Course on Stereochemistry
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Mod07 Lecture 34
Substitution and Elimination in Cyclohexane Systems

Okay welcome back, we were discussing the stereoelectronic effects or stereo electronic requirements for substitution and elimination reactions okay, but we will take some real examples and we will discuss mostly on the aspect of conformation and reactivity, because all these things are coming under dynamic stereo chemistry that is conformation and reactivity and we will discuss the reactivity of cyclohexanes towards substitution and elimination and different examples, okay.

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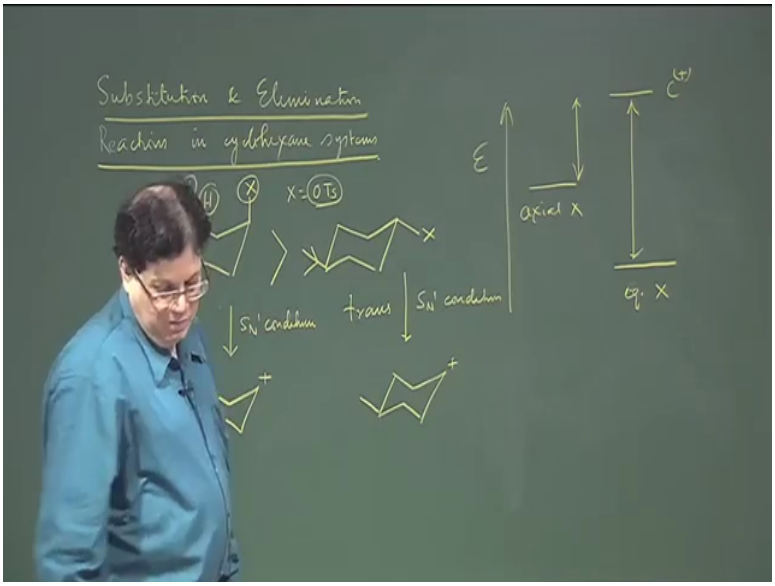

Now if we take a cyclohexane, suppose this is 4 tersary butyl and cyclohexane with a substituent with a leaving group at C1, okay. Now this can exist in 2 di-stereomeric forms, one is the Cis isomer another is the Trans isomer, okay. So this is the Cis-trans remember, the T butyl group is there, so that the conformations are locked. If this is not there, then they will become conformer they can flip to each other, okay we want to study the behavior of these towards substitution reactions, okay. Now there are different kinds of mechanism for substitution reactions, suppose we do it under conditions which favor SN1, under SN1 conditions and this one also subjected to the same SN1 conditions. So if it is SN1 that means there will be formation of the cation and this is a first step in SN1 reaction. It is a same cation that is generated here, okay same cation that is generated here.

Now what happens here which one will then react at a faster rate? There are again you can think in two ways, one is that when X leaves. In this system, there was if X is quite big, say (())(2:36) group. If X is say (())(2:38) OTs then that is quite big group. So when X leaves that leads to the release of the steric compression that it was having this 1, 3-diaxail interaction, in form of 1, 3-diaxail interaction. So that is released when X departs whereas, here X when X departs that will not be the case. The other thing you can other way you can think of that the energy level of this the axial compound the axial X will be higher than the energy of the equatorial X and if the carbo-cation that is same in both the cases is here, this is the cation then what happens? It will be easier for there will be less energy requirement for the axial X to be converted to the cation then the equatorial X to be converted to the cation.

So the axial isomer will react at a faster rate than the equatorial isomer, because of this if you remember if you carry it under the SN1 condition, okay. Ionization is favored in case of the axial, either you can say that release of this 1, 3 diaxial strain or you can also draw this energy the energy diagram to show the relative ease of the axial substituted compound over the equatorial substituted compound in forming the cation less energy is required, okay.

