Mechanisms in Organic Chemistry
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Lecture-25
Heavy Atom Isotope Effects

So welcome back. In the last class we were looking at secondary kinetic isotope effects. And we had seen that secondary kinetic isotope effects is usually associated with change in hybridization. So, we had seen that sp^3 to sp^2 leads to normal kinetic isotope effect.

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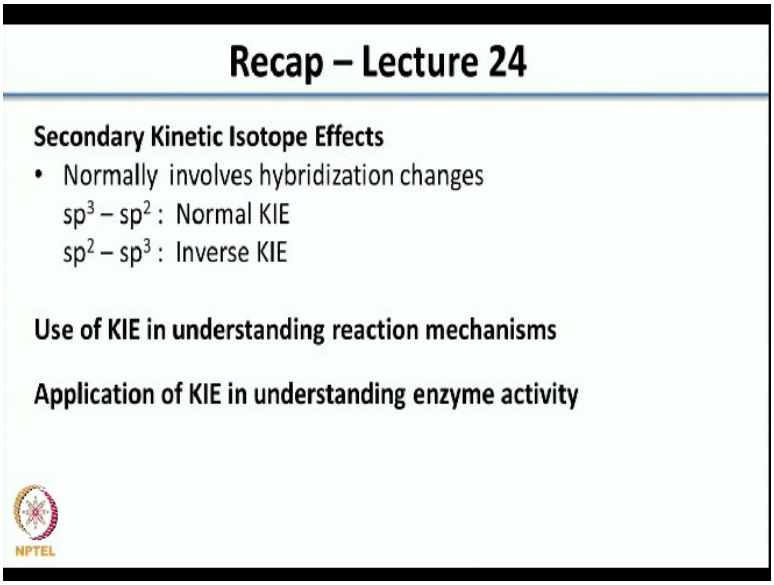

Whereas, sp^2 to sp^3 leads to inverse kinetic isotope effect, we had also seen the use of kinetic isotope effects in understanding reaction mechanisms. And also we had seen the application of kinetic isotope effects in understanding enzyme activity. So, in the introductory lecture, I had told you that, we will be looking at how basic principles in chemistry can also be used to understand biology.

So, this was one example, where you could use kinetic isotope effects to figure out the pathway how a particular enzyme works. So, when you think of isotope effects, I had left you with a problem, where I had told you that in this particular case,

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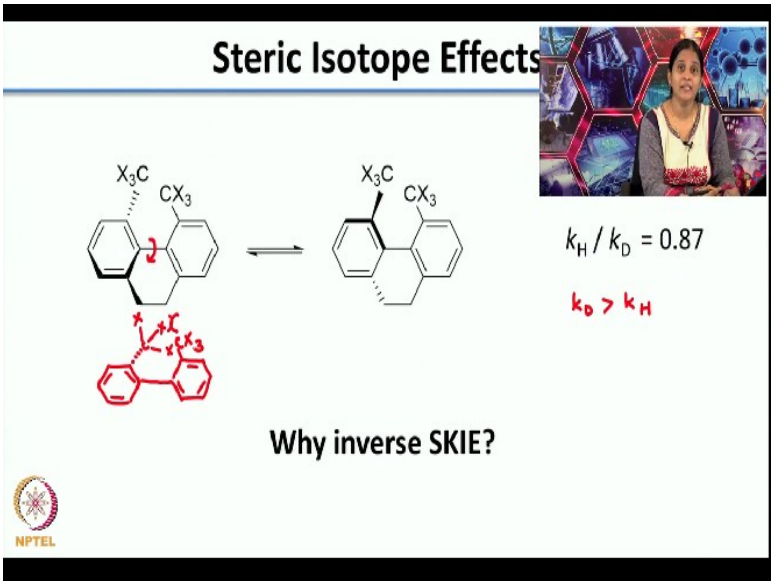

so, you have rotation around a single bond, so, the single bond we are talking about is this one. So, rotation around this single bond is restricted because you have a ring connecting the 2 aromatic rings. Usually, when you have 2 aromatic rings, they can rotate around the single bond quite easily. So, it can easily racemise. So, here the rotation is restricted. So, now the question I had told you is that, in this case, an inverse kinetic isotope effect is observed.

