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

**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
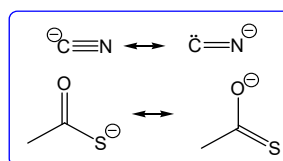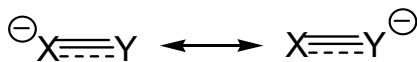
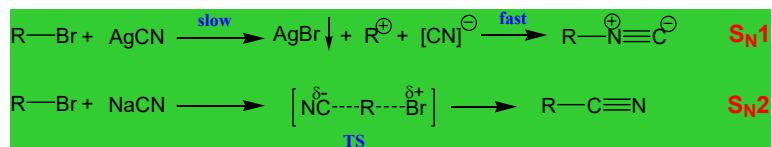**For soft nucleophiles → reactions are dominated by HOMO-LUMO interactions**
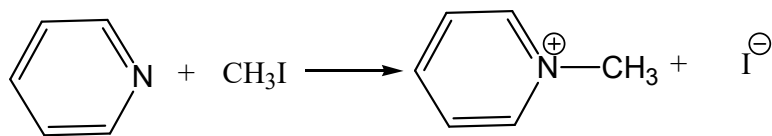
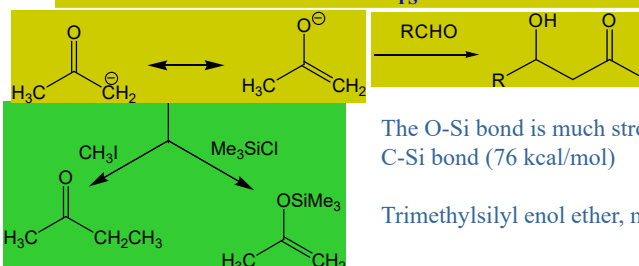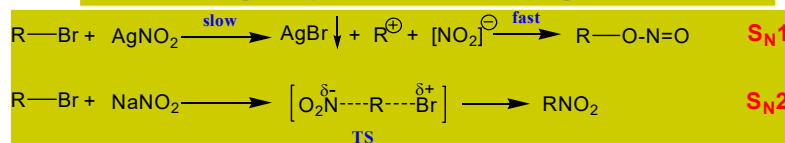Explain the relative rate

1.00   2.27   0.47   0.042
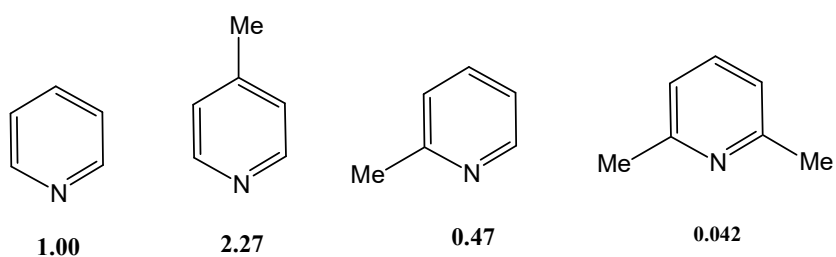
Ambident nucleophile: Nucleophiles which have more than one (generally two) suitable atoms through which they can attack the substrate.

2

R—Br + AgCN $\xrightarrow{\text{slow}}$ AgBr↓ + R$^{\oplus}$ + [CN]$^{\ominus}$ $\xrightarrow{\text{fast}}$ R—$\overset{\oplus}{N}\equiv C^{\ominus}$ **S$_N$1**

R—Br + NaCN $\longrightarrow$ $\left[\overset{\delta-}{NC}\text{----}R\text{----}\overset{\delta+}{Br} \right]$ $\longrightarrow$ R—C$\equiv$N   **S$_N$2**

TS

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.

R—Br + AgNO$_2$ $\xrightarrow{\text{slow}}$ AgBr↓ + R$^{\oplus}$ + [NO$_2$]$^{\ominus}$ $\xrightarrow{\text{fast}}$ R—O-N=O   **S$_N$1**

R—Br + NaNO$_2$ $\longrightarrow$ $\left[\overset{\delta-}{O_2N}\text{----}R\text{----}\overset{\delta+}{Br} \right]$ $\longrightarrow$ RNO$_2$ **S$_N$2**
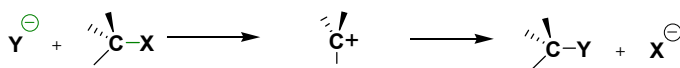
TS

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

Effect of leaving Group
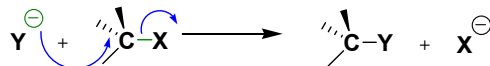
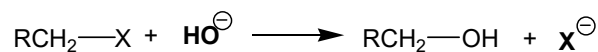**leaving group goes first and nucleophile comes later**

S$_N$1

nucleophile attacks and leaving group goes simultaneously

S$_N$2

There is an effect of leaving group!!!!

