Introductory Organic Chemistry
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Lecture - 43
Substitution & Elimination Part 5

One of the really good examples of where this anti-periplanar geometry place a role can be seen in this particular example.

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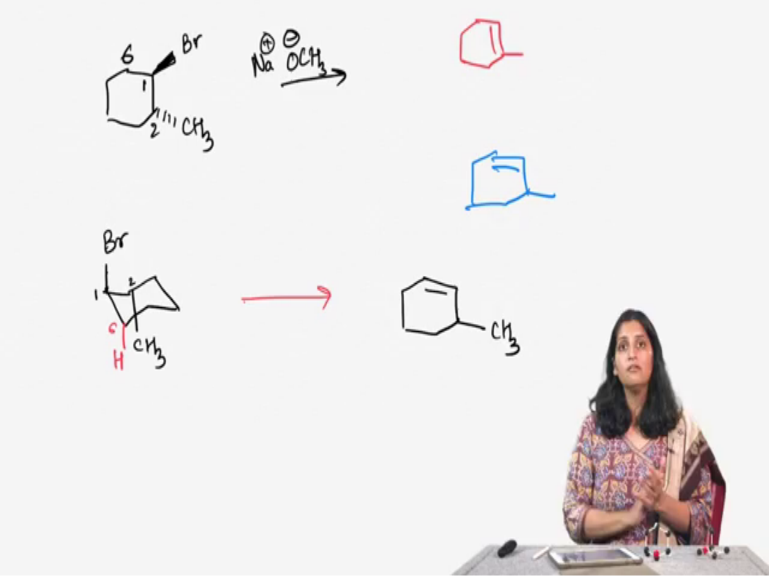

So, let me take an example here and I am going to start with the cyclohexane derivative. In this case I am going to start with this methyl bromo cyclohexane, right and we are going to react it with let's say methoxide for the E2 type of reaction. Now, when the elimination reaction is going to happen remember that the leaving group and the hydrogen, the beta hydrogen has to go anti-periplanar.

Now, if we were to ask what is the more substituted product of this particular reaction the answer would be this, right. Because it results into the formation of a more substituted carbon-carbon double bond. However, what we observe is that the major product of the reaction comes from this particular product.

So, how is this possible, why is the more substituted carbon-carbon double bond not form or why is the Zaitsev's rule not obeyed in this case? What we are going to do is first in order for us to do this reaction remember that we need to make the hydrogen, the beta hydrogen and the leaving group go opposite to each other or in the anti-periplanar geometry with respect to each other.

In order to do that what we are going to do is we are going to first convert it to the corresponding chair, okay. So, let’s draw the chair we know that let’s put the bromine going up and then 1 and 2 on the second carbon, the methyl should go down, okay. So, that is how the chair is going to look like, okay. Now, for the elimination to happen for it to go anti-periplanar what are the possible hydrogen’s that are anti-periplanar to this particular bromine.

As you can see when we draw the chair, the methyl group on carbon number two is really anti-periplanar to that bromine and that is kind of counterproductive because it does not help us to eliminate the beta hydrogen from that carbon, right. In fact, the beta hydrogen here on carbon number 6 is anti-periplanar to it, it is going in the opposite direction.

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Just to illustrate the point we are going to look at this model here; this is the bromine going up and the group anti-periplanar to it is actually the methyl that is going down. So, this does not help because what I need is the hydrogen that is going opposite to it. Remember that if the chair flips and if the axial goes to equatorial that also does not help because in this case the bromine does not have anything anti-periplanar to it right when the bromine goes equatorial there is no group anti-periplanar to it.

So, the bromine can be only eliminated or elimination reaction can happen when the bromine is in the axial position and that axial position is like this, right. Now, on this carbon you do not have any hydrogen that goes anti-periplanar, but on this carbon the carbon number 6 you have a hydrogen that goes in the opposite direction as compared to that bromine.

And as a result of which the elimination product will come when we eliminate from carbon number 6 here, okay and that is the reason why the Zaitsev's rule is not followed here. Although in principle any base can do an E2 reaction if we change the reaction conditions; more often it is seen that good bases are good at doing E2 kind of chemistry. So, when we want to employ bases to do elimination reactions, chemists choose bases that are really strong.

