Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach
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Lecture 35
Dynamic Stereochemistry: Stereoselectivity in Carbonyl Reduction

Hello. Welcome back to this course on Structure, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. In the last series of lectures, what we are discussing is what the topic what is called dynamic stereochemistry. Again, I repeat dynamic stereochemistry is basically the study of stereo chemical aspects in a dynamic process and that dynamic process could be a chemical reaction or it could be a conformational change.

We have discussed the addition to the carbonyl compound which is having a stereogenic center, an SP3 stereogenic center or what is called a chirality center at the alpha position. And at the alpha position, we have different groups of different sizes, different polar character or different chelating ability, and depending on that, the molecule adopts a particular conformation and that is what is shown by Cram’s rule or Cram’s model. And in that conformation the reaction takes place from the side of the smallest group.

And the other model that we discussed was the Felkin’s model, which is kind of a stereoelectronic requirement for a conformation to be adopted by the molecule in which the large or the polar group has to be orthogonal to the carbonyl, which enables sigma star 2-pi star conjugation, and that lowers the overall pi star of the carbonyl, so that the nucleophile can add its electrons or it can interact providing its HOMO and the pi star acting as the LUMO. So, that gap reduces and the reaction takes place in that favoured in that conformation, where stereoelectronic factor stabilizes the transition state.

Today, we will be discussing kind of a cyclic system now, where this rotation which was possible in the molecules that Cram or Felkin’s were using, well actually flexible molecules that is why they can adopt a particular conformation. But if you have a rigid conformation or a conformationally biased system, I call them, I told you that these are called an anancomeric systems.

So, conformationally biased systems, and if you have a carbonyl group, then it may be possible that the two faces of the carbonyl could be different, could diastereotopic. And if it is diastereotopic, then the question of the rate of attack by the nucleophile comes into play and there is a there could be a preferential attack from one side or the other.

So, let us talk about the reduction of the simplest carbonyl system, which is the cyclohexanone. But we need to have a conformationally bias system, so we will put a tertiary butyl group at the 4 position of the carbonyl, so that the molecule becomes conformationally biased.

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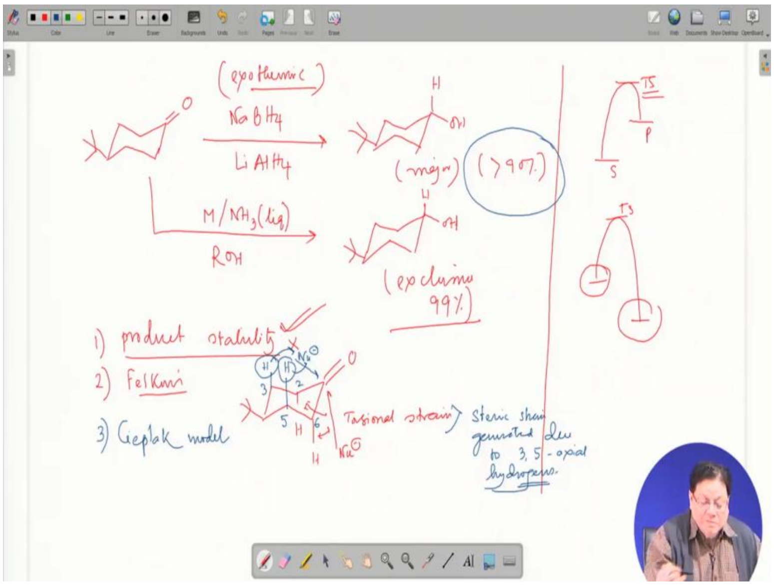

So, what we will be discussing is a system like this and the reduction of these systems. Now the reduction of carbonyl can be carried out by hydride mediated reagents, hydride mediated reduction processes, like sodium borohydride, or lithium aluminium hydride, or there are derivatives of sodium borohydride those are possible.

Now, the other way of reducing carbonyl is by the dissolving metal in liquid ammonia, like sodium in liquid ammonia and you need a proton donor in the form of an alcohol. In both the cases what you get is an alcohol. And in both the cases interestingly the major product is the equatorial alcohol.

