Symmetry, Stereochemistry and Applications
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Lecture - 31
Mechanism of Nucleophilic Substitution Reaction

Welcome back to the course entitled Symmetry, Stereochemistry and Applications. In the previous lecture, we started discussing about alkyl halides and we were talking about various aspects of substitution reaction. So in that we just talked about how the nucleophilicity and basicity can be understood.

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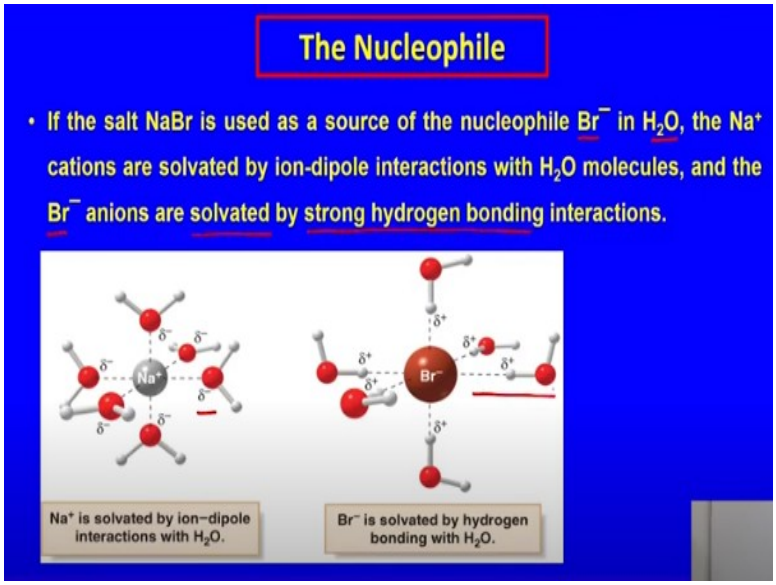

So when we try to understand how these reactions happen and what are the ions that are present in the solution and how are they stabilized in the solvent. If a salt sodium bromide is used as a source of a nucleophile, bromine or Br- in water, sodium plus cations are solvated by ion-dipole interaction as shown here with water molecules and the bromide anions are solvated by strong hydrogen bonding interactions as shown here.

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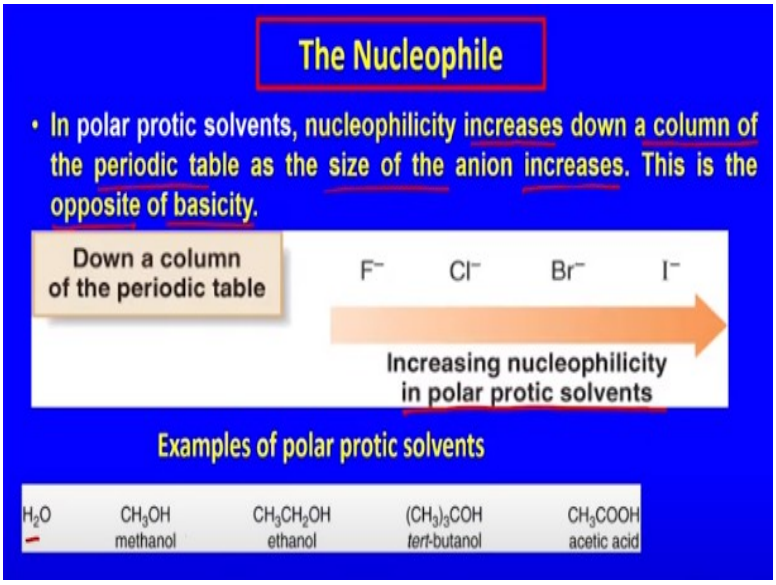

So in polar protic solvents like methanol, ethanol etc., nucleophilicity increases down the column of a periodic table as the size of the anion increases. This is opposite of basicity. So down the periodic table from fluoride to chloride to bromide to iodide, nucleophilicity increases in polar protic solvents because these larger groups are easily solvated by formation of hydrogen bond in solution.

Example of good polar protic solvents are water, methanol, ethanol, tertiary butyl alcohol, acetic acid, etc.

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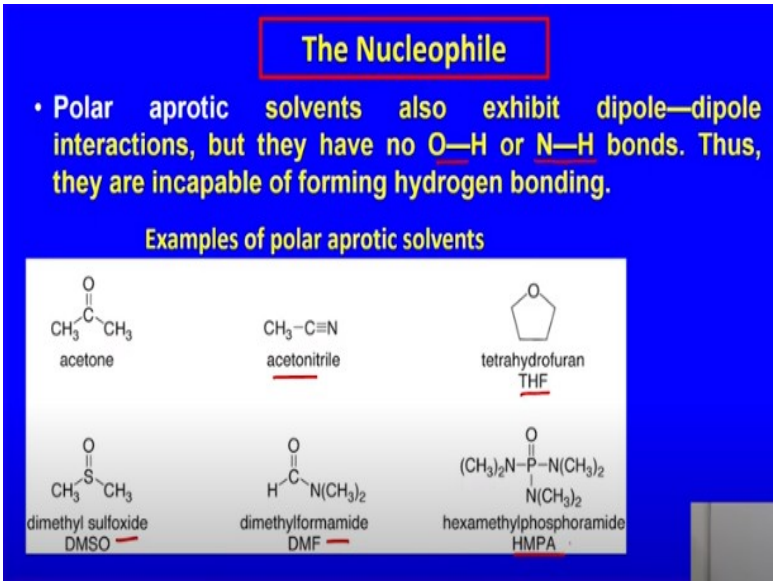

Polar aprotic solvents also exhibit dipole-dipole interaction, but they do not have any O-H or N-H bonds. Thus they are incapable of forming hydrogen bonds. See the

examples of polar aprotic solvents are acetone, acetonitrile, tetrahydrofuran, dimethylsulfoxide, DMF, HMPA, etc.

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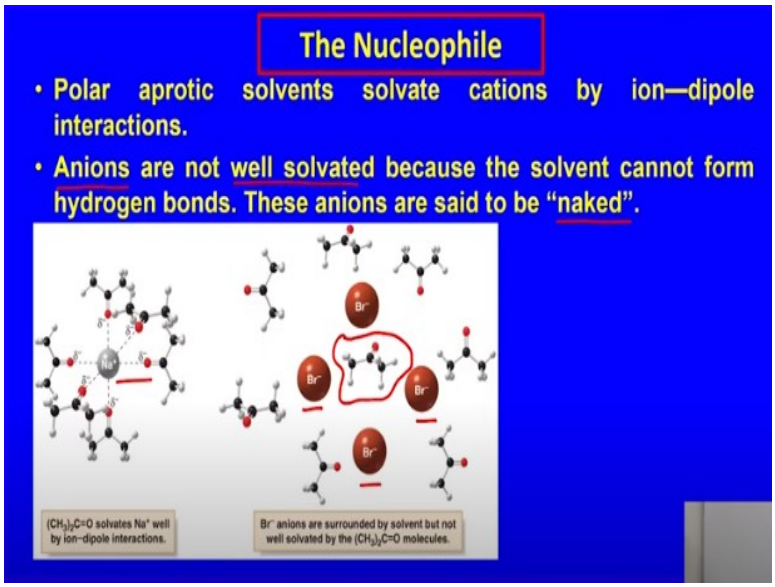

Polar aprotic solvents solvate cations by ion dipole interaction that we have already shown like in case of an acetone it forms ion dipole interaction. But anions are not well solvated because the solvent cannot form hydrogen bonds. So these anions are said to be naked. These anions do not interact, the anions which we have here, they do not interact with the solvent which is acetone. So Br- anions are surrounded by solvent but not well solvated.

