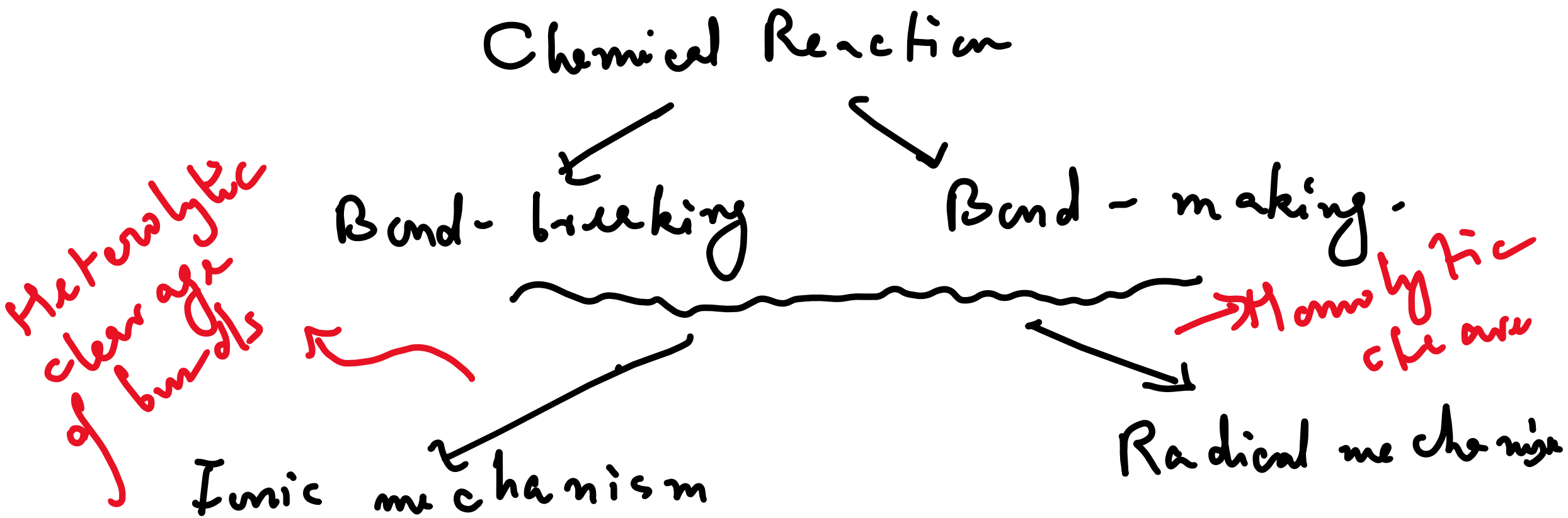
Organic Reaction Mechanism

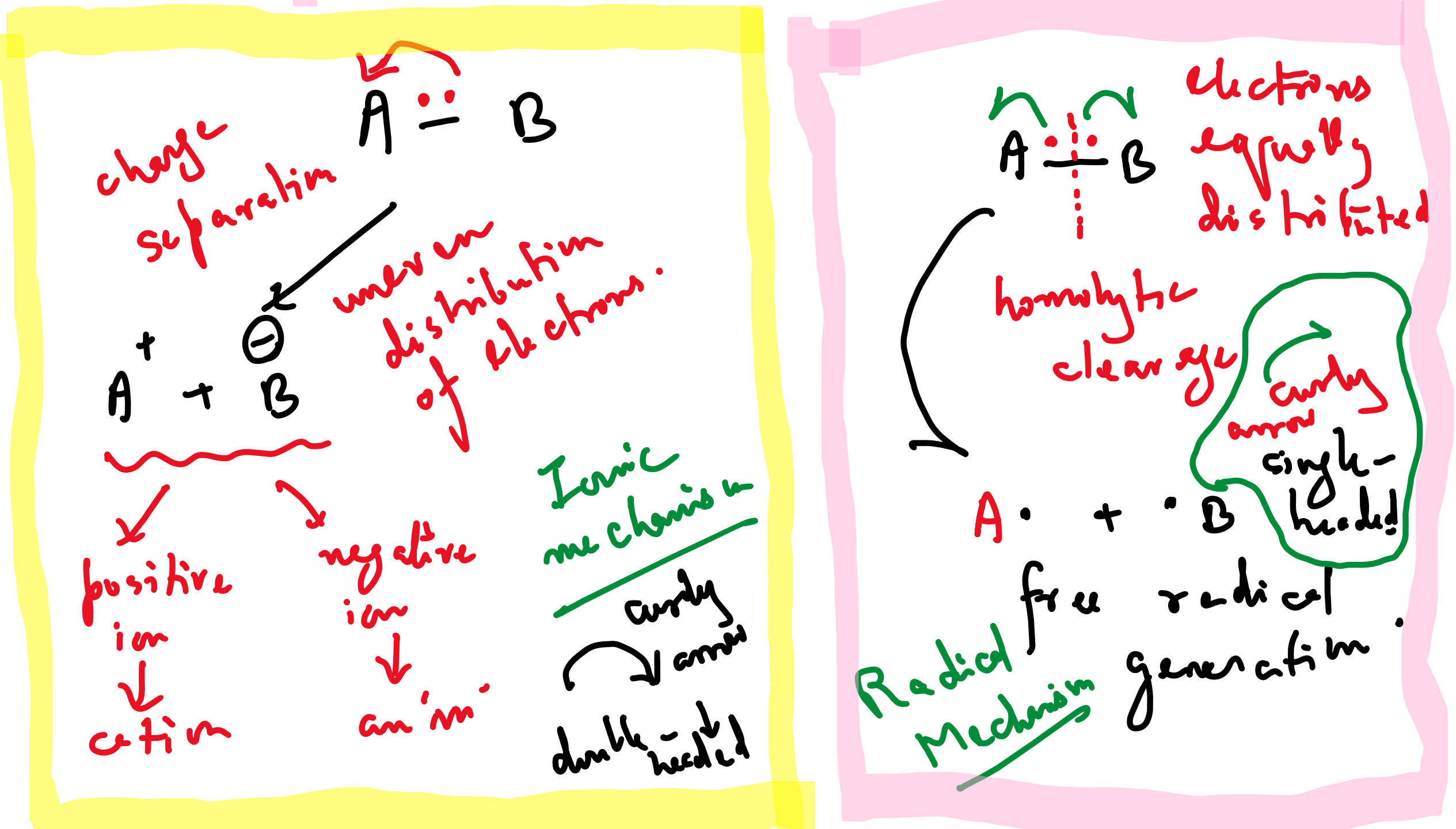
Why study organic reaction mechanism?

i) To know the complete, step-by-step account of how a reaction of organic compounds occur.

ii) To correlate the original structure of the reactants with final structure of the products.

iii) To account for the changes in structure & energy throughout the reaction process.




A : B
charge separation
uneven distribution of electrons.
A+ + B⊖
positive ion
cation
negative ion
anion
Ionic mechanism
curly arrow
double-headed
A : B
electrons equally distributed
homolytic cleavage
curly arrow
single-headed
A· + ·B
free radical
generation
Radical Mechanism

Ionic Mechanism:

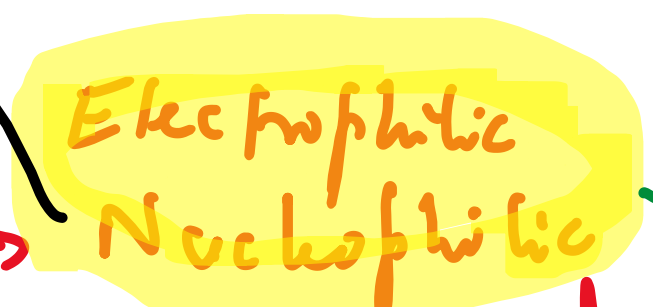
Electrophile

Nucleophile

Electrophile = electron loving = +ve ly charged species = $E^{\oplus}$

Nucleophile = nucleus " = −ve ly charged species = Nu

S_N1, S_N2, S_Ni



1. Substitution → Ionic
   Free − radical → Radical
2. Addition : 1. Electrophilic 2. Nucleophilic .
3. Elimination 1. E_1 2. E_2 3. E_1cB .

Type of Reaction	Mechanism	Which type of compounds respond?
Substitution:		
1. Nucleophilic	Ionic	Alkyl Halide: R–X X = –Cl, –Br, –I etc..
2. Electrophilic	"	Benzene & related aromatic systems
3. Free radical	Radical.	alkyl halide: R–X
Addition:		Alkenes, alkynes
1. Electrophilic	Ionic	Carbonyl compounds $>C=O$
2. Nucleophilic	Ionic	alkyl halide R–X
Elimination		

$Zn + H_2SO_4 = ZnSO_4 + H_2$

Substitution:

$$R-X + Y^{\ominus} \longrightarrow R-Y + X^{\ominus}$$

A class of chemical reactions in which an atom, ion or group of atoms or ions in a molecule is replaced by another atom ion or group.

Nucleophilic Substitution:

-ve ly charged.

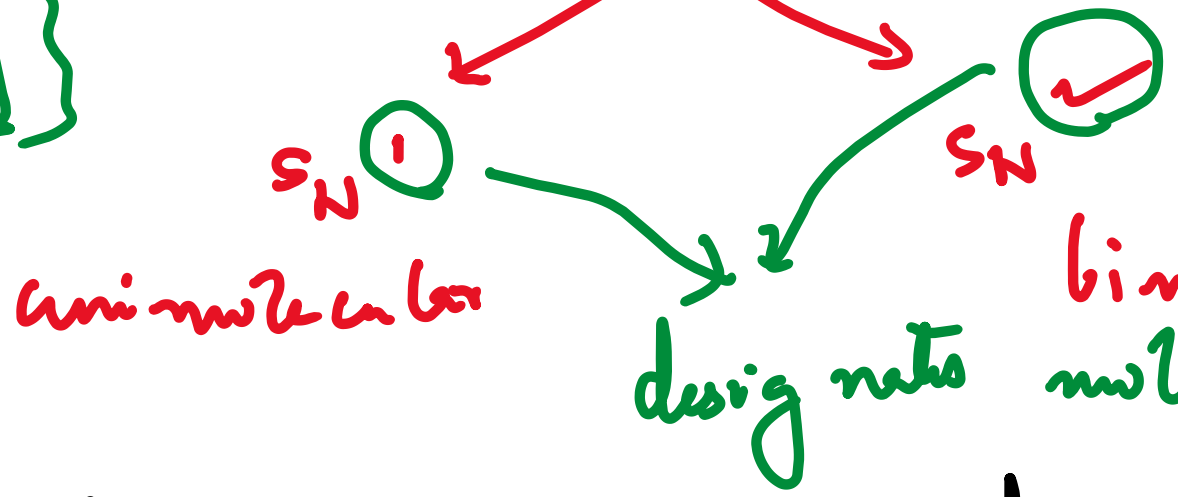
$$R-X + \overset{\ominus}{O}H \longrightarrow R-OH + X^{\ominus}$$

$X = -Cl, Br, I$

Nucleophile
↓
nucleus + phile ≡ nucleus loving

Order
Molecularity

Nucleophilic substitution.



Molecularity of a reaction can be defined as the total no. of reacting species in the rate-limiting or rate determining step.

Rate limiting step ≡ The step that determines the rate of the reaction, which is typically the slowest step.

1. Unimolecular reaction: Molecularity = 1

$A \longrightarrow$ Product

one reactant is involved in R.D.S.

2. Bimolecular: Molecularity = 2

$A + B \longrightarrow$ Product

↓ two reactants are involved.

3. $A + B + C \longrightarrow$ product : Termolecular reaction -

Molecularity represents the no. of molecules that comes together to react in an elementary reaction.

$PCl_5 \longrightarrow PCl_3 + Cl_2$

Unimolecular: do not look at the product side. Focus on the reactant side.

$2HI \longrightarrow H_2 + I_2$

stoichiometric coefficient = 2

∴ Molecularity = 2

$2SO_2 + O_2 \longrightarrow 2SO_3$ Trimolecular

$2FeCl_3 + SnCl_2 \longrightarrow SnCl_4 + 2FeCl_2$

Trimolecular. Molecularity = 3.

Order: The mathematical expression showing the dependence of rate on the concentration of reactants is known as rate-law or rate-expression. The sum of the indices (power) of the concentration terms appearing in the rate law, as observed experimentally is called as the order of the reaction.

$$2\,NO(g) + 2H_2(g) \longrightarrow N_2(g) + 2H_2O(g)$$

II

0

Kinetic experiment is carried out at 1100K upon this reaction has shown the following data.

$$2\,NO(g) + 2H_2(g) \xrightarrow{2:1} N_2(g) + 2H_2O(g)$$

Expt no	[NO] mol dm^{-3}	[H_2] →	Rate mol dm^{-3} s^{-1}
1.	5×10^{-3}	2.5×10^{-3}	3×10^{-5} (r_1)
2.	1.0×10^{-2}	2.5×10^{-3}	1.2×10^{-4} (r_2)
3.	1.0×10^{-2}	5.0×10^{-3}	2.4×10^{-4} (r_3)

reactant conc^n doubled

$\frac{r_2}{r_1} = 4$

$\frac{r_3}{r_1} = 8.$

Observation: From expt. ① & ②

When the concentration of NO is doubled, keeping the concn. of H_2 unaltered, the rate increases by 4 fold.

① & ③: When conc of both NO & H_2 are doubled, the rate increases by 8 fold.

$$\text{Rate} \propto [NO]^2 [H_2]$$

This is the rate law of the reaction as observed experimentally.

Order: $2 + 1 = 3$.

Order of a reaction can be defined as the number of molecules of the reactants whose concentration changes during chemical change.

Molecularity	Order
1. Total no. of reacting species (molecules, atoms or ions) which bring chemical change	1. Sum of the powers of mole concentration of the reacting species in the rate equation

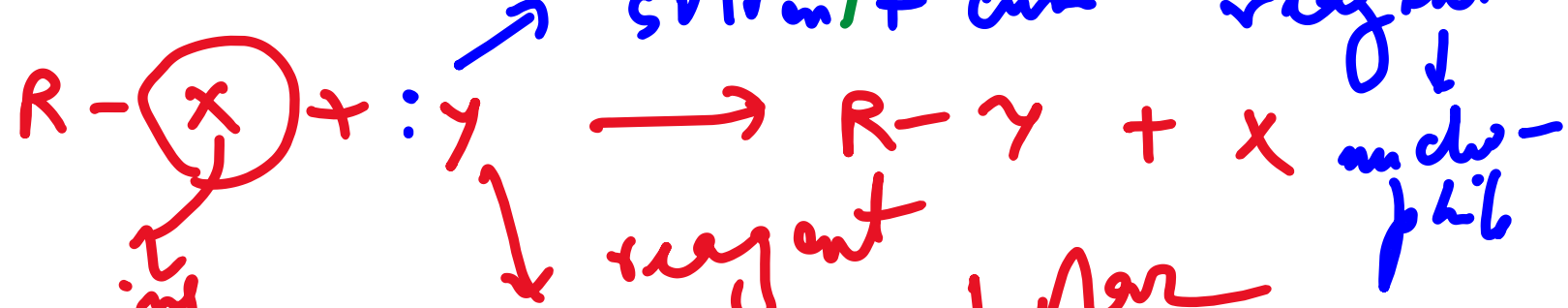
Molecularity	Order
2. It is an integer or whole no.	2. It may be a whole no., zero, or fractional.
3. Theoretical concept	3. Experimentally determined.
4. Meaningful only for simple reactions or individual step of a complex reaction	4. It is meant for the reaction & not for individual steps.

