Prof. Olomola's part

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. Sandberg
5. A guide book to mechanism in organic chemistry by Peter Sykes

Concepts in Theoretical Organic Chemistry

To the lame man, 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) h/hy 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 decription 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 specie 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 comprehesible way, mechanisms helps us to organize reactions.

Knowledge of reaction mechanism, similifies the work of a synthetic chemist by helping in the selection of the best reaction conditions for maximum yield 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 the margin or myth that might exist about molecular interaction.

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

The following are pre-requisite 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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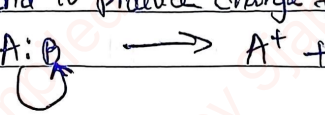
* bonds doesn't just break
* for heterolysis to happen, the atoms should be in different electronegativity or polarized

Types of Mechanisms

Organic mechanisms can be divided two three 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 charge fragment



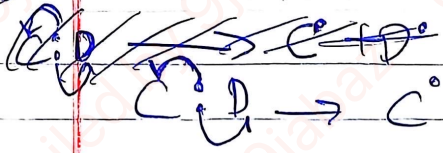
In heterolytic reaction, the reagent generally brings a pair of electrons to the substrate or takes a pair of electron from it

A reagent that brings an electron pair is called a nucleophile and 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) Homolytic Bond Cleavage: This occurs if a bond breaks in a way that each fragment gets one electron and free radicals are formed

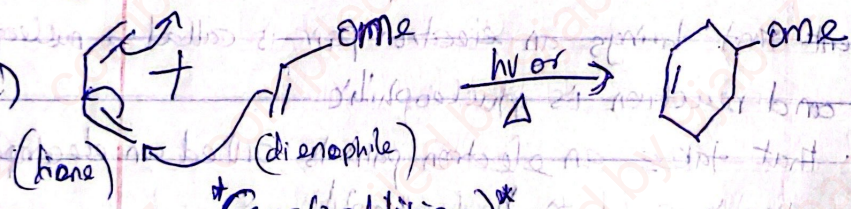


Free radicals often proceed by a chain reaction

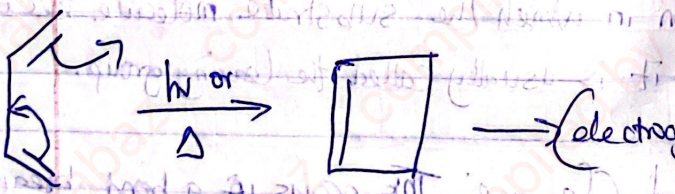
(3) Pericyclic Mechanism: (everything happens at the same time) This involves the stereospecific movement of electrons leading to the making and breaking of bonds in a single concerted step involving a cyclic transition state. There are no intermediates ions or free radical involved. The symmetry characteristics of molecular orbitals controls the overall course of the reaction

Electrocyclic and cyclo addition reaction involves the pericyclic mechanism

(i)



(ii)



(4) Transition Metal-Catalyzed and Metal — Mediated

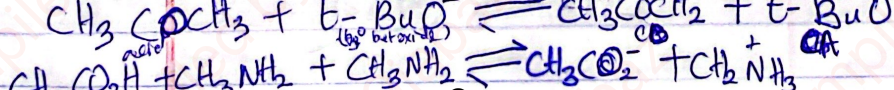
ACIDITY AND BASICITY

Many organic reaction are either acid-base reactions themselves, or involves an acid-base reaction at some stage. Acid-base reactions allows 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 gives 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 theory 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 constrast to strong acids such as HCl and H_2SO_4, acetic acid as a typical example of a weak acid

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

Since the equation is an equilibrium

$$K_{eq} = \frac{[H_3O^+][CH_3COO^-]}{[CH_3COOH][H_2O]}$$

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;

$$K_a = K_{eq}[H_2O] = \frac{[H_3O^+][CH_3COO^-]}{[CH_3COOH]}$$

In general, for any weak acid HA

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

* 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	pKa
Cl^-	-7
CH_3COO^-	4.75
OH^-	15.7

Arrang the order of decreasing basic strength,
OH^-, CH_3COO^-, Cl^-
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(2) Lewis Definition: A lewis acid is any specie with a vacant orbital or an electron pair acceptor.

$$BF_3 + :NH_3 \longrightarrow F_3B^{\ominus}-N^{\oplus}H_3$$

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

$$BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$$

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

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

Hard → Hard
Soft → 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 unshared 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

CH_4, NH_3, H_2O, HF

pK_a 48 38 15·7 3·2

increasing order of acidity →

CH_3^-, NH_2^-, OH^-, F^-

← increasing order of basicity

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

$RCOOH >> RCONH_2 >> RCOCH_3$

The acidity of MX_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, -I (negative inductive effect) 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	$(C_6F_5)_3CH$	
Pka	31.5	16	

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

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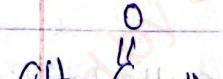
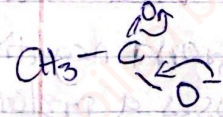
anion $C\equiv C^-$

(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 a alcohol

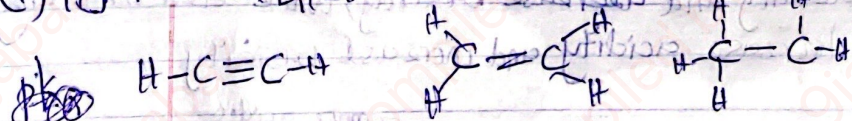


pKa 4.75 16



This also explains why amides are more acidic than amines

(4) Hybridization Effect

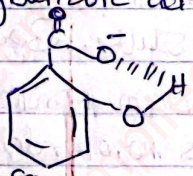


pKa 25 44 50

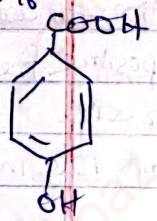
Electrons of 2s orbitals have lower energy than those of 2p orbitals because electrons in 2s orbitals tends to be much closer to the nucleus than electron in the 2p orbital with hybrid orbitals having more s character, it means that the electrons of the anion will on the average be lower in energy and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

It means that the $HC\equiv C^-$ is a weaker base than $H_2C{=}CH^-$. 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



pKa 2.98



pKa 4.58

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 pKa of about 130 in the gas phase (4.75) in solution/water. In the gas phase, seperation of oppositely charged particle is difficult

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

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 ($\varepsilon = 80$) and its ion solvanting ability. Solvation of any specie, 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

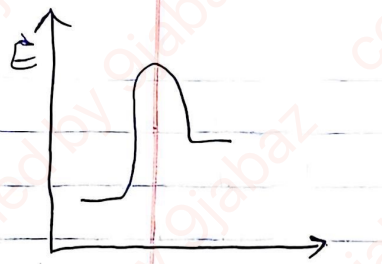
A reaction may be described as favourable or unfavourable fast or slow and as reversible or irreversible. These terms are useful parameters in describing an overall reaction mechanism. How far a reaction will go to give

Products depends on the energy change that takes place. Systems move forwards 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 that 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

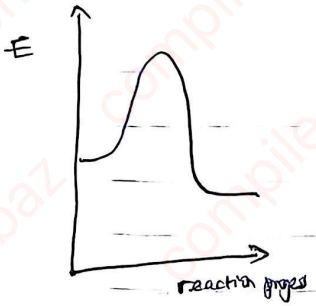
(ii) entropy change which is the measure of the degree of orderliness of a system. To favour spontaneity, enthalpy should decrease and entropy change should increase.

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 $T\Delta S^\circ$ is small compares to ΔH° for most reaction at ordinary temperature

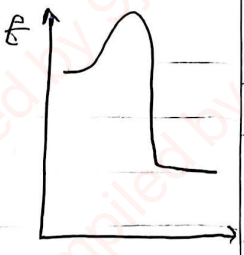
Thus if ΔH° is large and negative the reaction will favour product formation at equilibrium



$\Delta G^\circ > 0$
Unfavourable



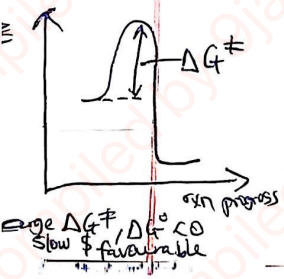
$\Delta G < 0$
favourable



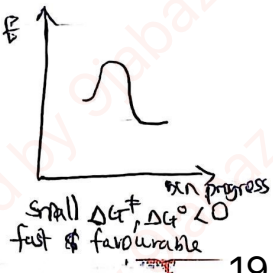
$\Delta G \ll 0$
highly favourable

Just because a reaction have a $-\Delta G$ 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 arrangment 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~~ the activation barrier. When the barrier is low, a reaction is fast and vice versa

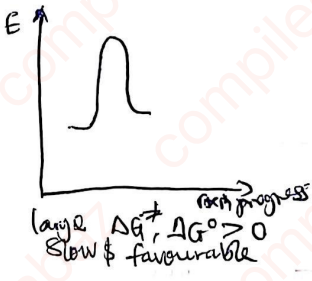
Note: $\Delta G^\ddagger$ and ΔG° (rate and energetics of a reaction) are independent of one another



large $\Delta G^\ddagger$, $\Delta G^\circ < 0$
Slow $ favourable



small $\Delta G^\ddagger$, $\Delta G^\circ < 0$
fast $ favourable



large $\Delta G^\ddagger$, $\Delta G^\circ > 0$
Slow $ favourable

According to the transition state theory, $\Delta G^{\neq} = -RT \ln K_{eq}$

Where K_{eq} is the equilibrium constant between the starting material and the activation complex

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

$\Delta G^{\neq}$ is also made up of enthalpy and entropy components

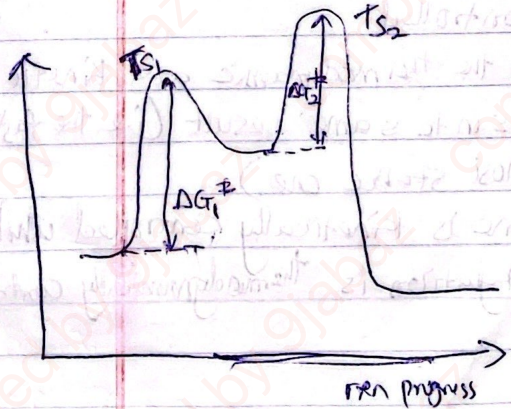
$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$$

where $\Delta H^{\neq}$ is the enthalpy of activation

$\Delta S^{\neq}$ is the entropy of activation

Several reactions involves more than one step. Such reactions involves the formation of one or more intermediate (s) and require more than one transition state complex.

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



The highest $\Delta G_{Tn}^{\neq}$ value corresponds to the rate determining step for the reaction

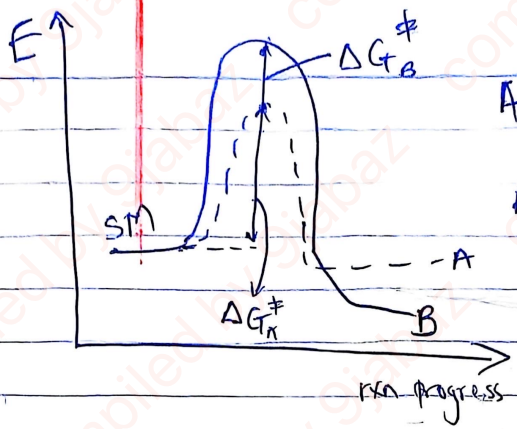
Whenever a starting material can be converted to two or more alternative products. The actual product formed is dependent on either the relative rate of formation of products, or their relative thermodynamic stability.

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 controlled and when the more stable product only or predominantly is formed, the reaction is said to be thermodynamically controlled

In some cases, the thermodynamic and kinetic controlled both results in to 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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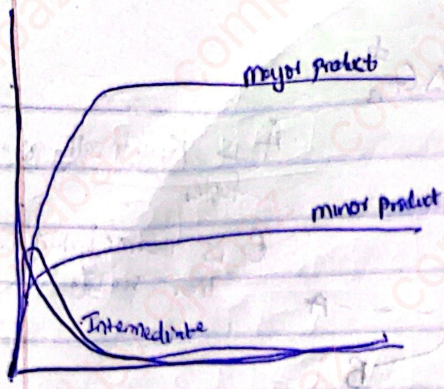
$CH_2=CH-CH=CH_2 + HBr \rightarrow$ 1,2 addition $CH_3CHBrCH=CH_2$ + $CH_3CH=CHCH_2Br$ 1,4 addition A

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

$CH_3CHBrCH=CH_2 \xrightarrow{\Delta} CH_3CH=CHCH_2Br$



$CH_2=CH-CH=CH_2 \rightarrow CH_3-\overset{+}{C}H_2-CH=CH_2 \longleftrightarrow CH_3-CH=CH-\overset{+}{C}H_2$

(more stable)

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 great $\geq 10^3$, 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 stable intermediate

A catalyst lowers the free energy of activation $G^{\neq}$, while the overall free energy of reaction G° remains unchanged. Acids and bases catalyse 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 base, 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 (LHA). 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 determing breakdown of the conjugate acid into products.

$$R + HA \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} RH^{+} + A^{-}$$

$$RH^{+} \xrightarrow[K_2]{\text{slow}} \text{prdts}$$

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

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

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

$\therefore$ rate $= \frac{K_2 K [R][HA]}{[A^-]}$

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Protonated Solvent = HA

$HA \rightleftharpoons H^+ + A^-$

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

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

Rate $= \frac{K_2 K [R][H^+]}{K_a}$

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

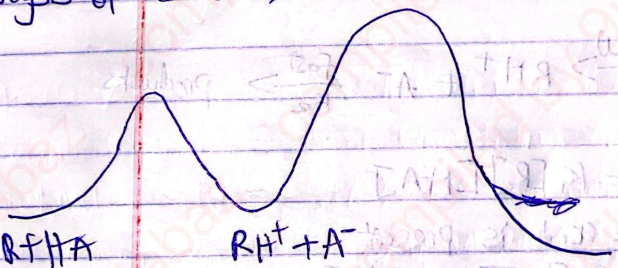
$\frac{K}{K_a} = \frac{[RH^+]}{[R][H^+]}$

$$RH^+ \xrightarrow{K_a} R + H^+$$

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

$$\therefore \text{Rate} = \frac{K_2}{K_{aRH^+}} [R][H^+]$$

This, the reaction rate depends on concentration of hydrogen ions $[H^+]$ and not on the concentration of $[HA]$ i.e the 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

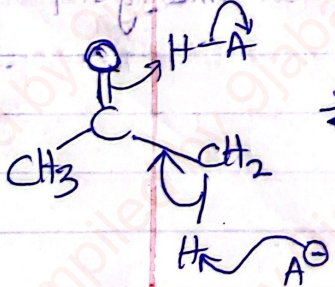
Due to the slowness of the proton transfer step, even the very weak acids participate in the proton transfer process

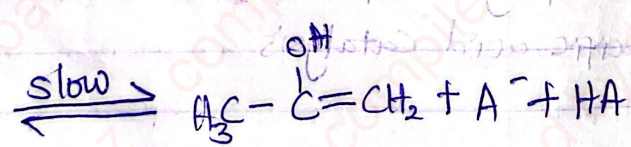
$$R + HA \xrightarrow[k_1]{\text{slow}} RH^+ + A^- \xrightarrow[k_2]{\text{fast}} \text{products}$$

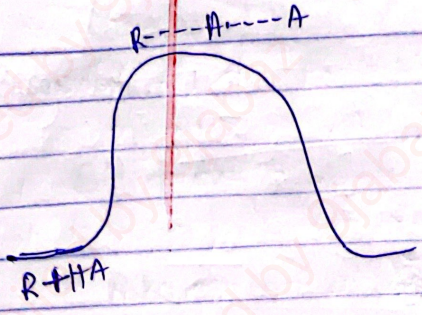
$$\text{rate} = k_1[R][HA]$$

If more than one acid is present

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







Consider the following reaction ~~x~~

$X + Y \longrightarrow$ product, with catalysis by H_3O^+, HA under pseudo first order condition, concentration of $[H_3O^+]$ and $[HA]$ is constant. Therefore, rate

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

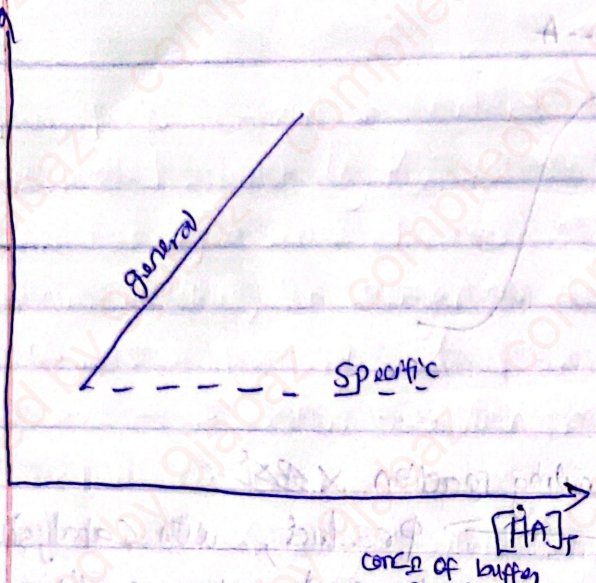
where $K_{obs} = K_H[H_3O^+] + K_1[HA] + K_w[H_2O]$

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 $\left(\frac{[A^-]}{[HA]}\right)$ constant but actually vary in values of concentration of $[HA]$.

Thus total buffer concentration keep changing

$$[HA]_T = [HA] + [A^-]$$

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



Specific Base Catalysis

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

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General Base Catalysis

Bases other than OH^- are involved

$$SH + B \xrightarrow[k_1]{\text{slow}} S + BH^+$$

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

$$= \sum k_i [A_i][B^-]$$

Examples of general base catalysis includes halogenation, isomerisation and racemisation 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 transfered. 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 catalysis equation.

$$\log k_a = \alpha \log K_\alpha + C$$

k_a is the rate constant for a reaction catalyzed

by an acid of ionization constant K_a. When $\log K_a$ is plotted against $\log K_x$ for the catalysis 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 suggest 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

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The Brosted relationship is an empirical one with several experimental deviation. It's limitations includes;

(i) It applies only to general acids or base catalyzed reaction

(ii) The law holds only for catalytic action of similar acids e.g carboxylic acid catalyst must be investigated as a group and not mixed with phenolic acid catalyst. Thus, α is a function of both substrate type and catalyst type

(iii) K_a and K_x being compared must be measured in the same solvent and at the same temperature

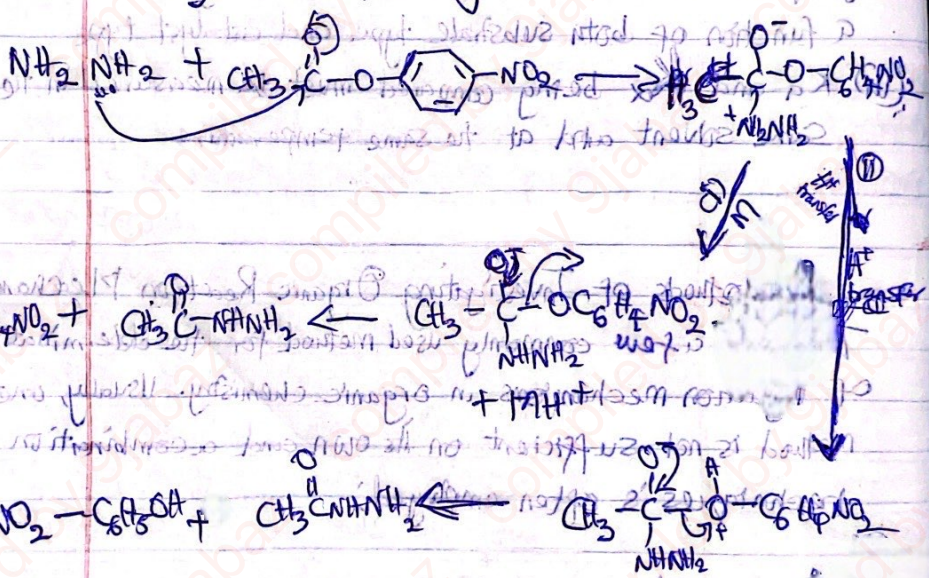
Methods of Investigating Organic Reaction Mechanism

They are a few commonly used method for the determination of reaction mechanisms in organic chemistry. Usually, one method is not sufficient on its own and a combination of techniques is often employed.

(iv) Product Identification: In most organic reaction, more than one product is obtained, knowing the proper identity and the relative proportion of all products is necessary in the determination of the reaction mechanism. An acceptable mechanism has to be able to account for all

the products of the reaction. For example, an acceptable mechanism for the halogenation of alkane must be able to account not just for the haloalkane but the several side product as well. Identification of products can be done by manual isolation of products, chromatography or using spectroscopy.

In the study of the following reaction:



P-nitrophenolate ion and P-nitrophenol absorb at different wavelength in the UV (λ_{max} = 400nm and 317nm respectively). On completion of the above reaction, the UV spectrum that was run, showed absorption at 400nm which

Suggest that Path(i) is correct

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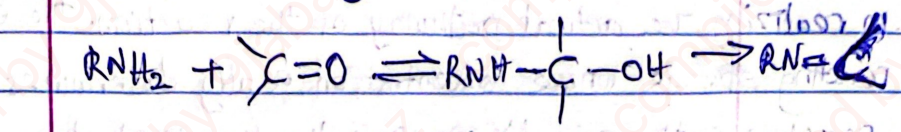
2. Kinetic studies: This provides the most general methods of determining the reaction mechanism. The experimental determination of a rate law for a particular reaction helps in realizing the actual pathway of the reaction. The effective reacting specie whose concentration really determines the reaction rate may differ from the known starting material. A study of the kinetics of the reaction involves measuring the change in concentration of either a product or reactant with time. This can be done either by a chemical or a physical method. The choice of method depends on its convenience and its applicability to the reaction being studied.