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

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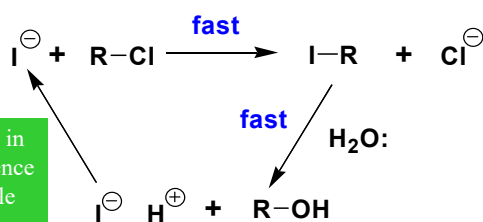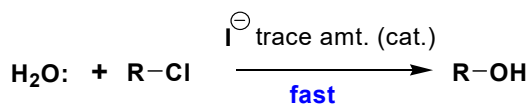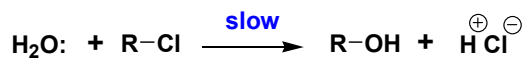
(c) & (d) becomes more important for following groups

$CF_3SO_3^-$

triflate ion
(a "super"leaving group)
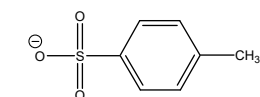
p-toluenesulfonate ion
(Tosylate)

Nucleophilic catalysis

$$H_2O: \ + \ R-Cl \ \xrightarrow{\text{slow}} \ R-OH \ + \ \overset{\oplus}{H}\overset{\ominus}{Cl}$$

$$H_2O: \ + \ R-Cl \ \xrightarrow[\text{fast}]{\overset{\ominus}{I} \ \text{trace amt. (cat.)}} \ R-OH$$

$$\overset{\ominus}{I} \ + \ R-Cl \ \xrightarrow{\text{fast}} \ I-R \ + \ \overset{\ominus}{Cl}$$

fast $H_2O:$

$$\overset{\ominus}{I} \ \overset{\oplus}{H} \ + \ R-OH$$

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

It is a good leaving and good entering group.

$$\overset{\ominus}{Br} \ + \ R-OH \ \xrightarrow{\ \text{X}\ } \ Br-R \ + \ \overset{\ominus}{HO}$$

$$\Big\updownarrow \ H^{\oplus}$$

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

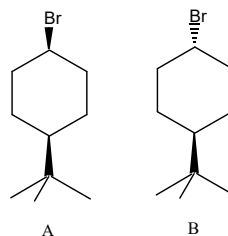$$\overset{\ominus}{Br} \ + \ R-\overset{\overset{\oplus}{O}-H}{\underset{H}{}} \ \longrightarrow \ Br-R \ + \ H_2O$$

Me₂C(Me)(Me)—OH $\xrightarrow[\text{shake 20 min. rt}]{\text{conc. HCl}}$ Me₂C(Me)(Me)—Cl $\boxed{S_N1}$

cyclohexanol —OH $\xrightarrow{\text{conc. (48\%) HBr}}$ cyclohexyl —Br $\boxed{S_N2 \ \& \ S_N1}$

R is also important

HO—CH₂CH₂CH₂CH₂—OH $\xrightarrow[\text{H}_2\text{SO}_4]{\text{conc. (48\%) HBr}}$ Br—CH₂CH₂CH₂CH₂—Br $\boxed{S_N2}$
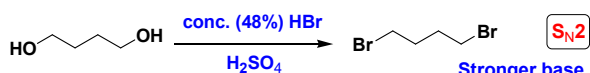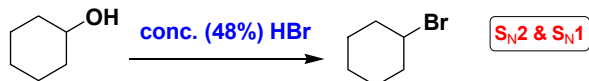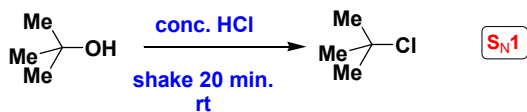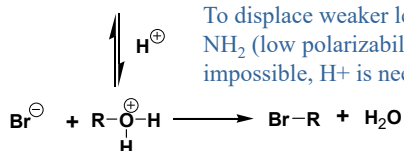
Stronger base better nucleophile

