Methods of Determination of Rx Mechanism

Since Chemical Rx proceed very fast ($\sim 10^{-14}$ sec), so these Rxs can't be studied directly.

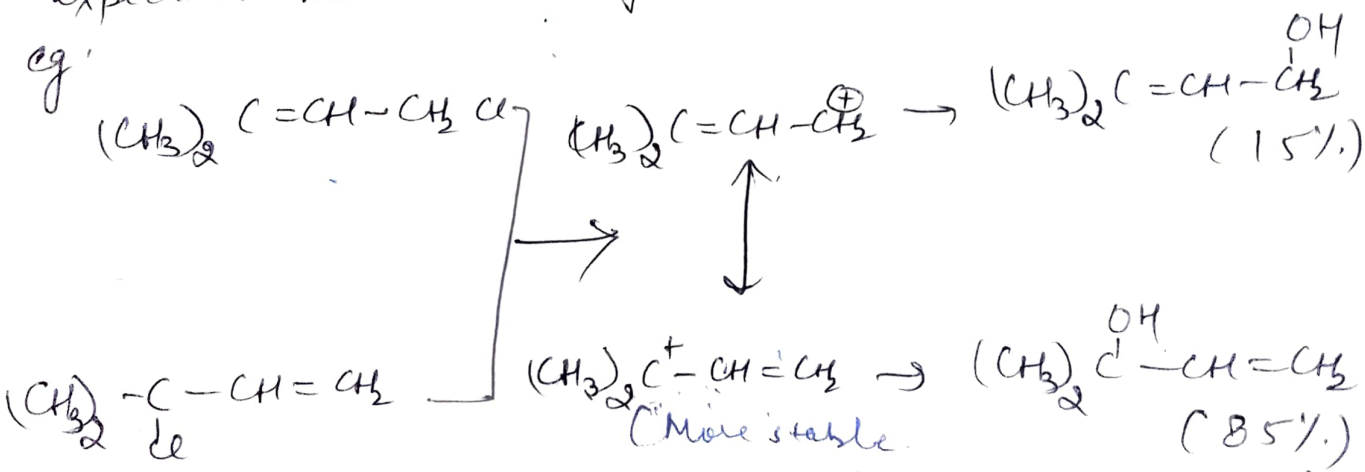
On basis of Indirect evidences, Mechanism can be found. :- (13)

Some Methods to find Mech. of Rx :-

1) Product analysis (उत्पादों की पहचान)
2) Presence of Intermediates (मध्यवर्ती यौगिकों की उपस्थिति)
3) Cross Over Experiments पारगमन प्रयोग
4) Isotope Labelling समस्थानिक अनुज्ञापक
5) Stereochemical Studies
6) Kinetic Evidences

1) Product Analysis :- By identifying the product, expected mech. can be found.

eg.



This shows that both isomers form a common intermediate, due to ⊆ Composition of product remain same.

A First step in determining the mechanism of Rx is identification of products & determining their relative amount

2) ~~Isolation~~ ~~Presence~~ of Intermediates :-

Intermediates are formed in some org. Rxs in which some stable intermediates can be obtained. Such int. can be isolated before completion of Rx.

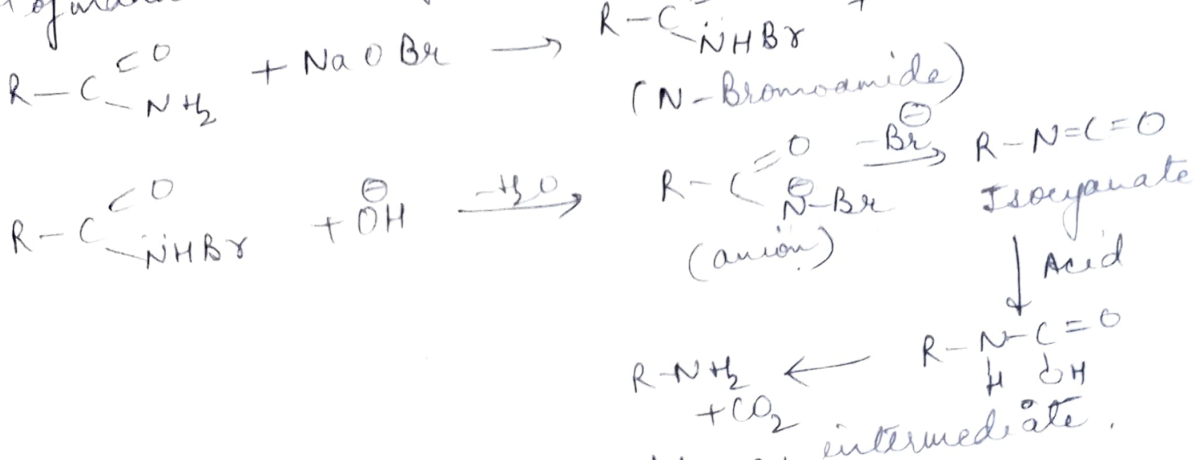
Unstable Intermediates can be detected by spectrometric methods or they can be trapped in the form of other compds. in chemical Rx.

