Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

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Lecture 19
Stereo electric Effects on Conformation and Reactivity

Hello, welcome back to this course on Structures Stereochemistry and Reactivity of Organic Molecules and Intermediates: A problem solving approach. Today we will be starting a new concept that is what is called the Stereo electronic Effect, which controls the conformation and reactivity of the molecule. And also, we will continue to apply the stereolectronic effect concept on to the, on to the cyclization, cyclization conditions that means a cyclic molecules to cyclic molecules conversion, how the electronic effect plays an important role and then we will go to the problem solving approach.

So, first we will discuss this stereo electronic effect now, which controls the confirmation and reactivity of a molecule. Now, we know that a molecule can suffer broadly two kinds of effects; one is steric effect and other is stereo electronic effect.

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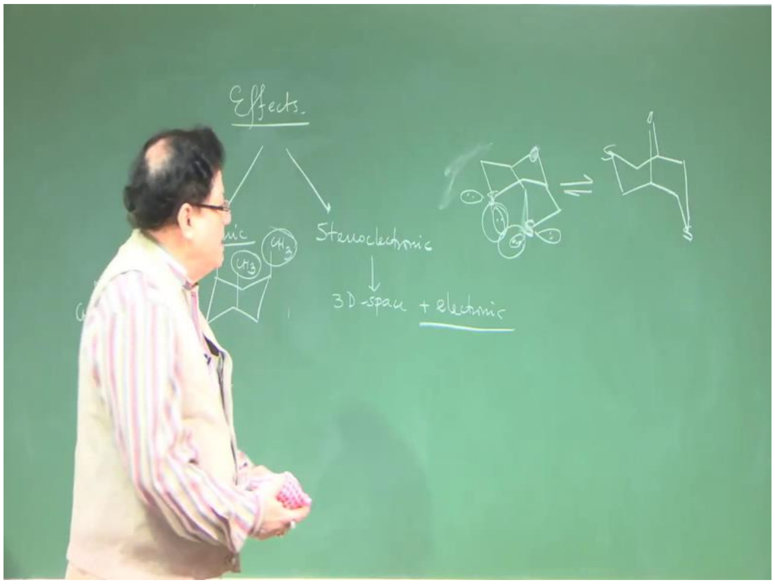

Now let me, so basically the effects that dictates the conformation of a molecule is broadly a steric and stereo electronic. Steric we know that, steric basically is the, when two groups become very close to each other, then there is a kind of repulsive force that, that occurs and that tries to pull the two groups away from each other. So, this is what is the steric effect and we say that the molecule is suffering from some static strain. Remember steric effect, if you think the, the atoms as rigid balls then steric effect is basically kind of a mechanical, mechanical effect.

But actually it is not, it is actually surrounded by electron clouds. So, whenever we talk about, steric effects basically it is the repulsion between the electron clouds when one enters the domain of the other. So, that is also a kind of electronic effect, but it is actually segregated from the stereo electronic effect. When you talk about stereo electronic effect, we are not considering the steric effect here it is mainly the electronic effect which is, which is possible due to the overlap of certain orbitals with electrons.

So, there is this distinction. Now, steric effect controlling the conformation of a molecule we are extremely aware of like, if I asked you that what is the preferred conformation of one 3 dimethyl cyclohexane, one 3 dimethyl cyclohexane cis then you know that this is possible one conformation which is possible, but the other conformation is more stable. So, here the two methyl groups become equatorial. And because of steric effect between these two methyl, as well as the steric effect with the axial hydrogen, axial hydrogen the molecule adopts the preferred conformation which is dye equatorial.

So, this is a classic example of how steric effect operates and how it dictates the conformation of a molecule. Now, stereo electronic effect is very similar that instead of these groups, if you have electron clouds here, in the form of orbitals, then if they are pointing towards each other, then what will happen they will repel each other and that also creates some kind of an effect and that is what is called stereo electronic effect.

That, so it means, that stereo means we know it is 3D space and electronic, so combined. That means the, the spatial orientation of the orbitals, orbitals can create stabilization or destabilization, it boths possible as the case may be stabilization or destabilization that can happen and that is, that effect is what is called stereo electronic effect. So, definition will be basically, they are stereo electronic effect is the effect that is operated between electronic, that operating between the, between orbitals or the bonding orbitals it could be or it could be bonding and nonbonding orbitals.

And the molecule try to adopt a conformation where the electronic repulsion becomes minimum and the molecule takes up a stable conformation. Like in the case of steric effect, the molecule tries to add up to conformation where the steric effect is minimum and the molecule gains stability by doing that.

