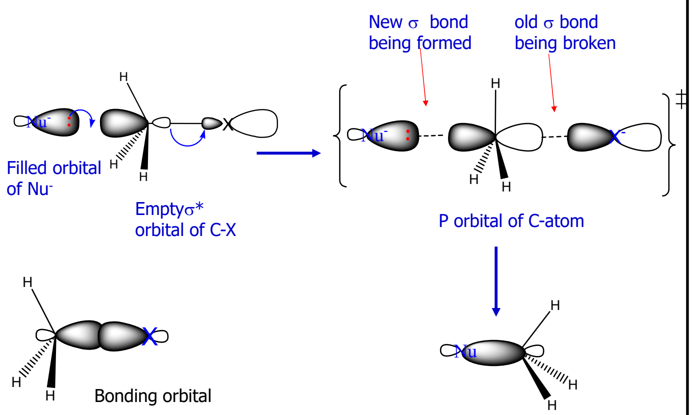


Rate = $K[R\!-\!X]\,[Y^{\ominus}]$

Pictures of bonding and antibonding Orbitals

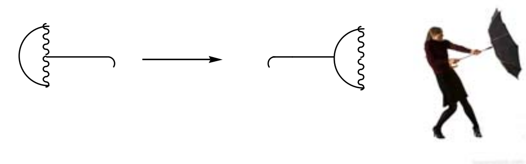


LUMO: lowest unoccupied molecular orbital
HOMO: highest occupied molecular orbital

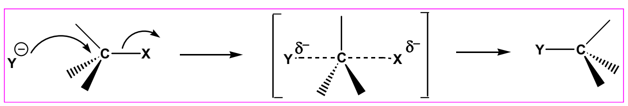


Important Point to Remember :

**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.**

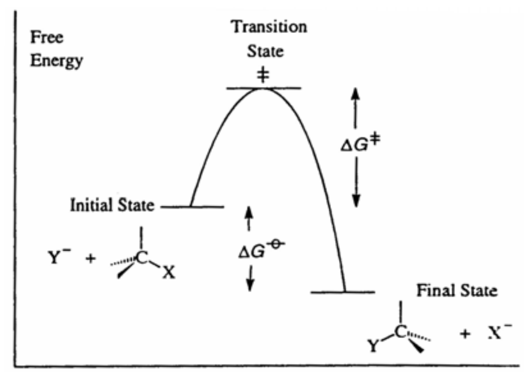


T.S. for S_N2

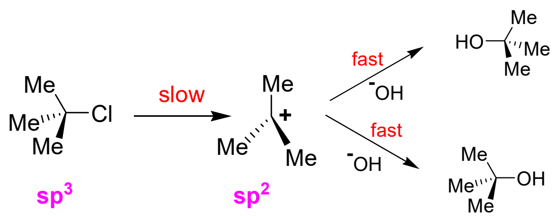


Inversion of configuration (Walden inversion)

Reaction profile for S_N2 reaction:

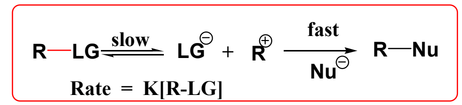


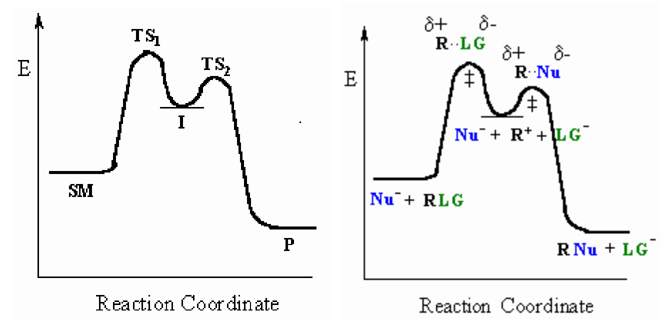
S_N1: Hydrolysis of *t*-butyl chloride by base proceeds according to Rate = k_1[*t*-BuCl] or independent of [OH^-]



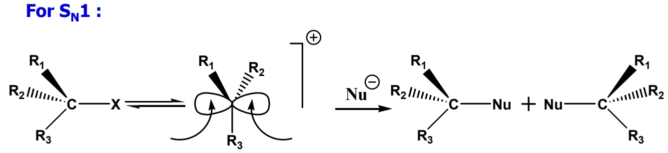
1. Halide undergoes slow ionization to yield the ion pair R^+ and Cl^- followed by first attack by ^-OH or solvent or nuleophile.
2. The energy necessary to effect the initial ionization is largely recovered from the energy evolved through solvation of the resultant ion-pair.

Reaction profile for S_N1 reaction





For S_N1 :

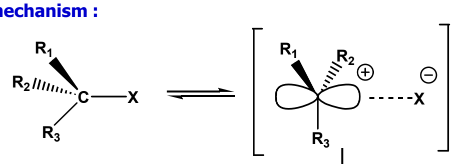


Racemization is expected

Extent of inversion = extent of retention

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

Ion pair mechanism :



More inversion than retention.

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

$H_3C{-}Br$ $\quad$ $\underbrace{H_3CH_2C{-}Br \quad Me_2HC{-}Br}_{\text{more resistant}}$ $\quad$ $Me_3C{-}Br$

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

Substituent	Compound	S_N2 Relative Rate, k_2	S_N1 Relative Rate, k_1
Methyl	$H_3C{-}X$	6×10^3	0.002
1°	$H_3CH_2C{-}X$	30	0.004
2°	$(H_3C)_2HC{-}X$	1	1
3°	$(H_3C)_3C{-}X$	0.00005	4×10^6

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.

