Course on Stereochemistry
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Mod07 Lecture 30
Conformation and Reactivity (Contd.)

Okay, so last time we have seen the differential reactivity of axial and equatorial functional groups, in a cyclohexane system, but the systems that we have handled were the locked, we are in locked conformations, okay like by putting the tersary butyl at the 4 position, but there may be there are plenty of systems where, which are freely convertible into one conformation and the other one, okay. There are various possible conformations unlike the locked conformation systems. So the situation will be little bit different when we deal with such a system, okay.

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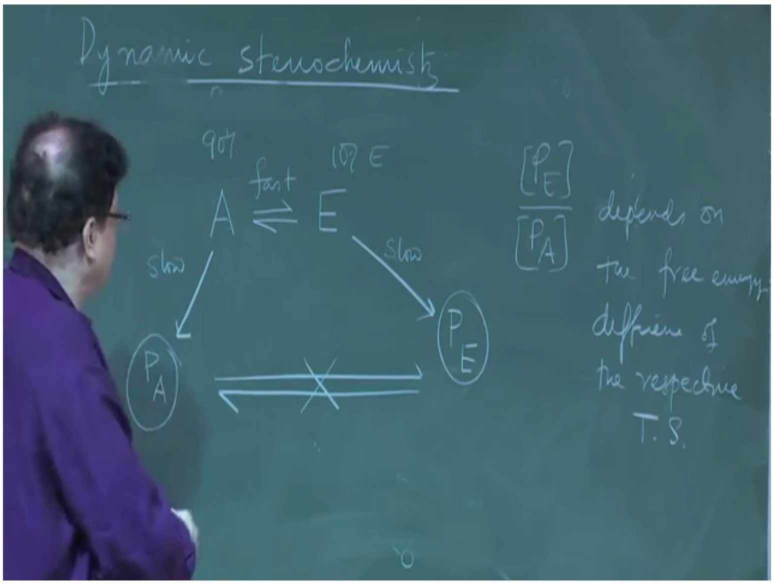

So let us first define the problem. Suppose a molecule has two conformations can exist in two conformer as two conformer, one is A another is E, okay and they are in equilibrium with each other. So what I am saying that a particular system can exist in two conformations or rather two conformers which are in equilibrium with each other. Now I try to do a reaction, a chemical reaction on this system. So this will react, because this is a different entity as, it is in the different conformation. So they will react with their own rates, okay. So E gives, suppose this also another criteria I put in here, that these generates a product, which is say I say pE and this generates a product which is pA, okay.

Now so basically I have a system where there are two conformers present A and E. they are inter-convertible and they are extremely rapidly inter-convertible that means if there is a (()) (2:21) of A then E goes to A or if there is (())(2:24) of A in the system then a goes to E. so that in inter-conversion is very fast as compared to the rate of the reaction. So rate of the reaction for this these are slower much slower as compared to this rate of inter-conversion between A and E and so that is the first restriction that this is the rapidly inter-convertible and these reactions that I am doing on E and A are slower than this inter-conversion rate and a 4th and the 3rd thing that I put is that there is no inter-conversion between the two products. So pA cannot be converted to pE or pE cannot be converted to pA.

Now in that case if all these things are satisfied that means rate of inter-conversion is fast, rate of reaction is much slower as compared to the rate of inter-conversion and the products are different and these products are not inter-convertible. Now question is what will determine the ratio of these two products pE by pA. So concentration of pE verses concentration of pA. So which parameter we will design? Now one might think that suppose I started with 90 percent of A and 10 percent of E that is the ground state population of A and E and just from the population difference one might say that pA will be formed, because a was present in 90 percent and pE will be less, because E was present only in 10 percent, but that is not true.

In a conformationally dynamic system, this is what is call conformationally dynamic system, what happens if these restrictions are followed that the rate of reaction is slower as compared to the rate of inter-conversion and the products do not lead to the cannot inter-convert then the ratio of the two products, first of all it does not depend on the ground state population of the conformers. It does not depend on the ground state population of the conformers, okay. Then what factor it really depends? The factor that decides, the ratio of these two is the difference in the Gibbs (())(5:01) free energy of the two transition state is a difference energy of the , so it depends on the free energy difference of the respective transition states, okay.

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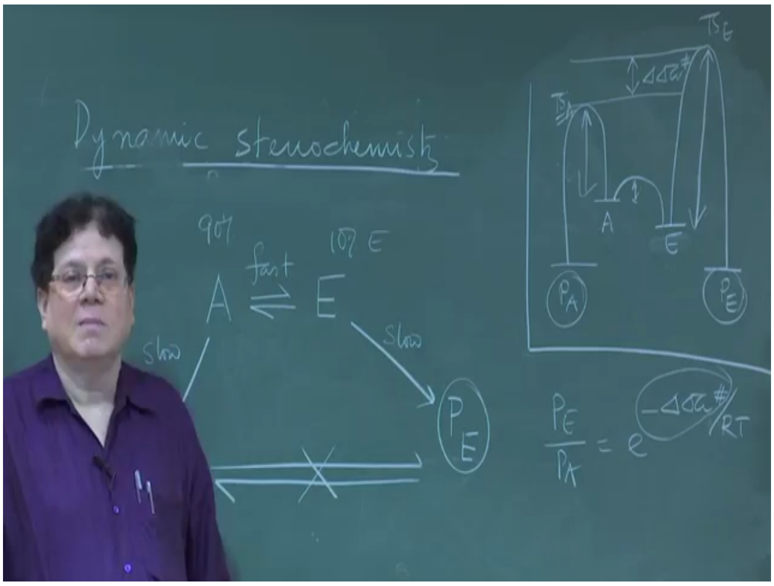

Now to I think this will be little bit clear if I draw the energy diagram to show you the case, okay. Suppose this is the conformer A and this is the conformer B, okay and they have a barrier of Course there will be a barrier to inter-conversion, but that barrier is very small, okay that barrier is very small. On the other hand suppose this is E we have consider this has E.

Now suppose this is reacting and giving a product which is pA that means one conformer leads to one product and the other conformer leads to another product, suppose that has got higher activation energy. So this is pE, so according to what is called now the Curtin-Hammett principle, the ratio of pE and pA will depend on the free energy difference. This is called del del G hash. The free energy nice between the two transition states. This is a transition state for reaction of A and this is the transition state for reaction of E, okay. So this difference will decide there is relationship there is a relationship that is pE by pA is equal to it will be e power minus del delta G hash by RT.