Similarly, if there is electron, electron repulsion, the molecule will orient or change into another conformation in such a way that those type of repulsion is minimized. That means, the molecule does it to gain stability. The other possibility, this is what is repulsive when there are repulsive that electron, electron interaction. Sometimes what might happen that the molecule adopts a conformation where there is a possibility of extra overlap between, between some orbitals, which was not possible earlier, if it takes another confirmation.

So, that is a stabilizing effect. That means, the molecule adopts a particular conformation where the orbitals are positioned geometrically in such a way that there may be some meaningful overlap between the orbitals and the molecule gain stability, that is one aspect. Other aspect is that if there is too much electron repulsion, then the molecule adopts, something some conformation where this repulsion, that mean the orbitals go away from each other.

All types of possibilities are there. So, let us give an example of a stereo electronic effect controlling the, the conformation of a molecule. See, let me try to draw it, two chair forms, there is a oxygen here. And if there are two sulphur at these two centers, now the sulphur has lone pairs like this. Now this is a molecule, it is a, it is a bicyclic molecule where it can adapt containing two sulphur and one oxygen and the sulphurs are pointing downwards. Both are, basically there are two chair forms in this, there are two chair forms.

So apparently, they should be quite stable, but what happens here that because the sulphur groups are pointing downwards, and their orbitals, that is the nonbonding orbitals which are containing electron pair, lone pair of electrons, they repel each other. So, there is a electronic repulsion if the molecule assumes this type of confirmation.

So, because of this stereo electronic effect, the molecule now changes its conformation and takes up, takes up a conformation where this is minimized. It is the same molecule, but the two sulphurs are pointing oppositely to avoid that electron, electron repulsion. So, now, so this is an example, a classic example, how street electronic effects dictate the conformation of a molecule. Now, let us try to see what is the origin of this stereo electronic effect.

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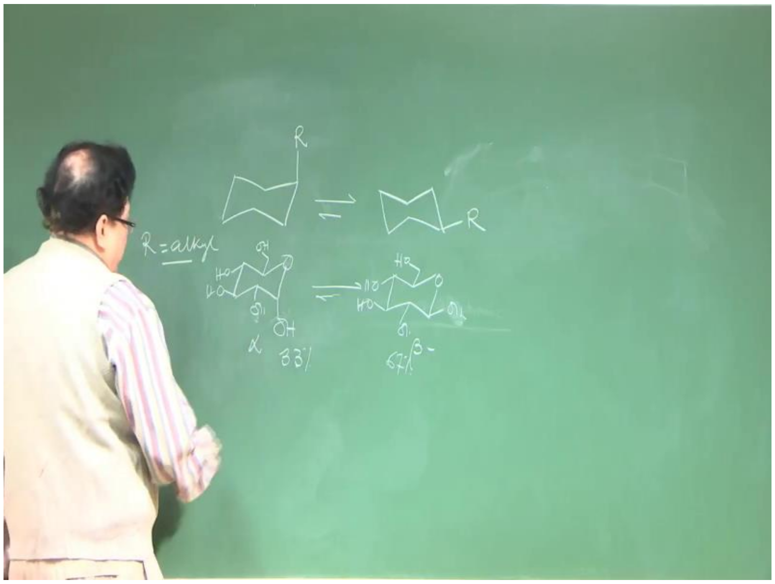

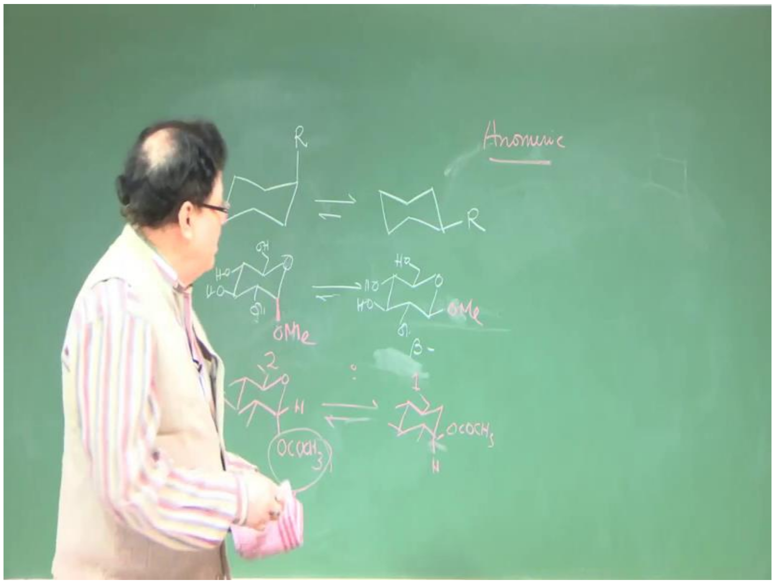

Remember, that in a cyclohexane system what happens, that if you have a cyclohexane system and if it is conformational locked, the way to do it is that a put a tertiary butyl. If it is conformationally locked, and if you want to or not, not conformationally locked. Suppose it is a flexible system and you put a group, an alkyl group. So, it is a mono substituted cyclohexane. And if you try to determine its preferred conformation, we know that the preferred conformation is the one where the R is equatorial, the R is in the equatorial form. And we know the reason for that.

