Course on Stereochemistry
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Mod08 Lecture 35

Stereospecific and Stereoselective Reactions and Asymmetric Synthesis

(Elementary Idea)

Okay welcome back yesterday we have seen the kind of stereo electronic requirements that are imposed in some reactions especially substitution elimination and rearrangement and we have seen that there are the stereo electronic requirements actually and along with conformation that dictates the major product formation, okay.

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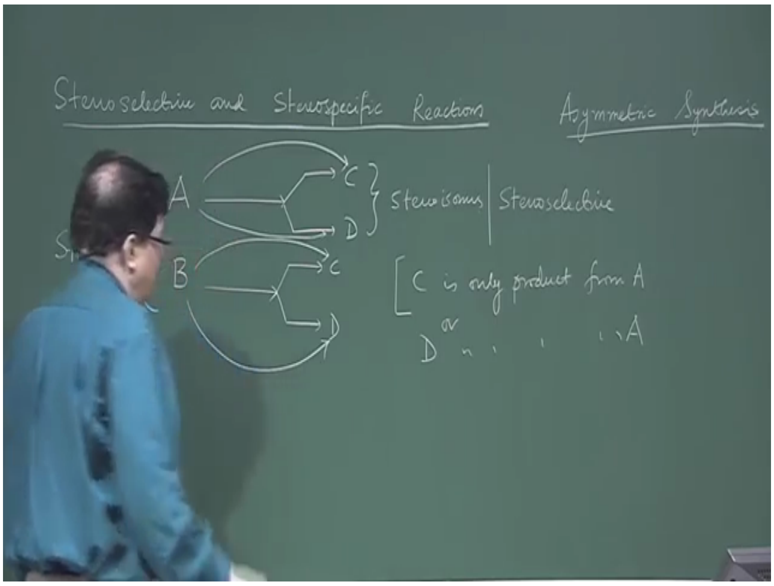

Now let us going to another important very important topic now, stereo selective and stereo specific reactions, okay along with that we will also discuss the asymmetric synthesis. Now suppose you have two compounds two isomers A and B. These are stereo isomers and if there is a possibility of formation of C and D from the stereo isomer A and the relationship between C and D are also stereo isomers and suppose, the same C and D can also be obtained from B. So what are we are talking about that we have taken two enantiomers two stereo isomers A and B and we are doing some reaction on these two compounds and suppose the possibility of product formation is designated as C and D as the products. So there is a possibility of C or D or both C and D formation from A and the same thing also happened from B.

So basically the two stereo isomers can give rise to the same set of stereo isomeric products. Now what can happen in many cases, suppose A only gives C and B only gives D, okay. Then that reaction that means one set of one set of stereo isomers is gone in the product. So only one major stereo isomeric product is obtained A going to C and not D and B also is going to D or B can also go to C. So lot of possibility, suppose C is the only product from A or that means out of the two di-stereo isomers, here the stereo isomers you have only one of them is formed on the reaction when the reaction was carried out on A. so this reaction will be individually called a stereo selective reactions, because out of the stereo isomeric products that are possible only one you are only one is obtained that one can be in in a meso form or it could be an optically active pair, both are possible, okay.

We will discuss examples this point to be clear. So basic definition is that whenever a reaction is done on an isomer A and then if there is possibility of formation of more stereo isomers and if only one stereo isomer is obtained in the product then that reaction is called a stereo selective reaction. So it could be C is only product or D is the only product, both are possible, but in both the cases the reaction is stereo selective.

Similarly, if B gives C or B gives D only one not both then the reaction is also individually stereo selective for with respective B that means B is undergoing a stereo selective reactions okay. So I hope this is clear that means if I take one compound and from that compound if there is a possibility of generation of different products different (())(4:50), the products are related by stereo isomerism and if only one product is obtained and not the other then that is called a stereo selective reactions, okay. Now actually in the, organic chemistry books, these terms are frequently used in place of one another ;however what I am talking is the strict definition of a stereo selective reaction.

