Mechanisms in Organic Chemistry
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Lecture - 24
Secondary Kinetic Isotope Effect: Part B

So welcome back. In the previous class we had looked at secondary kinetic isotope effects. So in secondary kinetic isotope effects essentially the bond that is broken in the rate determining step is not where you are doing the isotopic substitution.

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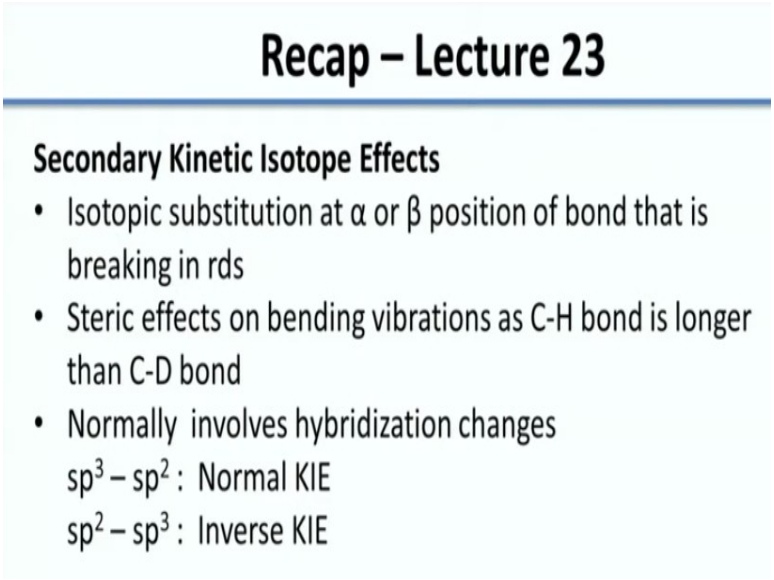

The isotopic substitution is done at the alpha or beta position of the bond that is breaking in the rate determining step. Second thing is, it is mainly bending vibrations that are important and the steric effects due to the fact that the C-H bond is longer than the C-D bond leads to this difference in kinetics between C-H and C-D. So usually you see secondary kinetic isotope effects when there is some sort of hybridization change.

So when you have a reaction which involves a change from sp^3 to sp^2, you see what is called as a normal kinetic isotope effect that is k_H would be greater than k_D. But when you have sp^2 going to sp^3, what you see is called an inverse kinetic isotope effect, where k_D is actually greater than k_H and the explanation for all of this was seen in the previous class.

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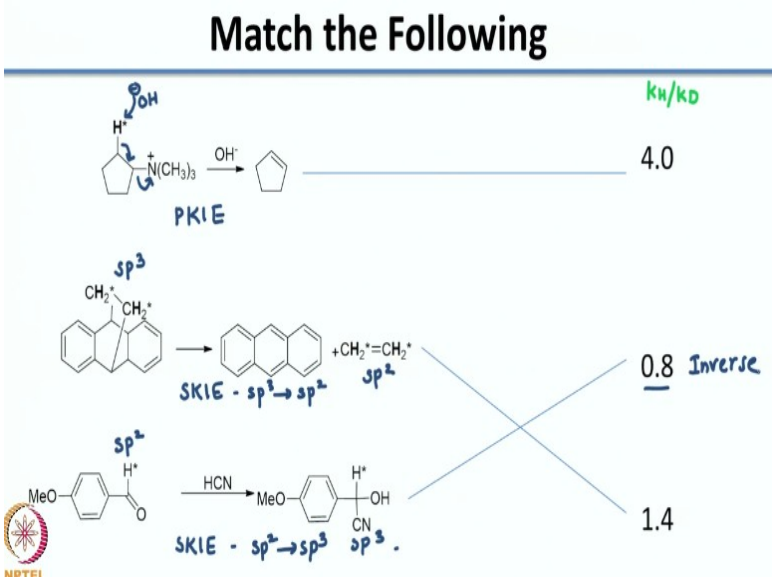

So now I had asked you in the previous class to match the following. So you have reactions given on the left and k_H over k_D values given on the right. You had to match the k_H over k_D values with the reactions that are given. So let us see if you have the answers correct. So in the first case, what is the mechanism of the reaction? So what you have here is you have OH^- coming in deprotonating and then you have these electrons coming in and eliminating the amine to give you a double bond.