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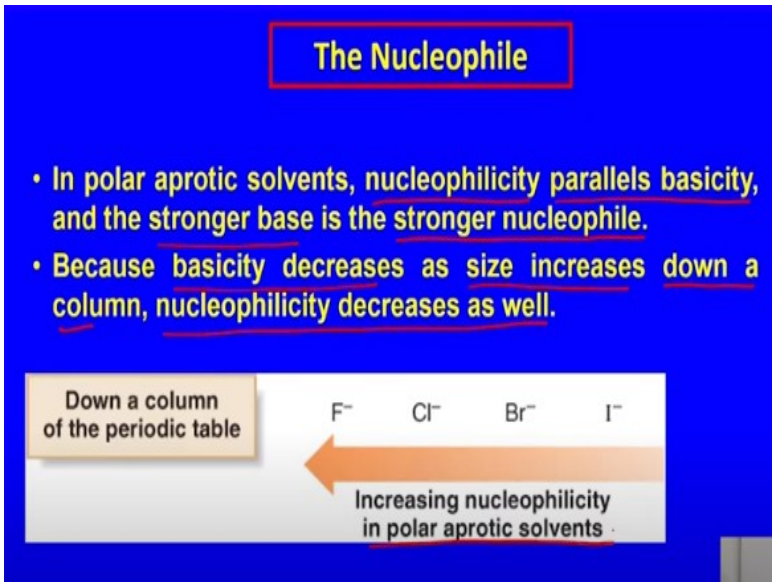

In polar aprotic solvents, polar aprotic solvents nucleophilicity parallels basicity and the stronger base is a stronger nucleophile because basicity decreases as the size

increases down a column, nucleophilicity decreases as well. So in case of halogens fluoride, chloride, bromide and iodide the nucleophilicity increases from iodide to fluoride in polar aprotic solvent. These trends will be very necessary when we try to understand what happens when you do a reaction of SN1 or SN2 reaction with these different types of nucleophiles.

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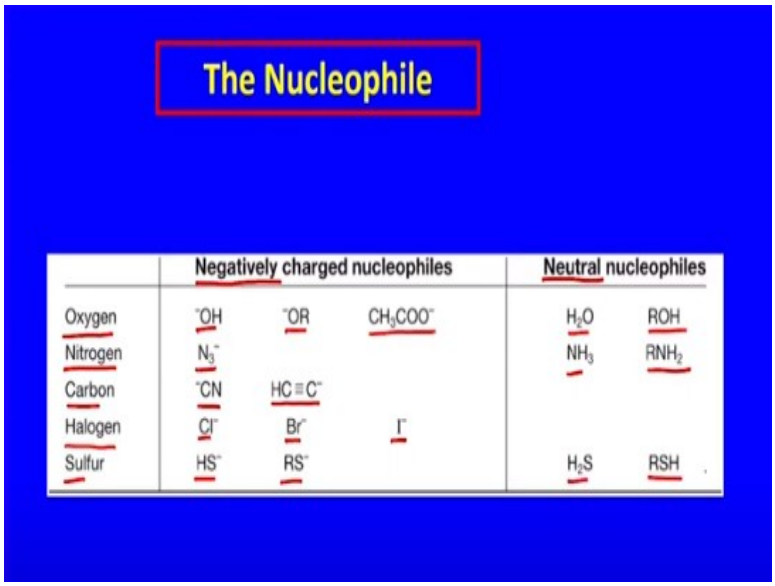

So when we try to understand what are possible nucleophiles that we may encounter, there are two different types of nucleophiles we can initially think of, the negatively charged nucleophiles and neutral nucleophiles. Negatively charged nucleophiles can be oxygen based, that is OH-, OR-, acetate or any other carboxylic acetate, carboxylic acid anion. Nitrogen based like as azides. Carbon based like cyanide or acetylate.

Halogen based which may be chloride, bromide or iodide. Sulfur based which is SH- or RS-. While the neutral ones are water and alcohol, for oxygen based nucleophile ammonia or any other amine. For nitrogen based and sulfur based maybe H2S, RSH and so on.

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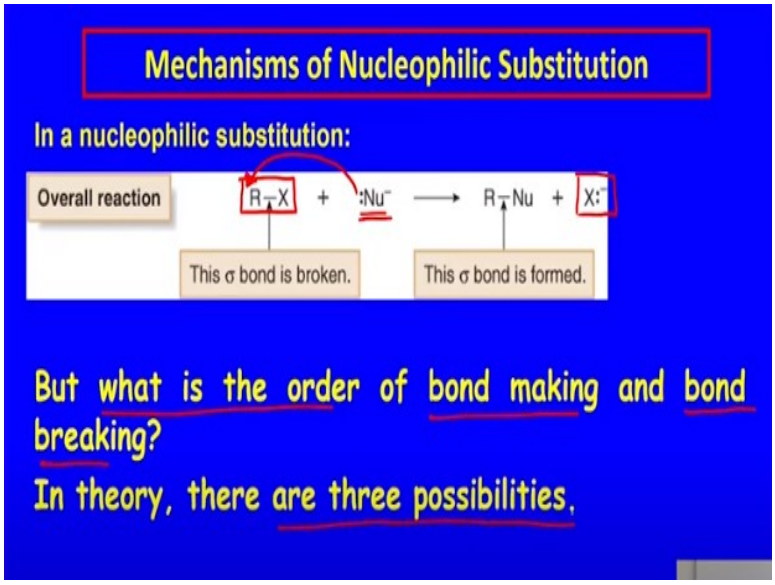

So the overall reaction that we are trying to understand in a nucleophilic substitution is that the sigma bond between R and X is broken, a nucleophile is required, which donates its electron to the alkyl halide carbon and forms a new sigma bond and the leaving group is thrown out of this molecule. Now the question is what is the order of this bond making and bond breaking process?

In which order these three things happen, bond breaking and bond making and elimination? Theoretically, there are three possibilities. Let us see those three possibilities one by one.