Chemical analysis involves direct determination of one of the concentration of reactant or product. e.g using titration. A physical method measures some physical property of the reaction mixture which changes with time. The property being measured must vary in some simple manner with concentration of reactant or product. The following are some of the common methods of studying kinetics of reaction:

(a) Periodic or continual spectra readings: Reactions can be carried out in a cell while it is inside an instrument that takes its readings continously or periodically.

Instrumentation method used for such includes infrared (IR), UV, polarimentary, NMR and ESR.



(b) Pooling and analysing

(b) Quenching and analysing: Aliquots can be withdrawn from a reaction medium at definite intervals and stucked either by temperature drop or by adding an inhibitor. The material is then analyzed using titration, chromatography or spectroscopy

(c) Measurement of changes in volume of solution or total pressure for gas phase reaction

(d) Calorimetric method: Heat gained or lost can be measured at time interval

(e)

(e) Stop flow technique: This is used for fast reaction. A sample is injected into the flow system and the flow is suddenly stopped. The variation of concentration with time is studied by oscilloscopic method

Kinetic data and reaction mechanism: The goal of kinetic study is to establish the relationship between mechanism and the rate law by determining the quantitative correlation between concentration of reactand and catalyst and rate of reaction. Kinetic data provides information only about the rate determing step and stops before it. A useful idea that is often employed in analysis and simplification of kinetic expressions is the steady state approximation. Consider the reaction;

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C$$

$$C + D \xrightarrow{k_2} E + F$$

Overall reaction: $A + B + D \longrightarrow E + F$

Assuming C is a reactive specie whose concentration remains small throughout the reaction (it is consumed as it is being formed). Therefore rate of formation of C = rate of consumption

$$k_1[A][B] = k_{-1}[C] + k_2[C][D]$$

Thus, $[C] = \dfrac{k_1[A][B]}{k_{-1} + k_2[D]}$

$$\text{Rate} = k_2[C][D]$$

$$= \frac{k_2 k_1[A][B][D]}{k_{-1} + k_2[D]}$$

If 1st step is faster,

$$k_1[A][B] >> k_2[C][D]$$

From 1st step,

$$k_1[A][B] = k_{-1}[C]$$

$$\Rightarrow k_{-1}[C] >> k_2[C][D]$$

$$k_{-1} >> k_2[D]$$

$$\text{Rate} = \frac{k_2 k_1 [A][B]}{k_{-1}}$$

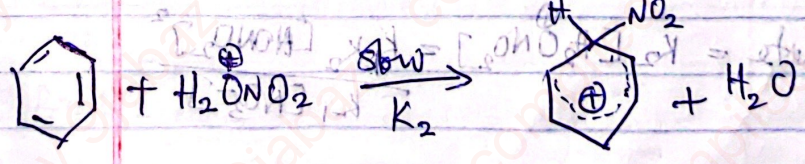
If 1st step is slower,

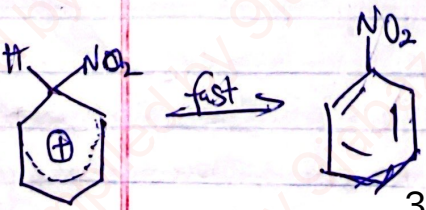
$$k_2[D] >> k_1$$

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

The normal cause of a kinetic investigation involves the postulation of likely mechanism, and comparison of the experimental rate law with what is expected for various possibilities. Consider the following mechanistic possibilities of aromatic nitration by nitric acid in organic solvent:

A.) $2HONO_2 \underset{k_{-1}}{\overset{k_1\ fast}{\rightleftharpoons}} H_2O^{\oplus}NO_2 + NO_3^-$





$$\text{Rate} = k_2 [C_6H_6] [H_2\overset{\oplus}{O}NO_2]$$

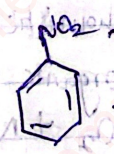
$$[H_2\overset{\oplus}{O}NO_2] = \frac{k_1 [HONO_2]^2}{k_{-1} [NO_3^-]}$$

$$\text{Rate} = \frac{k_2 k_1 [HONO_2]^2 [C_6H_6]}{k_{-1} [NO_3^-]}$$

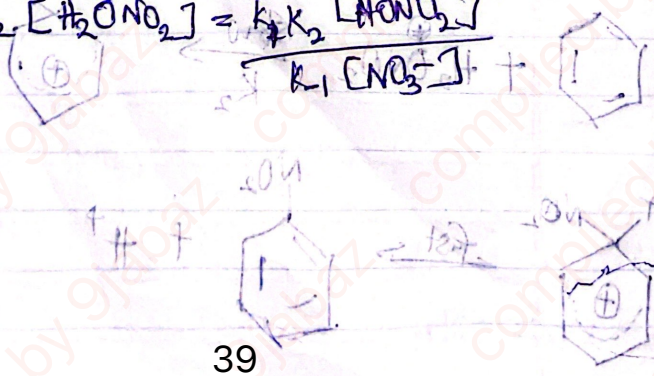
(B.) $2HONO_2 \underset{k_{-1}}{\overset{k_1, \text{fast}}{\rightleftharpoons}} H_2\overset{\oplus}{O}NO_2 + NO_3^-$

$H_2\overset{\oplus}{O}NO_2 \xrightarrow{\text{slow}} H_2O + NO_2^+$

$NO_2^+ +$  $\xrightarrow{\text{fast}}$ 

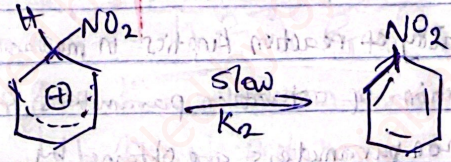
 $\xrightarrow{\text{fast}}$  $+ H^+$

$$\text{Rate}_2 = k_2 [H_2\overset{\oplus}{O}NO_2] = \frac{k_2 k_1 [HONO_2]^2}{k_{-1} [NO_3^-]}$$



(E) $2HONO_2 \underset{K_{-1}}{\overset{\text{fast, } K_1}{\rightleftharpoons}} NO_2^+ + NO_3^- + H_2O$

$NO_2^+ + \text{C}_6\text{H}_6 \underset{K_{-2}}{\overset{\text{fast, } K_2}{\rightleftharpoons}}$ 



$\text{Rate} = K_3[I]$

$K_2 = \dfrac{[I]}{[NO_2^+][C_6H_6]} \Rightarrow [I] = K_2[NO_2^+][C_6H_6]$ (1)

$\text{Rate} = K_2K_3[C_6H_6][NO_2^+]$

$K_1 = \dfrac{[NO_2^+][NO_3^-][H_2O]}{[HONO_2]^2}$ (3)

$\Rightarrow [NO_2^+] = \dfrac{K_1[HONO_2]^2}{[NO_3^-][H_2O]}$ (2)

$\therefore \text{Rate} = \dfrac{K_3K_1K_2[C_6H_6][HONO_2]^2}{[NO_3^-][H_2O]}$

Experimentally, the rate law of nitration of benzene in many organic solvent does not involve a benzene term.

So, mechanism B has to be the correct one

Activation parameters & Reaction Rate

One of the most important utility of reaction kinetics in mechanistic interpretation is in the derivation of activation parameters from kinetic studies. This activation parameters are obtained by applying the transition state theory.

The three basic assumptions of the transition state theory are;

(1) For a reaction to occur, reactants combine and pass through a ~~higher~~ transition state which has higher potential energy than reactants and products

(2) The activation complex although transitory in its existence is in equilibrium with the reactants i.e;

$$A + B \rightleftharpoons C^{\neq} \longrightarrow \text{products}$$

(3) The reaction rate is proportional to the concentration of the activated complex.

From these assumptions, the following rate expression is obtained;

$$K_r = \frac{KT}{h} e^{\frac{\Delta S^{\neq}}{R}} e^{-\frac{\Delta H^{\neq}}{RT}}$$

where K = boltzmann constant
h = planck's constant
$S^{\neq}$ = entropy of activation
$H^{\neq}$ = ethalpy of activation

For a reaction in solution $\Delta H^{\neq} = E_a - RT$.

$$\therefore K_r = \frac{KT}{h} e^{\frac{\Delta S^{\neq}}{R}} e^{-\frac{E_a}{RT}}$$

from Arrhenius equation

$$K_r = A e^{-\frac{E_a}{RT}}$$

$$\Rightarrow A = \frac{KT}{h} e^{\frac{\Delta S^{\neq}}{R}}$$

A (pre-exponential factor)

A negative value of $\Delta S^{\neq}$ corresponds to a small pre exponential factor A. In general, if $\log A > 13$, $\Delta S^{\neq}$ is positive. If $\log A < 13$, $\Delta S^{\neq}$ is negative.

$$\ln \frac{k_r}{T} = \ln \frac{K}{h} + \frac{\Delta S^{\neq}}{R} - \frac{\Delta H^{\neq}}{RT}$$

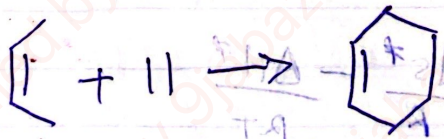
By plotting $\ln \frac{k_r}{T}$ Vs $\frac{1}{T}$, the slope $= -\frac{\Delta H^{\neq}}{R}$ and intercept $= \ln \frac{k}{h} + \frac{\Delta S^{\neq}}{R}$

This relationship shows that contrary to general assumptions, the pre exponential factor A is not strictly independent of temperature

Activation Parameters and Reaction Mechanism

The magnitude of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ reflects the transition state structure. The value of $\Delta S^{\neq}$ is diagnostic of the reaction mechanism. In general, the $-\Delta S^{\neq}$ usually indicates a more ordered transition state than the reactant as shown in bimolecular and concerted unimolecular reaction $A + \Delta S^{\neq}$ indicates a more disordered transition state like a decomposition reaction

$\Delta H^{\neq}$ is generally positive, but its magnitude varies from one reaction type to another. Concerted reactions where bond making accompanies bond breaking usually exhibit low $\Delta H^{\neq}$, while decomposition reactions usually exhibits high $\Delta H^{\neq}$. Thus SN2 has low $\Delta H^{\neq}$, while SN1 have high $\Delta H^{\neq}$



$\Delta H^{\neq} = 15.5$ kcal/mol

$\Delta S^{\neq} = -34$ Cal/mol.D

(gas phase)

$Bu-N=N-Bu \longrightarrow 2Bu^{\cdot} + N_2$

$\Delta H^{\ddagger} = +52$ kcal/mol

$\Delta S^{\ddagger} = +19$ cal/mol·K

For ionic reaction occuring in solution, there tends to be a resultant effect of both solvent and reactant entropy. The orientation of solvent molecule around an ion greatly restricts solvent freedom of motion. When a cation and an anion reacts to produce a neutral molecule, the charges are partially neutralized in the transition state, and this frees some solvent molecule leading to positive $\Delta S^{\ddagger}$

$C_2H_5NO_2^{-} + H^{+} \longrightarrow C_2H_5NO_2$

$\Delta S^{\ddagger} = 15$ e.u

Decomposition leading to formation of ions is assumed to have $+\Delta S^{\ddagger}$. However, due to the polar character of the transition state. A greater degree of ordering of the solvent molecule occurs relative to the ground state and this more than compensates for the intrinsic entropic gain leading to a negative entropy of activation. In general, reactions that generate electrical charge in solution, exhibit negative entropies of activation and those that destroy charge exhibit positive

entropies of activation in polar media

When a pair of anion or cation react accumulation of charge results in a greater increase in solvation leading to a large negative entropy of activation

$$R_2CHOH + OH^- \rightleftharpoons R_2CHO^- + H_2O$$

$$R_2CHO^- + MnO_4^- \rightarrow R_2C{=}O + MnO_4^{2-}$$

$$\Delta S^{\neq} = -2.2 \text{ eu}$$

The negative component of $\Delta S^{\neq}$ for formation of ions in neutral molecule is less for polar solvent than non-polar solvent. In polar solvents we have solvent-solvent ordering in the ground state of neutral molecule and solvent-solute ordering in the transition state

These two effects almost cancel out each other with the result that $\Delta S^{\neq}$ is only slightly negative

However, for non-polar solvents, the solvent-solute ordering is minimal as a result it is the solvent-solute ordering in the transition state which plays a major role.

Consequently, $\Delta S^{\neq}$ is largely negative

Thus formation of ions from neutral molecules is less favourable in non-polar solvent than in polar one. Conversely ion-molecule reactions where charge is being destroyed

in the transition state is more favoured by a less polar solvent than polar ones.

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$$AB \xrightarrow{[A^{\delta+} \cdots B^{\delta-}]} A^{+} + B^{-}$$

$$\Delta S_{r}^{\neq} = \Delta S_{solute}^{\neq} + \Delta S_{solvent}^{\neq}$$

(3) Isotopic labelling: Isotopic labelling is a technique used in chemistry to trap the movement of atoms through a chemical reaction by replacing certain atoms in the reactants with their isotopes. These isotopes maybe radioactive, e.g ^{14}C or stable, e.g ^{13}C, ^{18}O, & D (^{2}H)

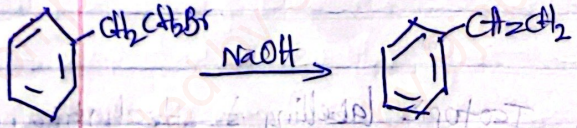
(4) Some kinetic data will often not tell us whether a particular bond in the rate limiting stage of the reaction or not. Consider the alkali permaganate oxidation of; ~~Ph2CHD~~

$$ph_2CHOH \longrightarrow ph_2C{=}O$$

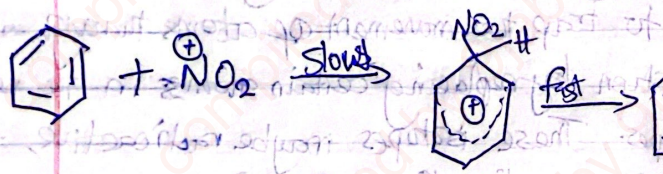
ph_2CHOH is found to be oxidized 6.7 times faster than ph_2CDOH. Such a reaction is said to exhibit primary kinetic isotope effect and the breaking of the C–H bond must occur in the rate determining step.

Kinetic isotope effect is the change of reaction rate from isotopic substitution of an atom in a reacting species of a reaction.

The new bond harder to break and it reactions are correspondingly slower at approximately 7 folds at room temperature.



$\frac{k_H}{k_D} = 7.1$



$\frac{k_H}{k_D} =$

Substitution of one isotope for another does not significantly alter the potential energy surface of a reaction. The differences in rate observed results from changes in the frequency of the vibrational mode of the bond. A C–H bond undergoes a series of characteristics vibration which impact some energy to the molecule known as the zero point energy and this energy is related to the mass of the vibrating atom. On substitution of Deuterium from hydrogen. Due to the higher mass, the vibrational

frequency is lower and therefore the zero point energy is lowered. In the transition state, the vibrational degree of freedom is converted to a translational mode

So, there is no difference between C–H and C–D at the transition state. The activation energy for dissociation of the isotopically labelled molecule will thus be higher than the unlabeled molecule and consequently, the rate of the unlabeled molecule is faster than the labeled one

The factor $\frac{K_H}{K_D}$ is known as the isotope effect for a reaction, and has a theoretical maximum of seven

Primary kinetic isotope effect can provide very useful reaction mechanism information

(1) The existence of a substantial isotope effect $\frac{K_H}{K_D} \geq 2$ is strong evidence that a C–H bond is broken in the rate determining step

(2) The magnitude of the kinetic isotope effect provides a guide on the position of the transition state wrt reactant and product. A relatively low primary kinetic isotope effect implies that the C–H is either almost or completely broken at the transition state

A high primary kinetic isotope effect (close to 7) implies that the transition state involves strong bonding of

the hydrogen to both its new and old bonding pattern.

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(b) Isotopic substitution at a bond that is not directly broken in the R.D.S is referred to as secondary kinetic isotope effect. This effect as expected is smaller than the primary kinetic isotope effect (usually $\frac{K_H}{K_D} = 0.7 - 1.5$)

Such isotope effect are either normal ($\frac{K_H}{K_D} > 1$) or inverse $\frac{K_H}{K_D} < 1$

They are also specified as α or β depending on whether the hydrogen being substituted is directly linked to the carbon atom undergoing rehybridization change (α) or is limited to the carbon atom.

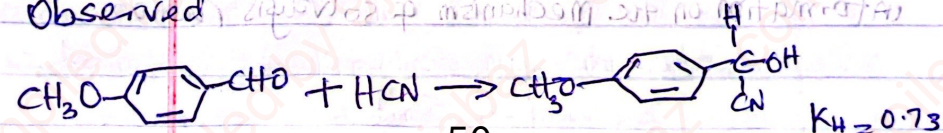
$\alpha - 2^\circ$ kinetic isotope effect arise from changes in the degree of coordination at the carbon atom going from ground state to transition state. If the C–X bond being broken is sp^3 hybridized in the ground state, and

its being converted to sp^2 in the transition state, the neighbouring hydrogen is experienced in decreased existence due to the out of plane C–H bending. The change of the out of plane bending mode will be greater for a C–H bond than for a C–D bond, because its frequency is larger.

The reaction will be faster for the unsubstituted case, a normal secondary kinetic isotope effect is observed, e.g. solvolysis of alkyl halides proceeding via ionization to a carbonium ion $\frac{K_H}{K_D} = 1.30$

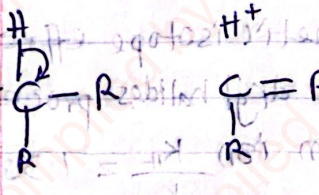
Note: α-2° KIE on direct displacement of substitution nucleophilic bimolecular (S_N2) are small because of the crowding in the transition state which alternates the bending frequency relief.

On the other hand, when hybridization changes from sp^2 to sp^3, the bending mode will experience increased restriction (which is more pronounced for C–H) and an inverse isotope effect will be observed.



$\frac{K_H}{K_D} = 0.73$

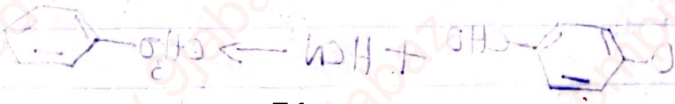
β−2° Kinetic isotope effect arises when the hydrogen being ~~reacting~~ substituted is not directly linked to the reacting side but is next to it. These effect have been studied extensively in nucleophilic substitution reactions and hyperconjugation is said to be responsible. A C−H bond adjacent to a carbonium ion will experience some hyper conjugation which stabilized the carbonium ion



Such hyperconjugation is however less significant for C−D because of the lower polarizability of Deuterium. This leads to the observed β−2° KIE.

Note: β−2° KIE is more significant for SN1 reaction than SN2 reaction. The more the carbonium ion character of the transition state, the more the 2° kinetic isotope effect.

Thus, the magnitude of β−2° KIE provides useful information on the mechanism of solvolysis reaction.



(4) Detection of Intermediate: Most organic reactions proceeds via more than one step. Some of the products of each of this step, either becomes transformed unimolecularly to the final reaction product or reacts with some molecule of another reactant to form the final product. This specie are called reaction intermediate. Evidence of presence of an intermediate comes from the comparison of the stoichometry of the overal reaction and the observed rate law. A concerted reaction must show a correlation between the kinetic order observed in the rate law and the stoichiometry of the balanced equation. If this correlation does not exist, at least one intermediate must be present

Reaction intermediate are molecules, ions or radicals that a sufficiently low in energy to be formed under the reaction conditions but are not sufficiently stable to be protected from further reaction

It is necessary to establish beyond all doubt that any specie isolated is really an intemediate and not really an alternative product. This is done by showing that such intermediate may be converted under normal reaction

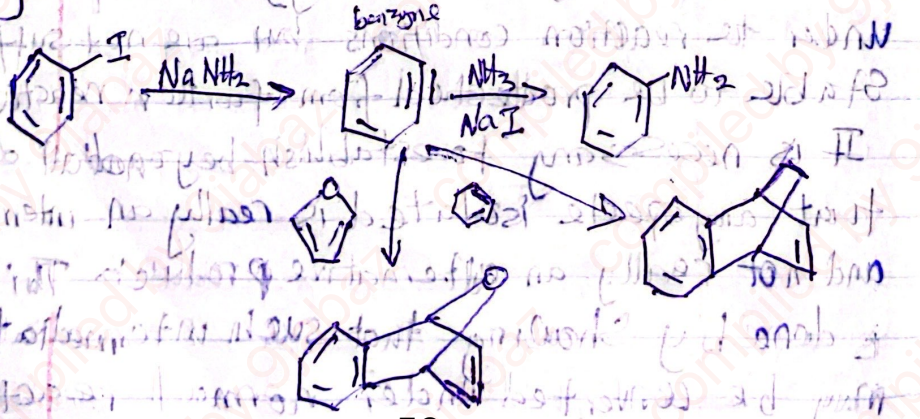
conditions into the usual reaction products at a rate at least as fast as the overall reaction under similar conditions characterization of reaction intermediate should be carried out under these techniques

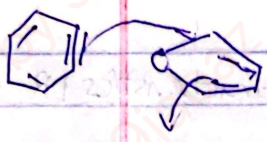
(i) Direct isolation: This is usually done by running the reaction at a lower temperature or otherwise controlled conditions, (e.g removing a catalyst), which could prevent rapid conversion of intemedrate to product. This is usally successful when $k_1 >> k_2$ in the following sequence

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_2} \text{products}$$

(ii) Trapping: This is done by adding a particular compound which reacts with the intermediate. The intermediate is thus diverted from its normal course and a new adduct is formed which can be characterized

e.g

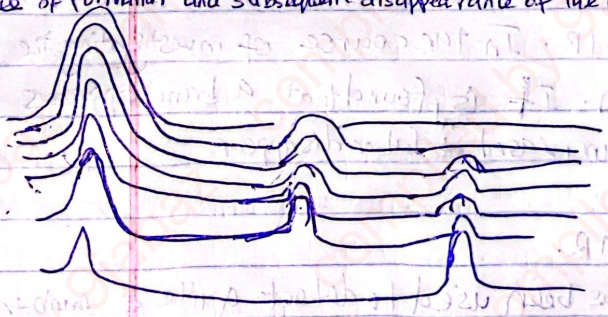




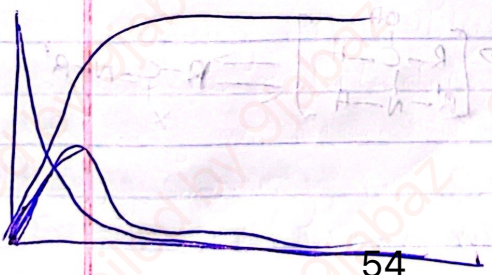
2.1.2.6 Detection

Indirect ~~detection~~ by Spectroscopic Method

(a) UV - Vis. Modern instrument can rapidly scan the UV-vis spectrum and the resulting info may provide definitive evidence of formation and subsequent disappearance of the intermediate species.

