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

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Lecture 33

Dynamic Stereochemistry: Conformationally Rigid and Mobile Systems

Hello. Welcome to this course on Structure, Stereochemistry and Reactivity of Organic Molecules and Intermediates: A Problem-solving Approach. Today, we will be discussing an important topic on Stereochemistry, which is called Dynamic Stereochemistry. Dynamic Stereochemistry is basically the Stereochemistry that is happening in a dynamic situation, a dynamic situation means, when one reactant or the substrate is converted into product. And what is the stereochemical implications of that process that means, what is the geometry of the transition state, what is the geometry of the product?

Basically, it is the correlation of product's stereochemistry with the substrate's stereochemistry by other transition state. So, it is a dynamic process that means a reaction which is going on and one studies these stereochemical aspects of that entire reaction pathway. That is one type of Dynamic Stereochemistry, the other is it could be not a reaction, but an interconversion between the conformational isomers.

And if you study the energetics, how the energy changes and when the inter conversion is taking place, that is also is a dynamic scenario. So, that is basically that means the stereochemistry which is going on in a dynamic situation. The dynamic situation can be a reaction or it can be an interconversion between conformational isomers.

Now, the question is basically how to deal with this situation? How to basically describe the stereochemistry of a chemical process? When I talk about the chemical process, the naturally two things come into mind, one is the rate of the chemical processes and the number two is the geometry or the stereochemistry of the product and the question of if there are possibilities of several pathways then there are possibilities of several products?

So, the question naturally comes that which process is faster that means, we are talking about rate. And how the rate is correlated with the geometry of the substrate. And the other thing is that what is the predominant product that is formed and what will be the geometry of that product? So, that is what is basically we are going to talk about in this lecture.

Now, the question is when there are many kinds of system, stereochemical system that we can think of. One system is which is stereochemically rigid, that means, basically, a molecule exists only in one conformation and that conformation, in that conformation only molecule reacts and gives the products, so that is one type of scenario.

The other is that where the conformation may be biased, that means, a molecule could have existed in several conformation, but due to some effects, some steric effects, the molecule adopts a particular conformation or which is called that means you lock the conformation in a particular form. And the other way of saying that is that the molecule is conformationally biased and that is what are called anancomeric systems.

So, one is conformationally rigid systems, which are relatively easy to tackle, that if you want to compare the rates of reactions between two conformationally rigid systems, then there is no question of interconversion. The other is that when there is conformationally bias systems, then also situation is simpler. But if it is a conformationally mobile system, then it will be, it is a little difficult to compare the rates of two conformationally mobile systems which are having a diastereomeric relationship that is we are talking about the relative rates of reaction of two diastereomers.

Then the issues that come up is basically the energetics of the transition state that is one issue, that which transition state is more stable or less stable depending on which rate is slower or faster, that is the one dominating factor. The other is also very important and that is that stereoelectronic requirement for a reaction. Because we know that stereoelectronic requirement demands that the orbitals that are involved in the reaction pathway should have the maximum overlap, so as to give the maximum stable transition state. So, these are different scenarios. So, let us now take up one by one examples of this scenario.

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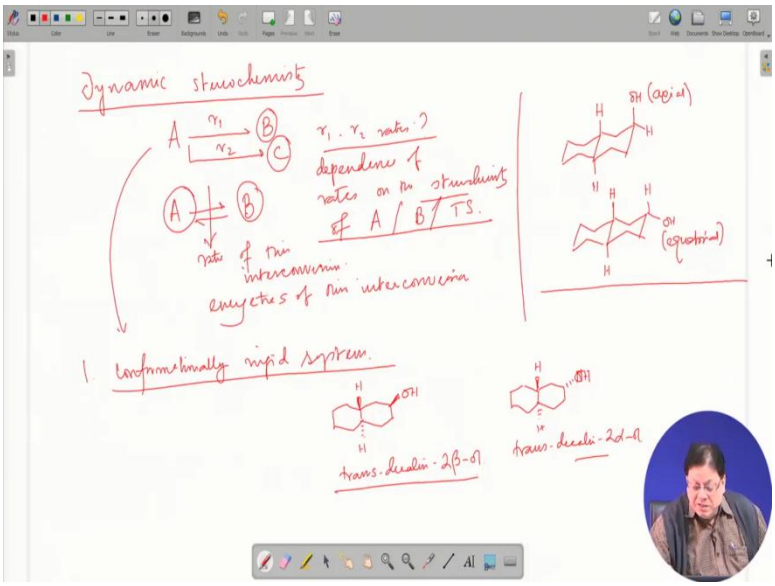

First it is the comparison. First take the which is called the so, first of all our topic is Dynamic Stereochemistry and basically what is again, I will define Dynamic Stereochemistry is that a molecule A going to B or it can also go to C. And if the question is what will be the energetics, what will be the rate of these reactions, these are rates, r1, r2 are rates.