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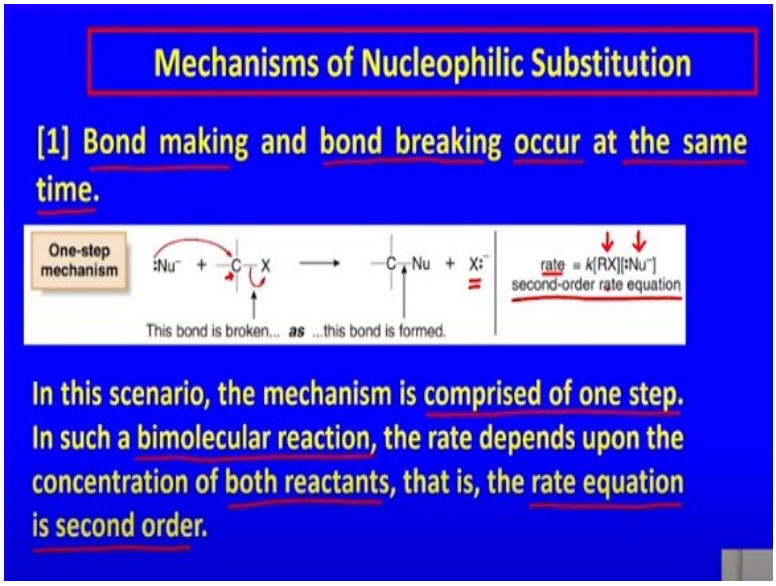

The first possibility is bond making and bond breaking occur at the same time simultaneously. That means, as soon as the nucleophile attacks at the nucleophilic

center, the C-X bond is simultaneously broken and a new bond is formed. So if the reaction happens like this, then the rate of reaction will have the component of RX and the nucleophile concentration.

So in this scenario the mechanism is comprised of one step in such a biomolecular reaction, because in this both the molecules are involved. The rate depends upon the concentration of both the reactants. That is the rate equation contains the concentration of RX and nucleophile both. So it is a second order rate equation.

So the rate of the reaction will change if you change the concentration of RX or if you change the concentration of the nucleophile.

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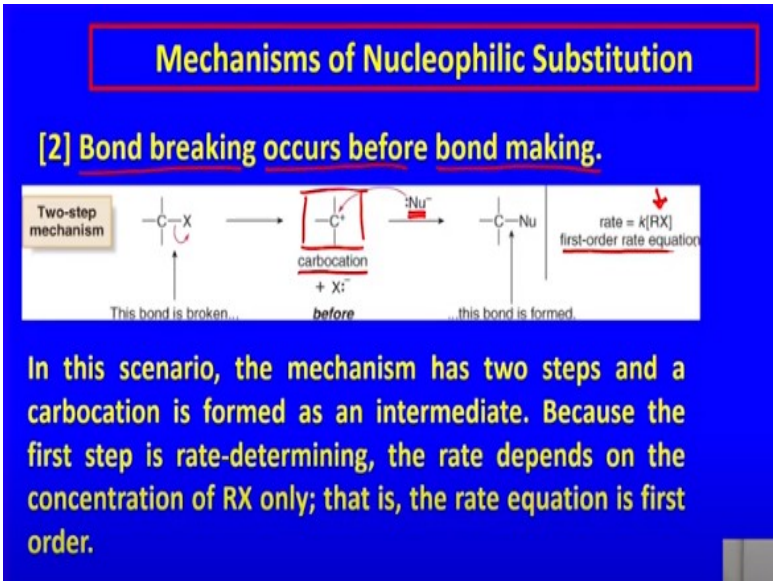

The second scenario is that the bond breaking process occurs before the bond formation process. So what happens is that the carbon halogen bond is broken. A new reactive species which is called carbocation is formed. And then that carbocation reacts with the nucleophile that is present in the solution and the bond is formed.

In this case, the rate of the reaction is only determined by the concentration of the RX that is the alkyl halide and that is why we call this as a first order reaction or first order rate equation. So here the mechanism has two steps and the carbocation is formed as an reaction intermediate because the first step is rate determining step. The rate depends on the concentration of RX only. That is this is a first order kinetics.

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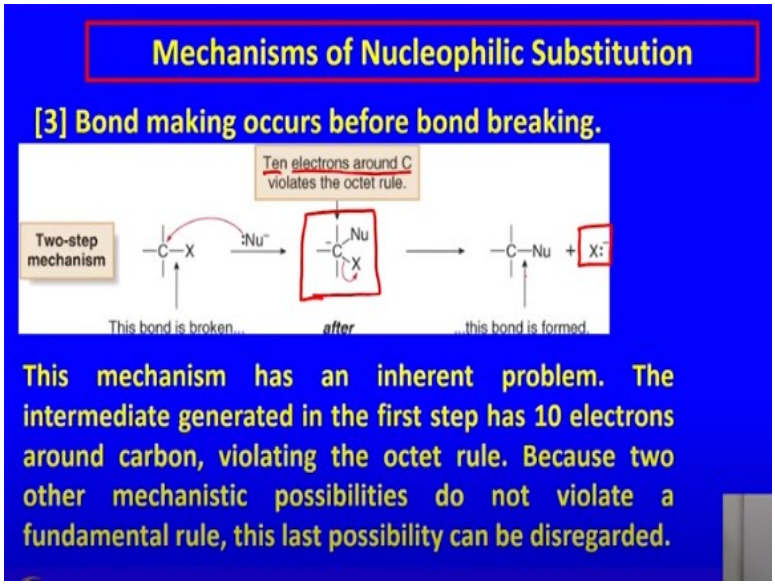

The third possibility, it is a possibility, theoretical possibility, is that bond making occurs before bond breaking. So if such kind of a reaction happens, the nucleophile attacks the carbon and you get a new species like this. What is wrong here? The central carbon atom now has 10 electrons which violates the octet rule. Therefore, this mechanism is not possible.

So it is not possible to form this compound and then eliminate the X and form the product. This of course, is a theoretical possibility, but it is not at all possible because it violates the octet rule that is there can be maximum eight electrons on a carbon atom.