However, this is major, and in this case it is not only major it is almost the exclusively, this is almost exclusive product that is formed, almost the exclusive around 99 percent of this equatorial alcohol is obtained. Here it is major, it is greater than 90 percent. However, the selectivity is more in case of the metal ammonia reduction. We will discuss both of these reduction processes.

In my stereochemistry course, that was for the beginners, we have some preliminary discussion on this reduction of carbonyl in a cyclohexanone system. And we will just go through quickly the different models that were proposed to explain the formation of the equatorial alcohol from a cyclohexanone carbonyl.

Now, let us see the molecule, let us see the model. So, this is the model of the cyclohexanone with the tertiary butyl group. So, this is my tertiary butyl group and that is in the equatorial position and this is the carbonyl. Now, if you look at the two faces of the carbonyl, let us look at the two faces of the carbonyl, this is one face, that is what is called the it is at approaching from the axial side, because the approach from this side makes the hydride which is ultimately attached to this carbon axial. So, this is the axial approach.

And there is another approach that is from the opposite side, that is from the equatorial face and that is the hydrogen ultimately becomes equatorial. So, this is the equatorial approach and that is the axial approach. And these two sides or these two faces are actually diastereotopic, because diastereotopic because you get diastereomers out of this reduction processes.

Now, one can visualize very clearly one thing or notice one thing very clearly and that is if the approach takes place from this side, remember the approach is actually according to the Burgi-Dunitz principle, if it approaches from this side at an angle of 107 to 109 degrees then what happens you see that it is actually very close to this axial hydrogens.

So, there is some, 1,3 di-axial interactions for this operating for this approach. On the other hand, the equatorial approach does not have this 1,3 steric interactions. So, the people might think that the hydride should approach from the equatorial side and that should result an axial alcohol and but the result is that you get the equatorial alcohol.

So, that means the steric factor is overrided by in some other stabilizing factor which is operating when the hydride approaches from the axial face. So, let us discuss that. Now there are initially it, people thought that since equatorial alcohol is the stable product, is more stable than the axial alcohol, so the reaction is guided by the stability of the product.

So, first model was based on product stabilization or product stability. Now, product stability will guide a reaction only when the transition state will mimic the product. That is the transition state is closer in energy to the product and not to the reactant. That happens only for an endothermic process, from endothermic process what you get is something like this.

So, now the product is nearer to the transition state, nearer means in terms of energy, so the transition state will resemble the product here. However, these type of reductions are extremely exothermic reactions. So exothermic reactions, if it is exothermic, so the curve will look like this. So, the transition state cannot resemble the product. The transition state cannot be correlated with the energy of the product.

On the other hand, it can it should be correlated on the energy of the starting material. And the starting material is actually only one starting material. The starting material is basically bifurcating into two products. So, the question is whether the, the model based on product stability is tenable or not? It is certainly not a tenable, because these reactions are exothermic, so product structure or product stability will not decide cannot decide on the preferential formation of one product. So, that is gone.

The second one was basically what is given by Felkin. Felkin's explanation was that again I bring the model, again show you the model, and if you see the attack from the equatorial, let me turn it this way, if you see the attack from this side, from the equatorial side, you see that there is these are the hydrogens, the axial hydrogens at C2NC6. So, there is a torsional strain or, so, they are kind of very, very close to eclipsing each other. So, there is a kind of torsional strain that is now operating when it approaches from the top.

So, there is a torsional strain which is basically generated by the C2 and C6 axial hydrogens. On the other hand, the top approach that is axial approach has 1, 3, this 1, 3 diaxial hydrogens, so that interaction. So, these two interactions are opposing each other. According to Felkin, now, according to Felkin that this interaction, the torsional strain, again I just show you the torsional strain.

So, when the nucleophile is approaching from this side, so you have a torsional strain like this. And when it is approaching from the top face, that was the axial face, these hydrogens, so now the nucleophile approaches from here. So, you have steric strain between this nucleophile and 1, 3 diaxial hydrogens. So, this is your 2, this is 6, this is 3, and this is 5.

So, these two are opposing each other, and according to Felkin, the torsional strain is greater than the steric strain generated due to 3 and 5 axial hydrogens. So, that is Felkin's model.

Still that is a little bit debatable, because it is hard to believe that the torsional strain will be higher than the steric strain, even if it is higher, but greater than 90 percent yield is extremely difficult to explain by this model. So, there is a third model which is the Cieplak model.

