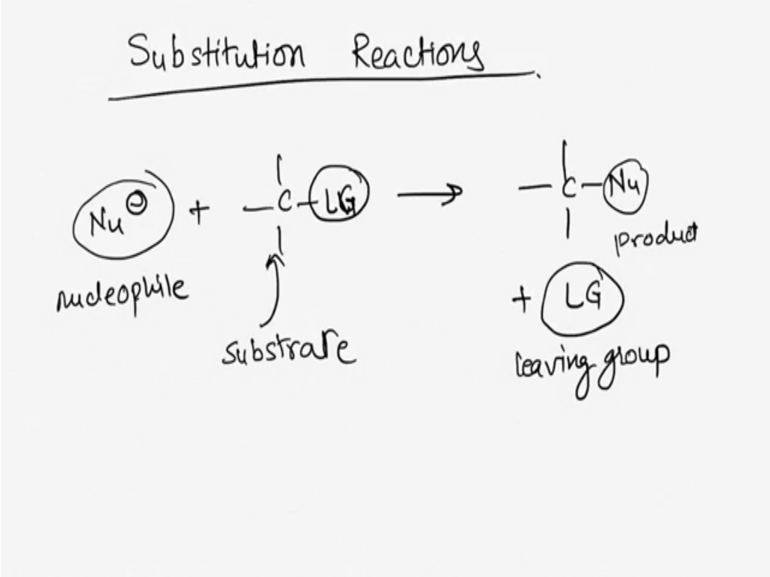
Introductory Organic Chemistry
Dr. Neeraja Dashaputre
Department of Chemistry
Indian Institute of Science Education and Research, Pune

Lecture – 39
Substitution & Elimination
Part 1

(Refer Slide Time: 00:15)



Welcome to Substitution reactions, the word substitution itself means that we are replacing something in a molecule with some other functional group. So, we are going to mainly cover nucleophilic substitution reactions and then there are two types of substitution reactions. Nucleophilic substitution unimolecular and nucleophilic substitution bimolecular reactions, but before we go ahead and look at each one of these I want to give an analogy, okay. So, just to discuss these two types, I am going to take an example of a football game; you must have heard the word substitution with respect to sports let's say football, right.

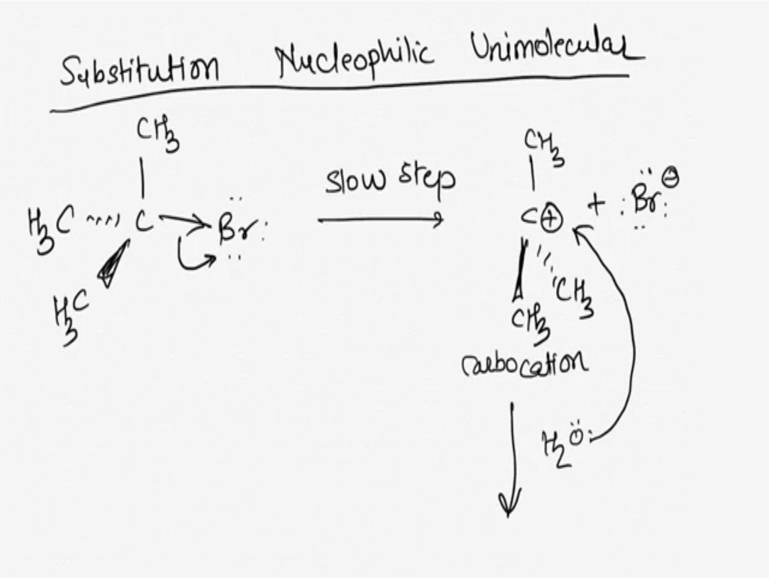
So, what happens is in a game for example, if one of the player gets injured he has to leave the field and then the coach has to substitute the place of this player with some other player, right. So, that is one way of substitution, but the other way of substitution is that that let's say that the coach feels that one player is not playing very well and in order to win he replaces this one player with a better player, right and kind of kicks this one player out, right. So, there are two different ways of substitution, even though the players are getting replace the same way; you can see that there are two different ways of substitutions that are happening here.

The first one where there is a vacancy on the field, because a player gets injured is somewhat similar to nucleophilic substitution unimolecular reaction, okay. And, the second one where a player is replaced by a better player is something similar to substitution nucleophilic bimolecular reaction. And, we are going to go over these reactions, but while going over these reactions just remember this analogy. okay. So, the word nucleophilic substitution really refers to any reaction in which the nucleophile which is really electron rich and is nucleus loving is going to replace something called as a leaving group, okay.