When you have, suppose I have an oxygen here and still I put a R group, where R is alkyl. Remember R is alkyl group, if R is alkyl then also the preferred conformation is the one where the R is assume an equatorial conformation. So, this is the way things were. Then suddenly, what happened that if you change this character of R, if you change the character of R and put a polar group, like if you have, before that let me see that even if you have OH here and OH there and suppose it is in the form of glucose molecule.

So, this is beta glucose, and this is alpha glucose. Still, the actual one is not the preferred one, the equatorial one that means the peta glucose is the preferred one. And the ratio is about approximately 33 and 67 percent. And you know, the classic case of Muta rotation that tells you that what is the equilibrium value and the equilibrium what is their percentage composition. So, up to this point, our original notion that a substituent when it is incorporated in a cyclohexane system, then it prefers to assume the actual orientation.

However, this concept got severely challenged when people found that if you have instead of OH if you have OMe a methoxy then there is complete reversal it is the other way around. That means this is almost 2 and that is almost 1, that is 1 and that is 2, so the ratio got reversed. The same is true if you, if you have OCOCa3 that means acetate. I am not writing the other groups like this, if you have acetate, then also the equate that axial one was preferred, and the preference actually got increased that means, the percentage of the actual one is even higher than what was for methoxy.

And then with CL here, you have a 90 to 10 percent of the, 90 percent of the axial Chloro compound versus 10percent of the equatorial total compound, so something happened. When you have a polar group like Cl methoxy or acetate attached to this carbon, by the way, this carbon is what is called, is what is known as the anomeric carbon.

The anomeric carbon is basically the original aldehyde carbon which is converted into an hemi acetal by intramolecular, intramolecular cyclization and then that hemi acetyl from that hemi acetyl the carbon came to know as an anomer, anomeric carbon because it is, it is as the alcohol as it forms the hemi acetal you create another stereo genic center and that is the genesis of alpha beta and anomer of glucose.

So, this is called the anomeric carbon. So, if you have a substituent at the anomeric carbon and if it is polar, then what happens the polar group tends to occupy an axial orientation, this is nothing but a stereo electronic, the reason is stereo electronic effect, the reason is basically exterior electronic. In origin, however, this has got a special name and that is what is called the anomeric effect. The anomeric effect, what is anomeric effect, the anomeric effect is basically the preference of a polar group at the anomeric carbon to adopt an axial orientation, in a, in an axial orientation in a sugar, obviously anomeric carbon is there, that is what is called the anomeric effect.

So, basically this is, this is the starting point of people then try to look at the genesis of this anomeric effect and when it was explained, when it was known that why the there is this particular preference, then they started looking at the reactivity of similar systems and they could come out with explanations that how to, how to explain the reactivity of a very similar systems, based on this stereo electronic, stereo electronic cum the anomeric effect. Again, I repeat, anomeric effect is a part of a stereo electronic effect.

Now, let us, there are two things now, basically one is we are obviously, we realize that there is a preference for the axial, axial orientation of a polar group at the anomeric carbon. But the question is, is there any quantitative measure of this anomeric effect in case of an ether system, is there any quantitative measure. So, that is, one, one aspect, yes there is, there is some quantitative measure that how much is the anomeric effect, what is the kilo calorie per mole. Like we have, we know that a Gauche butane contributes around 0.85 to 0.9 kilo calorie per mole. So, that is the evaluated parameter. So similarly, that is one aspect. And the other aspect is that explanation of the anomeric effect.