So, what that means is, k_D is actually greater than k_H. And I had asked you to think about why this would be the reason. So, to give you a hint, you can correlate this with what we had done in the previous class. So, what was the basis for secondary kinetic isotope effects? The fact that the CH bond is longer than the CD bond. So, now, if you look at this example, in this case you have on each aromatic ring, I am just writing this out so that it is clearer for you.

So, you have here I am just writing CX_3, because seems like there is steric crowding here as well. So, now when you have a longer CX bond, a longer CX bond will indicate greater static interaction between these 2 groups. So, now because the CH bond is longer than the CD bond, when you have these 2 CH bonds rotate, you will see that there will be a steric hindrance.

So, that is why what you see is when you have a CD_3 here, the kinetics is much faster. So, k_D is greater than k_H, which in turn means an inverse kinetic isotope effect. So, here again you see an isotope effect, because of sterics. So far we have only been looking at replacement of hydrogen with deuterium. So, all the examples we did so far, we saw CH bond being replaced by the CD bond. Now, why is that so?

So, if you remember the very first class, when we started talking about kinetic isotope effects, the origin of primary kinetic isotope effects is because of the vibrations that we had looked at. So, we said that vibrational levels are very very important to understand isotope effects.

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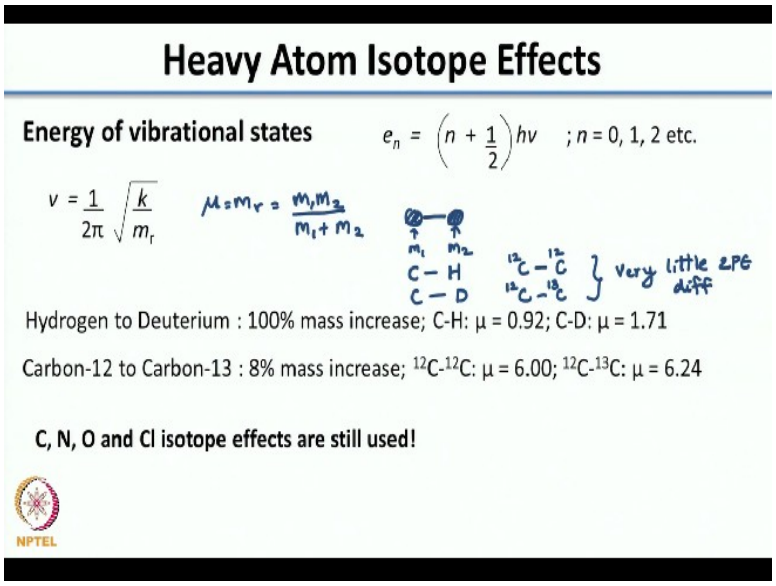

Now, the energy for these vibrational levels is given by e_n is given by $(n + ½) h\nu$. Now, what you would have is a large population of molecules would be in what is called as a first level. So, what is important is n = 0 and that is called as the zero point energy and the frequency is given by 1 by 2 pi root of k over m_r in this equation here. So, now, what is m_r? If you remember our earlier discussion, m_r is the reduced mass.

So, that is $(m_1 m_2 / (m_1 + m_2))$, where m_1 and m_2 correspond to the masses of the atoms that are attached. So, now that you understand this, you can calculate the reduced mass when you think of replacement of hydrogen with deuterium. So in this case when you think of replacement of hydrogen with deuterium, you are thinking of now CH versus CD, so your m_1 would correspond to mass of carbon and m_2 would correspond to either mass of hydrogen or mass of deuterium.

So, can you quickly calculate the reduced mass also sometimes denoted as μ for these 2 CH versus CD? So you can press the pause button on the screen and go ahead and calculate the reduced mass, you can assume the ^{12}C isotope of carbon. So, if you finish this exercise, I would also want you to do the same exercise for ^{12}C- ^{12}C and ^{12}C- ^{13}C bond. So, here the 12 and 13 you can use as the masses.

