Symmetry, Stereochemistry and Applications

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Lecture - 32
Stability of Carbocation

Welcome back to the course entitled Symmetry, Stereochemistry and Applications. In the previous couple of lectures, we have discussed about the reaction mechanism involving substitution reaction. And we have talked about two different methods, two different reaction mechanisms namely SN1and SN2 and we have found or we have learnt how the SN1 and SN2 mechanisms differ and what kind of alkyl halides prefer which type of reaction mechanism.

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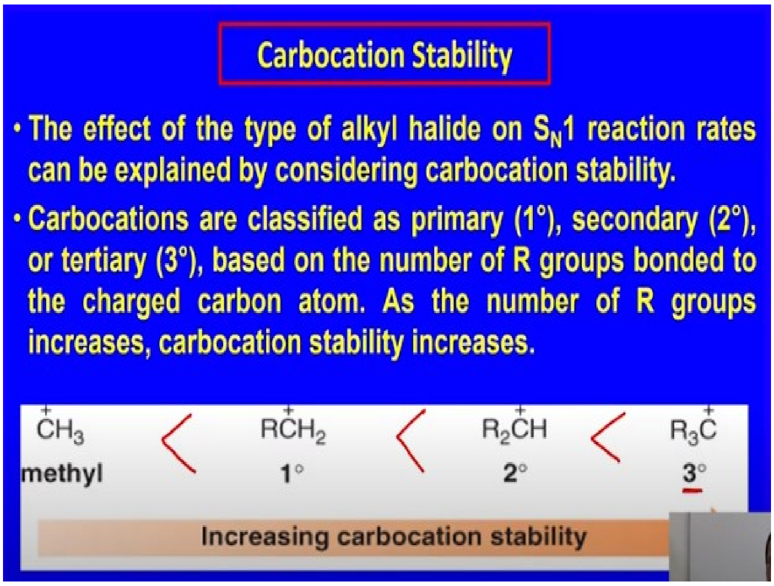

Carbocation Stability

- The effect of the type of alkyl halide on S_N1 reaction rates can be explained by considering carbocation stability.
- Carbocations are classified as primary (1°), secondary (2°), or tertiary (3°), based on the number of R groups bonded to the charged carbon atom. As the number of R groups increases, carbocation stability increases.

$\overset{+}{C}H_3$ methyl $<$ $R\overset{+}{C}H_2$ 1° $<$ $R_2\overset{+}{C}H$ 2° $<$ $R_3\overset{+}{C}$ 3°

Increasing carbocation stability

So in that context we would like to now continue and try to understand what are the factors that influence the stability of carbocation that is formed in case of SN1 reaction. The effect of the type of alkyl halide on SN1 reaction rates can be explained by considering the stability of carbocation.

Carbocations as you can easily understand that can be classified as primary, secondary and tertiary based on the number of alkyl groups added or connected to the charged carbon atom. As the number of R groups increases the carbocation stability increases.

So a 3 degree carbocation and a tertiary carbocation has better stability or higher stability compared to a 2 degree and 2 degree has a higher stability compared to 1 degree and methyl carbocation is the less or lowest stable carbocation. We need to know why this trend is followed.

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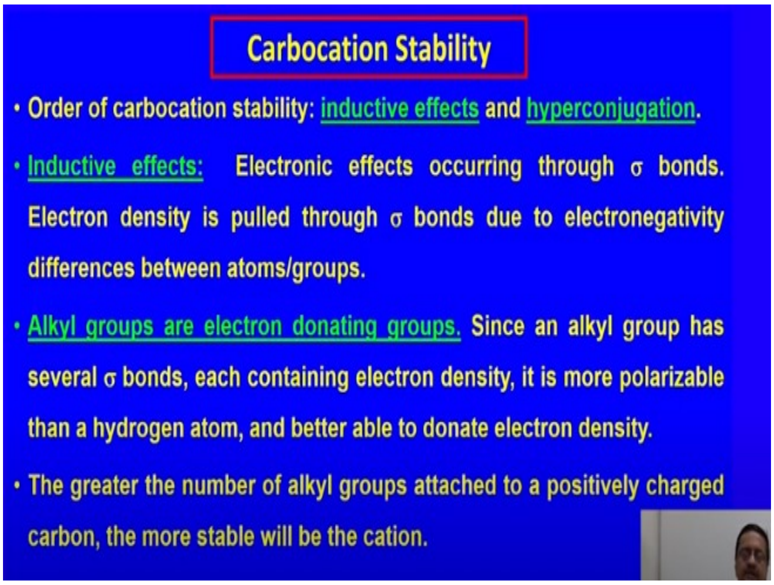

Carbocation Stability

- Order of carbocation stability: inductive effects and hyperconjugation.
- Inductive effects: Electronic effects occurring through σ bonds. Electron density is pulled through σ bonds due to electronegativity differences between atoms/groups.
- Alkyl groups are electron donating groups. Since an alkyl group has several σ bonds, each containing electron density, it is more polarizable than a hydrogen atom, and better able to donate electron density.
- The greater the number of alkyl groups attached to a positively charged carbon, the more stable will be the cation.