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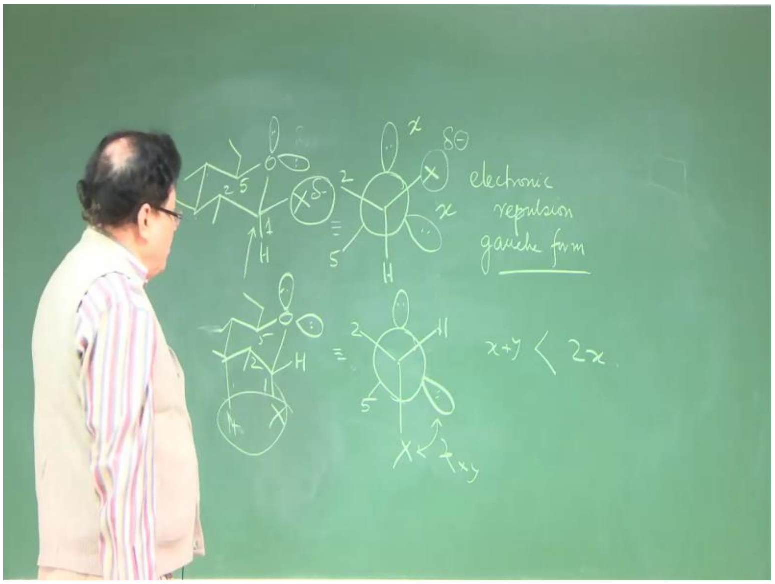

Now, the explanation of the anomeric effect is there could be, there could be two schools of thought. One school of thought, one school of thought is basically concentrating on the destabilizing effect on the equatorial isomer. See you can look into this problem into two ways; that either there must be something which is destabilizing the equatorial isomer, that means when the polar group is the equatorial position or you can look it into another way that there must be some stabilizing interaction which is absent in the equatorial, in the equatorial form.

So, one is a stabilizing effect, which stabilizes the actual isomer, another is the destabilizing effect, which destabilizes the beta isobar. So, you can try to explain in both ways, so these are the two schools of thought. Now, let us see the, the first one; that what makes the beta unstable, what, from what interactions it is, what extra interactions or strain it is suffering from. So, let us draw the, the beta isomer, remember this is a polar group. So, this atom is much more electronegative than the carbon which it is at us, that means the anomeric carbon.

So, when you have this molecule and you know that the put the oxygen lone pairs, so one is axial lone pair, another is equatorial lone pair. So, basically now, because of the inductive effect this will assume also delta negative character. And if you see there is the dihedral angle between this lone pair and this X is 60. So, also the (())(19:14) angle between this lone pair and X is 60. That means, if you draw a Newman projection along these, this is your C1 carbon, so how does it look. So, this is 1, so your hydrogen is at the bottom, then you have X and then you have the, this is your 6, this is, this is your number 2 carbon.

So, this is your number 2 carbon and, and then you have the, the behind is oxygen and the oxygen lone pair the axial lone pair is like this and the equatorial lone pair is like this. So, this is the situation and this is the other. This is basically the sixth not six, this is the fifth carbon 1, 2, 3, 4, 5. So, this is the carbon number 5. So, that is the Newman projection of this. So, if you draw the Newman projection, now you see, that this is basically a Delta negative, which is now sandwiched between, between two lone pairs. So, that creates a lot of electronic, electronic repulsion.

So, lot of electronic repulsion because they are actually in the gauche form because their dihedral angle is 60 degree the CX and the direction of the lone pair they are making an angle of 60 degree. So, that basically destabilizes the system. Now, the question is, is it present in the actual isomer or, or is it present, but maybe in a less, into a lesser extent, but let us try to draw that. So, draw the axial isomer, this is hydrogen, this is the lone pairs, this is the lone pair.

So, if you now try to draw the same thing, same Newman projection, so you will have now, the oxygen that lone pair is there, actual lone pair, this is the equatorial lone pair. And now, this is your C5 carbon. And you have on the top number one, so X is here, here it is hydrogen and on the other side it is 2. So, these are the two Newman projection for this. Now, in this case you see there is only one, lone pair X Gauche interaction. So, 1 versus 2.

So that means, because of these lone pair and the polar group interaction, so this is preferred, remember preferred, that means this interaction energy is quite high because, when X is axial then you have an axial, diaxial, 1 3 diaxial interaction. So, that must be overcome by this electronic interaction. So, even if you are inducing some repulsion here, but that is not sufficient, this is much more. So, what I am saying that if it is x kilo calorie per mole that is the x kilo calorie per mole and this is x. And the extra thing that it has is this one, suppose that is y, but we can say that x plus y is the stabilization is less than x.

So, that is what is basically. So, even if we induce some actual interaction, but you are actually that is much more being compensated by the reduction of one of the lone pair and x Gauche interaction which is an electronic repulsion. So, this is one idea that why the group x occupies the axial position, preferentially occupies the axial position.