So what kind of an isotope effect is this? Is this a primary or a secondary kinetic isotope effect? So it is a primary kinetic isotope effect. So which of these would be the correct answer then? It would be 4, okay? So now let us look at the second and third reaction. Now in the second reaction is the C-H bond broken? The C-H bond is not broken. So you know that it is a secondary kinetic isotope effect.

So now what you need to look at is you need to look at the change in hybridization. So let us look at the hybridization change. So what is the hybridization here? It is sp^3. And what is the hybridization in your product? It is sp^2. So the change that you have is sp^3 to sp^2, which is a normal secondary kinetic isotope effect. So the value would be greater than 1. And so the correct answer would be 1.4.

So now you know that the last answer is 0.8 and why is that? So here again is the C-H bond broken in the reaction? No. So it is a secondary kinetic isotope effect. And what does the hybridization change? Here you have sp^2 here you have sp^3. So you are

looking at sp^2 to sp^3. So which is why you have an inverse effect. So this summarizes whatever we had seen so far for primary and secondary kinetic isotope effects.

So let us do some more examples, let us solve some more examples together so that you get a better grasp on this concept of kinetic isotope effects. So as usual, you will have to think of the answer first and that is actually most beneficial for your learning because if you just watch me solve this example on the video, it will look easy for you. But then I am doing most of the thinking.

But if you want to learn it is better if you do the thinking so that you know what are the mistakes that you are making. And then once you look at me solving it, you can figure out how to rethink this the next time you get a problem like this. So shown is a problem in front of you.

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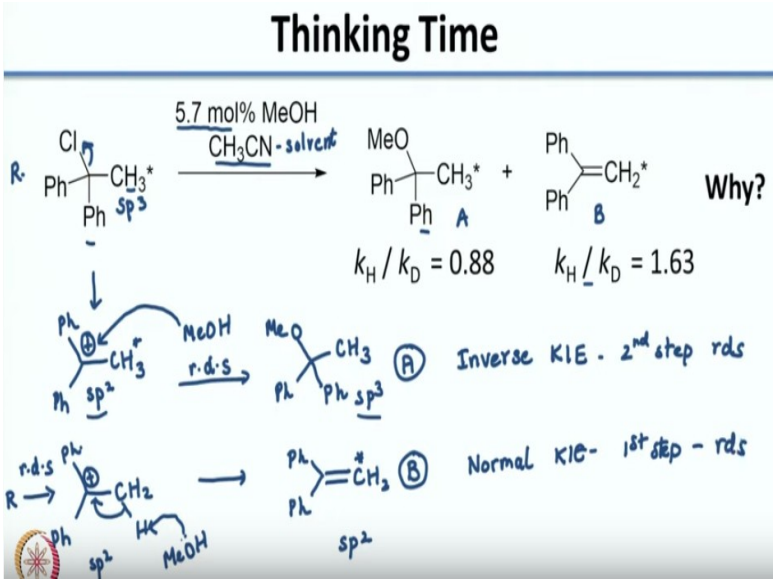

Now this reaction see carefully is done with 5.7 mol% of methanol. So that means the concentration of methanol in the reaction mixture, the solvent is acetonitrile, which is shown as CH_3CN. So this is the solvent. And here you have only 5.7 mol%, so small amount of methanol in the solvent. So now if you add 5.7 mol% of methanol to your starting material, there are two products which are formed, right?

