Course on Stereochemistry
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Mod07 Lecture 32
Stereoelectronic Effects

Okay, welcomes back, let us take that continue from whatever we have said last time. We have seen the kind of effects that control the stereochemistry of a molecule, specially we are looking at molecules where the axial orientation is preferred, alkyl ketone effect is one, the anomeric effect is the other and another is the allylic stress that pushes the groups in the axial orientation.

Now let us (())(0:54) a reaction, okay something is happening to the molecule that means the reaction. So when a reaction occurs in a molecule or when a molecule reacts, it has to go through a either a series of steps or it could be a one-step reaction whatever it may be every step has a transition states to be crossed, okay. Every step has a transition state to be crossed.

Now you know that the most the slowest step of the of all this steps is the rate determining step and if it happens to be only one-step then that has to be the rate determining step, okay. Now the stereo electronic effect is the one, which is such that the molecule when a transition state I created, the molecule the orbitals not the molecules the orbitals that are, see when a reaction happens to a molecule not all parts of the molecule are affected, certain parts of the molecule are affected that means certain orbitals associated to that part molecular orbitals associated to that part will be affected, okay.

Now this orbitals which are affected, they will be in such a orientation, they will take up a such a geometry, in relation to the other counter the attacking species, the such as a nucleophiles. So nucleophile has an orbital filled with electrons and it is attacking a carbon, suppose which is having a leaving group attached to it. Now the transitions state will be such the system will adapt a transition state in such a way that the orbitals are aligned, in 3D space so that to give up the to give the maximum stability that means to give the maximum overlap or in other way around stereo electronic effect demands that in the transition state, there should be maximum overlap of the orbital that are interacting during the reaction, okay.

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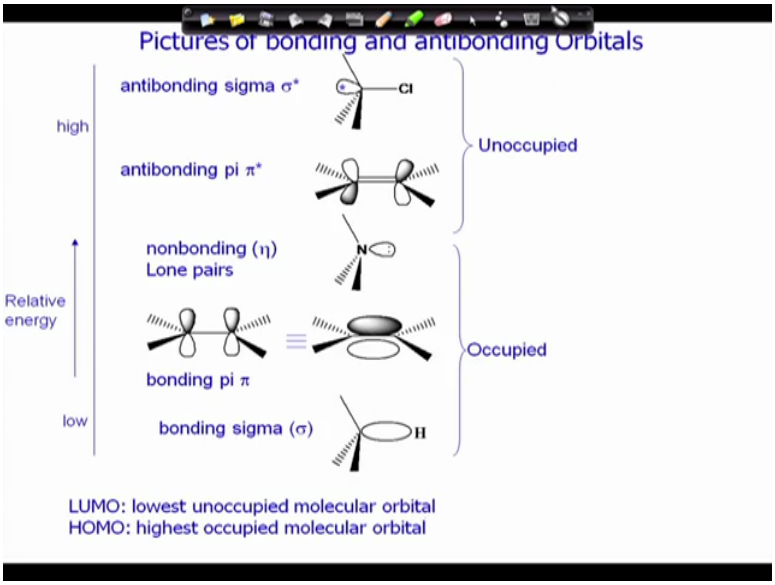

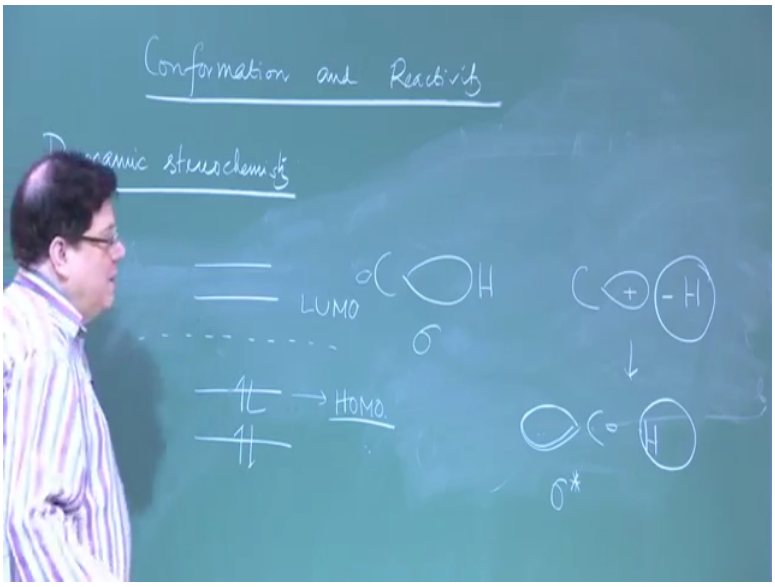

Now let us show these slides and come back to the board later on. Now when two orbitals combine with each other that generates, two atomic orbitals combine with each other that generates two molecular orbitals, one is called the bonding seen arrow when the two orbitals are in phase. So the energy goes down and the system is stabilized. So that is called the bonding seen arrow and the other is when the orbitals are in opposite phase then it goes up, they are mismatch and the energy goes up. So there is practically no overlap, because they repeal each other. There is no overlap and that is called an anti-bonding seen arrow.

So whenever two anti-bonding orbitals interact with each other, there will be atomic orbitals interact with each other. There will be two molecular orbitals, one will be bonding and another goes up that will be called anti-bonding, okay. So how does they look like if you have

a sigma bond, carbon sigma hydrogen bond, C-H bond not hydrogen bonds C-H bond. So the hydrogen S orbital and the carbon sp3 orbital. they interact with each other and it looks like this; however this is not the correct picture, I think there should be a tiny amount of space available here, which so what I am saying that actually it should be sometimes we overlook this, but there is a tiny amount on this side also. So this is the sigma C-H sigma, okay.

Now similarly you have C-H you have the C double bond. So when two p orbitals are combining laterally, so what will happen? There are two seen arrow that can happen, one is that they are in phase the just like this situation. So they will combine with each other. So there will be an electron cloud at the top and at the bottom, okay. This is the bonding pi orbital. So what is the anti-bonding pi orbital? The anti-bonding pi orbital when they are in opposite phase, you see the this phase is not matching with the top phase of this, so they will repeal each other and it will look like this if they bend they are bending away from each other. So this is the pi star orbital and what is a sigma star orbital. When these orbitals, so sigma star orbital is when the carbon has a has this orbital which is in say the plus phase and the hydrogen is in the minus. So they are dot is a same phase then actually the combination will lead.

So this will go back to here, so that means the bigger lobe on the back side and a very small lobe on this side. So this is and the hydrogen will also be deformed a little bit. So this is the sigma star C-H, okay. So that has got a bigger lobe on the back side of the hydrogen. So that is what is shown here, okay. So this is actually carbon chlorine, so you have the sigma star a bigger lobe on the back side, okay that is, usually the anti-bonding orbitals are empty, because when two atomic orbitals combine each usually have one electron and then so, both the electrons go to the boning level and the anti-bonding level becomes free, okay.

So that is this starting point and out of these there is a concept which is call lowest unoccupied molecular orbital that means out of these, out of these there will be a set of anti-bonding orbitals and then there will be a set of bonding orbitals. If you see that the bonding orbitals are all occupied, suppose this is the original level of the atomic orbitals and these are unoccupied.

So this orbital is what is called the highest occupied molecular orbital and this orbital is what is called the lowest unoccupied molecular orbital and whenever reaction takes place with another substrate, so it is the homo of 1 the highest occupied molecular orbital react with the lumo of the other, because there cannot be reaction between homo and see there cannot be

reaction between homo and homo, because that is that will not give any stabilization. So it can only react with an empty molecular orbital.