$$\overset{\ominus}{HO}$$
poorer leaving group

weaker base poorer nucleophile

$$H_2O$$
better leaving group

Q. Compound A reacts faster by the S$_N$2 mechanism than the compound B
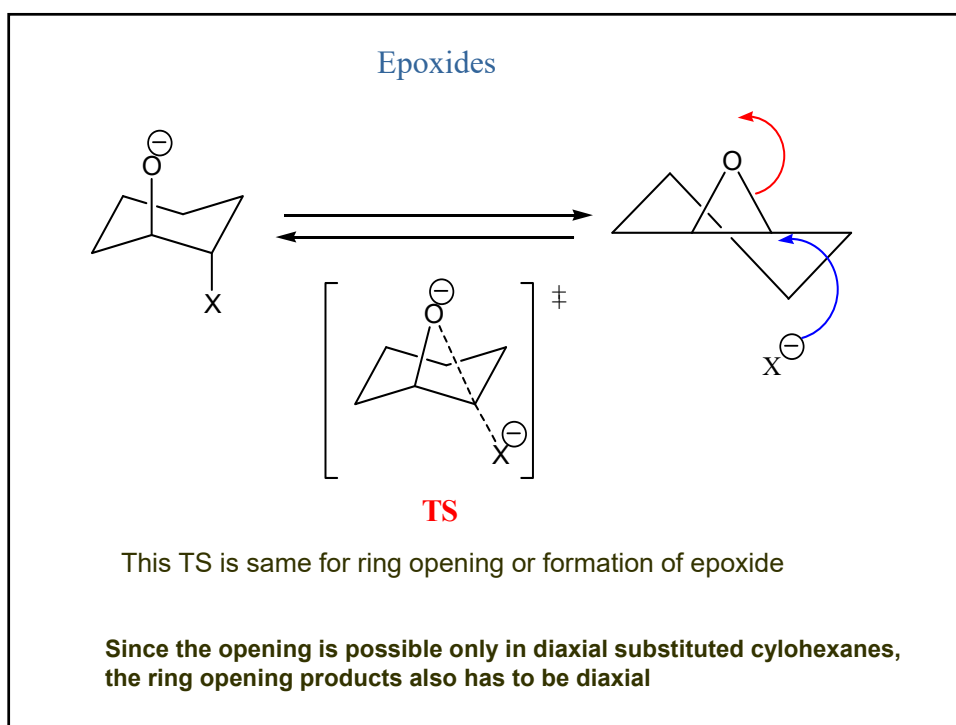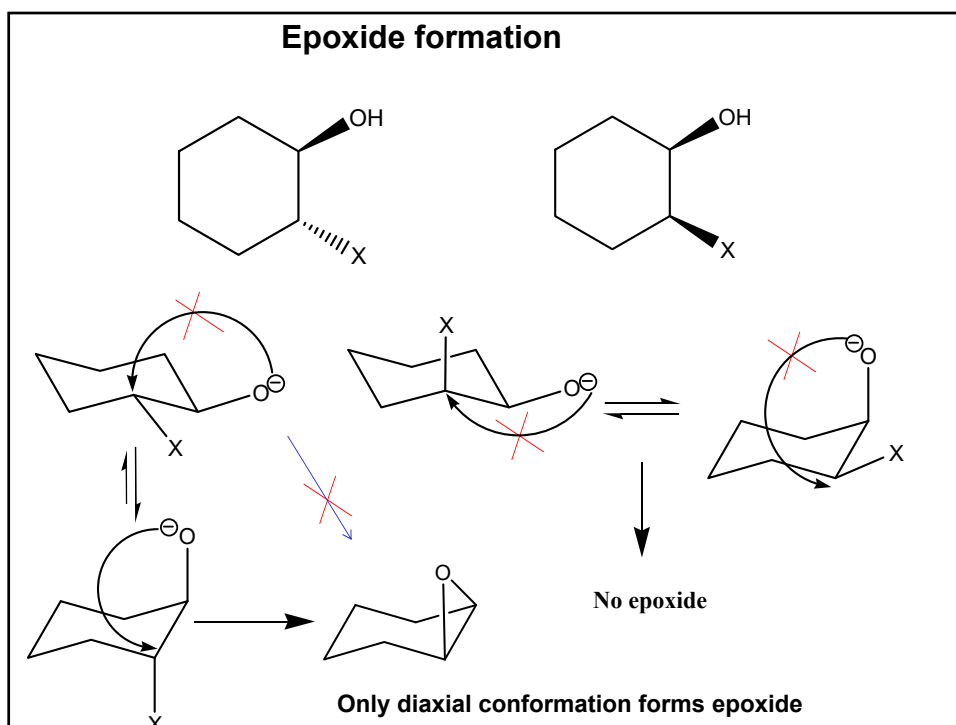
less hindered
approach
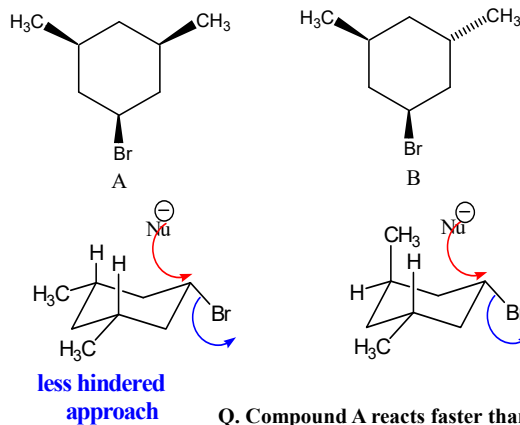
Q. Compound A reacts faster than compound B in NS reaction

A   B

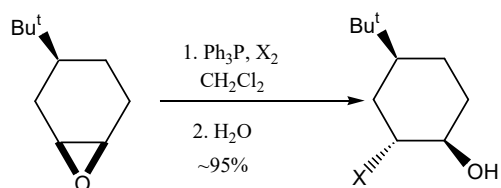**Reactive differences between axial and equatorial conformers**

TS

TS

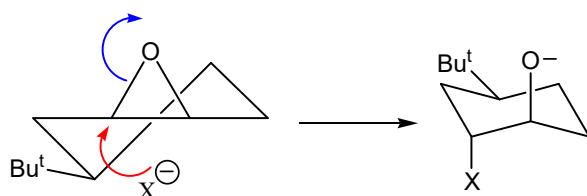Nu$^-$ = $^-$SPh
X$^-$ = $^-$OTs

Reaction 1 found to be 31 times faster than 2

hindered by
axial hydrogens

Epoxide formation

No epoxide

Only diaxial conformation forms epoxide

Epoxides

TS

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

Q.

Bu^t

1. Ph₃P, X₂
   CH₂Cl₂
2. H₂O
   ~95%

Bu^t

X⸝⸝⸝ ⸝⸝⸝OH

Whereas

Bu^t

1. Ph₃P, X₂
   CH₂Cl₂
2. H₂O
   ~95%

Bu^t

HO⸝⸝⸝ ⸝⸝⸝X

X = Cl, Br, I

O

Bu^t

X⁻

Bu^t   O⁻

X

OH

Bu^t

X⁻

Bu^t

X

• Twist boat, too high
  in energy to form.