So go ahead and also now calculate the reduced mass for ^{12}C- ^{13}C and ^{12}C- ^{12}C bond alright. So, let us see if you have the answers and if you have the correct answer. So, the first case where you look at hydrogen to deuterium replacement. So, in the first case, what you see is for the hydrogen to deuterium replacement you would get a reduced mass of CH 0.92 and CD it would be 1.71. So this is a pretty large difference.

Whereas if you compare ^{12}C- ^{12}C , so here you have 6 verses 6.24. So the increase in mass is not significant as compared to hydrogen, deuterium. And if you look at this equation, this is what dictates the zero point energy difference between C-H, C-D and in this case, ^{12}C- ^{12}C verses ^{12}C- ^{13}C . So the zero point energy difference in this case is very little. So that is why the value that you get for kinetic isotope effects

when you do replacement with these heavy items, is much smaller than what you see for hydrogen and deuterium. So we have seen k_H / k_D values close to 7. But that is not what you would see when you look at heavy atoms, but still people use carbon, nitrogen, oxygen, Cl, all these isotope effects are actually studied. So now the second question is, if the difference in kinetics is so small, how do you actually measure it?

Because that is a challenge too. We are talking about experiments to determine a particular mechanism. So, the experiment by itself has to be quite feasible. So a clever way to work around this is if you think of a reaction, so you have a reactant R going to a product P. So, let us not think about isotopic substitution. In general, you have a natural abundance of isotopes. So, if you have studied mass spectrometry, what you see is for halogens you would see the peaks corresponding to the different isotopes.

and the intensity of the peaks depends on the related abundance of each of these isotopes. Similarly, you see it for other elements as well.

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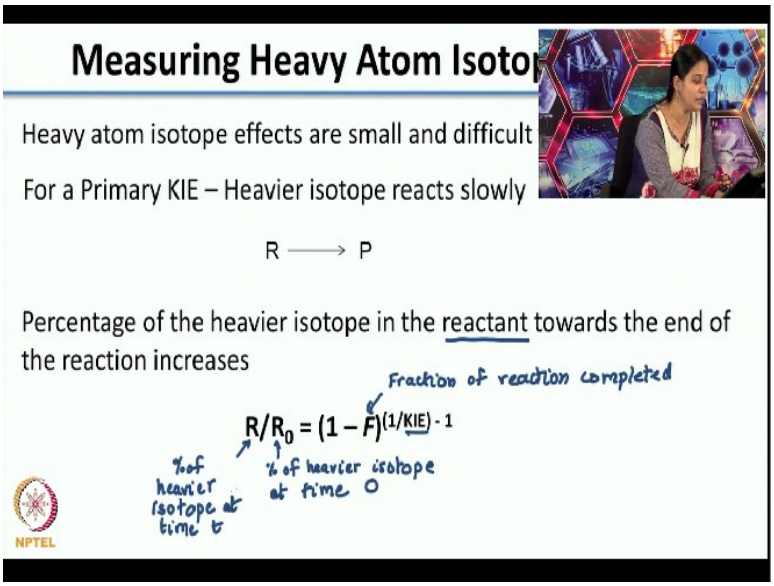

So, if you consider a reaction going from R to P and let us say we are trying to figure out the carbon isotope effect. So there is a natural abundance for the 2 isotopes of carbon. So when you do your reaction, your reactant will have both of these isotopes, alright? It would not be only ^{12}C or only ^{13}C, it would be a mix of ^{12}C and ^{13}C depending on their natural percentages.

So now imagine a reaction. So you have the reactant going to the product P. So let us look at a primary kinetic isotope effect. So in a primary kinetic isotope effect, if you remember what we had seen for CH versus CD, the lighter isotope reacts faster, right? Because the zero point energy for CD was less than CH, which is why the activation energy for CH is lower. So CH reacts faster. So this can be a generalization that for any heavier isotope the reaction goes slowly as compared to the lighter isotope.

