Prof. olonda's part

Fundamentals of Physical organic Chemistry can be divided into;

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

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

"how?"

Physical Organic chemistry is concerned with answering questions such as

(1) Why does compound A reacts one way and compound B reacts another way?

(2) If A is modified structurally, how is the reactivity affected?

(3) In the reaction of C with D to form E, what pathway is followed?

The mechanism for a reaction is the 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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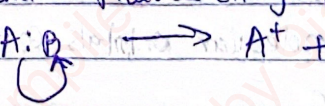
* bonds doesn't just break
* For heterolysis to happen, the atoms should be in different electronegativity or polarized

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



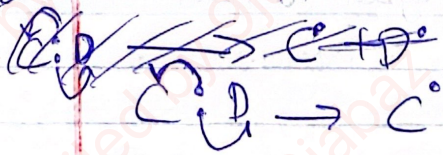
In heterolytic reaction, the reagent generally brings a pair of electrons to the substrate or takes a pair of electron from it

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

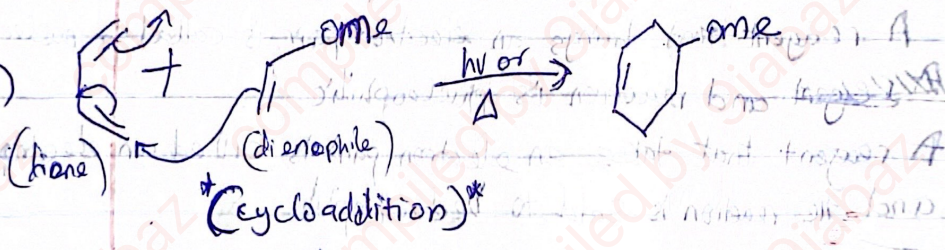


Free radicals often proceed by a chain reaction

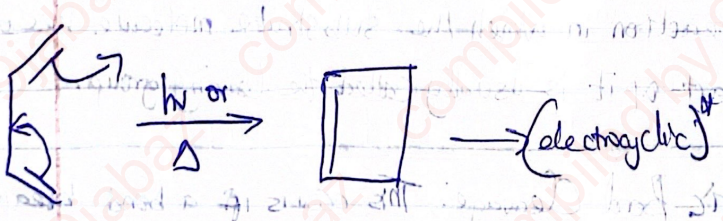
(3) Pericyclic Mechanism (everything happens at the same time): This involves the stereospecific movement of electrons leading to the making and breaking of bonds in a single concerted step involving a cyclic transition state. There are no intermediates ions or free radical involved. The symmetry characteristics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

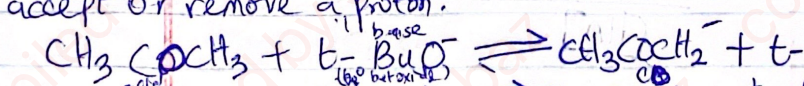
ACIDITY AND BASICITY

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.

Ka 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 pKa and the strength of the acid, the larger the value of pK_a, the weaker the acid.

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

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

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

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

(1) 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

		→ more acidic
	H_3CCOOH	$ClCH_2COOH$
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.

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

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

Nucleophile — substrate — Product — 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)