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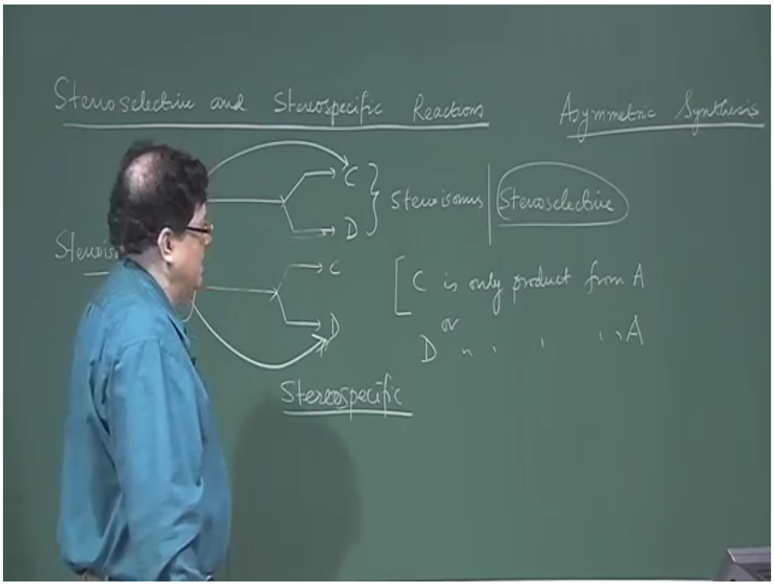

Now suppose what happens that if B, see A and B are stereo isomers and suppose A gives C and B gives D, if A gives C and B gives D that means the reaction (())(5:37) individually stereo selective, because only one set product is obtained. the other important thing is that the product formation is dependent on the stereo chemistry of the starting material, because now these are two stereo isomers. So depending on which isomer you are taking that will decide which product is being formed. So A giving C and B giving D and relationship between these two are stereo isomers and relationship between these two are stereo isomers also.

So what I am saying that the stereo isomer that is obtained from the reaction of A is different from the is different from the stereo isomer that is D here, obtained from B that means your product formation is dependent on the geometry of the starting compounds. If that happens then that is called a stereo specific reaction. So stereo specific reaction points out to the stereo chemistry of the starting materials, because the product formation depends on the what is the stereo chemistry or the geometry of the starting material. On the other hand, stereo selectivity is dependent on, which dependent on just number of products that you are getting in the reaction. So if one product is obtained, the reaction becomes stereo selective.

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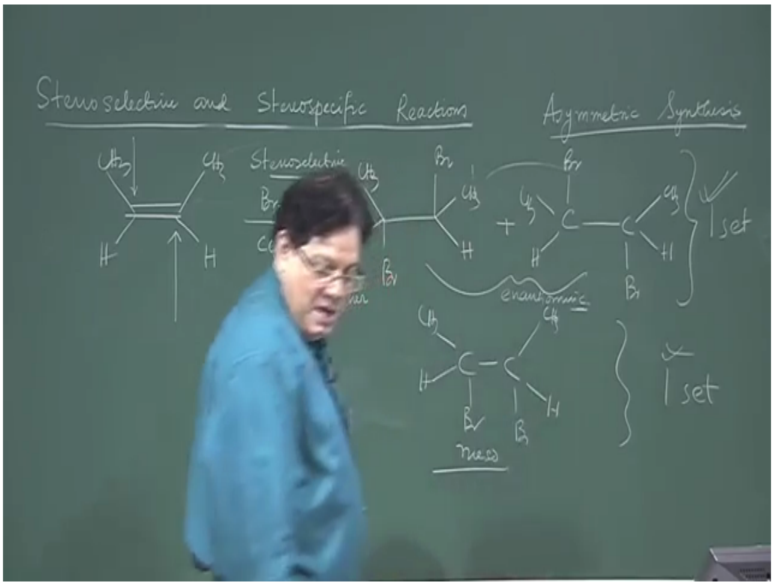

Now I give you one example, suppose I take Cis 2 methyl butane and if add bromine on to this, so I take a bromine in carbon tetra chloride, I know the bromines, bromine atoms add and the bromine atoms add in a trans manner, right an anti-manner, okay I take (())(7:35) that means one bromine, if it comes from the top then the other bromine coms from the bottom, okay and that is, because of the formation of a cyclic bromonium ion, okay. Now if that be the case, so the product that you will be getting is, so one is this when the bromine approaches from this side and the other bromine approaches from the other. So you get, this compound plus you will get the other compound the other possibility, the Br coming from this side and the other Br coming from the other side, okay. So you get Br here and you get methyl you get hydrogen and then you get Br in this side and then CH3 and this H.