They will use bases like hydroxides, they will use bases like alkoxides, amide anions, compounds like LDA which is lithium diisopropylamine or compounds like tertiary butyl lithium which is one of the strongest base that you will see; these are the bases that are used to do E2 kind of reactions. If you see the characteristics of all of these bases, all of these bases have conjugate assets with the pKa's that are above 11, okay.

So, if you see the pKa of alkoxide for example, alkoxide like, ethoxide will have its conjugate acid as ethanol and this ethanol has a pKa of 16, right or hydroxide which has a conjugate acid as water and water has a pKa close to 16, right. So, good bases are the compounds that have conjugate acids with pKa's above 11, okay and whenever we want the elimination reactions to favour we use bases that have pKa's of their conjugate acids above 11.

When we are using bases with the corresponding conjugate acids with the pKa's below or near eleven more often they can do substitution reactions as well. So, compounds like carboxylates, compounds like thiolates, cyanides, azides or compounds like really-really good nucleophiles like bromides, chlorides they all have their corresponding conjugate acids to have pKa's below 11, okay. Thus, chemists need to choose the kind of nucleophiles or the kind of base they want to employ to do a particular type of chemistry.

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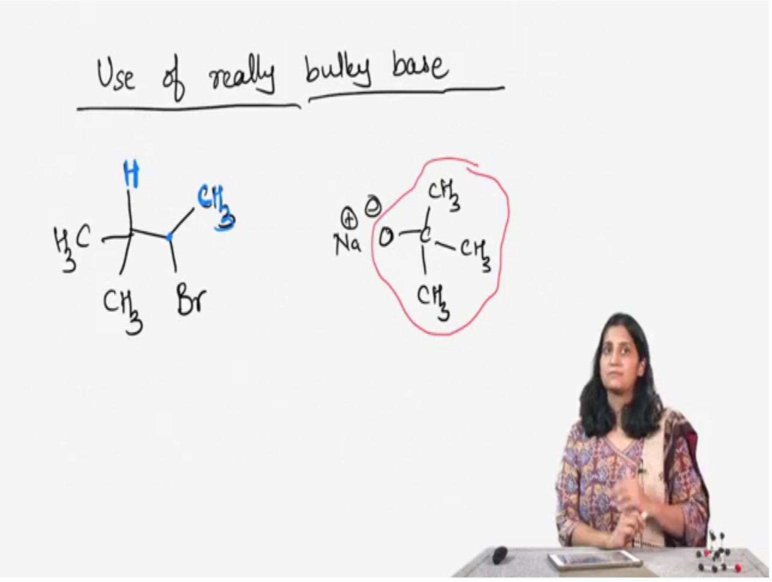

We just looked at an example where the Zaitsev’s rule was not followed and we formed the less substituted alkene because the right kind of geometry in the transition state could not be achieved, right. And we are gonna look at one more example where the Zaitsev’s rule is typically not followed and that is when we are using a really bulky base, okay and that happens for really-really bulky bases like tertiary butoxides sometimes it is also seen for compounds like LDA, okay.

So, tertiary butoxide is basically a compound which results when you deprotonate tertiary butanol, right. So, for example, here I have a sodium tertiary butoxide molecule, okay. As you can see this particular molecule tertiary butoxide is quite bulky; it’s a big molecule because it has the tertiary butyl group at one end of it. Now, when this molecule wants to attack on the starting material that I have shown here remember there are two types of beta hydrogen’s.

Now, since this is the alpha carbon, couple of beta hydrogens are present here and this particular hydrogen is also a beta hydrogen. So, I have kind of shown all the beta hydrogens in blue. What is seen is when compounds like tertiary butoxide react they want to approach the beta hydrogen but because of their size, because of the bulkiness of the base it cannot reach that particular proton effectively. In turn what it prefers to do then is to grab a proton from the less substituted carbon where there is lesser steric hindrance, okay.