Solvolysis

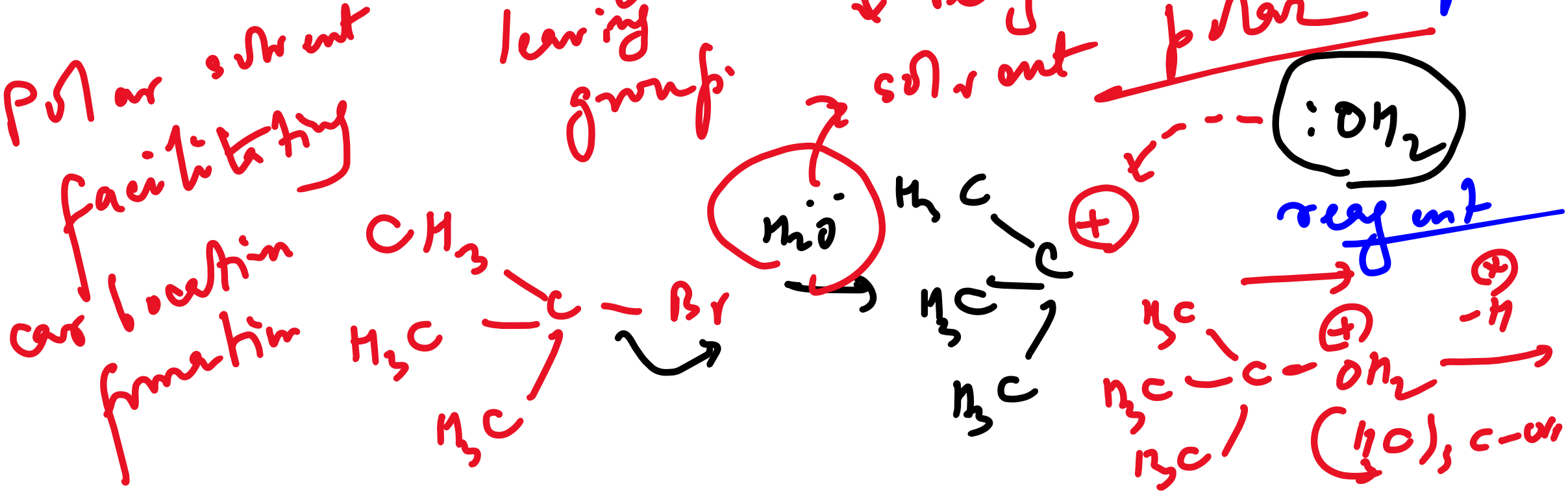
solvent — lysis

solvolysis

When the solvent acts as a reactant, the process is called solvent cum reagent



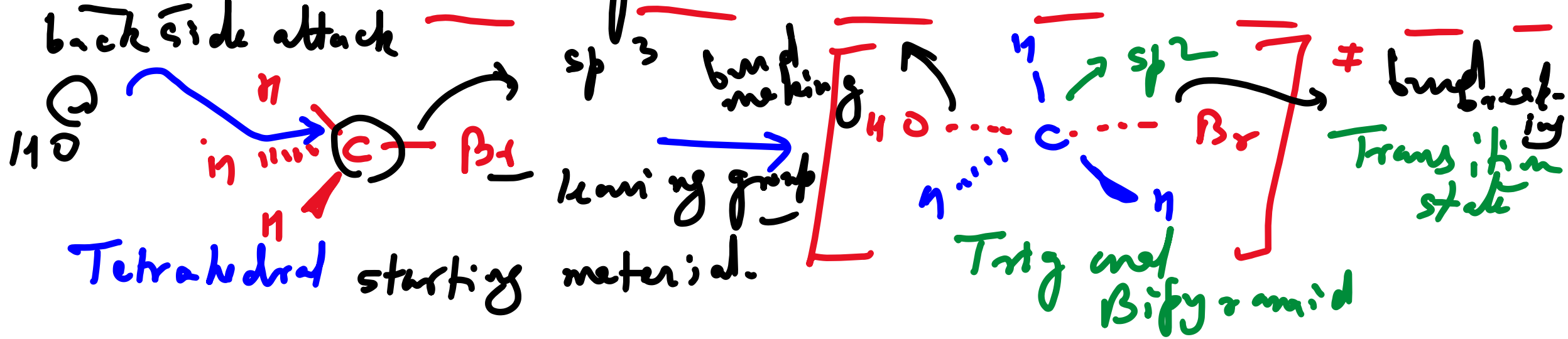
Polar solvent facilitates carbocation formation

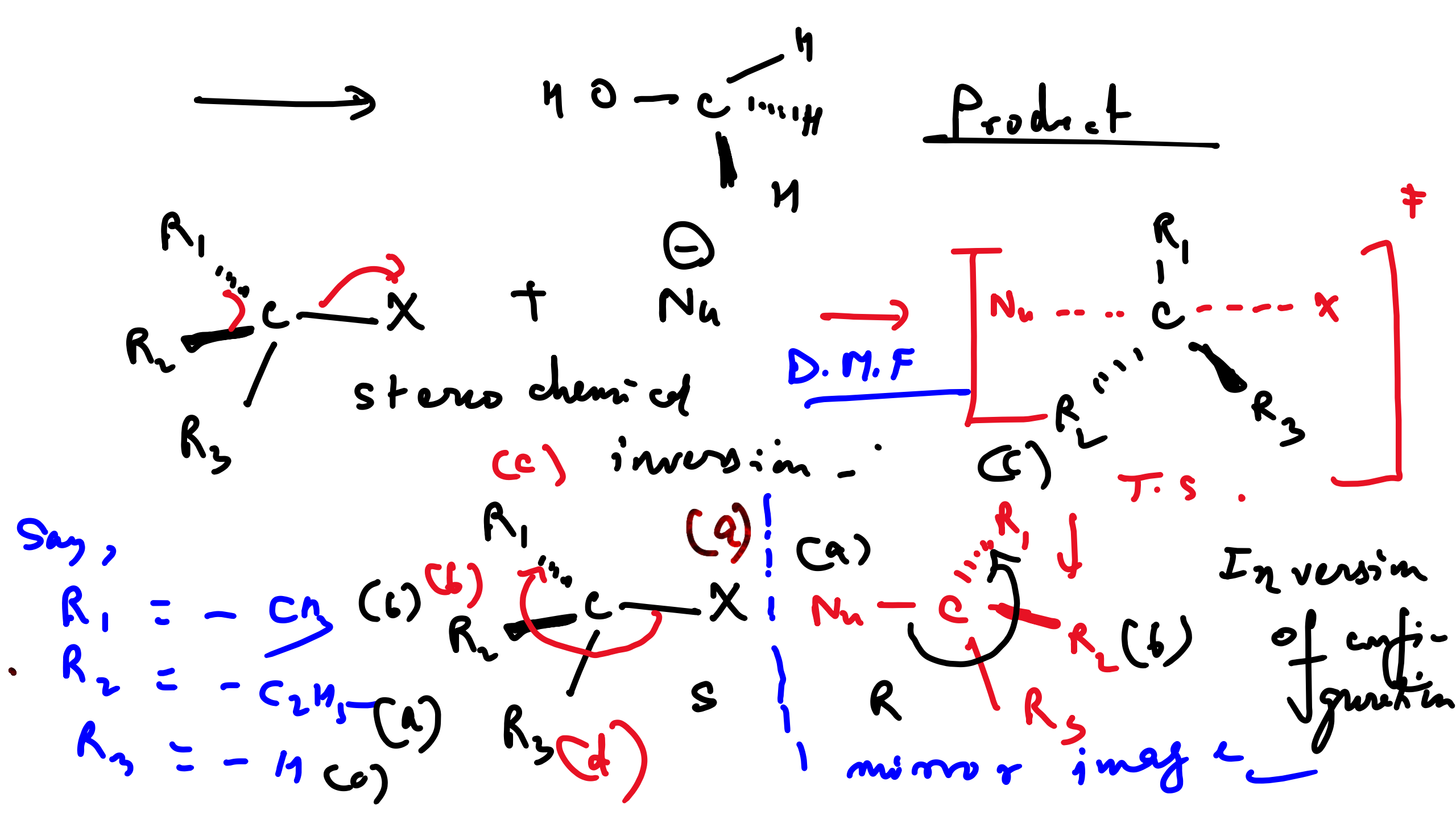


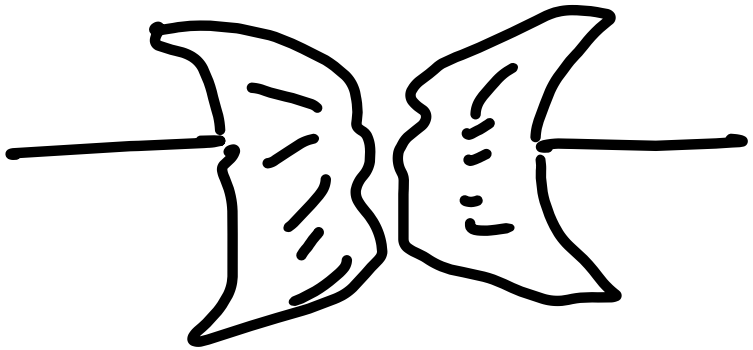
In a solvolysis reaction, the solvent plays the dual role of acting as a reaction medium & reagent.

Eg: H_2O:, CH_3OH ... neutral molecules

S_N2: Nucleophilic Substitution Bimolecular.




Product
stereo chemical
D.M.F
T.S.
(c) inversion
Say,
$R_1 = -CH_3$ (c)
$R_2 = -C_2H_5$ (a)
$R_3 = -H$ (d)
S
R
mirror image
Inversion of configuration



Stereochemical inversion in S_N2 is just like the inversion of an umbrella in storm.

Features of S_N2 reaction:

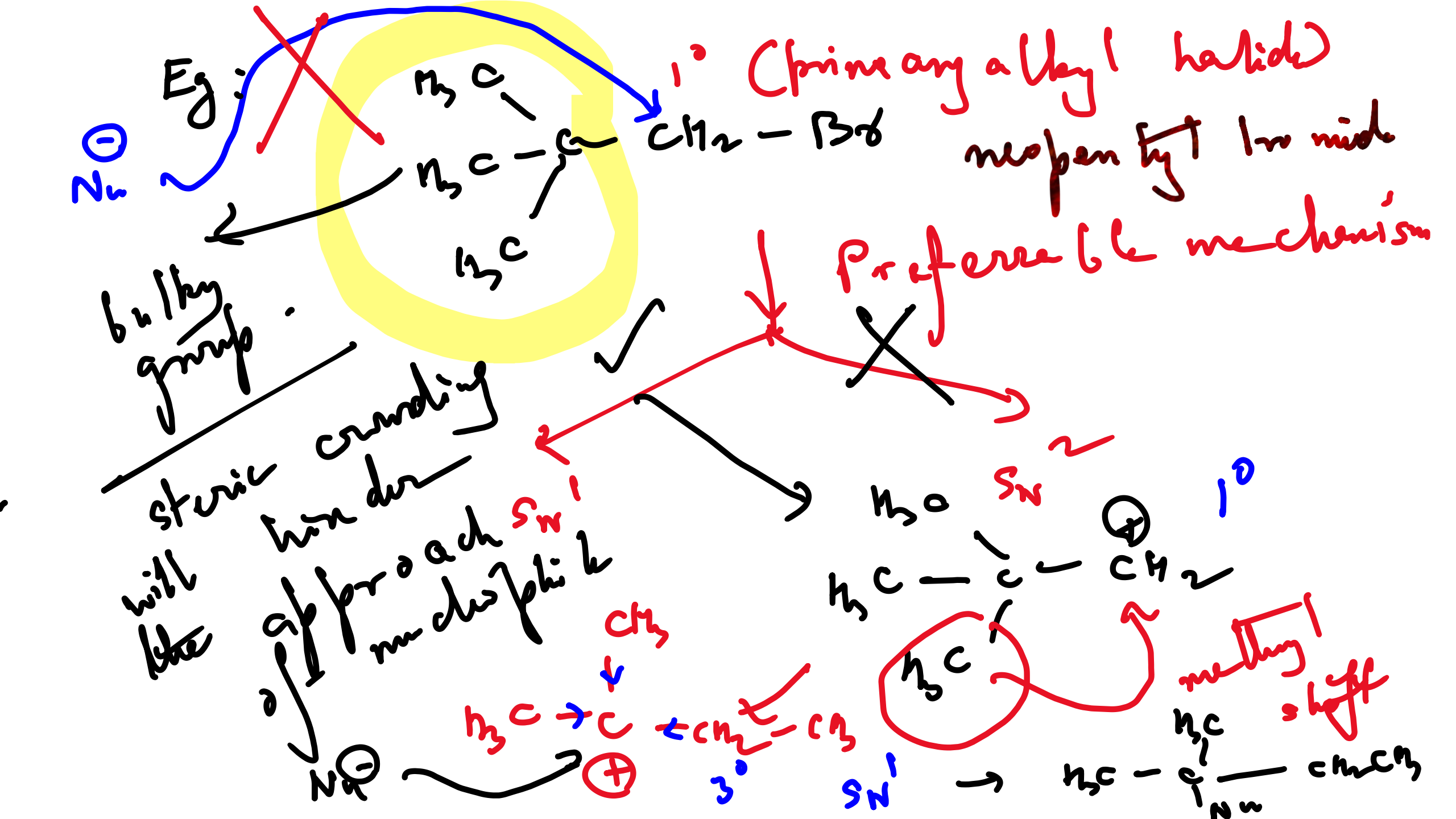
1. One step reaction.
2. Bimolecular reaction. Rate: $k[RX][Nu^{\ominus}]$

The rate of S_N2 reaction depends on the concentration of the nucleophile as the same is involved in R.D.S.

3. Synchronous, concerted reaction. No intermediate form. The reaction proceeds through a five-membered, T.B.P. transition state

4. Nucleophile attacks from back side. Hence higher the branching, and thus, steric crowding, the rate of S_N2 reaction decreases. Therefore, order of reactivity,

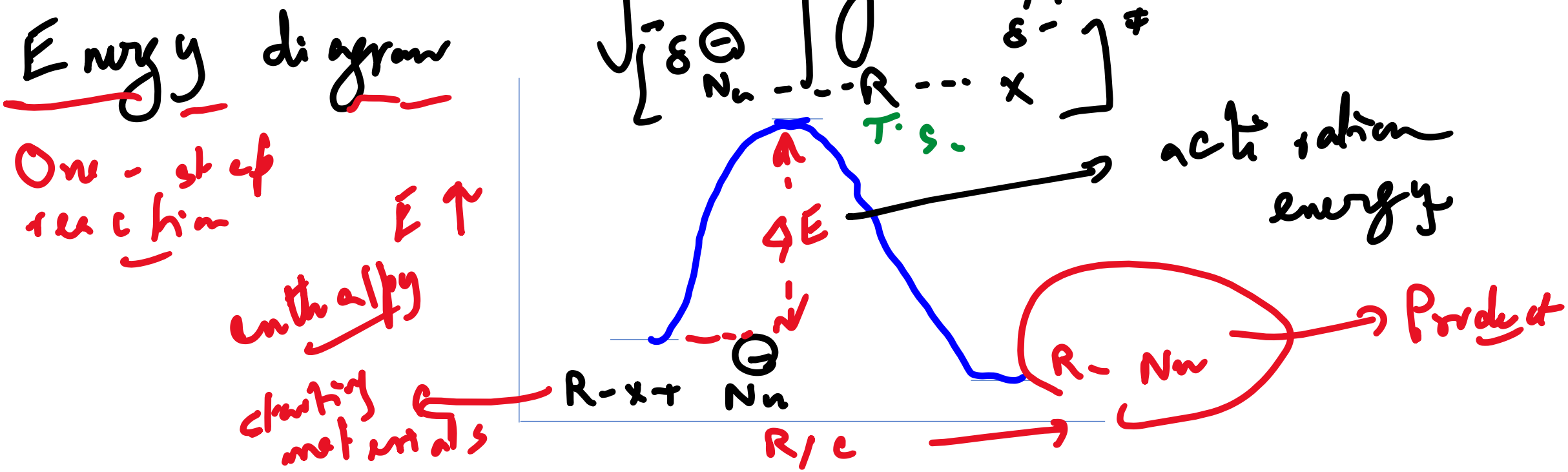
$$MeX > 1^\circ \text{ alkyl halide} > 2^\circ > 3^\circ$$