By them, Mech. can be known.

Isolation :-

Some stable int. obt. before completion of Rx. using mild conditions.

Eg. Hofmann Rearrangement Rx

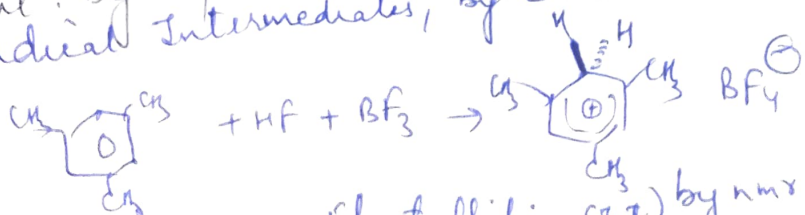


RCONHBr, RCO⊖NBr, RNCO → obt. as intermediate.

Detection :-

In SN1 & E1 Rx, Carbonium ion detected in form of int. by spectroscopy.

Radical Intermediates, by ESR.



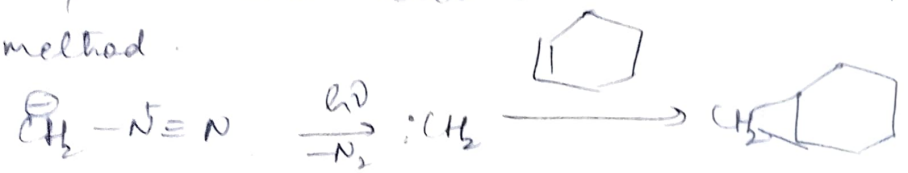
Electrophilic (I.T.) by nmr & electronic spectra

sub.

Trapping :-

Some int. can't be separated b'coz they are unstable.

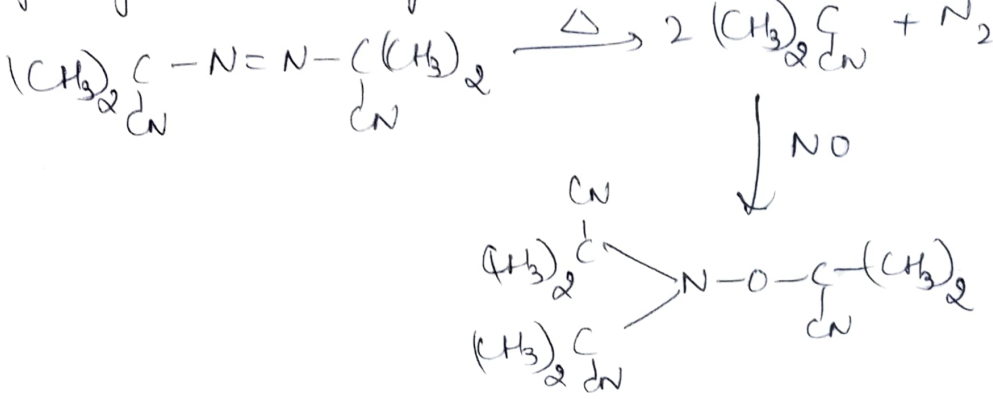
To detect such int., Rx. done in ~~the~~ presence of such compd to which ~~react~~ int. reacts c/a trapping method.



Carbene

Similarly, Benzyne in presence of anthracene form triptycene by trapping.

For trapping free radicals, Br_2 / NO added to which they fastly react. eg.