So let us say you are starting the reaction at time 0, and you let the reaction go for 2 hours. It takes 2 hours for the entire reaction to be complete. So when you have, say, at one and a half hours, where the reaction is closer, closer, closer to completion, what would you feel that if you measure the reactor and now? So reactant has been converted to product, and some of the reactants would be unreacted.

So it would be still sitting in your flask. Now, if you were to take this reactant after one and a half hours, and compare the percentage of the heavier isotope with the lighter isotope, what do you think would be the percentage now compared to beginning? Alright? What do you think it will be? Think about it. you can press the pause button and think about it. So the percentage of the heavier isotope will actually increase.

And it is also given there for you in front on your screen. Now why does it increase? Now the lighter isotope is reacting quickly, it is reacting faster, forming the product. So now the unreactive one would be more of the heavier isotope, which is slower to react. So this is similar to the case when you think of a marathon, you have people running the marathon, the faster runners will go to the finish line quickly.

But if you look at the finish line closer to say, 5 hours, 6 hours for the marathon, what you would see is you would see a greater percentage of the slow runners because the fast runners have already cleared the finish line and probably are even at home. So it is the same thing with these reactions. When you have the lighter and the heavier isotope, the lighter isotope would already be forming the product.

Whereas the heavier isotope would remain in the reactant as it is reacting slowly. So when you look at the reaction closer to the end, what you would see is you have a greater percentage of the heavier isotope in the reactant. And so it is very important, you understand we are only talking about the reactant and not the product here alright. So what has been done is that there is this expression which is used to determine the kinetic isotope effect.

So, in this expression, R and R_0 correspond to percentage of heavier isotope at times 0 and this is percentage of heavier isotope at any given time. And F gives you what fraction or percentage of reaction completed. So if the reaction is 98% complete, you would say that F value is 0.98. If it is 100% complete, the value would be 1. So when you look at F 0.98, that is closest to completion, there, you would see you will have a greater enhancement of the heavier isotope

and at that point the kinetic isotope effect actually is very important. Because depending on the difference in kinetics for the heavier and lighter isotope, the ratio R/R_0 will change. Alright? So if you measure the value of R_0, so you can measure the value of the reactant of a particular isotope, you can also measure the R concentration at any of the given times. So this is measurable, fraction of reaction completed, you can determine.

So, based on this you can calculate the kinetic isotope effect. So, this is an indirect method for calculating kinetic isotope effect when you look at heavy atom kinetic isotope effects. So, you are indirectly measuring it by measuring the concentration of the reactant with the heavier isotope. So now just to give you a feel for what these numbers look like,

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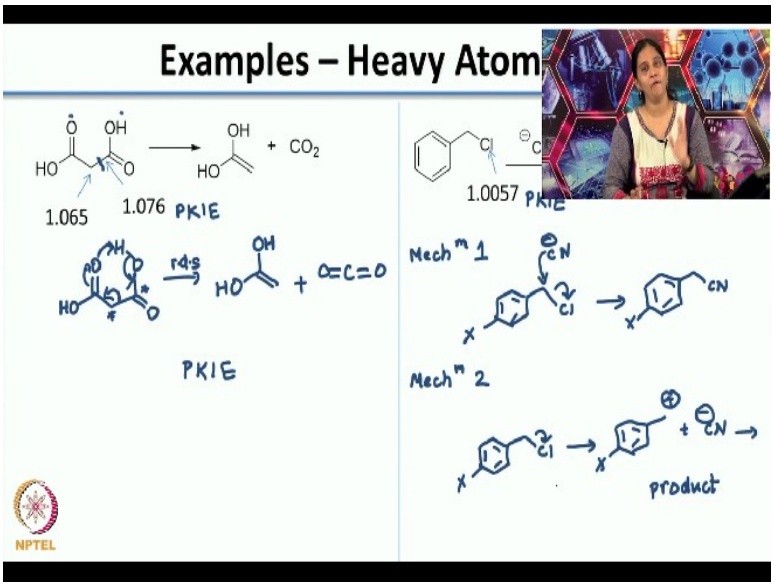

shown are 2 examples on your screen. So these are 2 different reactions and in one case we are looking at carbon isotope effects and the value was 1.065 and 1.076. Now by looking at it if you are correlating with the CH versus CD isotope effects, you would think that oh this is very small. But that is not the case. For carbon as we saw, putting in the equation the reduced mass difference is very small, remember?