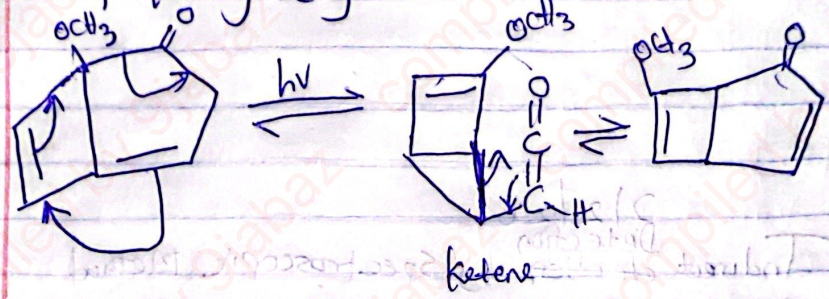


(b)



(b) IR

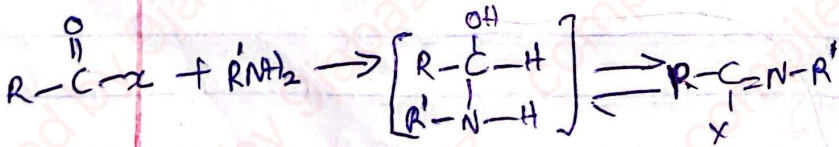
Intermediates can be detected by characteristics IR vibrational frequency e.g



Ketenes have characteristics absorption at 2100 and 2130 cm^{-1} in the IR. In the course of investigating the above reaction. It is found that a band appears at 2118 cm^{-1} and increased, later disappear.

(c) Stop flow NMR.

This method has been used to detect quite a number of intermediate



(d) Electron paramagnetic Resonance (EPR)

free radicals and other intermediate with unpaired electrons can be detected in extremely low concentration by EPR.

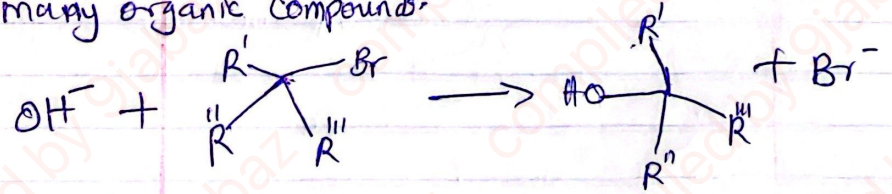
In some cases, concentration of radical specie in $10^{6} - 10^{9}$ m range can be detected

Examples of intermediates includes; carbocation, carbanion, free radicals, carbenes and nitrenes

(5) Stereochemical Evidence

This provides useful information in cases where the products can exist in different ~~isom~~ stereoisomeric form.

Instrumental techniques such as IR and NMR have made it possible to determine the stereochemistry of many organic compounds.



(6) Recent Methods Includes: ~~Computational Chem~~

(a) computational Chemistry

(b) Electrochemistry for electron transfer processes and reactions involving radicals

① Calorimetry

06/02/26

Hammett Relationship

Linear Free Energy Relationships (LFER)

They are a set of empirical relationship used in organic and physical chemistry to understand and predict the reactivity and properties of chemical reaction.

LFER are based on the assumption that there is a linear relationship between some experimental observables such as free energy change associated with a reaction or a process. This relationship provides valuable insight into the underlying mechanisms of chemical reaction

The Hammett equation is the oldest and most develop empirical relationship and many general features can be demonstrated by using it as an example.

The Hammett equation is a linear free energy relationship that studies the effect of subsequent changes on reactions.

The equation is often expressed as

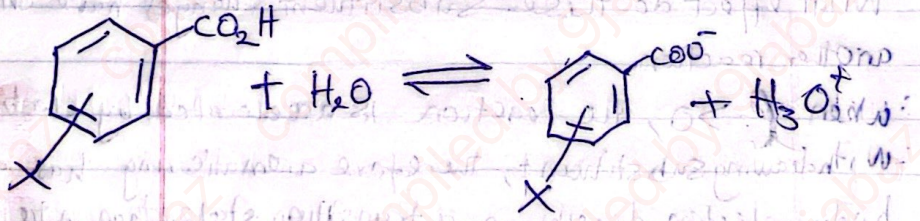
$$\log \frac{K_x}{K_H} = \rho \cdot \sigma$$

where ρ is the reaction constant / K_x & K_H can either be rate or equilibrium constant

σ is the substituent constant

In any linear free energy relationship, one of the first step that needs to be taken is to define the reference reaction.

Hammett chose the dissociation constant for substituted benzoic acid as the model reaction.



Hammett decided that hydrogen will be the reference substituent and he defined that when X = H, that $\sigma = 0$

The σ value for other substituent is thus determined by measuring the rate of benzoic acid dissociation with that substituent relative to when X = H

$$\sigma = \log\left(\frac{K_x}{K_H}\right) \quad \text{when } \rho \text{ is } 1$$

$\sigma > 0$ whenever substituents are more electron withdrawing

than hydrogen, because with electron withdrawing group, the rate of benzoic acid dissociation is faster.

$\sigma < 0$ whenever substituents are more electron donating than hydrogen, because with electron donating group, the rate of benzoic acid dissociation is slower

Due to steric effect, ortho substitution is not generally considered

The question with a linear free energy relationship is what effect do these substituent changes have on another reaction.

when $\rho > 0$, the reaction is accelerated by electron withdrawing substituent, therefore aromatic ring has a higher electron density in a transition state than in the starting material

When $\rho < 0$, the reaction is accelerated by electron donating substituent, therefore aromatic ring has lower electron density in the transition state than in the starting material

It is thus possible to predict the type of charge in transition state vs the starting material (either more or less negative by the sign of ρ)

The magnitude of charge is determined by the magnitude of ρ. If ρ is larger than +1, the reaction under consideration has a greater amount of electron density in the transition state than starting material relative to ~~transition~~ reference reaction

ρ describes the sensitivity of new reaction to substituent effect relative to the influence of substituent on the ionization of benzoic acid

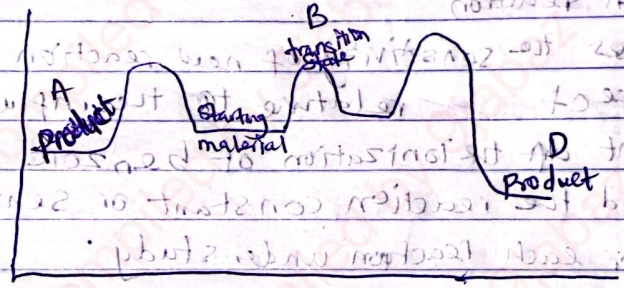
It is called the reaction constant or sensitivity constant for each reaction under study.

Test solution

(1a) (i) The proton transfer occurs the rate determining step eqn i is specific acid catalysis

(ii) The proton transfer occurs during the rate determining step eqn ii. is general acid catalysis

(b)



A is less stable, ~~it~~ is formed ~~faster~~ faster, it is ~~kinetically~~ Controlled product

D is more stable and it is thermodynamically controlled product

(2a) ~~For~~ solvation to really have an effect

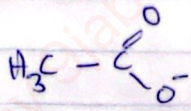
In the gas phase, there is no solvation between the molecules, therefore can be seperation of charges, but no solvation, because of the absence of water. both charges are only resonance stabilized

Therefore, there is no difference in the pKa values.

In aqueous phase, there is presence of water which will add acidity, therefore we not only considering resonance

stabilization, but also solvating effect.

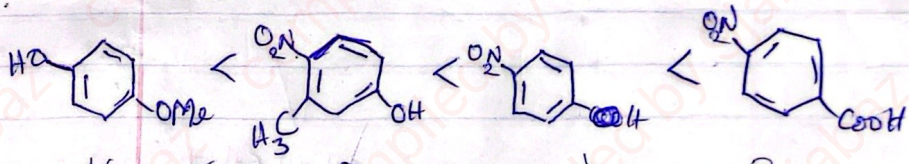
phenoxide



acetate

Solvating effect is a result of hydrogen bond, Acetate has two donor atoms for hydrogen bonding and phenoxide has just one therefore acetate is more solvated and therefore acetic acid is more acidic and has a lower pKa than phenol in the aqueous phase

(b)



4 < 2 < 1 < 3

Option 4 only has an electron donating group at the para position, it is the least stabilized, while option 2 has some amount of electron withdrawing effect, but the presence of $-CH_3$ (electron donating atom) makes it less stabilized than option 1.

Ethyl vinyl ether is hydrolysed in dilute acid according to the following equation.

$CH_3CH_2OCH = CH_2 + H_2O \longrightarrow CH_3CH_2OH + CH_3CHO$.

Given that; (i) The reaction is subject to general acid catalysis

(ii) The reaction is faster in water than in D_2O by a factor of 2.93

(iii) The ethanol obtained by hydrolysis in isotopically labelled water contains no ^{18}O.

With reasons suggest a mechanism for the hydrolysis which is consistent with these observation

State clearly which step is rate limiting

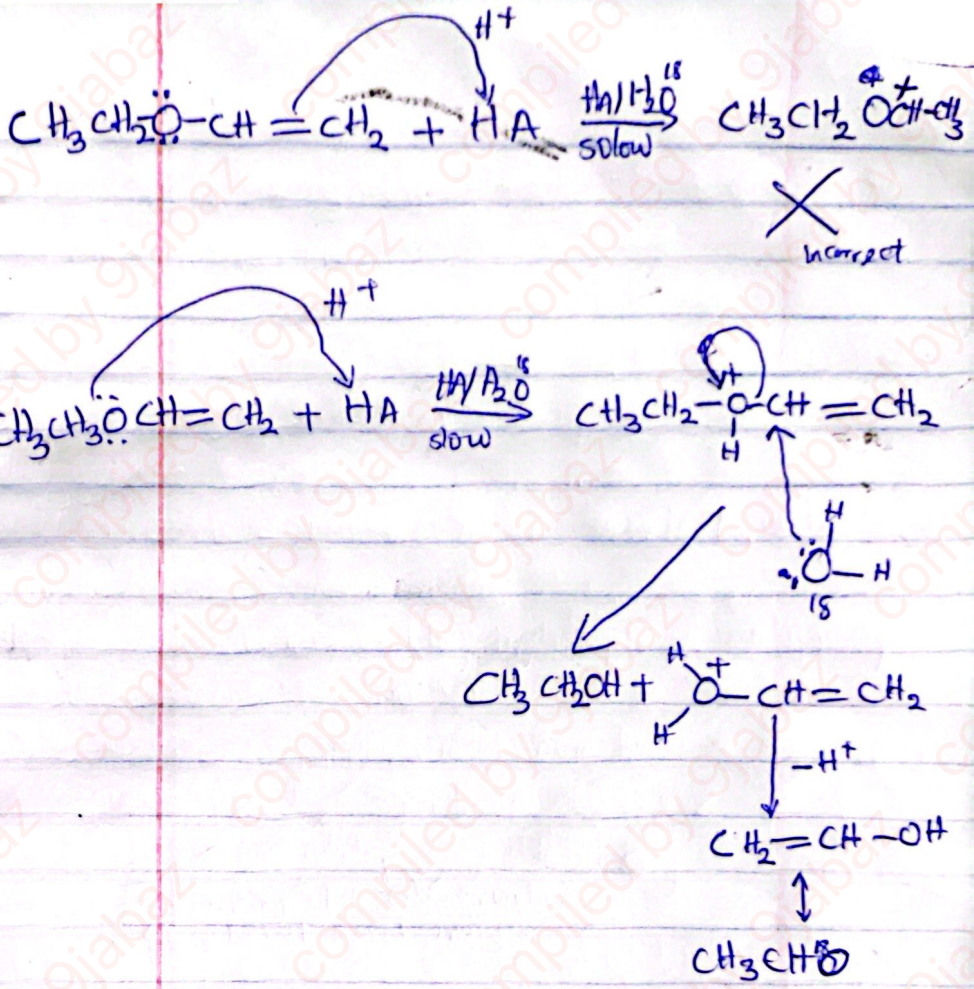
Explaining the observations

It is a general acid analysis

(i) The proton transfer occurs in the rate determining step of the reaction. The water will end up giving us H^+

(ii) $\frac{K_H}{K_D} = 2.93$, which means it is primary kinetic isotope effect, the C–H bond is broken in the rate determining step, hydrogen is lost in the rate determing step.

(iii) The water is attacking the C=C, not the ethanol side, the ^{18}O will be on the aldehyde side


H+
HA/H2O18
slow
incorrect
H+
HA/H2O18
slow
-H+

Dr Fadare's Part

Wade - 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

$Nuc^- + R-X \longrightarrow R-Nuc + X^-$

Nuc⁻ — nucleophile; R–X — substrate; R–Nuc — Product; X⁻ — Leaving group

Types of mechanism

(i) First order kinetics – Unimolecular reaction
(ii) Second order kinetics – bimolecular reaction

2nd order and bimolecular

Substitution Nucleophilic Bimolecular (SN2)

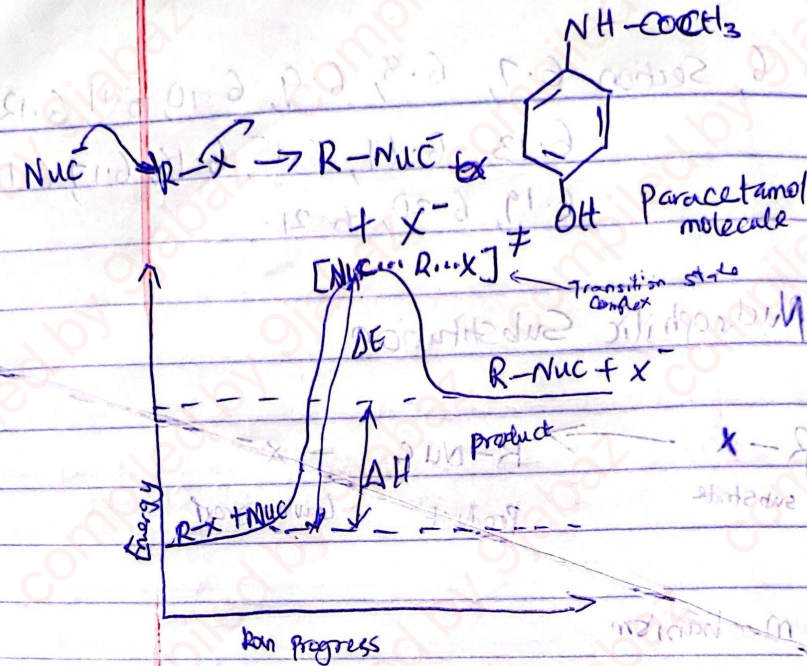
$R-X + Nuc \rightarrow R-Nuc + X^-$

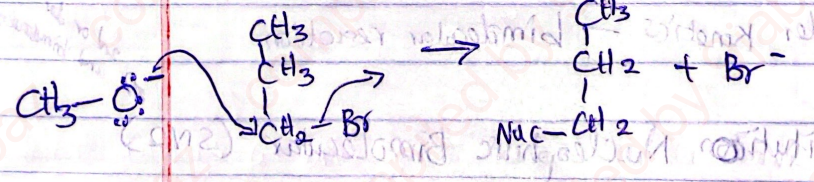
Rate law

Rate = $k[Nuc][R-X]$ 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.





P31/Q0/25

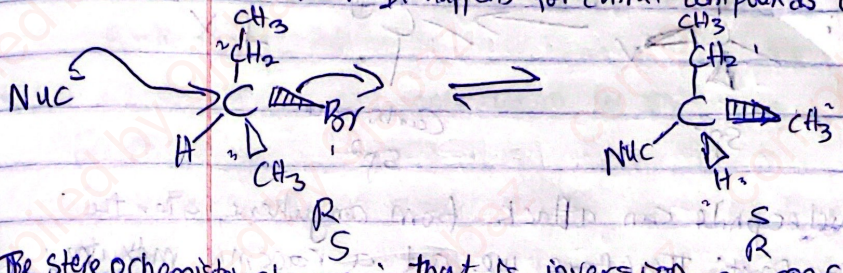
how to confirm SN2

(1) Kinetic evidence: rate of rxn is dependent on both nuc and ele

(2) Stereochemical evidence

(3) ~~What happens at bridge e.g.~~ 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

6/11/25

* What happens at bridge head carbon under SN2 conditions? If substrate has a leaving group at a bridge head carbon **

SN1 :

Steps;

Step1; formation of carbocation

$R-X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+ + X^-$ (slow step)

Step2; Nucleophilic attack

$R^+ + Nuc^- \xrightarrow{k_2} R-Nuc$

Kinetics

For SN1; Rate $= k[RX]$

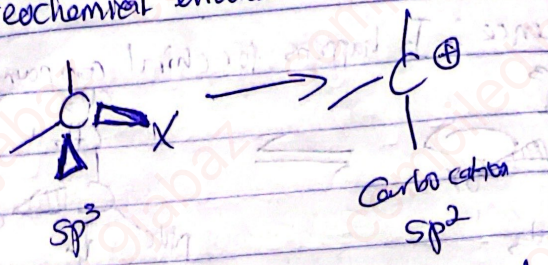
(1) The rate of reaction depends solely on the concentration of the substrate. It is first order and unimolecular

(2) Stereochemical evidence

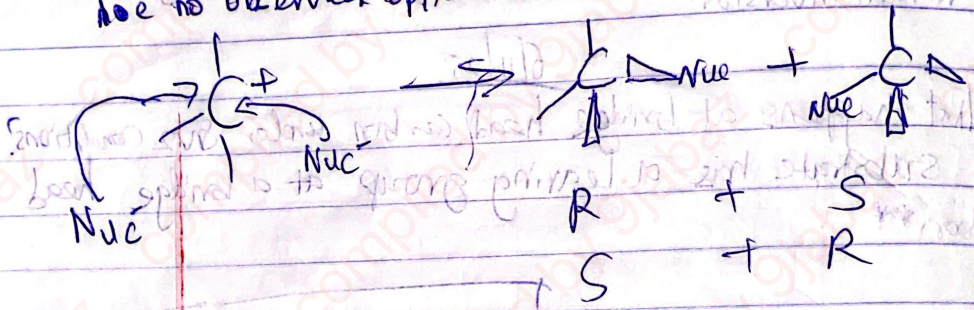
* Using these elementary step; derive the rate law.

(2) Stereochemical evidance

Step 1:



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



What happens at bridge head carbon under SN2 conditions

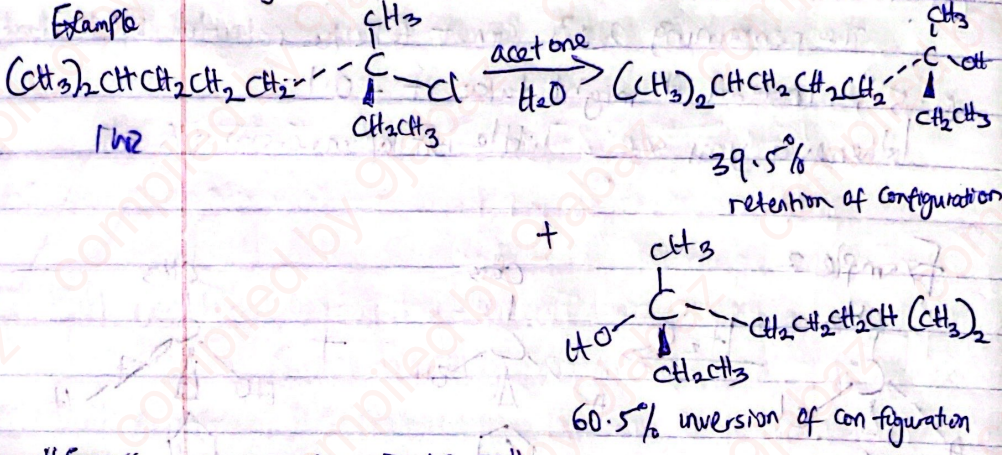
A bridge head carbon is the carbon at the point where two rings are fused together in a bicyclic compound. Therefore in an SN2 condition the backside attack is sterically and geometrically impossible due to the rigid bicyclic structure, preventing the required inversion of configuration.

stereochemical observation for SN1 = racemization

$R-X + Nuc \xrightarrow{SN1}$

But we don't always see racemization for SN1

Example



"Excess of inversion" → in SN1

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

$+0.5^\circ \xrightarrow{SN2} -0.5^\circ$

$+0.5^\circ \xrightarrow{SN1} 0^\circ$ (expected)

Bcs we will have 50% and 50%

$+0.5^\circ \quad -0.5^\circ$

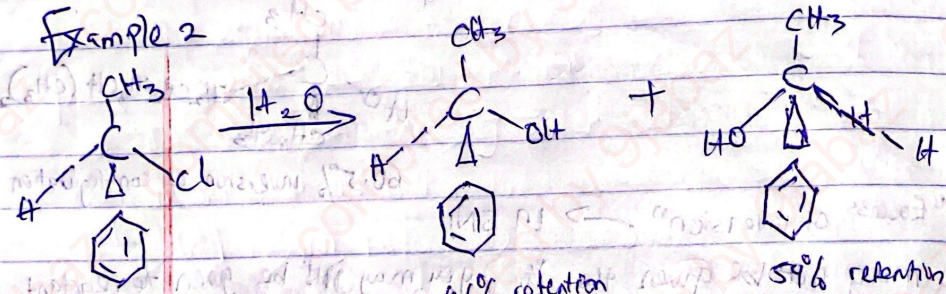
But what is most observed is;

$+0.5^\circ \xrightarrow{SN1}$ 40% $+0.5^\circ$ 60% -0.5°

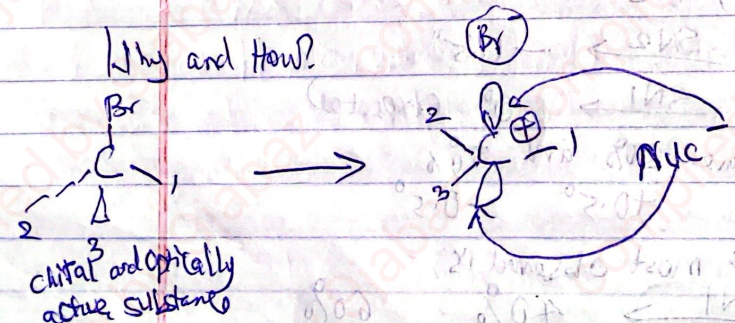
This means ~~the $+0.5^\circ$ and -0.5°~~ 40% of the molecule will go $+0.5^\circ$ and 60% of the molecule will go -0.5°, which means the 40% will cancel

some of the 60% rotation, remaining 20% which will figure in optical activity. But optical activity is a function of concentration
Concentration $\propto$ to the observed rotation
∴ The remaining 20% cannot take the rotation up to that -0.5°, instead it might take it -0.1
Whenever you see a little bit of inversion it is SN1

Example 2



Why and How?

