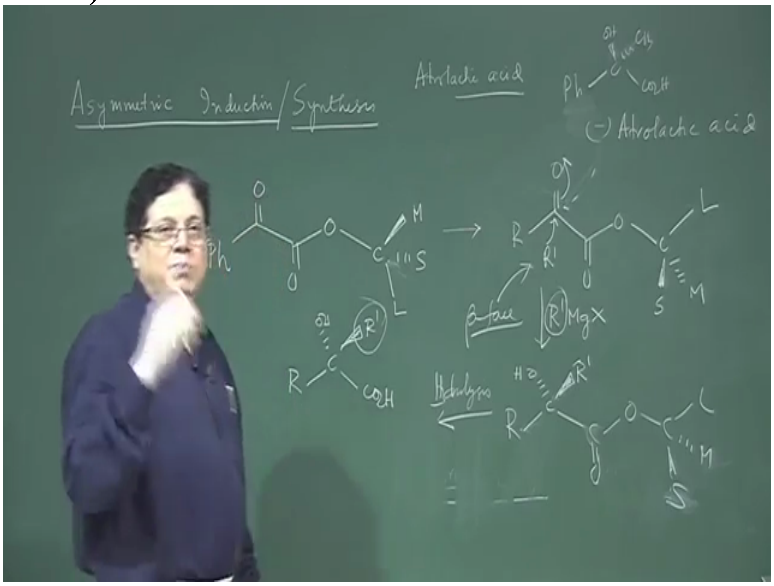
Course on Stereochemistry
Prof. Amit Basak
Department of Chemistry
Indian Institute of Technology Kharagpur
Mod08 Lecture 38
Asymmetric Induction (Contd.)

(Refer Slide Time: 0:31)



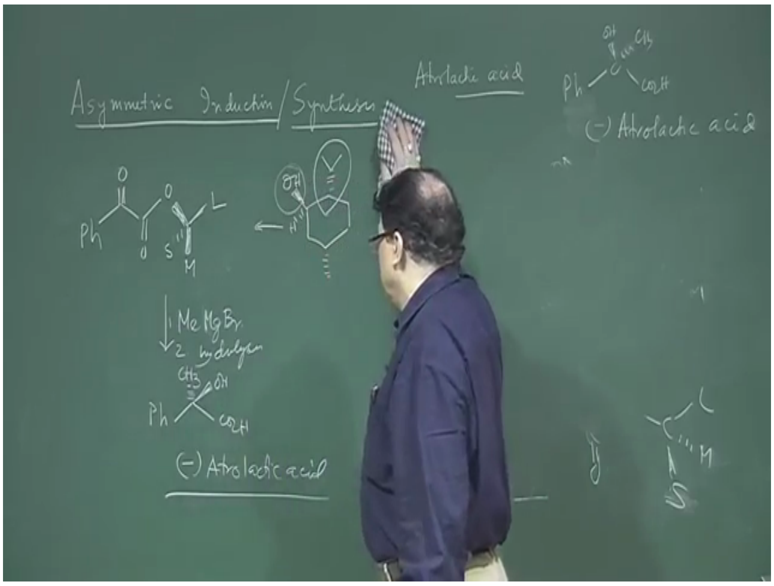
Okay, now let us, tell something about this Prelogs rule and work out a problem on based on Prelogs rule, okay. So what is Prelogs rule that if you have an alpha keto-ester like this attached to an alcohol ester of an alcohol, which is asymmetric at the alcoholic carbon center remember. So in this alcoholic carbon center you will have three groups. So one is in the plane, you have three groups another is in the, one is beta, one is alpha and the other is in the plane, actually you should write this way, okay. So these are the three groups. Now suppose this is your large groups, this is your small group. This is your medium group, okay.

Now according to Prelog the preferred conformation, in which this molecule reacts will be this will be where the Cl is syn to the ketone carbonyl O-C and then L is here that means you turn it up and down. So L 180 degree L goes there. So S becomes now beta and M becomes alpha, okay. Now you add suppose (())(1:53) reagent R dash MgX. So according to product, the R dash will now approach preferentially from side of the smaller group, okay. So if that happens, actually you should show it from this side R dash attacking here and this here. So it goes preferentially, from the beta face okay, because the beta face is occupied by the small group. So your ultimate product will be R-C, so OH will be alpha. If the nucleophile comes in a beta position from the beta face. So that will be alpha and the nucleophile will be nucleophile is R dash, the alkyl part of the (())(2:37) reagent and this will be CO-O and then this alkyl (())(2:45) L M and S, sorry S.