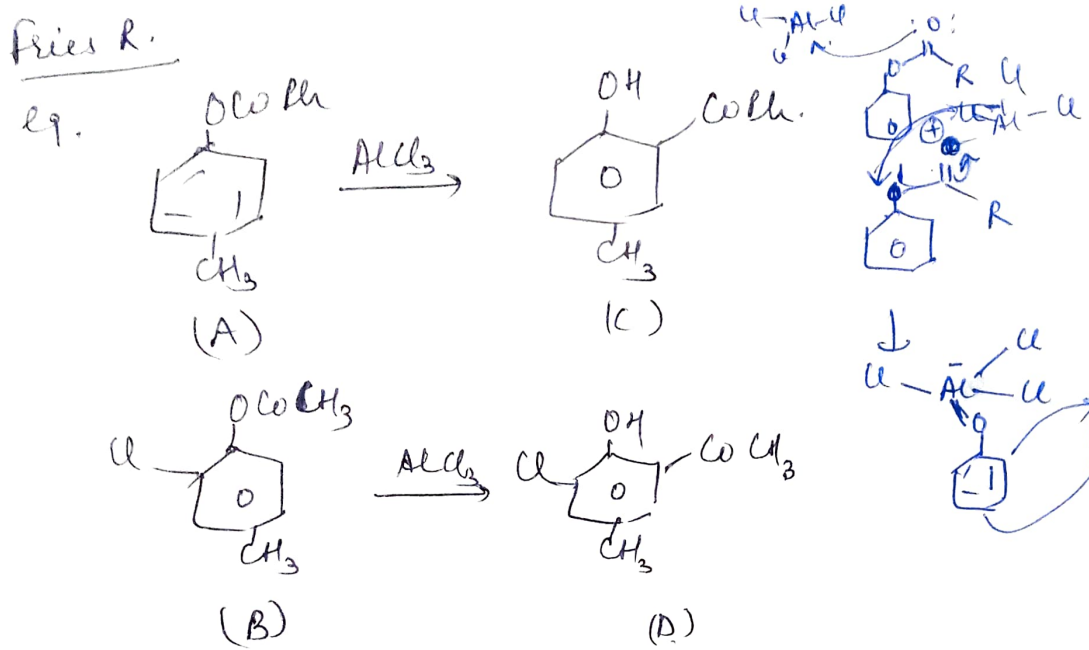


iii) Cross Over Experiments :-

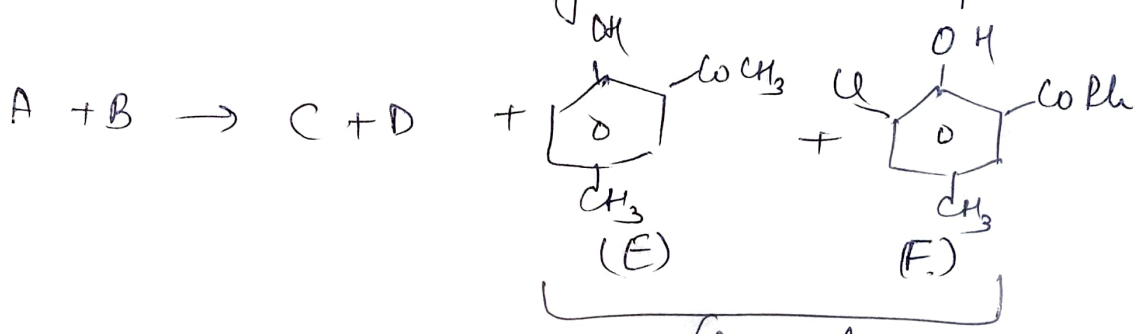
Rearrangement two types :- Inter molecular & Intra molecular cross over exp. are done.

To know mech. of these, two diff ~~p~~ are substituted & In the Mol. to be studied, products obt. from its mix. are studied.

Fries R.

