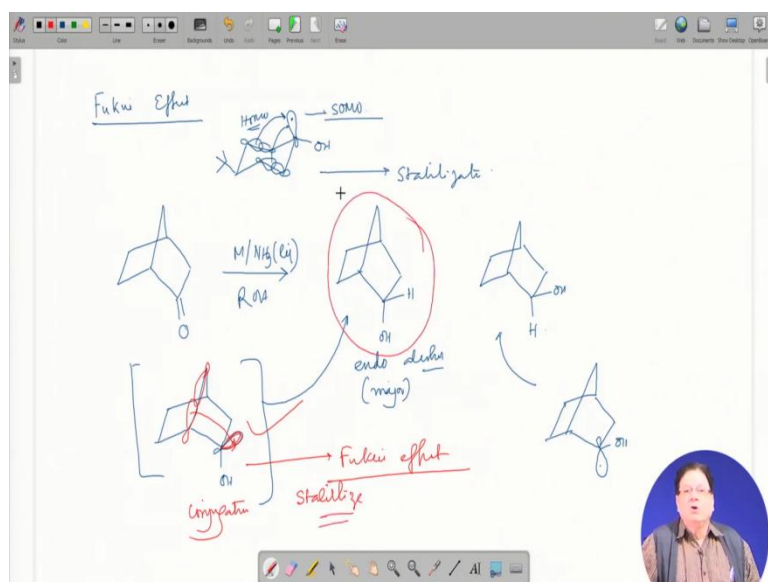


Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach
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Lecture 36

Dynamic Stereochemistry: Reactivity of Unsaturated Carbonyl and Enolate Systems

Hello. Welcome back to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. We have been discussing the reduction of carbonyls in cyclohexanone that was in our last lecture. In this session last lecture session, in this session, I will continue with the reduction of the carbonyl, but we may extend it, we will axially extend it to alpha, beta unsaturated carbonyl system, and then we will discuss the enolization and alkylation and halogenation of carbonyl systems.

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Remember, last time we were discussing the Fukui effect. Fukui effect, again, I repeat what is Fukui effect, Fukui effect is basically elongation of an orbital towards one side, towards one face or one side. And we have seen that in cyclohexanone reduction by metal dissolving ammonia then what happens this radical is elongated on the axial face. Why it is elongated? Just to enable that these CC bonds can interact with this.

Remember this is a three electron this is basically a single electron. We are talking about the stability of this of this SOMO. SOMO of the so, this is the SOMO and this is the HOMO. So, that type of interaction leads to stabilization, this is what is Fukui effect. Now, there are other

examples of Fukui effect, like a very good example is like this, reduction of this Norbornane system.

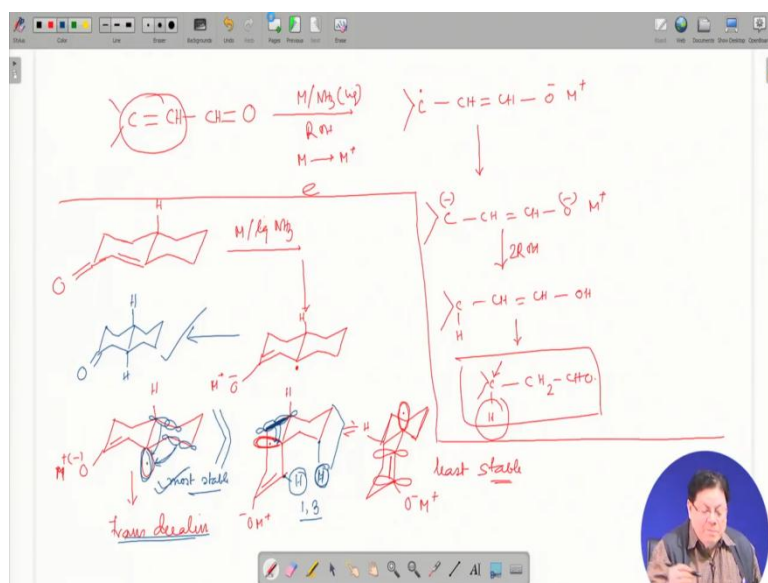
So, if you take this bi-cyclic compound carbonyl, the ketone, and if you again reduce with metal and liquid ammonia and a proton donor, then what was seen that it keeps as the major product this one, the endo-alcohol. This is what is that endo-alcohol. Because there is another one which will be exo-alcohol, that is this one.