So, I am going to draw a very typical nucleophilic substitution reaction here where the nucleophile plus let's say a carbon that has the leaving group is going to do this nucleophilic substitution reaction. And, what you end up with is the new bond between the carbon and nucleophile and the leaving group will leave in the end of the reaction, okay. So now, we are going to pay attention to each one of these terminologies. So, leaving group is really the group that leaves. So, it's easier to kind of picture; nucleophile is the group that either attacks or replaces the leaving group. So, that's my nucleophile and this one compound, the compound that we begin with is called as a substrate and of course, we have the product formed, okay.

So, we have a nucleophile plus the substrate reacting to give you the product as well as the leaving group, okay. We will discuss these terminologies in much more detail, but before that let us begin with the first example of substitution nucleophilic reactions and I am going to begin with S_N1 reactions, okay or substitution nucleophilic unimolecular reactions, okay.

(Refer Slide Time: 04:07)

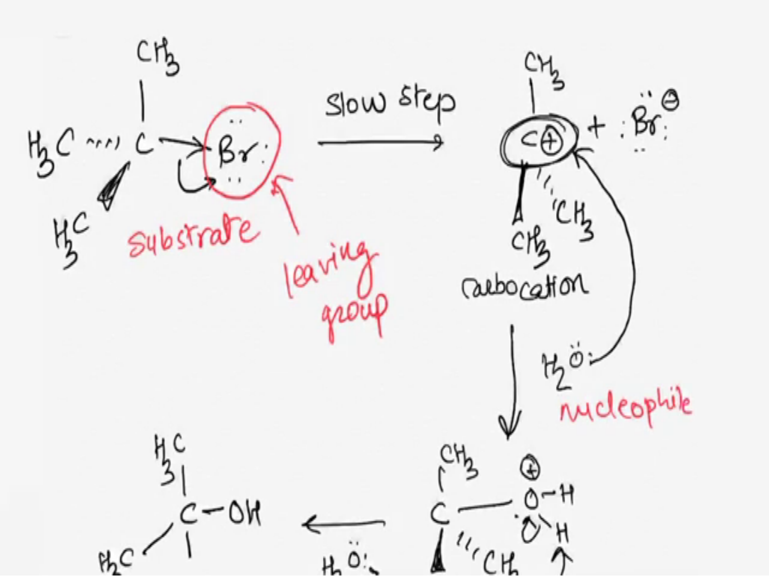


We will also go over what each one of these terms mean. So, let’s take a compound, tertiary butyl bromide. If we pay close attention to this particular compound which is also our substrate for this reaction, we know that the carbon-bromine bond is partially polarized. In the sense that bromine being more electronegative is pulling electrons towards it, kind of creating a delta positive on that carbon and a delta negative, a partial negative charge, on the bromine itself.

So, it’s a polar bond between carbon and bromine. Now, what happens is this bond between the carbon and bromine can break; it can break at a very slow rate not necessarily a very fast rate. But, it can break if I heat it up a little bit or warm the solution, what’s going to happen is that the bond will break such that carbon will be devoid of the bond electrons. So, what we create here is a carbocation and bromine will take both the electrons with it, right, kind of being the bromide ion, okay.

Now, this is a very slow step, it is not going to happen readily, but under certain reaction conditions the ionization of the carbon leaving group bond or the carbon-bromine bond here can happen and what you create is a carbocation. Now, this as we said is a slow step. Now, let’s say that we have water as the solvent in the reaction; seeing that there is a vacancy on that carbon which is a strong positive charge, water with its lone pair of the oxygen can now attack that carbocation, right.

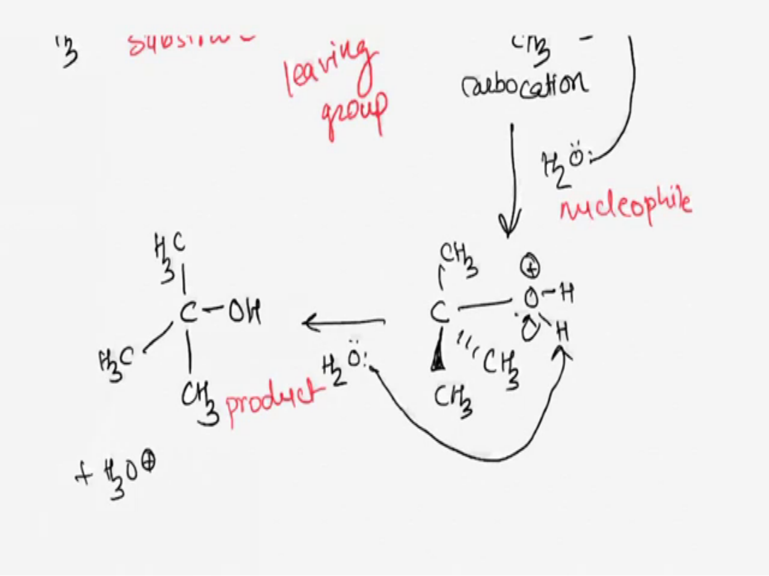
(Refer Slide Time: 06:40)



Creating a new bond between oxygen and carbon, okay; in turn oxygen loses one of its lone pair and is positively charged. Remember we have always said that this looks like an unhappy oxygen because it is charged right and nature hates charges. So, the next thing that happens is another water molecule will come and grabs this proton to give you your final product which is tertiary butanol plus H_3O^+. So, if I take tertiary butyl bromide and if I put it in water and heat it a little bit, what I will see is that the tertiary butyl bromide gets converted to tertiary butanol.