So basically temperature is a factor that another major factor is the free energy the would be difference in the Gibbs free energy of the transition state, so that we design. So it immediately tells you that it does not matter what is the population here. If the rate of E is more than the rate of conversion of A to pA that means if the that transition state of E lies lower than the transition state of A then, the product from E will be more or the vice versa.

If the transition state of A lies at a lower level than the transition state for the for the E then A will be react at a faster rate and, because that means the activation energy is also less otherwise why it will be at a lower level and if that is a case like here the activation energy of this is less and the activation of energy of this. So now I can say if this is a situation then pA will be more and pE will be less, okay. Irrespective of the fact that E was more stable than A. so in the ground states population E was more than A, but that is not the decide it (())(8:29) a factor.

The decide it (())(8:29) it factor is the is this difference that means basically, which transition state, the other way to speak it that which transition state is more stable and which activation energy is more or less that will the that will be the guiding factor, okay. So it is not always true that the population of the conformer, the conformer which is more populated will give the major product that is not true okay. Now that is what is called the Curtin-Hammett principle.

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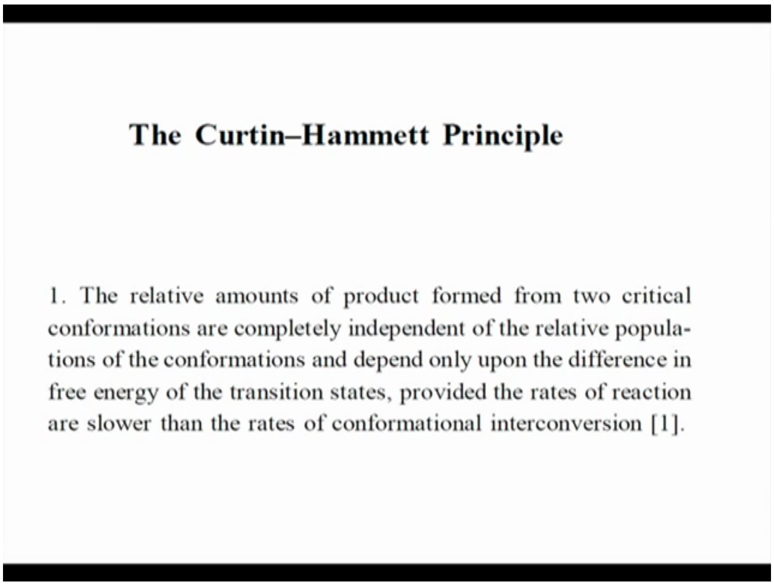

The Curtin–Hammett Principle

1. The relative amounts of product formed from two critical conformations are completely independent of the relative populations of the conformations and depend only upon the difference in free energy of the transition states, provided the rates of reaction are slower than the rates of conformational interconversion [1].

The Curtin-hammett principle can be said in different ways the relative amounts of one way to say, it is the relative amount of the product found from two critical conformation that means two extreme conformations are completely independent of the relative population of the conformations and depend only upon the difference in the free energy of the transition states as I said, provided the rates of the reactions are slower than the rates of conformational inter-conversion, as I said, the rate of inter-conversion should be very fast and the this is a other way to say the reverse way, the rate of reaction are slower than the rates of conformational inter-conversion.

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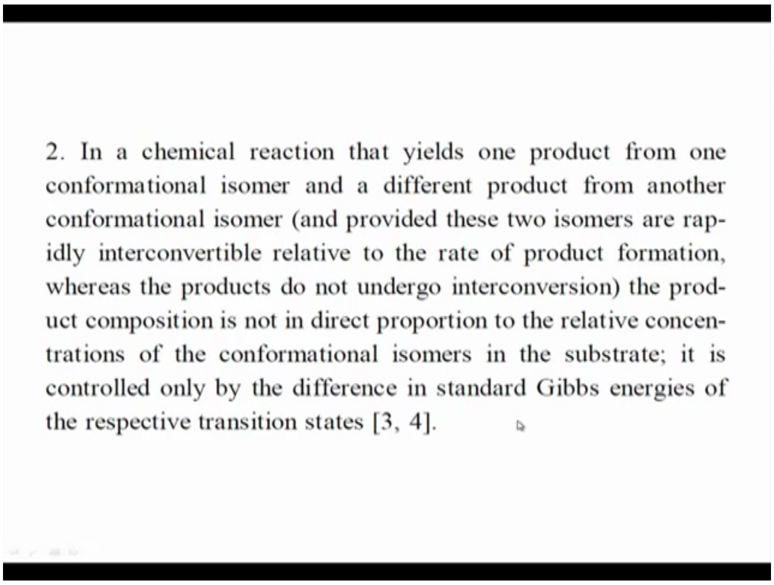

2. In a chemical reaction that yields one product from one conformational isomer and a different product from another conformational isomer (and provided these two isomers are rapidly interconvertible relative to the rate of product formation, whereas the products do not undergo interconversion) the product composition is not in direct proportion to the relative concentrations of the conformational isomers in the substrate; it is controlled only by the difference in standard Gibbs energies of the respective transition states [3, 4].

The in another way you can say it, in a chemical reaction more elaborately you can say, yields of one product from one conformer conformational isomer or a conformer and so in a chemical reaction that yield one product from one conformational isomer and a different product from another conformational isomer and provided that these isomers are rapidly inter-convertible relative to the rate of the product formation, whereas the products do not undergo inter-conversion.

So the first definition was not very correct, because it never said the inter-conversion between A and E that should not happen in a Curtin-Hammett system. So provided that there is the products do not undergo inter-conversion. The product composition is not indirect proportion to the relative concentrations of the conformational isomer in the substrate; it is controlled only by the difference in standard Gibbs energies of the respective transition states, okay.

