Essentials of Oxidation, Reduction and C-C Bond Formation. Application in Organic Synthesis

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Lecture – 30

Stereochemistry and Mechanistic Aspects of McMurry Coupling and Metal Mediated Reduction of alpha, beta-Unsaturated Ketones

Hello everyone, welcome to today's lecture, I hope you had an opportunity to go through the last class material and we can have a brief recap of what we did last time.

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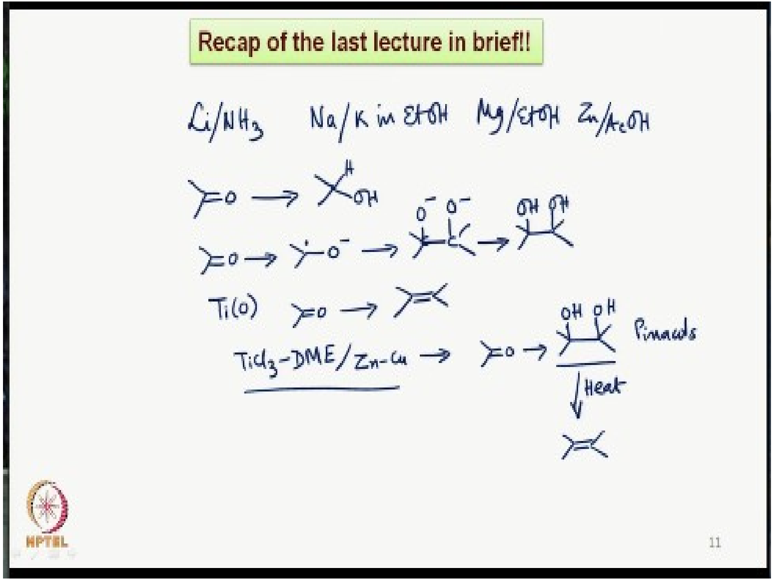

Recap of the last lecture in brief!!

So, we discussed the dissolving metal reductions in the last class where we had seen that reactions with lithium in liquid ammonia or say, sodium or potassium in alcoholic solvents like ethanol or magnesium in ethanol or some reactions with zinc in acetic acid. These are the reactions which allow the reduction of ketones to the corresponding alcohol and we discuss in great detail. How these reductions allow the thermodynamically more stable trans product in cyclic cases.

We also saw that the reaction proceeds via radical anion and this radical anion can allow the coupling to take place. And we can form the C-C bond easily and you can get a dianion of this type which can lead to the formation of 1,2-diol. We also saw that titanium zero permits the coupling of the carbonyl groups to form the corresponding olefin at one stretch in one go.

But also, we saw that titanium trichloride and DME together and then in the presence of zinc copper couple leads carbonyl in groups to form the corresponding diols. So, one can easily carry out the reaction at relatively low temperature with this system here and one can get diols. If one heats the same reaction by heating condition, then of course, one can get the olefin. This is what we discussed in the last lecture that titanium zero.

If it is done under normal McMurry coupling olefination conditions, then directly we get the olefin. On the other hand, if one wants diol to form the pinnacols to form, these are basically pinnacols. And if that is what is required, then the reaction can be carried out at relatively low temperature and with titanium zero form from TiCl3 DME crystalline complex with the reduction with zinc copper couple.

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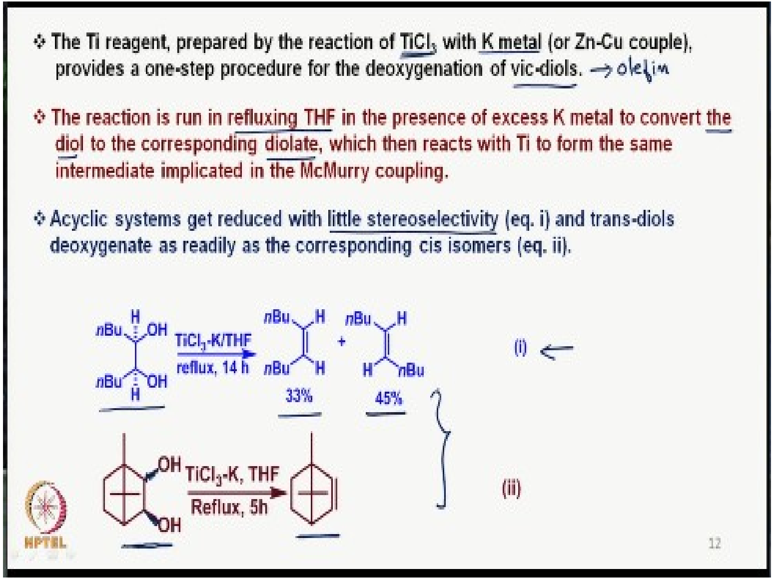