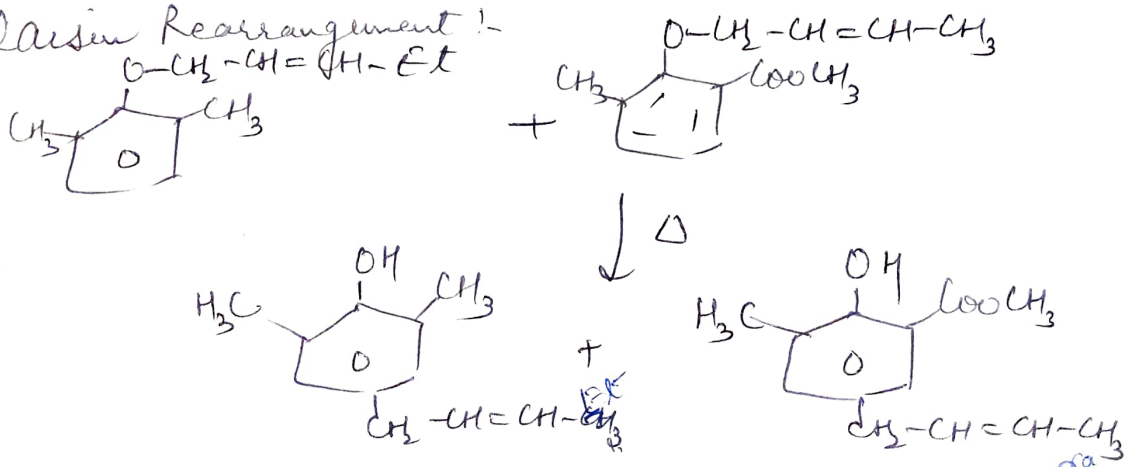


A & B separately give C & D.
While A & B on mixing give E & F along with C & D



This shows ~~reaction~~ mech. is intermolecular (2 steps)

2) Claisen Rearrangement :-



Here no cross product, thus mech → Intramolecular.

4) Isotope Labelling :-

Mech. of many Rxs have been investigated by using molecules in which isotope is substituted for an atom & then tracking the location of same in the products.

Eg: Whether hydrolysis of an ester involves acyl-oxygen or alkyl-oxygen fission has been solved by hydrolyzing amyl acetate in $H_2^{18}O$.

$$CH_3-\overset{O}{\overset{\|}{C}}-O-C_5H_{11} + H_2^{18}O \xrightarrow{HO^{\ominus}} CH_3-\overset{O}{\overset{\|}{C}}-{}^{18}O^{\ominus} + C_5H_{11}OH$$

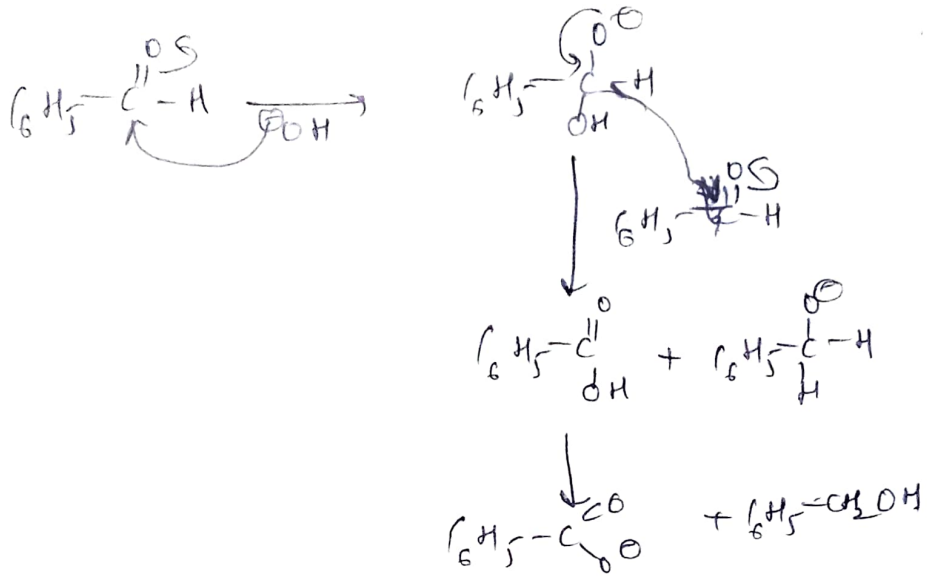
The fact that hydrolysis yields an unlabelled alcohol & a labelled acid has been taken as evidence for acyl-oxygen fission.

Cannizaro Rx → It involves transfer of H from one mol. to another, has been investigated by use of deuterated C_6H_5CDO instead of C_6H_5CHO.

$$2\,C_6H_5-\overset{O}{\overset{\|}{C}}-D + {}^{\ominus}OH \xrightarrow{H_2O} C_6H_5-\overset{O}{\overset{\|}{C}}-O^{\ominus} + C_6H_5-\overset{D}{\overset{|}{C}}(H)-OH$$

D is found to attach to that C of benzyl alcohol. on which OH gp. attached. So the possibility of exchange of H & Hydrogen atoms in the solvent is ruled out. Thus, there is transfer of H (or D) b'n C=O carbons of 2 aldehyde molecules & H/D never gets attached to oxygen atom.