The order of carbocation stability can be identified or determined by two different effects called the inductive effect and hyperconjugation. The inductive effect is an electronic effect that occurs through the sigma bonds. The electron density is pulled through the sigma bond due to electronegativity differences between the atoms and groups. The alkyl groups that are connected to the carbocation positive center are electron donating groups.

Since an alkyl group has several sigma bonds each containing electron density, it is more polarizable than a hydrogen atom and hence they are able to better donate electron density towards the positive center of a carbocation. The greater the number of alkyl groups that are attached to the positively charged carbon, the more stable will be the carbocation.

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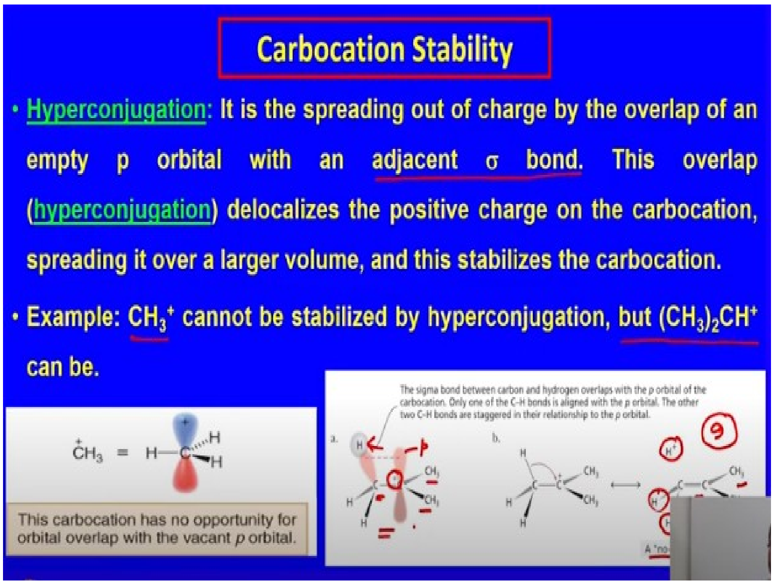

Carbocation Stability

- Hyperconjugation: It is the spreading out of charge by the overlap of an empty p orbital with an adjacent σ bond. This overlap (hyperconjugation) delocalizes the positive charge on the carbocation, spreading it over a larger volume, and this stabilizes the carbocation.
- Example: CH_3^+ cannot be stabilized by hyperconjugation, but $(CH_3)_2CH^+$ can be.

This carbocation has no opportunity for orbital overlap with the vacant *p* orbital.

The sigma bond between carbon and hydrogen overlaps with the p orbital of the carbocation. Only one of the C-H bonds is aligned with the p orbital. The other two C-H bonds are staggered in their relationship to the p orbital.

The other effect is called the hyperconjugation. It is the spreading out of the charge by an overlap of an empty p orbital with an adjacent sigma bond. You see we are talking about an adjacent sigma bond. This overlap delocalizes the positive charge on the carbocation spreading it over a larger volume or larger area in the carbocation and hence it stabilizes the carbocation. For example, methyl carbocation cannot be stabilized by hyperconjugation, but these isopropyl carbocation can be.

So when you have your isopropyl carbocation with a positive charge on this carbon, this empty p orbital interacts with the adjacent hydrogen, the charge is neutralized by the formation of a double bond and by release of this H+ ion. This is called a no bond resonance form. And this is possible for all the three hydrogens that are available on the adjacent carbon atom.

So this particular carbocation will have three equivalent hyperconjugative structures. So now you can easily understand that if a carbocation has three methyl groups associated with it, then 3 into 3, 9 such hydrogens will be there which can go for hyperconjugation.

And therefore we will have 9 hyper conjugating structures and they will be then giving the stability to the carbocation more than what we can see here in this case of carbocation. So here you see that there are three possible methyl groups. Each one of them can do the same. And then this can have 9 hyperconjugative structures.