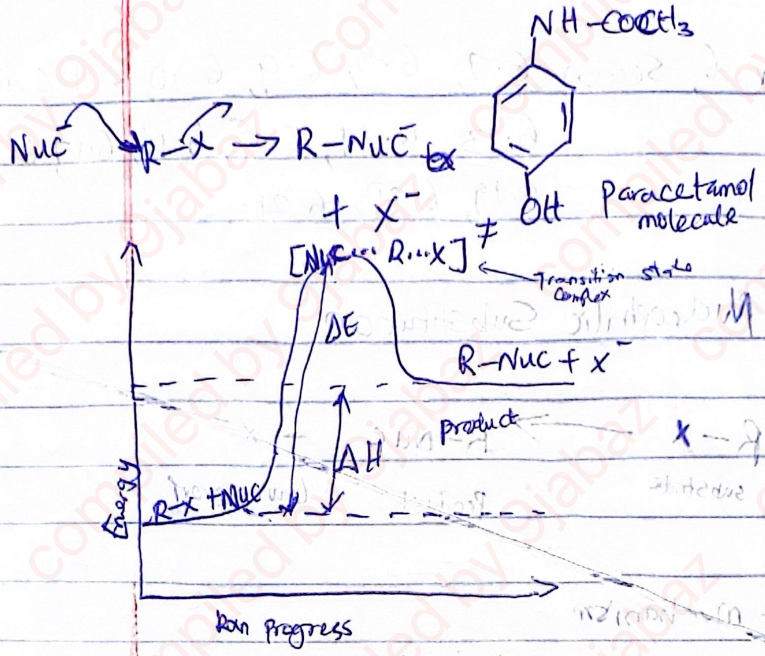
$$R-X + Nuc \rightarrow R-Nuc + X^-$$

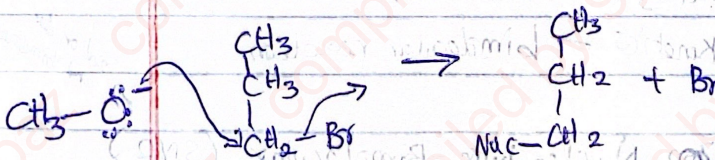
Rate law

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





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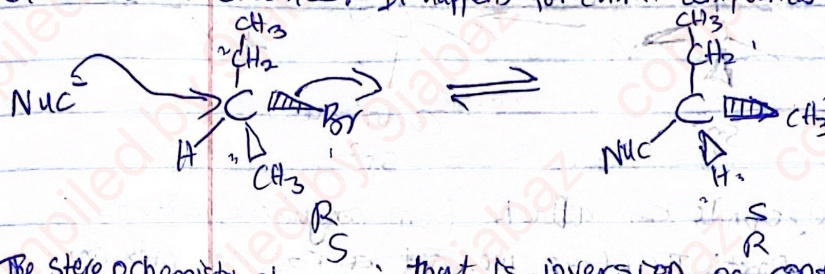
How to Confirm SN2

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

(2) stereochemical evidence

(3) ~~What happens at bridge ehd~~ 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

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** 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 $= k[RX]$

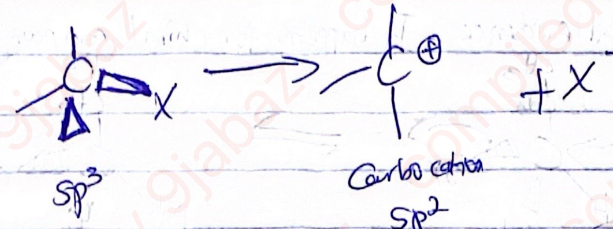
(1) The rate of reaction depends solely on the concentration of the substrate. It is first order and unimolecular

(2) Stereochemical evidence

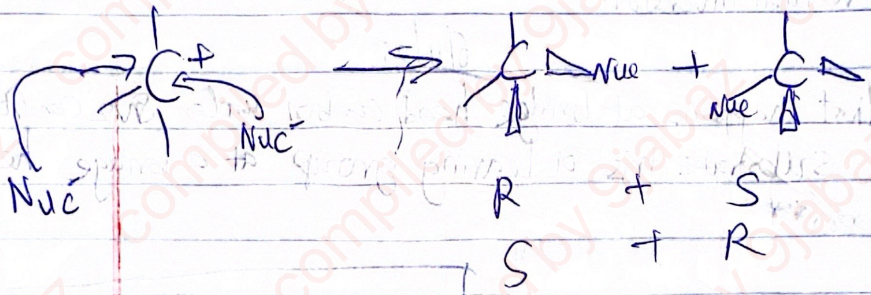
(*) Using these elementary step; derive the rate law.

