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

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Lecture 34

Dynamic Stereochemistry: Conformational Analysis of Elimination and Addition

Hello. Welcome back to this course on Structure, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. In the previous lecture, we were discussing the dynamic stereochemistry that means a stereochemical issues involved in a dynamic scenario and we have seen that the major issues that need to be considered are whether the system, starting systems are conformationally rigid or conformationally biased or conformationally flexible.

In case of conformationally mobile systems, then if there are multiple pathways possible then you have to compare the energetics of the transition states. It is not that you are not actually taking care or you are not basically forced to take care of an stereoelectronic requirement for the reaction. The last example that we have discussed was 2, 3, 4 triphenyl butyric acid and its acylation, intra-molecular acylation reaction, is a Friedel–Crafts reaction.

And we have seen that there are multiple pathways because of involvement of the different phenyl rings and it is basically the transitional state energetics that will decide which one which pathway will be followed by a particular reactant. Now, we will discuss, that if there is a stereoelectronic requirement for a reaction, then you have to then you are forced to really draw only a particular conformation and see particular conformation to satisfy the stereoelectronic requirement. And then, if there are two diastereomers that you are considering then compare the relative energies of the two transition states and then come out to a conclusion that which reaction will be faster, which one will be slower.

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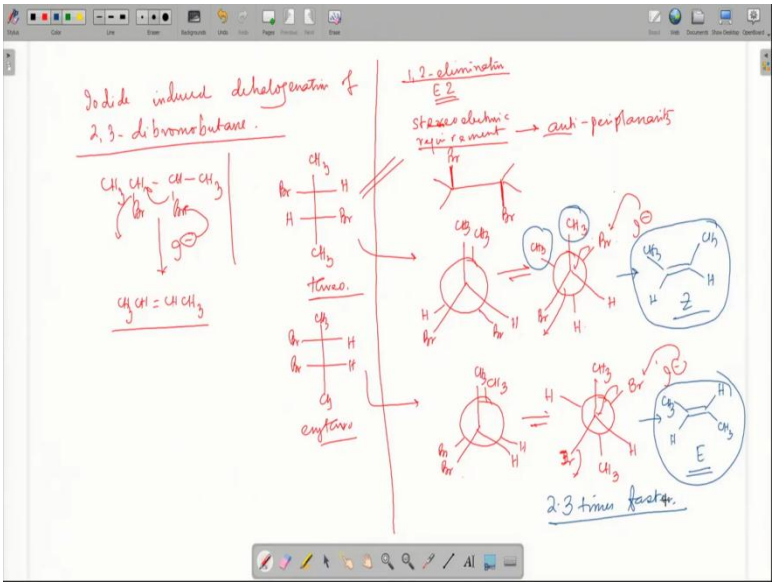

Now, let us talk about so, for this conformationally mobile system and reactions governed by stereoelectronic requirement, we will be discussing the iodide induced dehalogenation of 2, 3 dibromobutane. So, that means what we are talking about is this, CH3, CHBR, CHBR and CH3. Again this molecule can exist in the threo or the erythro diastereomers like CH3, CH3, BR, BR, hydrogen, hydrogen this is the threo and then you have the corresponding erythro also, BR, BR, methyl, methyl, hydrogen, hydrogen.

Now, the question is the reaction that you are trying to do is basically add iodide and we know that the iodide will this is the type of reaction that we are talking about. That iodide induced dehalogenation, so you form the double bond. So, the question is, which double bond will be formed E or Z, that is one stereochemical aspect. And the other stereochemical aspect is that the which reaction will have a faster rate? Which dehalogenation will have a faster rate? So, that is the point of discussion.

Now, to do that, you know that this is basically an 1, 2 elimination, 1, 2 elimination requires that and this is E2 also. That means, this is just basically one step reaction iodide attacking one of the bromine and then breaking the CBR bond and then at the same time the other bromine is expelled or that leaves as the BR minus.

So, we know that the stereoelectronic requirement for this reaction is what, anti-periplanarity. That means the two bromines which are actually leaving from the system, which are departing from the system, this CBR bond should be anti-periplanar to the other CBR bond. So, that is what is the stereoelectronic requirement. And this will ensure the maximum

overlap of the orbitals that are involved in this bond making and bond breaking process so that the transition state is stabilized to the maximum possible, maximum level possible.

