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Fundamentals of physical organic chemistry can be divided into

- (1) Concept in theoretical organic chemistry
- (2) Reaction mechanisms
- (3) Stereochemistry

Recommended text

- (1) Organic reaction mechanism by R. Breslow
- (2) Mechanism in Organic Chemistry by Alder, Baker and Brown.
- (3) Structure and Mechanism in organic Chemistry by C. Ingold
- (4) Advanced organic chemistry by F. A. Carey and R. J. Sundberg
5. A guide book to mechanism in organic chemistry by Peter Sykes

Concepts in Theoretical Organic chemistry

To the lame man, ~~the~~ chemical reaction seems like an act of magic. The process of unravelling what actually goes on during the chemical reaction involves answering the questions of "why?" and

"how?"

Physical Organic chemistry is concerned with answering questions such as

- (1) Why does compound A reacts one way and compound B reacts another way?
- (2) If A is modified structurally, how is the reactivity affected?
- (3) In the reaction of C with D to form E, what pathway is followed?

The mechanism for a reaction is the description of the event that takes place at a molecular level as reactant becomes product.

In cases where the reaction takes place in more than one step, it is important to know the chemical species called intermediate that intervene between each step along the way.

A mechanism is the actual process by which a reaction takes place; which bonds are broken, in what order, how many steps are involved, what is the relative rate of each step and so on. Any mechanism proposed for a particular reaction, must be

consistent with all experimental observations.

An important thing about approaching organic chemistry mechanistically, is that it helps organize what otherwise might be an overwhelmingly complex body of knowledge into an understandable form. The same way functional groups helps us to organize compounds in a comprehensible way, mechanisms helps us to organize reactions.

Knowledge of reaction mechanism, simplifies the work of a synthetic chemist by helping in the selection of the best reaction conditions for maximum ^{yield} ~~rate~~ in the shortest time. The study of reaction mechanism represent the deepest probe of a chemist into why molecules behave the way they do, thus ~~identifying~~ ^{defining} the margin or myth that might exist about molecular interaction.

For most reactions, there will be many conceivable mechanisms, but not all of these are reasonable.

The following ~~are~~ ^{prerequisites} are required for a reasonable mechanism;

i. an acceptable mechanism has to be able to rationalize all experimental facts, if a future experiment gives a result that contradicts a proposed mechanism, the mechanism is changed

- ii the mechanism must be as simple as possible while accounting for all available data.
- iii in a multistep mechanism, each of the individual steps should be either unimolecular or bimolecular
- iv each step should be energetically feasible, bonds that are broken in a particular step should be compensated by concurrent formation of new bonds
- v. each step should be chemically reasonable

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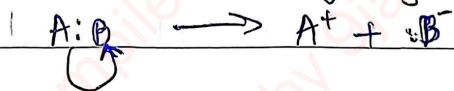
* bonds doesn't just break

* for heterolysis to happen, the atoms should be in different electronegativity or polarized

Types of Mechanisms

Organic mechanisms can be divided into two basic types

(1) heterolytic bond cleavage: This occurs when a bond breaks in such a way that one fragment takes away both electrons of the bond to produce charged fragments



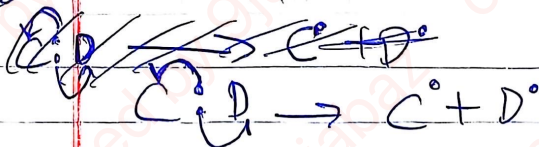
In a heterolytic reaction, the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it.

A reagent that brings an electron pair is called a nucleophile and the reaction is nucleophilic.

A reagent that takes an electron pair is called an electrophile and the reaction is said to be electrophilic.

In a reaction in which the substrate molecule becomes cleaved, part of it is usually called the leaving group.

(2) Heterolytic Bond Cleavage: This occurs if a bond breaks in a way that each fragment gets one electron and free radicals are formed.



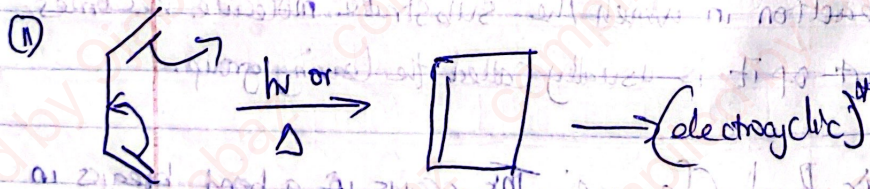
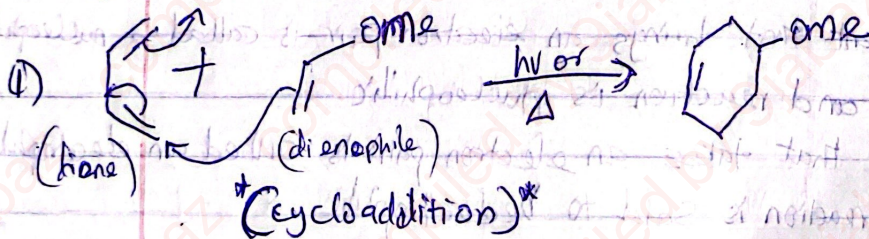
Free radicals often proceed by a chain reaction

everything happens at the same time. independent of each other

(3) **Pericyclic Mechanism**: This involves the stereospecific movement of electrons leading to the making and breaking of bonds in a single concerted step involving a cyclic transition state. There are no intermediate ions or free radical involved.

The symmetry characteristics of molecular orbitals controls the overall course of the reaction.

Electrocyclic and cyclo addition reaction involves the pericyclic mechanism.



(4) **Transition Metal-Catalyzed and Metal-Mediated**

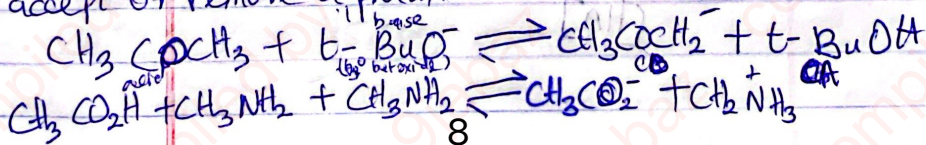
ACIDITY AND BASICITY

Many organic reactions are either acid-base reactions themselves, or involve an acid-base reaction at some stage. Acid-base reactions allow us to examine important ideas about the relationship between structure of molecules and their reactivity and to see how certain thermodynamic parameters can be used to predict quantity of products when a reaction reaches equilibrium.

Acid-base reactions also give a brief introduction to organic synthesis. They provide an illustration of the important role solvents play in chemical reactions, and enable one to see the process of bond breaking and bond making as molecules react.

Two acid base theories are used in organic chemistry today. Both are compatible and used for different purposes.

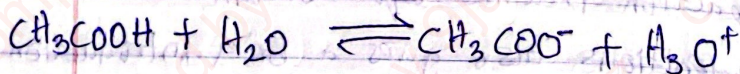
① ~~Bronsted~~ Lowry Theory: According to the Bronsted Lowry's definition an acid is a substance that can donate or lose a proton and a base is a substance that can accept or remove a proton.



Acids and Bases may be charged or neutral. Any acid base reaction is an equilibrium even if the equilibrium lies far to one side.

Strength of Acids and Bases

In contrast to strong acids such as HCl and H_2SO_4 , acetic acid is a typical example of a weak acid



Since the equation is an equilibrium

$$K_{eq} = \frac{[\text{H}_3\text{O}^+][\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}][\text{H}_2\text{O}]}$$

For dilute aqueous solutions, concentration of water is assumed to be constant at approximately 55.5M

So, rewriting the expression in terms of a new constant called activity constant, K_a ;

$$K_a = K_{eq}[\text{H}_2\text{O}] = \frac{[\text{H}_3\text{O}^+][\text{CH}_3\text{COO}^-]}{[\text{CH}_3\text{COOH}]}$$

In general, for any weak acid HA

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

the stronger the acid, the weaker the conjugate base

A large value of K_a means that the acid is strong, because the concentration of product of reaction is the numerator and the concentration of the undissociated acid is the denominator.

K_a value greater than 10 means complete dissociation in water

$$pK_a = -\log K_a$$

At room temperature, the acidity constant for acetic acid is 1.76×10^{-5} , $pK_a = 4.75$.

Note: There is an inverse relationship between the magnitude of pK_a and the strength of the acid, the larger the value of pK_a , the weaker the acid.

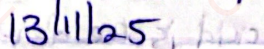
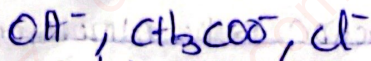
Because the minus sign in the pK_a definition, the lower the pK_a , the larger the acid equilibrium constant, K_a , and hence, the stronger the acid.

The pK_a of an acid is the pH where it is exactly half dissociated. At pH values above the pK_a , the acid HA exists as A^- in water and at pH below pK_a , the acid as undissociated HA.

* The stronger the acid, the weaker will be its conjugate base

Base	pK_a
Cl^-	-7
CH_3COO^-	4.75
OH^-	15.7

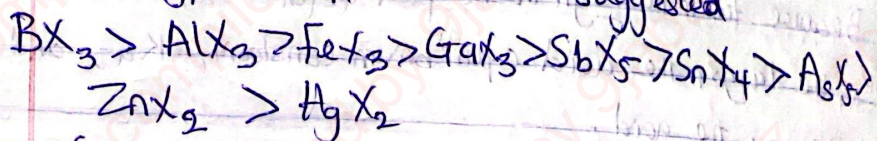
Among the order of decreasing basic strength,



(2) Lewis Definition: A Lewis acid is any species with a vacant orbital or an electron pair acceptor.



The advantage of the Lewis theory is that it correlates the behaviour of many more processes. Quantitatively, the following approximate sequence of acidity for Lewis acid of the type MX_n has been suggested.



Where X is a halogen or an inorganic radical. However, beyond acid-base strength, the hardness or softness of an acid or base is important in acid-base reaction.

(a) Soft Bases: Soft bases have donor atoms of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely, e.g. I^- , S^{2-} , PPh_3 .

Hard $\rightarrow$ Hard
Soft $\rightarrow$ Soft

(b) Hard bases: They have donor atoms of high electronegativity and low polarizability and are hard to oxidize. They hold their valence electrons tightly. Examples include, OH^- , F^- , NH_3 .

(c) Soft Acids: They have acceptor atoms that are large, have low positive charge and contain ~~sh~~ shared pair of electrons in their valence shell. They have high polarizability and low electronegativity. e.g., Ag^+ , I_2 , Pt^{2+} .

(d) Hard Acids: They have acceptor atoms that are small, they have high positive charge and do not contain unshared pair in their valence shell. They have low polarizability and high electronegativity. Example includes, H^+ , Na^+ , Al^{3+} .

Relationship Between Structure and Acidity or Basicity

(i) Periodic table Correlation: Moving down the group, bond strength to the proton decreases. This phenomenon is due to the decreasing effectiveness of orbital overlap between the hydrogen 1s orbital and the orbitals of successively larger elements in the group. The less effective the orbital overlap, the weaker the bond, and the stronger the acid.

Thus, acidity increases and basicity decreases in going down a group.

	pK_a	
H-F	3.2	acidity increases down the group
H-Cl	-7	
H-Br	-9	
H-I	-10	

Across the period, acidity increases from left to right, i.e. acidity increases as electronegativity increases across the period

pK_a	CH_4	NH_3	H_2O	HF
	48	38	15.7	32
	increasing order of acidity $\rightarrow$			

CH_3^-	NH_2^-	OH^-	F^-
$\leftarrow$ increasing order of basicity			

This effect is responsible for the difference in acidity of carboxylic acids, amines and ketone



The acidity of TX_n decreases down the group because

as molecular size increases the force of attraction between the nucleus and the incoming electron gets weaker, thus BCl_3 is a stronger acid than AlCl_3

② Inductive Effect: Any effect that results in electron withdrawal from a negatively charged center is a stabilizing effect because it spreads the charge. Electron withdrawing groups withdraw electron density from negatively charged anion produced when acid loses a proton.

Any factor that stabilizes the conjugate base of an acid increases the strength of the acid. Thus, ^{negative inductive effect} $-I$ groups increase acidity and decrease basicity, while electron donating groups decrease acidity and increase basicity

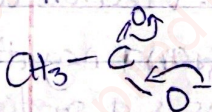
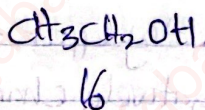
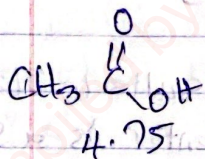
	H_3CCOOH	ClCH_2COOH	→ more acidic
Pka	4.75	2.86	
	Ph_3CH	$(\text{C}_6\text{F}_5)_3\text{CH}$	
Pka	31.5	16	

Note: Inductive effect weakens as the distance from the substituent increases.

