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

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Lecture 37

Dynamic Stereochemistry: Enolate as nucleophile

Hello. Welcome back to this course on structure, stereochemistry and reactivity of organic molecules and intermediates, a problem-solving approach. In the last lecture session, we are discussing the internalization of a carbonyl system in a cyclohexanone, giving us the model, and then followed by the addition of an electrophile.

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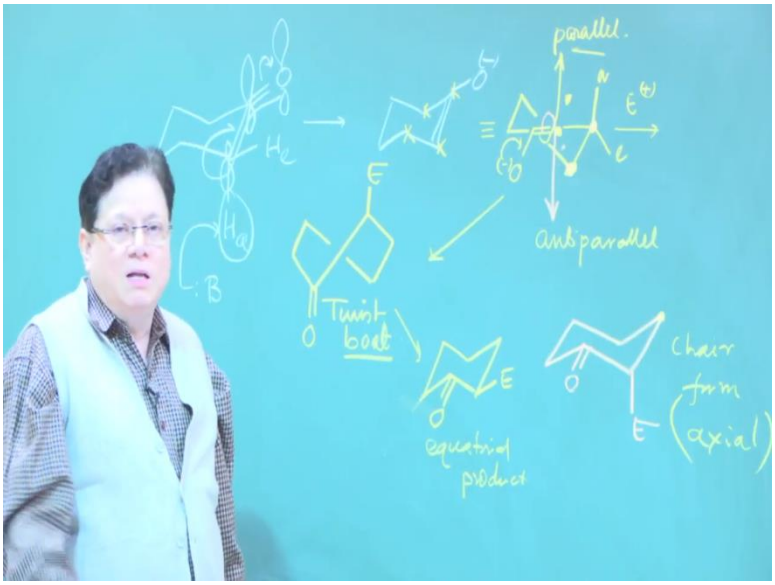

Now, the if I again go back to the very basic that, first of all, enolization, let me just, I will show you the model later on. First, I will show you the picture of enolization that what we are saying here that the enolization involves the actual hydrogen simply because the actual hydrogen is having a sigma bond which can interact favourably with the pi cloud of the carbonyl. Which is not possible for the equatorial bond?

So, it is the actual bond or actual hydrogen which is lost in this fashion. And that forms what is called an enolet. Although, the enolet is now written in chair form, but actually it is not by a perfect chair. It is a kind of, it take adopts, that is called a half chair form like this. So, this is because that this carbon that carbon and that means these double bond carbons as well as the adjutant carbons, all lie in a plane, that has to be planar.

And so, this is the geometry of the cyclohexanone, and this is the O minus. And now you have the addition of the electrophile, suppose the E plus is your electrophile. Now, the E plus can be captured, there are two possibilities, one from the top, that is this one, or the E plus can come can be captured from the bottom side.

And depending on these two approaches, we have given name to this, and the name is basically that the first find out the carbon where the electrophile is attached, and that is in this case that is this carbon, the electrophile is attached at this carbon. Then go to the next adjacent methylene where there is a pseudo actual bond and a (())(3:19) equatorial bond. And so, now, if the electrophile is captured from the side of the axial one, that means parallel, basically it is being captured parallel to the axial bond, so that is called parallel attack, and this is what is called the anti-parallel attack.

And there are consequences of the geometry that is involved in parallel as well as ant-parallel attacks. So, what happens in parallel attack you have this carbon as it takes up the electrophile this goes up. So, that means now you have a scenario where there is a carbon that will be here, there is a carbon already there, and there is a carbon at this position, these are prefixed, only that will go up.

If that goes up, so that takes up a geometry like this or this is typical of if you complete the cyclohexane product then that will be looking like this. So, this is what is called a twist boat confirmation. So, the electrophile will be added at this position and this is a twist boat confirmation.

And then naturally where is the carbonyl? The carbonyl is at this position and naturally it will not stay in this conformation, so it will go to more stable chair form. So, it will goes to the most of a chair form then you have the carbonyl sorry, the electrophile. The carbonyl is here and the electrophile is here. So, the electrophile ultimately occupies an equatorial position. So, this is the equatorial product.

On the other hand, if you have anti-parallel attack, then the situation is that, anti-parallel attack that means your carbon this carbon is there, this is prefixed positions and this carbon will go down and that will somehow say suppose go down. So, that means you have a situation where there is this carbon already there, another carbon already there, and you have another carbon going down. So, that is typical of the representation of a chair form.