So that is why the kinetic isotope effect values will also be very small. Alright? So what is seen is, values of 1.065 and 1.076 actually correspond to primary kinetic isotope effects and in the case of Cl, you can do the calculation of reduced mass for Cl as homework, but you would see

that there the differences even smaller, so what you would see is even a value of 1.0057 corresponds to a primary kinetic isotope effect.

And I wanted to show you these words use so that you understand that when you have heavy atom kinetic isotope effects, the values are small, and they correspond to primary kinetic isotope effects. Secondary kinetic isotope effects in this case are very very negligible. So you would not even see it. So a value of this would correspond to a primary kinetic isotope effect. So now that I have told you that both of these are primary kinetic isotope effects,

I would write this as PKIE, can you write the mechanism for both of these processes? You can press the pause button on your video and write the mechanisms for both of these, consistent with the fact that you are observing primary kinetic isotope effect. So, you can write a mechanism where you have this bond breaking and what you end up getting would be the product. Now, here if you see you have the C-C bond breaking in the rate determining step.

So, we have written a concerted process, which is why you observe a primary kinetic isotope effect. So, this is consistent with the experimental observation. Now, let us look at the second case. Here based on a primary kinetic isotope effect, I can write 2 mechanisms. Mechanism 1 is probably more likely given the fact that you have a good nucleophile. You have Cl and you have CN^-, comes in.

So this is an S_N2 mechanism. So you get your product. The other mechanism would be an S_N1 like mechanism where the first step would involve formation of this benzylic cation and then you would have CN^- added in give you the product. So, primary kinetic isotope effect is consistent with either of these mechanisms. So, what you can say here is that based on intuition, I can say that mechanism 1 is probably correct.

But based on the experimental observation, I can say either of these experiments could be correct. So, how would you figure out which of these mechanisms is the correct one based on whatever we have studied so far? Can you think of how you would figure it out? One way could

be where you could use a substitute here and you could look at linear free energy relationship to tell you whether it is a S_N2 like or S_N1 like or you could even use solvent effects.

So both of these we have studied so far. So you can use both of these experiments to figure out whether it is S_N2 like or S_N1 like. So, now we will look at another kind of effect. So remember we had looked at kinetic and thermodynamic control, we looked at kinetic isotope effects, there are also what is called as equilibrium isotope effects.

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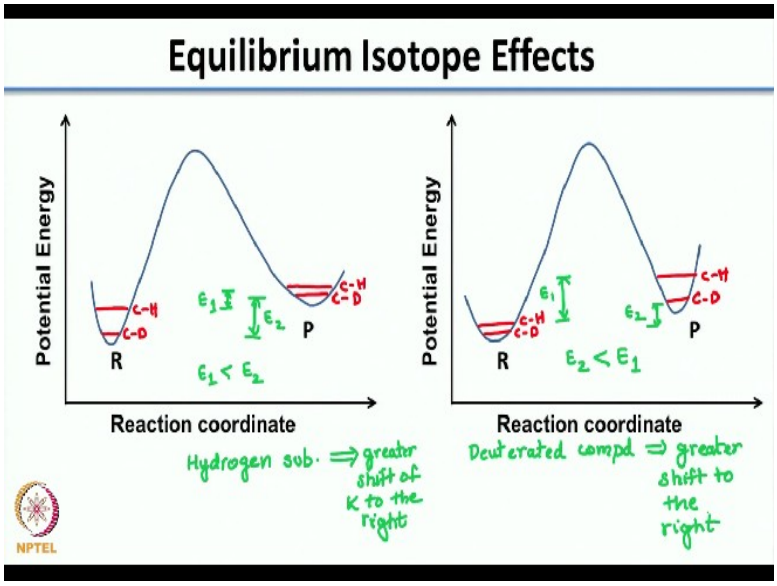

So in equilibrium isotope effects that can be 2 scenarios. Now 1 scenario would be where you have a large difference between CD and CH in the reactant and a small difference between CD and CH in the product or you can have the reverse scenario where you have a small difference between CD and CH in the reactant and a large difference between CD and CH in the product. So, these are the 2 scenarios. Now, if you compare both of these, let us look at the energy difference that we are talking about.