Now, you see that because this is major that means this radical the intermediate that is formed, remember the intermediate that is involved here is basically this one. Now, I am actually thinking of already that existence of Fukui effects. So, that the orbital is elongated on this side, this is elongated on this side. And the other one, so this will lead to the endo and the exo one will have if there is a Fukui effect, we will have enlarged orbital on this side.

However, there is no driving force for this orbital to be enlarged on this side because there is no donation, that CC bond there is the CC bond which is favourably positioned to interact with this orbital. On the other hand, if you look at the formation of the endo-alcohol the intermediate for the formation of the endo-alcohol, you see that there is these carbon, carbon bond.

Now that is in a position to undergo this type of conjugation. So, this will be there will be existence of Fukui effect in this intermediate. So, Fukui effect will stabilize this and leading to the formation of this alcohol as the major product, at the endo-alcohol as the major product.

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Now, let us discuss the reduction of alpha beta unsaturated carbonyl system, reduction of alpha beta unsaturated carbonyl system. So, if you do this metal ammonia reduction, you know that what happens here basically the double one gets reduced and the mechanism is like this, let me put the valency correct.

So, the mechanism is that first one electron is added, so M goes to M plus, donating one electron to the system, and that will become CH double bond CH and then O minus this is M plus, that goes to the another electron is dumped here minus CH, double bond CH, and then O minus M plus.

And finally, this is being quenched by two molecules of the alcohol and you get CH, CH double bond CH, OH, and that will ultimately become back to the ketone, back to the in this case it is aldehyde, so that will be back to the aldehyde. So, this is the product. So, basically you have reduced the double bond by this metal liquid ammonia reduction. So, this is the mechanism.

Now, the question is that there is a delivery of a hydrogen at this site, at this carbon, at the beta carbon. So, there is a question of stereochemistry in appropriate cases, not in this system, this is an acyclic system. So, there is a and it is not generating any stereogenic center here. So, there is the question of any preferential delivery for this molecule. But if you have a molecule where the delivery from two sides are different, then you can get two products. And let us take an example of that type of system.

So, suppose we have a decalin system, which has got a carbonyl at the 2 position sorry this, which has got a carbonyl at the 2 position and a double bond here, and this is hydrogen. So, we started with this molecule and now reduce it with the metal and liquid ammonia. So, basically what will happen as the mechanism is suggesting that it will form this O minus M plus double bond here and then a radical here, and this is the radical. Now, question is, what type of geometry this radical will adopt?

Let us see, first of all, it can adopt an axial orientation like this and this is the double bond O minus M plus or it can adopt see this is obviously that will lead to a trans decalin system ultimately, so that leads to trans decalin. And on the other hand, there is a there are possibilities that you can have since decalin type of system generated, so the radical will be something like this. This is the hydrogen, there is this double bond O minus M plus.

However, since decalin is flippable can undergo flipping, so you can also have the other form, the flip form. So, in the flip form this is the hydrogen and this is the radical, and this is the double bond, sorry, let me see, and this is the double bond and this is the O minus, M plus. So, these are the three scenarios.

Now out of these, the question is, which transition state or which radical will be more stable? We are talking about the intermediate now, which radical will be more stable? It is perfectly okay to discuss the stability of a transition state based on the intermediate, because intermediate is the closest one to the transition state. So, if you compare the intermediates then also we can finally get a conclusion from that stability order.

So, let us try to assign a stability order. First of all, this radical where this is see, because these are the P orbitals forming the double bond, but that is almost orthogonal to this radical, so this is the least stable. And this one and there is a see, there is no Fukui effect also here, this radical is not only orthogonal to this pi framework, but there is no Fukui effect also in this, because this is not properly aligned to this orbital.

On the other hand, in this one, the flip form of the other cis form, there is Fukui effect possible, obviously from this there is Fukui effect possible from this CC bond. And in this the one which is leading to the trans decalin, there is Fukui effect possible from two CC, carbon, carbon bonds like this, one is this one, another is this one. So, this should be the most stable.