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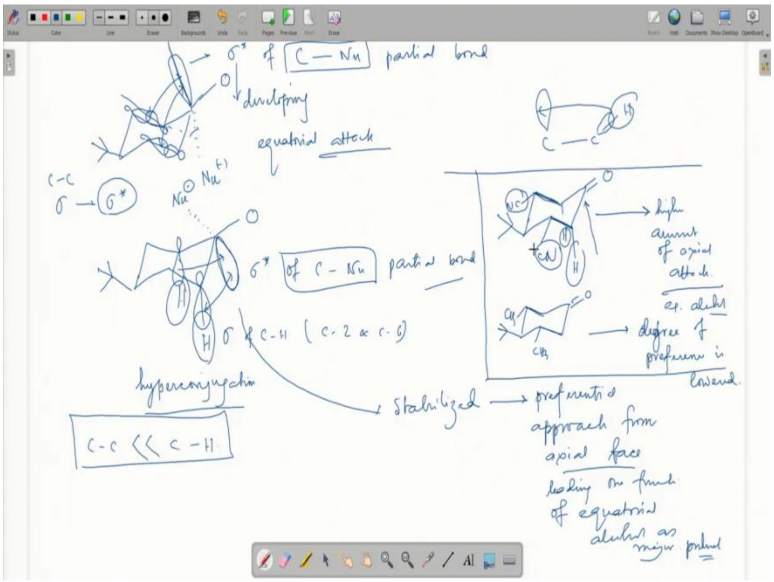

Now, the Cieplak model tells that when the nucleophile approaches the carbonyl, attacking the carbonyl. So, what happens there is some partial bond between the nucleophile, actually this should be according to the Burgi-Dunitz trajectory, let me draw it again. So, something like this. And so this is the nucleophile attacking from the equatorial face.

So, when the sigma bond is formed, at the same time, you will be forming an antibody, sigma star orbital also. So, this is one situation, now this is the sigma star of what of the carbon nucleophile that partial bond, and this is for the equatorial attack. And for the axial attack, you have now the nucleophile like this and now the anti-bonding orbital will be something like this. So, these are the two scenarios. So, this is the sigma star. Again of the carbon nucleophile partial bond.

Now the question is, what is the stability of these two transition states? Is there anything which stabilizes any factor which stabilizes these orbitals by some conjugation. So, what Cieplak suggested is that these hydrogens at C2 and C6, these hydrogens, so they have basically they have something like this, this is the sigma bond, sigma of CH at C2 and C6.

Both are having similar sort of angle with the developing sigma star orbital. You can also write that this is the developing sigma star orbital. And you see that they are not orthogonal, they are certainly not orthogonal and their angle is much less. So, that there is there is lateral overlap that is possible, yes. So, lateral overlap that is possible. This is nothing but very similar to your hyper conjugation.

But if there is an empty orbital at a carbon and if you have a hydrogen then this hydrogen can enter into hyper conjugation. So, this is nothing but hyper conjugation. And due to these hyper conjugation this sigma star will be stabilized. So, the whole transition state get stability due to this CH donation from this sigma of CH. Now the question is, can the other one that means when the nucleophile approaches from the equatorial face, whether that can be stabilized or not also? Yes, that can be stabilized, but that stability comes from donation from CC.

See, now you have although this is not there is some angle now between these two the orbital, the directions of these orbitals. However, there is still possibility of lateral overlap like this but this is, remember this is overlap between carbon, carbon sigma with the sigma star of that, that is developing. Now obviously the donation power of carbon, carbon is less, much less than CH. If that be the case, then this will be more stabilized, and if this is more stabilized that means there is preferential approach from axial face leading to the formation of equatorial alcohol as the major product.

Now if we now compare these two models Felkin’s model and Cieplak model, the success of Cieplak model over Felkin’s model lies in these examples. Like if you have suppose I put a cyanide here and a cyanide here, and then I trying to reduce the carbonyl. So, we know that now what is happening if you put electron withdrawing groups here, so these carbon, carbon bond will be even less able to donate to the developing sigma star orbital. So, in that case you expect even higher amount of axial attack, that means equatorial alcohol.