Now you hydrolyze this okay. So hydrolysis, so if you hydrolyze what you get is RCOH, R dash and then CO2H. So it is a hydroxy acid. Now this hydroxy acids some of these hydroxy acids in those days, their configuration was known by correlation studies, okay. Their configuration some of the acids are known like atrolactic acid or mandelic atrolactic acid. What is atrolactic acid that is ph-C-OH-CH3-CO2H. So if atrolactic acid is plus or minus then that configuration is known, like if OH is beta and methyl is alpha then that is minus atrolactic acid, okay that means the other is the OH alpha and the methyl beta. So this was known. So what was done then?

So if you want to know the configuration of an alcohol. So what you do? Take a phenyl here, so take phenyl, so then it becomes a phenyl glyoxalic acid ester, okay, but the general term is still remain. It is an alpha keto alpha keto-ester, okay. Now this is phenyl and then if you instead of R dash, so if you take now for R dash if you take methyl magnesium bromide then what you end up will be the atrolactic acid and since atrolactic acid plus or minus is known. So you just check what atrolactic acid is obtained, if it is plus you know what is the configuration if it is minus you also know what is a configuration and then you work backwards to find out the configuration of the alcohol, suppose I give you one example. This was first initially applied to a compound which is call menthol.

(Refer Slide Time: 5:15)



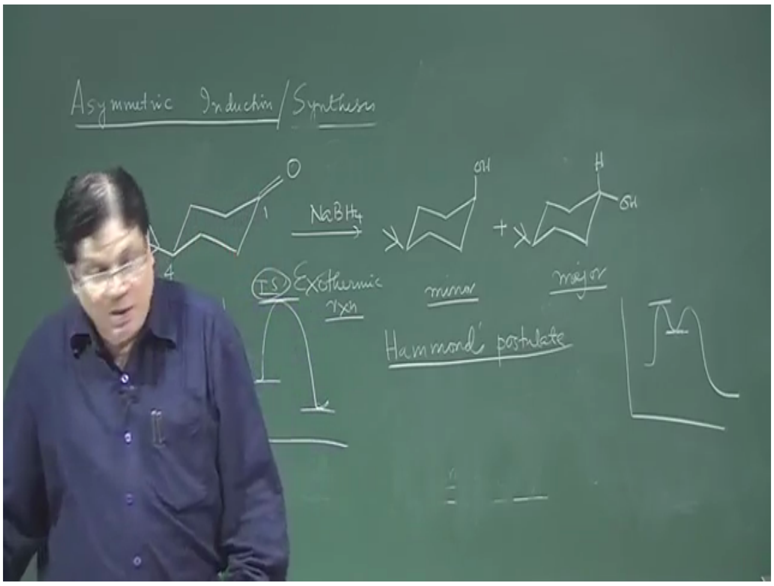
Now menthol has a structure, now we know what is the stereo chemistry of all the groups in menthol. So this was the menthol is actually is OH and there is a methyl, I think there is a methyl here, okay. So now we are interested in when people are interested that what is the configuration of this OH. So how did they do? They first made that ester that phenyl glyoxalate ester, okay and then also, try to check what is the, so this is because, it has got the isopropyl and this is the hydrogen. So that will be the L group the large group and this is the medium group and this is the small group, because of the hydrogen. So when you convert it into this ester, you know this is the preferred conformation Cl is in the syn direction with the carbonyl.

So now this methyl magnesium bromide what it will do, the methyl will come from the back side, because the small is in the back side. So ph so ultimate product after hydrolysis is ph then CH3, because the methyl comes from the back side OH and then CO2OH. So that is minus atrolactic acid, so once they know that they got the minus atrolactic acid. So they can immediately work backwards and find out what is the configuration of menthol carbon containing the OH okay.