So the interaction takes place between homo and lumo. So whenever another as I repeat whenever another substrate comes, it has got a set of homo and lumo. So if it supplies the lumo then that has to interact with the homo of this or if it supplies the homo then it has to interact with the lumo of the other system, okay. So it is a homo-lumo concept that reaction takes place via the interaction of homo and lumo, okay.

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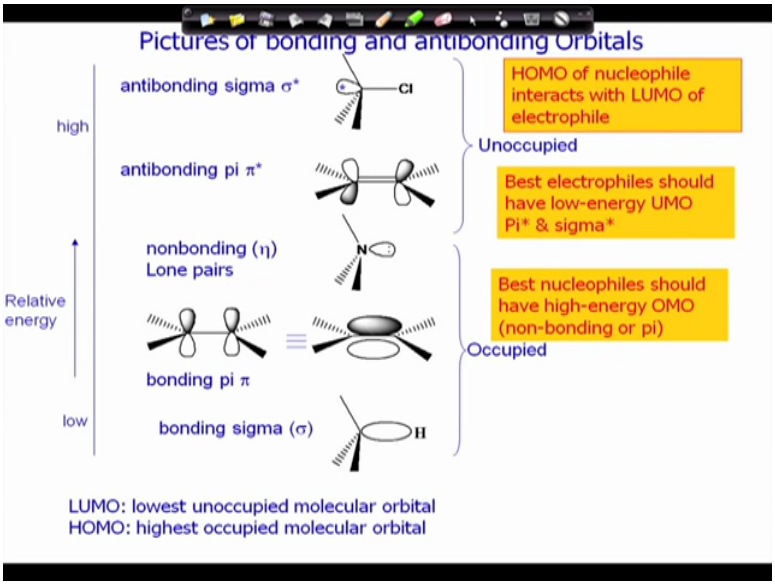

So now like, here it is between homo of nucleophile interacts with lumo of electrophile. So when the nucleophile comes and displaces the chlorine. So it is the it is this orbital which is the lumo, because it is the lowest unoccupied molecular orbital and then the homo that, the homo of the nucleophiles that comes and donates electrons to this and interacts with this orbital, okay. Base nucleophile should have a high energy; this is homo a non-bonding high energy. So the lower the gap between the homo and the lumo, the reaction the better is the situation. The lower the gap between the homo and the lumo, the better I the situation and the reaction will be more facile (())(8:57) okay.

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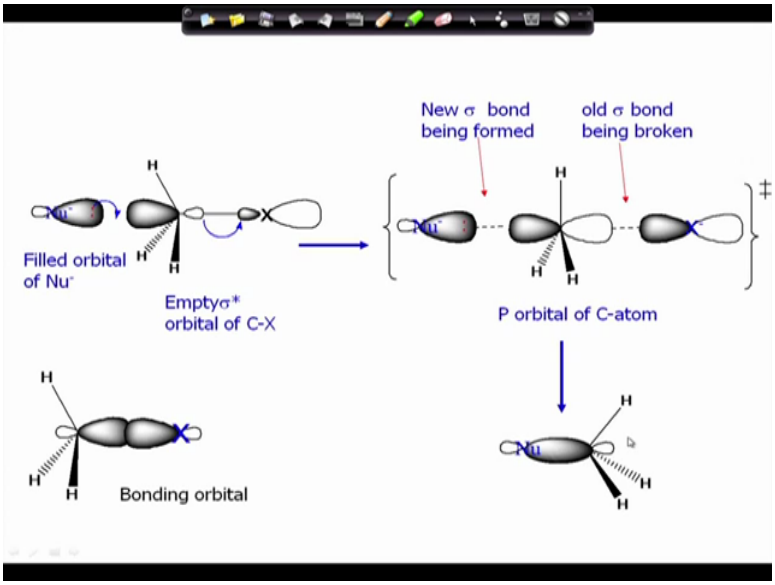

I think, so let us see again this, in case of say SN2 reactions, okay. In case of SN2 reactions what happens? This is the nucleophiles, suppose this has this are type of orbital and it has got two electrons and this is the C-X bond, okay. This is the C-X bond. Now what I am saying that because it is, now coming with the homo. So now it has to interact with a lumo of this C-X bond the lumo associated with the combination of carbon and X. Now here it is what is drawn is the is the anti-bonding orbital which is the empty orbital, first of all as I said that if this has also electron and this has got electron than they that combination will not lead to instability.

So stability will come only when this is empty and this is filled or the other way around, okay. Now in nucleophilic substitution, this is filled, so the carbon has to supply an empty orbital in the form of the sigma star, okay orbital of C-X. Now this nucleophile could have come from various sides from this side or from this side, but yesterday I was telling that it will approach in a line along the C-X axis, just opposite to it**.** Why it does so, because that gives the maximum sterilization of the two orbitals, okay.

Now this is what is the called the stereo electronic requirement. So what is the stereo electronic requirement of an SN2 reaction that the nucleophile should approach opposite to the C-X bond and along the C-X bond, okay opposite to the C-X bond that is true and it should be along that C-X bond axis? The approach should be along the C-X bond axis. Why it is so, because that ensures the stability highest stability of the transition state, see when the interaction is taking place that will be that will give the highest stability of the transition state, as I said stereo electronic effect demands that the orbital should be aligned in such a way, so

as to give maximum overlap that means the maximum stability. So that happens in the say SN2 reaction. So as it approaches the carbon becomes the it gets the pure p form and then there will be interaction between this and this is this X is started to break away from this system. So this is a transition state.

In a transition state, the carbon is becoming trigonal biperymid shape, okay. It is partly attached to this nucleophile and this is partly attached to the X, okay. Already there is started the detachment has been started and the attachment is also taking place. So new sigma bond and that is the old sigma bond being broken. So that is the stereoelectronic requirement for of for the SN2 reaction and after the completion of departure of X, this is the situation. So this anti-bonding, this is now anti-bonding whatever was the sigma star orbital, the anti-bonding orbital was being offered.

Now that has after combination become a bonding orbital, okay and the other important thing that these 3 hydrogens where on these sides on the left side, but now forming a cone. Now they are after the reaction they have gone to the right side. So they are form a cone from the right side, okay that is important to notice.

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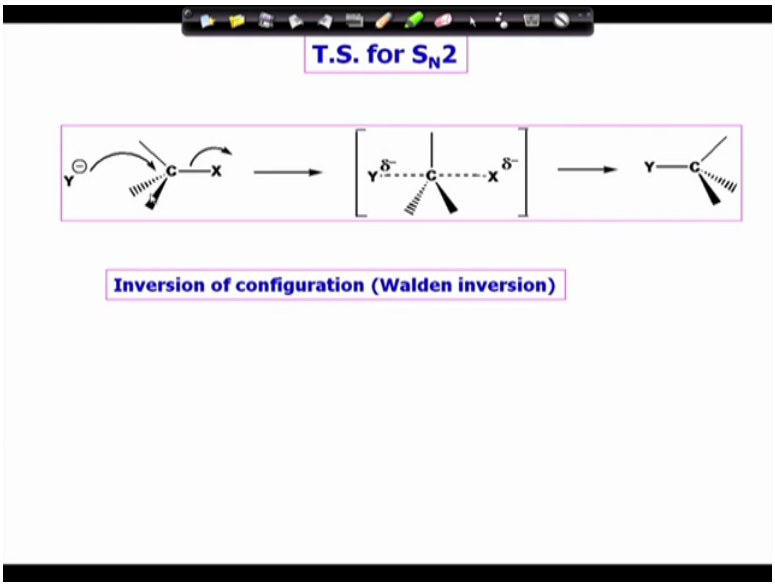

So that is again read (())(12:49) they are that means the mechanism for SN2 is this. This is the transition state and this is the product, okay. So there is what is called an inversion of configuration, because if these 3 groups are different then this has got an absolute configuration, because X is also different. The after the reaction, it is again stereo genic center, but there is a earlier the X was on the right side and now the entering group is on the

left side and these three groups have been inverted from one side to the other, okay has been inverted from one side to other.