• Barrier to reaction
  that matters not the
  final product

X⁻

Bu^t

O

Bu^t   X

O⁻
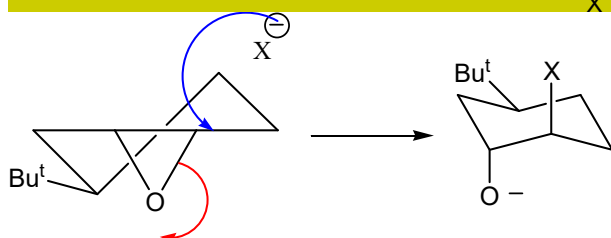
• Ring opening of
  cyclohexene oxides
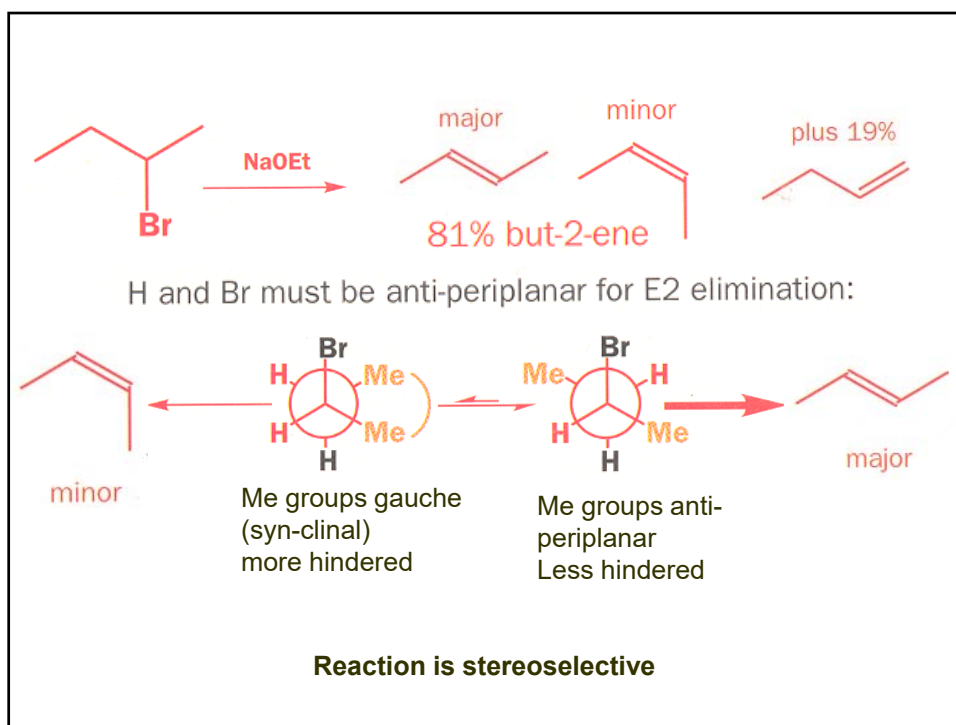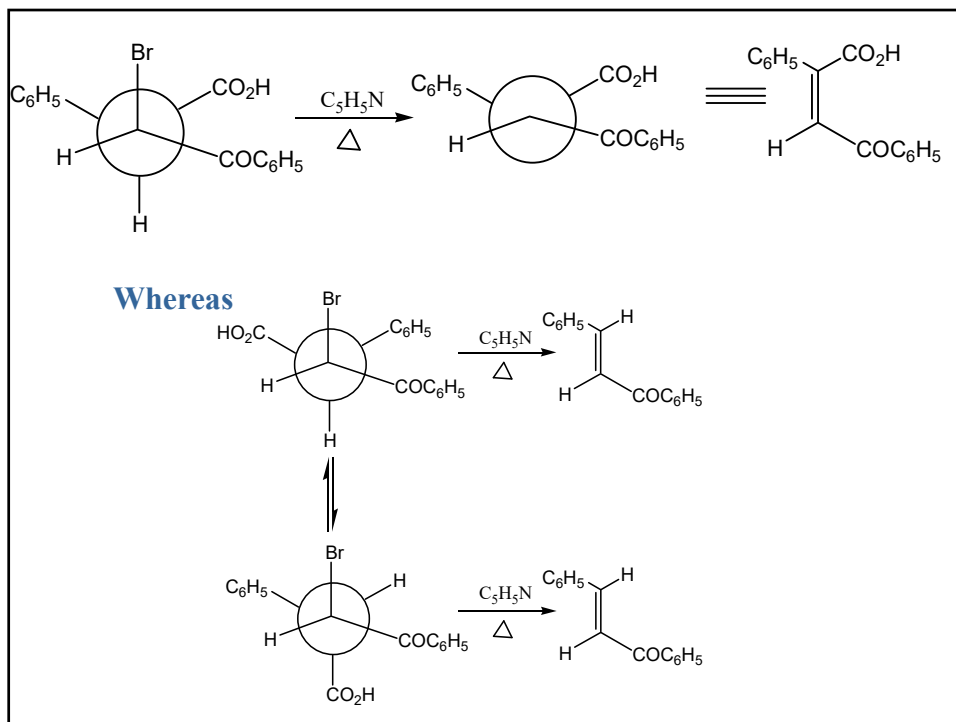 always leads directly to
  diaxial products