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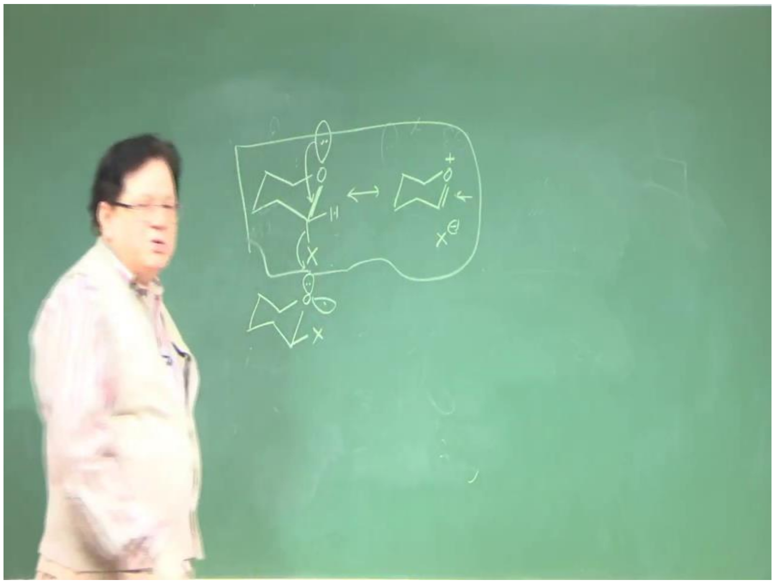

Another, another school of thought is basically based on the, on the no bond type of resonance, no bond resonance you know what is a no bond resonance that is also known as hyper conjugation. So, another school of thought explains it on the basis of resonance. See this lone pair is exactly anti parry planar to the CX bond. If that be the case, then what happens this lone pair can come on to the side and then break the CX bond. And in the process, it can generate a structure which will look like this, it is a resonance structure O plus X minus.

This is happening because of the, the geometric relation between the CX orbital and this lone pair because they are positioned in space, in such a way that this type of displacement can take place. This is very similar to your any addition or elimination, beta elimination or one to addition you know that the groups are adding in an anti-pair planner sense or when they eliminate, they eliminate in an anti-pariplanner, they have to be in an anti pariplanner position That is also, this anti pari planarity for a beta elimination is also what is called the stereo electronic requirement for the reaction.

So, you see the stereo electronic term is, is used, is used in many places in many places. It is basically in case of confirmation, if we are talking about the confirmation and stereo electronic effect then the confirmation, the preferred confirmation becomes such that the repulsion between the, between the orbitals that are positioned in the space becomes minima that means, the orbital takes up a position in the 3-dimensional space in order to minimize, the minimize the repulsion between the, between the electrons, that is when you are talking about the confirmation.

When you are talking about the reactivity of a molecule then what is the stereo electronic effect or what is the stereo electronic requirement that we say. The stereo electronic requirement is that the molecule must adopt a transition state while it reacting, when it is reacting with the reagent, with the attacking reagent it actually should take up a geometry where the orbital overlap is maximum, orbital overlap is maximum.

Means, when a reagent approaches a molecule there must be an interaction between the two. And this interaction is what, interaction overlap of the orbitals, interacting orbitals. So, the attacking reagent must approach from a side which assures maximum overlap that is possible. Similarly, when the group leaves and a new bond is formed, so the bond formation also has to be done with maximum overlap principle. So, this is, that means the orbitals should be positioned in the space in such a way so that it gives the maximum overlap possible and that is the stereo electronic requirement of (())(27:17) elimination.

The electronic requirement of an SN2 to the action is that, is that the nucleophile approaches opposite to the side of the living group not only that, it approaches collinear, its line of attack is collinear with the carbon living bond. Why is that, because if it approaches only in a collinear fashion and opposite to the living group, then there is maximum possibility of overlap with the back, with the back antibonding orbital that is there for the Cl, for the Cl bond. Cl sigma star has a lobe at the backside.

So, when the nucleophile attacks from the backside and exactly aligned with the Cl bond then only the maximum overlap takes place and that is what is called the stereo electronic requirement for a, for an SN2 reaction. So, in terms of confirmation, the electronic repulsion has to be minimized or there must be some possibility of new type of interaction which stabilizes the, stabilizes isomer. Like in anomeric effect, what I am saying that when X was equatorial, when the X was equatorial there is no chance of this type of resonance possible because of the, because of the positioning of the CX and the lone pair, they are not antipari planner in case of the equatorial isomer.

So, there is no anti pari planarity here. So, such type of resonance is not possible. So now, you can say that this molecule is a resonance hybrid of this and that gives the extra stability to the molecule. Now, if that be the case, if it is a resonance hybrid of the two, how can you prove this experimentally, the way to prove is that this CO bond should be now shorter, should be shortened due to this resonance, which is indeed had been found to be true that the CO bond is shortened in this case of anomeric system.