So that was beautiful this disposition of Prelogs rule and many of the alcohol including steroids the geometry of the stereo chemistry of the carbon bearing alcohol was proven by applying Prelogs rule, okay. Problems will be given in a different way that you have been given an alcohol and then you can ask what is the ultimate product or you can give the ultimate you have been given the ultimate product and you have you will be ask to work backwards to tell the what is the configuration of the original alcohol, okay, I hope this is clear. This is what Prelogs rule.

Now these are more or less outdated not from historical perspective and understanding of stereochemistry, these are important, outdated, because now there are spectroscopic means NMR spectroscopy, which can tell from the coupling constant of adjacent carbons that what is the stereochemistry of different systems of specially vicinal carbons and then X-ray crystallography is there that has been improved so much that now stereochemistry of molecules can be determine quite easily, but these are important these are very various historical milestones as we say in stereochemistry, because this has enriched the subject of stereochemistry.

(Refer Slide Time: 8:59)



Now we move on to a cyclic system whatever we are dealing with the acyclic system. Now we move on to a cyclic system and very interesting that we have seen that what happens to the carbonyl when you add a nucleophile when there is a adjacent stereo genic center, we have like crams rule, felkin model whatever it is, depending on the substituent you get the major product, okay. Now by the way those are all examples of asymmetric synthesis; however the degree of asymmetry may not be very high in those cases, but later on, today the asymmetric synthesis has reached new high where one compound one isomer is obtained almost in close to 99 percent enantiomeric excess, okay.

Now we are talking about what happens to the reduction or addition of a nucleophile to a carbonyl in a cyclohexane system, which is locked in a conformation. So suppose, I take tersary butyl cyclohexanone 4 tersary butyl cyclohexanone. So this is a 4^{th} position. Now if I add a nucleophile, suppose my first reaction is that I try to react with sodium boro-hydried, okay carbonyls are easily reduced by sodium boro-hydried and how many products I should expect, I expect 2 products one is the axial alcohol and the other is the equatorial alcohol.

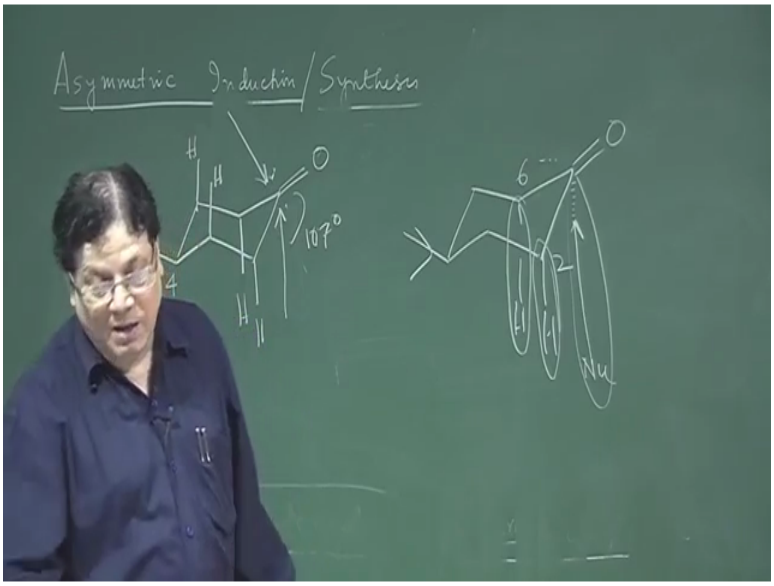
The question is which one is the major product, okay apparently the problem looked very simple apparently, because in sodium boro-hydried reduction of this, this is the major product and this is the minor product and you might say that, because this is more stable than this. So what is the big deal out of it, because the major the more stable compound is obtained in major amount; however there are problems, always there are scientist, who look at very carefully that what are you saying is true or not, okay.

Now reaction of sodium boro-hydried to a carbonyl is a highly exothermic reaction. So if that be the case highly exothermic reaction. So the energy diagram will be what is an exothermic reaction? The product lies lower, okay. So this is cyclohexanone, this is the cyclohexanol and this is the transition state. So if you argue on the basis of stability of the product for an exothermic reaction you are making a mistake, because there is a rule or there is a postulate, which is call Hammonds postulate**.** What Hammond said that, because we really do not know the exact structure of the transition state? How does it look like, it is so transitory in nature that it is very difficult to exactly ping point the transition state or know it structure, but we have some approximation to know the what are the approximate? What is the approximate structure of the transition state? How does it look like, okay?