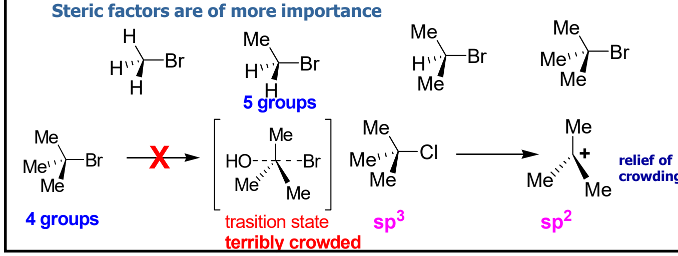
Increase in Me groups: •Inductive effect increases

Increase in crowding

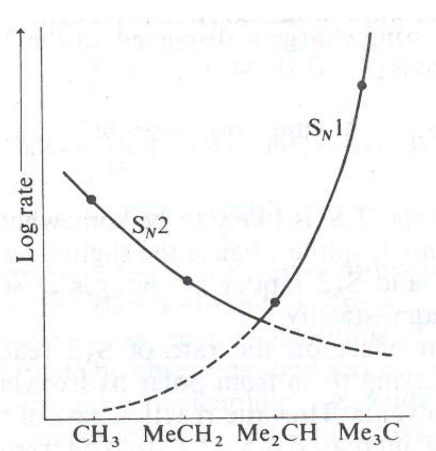
OH^- finds it more difficult to attack at C-Br

$\underbrace{H_3C{-}Br \quad H_3CH_2C{-}Br}_{S_N2}$ $\quad$ $\underset{S_N2\ \&\ S_N1}{Me_2HC{-}Br}$ $\quad$ $\underset{S_N1}{Me_3C{-}Br}$

Steric factors are of more importance

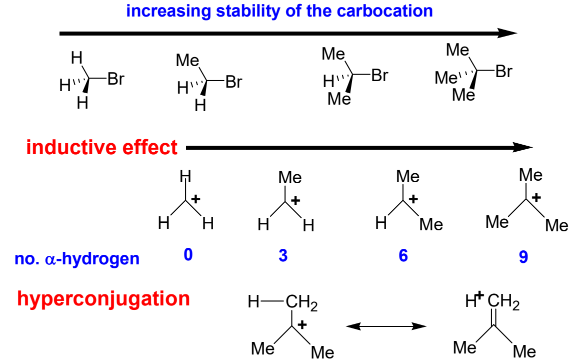


Rates of Hydrolysis in aq. ethanol NaOH solution



For S_N1 : ion pair formation

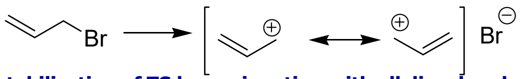
increasing stability of the carbocation



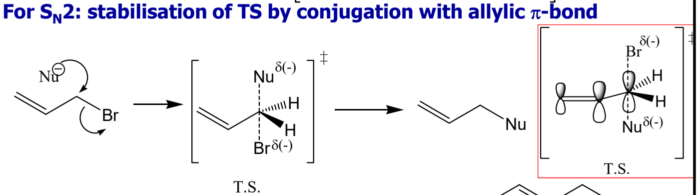
Stability of carbocation is important for S_N1

True for both S_N1 and S_N2

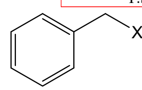
For S_N1: stabilisation of carbocation by delocalisation



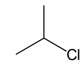
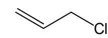
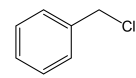
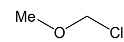
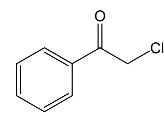
For S_N2: stabilisation of TS by conjugation with allylic π-bond



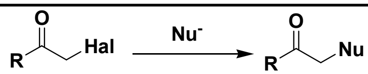
The benzyl group acts in much the same way:



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

Alkyl chloride	relative rate
Me—Cl	200
	0.02
	79
	200
	920
	1,00,000

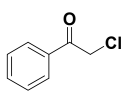
The rates are given with respect to n-BuCl



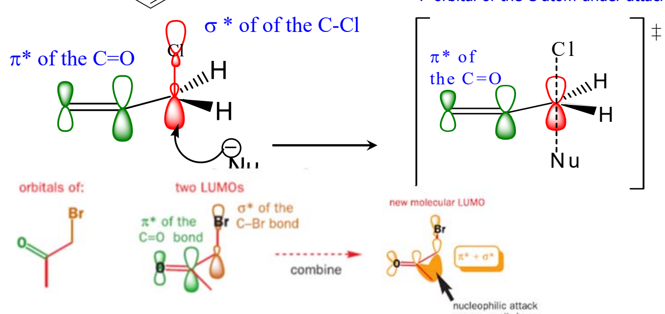
only S_N2, no S_N1

R = alkyl, aryl, OR'

Relative rates of S_N2 reactions with iodide ion

Me—Cl  1:500

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 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 :

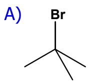
1) S_N2 reaction by EtO^- in EtOH:

	CH_3CH_2-Br	$CH_3CH_2CH_2-Br$	Me_2HCCH_2-Br	Me_3CCH_2-Br
relative rate	1	$2.8X10^{-1}$	$3.0X10^{-2}$	$24.2X10^{-6}$

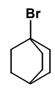
Explain ?

2) Rate of solvolysis in EtOH :

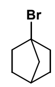
A)



1



10^{-6}

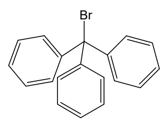


10^{-14}

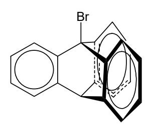
Explain?

cc at bridge head, less stable, difficult to attain planarity due to rigidity

B)



1



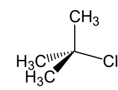
10^{-23}

1-bromotriptycene

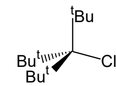
Explain ?

Rigid structure, cation empty p-orbitals are at right angles to π orbitals of Ph

Q. Compare the relative rates of solvolysis of



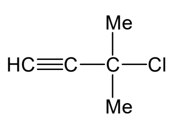
&



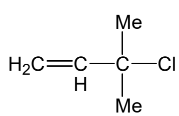
Which reaction is faster?

600 times faster
Steric acceleration

Q. Relative rate of solvolysis under S_N1 condition



1.0

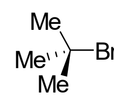


10,000

Explain?

