Mechanisms in Organic Chemistry

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Lecture - 22
Primary Kinetic Isotope Effect

So welcome back. In the last class what we had looked at was kinetic isotope effects and how kinetic isotope effect is a method that gives you information about the rate determining step.

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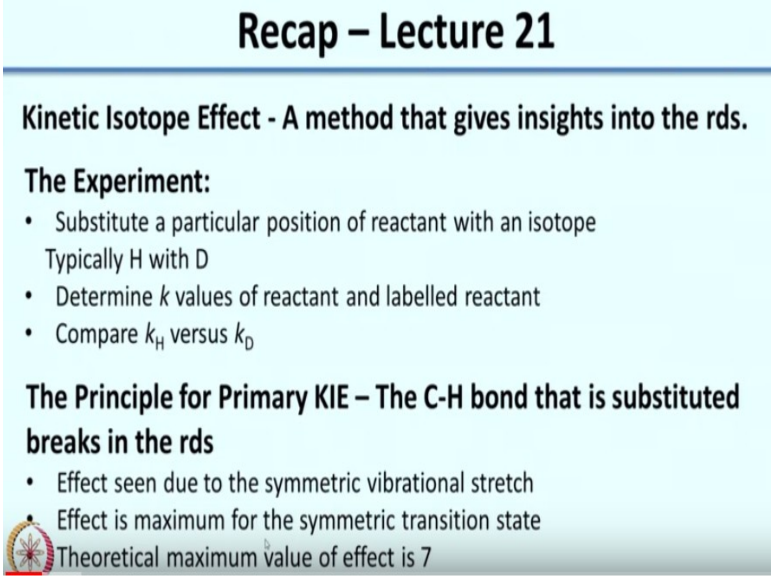

Recap – Lecture 21

Kinetic Isotope Effect - A method that gives insights into the rds.

The Experiment:

- Substitute a particular position of reactant with an isotope
  Typically H with D
- Determine k values of reactant and labelled reactant
- Compare k_H versus k_D

The Principle for Primary KIE – The C-H bond that is substituted breaks in the rds

- Effect seen due to the symmetric vibrational stretch
- Effect is maximum for the symmetric transition state
- Theoretical maximum value of effect is 7

So the experiment involves substituting a particular position of the reactant with an isotope. So typically you substitute hydrogen with deuterium. Determine k values of the reactant and labeled reactant independently and compare the k_H versus k_D. Specifically, we had looked at the primary kinetic isotope effect. Primary kinetic isotope effect means that the bond where you are substituting say hydrogen for deuterium is breaking in the rate determining step.

So now if this bond is breaking, you would see an effect due to the symmetrical vibrational stretch and the effect is maximum when you have a symmetric transition state and theoretically maximum value for k_H over k_D is 7. So these were the things we had looked at in the previous lecture. So in this lecture, we will try to look at how this can be used to determine the mechanism for a particular reaction.

So before stopping the previous lecture, I had given you two reactions and asked you to write the mechanism and see if your mechanism is correct based on the k_H over k_D values given.

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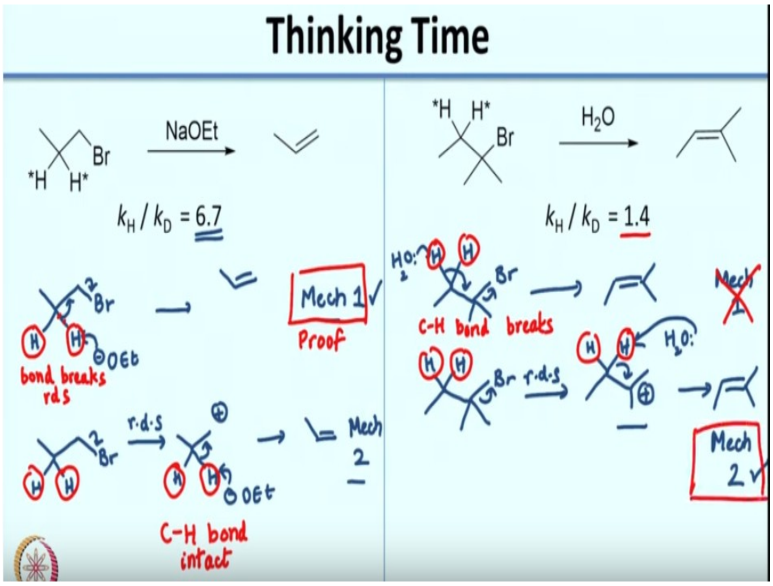

Thinking Time

NaOEt

$k_H / k_D = 6.7$

H_2O

$k_H / k_D = 1.4$

So let us look at each of these reactions. So in one reaction, one mechanism I can write could be where I have with the base. So your base is your ethoxide and then once your base abstracts this proton it gives you the product. So this is mechanism 1. Let us think of another mechanism where you have in the first step you have formation of a carbocation.