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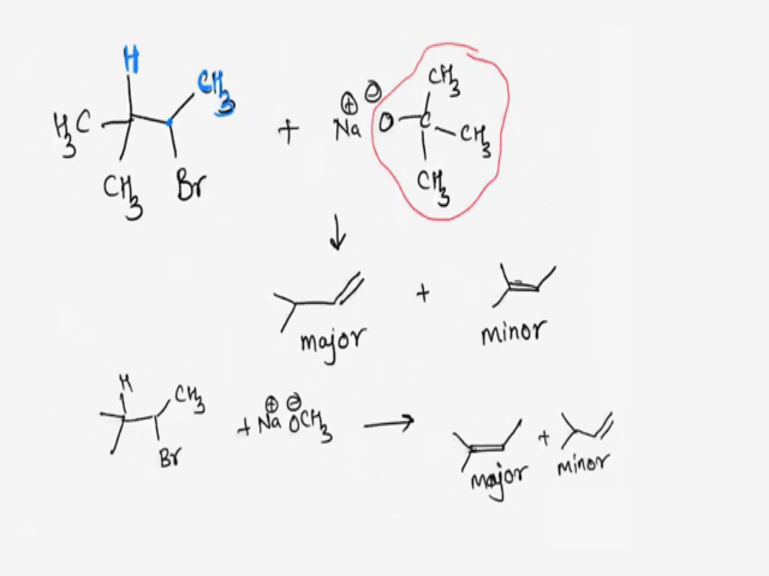

So, what we see is when these kind of reactions take place, it results into the formation of this as the major product whereas, the more substituted alkene is seen as a minor product and this is one of the case when the less substituted alkene is preferred. Now, if I take the same compound and if I react it with a smaller base like a sodium methoxide, this base would prefer picking up that proton from the more substituted carbon and it would result into exactly opposite ratio and we would form this as the major product and this as the minor product.

So, one thing to pay attention to, is also what kind of base we are using? Typically, really bulky bases prefer to form the less substituted product to avoid steric hindrance, okay. So, we have seen now 4 types of reactions; one is S_N1, S_N2, then E1 and E2. And we have said that S_N1 and E1 kind of compete with each other, right because both of them go through a carbocation formation and once the carbocation is formed either it can result into an elimination product or it can result into a substitution product.

Similarly, since both S_N2 and E2 both require strong base or correspondingly strong nucleophiles what you can see is that they compete with each other too and you will get a product that comes out of S_N2 or E2 or a product ratio in a particular reaction. And more often it can be really confusing to determine which one of these two processes will dominate or what kind of reaction will happen given a particular alkyl halide and the particular nucleophile or a base, right; it could be confusing to come up with the products.

So, what I am going to do is we are going to walk through the step by step process to determine which products will arise from which reactions, okay. So, now, let us begin our discussions with the methyl alkyl halides.

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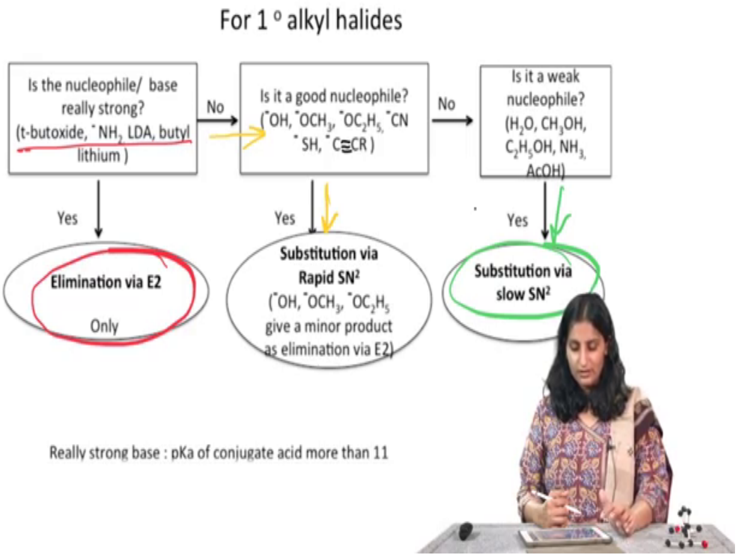

For 1 ° alkyl halides

Is the nucleophile/ base really strong? (t-butoxide, $^-NH_2$ LDA, butyl lithium)

Is it a good nucleophile? (^-OH, $^-OCH_3$, $^-OC_2H_5$, ^-CN ^-SH, $^-C{\equiv}CR$)

Is it a weak nucleophile? (H_2O, CH_3OH, C_2H_5OH, NH_3, AcOH)

Elimination via E2 Only

Substitution via Rapid SN^2 (^-OH, $^-OCH_3$, $^-OC_2H_5$ give a minor product as elimination via E2)

Substitution via slow SN^2

Really strong base : pKa of conjugate acid more than 11

Now, methyl alkyl halides are compounds like CH_3X, right or CH_3Br, CH_3Cl, CH_3I, right and these are compounds which are very easy to predict because they will never undergo an elimination reaction because there is no beta carbon, there is also know beta hydrogen present, right. So, they will never undergo elimination reactions. For methyl alkyl halides, S_N2 is typically a favoured reaction because it is favoured with good nucleophiles and it will proceed in a polar protic or polar aprotic solvent, but typically polar aprotic solvent is preferred for S_N2 reaction, okay.