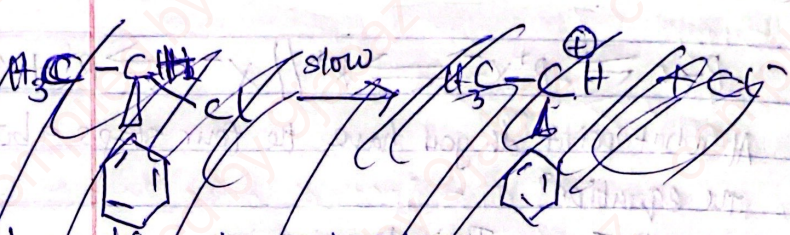


Because Br^- is still hanging around, there is repulsion between Br^- and Nuc - which makes inversion slightly more than retention.
When we don't get complete racemization, you get slight

excess of inversion

6 Quiz

Consider the role of solvent on the stereochemistry of the SN1 reaction (hydrolysis of 1-chloro-1-phenyl ethane)



In SN1 reaction, the carbocation

Ans

In SN1 reaction, the carbocation intermediate 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 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 the same (perfectly equal) leading to partial racemization, often with a small excess of inversion.

Concept of ID

(i) Internal return

(ii) Intimate ion pair

(iii) solvent seperated ion pair

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

$$R\text{-}X \rightleftharpoons R^+X^- \rightleftharpoons R^+ // X^- \rightleftharpoons R^+ + X^-$$

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

$R\text{-}X \longrightarrow R^+X^-$ — Intimate ion pair

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

$R^+X^- \rightleftharpoons R^+ // X^-$ — Solvent-separated ion pair.

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

$R^+ // X^- \rightleftharpoons R^+ + X^-$ — fully dissociated (solvated) ions

Ions are fully separated and each is solvated by many solvent molecules

Factors that Affect Rate of SN2 Reaction

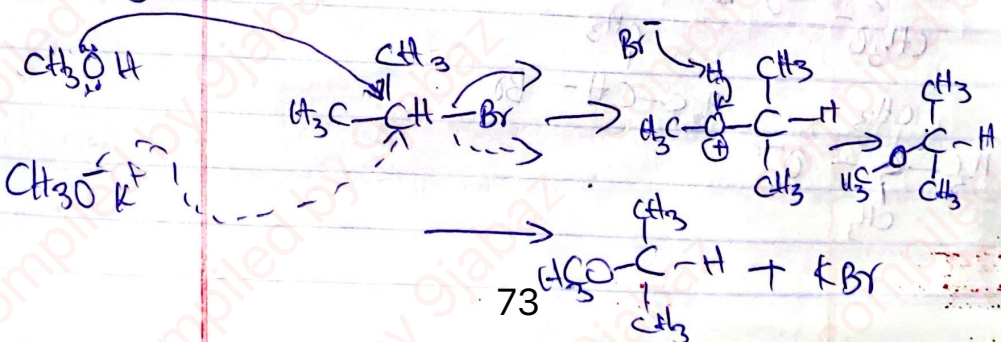
1. Substrate type
2. Effect of nucleophile
3. Effect of solvent
4. Leaving group type

1) **Substrate type:** In SN2, the nucleophile attacks from the back, but when the back side is crowded, the nucleophile will be sterically hindered. In a ~~methyl~~ substrate we could have methyl, 3°, 2°, 1°. In a 3° substrate S_N2 cannot occur due to steric hinderance. 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 is faster than the methyl substrate. Why? Test question.

2) **Effect of Nucleophile:** When we have a negative charged nucleophile it make the reaction ~~faster~~

E.g



Trend in Nucleophilicity

(1) A negatively charge nucleophile is better than a neutral nucleophile e.g HO^- / H_2O

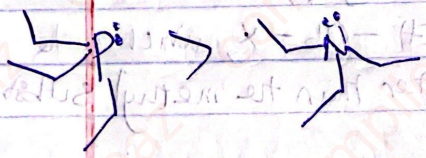
(2) Nucleophilicity decreases from left to right in the periodic table following the increase in electronegativity from left to right

$NH_2^- > OH^- > F^-$

$NH_3 > H_2O$

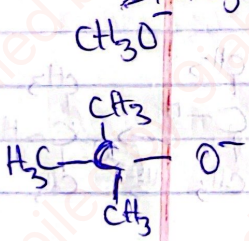
(3) The nucleophilicity also decreases down the group due to increase in size and polarizability

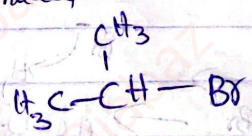
$I^- > Br^- > Cl^- > F^-$



(4) Steric Hinderance: When the nucleophile is getting bigger or bulky it slows down the nucleophilicity

Stronger nucleophile





Effect of Solvent on Nucleophile

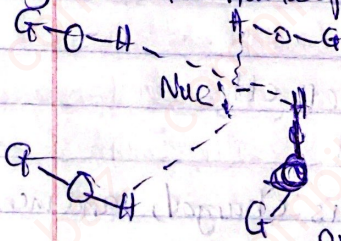
(I) Protic solvents (→ Polar): $-SH$, $-OH$, $-NH$

(II) Aprotic solvents; (→ non-polar): CH_3-O-CH_3, $CH_3CH_2-O-CH_2CH_3$, $CHCl_3$, CH_2Cl_2, THF

(III) Polar Aprotic solvents; eg, DMF (dimethylformamide $\left(H-\underset{}{\overset{O}{\overset{\|}{C}}}-N(CH_3)_2\right)$, Acetonitrile ($CH_3-C\equiv N$), DMSO, Acetone

Solvent can affect SN2 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 no really react, and the reaction becomes very slow especially when the nucleophile is negatively charged



In aprotic solvent 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:

$(CH_3-CH_2)_3N:$ + $CH_3-\underset{CH_3}{\underset{|}{CH_2}}-I$ → $\left[(CH_2CH_3)_3\overset{\delta+}{N}\cdots\underset{CH_3}{\underset{|}{CH_2}}\cdots\overset{\delta-}{I}\right]^{\neq}$ → 

neutral reactant

transition state

partially charged activated complex

$(CH_3CH_2)_3\overset{(+)}{N}-CH_2CH_3$

Charged product

The reactants are neutral and not charged, moving to a charged transition state will be favoured by ~~lowering~~ increasing the polarity of the solvent

$$(CH_3CH_2)_2\ddot{N}:^{\ominus} + \underset{CH_3}{\overset{|}{CH_2}}-I \longrightarrow \left[(CH_3CH_2)_2\overset{\delta-}{N}---\underset{CH_3}{\overset{|}{\overset{\delta+}{CH_2}}}---\overset{\delta-}{I}\right]^{\neq}$$

Charged

$$\longrightarrow (CH_3CH_2)_2N-CH_2CH_3$$

Neutral

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 serves two purposes in SN2

(i) Leaving group polarizes the $-\overset{\delta+}{C}-\overset{\delta-}{X}$ (withdraws electron more)

A leaving group that strongly polarizes the $-\overset{|}{C}-X$ makes the substrate carbon more partial positive and makes it more electrophilic and susceptible to nucleophilic attack

(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 serves two purposes in SN2

(i) Leaving group polarizes the $-\overset{|}{C}-X$ ($\delta+$ on C, $\delta-$ on X; withdraws 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 attack

(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

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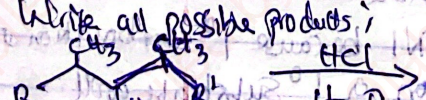
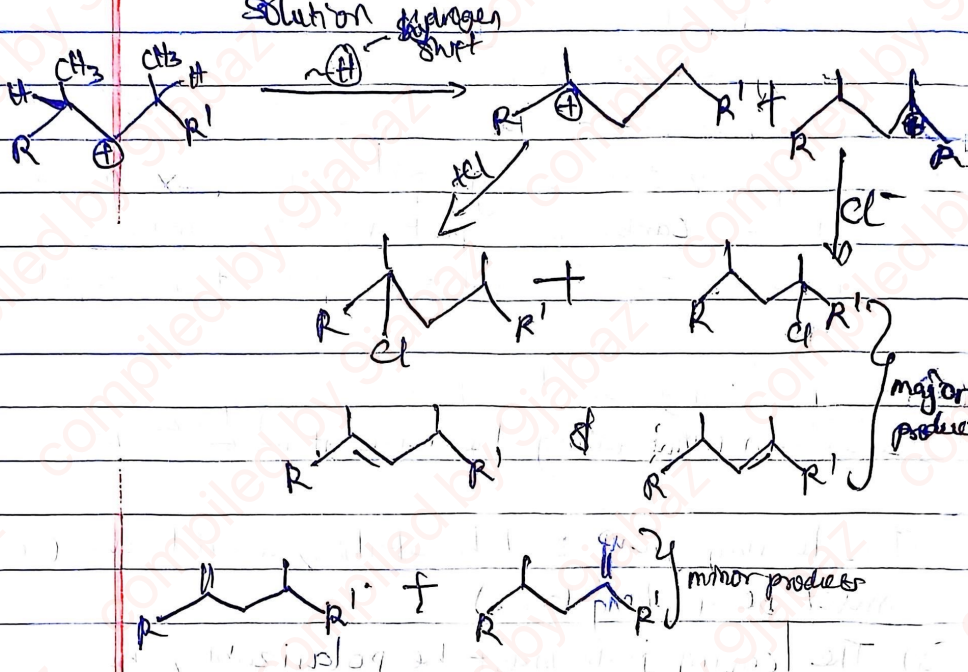
for a strong nucleophile: Nucleophilic attack will occur faster than the carbocation can form. Because of a strong nucleophile. It undergoes SN2 but if it is a weak nucleophile, Carbocation will be formed

Write all possible products;





Factors that affect the rate of SN1 reaction

(1) Substrate type
(2) Leaving group
(3) Solvent effect

(1) Substrate type: $3^0 > 2^0 > 1^0$

3^0 substrate, the kinetics will be SN1 and will be fast

2^0 substrate for SN1 is possible, but not as 3^0 substrate

1^0 substrate do not undergo SN1 because 1^0 carbocations not stable. The only condition a 1^0 substrate will

undergo is rearrangement.

Carbocation determines the rate in SN1. 3° carbocation is formed faster

Stability of carbocation drives SN1 reaction

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

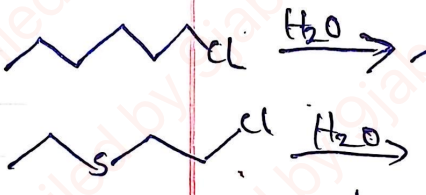
(2) Effect of the leaving group: same as that of SN2

(3) Solvent effect

Consideration for solvent in SN1 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

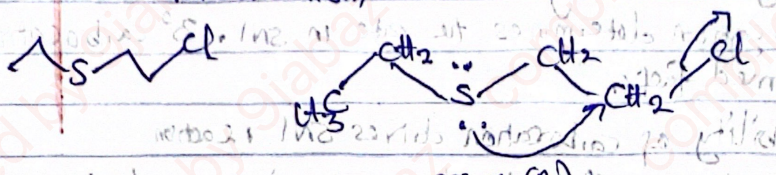
INTRAMOLECULAR REACTIONS & NEIGHBOURING GROUP PARTICIPATION



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

What is neighbouring group participation?

Mechanism



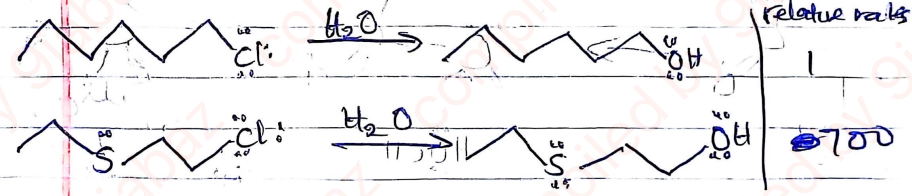
The lone pair on sulphur makes it behave like a nucleophile. The leaving of leaving group is being assisted which is called Anchimeric assistance.

Video

Intramolecular Reactions and Neighboring Group Participation

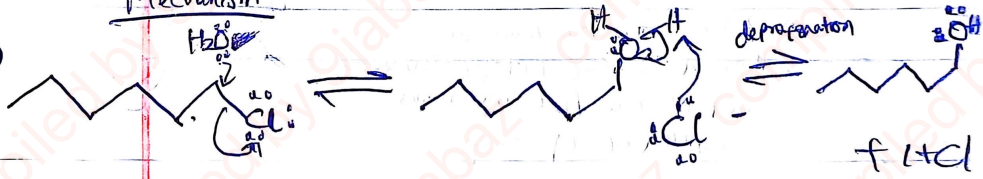
A neighbouring group effect is the role that neighbouring groups (other functional groups on the substrate) play in the reactions that the substrate undergoes.

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



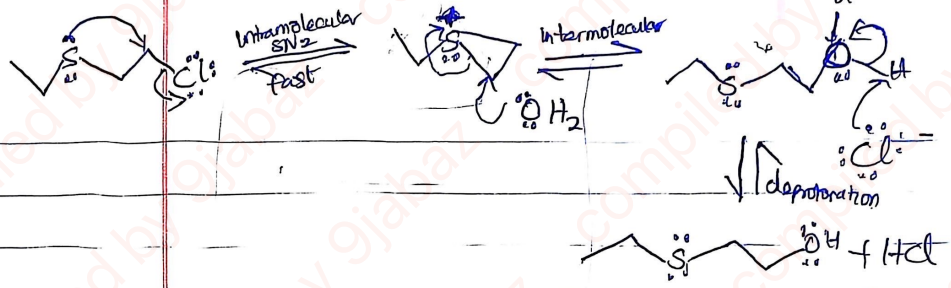
Mechanism

(1)



f (+Cl

(vi)



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

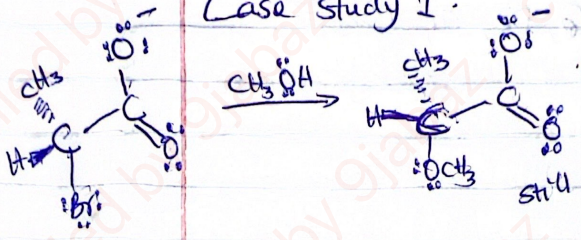
If there is a neighbouring group effect in operation; we have to watch out for three things;

(i) An usual stereochemical result, usually retention of configuration where inversion is expected

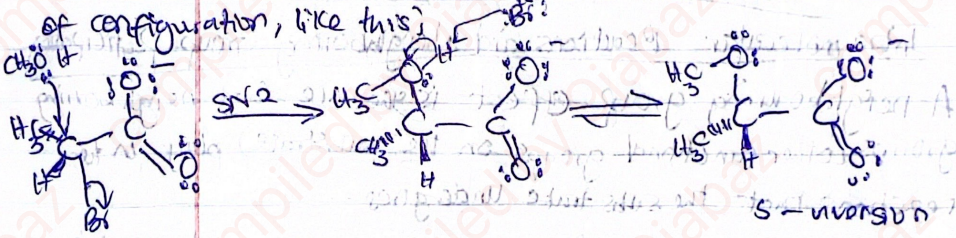
(ii) A strange rearrangement, often involving a labeled molecule

(iii) An unexpected fast rate

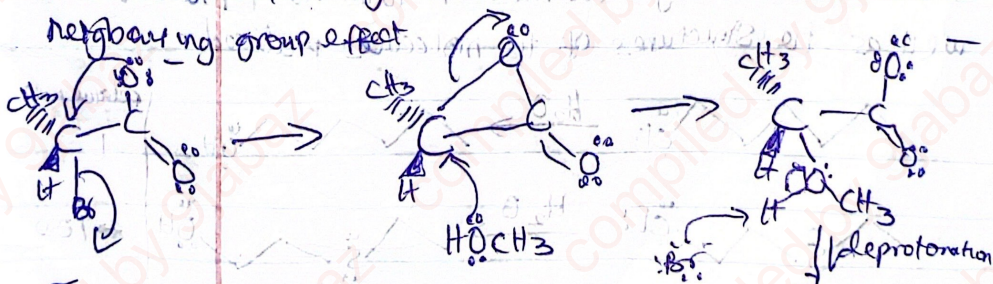
Case Study 1.

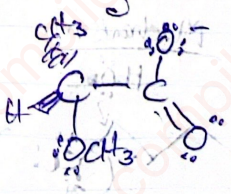


The expected stereochemistry of the product should be an inversion of configuration, like this;



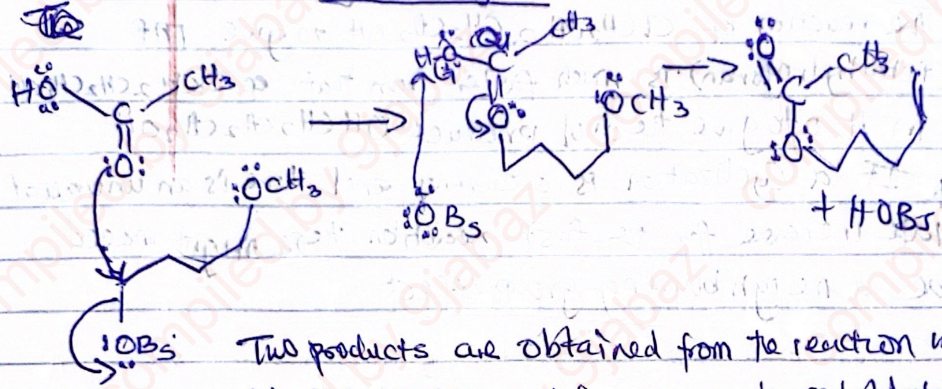
The observation of strange stereochemical result is due to the neighbouring group effect



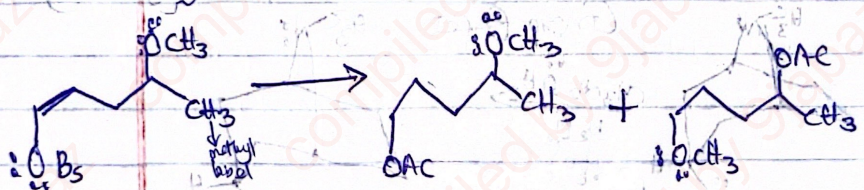


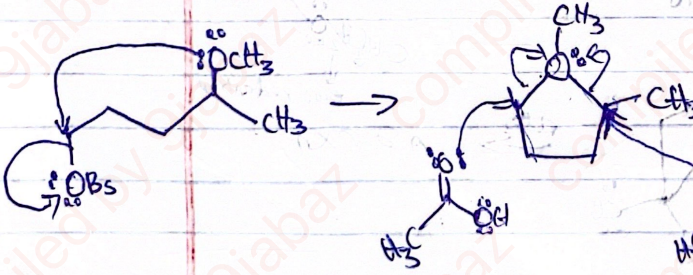
There is an inversion of configuration in the first step (SN2) and another inversion of configuration in the second step (also SN2) So the combination of the two inversions is equivalent to retention of of configuration

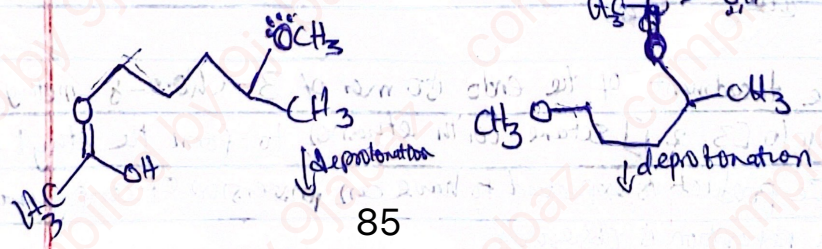
Case study 2



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





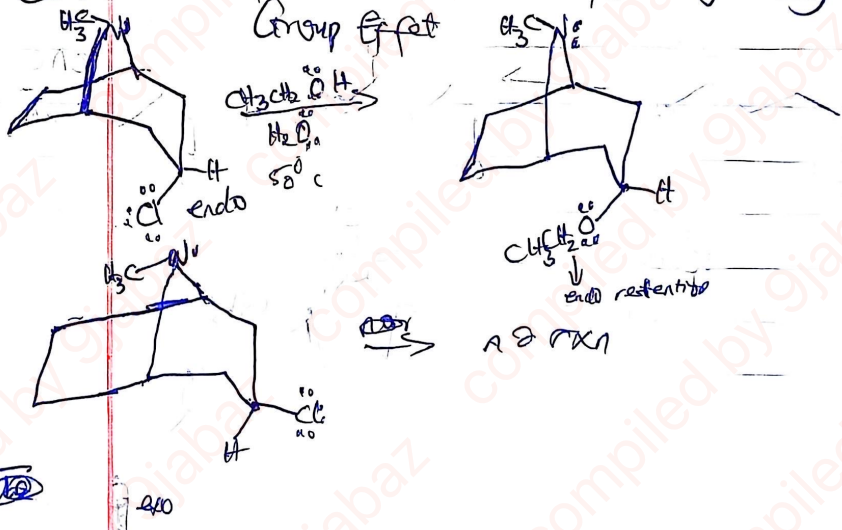


Case Study 3

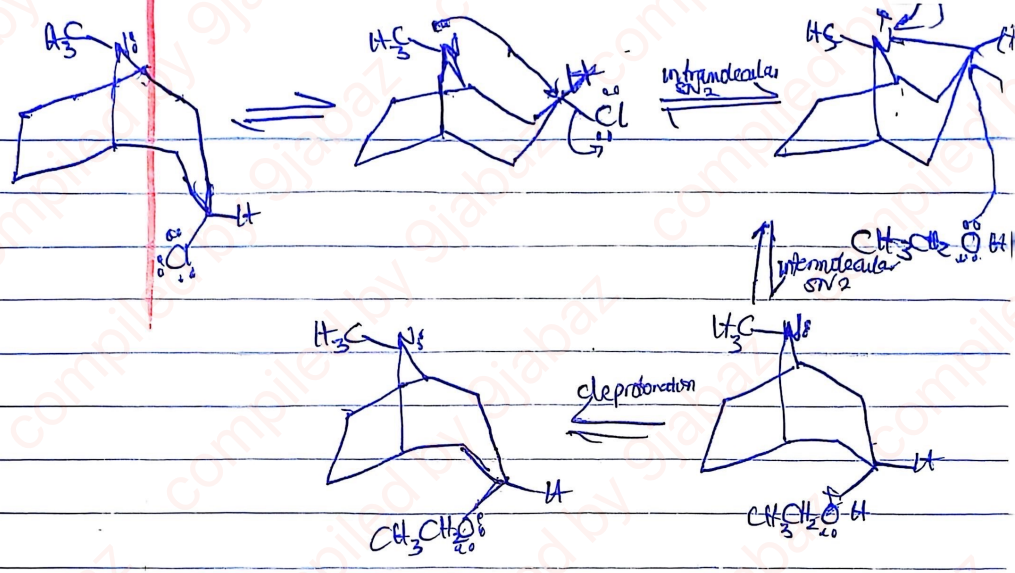
The reaction of $ClCH_2CH_2CH_2CH_2OH$ to give THF (tetrahydrofuran) is much faster than that of $ClCH_2CH_2CH_2OH$ in H_2O to give the diol product $OHCH_2CH_2CH_2OH$

If a cyclization is occurring and there is an unusual rate increase for the first reaction there might indeed be a neighbouring group effect.