Epoxides
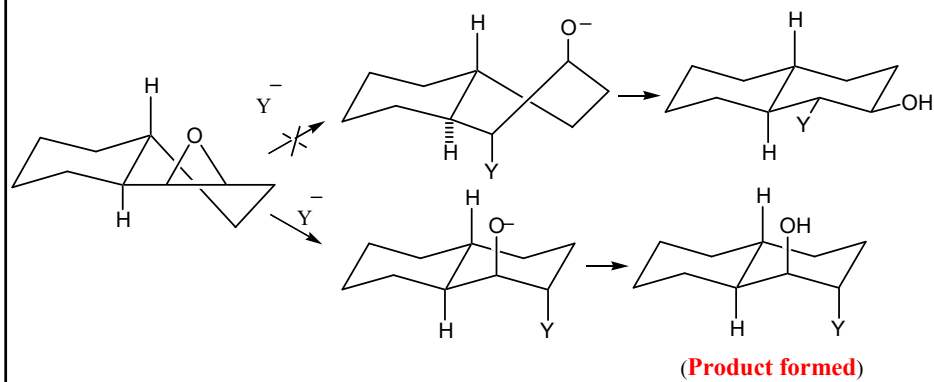
(**Product formed**)

Two conformations with H and X coplanar

syn-periplanar
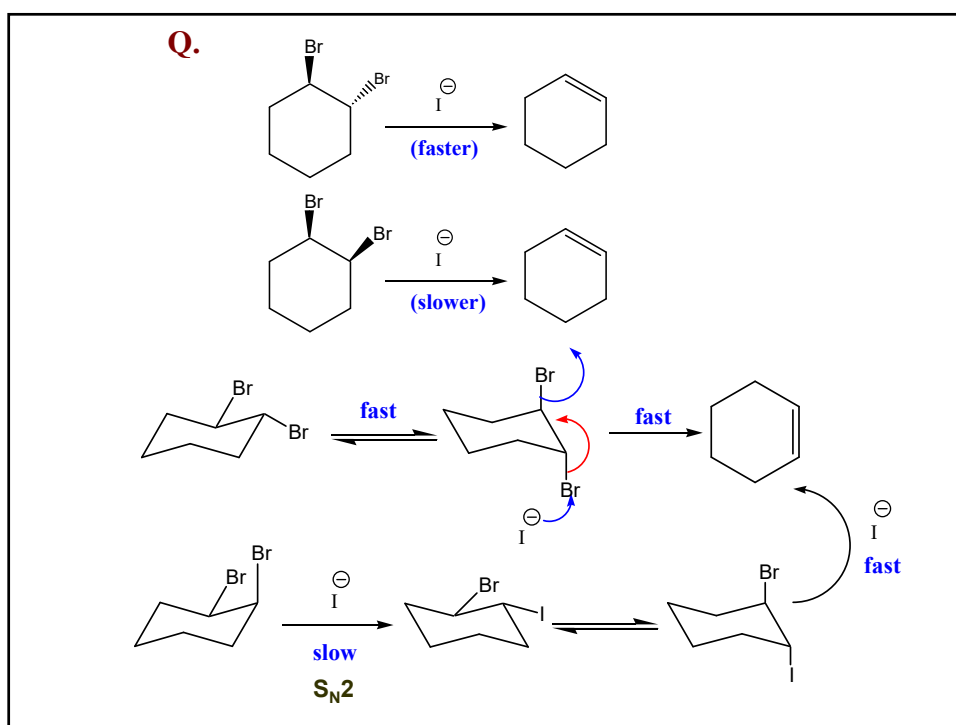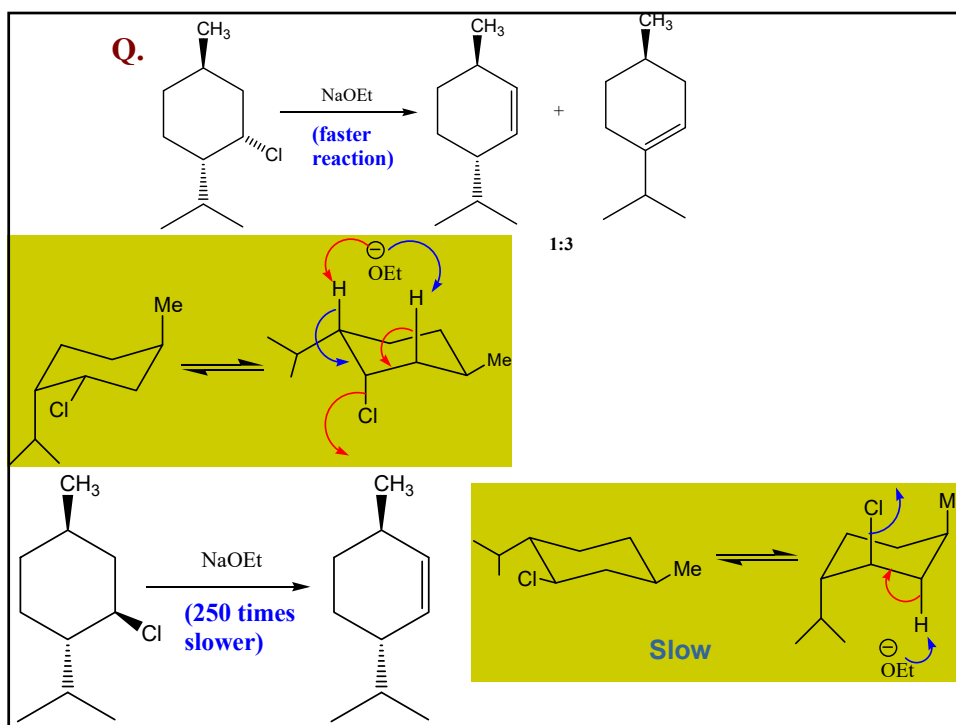(eclipsed)