And then in the second step you have the base abstracting the proton to give you your product. So this is mechanism 2, alright? So these are the two mechanisms you can write. One is an E2 type of a mechanism and the second is an E1 type of mechanism. So typically in the E1 mechanism your rate determining step is formation of the carbocation, alright? And you might have written other mechanisms also for this.

But these are two probable mechanisms one can say. Now let us look at the second example. In the second example, again I can write a mechanism where I think of just like before I do not have a base here. So if I think of a similar mechanism like before it will give you the product. The other mechanism is again like an E1 mechanism. The first step which would be the rate determining step.

So it will be formation of the carbocation followed by elimination to give you the product. So this is mechanism 1 and this is mechanism 2. Now based on whatever we had studied during the first week where we were writing reaction mechanisms, just looking at the substrates, you can probably tell me that among mechanism 1 and mechanism 2 for the first reactant, which do you think would be more probable?

You can press the pause button and think now that I have written all the mechanisms. In each case, tell me which would be the most probable mechanism. Alright. So in the first case, since you are generating a primary carbocation, if you do the E1 mechanism, it tells you that the primary carbocation is not very stable.

And since you have a good base, which is ethoxide, probably the reaction goes via mechanism 1. Whereas in this case, you are generating a tertiary carbocation which is pretty stable. So maybe this goes by mechanism 2. Now I can sit and argue with you that oh maybe mechanism 1 is correct in this case, mechanism 2 is correct in the other case. But now let us look at the k_H over k_D value.

Now in this case you have a k_H over k_D value of 6.7. That indicates that you have a primary kinetic isotope effect. Remember, I told you the theoretically maximum value is 7. So now, if you look at both of these mechanisms, now these are the hydrogens that were labelled, right? So in the first case, this bond is actually breaking in the rate determining step. So this bond breaks in your rate determining step.

Whereas in this case, in the rate determining step the C-H bond is intact. So that means that had it gone through mechanism 2 it would not have shown such a great k_H over k_D value, but the fact that it is showing a large k_H over k_D value gives you evidence that the reaction is going via mechanism 1, alright? Now let us look at the second case.

Now in this case k_H over k_D is greater than 1 but the value is not too large. So that means the effect is not as pronounced. So if you look at mechanism 1, what you see is C-H bond breaks in the rate determining step. Or C-H bond breaks in the rate determining step. But the k_H over k_D value is 1.4. So that indicates that this mechanism may not be operative.

But then in the mechanism 2 your C-H bond does not break in the rate determining step. So it is probably going through this mechanism. So in general, a thumb rule that you can use, when you are trying to see if the reaction shows a primary kinetic isotope effect is that if you have a k_H over k_D value greater than 2, you can consider that the C-H bond that you have replaced is probably taking part in or breaking in the rate determining step.

Or probably essentially what it means is it shows a primary kinetic isotope effect. So you can use this as a thumb rule, k_H over k_D greater than 2 indicates a primary kinetic isotope effect. So now that you have a feel of this concept, I have shown you three reactions on your screen in front of you.

What I want you to do is I want you to look carefully at each of these reactions, write the mechanism for each of these reactions and tell me based on your knowledge of writing mechanisms, do you think they will show a primary kinetic isotope effect? So for each reaction, I want you to write the mechanism and let me know or write it on a piece of paper, whether they will show a primary kinetic isotope effect.