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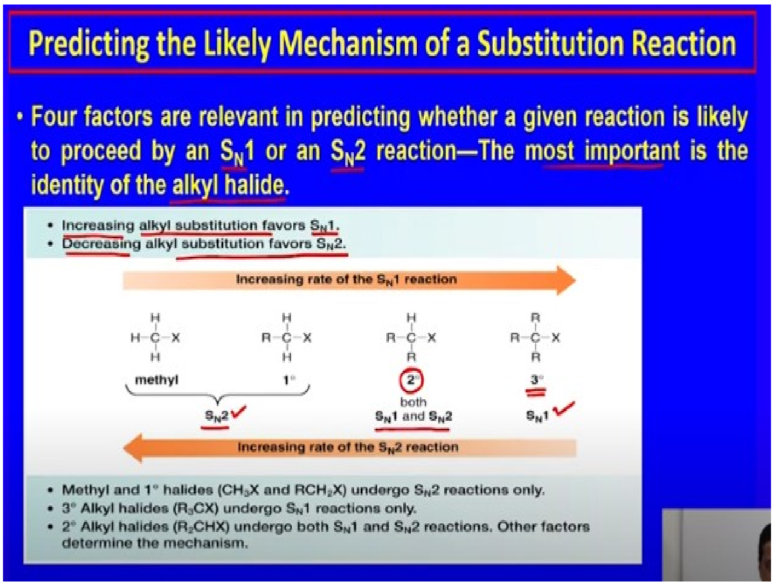

Predicting the Likely Mechanism of a Substitution Reaction

- Four factors are relevant in predicting whether a given reaction is likely to proceed by an S_N1 or an S_N2 reaction—The most important is the identity of the alkyl halide.

- Increasing alkyl substitution favors S_N1.
- Decreasing alkyl substitution favors S_N2.

- Methyl and 1° halides (CH_3X and RCH_2X) undergo S_N2 reactions only.
- 3° Alkyl halides (R_3CX) undergo S_N1 reactions only.
- 2° Alkyl halides (R_2CHX) undergo both S_N1 and S_N2 reactions. Other factors determine the mechanism.

So four factors are relevant in predicting whether a given reaction is likely to proceed by SN1 or SN2 reaction pathway. The most important is the identity of the alkyl halide. Increasing the alkyl substitution favors SN1. Decreasing the alkyl substitution favors SN2. So that means a more substituted alkyl halide will prefer SN1. A less substituted alkyl halide will prefer SN2.

And the intermediate one which is 2 degree alkyl halide can have SN1 and SN2 pathways depending on other factors that may be influencing the reaction.

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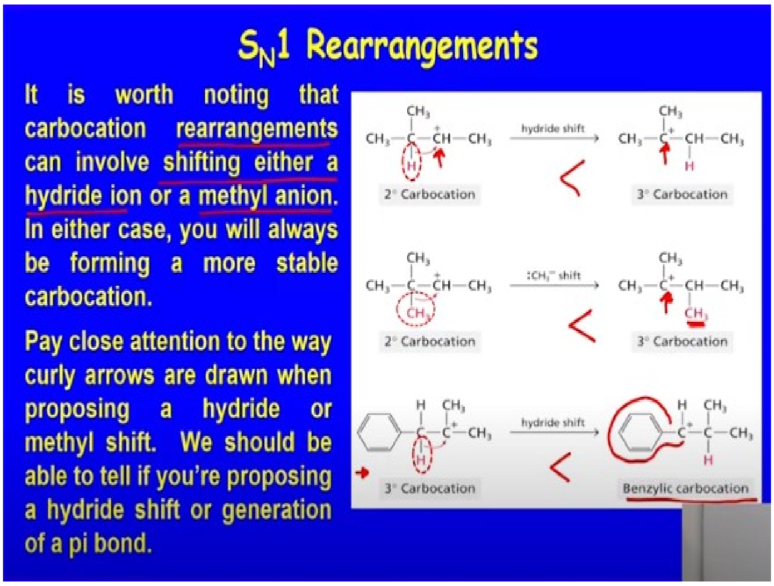

S_N1 Rearrangements

It is worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion. In either case, you will always be forming a more stable carbocation.

Pay close attention to the way curly arrows are drawn when proposing a hydride or methyl shift. We should be able to tell if you're proposing a hydride shift or generation of a pi bond.

So in case of SN1 reaction we must now introduce you to a fact that there may be a rearrangement of ions or atoms in the carbocation which can generate a more stable carbocation in a process which we call as a hydride shift or a methyl shift. So it is worth noting that carbocation rearrangements can involve shifting of either hydride ion or a methyl anion. So here what we have is a 2 degree carbocation.