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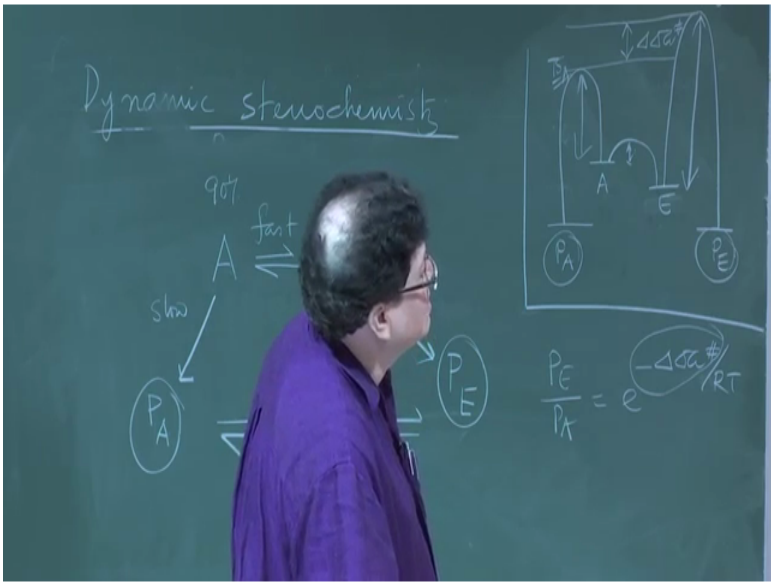

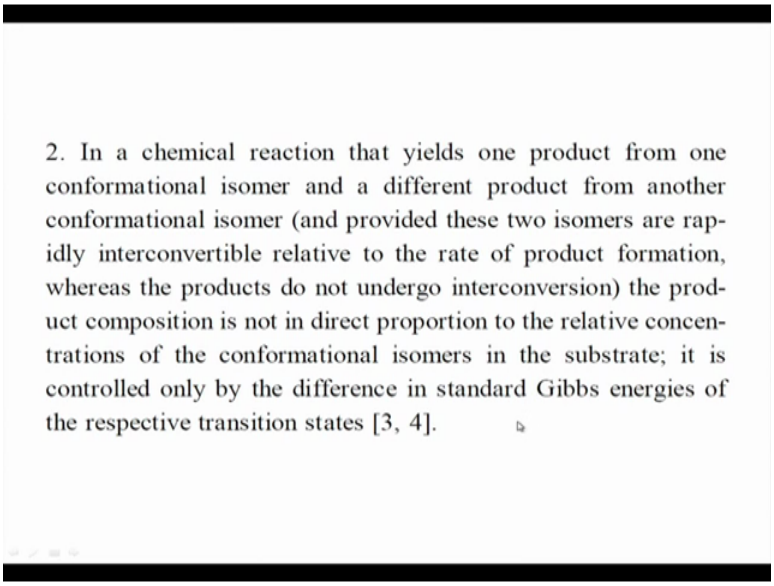

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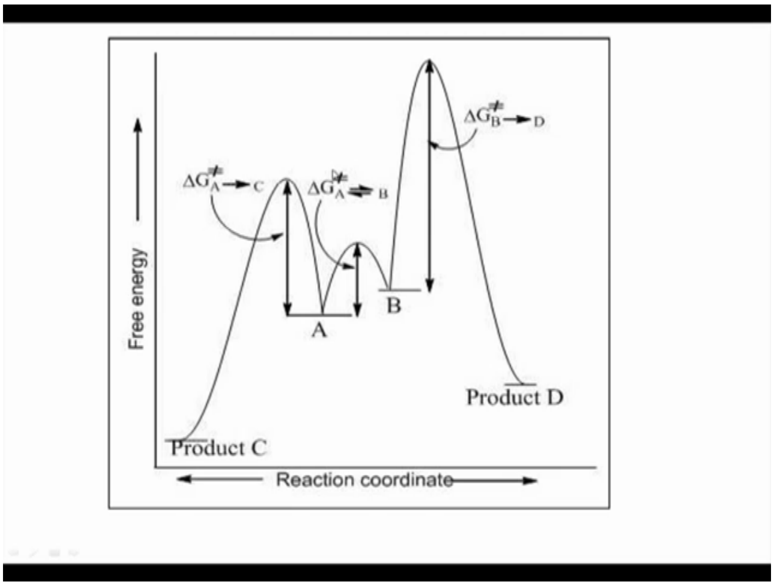

So this is I think the more correct version of Curtin-Hammett principle and gave you the equation, but this can be derived also, this equation but that is not within (())(10:55) the scope of this of this (())(10:58). So again I go to the energy diagram, so what Curtin-Hammett Principe says that first of all this barrier is much less as compared to the that activation energies that is number one, so they rapidly inter-convert to each other, and the product ratio of products C and B will depend on the difference, difference of this energy this minus this and that is the deciding factor (())(11:25), okay.

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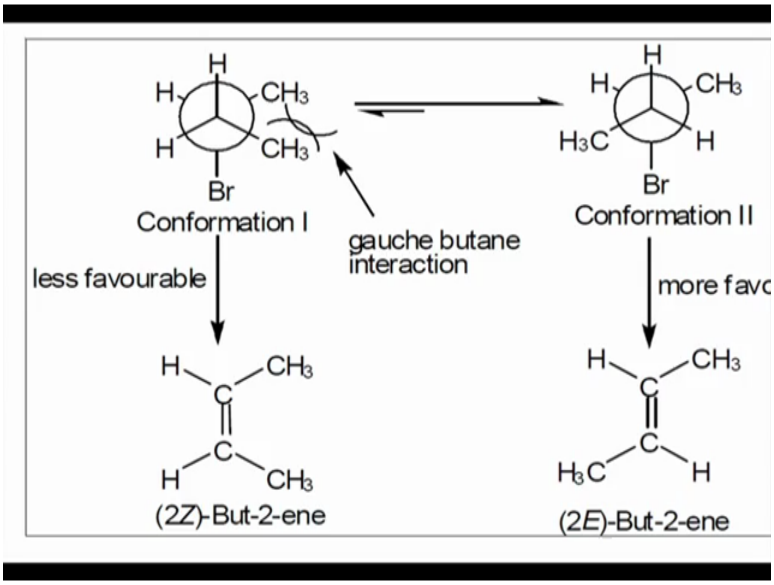