And so, which one is higher, which one is smaller these things, and whether that basically dependence, I can say dependence of rates on the stereochemistry of A or B or even the transition state. So, that is one type of scenario I said, another is the interconversion between conformational isomers. So, what is the rate of these interconversion and the energetics of this reaction, of this when it is under reaction of this interconversion. This is conformational isomers. So, these two are basically conformational isomers. So, these are the things.

Now, as I said, that this the scenario can be of different types that one can deal with conformationally rigid systems, that is the first one. So, we will take about, we will take the example of 2 molecules. This is a decalin system with a beta OH at the two position. So, this will be, if these are hydrogens, then this will be called trans decalin 2 beta-ol, and then you can have another trans molecule, another isomer, basically an epimer, which is also trans decalin, but that is trans decalin alpha or trans decalin 2 alpha-ol.

Now, these are stereochemically rigid system, because we know that trans decalin because of the steric restriction that the hydrogens at the ring junction they have to occupy actual

positions, so you cannot really flip the ring. So, it is conformationally rigid. And then, so we are talking about a conformationally rigid system where in one molecule the OH is beta and in the other molecule the OH is alpha. So, that makes in one molecule OH as axial and is where the hydroxy is beta, so this becomes axial and this is equatorial.

Now, if you compare these two molecules, you will see that everything is same up to this point. Only the difference is that the orientation of the two hydroxy groups that is axial or equatorial. So, this is a very good models, these two are very good models for comparing the reactivity of an axial functionality in this case OH, again and the equatorial functionality. Because the remaining part of the molecule are virtually are same.

Now, the different types of reactions can be carried out on these and then we can compare their rates of reactions like if I do acetylation suppose. So, if I do acetylation then this OH will be acetylated. And what we will get is this 2 beta acetate or COCH3 or 2 alpha acetate. Now, the question is which one should react faster? This is, sorry, this is OCOCH3. The reagent is, there could be different types of reagents, so the standard is acetyl chloride and you have to use base tertiary base like triethylamine or pyridine. Now this acetylation reaction we know that basically increases the state bulk of this OH.

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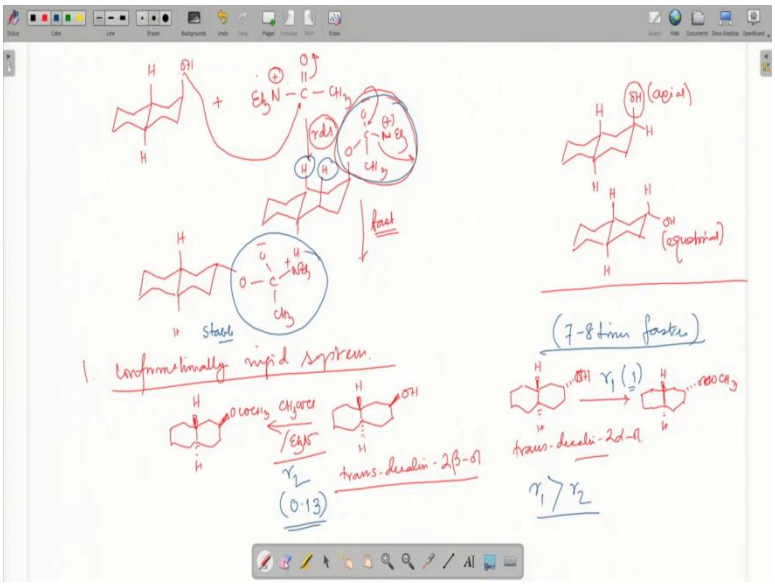

So, in the reaction mechanism, if you try to draw the mechanism, let us erase this part. So, if we try to draw the mechanism then we know that this is a case of nucleophilic catalysis. The tertiary amine like triethylamine forms this type of intermediate COCH3, and this is plus. So, first the triethylamine reacts with acetyl chloride forming this species, the acyl ammonium

species and then the suppose the OH that now reacts and forms a tetrahedral goes via a tetrahedral intermediate.