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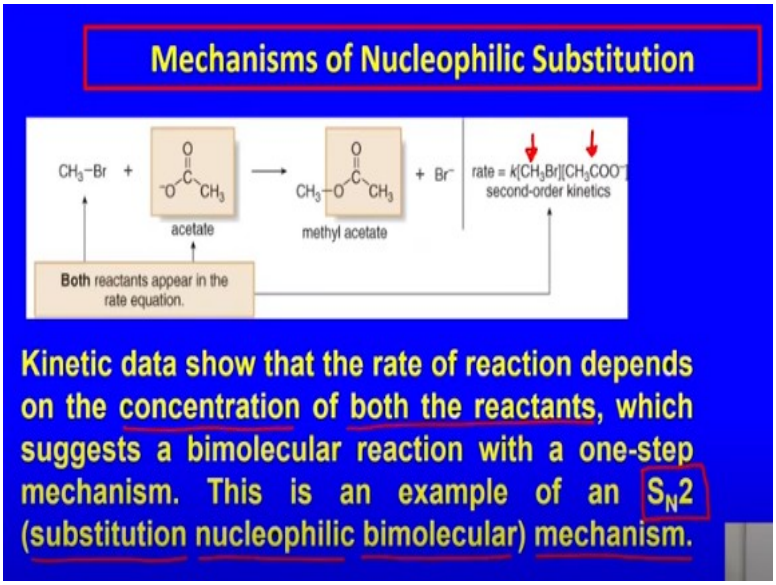

So when we are trying to understand these reactions, any of those reactions with example, we try to first see how the reaction rate is determined. We try to determine the rate of that those reactions by following the concentrations of the alkyl halide and the corresponding nucleophile.

So the kinetic data show that the rate of reaction depends on the concentration of both the reactants, which suggests a bimolecular reaction with a one-step mechanism and this is an example of SN2 mechanism, which means substitution nucleophilic biomolecular. So this is S, nucleophilic N, and 2 means it is a biomolecular process.

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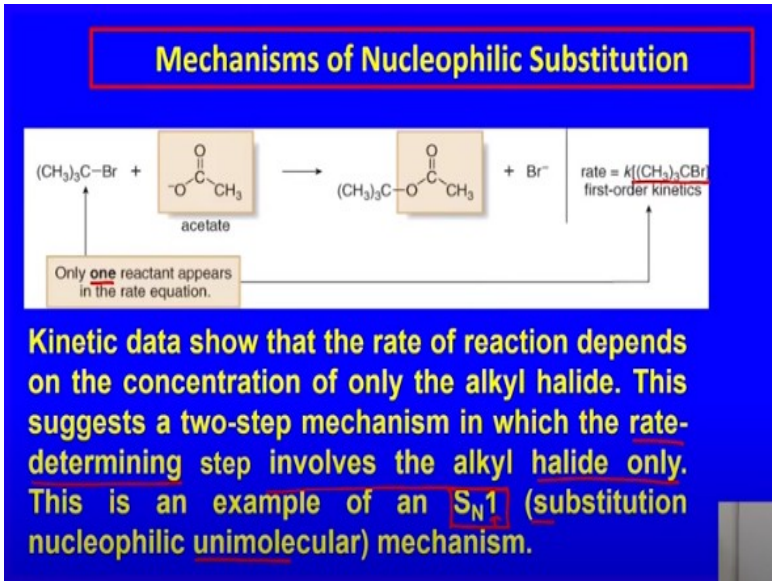

The next method that is the second process where the bond breaking and bond making happens separately, there only one reactant appears in the rate equation. Here it is only dependent on the alkyl halide, kinetic data shows that the rate of reaction depends only on the concentration of alkyl halide. So this mechanism suggest a two-step process in which the rate determining step involves the alkyl halide only.

That means the bond breaking step is the most important and slowest step. So then we call that reaction as SN1 or substitution nucleophilic unimolecular. So that 1 means you unimolecular. So that means in the rate determining step you have only one molecule.

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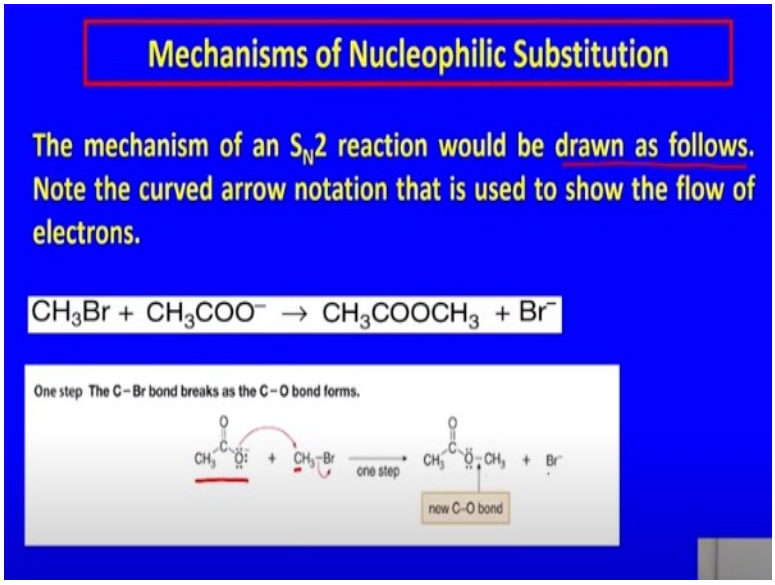

The mechanism of an SN2 reaction would be drawn in the following way. Note that the curved arrow notation is used to show the flow of electron which I have been using from the beginning itself. So when you have a nucleophile like acetate, the electron from oxygen attacks the carbon which is bonded to the bromine atom and in one step the product is formed and bromine, bromide ion is eliminated.

(Video Starts: 12:04) So this is how the reaction happens. Suppose here we have OH- which comes and attacks a methyl halide, it attacks the carbon from the backside and the halogen group or halide group leaves the reaction media immediately. So this mechanism which is happening in one step is the most important part of SN2 reaction. It is a biomolecular process and the bond making and bond breaking process happens simultaneously. **(Video Ends: 12:43)**

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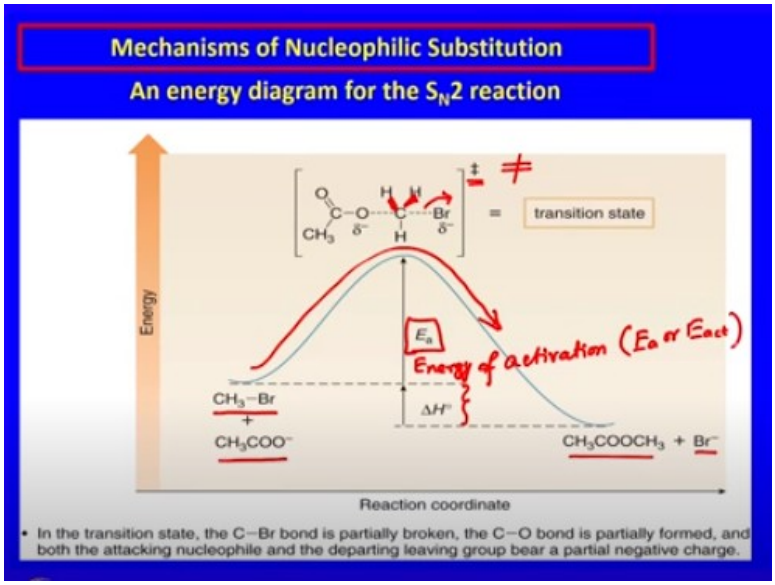

So when we try to draw the energy profile diagram for this SN2 reaction, we should draw something like this. When we start the reaction, we have methyl bromide and the acetate anion. When the acetate anion attacks methyl bromide, it forms a transition state like this, where if we try to draw it correctly, these hydrogen atoms are above and below the plane.