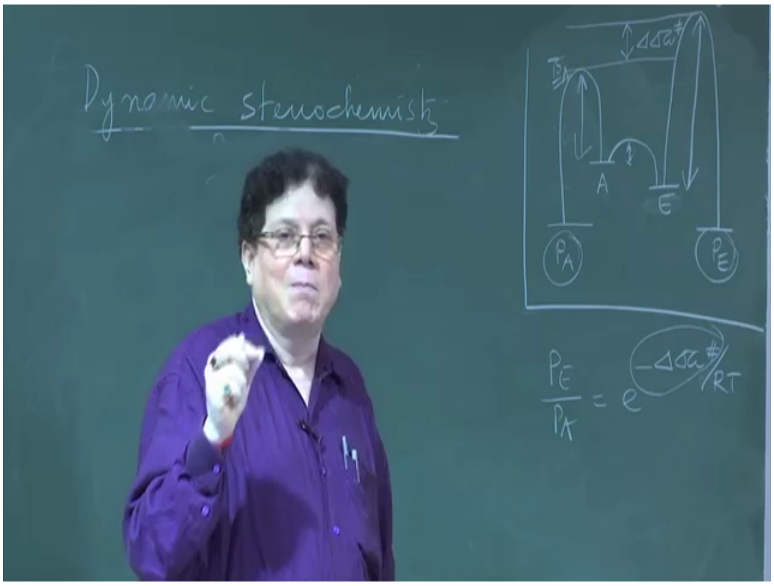

Now the question is whether we will come to the examples of Curtin-hammett principle. So the most striking example for a Curtin-hammett principle will be to show that a conformer, which is the least expected conformer is giving the major products, which is however very hard to find hard to find, because most of the time, it has been found that the major conformer is actually having a higher rate of reaction that means a lower activation energy that is in most of the cases, but we will go we will discuss all these cases and try to find out a case where the minor conformer gives the major product, because that will be direct proof for the Curtin-hammett principle, if the major carbon conformer gives the major product then you might say that actually in the ground state population ,which is dictate in the process. So it is the best process the best way to prove the Curtin-hammett principle is to show that the minor conformer gives the major product, okay.

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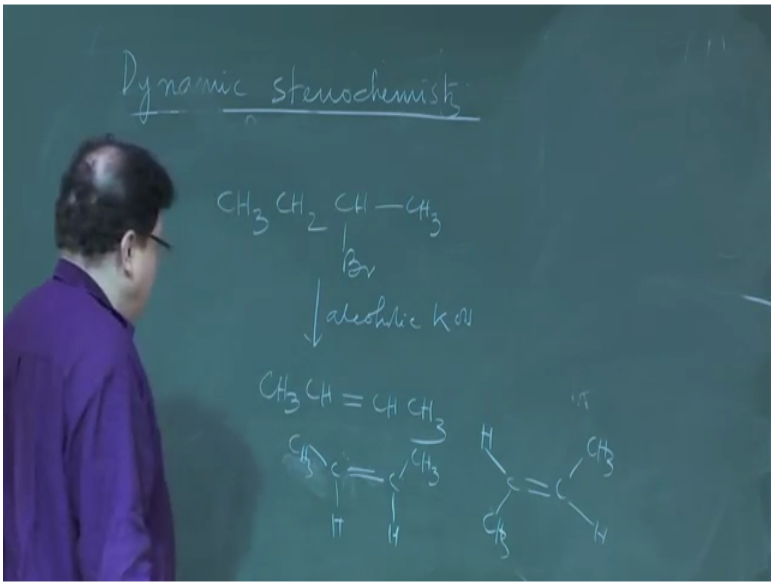

So we will come slowly into that the first example, again I remind you now we are now dealing with a conformationally (())(12:43) system, okay. So conformationally (())(12:46) system that means molecules which can exist in various conformations. So if I want to make two butene from two bromo-butane by elimination by E to elimination, you know that if I treat this with alcoholic KoH then what happens? This is eliminated the beta hydrogen most of the product is the (())(13:20) product and not the Hoffman, because there is another possibility of beta elimination from this side, but the major product is this one.

Now this major product again can be Cis or trans, so you have the Cis verses the trans. So the actual diagram is this the methyl on this side. So either this product or you can have the trans isomer. The question is which one will be formed in major amount?

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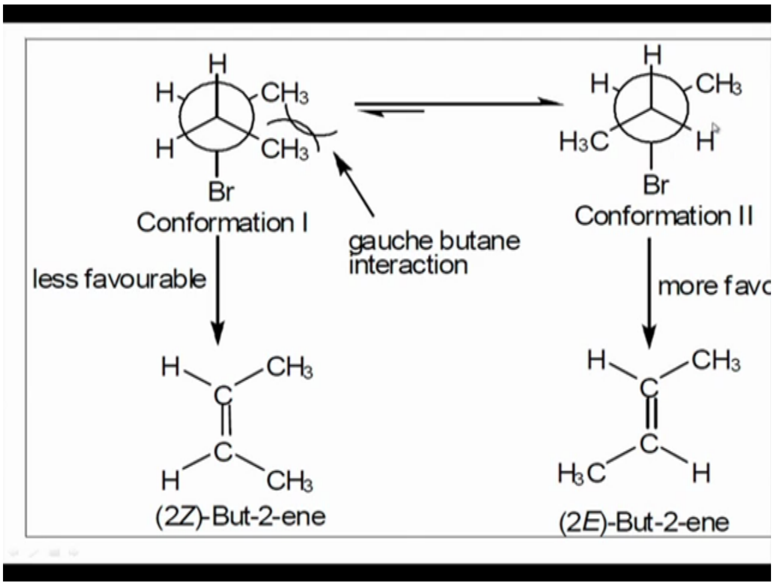

Now here we know that this molecule this 2 bromo-butane, we can consider it, it existing in two conformations, one where the methyls are in the gauche form, okay. So there are two staggered conformations we are considering, in one the methyls are in the gauche positions whereas, in the other the methyls are in the anti-position, okay. Now we are considering these two staggered conformations, in order to have a hydrogen a beta hydrogen, which is align opposite to the bromine atom. The bromine atom is leaving, so also the hydrogen, it is an E2 elimination and so we have to have a hydrogen opposite to the bromine and while doing so we can find two conformers, one is this one. This is the gauche conformer and this is the anti-conformer.

Obviously, the anti-conformer will be the major conformer, because of this gauche butane interactions. It will be less and this methyl bromine interaction is there in both the systems. So this will be the conformation which is less, because of the gauche butane interaction, this is more, okay.