S_N1 reactions for methyl alkyl halides are very-very rarely seen because it involves the formation of a primary carbocation which is really not stable; we don't see an S_N1 reaction happening on a methyl alkyl halide. So, more often methyl alkyl halides have only one fate that they can undergo S_N2 type of reactions, okay. Now, let us talk about primary alkyl halides and after primary the thing gets a little complicated right, let's talk about primary alkyl halides.

Now, for primary alkyl halides compounds like ethyl, propyl, 1-butyl bromide when the leaving group is attached to the primary carbon, okay. Now, primary alkyl halides are going to do S_N2 when they are put in with good nucleophiles okay; good nucleophiles but weak bases like azides like cyanides like bromides like thiolates and all of these will be good nucleophiles for an S_N2 reaction.

And this will prefer a polar aprotic solvent over a polar protic solvent, but however, it is not like the polar protic solvents will not do the reaction; the reaction will happen but it will just prefer or will happen better will happen faster in a polar aprotic solvent. Primary alkyl halides also do E2 type of reactions and E2 will happen in a really strong base, okay and also a bulky base and S_N1 and E1 typically on a primary centre since they both involve carbocation formations are not seen.

So, we do not see carbocation formation on the primary carbon very effectively. So, S_N1 and E1 are also not allowed for primary alkyl halides. So, if I have to think about primary alkyl halides doing a reactions, the first thing I ask is, is a nucleophile or a base really strong, right. So, these include bases like tertiary butoxide, $NaNH_2$, LDA, butyl lithium really-really strong bases; then more often rather than substitution these strong bases want to do elimination because it is more basic than more nucleophilic and so it will form elimination products, okay.

If the answer is no and if you have really good nucleophile. So, as I said compounds like cyanides, azides, bromides, iodides even some of the really good smaller bases like hydroxides, alkoxides if all of these are the condition as you can see, then the substitution reactions S_N2 reaction is preferred, okay. Although S_N2 is the major product you also see a minor product resulting from elimination reactions from compounds that are really good bases as well.

So, for alkoxides and hydroxides for example, you will see a minor component coming from the elimination reaction as well, okay; that is one case. If that is still not the case and if you have a really weak nucleophile like water, like ethanol, methanol, compounds like ammonia or acetic acid all of these are really-really weak nucleophiles. And if that is the case then the substitution will happen, but it will happen very slow with the help of S_N2 type of reaction. Again it will be a slow reaction because S_N2 requires a really good nucleophile, okay.

So, the final thing that can do is substitution via S_N2. So, that's the fate of primary alkyl halides, okay. Now, let's come to the more tough part which are the secondary alkyl halides.

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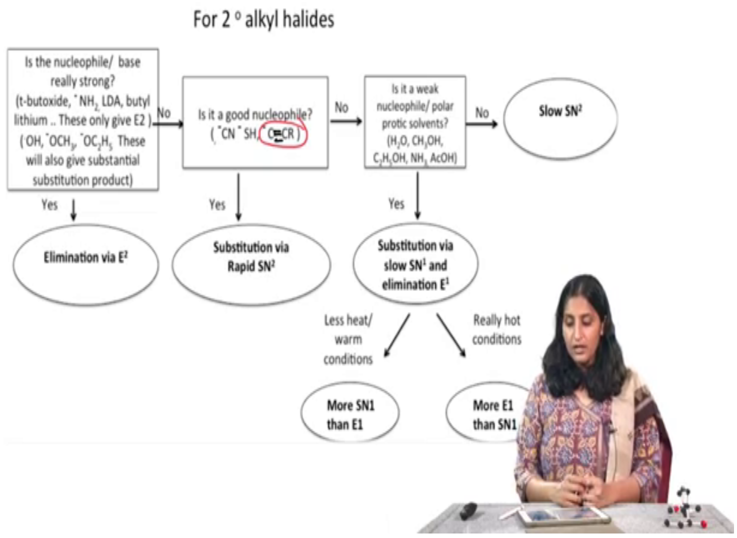

