Course on Stereochemistry
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Mod07 Lecture 33
Stereoelectronic Effects (Contd.)

Okay start, okay welcome back yesterday, we were discussing the stereo electronic parameters for Sn2 reactions and we saw this SN1 reactions. We have seen that in SN2 reactions, the nucleophile should approach, in a linear fashion to the C-X axis X being the leaving group and it should come from the back side, okay. The reason for that that it gives the maximum possible stable transition state, because the overlap when it comes from the back side. The overlap of the orbitals of the incoming nucleophile and the orbital that the carbon is having that gives the maximum overlap when it approaches along the C-X axis, okay.

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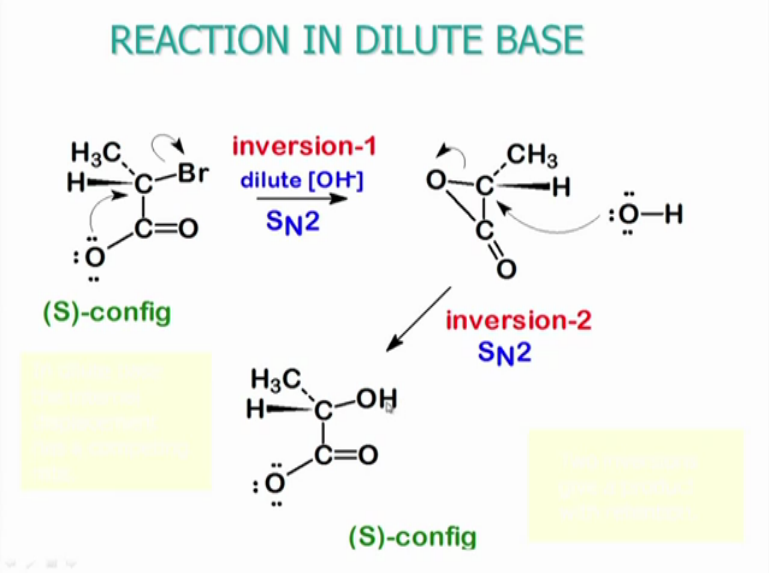

Then we so basically in SN2 reactions, there will be inversion which is called Walden inversion, inversion of configuration again, I repeat this inversion does not mean R going to S or S going to R that may happen that may not happen or it does not mean also plus going to minus rotation or minus rotation going to plus rotation that may happens that may not happen. It all depends on the nature of substituents and the priority of the substituents, okay. So we have seen that there are cases which go by SN2 reactions SN2 reactions. There are cases where double inversion can occur double inversion means double SN2 reactions can

occur, okay and these are called, these are these takes place when there is anchimeric assistance from the neighboring nucleophile within a molecule.

So intra-molecular, it is a intra-molecular attack by a neighboring nucleophile. So one example we have seen is the case of hydrolysis of alpha bromo or 2 bromo propionate, okay 2 bromo propionate we have seen that the carboxylate in dilute sodium hydroxide the carboxylate is formed and the OH minus being less in number. So the before the OH minus attacks this carbon from the back side, it is carboxylate which attacks from the back side and the Br leaves. So that is one inversion and then the OH minus comes and opens up the alpha lactone. This is a very strange molecule, so it also wants to open up and that is assistant opening is assistant by the nucleophilic attack by OH minus from the back side of this C-O bond.

So basically another inversion takes place. So there are two SN2 reactions and the overall, it leads to retention of configuration. What is this retention that means the Br was occupying a place, which now the OH minus is placed, the OH is placed okay, so that is retention of configuration.

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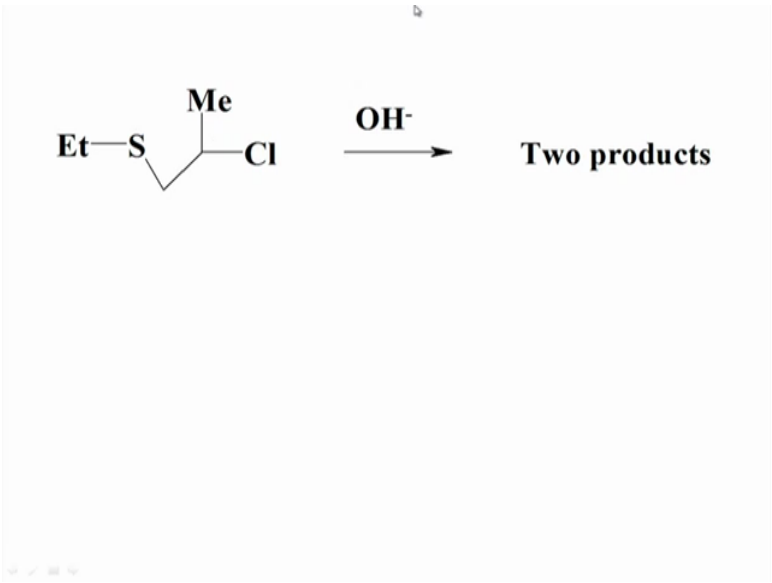

Now we have also seen that, we have to be careful that always neighboring group participation does not lead to retention of configuration. It will lead to the retention of configuration provided; the center that is the neighboring group is attacking is also attack by the nucleophile. If the incoming nucleophile attacks another carbon like this sulpher compound if it attacks here then there will be inversion of configuration at this center. Now

the OH minus can attack this carbon or that carbon. So if it attacks this carbon then this bond will break, but inversion will still be retained. So in that case, it is the inverted product that is obtained. On the other hand if OH minus attacks at this carbon and breaks the carbon sulpher bond, then it is the retention of configuration. So you have to be careful, which center the nucleophile is attacking, is in the same center as the internal nucleophile is attacking or it is a other center and depending on that whether inversion will take place or not that will be decided, okay.