So, in one case, if you look at, so this is the energy for CD, let us call it E_2 and this is the energy difference for CH. So, this is the energy difference for CH, we will call it E_1. So, what you see here is E_1 is less than E_2. So, what happens here is that if you compare the equilibrium for the case where you have hydrogen versus the case where you have proton, you have the hydrogen substituted reaction shows a greater shift of equilibrium to the right, which is towards the product.

Now let us look at the second case. Now in the second case, if I were to compare the energy difference again for CH it is E_1 and for CD it is E_2. Now in this case E_2 is less than E_1. So, the energy for CD is less than CH. So, the deuterated compound would show a greater shift to the right. So now that you have an understanding of equilibrium isotope effects, let us look at how this has been used to understand reaction intermediates.

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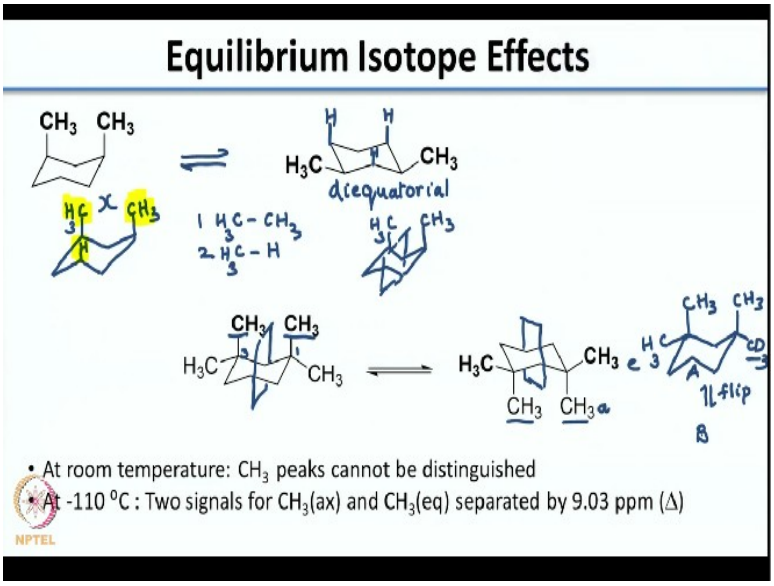

So, if you see shown here are 2 different structures. So, you have 1,3-disubstituted cyclohexane and you have 2 methyls and what is the relationship between these 2 structures? Do you know? If you have studied confirmation analysis, you would know that these are 2 conformers. So, cyclohexane as you know can flip quite easily.

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So shown here is the chair form of cyclohexane. So you can see the chair form here. And if you look at it in another angle, you would also be able to see the Newman projection. So this is what the Newman projection looks like if you have seen in your textbook. So there are 2 different types of substitutes here, you have the actual substitutes. So, the axial substitutes are the one shown in red, and you have the equatorial substituent.

So I will again show you the chair form, so maybe you will be able to see the axial and equatorial substitutes much better in the chair form. So in the chair form, what you see is the

axial substituents are actually parallel to the axis. So if I show this as the axis of the molecule, your axial substitutes are parallel to this axis of the molecule. And the equatorial substituents you can think as along the equator. So you can see the chair form very nicely again.

And you can see the axial and equatorial substitutes. So to make it easy for you, I have shown axial in red and equatorial in blue. So now cyclohexane can undergo what is called as the ring flip. So when it undergoes the ring flip, what will happen? So remember now I have axial red and equatorial blue. So I am going to go ahead and do the ring flip. So, when I do the ring flip, what I have done here now is that I have switched it such that I have the equatorial red and the axial blue.