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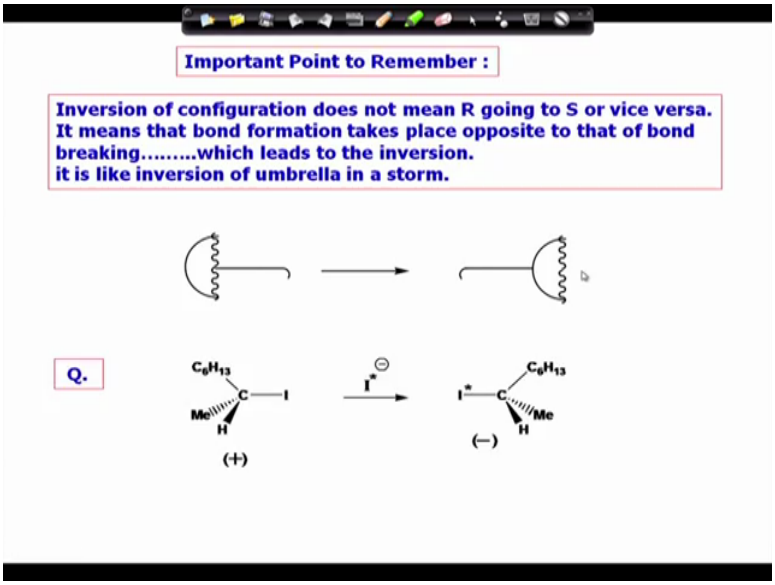

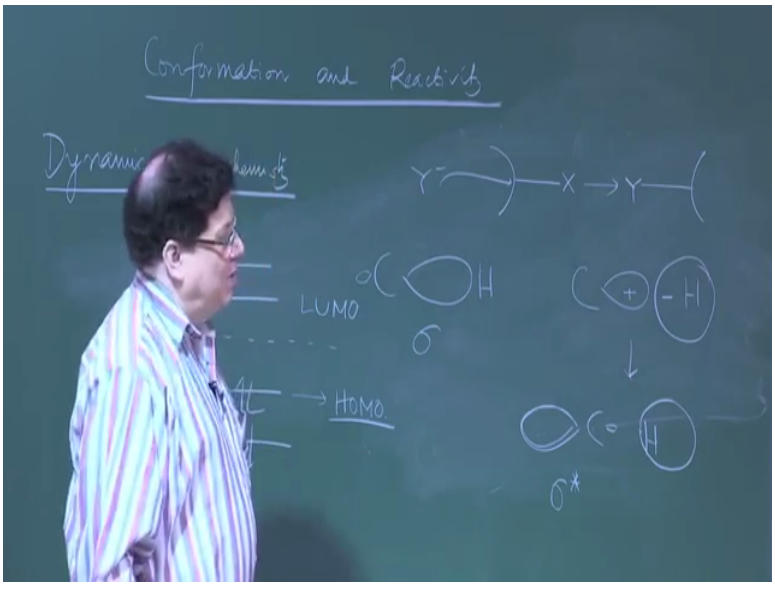

Now inversion of configuration does not mean that R going to S, okay that is very important you should always notice this that inversion of configuration does not mean R going to S or vice versa. It means that the bond formation takes place opposite that of the bond breaking, which leads to the inversion, okay. It does not means R going to S or it does not even mean that plus compound is going to a minus compound; okay do not think that way. It is a change of configuration, okay change of configuration from one to the other that means the incoming group is occupying the opposite side of the of where the leaving group was, okay.

So it is like you can compare this with this umbrella that earlier, this was the this was the leaving group and when the nucleophile come then it attacks from this side. So this is a nucleophile bond, but what happens? Now this whole portion has to be inverted. These are the three alkyl groups. So that portion now that is not shown here, this whole portion, sorry these are the things that is still there. So that is may be that picture may not be very correct, I think the other way the better way to do it is that if you have an umbrella like this inverted umbrella like this and if you do the reaction, so the inversion means, so this is X, now the Y comes and attacks this carbon.

So now this takes a another inverted envelop. So this is, this should be the picture not the other one, I think other one has some difficulty, okay. It does not really show the inversion clearly, it just shows that this is opposite to that, but this remaining the same that should not remain the same that should be in the opposite direction, okay.

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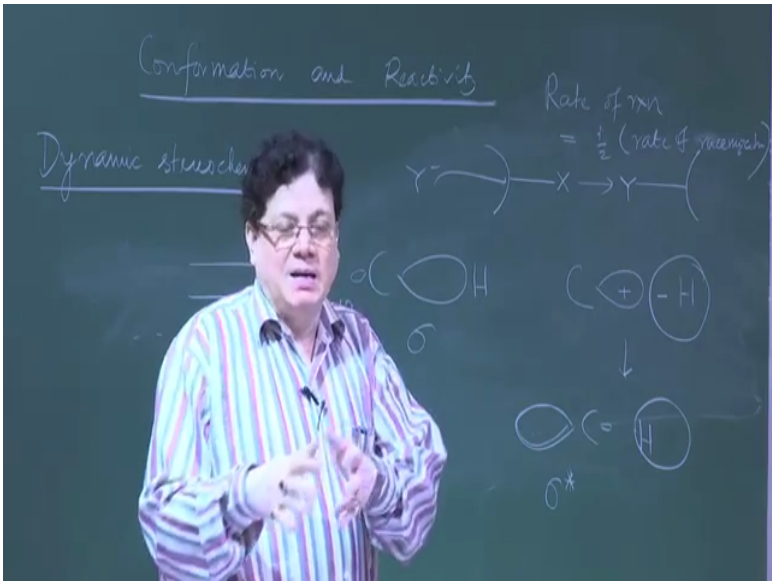

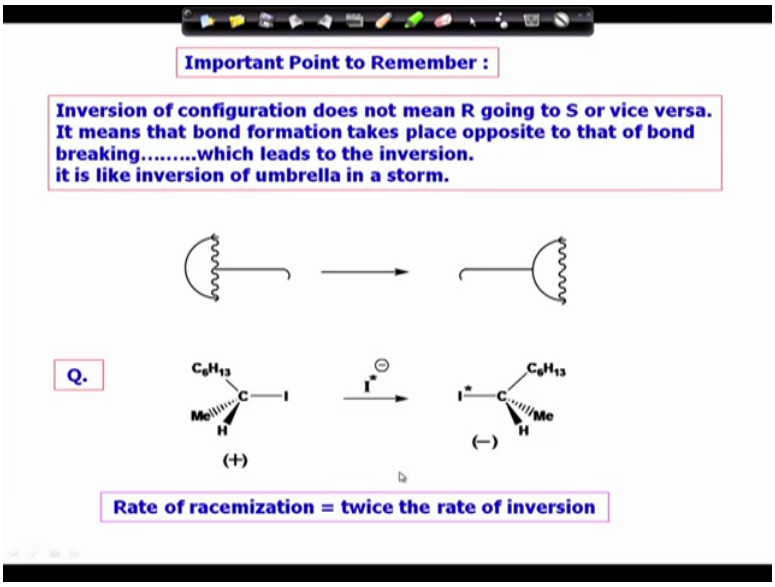

Now how do you know that the there is inversion in the SN2 reaction? There is a classic experiment that was done that the two idooctane ())(15:37) this is 2 idooctane (())(15:37) a plus form of 2 idooctane was treated with radioactive iodide, okay. So what happens with radioactive iodide? The radioactive iodide will approach from the back side. Now in this case, the product is the same as the original, only this is radioactive and this is not radioactive that is the only difference; however if iodide comes from the back side, it will give a molecule which will have minus which is a mirror image of this. So this will have minus rotation and this has got plus rotation. So suppose I have I started with two molecules of this and two molecules of plus compound.