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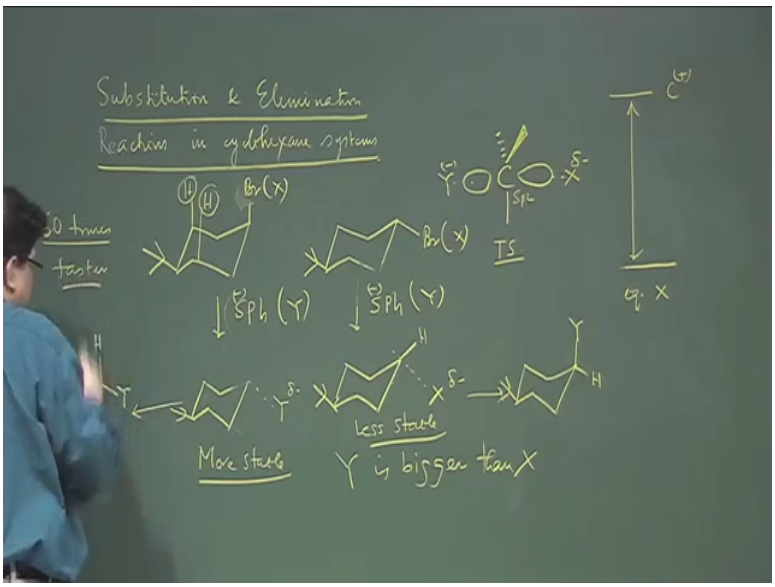

Now if you now do the same reaction under the SN2 condition, so I add Y minus and here Y minus. In the first case, I did not add the nucleophile, because it was a SN1, so the anyway whatever nucleophile you add, that is the very fast step the very fast that step. So there will be formation of both axial and equatorial products there, okay. So what I am saying that when the cation is the carbo-cation is formed, because the next step is very fast , so the nucleophile can attack from both sides, but there may be some discrimination equatorial product may be

little bit more, but in theory, because the product is very fast. So there should not be any selectivity in this attack in SN1 conditions, okay whereas, in SN2 now you have a you have the requirement of the Y minus should approach and attack from the back side of C-X that is number one and number 2 is, the transition state involves a carbon that is a carbon which is being attack that is transform from a Sp3 to a trigonal bipyramid structure that means what happens when Y minus take the simple SN2 reaction.

So in the transition state what happens? You have this is suppose X delta minus and this is Y that is your nucleophile and the three groups that are there. So this is the transition state trigonal bipyramidal, okay Sp2 hybridized carbon, but since both are holding X and Y a not very tightly, but loosely, because the bonds are, now more or less half. This is half brocken and this is half bond (())(6:25). So the transition state is a bipyramidal transition state.

So the same thing will happen here. So the transitions state will look like, this see these 3 groups will be these 3 groups resemble these three bonds. So these three bonds are will be in the plane and here, it will be Y delta minus and here it will be X delta minus, okay and in this case, what will happen? X here it is X delta minus and Y delta minus and then the final product. Here, the final product is sorry, put the T butyl, the final product is Y in the equatorial position, because you are replacing the X which was axial and, because it is SN2. So there will be inversion of configuration and that exactly what happen and in this case the product will be the axial one, okay.

Now the question is which one will react at a faster rate that depends on the relative size of X and Y**,** okay. If Y is big if Y is bigger than if the size of Y. So we are saying Y is bigger than, if the size of Y, so we are say Y is bigger than X then what happens? If Y is bigger than X then, this transition state will be less stable and this transition state will be more stable, okay. So if that be the case then we can say that the axial (())(8:37) will react at a faster rate than the equatorial tossile ((()))(8:42) and in fact, reaction has been done where Y is, but remember Y has to be bigger than X. so X was, suppose chlorine, here that was not (())(8:58) X was chlorine or may be bromine you can also tolerate bromine and you are replacing it with, your Y minus is Sph minus suppose, which is quite big thiophenoxide, okay. So if you do that.

So now this is your Y, so Y is bigger than your X. So what was actually reported that this reacts about 60 times faster, but that the number is not very important? The important thing is that the concept that why this reacts faster than this, because of the size of the nucleophile is

bigger than the size of the leaving group. So now in the case that will cause, destabilization of the transition state, obtained from the equatorial bromide, okay, I hope this is clear.