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unon $C \equiv C^+$

(3) Resonance Effect: Resonance that stabilizes its base much more than its conjugate acid results in the acid having a higher acidity than usual. This explains why a Carboxylic acid is more acidic than an alcohol.

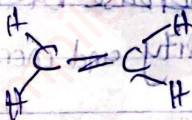


This also explains why amides are more acidic than amines.

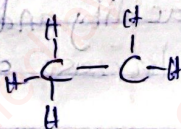
(4) Hybridization Effect



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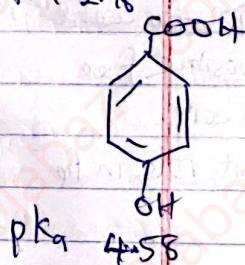
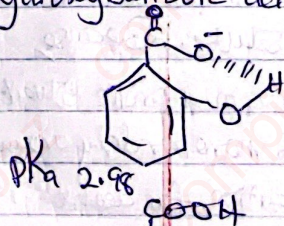


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Electrons of 2s orbitals have lower energy than those of 2p orbitals because electrons in 2s orbitals tend to be much closer to the nucleus than electrons in the 2p orbital. With hybrid orbitals having more s character, it means that the electrons of the anion will on the average be lower in energy and the anion will be more stable.

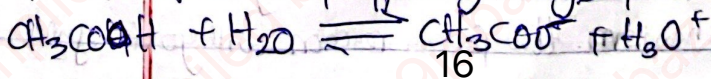
It means that the $\text{HC}\equiv\text{C}^-$ is a weaker base than $\text{H}_2\text{C}=\text{CH}^-$. This explains the relatively high acidity of acetylene and nitriles.

⑤ Hydrogen bonding: Internal hydrogen bonding can greatly influence acid or base strength. Internal hydrogen bonding with OH and COO^- groups of carboxylate base ortho hydroxybenzoic acid gives stability and an increase in acidity over the para analog.



Effects of Solvent in Acidity and Basicity

In the gas phase, most acids are weaker than they are in solution; acetic acid for example has a pK_a of about 130 in the gas phase (4.75) in solution/water. In the gas phase, separation of oppositely charged particles is difficult.



The influence of solvents on dissociation of acids and bases can be profound. Thus, hydrogen chloride which is a strong acid in water is not ionized in benzene. Water is an effective ionizing solvent on account of its high dielectric constant ($\epsilon = 80$) and its ion solvating ability. *Kim*

Solvation of any species, decreases the entropy of the solvent, because the solvent molecules become much more ordered as they surround molecules of the solute. Because solvation of acetate ions is stronger in a protic solvent like water, the solvent molecule becomes more orderly around the ion. The entropy, ΔS° for the ionization for acetic acid is therefore negative, this results in a positive free energy change for the ionization of acetic acid.

In general, solvents play a significant role in the acidity and basicity of a system.

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Thermodynamics and Kinetics of Reaction

A reaction may be described as favourable or unfavourable, fast or slow and as reversible or irreversible. These terms are useful parameters in describing an overall reaction mechanism. How far a reaction will go to give

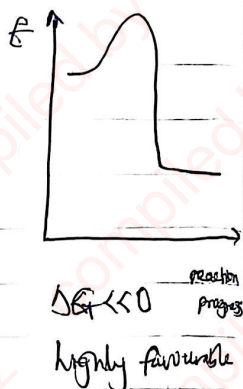
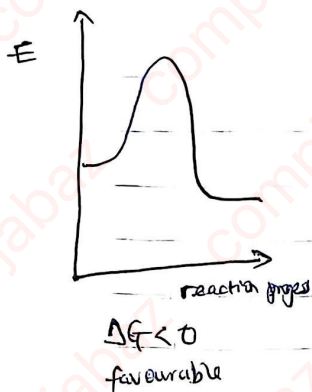
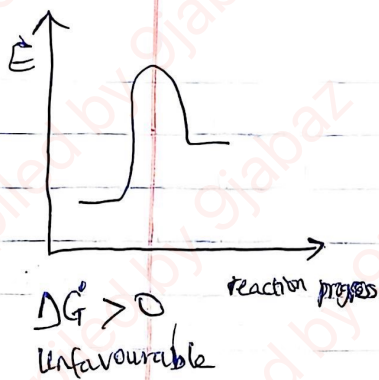
Products depends on the energy change that takes place.

Systems move ~~forwards~~ towards their most stable state. So, the more stable the product of a particular reaction in comparison with the starting materials, the more the equilibrium will lie to the right. (i.e. favour product formation). For a spontaneous reaction, free energy of product must be lower than free energy of the reactant, i.e. $-\Delta G$ must be negative. Free energy is made up of two components, (i) the enthalpy change which is the difference in bond energy between reactants and products

(ii) entropy change which is the measure of the degree of orderliness of a system. To favour spontaneity, enthalpy should decrease and entropy change should increase.

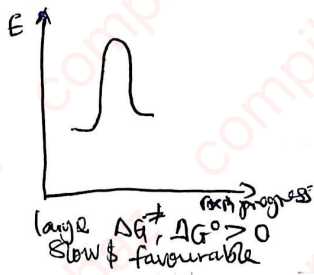
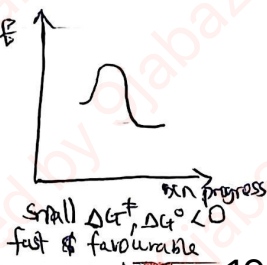
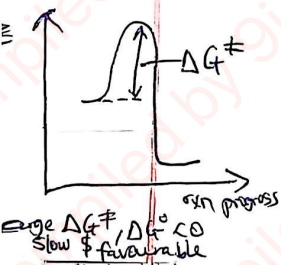
In practice, it is the enthalpy and not the free energy that is usually used to determine whether a reaction is favourable or not. This is because ΔH° is easier to measure and ΔS° is ~~for most reactions at ordinary temperature~~ small compared to ΔH° for most reaction at ordinary temperature.

Thus if ΔH° is large and negative the reaction will favour product formation at equilibrium.



Just because a reaction has a ΔG value is not sufficient for it to be spontaneous. Starting materials have to go through an energy barrier to become product. This barrier is called the activation energy $\Delta G^\ddagger$. The arrangement of the reactant at the top of the barrier where they can go either backward to starting material or forward to product is called the transition state (or activated complex). The rate of a reaction is dependent on the size of the activation barrier. When the barrier is low, a reaction is fast and vice versa.

Note: $\Delta G^\ddagger$ and ΔG° (rate and energetics of a reaction) are independent of one another



According to the transition state theory, $\Delta G^\ddagger = RT \ln K_{eq}$ where K_{eq} is the equilibrium constant between the starting material and the activation complex.

$\Delta G^\ddagger$ is -ve with reactions where $K_{eq} > 1$

$\Delta G^\ddagger$ is also made up of enthalpy and entropy components

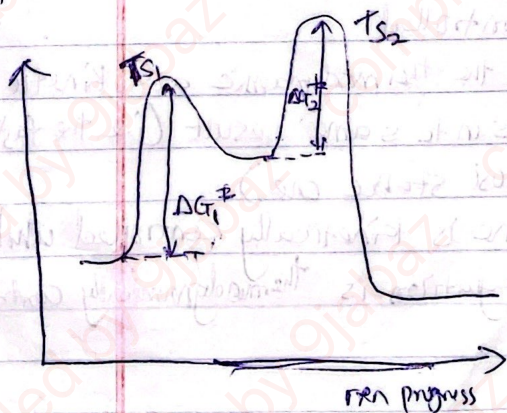
$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

where $\Delta H^\ddagger$ is the enthalpy of activation

$\Delta S^\ddagger$ is the entropy of activation

Several reactions involve more than one step, such reactions involve the formation of one or more intermediate ~~mes~~ (S) and require more than one transition state complex.

Intermediates are real species that can be isolated though their existence is usually short. e.g. Carbocation, Carbanions and free radicals



The highest $\Delta G^\ddagger$ value corresponds to the rate determining step for the reaction.

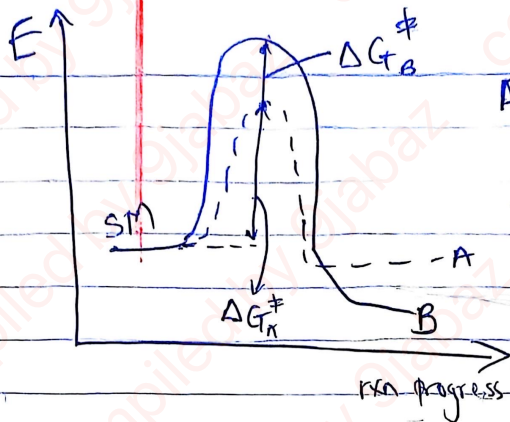
Whenever a starting material can be converted to two or more alternative products. The actual product formed is dependent on either the relative rate of formation of products, or their relative thermodynamic stability.

The product that is obtained most quickly (referred to as the kinetic product) is not necessarily the product that is lowest in energy (referred to as a thermodynamic product).

Whenever the fast product only, or predominantly is formed, then the reaction is said to be kinetically ~~product~~ controlled and when the more stable product only or predominantly is formed, the reaction is said to be ~~thermodynamic~~ thermodynamically controlled.

In some cases, the thermodynamic and kinetic controlled both results in the same result (i.e. the fastest one formed and the most stable one).

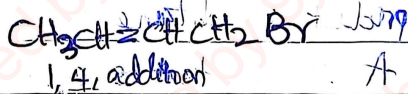
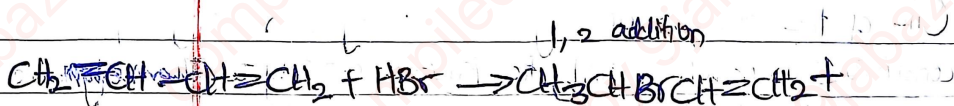
eg Nitration of toluene is kinetically controlled while its Friedel-Craft alkylation is thermodynamically controlled.



A is kinetically controlled, more faster

B is thermodynamically controlled, more stable

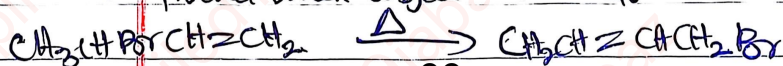
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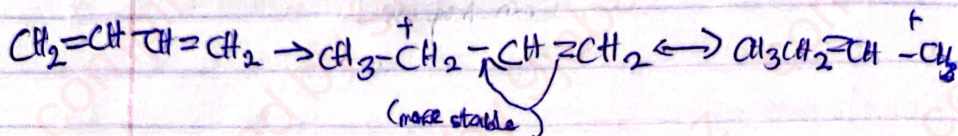
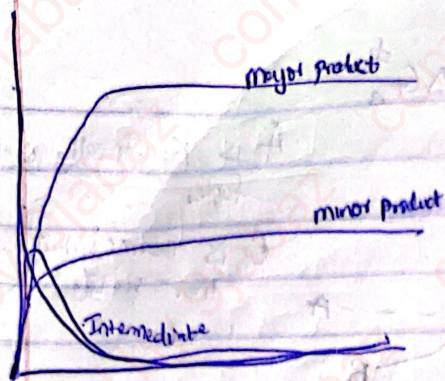


The 1,2 addition product, is the kinetically controlled product, because it is easy to add HBr to carbon 1 and carbon 2.

However, ~~with time~~ ^{and/or} under more rigorous conditions, the more stable product predominates i.e. the 1,4-addition product because it is more substituted.

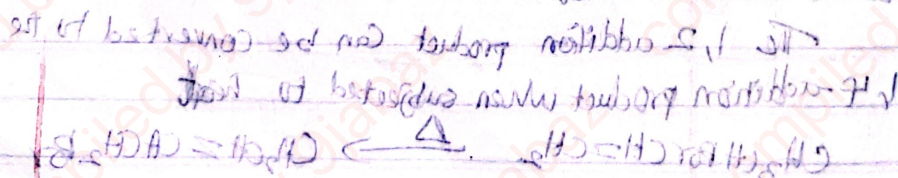
The 1,2 addition product can be converted to the 1,4-addition product when subjected to heat.





One of the strengths of organic chemistry is in designing conditions under which only the kinetic or only the thermodynamic product is obtained.