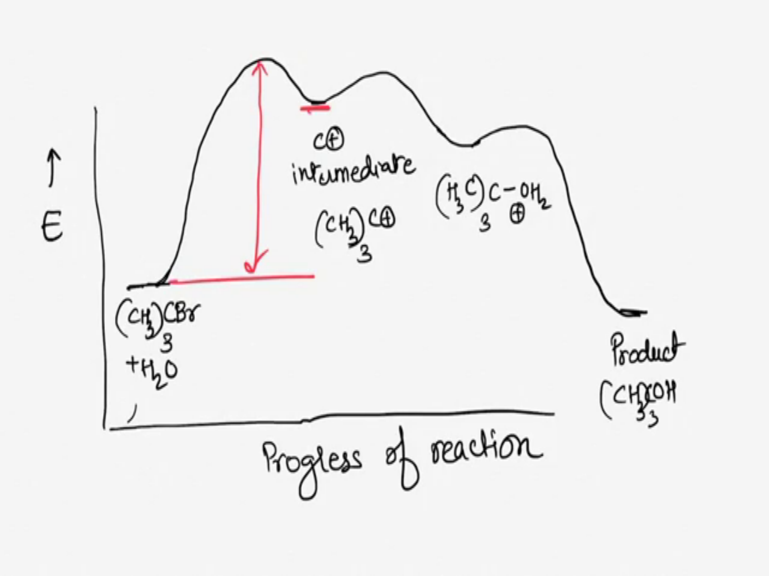
This whole reaction is very similar to that first part where we talked about a player getting injured. Because, what it goes through is that at first there is a vacancy created on the carbon, right; the carbocation is created and then the nucleophile is going to attack, right. So, if I really have to look at it the terminology, this is my substrate; bromine here acts as a leaving group; so, it is what leaves in the beginning. So, it is going to be the leaving group of the reaction, right; water is going to attack as the nucleophile because it attacks a carbocation. So, this is going to be my nucleophile and this is going to be my final product.

(Refer Slide Time: 08:36)



So, as you can see we end up creating a substitution on that carbon where we have substituted the bromine with OH group or alcohol functionality.

(Refer Slide Time: 08:56)



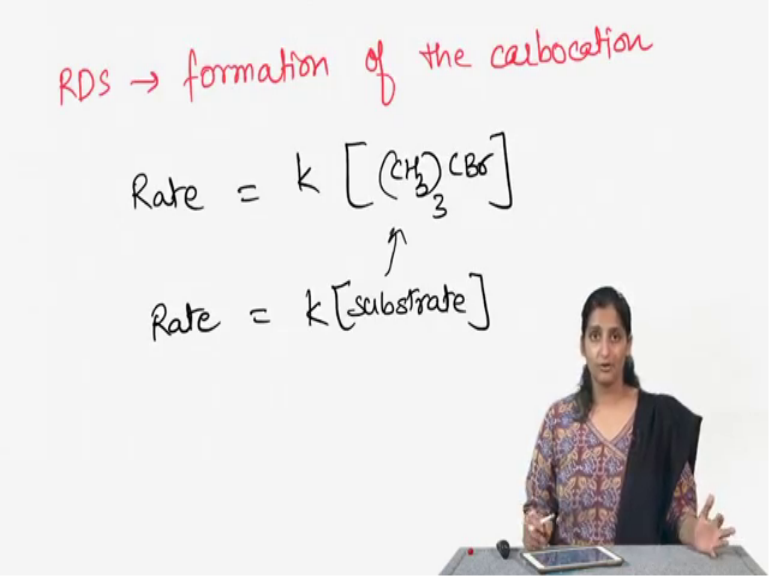
So, now let us create the energy profile diagram of this reaction, if I remember the mechanism we started with tertiary butyl bromide and water together. And, then what happened was initially it was a slow step, but we ended up creating a carbocation, right. So, this is energy if we are plotting on the y-axis and if the progress of reaction is plotted on the x-axis, initially the energy needs to go up towards the formation of the carbocation intermediate.

Now, as we create this carbocation intermediate remember that carbocations are not as stable as the starting molecule or the end product. Because the octet rule is not complete, carbon is having a strong positive charge; it is going to be the most unstable species created in this chemical reaction. Then on this carbocation a water molecule attacked and you created a new intermediate. And, this particular intermediate was such that the carbon and oxygen had formed a bond.