Solvent effect

Solvolysis rate of



in EtOH	1
in EtOH-H_2O (1:1)	$3X10^4$

Dielectric constant (ε, at 25 ^{0}C): H_2O 79

EtOH 25

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

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

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

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

- 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.

$$Me{-}I + N_3^-Na^+ \xrightarrow{\text{solvent}} Me{-}N_3 + NaI$$

Rate in MeOH (ε = 33)	1		
DMF (ε = 37)	$4.5X10^4$		DMF: $HCONMe_2$
DMSO (ε = 46)	$1X10^9$		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**

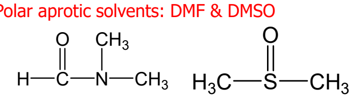
Q. Which reaction will take place more rapidly?

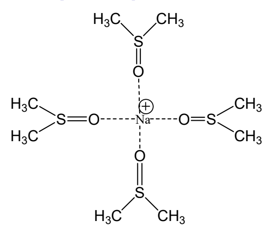
$$CH_3Br + NH_3 \xrightarrow{Et_2O} CH_3\overset{\oplus}{N}H_3 + \overset{\ominus}{Br}$$

$$CH_3Br + NH_3 \xrightarrow{EtOH} CH_3\overset{\oplus}{N}H_3 + \overset{\ominus}{Br}$$

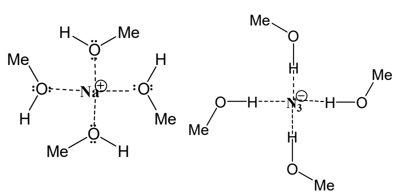
- **When RX is capable of undergoing both S_N1 and S_N2 reactions:**
- **S_N2 reaction will be favored by a high concentration of a good (negatively charged) nucleophile in a polar aprotic solvent,**
- **S_N1 reaction will be favored by a poor (neutral) nucleophile in a polar protic solvent**

Polar aprotic solvents: DMF & DMSO





Polar protic solvents: H_2O, MeOH, EtOH

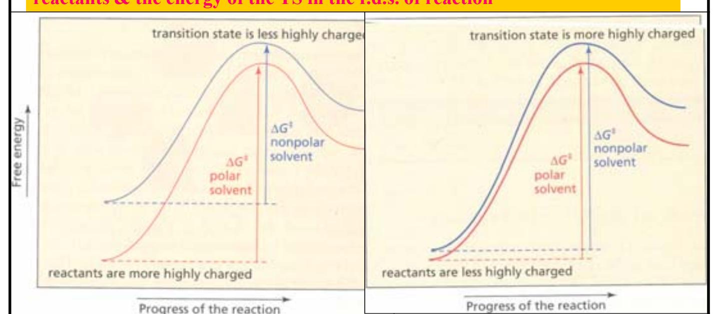


Increase in solvent polarity & ion-solvating ability may change the reaction mode from $S_N2 \rightarrow S_N1$

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

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

$$CH_3O^{\ominus} + H_3C\text{—}I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^{\ominus}$$

$$CH_3OH + H_3C\text{—}I \xrightarrow[\text{slow}]{\text{very}} CH_3OCH_3 + HI$$

Nucleophilicity of $CH_3O^{\ominus} > CH_3OH$

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

Stronger base better nucleophile		weaker base poorer nucleophile
$HO^{\ominus}$	>	H_2O
$CH_3O^{\ominus}$	>	CH_3OH
$H_2N^{\ominus}$	>	NH_3

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

Nucleophilic power towards saturated carbon

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

$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$$

$$RSe^{\ominus} > RS^{\ominus} > RO^{\ominus}$$

$$R_3P: > R_3N:$$

Halide ions nucleophilicity

increasing size

F^-

Cl^-

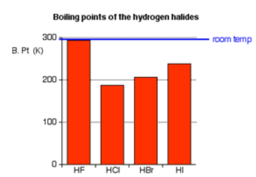
Br^-

I^-

increasing basicity

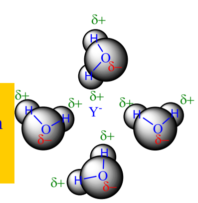
increasing nucleophilicity in gas phase

increasing nucleophilicity in a protic solvent



pKa (aq)
3.17
-7
-9
-10

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



Effectiveness of different nucleophiles in SN2 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

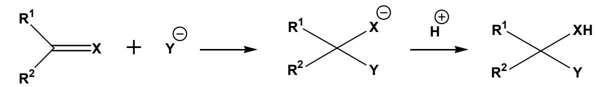
PhO^- (RO^-) is more basic than PhS^- (RS^-)

Relative nucleophilicity toward CH_3I in MeOH

RS^-
I^-
^-CN
CH_3O^-
Br^-
NH_3
Cl^-
F^-
CH_3OH

increasing nucleophilicity

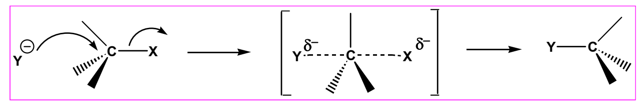
There are two main factors controlling bimolecular reaction:
i) Electrostatic attraction (simple attraction of opposite charges)
ii) Productive interaction between the HOMO of the nucleophile and the LUMO of the electrophile

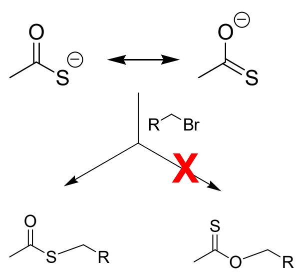


X = O , NH

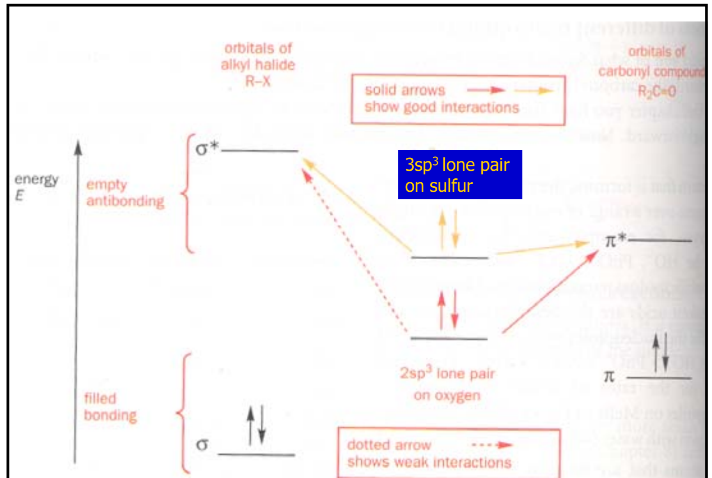
Heavily influenced by electrostatic attraction (as well as by HOMO-LUMO interaction).