This carbon is a 2 degree carbocation. And if this hydride shifts from the adjacent carbon to this carbocation site with its electron, we generate a new carbocation which is a 3 degree carbocation and is more stable compared to the 2 degree carbocation. Therefore, as soon as this 2 degree carbocation is formed, this hydride shift is possible and it generates a more stable carbocation.

Similarly, here in the second example, you have a methyl group connected to the carbocation, which is a 2 degree carbocation. And if this methyl group shifts to the carbocation positive site with the one pair of electrons we get a new 3 degree carbocation which is again more stable than the original 2 degree carbocation.

Therefore, this type of hydride or methyl shift is very common, when you are having a reaction going through SN1 pathway. In this particular case, in the third reaction here, where the hydride is shifting from the benzylic position to the carbocation site, making a new carbocation which is a benzylic carbocation, which can get delocalized over the aromatic ring and hence it can have better stability.

Therefore, this benzylic carbocation is again higher stability than compared to the 3 degree carbocation from which it got generated. So depending on the nature of carbocation and the groups that are associated with the adjacent carbon atom, it is always possible to have a new carbocation, which is more stable than the original carbocation that had formed in the first step of the reaction.

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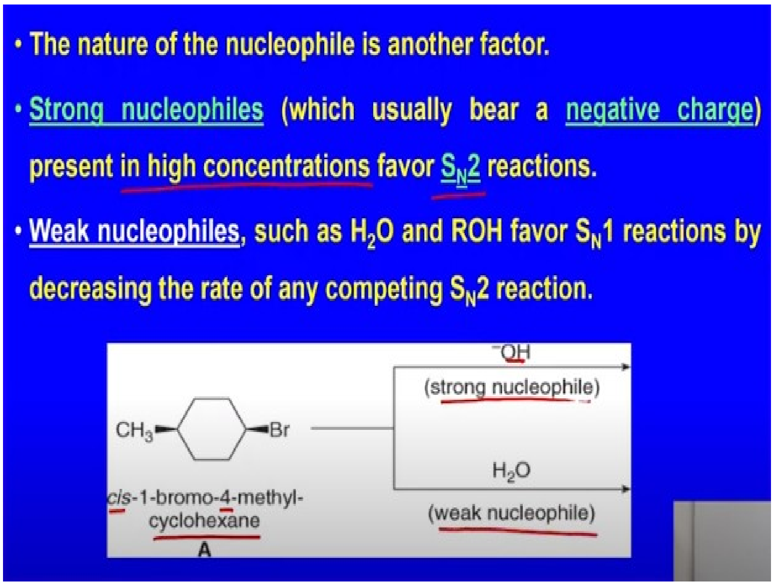

- The nature of the nucleophile is another factor.
- Strong nucleophiles (which usually bear a negative charge) present in high concentrations favor S_N2 reactions.
- Weak nucleophiles, such as H_2O and ROH favor S_N1 reactions by decreasing the rate of any competing S_N2 reaction.

The second factor is the nature of the nucleophile. A strong nucleophile which is which usually bear a negative charge present in high concentration favors SN2 reaction. A strong nucleophile favors SN2 reaction. A weak nucleophile such as water, alcohol, etc., favor SN1 reaction by decreasing the rate of any competing SN2 reaction. So let us try to understand this using a given example here.

If we start the reaction with cis-1-bromo-4-methyl-cyclohexane and we use separately a strong nucleophile like OH- and a weak nucleophile like water, let us see what happens to these two different reactions.

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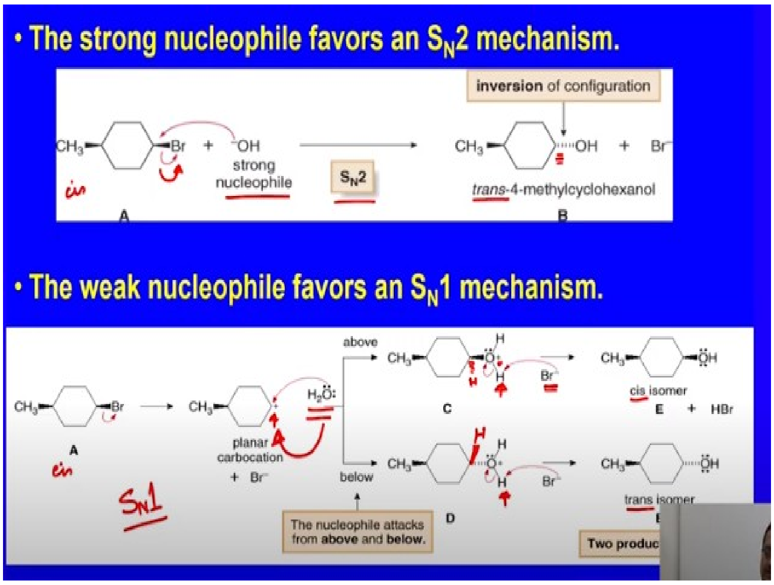