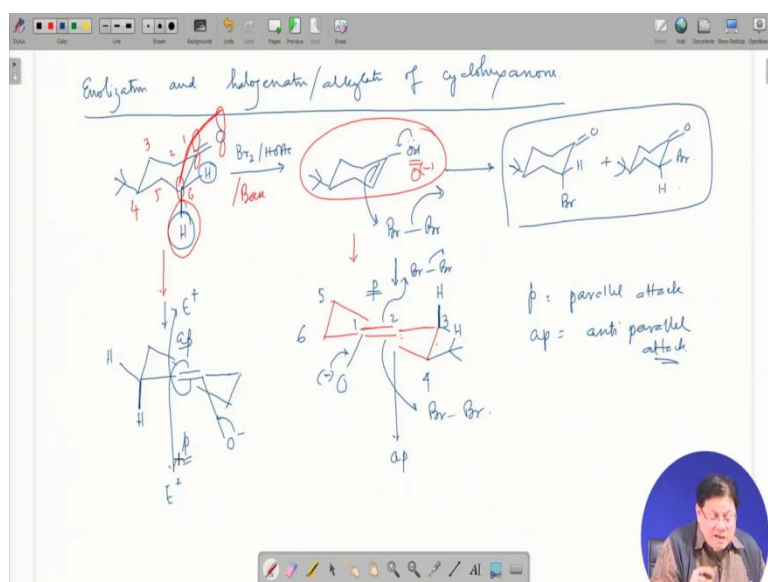
Another factor we should not ignore is that there is a hydrogen here and there is a hydrogen there. So, there is steric interaction between these two hydrogens, 1, 3 interaction, and that is causing destabilization of this radical.

So, basically the stability order is this is much greater than this one and this is more stable than that one. So this is although, this has got some Fukui effect, which is shown here, but this is also this there is a destabilizing factor which is generated due to the presence of this axial hydrogen at the 3 position.

And on the other hand, this one is this radical is not is having a Fukui effect from two adjacent carbon, carbon bonds, and it is not suffering from any sort of 1, 3 di-axial interaction. So, this is the most stable one and you get ultimately the product, now you can write that what is the major product, the major product will be the trans decalin system. So, this is the major product.

So, that is a very another example of Fukui effect operating in an alpha beta unsaturated carbonyl system. So, we have seen a nor bond and then bond in the system which are there is a carbonyl and in this decalin system where there is an alpha beta unsaturated carbonyl system present.

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Now let us consider the enolization and halogenation or alkylation of cyclohexanone. See, we always take cyclohexanone as our model system, because that is where the geometry is very well known, that is number one, and it is easy to it is also that they are present the six

membered rings are the most stable. So, naturally the natural products the majority of the natural products will have the six membered rings.

So, let us consider the enolization and then followed by this halogenation or alkylation of a cyclohexanone. So, if you again take the same conformationally bias system and if you add suppose I add bromine in acetic acid. So, the mechanism says that it first goes to an enol form and then it comes back and then attacks the bromine and bromination takes place. Again there is formation there is the chance of formation of two products. So, you can have a equatorial bromine or you can have axial bromination.

So, both these diastereomers are possible, but we have to see which one will predominate that depends on the structure of the system. First of all, first it will enolize that is the first step. Enolization, now there are two hydrogens here two diastereotopic hydrogens, now these diastereotopic hydrogens, one will be preferentially lost, because and which one it is the axial one, because the axial one when it is released that because the orbital that is involved here is can form the conjugation with the carbonyl, which is absent in case of the equatorial CH.

So, when we say that there is a enolization, the enolization will remove the axial hydrogen. So, this can be proven by putting a deuterium here, a hydrogen here, and you can see that these deuterium is lost and the hydrogen is retained. So, that is the first step. So, when you have the enol form now, enol form contains a cyclohexane ring with a double bond. You know cyclohexane ring with a double bond is not really in the perfect tier form, rather it exists what is called a half tier form, like this.

So, this is the actual geometry of a cyclohexene system. So, cyclohexene, now this is cyclohexene, only difference that there is a OH attached to the double bond or there could be if you are doing it with a base then there could be O minus here. If you are doing the bromination with the base, then there will be an O minus instead of OH. So, O minus or OH.

So, on one side there will be so let us consider this, suppose we number it now, this is 1, 2, 3, 4, 5, 6. So, now you have your this is suppose your O minus or OH, so that will be your 1, then that will be your 2, this is 3, this is 4, actually this will not lead to the right one, let us see, I think I erase this put the carbonyl, sorry, let me erase it and then again draw it.