Eg:
Nu⊖
1° (Primary alkyl halide)
neopentyl bromide
bulky group.
steric crowding hinder
will the approach of nucleophile
Preferable mechanism
SN1
SN2
1°
3°
SN1
methyl shift

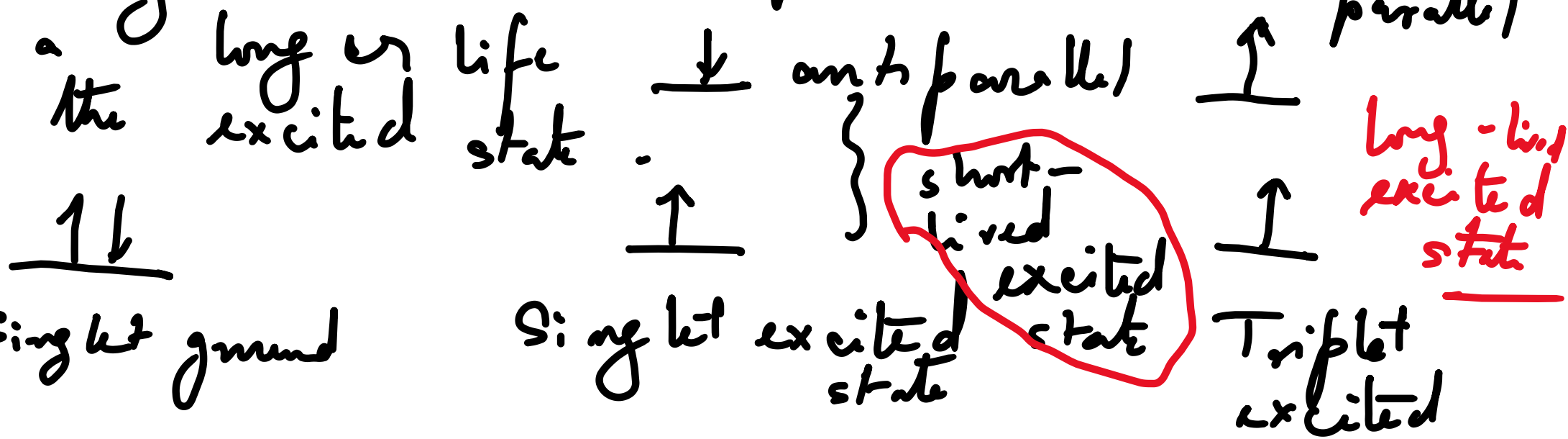
⑤ S_N2 reaction occurs in polar aprotic solvent like DMF, DMSO etc.

⑥ The reaction is stereo specific & occurs with inversion of configuration.

Energy diagram



In phosphorescence, there is a change in electron spin, which results in a longer life of the excited state.



Fluorescence differs from phosphorescence in that the electronic energy transition does not change spin.

same spin

that is responsible for fluorescence

Organic Reaction Mechanisms

S_N1 :

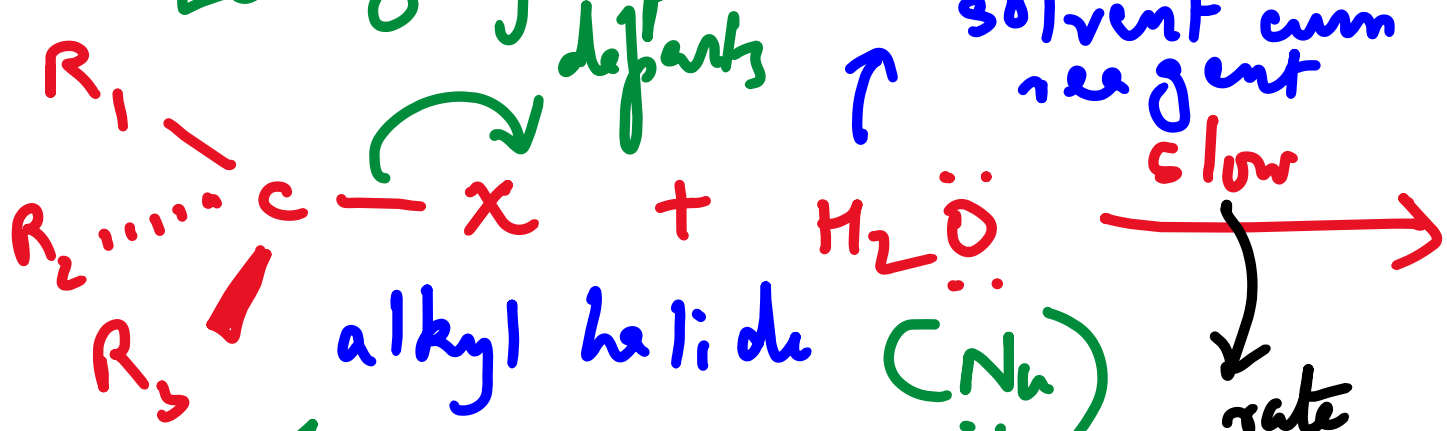
S = substitution

N = nucleophilic

1 = Unimolecular

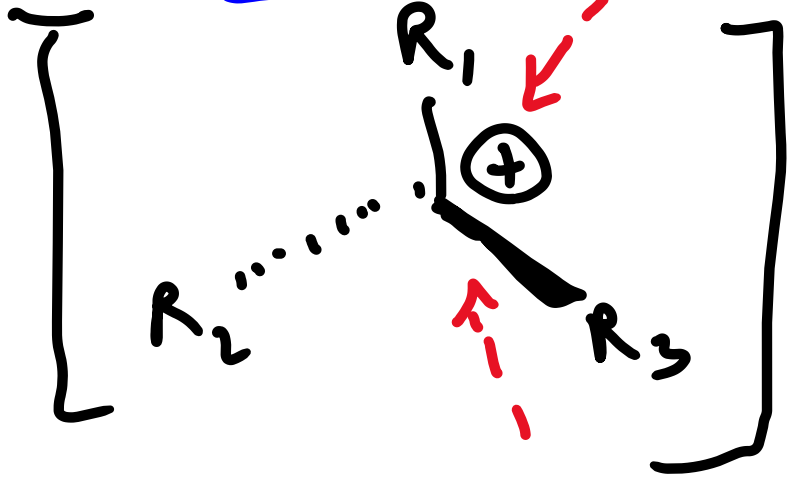
Two-step reaction

Step-I: Leaving group departs



Step II

Planer



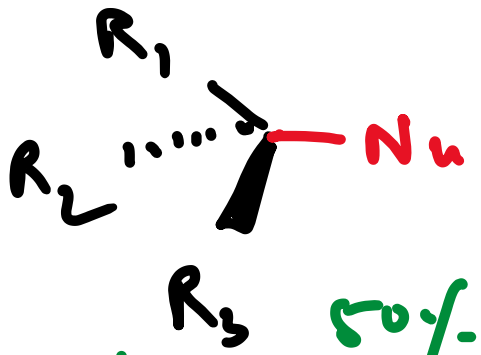
+ :Nu

50% — Bond making

fast

can attack equally from both top & bottom face

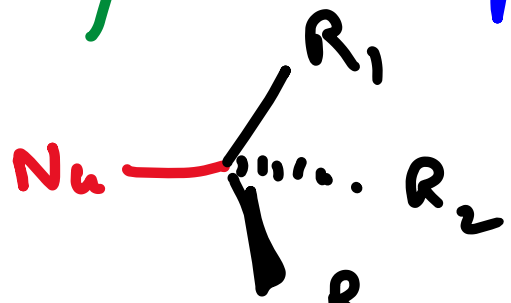
50%



50%

Racemisation

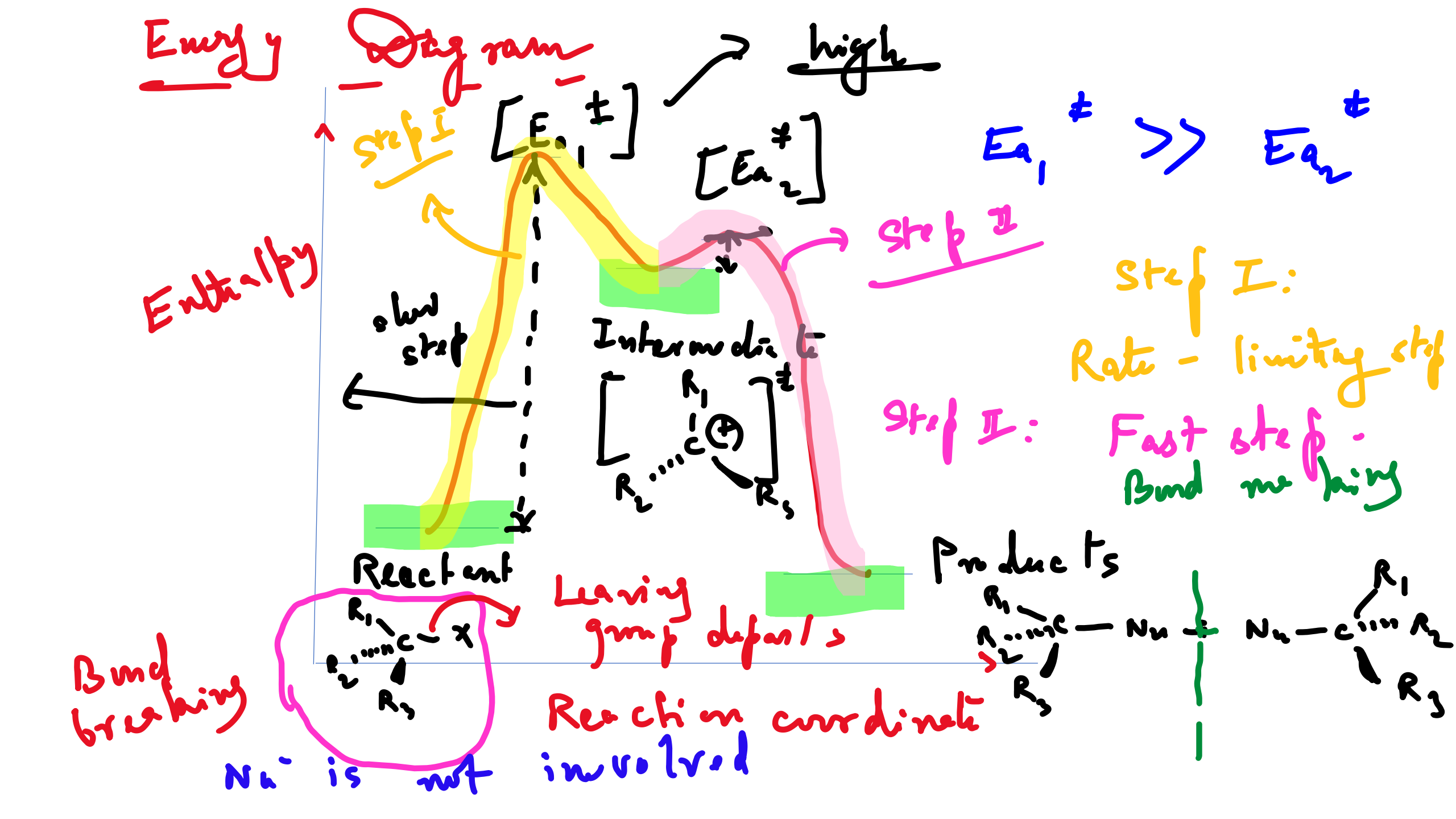
+ mirror image



50%

Enantiomeric pair (±)

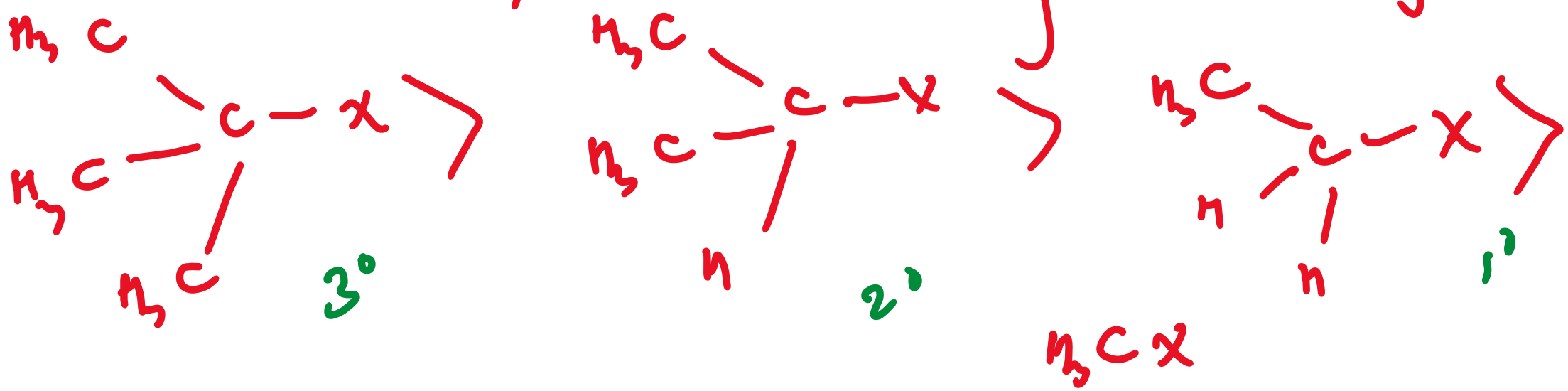
non superimposable


Energy Diagram
high
Enthalpy
Step I
Step II
slow step
Intermediate
Reactant
Products
Leaving group departs
Bond breaking
Bond making
Reaction coordinate
Nu⁻ is not involved
Eₐ₁‡ >> Eₐ₂‡
Step I:
Rate - limiting step
Step II:
Fast step

The rate of S_N1 reaction is independent of the nucleophile concentration but is dependent on the nature of leaving group.

Better the leaving group (for both S_N1 & S_N2) faster the reaction

In S_N1 reaction, the order of reactivity is



This is because S_N1 reaction involves the formation of a carbocation intermediate.

Higher the no. of alkyl substituents, greater is the stability of resulting carbocations due to +I effect.

Greater the carbocation stability, lower is the activation energy required to reach the T.S. & faster is the reaction.

Features	S_N1	S_N2
1. Molecularity	1	2
2. No. of steps	Two	One only transition state
3. Intermediate	✓ Planar (Carbocation)	X (T.B.P.)
4. Nucleophile affect reaction rate?	X nucleophile not involved in R.D.S.	✓ nucleophile attacks and leaving group departs at the same time.
5. Mechanism →	Stepwise	Synchronous

Features	S_N1	S_N2
c. Nature of leaving group affect reaction rate?	✓	✓
	Leaving group involved in RDS	Reaction rate depends on C–X bond strength

Bond strength: C – Cl > C – Br > C – I

Higher the bond strength slower is the rate of reaction.

This condition applies to both S_N1 & S_N2 as in both case bond breaking occurs in the R.D.S.

Features	S_N1	S_N2
7. Solvent	Polar protic Carbocation → charged intermediate stabilized in polar protic solvent Eg. H_2O, CH_3OH	Polar aprotic Eg. DMSO DMF
8 Stereochemistry	Racemization Non-stereospecific	Inversion Stereospecific

Order of reactivity: S_N2 : $1^0 > 2^0 > 3^0$

S_N1 : $3^0 > 2^0 > 1^0$

Organic Reaction Mechanism

Stereochemical outcome of S_N1 reaction :

In S_N1 reaction, racemisation will occur yielding an optically inactive (±) product.

In practical scenario, 100% racemisation is rarely observed.

Although racemisation might be the major outcome of S_N1 reaction, there may be certain degree of inversion; depending

the structure of the intermediate carbocation and solvent.