So, whenever you draw a conformation and do the reaction the two bromines have to be anti to each other, and that is the conformation in which it will react. So, first talk about the threo. So, let us draw the conformation. So, this is methyl, that is methyl, this is BR, that is hydrogen, and this is BR, and that is hydrogen. So, this is eclipse form and that will definitely go to the staggered form.

Now, which staggered form you should draw, there are many staggered forms possible. So, we will directly go to the staggered form in which the two bromines are anti to each other. So, without disturbing the top carbon, let it remain as it is, this bromine, so you do it a 60 degree turn, sorry, this bromine is here and this is the so this is the methyl and this is the hydrogen.

So, this is the reactive conformation for the debromination from the erythro compound. So, this is iodide that comes here and this goes off. On the other hand, the erythro 1, if you draw the same thing the methyl, BR, hydrogen, and then BR, hydrogen and the methyl. So, convert it to the or draw the conformation in which it will react, which will satisfy the stereoelectronic requirement.

So, again without disturbing the top one methyl, bromine, hydrogen and then bring this bromine here. So, that will bring the methyl and the hydrogen here. Now do the in this conformation, this is going to react. Now, let us see the that in this form in the threo 1, you have this methyl, methyl Gauche butane interactions, which is absent in case of the from the erythro. So, the erythro 1 is going to react faster, not only that, the product from the erythro will be basically now when you do this reaction, so you have a double one and this is the, so it will be the E compound, that is E geometry that will be formed.

So, the alkene will have the E geometry. Whereas here as the reaction takes place, the two methyls are basically eclipsing each other that means it will be the, the Z compound. So, that will give the Z alkene and that will give the E alkene. And so, there are two things now, two stereochemical issues that we are talking about, one is the geometry of the final product, that is one issue. And the other is the rate of the reaction, so relative rates of the reaction.

So, not only the two products have different geometries that is one issue, the other is the two rates of formation, the rates of formation of the two products are also different. So, the erythro 1 reacts faster and what has been found that it reacts about 2.3 times faster than the threo isomer. So, this is a dynamic scenario, but the whole thing is dictated by the stereoelectronic requirement for a reaction.

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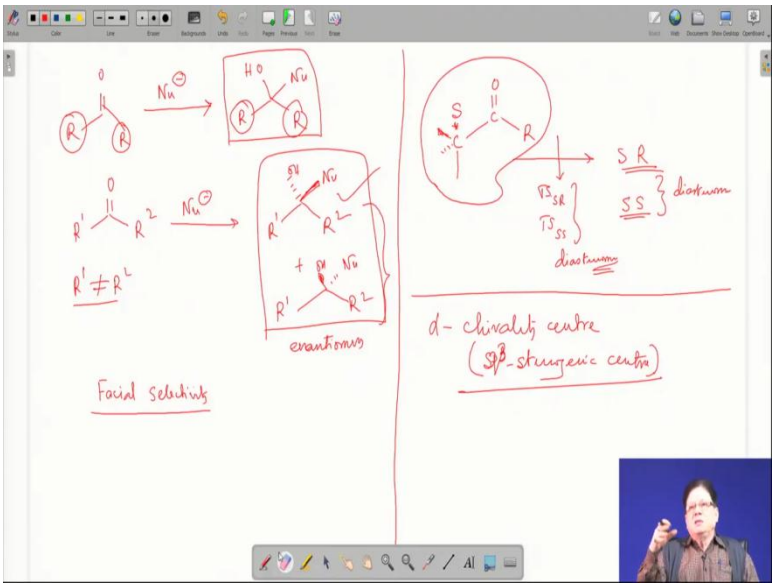

Now, let us go to a reaction which is now let us talk about reactions involving carbonyls. So far, we have not, we are discussing different reactions, different types of reactions, acylation, and then we have discussed acylation and then we have discussed the Friedel–Crafts intramolecular cyclization, we have discussed the dehalogenation.