For 2 ° alkyl halides

Is the nucleophile/ base really strong? (t-butoxide, $^-NH_2$, LDA, butyl lithium .. These only give E2) (^-OH, $^-OCH_3$, $^-OC_2H_5$ These will also give substantial substitution product)

No

Is it a good nucleophile? (^-CN ^-SH, $^-C{\equiv}CR$)

No

Is it a weak nucleophile/ polar protic solvents? (H_2O, CH_3OH, C_2H_5OH, NH_3, AcOH)

No

Slow SN^2

Yes

Elimination via E^2

Yes

Substitution via Rapid SN^2

Yes

Substitution via slow SN^1 and elimination E^1

Less heat/ warm conditions

Really hot conditions

More SN1 than E1

More E1 than SN1

Now, why they are tough is because they are kind of in between; for the primary alkyl halides as we had seen you cannot form a carbocation very effectively. So, S_N1 and E1 kind of do not happen for primary alkyl halides whereas, for the tertiary alkyl halides as you will see S_N2 does not happen very effectively because there is a lot of steric hindrance. But secondary alkyl halides are kind of in between and they are I call it as a mushy zone it can do both S_N1, S_N2, E1, E2 all sorts of reactions depending on the kind of nucleophile that you are using.

So, let’s go over the secondary alkyl halides in detail, okay. So, for S_N2 reactions remember that the secondary alkyl halide is little more hindered than primary alkyl halide and therefore, it prefers doing elimination a little more than substitution, okay. However, it is not like substitution does not happen; substitution will happen, but there is a little more preference given to the elimination of the secondary alkyl halide, okay.

So, when we are using really good nucleophiles such as bromides, cyanides, azides, but not really good bases. So, all of these compounds are great nucleophiles they are not great bases. So, a rule of thumb that we talked about was that compound is a good base, if the pKa of its corresponding conjugate acid is more than 11.

So, if the nucleophile employed here is such that the pKa of its conjugate acid is less than 11, then it’s a really good nucleophile, so it would prefer doing S_N2 reaction, okay. And of course, it is important to use a polar aprotic solvent here because the reaction is already slow due to the steric hindrance. So, you want to aid it by giving the right kind of conditions.

So, you want to use the polar aprotic solvent. In the case of secondary alkyl halides remember E2 is also a possibility, but for E2 you are going to require a really good base and for E2 especially you want the pKa of the conjugate acid of the base to be above 11, okay.

If that is the case then the compound will probably do an E2 kind of reaction. For the secondary alkyl halide, S_N1 or E1 is also a possibility; you are forming a secondary carbocation and those are considerably stable molecules although not the best carbocations as we have seen they can form, but again it's going to require some aiding. So, you will need polar protic solvents in this case because in order to stabilize the carbocation formation and also we will need nucleophile that do not have a negative charge.

Remember when we want to form a carbocation we are forming a molecule with a positive charge on it and any time we have a really strong base which has a good amount of negative charge on it, the carbocation is not stable enough and so for the S_N1 kind of reaction to happen we need nucleophiles that are weak and also the nucleophiles that do not have a strong negative charge, okay.

The only exception to that is nucleophiles like chloride, bromide, iodide which have a negative charge, but will not act as strong bases, okay because of course, they are one of the most weak bases that you have seen, right. One of the things to remember here is whenever you form a secondary carbocation there is a possibility of rearrangement. So, always be careful about the potential rearrangement that can happen whenever you form a secondary carbocation.

So, let's go over the chart for secondary alkyl halides here. The first question to ask is, is the nucleophile or the base really strong; if the base is really strong that is tertiary butoxide, again LDA, butyl lithium, these will only give E2 kind of product. So, they will undergo elimination via E2.

Compounds which are not really-really basic, but are strong bases like hydroxides, ethoxides, methoxides will do an elimination reaction, but remember they will also do some kind of substitution reactions. So, you will see a mix of substitution and elimination product. If that is not the case and if you have a good nucleophile, but a weak base. So, a good nucleophile like cyanides, like thiolates then you will see substitution product and again with acetylide ions, this one that I have shown here, it is a really good nucleophile but it is also a considerably good base.