Now if the iodide comes from the back side, if the reaction happens to only one molecule then I have one molecule of minus compound and one molecule still remaining of plus compound, but that is what is called racemic (())(16:32) mixture that means the rate of reaction for each iodide incorporation I get two molecules as a (())(16:38) pair. So the rate of the rate of reaction is, so the rate of reaction is half of the rate of inversion a rate of is half of rate of racemization. Rate of reaction is half of rate of racemization, because the racemization is happening at a double speed okay, for each one molecule getting inverted, you get two molecules being recemised, okay. So the rate of reaction is half the rate of racemization and this was really proved the check the rate of iodide incorporation that will tell you the rate of reaction and they also checked the rate of racemization that means the dropping of the optical activity how quickly it is dropping.

So from they figure out that it is exactly following that rule, okay. So that was a very excellent proof that rate of racemization is twice the rate of inversion. It is the other **other**

way of same thing rate of racemization is twice the rate of reaction, one rate of reaction means one inversion, it is a same thing. So one rate of reaction, I repeat one rate of reaction is rate of reaction is same as rate of inversion and, because every reaction is associated with inversion. So that is why you can say that, okay.

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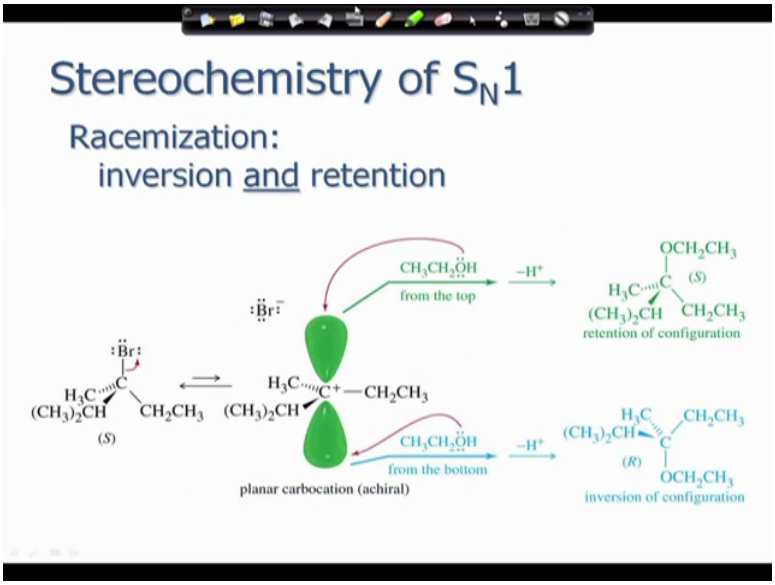

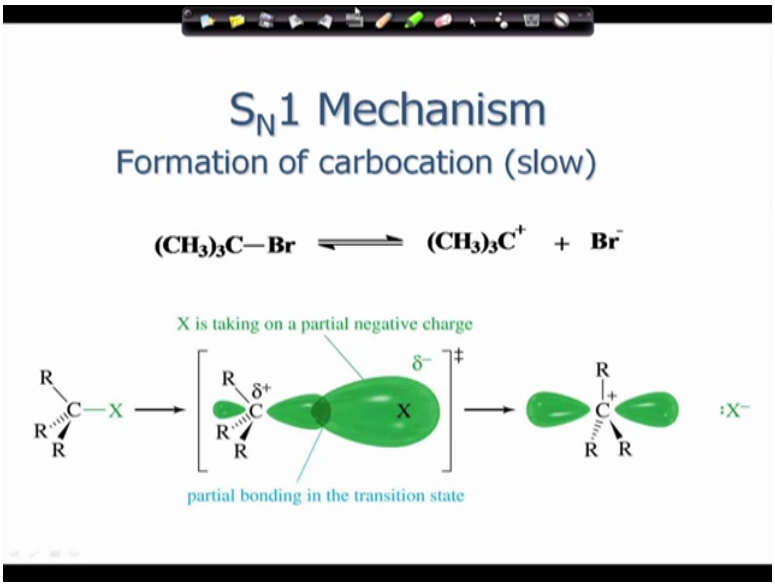

Now in so what happens in SN2, there will be inversion of by the way this inversion is called the Walden inversion, because Walden who first pointed out that conformational inversion of configuration in an SN2 reaction. In Sn1 reaction what happens? The SN1 reaction we know that there is formation of this carbocation that is as the first step rate determining step. So here what will happen? This basically leaves and this happens when only when this is a stable carbocation, okay. Now you have both the lobes are free.

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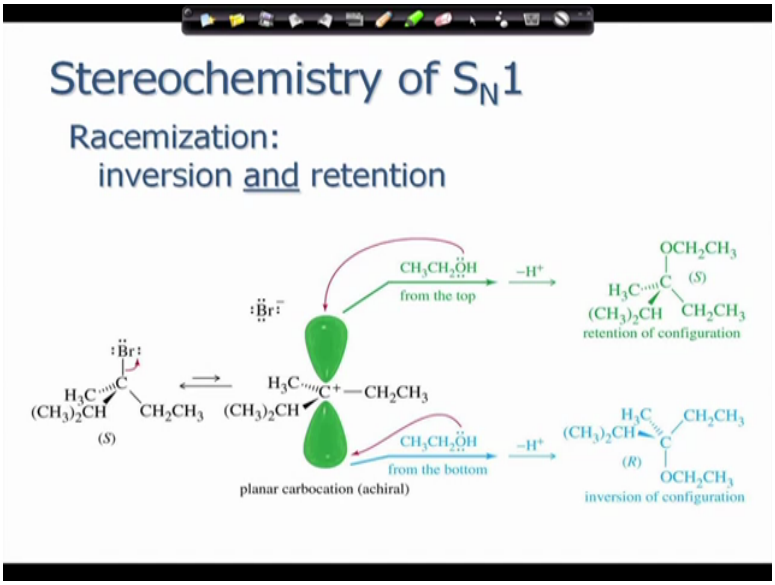

So the nucleophile, now can approach, it is the other you can show it in the orbitals in the vertical direction. So you have one half of the orbital here and one half of the orbital in a down phase. So if the, but this is planar again. This is a plane carbocation is planar. Now if the nucleophile attacks from the top, so it will give this compound and if you work out the configuration it turn it will turn out to be S and if it comes from the bottom then it will the turn out to be R. so what you will get is a racemic mixture of these two compounds, okay. So in SN1 in a ideal SN1 reaction, that what happens. So in an ideal SN1 reaction there is complete racemization; however what happens?