On the other hand, if you have donor groups attached to these centers, say like methyl, then what will happen, then the ability of these carbon, carbon bonds to donate to the sigma star increases a little because of the electrode pushing by the methyl. And so you will see a little less of, although less of or loss of preference I can say, you have to use the right word if you say less that is that means that the axial alcohol by equatorial will be less, that is not true. It is basically the preference, the degree of preference, I can say, the degree of preference is lowered.

Now, if you this can be so this substitution effect can be quite easily explained by Cieplak's model. However, this Felkin's model cannot explain these types of observations, because Felkin's model is basically there is no stereoelectronic factor. It is basically this torsional strain which remains the same whether there is cyanide or there is methyl that does not matter. So, it fails to explain the substitution effect. So, that is where one of the success of the Cieplak model. Now, let us discuss the other type of reduction, that is the reduction by the dissolving metal in liquid ammonia.

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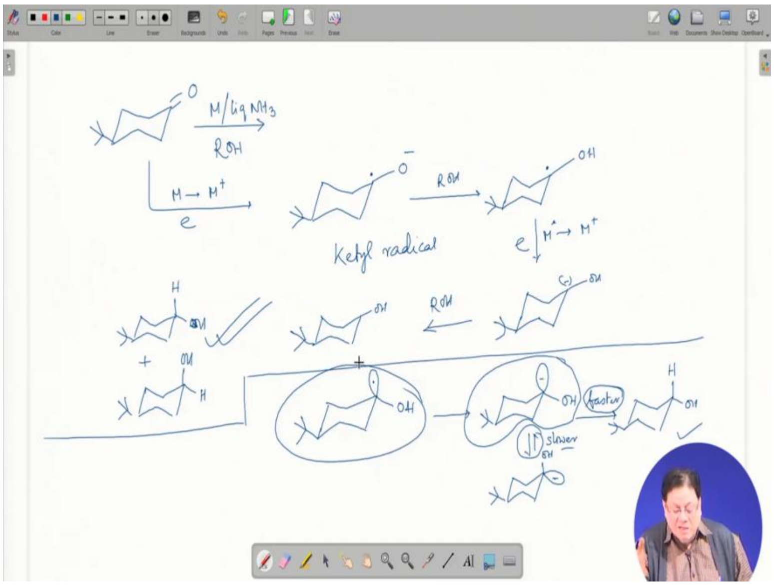

So, this is C again, we take the same conformationally bias systems. So, we have a metal and liquid ammonia and you have a proton donor which is ROH. Now, the mechanism of this reaction is basically that the metal ion, the first the metal goes to metal ion, with release of one electron and that electron is added to the carbonyl carbon. So, what you get is basically this one. This is what is called ketyl radical.

Now, this ketyl radical is quenched by the proton donor. So, you can have OH here, and the radical, and then another electron is added, so that this becomes now this attends a negative character and now this is quenched by the alcohol and you get the ultimate formation of the alcohol, this cyclohexanol. Now, there are two possibilities here also, equatorial and axial. And I already told you that it is, it gives almost exclusively the equatorial alcohol. So, this is the one which is formed almost exclusively.

Now, what is the reason for that? First of all, when we discuss the radical reactions, the geometry of a radical usually is planar, SP2 hybridize because of donation from adjacent groups, like hyper conjugation or electron donation from a donor group. So, usually the radical adopts a planar conformation a planar geometry that means SP2. So, the radical recites in a P orbital, except in the case of CF3, CF3 we have discussed that CF3 is pyramidalized to some extent.

Now, to explain the formation of this equatorial alcohol what has been proposed is that, that this radical is, see this is one of the intermediate, and then it goes to the anion. And then it goes to the anion and this anion is then quenched to give the alcohol. So, one thing is clear that we know that this anions, like the nitrogen lone pair, that can undergo inversion.

So, if it undergoes inversion, then the negative charge will be on the equatorial face and the OH will be on the OH will be axial configuration. So, this is much slower compared to this aspect, this is faster. If this is faster and if this is the preferred geometry of the anion, then you expect that the equatorial alcohol will be formed.

Now, the question is, why this geometry will be preferred? If you think that this geometry is preferred, that means the radical assumes this geometry where the orbital is basically pointing towards the axial position, so that the hydrogen the proton ultimately is donated from the axial side before that one electron is added from the axial side.