So, that will be hydrogen, hydrogen and then you have OCO minus N83 plus, and then this is CH3. And this is the rate determining step. And then this is followed by expulsion of the triethylamine group and you get the acetate. So, this is the first step. So, if this is a rate determining step, you are actually increasing a steric bulk of the system and if the group is axial and if you increase the steric bulk that means, you are increasing the 1,3 diaxial interaction between this, between this group and these hydrogens.

So, that means, you are increasing the steric repulsion and that will make it to react or the transition state for this step at a higher level. Then the transition state which is involved in case of the other isomer, that means the alpha isomer, the alpha isomer the OH is so the intermediate, we are drawing the intermediate N83 plus and then CH3.

So, basically this steric increase in steric bulk does not affect, is not suffering from the one three diaxial interaction. So, this is more stable and that means this will this acetylation will be faster. So, if this is r1 and if this is r2, then r1 should be greater than r2. In fact, the relative acetylation rate is if it is considered as 1 then that is 0.13. So, actually about 7 to 8 times faster, this reacts about 7 to 8 times faster.

So, this example clearly now indicates that an axial alcohol will undergo acetylation or if you do benzylation all these things will, axial alcohol will react at a slower rate and at the rate the relative rates will be something between 7 to 8 times. But that may not be followed in all the cases, but at least the qualitative analysis that means axial alcohol reacts at a slower rate that will be valid for other systems.

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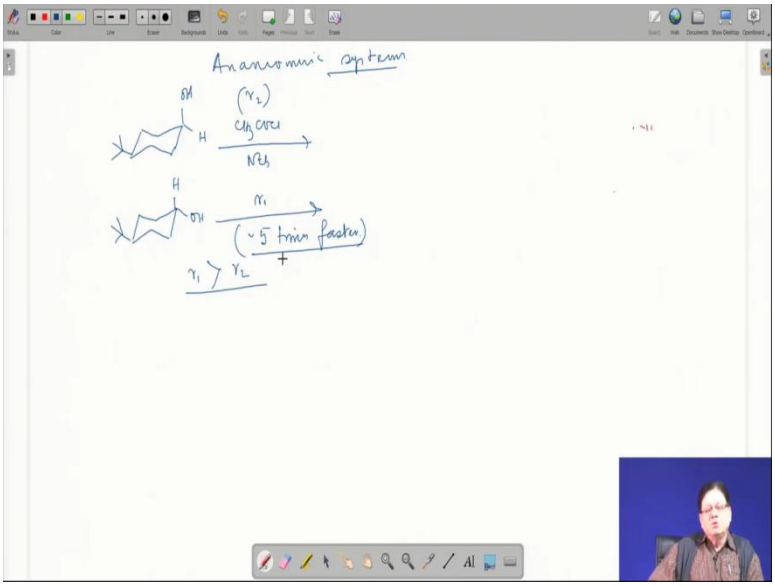

So, what is the other system I was talking about, the other system I was talking about is the conformationally, what are called conformationally biased systems. The other name of conformationally bias systems are called anancomeric systems. So, for anancomeric systems like you already know this that if you put a tertiary butyl group in a cyclohexane then what happens the cyclohexane molecule becomes locked in a particular conformation because of the because the tertiary butyl group has to occupy an equatorial position. So, if you take this one, that means the cis, one cis 4 tertiary butylcyclohexanol versus the trans one.

Now, also again you can compare the difference in the rates of these two systems. They are basically virtually locked in one conformation. They are not like the earlier one decalin where it is exclusively trans, there is the flipping is other conformations are just forbidden. Here what happens, it is conformationally biased. So, maybe in 10,000 molecules one or two molecules will occupy will have a conformation where the tertiary butyl is occupying an actual position. But mostly it is the equatorial position.

So this is called anancomeric systems. So, anancomeric systems like this, again will be very similar if you do acetylation, we can say that the rate if this is r2, and if this is r1, then r1 should be greater r2. Now what is the actual experimental result, experimental result is basically around unlike 7 to 8 times. Now, it is not it does not reach up to that point, but it is about approximately 5 times faster. It is slightly less than what was observed in case of the decalin system, because this is conformationally biased. Now, earlier one was conformationally rigid.