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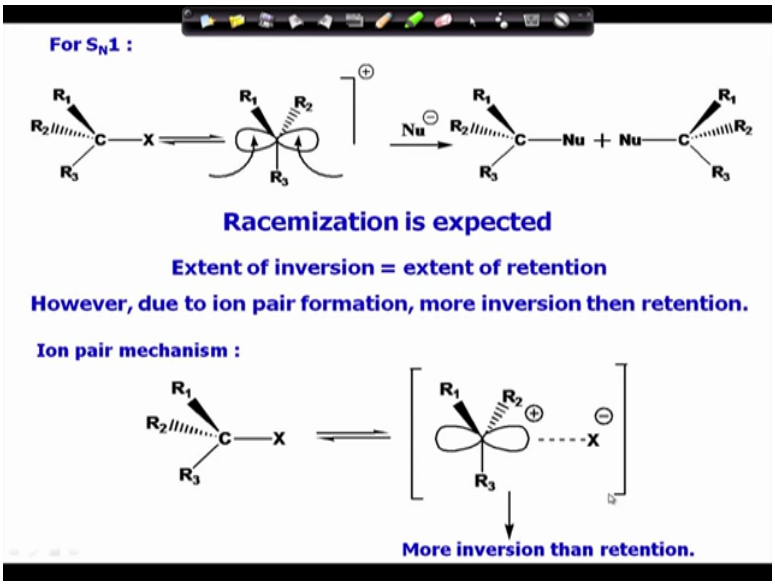

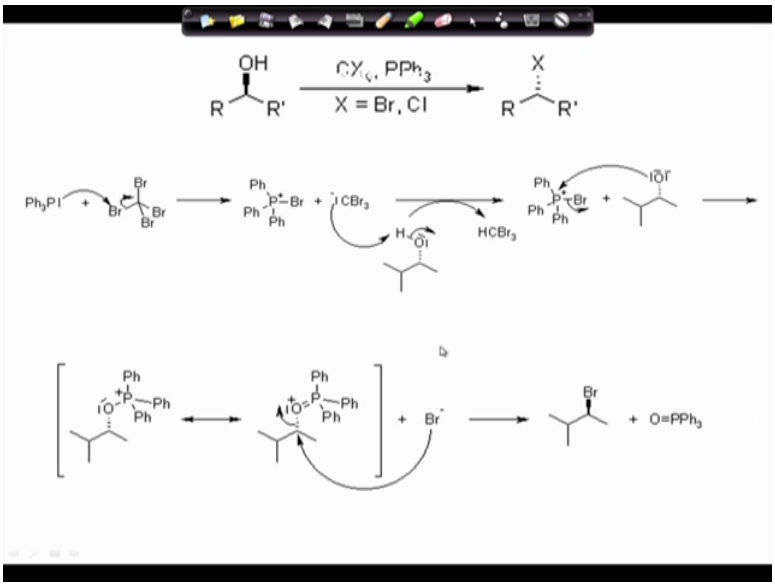

In many cases, there is what is call ion pair effects. So this is the what I have shown that if this breaks and if this is completely free out of the leaving group, if the leaving group has departed a long way then both the lobes are available for attack by the nucleophile. So you get a plus minus mixture of these; however so racemization is expected extent of inversion is extent of retention the same thing; however due to ion pair formation there is more inversion than retention. What is ion pair that means this is now when it is departed it is a plus carbocation and a minus the leaving group, okay minus.

So now there will be some interaction still electrostatic interaction that may be present here and thus so this may exist as a ion pair. If it exist as a ion pair then this side is little bit blocked for the nucleophile to gain entry from this side, but this side is open. So there will be nucleophile we have preferential attack from this side rather than from this side, because this is little bit hindered. The hindrance is coming from the counter ion that means the X minus of the ion pair. So there will be more inversion than retention. So in in SN1 in many cases that racemic mixture is not obtained, but it there is more inversion, okay and that is due to that signifies that there is a ion pair mechanism, okay.

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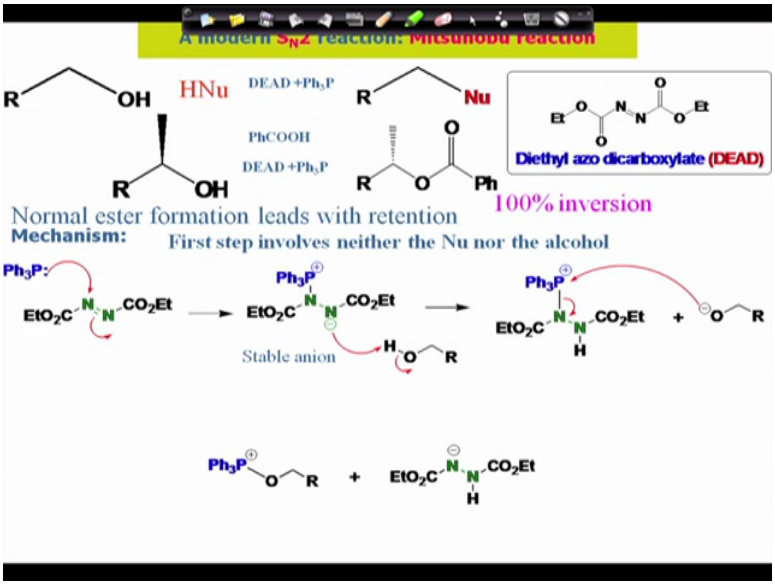

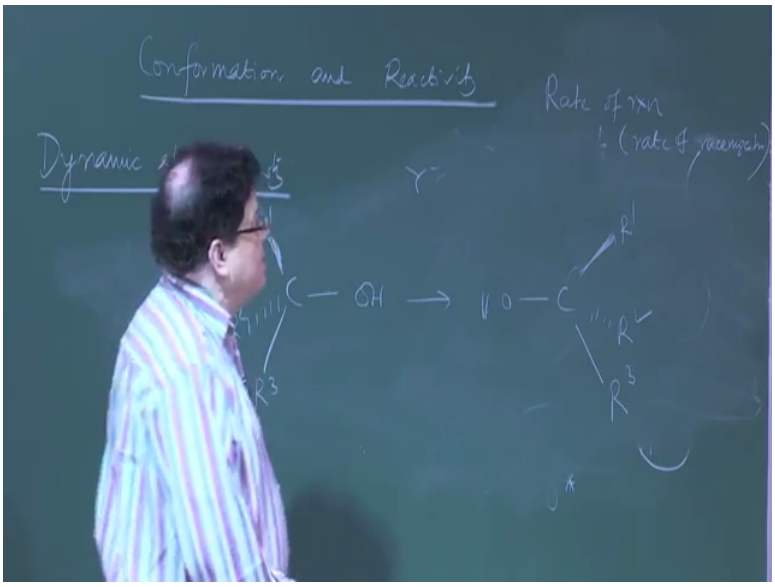

Now there are, I think I just keep these you can come back to these type of problems, okay. This is possibly quite interesting I will not go to the mechanism, see suppose, I have a I have you know that in SN2 reaction there is inversion, but if I start with a chiral compound R1,R2, R3and have a OH. In many cases, I may need to invert the configuration that means I need a compound where is exactly the mirror image of this. So how to convert this into the mirror image? So this is the inversion, but the problem is that I cannot actually attack this OH by another OH minus. So there is no direct way of converting this into the mirror image by a reaction, not by another OH okay. So another OH will not do anything any way even if it comes you are ending up with a racemic mixture you cannot get this compound. So one step or even a two-step conversion will be okay.