One is based on substitution and the second is the elimination product and the isotopic substitution is done here. So what is seen is that the k_H over k_D value for this product if you remember our class on kinetics, you can study the kinetics for formation of

multiple products. So if you study the kinetics for formation of this product, you get a k_H over k_D value, which is 0.88 an inverse kinetic isotope effect.

Whereas, in the case of elimination, you get a k_H over k_D value of 1.63, which is a normal kinetic isotope effect. Now what I would like you to do is, I would like you to write the mechanisms for formation of each of these products. And then based on the mechanism, see if you can justify the k_H over k_D value. So I will repeat the question. I want you to write the mechanism for formation of each of these products.

Let us call this product A and let us call this product P. And then based on your mechanism, you should be able to justify why you see an inverse kinetic isotope effect in one case and why you see a normal kinetic isotope effect. So go ahead press the pause button on your video and work out this problem. So you can now see if you have worked out the problem correctly. So let us first start with the mechanism.

So the first step in the mechanism would be formation of the carbocation. So you form the carbocation where you have, so this is the carbocation. Now once you form the carbocation you can have methanol add in. So if methanol adds in you will get product A. This is product A; now the same carbocation. In one case methanol is acting as a nucleophile whereas in the second case it acts as a base, grabs the proton.

So you get product B. So now hopefully you were able to write these mechanisms. For each step you can write the hybridization that you have. So here you have sp^3. Here you have sp^2. So remember this is next to the carbon hydrogen bond that is being substituted, which is what you see in a secondary kinetic isotope effect. And here again the bond is not broken. So you have sp^3.

Here again, it is sp^2 and here you have sp^2. Now here you have the bond breaking. But what do you observe? In the first case, you observe an inverse kinetic isotope effect. Whatever you have studied so far for S_N1, we have always said that the first step is rate determining, right? Now if the first step were rate determining for formation of A. So let us call this as reactant R.

So if the first step were rate determining for formation of product A, what would you see? You have a change from sp^3 to sp^2. Now based on whatever we have studied in the previous class, a change from sp^3 to sp^2 would indicate a normal or an inverse kinetic isotope effect? It would indicate a normal kinetic isotope effect. But what you are observing is an inverse kinetic isotope effect.

So what that suggest is now if you look at the next step you have so if you look at the next step you have sp^2 going to sp^3. So here you would observe an inverse kinetic isotope effect. Now whatever steps usually come after the rate determining step do not usually impact the kinetics. So what that tells you is that actually what you have is the second step which is rate determining.

Now some of you might be confused thinking why is that the case? We have always studied that S_N1 means the first step has to be rate determining. But here you see that second step is rate determining and why is that? Remember I told you one thing is very important. You are using a very very small amount of your nucleophile which is methanol.

And methanol, you are using such a small amount and it is not that great a nucleophile. So what you see is that the rate for the second step is actually slower than the first step here. So the second step becomes rate determining and which is why you observe an inverse kinetic isotope effect, alright? This is all because the second step is the rate determining step?

Now let us look at formation of product B. So the first step you have R giving you the carbocation. R is the reactant. So once the carbocation is formed, it appears that the elimination occurs quickly. Now the elimination and here you do not see much of a change in hybridization. So in this case what you have is you have the first step being the rate determining step, alright?

So this is a very nice example. So here you have a normal kinetic isotope effect because your first step is the rate determining step. So this is nice illustration of how you can get two products and each actually have a different rate determining step. So now let us see another example, where the kinetic isotope effect information could be

used to determine the nature of the transition state and what is the mechanism of a given reaction. So the reaction is shown on your screen.