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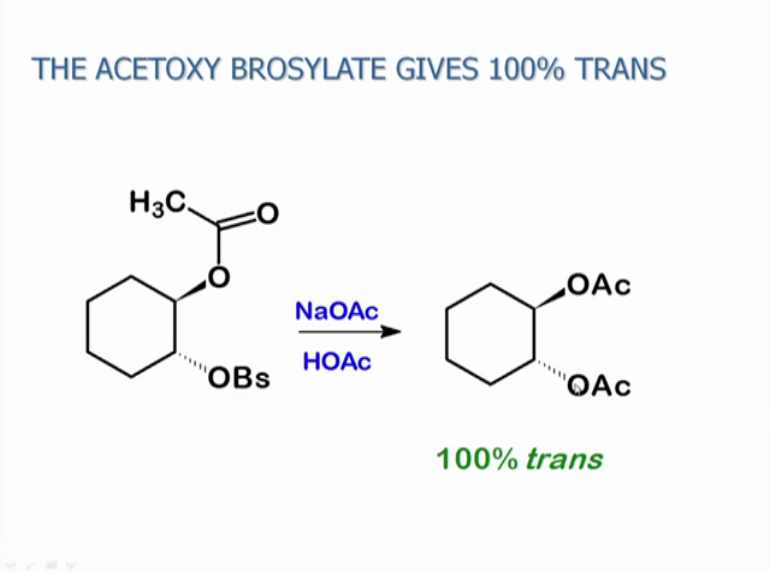

Now this is one example of a cyclohexane system, cyclohexane system where, this type of anchimeric assistance can take place. This is sodium acetate. This is a reaction of, so you start with cyclohexane 1,2-diol trans and one of the oxygen is protected as the acetate and the other is converted to a brosile (())(4:50) group, okay to a (())(4:53) okay ortho that is Para-bromo sulphonil that is the brosile (())(4:59) group and then sodium acetate.

Now in theory sodium acetate should approach from the top side and do an SN2 reaction to the to force this to go out and the acetate should have been beta, but you see the product. The product is here, the acetate retains, its configuration whatever was there and this acetate also retains the same configuration as the brosilate (())(5:29) had, okay. So it is also now alpha and the mechanism of this is, I can write it down, the mechanism is given here.

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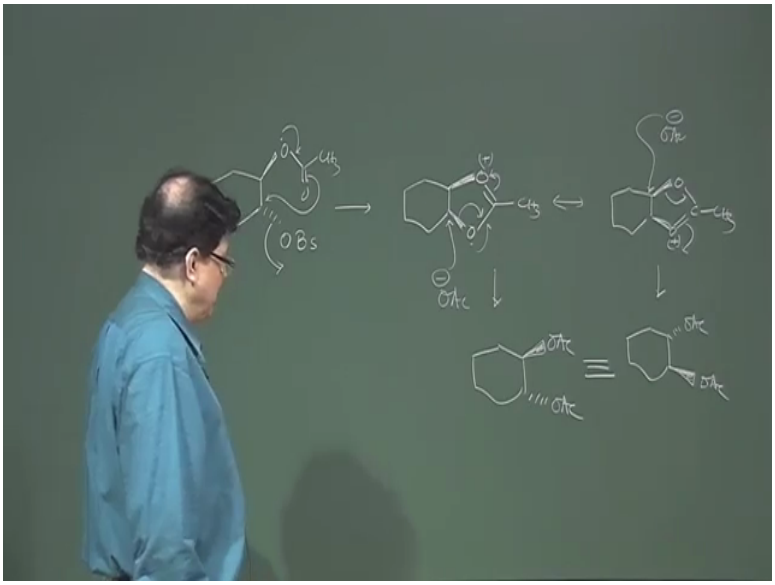

So you have to if you write in the cyclohexane form, so what happens here? This is the beta O-CoCH3 and this was the alpha that is the brosile group. So initially, this is what is going to happen. So this attack as a internal nucleophile, so that comes from the top side and if it comes from the top side, so the this, there will be an intermediate which will be, so this will be also beta, because it is from the opposite side the back side, it should attack and there will be CH3 and this is plus.

Now this will be a resonance hybrid of these two**.** Now what happens, the acetate which comes, the OAc minus that will come from the back side and this opens up like this. So you get the retention of acetate here and this OAc comes from the alpha side, okay. So that is the mechanism of the reaction, you can also think of that the, because there is no distinction between these two oxygens here. If you write the other resonance structure, so you have O then C then here, it is the O plus, this is CH3. Now if the acetate attacks the other carbon, because there is no distinction between these two carbons. So it can attack here that goes there that go there, say remember this is beta. So now you have the same situation OAc and OAc, they are Trans to each other, since this is C2 symmetric molecule, these two molecule cell same, okay.

So it is note that it is attacking only the carbon where the brosile (())(7:52) group is there. It can also attack the other carbon and this is the mechanism. So basically it is a anchimeric assistant from the acetate, first to kick out the brosyte (())(8:02). So that is one inversion and then it decides to attack from the back side. So that is further inversion. So that gives it

retention, okay. So ultimately the result is that the 2 acetate groups are trans to each other, okay 100 percent trans.