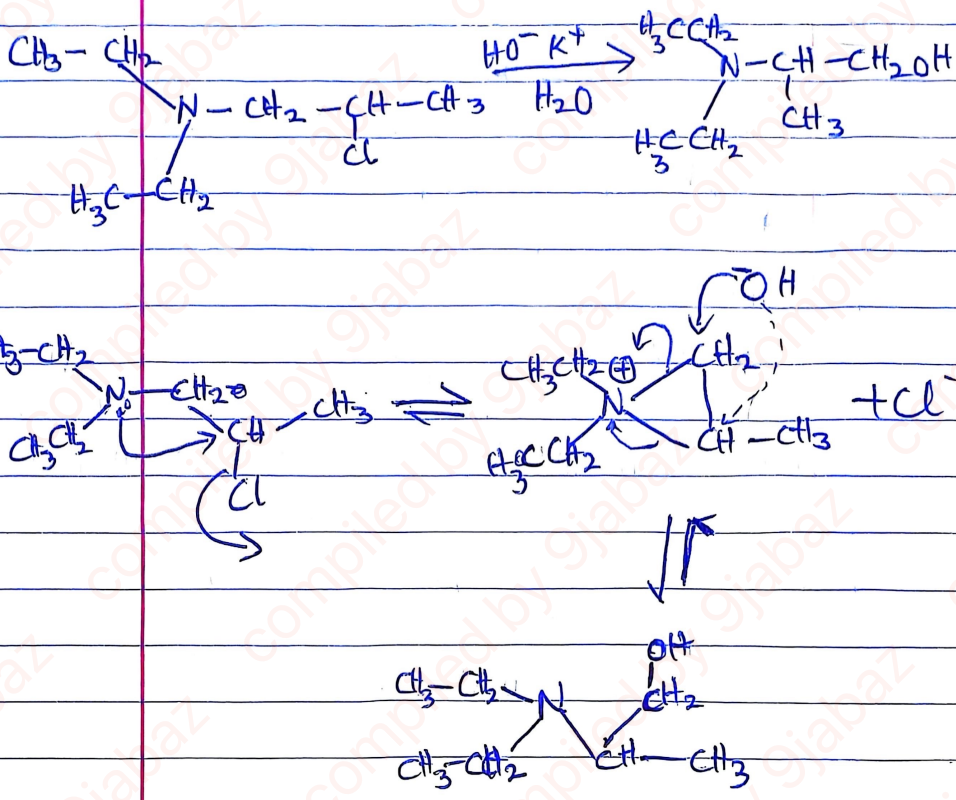
Consideration of Other Heteroatoms for Neighbouring Group Effect



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


intramolecular SN2
intermolecular SN2
deprotonation

4/12/25



Substitution Nucleophilic Internal (SNi)

In a few reactions, nucleophilic substitution proceeds with retention of configuration even where there is no possibility of a neighbouring group effect. In the SNi mechanism (substitution nucleophilic internal) part of the leaving group must be able to attack the 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 SN1 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

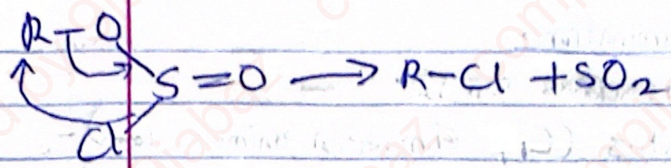
Illustration

$$R-OH + SOCl_2 \longrightarrow RCl + SO_2 + HCl$$

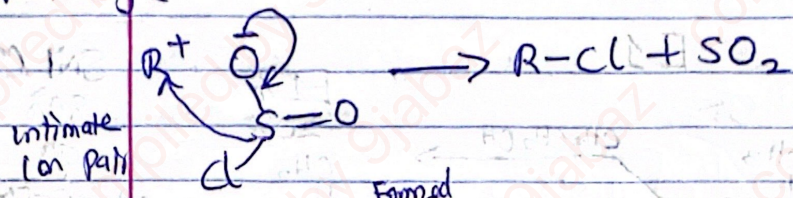
R-OH and $SOCl_2$ combines to form a stable, isolable intermediate $[R-O-SO-Cl]$

$$+ ROH \longrightarrow R-O-\overset{\overset{O}{\|}}{S}-Cl + HCl$$

Possibility 1

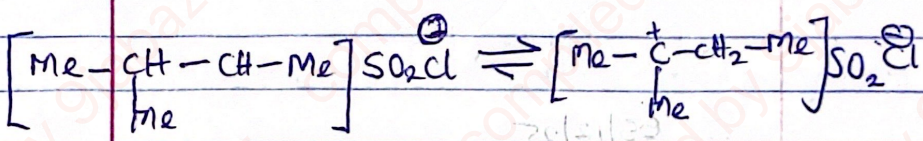


Possibility 2



* When the product formed 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

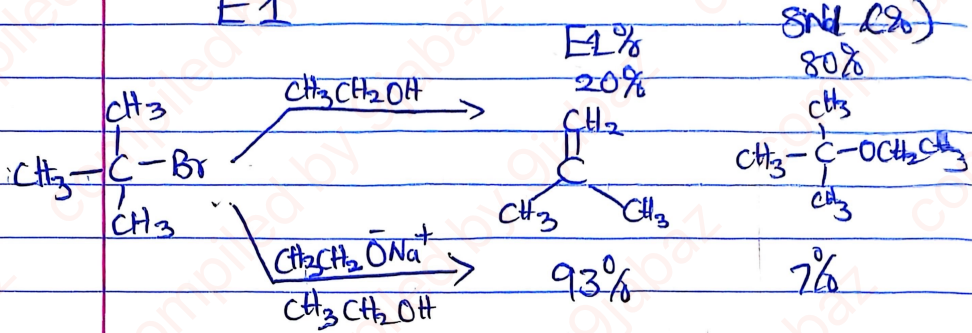


The SNi mechanism is relatively rare; another example of it is the decomposition of ROCOCl (alkylchloroformate into RCl + CO_2

Eliminations

Elimination reactions can be;
First order kinetics (E_1, elimination unimolecular)
Second order kinetics (E_2, elimination bimolecular)

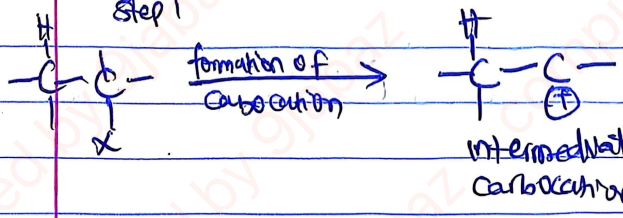
E1



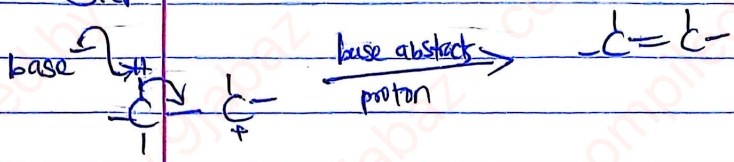
For first order kinetics, we always have competition b/w E1 vs SN1

05/12/25

E1



Step 2



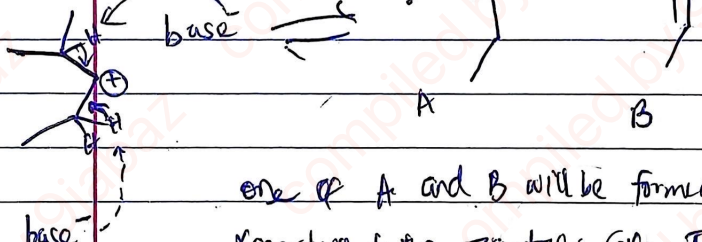
Reactivity of substrate in E1

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

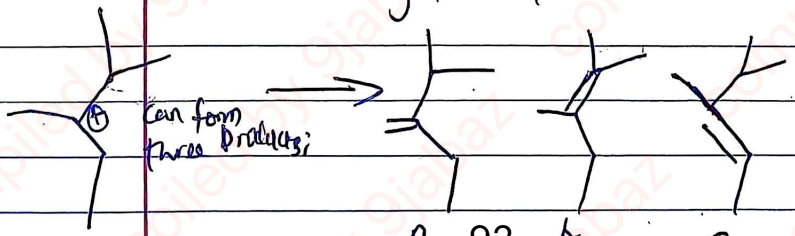
$3^{0} > 2^{0} > 1^{0}$

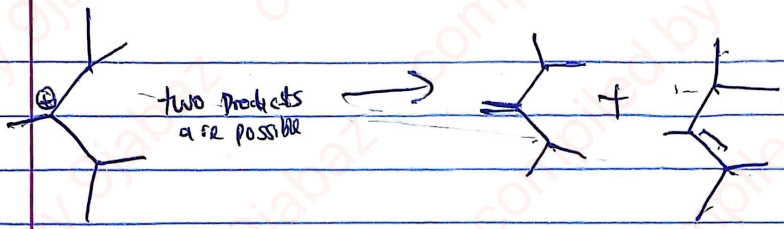
decreasing order of reactivity

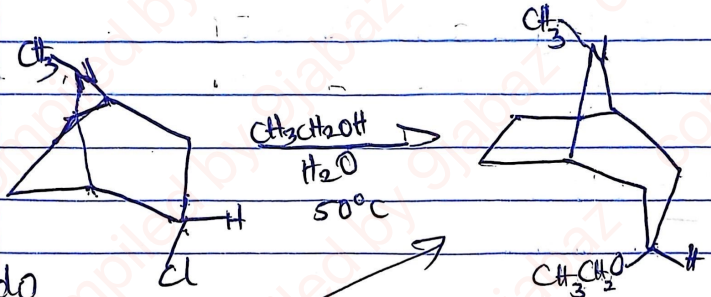
Selectivity

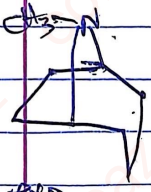


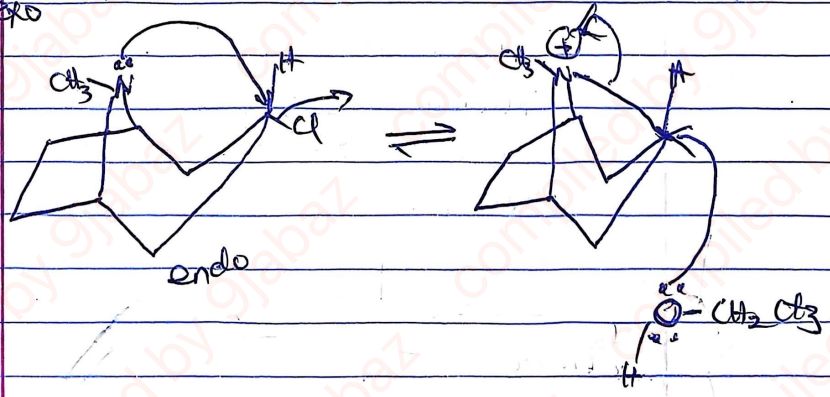
one of A and B will be formed preferentially according to the Zaytzev rule. The more substituted alkene is more stable and has a greater tendency to be formed

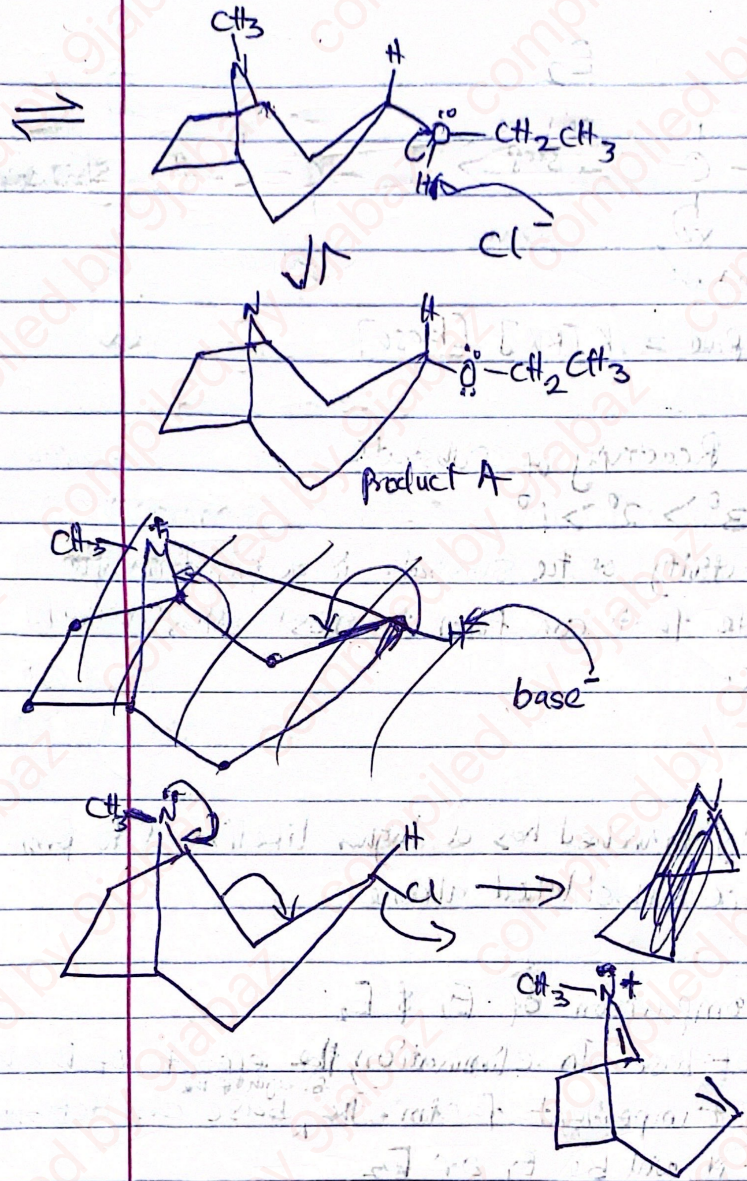


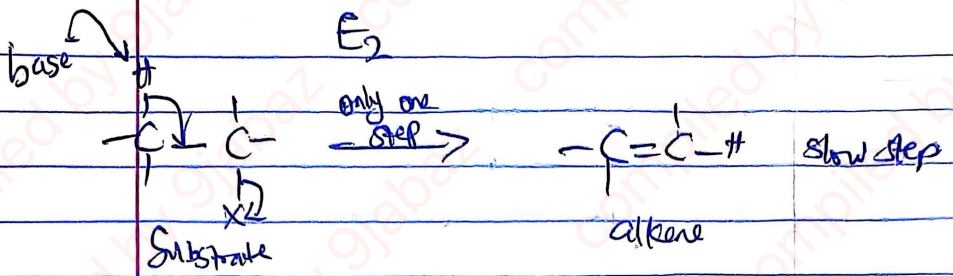

two products
are possible


CH_3CH_2OH
H_2O
50°C
endo
no reaction


exo


endo


CH3
H
CH2CH3
Cl⁻
Product A
base⁻
minor product



Rate = K [RX] [base]

Reactivity of substrate

$3^0 > 2^0 > 1^0$

The reactivity of the substrate is a function the substrate that can form the most substituted alkene.

A highly branched has a higher likelihood to form a more substituted alkene.

Comparison of E_1 & E_2

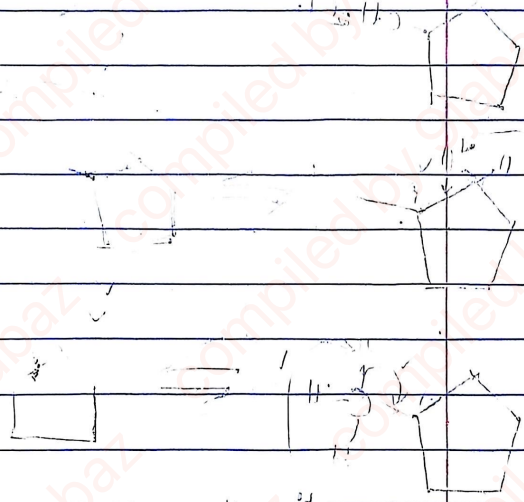
1) Effect of base: In elimination, the effect of the base is the most important factor. The strength of the base can determine whether it will be E_1 or E_2

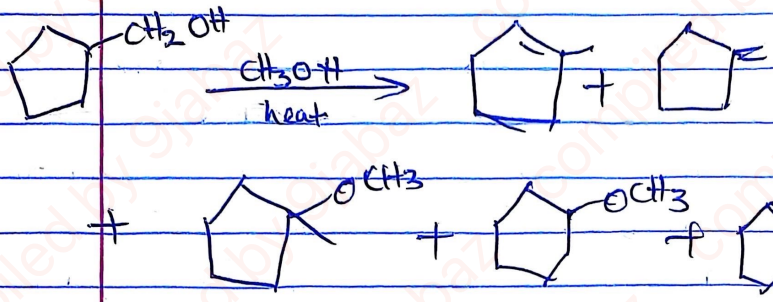
If a strong base is present, the E_2 mechanism will be preferred, but if a weak base is present,

It will likely be via E_1 m
A strong base will attack the ~~Substrate and attack~~ proton before the substrate forms a carboncation But a weak base will allow the substrate to form a carbocation before it abstract 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) Kinetic
(iv) Stereochemistry
(v) Rearrangement

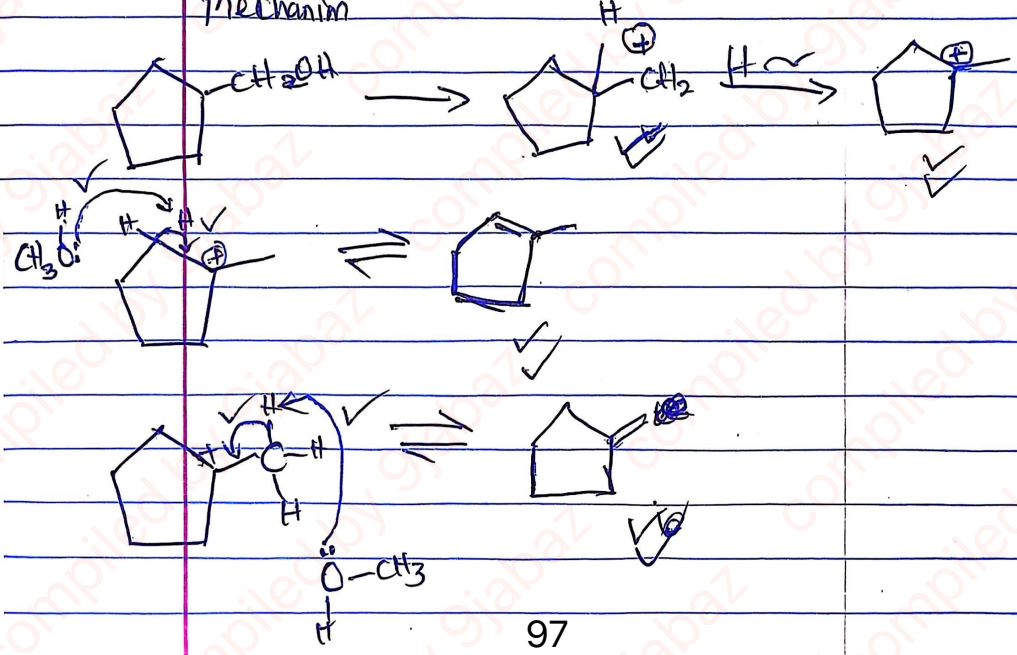


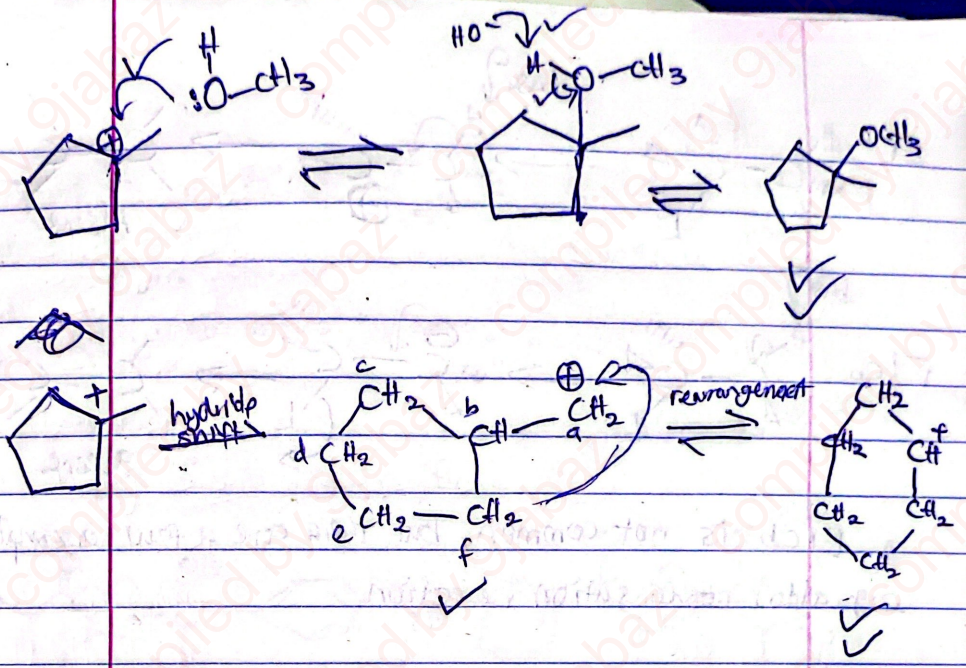


Solution

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

Mechanism





17/12/25

E1cb Elimination.