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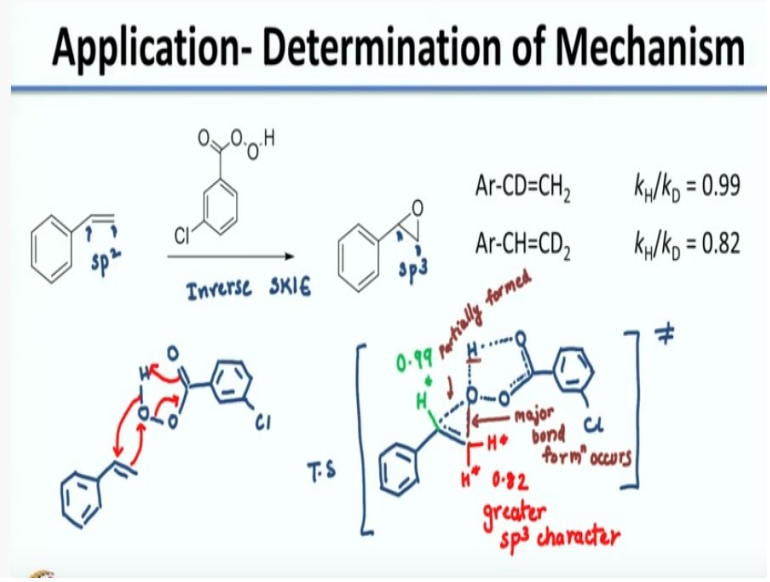

This is an epoxidation reaction. So you have your double bond getting converted to an epoxide using a reagent which you must have heard as mCPBA, that is meta-chloroperbenzoic acid. So what I would like you to do is again press the pause button on your video, write the mechanism for this reaction and see if you can justify the kinetic isotope effects observed.

So let us see if your mechanism explains the kinetic isotope effect. So you are starting material here is styrene. So let us draw the structure of styrene and then it is interacting with meta-chloroperbenzoic acid. So that is the reason why I am writing the structure like this. So now let us try to push the arrows. So when you push the arrows, what you would see is you have, so essentially what is happening is, you have the carbonyl group here grabbing the hydrogen here.

So it is grabbing it as the proton and so you have this coming in. So now if you were to write the transition state for this, people call it what, call this mechanism as a butterfly mechanism. So if you were to write the transition state for this, so nothing happens to these bonds. The bonds are partially formed with the hydrogen. This bond is breaking. This bond is also breaking. Then it is forming a new double bond here.

And then you have a new bond being formed between the oxygen and the hydrogen and here again nothing happens. So we are just going to rewrite it. So this is what your transition state will look like and finally you have the product. So what you would see here is that in this case, you have sp^2 going to both these centers as sp^3. So you see an inverse kinetic secondary kinetic isotope effect.

So you see an inverse secondary kinetic isotope effect. So now let us look at each of these examples. So in the first example, you have isotopic substitution at this position. So if I draw this C-H here. So you have isotopic substitution at this position. So it is again a secondary kinetic isotope effect, because this C-H bond is not broken. Now what you see is that when you do an isotopic substitution here, you see that the k_H over k_D value is not that high, alright?

So you see that the k_H over k_D value is 0.99 almost close to 1. Whereas so I will just write the value here, it is 0.99. Whereas if I do the isotopic substitution here, so here you have the value is 0.82. So it is actually much lower than the isotopic effect that is seen at the position right next to the aromatic ring. So what that tells you is that there must be some difference between these two positions.

What you see is that in this position, there is greater sp^3 character as compared to this position, because you see a value of 0.99. So what that tells you is that, so if I were to think of the position of transition state with respect to this bond I can say that major bond formation occurs in the transition state. So that means it is a late transition state compared to formation of this bond.

Whereas this bond is partially formed. So what that tells you is that the transition state is not as symmetric as one would expect as shown in the drawing in front of your screen. What it tells you is that you have major sp^3 character at this position and smaller sp^3 character at the position next to the phenyl ring. So what it tells you is that although the process is concerted, you have different extents of bond formation.

So it tells you that you have a greater extent of this bond formation as compared to the other bond. So the kinetic isotope effects can not only give you insights into the nature of the transition state, it can also give you insights into the extent of bond

breaking and bond making that happens in the transition state. So this is a nice illustration of this, the epoxidation of styrene using meta-chloroperbenzoic acid.