Now, remember there is also a strong positive charge present in this compound, but the octet of each atom is complete and, hence this particular species is not as reactive or is not as unstable as the initial carbocation. Then this particular molecule lost that proton in the final step to give us the product which was our tertiary butyl alcohol, right.

So, if I look at this energy profile diagram as you can clearly guess the rate determining step of the reaction, that is the step that takes the longest time or that is the slowest step of the reaction is the first step towards the formation of this carbocation right. Because, you are going to take the longest to go over that first hill then after that everything else is a downhill process. So, the first step is the rate determining step of the reaction and in any substitution nucleophilic unimolecular reaction, S_N1 reaction and we will go over why it is S_N1; the rate determining step of the reaction is always the formation of the carbocation, okay.

(Refer Slide Time: 11:44)



RDS → formation of the carbocation

$$\text{Rate} = k\,[(CH_3)_3CBr]$$

$$\uparrow$$

$$\text{Rate} = k\,[\text{substrate}]$$

So the RDS; remember that the rate of the reaction is proportional to the rate of the rate determining step or rather it is governed by the rate determining step. So, if I want to write down the rate equation for this particular reaction, I would write it as the rate is equal to some rate constant K into the concentration of the species that are taking part in the rate determining step.

Now, the compound that is taking part in the rate determining step that is the rate determining step which is the first step or the slow step is actually the tertiary butyl bromide. If you really pay attention water which was my nucleophile is not present in the rate determining step. It does not play any role in the rate determining step of the reaction and thus the tertiary butyl bromide's concentration will really affect the rate of the reaction, right.

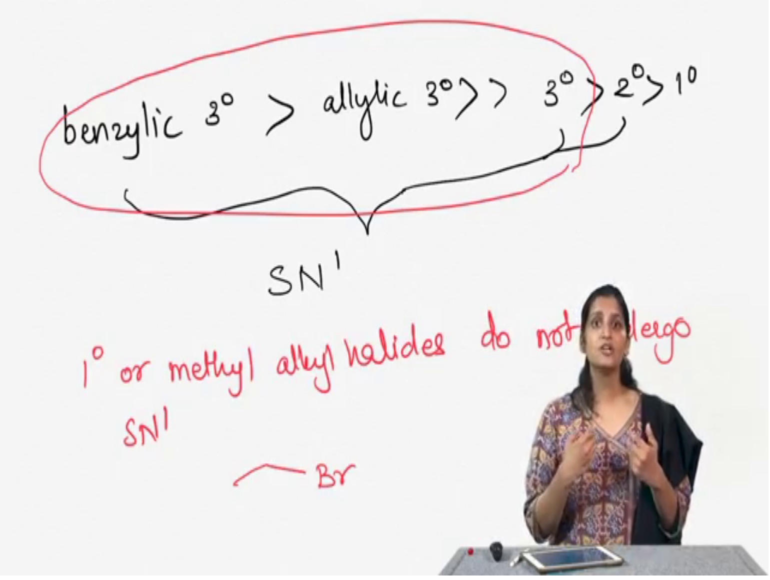
Since, the bond breaking between the carbon and the leaving group is almost completed before the bond forming of the nucleophile, this is a unimolecular reaction. Meaning that the rate is only dependent on one type of the molecule which is your substrate, it is not dependent on the nucleophiles concentration, right. So, you can generalize this as the rate of these types of reactions is equal to some rate constant K into the concentration of substrate and thus this is substitution nucleophilic unimolecular reaction, okay.

So, S_N1 meaning there is some substitution happening, N meaning there is some nucleophilic attack happening and 1 meaning there is only one type of species that is taking part in the rate determining step of the reaction. So, if I let's say if I am doing this reaction and if I increase the concentration of water will it play any role on the reactions rate? The answer is no, because water does not play any role in the rate equation. If I increase the concentration of the tertiary butyl bromide instead what we will see is that the rate will also get enhanced.

Now, since we are talking about rates let's also think about the factors that affect the rate of this S_N1 reaction or the factors that govern, if a reaction like substitution nucleophilic unimolecular reaction happen or not, okay.

One of the key things to remember is that remember this carbocation being formed was the slow step. So, if anything can stabilize the carbocation, bringing down the energy of the carbocation will also bring down the energy of the corresponding transition state and the rate will be faster, right. And so, what we are going to do is whenever we are going over all of these factors that affect the rate of S_N1 reaction, we are going to pay close attention to whether that particular factor affects the stability of the carbocation or not.

(Refer Slide Time: 15:22)



benzylic 3° > allylic 3° >> 3° > 2° > 1°

S_N1

1° or methyl alkyl halides do not undergo S_N1

Now, one of the things to think about is we have seen the stability of carbocations, right. And, we had said that tertiary benzylic carbocations are more stable than an allylic tertiary, right, in general which are kind of more stable than tertiary carbocation then secondary then primary, right. Benzylic and allylic are really stabilizing the carbocation by a resonance effect and tertiary carbocations are more stable than secondary carbocations due to the hyperconjugation that happens in the case of tertiary versus secondary, right.