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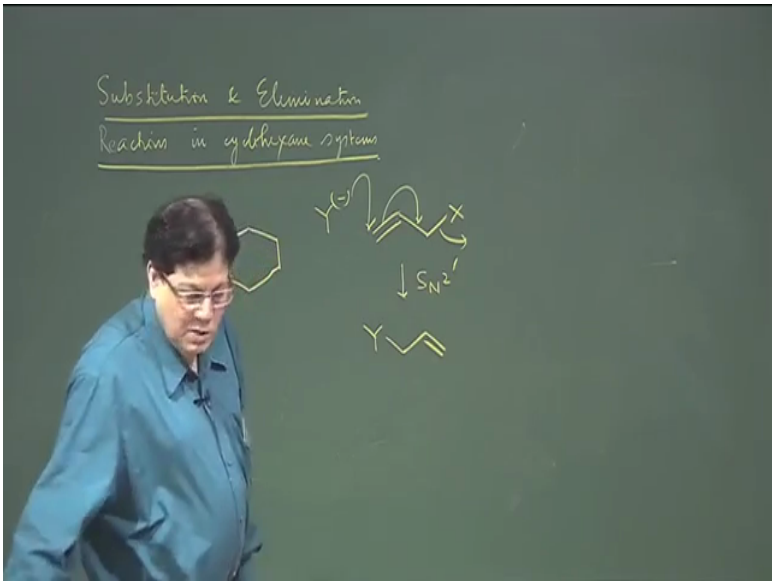

Now next is, so this is, so we have discussed SN1 first and then we have discussed the SN2. In both the cases you see, the axial isomer is, reacting at a faster rate, of course provided that size requirement was there. Now the in the SN2 case, that the nucleophile has to be larger than the leaving group. So if that be the case, in both the cases, the SN1 case or the SN2 case, the axial is reacting at a faster rate, okay.

In case of, see there are reactions which are called reactions which go via allylic rearrangement that means, if you have a leaving group here and allyl (())(10:50) system and if you add the nucleophile, the nucleophile can attack this carbon and then the process can go in this way. So Y is attached, it is not directly attacking the carbon bearing the leaving group. it is attacking the end carbon of the double bond, okay the allylic carbon or the double bond and the gamma carbon of the double bond, okay. Then, so what is happening this is Y and the product is this, okay. This is what is the this is called SN2 prime. This is prime that means SN2, but it is not attacking the same carbon as the which is contains the leaving group. It attacks another carbon, so that is why this is SN2 prime not direct SN2, okay.

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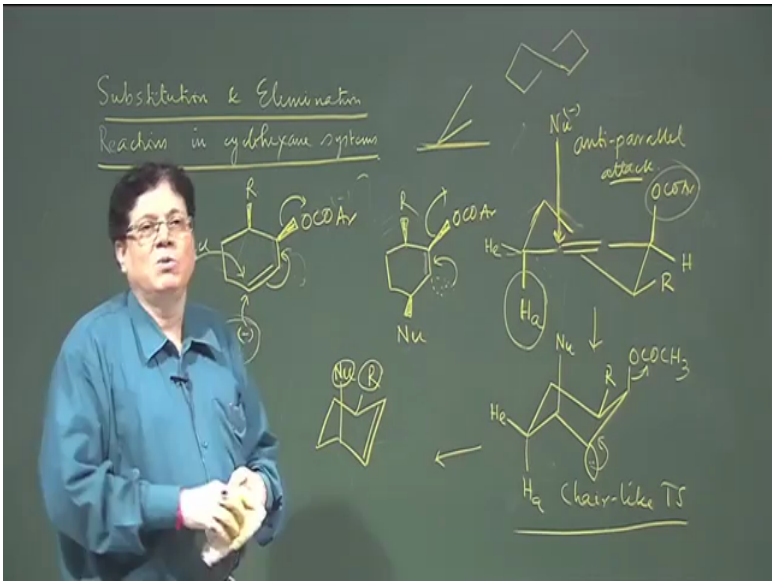

In SN2 prime, in cyclic systems, so if you have a cyclohexene kind of thing, I am sorry, let see if you have a cyclohexene and you have a leaving group here, O-CO say Ar a leaving group and acetate benzoate kind of thing leaving group and the group R here, okay. So now the nucleophile, whatever nucleophile you have, we will attack in an SN2 prime fashion. So it attacks here, it goes there and that goes out, okay. Now the question is from which side it should attack**.** In direct SN2, it should attack from the opposite side of the benzoate, okay the leaving group. In SN2 prime, the nucleophile is the other way around. The nucleophile attacks from the same side of the leaving group**.** Now you can say why is that? That means I am saying the nucleophile should attack from the beta face, okay. Why beta face, because this is the leaving group is also in the beta phase okay. Now the question is why?