Now we will discuss the stereochemistry, the dynamics stereochemistry of carbonyl reactions, that means reactions occurring at carbonyl centers mainly from ketones or aldehydes and what happens what does that stereochemical issues involved in that addition reaction.

Because we know that carbonyl chemistry is dominated by nucleophilic addition. So, if you have a symmetry carbonyl compound like this and if you add the nucleophile, then you have a product which will be this. But this is now only one product, because the two faces, first of all because the two this is not an isometric center, so it is only one product. That is one way to look at this molecule.

The other way is that look from the starting material that you have two faces of the carbonyl, one is the top face, another is the bottom face. If the two faces are homotopic that means they lead to the same compound of the same compound then they are homotopic faces. And homotopic faces basically when you have these two substituents same then the two faces are same, so they are homotopic faces. Homotopic faces will give only one compound and in that case there is no stereochemical issues involved for the process.

On the other hand, if you have R1 CO and this is R2, and R1 not equal to R2. So now, what you have is basically two faces two Enantiomeric faces or Enantiotopic faces. Now the top face and the bottom face are not the same. Because if the nucleophile approaches from the top face then what you will get is the wedge as alpha and the nucleophile as beta, and then this is R2, plus if the nucleophile approaches from the bottom face then the wedge will be beta and the nucleophile will be alpha. So, these two.

Now these two are basically in this case enantiomers provided R1, R2 at the nucleophile does not do not have any stereogenic center. So, they are enantiomers and they will be formed in 1 is to 1 ratio. Now, the question is, how can you disturb this 1 to 1 ratio? There are many ways to do that. First of all, that is we are talking about a scenario where the question is asked that how can you generate facial selectivity, because if you want to have one compound in excess over the other, what you need is what is called facial selectivity. That means your nucleophile should be biased to approach from only a particular face, either the top face or the bottom face.

Now the because we are not doing any priority here, you know, that the other way because top and bottom face does not really mean much unless you fix the molecule in a particular form. Otherwise, we have this notion of re and si face. Here because we have drawn this molecule R1 on the left side R2 on the right side, so we say that the top face or the bottom face.

So, if you want to have only one type of isomer here, so you have to bias the nucleophile to approach from one of these faces. So, that is what is called facial selectivity. So, the question is how can you introduce facial selectivity into this type of reaction, the addition to the carbonyl. Now there are there are several ways to do that. One is that you have to first of all disturb the transition states, the transition states for the formation of the product.

If you have generating only enantiomers, then what will happen the straightforward way of doing this reaction will involve transition states which will be enantiomeric. And enantiomeric transition states will have same energy. That means they will have involved that both the reaction pathways will be have same rates, so you cannot discriminate between the two. Both will be formed at equal rates, so it will be 1 is to 1.

So if you want to introduce facial selectivity, so then you have to make these transition states diastereomeric in nature, so that their energy there is an energy difference between the two transitional states, then only you have different rates and then only you have different ratio of the products.

One way of doing this is to have existing chirality in the molecule, in the ketone itself or the aldehyde, whatever it is. In the carbonyl compound, if you have already a stereogenic center like a SP3 stereogenic center or chirality center, then what you will be generating as products they will have a diastereomeric relationship. Because you have already a particular configuration of a stereogenic center already present in the molecule.

Like if you have suppose this and you have a stereogenic center or chirality center here, and suppose this is in the S conformation, sorry S configuration. And then after the reaction when the nucleophile adds, so you have two possibilities, either you get SR product or you get SS product. And their relationship is, they are diastereomers. So, that means their transition states for SR and transition state for the formation of SS, they will be diastereomeric.

So, then you have a possibility of bringing in large energy difference, so that a large stability difference, so that 1P dominates over the others. So, this is the what is the principle of what is called asymmetric synthesis. And so this is one way of achieving asymmetric synthesis. The other is basically you can use chiral nucleophiles, the nucleophile which is being added on to the carbonyl that could be chiral. Then also you will have diastereomeric relationship in the product.

And the third one is that you can use catalysts which are chiral, because catalysts are going to play a role in nucleophilic addition. Because if you have a Lewis Acid catalyst, it will complex to the carbonyl oxygen. And then if the catalyst is chiral then what will happen you are again inducing diastereomeric relationship in that between the transition states. The catalytic reaction is very advantageous because you do not have to, you can always detach to that catalyst at the end of the reaction.