Elimination Unimolecular Conjugate Base

The E1cb is a first order kinetic elimination like E1 but the sequence is the reverse version of elimination. The the E1cb, the hydrogen is lost first to generate anion. This is followed by the ejection of the leaving group by the anion to form the alkene.

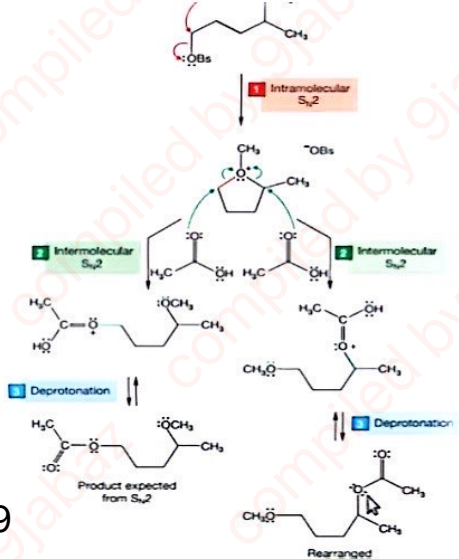
Recall that in the E1 reaction, the leaving group is lost first to give the carbocation and a proton is lost in the second step to give the alkene

QUIZ

A third product is also formed in small quantity –

2-methyltetrahydrofuran.

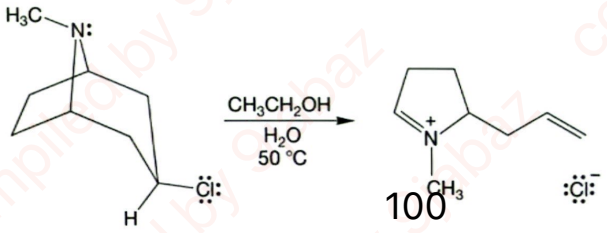
Can you explain the formation of this molecule. Use arrows to show movement of electrons in any mechanism you propose



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 $ClCH_2CH_2CH_2CH_2OH$ in H_2O to give THF (tetrahydrofuran) is much faster than that of $ClCH_2CH_2CH_2OH$ in H_2O to give the diol product $HOCH_2CH_2CH_2OH$.

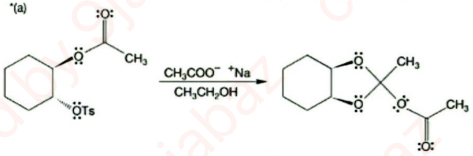
The two reactions are expected to be simple substitution reactions with no significant rate difference. However, if a cyclization is occouring and there is an unusual rate increase for the first reaction, there might indeed be a neighboring group effect.

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

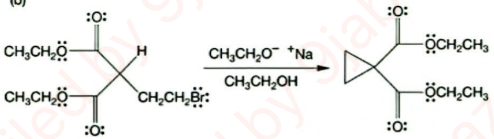
TUTORIAL

Write mechanisms for the following reactions:

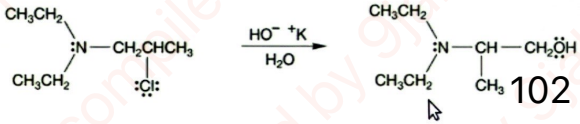
*(a)



(b)

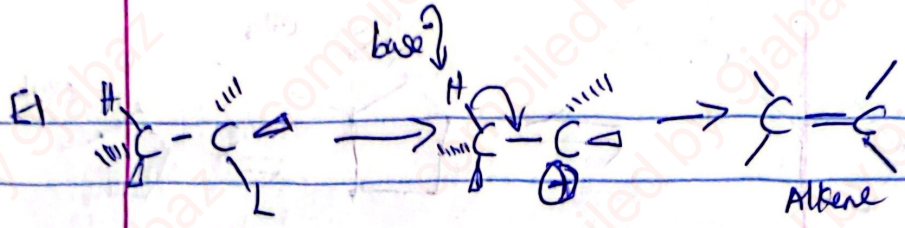


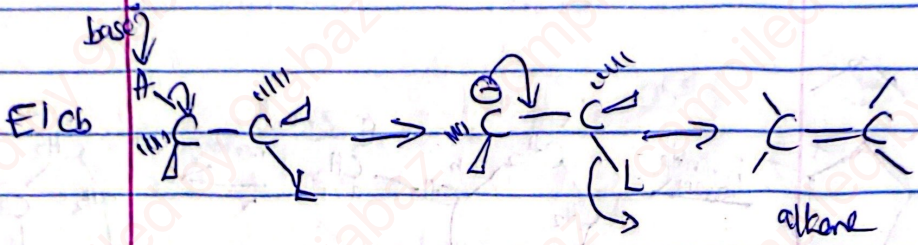
(c)



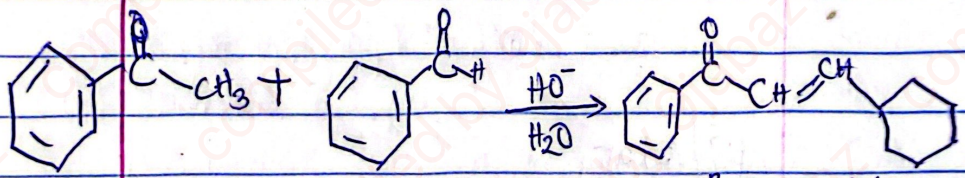
NOTE

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



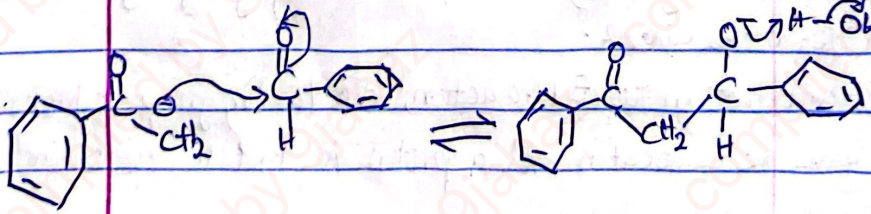


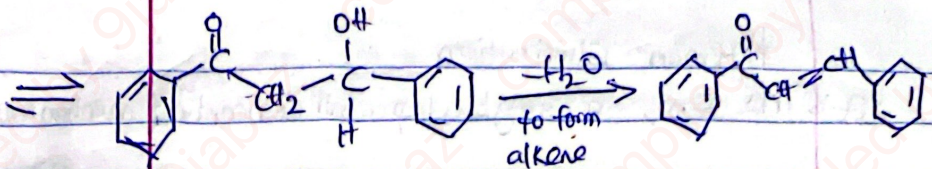
* E1cb is not common, but there are a few examples
e.g aldol condensation reaction



α-β-unsaturated carbonyl + H_2O

Mechanism

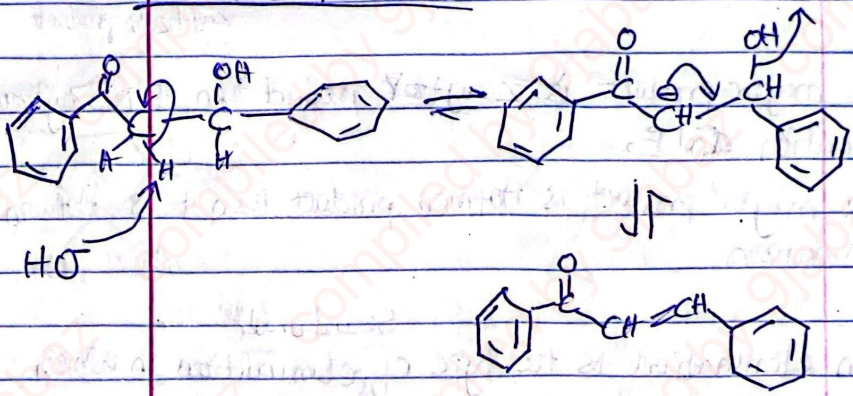




aldol product
(This is not the final product)

^-OH is a very poor leaving group

The E1cb Mechanism



Home Work

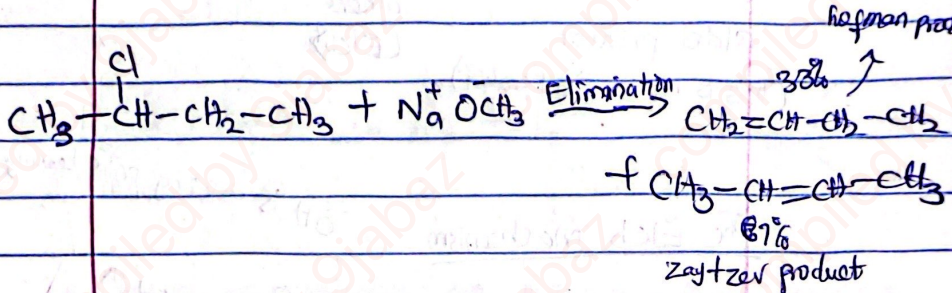
Find out other examples of E1cb apart from aldo condensation

How do we tell if E1cb ~~can~~ happen?

* Leaving group is very electronegative, eg F^-

Hofman Elimination

It is like E_2, a single step and concerted mechanism.



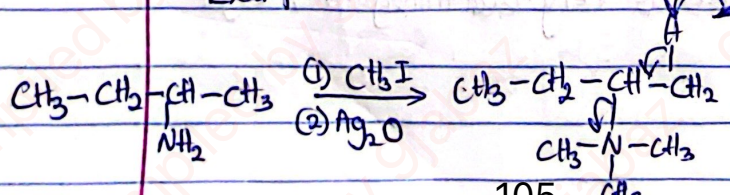
If the major product is Zaytzev product then it is Zaytzev elimination and E_2

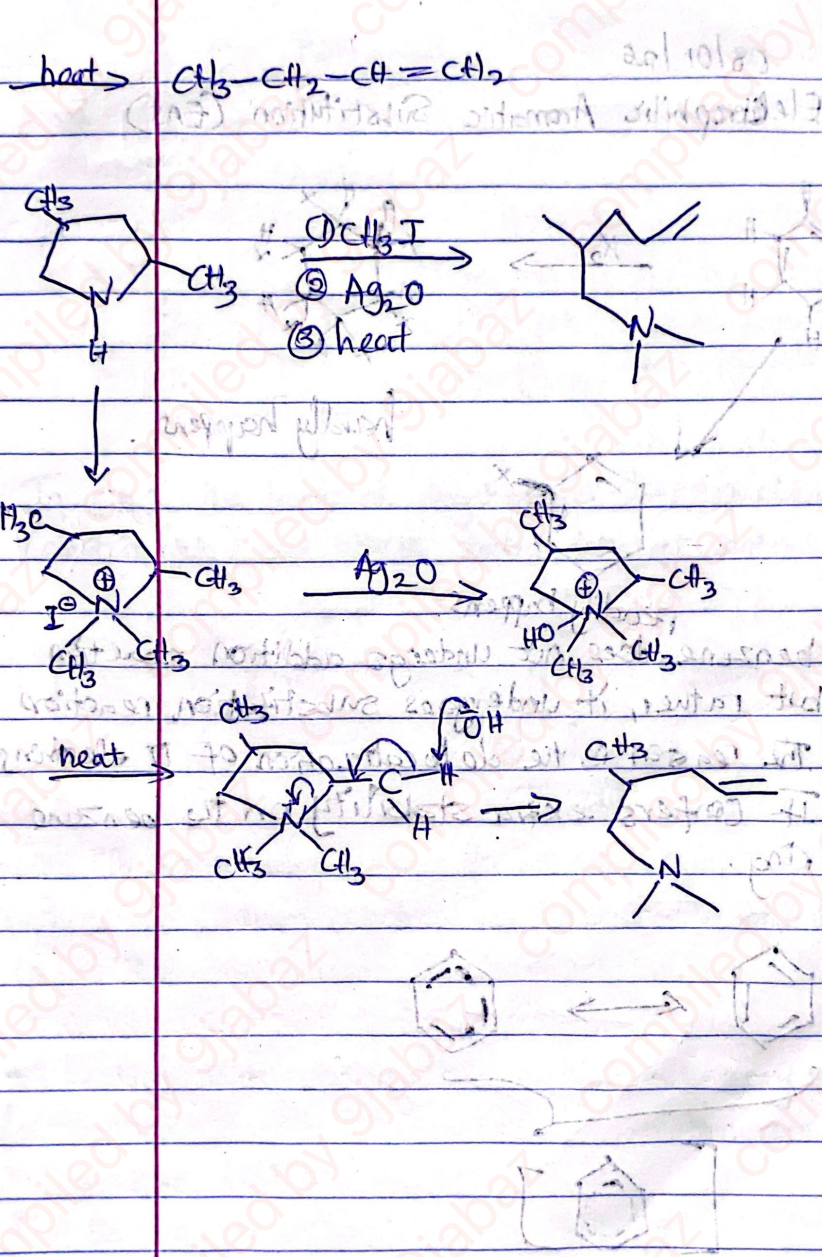
If the major product is Hofman product then it is Hofman elimination

Hofman elimination is the type of elimination (second order) in which the least substituted alkene is the preferred product

The Hofman elimination occurs when the leaving group is very bulky. It is driven by steric factors

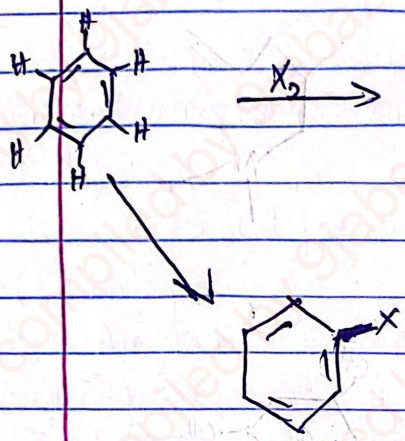
Example




heat
CH3–CH2–CH=CH2
① CH3I
② Ag2O
③ heat
Ag2O
heat

08/01/26

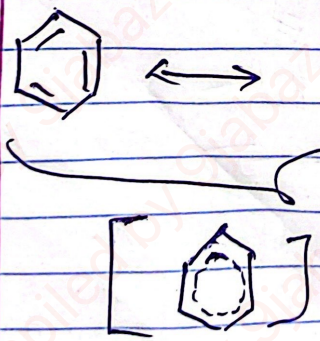
Electrophilic Aromatic Substitution (EAS)



hardly happens

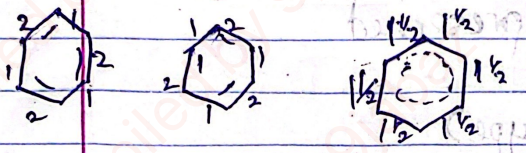
readily happens

benzene does not undergo addition reaction but rather, it undergoes substitution reaction. The reason is the delocalization of π electrons. It confers extra stability on the benzene ring.



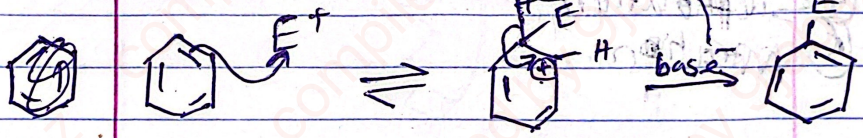
Assignment

Use energetics (i-e bond energy estimates) to prove the stability of benzene.



which means benzene has pseudo double bonds

In EAS, the benzene ring behaves like a nucleophile (electron rich) and attacks electron deficient centers (eg electrophile

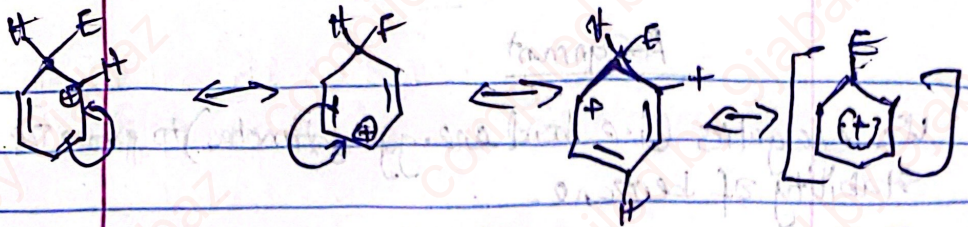


Positively charged intermediate Carbocation.

Note: The reason why benzene is not very reactive or will not partake in addition reactions is because it does not like to lose the arrangement of π-electrons in the ring

The intermediate carbocation of benzene is very stable (meta-stable) as conjugated carbocation are more stable than tertiary carbocation

But the final product is more stable than the carbocation

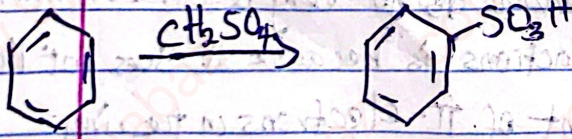


At the end of the reaction, the aromaticity of benzene ring is preserved

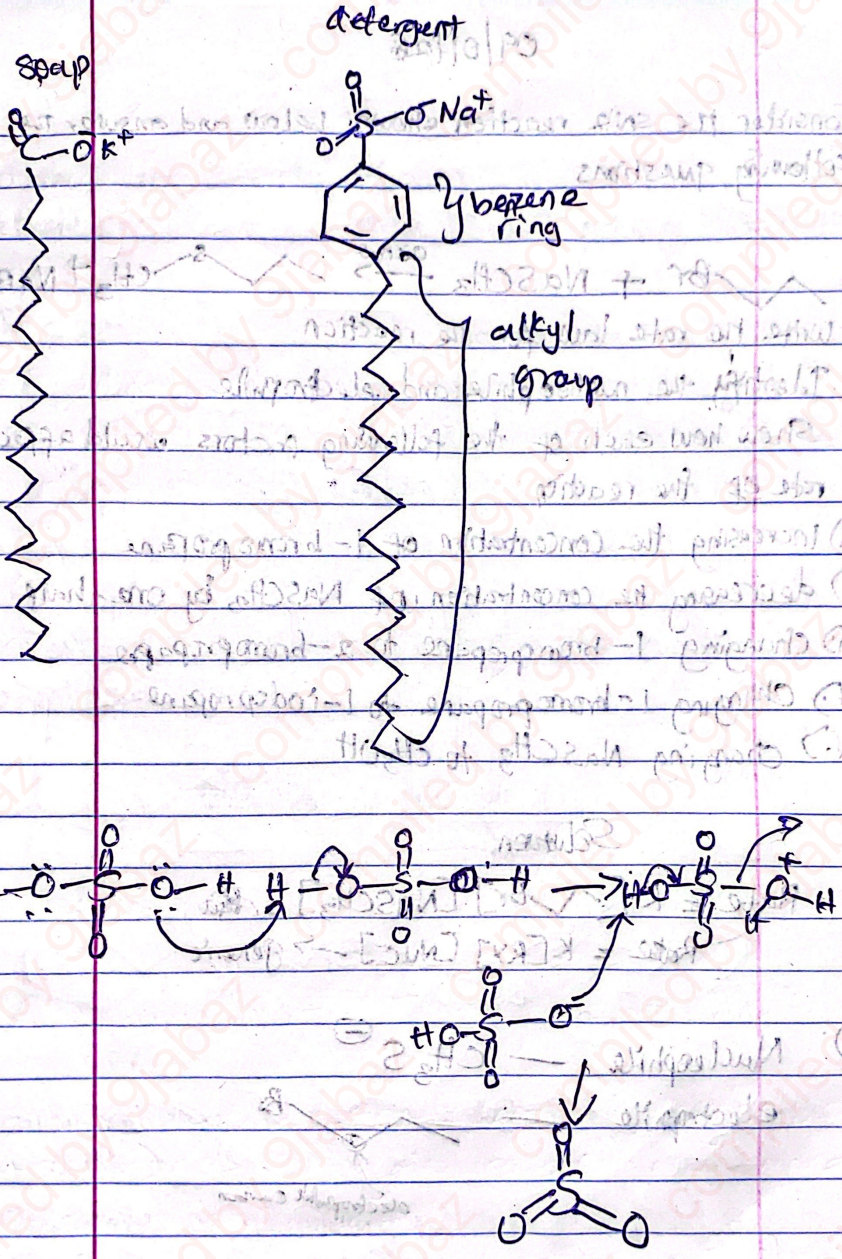
EAS (type)

1. halogenation
2. Alkylation
3. Acylation
4. Sulfonation
5. Nitration

Sulfonation

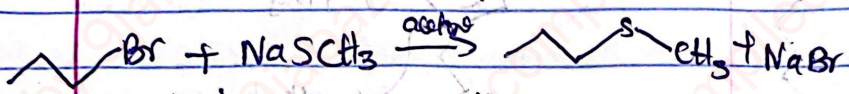


benzene sulfonic acid


detergent
soap
benzene ring
alkyl group

09/01/26

Consider the SN2 reaction shown below and answer the following questions



(a) Write the rate law for the reaction

(b) Identify the nucleophile and electrophile

(c) Show how each of the following factors would affect the rate of the reaction

(i) Increasing the concentration of 1-bromopropane

(ii) decreasing the concentration of $NaSCH_3$ by one-half

(iii) Changing 1-bromopropane to 2-bromopropane

(iv) Changing 1-bromopropane to 1-iodopropane

(v) Changing $NaSCH_3$ to CH_3OH

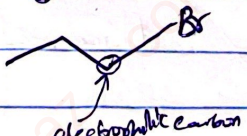
Solution

(a) : Rate = $K[\text{  }][NaSCH_3]$, Ans

Rate = $K[RX][Nuc^-]$ → generic

(b) Nucleophile — $CH_3S^{\ominus}$

electrophile —



(i) Rate increases

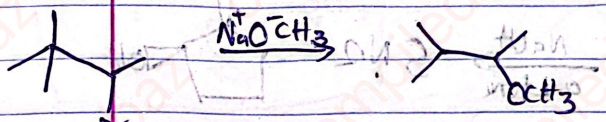
(ii) Rate decreases by $\frac{1}{2}$

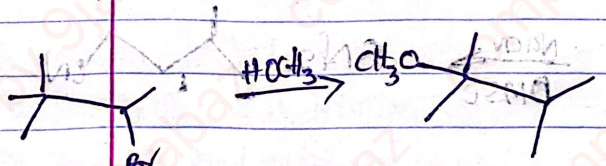
(iii) Rate decreases but SN2 favours primary substrate than 2°

(iv) There will be increase in the rate of reaction because iodine is a better leaving group

(v) There will be a decrease in the rate of reaction because CH_3OH is a weak nucleophile.