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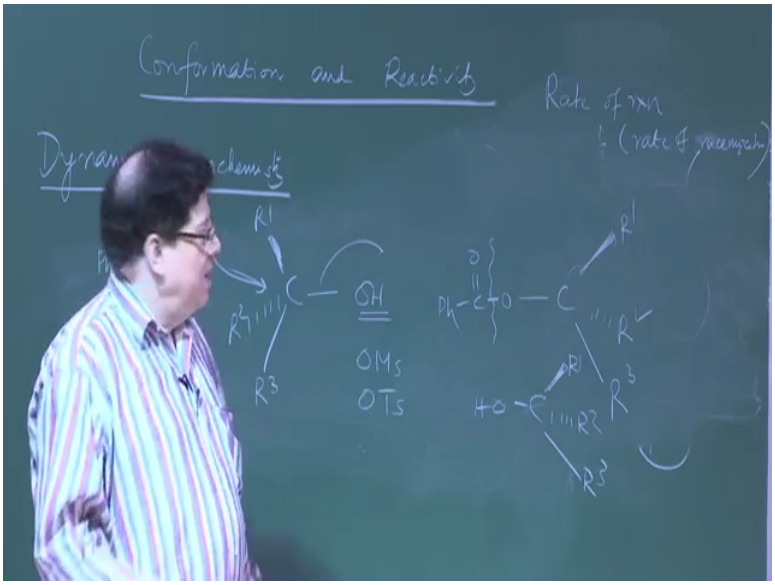

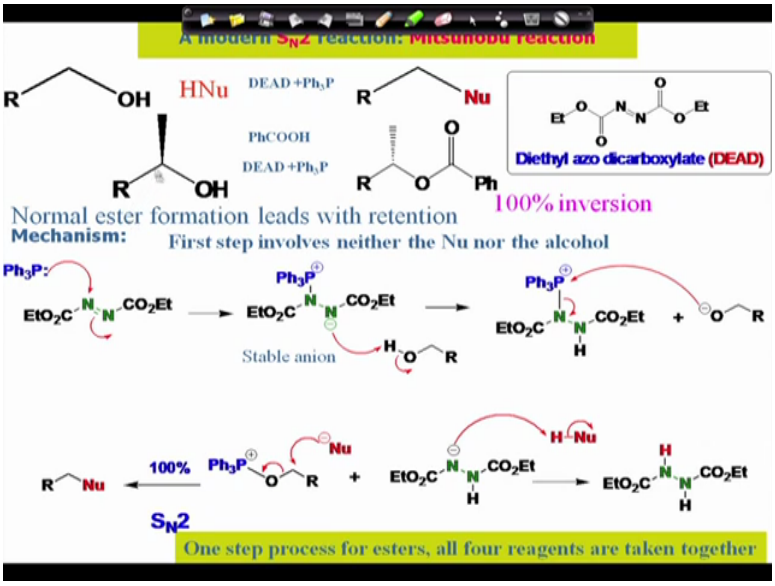

So there is a very beautiful reaction which was called the (())(22:39) reaction. Now there are ways to do it that the ways to do it means you have to, but that is that will take many steps, see you can convert into a good leaving group. First of all OH is the not a good leaving group. So it very difficult to expel OH by a nucleophile. So in order to do that you have to make it a good leaving group like O methyl or OTs okay. So if you do OTs and then you now attack with a nucleophile so that this goes out and there is inversion of configuration and this nucleophile should be such that it can be converted into a OH without disturbing this the stereogenicity of the carbon, so you understood what I said. So first convert it into a good leaving group and then add a nucleophiles suppose O-C-O (())(23:42) that means a benzoic acid, a benzoate as a nucleophile, okay.

So now the benzoate will attack from the back side and this will go out. So the product will be now O and then C-O ph. Now if you can break this bond by hydrolysis without disturbing a stereogenicity of this then you will end up with, the inverted compound. In many synthetic operation what we need at different stages is to invert the configuration of the carbon and this is a this is one way of doing this and I will show you another way that is called what is called mixonobo (())(24:25) reaction.(24:21) this is a quite modern reaction that is why I brought this here.

So the problem is that if you have R, this is a chiral center, right, this is a chiral center OH and I want the opposite isomer. So if the opposite isomer that means the methyl should be alpha. So what I need basically opposite isomer we have to react we have to put a benzoate kind of things, so that this can be converted into OH, okay. This is not simple benzylation of OH. If you do if you put the OH if you make the OH to O-C-O-ph then this methyl will remain the same. So in order to make this you have to you have to convert this OH into a leaving and then attack that with a benzoate so that you get this compound, okay.

Now this is how do you do it in one step. So what you do here, there are you have to convert the OH into (())(25:22) instead of doing that what you can do? This is a compound call diethyl azo dicarboxylate DEAD abbreviation diethyl azo dicarboxylate and tri-phenyl phospen (())(25:34) is a another compound. So you add this two along with this alcohol plus the benzoaic acid. So what will happen?

The tri-phenyl phosenel ())(25:42) attack this nitrogen, the double bond breaks, so it becomes n minus and that picks up the hydrogen from the alcohol your starting as (())(25:50) okay. So the starting alcohol now becomes alcidine, so I this is there should be a methyl here if you start from this compound then it attacks the phosphorus, phosphorus is now positive and oxygen as high affinity for phosphorus. So this breaks, so another inion is formed. So ultimately you are having this R-CH2O if it is the methyl is there then there should be a methyl here and then this phosphate.

Now what will happen the benzoic acid will come from the back side, because this has become a very good leaving group, see your ultimate objective is to make the OH a very good leaving group, either in this case it was by misilation (())(26:30)earlier. Now it is by you have to you are making a phosphor as phosphate bond okay a phosphate bond and a with a phosphorus positive. So this is now become a very good leaving group. So now the nucleophile comes and attacks from the back side and this breaks, so that is shown in the

next. So now this opens up the nucleophile that is the benzoic acid goes to the this n minus abstracts the hydrogen from benzoic acid that goes to the Nu minus and then Nu minus attacks this from the back side. So if it is and chiral center that will undergo inversion. So you get R-CH R carbon and Nu, okay.

If again I repeat if it is a if you start with a methyl here, like this compound then it will be the inverted compound with a benzoate here is the nucleophile happens to be benzoic acid. So this is a nice way then you hydrolyze the benzoic acid and get to the OH. So this is the (()) (27:29) one step process of inversion. Here it is says one step process for ester formation yes it is, it forms the ester O-C-O-ph, so one step process for ester formation and there are so many reagents acting together here , okay. Then triphenyl phosphine and the nucleophile as well as the starting (())(27:51). So 4 compounds are reacting together. It is a high yielding reaction and you get the product.(27:51)

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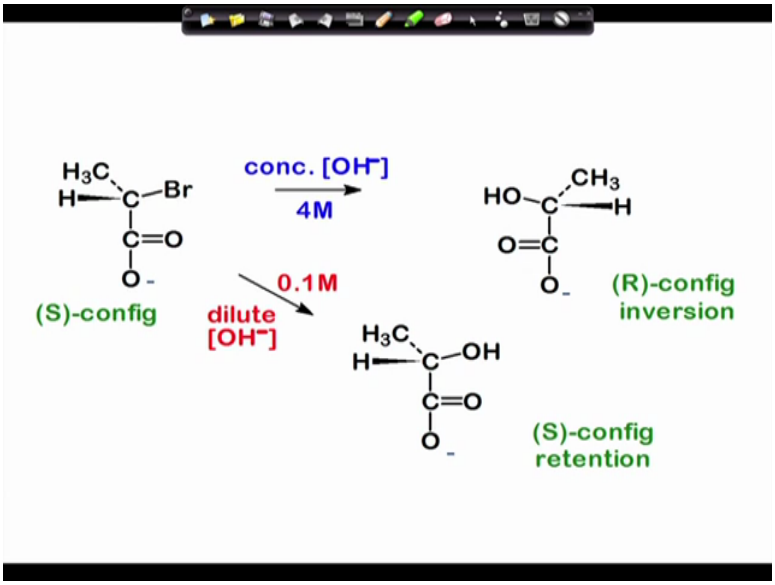