This acetate attacks the methyl group from one side and bromine gets released from the other side. So to achieve this state which is a transition state, normally we identify a transition state with a symbol hash is a transient species. And when the bromide is eliminated, you get the ester and the bromide separated. So when we try to calculate the delta H of a reaction, this difference is called the heat of reaction.

And the barrier, energy barrier that we have to cross through for this, this energy barrier that we need to cross through for this reaction is called the energy of activation generally written as Ea or Eact, okay.

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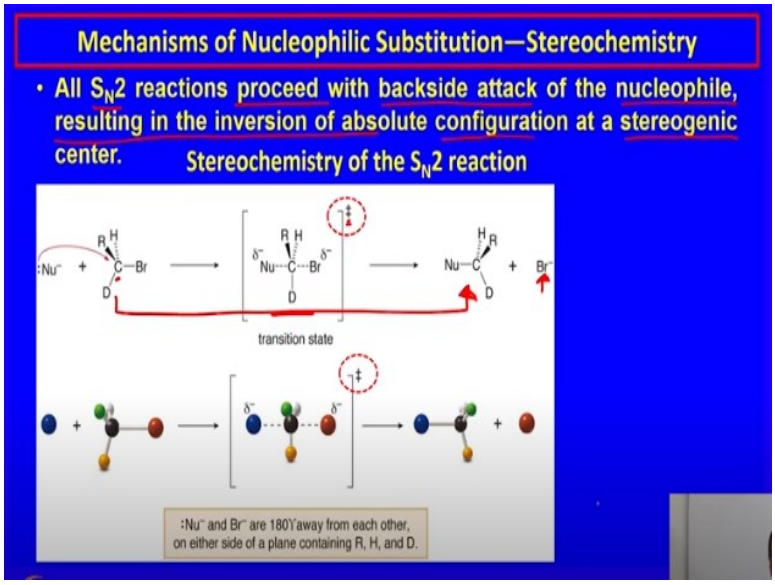

By now you must have seen that the SN2 reaction proceeds with a backside attack of the nucleophile resulting in the inversion of absolute configuration at the stereogenic center. So if you are doing a reaction with a chiral center which is here in this case, the nucleophile attacks from the backside. You form a three dimensional transient, transition state, transition state species, which is identified by that hash sign.

And then when the bromide leaves you get a stereochemically inverted molecule, right? So the absolute configuration of this gets changed to that during the reaction process. So in the case of a SN2 reaction on a chiral center, the absolute configuration gets inverted.

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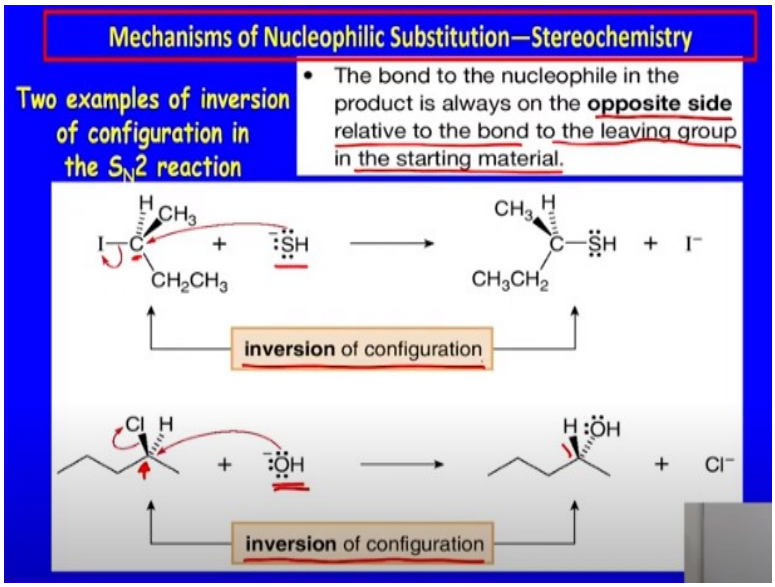

There are two examples of inversion of configuration in SN2 discussed in this slide. The bond to the nucleophile in the product is always on the opposite side relative to the bond to the leaving group in the starting material. So here if you attack with this SH group to this nucleophilic center, iodide is left. So the umbrella which was like this and because of the attack from this side, the umbrella gets inverted like that.

Similarly, in this case when OH- is used to attack this particular nucleophilic center, we get an inversion of configuration. Chlorine which was above the plane has left. The hydrogen which was below the plane has come to the above the plane, and OH has come from the backside. So what we see in these two cases is that the inversion of absolute configuration is taking place when the reaction happens through an SN2 mechanism.

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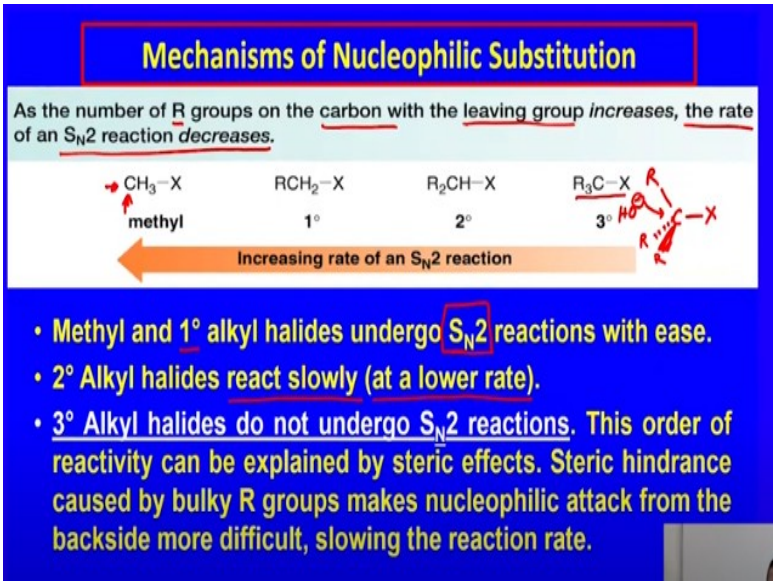

As the number of R groups on the carbon atom with the leaving group increases, the rate of SN2 reaction decreases. Why? Can you tell me? It is because when the attack happens from the backside, if this carbon is sterically hindered, then the backside attack is less visible and therefore, the probability of SN2 reaction decreases.

So in case of a 3 degree alkyl halide, when the molecule is like this, any nucleophile coming from the backside will have a steric hindrance. And therefore, this group will have less propensity for SN2 reaction. Whereas this methyl halide will have a better propensity for SN2 reaction. That is why methyl and 1 degree alkyl halides undergo SN2 reaction readily.