S_N1 reaction

Solvent

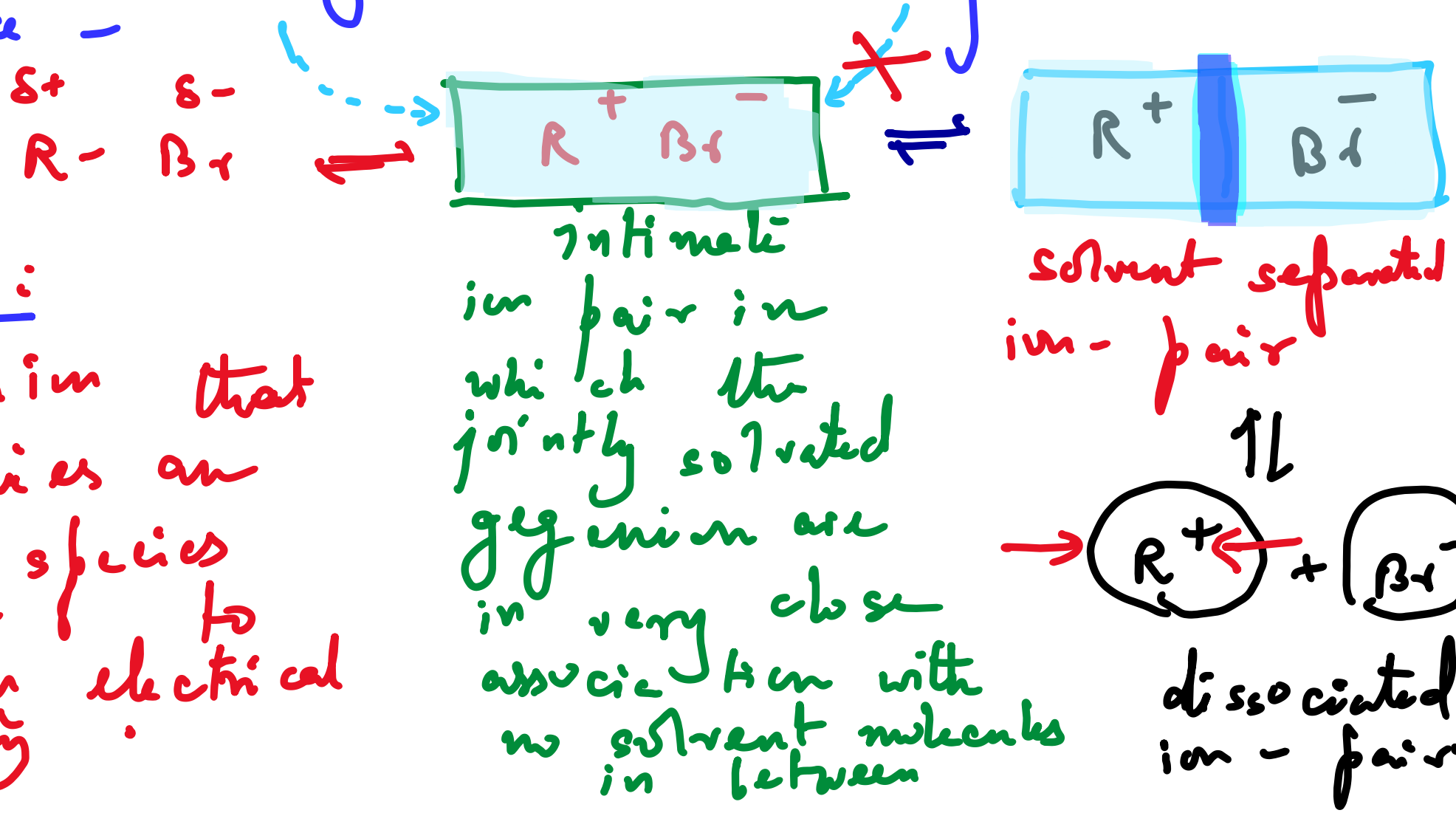
More stable the carbocation, greater is the degree of racemisation.

The more nucleophilic the solvent is, greater is the degree of inversion.

Carbocation.

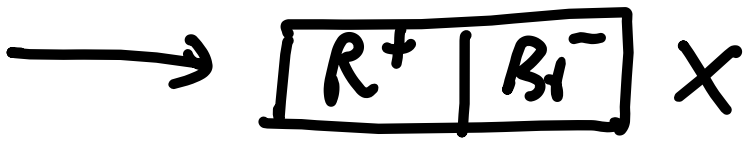
Depends on structure of the carbocation.

These observations become understandable if the rate limiting SN1 ionisation follows the sequence –



Geminate:
A counter ion that accompanies an ionic species in order to maintain electrical neutrality.

In a solvolysis reaction, attack on R^+ by a solvent molecule e.g. H_2O is likely to result in inversion as attack can take place by the solvent envelope on the back side of R^+ but not on the front side where there are no solvent molecules which is shielded by the Br^- group.

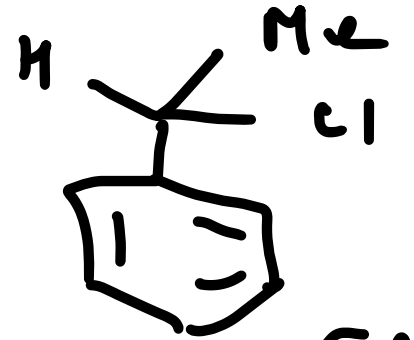


Attack on the solvent separated ion pair is likely to lead to racemisation

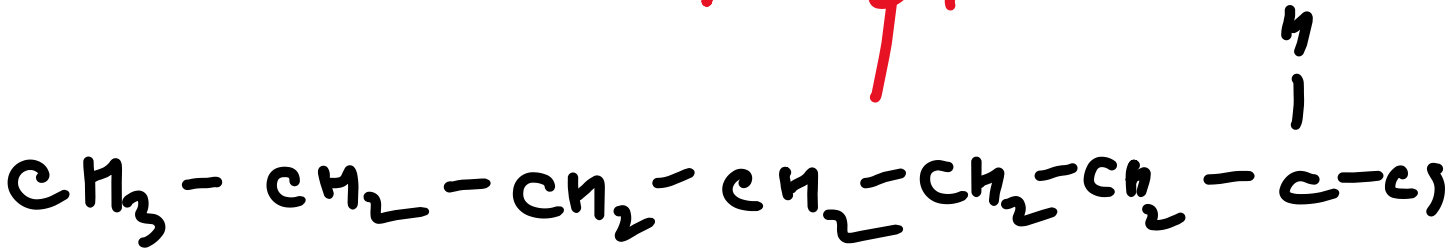
because at this stage R^+ is not shield by Br^-, so that attack can take place from both sides, leading to S_N1 mode of reaction.

Q Solvolysis of (+) $C_6H_5CHMeCl$ leads to 98% racemisation whereas in case of $C_6H_{13}CHMeCl$, only 34% racemisation occurs- Explain.

S_N1

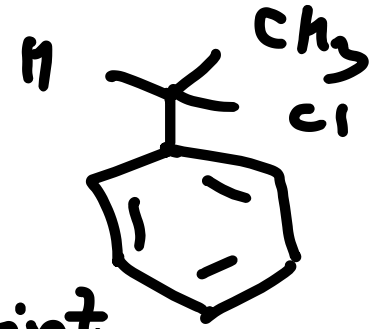


(A)

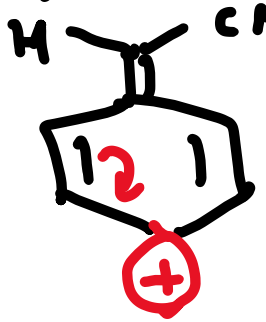


(B)

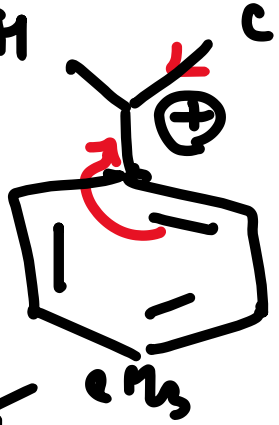
A:



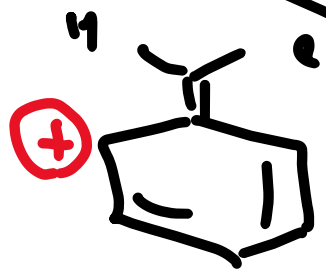
S_N1 reacting



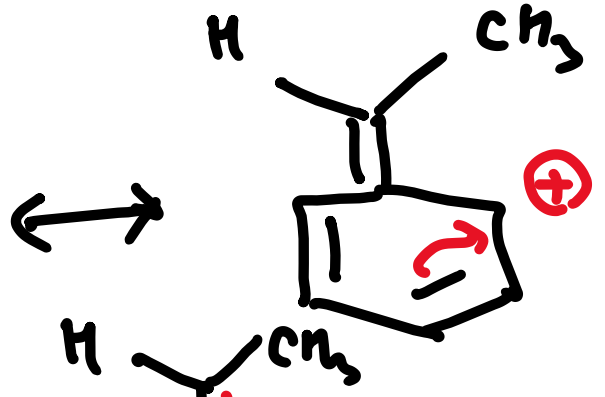
much higher



resonance stabilized c.c.



+I, +R



highly stable c.c.

B: $C_6H_{13}-\underset{\underset{Me}{|}}{\overset{\overset{H}{|}}{C}}-Cl$ ⇌ $C_6H_{13}-\overset{\overset{H}{|}}{C}\oplus$ (Me)

Cross-resonance

Creation of solvent

+I effect will stabilise the carbocation

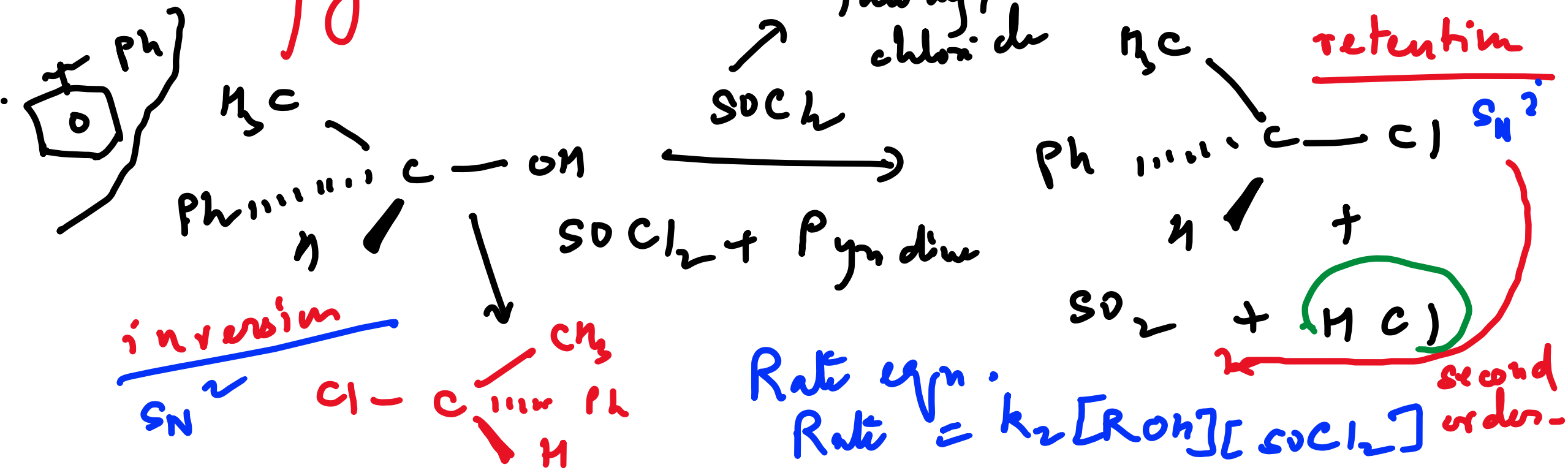
S_N1 + S_N2

Racemisation

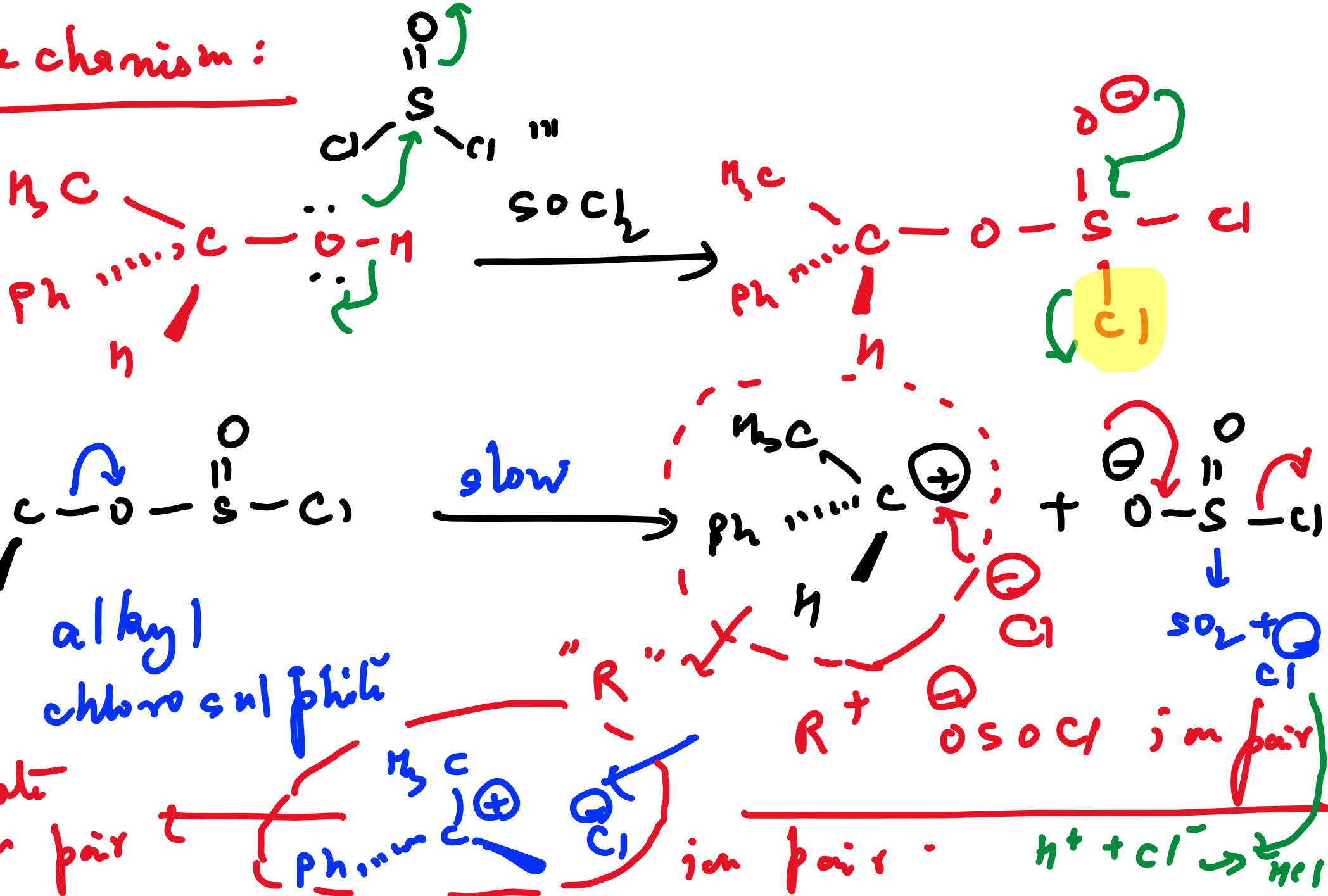
Inversion

S_Ni mechanism : Retention of configuration

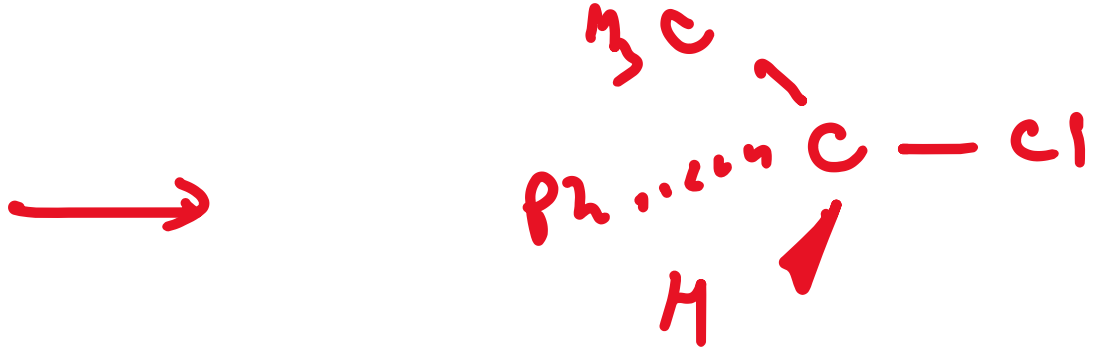
A number of cases are known where the reactions proceed with retention of configuration.