So, you will see a mixture of elimination and substitution products. So, S_N2 or E2 can happen. Now, if you are dealing with really weak nucleophiles and in polar protic solvents like H_2O, like methanol, like ethanol and all of these cases you will see is S_N1 or E1 happening. Now, typically it is seen that elimination products are favoured in the case of higher temperature conditions.

So, E1 will predominate if the temperature conditions of the reactions are high enough; S_N1 will predominate if at a lower temperature, okay. So, that is the case for secondary alkyl halides.

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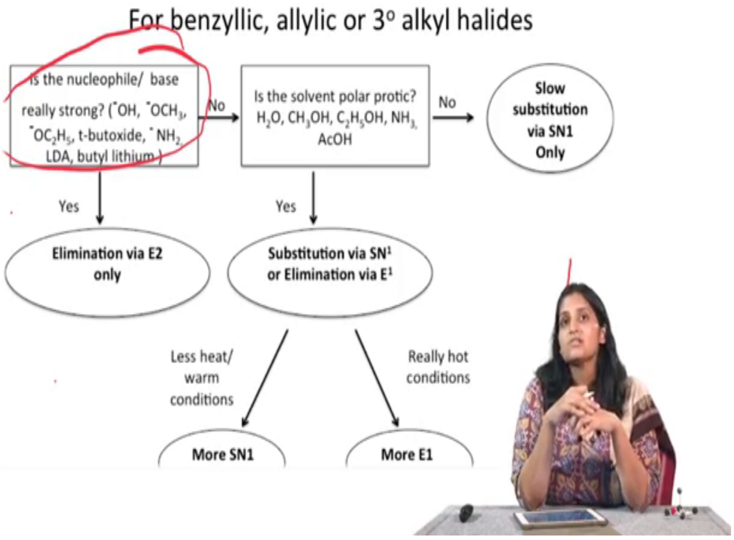

For benzyllic, allylic or 3° alkyl halides

Is the nucleophile/ base really strong? (^-OH, $^-OCH_3$, $^-OC_2H_5$, t-butoxide, $^-NH_2$, LDA, butyl lithium)

No

Is the solvent polar protic? H_2O, CH_3OH, C_2H_5OH, NH_3, AcOH

No

Slow substitution via SN1 Only

Yes

Elimination via E2 only

Yes

Substitution via SN^1 or Elimination via E^1

Less heat/ warm conditions

Really hot conditions

More SN1

More E1

Now, let us look at compounds that are benzylic allylic or tertiary alkyl halides. So, basically the kind of compounds that will form a very stable carbocation, okay. These are also the compounds that have bulky substituents present on the carbon bearing leaving group, okay.

Now, whenever you are dealing with tertiary alkyl halide since they form carbocation so effectively one of the major pathways for them to react is S_N1 and E1, okay. S_N2 pretty much does not happen because there is so much steric hindrance that S_N2 on a tertiary alkyl halide is very rarely seen, almost not seen, right.

So, it is not allowed we can even say that. E2 will occur if we use really strong base like hydroxide, tertiary butoxide, ethoxide, methoxide or even stronger bases like LDA, like butyl lithium if we use compounds like these then E2 type of reactions will happen; but again the major pathway for tertiary alkyl halides is either S_N1 or E1.

Typically S_N1 and E1 both are favoured in polar protic solvents, okay. Typically, the compounds that will do this kind of reaction will be like alcohols, will be water and also the compounds like chlorides, bromides, iodides ,right, all of these will be performing S_N1 type of reaction. So, S_N1 and E1 since they involve the production of carbocation again we do not want really strong bases to be present because the carbocation is not favoured in that particular medium, okay.

Now, for tertiary alkyl halides if we have to go over the chart, for tertiary alkyl halides the question is, is the nucleophile or the base really-really strong? If yes then it will do mainly elimination via E2 reaction. If not, if you have polar protic solvents like water, ethanol, methanol, ammonia, acetic acid all of these compounds will prefer doing S_N1 and E1; and which one amongst S_N1 or E1 will predominate will depend on the temperature more often.

And what we will see is at a higher temperature we do see elimination being preferred over substitution. If that is not the case then more often the only way the tertiary alkyl halides can react is S_N1 kind of conditions, okay. So, this kind of sums up our summary of substitution and elimination reactions.

Now, the tutorial for this one is going to be very important one because in that tutorial we will go over exact examples of which is the more preferred product S_N1, S_N2, E1 or E2 depending on the given reactants, okay. So, let’s meet for the tutorial.