Now according to Hammond postulate, the transition state will look like, the closest minima in the energy profile diagram. So in this case, you have two minima. One is this substrate, the cyclohexanone another is the product that is cyclohexanol, but since this is closer to the cyclohexanone. So this transition state will cannot resemble the product. So this transition state cannot resemble the product. It is not product like transition state. So if it is not product like transition state, you cannot base your argument on the stability of the product. Had the transition state been product like then your stability of the product will dictate the which is the major which is the minor product, but here there is a problem, because the transition state is reactant like okay, just to clarify a little bit about hammonds postulate. This is a one-step reaction, but if there is a multiple step reaction then this transition state will resemble mostly, because it resembles the nearest energy structure energy minima structure.

So this resembles the intermediate of the reaction and this also a resembles the intermediate of the reaction, because this is the closest to the highest point that means the transition states. So that should be clear that is Hammond postulate. So the problem remains here that this is exothermic reaction. So whatever reasons you are giving cannot be based on the stability of the product.so what is the actual reason for getting the equatorial compound as the major product.

(Refer Slide Time: 14:22)

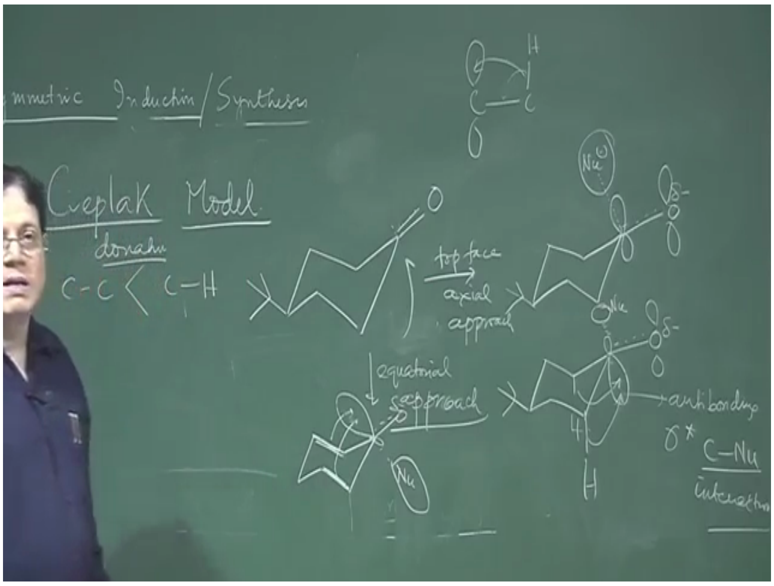


Now to interestingly, if you want to get the equatorial compound, the hydride should approach from this side and while approaching from this side, people will argue that there are hydrogens in the 1, 3-diaxail position, so that will put steric strain to the approach of the hydride okay, but that is giving the equatorial alcohol, on the other hand if the hydride approaches from this side, from the equatorial face, which is much easier to approach you get the axial alcohol. So apparently it appears that the axial alcohol should have been more, but it is not, there is always a preferential attack of the hydride from this side from the from the axial face and not from the equatorial face. In spite of the fact that there is these hydrogens at the 1 and the 3 and the 5 positions of the carbonyl which can pose a steric strain to the approach of this nucleophile, okay.

Then what is the then something must be happening to stabilize the transition state that is formed from the axial approach, okay mean while felkin said felkin tried to give an argument and he said that although, it is true that when it approaches from this side. These hydrogens these hydrogens come in the way of the approach that means they offers steric strain, but it is not true that when it approaches from the equatorial side, it does not suffer from any strain. He actually introduce that barge donage principle. He said that the nucleophile does not approach in a 90 degree fashion. It approaches in an angle of 107 degree that is the barge donage trajectory and if it does that then what happens? See this is your cyclohexanone, may be I can do this. So what I was talking about is right. This is a cyclohexanone. So these are the carbonyls are the 1, 3 positions are not here.