So, when X is axial, when X is equatorial, you do not see the lengthening of the CO bond. So, that is a good proof that this type of resonance is happening. However, this type of no bond resonance, this is a valence bond approach these type of resonance structures, some people may not may not, may not like specially, specially when you use the molecular orbital picture. So, there must be a molecular orbital picture of this type of resonance and that is we can discuss that now.

So, now we have two, two theories; one is that, that lone pair and the CX Gauche interaction that has, that is more in the case of equatorial isomer and the second one is this type of resonance, no bond resonance, say hyper conjugative resonance which is possible only for the axial isomer.

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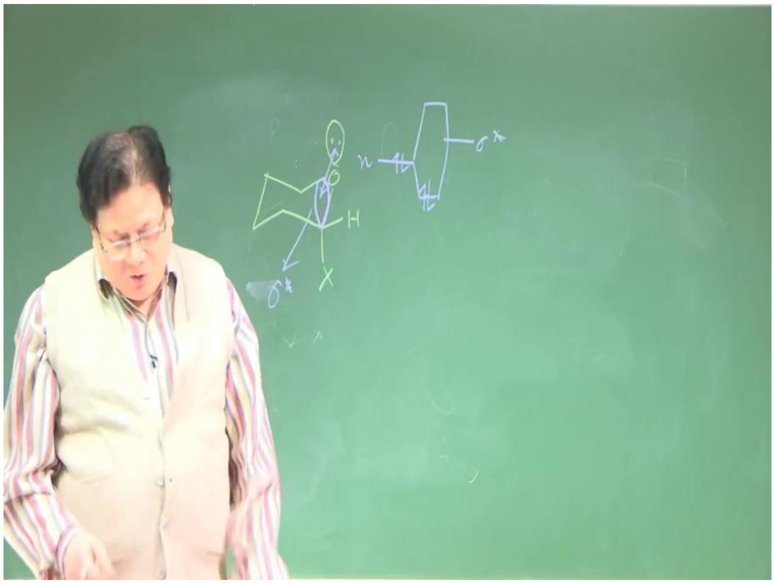

Now, the third one is a molecular orbital approach what it says, what it says that when you have this X, C X sigma bond, so there is an antibonding orbital for the CX and that has got a lobe on the opposite side, and that has got a lobe on this side which is vacant. And these two, this lone pair and this vacant, this the in C, this is the sigma star, stigma star of the CX bond. So, that orbital is vacant, but this is lying exactly parallel to the lone pair. So, now there is lateral overlap which is possible. So, if there is lateral overlap possible, that means these, that will be, basically this is empty that is the sigma star and that is the lone pair, that is the nonbonding lone pair.

So, that gives it stabilization, overall stabilization of the system. So, basically the third one which is basically the modern approach, the modern approach, this says that the anomeric effect is due to the fact that there is a, there is a lower, there is an overlap between the axial lone pair on the oxygen and the antibonding, and the antibonding sigma, sigma antibonding orbital of that CX bond because they are in 3D space, they are perfectly positioned to interact with each other.

It is like a pi bond that when you have a pi bond the p orbitals are lying parallel to each other and then you have the side wise overlap. So, that same thing can happen here and that gives the extra stability for the axial isomer and that is why you see the anomeric effect dictating the X to be at the, at the axial position. So, that is what is the anomeric effect.

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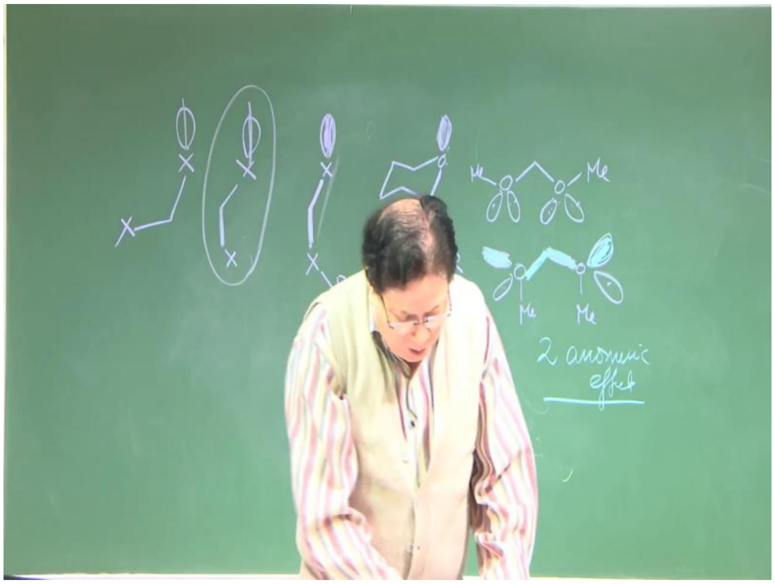