- The strong nucleophile favors an S_N2 mechanism.
- The weak nucleophile favors an S_N1 mechanism.

In the first case when we use a strong nucleophile, this prefers SN2 reaction pathway and OH- attacks from the backside and removes Br- and makes a product with inversion of configuration. Here this was a cis compound, here this is now a trans compound. But when we use the weak nucleophile, the water molecule, the first thing that happens is the C-Br bond is broken and a carbocation is formed.

And then this carbocation is attacked by water molecule either from top or from bottom. So when water molecule comes from top, the hydrogen goes down. When the water molecule comes from bottom, the hydrogen goes up. And then this water molecule being added carries a positive charge. In the medium we have Br- which takes up a proton and makes it a neutron species.

And we started with a cis isomer and have got a cis isomer if the attack comes from the top. But if the attack happens from the bottom, the same reaction pathway is followed, if proton is abstracted and a neutral compound is formed, we get a trans isomer. So in this particular case, when we are using a weaker nucleophile the reaction is going through SN1 mechanism and from a cis compound, we get a mixture of cis and trans.

Whereas in case of SN2 mechanism using a strong nucleophile, the same substrate gives you only one product which is a trans compound. So this is how the nature of nucleophile can dictate the reaction pathway for SN1 and SN2 reactions or the other substitution reactions.

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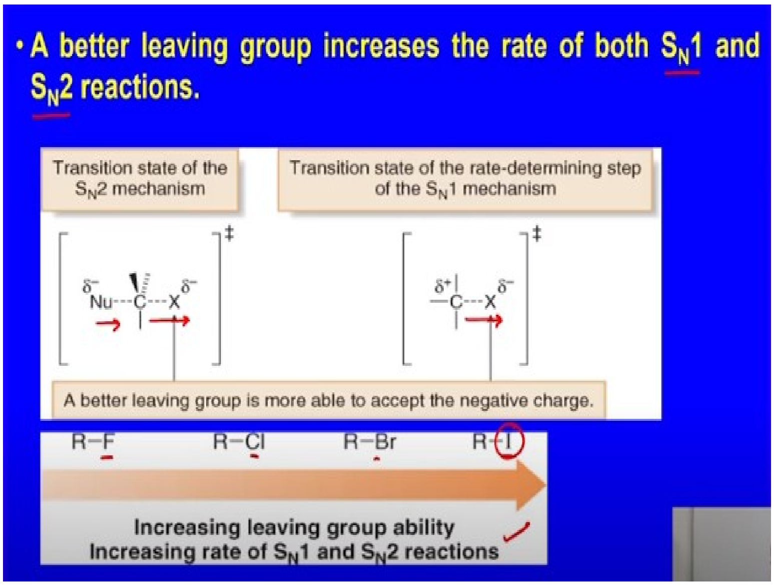

- A better leaving group increases the rate of both S_N1 and S_N2 reactions.

Transition state of the S_N2 mechanism

Transition state of the rate-determining step of the S_N1 mechanism

A better leaving group is more able to accept the negative charge.

R−F R−Cl R−Br R−I

Increasing leaving group ability
Increasing rate of S_N1 and S_N2 reactions

A better leaving group increases the rate of both SN1 and SN2 reaction. This is obvious. Why? Because in both the reactions, the leaving group breaks the bond with the carbon center and allows the reaction to happen. So a better leaving group is capable to break the bond easily and hence, it facilitates the reaction. So in case of SN2 reaction, when a new bond is formed, the C-X bond gets broken.

In case of SN1 reaction the first C-X bond is broken. So in both the cases the bond breaking is very important and weaker the bond It is easy to break them. So increasing the leaving group ability increases the rate of both SN1 and SN2 reactions. So fluoro to chloro to bromo to iodo, iodide being a better leaving group, this C-I bond breaks faster in case of both SN1 and SN2 reactions.