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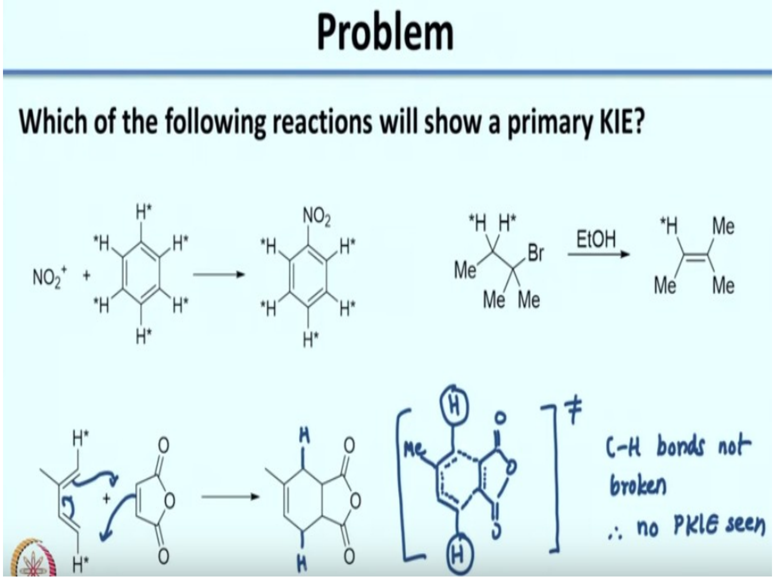

Problem

Which of the following reactions will show a primary KIE?

C-H bonds not broken

∴ no PKIE seen

So you can press the pause button and work this out in a sheet of paper. So let us try working these out. I will start with the third reaction, because it is an example of a Diels-Alder reaction. And this reaction, the mechanism is it is a concerted mechanism. So I can directly draw the arrows here. So you will have a transition state which looks, so your partial bond formation and partial migration of the pi bonds.

You have a methyl here and these are the hydrogens that have been labelled. So this is what your transition state will look like. Now looking at the transition state, are the C-H bonds broken? No. So the C-H bonds are not broken. Therefore, no primary kinetic isotope effect will be seen. Okay, this is quite straightforward because in your product also you have these C-H bonds and they are not broken. So you can say that this reaction will not show a primary kinetic isotope effect.

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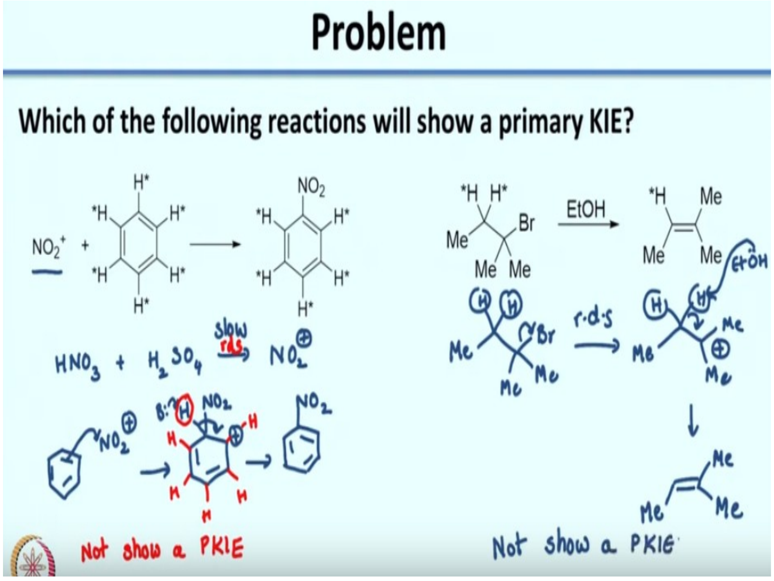

Problem

Which of the following reactions will show a primary KIE?

Now what about the other two reactions? Now when you think of the electrophilic aromatic substitution reaction, the first step here is generation of the electrophile. So you have HNO_3 + $H2SO_4$ which gives you NO_2^+. Now this reaction is known to be very slow. So once you generate the electrophile this is your aromatic ring. You have your NO_2^+.

you generate this intermediate and you can write several resonance structures for this. I am just showing you one. So now once you generate this intermediate you have a hydrogen here. So what you do is you can then have the hydrogen leave to give you your nitrobenzene. Now in this case what you see is you do have a C-H bond. So you do have a C-H bond, which is breaking, correct?