Now these two are racemic mixtures. They are optically active, but both the compounds are formed in one is to one amount, okay. Now there is a third possibility, the third possible compounds with this formula is the meso compound, where which has a plane of symmetry that we know. This is the meso, but what is obtained in this addition trans addition of bromine that you get only these two, okay. So these two are one enantiomeric pair. So you get one enantiomeric pair and not the meso compound, okay.

So this reaction is stereo selective, remember stereo selectivity does not discriminate between the extent of the enantiomers, even if you get plus minus one is to one, the reaction is stereo selective that means this is considered as a as one set and this is the other one the other set, but here it is not set, because it is a meso compound. So it is exist only in one isomer however if you get either this or this the reaction becomes stereo selective. So here you are getting only this compound, so it is stereo selective.

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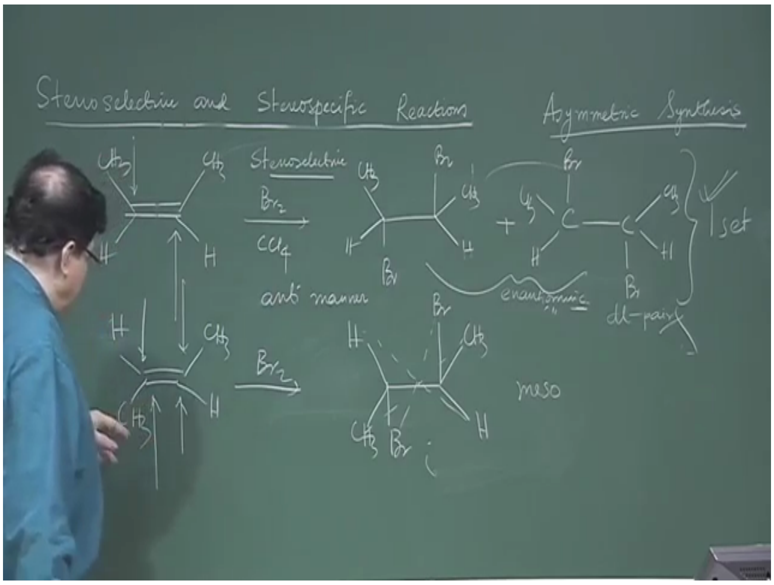

Now if you take the trans compound, the trans alkene, sorry the trans alkene then what will happen after bromine addition if the bromine adds from this side or that side. So you are, I erase this actually that is not the way to write, you will get a compound which will have a center of symmetry now. So one bromine comes from here, another bromine comes from the other side and now you have a center and I present in the compound, okay. So it got it has an I (())(10:50) okay. It also has the plane of symmetry but not in this conformation.

In the eclipse fully eclipse conformation; you get the plane of symmetry. So it has got I (())(11:01) . So this is now you are not getting the di-pair you are not getting the dl-pair. So that is not obtained. So what you get is the meso, I am not doing the other side of addition, because that gives the same product, okay.

Now you can have a very, see which product which will give which product is there is a mnemonic device you can apply that, because the bromine adding opposite that means that will have a that will bring a I at this point, but this molecule does not have I. so what happens, it has sigma. So if the bromine add from the same side the sigma is retain, but the bromine is adding from the opposite side. So the sigma is disrupted. So that is why you get enantiomeric pair.

Here, already I is present and bromines are adding in a center of symmetry fashion. So it will the I will be maintained will be retained and in then the meso compound. So this is what is stereo both the individual reactions are stereo selective and the overall reaction bromine addition to alkene is stereo specific also, because the products depends the product geometry depends on the geometry of the starting material, okay that is clear.