Otherwise you have to introduce a chirality in the molecule, substrate molecule itself or in the nucleophile. And then that will be more difficult if these chiralities are really not, is not really wanted in the final product, then you have to take up this whatever the chiral appendages that you have already added to your substrate or to the nucleophile. How about the catalytic reaction, again I repeat, the catalytic reaction we have the advantage to get the final product without this extra chiral appendage.

Now, let us talk about the reaction of carbonyl systems where there is an alpha chirality center, this is also called SP3 stereogenic center, now this SP3 stereogenic center. So, now the question is what is the dynamic what is the stereochemical dynamics of this reaction? That means, we are saying that there are possibilities of two products because it is diastereomers, but can we really predict which diastereomer will be formed?

Now, again you will go back to the very basic if you want to really figure out, which diastereomer is formed in a major amount, that means you have to study the reaction pathway, that means you have to study that transition state. And then see that the path of the nucleophile, remember again the path of the nucleophile is basically the nucleophile is coming from two faces, the alpha face or the beta face or the re or the si, you have to do a facial discrimination.

So, you have to see that if nucleophile comes from a particular face, what are the interactions that are taking place or vis a vis if the nucleophile approaches from another face. However, if this is another important issue is that if this is an a acyclic system, that means it is conformationally mobile system. So, whether there is any, whether it has got any preference for a particular conformation, reacting conformation, a particular conformation in which it is reacting. So, these type of issues are there.

It was first Donald Cram, who studied these stereochemistry of nucleophilic addition on to the carbonyl where there is an alpha stereogenic center, SP3 stereogenic center or a chirality center. And he proposed several types of rules and that we are going to discuss now the, Cram's rule, and then after Cram's proposition, then came another model which is called Felkin-Ahn model which can also successfully explain the formation of the major product.

The difference between the Cram's formulation versus Felkin-Ahn model is basically that Felkin-Ahn model takes care of the orbital interactions that means there is the stereoelectronic factor that is involved in the Felkin-Ahn model which is absent in Cram's

model. Cram's model is basically mainly on steric factor which has involved in the transition state.

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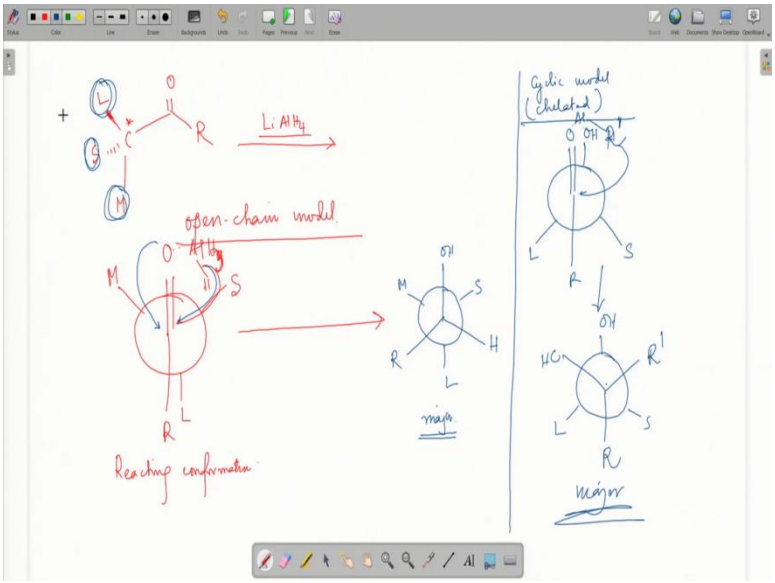

So, let us see the what are the different models that Cram proposed. First of all, we are having an alpha stereogenic center. So, whenever there is an alpha stereogenic center, so one of the, these three groups are different, so they are different in sizes also, most likely, unless there is a deuterium and hydrogen where the sizes are almost same. So, if there is significant difference in the sizes then only actually Cram's rule is successful. So, if one group is large, another group is medium and the third group is small, so that will happen one will be small, another will be medium size, another is a large size.