A reaction that is equilibrium is reversible in principle, all reactions are reversible, but in fact some reactions have equilibria that lie so far to the right that no starting material can be detected at equilibrium. As a rule of thumb, if the equilibrium constant is $\geq 10^3$, the reaction is irreversible.



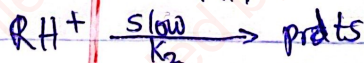
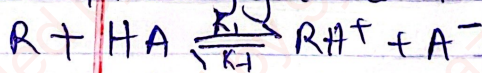
Acid-Base Catalysis

In general, catalyst provide an alternate path of less energetic demand, often through the formation of a new and more stable intermediate.

A catalyst lowers the free energy of activation $G^\ddagger$, while the overall free energy of reaction G° remains unchanged. Acids and bases catalyze several reactions by proton transfer between the catalyst and the substrate.

Such acid-base catalysis are carried out with the aid of a buffer. Reactions can be catalyzed by acids or bases, in two different ways; General and specific catalysis.

1. Specific Acid Catalysis: This arises when the reaction rate depends only on the pH of the solution or more generally the protonated solvent (HA). The acid added to the solvent may be stronger or weaker, but the rate is proportional only to the protonated solvent that is actually present in the solution and independent of the concentration of the undissociated acid in the buffer system. The reactant is converted into its conjugate acid in a rapid equilibrium step followed by rate determining breakdown of the conjugate acid into products.



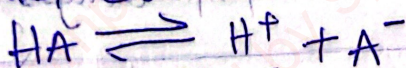
$$\text{Rate} = k [RH^+]$$

But $k_2 = \frac{[RH^+][A^-]}{[R][HA]}$

$\Rightarrow [RH^+] = \frac{k_1 [R][HA]}{[A^-]}$

rate $= \frac{k_2 k_1 [R][HA]}{[A^-]}$

Protonated Solvent $\rightarrow HA$



now $K_a = \frac{[H^+][A^-]}{[HA]}$

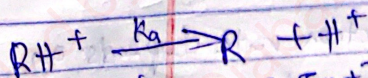
therefore $\frac{[HA]}{[A^-]} = \frac{[H^+]}{K_a}$

rate $= \frac{k_2 k_1 [R][H^+]}{K_a}$

stop $\frac{k}{K_a} = \frac{[RH^+][A^-]}{[R][HA]} \times \frac{[HA]}{[A^-][A^-]}$

$\frac{k}{K_a} = \frac{[RH^+]}{[R][H^+]}$

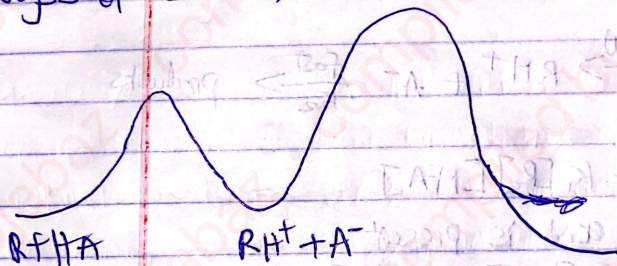
$[H^+] = 10^{-7}$



$$K_1 R + H^+ = \frac{[R][H^+]}{[R + H^+]}$$

$$\therefore \text{Rate} = \frac{k_2}{K_1} [R][H^+]$$

Thus, the reaction rate depends on concentration of hydrogen ions $[H^+]$ and not on the concentration of $[HA]$ i.e. to protonated solvent. Example of this is acid catalyzed hydrolysis of acetals, esters and ethers.



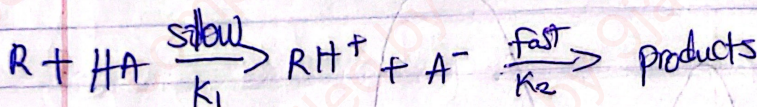
Proton is fully transferred before the rate determining step in a specific acid catalysis.



General Acid Catalysis

In general acid catalysis, the reaction rate depends on pH and on the concentration of the undissociated acid present in the buffer system. In terms of the mechanism, the proton transfer step is the slow rate determining step followed by rapid conversion of the protonated reactant to product. Thus, in this case, the first step is the rate determining step.

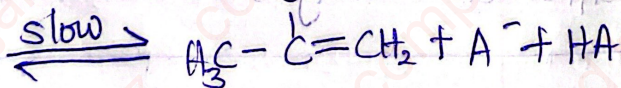
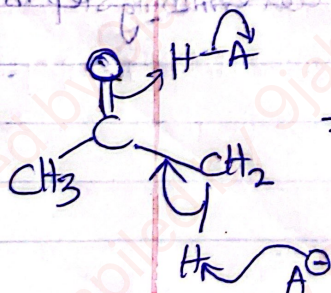
Due to the slowness of the proton transfer step, even the very weak acids participate in the proton transfer process.

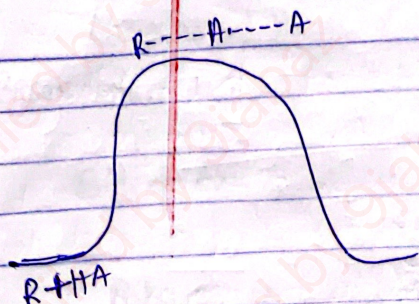


$$\text{rate} = k_1 [R] [HA]$$

If more than one acid is present

$$\text{rate} = [R] \sum_{i=1}^n k_i [HA_i]$$





Consider the following reaction ~~$X + Y \rightarrow \text{Product}$~~

$X + Y \rightarrow \text{Product}$, with Catalysts by H_3O^+ , HA under pseudo first order condition, concentration of $[\text{H}_3\text{O}^+]$ and $[\text{HA}]$ is constant. Therefore, rate

$$\text{rate} = K_{\text{obs}} [X] [Y]$$

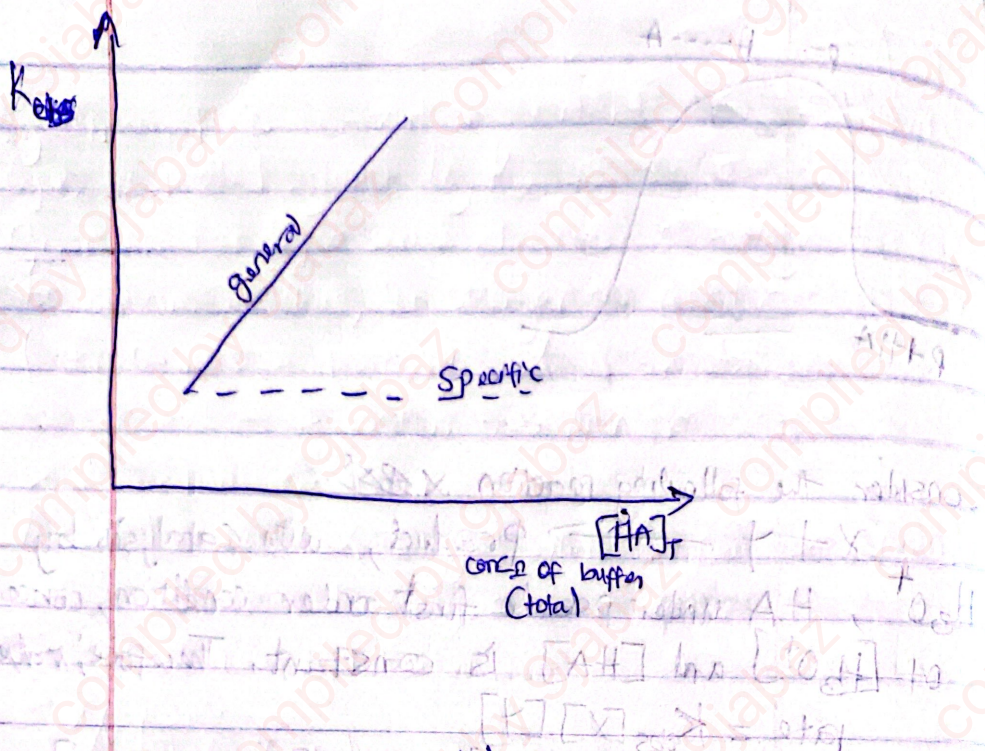
where $K_{\text{obs}} = K_{\text{H}} [\text{H}_3\text{O}^+] + K_1 [\text{HA}] + K_{\text{A}} [\text{H}_2\text{O}]$

To do this, we measure reaction rate at a specific pH for different buffer concentrations. The pH is set by keeping the buffer ratio i.e. $\left(\frac{[\text{A}^-]}{[\text{HA}]} \right)$ constant but actually vary in values of concentration of $[\text{HA}]$.

Thus total buffer concentration keep changing

$$[\text{HA}]_{\text{T}} = [\text{HA}] + [\text{A}^-]$$

For a plot of K_{obs} versus $[\text{HA}]_{\text{T}}$ i.e. total concentration of buffer, General acid catalysis changes with time but specific acid catalysis remains constant.



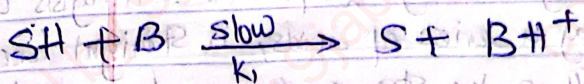
[0] Specific Base Catalysis

This occurs whenever a reaction is catalyzed only by hydroxide ions (OH^-) derived by the protolysis of solvent of the molecule. If only OH^- catalyzes a reaction and not other bases in solution, it is a specific base catalysis. e.g. Aldol, Claisen and Favorskii condensation.



General Base Catalysis

Bases other than OH^- are involved



$$\text{Rate} = k_1 [\text{SH}] [\text{B}]$$

$$= \sum k_i [\text{A}_i] [\text{B}]$$

Examples of general base catalysis includes halogenation, isomerisation and racemization of organic compounds containing hydrogen

Bronsted Catalysis Law

Although acidity is an equilibrium process while rate is a kinetic process. There tends to be a relationship between both. This occurs because at transition state a proton has been partially transferred. Hence, the effect of acidity plays a partial role. The relationship between acid strength of a catalyst and its catalytic ability can be expressed by the Bronsted Catalyst equation.

$$\log k_r = \alpha \log K_a + C$$

k_r is the rate constant for a reaction catalyzed

by an acid of ionization constant K_a . When $\log k_a$ is plotted against $\log K_a$ for the catalysts of a given reaction by a series of acids, a straight line should be obtained. Thus, the stronger the acid catalyst, the faster the rate of reaction. α is an approximate measure of the extent of proton transfer in the transition state and varies from 0 - 1.

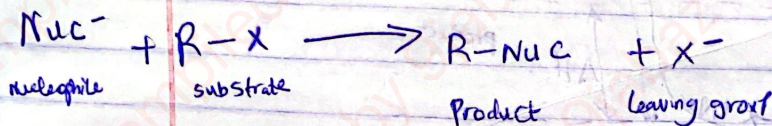
A small value of α suggests that the reaction is not very sensitive to acid catalysis and it indicates that the transition state is reached before the proton transfer becomes significant.

A large α value indicates that the proton transfer is almost complete by the time transition state is reached. Hence, such reaction is sensitive to acid catalysis, i.e. reaction is very slow on its own and the effect of the acid catalyst is quite significant.

Values of α can thus be used as probes of transition state structure and reaction mechanism.

Lab - chapter 6, Section 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13, 6.14, 6.15, 6.16, 6.17, 6.18, 6.19, 6.20, 6.21.