Now, if I want to put this into perspective we observe the S_N1 type reactions happening mainly for this group, okay. These compounds will undergo S_N1 type of reactions, some of the secondary compounds can also undergo S_N1, but it is not really favoured for them or it happens at a much slower rate.

But, we pretty much do not see any primary alkyl halide undergoing this kind of reaction; we also do not see any methyl alkyl halide undergoing this reaction. So, the reaction works mainly for tertiary, allylic, benzylic compounds. It does not work very effectively for secondary and it certainly does not work for primary or methyl alkyl halides, okay.

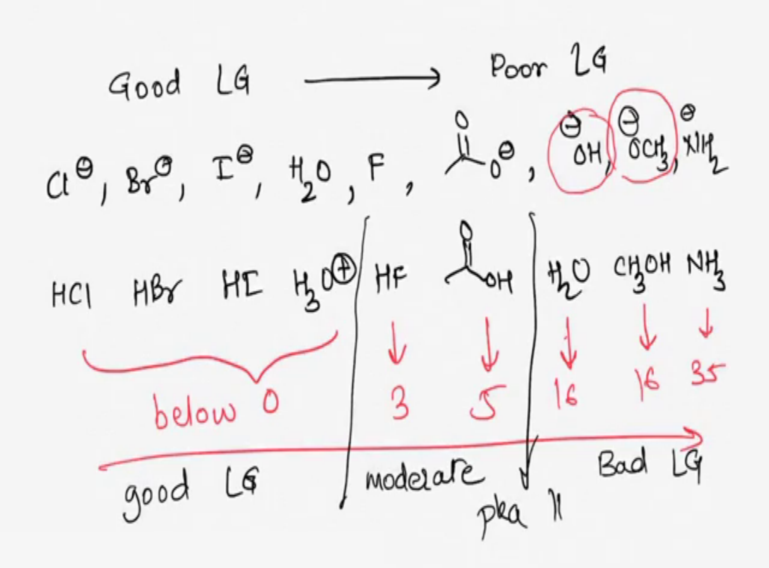
So, we have to reason out, the reason becomes very simple is that primary alkyl halides let's take for example, ethyl bromide. The bromine will not leave, right, creating a primary carbocation because what you are creating is something so unstable that the reaction, the first step of the reaction itself will not happen, right or for the same analogy goes for methyl bromide as well. You will not create a methyl carbocation and it will be impossible to create that carbocation. Thus, the reaction will not be happening for these two kind of species.

The next thing that we are going to look at is the leaving group ability and in this particular example leaving group was bromide, right. Remember that in order for the molecule to undergo this type of reaction the first step is of course, the leaving group leaving. So, the leaving group also has to be stable as it leaves; remember you are not going to create something very unstable in the middle of the reaction. So, if bromide was not stable on its own, the reaction would not happen. So, for example, we don't see very-very poor leaving groups doing this kind of reaction, okay.

So, how do we determine which one is a better leaving group? So, one of the key things to know is that we look at the stability. So, most of the halogens, chlorides, bromides, iodides actually function as a very good leaving groups because they can be stable as they leave and create a stable anion. But, if you have to really come up with a rule of thumb and think of which compounds would function better as a good leaving group; one of the things that we have looked at when it comes to stability is the stability of the conjugate base, right. So, chloride, bromide, iodide are also very stable conjugate bases and as a correlation the corresponding acids are quite acidic.

So, what we will observe is that the leaving group ability can be also correlated with the stability of the conjugate bases, right. So, the best leaving groups are actually very weak bases. And how do we identify weak bases? Their conjugate acids are really-really strong, okay.

(Refer Slide Time: 19:34)



If I write down the good leaving groups here okay, these are compounds like chloride, bromide, iodide; I also have water and slowly I am going to start going towards the poor leaving groups, okay. Now, we have looked at water then comes the fluoride then you have a acetate, right and slowly if I go to hydroxide or alkoxides, right, these are the poor leaving groups, okay.

So, we have noted down the leaving groups from good leaving groups to really poor leaving groups. Now, what I am going to do is I am going to draw their corresponding conjugate acid. So, we have looked at HCl, HBr as the conjugate acids, HI, H_3O^+, HF, right, acetic acid, water, methanol and ammonia, right.

And, if I note down the pKa's of the conjugate acids you will see that these are kind of below 0, this one is close to 3, this is close to 5, 16, 16, 35. So, what do we observe? We observe that the leaving group ability goes on decreasing as we go towards ammonia, right which also means that the stability of the leaving group NH_2^- is really-really poor as compared to, let's say, the chloride or bromide.