So, this directly goes into a chair form and where is your this is the carbonyl that has gone down, this is the back one, this is the back one. So, you have an anti-parallel attack, so that is the electrophile and this is the carbonyl. So, it goes directly to the product. You do not need any interconversion of the confirmer. So, that goes directly into the chair form and it is the axial product.

So, that is an interesting fact that the equatorial product is more stable, but to have to go to the equatorial product, you need to go to the twist boat form. And on the other hand, axial one is the less stable product, but you can directly go access that going through the chair form. So, this is the basic principle of parallel attack and anti-parallel attack.

Just remember parallel attack gives you the equatorial product but it goes through a twist boat confirmation whereas the anti-parallel attack gives the axial product which goes through chair form, directly into the chair form. Now, let us so in absence of any overriding factors, like steering factors, stereo electronic factors, what happens that both the products are formed in appreciable amounts.

And another case, another important point that one has to remember is that, if the transition state is early transition state, then it does not matter whether it is going ultimately through a chair or a boat form, then also the product the both the products will be formed in appreciable amount. But if the transition state is a late transition state, then obviously the twist boat have higher energy than the chair form and then there will be differences in the ratio of the two products.

So, there you do not expect any differences. If there is an early transition state that means it is not the geometry is not very important and if there is no other overriding factors like steric factor or streo electronic factor, then you can expect both the forms in appreciable amounts. However, in real scenario that does not happen as you know. There are other factors that come into play and that makes the products deviate from 1 is to 1 ratio.

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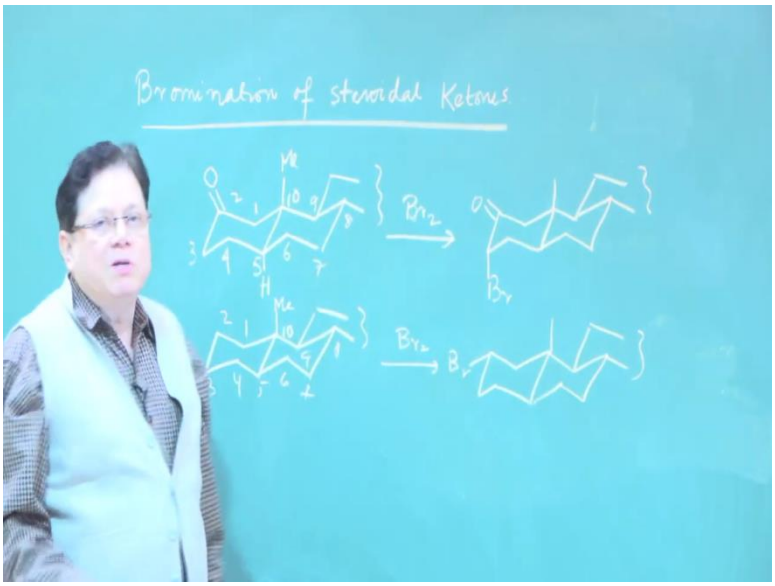

So, let us do some examples. Bromination of steroidal ketones. So, let us take a steroid molecule, we are not drawing the C or the D rings. If the ketone form, it says steroidal ketone. So, let us take the 2 ketone steroid and there is a methyl here, there is a hydrogen. So, it is a transfused ring junction and you are trying to do, so this is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. And you are trying to do the bromination. So, that is one scenario.

The other molecule that we have is the 3 ketone system. And it has been found that there is a perceptible difference in the bromination product. And what is the difference? That in case of the 2 ketone steroid the product that is formed is an actual bromine. On the other hand, from the 3 ketone steroid 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, on the three ketone steroid, the product that is formed is a two equatorial bromine. So, the bromine goes here, in the equatorial position. Now, weather how to analyze these dynamics stereochemistry, that is the problem.