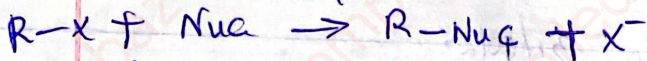
Nucleophilic Substitution



Types of mechanism

- (i) First order kinetics - unimolecular reaction
- (ii) Second order kinetics - bimolecular reaction

Substitution Nucleophilic Bimolecular (SN2)



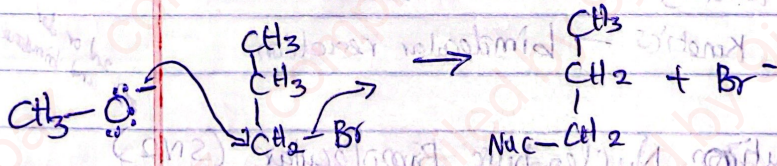
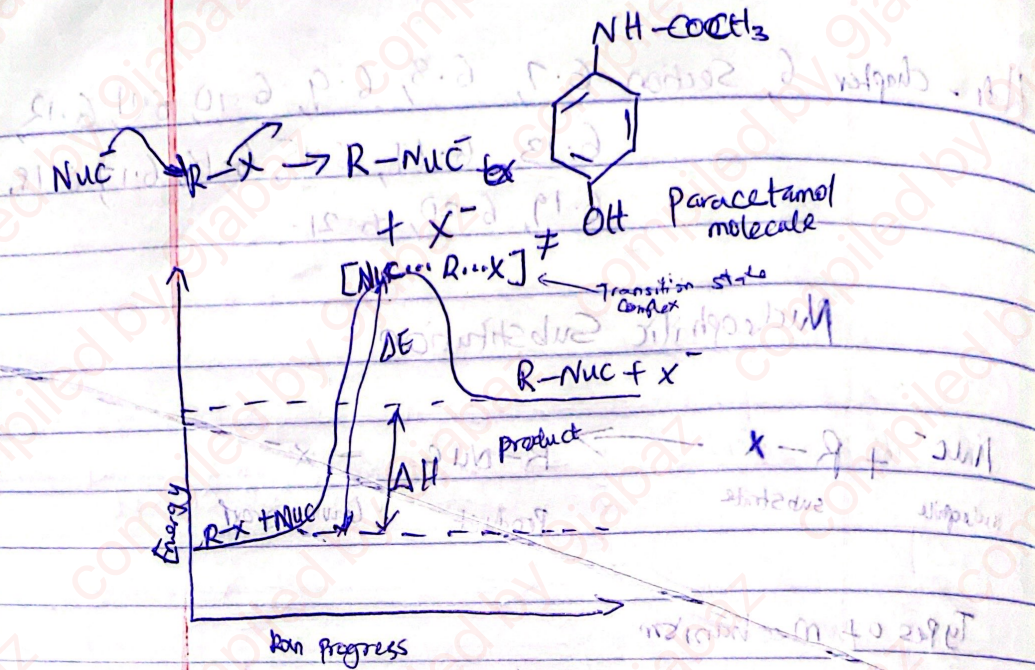
Rate law

$$\text{Rate} = k[\text{Nuc}][\text{R-X}]$$

Overall order is 2nd order

The slow step involves collision between two molecules, i.e. the reaction is bimolecular.

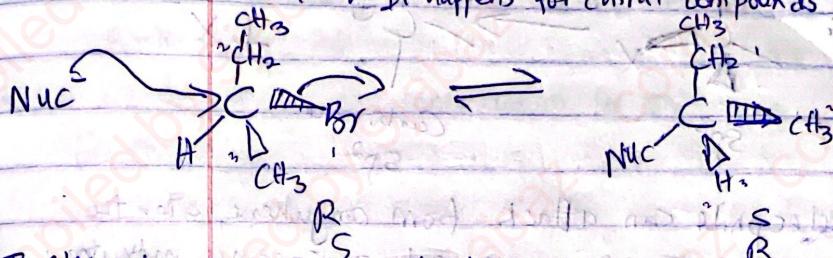
The SN2 mechanism is concerted, i.e. two molecules collide, a bond is being formed at the same time a bond is being broken.



How to Confirm S_N2

- (1) Kinetic evidence: rate of rxn is dependent on both nuc⁻ and rxn
- (2) Stereochemical evidence
- (3) ~~What happens at bridge head~~ Substrates with leaving groups at bridge head

Stereochemical evidence: It happens for chiral compounds (Substrates)



* The stereochemistry changes: that is inversion of configuration or Walden inversion

6/1/25

* What happens at bridge head carbon under S_N2 conditions?
If substrate has a leaving group at a bridge head carbon **

S_N1

Kinetics

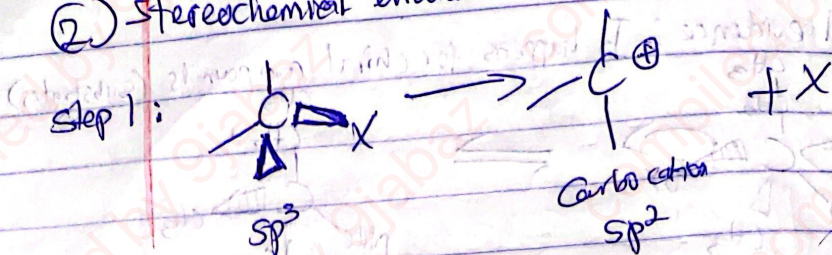
For S_N1; Rate = k[RX]

Steps;
Step 1: formation of carbocation
 $R-X \xrightarrow{k_1} R^+ + X^-$ (slow step)
Step 2: nucleophilic attack
 $R^+ + Nuc^- \xrightarrow{k_2} R-Nuc$

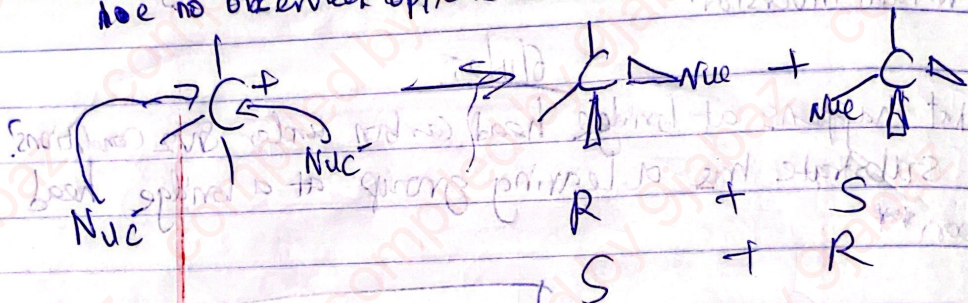
- ① The rate of reaction depends solely on the concentration of the substrate. It is first order and unimolecular.
- ② Stereochemical evidence

⚡ using these elementary step; derive the rate law.

② Stereochemical evidence



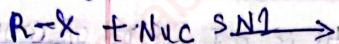
The nucleophile can attack from anywhere, either the back or front; Therefore, we get a racemic mixture. No observed optical activity; the rotation cancels out.



What happens at bridge head carbon under SN_2 conditions

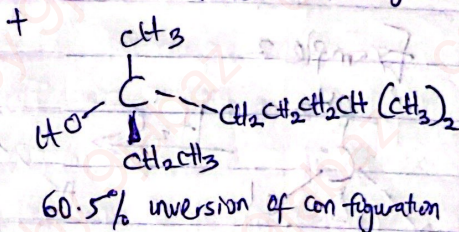
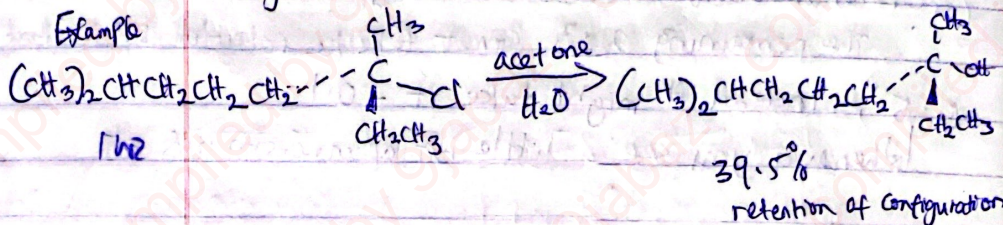
A bridge head carbon is the carbon at the point where two rings are fused together in a bicyclic compound. Therefore in an SN_2 condition the backside attack is sterically and geometrically impossible due to the rigid bicyclic structure, preventing the required inversion of configuration.

stereochemical observation for $S_N1 \approx$ racemization



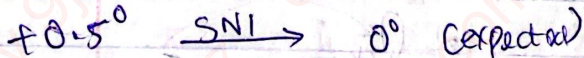
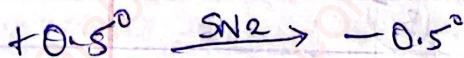
But we don't always see racemization for S_N1

Example



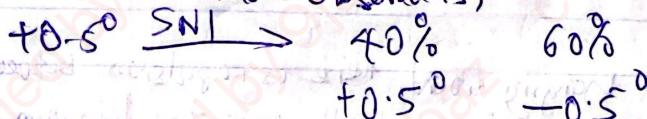
"Excess of inversion" $\rightarrow$ in S_N1

You may not be given the %, you may just be given the reactant from the machine, i.e. the rotation



As we will have 50% and 50%
 $+0.5^\circ \quad -0.5^\circ$

But what is most observed is;

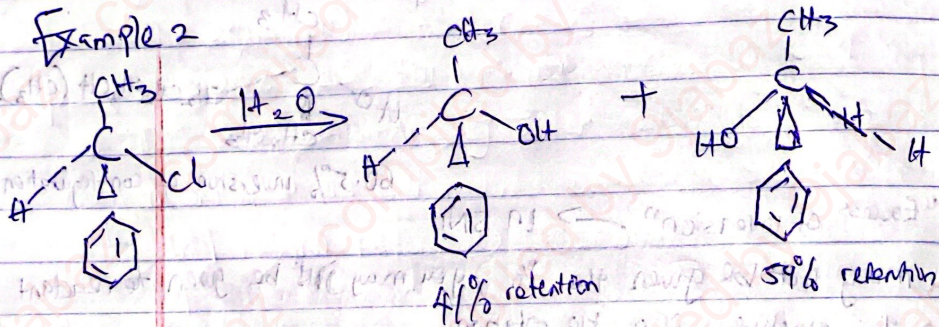


This means the ~~$+0.5^\circ$~~ and ~~-0.5°~~ 40% of the molecule will go $+0.5^\circ$ and 60% of the molecule will go -0.5° , which means the 40% will cancel

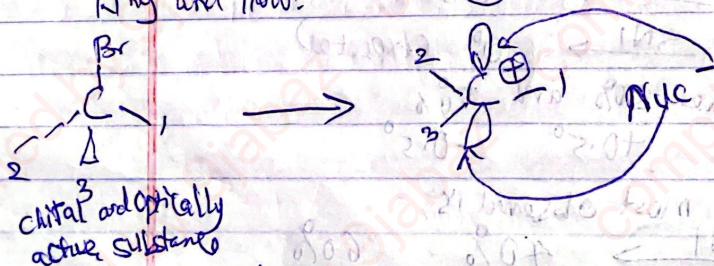
Some of the 60% rotation, remaining 20% which will give us optical activity. But optical activity is a function of concentration. Concentration $\propto$ to the observed rotation

The remaining 20% can't take the rotation up to that -0.5° , instead it might take it -0.1° . Whenever you see a little bit of inversion it's SN1

Example 2



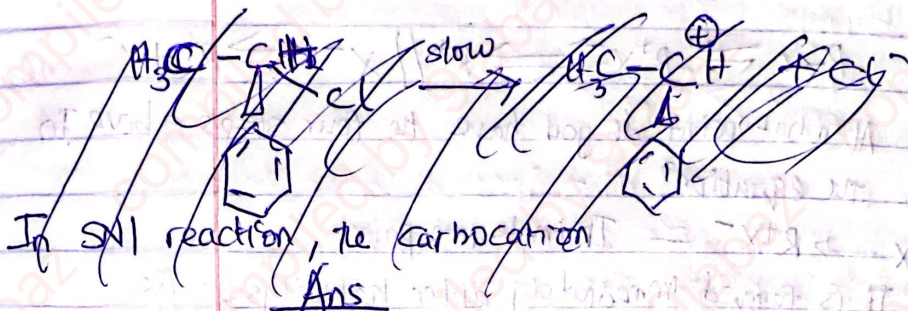
Why and How?



Because Br is still hanging around, there is repulsion between Br and Nuc - which makes inversion slightly more than retention. When we don't get complete racemization, you get slight

excess of inversion

Ques
Consider the role of solvent on the stereochemistry of the S_N1 reaction (Hydrolysis of 1-chloro-1-phenylethane)



In S_N1 reaction, the carbocation intermediate is attacked by the nucleophile from either side, while polar protic solvents (like water, ethanol) stabilize both the carbocation and the leaving group (Cl^-) through solvation and hydrogen bonding, which increases the rate of ionization.

Immediately after ionization, the solvent molecules experience the solvent cage effect, where sometimes the leaving group Cl^- or solvent molecules partially block one side of the carbocation. As a result, the attack by the nucleophile on each side is not perfectly equal, leading to partial racemization, often with a small excess of inversion.

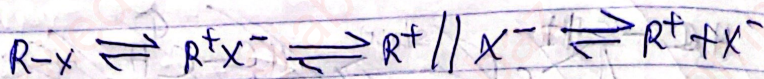
Concept of ~~the~~

(i) Internal return

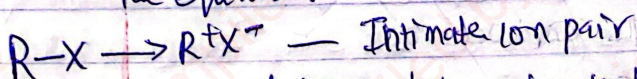
(ii) Intimate ion pair

(iii) Solvent separated ion pair

(iv) Dissociated ions (each surrounded by molecules of solvent)

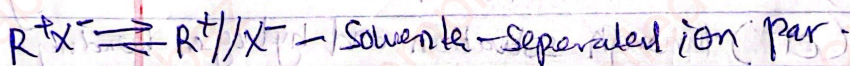


At what point do you have the four steps above in the equation?