So you can also think as a homework as to what will happen if you do an isotopic substitution at this position. So at this hydrogen. So I want you to think about this. If you make an isotopic substitution at this hydrogen, what kind of an isotope effect would you see? All right? Would it be a primary, would it be a secondary? What do you think would be the magnitude and you can have this discussion in the discussion forum.

So now we look at an application of kinetic isotope effect in understanding biology. We have been doing that throughout this course, where each of these, so even in case of the linear free energy relationships, we saw how you can simplify complex problems in biology by using model systems and looking at the simple chemistry behind it. So in our body, we have an enzyme which oxidizes amino acids.

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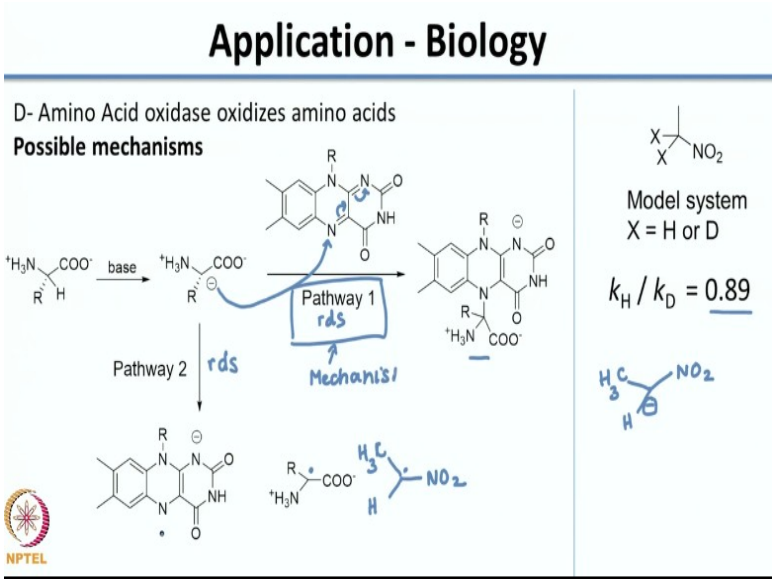

It is called a D-amino acid oxidase enzyme. So what it does is in the presence of this enzyme, the amino acid gets oxidized. And there are two pathways that are proposed for this. It is proposed that the reaction takes place in the presence of a base. So you have your amino acid bound to your enzyme. It gets deprotonated to give you this anion. Now once this anion is generated, there are two possible pathways.

It can interact with this co-factor shown here, where you have an ionic mechanism. So you can imagine this. So you can imagine this acting as a nucleophile to give you the product that is shown here. The other option is where you have a radical like mechanism. So here what happens is once you form the anion so once you form the anion instead of the anion acting as a nucleophile, it can actually undergo electron transfer.

So what it has done is, it has given an electron to the system here. So you are again pushing electrons as shown earlier. So you have the electrons going towards, so you have this conjugated system. So you have a negative charge that comes on the nitrogen and you have a radical that is generated here. And of course, because it is an electron transfer, single electron transfer you have another radical generated at the amino acid.

Now to understand which of these pathways is taking place, is it pathway one or is it pathway two a model system was used. The model system is nitroethane. So we have seen nitroethane before, right when we were looking at primary kinetic isotope effects. So what was seen was that when nitroethane was used, you get a k_H over k_D value of 0.89.

So now that you have this information, I have shown you both the pathways, one involves a nucleophilic attack or an ionic mechanism and the other one goes via a radical pathway. So now that you have both these pathways in front of you, what I want you to do is I want you to figure out which is the actual pathway based on the k_H over k_D value given.

So you can press the pause button on your screen and see which is the pathway taking place. And as a hint, I can tell you that you can write the hybridization change at each position to tell you whether you would have a normal or an inverse kinetic isotope effect. So let us see if your understanding is correct. So in one case, you have formation of a tetrahedral product.