Now, another interesting point I should also mention here that is this anomeric effect. Now can be, actually can be very general it does not have to be in a sugar molecule, it can be of any system where you have this type of like (())(33:22), what is the anomeric system, oxygen, then a carbon, then an oxygen and here you have a lone pair. So, this type of system is also can be present in other, other molecules, can be present in other molecules. Like, if you have say O then

Me and then a CH2 and then O and then a Me. So, now you have this lone pair here, lone pair there, lone pair here, lone pair there.

Now usually, this type of linear molecules take a zigzag orientation conformation. However, this molecule, this molecule takes up an orientation which looks like this contrary to what the, what we, what we usually think. So, now there will be a lone pair here, there will be another lone pair somewhere there, there will be lone pair here, there will be there. Now, this is again because of the anomeric like effect that, the effect that we have seen in the sugar moiety.

Now, when you have, when you have these, remember in the anomeric effect, the lone pair, which is participating in the anomeric effect is attached to the hetero atom is not necessarily always oxygen it would be nitrogen also. And then you have, a bond and then another one which is at us to another hetero atom. So, basically now you can say that, that anomeric effect can take place in any system which will have this type of attachment, this type of attachment. So, X carbon X and this X should have this, here O had a R group because this is either methoxy or acetate those types, so you can say that this has got a R group.

So, this type of system will also show anomeric effect. Now, the point I was trying to make out is that this lone pair on the X is, is basically anti to the, is anti to the bond, to the beta bond, to the beta bond which is attached to another heteroatom. That means, I can say that if a molecule looks like this, adopts this type of conformation versus, versus suppose, versus this, these two.

Now, this is exactly the system which can generate anomeric effect because this is anti to the this beta bond. However here, this is not anti to this one, so if a system adopts this type of confirmation there is one anomeric effect, if a system adopts this type of confirmation there is no anomeric effect. So, this concept is very important because sometimes you may be asked that how many, a molecule can have multiple anomeric effects present and the way to find out is basically you have to check the lone pair and then see the whether there is a beta bond which is attached to another hetero atom and that is anti to it, then only you can have an anomeric effect.

Like here, these two systems there is, see there is no anomeric effect in this, in this confirmation. But here, now you have this is the lone pair and this is your the bond I am talking about which is anti to each other. So, there is one anomeric effect here. And there is another anomeric effect which is between this and between this. So, there are two anomeric effects. So, this concept will, we can do one problem I think that will clarify the number of anomeric effects that are possible in a molecule or that are present in a molecule. Let me try to find out the system.

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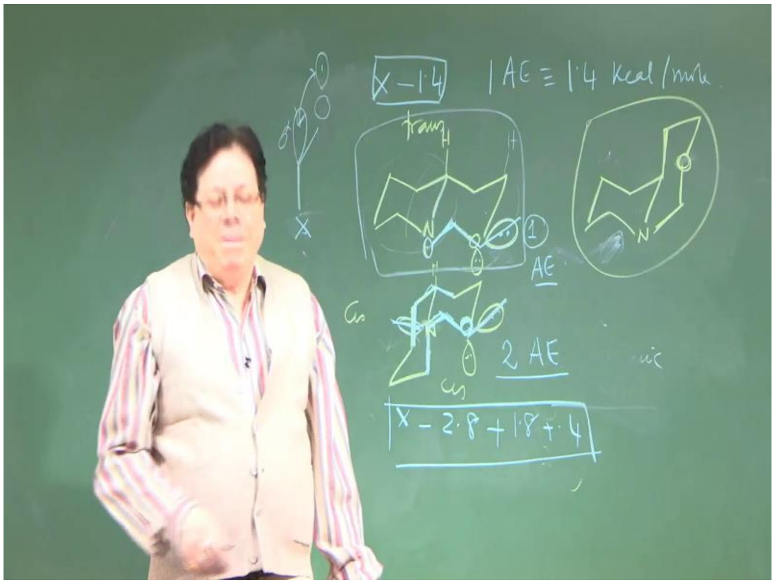

There is one molecule which is a fusion of a pieridine and something which is called an oxygen. You know that hetero cyclic ring, these are of course tetra hydro that parhydro pieridine tetra hydro pieridine and this is also the fully hydrogenated form. This is what is called oxygen, this system and this is what is called pieridine, means loosely speaking these are actually reduced pieridine and reduced oxygen. So, we have a few system between the two. Now it can exist in the transform or it can exist in the sis form also. Let me try to draw the cis form in and the cis form is, so this is the, this is the cis form.