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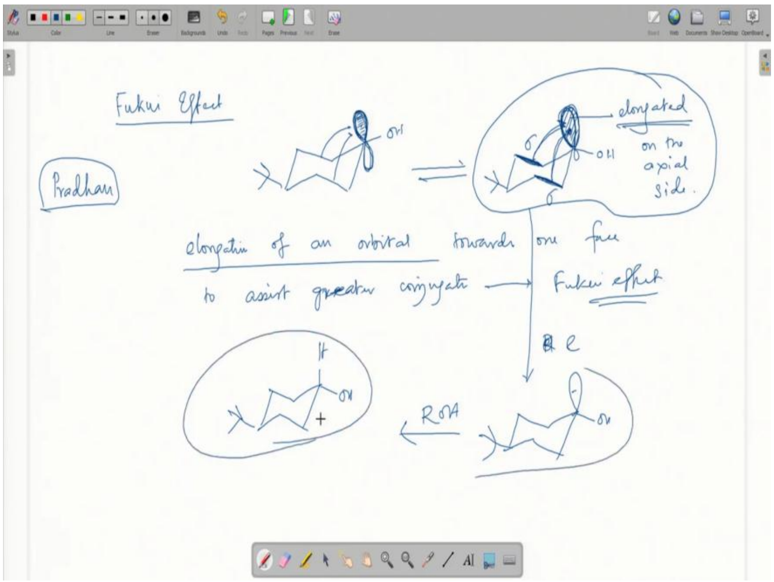

Fukui Effect

elongation of an orbital towards one face to assist greater conjugation → Fukui effect

So, that was a little bit difficult to explain until one Indian Scientist Professor Pradhan, he proposed the application of an effect which is already known which was already known at that time and that is called Fukui effect, that is called Fukui effect. What is Fukui effect? Fukui effect is basically a radical like when we have this ideally this radical should have been SP2. However, because of Fukui effect, this assumes a kind of SP3 character or not purely SP3 but what we can say that the orbital is more elongated on the axial side.

Now, why is that? That is the question. The reason is that these we have just seen the Cieplak model is very similar that these carbon, carbon sigma they can now donate to these orbital to stabilize this radical. Now, if this radical has this contour that means the geometry of this orbital is such that this area, that the volume occupied by this top loop is less then there will be less conjugation.

On the other hand, if you can increase the volume in this side, on the axial side, that means the orbital gets elongated, then what happens then you get better or stronger conjugation from the sigma of the carbon, carbon bond. So, this is basically what is that means elongation of an orbital towards one face to assist why this is happening greater sorry, greater conjugation, is what is called Fukui effect. So, due to this Fukui effect, the radicals become stabilized.

So, now you can explain the greater formation of the equatorial alcohol. That because of the Fukui effect the radical that is formed that assumes a higher, at elongated orbital on the axial side and so, there will be a preferential protonation first the electron will be delivered, so electron delivery will take place. So, that will be negative OH and then the ROH delivers the proton.

So, everything depending on this stability of this radical, this radical again I repeat has an elongated loop on the axial side so that the electron and the subsequent proton donation takes place preferentially from the axial side. So, because of this Fukui effect that is according to the what Professor Pradhan in a paper they proposed this type of effect to explain the formation, the preferential formation of the equatorial alcohol.

So, that takes care of the reduction of a carbonyl. First, we have discussed the reduction of a carbonyl by hydride transfer agents and we have discussed the different models. But we have taken cyclohexanone as the model system, and not only cyclohexanone, it is a conformationally biased cyclohexanone and that leads to preferential formation of equilateral alcohol.

In case of hydride transfer agents, there are different models, first it was product stability, that model which was discarded because it is exothermic process. Then Felkin’s model that also cannot explain the effect of substitution and followed by Cieplak’s model, which can efficiently explain the substitution effects on the reduction, course of reduction.

Then we have discussed the metal ammonia system, and we have seen that because of Fukui effect, now which is basically the elongation of the radical on one side to enable stability by donation from the adjacent carbon, carbon bond is what is guiding the whole course of reduction and giving the equatorial alcohol as the major product. Thank you very much.