Explain why the two reactions below provide constitutionally different products





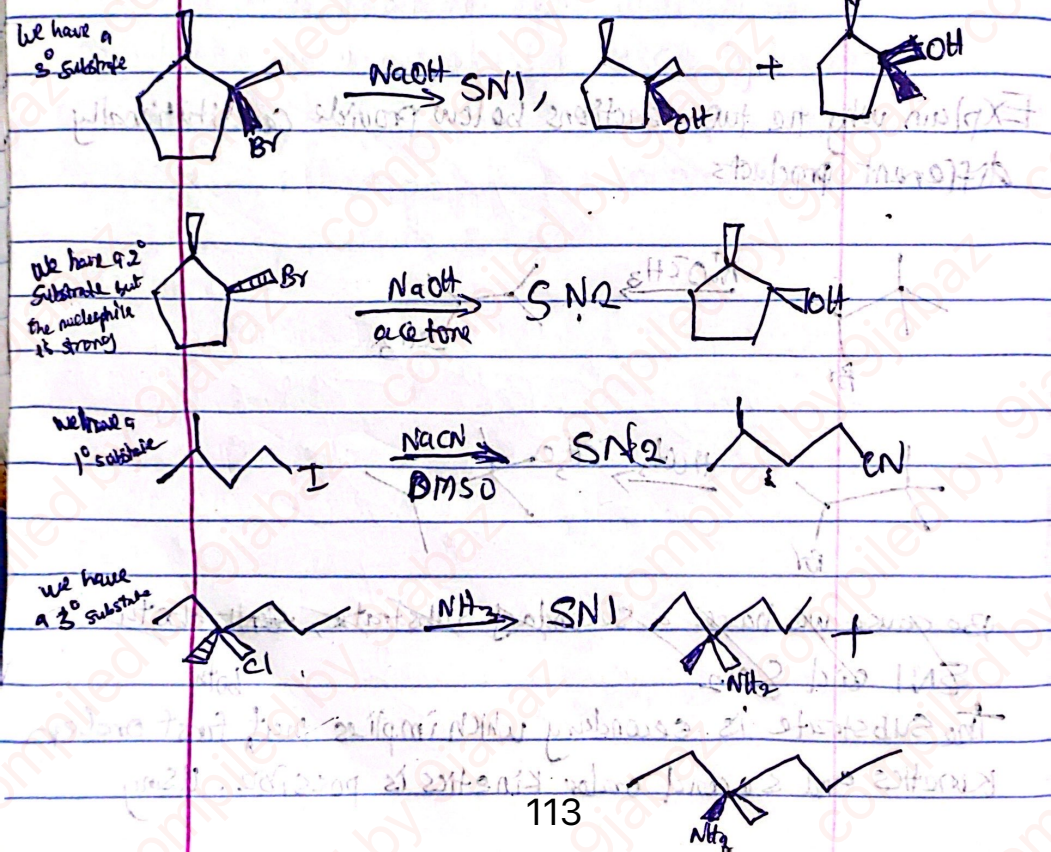
Because we have a secondary substrate, both SN1 and SN2

The substrate is secondary which implies that first order kinetics and second order kinetics is possible. Using

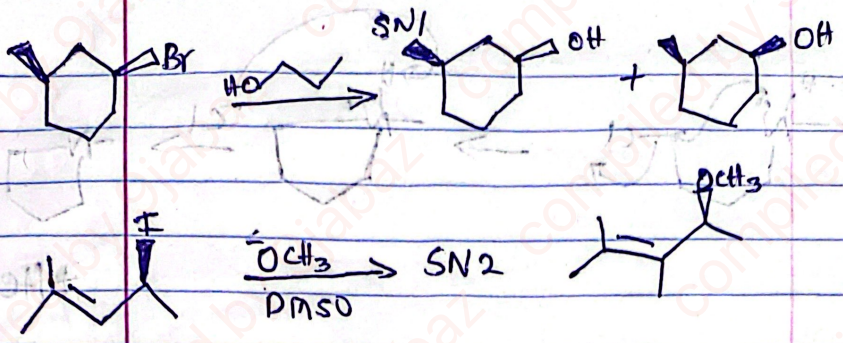
1° always SN2

a strong nucleophile will favor 2° kinetic and using a weak nucleophile will favor 1° kinetics

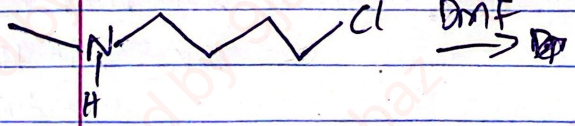
Assuming each reaction below undergo nucleophilic substitution. Predict the mechanism (SN1 or SN2) and draw the major product, include the stereochemistry where appropriate

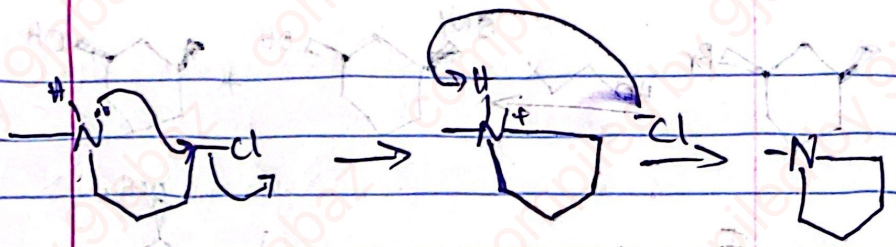


2° substrate but a weak nucleophile

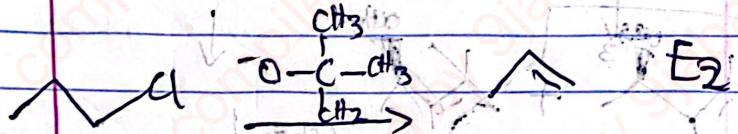


The compound below can undergo an intramolecular nucleophilic substitution via an SN2 mechanism. Draw the products and mechanism by which it is formed

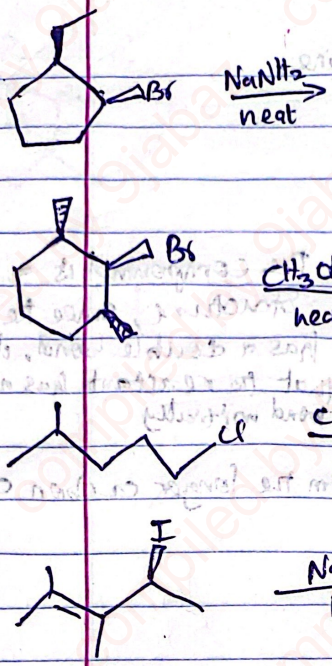




For each of the following reactions, predict the major mechanism SN1 or SN2 or E1 or E2 and provide the major product. Show correct stereochemistry where appropriate.

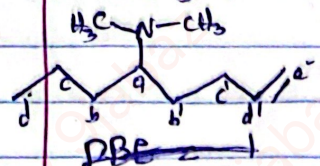


Primary substrate shows it will be second order kinetics but the ~~base~~ is too bulky, due to steric effect it will not undergo SN2, it will undergo E2



The alkaloid conine has been isolate hemlock and purified. It molecular formular is $C_8H_{17}N$. Treatment of conine with excess methyl iodide (CH_3I) followed by Ag_2O and heating gives the pure S-entantiomer; N,N-dimethyl oct-7-ene-4-amine. propose a complete structure for conine

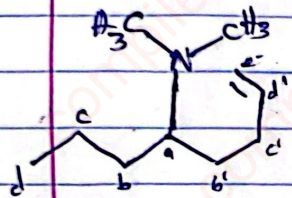
N-N-dimethyl) oct-7-ene-4-amine.



DBE = 1

DBE of $C_8H_{17}N$ = 1, The compound is a ring structure, since the product has a double bond, it shows that the reactant has no double bond initially

Drawing the ring structure from the longer carbon chain



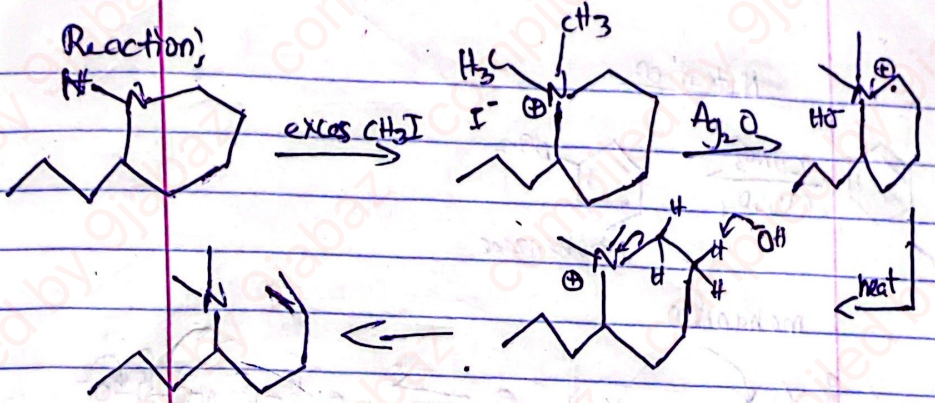
That means before exhaustive methylation; we have

$C_8H_{17}N$

Structure for coniine

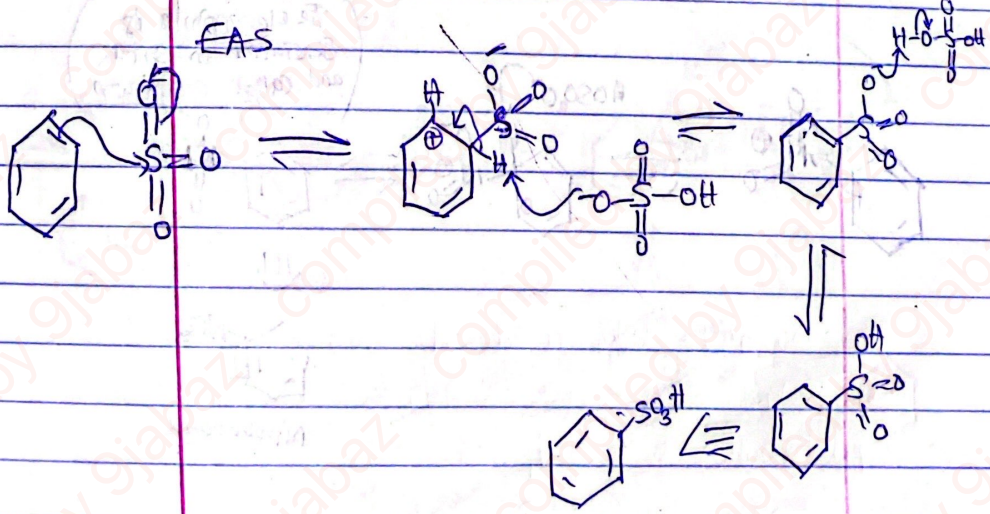
Alkaloid are bitter and used for medicinal purpose but are toxic in excess

Reaction;



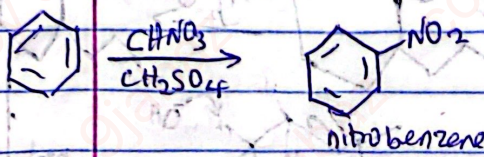
16th January, 2025

EAS



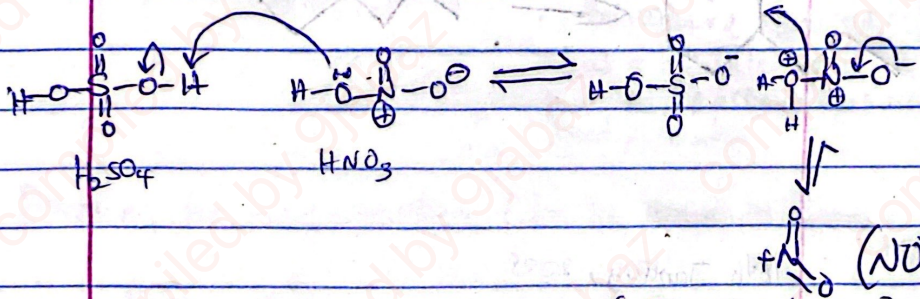
Mechanism for sulphonation

Nitration

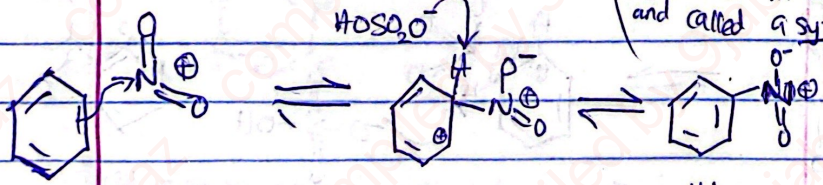


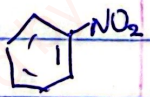
nitrobenzene

mechanism



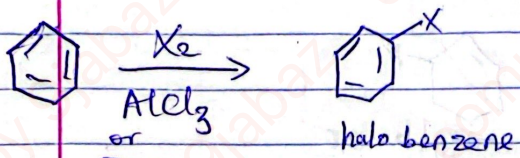
(The electrophile is generated in-situ and called a synthon)





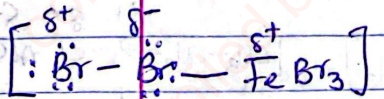
nitrobenzene

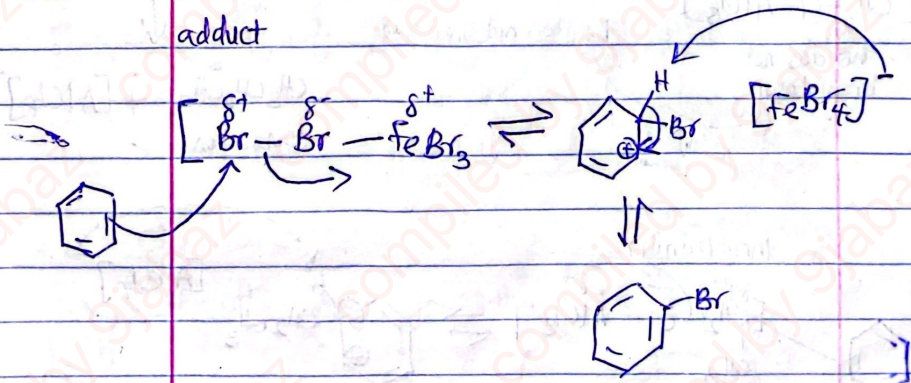
Halogenation



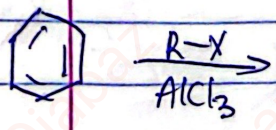
mechanism

$Br_2 + FeBr_3$



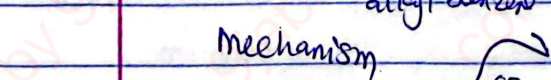


Friedel Craft's Alkylation



alkyl benzene

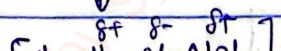
Mechanism



carbocation

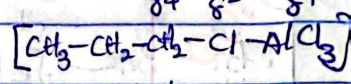
CH_3Cl or CH_3CH_2-Cl

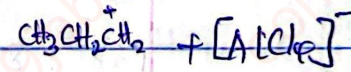
this does not breakdown



this does not breakdown

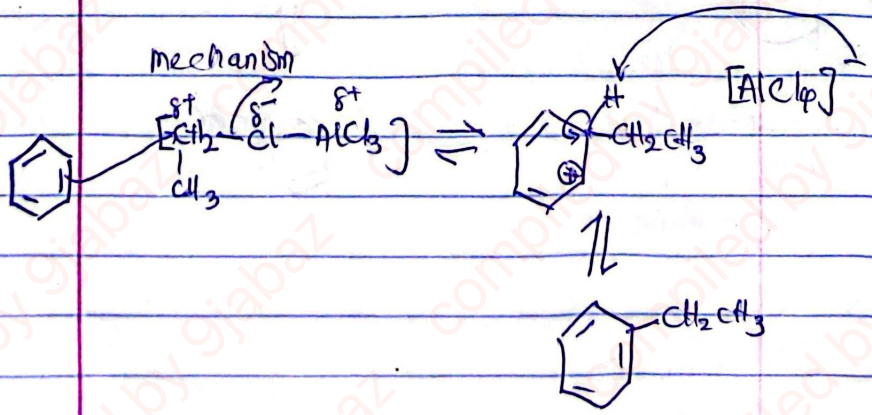
"why? " exam



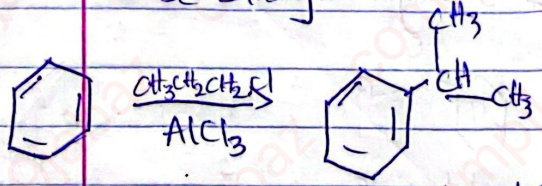


Carbocation

Mechanism

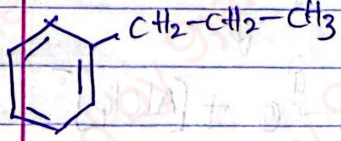


Case study

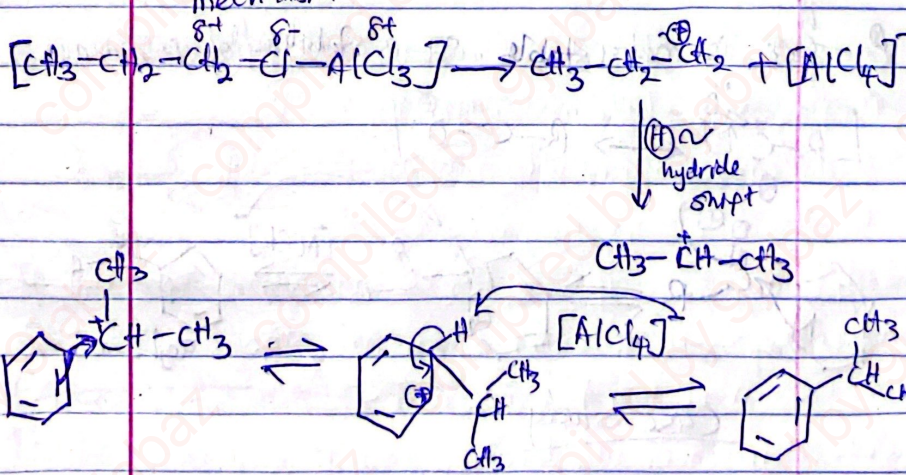


Observed product

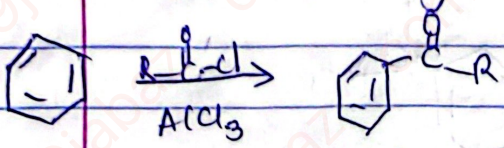
Note: the expected product



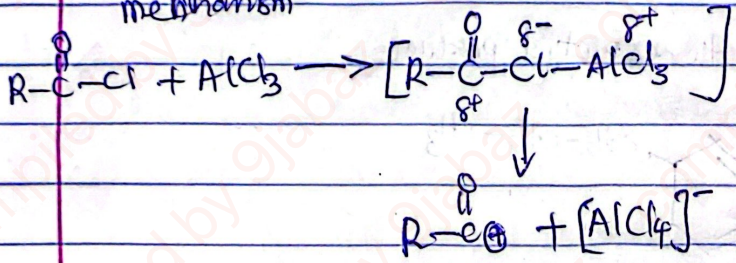
mechanism



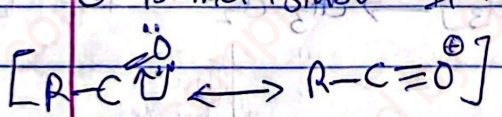
Friedel- Craft's Acylation

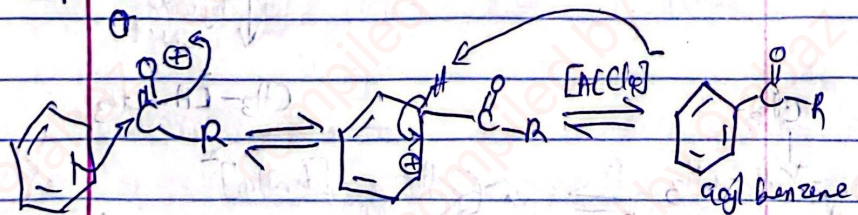


Mechanism

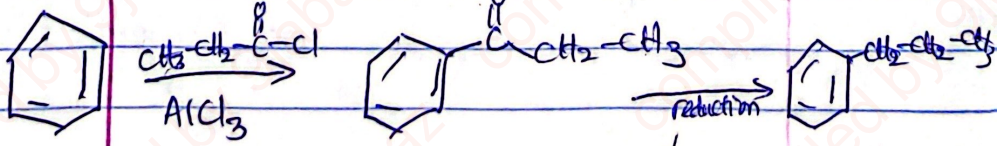


$R-C\equiv O^{\oplus}$ is meta stable. It is stabilized by resonance





Case Study



Which type of reduction is this?