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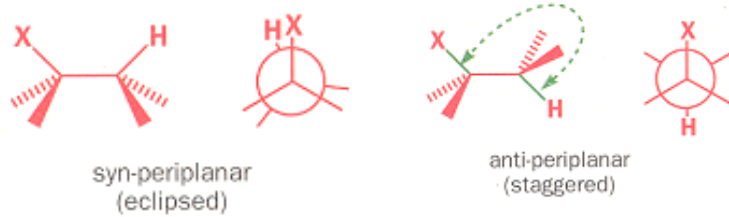
In E2 eliminations, the new π bond is formed by overlap of the C-H σ bond with the C-X σ* antibonding orbital

major   minor   plus 19%

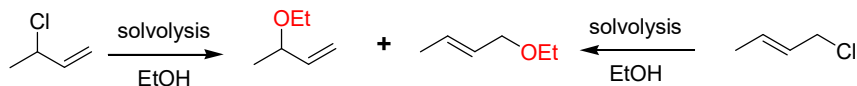**NaOEt**

81% but-2-ene

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

minor   Me groups gauche (syn-clinal) more hindered   Me groups anti-periplanar Less hindered   major

Reaction is stereoselective

Only one proton for removal

$OH^{\ominus}$

(faster)

$OH^{\ominus}$

(slower)

Whereas
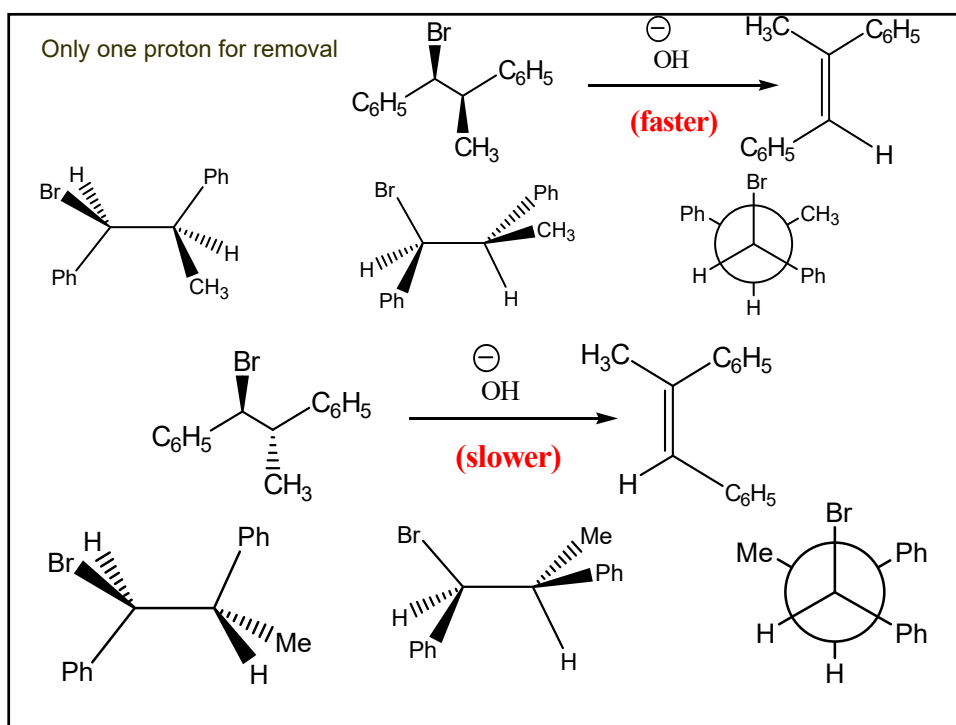
Predict the product of following reaction

Q.

CH₃ ... NaOEt **(faster reaction)** → CH₃ + CH₃

1:3

Me

Cl

⊖ OEt

H   H

Me

Cl

CH₃

NaOEt **(250 times slower)** → CH₃

Cl

Slow

Cl Me

Me

Cl

H

⊖ OEt

Q.

Br
Br
⊖ I **(faster)** →

Br
Br
⊖ I **(slower)** →

Br
Br **fast** ⇌ Br
Br
⊖ I **fast** →

⊖ I

Br
Br
⊖ I **slow**
S_N2 → Br
I ⇌ Br
I
fast

12

Reactions of 2-bromo-4-phenylcyclohexanols with base and silver oxide

Ag$_2$O or OH$^-$

Ag$_2$O or OH$^-$

Ag$_2$O Or OH$^-$

Stable not suitable for -HBr

Ag$_2$O

Ag$_2$O induces –Br$^-$

OH$^-$

NaNO$_2$, HCl

NaNO$_2$, HCl

NaNO$_2$, HCl

NaNO$_2$, HCl

13

S_N1 solvolysis
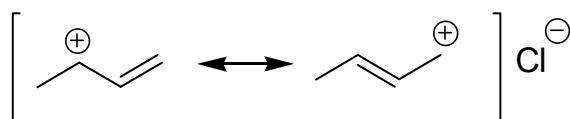
In presence of high concentration of EtO⁻ in EtOH
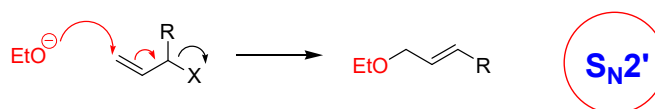
S_N2'