S_Ni mechanism:



Attack of $Cl^{\ominus}$ occurs on the same side from which $\overset{\ominus}{O}-\overset{O}{\overset{\|}{S}}-Cl$ departed

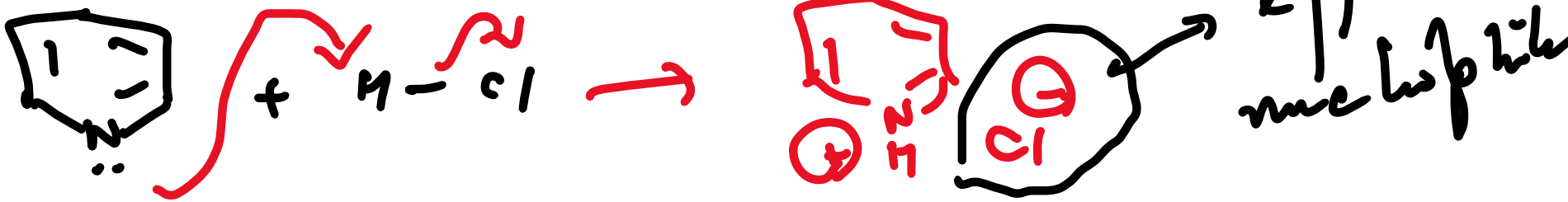


Leading to retention of configuration.

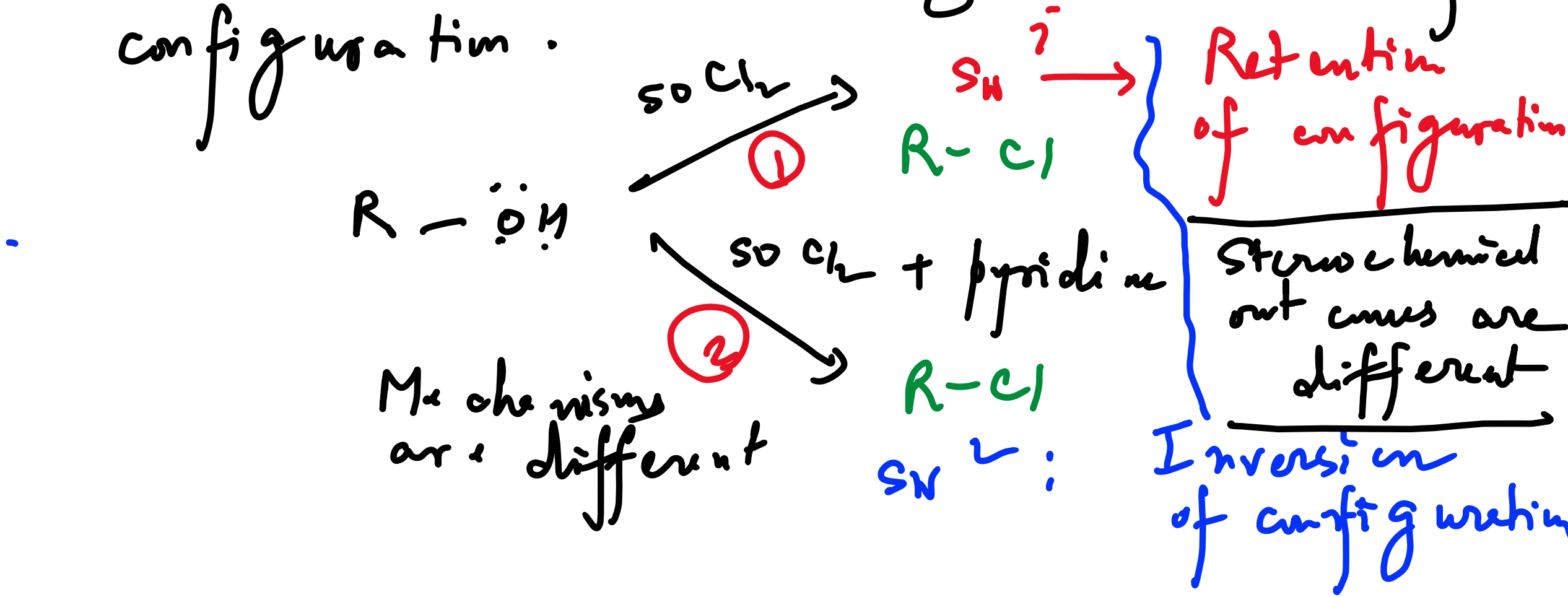
$S_N i$ reactions are second order rate equation like $S_N 2$. However, unlike $S_N 2$, this reaction proceeds with retention of configuration.

When pyridine is used along with $SOCl_2$, the product RCl is found to have undergone inversion of configuration

This occurs because the HCl produced during the formation of R-OH & $SOCl_2$ is converted by pyridine to pyridinium chloride.



$Cl^{\ominus}$ being an effective nucleophile will attack from the back in a normal S_N2 reaction mode leading to inversion of configuration.



Organic Reaction Mechanism

Like dissolves Like

Nucleophilic Substitution

S_N1

unimolecular

polar, protic solvent

1. Two-step mechanism
2. True carbocation intermediate
3. Racemisation → inversion

S_N2

bimolecular

polar aprotic solvent

1. Synchronous, Concerted
2. No intermediate Only T.S. complex
3. Inversion

S_Ni

Second order rate

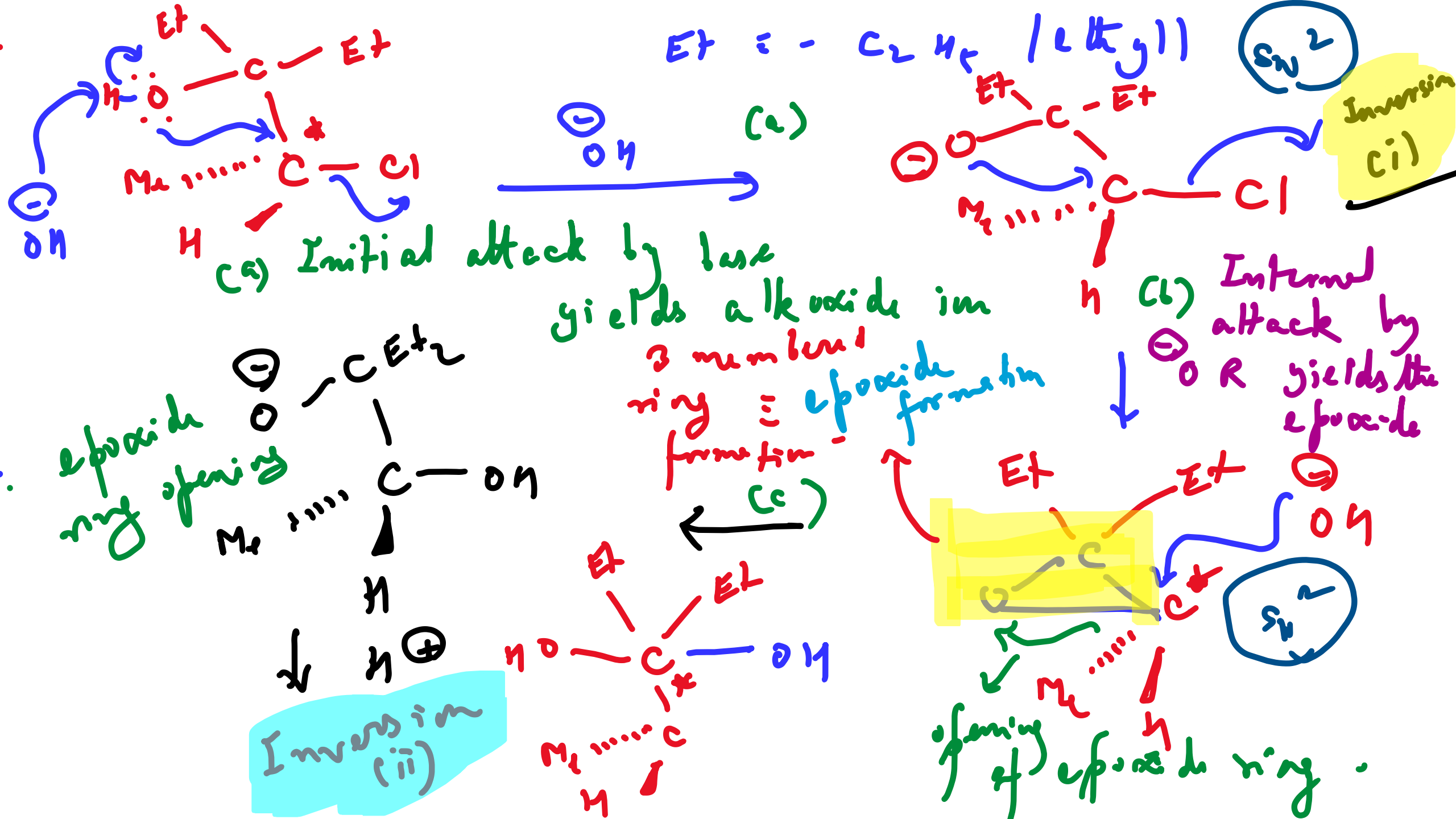
different ←

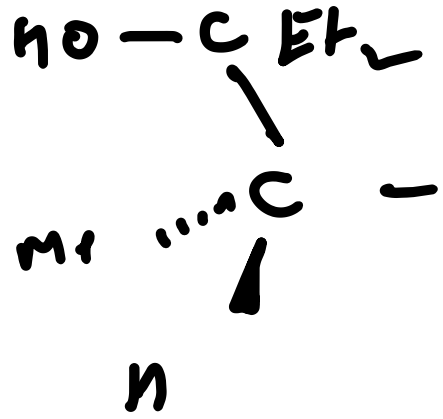
1. Multi-step
2. True intermediate
3. Retention of configuration

Neighbouring group participation

In nucleophilic displacement reactions, there are some examples where the common feature is an atom or a group close to the carbon undergoing attack, has an electron pair available.

The neighbouring group can use its electron pair to interact with the backside of the carbon atom undergoing substitution, thus preventing attack by nucleophilic reagent.


Et = - C2 H5 (ethyl)
(a)
(b) Initial attack by base yields alkoxide ion
(c)
3 membered ring ≡ epoxide formation
epoxide ring opening
Inversion (i)
Inversion (ii)
(d) Internal attack by OR yields the epoxide
SN2
SN2
ring opening of epoxide ring.

Final product: 

↓

result of inversion + inversion

= double inversion

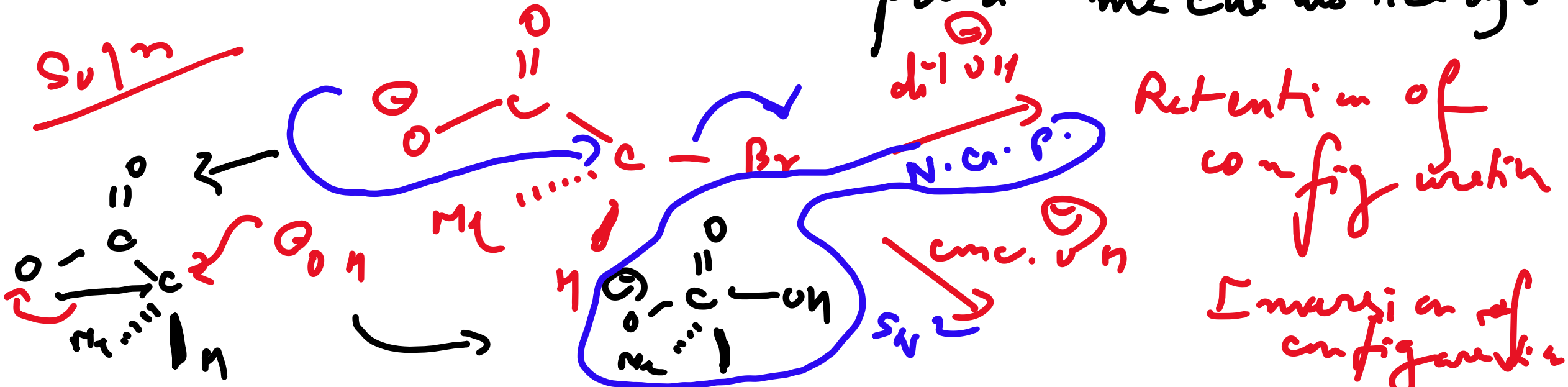
= retention of configuration

stereochemical configuration same as the starting material

The apparent retention of configuration is brought about by two successive inversions.

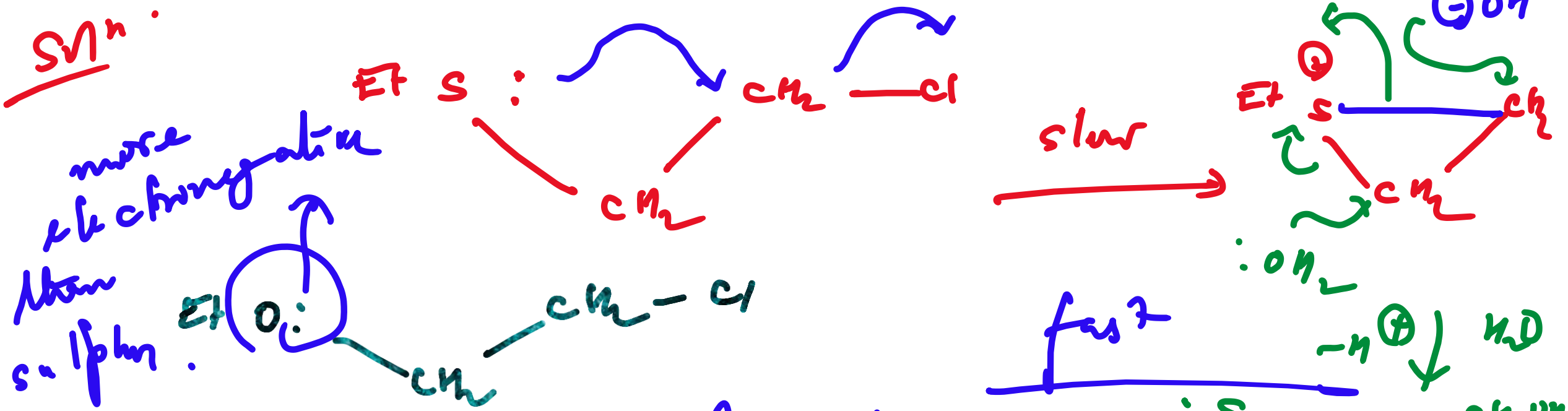
Q. Hydrolysis of 2 bromopropanoate

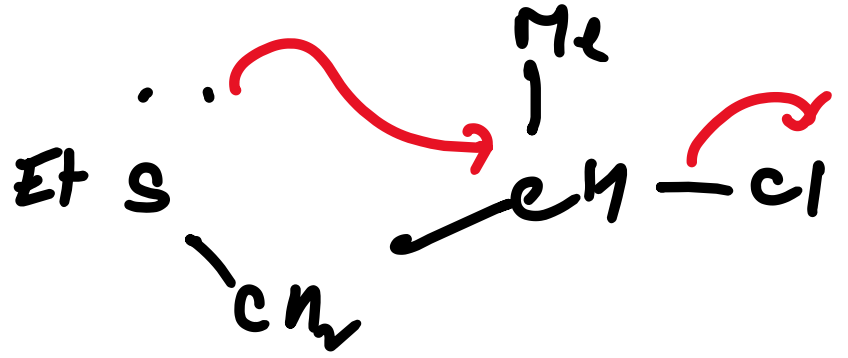
anion at low $[^{\ominus}OH]$ concentration proceeds with retention of configuration. However, as the concentration of the nucleophile $[^{\ominus}OH]$ is increased, an increasing proportion of inversion of configuration is observed. Explain mechanistically.