- The Ti reagent, prepared by the reaction of $TiCl_3$ with K metal (or Zn-Cu couple), provides a one-step procedure for the deoxygenation of vic-diols. → olefin
- The reaction is run in refluxing THF in the presence of excess K metal to convert the diol to the corresponding diolate, which then reacts with Ti to form the same intermediate implicated in the McMurry coupling.
- Acyclic systems get reduced with little stereoselectivity (eq. i) and trans-diols deoxygenate as readily as the corresponding cis isomers (eq. ii).

So, the same zinc copper couple, either we can also use a potential metal as such and with the TiCl3, it allows deoxygenation of vicinal diols to the corresponding olefin, if the reaction is carried out at a high temperature. That means if the reaction is run, refluxing THF with excess of potassium metal, the diols are essentially converted to the corresponding diolate.

And they react with titanium to form the same intermediate, which is implicated in the McMurry coupling. We will discuss that in a minute, how the 2 are converging into the same intermediate. But, if we start with acyclic systems, such as here, we can see that there is not much of stereoselectivity that is observed. This is the equation 1. And trans diols deoxygenate as readily as the corresponding cis isomers, for example, here is a mixture of cis and trans.

So, if this is beta oriented, for example and this is a mixture, so, we can expect both cis and trans diols. But, then a mixture of cis and trans diols directly gives the corresponding olefin. This is what indicates that the mechanism must be involving in a non-concerted fashion. So, you have a diol which is stereo chemically properly oriented, however, it leads to the 33% formation of cis olefin and 45% formation of the trans olefin.

So, when the reaction is carried out in such a way that the vicinal diols are allowed to react under the same conditions in which we had originally formed the diol, but now, we start heating then the corresponding olefins form. So, these 2 cases are very good indications of how the reactions may proceed and therefore, it will reflect on the mechanism of reaction.

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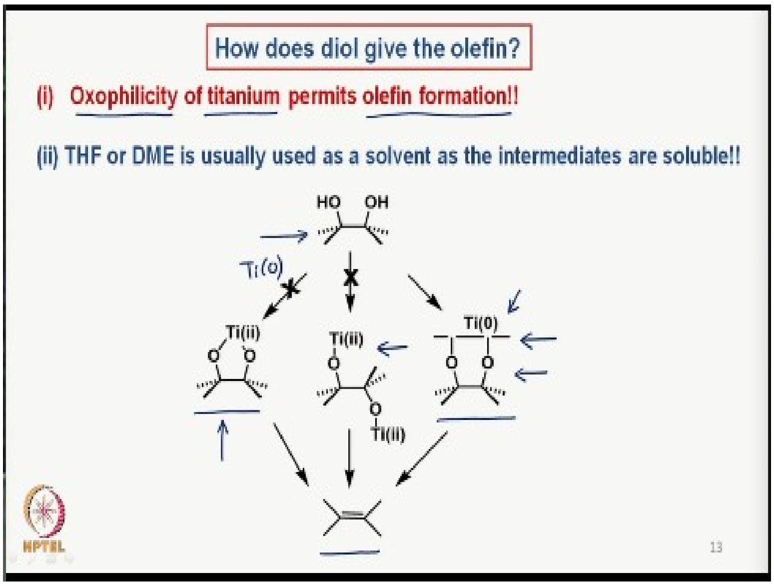

How does diol give the olefin?

(i) Oxophilicity of titanium permits olefin formation!!

(ii) THF or DME is usually used as a solvent as the intermediates are soluble!!

So, a lot of work has been done by McMurry and others. And how does this diol give the olefin? So, essentially first thing is that there is an oxophilicity of the titanium that allows the formation of the olefin, because, there has to be a tendency of the oxygen of the diol to interact with the titanium. So, there are 3 such possibilities which have been implicated. One is that we start with diol like this 1,2-diol, it could form acyclic trasitions or intermediate of this type where only one titanium is involved.