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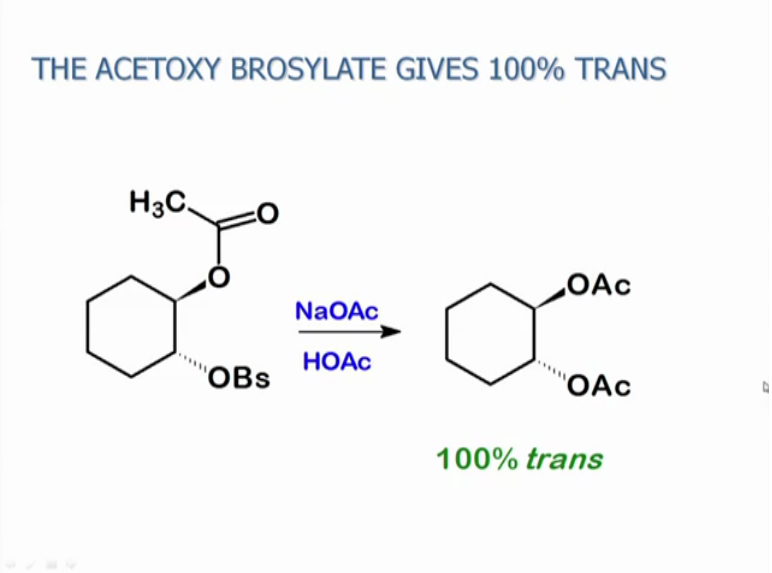

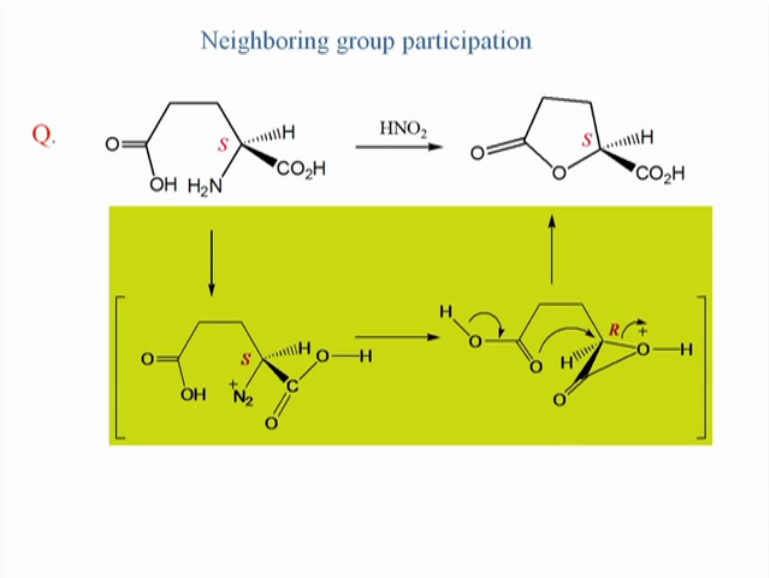

Another example is, this amino acid, you know amino acids, the primary amines can be converted to the di-azo and then that can be replaced by OH, okay. So if you take a primary amine and if you treat with HNO2, so one of the product is ROH. Now in this case if you do the same reaction with an amino acid. So basically you can think of that this is becoming OH and this carboxy and OH, now form a lactone. So the product is a gamma lactone, okay. So basically the reaction is we virtually the same. This is replaced by OH, but since this is hydroxy and acid (())(9:03) and carboxylic acid are together and this is an acidic medium. So there will be acid catalyzed esterification, you can think in that fashion, okay.

Actually the mechanism is not like that, that this is just replaced by OH coming from the back side OH means OH from water, okay, because if you look at the configuration, this is S and the product that is also S that means there is retention of configuration, that means this oxygen has not come from the water from the back side, because then it would have been R. so it is coming from the from obviously, this oxygen is taking the place of the nitrogen. So what is the mechanism of this reaction that is given here? So first there is there is that means here, it is retention of configuration, although there is SN2 attack if the OH attacks in an SN2 fashion and directly kicks out the NH2 then it would have been, you have to rotate it, so and then change the then oxygen will come I can show it here in the board, then the carboxy oxygen should come.

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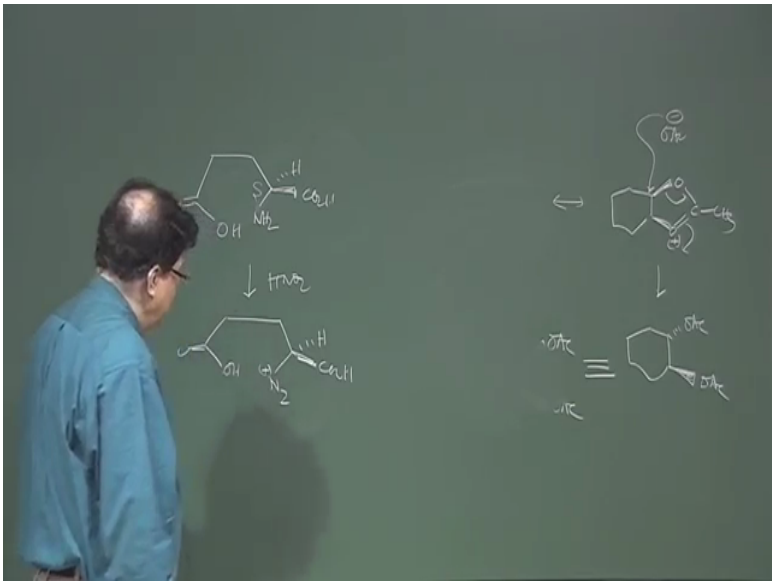

So there are two possibilities, so one is that you have, this this is by the way is a is an amino acid called glutamic acid. So you have NH2 on this side, okay and then you have carboxy, the beta carboxy and you have alpha hydrogen. Now there are two possibilities. First of all if HNO2 comes, so that will be converted to the di-azo the amine will first converted to the di-azo, remember this is S configuration, okay. So this is CO2H that is H.

Now if this has to kick out this nitrogen. This is a leaving group, the N2 plus. So this has to rotate and then oxygen will attack and the nitrogen will go out, but if that happens then this will be converted to the R configuration, because you are already rotating it and then the oxygen comes and so if you rotate, the carboxy will go to the back position and hydrogen will come to the front position. So that will create an R configuration; however the configuration still remains S, so what happens there is neighboring group participation.