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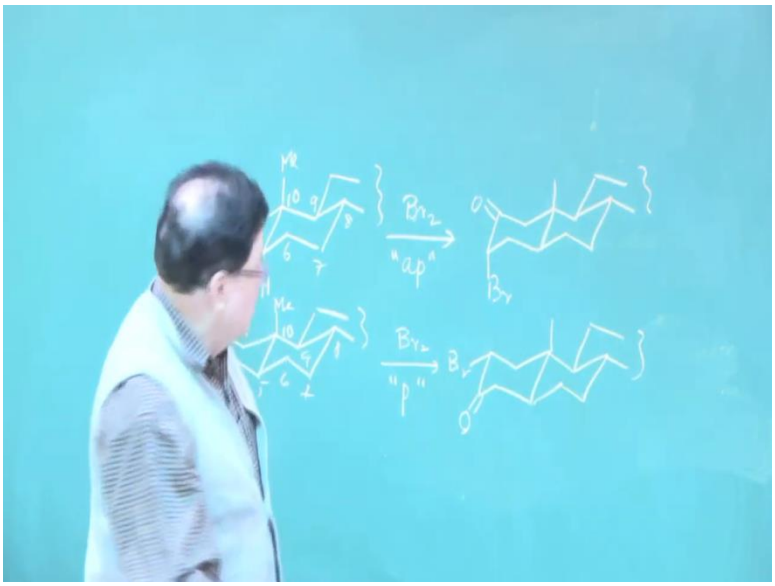

So, let us try to draw the enolet, see the way to solve it is basically you have to go back and just analyze the products. If the products are given from the products you can make out that what type of attack is taking place on the enolet, whether it is parallel attack or anti-parallel attack.

If it is giving that actual bromination, halogenation, then definitely axial product is obtained via anti-parallel attack, right? And the sorry, there is a ketone here, the equatorial product is obtained in case of a parallel attack, if parallel attack is more. So, actually this gives the answer but you have to now provide a reason for this that why there is anti-parallel attack here preferred and why there is a parallel attack that is preferred over here.

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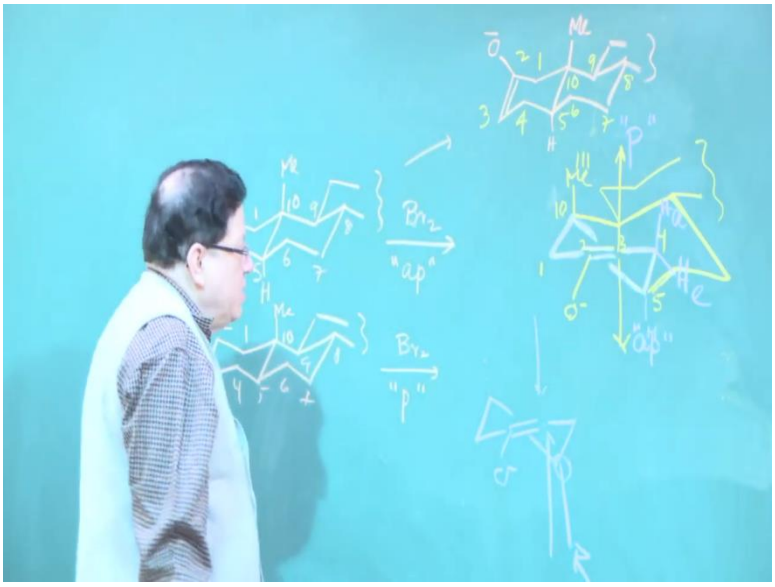

So, let us draw the let us first erase these two, because I need space. So, the enolet that is formed is this is from the 2 ketone system. This is the enolet. And if you draw the true picture of a cyclohexene, if you draw the true picture means true confirmation, then that will be is basically equivalent to this is again remember 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10.

So, now this will be your 2, so that will be O minus, this is 1, that is 2, 3, 4, 5, and then this is your the other the 10, 5 is connected to remember 10 in the same ring, 6 is the carbon belonging to the BV. So, now you have to draw the other ring. The other ring is basically that will look like something like this. So, this is the scenario. Where is your methyl? The methyl is at this position. So, if I can use another chalk, another colour, then this is your the front side, this is the A ring and that is the B ring. This is your B ring and then the C ring comes from this side. So, this way it goes.

Now, see, parallel so you have to find out where the electrophile is approaching or attacking. The electrophile is attached either this position or from the bottom. Now, which one is parallel and which one is anti-parallel attack? That we have to go for the where is the axial group at the four position, the four position has axial here, hydrogen, and that is your equatorial. So, equatorial and axial. So, that means this is parallel attack and this is anti-parallel attack.

Now, there is basically usually what happens that anti-parallel attack when you have, anti-parallel attack has may have some interaction with the some, 1 3 it can suffer from 1 3 dipolar 1 3 steric repulsion, like again I draw the only the cyclohexene geometry. See, if you have these, O minus and anti-parallel attack means it is approaching from this side.