And therefore, we have 2 oxygens of the diol interacting with one titanium and that is in titanium2 form that is if we take the diol and have only one titanium zero giving 2 electrons and then combining by the loss of hydrogen. So, we can get this type of cyclic 5 member intermediate or a species of this type. The other possibility is that each of the hydroxy group interacts with the titanium and forms an intermediate of this kind, where the 2 oxygen titanium bond this particular part of the molecules are away from each other.

So, this also can lead to the formation of the olefin here and this also can lead to the formation of the olefin here. And the third possibility is that there is a basically simple co-ordination that means the OH or the O minus that is formed during the reaction simply coordinates, simply attaches itself to the titanium zero part. And then of course, there is a transfer of the oxygen to the titanium.

Of course, when we talk about these and if there is a formation of the kind of species under the surface of the titanium zero, there will be titanium one; there will be titanium 2 and of course, titanium zero. So, what these possibilities suggest that we can expect such intermediates which are likely to form, how do we rule out one or the other and see which exists or which forms the best way.

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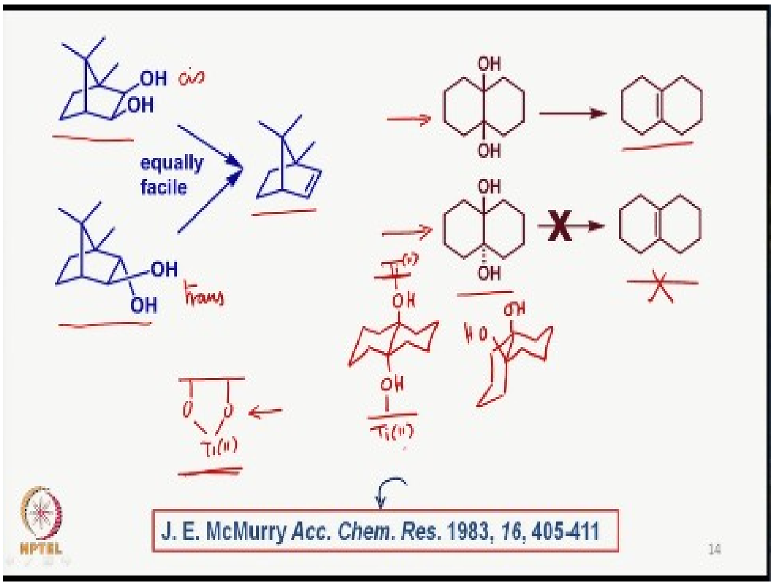

J. E. McMurry *Acc. Chem. Res.* 1983, *16*, 405-411

Now, many experiments have been done and this McMurry has written a review, which you can check it here, Accounts of Chemical Research in 1983. So, what happens in here is that McMurry took 2 different types of rigid and locked alcohols which can easily come from this norbornane system. And one of them is a cis diol and the other one is a trans diol.

So, obviously, one can expect that the intermediate that we discussed, where we had this oxygen and oxygen. And then coming on to the same titanium to coming and forming this type of intermediate. One can expect that to happen with the cis diol. But, it was found that both cis and the trans diol, they are equally reactive and they form the corresponding olefin without any problem.

So, it is very clear that the formation of such intermediate. It is very unlikely because both of them react equally facile. If there was difference, then of course, the trans would have reacted slower than cis, because formation of such 5 member intermediate would be better and easier with cis diol. The other reaction that they carried out was this cis diol and trans diol and it was found that the cis diol react very easily and the trans one does not react at all.

So, what does it mean? If we look at the conformations of these diols, we can see that the 2 hydroxy group in the trans diol would be here like this. And the second possibility which we considered earlier was that each hydroxy groups coordinates to the titanium species here, where the 2 of them are interacting separately. But then that obviously is not happening because this is not reacting.

So, there is no reaction here. It means there is no product formation; it means that this binding of the oxygens to individual titanium is not possible. On the other hand, if we take the cis diol where we can anticipate that such a reaction will allow the OH here and the OH here both are cis to each other, then of course, they can go to the same intermediate as this, but obviously, they need not go through this 2 different titanium binding. So, these 2 possibilities are completely ruled out.