The answer you can , simply answer without writing any conformation, you can say that if the nucleophile attacks from the top phase then the negative charge that will be formed here, will be in the bottom phase and that negative charge, now will be in a will be anti to the will be anti to this OCOph. So it will be easier for that negative charge to come back and kick out the benzoate, again I repeat, this appears from the beta face, because the negative charge that will be generated here, will be in the alpha face and then that alpha face negative charge for the alpha face negative charge we will have easier elimination of the benzoate. The alpha phase negative charge can easily displays the beta benzoate, okay because they are anti to each other.

On the other hand, if it approaches from the alpha face, then the negative charge is formed in this side and now it will be difficult, because they are on the same side, okay. So there will be

difficulty in kicking out the benzoate, because they are on the same face and they are both having the negative charge, see this is the you are trying to generate a negative charge, in the same face as the negative charge itself where it is generated okay. If you want to go to the conformational level, so what I have said that the if the nucleophile without going into the conformation, you can said if the nucleophile approaches from the beta face then the double bond is here. So initially that means the negative charge that is generated will be in the alpha phase, okay and then this is beta.

So it will be now, it is like a Trans elimination as I said in the, in the case of E2 elimination. it is a kind of a Trans anti elimination Trans elimination, the same thing here that this comes out, this comes back and this goes out. So there will be, it is much, it will be good that if they have anti relationship. So this is without going into the detail conformation analysis, but you can do a quick conformational analysis by drawing the cyclohexene you know that is drawn in the half chair conformation. So you can without going into any complication, I will just show you one approach of how to really draw the conformation and make this thing look is more look , the go into the actual conformational analysis of this SN2 prime reaction.

See this is kind of not correct because you are is in a plane hexagonal cyclohexane, but that is not the correct. It is actually, the cyclohexene has this type of conformation. So now what happens where is the your benzoate? The benzoate is here, OCOAr, okay actually, see in cyclohexene, this groups are pseudo axial and pseudo equatorial, okay. So the here the group will be up and so this will be pseudo axial OCOAr and this will be hydrogen and here there will be the pseudo axial hydrogen and here this will be pseudo equatorial hydrogen, okay.

Now let us actually draw these two bonds, just to make it less complicated, because we are only concerned about**,** this carbon that carbon and these two aliphinic (())(16:47) carbons, okay. Now the nucleophile can approach from the, because this is beta. So I said the nucleophile has to approach from the top, okay. So if it approaches, it has to approach from the top, so if it approaches now, so what will happen? This will see this will change; this will become a cyclohexane system, interestingly. Now you are dealing with a cyclohexane system as there is connection between the nucleophile and this double bonded carbon. So this will now, form, see this carbon will little bit push up as the nucleophile comes here. So as if there are positive interaction. So this carbon is going up. So if carbon is going up that means you will get what is called a chair like transition state, see this is the nucleophile. This is the Ha I

am showing these two I will tell you the reason, why I am showing this Ha and He, although they are not participating any in the reaction.

Now you have a negative charge here, okay and you have OCOCH3. So now the negative charge and actually we have a R group to start with, where was that R, the R was the beta. So R was here, okay and so the R was now here, remember it was on the back side. So R was this part is in the back side. So R is here. So now this comes and kicks (())(18:26) out the acetate and the product is the cyclohexene again.

Now the product will if you draw it in the chair form, so you have a double bond here, you have R here and you have nucleophile here. So the important thing is this R and nucleophile will be Cis to each other and there is a chair like transition state and this attack is what is called an anti-parallel attack, because this is based on the relationship on the attack with the axial hydrogen on the on this side, okay. On the axial hydrogen on this carbon. So because the axial hydrogen is alpha, so pseudo axial. So the nucleophile is approaching from the opposite direction, so this is call anti-parallel attack. If the attack takes place from this side that will be call parallel attack, but this cannot happen, because the stereo electronic requirement says that this has to come from the same phase, as the benzoate, okay. So this is one way of doing.

There are other, see there will be anti-parallel attack also, but that cannot involve these type of cyclohexene, you have to flip it and then do it, okay but we are not going into, because this is a foundation course. So we are not going into that detail, but remember that the way I do the chair, because I know that in the chair form**,** when you write a chair form, these carbons and these carbons are both above this above the plane horizontal plane containing this carbon.

So when I brought the nucleophile, I know that this is going to go up that means there is already a carbon up and this is up. So that gives you a chair. If the nucleophile attack from this side, which is not happening in this case, but that will go through a even if that happens, so this carbon will go downwards and in the in the that twist boat conformation, this is what is the geometry of a twist boat. So in the parallel attack, a there will be the formation of the twist boat, because that is going down. So you remember these things that will be useful in your future courses when you take an advance stereochemistry course, okay, because again I tell you, stereochemistry is nothing but visualization of the 3D molecules.