(2) Stereochemical evidance

Step 1:



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



What happens at bridge head carbon under SN2 conditions

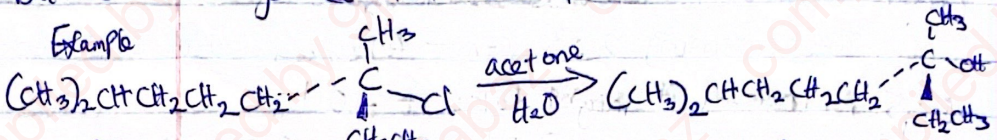
A bridge head carbon is the carbon at the point where two rings are fused together in a bicyclic compound. Therefore in an SN2 condition the backside attack is sterically and geometrically impossible due to the rigid bicyclic structure, preventing the required inversion of configuration.

Stereochemical observation for SN1 = racemization

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

* But we don't always see racemization for SN1

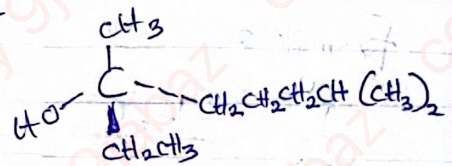
Example



Inv

39.5% retention of configuration

+



60.5% inversion of configuration

"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

$+0.5^0 \xrightarrow{SN2} -0.5^0$

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

Bcs we will have 50% and 50%

$+0.5^0 \quad -0.5^0$

But what is most observed is;

$+0.5^0 \xrightarrow{SN1}$ 40% $+0.5^0$ 60% -0.5^0

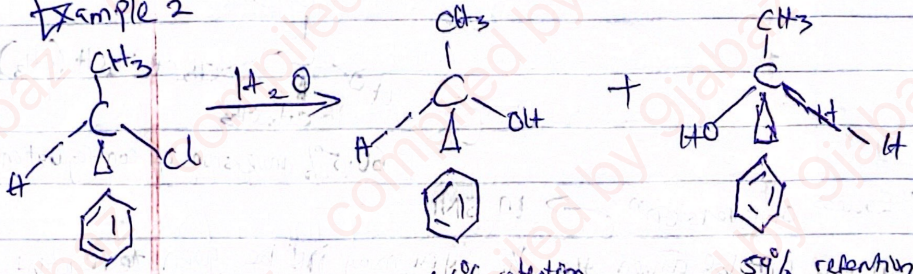
This means ~~the +0.5 and -0.5~~ 40% of the molecule will go $+0.5^0$ and 60% of the molecule will go -0.5, which means the 40% will cancel

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

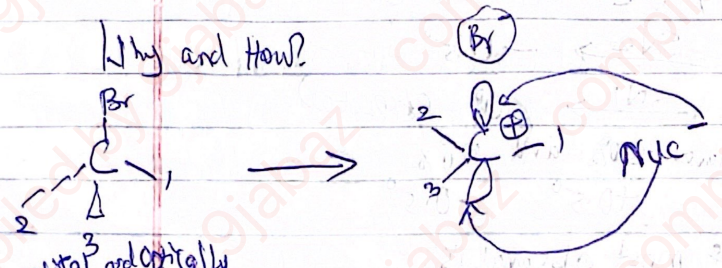
∴ The remaining 20% cannot take the rotation up to that -0.5°, instead it might take it -0.1

Whenever you see a little bit of inversion it is SN1

Example 2



Why and How?



chiral and optically active substance

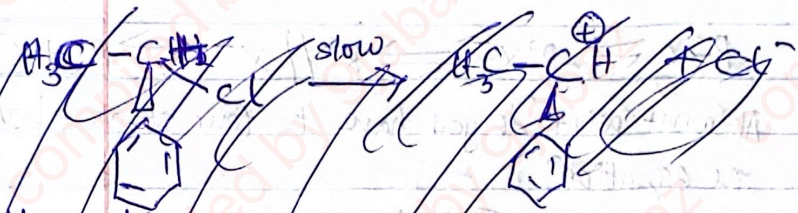
Because Br is still hanging around, there is repulsion between Br and Nuc - which makes inversion slightly more than retention.

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 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?