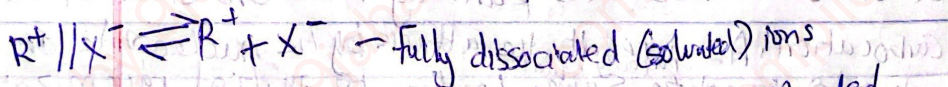


* It is formed immediately after heterolysis - the cation and anion are still in direct contact (no solvent between them).

* Internal return refers to recombination at this stage



* A solvent molecule (or a few) inserts between the ions. They are still associated but no longer in direct contact; mobility increases.



* These ions are fully separated and each is solvated by many solvent molecules.

Factors that Affect Rate of S_N2 Reaction

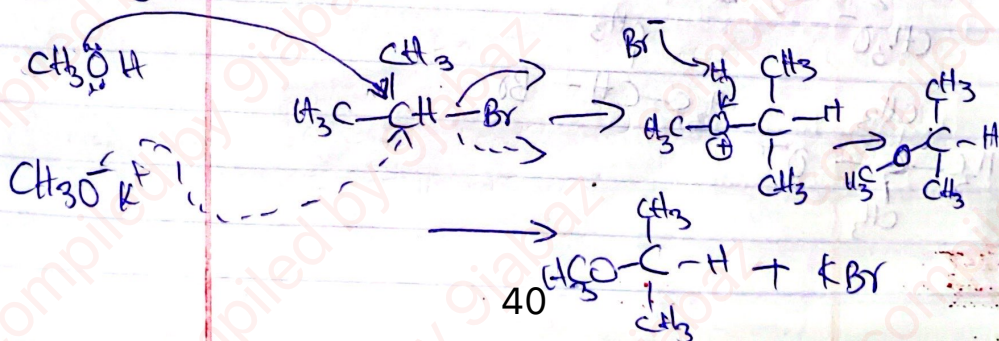
- (1) Substrate type
- (2) Effect of nucleophile
- (3) Effect of solvent
- (4) Leaving group type

1) Substrate type: In S_N2 , the nucleophile attacks from the back, but when the back side is crowded, the nucleophile will be sterically hindered. In a ~~methyl~~ ^{methyl} substrate we could have 3° , 2° , 1° . In a 3° substrate S_N2 cannot occur due to steric hindrance. The rate of methyl substrate is the fastest, followed by 1° , then 2° .

We can also have $CH_2=CH-CH_2-X$, which is the allylic substrate, it's faster than the methyl substrate. Why? Test question.

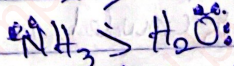
2) Effect of Nucleophile: When we have a negative charged nucleophile it makes the reaction faster.

Eg

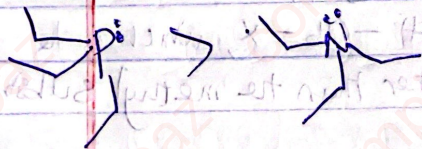
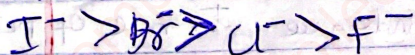


Trend in nucleophilicity

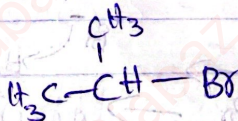
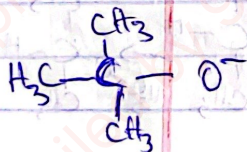
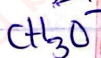
- ① A negatively charged nucleophile is better than a neutral nucleophile e.g. $\text{HO}^- / \text{H}_2\text{O}$
- ② Nucleophilicity decreases from left to right in the periodic table following the increase in electronegativity from left to right



- ③ The nucleophilicity also decreases down the group, due to increase in size and polarizability



- ④ Steric Hindrance: When the nucleophile is getting bigger or bulkier it slows down the nucleophilicity

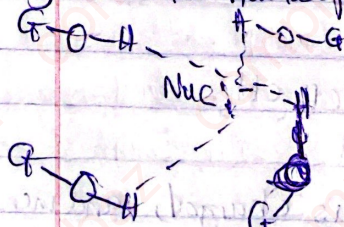


Effect of Solvent on Nucleophile

- (i) Protic solvents: $\xrightarrow{\text{polar}}$ $-\text{SH}, -\text{OH}, -\text{NH}$
- (ii) Aprotic solvents: $\xrightarrow{\text{non-polar}}$ $\text{CH}_3-\text{O}-\text{CH}_3, \text{CH}_3\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_3, \text{CHCl}_3, \text{CH}_2\text{Cl}_2, \text{THF}$
- (iii) Polar Aprotic solvents: eg, DMF (dimethylformamide) $(\text{H}-\overset{\text{O}}{\parallel}-\text{N}-\text{CH}_3)$, Acetonitrile $(\text{CH}_3-\text{C}\equiv\text{N})$, DMSO, Acetone

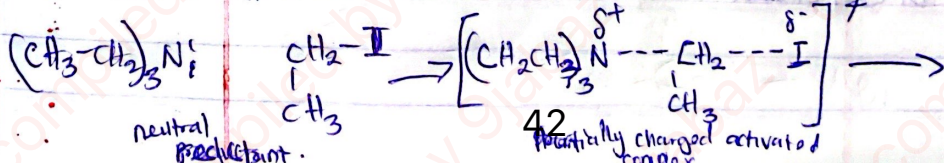
Solvent can affect $\text{S}_\text{N}2$ reaction in two ways;

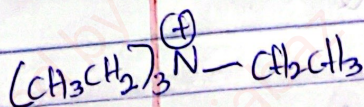
- (i) effect on Nucleophile: Nuc^- will be strongly solvated in protic solvents, it stabilizes the nucleophile, ^{due to hydrogen bond} therefore Nuc^- does not really react, and the reaction becomes very slow especially when the nucleophile is negatively charged.



In aprotic solvent ~~may not~~ nucleophile will not dissolve, but in polar aprotic solvent, the nucleophile dissolves but due to less hydrogen bonds, the nucleophile is more free for reaction.

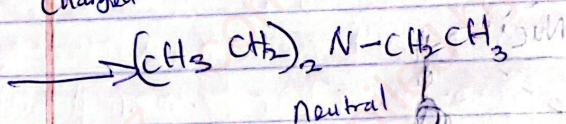
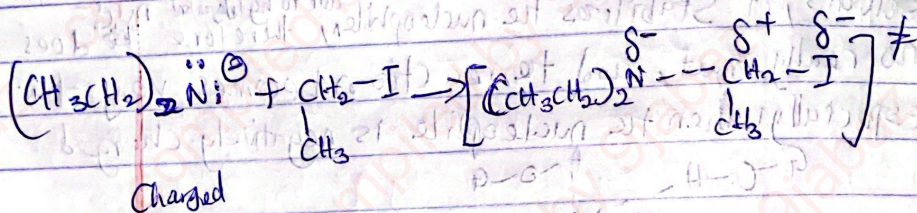
- (ii) Solvent effect on Substrate: ^{transition state}





Charged product

The reactants are neutral and not charged, (moving to) a charged transition state will be favoured by ~~increasing the~~ ^{increasing the} polarity of the solvent.



In this reaction, the reactant is charged, and increasing the polarity of the reactant favours the reactant and not the TS, decreasing the polarity will increase the rate of reaction as it favours TS.

How we increase/decrease polarity?

E.g. DMSO/Ethanol

The Effect of Leaving Group

The Leaving Series two purposes in S_N2

- (i) Leaving group polarizes the $-C-X$ (withdrawing more electron)

A leaving group that strongly polarizes the $-C-X$ makes the substrate carbon more partial positive and makes it more electrophilic and susceptible to nucleophilic attacks.

(ii) A good Leaving should therefore

- (i) electron withdrawing because it ~~make~~ polarizes the carbon more

(ii) The leaving group must be stable, as it leaves (it must be a strong base)

(iii) The leaving group must be polarizable, because it stabilizes the transition state

The Effect of Leaving Group

The leaving group serves two purposes in S_N2

(i) Leaving group polarizes the $-C-X$ bond. (withdrawing more electron)

A leaving group that strongly polarizes the $-C-X$ bond makes the substrate carbon more partial positive and makes it more electrophilic and susceptible to nucleophilic attack.

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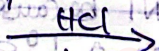
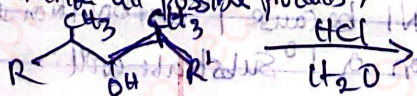
(ii) The leaving group must be stable, as it leaves (it must be a strong base).

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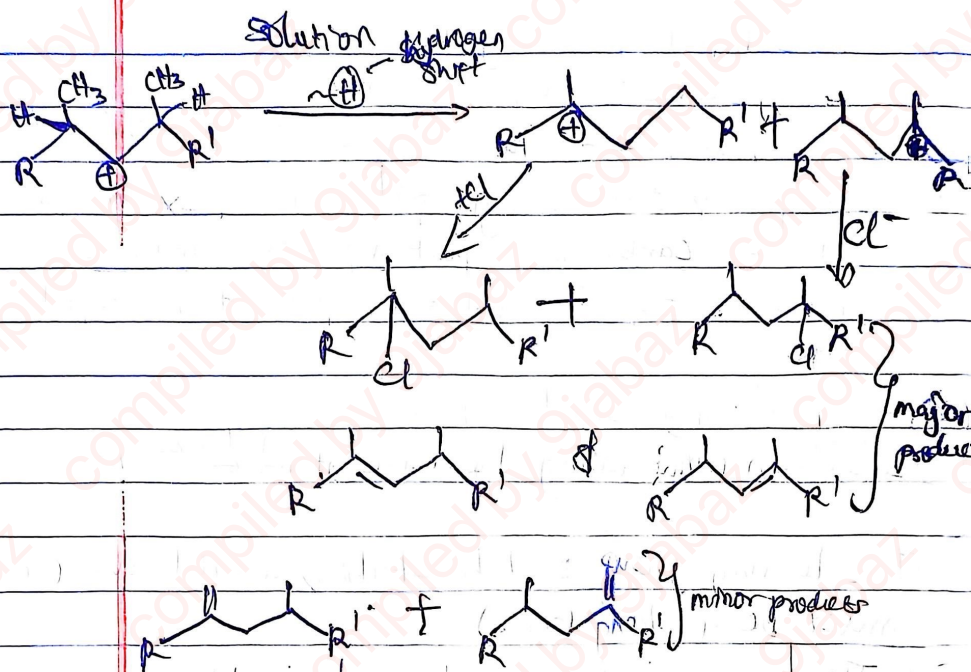
28/11/25

For a strong nucleophile: Nucleophilic attack will occur faster than the carbocation can form. Because of a strong nucleophile. It undergoes S_N2 but if a weak nucleophile, carbocation will be formed.

Write all possible products:



Cl^- is a moderate nucleophile



Factors that affect the rate of S_N1 reaction

① Substrate type

② Leaving group

③ Solvent effect

① Substrate type: $3^\circ > 2^\circ > 1^\circ$

3° substrate, the kinetics will be S_N1 and will be faster

2° substrate for S_N1 is possible but not as 3° substrate

1° substrate do not undergo S_N1 because 1° carbocation is not stable. The only condition a 1° substrate will

undergo $1,2$ rearrangement.

Carbocation determines the rate in S_N1 . 3° carbocation is formed faster.

Stability of carbocation drives S_N1 reaction.

Strength of nucleophile does not play any role because nucleophile has nothing to do with the slow step, since only the rate of carbocation factors in.

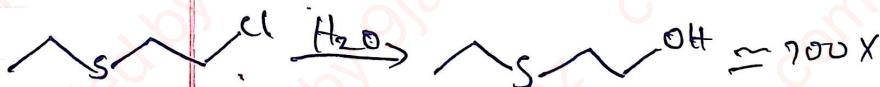
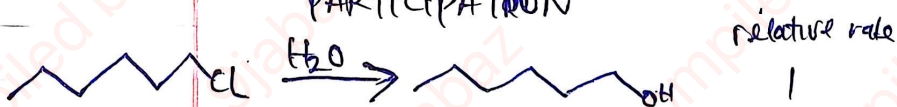
(2) Effect of the leaving group: Same as that of S_N2 .