So, basically you are handling only one conformation there, here there is a certain percentage of the other conformation, although the percentage is very low, but that actually makes the difference slightly less than what was happening in the decalin system. So, that is about the conformationally rigid system. Let us talk about conformationally rigid and conformationally biased, those two systems we have discussed.

Now, let us talk about conformationally mobile systems. If it is conformationally mobile systems, then as I said that there are two issues, one is that out of several conformations, one conformation maybe predominant and the rate can be correlated with the most favoured conformation provided, provided that is important, provided the conformation which is present in less amount has is not exceptionally reactive. Because if it is exceptionally reactive then what will happen the whole equilibria will be shifted towards the less populated conformation and then the whole scenario may change. So, that is one type. The other is that the stereoelectronic requirement for a reaction.

So, let us talk about both these type of scenarios. So, in one case when we draw the transition state for the reaction, we have to see the what type of interactions that are going on in the transition states. And then if there are multiple pathways then compare or come to a conclusion that which transition state will be favoured and which will be followed, and that will give the product that will be obtained via that pathway.

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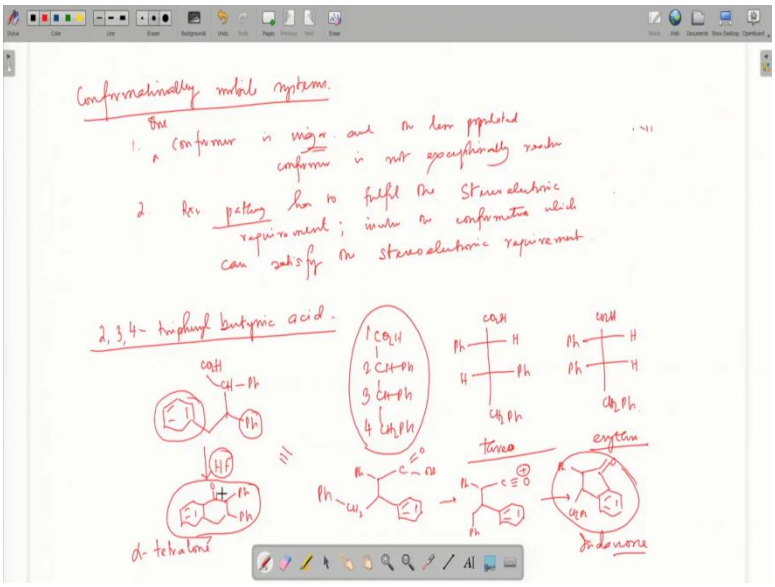

So, let us take an example. So first of all this is we are discussing conformationally mobile systems. So, conformationally mobile systems, as I said, again the two scenarios can happen,

one is the conformer, one conformer is major, one conformer is major and the least populated conformer is not exceptionally reactive. The number 2 scenario is that the reaction pathway has to fulfil the stereoelectronic requirement. So, in that case you have to involve the conformation which can satisfy this stereoelectronic requirement. So, you do not have any choice here, stereoelectronic requirement.

So, it has to be a particular conformation or there may be other possibilities. If suppose there are two hydrogens, one has to be eliminated then you can actually eliminate try to see the conformation in which a particular hydrogen is eliminated versus the conformation where the other hydrogen is eliminated. So, those type of scenarios are there. So you can again compare the trio relative stability of the transition states for elimination of these hydrogens.

So, let us I think it will the examples will make these concepts clear. Suppose, we are thinking of a molecule which is 2, 3, 4 triphenylbutyric acid, that means you are what is 2, 3, 4 triphenylbutyric acid, that is CO2H then you have CHPH, then you have CHPH and you have CH2PH, so this is 1, 2, 3, 4, so triphenylbutyric acid.

Now triphenylbutyric acid obviously can exist in two diastereomeric forms, one is the threo so let us draw that, and the other is the erythro isomer. So PH, PH, H, H and CO2H, and this is CH2PH. So, this is threo isomer and this is the erythro. Now, if you try to draw this in a linear fashion like not as a Fischer projection, so you have a phenyl, suppose this is the, so, you have this phenyl, then you have a CH2, then you have a CHPH, then you have a CHPH and then you have this carboxy.