And then we are talking about a reaction on a carbonyl and this is R. So, now, suppose what we are doing, suppose we are doing a say lithium aluminium hydride reduction. So, this can give two products, the hydride can approach from the top or from the bottom. Remember, this stereochemistry of this is fixed, so we have the only starting from a stereochemically pure compound.

Now, according to Cram's model this is also called open chain model. That means it immediately tells that there is another model which is acyclic model, we will come to that. So, open chain model what happens that the molecule will react in a conformation where the large group is anti to the carbonyl or the large group is eclipsing the R group, both are basically same.

And now you have a small and the medium, that means in the Cramp's model, the carbonyl is flanked between the small and the medium group. And that forces the large group to be eclipsing with the R group. So, this is according to Cram, this is the reacting conformation. And then, we know that the lithium aluminium hydride mechanism is that it first complexes with the aluminium and then the hydride is basically I can write CH3 and then one hydrogen. So, this hydride will now have two possibilities. It can approach from this side from the side of the small group or it can approach from the side of the medium group.

Obviously, for steric reason it will approach from the side of the small group. So, the major product that we will form, that will be formed, this will remain the same, L. So, now the if this is OH, so the hydrogen has come from this side, remember this is not the delivery of the only the hydride is delivered that is true. But the whole thing is the complex, and oxygen aluminium complex. So, that is a quite a big group. So, that is why the steric considerations are there and that will be your R group. So, this is the major product. So, that is the what is called the open chain model.

Another model is there where that is called the cyclic model or sometimes also called chelated model. In this case what happens that if a group is there which may not be the large group, if any of these groups have the ability to form a complex with the reagent, like lithium aluminium hydride or say you are adding methyl lithium, alkyl lithium you are adding to the carbonyl or sodium borohydride, any of these.

So, if any of these groups can form a complex with the reagent, then what happens the molecule will adopt a conformation or the conformation in which it will react will be something like this. Suppose this is a OH a hydroxy group, so then what will happen, so that will form a complex like this. So, then you have the choice only between these two groups. So, one large another small. There is the concept of medium here now.

Because, if one of the groups have the ability to form complex with the reagent then it will form a network, see the complex is a cyclic one. It is a chelate where the carbonyl oxygen is donating to the metal ion as well as the other group of this stereogenic center which is in which could be OH, which could be a nitrogen, which could be sulphur, all these are possibilities.

Something which can donate electrons which can act as a chelating group. Then the whole scenario changes, then you do not have to bring the large group eclipsing with the R group,

that scenario changes. So, this will dominate now, this is what is called the cyclic model. And now the whatever reagent you are adding, if it is aluminium hydride, the hydride will come from this side. If it is methyl lithium the methyl will come from this side. And the product will be, so I just write R something and now R1. So, that will give rise to a product which will be L, S we started with OH.

So, that will be OH that will be R1 and this will be R. So, this is the major product. So, depending upon the type of the groups that are present, so you have to adopt different models. So, first of all, if there is no, there if all these things that S, L, M are non-chelating, then open chain model you just apply, Cram's open chain model. If it is a chelating group then you have to apply irrespective of the size of the chelating group, you have to adopt the cyclic model or the chelated model. In both the cases, however, the nucleophile is delivered from the side of the small group.

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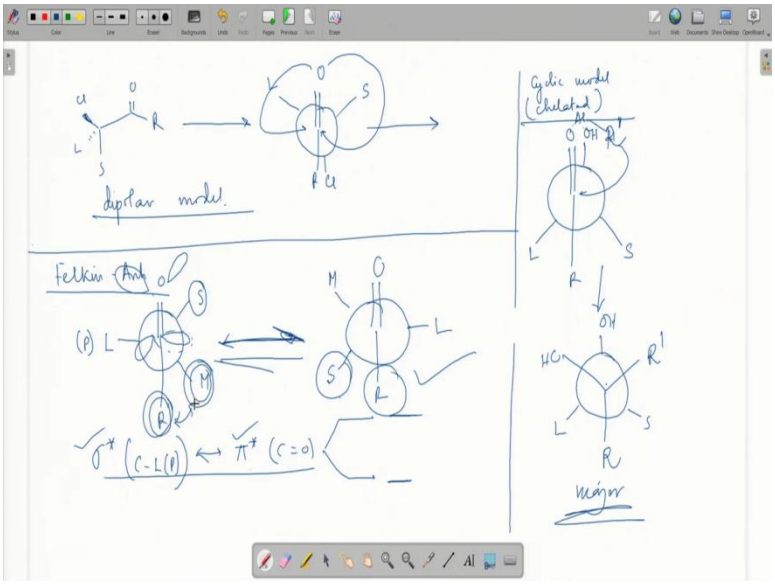