(3) Solvent effect

Consideration for solvent in S_N1 is straightforward. The best to stabilize the carbocation is a polar solvent. A non-polar solvent doesn't work.

Polar solvent whether protic or aprotic.

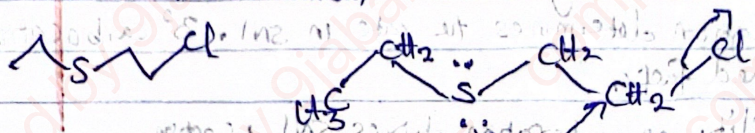
INTRAMOLECULAR REACTIONS & NEIGHBOURING GROUP PARTICIPATION



The reason the second is so fast is due to neighbouring group participation.

What is neighbouring group participation?

Mechanism



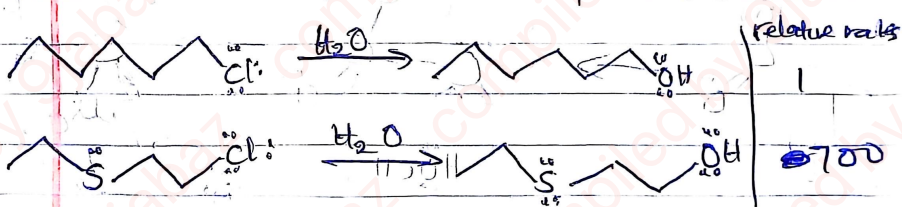
The lone pair on sulphur makes it behave like a nucleophile. The leaving of leaving group is being assisted which is called Anchimeric assistance.

Video

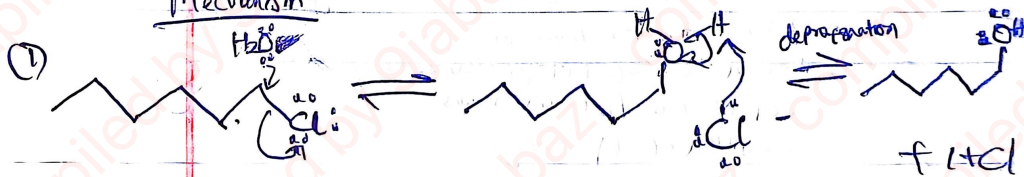
Intramolecular Reactions and Neighboring Group Participation

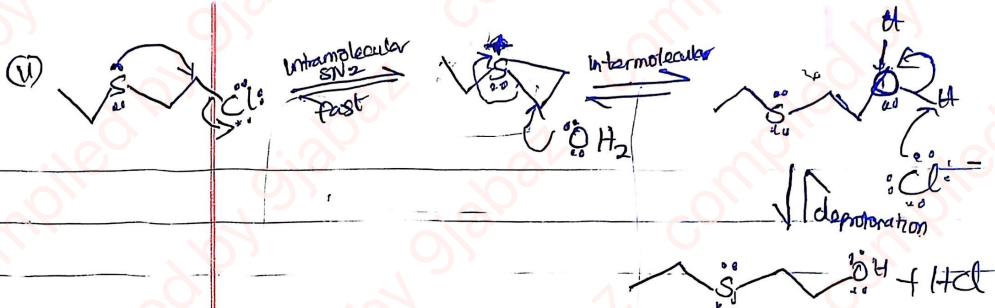
A neighbouring group effect is the role that neighbouring groups (other functional groups on the substrate) play in the reactions that the substrate undergoes.

The neighbouring groups' participation in the reaction of the substrate can change the rate of formation of products as well as the structures of the molecules produced.



Mechanism





General Observations for Neighbouring Group Effects

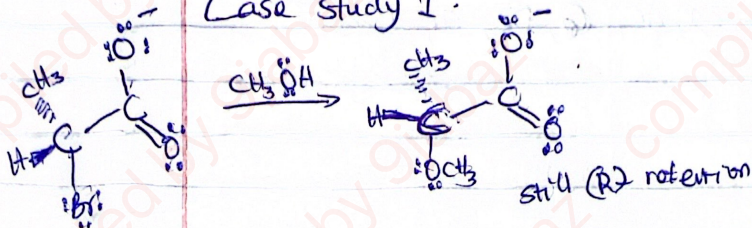
Intramolecular reactions are often faster than intermolecular reactions because there is no need for the nucleophile and substrate to find each other in solution.

When the rate-limiting step is the step that involves the neighbouring group effect, such is called ANCHIMERIC ASSISTANCE.

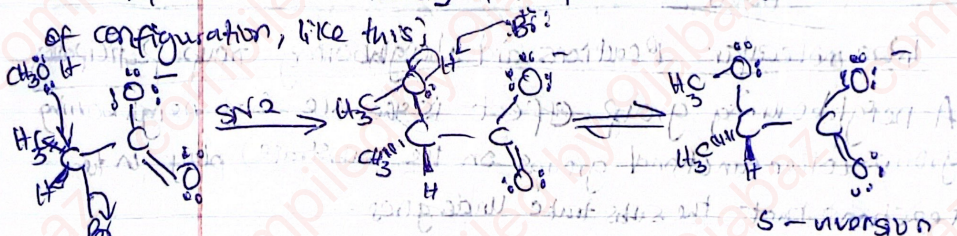
If there is a neighbouring group effect in operation, we have to watch out for three things:

- (i) An usual stereochemical result, usually retention of configuration where inversion is expected.
- (ii) A strange rearrangement, often involving a labelled molecule.
- (iii) An unexpected fast rate.

Case study 1.

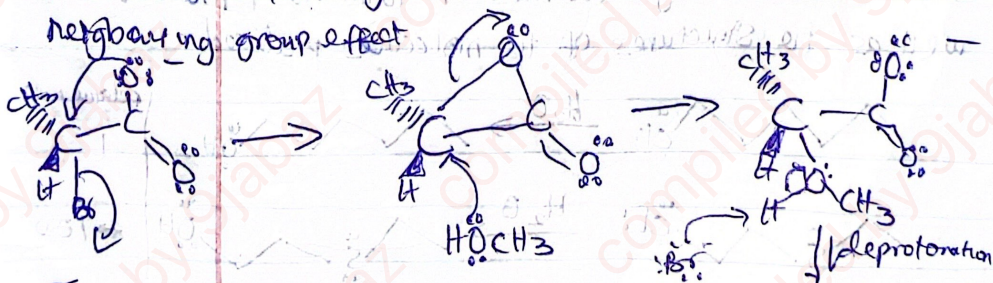


The expected stereochemistry of the product should be an inversion of configuration, like this?

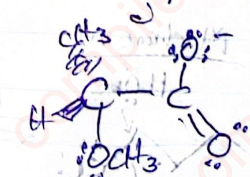


The observation of strange stereochemical result is due to the

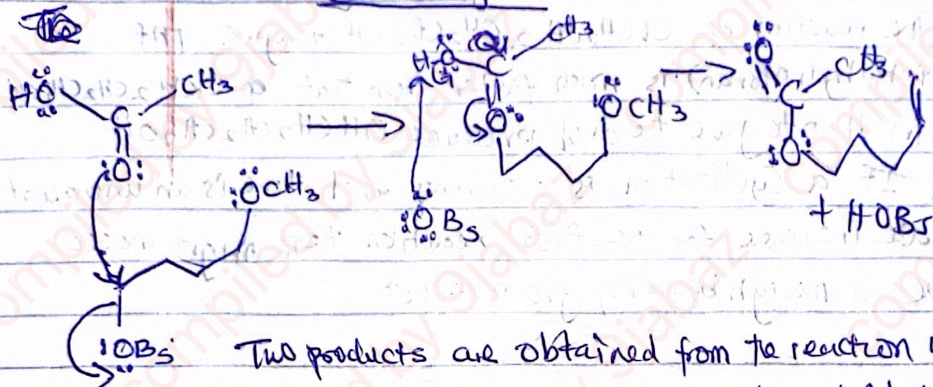
neighboring group effect



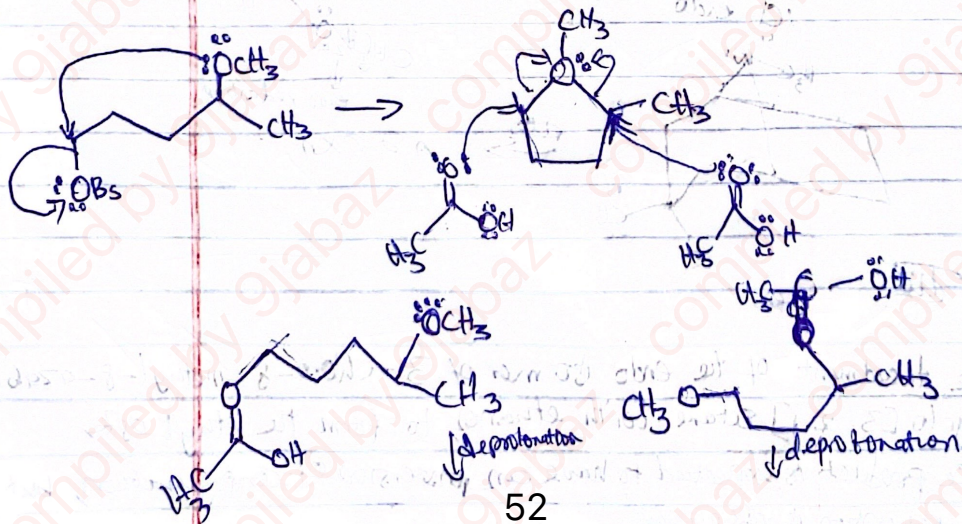
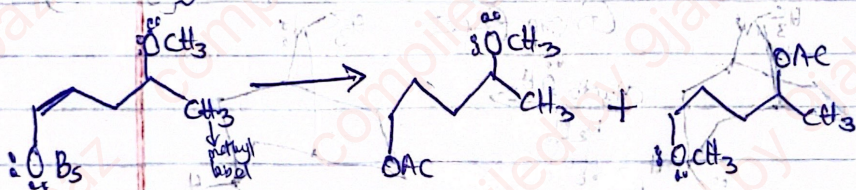
There is an inversion of configuration in the first step ($\text{S}_\text{N}2$) and another inversion of configuration in the second step (also $\text{S}_\text{N}2$). So the combination of the two inversions is equivalent to retention of configuration.



Case study 2



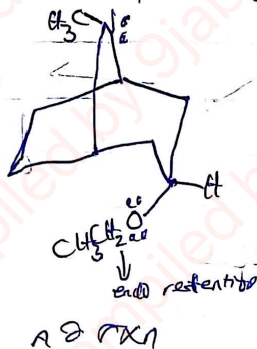
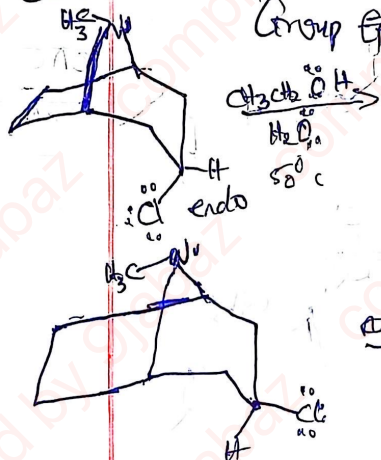
Two products are obtained from the reaction as expected from a regular substitution reaction.



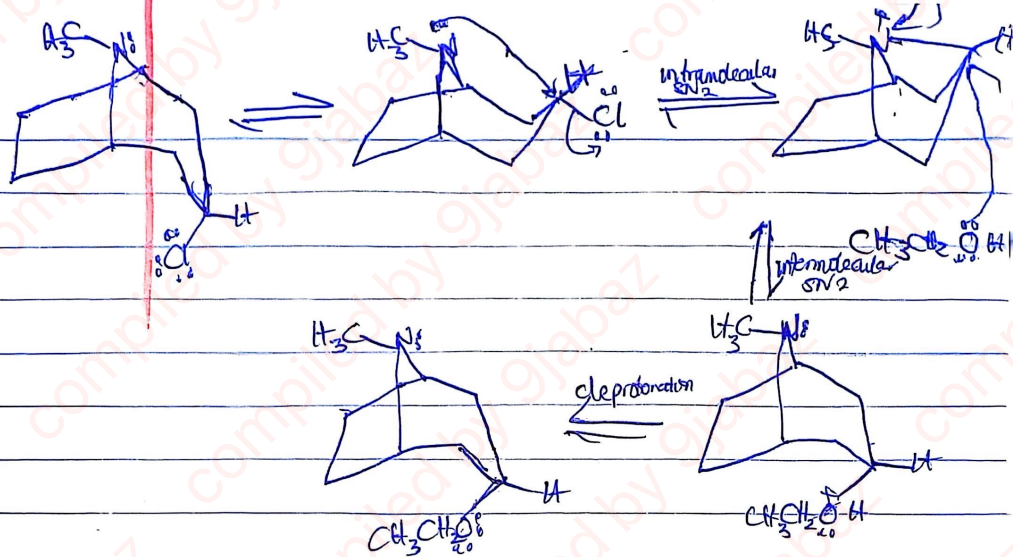
Case Study 3

The reaction of $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ to give THF (tetrahydrofuran) is much faster than that of $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ in H_2O to give the diol product $\text{OHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$. If a cyclization is occurring and there is an unusual rate increase for the first reaction there might indeed be a neighbouring group effect.