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

S_N2: Inversion of configuaration
S_N1: ideally Racemization

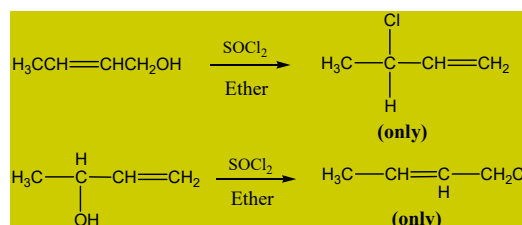**Retention of configuaration :** S_Ni (substitution nucleophilic internal)

Rate = K [ROH] [SOCl₂] ⟶ S_N2

Then how the configuration is retained?

Ion pair

Cl⁻ attacks from the same side with retention configuration

Problem:

Inversion

S_N2

Examples of $S_Ni^{/}$ **reaction**

(only)

(only)

Mechanism

$+$ SO_2
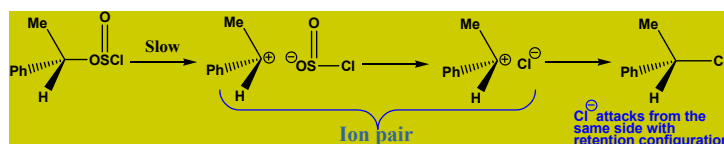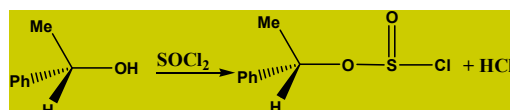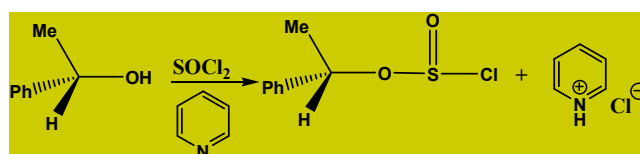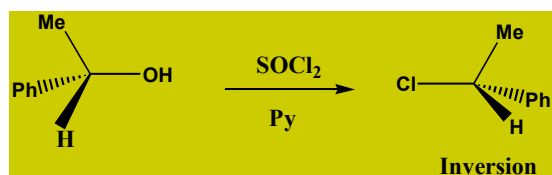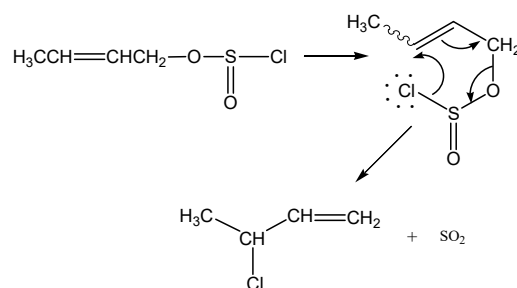
Neighboring Group Participation (Anchimeric asssitance)

Hydrolysis of EtS–CH$_2$CH$_2$ – Cl is 10^4 times faster than that of EtO–CH$_2$CH$_2$–Cl. Why?
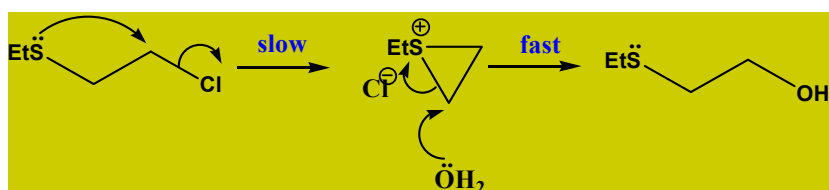
Reaction of CH$_3$COOH with

MeO ~~~ OSO$_2$Ar
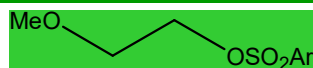
reacts four times slower than

Reaction of ROH with
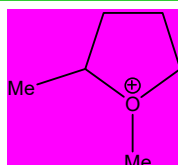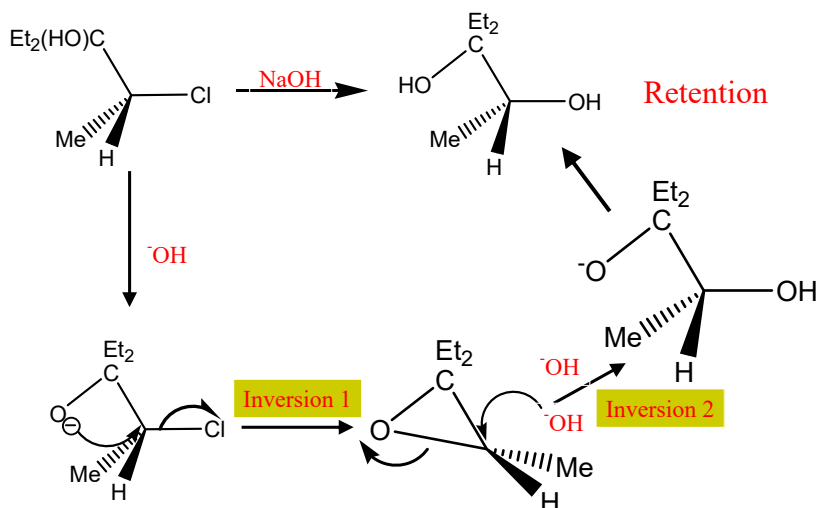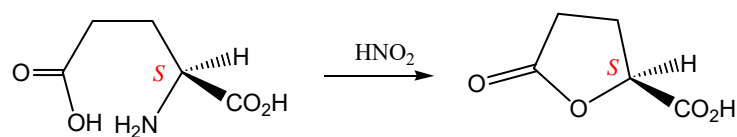
~~~ OSO$_2$Ar
OMe

reacts 400 times faster than