Electrostatic attraction is unimportant in S_N2 reactions, only HOMO-LUMO interaction matters





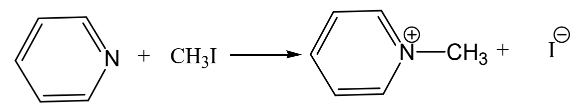
So, sulfur is a better nucleophile than oxygen for saturated carbon. Why should this be ?



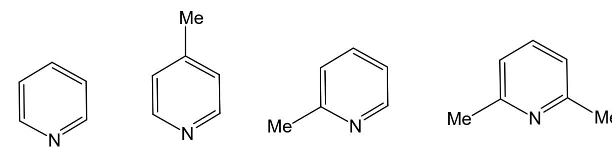
Hard nucleophiles and Soft nucleophiles

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: $N_3^{\ominus}$, $CN^{\ominus}$, $Br^{\ominus}$, RNH_2



Explain the relative rate



1.00 2.27 0.47 0.042

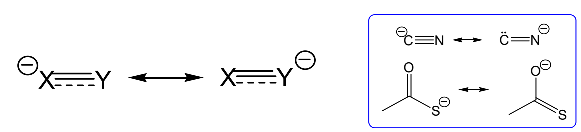
Soft nucleophiles are rather large and flabby with diffuse high-energy electrons

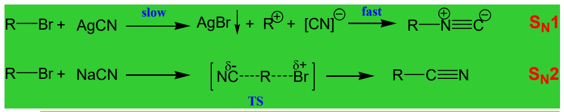
Hard nucleophiles are small with closely held electrons and high charge density

For hard nucleophiles → reactions are dominated by electrostatic interactions

For soft nucleophiles→ reactions are dominated by HOMO-LUMO interactions

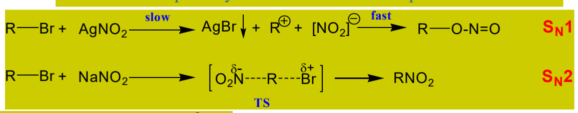
Ambident nucleophile: **Nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate.**

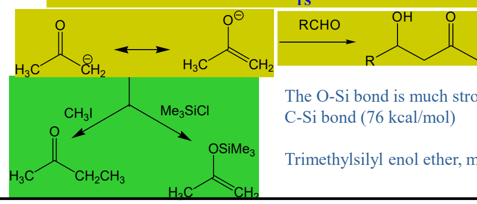




Ag+ promotes the formation of R+ by the formation of AgX ppt.
Nu attacks from the side that has more electro negative atom.

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





The O-Si bond is much stronger (108 kcal/mol) than C-Si bond (76 kcal/mol)

Trimethylsilyl enol ether, method to trap in enolate

The leaving group:

$$RCH_2—X + HO^{\ominus} \longrightarrow RCH_2—OH + X^{\ominus}$$

X:	I	Br	Cl	F
Relative rate	30,000	10,000	2,00	1

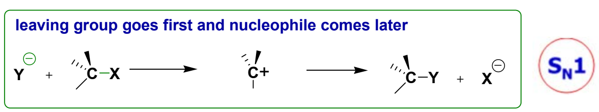
Halide (X)	Strength of C-X bond (kJ mol^{-1})	pk$_a$ of HX
Fluorine	118	+3
Chlorine	81	-7
Bromine	67	-9
Iodine	54	-10

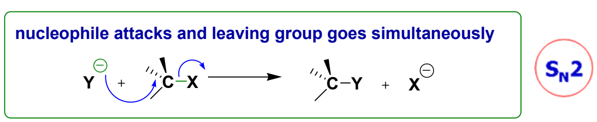
Low C-X energy, ionizes easily

I^- is weaker base
The weaker the basicity of a group, the better is the leaving ability.

Size is more important than the electronegativity

Effect of leaving Group





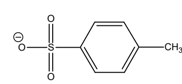
There is an effect of leaving group!!!!

Influencing Factors of Leaving groups

a) The strength of R-X bond
b) The polarisability of the bond
c) The stability of $X^{(-)}$
d) The degree of stabilisation through solvation of $X^{(-)}$

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

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

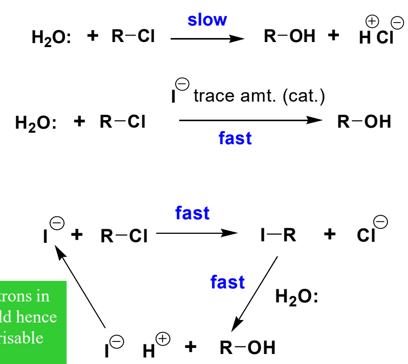


p-toluenesulfonate ion (Tosylate)

$CF_3SO_3^-$

triflate ion
(a "super"leaving group)

Nucleophilic catalysis

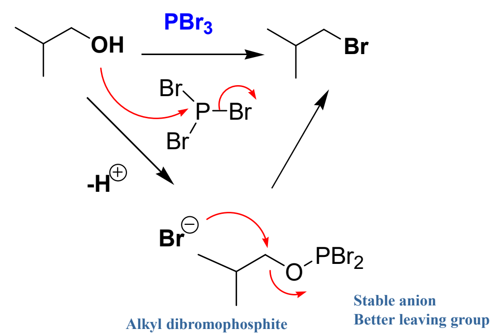


Outer shell electrons in I⁻ are loosely held hence it is highly polarisable

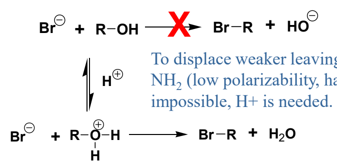
It is a good leaving and good entering group.

