Symmetry, Stereochemistry And Application
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Lecture No-42
Cram's Rule and Felkin-Anh Model

Welcome back to the course entitled symmetry, stereochemistry and applications, in the previous lecture we were discussing about Cram's rule and how Cram's rule can be utilized to identify which diastereomeric product will be formed as a major product and which will be formed as minor product in case of carbonyl addition reactions.

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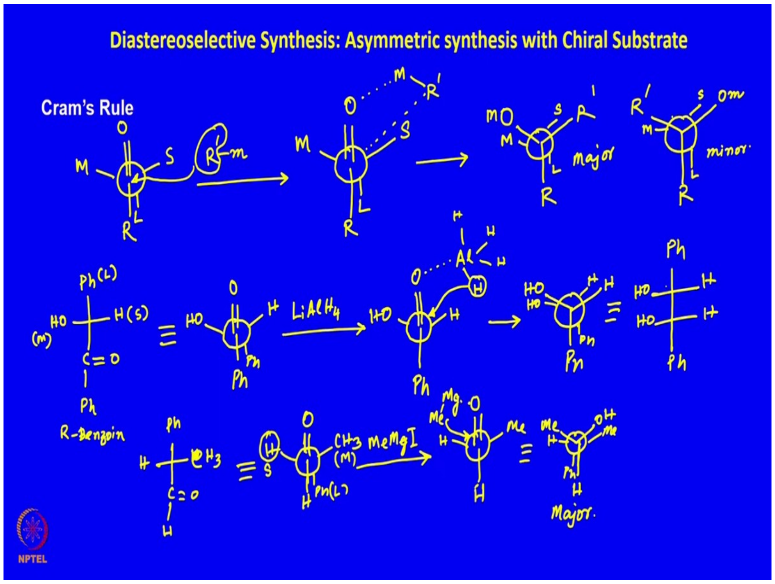

Diastereoselective Synthesis: Asymmetric synthesis with Chiral Substrate

Cram's Rule

So we have discussed two examples in the last class. So, you can see here as we are discussing the formation of the major product is based on the understanding of making the molecule like this which was proposed by Cram where he proposed that the large group will be in eclipse condition with the other group in the carbonyl compound in and it will be anti to the C double bond O.

So, with that understanding there are couple of problems and there are certain deviations from the Cram's rule.

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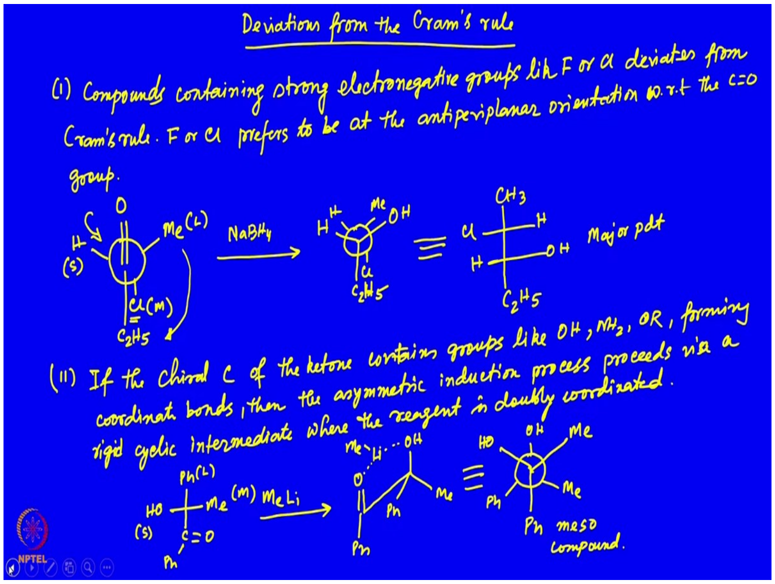

Deviations from the Cram's rule

(I) Compounds containing strong electronegative groups lik F or Cl deviates from Cram's rule. F or Cl prefers to be at the antiperiplanar orientation w.r.t the C=O group.

(II) If the chiral C of the ketone contains groups like OH, NH₂, OR, forming coordinat bonds, then the asymmetric induction process proceeds via a rigid cyclic intermediate where the reagent is doubly coordinated.

So, two well known deviations should need to be discussed here. So, the compounds containing strong electronegative groups like fluorine or chlorine deviates from Cram's rule, F or Cl prefers to be at the antiperiplanar orientation with respect to the C double bond O group even though they may not be the largest group in the substitution.

So, in such a case we may have a particular molecule which I am drawing here, may have a methyl substitution, a chloro substitution and a hydrogen where methyl is the large group chloro is the medium group and hydrogen is the small group but this is the preferred geometrical orientation of the backside carbon which is chiral carbon as chlorine is highly electronegative and it tries to stay at an antiperiplanar orientation with respect to the carbonyl group.