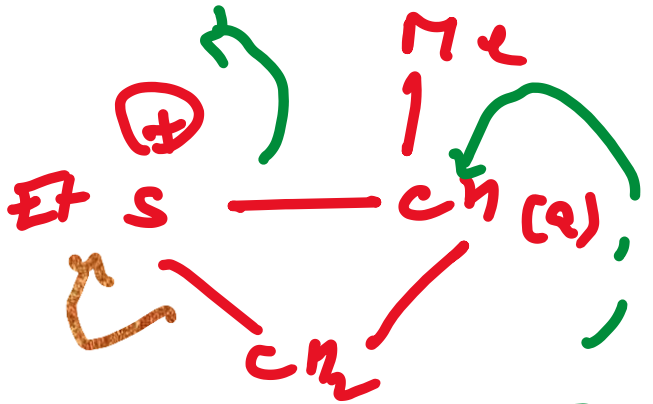
Q. Et S CH_2CH_2Cl undergoes hydrolysis 10^4 times faster than Et O CH_2CH_2Cl in dil. comparable conditions — Why?

S_N1

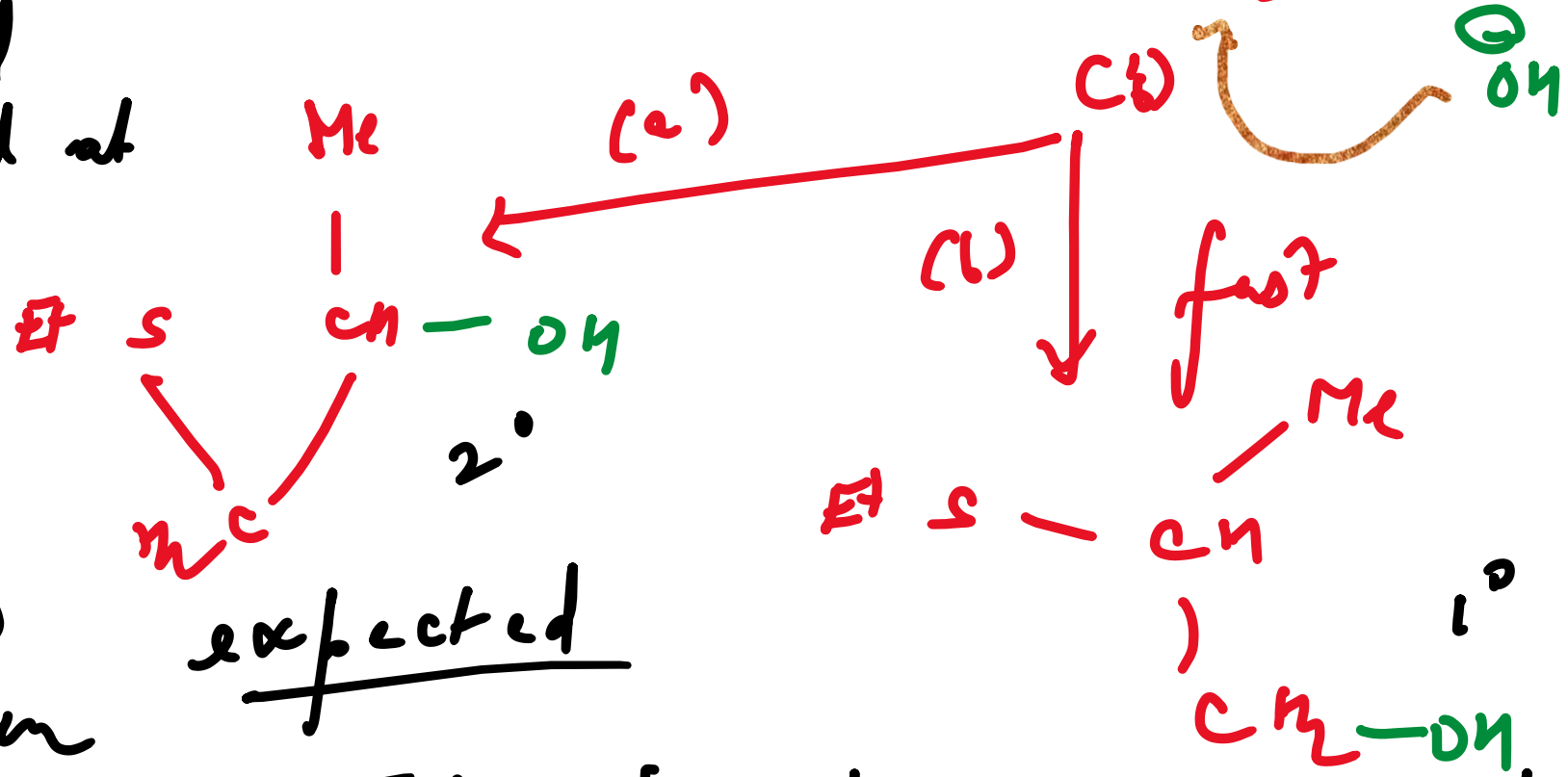




slow



The unexpected one is formed at a greater rate than the expected one indicating the participation of an unsymmetrical intermediate

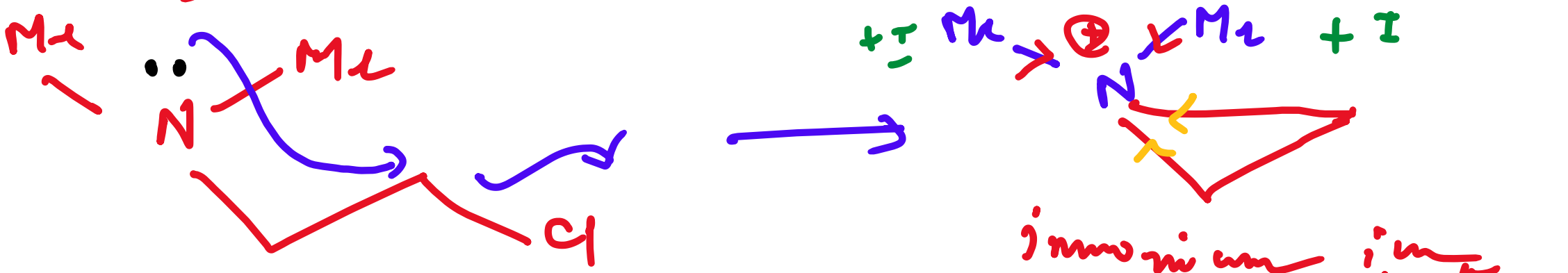


unexpected

Unlike sulfur, oxygen is sufficiently electronegative so as not to donate an electron pair like OR or $R\text{-}CO_2^{\ominus}$ and therefore hydrolysis of ETOCH$_2$CH$_2$Cl proceeds via ordinary S_N2 attack by an external nucleophile which is likely to be much slower as compared to the internal nucleophilic attack that we have observed in case of neighboring group participation with sulfur atom.

Nitrogen (N) can also act as a neighbouring group just like S.

Hydrolysis of $Me_2N CH_2CH_2 Cl$ is markedly slower under comparable conditions



The hydrolysis is slower in this case because of the greater stability

of the cyclic immonium ion intermediate.

Such cyclic species are formed during the hydrolysis of mustard gas $S(CH_2CH_2Cl)_2$ & the related nitrogen mustards. such as $MeN(CH_2CH_2Cl)_2$

The cyclic immonium salts derived from the latter are powerful neurotoxins. → Peripheral N.S!

Neurotoxicity M. fatty

cause damage of CNS ✓ such as persistent memory impairments, epilepsy & dementia. ←

intellectual disability

Which factors affect the rate of S_N1 & S_N2?

1. Structure of the substrate
2. Concentration & reactivity of the nucleophile.
3. Solvent.
4. Leaving group.

① Substrate: S_N2: Order of reactivity:

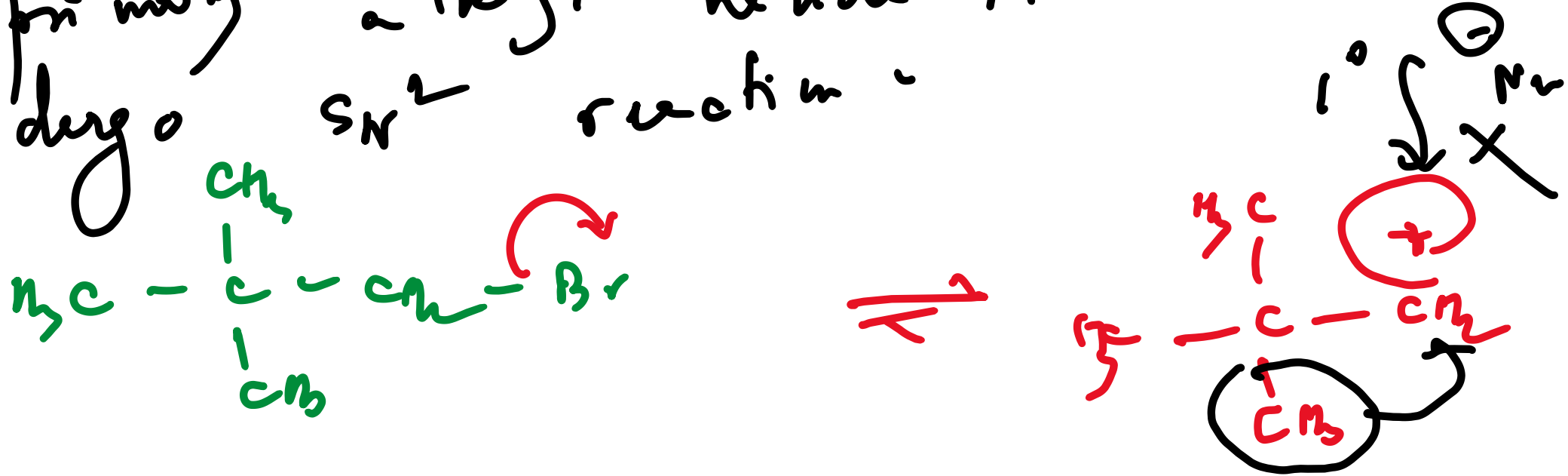
$-CH_3$ > Primary > Secondary > Tertiary

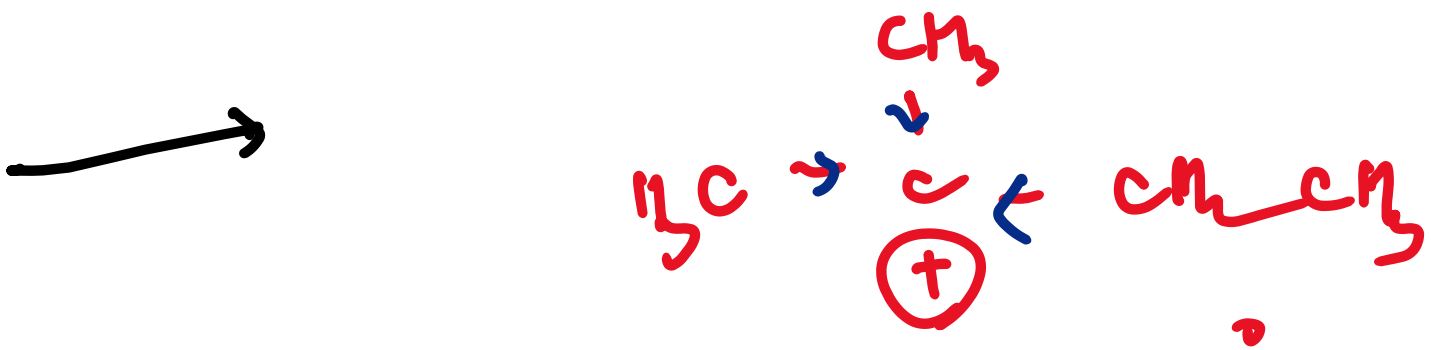
CH_3-I > CH_3CH_2I > $(CH_3)_2CHI$ > $(CH_3)_3CI$

In S_N2 reaction, nucleophile attacks from back side of the L.G. So, higher the steric hindrance, slower the reaction rate.

N.B:-

Although neopentyl chloride / bromide is a primary alkyl halide it will not undergo S_N2 reaction.





more stable 3° due to +I effect.

For bulky substituents with steric hindrance, S_N1 is preferred than S_N2.

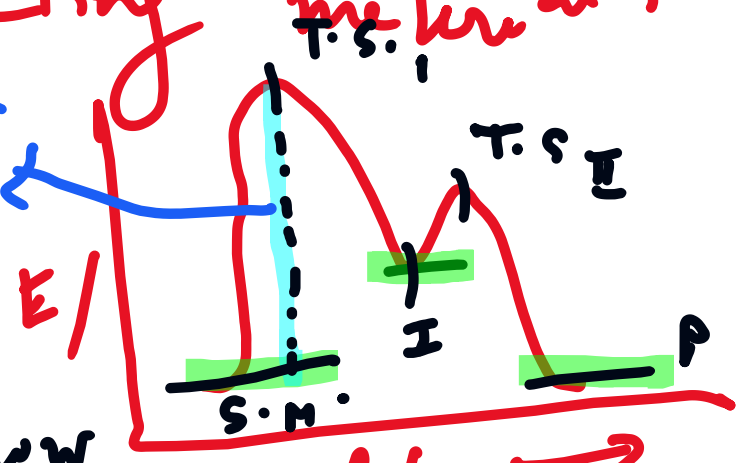
S_N1 : Reactivity order is reversed

3° > neopentyl > 2° > 1° > $-CH_3$

S_N2 : $-CH_3$ > 1° > 2° > neopentyl > 3°.

In S_N1 reactions, greater the stability of intermediate carbocation, faster is the reaction rate.

More stable the intermediate lower is the activation energy barrier. The transition state & intermediate are uphill in energy w.r.t. starting material.



Hammond's Postulate

The transition state for a step that is uphill in energy should show a strong resemblance (in energy) to the product of that step

Since the product of R.D.S of S_N1 reaction is a carbocation, any factor that stabilize the carbocation should also stabilize the T.S.

Solvent effect: Intermediate in S_N1 reaction is a planar carbocation, which is a charged species. Polar, protic solvent will promote S_N1 reaction whereas polar, aprotic solvent will favor S_N2,

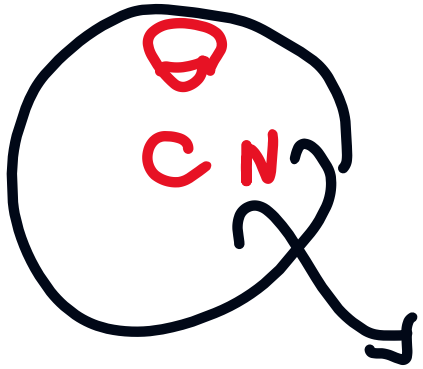
Molecularity of S_N1 is 1 $\Rightarrow$ only 1 molecule involved in R.D.S. The nucleophile does not participate in R.D.S. S_N1 concentration of S_N1 is nucleophile independent. But in case of S_N2 strength & concentration of the nucleophile is important, S_N2 if the concentration of the nucleophile is increased the rate of S_N2 reaction will increase proportionally

Q. Halides that do not readily undergo S_N1 attack can be promoted by the use of silver salt as anion.

$R-N\equiv C$

In S_N1 reaction, attack takes place on the intermediate carbocation R^+ through the ambidentate nucleophile

atom in the nucleophile that has higher electron density.



+ R – Br $\xrightarrow{S_N 2}$

NaCN

[$\overset{\delta-}{N}C \cdots \overset{\delta+}{R} \cdots \overset{\delta-}{Br}$]

T.S.