Let me make the 1, 3 positions clear. So this is the red ones are the 3, 5 positions, so the red ones are the 3, 5 positions and if the nucleophile approaches from the top then this is a cyclohexanone. If it approaches from the top then these hydrogens will offer steric hindrance. Now what happens felkin said that it is not true that the equatorial position is also very free, because the nucleophile does not approach, in a perpendicular direction rather, it approaches at angle of 107 degree, which is according to barge donage principle trajectory, okay. So if it does that you see, there is eclipsing interaction between these hydrogens. So it is more inclined towards this equatorial the axial hydrogens when it approaches from the equatorial position. So just to show it in the board. So when it approaches, so what is felkin saying is that when it approaches from the equatorial face, so this is a 2, this is a 6 carbon, so this is your nucleophile. So now there is this bond formation transient bond formation of the nucleophile, which is now eclipsed by these hydrogens the C-H hydrogens the axial hydrogens at C2 and C6, so that is felkins model, okay.

(Refer Slide Time: 18:17)



Later on later on, there is another person, whose name is Ceplak, I will quickly do that Ceplak, he gave model which was well accepted by the community. He gave a model a based one based on orbital overlap, because I told you that all reactions are govern by what, there are two forces that govern, the stability of the transition state, one is that stereo electronic factor, which compiles the orbitals to be lying in in a particular geometry so that maximum overlap is possible. The other is steric factor which sometimes stabilize destabilizes the transition state. So these two factors that need to be considered while considering the stability of the transition state, okay. The more the overlap in the transition state the better, okay.

Now according to Ceplak, he gave a very interesting model. According to him that if you have this carbonyl, now when the nucleophile approaches from the top. So this carbonyl, there will be partial breakage of the carbonyl. So what is the transition state look like? The transition state will look like the Tau elongated delta minus and this is the new bond that is being formed at an angle of say107 degree. The barge donage trajectory, okay.

Now what Ceplak says that when the nucleophile approaches from the top, okay. This bond is interacting with the p orbital of the carbon p orbital, okay the nucleophile has some kind of orbital, suppose and that is interacting with this orbital with the p orbital. Now any interaction will lead to a bonding interaction another is anti-bonding interaction, okay. So when it is trying to interact with this orbital. So there will be a bonding interaction where these two orbitals are in phase and there is an anti-bonding interaction. So in the anti-bonding seen arrow what happens? You know in the anti-bonding seen arrow, the lower lobe becomes bigger and this is the smaller and this is the nucleophile and they want to repeal each other, okay.

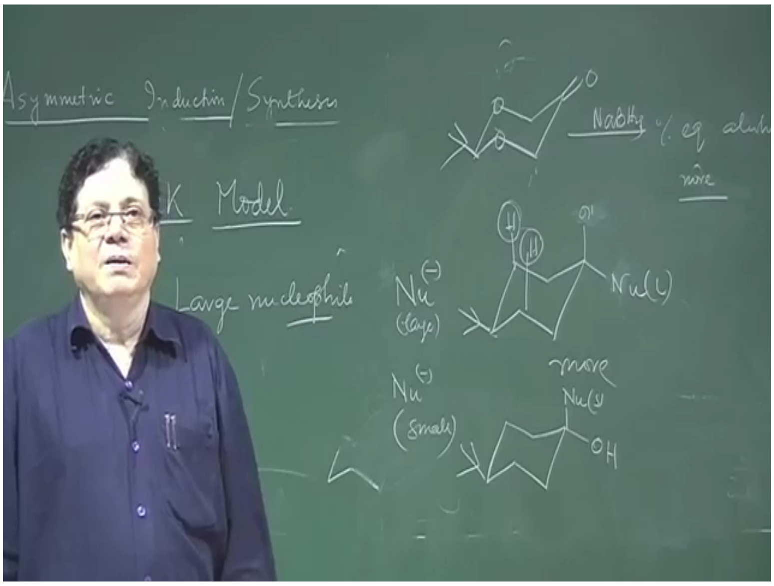
So this is the anti-bonding orbital, which has got a lower lobe at the back side, okay. So now look at these hydrogens. These hydrogens are almost nearly planar to this empty anti-bonding orbital. So what they will do like hyper conjugation, they can participate and donate the electron. This like hyper conjugation, see suppose here the carbon, which has got empty orbital and in the adjacent carbon you have hydrogen what is called a, so these hydrogens now donate here. So what you call is basically you have a no bond resonance.