So, in this case if you do the reaction with sodium borohydride the product that one would get is the product where the C2H5 is here and the hydride is added from the side of hydrogen. So, you get hydrogen here and OH is formed at the right hand side, keeping the chlorine, methyl and hydrogens intact. So, it is equivalent to this particular compound which I am drawing here as the major product.

If you had followed the Cram's rule, if it had followed the orientation of Cram's rule then this methyl would have come it down chlorine would have gone here and then the reaction would have taken place from the right hand side. So, you would have got a different product different compound as a major product but in this particular case the strong electronegative chlorine deviates from the original prediction of Cram's rule and gives a different product.

The second deviation that is observed is in the case where, if the chiral carbon of the ketone contains groups like OH, NH2 or OR which are capable of forming hydrogen bonds or forming dative bonds or forming coordinating bonds, then the asymmetric induction process proceeds via a rigid cyclic intermediate where the reagent is doubly coordinated. Let us see with one such example suppose we have a compound where we have a phenyl, methyl, OH associated with a ketone obviously this phenyl is large, methyl is M and OH is a small group.

So, when we try to treat this with methyl lithium reagent, the intermediate that is formed is this one and then the addition of methyl group happens in such a way that you get the product as this one the meso isomer.

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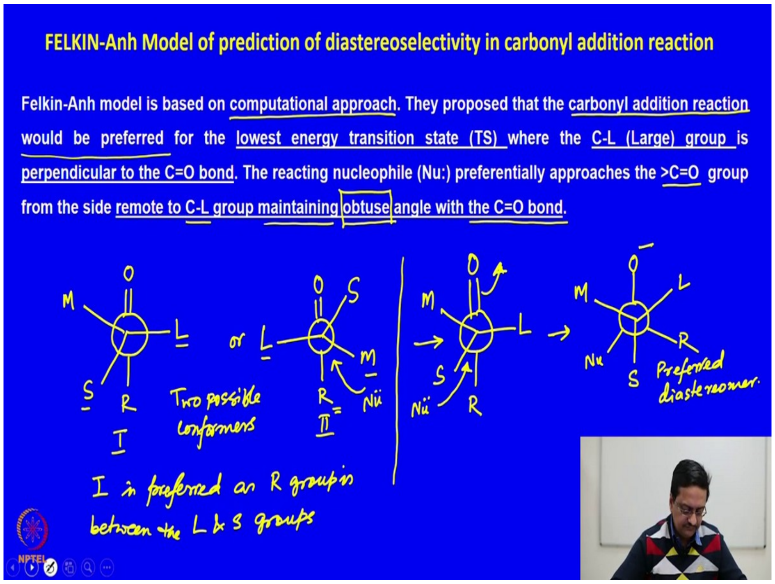

FELKIN-Anh Model of prediction of diastereoselectivity in carbonyl addition reaction

Felkin-Anh model is based on computational approach. They proposed that the carbonyl addition reaction would be preferred for the lowest energy transition state (TS) where the C-L (Large) group is perpendicular to the C=O bond. The reacting nucleophile (Nu:) preferentially approaches the >C=O group from the side remote to C-L group maintaining obtuse angle with the C=O bond.

If this reaction had undergone following the Cram's rule of addition then you would have got a different product in this case. So, based on these differences and these problems that are associated with Cram's rule and the prediction of product there is a second method or second proposal by Felkin and Anh model of prediction of diastereoselectivity in carbonyl addition reaction.

So, the model by Felkin and Anh is based on computational approach that means theoretical computational chemistry where people have used reaction mechanisms and calculated the energies of the reaction intermediates, transition states and all that and based on those energies and calculated energy values and their relationship with the substrate they proposed that the carbonyl addition reaction would be preferred for the lowest energy transition state where the carbon and L large group is perpendicular to the CO bond.

So, in the transition state the bond between the chiral carbon and the large group is at 90 degree with respect to the carbonyl bond. So, the reacting nucleophile then preferentially approaches the carbonyl group from the side remote to the C-L group maintaining obtuse angle with the CO bond.

So, let us try to visualize this using the example. So, suppose for a particular compound you can have two different orientations in the transition state. So, these two different conformers are possible at the transition state where the L group the C L bond is perpendicular to the carbonyl compound. So, now this conformer 1 and 2 among them the conformer one is preferred as R group is between the L and S groups while R here is between L and M. So, this conformation one for the transition state is favoured over the 2.