Another way to convert OH group into a better leaving group

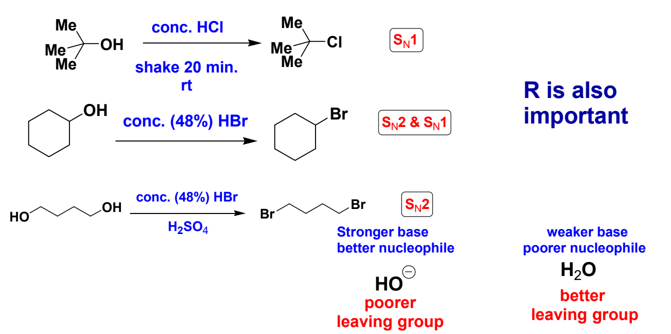
Combination with an element that forms strong bonds with oxygen



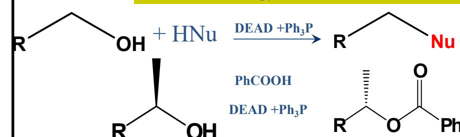
$HOPBr_2$ H_3PO_3

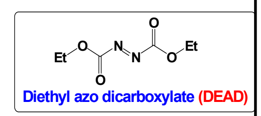


To displace weaker leaving groups such as ⁻OH, ⁻OR, ⁻NH$_2$ (low polarizability, hard bases) is almost impossible, H+ is needed.



A modern S_N2 reaction: Mitsunobu reaction

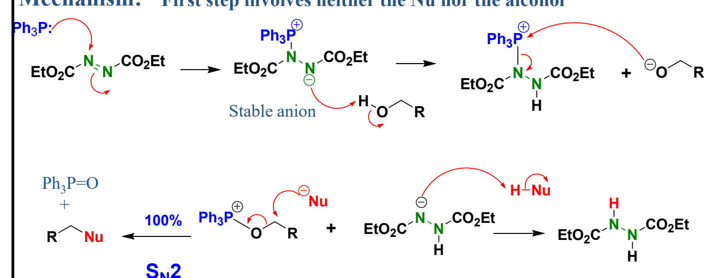




Normal ester formation leads with retention

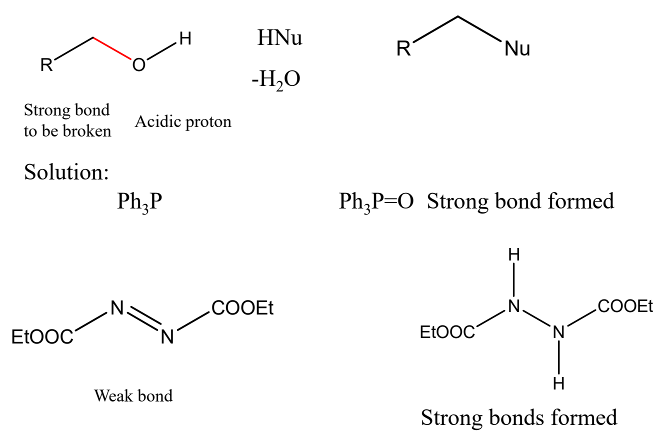
100% inversion

Mechanism: **First step involves neither the Nu nor the alcohol**

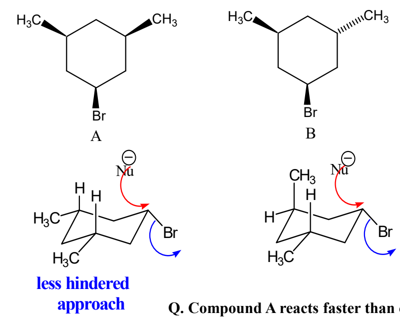


One step process for esters, all four reagents are taken together

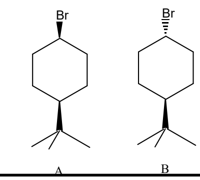
Problem:



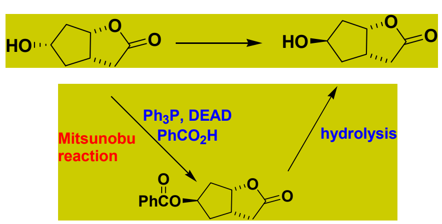
Q. Compound A reacts faster by the S_N2 mechanism than the compound B



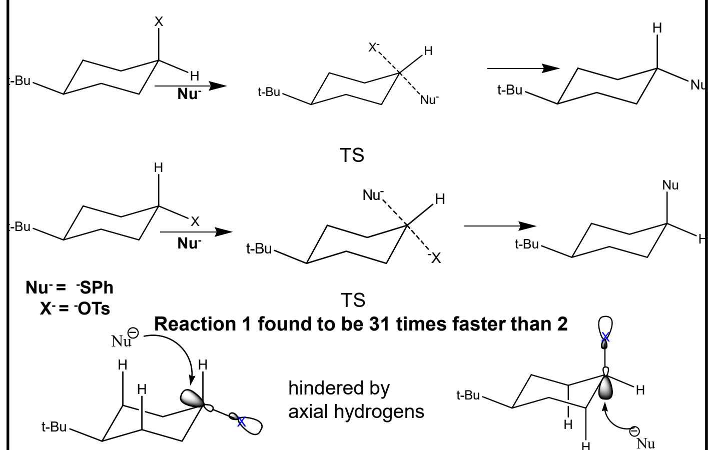
Q. Compound A reacts faster than compound B in NS reaction