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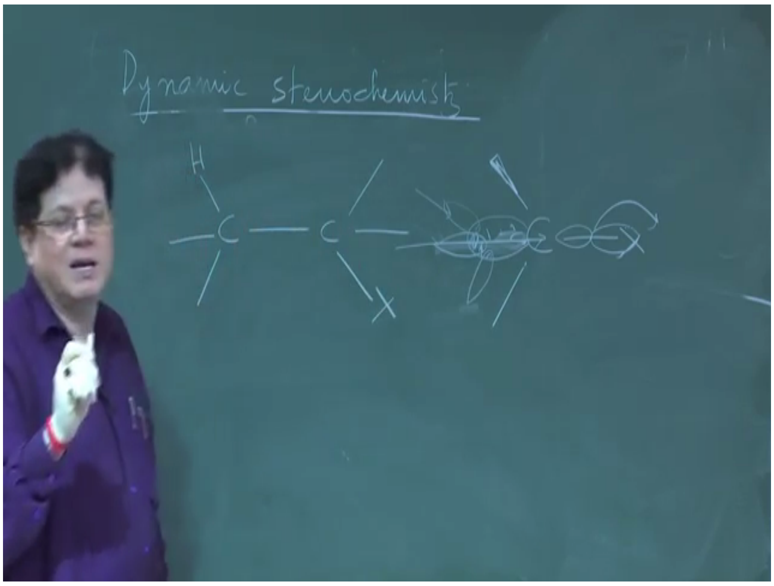

Now the mechanism of E2 elimination okay, we have not done any stereochemistry of SN1, SN2 or E2, but just to say the E2 elimination. In the E2 elimination what is happening that you have a X here and you have a hydrogen, okay beta hydrogen we are talking about beta elimination, okay. Now in all the reactions there is something which is called stereo electronic factor. What is unsteric factor? Steric factor we know is the repulsion between two groups between two bulk y groups when they come very close to each other and that affects the rate of reaction. The other thing is the most important parameter is the stereo electronic parameter.

What is that? Stereo electronic parameter is says that in a chemical reaction, the reaction will take place in such a way that the transition state involved in the reaction is stabilized to the maximum, that means in order to do that the orbitals that are, see what is a chemical reaction? Bonds are Brocken and new bonds are made. So when these bond breaking and bond making processes are going on, the orbitals are (())(16:42) aligned, okay. They are pairing in differently than substrate, okay like in elimination, we know that there is a formation of a double bond here and with a expulsion of H plus and X minus, okay. So there is now the orbital are now changing their partners, okay.

The stereo electronic factor says that the orbitals in the transition state, the orbitals are in aligned in a such a way, so as to maximize the overlap that is involved in the transition state. To maximize the overlap of the orbitals in a transition state, again I repeat, stereo electronic factor says that in a reaction chemical reaction, the transition state should be such that allows maximum overlap of the involved orbitals that are been brocken or that are or orbitals that are participating in the reaction, okay like in, this is the E2 elimination.

Here, the stereo electronic requirement is that the hydrogen and the X should be anti to each other and in SN2 reaction, the stereo electronic requirement is that this the nucleophile should approach from that back side not only from the back side, but it should be aligned to the C-X axis opposite to the C-X axis, okay. So stereo electronic factor demands that it approaches the carbon, which is undergoing substitution, approaches the carbon from behind the leaving group not only behind the leaving group, it should be just a aligned with a C-X axis. So that is the stereo electronic requirement. Now why are these, I said because the transition state in the transition state there is maximum overlap of the orbitals that are involved like, here we know that there is this is, the suppose this is the orbitals, there is a small part of the orbital here, okay.

Now if you consider actually I put it small this is the bonding seen arrow. In the anti- bonding seen arrow there is a bigger lob on the back side, which is empty and the bonding orbital. So when the nucleophile comes, so if the nucleophile comes through this side there will be less overlap of the orbitals, only if it comes from the from just exactly opposite to the C-X axis then the overlap is much more, on the other hand if it comes from inclined position, which is also beck side of C-X, but the extant of overlap will be less. So it approaches from the back side and opposite to the C-X axis, okay. So that is the stereo electronic requirement of SN2 reaction and you know the consequence of this. This leads to what is called (())(19:45) inversion that is inversion of configuration.

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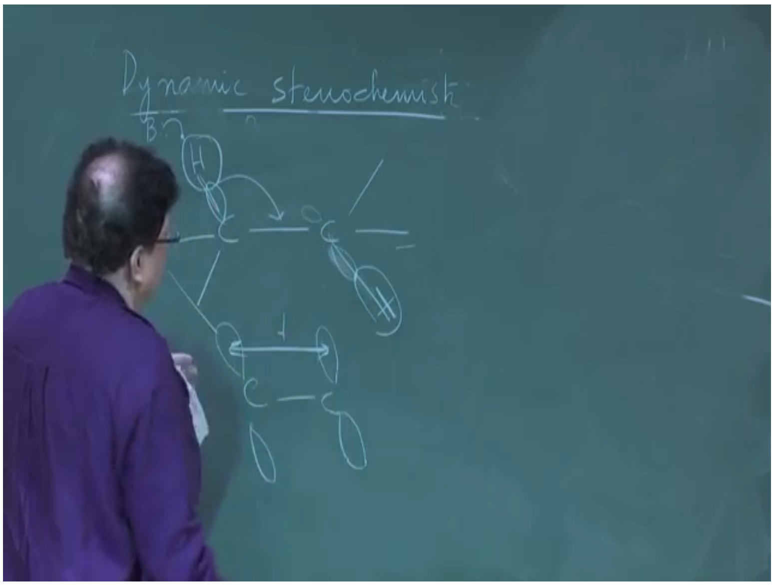

In E2 elimination, very similar things happen that the base approaches from here, takes the hydrogen, E2 means it is a bimolecular reaction so the base involved in the rate determining step. So now that comes here and this goes there. So in terms of orbital approach if you break it into orbitals and this was the hydrogen. So in the transition state what will happen now this carbon are becoming almost a sp2. So there will be maximum overlap between these orbital if it approaches if they are perfectly anti to each other, because if there is an angle between the or between these lines C-X and C-H then the p orbital or semi P orbitals, which are generated during the reaction they cannot be aligned to each other.