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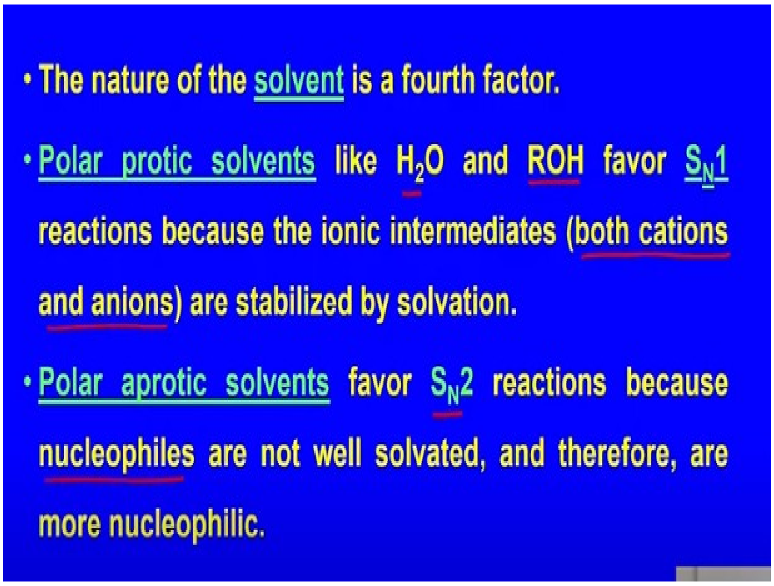

- The nature of the solvent is a fourth factor.
- Polar protic solvents like H_2O and ROH favor S_N1 reactions because the ionic intermediates (both cations and anions) are stabilized by solvation.
- Polar aprotic solvents favor S_N2 reactions because nucleophiles are not well solvated, and therefore, are more nucleophilic.

The nature of the solvent is a fourth factor. Polar protic solvents like water, alcohol etc., favor SN1 reactions because the ionic intermediates that is your carbocation and the anion that is released from the leaving group are stabilized by solvation and hydrogen bond formation. And polar aprotic solvents favor SN2 reaction because nucleophiles are not well solvated and therefore are more nucleophilic.

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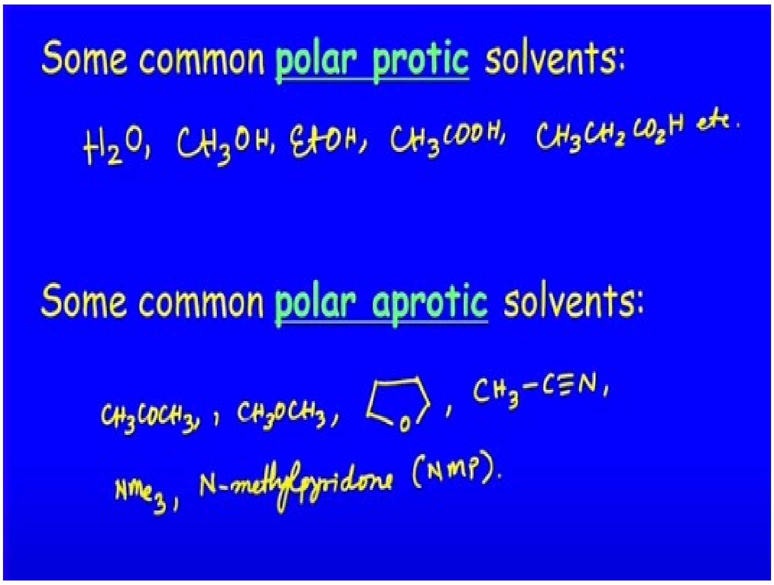

Some common **polar protic** solvents:

H_2O, CH_3OH, EtOH, CH_3COOH, $CH_3CH_2CO_2H$ etc.

Some common **polar aprotic** solvents:

CH_3COCH_3, CH_3OCH_3, , $CH_3-C \equiv N$,

NMe_3, N-methylpyridone (NMP).

So what are the common polar protic solvents? Of course, water, methanol, ethanol, acetic acid, propionic acid etc. And common polar aprotic solvents are acetone, ether, tetrahydrofuran, acetonitrile, triethylamine and N-methylpyridone or NMP. So these are different solvents that are used in various substitution reactions.