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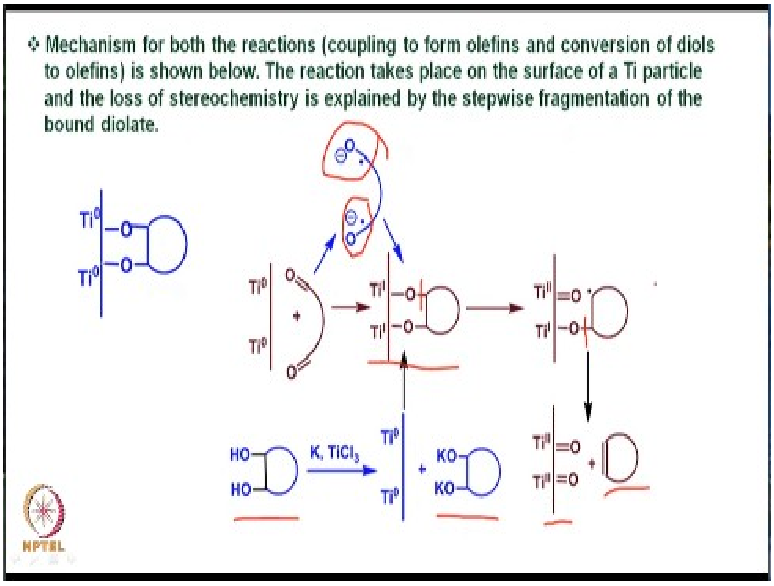

- Mechanism for both the reactions (coupling to form olefins and conversion of diols to olefins) is shown below. The reaction takes place on the surface of a Ti particle and the loss of stereochemistry is explained by the stepwise fragmentation of the bound diolate.

Now, the third type of possibility of the mechanism basically involves attachment of the oxygen to the titanium surface and that eventually leads to the formation of the olefins. Now, for both the types of reactions that is coupling of carbonyl compounds to form olefins and conversion of diols to olefins can be considered and that is shown below here, the reaction takes place on the surface of the titanium particle.

And we can also explain the loss of stereochemistry by invoking stepwise fragmentation of the bound diolate. Now, what is happening is the titanium surface in which generally we show as titanium zero, but it also has titanium +1 and titanium +2 species, when a carbonyl compound or a dye carbonyl compound of this kind, where 2 carbonyl groups are attached to the same molecule, when such a molecule comes in contact with the titanium surface.

Then, there is a transfer of an electron from titanium to carbonyl carbon presenting into a radical anion of this particular type here, as I have shown on the top. And in a similar fashion, there is a transfer of an electron from the titanium surface to the other carbonyl leading to another radical anion. Now, these anions on the oxygens will of course, have an interaction or attachment to the titanium surface and the radicals which are on the carbons would couple to form a carbon-carbon bond.

Now, since the titanium surface has lost an electron, so, we are showing it here as a titanium 1 and of course, then you have the oxygen titanium attachment. Now, what happens is, we then allow or we invoke or we propose that there is a carbon oxygen bond cleavage resulting into a radical formation. And of course, the oxygen radical would take an electron from the titanium surface. And the titanium surface will become titanium 2 for example, from titanium 1 to titanium 2 and there is a titanium oxygen double bond.

And then, in a stepwise manner, the second carbon oxygen bond then would break and that leads to another radical here and of course, oxygen radicals. The oxygen radicals will form the titanium oxygen double bond, the way I have shown it up and the radical, which is generated here would couple with this radical to form this particular olefin as the final product.

Now, this titanium oxygen double bond would lead to what is proposed to be a titanium dioxide eventually. Now, obviously here the stepwise fragmentation has been suggested mainly because it allows you to loose the stereochemistry because, if we start with a particular diol of a particular stereochemistry, it is found that eventually it looses the stereochemistry and that is the reason why stepwise Fragmentation has been proposed.

Now, if we take a diol of this kind and treat it with the potassium and titanium trifluoride under the McMurry coupling conditions, then of course, we expect that potassium diolate will form and it will have similar type of interactions on the titanium surface as we have discussed that the titanium zero surface not only has titanium zero particles, but also other low-valent titanium particles like titanium+ 1 or titanium+2.

And therefore, the interaction of the protection dilate with the titanium surface leads to similar type of intermediates of this kind, which then eventually lead to the formation of the olefin and of course, titanium dioxide or similar type of titanium species, but this is how the mechanism is perceived and this is the mechanism that is believed to be operating in this particular McMurry coupling case.