Mech :-



Isotope Effect :-

In above discussion of isotopic labelling, we assumed that there is no diff. in chemical behaviour of diff. isotopes & hence chemical prop. of comp. are not qualitatively changed when isotope is sub. for an atom. Inspite of their chemical similarity, isotopes are not exactly identical & often rate at which Rx may occur may vary ~~c~~ isotope. This variation in rate of Rx. due to diff. in isotope but in mol. c/a isotope effect. & it is usually small. However, in a Rx in ~~c~~ Cleavage of a bond binding particular atom (or its isotope) is Rate det. step, then isotope effect can be of relatively large magnitude c/a Primary isotope effect.

shown as K_H/K_D or K_H/K_T. > 1. (always) shows that comp. cont. H reacts faster than to D & T.

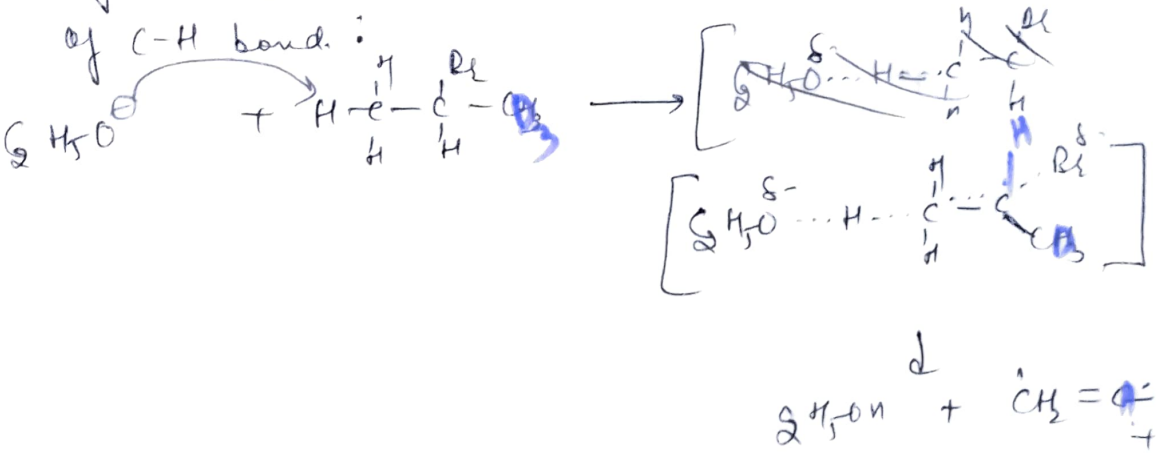
Reason → When C–D & C–H bonds broke in R.D. Step. of a Rx → greater Bond dis. En. of C-D than C-H, so Ea would be greater for Rx involving cleavage of C-D bond thus rate get slower.

Eg. $(CH_3)_2CHBr + C_2H_5O^{\ominus} \rightarrow CH_3-CH=CH_2 + C_2H_5OH + Br^{\ominus}$ 1.0

$(CD_3)_2CHBr + C_2H_5O \rightarrow CD_3-CH=CD_2 + C_2H_5OD + Br^{\ominus}$ 0.15

$$K_H/K_D = \frac{1.0}{0.15} = 6.66$$

Large I effect shows that R.D. step involves breaking of C-H bond:

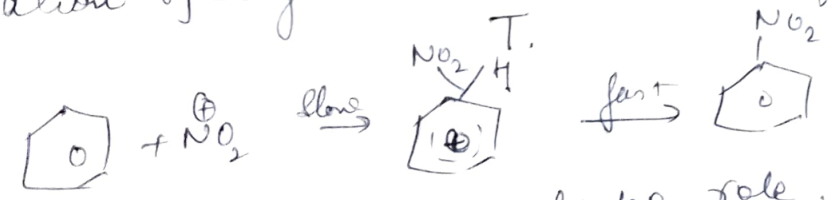


$C_2H_5OH + \dot{C}H_2=CH-CH_3 + Br^{\ominus}$

Rules out Mech:-

$(CH_3)_2CHBr \xrightarrow{slow} (CH_3)_2\overset{+}{C}H \xrightarrow[fast]{C_2H_5O^-} CH_2=CH-CH_3 + C_2H_5OH$ ✗

(2) Nitration of benzene → No isotope effect on using T.