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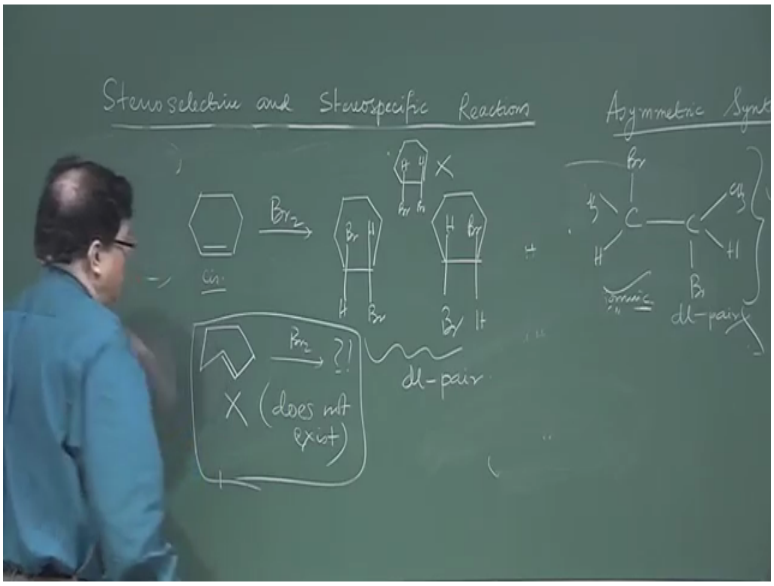

Now let us take an example, if we do the same reaction with cyclohexene, see I am talking about the very very see if you are very pure stereo chemist then this is what is followed, that means this these terms have to be followed very very seriously very rigorously, like when you say that bromine addition took Cis or trans to butene is stereo selective as well as stereo specific okay, but that is only meant for the butene system. If you take the cyclohexene system, the bromines will add from the opposite side, so you get bromine here, hydrogen there, because they will be adding in a trans fashion. Now this is the this is one product and you get the other product, because this is now optically active. So hydrogen bromine hydrogen. So this dl-pair you will obtain, okay.

Now what was the other possible product? Other possible product was the meso, but this is not obtained. So this is not obtained, only one pair enantiomeric pair is obtained, so the reaction is stereo selective. Now the question is if the reaction if the question is asked that is this reaction stereo specific? Now to know that answer, you have to make, the other isomer of cyclohexene. This is the Cis double bond. So we have to make the other isomer of cyclohexene and do the same reaction and see which product is obtained that means you have to make, the trans form of the trans form of like this, but this 1,2,3,4,5,6, these does not exist. This is sterically not accessible does not exist. Why it does not exist, because you cannot introduce a trans double bond and make a 6 membered ring, see basically these are the 4 carbon atoms already gone and if you want to make the trans compound. So then you have only two more carbons and this is not possible to add like this. So you need later on you will be knowing this or you should know this that, it needs 8 total 8 carbons that means 4 carbons more to introduce a trans double bond in a cyclo in a cyclic ring.

So trans octane is the first one, of course this does not exist in this form, this is a special geometry and this is optically active, but just to know the trans double bond exist only when n, n is the number of carbon atoms in the ring when n is equal to 8 greater than or equals to 8 okay, then you can introduce the trans double bond. So this compound does not exist so you will not be able to do this bromine addition on to this and see what happens. This is not possible, nobody has done that and nobody could do that, because this does not exist.

So now according the strict definition of stereo specific reaction you cannot say, that this reaction is stereo specific, okay, because simply to know the stereo specificity you have to take both the isomers both the substrates and do the reaction and one substrate should give one product, another substrate should give another product then it is stereo specific. It is the reaction is stereo selective, because there is no problem, because of these, this is pair dl pair and this is the meso, you are not getting the meso you are getting only this di-stereomeric pair. So this reaction is stereo selective, okay.