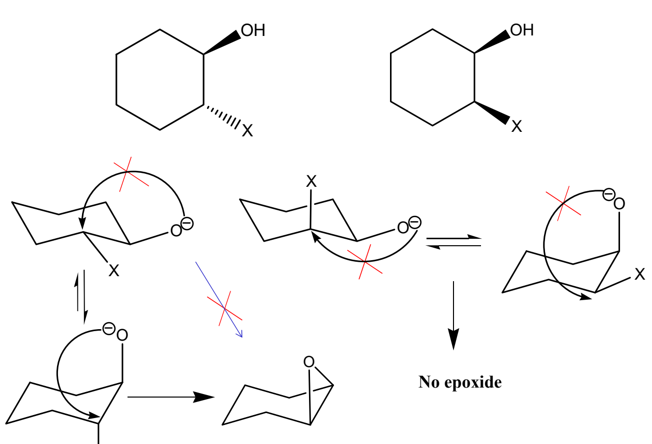
Problem:



Reactive differences between axial and equatorial conformers

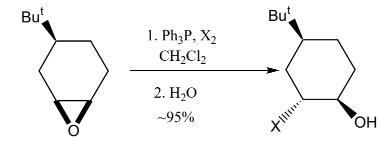


Epoxide formation

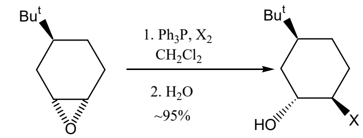


Only diaxial conformation forms epoxide

Q.

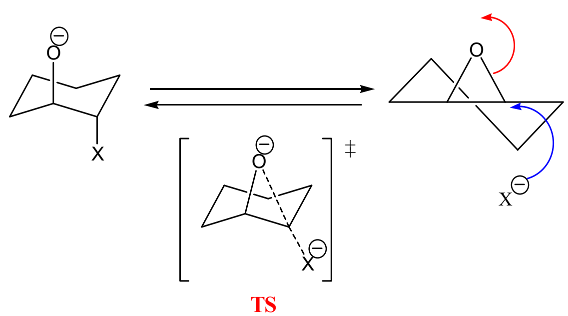


Whereas



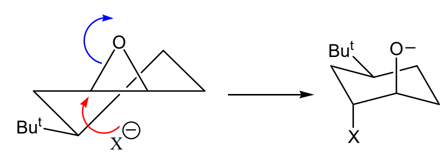
X = Cl, Br, I

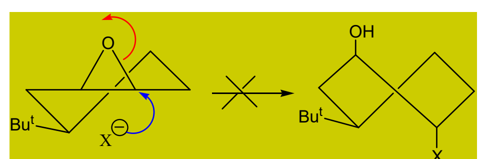
Epoxides



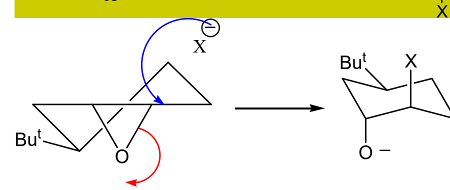
This TS is same for ring opening or formation of epoxide

Since the opening is possible only in diaxial substituted cylohexanes, the ring opening products also has to be diaxial



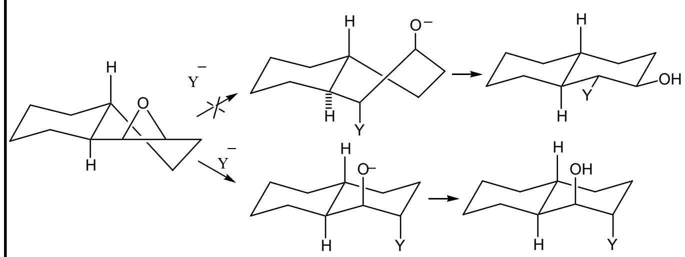


- **Twist boat, too high in energy to form.**
- **Barrier to reaction that matters not the final product**



- **Ring opening of cyclohexene oxides always leads directly to diaxial products**

Epoxides



Substitution *vs* Elimination

3° Alkyl Halides

With strong bases: E2 elimination occurs

With weak nucleophiles or bases: A mixture of products from S_N1 and E1 reactions

1° Alkyl Halides

With strong nucleophiles: Substitution occurs by an S_N2 mechanism

With strong sterically hindered bases: Elimination occurs by an E2 mechanism

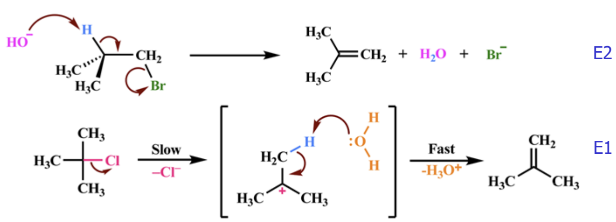
2° Alkyl Halides

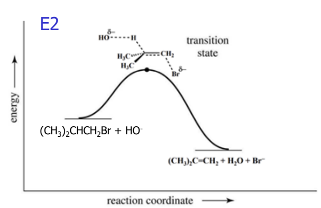
With strong bases and nucleophiles: A mixture of S_N2 and E2 reaction products are formed

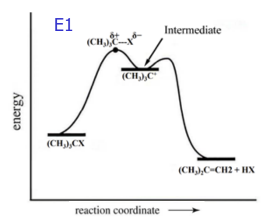
With strong sterically hindered bases: Elimination occurs by an E2 mechanism