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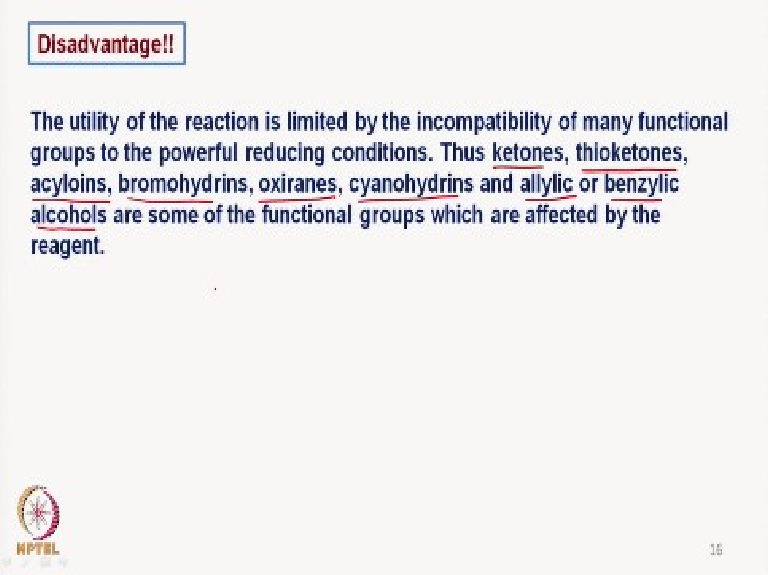

Disadvantage!!

The utility of the reaction is limited by the incompatibility of many functional groups to the powerful reducing conditions. Thus ketones, thioketones, acyloins, bromohydrins, oxiranes, cyanohydrins and allylic or benzylic alcohols are some of the functional groups which are affected by the reagent.

What is the disadvantage of this McMurry coupling is that the reaction is limited because many functional groups are not easily tolerable under these conditions. So, they can also get reduced because it is powerful reducing system. Thus, the ketones, thioketones for example, ketones, thioketones, acyloins, the hydroxy ketones, bromohydrins, oxiranes that is epoxides, cyanohydrins, allylic or benzylic alcohols are some other functional groups can also get affected by this particular reagent.

Though, there is a disadvantage, but at the same time, the advantage is that we can easily carry out the coupling either in an inter-molecule fashion or an intra-molecular fashion, we can stop at the diol stage, we can also make an intra-molecular coupling and get medium sized ring or larger rings. And of course, we can convert the diols to the corresponding olefins using the same condition but by refluxing or heating at high temperature under the same reducing system conditions.

So, there are advantages and there are also disadvantages, but, because of the simplicity of the reaction, it has been used in making different types of olefins or diols using this reaction.

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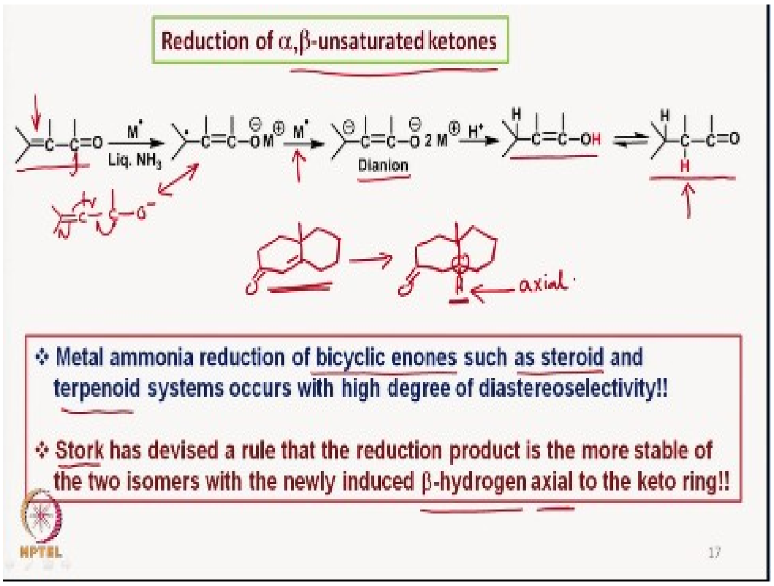

Reduction of α,β-unsaturated ketones

- Metal ammonia reduction of bicyclic enones such as steroid and terpenoid systems occurs with high degree of diastereoselectivity!!
- Stork has devised a rule that the reduction product is the more stable of the two isomers with the newly induced β-hydrogen axial to the keto ring!!

We go for the next part of this particular dissolving metal reductions, where we take say for example, sodium or potassium or lithium liquid ammonia conditions and try to look at the reductions of alpha, beta-unsaturated ketones. We had seen the normal reductions of cyclic ketones or a simple ketone where reduction gives the corresponding alcohol. Here, if we take an alpha, beta-unsaturated ketone like this and transfer an electron from lithium or potassium or sodium.