So this is one case where students gets stuck that why it is a how do, I know that it is going through a chair conformation, I said that in the chair, study the chair conformations that these two carbons are above this carbon, if you take a horizontal plane. So that is what is happening. This is your horizontal plane. This is this carbon and this is going up okay. So that type of tricks you have to have in your mind so that that will enable you to draw these type of structures, okay. So the stereo electronic requirement for SN2 prime is that the attacking group the nucleophile should be coming from the same side of the leaving group, okay. So that takes care of the SN the substitution nucleophilic substitution reactions, in cyclohexane.

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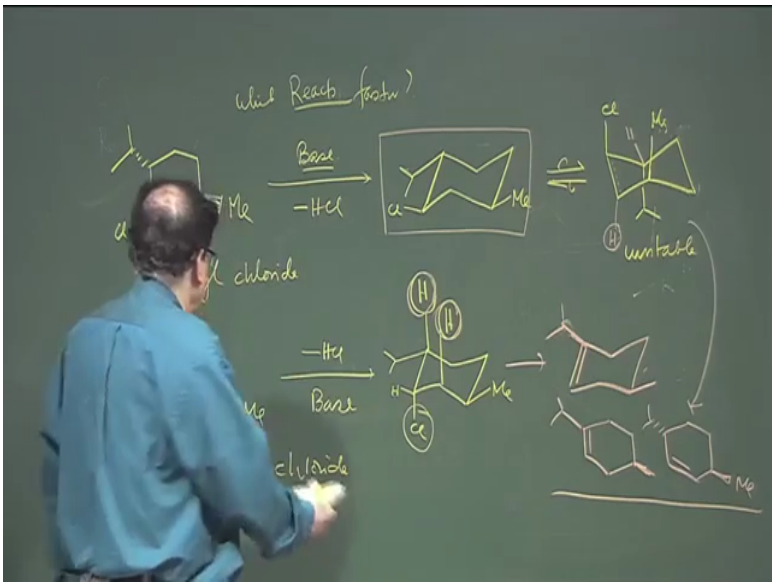

Let us now take the let us take the elimination aspect and do some problems, okay. First problem let us try to do. There are these types of questions can be given that suppose, you have this compound, a cyclohexane substituted tri-substituted cyclohexane. This is what is called menthyl chloride you have heard of menthol a natural product menthyl chloride, which gives an aesthetic sensation. This menthyl chloride has this type of configuration. There is another compound which is very similar, but only the chlorine is alpha.

Here, the iso propyl is alpha, chlorine is beta, methyl is beta you have another compound where chlorine is alpha as well as isopropyl, but the methyl remains beta. This is called iso-menthyl chloride, okay. Now if you want to do, dehydro halogenation, see base okay, you want to replace HCl dehydro halogenation minus HCl by a base. Question is which one reacts faster or which one which one reacts faster, but there may be some problem with some molecule, or which molecule has that problem.

So in order to solve tis type of problem, this is the reactivity that means which reacts faster that is which reacts faster. So what will how do you answer these type of question you draw the the conformation, the correct chair form of this molecule. So where is your iso-propyl, you see the iso-propyl is alpha is having an alpha orientation. Now you have lot of flexibilities, see alpha you can put anywhere, this is see, but you have to see the you have to pick up the correct bond, either equatorial or axial.

Now since to start with seen this is the big group. So I will try to put it in the alpha as well as in the equatorial position. So my base (())(24:25) is that I put this here, okay. If I put that there then the next is chlorine, chlorine is beta that means chlorine is also equatorial and then the methyl after one carbon. So the methyl is also beta. So this is a preferred conformation, because if you flip it, you will get all this as. So the methyl is here now, axial the chlorine is here axial and the isopropyl is here that is also axial, so unstable, okay.

On the other hand if you would write the conformation of this. So this will be again iso-propyl, I put in the alpha equatorial position then the chlorine, now it is alpha. So it will be axial and now the methyl remains in the equatorial position. If you flip it, now there is no requirement of flipping, because this has got an axial chlorine. An axial chlorine and that means, you have to check whether, it has got any hydrogen, which can eliminate axial hydrogen yes, there are two sets of axial hydrogens, which can be eliminated, so either this can be eliminated, this HCl or this can be eliminated.