With weak nucleophiles or bases: A mixture of S_N1 and E1 products results

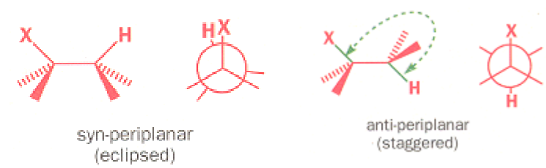
Elimination Reactions





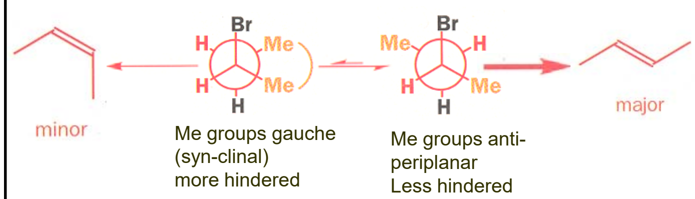


Two conformations with H and X coplanar

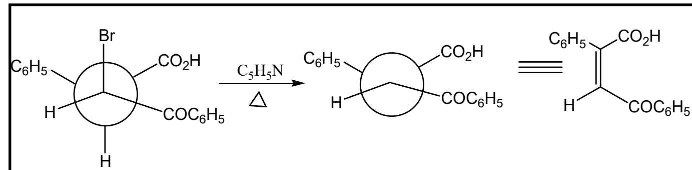


In E2 eliminations, the new π bond is formed by overlap of the C-H σ bond with the C-X σ* antibonding orbital

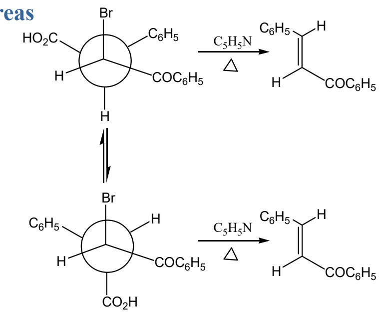
H and Br must be anti-periplanar for E2 elimination:



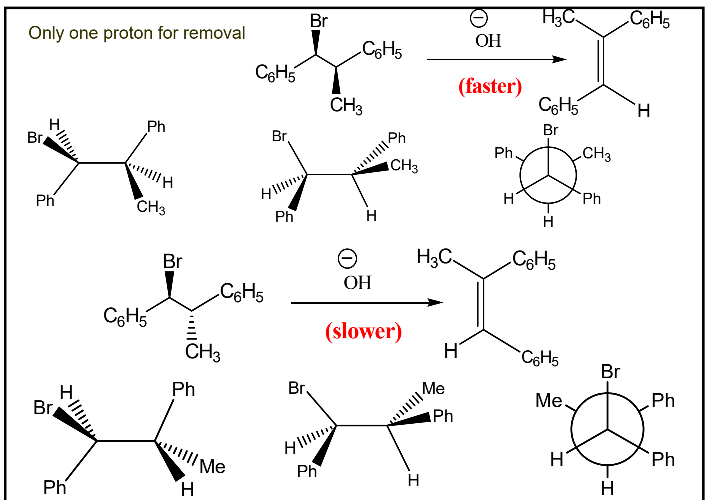
Reaction is stereoselective



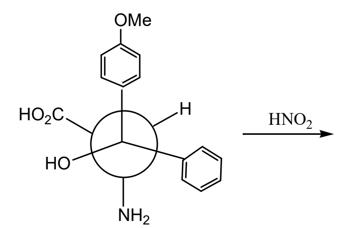
Whereas

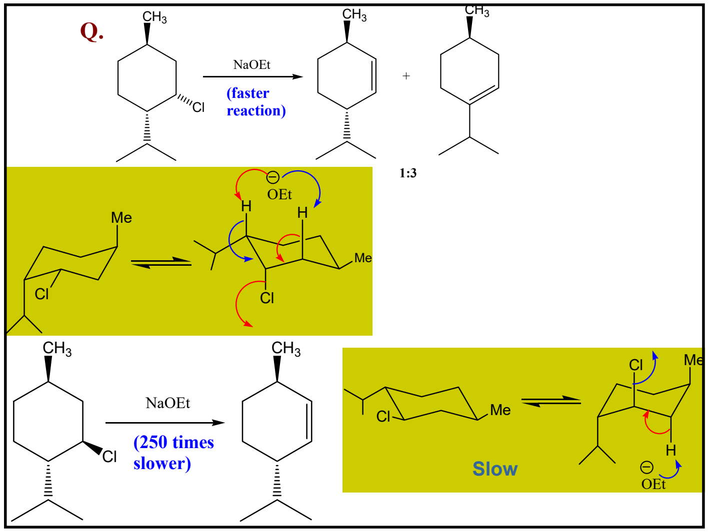


Only one proton for removal

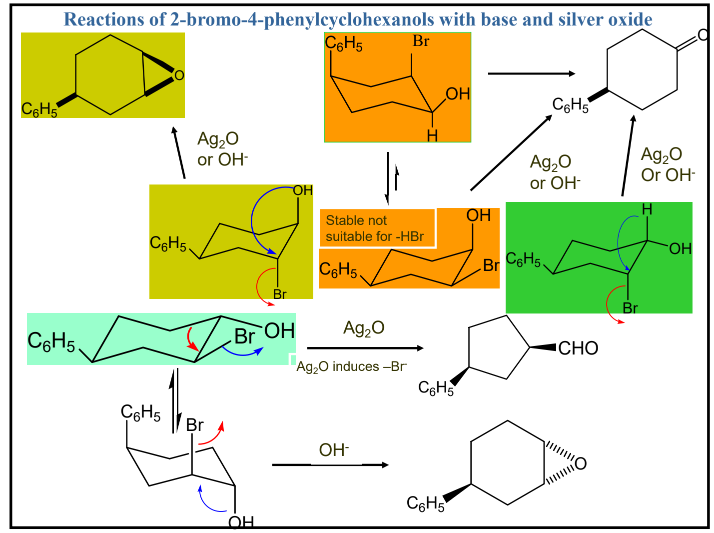


Predict the product of following reaction

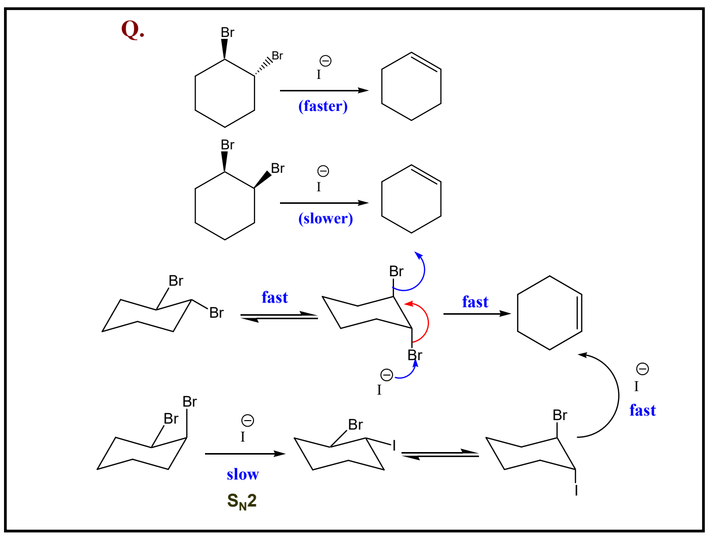




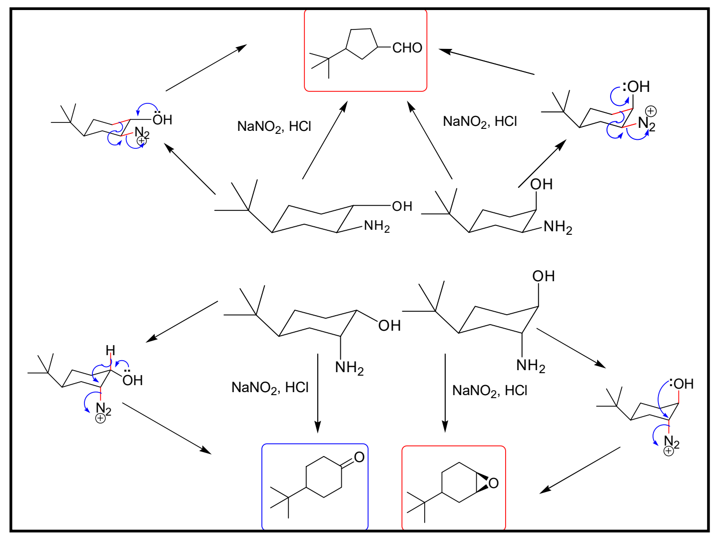
Q.
NaOEt
(faster reaction)
1:3
Me
OEt
Cl
NaOEt
(250 times slower)
Slow



Reactions of 2-bromo-4-phenylcyclohexanols with base and silver oxide
Ag2O or OH-
Stable not suitable for -HBr
Ag2O or OH-
Ag2O Or OH-
Ag2O
Ag2O induces –Br-
CHO
OH-

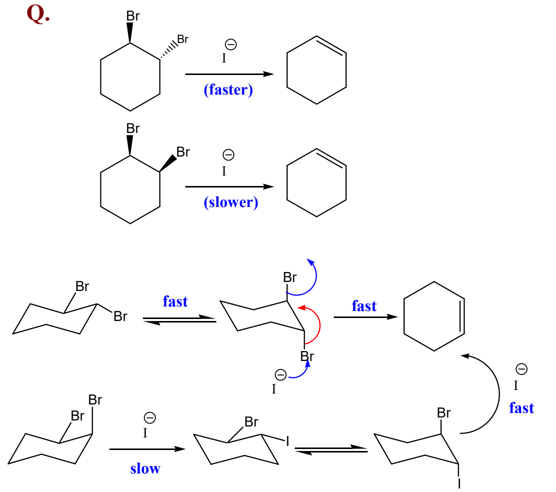


Q.
(faster)
(slower)
fast
fast
fast
slow
SN2



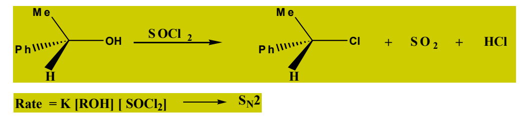
CHO
NaNO2, HCl
NaNO2, HCl
NaNO2, HCl
NaNO2, HCl

Q.

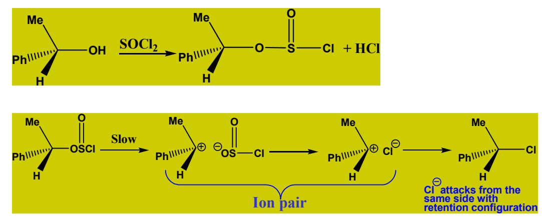


S_N2: Inversion of configuaration
S_N1: ideally Racemization

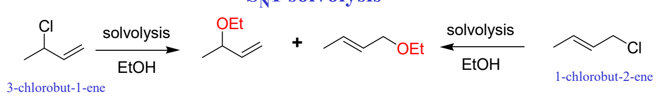
Retention of configuaration : S_Ni (substitution nucleophilic internal)

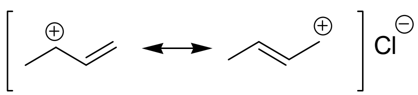


Then how the configuration is retained?



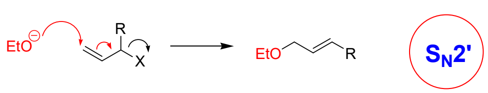
S_N1 solvolysis





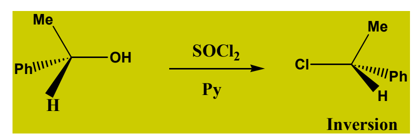
Allylic rearrangements

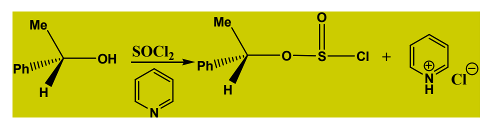
In presence of high concentration of EtO^- in EtOH

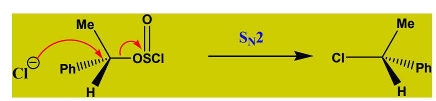


Tends to occur when "R" is bulky enough to reduce markedly the rate of direct S_N2 displacement on C_α.

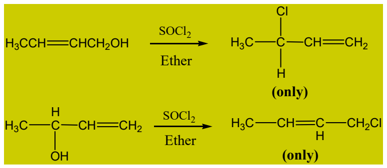
Problem:







Examples of S_Ni' reaction



Mechanism