Obviously, first thing will happen is the transfer of the electrons occur at the carbonyl carbon here. So, you can anticipate to form something like this. Here, you have an O-and you have an electron here, which of course, will go to this particular carbon atom and form this intermediate of this type. So, we have a possibility of such a movement of, here is an electron. So, you can anticipate such a resonance structure of the radical anion to form.

And when second electron is transferred by the metal here, we can expect that a dianion is formed and this dianion protonation gives the corresponding enol. Thus, enol will obviously be in equilibrium with the corresponding ketone. So, under these conditions, what is found that reduction of an alpha, beta-unsaturated ketone with metal liquid ammonia system will leads to the formation of the corresponding saturated ketone. That means the only double bond that has been reduced, this is a very important reaction.

And especially, it is very useful when there are bicyclic enones or in a system like steroids and terpenoids, we look at the reductions and it helps in designing the stereochemistry of the molecule. So, you have a system like this here, say, you have a ketone of this type and then how does the reduction occur. Now, obviously, we expect the reduction should give the corresponding ketone.

But more importantly, what is the hydrogen that is coming here, what is the stereochemistry of the hydrogen at this stage that is what is most important. And in that respect, a lot of work has been done and Gilbert Stork at Columbia University has devised a rule that reduction product is the most stable of the 2 isomers with the newly induced beta hydrogen being axial to the ketone ring.

For example, if this particular hydrogen which is what is expected to come after the reduction, it prefers to remain axial. So, this particular hydrogen is axially oriented in the ring that contains the ketone. We will see how does this happen.

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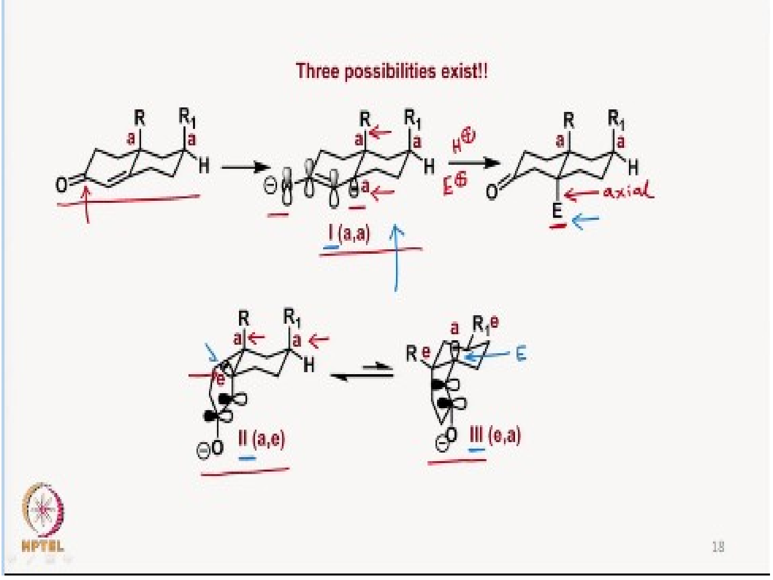

Three possibilities exist!!

So, there are essentially 3 possibilities. So, we can write that bi-cyclic ketone into this particular conformation. And as we can see, that one of the left side ring is obviously half chair and the other one is expected to be chair and therefore, we have written like this particular way of chair and the normal chair and once the electron is transferred to this particular carbon atom, the anion, dianion which we had discussed earlier would be something like this here.

And we can expect that the anion at the junction would be axially oriented and such an intermediate when it gets protonated or when we can also use either a proton as an electrophile or we can use any other electrophile which you can term it as E+, then the electrophile comes in this fashion and what we are expecting is that is what Gilbert Stork suggested that the proton or the electrophile would come in the axial orientation.

Now, we can write in a slightly different way, that is we can write that the conformation of the dianion maybe somewhat like this, where it is cis orientation. For example, here, we had this R group axial and this 9 is also a and therefialore, 1,2-di-axial would be trans relationship. But now, we are talking about this being axial and this being equatorial. Therefore, we are talking about a cis declain type of system.

We can also write slightly differently another declain, which is also cis and in this particular case, for example, this was axial here; this was also axial and this is equatorial oriented. The anion is equatorial oriented. So, we can write flip the rings in such a way that these R 1 is equatorial, R is equatorial which were earlier axial and since the anion was equatorial, now it has become axial. So, we have basically flipped.