So basically you get two products, one is this one. This is iso-propyl, sorry this is the iso-propyl and this is the methyl of course, here alpha beta, it is not in the chair form, so you can convert it into the write it in the cyclohexene. So double bond this is iso-propyl and this is your methyl that is one product and the other product is on this side. So other product will be iso-propyl remains and the double bond is here and the methyl is here. So these are the two products, a mixture of two products, but elimination will (())(26:45), because the chlorine is occupying an axial position and there are hydrogens opposite to it.

On the other hand, this molecule has a problem. This molecule, in the preferred conformation is this one, where the chlorine is equatorial and all other substituents are equatorial. Now in order to have dehydro halogenation, this molecule has to flip, but that requires enormous energy, because you not only make chlorine. Here if chlorine is axial if you flip it then chlorine becomes axial and yes you have a hydrogen here, which is anti to it. First of all, it requires much more higher temperature to do this dehydro halogenation reaction that is

number one and number 2 the difference with this is that, it can only give one product, the double bond can only be here, that means it only give this product and not the other one, because other one other place the hydrogen is equatorial. It is not and the Trans diaxial to the, it is not having the trans diaxial relationship, okay.

So there are two things, first of all this reacts very (()(27:55) if you want to do dehydro halogenation you have to heat it up and then the other difference is that it can only give, this product and this product cannot be obtained from that, because there is no anti hydrogen in this case, okay. So that is one interesting problem menthyl chloride and iso-menthyl chloride, okay.

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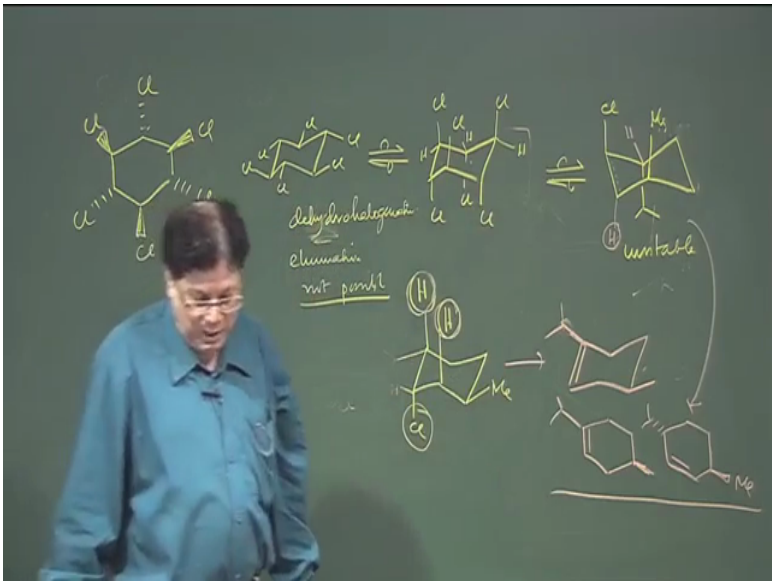

Let me see, another interesting example is dehydro halogenation of this compound, okay. Dehydro halogenation of this compound. This will never undergo dehydrogenation dehydro halogenation. Why, because if you draw the preferred conformation, so you have alternate alpha and equatorial alpha and beta chlorines, but the interesting part is all the chlorines are in the should be in the equatorial position, that should be the most favored conformation, okay.

So there is no question of any elimination here, because the chlorine is not occupying any axial orientation. If you flip it by applying energy thermal energy yes, it will flip, but the problem is it requires lot of energy that is one and the other problem is even if you flip it, you see, there is still no axial hydrogen a adjacent to the chlorine, okay. All the hydrogens are now equatorial. So you do not have any situation where there is hydrogen and chlorine which

are trans to axial. So it cannot eliminate. So elimination is not possible means dehydro elimination not possible, I am talking about dehydro halogenation, okay. I am talking about dehydro halogenation, so this is interesting, so many chlorines are there, but it cannot eliminate, simply because, in the ground state, it is in the ground state, it exists in this all equatorial conformation, if you heat it strongly, it will go to the diaxial, but still that is not capable of doing any elimination as no hydrogen is anti to the chlorine, okay.