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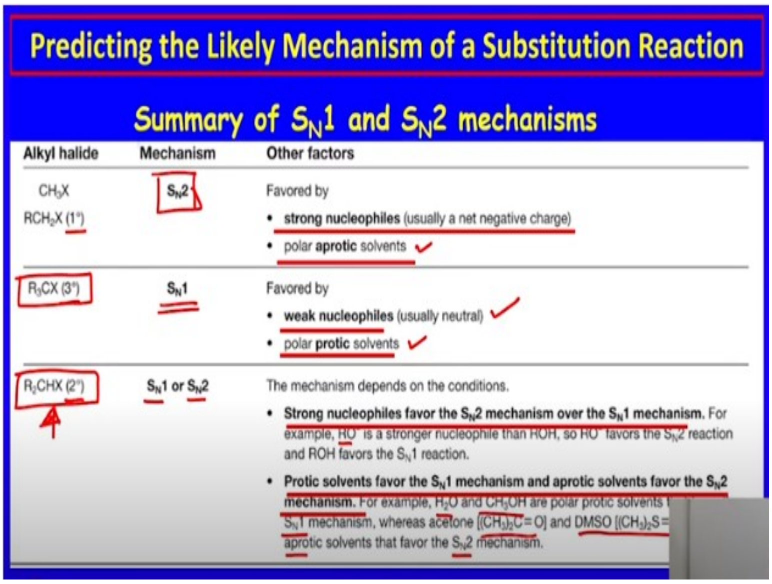

Predicting the Likely Mechanism of a Substitution Reaction

Summary of S_N1 and S_N2 mechanisms

Alkyl halide	Mechanism	Other factors
CH_3X RCH_2X (1°)	S_N2	Favored by • **strong nucleophiles** (usually a net negative charge) • polar **aprotic** solvents ✓
R_3CX (3°)	S_N1	Favored by • **weak nucleophiles** (usually neutral) ✓ • polar **protic** solvents ✓
R_2CHX (2°)	S_N1 or S_N2	The mechanism depends on the conditions. • **Strong nucleophiles favor the S_N2 mechanism over the S_N1 mechanism.** For example, HO^- is a stronger nucleophile than ROH, so HO^- favors the S_N2 reaction and ROH favors the S_N1 reaction. • **Protic solvents favor the S_N1 mechanism and aprotic solvents favor the S_N2 mechanism.** For example, H_2O and CH_3OH are polar protic solvents S_N1 mechanism, whereas acetone [$(CH_3)_2C=O$] and DMSO [$(CH_3)_2S=$ aprotic solvents that favor the S_N2 mechanism.

So if we want to summarize the SN1 and SN2 reaction mechanisms in predicting the likely mechanism for substitution reaction, we have three factors to talk about the alkyl halide, which can be 1 degree, 3 degree and 2 degree. In case of methyl and 1 degree SN2 reaction is favored. It is favored by strong nucleophiles usually a negatively charged nucleophile and it is favored in case of polar protic solvents.

3 degree alkyl halides prefer SN1 reaction mechanism pathway. And normally it proceeds using the weak nucleophiles and usually neutral nucleophiles and they prefer polar protic solvents which can solubilize or which can form hydrogen bonds with both the carbocation and the anion that are formed after the bond breaking process. The secondary alkyl halides can undergo both SN1 or SN2 depending on the nature of the nucleophile depending on the solvent and so on.

So strong nucleophiles favor SN2 mechanism over SN1 mechanism. For example, RO- is a stronger nucleophile than ROH. So RO- favors SN2 reaction over SN1 reaction in case of 2 degree alkyl halide. On the other hand, polar protic solvents favor SN1 mechanism and aprotic solvents favor SN2 mechanism for a 2 degree alkyl halide.

So for example, water, methanol or any other alcohol which are polar protic solvents, they favor the SN1 mechanism for a 2 degree alkyl halide. Whereas the acetone, DMSO etc., which are polar aprotic solvents that favor SN2 mechanism in case of 2 degree alkyl halides. So this slide actually summarizes the preference for SN1 and SN2 reactions for different types of substrates and different types of nucleophiles and different solvents.