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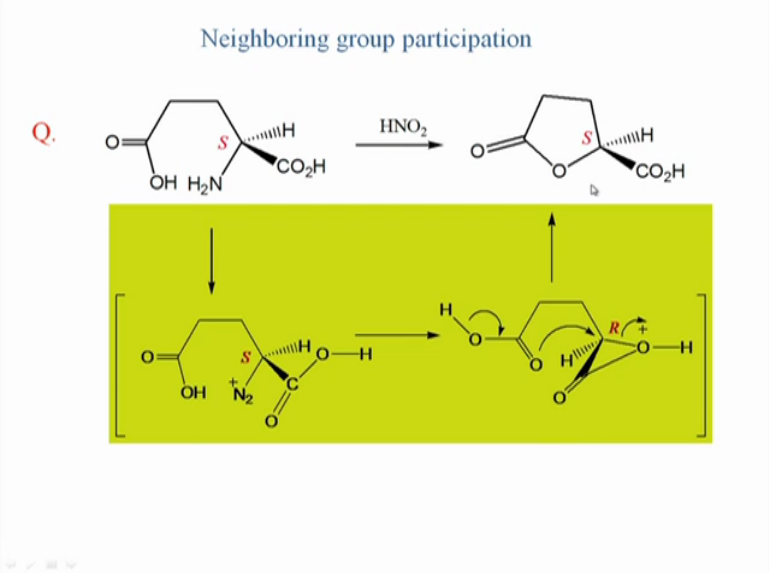

Now you come back to the slide, there is neighbor (())(11:46) group participation. This oxygen the carboxy t is a very similar to that alpha bromo propionate case. Now this oxygen at acts as a nucleophile and attacks this (())(11:57) carbon and the nitrogen goes off. So that forms an alpha lactone. In this case, you can write OH plus, because it is not the basic medium. It is acidic medium. So the plus charge is still on the oxygen and then the lactonization, this is alpha lactone replace by a gamma lactone, because that is more stable. So this is lossed and that acts as a nucleophile attacks the carbon and this carbon oxygen bond is Brocken. So if that is the case then you get what is call the, you get the same (the) what was the amine occupying the position.

Now this oxygen occupying the same position as the amine. So this goes to the S configuration. So in between it has been converted into the R configuration, because now, this oxygen is has replaced in the intermediate, the oxygen has done an SN2 attack on to the azide (())(12:55) okay, on to the sorry on to the di-azo and that forms alpha lactone, but the configuration has changed in that in that attack, because now the most, the priority the highest priority group is C-R, on the right side here, the highest priority group is on the left side, okay. So the there is a change in configuration R and then goes to S, okay. So these are some of the examples of that intra-molecular a reactions, intra-molecular cases where there is neighboring group participation, okay.

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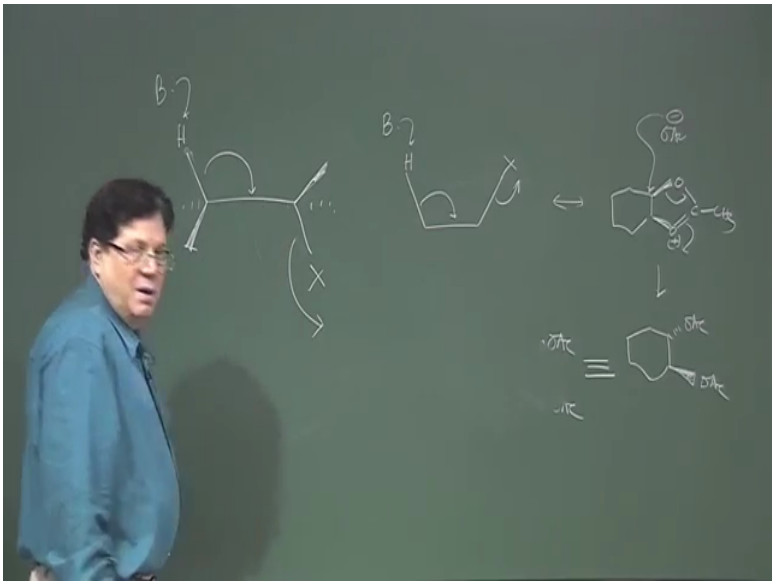

Now let us come to the stereo electronic requirement for E2 elimination, okay. Now in E2 elimination what happens? E2 elimination is that the if it is a elimination involving, say dehydro halogenation. So you have system like this, okay. So E2 elimination is the base attacks the takes the hydrogen if it is dehydro halogenation, then this is the mechanism. Now what is the stereo electronic requirement for this process that is what we are considering now? Now there are two possible ways you can write this that either it could be a syn type system orientation or it could be an anti-type orientation between the C-X and the CH, that means the two leaving groups, because here hydrogen is lossed X is lossed.

So the two leaving groups can be anti to each other or they could be syn to each other and but the most important thing is that they should be peri-planar means this plane. The plane containing these bonds and the plane containing this plane containing this (())(14:52) actually I should make it, only single and this is the beta bond, okay. So this CH and this C-X should be peri-planar, so also this C-H and C-X has to be peri-planar, because if they are not peri-planar then what happens, there will be problem with overlap of the p orbitals that are been generated here, because ultimately there is double bond. So p orbitals are generated if they are not in the same plane then there cannot be overlap between them. So for efficient overlap, they have to be syn, okay.