So, you can get a good gaze of what will act as a good leaving group looking at the pKa's of the conjugate acid. And, remember when we went over the acids and bases chapter, we talked about how this one chapter will really help us out in future. This is one of the examples of where the acids and bases are really important. In the sense given a chemical reaction you can predict, if a species will act as a good leaving group or will not leave because, it is a bad leaving group.

One of the cutting points of the leaving group ability comes around pKa 11. In the sense that the leaving groups whose conjugate acids have pKa below 0 are really the good leaving groups; from around pKa 0 to pKa 5 they are kind of moderately good leaving groups. But, everything above pKa 11 pretty much is a very bad leaving group, okay. So, you will never see an OH^- leaving in a chemical reaction just like that or you will never see an OR^-, methoxide, ethoxide just leaving in a chemical reaction; same goes with that NH_2^- anion. Thus, knowing the pKa's you can kind of correlate the leaving group ability.

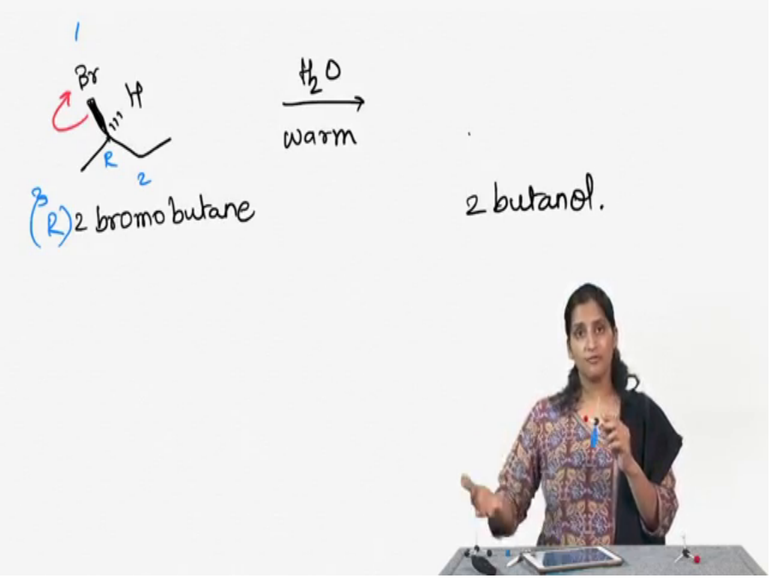
Now, we have paid attention to the substrate where we have said that the substrate has to be at least a secondary, if not really a good tertiary alkyl halide to begin with. And, then we have looked at the leaving group such that the leaving group needs to be a very good leaving group for this reaction to happen. What about the nucleophile? Do you need a very strong nucleophile for the reaction to happen? First of all how do we judge the nucleophilicity of a particular compound? So, one of the rule is that the nucleophilicity is basically how much the compound loves the nucleus, right, or loves the positive charge.

How much it needs the positive charge to get stabilized, right; good rule of thumb is that most good nucleophiles are really good bases. So, for example, if we take hydroxide versus water, hydroxide is a good base as compared to water; hydroxide is also a very good nucleophile as compared to water, okay. The reason is that hydroxide on its own is more unstable than water and hydroxide would want to do the reaction to become more stable, right. So, most good nucleophiles are also good bases, but that's not it; with nucleophilicity you also want to look at the ability of the compound to go and attack, right. So, you also have to look at whether something is a bulky nucleophile or whether something is a very tiny nucleophile, right.

So, one of the things about nucleophiles is that they also should be able to attack the particular carbon and do the chemistry. In the case of S_N1 reactions as you know that the nucleophile does not really play any role in the rate of the reaction. It also does not need to attack on the carbon before the carbocation is created, right. So, in the case of S_N1 reaction even poor nucleophiles can do a very good S_N1 reaction. In fact, most of the S_N1 reactions that are seen are done by really poor nucleophiles. So, for example, water which is a poor nucleophile or methanol, acetate, all of these compounds are poor nucleophiles because they are not really strong bases.

They do not have the need to go and attack the carbon, are going to do S_N1 kind of reaction. Now, let us discuss this stereochemistry of a reaction. The example that we saw actually was based on tertiary butyl bromide in which there was a carbon which had 3 methyl groups attached to it. So, it's very difficult to determine if the stereo chemical course of the reaction is such that it retains the stereochemistry or changes the stereochemistry, right. So, one of the compounds study to determine the stereochemistry of S_N1 reactions is actually the following reaction.