So if there is a angle so the the overlap will be less that means the transition state will be less steremised. So that is the reason that this should be perfectly anti to each other. So that is E2 eliminations stereo electronic requirement of E2 elimination. So it the hydrogen, which is eliminated should be anti to the group to the leaving group, okay.

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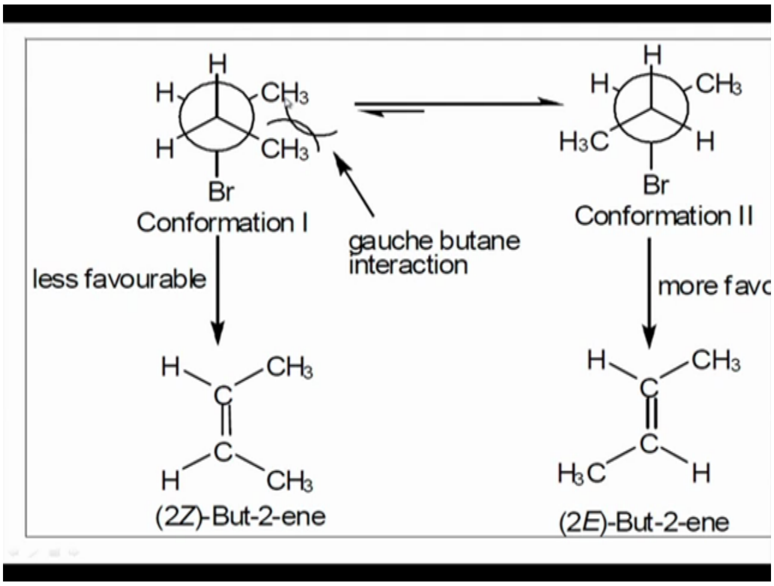


Conformation I

gauche butane interaction

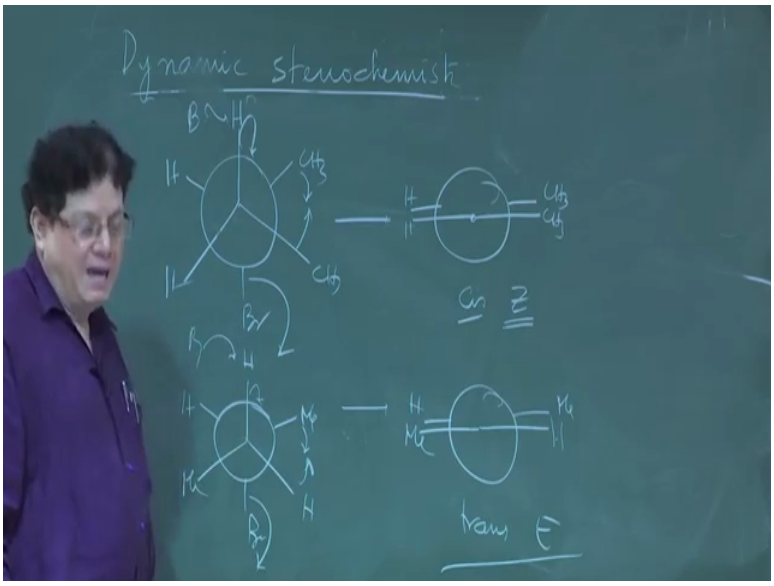
Conformation II

less favourable

more favc

(2*Z*)-But-2-ene

(2*E*)-But-2-ene



Now let us come back to this slide again. So this is your one conformation and this is the other conformation. Now the hydrogen both the conformations there is a hydrogen which is anti to the bromine. So the base abstracts this hydrogen and it comes attacks the back carbon bearing the bromines. So bromine leaves. So in the process what happen, this carbon becomes sp2 and the back carbon sp3. So the hydrogen now and the methyl will eclipse each other. So hydrogen in methyl will eclipse each other and so that will lead to, because the methyls are in the opposite direction. So that will lead to the formation of the trans product, which is the 2E also, the called E configuration, right we know the EZ stereochemistry now.

On the other hand if there is elimination here, then what happens this hydrogen is lossed, this bromine is lossed. These methyls will now come closer to each other and methyls will come closer to each other and that will form the Cis 2 butane, okay Cis 2 butane. Now the rate of reaction of this is more, because of the said that there is much less interaction. So as this hydrogen approaches this methyl here. Here these two methyls become eclipsing to each other, as the reaction proceeds you can again draw it, continue numen projection. So this was the hydrogen. This is bromine, this is a methyl that is a methyl and this is a hydrogen. So when this hydrogen is taken up by the base, so this comes here. The bromine goes out, so what happens?

In the numen projection, it will look like this. So this is methyl and that is methyl. This is hydrogen, this hydrogen that means they are now, approaching in a an eclipsing orientation. So that is the Cis compound or the Z isomer. So the Z isomer, there is increases of eclipsing interaction as the reaction goes. So that has got higher activation energy as compared to the other isomer. What is the other isomer? There is methyl here and methyl here, this bromine, this hydrogen here. So this is the other isomer. So as the reaction proceeds, sorry this hydrogen here, as the reaction proceeds the base, so that goes here, this goes out and there is now eclipsing interaction between hydrogen and methyl, which is much less as compared to a methyl-methyl. So the product will be the top one will be the hydrogen, the bottom one will be methyl and here the top one will be methyl and the bottom one will be hydrogen. So this is the trans that means E isomers.

So the E isomer will obviously more irrespective of the population of these two, but here unfortunately, this is the major population, major the conformer which is more populated, and , but the reason for getting the trans isomer is not due to that, this is populated in a populated more, the reason is that there is this has got less activation energy for conversion compared to the gauche compared to this conformation. So that is the reason why this is more and this less, okay, but as I said that if the major conformer gives the major product then it is very difficult to convince students that the reason is actually is the kinetic reason not the ground state population, but it is very difficult to convince the student.