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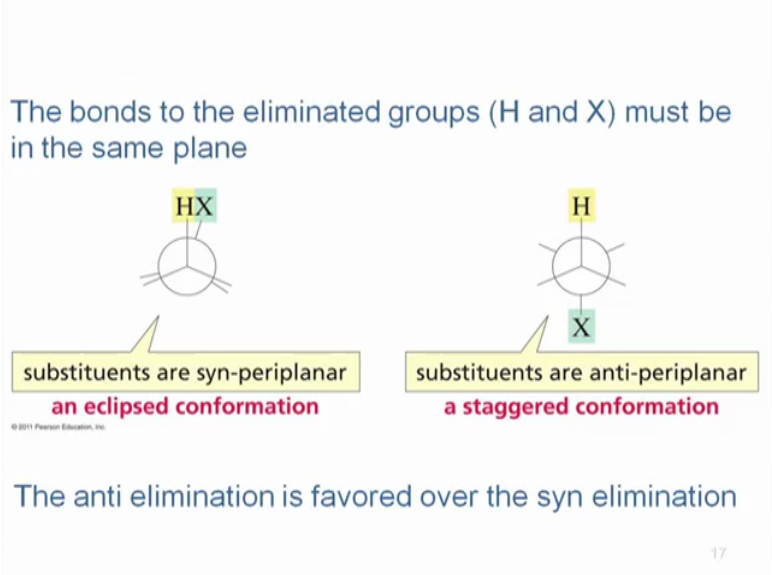

Now let us show this, the bonds to the eliminated or the eliminated groups H and X must be in the same plane that is number one. Now same plane means two types, one is this eclipsed conformation H and X are syn to each other or other could be the anti peri-planar. So one could be syn periplanar that means syn configuration as well as peri-planar, the other could be anti periplanar H and X are in the same planar system, but they are now anti a staggered conformation. So these two are possibilities. So what happens in elimination?

The normal process involves, the anti-elimination is favored over the syn elimination. There are cases where syn elimination takes place, but that is through a different kind of mechanism when 6 membered transition states are involved, then it could be syn elimination, but otherwise if there is this joint end are a base comes and attacks takes up the hydrogen and the X leaves then it is always the anti-type of elimination that takes place, okay.

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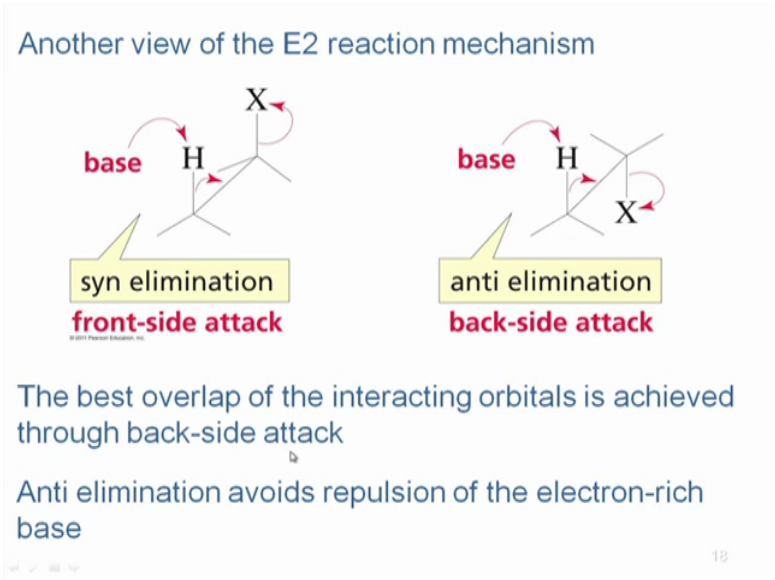

Now the reason for anti-elimination is that, there could be several reasons, one is at a, this is the syn elimination and there is a front side attack that means the base is coming from the same side as a both the groups that the same side of the groups that are be eliminated. So H and X are facing the same side and the base is coming from the same side. So you can expect repulsion, because base is after all, a negatively charged system, it is it could be a nucleophile, it could be an anionic species or it could be a species containing lone pair of electrons, okay. We are talking about leave is base (())(17:09) and then there will be repulsion with the, because as X is coming as coming out as X minus. So there will be repulsion to the approach of the base. So that may this favor this front side attack or the syn elimination.

On the other hand, in anti-elimination you do not face that problem, because x is on the other side on the anti-side, okay. So the that is one aspect, the anti-elimination avoids repulsion of the electron rich base, with the leaving group that means the X and the other, more important thing is that anti-elimination, the best overlap of the interacting orbitals is achieved through back side attack, the best overlap is achieved through back side attack.

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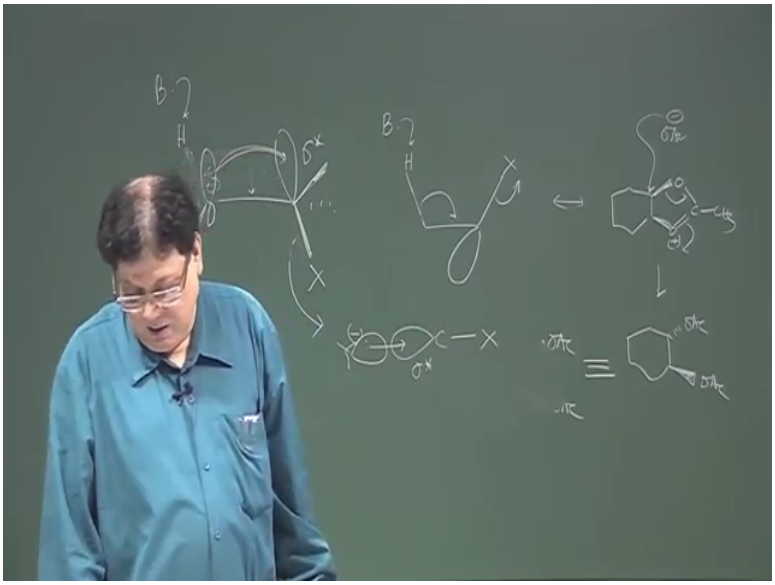