And for the carbonyl, we put the carbonyl here suppose this is O minus, so that becomes 1, this is 2, sorry, so this is 1, 2, 3, 4, 5, 6. So, at the 4 position you have a tertiary butyl. The

earlier diagram I removed that because the tertiary butyl was adopting a pseudo-axial position which is not turnable, so that is why I changed the diagram a little bit. So, specifically the O minus I put from put at this carbon. So, this is the structure of the enolate or enol.

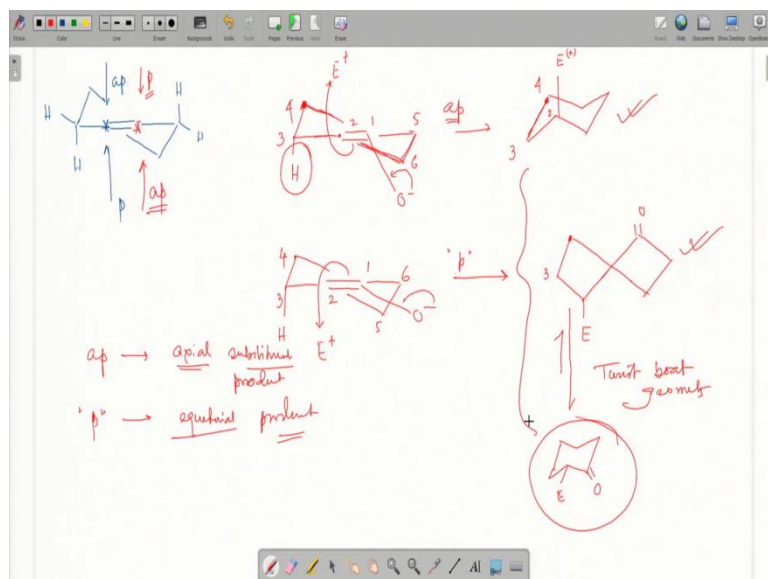
Now this comes back and this takes up the bromine either from the top face or it can be from the bottom face, these two. Now if you look at the substituent here. One is pseudo-axial another is pseudo-equatorial. Now when the electrophile in this case, this is the bromine is approaching from the side of this parallel to this axial hydrogen at C3, because this is the axial pseudo-axial hydrogen.

So, bromine is basically approaching from the in a parallel fashion to this CH bond. So, this is what is called parallel approach or parallel attack. On the other hand, the other side, which is just opposite to the CH, this is called anti-parallel. So P means parallel attack and AP means anti-parallel attack. I can just explain it again with the help of another diagram.

Suppose I have the structure which is like this, and the O minus is here suppose. So, now if O minus is here and so it comes back and then it either goes to the top and then whatever the approaching electrophile is here, suppose E plus, or it can take the E plus from the bottom side.

You can visualize this in the like you can also when this is attacking the E plus, I can also say that the E plus is basically approaching from this side, which is this is now the hydrogen which is all the pseudo-axial hydrogen and this is this the pseudo-equatorial. So, this approach is now anti-parallel to this CH, the pseudo-axial hydrogen. So, this is now anti-parallel attack and this is the parallel.

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So, let us see that what is the consequence of this parallel attack and the anti-parallel attack. I hope, this parallel and anti-parallel that is now very clear. What you have to do, you have to just see the where is your axial hydrogen pseudo-axial, these are not perfectly axial. So, if the approach first of all, which carbon the electrophile is added. The carbon, the electrophile is added is if this is happens to with this carbon then that will be your anti-parallel attack and this will be your parallel attack.

On the other hand, if this is the carbon which is being which is actually reacting with the electrophile or even it is a nucleophile which is approaching from one side or the other. Now if this is the situation that you are involving this carbon for the attack then this will be parallel attack and that will be anti-parallel attack. So, this is the scenario.

Now let us take some let us see that what is the consequence of this parallel and anti-parallel attack. If you let us talk about only one carbon otherwise what happens the situation becomes more complicated. So, this is the one. So, now suppose we are having a O minus here, this is coming back enolate and this is now undergoing this is attacking the electrophile.

Now if it attacks from the top side that is what will be called anti-parallel attack. So, anti-parallel attack the transition state will look like what, this carbon when it attacks the electrophile that also goes up. So, now you have this is a top carbon and that also becomes a top carbon that means there is 1, 2, 3.

So 1, 2, 3 that means this carbon is the original carbon. Suppose this is your again I number it, 1, 2, 3, 4, 5, 6. So, this is your fourth carbon and third carbon is basically your, the bond is going down and then it is going up. So, that is your number two carbon. So that means, this is now taking the shape of a chair, if you complete the whole thing.