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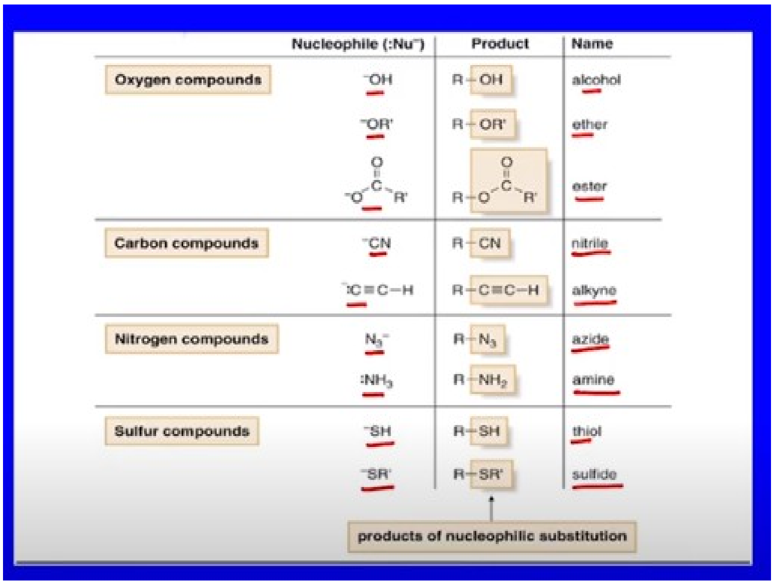

	Nucleophile (:Nu⁻)	Product	Name
Oxygen compounds	^{-}OH	$R-OH$	alcohol
	$^{-}OR'$	$R-OR'$	ether
	$^{-}O-C(=O)-R'$	$R-O-C(=O)-R'$	ester
Carbon compounds	^{-}CN	$R-CN$	nitrile
	$^{-}:C\equiv C-H$	$R-C\equiv C-H$	alkyne
Nitrogen compounds	N_3^{-}	$R-N_3$	azide
	$:NH_3$	$R-NH_2$	amine
Sulfur compounds	^{-}SH	$R-SH$	thiol
	$^{-}SR'$	$R-SR'$	sulfide

So in this table what I am trying to show are different types of oxygen containing compounds, carbon compounds, nitrogen compounds and sulfur compounds which are different types of nucleophiles. So in that case, the products are alcohol, ether or ester. When it is carbon based nucleophile then it is cyanide or acetylide.

So the products are nitrile and alkyne. The nitrogen based nucleophiles are azide and ammonia. So azide is forming with alkyl azide or it forms an amine. Sulfur compounds are SH and SR. So it can form thiol or a sulfide. So these are the products of nucleophilic substitution reaction.

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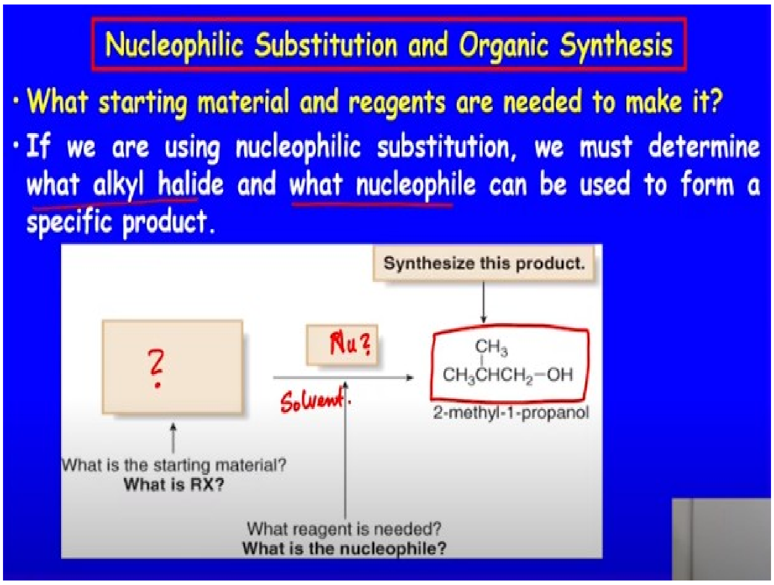

Nucleophilic Substitution and Organic Synthesis

- What starting material and reagents are needed to make it?
- If we are using nucleophilic substitution, we must determine what alkyl halide and what nucleophile can be used to form a specific product.

Synthesize this product.

$$\overset{CH_3}{CH_3CHCH_2{-}OH}$$

2-methyl-1-propanol

What is the starting material?
What is RX?

What reagent is needed?
What is the nucleophile?

So nucleophilic substitution reaction and organic synthesis. If we are trying to target a molecule, we need to identify what substrate we should use. And based on that we need to identify what should be the nucleophile and what should be the solvent. So I am giving you a problem here to solve at your home that what starting material and reagents are needed to make this particular compound.

I want to know what starting material or what RX you should use? What nucleophile should be used? And what should be the solvent that should be used for this particular reaction? So if we are using nucleophilic substitution reaction, we must determine the alkyl halide, the nucleophile to form this particular specific product.

So with this for the time being we will conclude the discussion on the substitution reactions. In the following lecture we will start talking about the other type of organic reaction, which are elimination reactions.