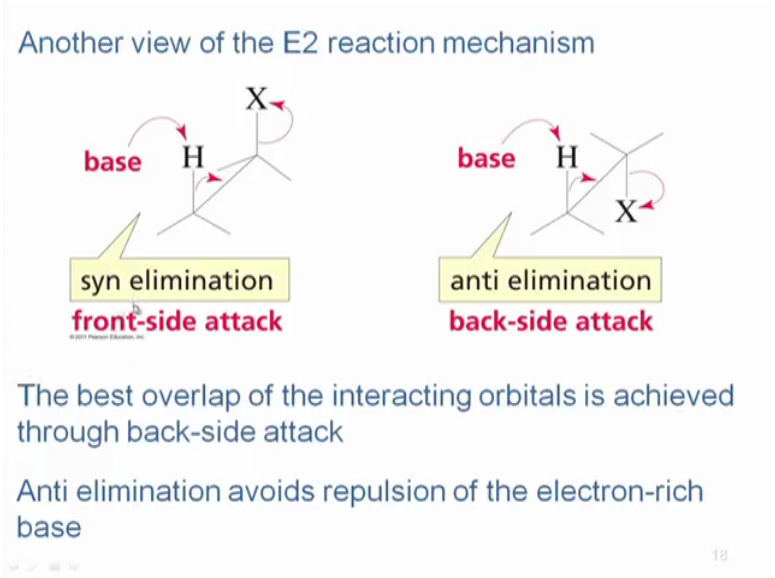

Actually what happens you can think in this way that when this H is lossed, so basically you are generating an anion here and the anti-bonding orbital of this C-X is empty on this side and this anion can now, can overlap means this anion means this is occupying another when the hydrogen is lossed. So this is occupying Snp orbital. So there will be a very good overlap between the anti-bonding orbital of this and the anion that is being created. So that will stabilized the whole system. So that is why, it is coming from the back side.

If it come from the front side then the anti-bonding orbital portion will be, on this side whereas, the anion is created in the front side. So this will be back side that will be on the front side. So there will not be efficient overlap if it happens in the syn direction, I hope this is clear. This is very similar to your SN2 that in SN2, the back side attacks takes place,

because the backside has anti-bonding empty orbital and this is the nucleophile. So the nucleophile orbital, now that is filled up with electrons. So that can efficiently overlap in the sigma star. So it is very similar.

Now instead of the nucleophile you have a negative charge and the negative is placed on the front side, front means up side and here the up side you have the anti-bonding orbital. So there will be efficient overlap between these two. In this case, it is not possible. So now we know that in E2 elimination, so we are convince that E2 elimination is mostly taking place when the two groups are anti peri-planar. So the stereo electronic requirement for E2 elimination is that that groups which are departing should be anti peri-planar, okay. So that is the important fact.

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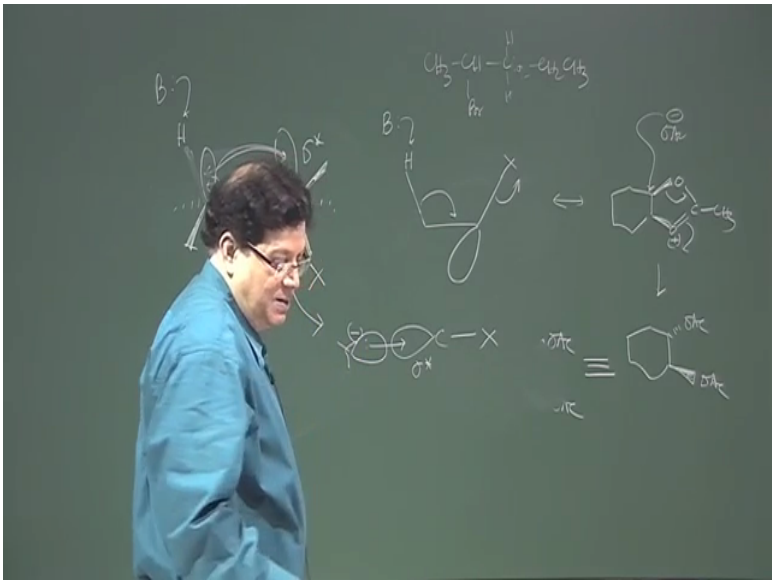

Now let us take few cases, I think I discussed about this, there are this is actually, CH3CHBr then you have CH2 then CH2-CH3. So CH3 you have what, you have CH3 then CHBr then CH2 then CH2then CH3. So if it undergoes elimination. So there are two types of the elimination possible, but let us consider the (())(20:29) elimination that is the more substituted double bond. So this hydrogens, one of these two hydrogens will be **will be** eliminated, but while doing so you are creating a Cis and Trans double bond, okay. Now in order to form the, first of all the to eliminate, the hydrogen and bromine should be anti to each other. So in one conformation, you have done the hydrogen-bromine anti and while doing so you have put the methyl and the ethyl group**.** So this is the methyl and this is the ethyl, the methyl and the ethyl group the methyl anti to each other the methyl, okay.