There is a another a third model which is there in which if one of these groups that small, medium, or large, if one of these is polar, like say halogen, then also that will disturb the conformation that will also disturb the reacting conformation as was predicted in the open chain model. So, now what we are talking about is suppose one of these groups is a chlorine and then one is large, another is small and then you have carbonyl R.

So, if this is the scenario, then it will adopt to conformation, a reacting conformation, in which the two poles are farthest apart. Like this is anti to each other in order to avoid the dipole, in order to avoid the dipole-dipole repulsion, dipolar repulsion. So, in that case, now

you have S and L, so this will be the reacting conformation. And again the reagent will be delivered from the side of the small group, so you get, accordingly you will get the product. So, this is what is called dipolar model. So, Cram's model, he had to modify the model according to the different types of substituents that are present in the stereogenic center.

Now, there is as I said (()) (32:45) Cram's model is basically based on the reacting transition state, which is dependent upon several factors in a simple case that the normal case where these are simple substituents, the large, small, and medium, non-chelating, non-polar. Then you have the carbonyl flank between the small and medium, that is the reacting conformation.

In case of the any of these groups is a chelating group, then the reacting conformation will be different because it will go through a chelated complex or a cyclic model. And the third one is a dipolar model, where to avoid the dipolar repulsion, dipole-dipole repulsion, it adopts a conformation in which the polar group becomes anti to the carbonyl.

But in all the cases the nucleophile is delivered from the side of the or from the face where the small group is residing, so that means you are getting a facial selectivity. See the carbonyl is delivered, the moment we say that it is delivered from the side of the small group, that means, you are now saying that this will be less favoured. So, there is a facial selectivity that is happening.

Now, apart from this there is another model which is called the Felkin-Ahn model. In the Felkin-Ahn model, now let me actually, let me first tell what is in Felkin-Ahn model. Felkin-Ahn actually criticized Cram's model because of especially the open chain model, where you are actually having eclipse in interactions between the substituents attached to the carbonyl and the large group, so that was one type of criticisms, where you are adopting an eclipse conformation.

So, in Felkin-Ahn model, what happens that the reacting conformation according to this model, Felkin-Ahn model is that the large group or the polar group, it will be a polar group also. That is orthogonal to the carbonyl and which makes the other two ones, the small and the medium. So, basically what happens, now the reacting conformation there is a drastic change now. Felkin model is saying that the large group or a polar group has to be orthogonal, orthogonally placed to the carbonyl.

Now, why that is? What they are saying that if you place it orthogonally, then what happens that the sigma star of this carbon polar group or the large group, the sigma star of this bond, the sigma star of carbon L or P and the pi star of the carbonyl. So, something like this, pi star which is, which will be like this, and the sigma star which will have a larger love on this side.

So, they are now basically on top of each other. And then there could be overlap between this. So, sigma star, Pi star of the carbonyl that overlaps. And that basically what will happen now, that the energy level of this star will be this combination, the sigma star, Pi star, combination will lower the energy of the Pi star. So, one set, one orbital goes down, another goes up, but both are vacant.

So, what is happening that due to the sigma star, Pi overlap, the overall energy of the Pi star of the carbonyl goes down. Now what is the consequence of that? When the nucleophile comes and attacks the carbonyl carbon, for the first it donates the electrons to the Pi star orbital, because that is the HOMO LUMO interaction. The nucleophile comes with the or donates the HOMO, which is occupied by a pair of electrons, that is why it is negatively charged. And then that is donated to the LUMO, LUMO is the Pi star.