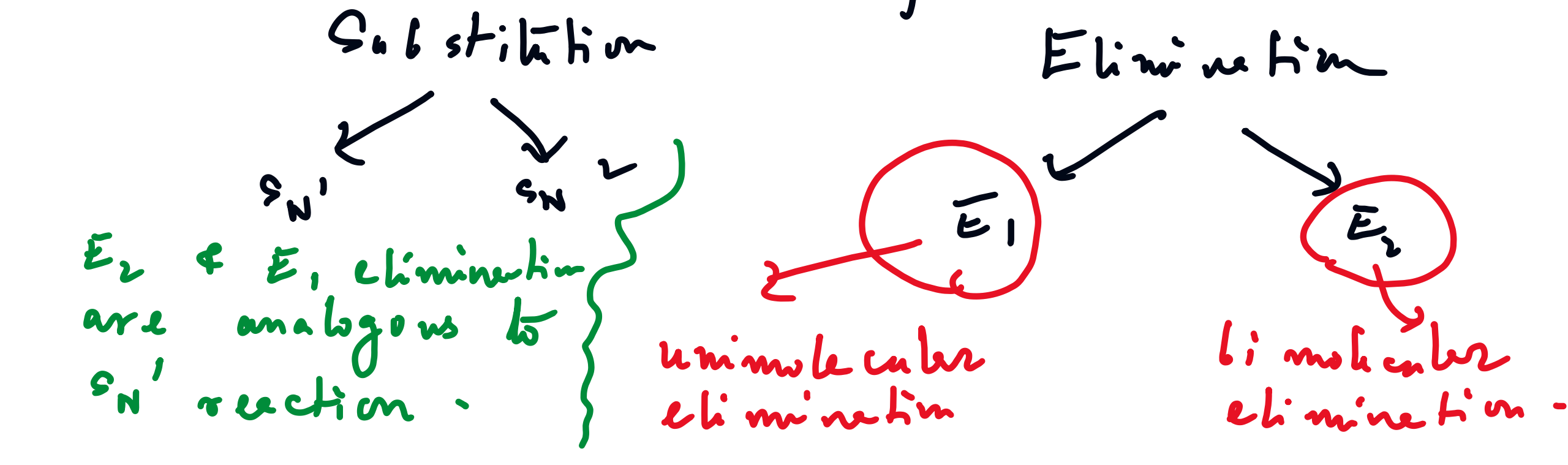
$N \equiv C - R$ + Br^-

Of mediated formation is ab

Attack takes place through the atom which is more favorable

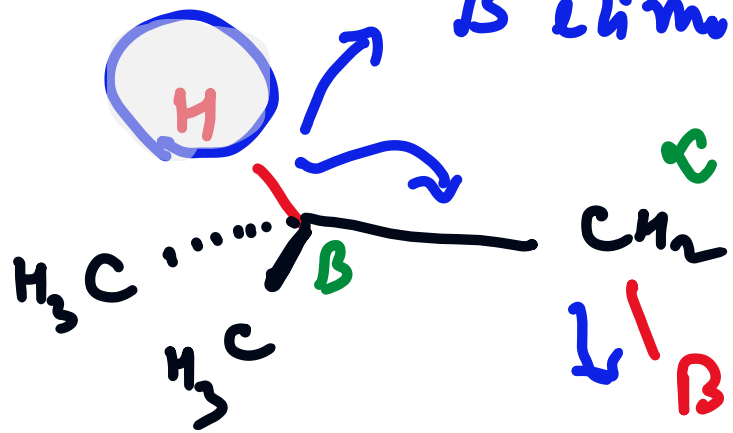
Elimination Reaction

Just as there are two mechanisms in case of substitution (S_N2 & S_N1), there are two mechanisms of elimination (E_2 & E_1)



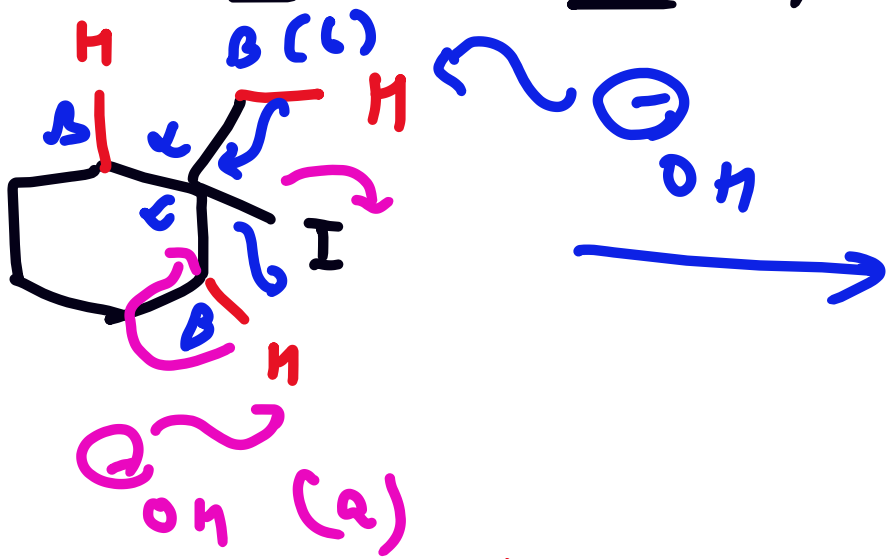
E_2 & S_N2 shares some common features

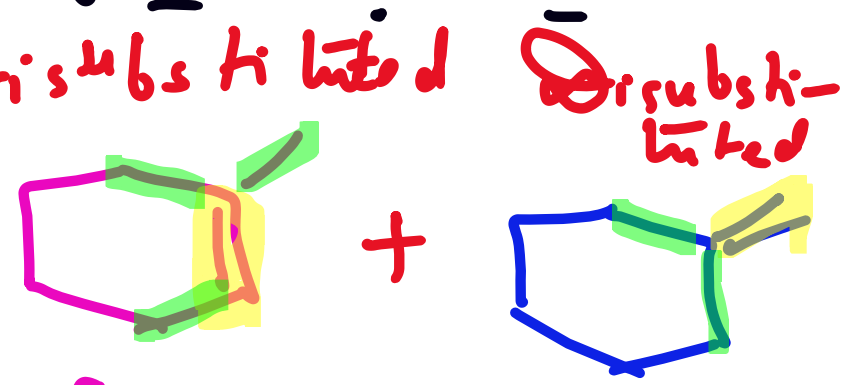
E_1 & S_N1 " " " "



Base removes a proton from the β-carbon atom, while the halogen atom leaves from the α-carbon resulting in π bond.

The Zaitsev Rule / Saytseff Rule.





(2) major product

(1) minor product

When alkyl halides have more than one β carbons i.e. two or more β carbons, more than one alkene product is formed.

In such cases, the major product is the more stable product - i.e. the one with

more substituted double bond. This phenomenon is called the Zaitsev rule.

Zaitsev product or more substituted alkene product has higher stability than the less substituted ones. More substituted alkenes have greater stability due to a number of contributing factors including hyperconjugation. Each alkyl group that can involve in hyperconjugation with the double bond stabilizes it by approx 6 cal/mol.

E_2 mechanism

One step, concerted reaction

Dehydrohalogenation:

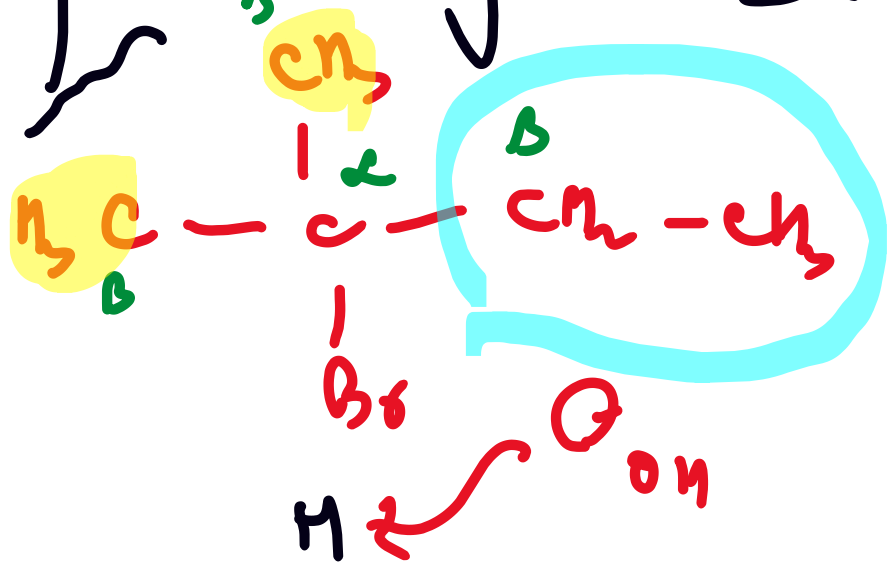
Kinetics: Second - order.

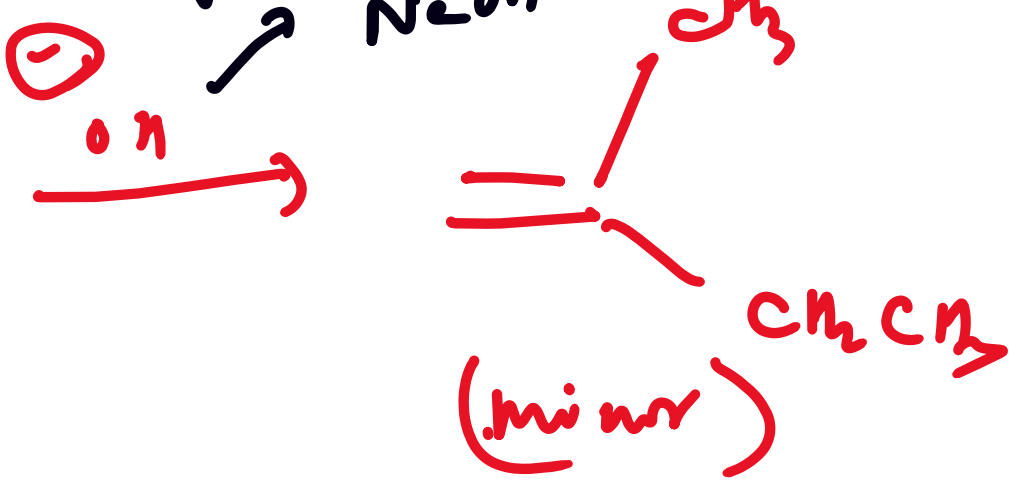
$$\text{Rate} = k\left[(CH_3)_2CH-CH_2Br\right]\left[OH^-\right]$$

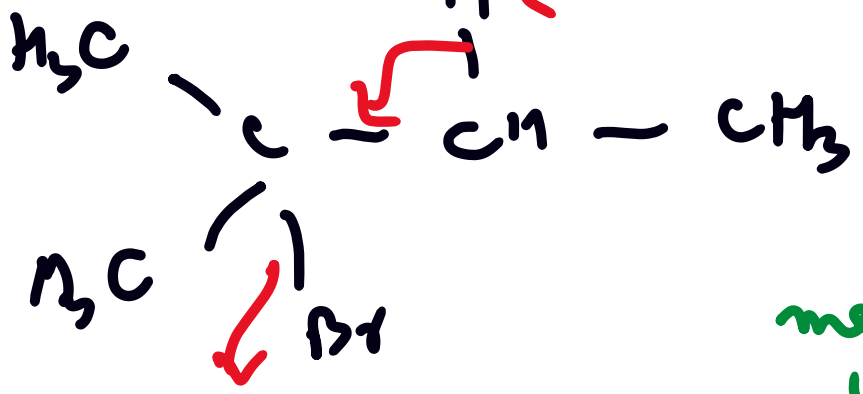
Both alkyl halide & base appears in rate equation. The reaction is concerted $\Rightarrow$ all bonds are broken & formed in single step

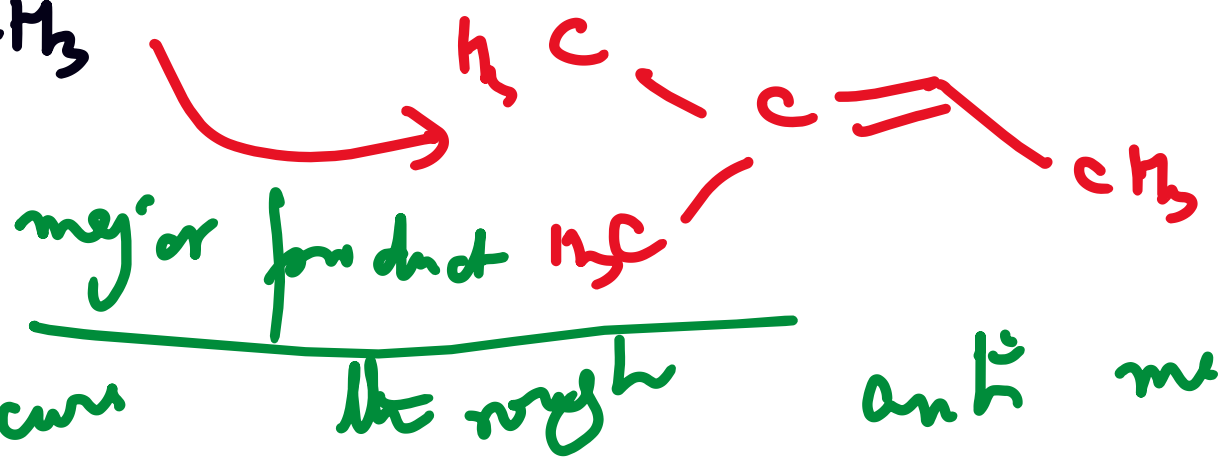
E_2 reactions are regioselective & favor the formation of Zaitsev products.

similar









major product

E_2 elimination occurs the anti mechanism.

Elimination

Antiperiplanarity is a condition for E2

syn ← ——

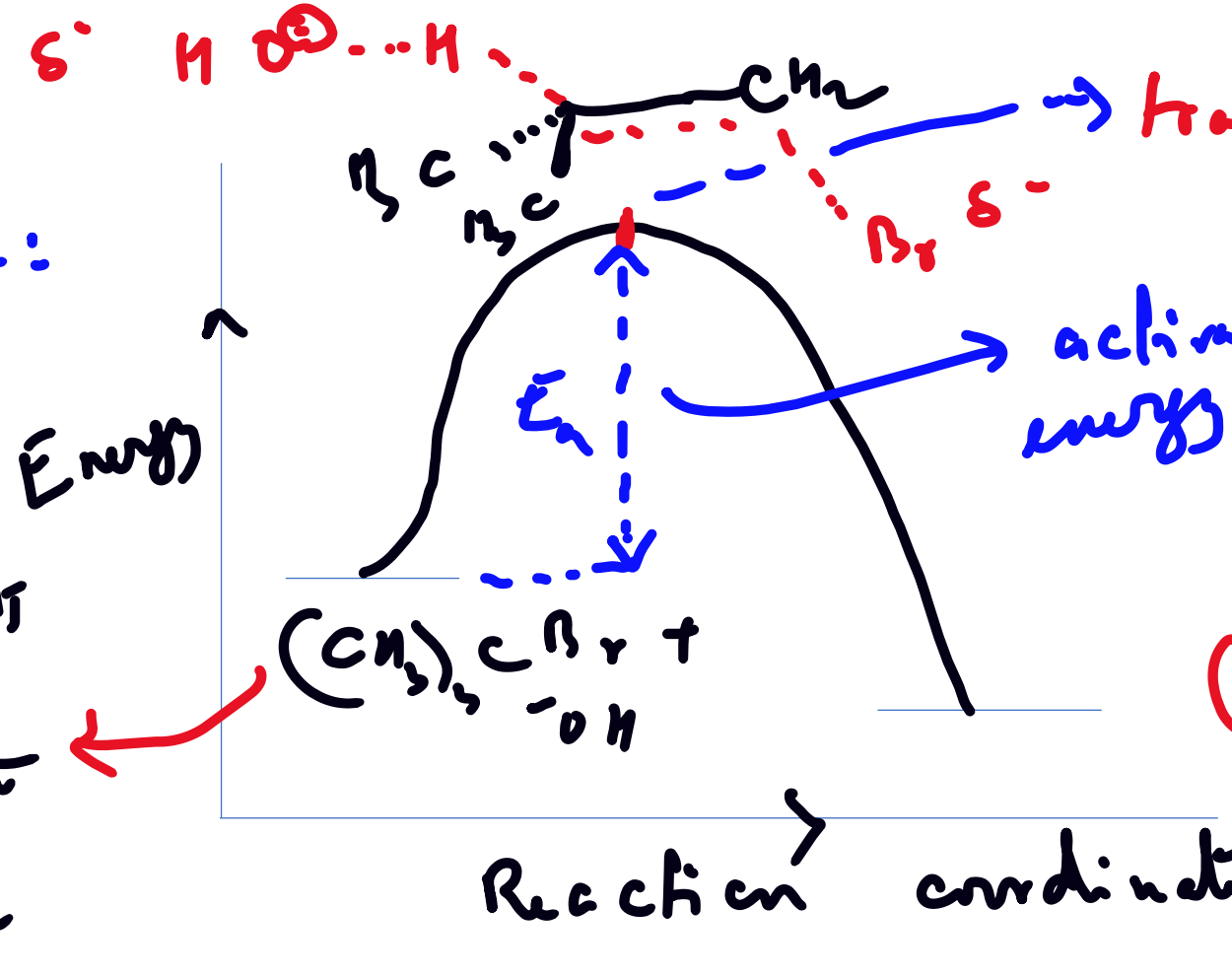
Base attacks the β hydrogen on the same side of leaving group.

anti →

Base attacks β hydrogen on the opposite sides of L.G.