2 degree alkyl halides react slowly, that means at a slower rate. Sometimes you may have to do the reaction for several hours at a higher temperature and so on to facilitate the reaction. 3 degree alkyl halides do not undergo SN2 reactions. This order of reactivity can be explained by steric effects because you can see because of bulky groups, the nucleophile cannot attack the nucleophilic center of that alkyl halide and hence it lowers or reduces the reaction rate.

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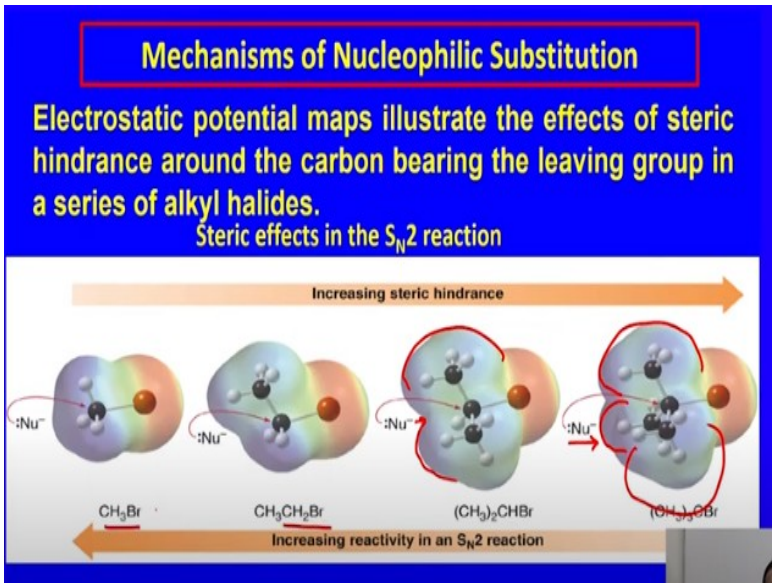

Electrostatic potential maps illustrate the effect of steric hindrance around the carbon bearing the leaving group in a series of alkyl halides here. So you see what I have tried to show in the previous slide, when you have three methyl groups, they are very bulky group and this backside is totally blocked, and hence the nucleophile does not get a chance to enter.

When you have two methyl groups, still the backside has little bit of entry. So it is possible that a nucleophile can attack these 2 degree alkyl halide and the reaction takes place for much much longer period of time. Whereas for 1 degree halide or methyl halide, this reaction happens almost readily.

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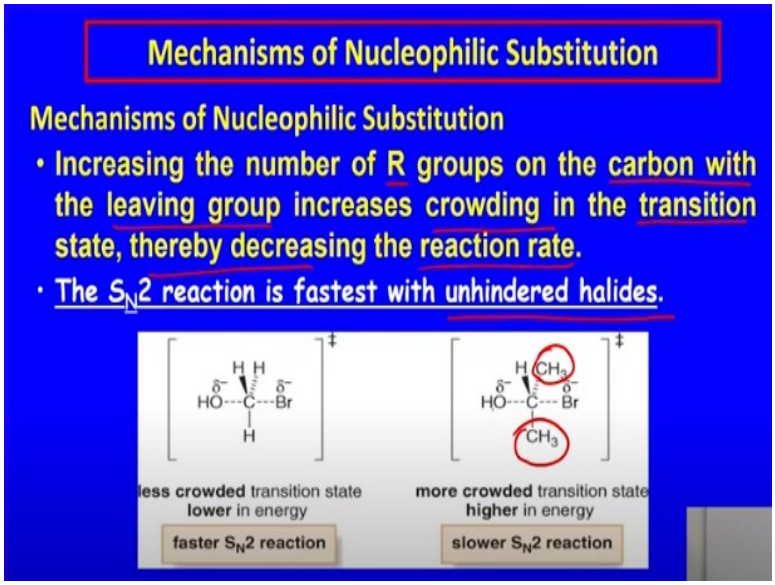

Increasing the number of R groups on the carbon atom with the leaving group increases the crowding in the transition state and therefore, decreasing the reaction rate. So the SN2 reaction is fastest with unhindered halides. So that means for one degree and methyl halide, you will have very high possibility or higher rate of SN2 reaction.

But when you have two or more methyl groups on the transition state that would be formed due to the backside attack of the nucleophile, then the reaction rate for SN2 reaction is much slower.

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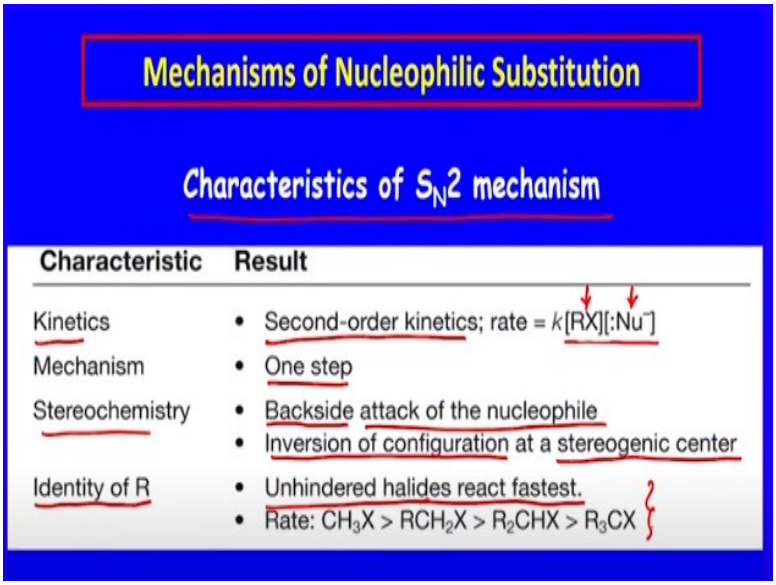

So what we learn from here is that the characteristics of SN2 mechanism can be tabulated like this. The kinetics, it is a second-order reaction, where the rate is

determined by the concentration of both alkyl halide and the nucleophile. The reaction mechanism happens in one step.

The stereochemistry indicates that backside attack of the nucleophile and inversion of absolute configuration at any stereogenic center and it depends on the identity of R. Unhindered halides react faster compared to the hindered halide groups. So here we could understand a few features of SN2 reaction.