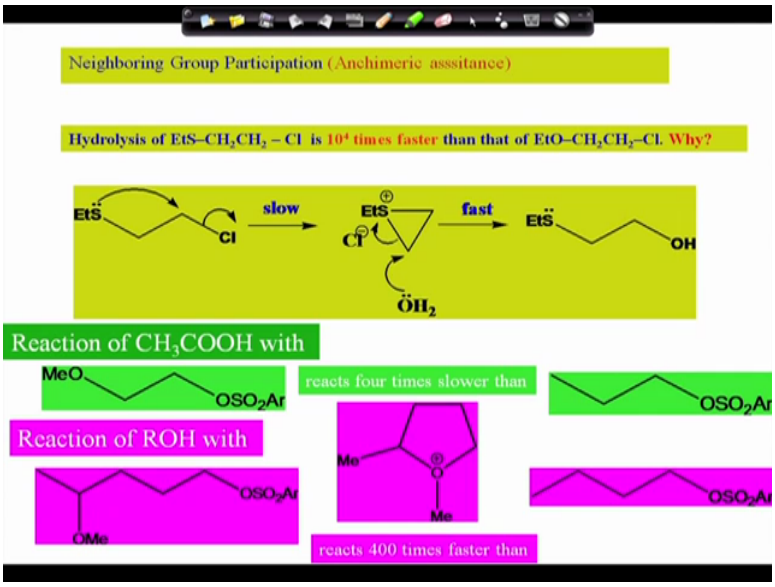

Another now SN2 reactions lead to inversion, SN1 reactions ideally it should be little racemic mixture, but because of ion pair formation must in many cases we see mode of inversion than of retention and there is some cases where, there is complete retention of configuration that is possible that is in case of where neighboring group participation occurs like you know that if a if a nucleophile is already present in a molecule like this the sulpher and you are trying to kick out this chlorine with a external nucleophile and before the external nucleophile comes the sulpher attacks the this carbon from the back sides and so you get this sulphonium ion, but this is not a stable compound.

So now the nucleophile, the actual nucleophile if it is water comes attacks the carbon attacks one of these carbons, these two identical and then breaks the these two are identical, say this and this. So it can attack here or this can attack there. These two bonds are identical. So if it attacks here then this breaks and the product is ultimately OH. So it is not a direct displacement of chlorine by chloride by OH rather, it is a assistant replacement. So this is called neighboring group participation or anchimeric assistance. Now when this anchimeric assistance takes place you have to be then there is a question of retention of configuration that can takes place.

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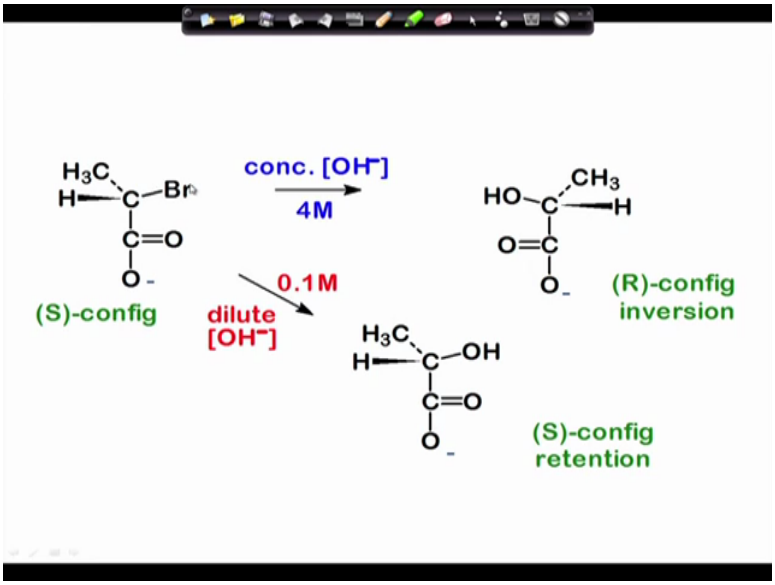

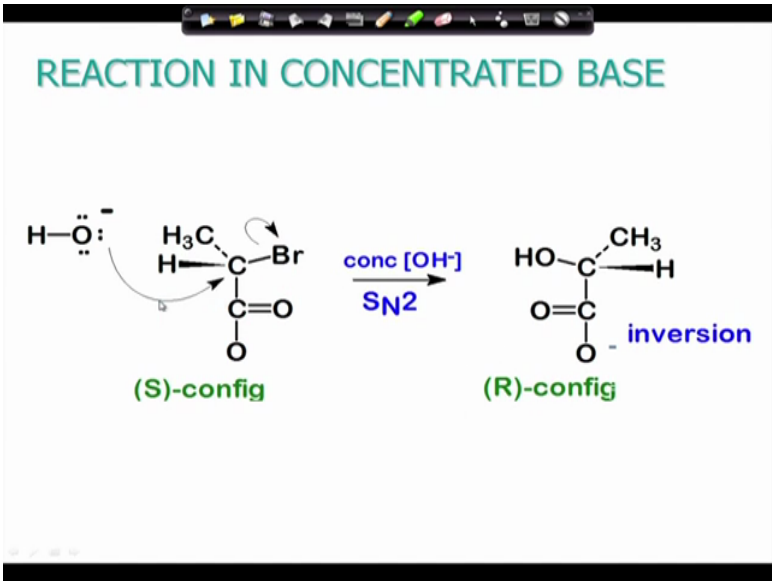

So this example will tell that that if you take alpha bromo propionic acid propionate form, okay means alpha bromo propionic acid, you add dilute OH a dilute sodium hydroxide. If you add dilute sodium hydroxide what happens? This will be O minus now and dilute sodium hydroxide means there is lot of water and less OH minus. So what happens before the water as the nucleophile or OH minus, but which is present in much less concentration acting as a nucleophile, before that nucleophile comes you have a nucleophile inbuilt nucleophile here O minus and that now attacks that can attacks the carbon. So make an SN2 displacement on the bromine and forming what is called lactone, okay.

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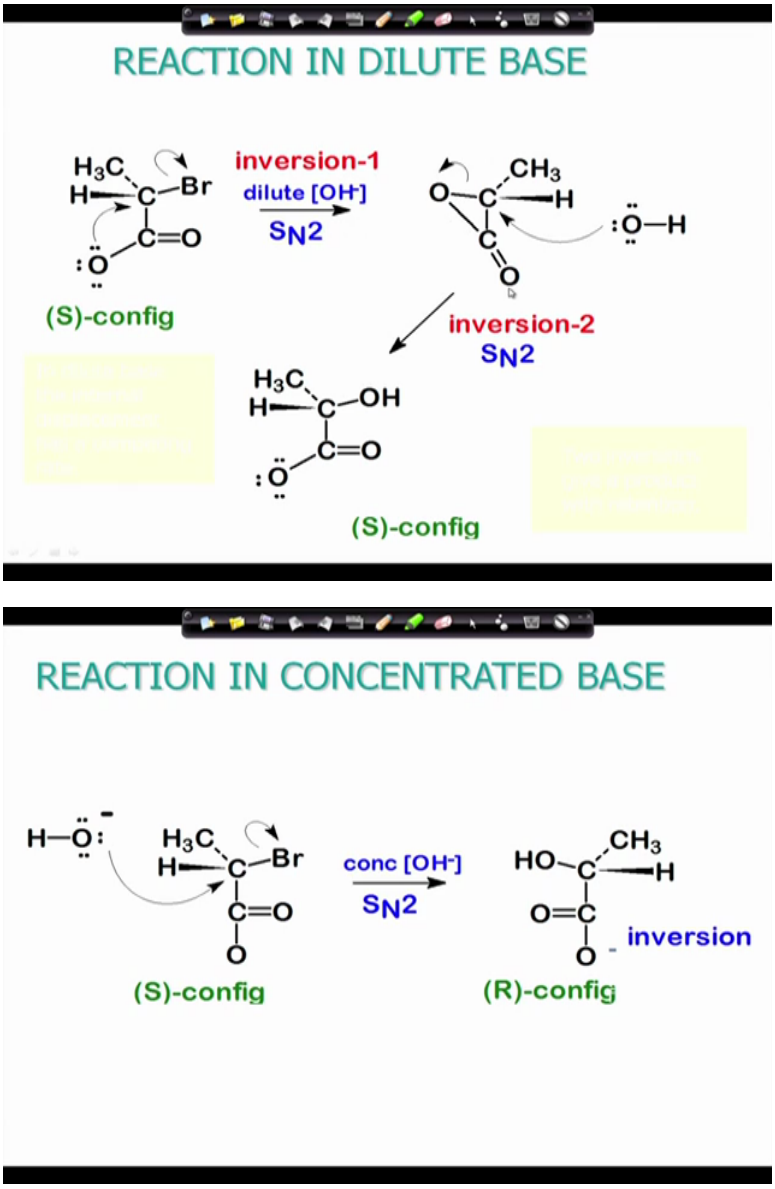

First what is that is in the next slide. So what I am saying that this can attack the carbon and bromine expels. So there is an inversion at this configuration. So that is inversion one then OH minus whatever is there much less concentration. So that is why it took so much time, it was waiting for this lactone to be formed. So once the lactone is formed this is called alpha lactone. So it comes and attacks this carbon and this carbon oxygen bond again opens out.