(Refer Slide Time: 26:13)

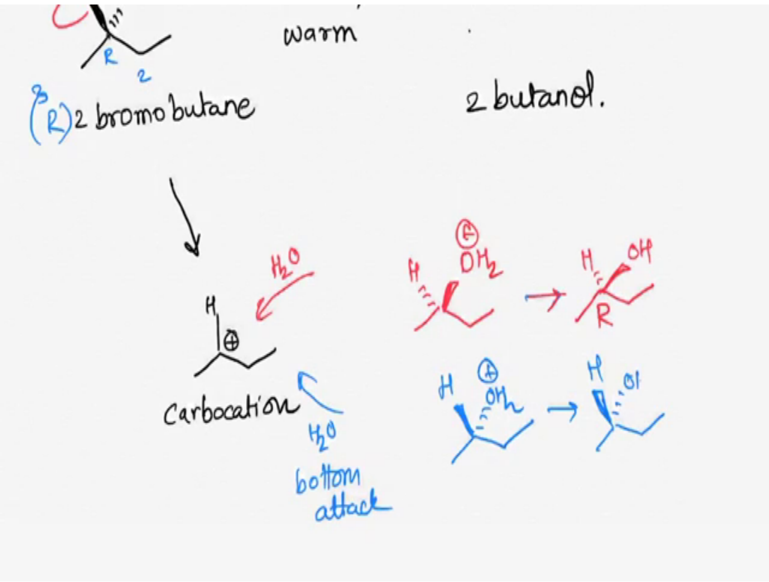


In this case what we are going to do is I am going to take simple 2-bromobutane and if you want to pay attention to the stereochemistry of the starting material; we know that this is 1, 2, 3 it moves like R and it is R. So, this is (R)-2-bromobutane, now let's start with (R)-2-bromobutane and let's do the reaction with water as the solvent. And, if I warm it up a little bit what will I observe is that I will see the formation of 2-butanol, okay. Now, the question in hand is do we form (R)-2-butanol or do we form (S)-2-butanol? Let's think about it; we know that the first step of reaction is such that the bromine will leave in the reaction creating a carbocation.

So, I have this starting material, it is tetrahedral carbon in the middle and that's the compound. But, what's going to happen is this particular compound is going to react such that let's say this is the bromine; it leaves to form a carbocation. And, we know that the nature of the carbocation is that it is sp^2 hybridized, it is flat and planar such that the p-orbital, the empty p-orbital goes above and below the plane of this carbon-carbon bonds. So, if you think about it, once the carbocation is created the carbocation can be attacked from either ends, right. So, it can be attacked from the top as well as the bottom in this particular reaction, right.

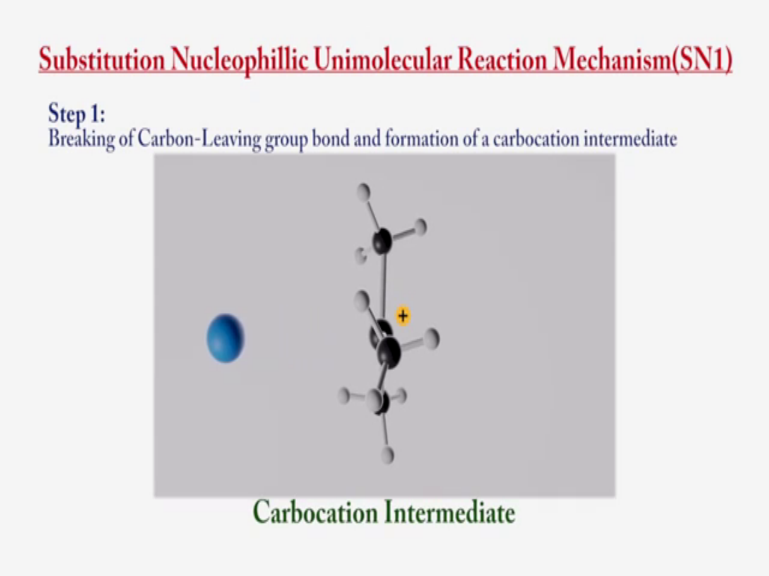
And, thus when the nucleophile in this case water when it attacks, it's going to attack from the top; it is also going to attack equal probability from the bottom really creating a mixture of (R) and (S)-2-bromobutane.

(Refer Slide Time: 28:35)



So, if I have to draw this reaction and represent it, what I will show is that it's a carbocation, right; it is flat and planar. So, once let's say if the water attacks from the top, the product that will be formed will be such that the water is coming towards you and hydrogen is going away. Whereas, if the water attacks from the bottom what you will see is that water will be at the back and hydrogen will be in the front. Really creating both the molecules in one case you will form (R)-2-butanol and in the other case you will from the (S)-2-butanol, right.