~~~ OSO$_2$Ar

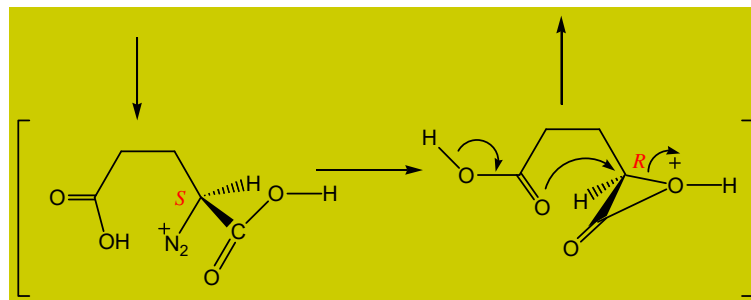## Neighboring Group Participation : Retention of configuration
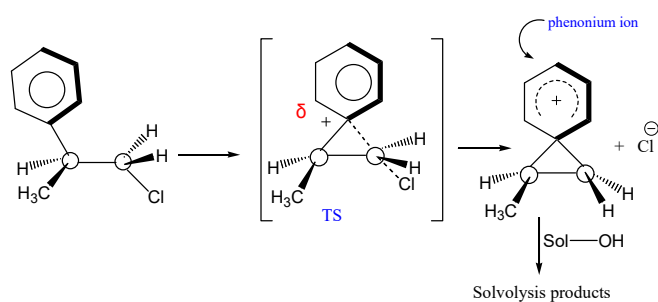

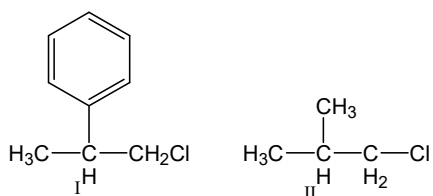Retention

Inversion 1

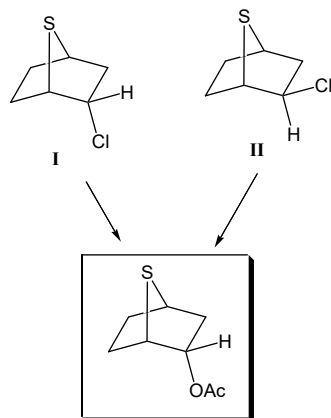Inversion 2

Neighboring group participation

Q.

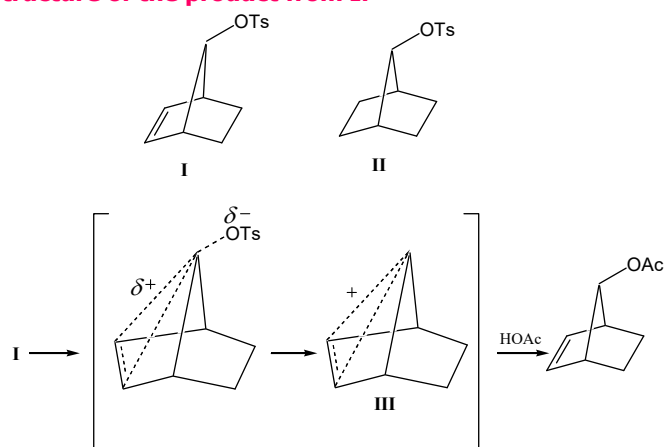Q. **Which one will undergo S_N1 solvolysis faster? Exaplain?**

Q. Which compound solvolyses faster in HOAc containing NaOAc (I or II)?

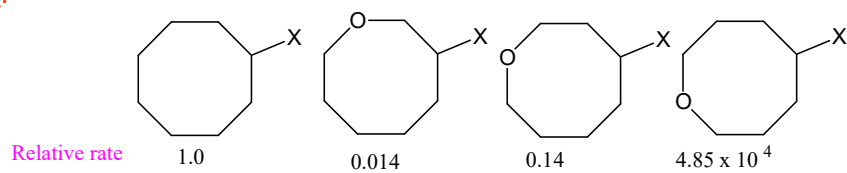**The product is the same from either I or II. What is the structure of the product?**

Q. Which compound solvolyses faster in HOAc? (I or II). Give the structure of the product from I.
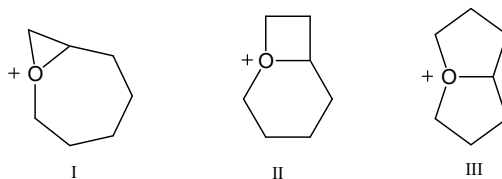

Participation of the π electrons of the double bond gives the ion III, which would be stabilized by delocalization of the positive charge.

I undergoes 10^{11} times greater rate than II

Q.

Relative rate   1.0   0.014   0.14 4.85×10^4

Transannular participation of ether oxygen

I   II   III

- III is more favorable than either I or II
- Unfavorable polar effect of the C-O bond

Q. Which one reacts with MeI more rapidly ?

I   II