So now, the question is which one will be more stable, which one will be more stable. The other way I think, the other way I should I can draw it is, rather than changing that let us change the this part. So, this is the nitrogen, let us, this is also perfectly okay, we will leave it here that but we draw conformation which is same as that. This is the cis, and because the lone pair is this and this the hydrogen. Here the lone pair and hydrogen are trans, so this is the trans system and this is the cis system.

Now, let us try to find out, whether there is any anomeric effect present in this system or there is and if it is present how many are there. Now one more thing that comes into mind that we started with anomeric effect with a substituent at the anomeric carbon, here there is no substituent as such. But you can think that one, one hetro cycle can act, can provide subsituence to the other hetro cycle, so that creates the, creates the genesis o the anomeric effect in this system. Now, in order to find out the anomeric effect correctly draw the lone pair of electrons and the hetero atoms. So, this the first one the trans and the second one is this, and there is a lone pair here and there is a lone pair there.

Now, try to find out what I said, that you have to find out that way there against the lone pair there is a a beta bond which is anti, and that beta bond has to be a, has to be attached to the to a hetro atom. It is not that the beta bond has, will attach to a, suppose if you have these and then there is a carbon and there is a carbon, then there is no anomeric effect, it is only possible if there is a hetero atom here, then only its sigma star can meaningfully interact with this.

It is not carbon if it is another hetero atom. So, let us see this is the lone pair on the nitrogen and I could see that the lone pair then this, the beta bond which we are talking about, that means the lone pair then a carbon, then a atom, and then the next bond So, the lone pair this is the bond and then there is basically no atom which is highly electronegative So, basically this lone pair does not provide any anomeric effect. On the other hand, this lone pair, the oxygen lone pair which is equatorial, so if you look at this, this actually satisfies the condition of anomeric effect.

So, that gives one anomeric effect, this oxygen lone pair which is axial again that is not giving any anomeric effect because nothing is, what is anti to it is a hydrogen, that cannot give it anomeric effect. So, there is one anomeric effect present in this. And in the equatorial one this lone pair and then this bond and this is the one and a hetero atom, is a perfect positioning to give an anomeric effect. So, this is one anomeric effect, and this is another one. Because the lone pair, then oxygen, then carbon, then nitrogen.

So, that means this molecule is suffering, is actually not suffering is having a stabilizing interaction because anomeric effect is a stabilizing interaction, is adding two anomeric effect and this is one anomeric effect. And you can actually calculate the energy difference between these two. One anomeric effect, I have not talked about the, how the anomeric effect has been evaluated maybe in the next lecture I will do that. The anomeric effect can be evaluated and, just take it from me the anomeric effect has been estimated to be about 1.4 kilo calorie per mole, one anomeric effect is equal to 1.4 kilo calorie per mole.

So, if I ask you that what is the energy difference between the two, first of all see the destabilizing forces because this is transferring junction this does not have any gauche type systems, we know trans deca lean does not induce any extra gauche butane unit. Similarly, there is no extra gauche unit here. So, it has got a stabilizing interaction of one anomeric effect. So, the overall energy, suppose this whole skeleton because it is called carbon, carbon, carbon nitrogen bonds. So, if the whole skeleton has an energy of X, then it will have X minus 1.4.

So, that will be the energy of the system or the trans. On the other hand, the cis, now it is made up of the same molecular formula. So, it will have X but now, it has got to anomeric effects, so minus 2.8 but then it has got some plus because it is cis link junction. First of all, it has got two gauche butane type interactions; one is this, another is this. So, two gauche butane interactions that gives about, if it is 0.9, so that gives about 1.8 and it has got again another one which is also gauche not butane, now it is got a it is like a carbon if you think this is a (())(45:56) nitrogen, but if it is all carbon framework that will be propyl alcohol.

So, this is nothing but called a gauche propyl alcohol system and that gives some additional energy I, I think that is about 0.4. So, that is about 0.4. So, now, you can, so this is the energy of the cis system, this is the energy of the trans system. So, you can easily make the difference between the two and you can predict that at equilibrium mixture what will be the ratio of the cis and the, and the trans. So, I think that is, we have given some concept some clarification.

And on stereo electronic effects, we first introduced stereo electronic effect, then we started talking about that the genesis, it all started with the anomeric effect, namely in the sugar chemistry and then what is the reason for having this anomeric effect we have seen there are various explanations that can be provided to explain the anomeric effect, and then how to calculate the number of anomeric effects that are present in a system. Thank you very much.