All the others might be intact, but you do have a C-H bond that is breaking. Now, but the bond breaking is happening after the rate determining step. So since this is happening after the rate determining step, this will not show a primary kinetic isotope effect. Remember all the steps that take place after the rate determining step do not influence the rate constant much, which is observed for a particular reaction.

So what happens is since you have the C-H bond breaking after the rate determining step, it will not show a primary kinetic isotope effect, although you see in the product, you have the C-H bond broken, but since that happens after the rate determining step, no primary kinetic isotope effect is observed. Now let us look at the other reaction.

Now this is very similar to the reaction that we had seen in the previous lecture except you have methyl groups here. So here how the reaction works is you have, the first step would be formation of a stable tertiary carbocation. Once you form the carbocation you then have elimination to give you your product. So this is again a very interesting example where in the rate determining step, you have the C-H bonds intact.

So you will not see or this reaction will not show a primary kinetic isotope effect. So we saw three different reactions where in two reactions, the C-H bond was broken after the rate determining step. So you did not observe a primary kinetic isotope effect. Whereas in one case the C-H bond did not break at all, which is why you will not observe a primary kinetic isotope effect. Now let us look at another highly interesting observation.

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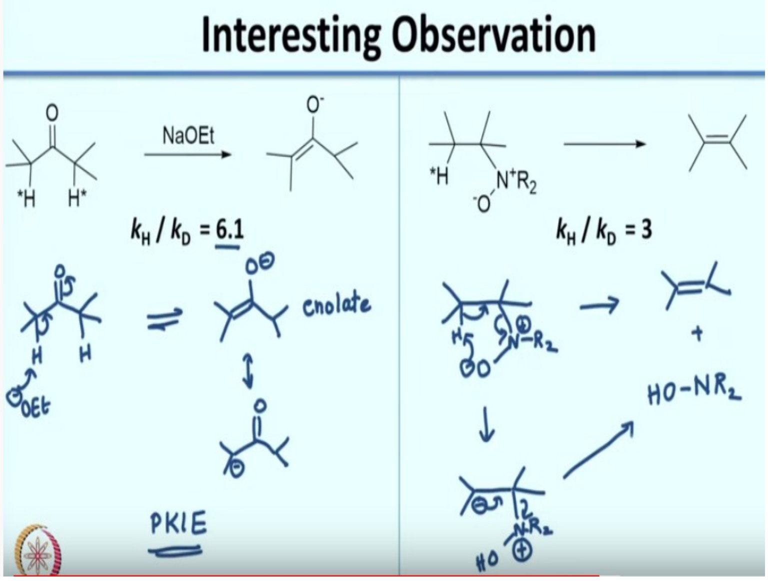
Interesting Observation

Now shown are two reactions on your screen. What is seen is both are deprotonation reactions, but in the second case you have deprotonation followed by elimination. So in the first case, the k_H over k_D value seen is 6.1. Whereas in the second case, the k_H over k_D value seen is 3. So what I want you to do is I want you to write the mechanisms for each of these and I want you to think as to why you have a lower k_H over k_D value in this case.

As you can see in both cases you have deprotonation taking place. But in one case, the effect seems to be lesser than the other case. So you can go ahead, press the pause button on your video and work out these two problems. Alright, so let us see if you were able to get a solution for this. This is quite challenging, so it might not be very obvious for you as to why there is a lower k_H over k_D for the second reaction.

So let us see if your answer is correct. So as you have studied the alpha hydrogen next to a ketone is acidic. So here you have two alpha hydrogens. So let us deprotonate one with a base. So what you get would be, so this product is called an enolate. Of course its other resonance structure is a carbanion. And of course, this is the more contributing structure because you have a negative charge on electronegative oxygen.

So now when you look at formation of this enolate what you would see here is you have the C-H bond breaking in the rate determining step. And probably you have quite a symmetric transition state. So your k_H over k_D is 6.1. So it is a primary kinetic isotope effect. Now in the second case, the mechanism is, so here again you have a deprotonation to give you your product.

So these are the two products that are formed. You can think of it either in a concerted fashion or you can think of it in a stepwise fashion. But since you have such a nice leaving group right here, there is a good likelihood that it goes via the concerted process. Now when you look at this either way or either mechanism you write what you will notice is the C-H bond is breaking in the rate determining step.

Then why do you have a lower k_H over k_D value? Now to answer this we need to understand a linear versus a nonlinear transition state.