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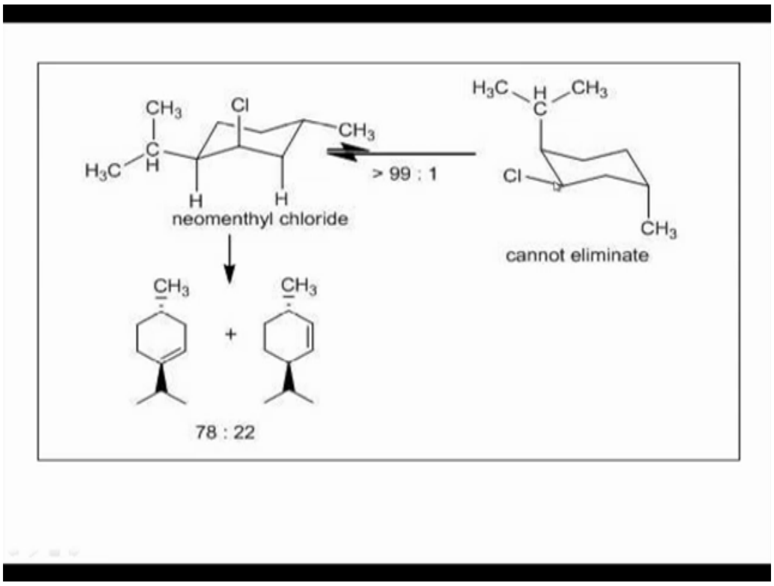

So I said that we should have an example where the minor population the minor populated conformer gives the major product, okay. This is an extreme example that this is neomenthyl chloride, I talked you about the menthol neomenthol where chlorine is replaced by OH, but this is suppose the neomenthyl chloride. Now this has got two conformation conformers, but one is highly populated that is where the chlorine is axial methyl is equatorial and this isopropyl is equatorial. If it flips then the isopropyl becomes axial that is what (()(26:11) is the big group and this is also quite big only the equatorial the only the benefit you have is putting the chlorine in equatorial position, but you gain you actually forcing these big groups in the axil position. So this is only present in 1 percent and that is about 99 percent. So this is the this is the one which is not present at all (())(26:39).

So again here is that the chlorine has to eliminate if I want to produce the beta elimination then either this hydrogen is lossed or this hydrogen lossed (())(26:48). So again only these two compounds are formed and not the compounds from this conformer not from this conformer. So that is that is not a correct example again a true example or an example which proves the Curtin-hammett principle, here also again the major conformer giving the major products. So again one can argue whether, it is due to population difference or due to the kinetic that is plane a part. Here the kinetic say that this cannot eliminate, because there is no hydrogen opposite to chlorine. So we this can produce the product, okay.

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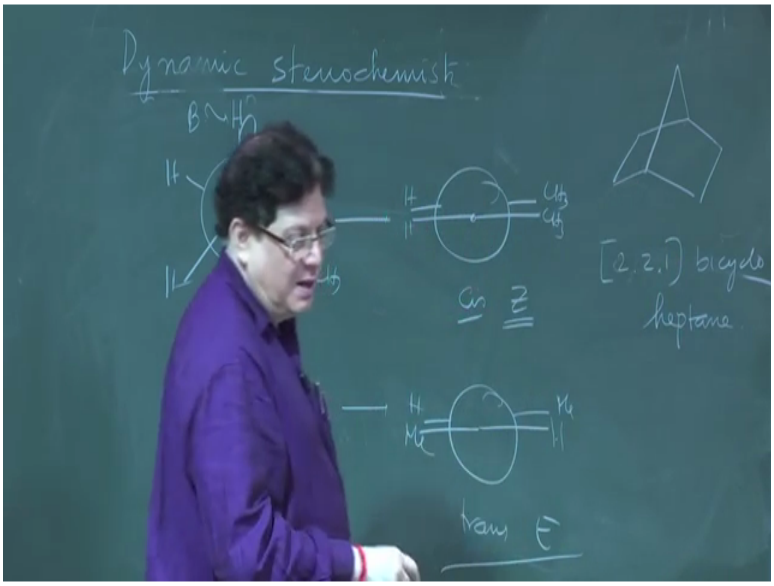

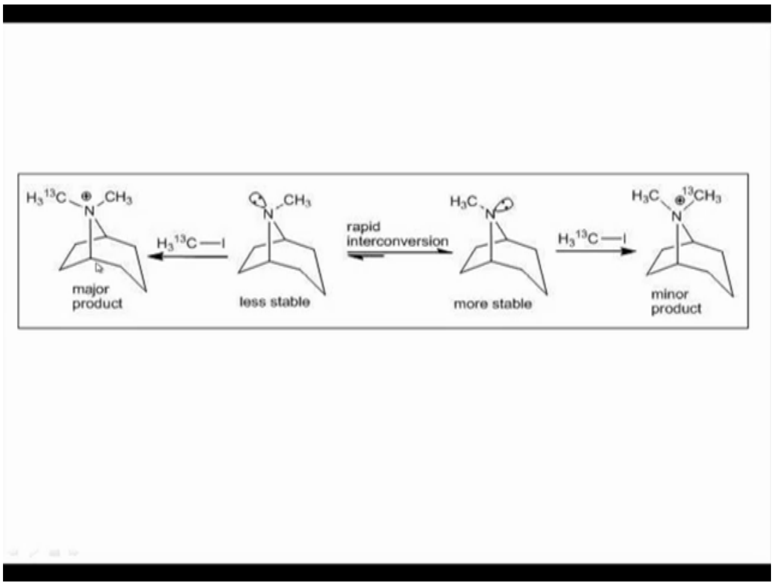

Now let us come to a real example, where the actual where the minor isomer gives the major product, okay. So this is a compound a bicyclic compound. It is bicyclo as a bicyclo compound as which is a bicycle compound, the like this you have, this is a example of a bicyclic compound, okay. These are named probably whether you know this or not. This is 2 to 1 bicyclo the n the total number of carbons 1,2,3,4,5,6,7, so this is 2, 2,1 bicyclo heptane 2,2,1 bicyclo make it is a dots (())(28:22) 2,2,1 bicyclo heptane, okay.

So similarly if you look at the look at this compound what is shown here this is your 2, this is 3 carbons here. So 3,2,1 bicyclo as a and the total number of atoms is 1,2,3,4,5,6,7,8, so bicyclo as a octane. So this is bicyclo as a octane.