So, now if you have a group here, large group, so that can hinder the approach of the electrophile from that side. So, you have to try to find out whether there is an big axial group at this point. On the other hand, parallel attack, this is a parallel attack, parallel attack does not encounter such type of 1 3 di-axial interaction, because the closest axial position will be here, but that is too far away. Because that is this 1, 2, 3, so, 3 carbon it is actually 3 carbon array, but this is the 1, this is 2 carbon. So, that is the perfect orientation of 1 3 di-axial interaction. So, that is your that you have to look that whether there is any 1 3 di-axial interaction. See, we are one three di-axial interaction or not. In this case there is only a hydrogen here.

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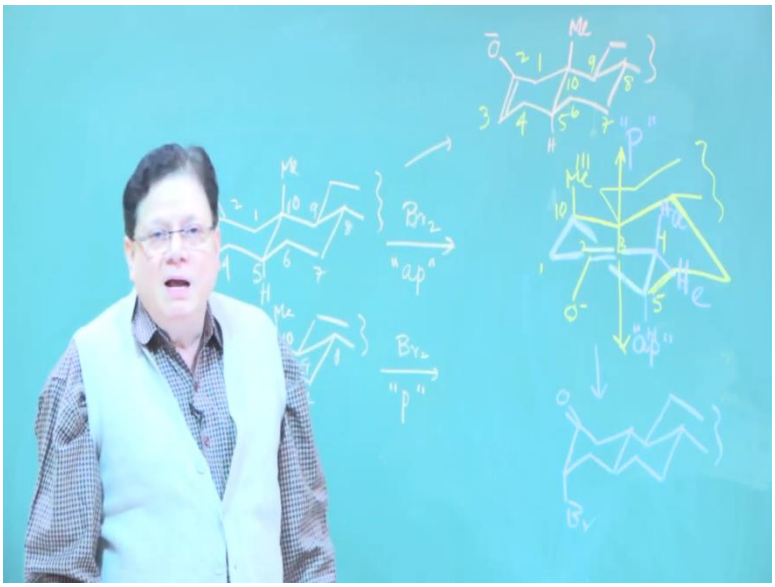

So, basically, if there is only hydrogen, so then there is this because the anti-parallel attack goes via the directly to the chair. So, in this case what has been found it must be a quite delayed transition state. So, what has been found that major attack takes place from the anti-parallel side. Anti-parallel side attack means what? Anti-parallel attack means, your electrophile will assume an actual orientation and that exactly what happens. So, that you get a product which looks like this, this is your bromine.

So, that is the first molecule, that anti-parallel attack takes place. Because in absence of any other overriding interactions, no such strong di-axial interaction, so anti-parallel attack is taking place that means it is actually probably a kind of a late transition state.

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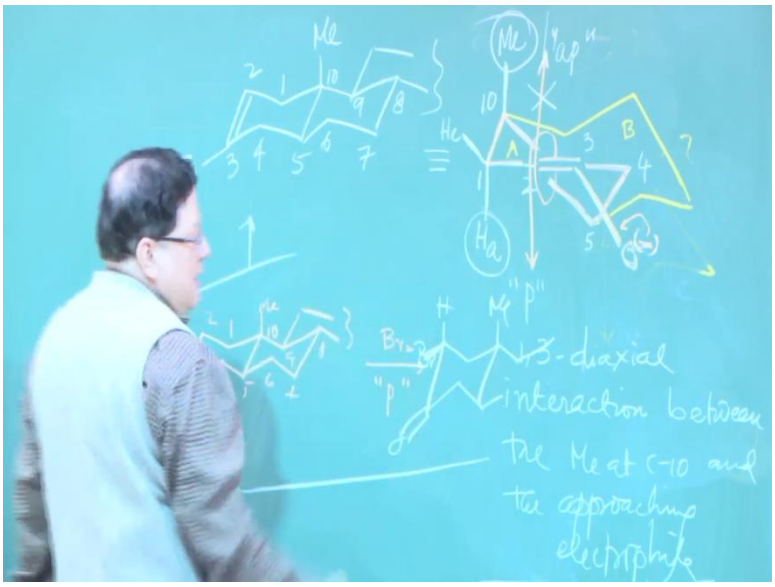

The second one means the 3 ketone system. So, let us erase the 2 ketone system and go to the 3 ketone system. The 3 ketone system basically the enolet will look like this, this is your enolet, this is the methyl. Put the numbering, it is always what would give the numbering otherwise you may lose track while drawing the actual geometry. So, this is the scenario.