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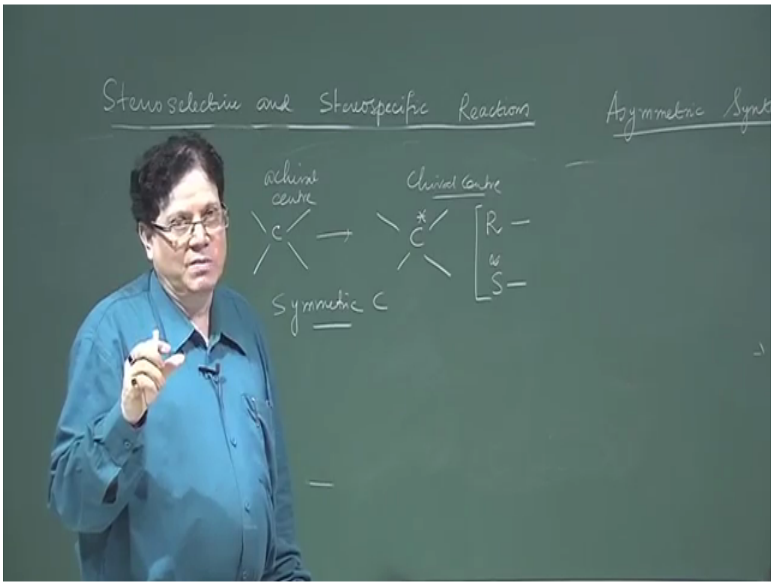

Next is the question of asymmetry, okay. Asymmetric synthesis. What is asymmetric synthesis in true sense, see as I said all these terminologies have been quite misused in the organic chemistry text books, okay, but what I am telling today is the actual meaning of this terms, but later on we may also as you go along the terms can interchange with each other like the other like the books are doing, but it is better to know the exact meaning of this and try to avoid those type of complications by using randomly one over the other, okay that should might be done.

Now what is asymmetric synthesis? Asymmetric synthesis is if you take a molecule and if you have a pro-stereogenic center. Pro-stereogenic center means, or if you just do not tell about process-stereogenic center. If you have a molecule where there is a carbon, suppose a carbon is there and if you want to convert this carbon, it was symmetric carbon and you want to make it asymmetric. If you want to convert it into asymmetric carbon. So a symmetric carbon is converted or in the chiral center is can say, an achiral center is converted into a chiral center or the modern terminology just a stereogenic center. Now when you make this chiral center, so there is a possibility of formation of R and S configuration, both and usually both are formed in 50-50 that is what is expected, but if you can do it in such a way that only one of these it is the (())(18:39) product or could be the major product then that reaction will be called an asymmetric synthesis.

So what I am saying again that if you convert an achiral carbon into a chiral carbon and if you get only one configuration as the major one or even possibly 100 percent then that reaction will be called the reaction that we have taken help to do that will be called an asymmetric reaction, okay will be called an asymmetric reaction and if it a part of synthetic protocol that is called an asymmetric, okay. now the there is a thing of degree of asymmetry, as I said that you can get 100 percent of this almost 100 percent or you can get 90 percent of this 10 percent of this, okay. So there is a thing that is called degree of asymmetry which is expressed in terms of you remember I gave you what is called enantiomeric excess (()) (19:42) or optical purity of the molecule that optical purity or enantiomeric excess will tell you or even di-stereomeric excess if they happen to be di-stereomers, in this case enantiomers.

Now there are cases where the product can be di-stereomers, so that di-stereomeric excess or the enantiomeric excess or the optical purity will tell you about the extent of asymmetry that you have achieved during the reaction, okay. Now the question is how can you achieve how can you achieve these type of asymmetric synthesis.