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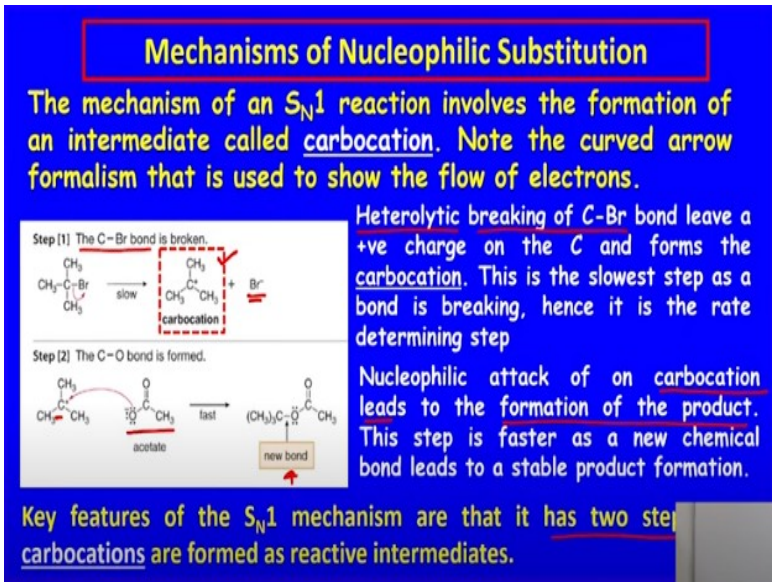

The mechanism of SN1 reaction involves the formation of an intermediate called carbocation. So what happens is in this case is the C-R bond is first broken, C-Br bond. And this bond breaking process is slow and what it forms is called a carbocation. So what happens is an heterolytic breaking of C-Br bond takes place and Br- leaves with the electron of the bond.

And then the nucleophile comes and attacks the nucleophilic carbon center of that CH3, sorry the carbocation and the new bond is formed. So nucleophilic attack of the on a carbocation leads to the formation of the product. So this step is faster as new chemical bonds leads to a stable product. Key feature of SN1 mechanism are that it has two steps. And carbocations are formed as reactive intermediate compared to the transition state in SN2 reaction.

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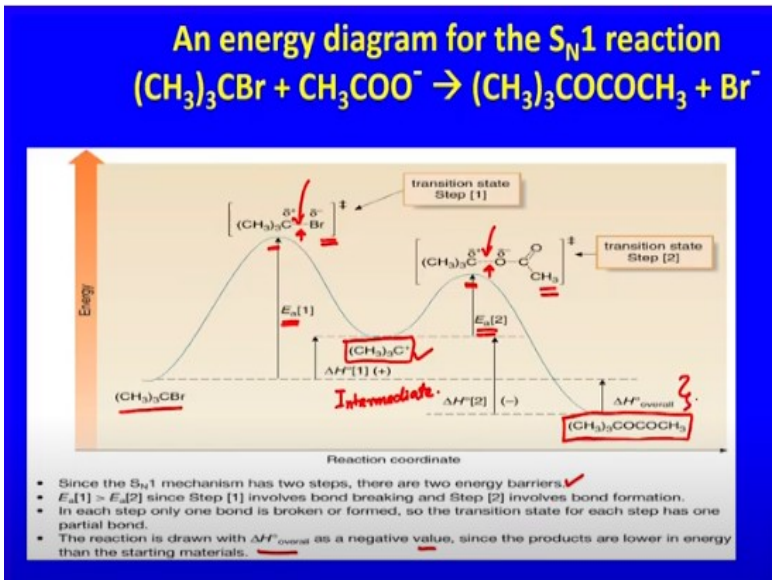

So when we try to draw the energy profile diagram for SN1 reaction, what we see are two humps. The first one is when the C-Br bond is about to break. The bond gets slightly elongated in the transition state when you give some heat and then that bond is broken and we form a stable species called a carbocation.

Under certain circumstances, one can isolate this carbocation and then this carbocation starts to form a new bond and the product is formed when the new bond has formed. So there are two different steps. There are two different transition states and one reaction intermediate. So the SN1 mechanism has two steps and there are two energy barriers.

The first energy of activation is always higher than the second energy of activation, because the carbocation is already energized. In each step, only one bond is broken or one bond is formed. So the transition state for each step has one partial bond. Unlike SN2 reaction you have two partial bonds.

The reaction is drawn with delta H zero overall as a negative value, which is this one, the energy difference between the starting alkyl halide and the final product.

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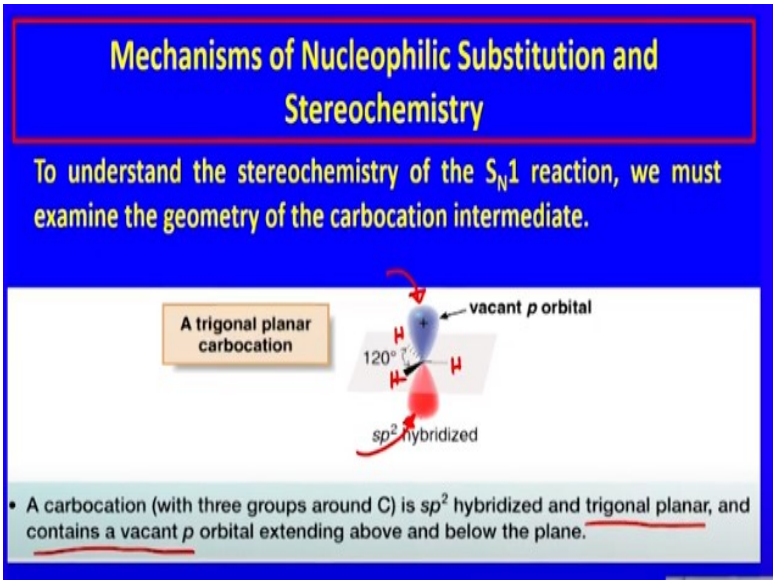

Now to understand the stereochemistry of SN1 reaction we must examine the geometry of the carbocation intermediate. The carbocation intermediate has a planar trigonal geometry having three bonds like that and we have a vacant p orbital. So the carbocation with a vacant p orbital is sp2 hybridized and trigonal planar in geometry and it contains a vacant p orbital which is now capable of accepting electron from the nucleophile.

And now what happens is the nucleophile can come from top or nucleophile can come from bottom.

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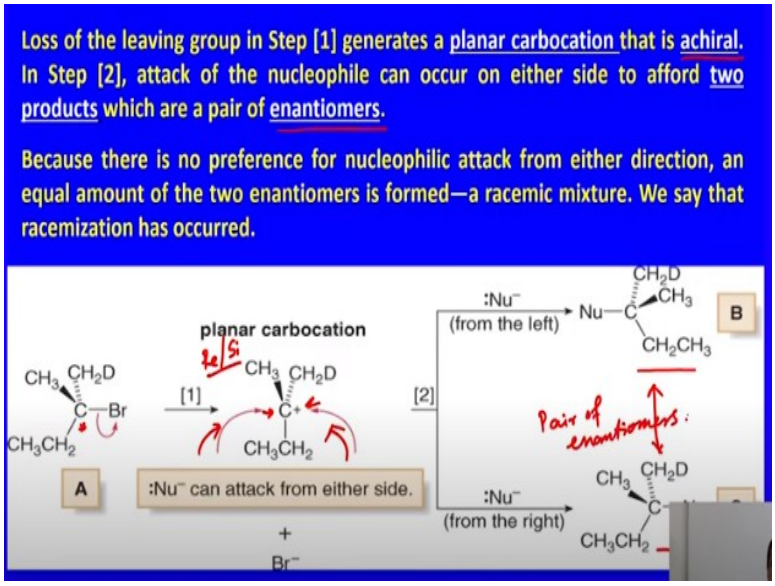

As a result, what happens that when the nucleophile is capable of attacking from either side, there are possibility of formation of two products which are isomers,

which are a pair of enantiomers. So loss of the leaving group in step 1 generates a planar carbocation which is achiral. In step 2, the attack of nucleophile can occur on either side of the carbocation to result in two products, which are a pair of enantiomers.