We have got another confirmation, but cis confirmation of course, cis declain system but in a different conformation. So, cis expect these 3 types of orientations, one being this number one here, which is trans declain type, then we have second, which is cis declain type and the third also cis declain type. So, these are the 3 possibilities, we exist. And here of course, the electrophile comes in an axial fashion and here as you can see that this will give an axiall electrophile and this will give an equatorial electrophile.

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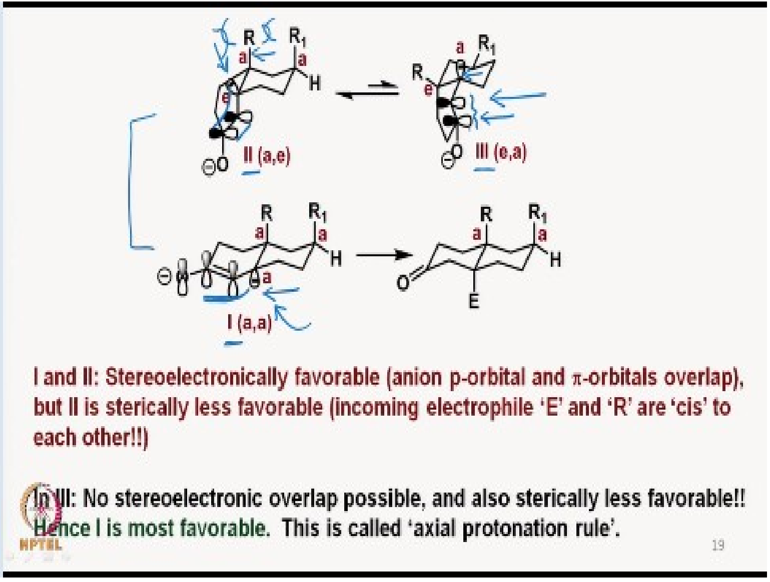

I and II: Stereoelectronically favorable (anion p-orbital and π-orbitals overlap), but II is sterically less favorable (incoming electrophile 'E' and 'R' are 'cis' to each other!!)

In III: No stereoelectronic overlap possible, and also sterically less favorable!!
Hence I is most favorable. This is called 'axial protonation rule'.

So, let us see which one would be the best. So, we have this number 2 here, we have number 3 here and we have number 1 here. If we look at number 1 and number 2, if we take these 2 cases, they are stereoelectronically favourable that is because the anion p-orbital either here or here for example and you consider the pi-orbital of the double bond, this is the double bond, this is the double bond, if we look at the pi-orbital, so, they are all planar and this is also essentially planar around.

So, there will be a proper overlap and stereoelectronically, these are favourable conformations. So, the only other problem is that when the electrophile either a proton or any other electrophile when that approaches as you can see that in the second case, where the R group here is axially oriented and when the electrophile approaches from the equatorial side, we are talking about 1,2-axial equitorial which is cis and there will be a steric hindrance.

In addition to the steric hindrance that of course, one has it here, but that is anyway existing in all the cases. So, when the incoming electrophile comes in and approaches this particular anion, you have a steric hindrance offered by the R group, which is at the junction. Whereas, that is not the case in this case here because the incoming electrophile is coming from the axial side from the below and has nothing to do with the R group or R 1 on the top.

On the other hand, if we take the third confirmation here, like this, we can see that the anion, there is no stereoelectronic overlap possible if we look at the anion which is axially oriented and that is actually orthogonal to the double bonds p-orbitals or the pi-orbitals which are here. So, basically there is no overlap between the p-orbital containing anion and the pi bond; there is no overlap at all.

So, stereoelectronically, it is not possible and also if you look at the approach of the electrophile to this particular anion, then also you have, there is a cis interaction or the 1,2 orientation will be like a axial equatorial, this is going to be actual and therefore, there will be a steric hindrance here. So, the third one is the worst among the three that is both stereoelectronically as well as sterically, it is not feasible.

And therefore, the only way reaction occurs is via the conformation of type 1, which leads to the formation of the electrophile coming in from the axial side and that is what is in conformity with the Stork’s rule. So, we will stop it at this stage and will take up other aspects of reduction in the next class. You can study these reductions carefully and we will discuss it during our question answer if you have any questions. Thank you and bye.