23/01/26

Substituent Effects on EAS

prefers substitution reaction as against addition reactions. because substitution allows the benzene ring to retain its aromaticity.

Ordinarily, benzene undergoes EAS, reluctantly. Benzene is usually forced, through;

1. excess reagent
2. Catalyst

Substituent Effect

substituent can either activate the benzene ring or deactivate the benzene ring.

If benzene ring is activated, then it will undergo EAS more readily i.e EAS reactions are faster and more feasible.

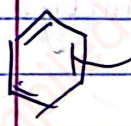
If benzene ring is deactivated, then it will undergo EAS less readily, i.e, reactions are slower (or may not occur) and less feasible

EWG (electron withdrawing group)

EDG (electron donating group)

EWG deactivates the benzene ring
EDG activates the benzene ring

How does EWG deactivates the benzene ring?



mechanistically, benzene behaves like a nucleophile — donating electrons towards E^+. If benzene will donate electrons in a nucleophilic attack, the electrons must be available for donation.

Substituents that draw electrons away from the benzene ring prevent electron donation by the benzene ring from happening readily. This results in the deactivation of the benzene ring.

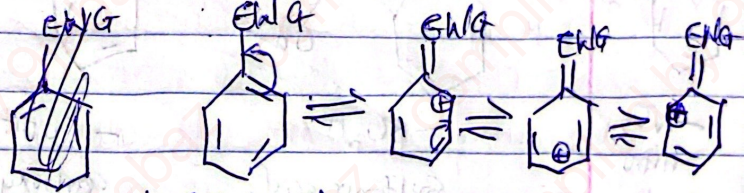
The opposite applies for a substituent that ~~activates~~ donates electrons to the benzene ring. This results in the activation of the benzene ring.

Electron withdrawal/donation can happen either
(i) Inductively or
(ii) Mesomerically

Inductive effect is ~~operates~~ operates like a pull of electrons

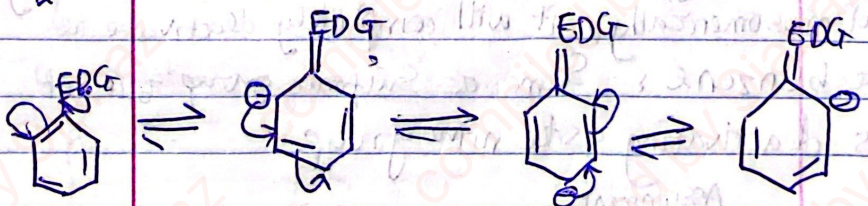
inductive effect (weak)
mesomeric effect (strong)

mesomeric effect operates by complete translocation of electrons



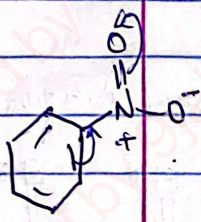
The positive charge is on the ortho and para position, therefore ~~electrophile~~ will not be able to attack that position. Therefore they are meta directing if the reaction eventually occurs.

E^+

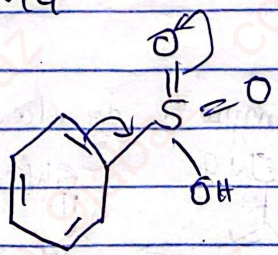


only ortho and para position is delocalized.

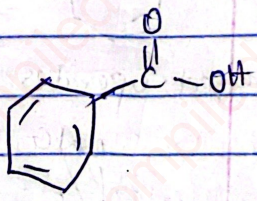
EWG



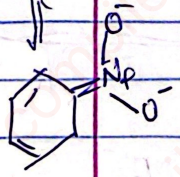
$-NO_2$
nitro

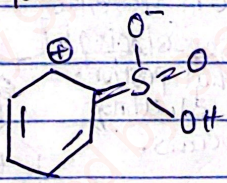


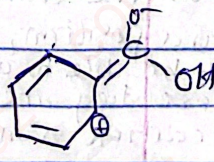
$-SO_3H$
Sulfonic acid



$-COOH$
Carboxylic acid.







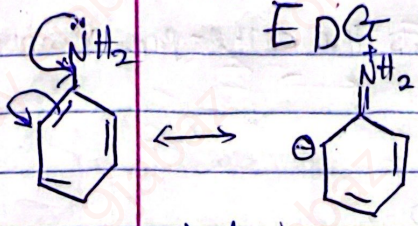
The nitro group can withdraw

The nitro group can withdraw electron both inductively and mesomerically, it will completely deactivate the benzene. Same as Sulfonic group but not as deactivating as the nitro group.

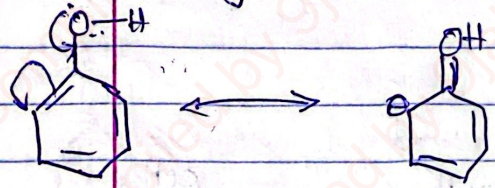
Assignment

List all EWG from strongest to weakest

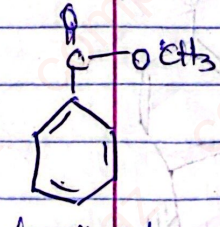
EDG



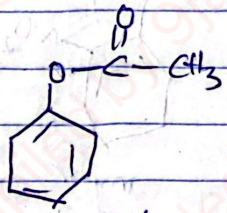
NH_2 can ~~donate~~ withdraw electron inductively but because of the lone pairs it can also donate mesomerically. It is the strongest electron donating group.



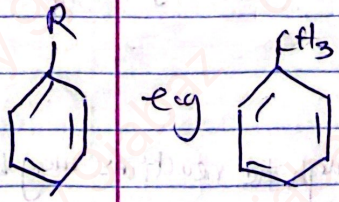
Overall Mesomeric effect



deactivated

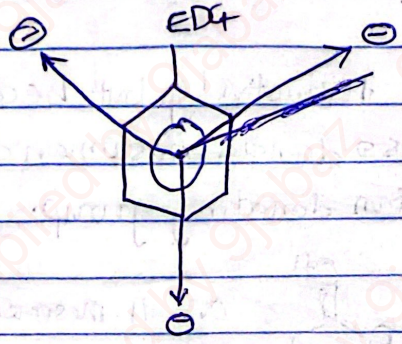


activated

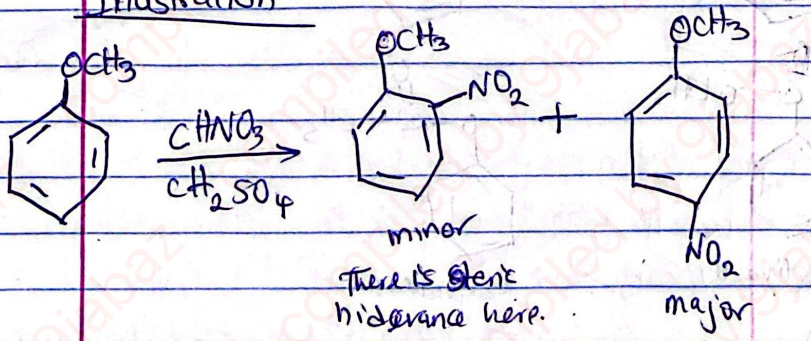


R-groups donate electrons inductively, no mesomeric effect.

EDG directs electrophiles towards the ortho-para position in the benzene ring



Illustration



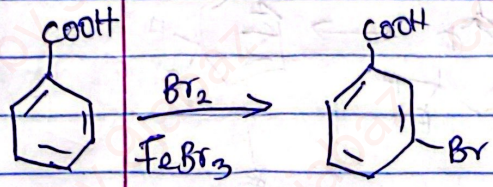
minor

There is steric hinderance here.

major

EWG are meta directing though the reactions may be slow (very slow) or hardly occur, i.e. it eventually occurs, the E^+ will go to the meta position.

Example



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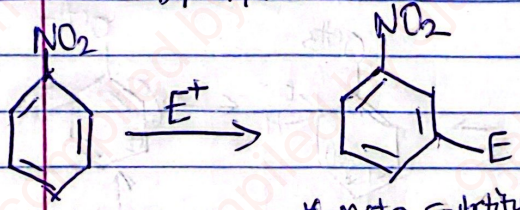
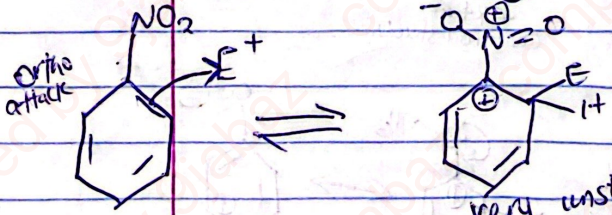
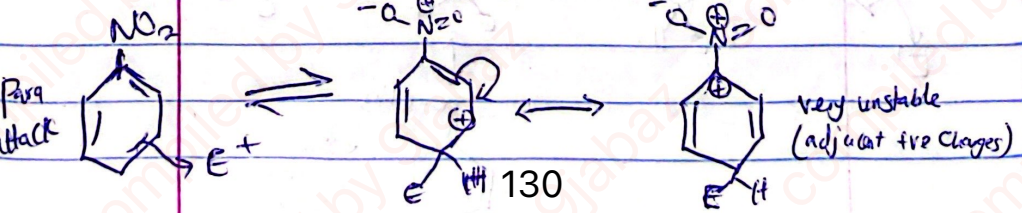


* Meta substituted cos $-NO_2$ is meta directing
* Reaction is going to be very slow $-NO_2$ deactivates the benzene ring

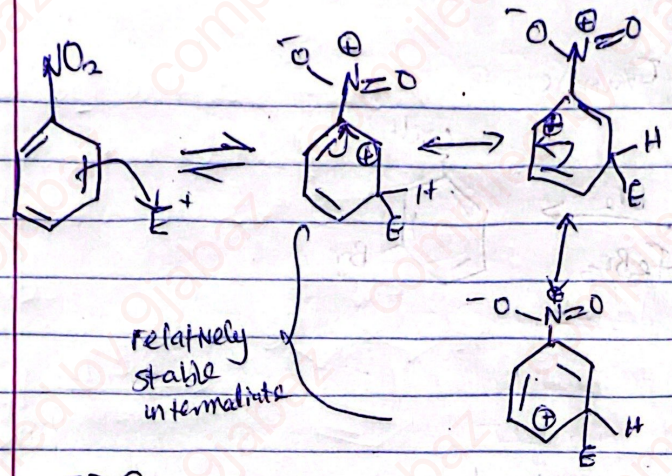
Reason it is meta directing:



very unstable (adjacent +ve charges)

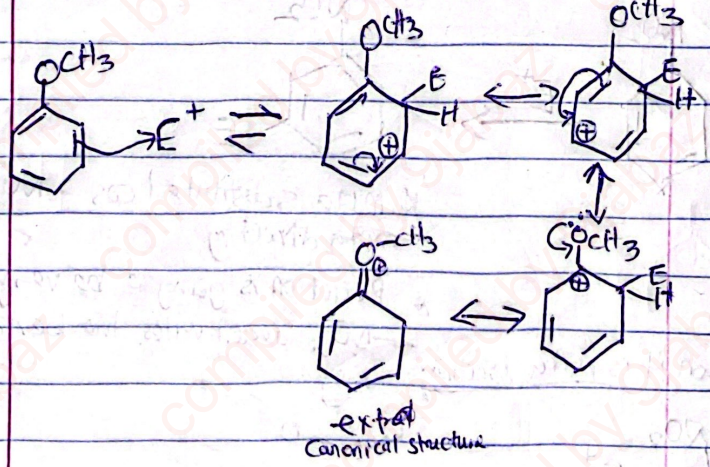


meta attack

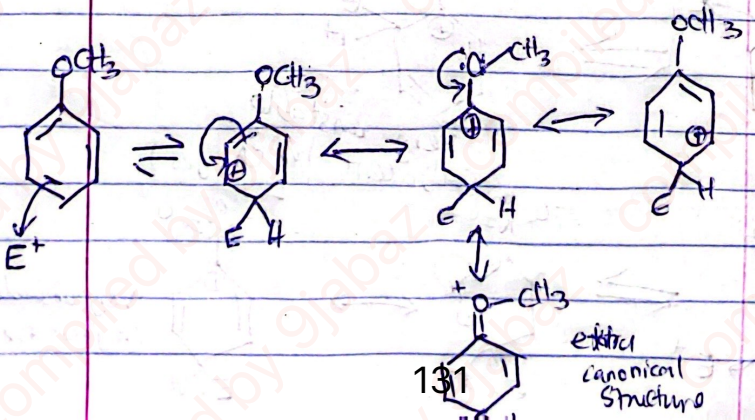


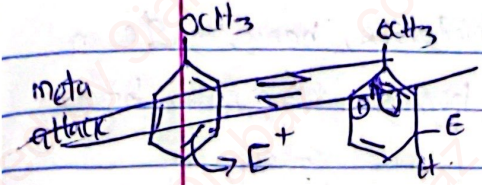
In an EDG

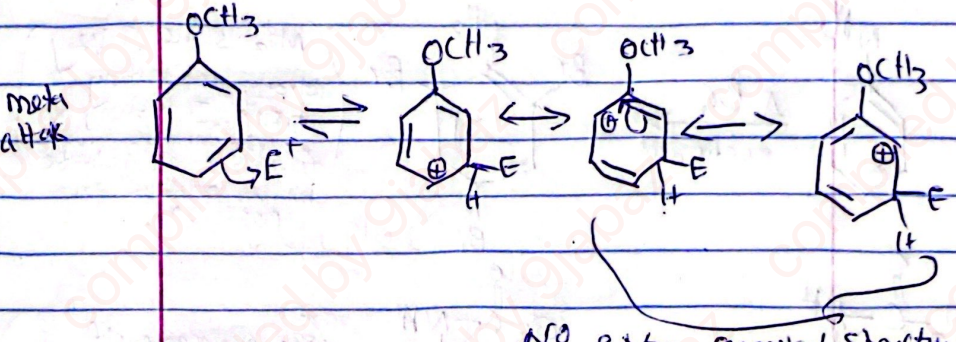
ortho attack



Para attack

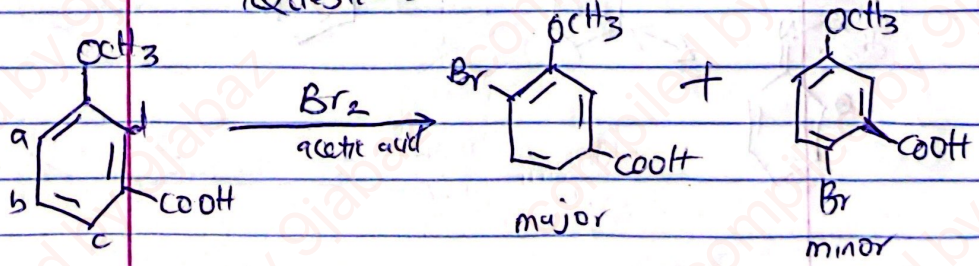






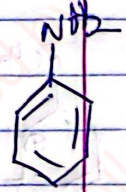
NO extra canonical structure. The intermediate is stable but the intermediate from the O- & P- attack are more stable. Therefore, the O- & p- attack are favoured.

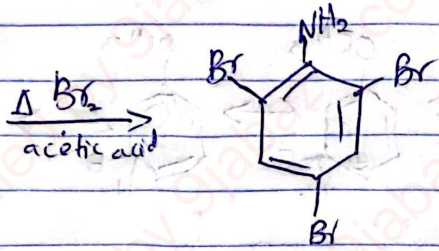
Questions



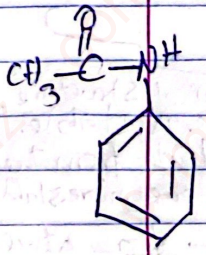
* Groups that activates the benzene ring usually overide groups that deactivates the benzene ring
* $-OCH_3$ will determine where Br will be attached on the benzene ring. (a, b, or c)

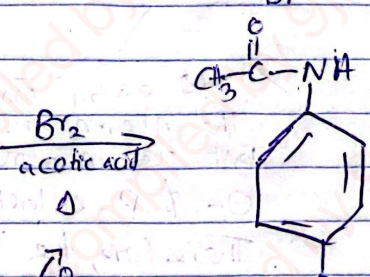
* d is unlikely because of steric hinderance, hence, a, b, c on contention, but a is more likely because there is a bit of steric hinderance at c



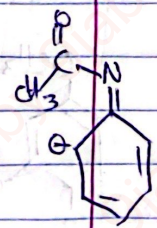


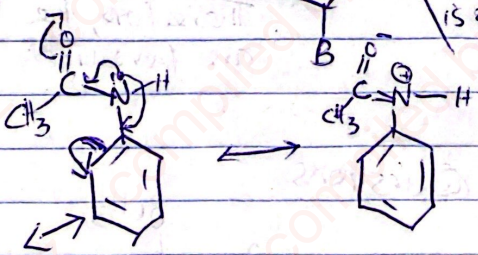
NH_2 is the a very strong activating group. It a strong electron donating group Therefore it will activate both the ortho and para position





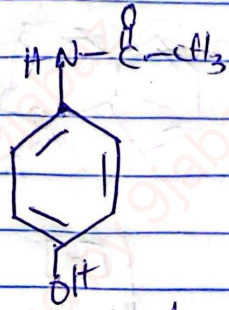
The presence of CH_3-C- instead of H, reduces the activating effect of NH_2. So, it is only para directing



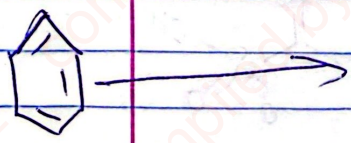


Case Study

(1)

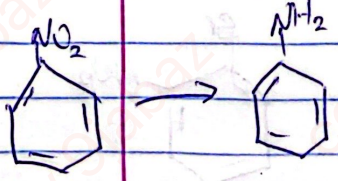


Paracetamol



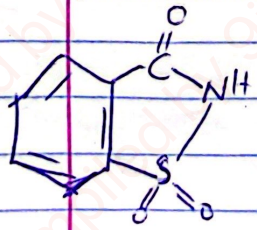
route 1 (convert benzene into phenol)

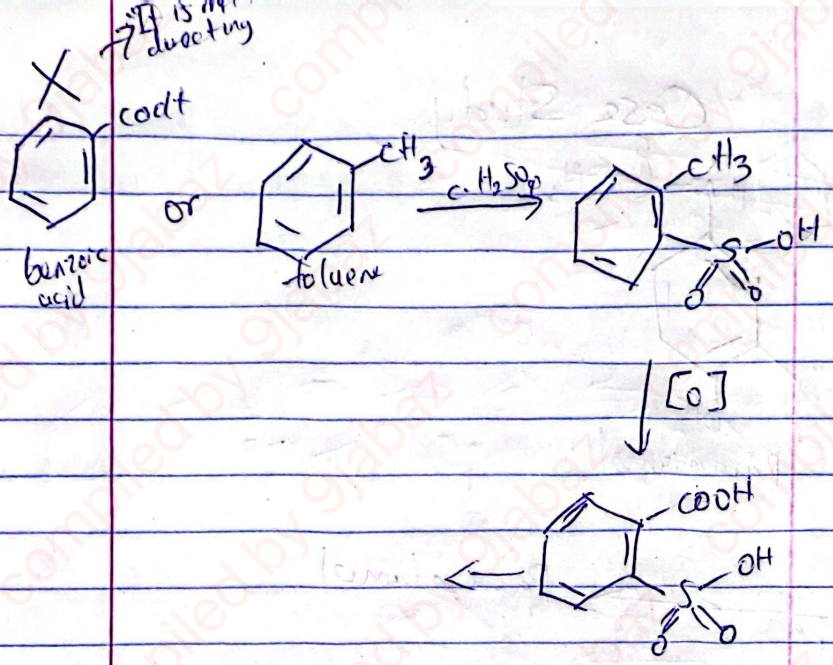
route 2 (convert benzene into nitrobenzene)



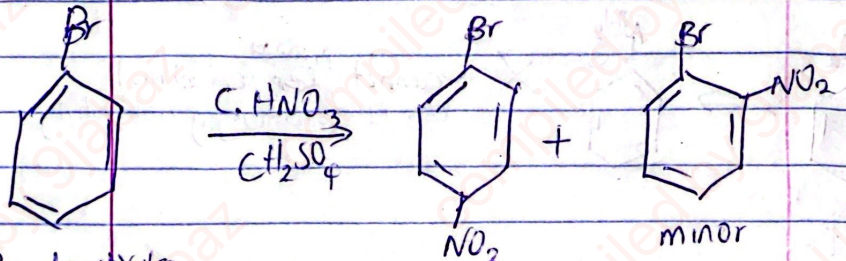
cannot ~~for~~ produce paracetamol cos it is strongly activating.

(2) Saccharin





Exam question



Br deactivates benzene ring

Why?