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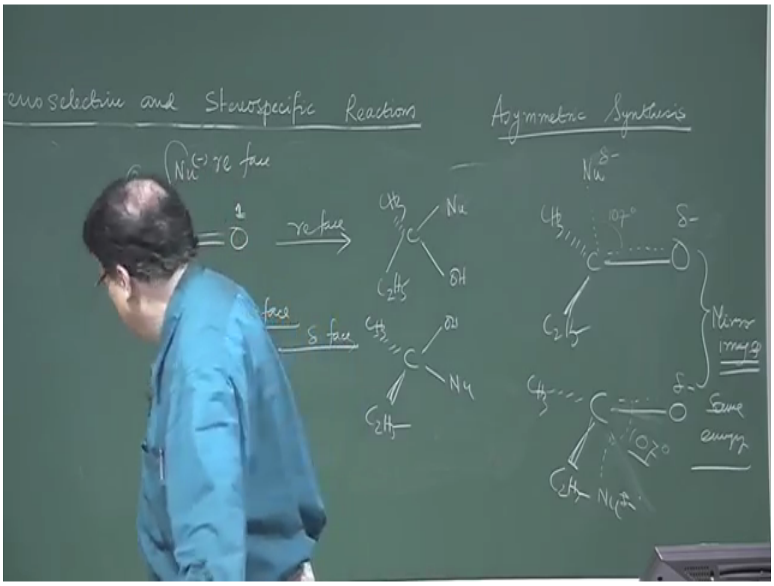

Suppose I take a carbonyl compounds, okay suppose there is a methyl, suppose these two groups are different R1 and R2, okay. Now I have told you earlier that whenever you have this better way, it is write that carbonyl carbon is in the plane of board then these two carbons one will be so this is vertically placed, so the R1 this is vertical to the double bond to the board, so that is placed along this line. The carbon oxygen is in the plane of the board, but this R1 and R2 they are one is going this way and the other is going in a back side okay. So R1 R2 and this carbon and oxygen that makes a vertical plane, but if the carbonyl is in the plane of the board okay. If it is placed in that way, now what happens, I know that carbonyls are susceptible to nucleophilic addition, okay. So suppose I add a nucleophile.

Now whenever I place the carbonyl, now we have two faces of the carbon. The nucleophile can approach from this side or the nucleophile can approach from this side, okay. Now what are these side how do you define these sides? We have seen the ray and the phi phase. First of all these faces are either enantio topic or di-stereo topic depend on what type of products you ultimately get here, okay.

If you end up getting enantiomers then that will be there will be enantio topic faces, suppose these two are not a or not chiral. They are achiral groups okay. Suppose these two groups are achiral groups so take an example, suppose methyl, this is methyl and this is ethyl, okay. Now the top group you know how to number this the top group is the top face is now one, if you do the preference the priority sequence, this is one, this is two and this is three. So if you see from the top, so one then one then two and then three. So that means it is going in a clockwise direction. So this is a ray face okay this is a ray face and if you do the if you check this one. So this is one, this is two and this is three. So now it is going in an anti-clockwise direction. So this will be phi face that we have done earlier, right. This is ray face and that is phi face.

So if the nucleophile approaches from the ray face then the product will be C2H5 carbon and this will be OH and sorry, now the nucleophile will be on this side and OH will be on that side okay and if the this is the ray face approach and if it is from the psi face then the product will be, this is OH, this is nucleophile and this methyl and this is your ethyl. So what is a relationship between these two? They are mirror images okay. They are enantiomeric pairs that is why I called this as enantio topic faces, okay.

Now the transition state that is involved when the attacks takes from the ray face, you can depict it as without much deformation you can say that the carbonyl oxygen has brocken to some extent and this is the C2H5. This is the nucleophile. So that is forming a bond half bond. So this is the transition state, okay. So that will be delta minus and if it is approaching from psi face, the transition state will be, so C2H5 and now the nucleophile will be from nucleophile will be from this side okay.

The nucleophile actually approaches at an angle of about 107 degree. This is what is called barge donage trajectory. So whenever something attacks to a carbonyl, see this is a carbonyl carbon**,** suppose this is oxygen. So the nucleophile does not approach at perpendicular direction, it approaches at an angle of about 107 degree, close to the angle of an sp3 carbon, remember that this carbon after the addition will become an sp3. So it is close to that sp3 carbon. So this trajectory is called barge donage trajectory and the angle is calculated to be around 107 degree. So that is why I make it slightly slant in that sense 107 degree. Now the important thing is that, these two are now mirror images**.** So energetically, they are same, so same energy.