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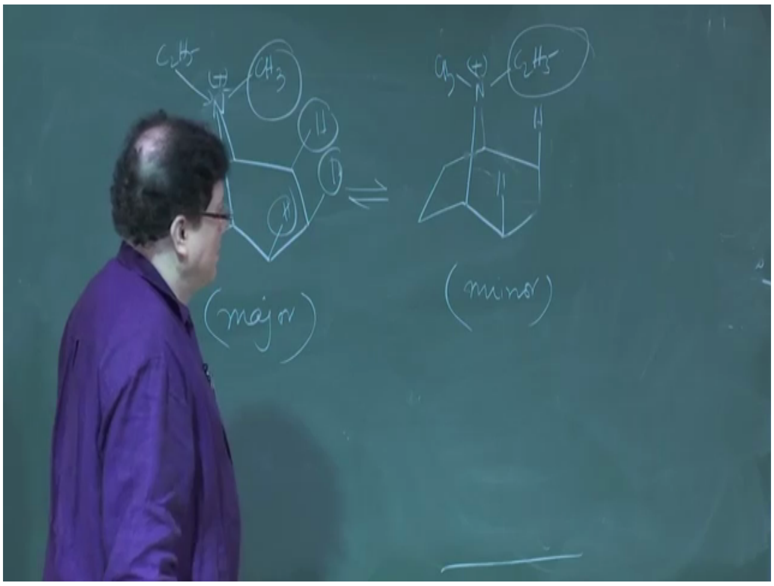

Let me draw it here, in the board okay. So what we are talking about is a system and there is a nitrogen here. So this is the as I said, this is 2, this is 3. So 3, 2, 1bicyclo as a, so number of atoms in the ring is 1, 2,3,4,5,6,7,8, including the nitrogen. So that will be as a octane bicyclo as a octane. Now this has got a suppose, I take the methyl group, so n methyl n methyl bicyclo as a octane. Now this has got 2 conformations depending on (the) that is due to the that is inversion of the nitrogen, okay. So either the methyl is on this side or methyl is on the other side. So methyl is on this side as a lone (())(30:22) pair on this side. Now between these two, because of the presence of the larger portion of the ring so you have lot of hydrogens on the top. Here you have hydrogens here and there. So there are more interactions of these hydrogens with these methyls, okay.

So as a result, this one will be the major conformer and this one will be the minor conformer this one will be the minor one. Now suppose I do an n alkylation (())(31:02). In the literature, they have done the alkylation with a labeled methyl iodide, but I can to simplify the system, suppose I add ethyl bromide. So what will happen? The ethyl bromide will react the nitrogen will attack it in a SN2 fashion. So there will be now ethyl group, so I can erase this lone pair, now there will be ethyl group on this side, the nitrogen plus and there will be ethyl group on this side, okay.

Now the question is which one is this compounds are not same. Now the inversion is also not taking place. So they are mirror images of each other, okay which compound is more. First of all this is major conformer and the problem is, the approach of this ethyl, because of these hydrogens the approach of the ethyl bromide from this side will be difficult as compared to the approach of the ethyl from this side, okay. So now the major product will be this one that is coming out minor isomer from the minor conformer whereas, the major conformer leads to an minor product, okay.

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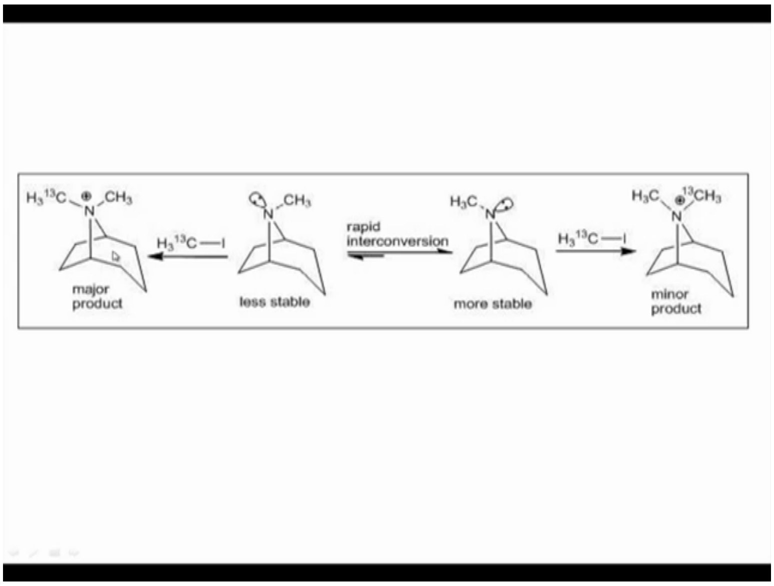

So major I can show it to here and that will end up this lecture session that you have this compound and this compound, as I said, because of the longer, because of three carbons here, so you have more steric repulsion with the methyl. If the methyl is on this side that is why this one is less stable and this one is more stable as you have less hydrogens, less carbons here that means less number of axially oriented hydrogen. So this is the less stable conformer, this is the more stable conformer.

Now this was treated with not ethyl iodide not ethyl bromide, but for simplicity I said ethyl bromide. This was treated with a 13 C level methyl iodide. 13 C level means that is a different carbon. So what will happen? Now the methyl is when the nitrogen lone pair ion this side, then this attacks here, in the methyl, but the problem is the approach of this methyl iodide to this lone pair is difficult, because this is a larger portion of that ring (())(33:35). So that is less accessible.

On the other hand, it is easier for this lone pair to attack the ethyl bromide from this side, because this side is easily accessible. So again I repeat, this side is less accessible that is why the lone pair attack on to the methyl iodide will be less (())(33:55) from this side than the lone pair attack from this face to the methyl iodide. So what happens? This becomes the major product, because this side is more this phase is more is more available satirically accessible. So this becomes major product and that becomes minor product, okay. So this is a classic example where the more stable conformer that is more populated conformer is giving a minor product and the less populated conformer is giving the major product, I think this is the best example, which proves the validity of the Curtin-hammett principle okay.

So we will discussed more problems next day, today I think that is the it thus we end up with saying that population is not the determining step for systems, which follows Curtin-hammett principle systems where equilibration is very rapid between the conformers, but the rate of the reaction is slower then what happens? The product ratio is not govern by the population ground state population, it is govern by the by free energy difference between the transition state, okay. That is the very important concept in stereochemistry dynamic stereochemistry with conformational (())(35:16) systems. Thank you.