Whereas in pathway two if you have the first step, which is rate determining, what you have is you have a carbanion getting converted into a radical and then what you

have especially for the amino acid because that is where you are going to make the substitution. Instead of amino acid what you have is you have nitromethane. So you would have a situation like this, where you have NO_2 and then $CH_3H^{\cdot}$.

Whereas in the case of your reactant, your reactant anion would be, I will write it on the right because we have space here it would be $CH_3CHNO_2^{-}$. Now why you have chosen why was this particular model system chosen is that the abstraction by base will not be rate determining, it would happen pretty quickly because you are using nitroethane here. So this step is not rate determining.

One of these would have to be the rate determining step. Now in the case of pathway two you would have this anion versus the radical. And now if you are imagining, so you have hydrogen here. So if you look at the transition state and whether the C-H over C-D bond length will make a huge impact; in the case of pathway two the impact would be minimal as compared to pathway one, where you have some sp^3 character coming in because of your tetrahedral product.

So you have the bond angles would be such that your C-H over C-D bond length would have a greater impact and because you see an inverse kinetic isotope effect, you can say that the reaction follows pathway one. So this is what would be the mechanism. So using a clever model system one can understand the pathway for formation of a particular product even in biology. You need not use a very complex system. So before we leave, I have a question for you.

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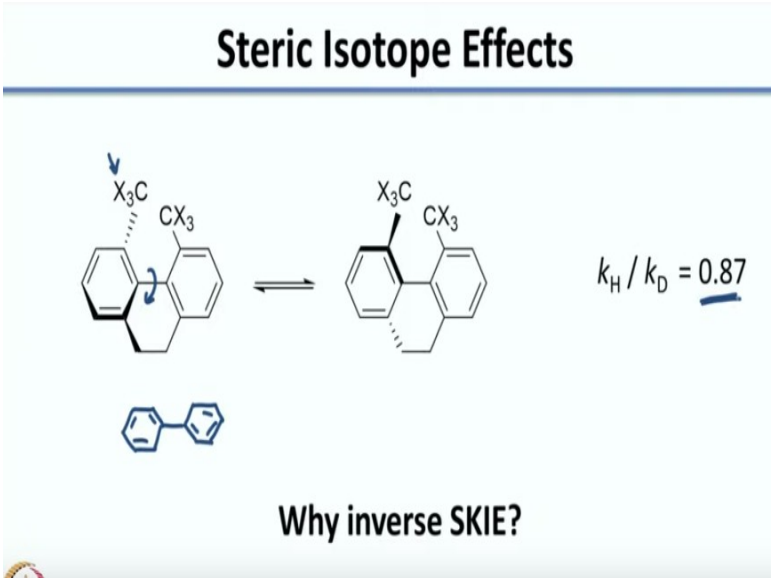

So shown here is a, it is not a reaction. It is essentially an equilibrium for rotation about this C-C bond. So we are talking about rotation about this C-C bond. Now what you see is if you have a biphenyl system. So if you have a biphenyl system, you can imagine the two phenyl rings connected by a single bond. The single bond has free rotation, so it rotates very very easily.

But in this case, we have restricted the rotation by interlocking the molecules. So because the two aromatic rings are now interlocked you have restricted rotation. So now the question to you is the kinetics for this rotation from going for A to B, k_H over k_D, so you are actually making substitution at this position. So when you have X is equal to CH_3 versus X is equal to CD_3, you observe an inverse kinetic isotope effect, and the value is 0.87.

So what I want you to think about is why do you observe an inverse secondary kinetic isotope effect? So you can use whatever principles we have learned in today's lecture to understand why this inverse kinetic isotope effect is observed. So thank you, and I will see you in the next class, where you will have the answer for this problem and we will also look at some other isotope effects. Thank you.