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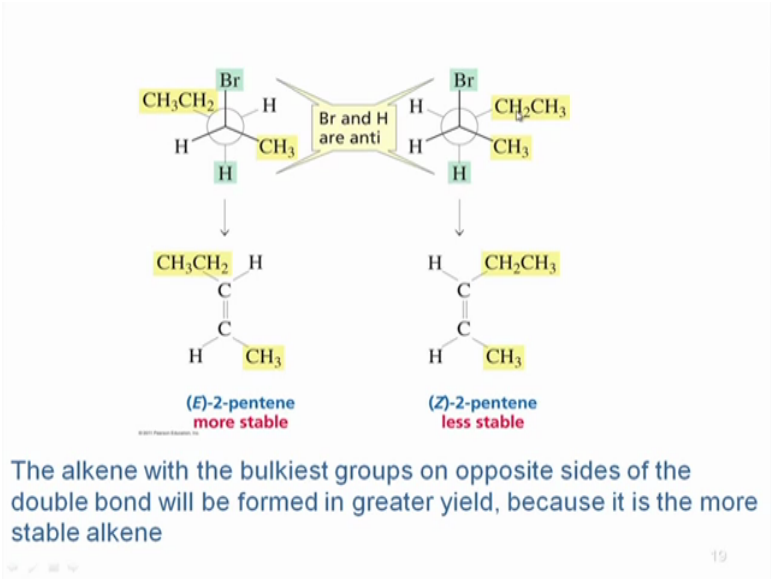

Now this, but you can draw another conformation, in which the hydrogen and bromine are again in the anti-position, by doing a 120 degree rotation. So if you do a 120 degree rotation, the methyl will come here. This hydrogen this hydrogen will come here and this hydrogen will go there, but the still you have an anti peri-planar a relationship, okay but out of these we know that this is the higher energy conformer as there is, this steric repulsion between this ethyl and the methyl which is not present here. So this will be this will be the favored conformer and then when the elimination takes place, there will be the methyl eclipse this hydrogen and this hydrogen will be eclipsed by this ethyl. So that is also less energetic than methyl ethyl eclipsing.

So in that case, this will have lower activation energy and this will be the major product that is obtained, okay. So here the more that means this is the, here all the this is the more populated conformer and the most populated conformer also giving the more stable product the or the also reacting the faster rate and resulting in a , more stable product via a transition state which, is more stable than the transition state which is , involved in this elimination from this conformation.

Here, there will be tremendous methyl ethyl eclipsing interactions as the elimination is taking place, okay. So this is how you convince yourself that why this is the major product formed in the elimination of this compound. This is 2 bromo pentene, okay. So that is written here. The alkene with the bulkiest group on opposite sides of the double bond will be formed in greater yield, because it is the more stable alkene, but actually stability is not the matter, I think that is one aspect, but the more important aspect is that, this is during the in the

transition state less repulsion, because two large groups eclipsing each other is consider to be having a much more interaction, steric interaction than the interaction between a small hydrogen and an alkyl group.

Although, there are two such interactions are there, but the combined interaction between methyl and hydrogen and ethyl and hydrogen is less than the combine eclipsing interaction than the eclipsing interaction of methyl and ethyl, okay. So ultimately this is the product that is obtained.

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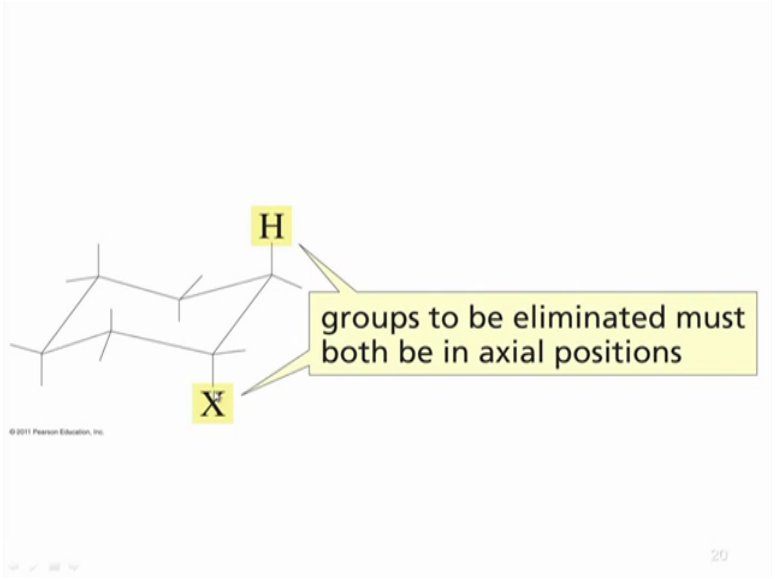

Now in case of cyclohexane, if it is not an acyclic system. In acyclic system, what you do? You draw the numen projection and ultimately draw a conformation where the leaving groups are anti to each other anti peri-planar to each other, okay. In case of cyclohexane, if you have hydrogen if you are doing a dehydro halogenation then the hydrogen and X are have to be eliminated from vicinal positions and then what happens? The hydrogen and X should be anti peri-planar, in order to in order to undergo the elimination, but that makes it (())(24:43) that both the hydrogen and the X are have to be axial, okay. One is beta axial, the other is alpha axial, okay or vice versa. So they have to be trans di-axial that is what is said that the leaving group and the both the leaving groups have to be trans have to have a trans di-axial relationship, okay.

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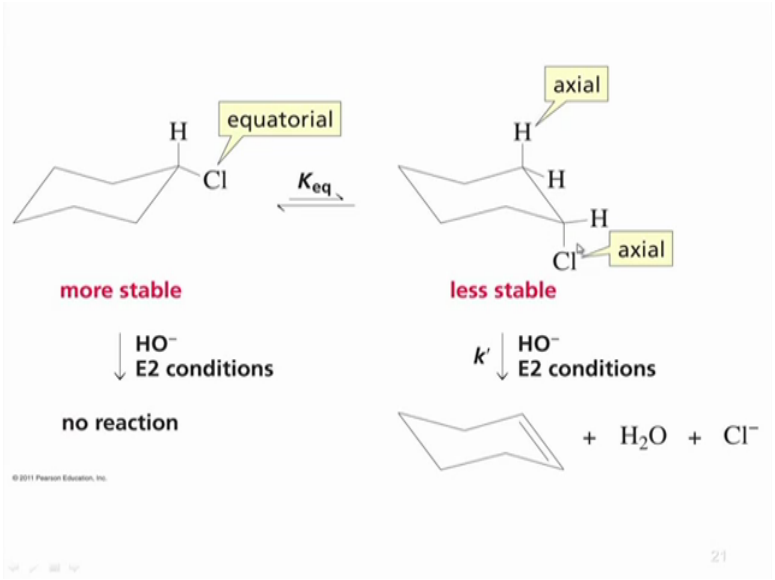