(Refer Slide Time: 29:53)



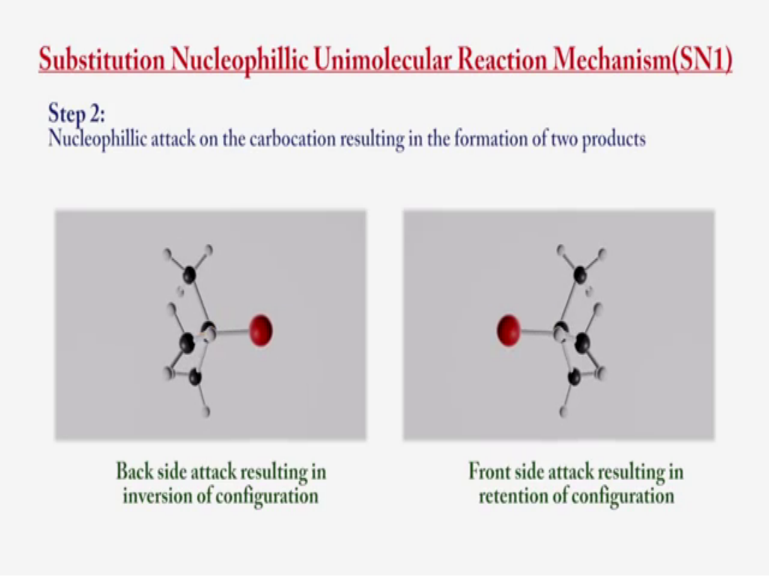
Substitution Nucleophillic Unimolecular Reaction Mechanism(SN1)

Step 1:
Breaking of Carbon-Leaving group bond and formation of a carbocation intermediate

Carbocation Intermediate

So, now we will look at the animation of this reaction.

(Refer Slide Time: 29:59)



Substitution Nucleophillic Unimolecular Reaction Mechanism(SN1)

Step 2:
Nucleophillic attack on the carbocation resulting in the formation of two products

Back side attack resulting in inversion of configuration

Front side attack resulting in retention of configuration

Let’s say we create a mixture, will it be a 50-50 mixture, in the sense will it be a racemic mixture? The answer is yes and no, okay; there have been reactions for which a perfect racemic mixture has been isolated as a product. But, more often what we see is that the perfect racemization is not observed. Why is that? Right. So, let us look at what really happens, okay; remember that the bromine is going to leave in the first step.

(Refer Slide Time: 30:39)

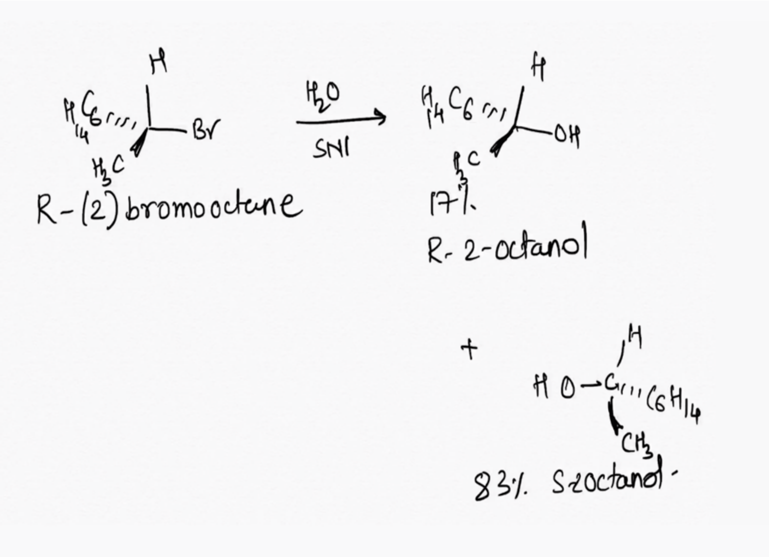
In the sense that let’s say in this particular reaction the bromine leaves, really disconnecting the bond between carbon and bromine.

(Refer Slide Time: 30:43)

As a result of which this particular carbon here is going to have a positive charge on it and the bromine is going to be negatively charged. So, as the bromine leaves, remember there is going to be an attraction between this positively charged carbocation and negatively charged bromine. So, the bromine here even though it leaves, it does not go far away from it, it kind of stays nearby and what we really create is an ion pair, okay. So, when the incoming water molecule wants to attack, it is not attacking from the side of the bromine; it is going to find steric hinders where the bromine is already present.

So, what it does is it attacks from the other end and you will get more product resulting from when the water attacks from the other side that is away from the side where the bromide is present, okay. So, this ion pair effect really results into more inversion of configuration, meaning if I start from R, I will form more S, okay, than the retention of configuration, okay. So, although we would expect 50-50, more often it is 80-20 where the inversion is often seen to be more predominant than the retention of the reaction; in fact, I have this particular reaction here.

(Refer Slide Time: 32:17)



Now, in this case this is (R)-2-bromooctane, when this reacts with water in an S_N1 reaction, what we observe is 17 percent of (R)-2-octanol and around 83 percent of a (S)-2-octanol, okay. So, what we will observe here is that, that the retention is very less and the inversion is really high, okay. Now, whenever we find a mixture, in the sense that we have created a mixture of R and S; typically it is a good indication that S_N1 type of reaction is happening.