So this is another inversion, the result is that you have displays the bromine with a OH. So result is a alpha hydroxy carboxylic acid, but in this case if the mechanism is via this there is a two-step process via this neighboring group participation then the overall product we will have the same configuration S config, actually there is no inversion or configuration; however as I said inversion of configuration does not mean R goes to S or S goes to R, but

here, because that depends whether S will remain as S that depends of the priority of the departing group whether and the priority of the incoming group whether they are same or not in the final product.

So here bromine is number one, in this which is attached to this carbon OH is also number one. So that is why this is S and that still remains S, okay but do not be confuse. There may be cases, if suppose this is replaced by a carbon then that inversion of configuration takes place, but the that rotate R between S will become R, because the priority matching will not be there. So there has to be priority matching if S remains (())(32:02) or R wants to be go to the R.

So this happens with dilute NaOH remember, if it is concentrated NaOH then before this inion can attack to this carbon, because of the high concentration of OH minus is directly attached to this carbon and replace the bromine. So that becomes the inversion, okay. So that is the is the inversion case, okay. So R so it can be inversion depending on the concentration, for low concentration there is this anchimeric assistance followed by alpha lactone and then breakage of the alpha lactone. In that case the S remains S, again I repeat S remain S, because of the same priority OH has as the bromine has in a original compound, okay.

The best thing is that there is retention of configuration, in anchimeric assistance reactions assistant reactions and there is retention inversion of configuration if it is a direct displacement. Direct displacement only happens with concentrated alkali, okay.

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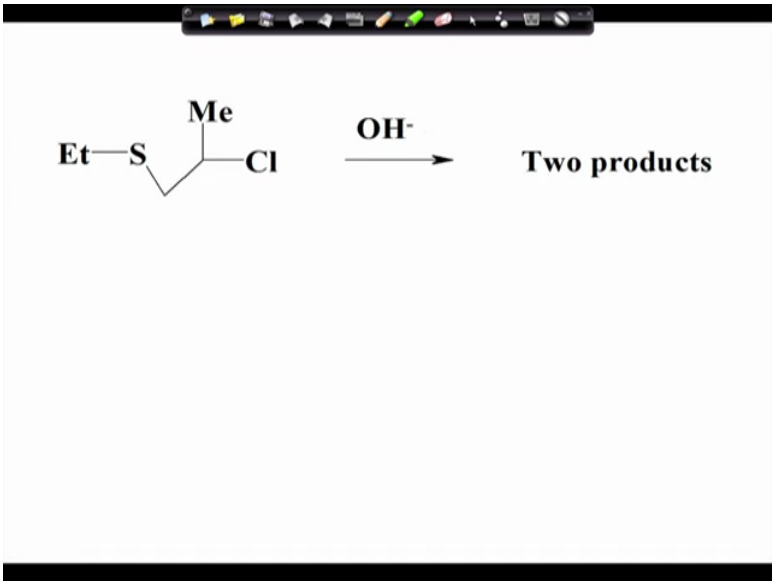

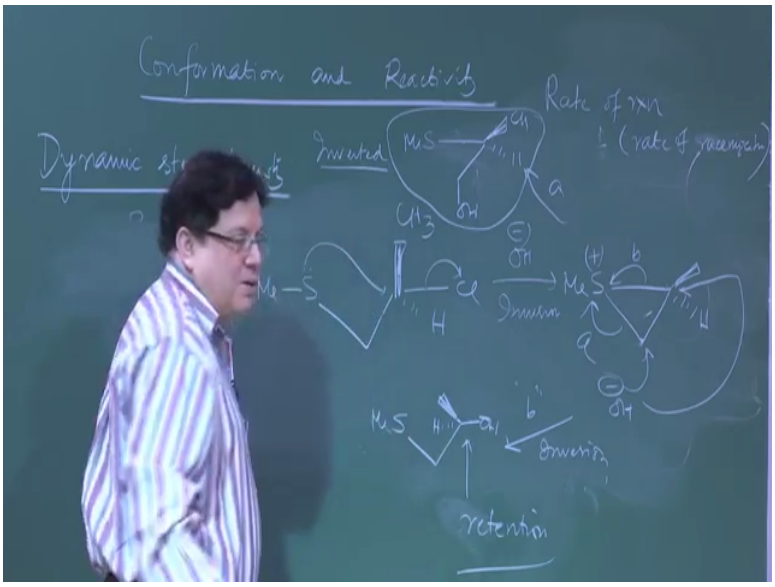

This is the same example, but you have to see, this is says that two products, okay. This is we can take it up very quickly before we finish this part, see what was the problem that S-Me and this was a chiral center a CH3and a hydrogen, okay and HCl so that was the product that was a starting material. So if you now, do the reaction trying to displace with OH minus, suppose, so before OH comes, there will be anchimeric assistance okay, the chlorine leaves. So now you have SMe and so there will be inversion here, so there will be methyl on this side and this side, this is the case; sulpher is now plus, okay.

Now it says two products, two products this is hydrogen. So now the nucleophile can attack this carbon and opaque this up. This is path A suppose or the nucleophile can come and attack this carbon and that is path B. So if it is path B then the product, in the product there is

retention of configuration. This is important, so suppose path B product is what? SMe and then there is a CH2 then this and then you have again beck to the this is the hydrogen this is the OH and this is the hydrogen. So this is the product in path B.

So this configuration is inverted, sorry, it is a retention of configuration, because it has undergone two inversions, one is here when the this attacked. So inversion here and then another inversion here. So overall this is retention; however if the OH attacks at this carbon, which is the which is most likely to be, because this is CH2 verses a tersary carbon, so if that attacks. So path A that will give SMe and then CH2OH-CH2-SMe sorry, SMe and then you have this CH3 hydrogen then CH2OH, okay. This is a product, again I repeat a path A, so this is attacking here. This is Brocken and if this breaks then you have CH2OH then this stereo genic center then this SMe. So what happens here now? Interestingly, the inversion if there is no question of inversion or retention at this carbon, because this is not chiral center. So whatever inversion has taken place that remain.

So now you have only the inverted product, okay. Now you have only the inverted product. So depending on where it is attacking, do not think that on in all anchimeric assistance product there will be retention of configuration. It depends on where the nucleophile is attacking. If the nucleophile is attacking the same carbon where the anchimeric assistance has taken place then, there will be retention of configuration, but if the nucleophile is attacking at a different carbon like here, in path A then the inversion of configuration retain that happen in the anchimeric assistance, okay. I think that means that is clear, so we end here about this SN1, SN2 and this neighboring group participation and associated stereochemistry. Thank you.