Factors that Affect Rate of SN2 Reaction

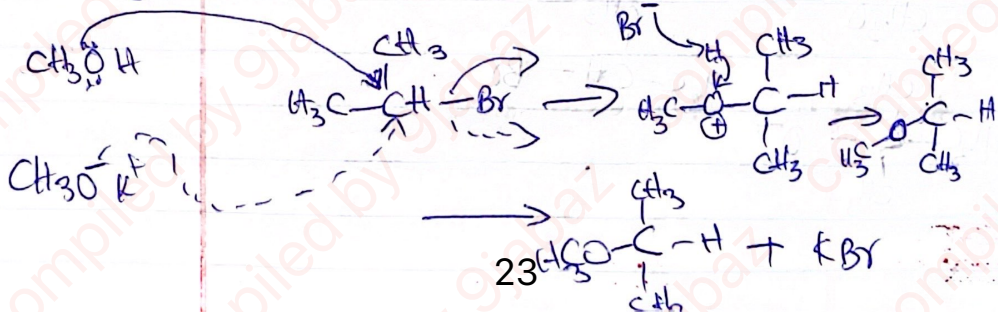
1. Substrate type
2. Effect of nucleophile
3. Effect of solvent
4. Leaving group type

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 SN2 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 Nucleophicity

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

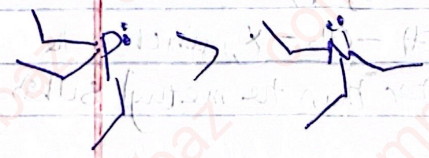
(2) Nucleophilicity decreases from left to right in the periodic table following the increase in electronegativity from left to right

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

$NH_3 > H_2O$

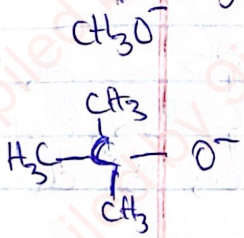
(3) The nucleophilicity also increases down the group due to increase in size and polarizability

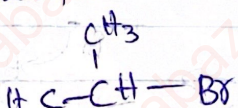
$I^- > Br^- > Cl^- > F^-$



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

→ Stronger nucleophile





Effect of Solvent on Nucleophile

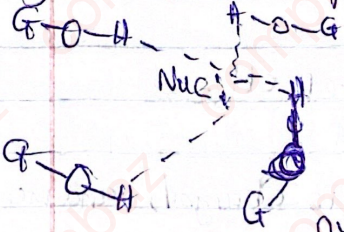
(i) Protic solvents (polar): $-SH$, $-OH$, $-NH$

(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 $\left(H-\underset{\underset{CH_3}{|}}{\overset{\overset{O}{\|}}{C}}-N-CH_3\right)$, Acetonitrile ($CH_3-C\equiv N$), DMSO, Acetone

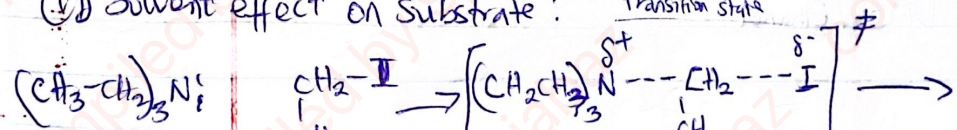
Solvent can affect SN2 reaction in two ways;

(i) effect on Nucleophile: Nuc^- will be strongly solvated in protic solvents, it stabilizes the nucleophiles, 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

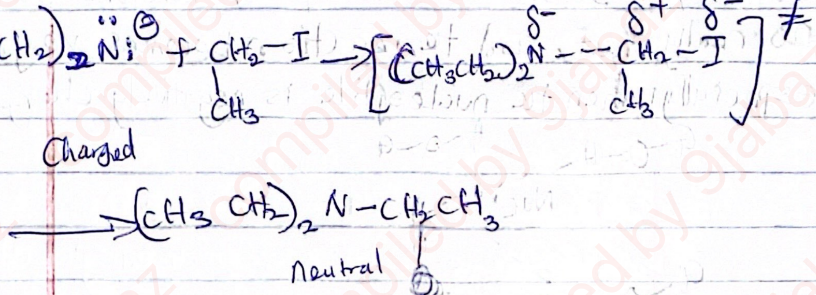
(ii) Solvent effect on substrate:



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

Charged product

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



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

How we increase/decrease polarity?

Eg 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 $-\dot{C}-X$ 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