Now, you draw the that cyclohexene confirmation, so this is the scenario. Now, this is your 1, that is 2, that is 3, so this is the O minus, and that is 4, then 5, and 10, and like before you can now draw the B ring, the B ring will go like this. This is the B ring and this is your A ring, if I put a different colour this is your A ring, this is the O minus, and this is the scenario.

Now this O minus will come back and this will grab the electrophile either from the side or from this side. So, if you are adding the electrophile at the 2, that means now you have to look at remember there is a methyl here at the 10 position. Now, we have to look at the axial and the equatorial bonds at the adjacent carbon. In this case the adjacent carbon is 1. So, this is the axial and this is the equatorial.

So, this is the parallel attack and this is the anti-parallel attack. Anti-parallel, because this is now opposite to the axial, this approach is opposite to the axial hydrogen, which is of the any

substituent could be there at the adjacent carbon. And this is parallel to that axial hydrogen. So, this is the scenario.

Now, which one will be preferred? In this case, you see the anti-parallel approach suffers from a severe 1 3 di-axial interaction from this methyl. So, there is 1 3 di-axial interaction between the methyl at 10 and the approaching electrophile. And due to this factor, you now do not get much of this anti-parallel attack. So, you will get both the parallel attack, remember, parallel attack will give you ultimately the this also tells you the alpha, beta nature of the substituent.

The substituent is coming from the alpha side of the ring, so it is alpha, and it will be alpha equatorial. And so, that is why the product what we drew here was a carbonyl here and an alpha equatorial bromine. Remember that was the structure, and this is methyl. So, that is a very good example of that in one case parallel attack is taking place another case anti-parallel attack is taking place. Simply because the carbonyl is at two different positions. One is located at C2 and in another time it is located at C3. So, that makes a difference.

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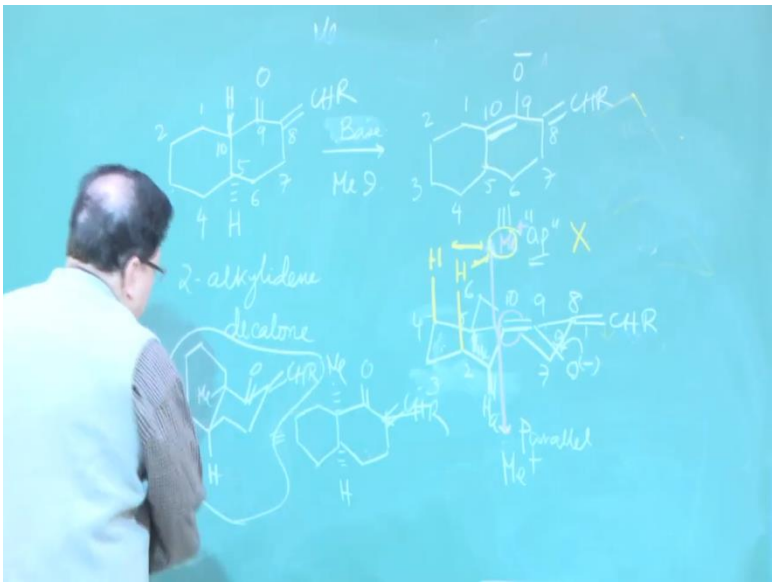

Now, let us take another example. This is now this is this was halogenation. Now, let us take an example where alkylation takes place. So, the molecule is a decalone system. It is a decalone, it has got sorry, it is not a decalone system, it is a decalone, but the carbonyl is here, CHR, and there is yes, this is the starting material, a decalone, but at the alkylidene, a two alkylidene decalone.

So, that will be methyl lithium. So, what will happen the sorry, a base not methyl lithium, a base and then suppose methyl iodide. So, the base will abstract this hydrogen, it forms the enolet, and then the enolet will be alkylated, methylated at this position. So, this is the C10 position, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10.

So, the question is, what is the geometry of this product? So, let us try to draw the first the enolet. So, this is the enolet from this one decalone system. And if you try to draw it properly, then what will happen, you have, now this actually this is the front ring from this side and this is the back ring. So, what you do in order to now, this is okay I think, let us see whether we can draw it properly, if we do this.