H removed in fast step, so no role.

5) Stereochemical evidences :- (त्रिविम रासायनिक प्रमाण)

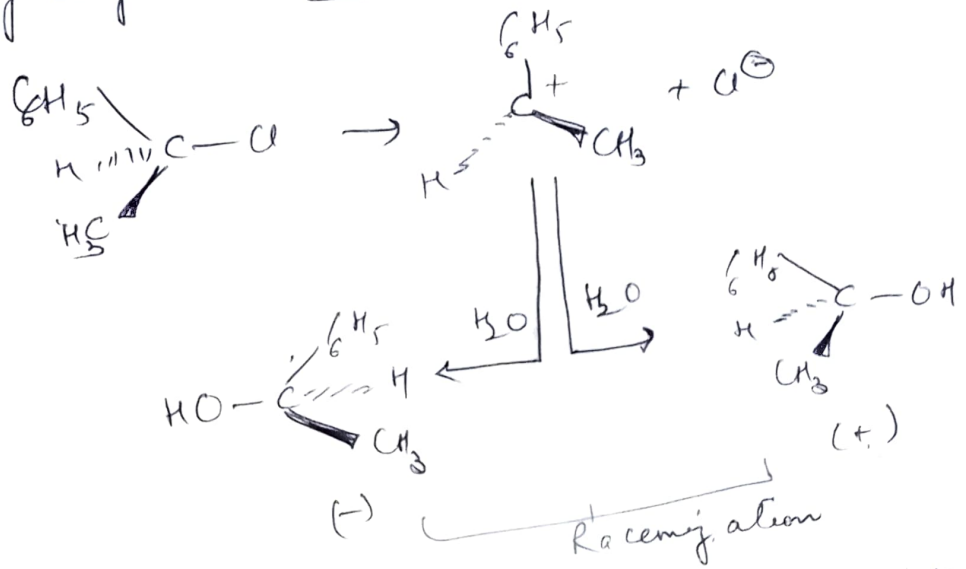
Sometimes mechanistic course of a Rx can be known by its stereochemistry.

For this, optically active compds. are taken & then optical activity of products is checked.

Racemization of Product indicates → Participation of a planar intermediate eg. Carbonium ion.

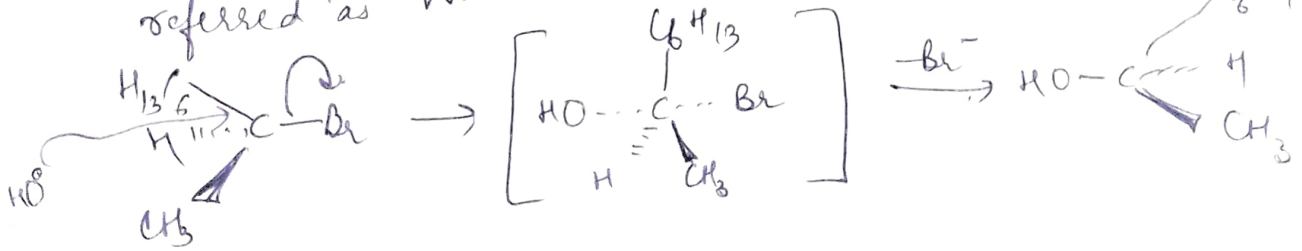
which is equally likely to be attacked by $Nu^{\ominus}$ on either side producing a mix. of eq. no. of mol. i.e retention & inversion of conf.

S_N1 Rx



When product is optically active but its conf. is diff. from that of reactant, the process K/n as inversion of conf. Eg.

In basic hydrolysis (S_N2) of 2-bromooctane, Nu (OH^-) attacks side of C atom opp. to that of leaving gp (Br^-), & reaction proceeds i.e stereochemical inversion (~~R → R~~) referred as Walden Inversion.