So, basically the electrophile will be added from the axial face and it is assuming an axial orientation for anti-parallel attack. Anti-parallel, why? Because this is the pseudo-axial hydrogen, so the electrophile is basically coming from the opposite side or the nucleophile is attacking from the opposite side, anti-parallel.

On the other hand, if it is parallel attack that means, this comes and that takes up the electrophile. So, again I number 1, 2, 3, 4, 5, 6. So, if that happens, this is what is parallel attack, because hydrogen, this is from the same side of this hydrogen, so the bond formation is almost parallel to the CH. So, this is the parallel attack.

So, if it is parallel attack then what happens, see you have a top carbon here then the bond goes down, this is 3, and then it also again further goes down. So, you see that this is the, what is the configuration of a or the sorry, conformation of a cyclohexane twist boat. So, when there is approach from the parallel side or where there is parallel attack, the electrophile the first of all the intermediate or the product sorry, the product that is formed initially adopts a twist boat geometry. This is a twist boat geometry.

And then it will and the carbonyl will be here and then it will flip because twist board is not stable, so then it will flip to the chair form. So, this will be the electrophile and that will be the carbonyl. So, basically what is the consequence of anti -parallel and parallel attack that is demonstrated in this diagram. So, anti-parallel attack gives axial substituent or axial product you can say and parallel attack gives equatorial product.

Now, one might think that the equatorial product will be more, but that is not true. Because there is some other factor you need to consider. Because it is going through a twist boat which is of higher energy and this is directly going to the chair form.

Now, if the reaction, the bond formation bond forming, if there is not sufficient bond formation in that transition state, that it is an early transition state, then what happens this the adoption of a twist boat or a chair will not matter much. That means then you can expect that

both of these products equatorial and the axial alcohol are to be produced and usually that happens.

That if there is a early transition state and if there is no other factor, other than just this twist boat and the chair form then you expect that both these products will be formed in appreciable amounts. However, in many cases, as you know in many cases, there will be different factors that can guide the formation of one product as the major over the other.

So, this is one of the very important concept in dynamic stereochemistry, that is the alkylation or the halogenation of enolix. And to summarize what we have discussed is that concept which is called parallel and anti-parallel attack. Again, I now I show you the model to so that you have a better grasp of what is going on here, what is this parallel attack and what is this anti-parallel.

So, let me show this show the model to you, just a second, yes. So, this is your let me first point out what are the substituents here. So, this is the oxygen minus, this is the double bond, and that is the cyclohexene system. If we look at the cyclohexene system in this fashion, let me just try to find out which view will be best for you, maybe I think I will rotate it this way.

So, you see now this is the O minus, this is the double bond, and then you have this. So, this is your pseudo-axial. So, when O minus comes here, the double bond takes the electrophile from this side, so that is what is parallel attack. Because this is almost parallel to this pseudo axial hydrogen. And if it comes from the bottom side, now it is anti to the pseudo-axial hydrogen, so that is what is called anti-parallel attack, that is one.

And then what we are saying about the product conformation, that when parallel attacks takes place this carbon goes up, so you have a down carbon then in the level of this double bond a carbon, and when the reaction takes place it goes up. So, that assumes a kind of twist boat conformation.

On the other hand, if there is anti-parallel attack, that means from this side, then what happens, this is the down carbon then followed by the carbon in the plane of this double bond. But now the double bond is broken, so this carbon comes down. So, what you are getting is basically a chair, I can now force this. As it goes down, you see that it is slowly adopting chair conformation.

On the other hand, if it goes up, if this carbon goes up, then that is adopting a kind of boat type of twist boat conformation. So, that is the visual thing that in terms of the model you can explain the parallel and the anti-parallel approach.

Look at this anti-parallel approach, one thing I can show you is that, when the approach takes place from this side, you have this hydrogen if there is a substituent here, which is kind of again a pseudo-axial hydrogen, so there could be and there is another one, another pseudo-axial substituent here, then they are could be seen here 1, 3 di-axial interaction. So, anti-parallel attack sometimes may be inhibited by this 1, 3 di-axial interaction.

On the other hand, the parallel attack does not have, because this is the axial one but that is in the 1, 4 position. So, we will discuss the problems involving this parallel and anti-parallel attack in our next lecture series, when we discuss the bromination and the alkylation of cyclohexanone, especially the ones which are present in decalins and steroids systems. Thank you.