Now, if you can lower down the Pi star by this interaction with the sigma star, then the reaction will be more fissile. So, that is exactly the reason why this conformation was considered by Felkin and Ahn. Now, when you take a particular molecule there will be two scenarios, one is that the there will be the medium group on this side, this is the R group. And the other one is that you can have this is not resonance, sorry, this will be this.

So, there are two possibilities, the other is the L is on the right side. See, there are two possibilities, two orthogonal positions, one is on the left, another is on the right. And then what will happen your medium will be here and small will be here. So, which one will be more preferred, basically is the interaction between this R and the S, and this R and the medium. So, that will decide obviously, this will be favoured.

Because in both the cases that sigma star, Pi star overlap is there, so that is not disturbed. But what is the basically that this will be favoured because there is more interaction here because of the R and M. So, this is the basis of the Felkin model, and you can apply into the same problems which Cram dealt with, so you can apply the Felkin model and you will see that the same product, same remember, the same product is predicted by both the models.

However, the reacting conformation is different in them two models. Felkin models is basically guided by a stereoelectronic. So, this is a now the stereoelectronic requirement. That the large group should be orthogonal or the polar group should be orthogonal to the carbonyl which will assist in the sigma star, Pi star overlap, and bring the Pi star level down. And so that now the HOMO LUMO interaction between the LUMO, between the nucleophile HOMO and the LUMO of the carbonyl is the energy difference is less so that will be more fissile. So, that is basically the what is the model all about.

So, that basically I can now show you about these type of interactions by with the help of this model. So, whatever we are talking about is this one. So, this is the carbonyl and this is the carbon which is the stereogenic center. There is one red another green and this is the say the large group. So in the Felkin model, Felkin model what you have to do, the large group has to be orthogonal to the carbonyl.

So, you see this is orthogonal to the carbonyl. And if it is orthogonal to the carbonyl, so this CC bond you see. If you now take the sigma star that goes in the opposite direction and the Pi star is on this side so there is overlap possible between the sigma star and Pi star. You can talk about that what about the overlap with the Pi system? See, Pi system overlap does not affect, stabilization does not affect the reaction, because the nucleophile is donating the electrons to the LUMO, which is the Pi star.

So, we have to take the Pi star and think of its stability and not the Pi itself. So, this is the Felkin the reacting conformation in the Felkin model. In the Cram's open chain model, this is the scenario that the carbonyl is flanked between the green and the red which is the small and the medium. And in the chelated model, suppose this red one is the hydroxy, so that this is chelated model, so that will form the complex here.

And in the dipolar model, suppose this is the red is a polar group, so the dipolar model, so this is the scenario in that dipolar model. So, the carbonyl and the polar group are anti to each other. So that is, so with the help of the model it is it you can visualize. I am sure that when the scientist this develop their models they have actually definitely handled or made these type of molecules and then because there is a model called (()) (42:57) model, so where you can have perfect bond angles maintained, bond length maintained, and then you can actually compare the energetics of the various transition states.

Remember these were the days when these computational facilities were not available. The computational chemistry was not developed at that time, so 50s. And so the only thing or the only tools that the chemist had was the molecular models. And then by inspection of these molecular models but they have to be very perfect where the bond length to the bond angle there need to maintain and then you can compare the relative energetics of the transistor state.

So, on those basis, actually these models were developed. I think a due credit to be given to the scientists because that is basically those were the days when stereochemistry was being developed and dynamics stereochemistry was the more difficult challenging ones. So, Cram contributed a lot in this scenario.

So, I think with this let me summarize. What we have done initially in this lecture, we have first taken a conformationally mobile system and then see how the stereoelectronic effect controls the rate of formation of the product as well as the product geometry, that is the dehalogenation. Then we talked about the facial selectivity in a carbonyl system, where there is a alpha stereogenic center and the nucleophile is added from one face or the other face.

And there are different models to predict which side or which face will be more favoured, basically there are Cram's model and there are this there is the Felkin-Ahn model. Felkin-Ahn model, again I repeat, is has got a it has brought in a stereoelectronic requirement for the conformation, for the reacting conformation. So, I think with this, we will conclude this lecture session. Thank you very much. We will discuss more on the carbonyl chemistry in the next set of lectures. Thank you.