So, this is the double bond, this is your O minus, this is your double bond CHR up to that point is, and your next ring, so double bond carbons are basically 1, 2, 3, 4, 5, 6, 7, 8, 9, 10. So, this is your 9 and this is your 10, and 10 is connected to 1. So, that is your 1. That means the next ring that is basically you have to draw it in this fashion I am sorry, this is your A ring.

So, better not first draw the B ring in the cyclohexene that conformation and then complete the construction of the A ring. So, this is your A ring and this is the B ring. So, now you complete the numbering. This is 1, this is your 2, this is 3, this is 4, 5, and then 5, then you have to 5 is connected to there is some problem, just a second. 5 is connected to 6 sorry, I am really sorry.

This is not 1, you have to do it in the opposite way 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, this way. So, one will start from here. This 10 is connected to 1 as well as 5. But since 5 has is connected to 6, so we have to do it in this opposite fashion. So, that is the molecule. Now, the question is, when it comes back and now there is again possibility of two approaches, one is the methyl plus can attack from here or it can approach from the bottom.

You have to find out which is parallel and which is anti-parallel. So, you see, you have to come to this next carbon. The next carbon is you see this, these are the axial hydrogens. Of course, it is then that means, this is the just a second, so this is the parallel attack, because this is the axial hydrogen.

See, the carbon that is attack to go to the next adjacent carbon. In this case, there are two carbons, which are attached at this carbon. So, there are there are two axial hydrogen, so you

can take any of these as reference. So, that is the electrophile approaching from this side is a parallel attack and electrophile coming from this side is anti-parallel. So, that part is clear.

Now, the question is which one will be the favoured one? So, this is basically you can see, so this is your parallel attack, why? Because, I said that this is the axial hydrogen's adjacent to the carbon which is being attacked by the electrophile or where the electrophile is captured. So, this is the parallel attack. So, no doubt about that, and this is the anti-parallel attack. The question is which one will take place preferentially?

Remember, what I told is that anti-parallel attack, you have to always keep in mind that the anti-parallel attack maybe subjected to steric interactions like 1 3 di-axial interactions. In this case, there are I could see hydrogen's at these positions, which are actually basically having 1 3 di-axial interaction.

Earlier case we saw only one hydrogen offering the di-axial type of interaction to a bromine. Now, this is a 1 3 di-axial interaction offered to a methyl. The methyl is obviously bigger than bromine, that is number one, and number two is that there are two hydrogen's now, offering steric entrance to the approach of this methyl plus.

So, that says that the anti-parallel attack will not be favoured. On the other hand, it is a parallel attack that will be favoured. So, when you decide between anti-parallel and parallel, you just try to check whether the anti-parallel attack is suffering from any 1 3 di-axial interaction or not, CBR 1 3 di-axial interaction or not. In this case, there is these 1 3 di-axial interactions.

So, the bottom line is that your methyl is approaching from the alpha phase, number one. Number two, it will occupy an equatorial position. So, the two-dimensional structure will be something like this, this is double bond CHR and this is the methyl and this is the hydrogen. Now you can draw cis-Decalin structure, if you wish.

cis-Decalin structure, not this structure, because in this structure you maybe little confused that what is happening, because methyl is… so, this is the methyl and this is the hydrogen. This is the carbonyl, this is CHR, so that is the one of the this is the preferred geometry. Because methyl will try to add up to the equatorial position. It is always flappable, this molecule can flip, the methyl can flip to the axial position, but that will be the less stable one.

So, I think this summarizes this lecture session where we have discussed the electrophilic bromination and alkylation of an enolet. We have discussed again what is parallel and what is anti-parallel, and how judiciously you can distinguish between the preferential attack based on the parallel or anti-parallel. Remember parallel, anti-parallel is based on the axial nature of the substituent which is attached to the carbon next to the carbon where the electrophile or even it could be a nucleophile, we have not given any example, that is attacking at that position.

Based on that, we decide parallel or anti-parallel. And we have to remember that anti-parallel attack may suffer from 1 3 di-xial interaction. And if that happens, then parallel attack will predominate. This also tells you that what will be the ultimate orientation alpha or beta, the nature of the substituent that is entering into the system, either the electrophile, the bromine or the methyl or any other alkyl group. Thank you very much.