E2 reactions are stereoselective - resulting in the formation of trans-double bonds preferentially.

Energy diagram:



bond breaking + bond making occurs simultaneously

$(CH_3)_2C{=}CH_2 + Br^-$

product ↓ alkene (preferentially trans)

Factors affecting the rate of E_2:

There are close similarities/analogies between S_N2 & E_2 in how the identity

of the base & leaving group, as well as the solvent affect the reaction rate

1. Base appears in rate equation. So rate of E_2 reaction is dependent on the concentration & strength of the base used.

Rate of E_2 reaction $\propto$ Strength of base

Analogy: S_N2 reaction rate increases with increasing nucleophile concentration

(increases)

as the strength of the base is increased, rate of E_2 increases

2. Because there is a partial bond breaking in the T.S., better the leaving group, faster the rate of E1 reactions

Order: R-I > R-Br > R-Cl > R-F

3. E1 reactions require strong, negatively charged bases like $\ominus OH$ or $\ominus OR$.

4. Polar protic solvents increase the rate of E1 reactions. / just like S_N2

S_N2 & E_2 mechanisms differ in how the R group affects the reaction rate.

As the number of R groups on the carbon with l.g. increases, the rate of E_2 reaction increases.

Characteristics of E_2 reaction

1. Kinetics – Second Order
2. Mechanism – Single step / Concerted path way
3. Intermediate – X No free intermediate (only T.S.)
4. Identity / Nature of R group – More substituted halide reacts faster.

Rate : $R_3CX > R_2CHX > RCH_2X$.

5. Strength of the base: Stronger base will favor the reaction.

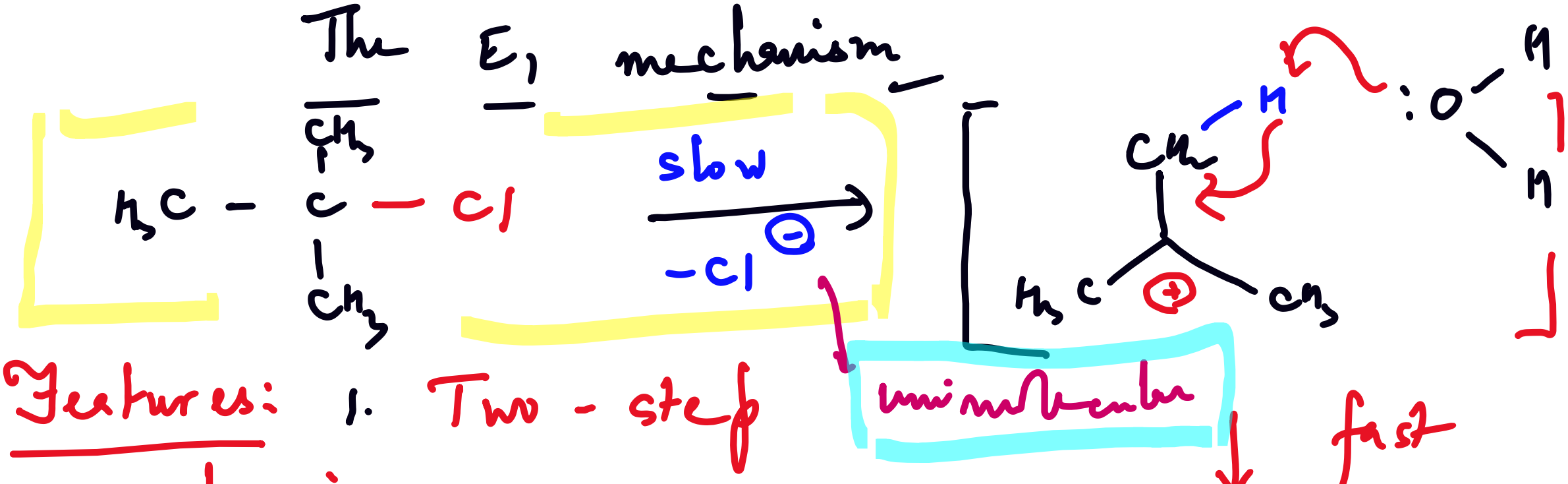
6. Leaving group: Better leaving group leads to faster reaction rate.

7. Type of solvent: Favored by Polar aprotic solvent.

8. Stereochemistry: Stereoselective reaction
Route Preferred: Anti elimination

E2 reactions are regioselective.

The E_1 mechanism



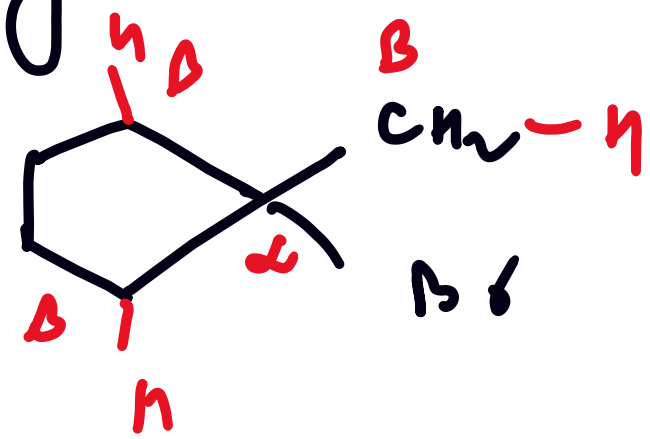
Features: 1. Two-step mechanism: a) Leaving group departs / bond-breaking occurs to form a carbocationic intermediate

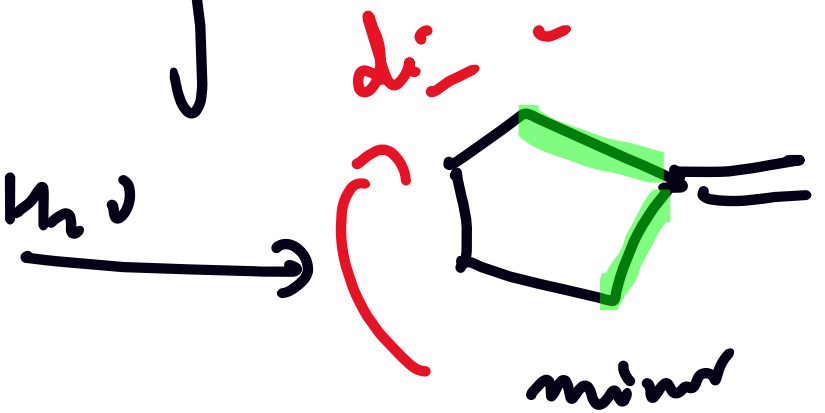
b) π-bond is formed C bond-making step

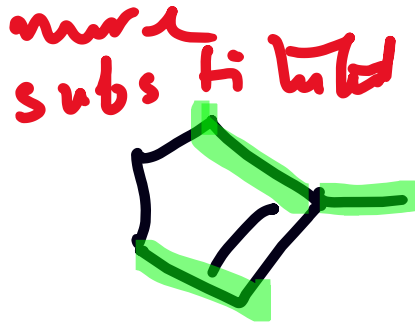
2. Kinetics: First order:

$$\text{Rate} = k\,[(CH_3)_3CCl]$$

3. **Regioselectivity:** E1 reactions are regioselective & follows Zaitsev rule -



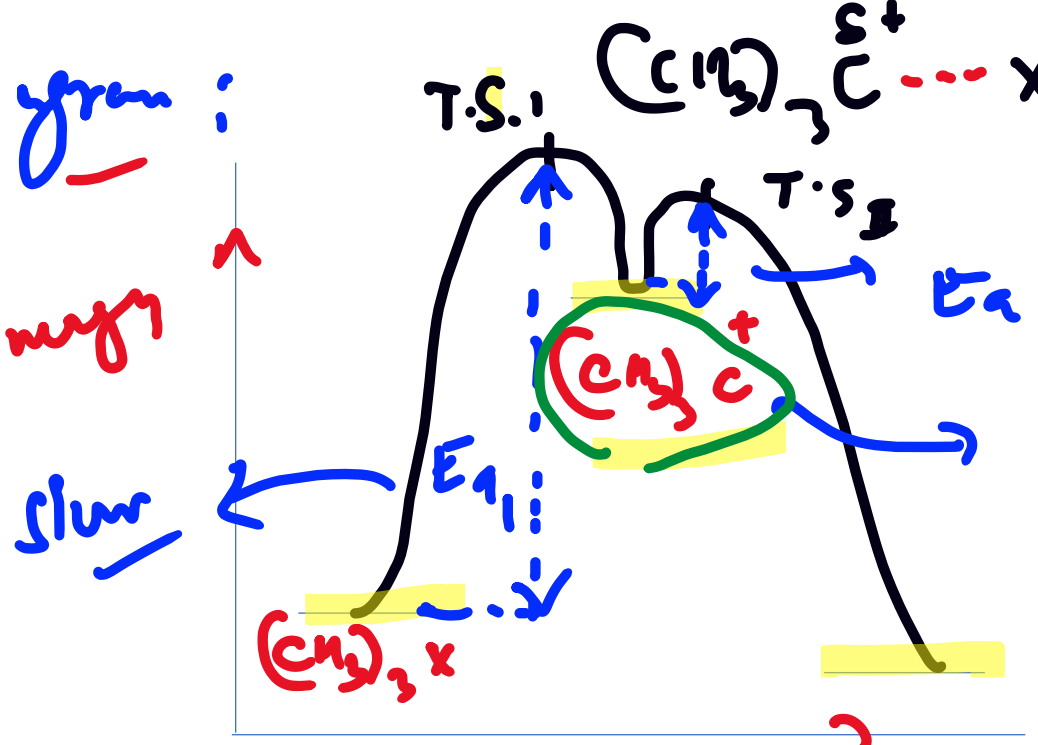




less substituted, d-alkene

major

Energy Diagram :



$(CH_3)_3C^{\delta+} \cdots X^{\delta-}$

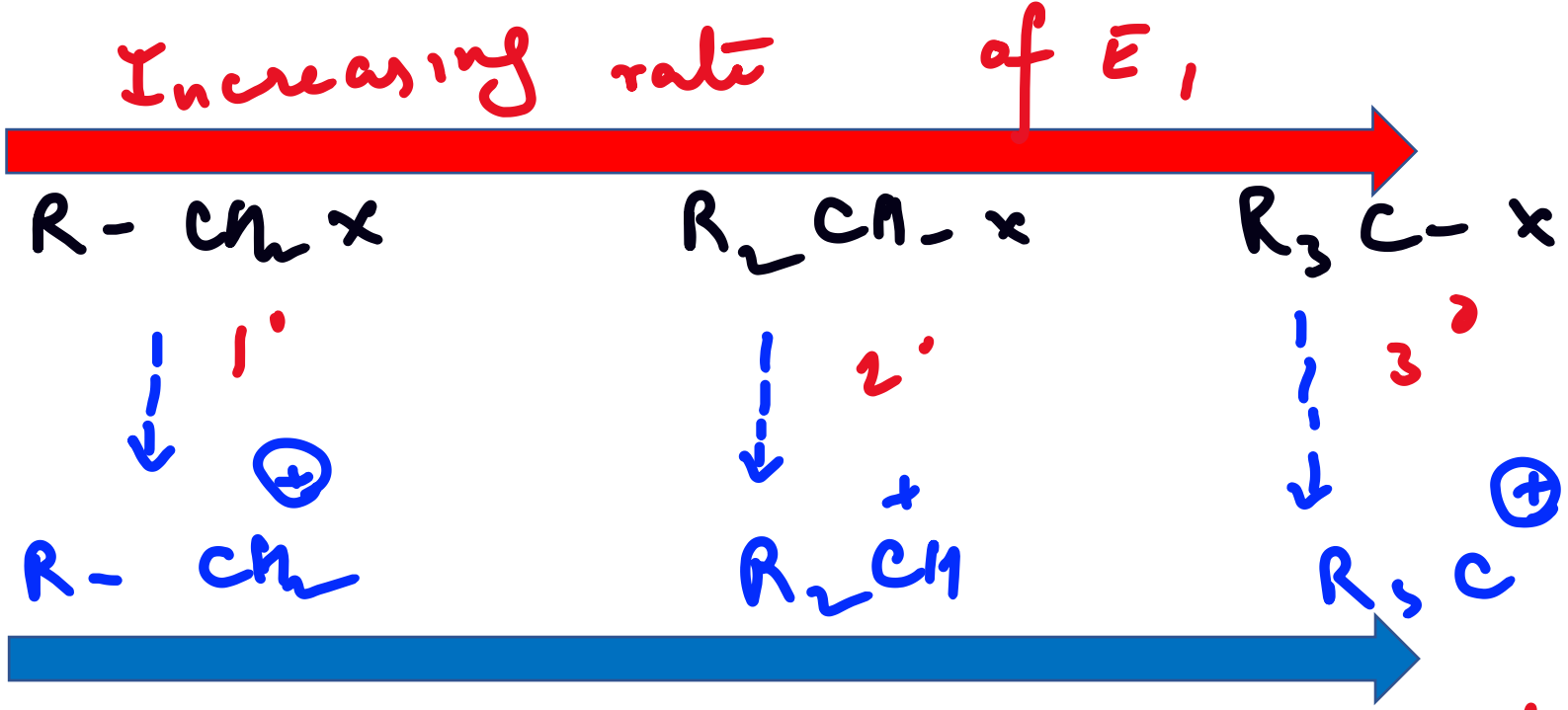
$(CH_3)_3C^+$

$(CH_3)_3X$

$(CH_3)_3C = CH_2 + HX$

Factors :

1. The rate of an E1 reaction increase as the carbon with no. of R groups in the leaving group increase s



Identity of R. grp : $S_N2 \neq E_2$

$S_N1 \equiv E1$

Q. Strong base like $\ominus OH$ or $\ominus OR$ favour E_2 whereas, weaker base like H_2O & ROH favour E1. reaching

Characteristics of S_N1 reaction:-

1. Kinetics: 1st order
2. Mechanism: 2 steps
3. Intermediate: Tertiary carbocation.
4. Identity of R group: More substituted halides react faster.

   Rate: $R_3CX > R_2CHX > RCH_2X$
5. Strength of base: Favored by weaker bases. such as H_2O or ROH

6. Leaving group: Better leaving group leads to faster reaction as the R.D.S. involves C – X bond cleavage.

7. Type of solvent: Polar protic solvent as it can stabilize carbocation intermediate.

8. E1 reactions are regioselective but not stereoselective.