So that donation comes from the C-H, in hyper conjugative fashion. So now there are two CHs they can donate to this empty sigma star which sigma star that is the carbon nucleophile interaction obtained due to carbon nucleophile interaction, okay? So when it approaches from the top, you have an anti-bonding orbital here, which is empty and that is stabilized by these hydrogens, okay. So what happens when it comes from the bottom? So when it comes from the bottom, so this is top approach top face that means the axial approach and if it is coming from the this side then it is the equatorial approach, okay. So if it is equatorial approach then what happens? You get the anti-bonding orbital in the opposite direction, because it is approaching from this side. So anti-bonding orbital (will be) will have the lobe on this side, so that will be delta minus this is dot. So this is the anti-bonding orbital, okay. This is the nucleophile and the nucleophile orbital will also be bigger on the reverse side, okay.

Now these hydrogens cannot participate in hyper conjugation, because this orbital is on the opposite side. On the other hand what can possibly participate is the C-C bond, which are nearly parallel to this to the axis of this orbital of this anti-bonding orbital, okay. So now the C-C bond can donate. Now you know that C-C bond hyper conjugation or C-C bond donation is much less than C-H bond donation. So if that be the case if that donation happens that this donation is much less, but this donation is much more. So this transition state will be more stabilized that means the transition state, which is obtained when the nucleophile approaches from the from the axial face.

So remember the anti-bonding orbital is bigger in the equatorial face means the nucleophile is approaching from the axial face. So when it approaches from the axial face then you get then you that is the reason that you get stability of the transition state by this hydrogens, hydrogen donation C-H donations like a hyper conjugating effect on to this anti-bonding orbital. Here it is the C-C bond that has to donate, but C-C bonds are very poor donors we know unlike the C-H. So ultimately this transition state is more stable than the transition state obtained by attack from the equatorial face, in which case the anti-bonding orbital has the bigger lobe on the side of the carbon-carbon, which are in apposition to interact, but that is a poor interaction. So that does not happen okay.

(Refer Slide Time: 25:20)



So generally what happens that if you do boro-hydried reduction, it is true that the alcohol equatorial alcohol is **is** produced in large amount, only when you have a very large reagent large nucleophile. So if you have a large nucleophile attacking a cyclohexanone, large nucleophile, suppose nucleophile large, okay large nucleophile then what happens? Then your steric factor then these hydrogens steric factor wins and then you get the axial alcohol more. If the nucleophile is small, so this is maybe I can write large if the nucleophile is small like the boro-hydried kind like of (())(25:59) hydride then what you do? Then you get, so it should be nucleophile, this is OH okay and this is nucleophile and you get the Ceplak model holds good there. This is small this is large, okay. So that is the fundamental principle, more over if you try to put more alkyl groups here, axial more axial groups bigger bulky axial groups then the nucleophile will always approach from the equatorial face, okay.

So that takes care of the of these type of systems. This Ceplak model is quite useful in explaining some of the some of the reduction characteristics of not carbocyclic or say a system which is a (())(26:56) type system. If I give if I ask that what is the if I take a system and do a sodium boro-hydried reduction. So it changes a little. So now it is earlier, it was C-H donation verses C-C donation. Now C-H donation verses C-O donation, okay. So C-O donation is inverse (())(27:22) than C-C, oxygen does not want to donate anything. So in this case the percentage of equatorial alcohol will be even more will be more than all carbon system than cyclohexane system. So I hope it is clear this is a Ceplak model.

So ultimately we have done this stereochemistry of reduction in acyclic systems, which are controlled in acyclic systems having stereogenic centers, which are controlled by various rules by crams rule then felkins model and now this cyclohexanone system we have the initial rules based on the stability of the alcohol, but that did not stand (())(28:13), because of hammonds postulate. Then felkin gave a model which depends on the eclipsing interaction of the carbon nucleophile bond with the axial C2 and C6 hydrogens and finally the Ceplak model, which is based on the stereo electronic effect offered by the axial hydrogens at C2 and C6, okay just donation to the anti-bonding orbital. Thank you.