6) Kinetic Evidences (अभिक्रिया गतिकी प्रमाण):

Knowledge of Rx order is the most imp step to know the mech. of Rx.

eg → Hydrolysis of alkyl halides.

$$CH_3Br + \overset{\ominus}{O}H \longrightarrow CH_3-OH + Br^-$$

$$-\frac{d[CH_3Br]}{dt} = K[CH_3Br][OH^-]$$

This shows that rate of Rx depends on $[CH_3Br]$ & OH^- thus 2nd Order Rx, Thus S_N2.

$$(CH_3)_3C-Br \xrightarrow{slow} (CH_3)_3C^{\oplus} + Br^-$$

$$(CH_3)_3\overset{\oplus}{C} + OH^- \longrightarrow (CH_3)_3C-OH + (CH_3)_3C-OH$$

$$-\frac{d}{dt}[(CH_3)_3C-Br] = K[(CH_3)_3C-Br]$$

It is unimolecular Rx.

Isotope effects:-

- Primary kinetic isotope effects
- Secondary Kinetic isotope effects
- Solvent isotope effect

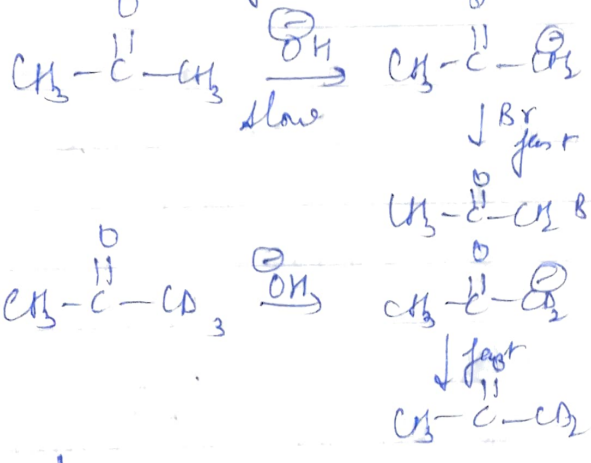
Secondary: α, β

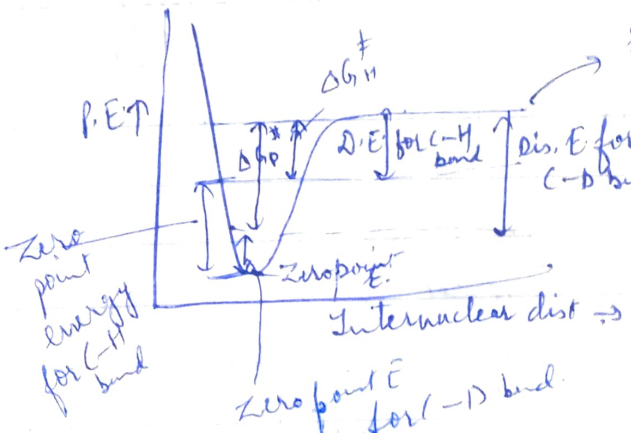
$$KIE = \frac{K_H}{K_D} > 1 \text{ (always)}$$

~~Eg. Bromination~~ Changing H for D/T can affect rate of rx only if H/D is involved in rate determining step. In this case, K_H/K_D is K/n as Primary isotope effect.

Max. value = 7

Eg. Bromination of acetone





$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k(m_1+m_2)}{m_1 m_2}}$$

Bond energy depends on freq. of vibration

↓

depends on reduced mass

More mass of D, so less freq

α (correlated C⁻ carbocation ch. (Hyb. change)
β (sub. of D for H β to position of bond breaking) (Hyperconjugation)

Secondary Kinetic isotope effects:-

→ When sub. H atom is not directly involved in the Rx, then such isotope effects are of a secondary isotope effects.
→ They are smaller than 1° & usually in the range of $K_H/K_D = 0.7 - 1.5$.
→ They may be normal ($K_H/K_D > 1$) or inverse ($K_H/K_D < 1$).

→ They result from a tightening or loosening of C–H bond at T.S.
→ Strength of bond may change b'coz of hybridization change or change in extent of hyperconjugation.

→ When carbocations are involved as intermediates, substantial β-isotope effect are observed. Since hyperconjugative stabilization by β-H weakens C–H bond.

$\frac{K_H}{K_D} = 1.15$

β
$CH_3-\overset{\alpha}{\underset{}{C}}H-Ph \longrightarrow CH_3-\overset{\oplus}{C}H-Ph$ ($sp^3 \to sp^2$)
$CD_3-\overset{\alpha}{\underset{}{C}}H-Ph \longrightarrow CD_3-\overset{\oplus}{C}H-Ph$ { Stab. by hyperconjugation by H/D }

D stabilize less effectively than H, thus, fall in Rx rate.