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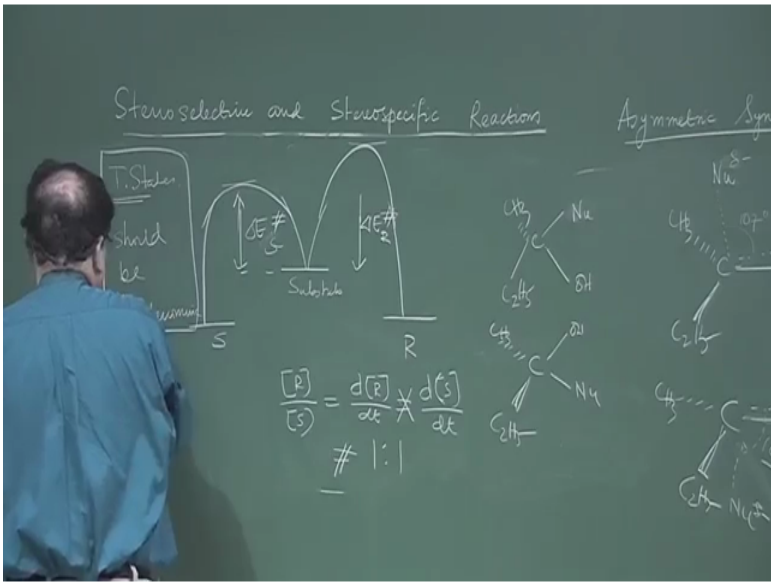

If you do this type of reaction where the transition states are enantiomeric that means you start from the carbonyl that is their carbonyl compound that is the ethyl methyl ketone that we will have started and what you have getting two products. So one product is suppose this is the R compound and this is the S compound, but the problem is at a both S and R we will have the same energy, but here the problem is the transition states and this is the transition state this is transition state for R compound formation transition state for S compound formation.

These transition states are enantiomeric. If that is the case that means they have same energy and if that be the case. If this is your substrate that means the starting ketone. So the activation energy for the formation of the R compound is the same as the activation energy for the formation of the, so this is the delta E this is delta E, they are same. So delta ER and delta, so this is delta ER and this is delta ES, (())(27:36) may be a hash. So these two are same.

So if these two are same then the rate of formation of R will be equal to rate of formation of S and that means your R and the S will be produced in equal amount. So R by S will be dependent on rate of formation of R is and that will be equal to rate of formation of S, because both are the same activation energy, okay. So this is a symmetric synthesis, because what is asymmetric synthesis?

If you can make one of these as the major product then that becomes an asymmetric synthesis, okay, but this way you cannot achieve this. If the transition states are enantiomeric then you cannot achieve asymmetric synthesis. So you have to introduce di-stereo di-stereomeric relationship between the transition states, in order to achieve an asymmetric synthesis. So that is the principle of asymmetric synthesis that when you consider the transition states. The transitions states cannot be enantiomeric. So they have to be di-stereomeric and you know the diastereomers of different energy, okay.

Di-stereomers are not mirror images that is they are called di-stereomers and they have different energy levels and if they have different energy level then the activation barrier changes for the formation of both the compounds and then there is a possibility of formation of one compound over the other, one configuration over the other. So that is the principle of asymmetric synthesis that means whatever you do, you have to make this transition states differ in energy, okay differ in energy, suppose, this will be bigger and this will be smaller.

Now the question is how do you do it, okay? So this is what is then this will not be equal to this will not be equal to this and if that is not equal to this and this is not equal to 1 is to 1. So you have an asymmetric synthesis. The question is what is a asymmetry that depends on the type of reaction that you are doing, okay.

So the to achieve asymmetric synthesis, the transition states the rule of thumb is the transition states should be di-stereomeric, okay. Then only you can have an asymmetric synthesis, because then only the rate of formation of one compound over the other will be different, okay. So in the next lecture we will consider how to achieve asymmetric synthesis with some examples and then how to predict which compound or which di-stereomers or which isomer is obtained in major amount over the other. There are certain rules which governs the which can predict the configuration of the major configuration, but that will be in the next lecture. Thank you.