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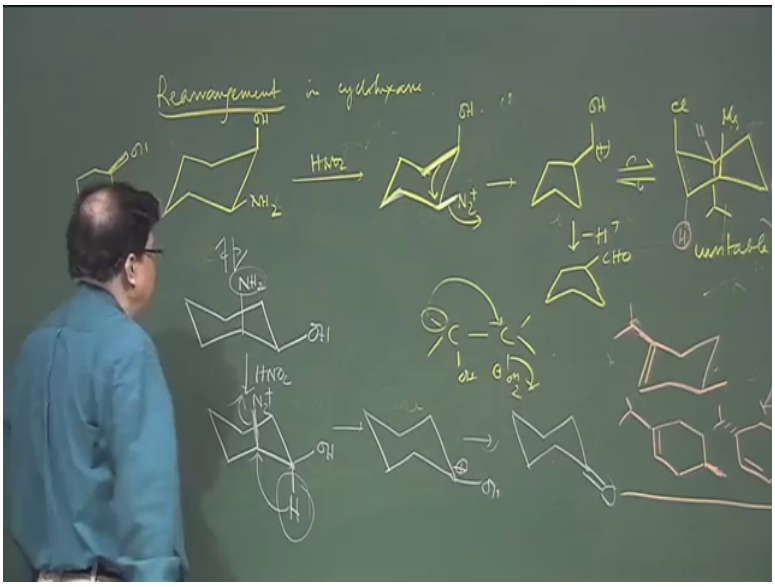

Let us do just one more example of where bond migration, see where rearrangement reactions is cyclohexenes, rearrangement in cyclohexenes. Now suppose you take, no tersary butyl, suppose you take Cis 1 and Cis 1 amino 2 amino, I do not know which one is 2 amino 1-cyclohexanol, okay. If it is Cis then basically what you have? You draw the Cis compound OH and NH2. So OH will both are beta, because it is Cis. So if both are beta then one has to be axial another has to be equatorial, okay.

Now you know that it is like, if you add HNO2 in this system, so this will be converted into di-azo group and that will be tis compound and it is very similar to what is known as pinacol–pinacolone rearrangement that in pinacol–pinacolone rearrangement you have OH and OH and OH the moment you make OH to plus here. This goes out and one of the group migrates here, okay. Now group that migrates again like elimination here, again in cyclohexane system that is true for here also, the group that migrates will migrates the group that is anti to it or the bond that migrates should be anti to the carbon d-azonium bond, okay. So now in this case you have to look that if the nitrogen leaves, this bond is brocken, so what is anti to it, you can

see the anti-bonds of this is that one and also of course this one also. These two are the anti-bonds to this nitrogen.

So in theory, both can migrate, either this can migrate and this leaves or this can migrate and this leaves, but resulting in ring contraction, there the contraction in the; however in reality only this migrate and that goes out. Why this migrates, because the cation that is generated is stabilized by the oxygen. So this does not migrate, because there so no assisting group to help the cation to be stabilized. So this migrates and what you get is this compound. This will be the cation and finally a proto is lossed and you get cyclopenten aldehyde, okay. Now this is one conformation of Cis amino cyclohexanol. There is other if you flip it you get another conformation and in that conformation, this OH will be equatorial and NH2 will be axial, okay.

Now you see the difference, if you treat that the same thing, because it is the same thing with HNO2, so HNO2 will make the amine the di-azonium, so that will be N2 plus and this will be, sorry this will be OH, but now you have a hydrogen, the CH bond which is anti to the carbon nitrogen bonds. So this hydrogen will now migrate, is in a position to migrate, because it fulfills that stereo electronic requirement that the migrating group should have the bond, which is anti to the bond that is being brocken that is leaving.

The bond which is containing the leaving group. So this leaves now, so resulting in OH and this is plus, so that is nothing but cyclohexanol, sorry that is nothing but cyclohexanone, sorry that is nothing but cyclohexanone, okay. So in one case you get cyclopenten aldehyde and in the other case, what you get is a cyclo is a cyclohexanone. So ultimately you will get a mixture of the two, because there is hardly (())(35:51) any energy difference between this between these two conformations, because their steric bulk is more or less very similar and in both the cases, one is equatorial and the other is axial, okay. So I think that is the type of one we are rearrangement reaction we have discussed in cyclohexane and there are lot of problems that can be generated from this type of pinacol-pinacolone type of rearrangement, okay or epoxide formation. So those are will be given in the in the assignment when we give the assignment when you attempt this online course, okay. Thank you.