So here in this example, if you have a group, a compound A, which has a chiral center here, after removal of Br-, this particular carbocation has two faces, as we have already seen in our stereochemistry course. These two faces can be identified as Re or Si faces. And they can be also called as pro-R or pro-S faces and when the nucleophile attacks from the left hand side or from the right hand side, you get two different products B and C and these two compounds are a pair of enantiomers, right?

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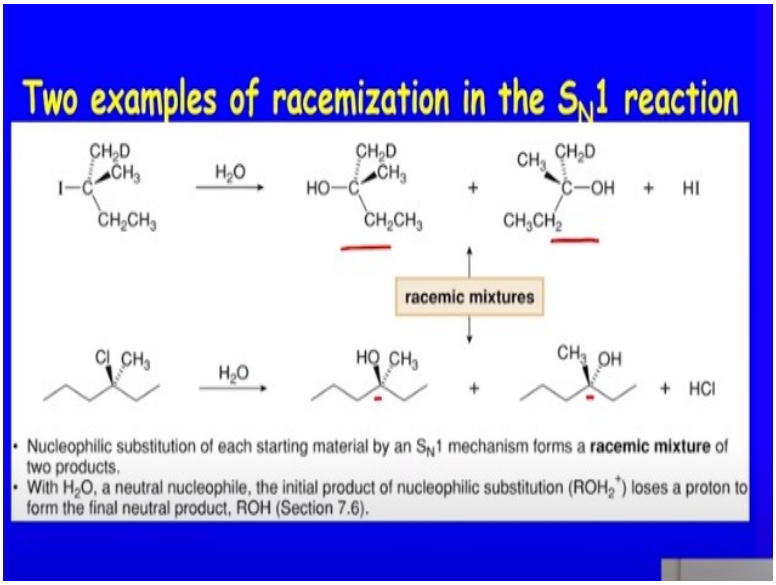

So again there can be two examples, which we can discuss. Here if you have water as your nucleophile you can get this or that which are enantiomers. Again with water being nucleophile one can react at the center and when chlorine leaves it form a carbocation here and then the carbocation reacts with water molecule, so the water can come from top or it can come from bottom giving you two different products.

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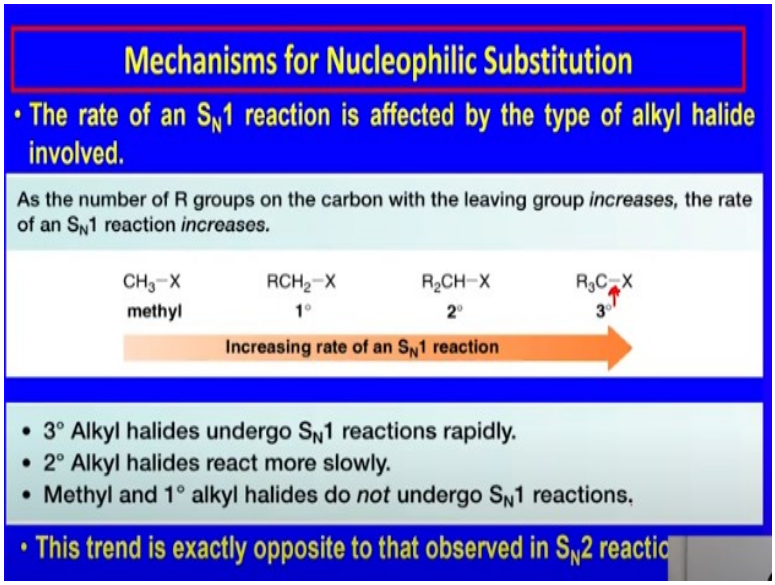

So the rate of SN1 reaction is affected by the type of alkyl halide that is involved. As the number of R groups on the carbon atom with the leaving group increases, the rate of SN1 reaction increases. That means more the, more polar the bond is, it is more prone for SN1 reaction. 3 degree alkyl halides undergo SN1 reactions rapidly. 2 degree alkyl halides react slightly slower. Methyl and 1 degree alkyl halides do not undergo SN1 reaction. This trend is exactly opposite to that we have seen in case of SN2 reactions.

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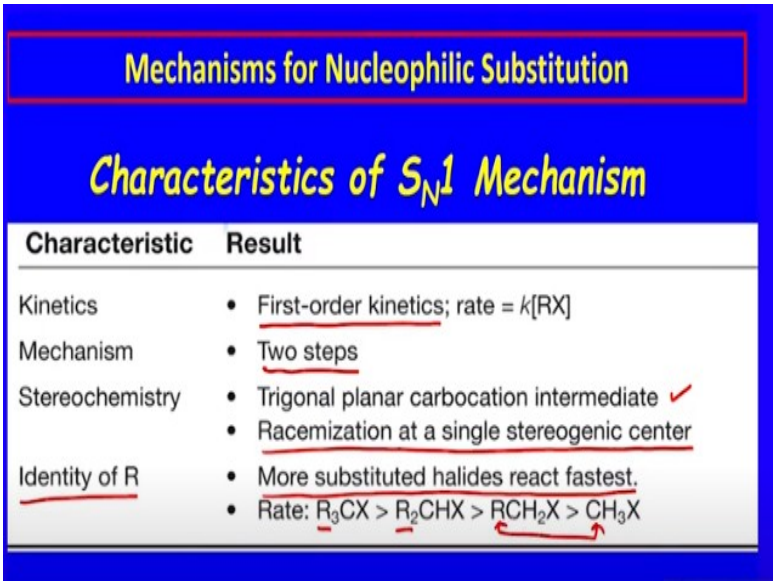

So to summarize the characteristics of SN1 reaction, it is a first order reaction. It has two steps. It forms a trigonal planar carbocation as an intermediate. It goes through a racemization process so the stereocenter gets racemized and more substituted alkyl

halides react faster. The identity of R involved influences that the more substituted alkyl halides react the fastest.

So the 3 degree alkyl halide has a much faster reaction than compared to a 2 degree halide and generally 1 degree alkyl halide and methyl halide they do not go through SN1 reaction mechanism. So we will continue from here in the next lecture.