Now, we know that there is a Friedel–Crafts type reaction the acylation, where if you add say acids like HF or PPA, then it will form this CO plus, the electrophile and then there will be electrophilic substitution in the aromatic ring. So, what you can get is this type of molecule PH, PH. So this is one possibility.

The other possibility is that instead of this phenyl that means the phenyl at the 4 position involving in the reaction the other possibility is that this phenyl, I can draw it in a suppose I would draw it PH, then there is a CH2 then there is this PH. So, I write it in the form of a benzene ring then this is PH and then there is CO2H. So, now, the other possibility is that this forms the CO plus, the electrophile and the substitution takes place on the benzene ring at the 3 position and not at the 4 position.

So, this will be CH2PH and that will be PH. So, in that case you will get a 5 membered ring fused onto the benzene ring. So, this is what is called in indanone. This is the indanone ring system. So, there is a PH here, there is a CH2PH here and this is the benzene ring. So, indanone and the other possibility is that this is tetralone, alpha-tetralone. Because tetralone can be also a beta-tetralone, this is alpha-tetralone derivatives. So, these are the two possibilities. Now which one will be formed that depends on the transition state for formation of these products. So, let us try to draw the transition state one-by-one. So, let us erase this.

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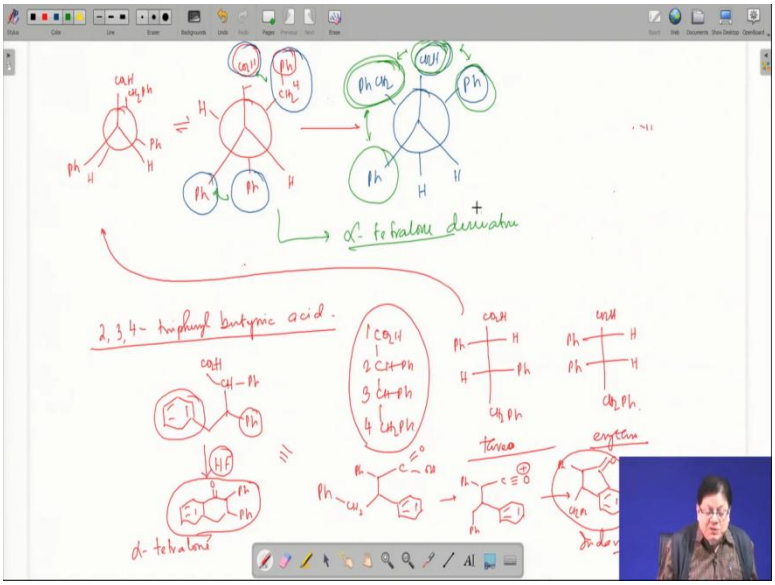

So, if you carefully draw the Newman projection of this which is the threo-form. So, the first form, the first one is basically CO2H. So, you know that Fischer projection is drawn in an eclipsed and it represents the eclipsed form of a molecule. So, CO2H and then you have this PH and this is H and you have CH2PH here, and you have PH here, and you have H here.

So, this is the corresponding Newman projection formula with threo-form. But this will definitely be, not be present and so what will happen? Now, it will go to the staggered one. So, this is CO2H, this is CH2PH. And then you have so, basically you just turn the CH2PH, the remaining the top one remains the same, PH, H, and this will be PH and that will PH.

Now, in this conformation if you try to do the cyclization that means now this phenyl, remember this is the phenyl at the 4 position. So, this phenyl, if it reacts with that electrophile, then what will happen, then you will get the tetralone. Now, let us try to see how many Gauche type interactions are there in this system. So, this is one, maybe I can do a different coloured. This one is one interaction and this is another interaction.

On the other hand, if you want to involve the phenyl ring at the 3 position that means you have to bring this phenyl now, you have to bring, so we have to draw another conformation where there is CO2H, then PH, H and then bring this phenyl here because you want to react with this phenyl that forms the indanone but you will see that the conformation that is required for the formation of the indanone, now, involves one interaction is here, maybe another colour we use.

So, one interaction is this, another interaction is between these and that, and the third interaction is between that and that. So, you are now having 3 Gauche interactions between the large groups. On the other end here it is only two. So, two versus three. So, naturally this will give the alpha tetralone derivative.