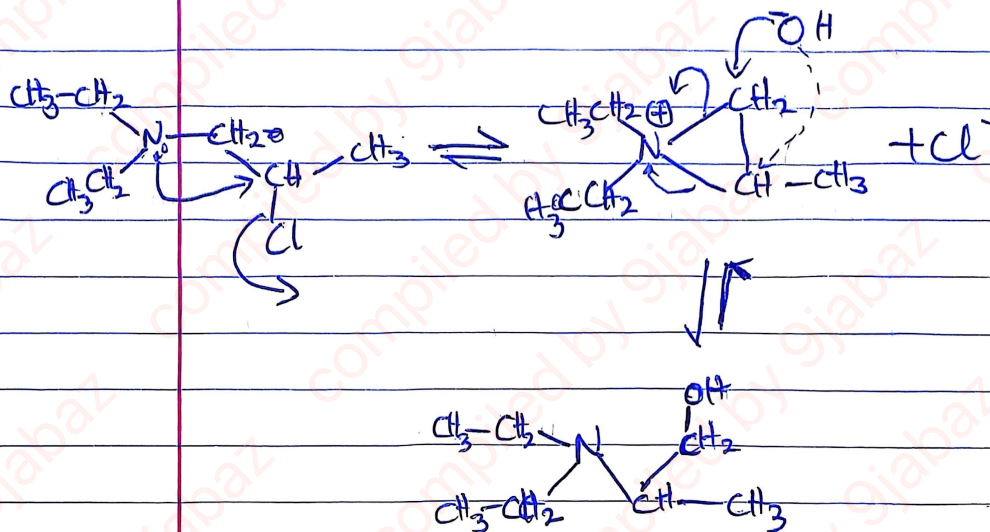
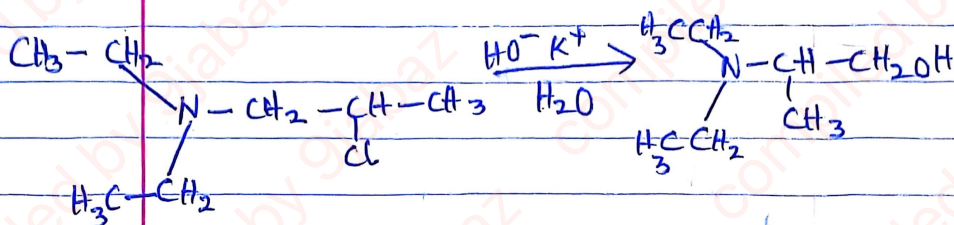
Consideration of Other Heteroatoms for Neighbouring Group Effect



The treatment of the endo isomer of 3-chloro-8-methyl-8-azabicyclo[3.2.1]octane with ethanol to form the ethyl ether. The product is expected to have an inversion of configuration, but a retention is observed.



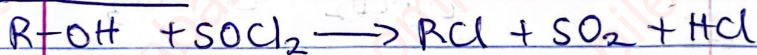
4/12/25



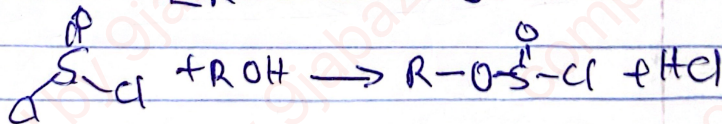
Substitution Nucleophilic Internal (S_Ni)

In a few reactions, nucleophilic substitution proceeds with retention of configuration even where there is no possibility of a neighbouring group effect. In the S_Ni mechanism (Substitution Nucleophilic Internal) part of the leaving group must be able to attack the ^{substrate} ~~substrate~~ detaching itself from the rest of the leaving group in the process. The first step is the same as the first step of the S_N1 mechanism: Dissociation into an intimate ion pair. But in the second step part of the leaving group attacks, necessarily from the front, since it is unable to get to the back and this results in retention of configuration.

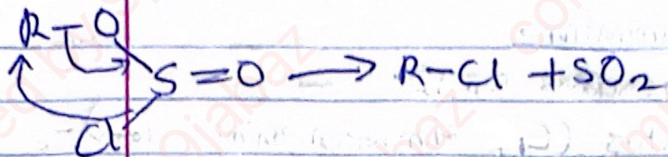
illustration



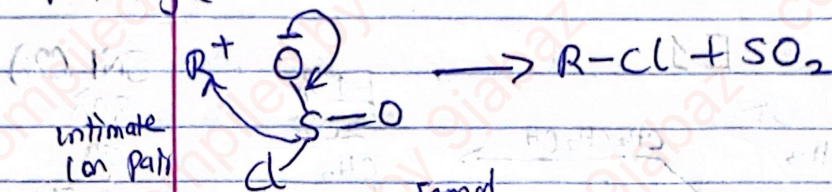
R-OH and SOCl₂ combines to form a stable, isolable intermediate [R-O-SO-Cl]



Possibility 1



Possibility 2



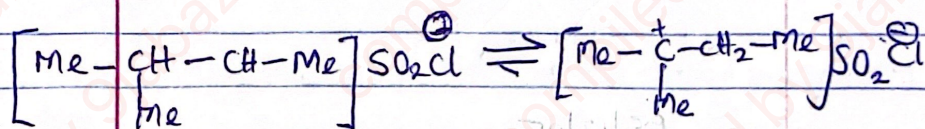
intimate
(ion pair)

formed

* When the product can rearrange, it is the correct mechanism

Carbocation rearrangement is possible in the observed product.

This implies a carbocation must have been formed somewhere during the mechanism



The $\text{S}_{\text{N}}\text{i}$ mechanism is relatively rare; another example of it is the decomposition of ROCOCl (alkylchloroformate) into $\text{RCl} + \text{CO}_2$

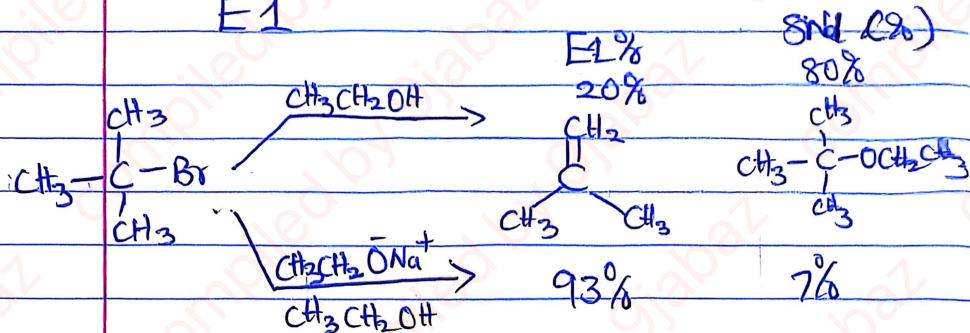
Eliminations

Elimination reactions can be:

First order kinetics (E_1 , elimination unimolecular)

Second order kinetics (E_2 , elimination bimolecular)

E_1

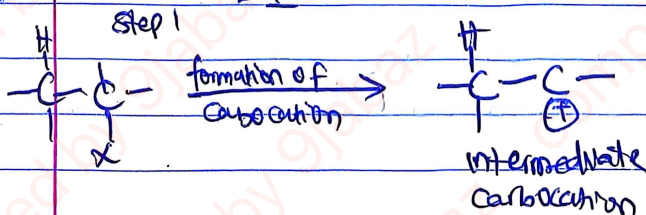


For first order kinetics, we always have competition b/w

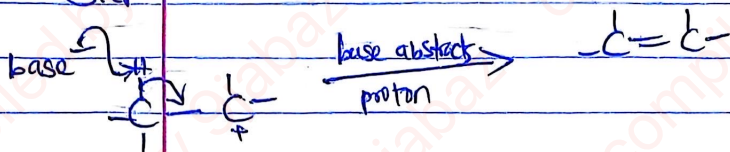
E_1 vs SN_1

05/12/25

E_1

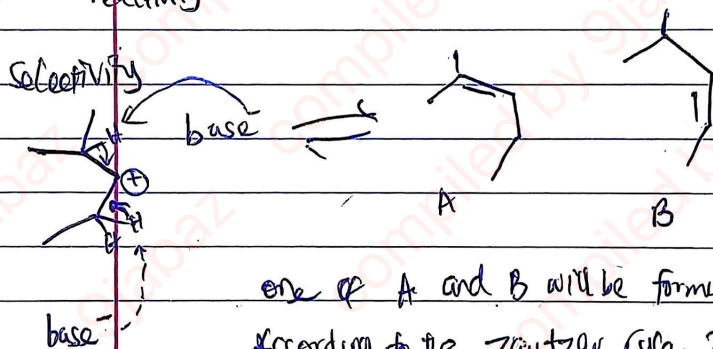
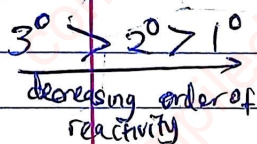


Step 2

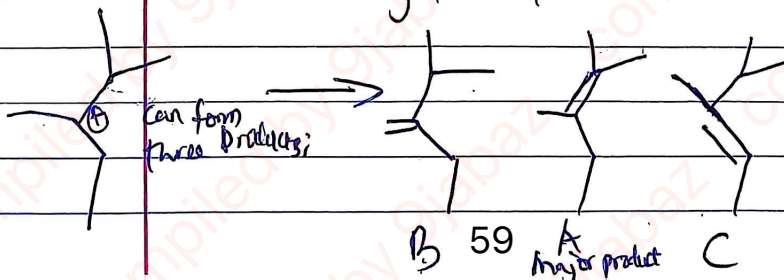


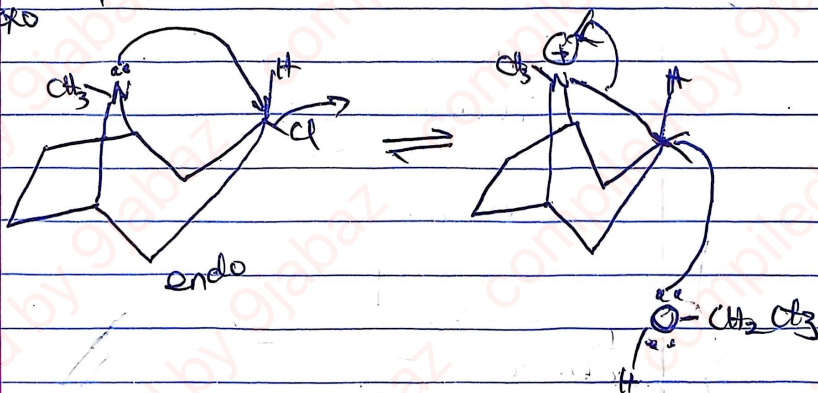
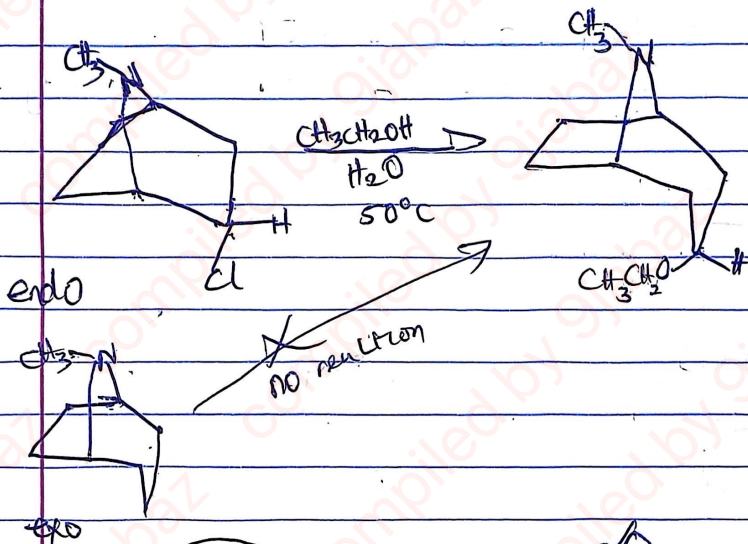
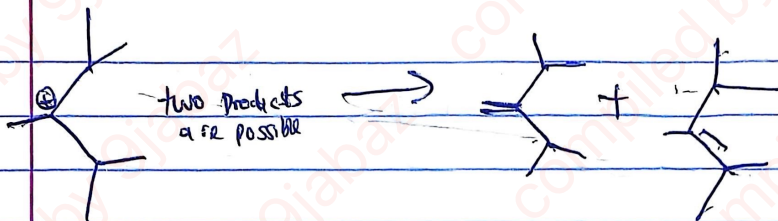
Reactivity of substrate in E1