So do you see it here? Now that have I flipped it, so, again, the Newman like projection, you can also look at the chair form. So, here is the chair form, so in the chair form what you see is now the blue is axial and the red has become equatorial, and this chair flip happens quite easily. Alright?

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So, now, if you compare this particular example that I have shown you, so if I can I can write this equilibrium. So, these 2 conformers can flip. Now, among the 2 conformers, one is actually more stable and you might have studied this in stereo chemistry. The more stable conformer is the diequatorial conformer. The diequatorial conformer is more stable. So, what happens in the diaxial conformer is that, I have a hydrogen, I have the 2 methyls.

So, I have steric interactions between these 3 atoms. So, these 3 groups would have steric interaction, because of which this is unstable. In the case of the equatorial conformer what you see is that you do not have this kind of steric interaction at the axial positions you have hydrogens and the hydrogen hydrogen 1,3-diaxial interactions are not that bad as compared to the hydrogen-methyl or the methyl methyl 1,3-diaxial interaction.

So, these are called as methyl-methyl and these two are hydrogen-hydrogen. So here you have one methyl-methyl, 1,3-diaxial interaction, and two methyl-hydrogen, 1,3-diaxial interaction. So

now this destabilizes the conformer on the left as compared to the conformer on the right. So, you can look at the 2 substituents. We are only looking at 2 substitutes now.

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I will remove all the other substitutes to make it easier for you to understand. So, this is so this is now your less stable conformer shown in blue are your methyl-methyl diaxial conformer and as I told you this is bad. So, let us go ahead and flip this ring. So, when you flip this ring, you have now the methyl-methyl will be diequatorial. So you have the methyl-methyl diequatorial now. This is the more stable conformer.

Now what are the elements of symmetry here? So when you look at this molecule, so let us again, look at the chair form. So when you look at the chair form, are you able to see a plane of symmetry? So I will draw it here.

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So if you look at both of these molecules. So if you have methyl-methyl, what you see is you have a plane of symmetry here. Alright? So now coming back to the equilibrium isotope effects, it is very important for you to understand this so that you understand equilibrium isotope effects. So to understand equatorial isotope effects, I will show you another example. Now in this example, instead of one methyl at 1,3 position, so if this is the 1 position, and this is the 3 position.

I have 2 methyls and as before we will have a mirror plane in both these molecules. But now, what happens in terms of energy in each case you have 1,3-diaxial interaction. So you have it in this case, you also have it in this case. So both of these are almost equal in energy. So what you see is, if you try to look at the NMR spectrums, so NMR is nuclear magnetic resonance spectroscopy, so when you measure the NMR spectrum at room temperature,

because both of these can flip very easily, you cannot distinguish between the axial and equatorial peaks. So all you get at room temperature is all merged CH_3 peaks. So you cannot distinguish axial and equatorial. But what happens is at -110 degrees, so now you are cooling it,

when you cool it, you are not giving the molecule enough energy to flip. So like we were flipping before now the molecule does not have enough energy to flip.

So now how many signals would you see? You would see 2 signals because you have this mirror plane, one corresponding to the axial and the other corresponding to the equatorial and the 2 signals for axial and equatorial are separated by 9.03 ppm. So before we stop this lecture and continue with equilibrium isotope effects, I have a question for you. So think of the molecule, I am going to draw it here where I have CH_3, CH_3, and then CH_3, CD_3.

So now I have done the isotope substitution, because we were talking at equilibrium I mean we were talking about equilibrium isotope effects. So now I have done the isotopic substitution. So, if I have this molecule, what I want you to do before the next lecture is, I want you to write the conformer for this molecule. So for the conformer, you will have to flip this ring. So when you flip this ring now the CD_3 will go to the actual position.

So what I want you to think about is, between these two conformers, so let us call this conformer A and conformer B, which would be more stable? It can be slightly more stable, but I want you to think about it and tell me which conformer will be more stable. So, thank you. We will get back to this question in the next class and continue with equilibrium isotope effects.