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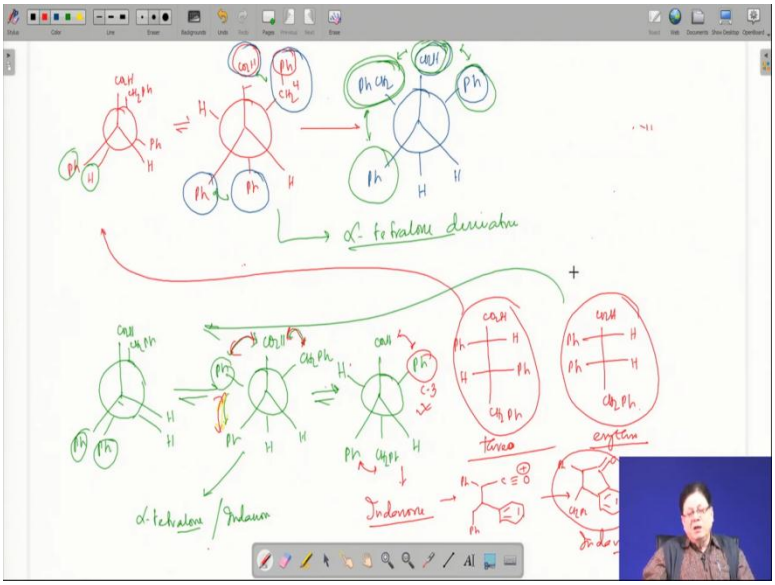

And for the other isomer let us see. If I want to draw the again I will do the same thing, draw the a Newman projection in the eclipse form and then change it to the correct staggered form. So, we are now taking this molecule. So, the first form, the eclipse form will be CO2H then this will be PH, that will be H, and then this will be PH, and that will be H sorry that will be H, and this will be your CH2PH.

So, here PH, H are eclipsing and here PH, PH are eclipsing. So, that is not the form, so it will go to the staggered form. So, now, if you want to have the tetralone formation, let us see. If you want to have the tetralone that means CH2PH will be here and then PH will be there and H will be here. So, now the reaction if the reaction takes place between that and that you get the tetralone.

On the other hand, if you this is your phenyl at the 3 position. So, if you want to make that reaction feasible, then draw the transitions or change the feasibility of that reaction, then you draw the other reactive conformation. Of course, here see the CO2H had the option of reacting with this phenyl or this CH2PH. So, both are possible from this conformation, I should mention that both are alpha tetralone or indanone both are possible.

However, here how many interactions are there? Again, you see the number of interactions, maybe red is better. This is one, that is another one, and this is the third one. So, number of interactions, Gauche interactions between large groups are three. Now, if you bring the phenyl, the 3 phenyl or draw another conformation. So, this phenyl you turn it by 120 degree, so phenyl and then this your this will be your CH2PH and that will be your H.

So, this is the conformation. If this this is favoured because now you have only two interactions, Gauche interactions between large groups. So, this is the favoured one. If this is the favoured one, so the reaction pathway will now favour the formation of the indanone, because this is the phenyl at the C3 position, so that makes the indanone. So, this is a good example.

So, you see that depending on the stereochemistry of your starting compound, the final product structure will depend. And so, basically what we are doing, we are discussing the transition state for different pathways and then trying to figure out what type of interactions are there, how many are there, and then decide on the course of the reaction.

So, in one case the threo gives the tetralone as a major product, and the erythro gives the indanone as the major product. Remember this is not exclusive that one product is formed, this is the major product. A major product is alpha tetralone from the threo isomer and indanone derivative from the erythro isomer. So, that is basically one type of reaction that we have discussed.

Now, I think we will discuss more examples in the following lecture. So, at this moment, just to summarize what we have done. We have just discussed or defined what is dynamic stereochemistry. That is these stereochemical issues that are involved in a dynamic scenario, when one compound is converted into another compound or several compounds. And the other is that one conformation is converted into another conformation.

But while dealing these issues to your chemical issues, we have to think of the originality of the basically they are stereochemical origin of the starting material that whether they are conformationally rigid, they are conformationally biased or they are conformationally flexible. So, everything you have to think and then proceed step-by-step to arrive at the relative rates of the reaction or sometimes what is the final measure product for the reaction. Thank you.