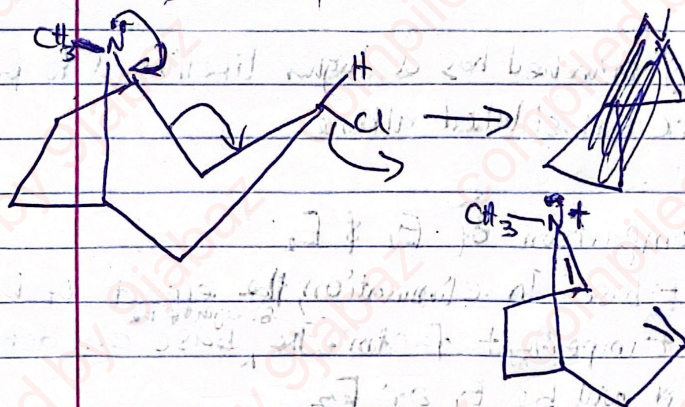
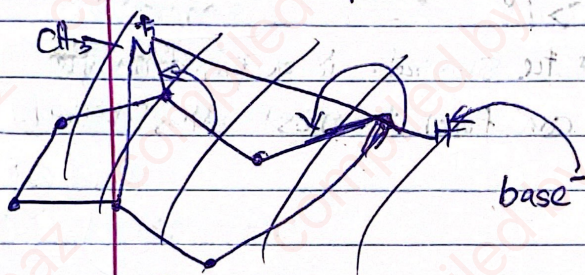
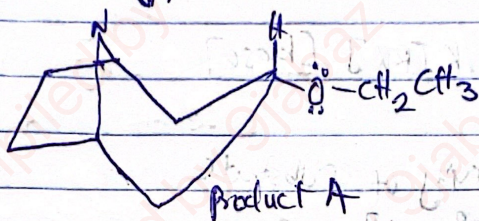
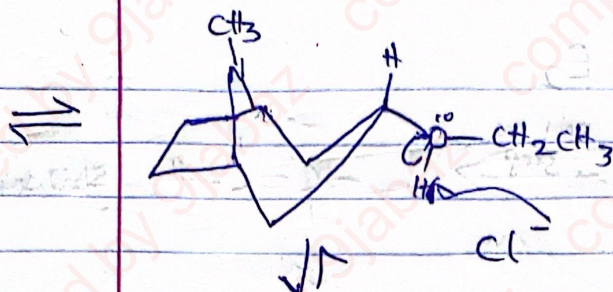
The reactivity of the substrate is a function of the stability of the carbocation



one of A and B will be formed preferentially according to the Zaitsev rule. The more substituted alkene is more stable and has a greater tendency to be formed







minor
 product

It will likely be via E_1 or

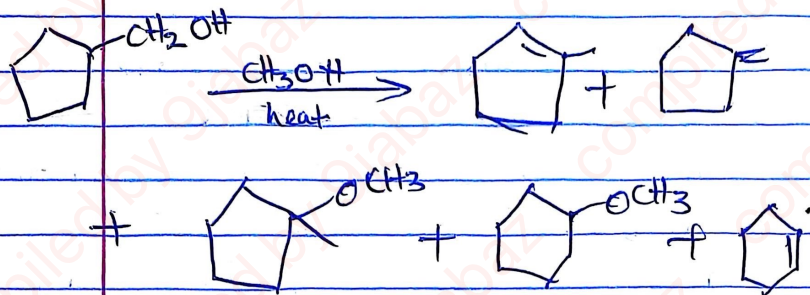
A strong base will attack the ~~proton~~ ~~substrate~~ ~~and~~ ~~abstract~~ ~~proton~~ before the substrate forms a carbocation

But a weak base will allow the substrate to form a carbocation before it abstracts a proton. Therefore, a strong base favours E_2 mechanism while a weak base favours the E_1 mechanism

Assignment

- (i) Effect of solvent
- (ii) Effect of substrate
- (iii) Kinetics
- (iv) Stereochemistry
- (v) Rearrangement

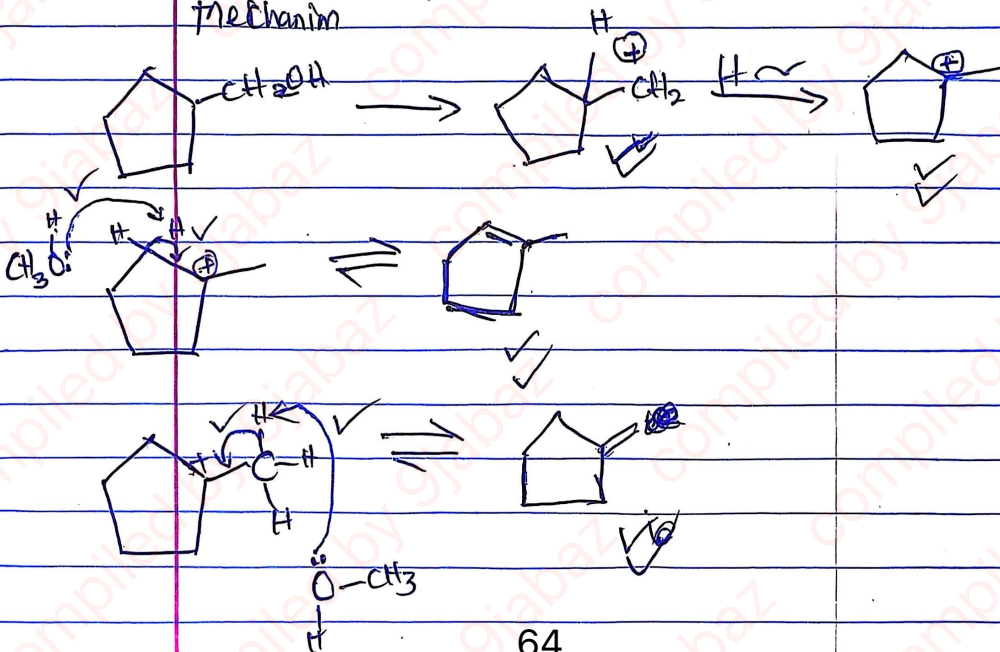


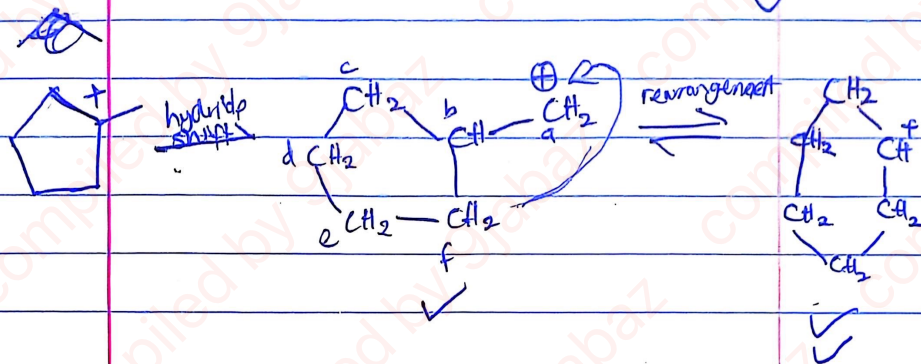
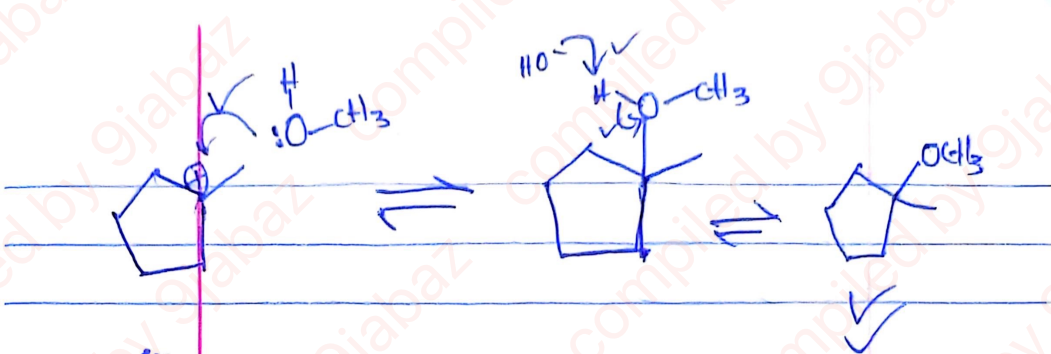


solution

Products appear to have some form of rearrangement which implies that it is a first order kinetics (or formation of carbocation) ✓✓

Mechanism



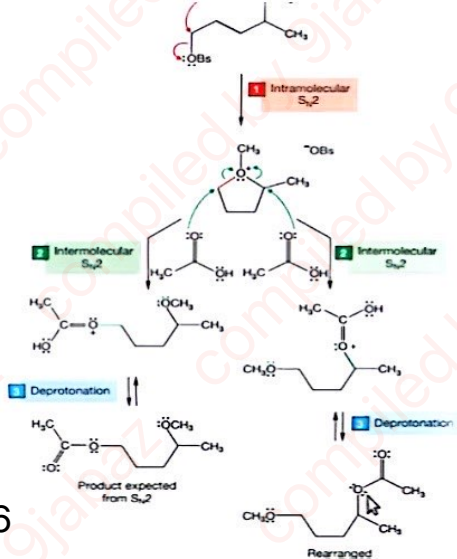


QUIZ

A third product is also formed in small quantity –

2-methyltetrahydrofuran.

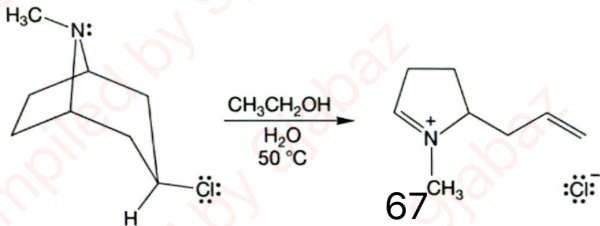
Can you explain the formation of this molecule. Use arrows to show movement of electrons in any mechanism you propose



QUIZ

The exo compound does not react to form either the exo or endo product under the same reaction conditions as the endo product. Why does the exo compound not react in the same way as the endo compound?

PROBLEM 21.7 The exo isomer of Figure 21.14 gives the product shown below. Suggest a mechanism for this reaction.



CASE-STUDY 3

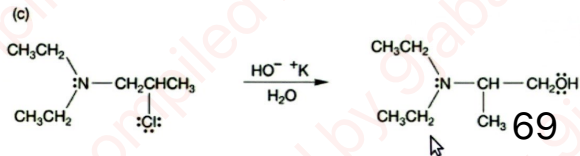
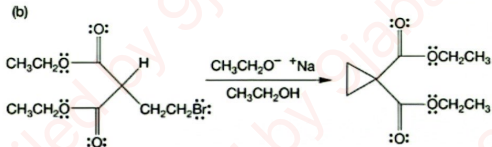
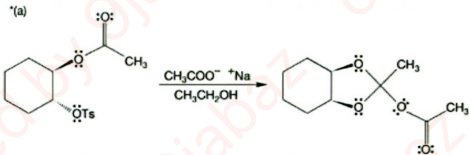
The reaction of $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ in H_2O to give THF (tetrahydrofuran) is much faster than that of $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{OH}$ in H_2O to give the diol product $\text{HOCH}_2\text{CH}_2\text{CH}_2\text{OH}$.

The two reactions are expected to be simple substitution reactions with no significant rate difference. However, if a cyclization is occurring and there is an unusual rate increase for the first reaction, there might indeed be a neighboring group effect.

QUIZ = Propose a mechanism for the formation of THF in the reaction described above

TUTORIAL

Write mechanisms for the following reactions:



NOTE

Use arrows to show the movement of electrons in the mechanism that you propose.