Now let us see whether there is a anymore problem here, okay we will do some problem here, suppose we want to eliminate this chloro-cyclohexane. So in the equatorial form there will be no reaction, because you do not have a see want to do the dehydro halogenation. So this is a alcoholic potassium hydroxide, okay and then in alcoholic potassium hydroxide you know the elimination takes place, but there will be no E2 elimination, because in this conformation, because there will be the, you do not have a trans and you do not have any hydrogen, which is anti to the chlorine, okay because the chlorine is not in an axial position. On the other hand if you do a that, so if you see if you do a forcing condition, if you heat it, so this will now be converted to the axial conformer.

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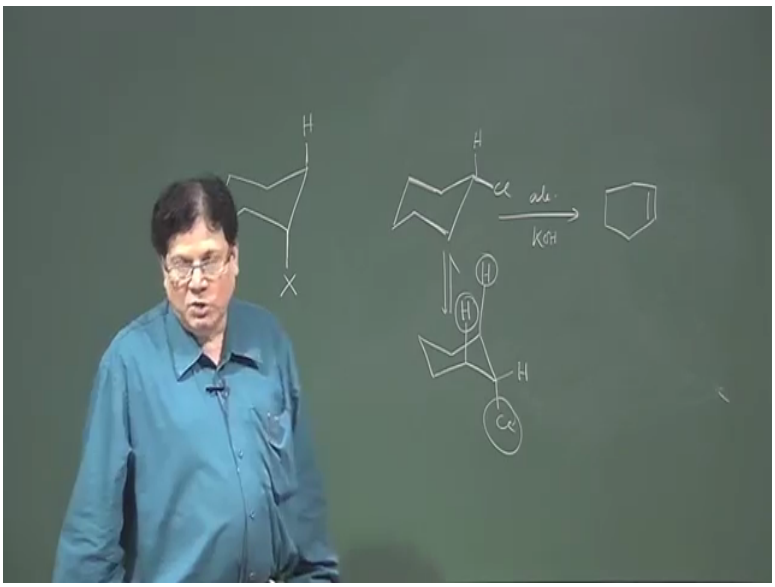

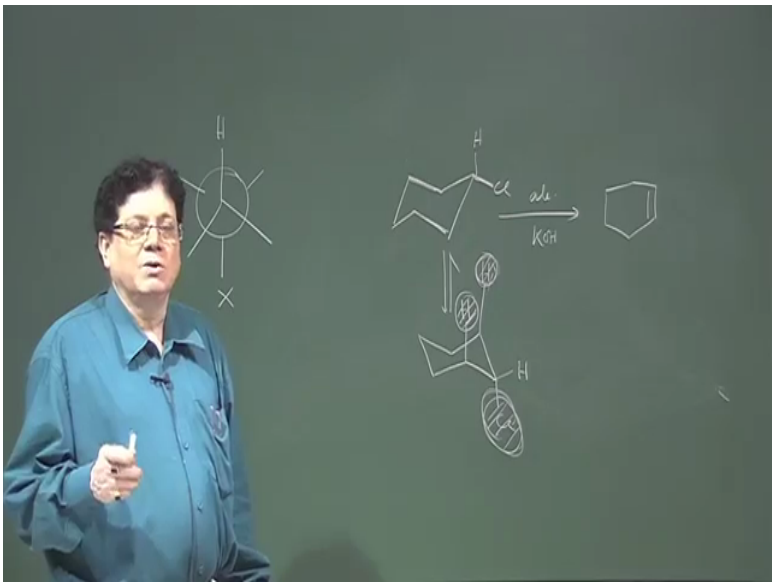

So we have seen that this stereo electronic requirements of E2 elimination, in what we have said in the last slide is that in a cyclohexane system, the groups that are being eliminated if it is dehydro halogenation then that has to be in the diaxial position, that makes it anti periplanar, okay and suppose you take the chloro benzene which will normally exist in the equatorial position. If you want to do the dehydro halogenation say with alcoholic KOH. It requires forcing condition to get into the cyclohexene. Why forcing condition, because in this equatorial position, there is no hydrogen which is anti to this chlorine. The anti-bond that is to the that is present is the C-C bond, okay but here the hydrogen has to be lossed. So hydrogen has to be anti.

The other way you can say the chlorine is occupying equatorial position. So there cannot be any anti hydrogen, okay. It has to be in the axial. It has to be in the axial position. so there is, if you force it, so then this conformation can flip and chlorine can go into the axial position, but that requires little bit of energy and then, so in under forcing condition you get this di-axial arrangement, in fact you have two hydrogens which are di-axial to this chlorine, okay. So that is these are the important issues that you have to consider while considering the elimination of cyclohexane system, again I repeat, in case of acyclic system, you have to consider the best is consider in numen projection and your hydrogen and X have to be like this and in the cyclohexane system your H and X should be occupying this type of diaxial orientation, okay.

So next we will work on the again some problem solving session. what happens in cyclohexane system, mainly focusing on cyclohexane system about SN1, SN2 and SN 2 prime those type of reactions that and then we will take some cyclohexane’s to do the

elimination reactions that means we will talk about conformation and the activity in cyclohexane systems with respect to substitution and elimination reaction that will be in the next lecture. Thank you.