So, when that is established that one conformation is preferred then how the reaction would proceed, the reaction would proceed in a way such that the nucleophile would attack from the side of from the rear side of L which means from this side but then it has to maintain obtuse angle with the carbonyl group which means the nucleophile has to attack from here and if such nucleophilic attack happens the carbonyl group 1 would open up to give you a product which would look like this.

So, this will be the preferred diastereomer of this particular reaction of course it is possible that some of the compounds may have the unfavoured conformation too and would give rise to a product in that case that Nu would approach from this side which is the opposite or rear side of L and also makes an obtuse angle. So, you will get a different diastereomer with much lesser amount. So, let us try to see this with a real example. So, this particular compound is treated with lithium aluminium hydride.

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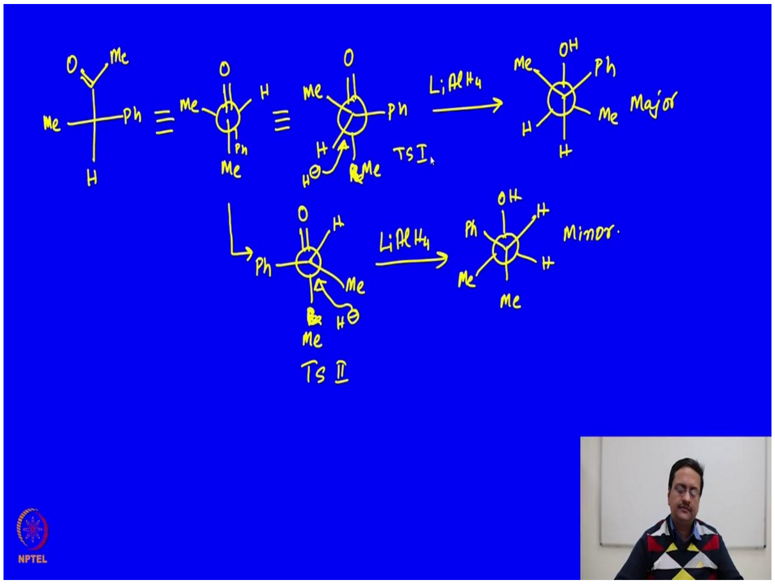

So, for this compound the preferred geometry as per Cram's rule if we try to draw would be this one but as per Felkin and Anh model if we try to draw the transition state or the geometry of the molecule it would be like this. So, when we treat this with lithium aluminum hydride the hydride would attack the carbon center from this side and give rise to this particular product. The other possible transition state for this compound would be this one and in that case if we treat with lithium aluminium hydride, H minus would attack from this corner and remember this R is methyl group. So, what will happen is we will get the minor product as this one.

So, this will be the transition state 2 and this will be the transition state 1. So, based on the transition state one can predict which enantiomer will be rather which diastereomer will be formed in excess compared to the other one.

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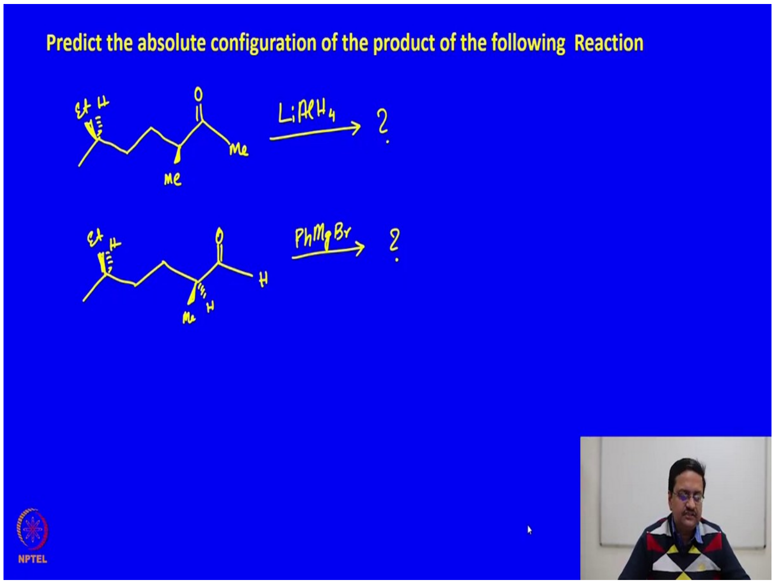

Predict the absolute configuration of the product of the following Reaction

So, now I would like to give you a couple of problems to solve yourself, this is treated with aluminum hydride what will be the product or which will be the major product of this reaction and in this reaction what will be the product of this reaction. So if you are able to solve these two problems yourself then you should solve other problems related to this Cram’s rule and Felkin Anh rule available in some standard text books.

So, those things you should practice yourself and we may discuss some other problems on this set of reactions this type of stereo selectivity and stereo specificity at a later stage if we get time in this course thank you.