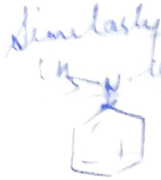
α
$Ph-\overset{O}{\overset{\|}{C}}-H + CN^{\ominus} \xrightarrow[K_H]{25°S} Ph-\overset{O^{\ominus}}{\underset{CN}{\overset{|}{C}}}-H$
$Ph-\overset{O}{\overset{\|}{C}}-D + \text{"} \xrightarrow{\text{"}} Ph-\overset{O^{\ominus}}{\underset{CN}{\overset{|}{C}}}-D$

→ Here effect is due to conversion of sp^2 hybrid C into sp^3 hybrid C.

$\frac{K_H}{K_D} = 0.83$

$sp^2 \longrightarrow sp^3$ ($K_H/K_D < 1$)
$sp^3 \longrightarrow sp^2$ ($K_H/K_D > 1$)

Similarly,



less base

(More base)
due to steric hind.
. lone pair is not shared.

~~Reactivity~~ :-

Effect of of structure on Reactivity - Resonance & Field effects, steric effects

→ On replacing H atom by another atom or gp of atoms, there is a change in rate constant. The sub. effect may be result of size of substituent (steric effect) or its influence on availability of e⁻ (electronic effect) on site of Rx (e⁻ withdrawing or e⁻ releasing).

E effects

Inductive — +I, -I

Mesomeric effect — +R, -R.

→ Ind. effect is transmitted thru σ bonds & weakens as dist. b/n subst. & reactive center ↑es.
→ The effect is greatest for adjacent bond.

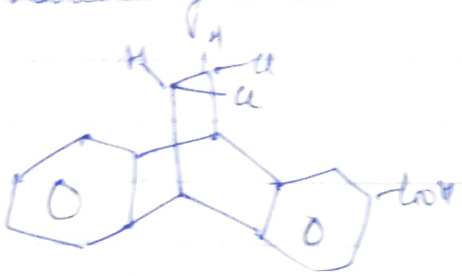
→ Field effect → operating either thru space surrounding the molecule or in solution, via molecules of solvent that surround it.

sp - sp

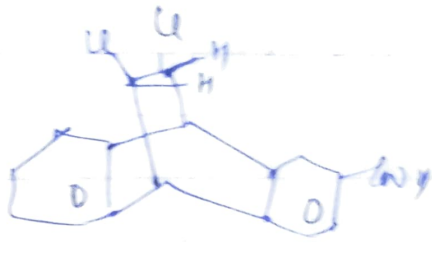
Steric effect

→ Usually, it depends on geometry of molecule while Ind. effects depends only ~~on geometry of~~ nature of bonds.

Eg



pKa = 6.07 (I)



pKa = 5.67 (II)

→

→ Both have diff field effects since Cl atoms in (I) is closer to carboxylic gp & thus I ses the stability of carboxylate ion by steric hindrance & as a result, II is more acidic.

(0.81 - 1.26)

α-isotope effect → related to carbocation character

→ results from replacement of H by D at C containing gp.

S_N2 RX → α isotope effects ≈ 1.

S_N1 " → " " > 1 (depending upon nature of leaving gp.)

→ Reason

→ One of the bending C-H vibrations is affected by sub. of D for H more or less strongly in T.S. than in ground state. It may ↓ or ↑ rate of rx, depending on nature of T.S.

Solvent isotope effect :- When solvent is changed from H_2O to D_2O or from ROH to ROD.

β- Isotope ratio — Normal ratio $k_H/k_D > 1$

Inverse ratio $k_H/k_D < 1$

Mode	F (cm^{-1}) C—H sp^3	O—H sp^2
1) Stretching	2900	2800
2) In plane bending	1350	1350
3) Out of plane bending	1350	800

Here major diff. b'w two hyb. states is in their out of plane bending freq. → Higher freq, greater will be reduction due to deuterium labelling.

Thus change in ZPE for sp^3 system > than sp^2

Thus $sp^3 - sp^2$ transformation → Normal isotope effect

$sp^2 - sp^3$ " → inverse isotope effect