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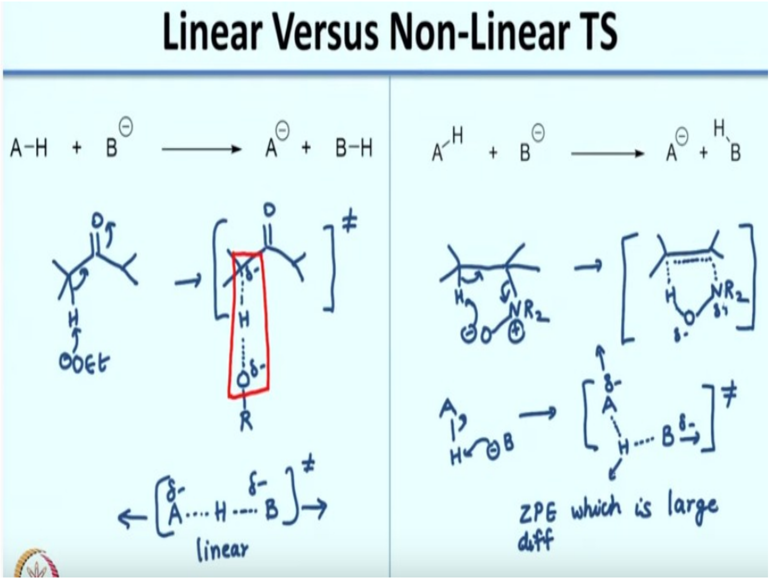

Linear Versus Non-Linear TS

So in the first case that we studied where you had, so we were looking at hydrogen abstraction. Now when you write the transition state for this, the transition state can be written like this. And of course then you have the R group attached to it. And then let us not bother about this either. Let us draw the rest of the molecules. You have your δ^-, δ^-.

So this is what your transition state would look like. This transition state is very similar. So if I were to focus just on this part. So the transition state is very similar to what we had seen earlier. So this is very similar to this, this is a linear transition state. So where you have the symmetric stretch contributing to k_H over k_D. So you have a value which is close to 7, so it is around six point something.

So you see a proper or whatever you have studied earlier, you see a primary kinetic isotope effect. Now what is happening in this case, in the other case, which we saw, we had, so if I were to draw the transition state for this these bonds are not broken. This is partially broken, this is partially broken and you have this partially formed and you have the double bond partially formed.

You have a δ^+ here δ^-here. So now what you see is your transition state is not linear anymore, right? Just because you have, in this case a base, which is a neighboring group, so the base is actually abstracting the proton. And because it is a neighboring group, the geometry is constrained. It is not linear like you had seen in the earlier case, it is quite constrained. So now what does this constraint do?

So if I were to translate this, so I have A-H and then I have B which is coming at an angle now. Correct? So now what you have is B is coming at an angle. So your transition state looks something like this. δ^-, δ^-. So this is what your transition state looks like. So now when you are thinking about the vibrations that are taking place, they are taking place like this which is essentially like a bending vibration, right?

So you have a nonlinear symmetric stretch kind of thing, but what you end up getting is something which is similar to a bending vibration. So what do you see in your transition state would be that instead of the other case, remember I told you elephant or man, both are being pulled on the opposite sides. So it does not matter what the mass is in the center, you have equal forces on both sides.

But in this case, because you have a nonlinear transition state, you would get a zero point energy which is, so zero point energy difference, which is large. So now what you have when you look at the reaction coordinate is you have reactants as well as transition state with the large zero point energy difference, which is why the kinetic isotope effect observed will not be as pronounced.

So you still see a primary kinetic effect isotope effect of 3, but it is not as pronounced as when you have a symmetric linear transition state. So now that we have seen different types of primary kinetic isotope effects, so we saw the origin of primary kinetic isotope effects and we also saw how the position of the transition state has an effect on the magnitude of k_{H} over k_{D}.

We also saw how the geometry of the transition state can have an effect on the k_{H} over k_{D}. So if you have a linear geometry, you would have a greater k_{H} over k_{D} as compared to a nonlinear transition state. So in the next class, what we will do is, we will look at another kind of kinetic isotope effect. This involves C-H bonds, which are actually not broken in the rate determining step.

So these are called as secondary kinetic isotope effects and we will see more about that in the next lecture. Thank you.