Mechanisms in Organic Chemistry
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Lecture-26
Equilibrium Isotope Effects

So welcome back. In the last class we had looked at steric kinetic effects and these were seen because the CH bond is longer than the CD bond. We had also looked at heavy atom kinetic isotope effect

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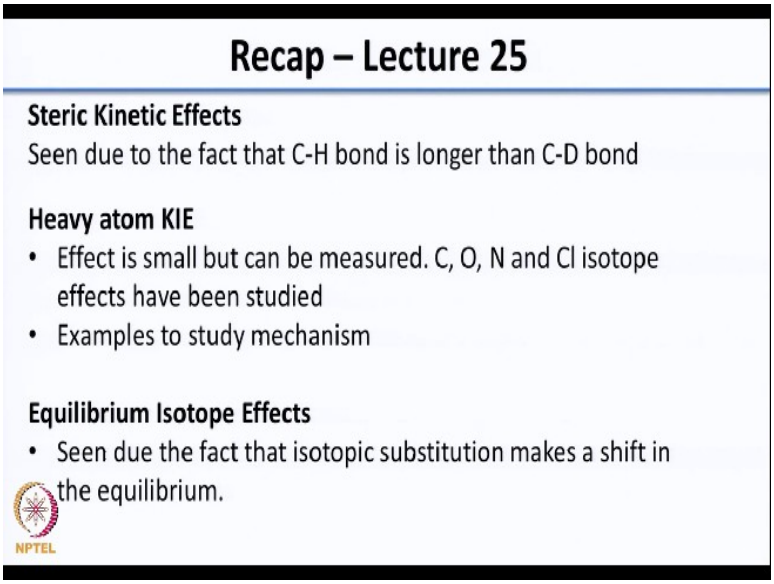

and I had told you that these effects are very very small because the reduced mass difference when you substitute with the heavier isotope is very little compared to substitution of hydrogen with deuterium. So to study this simple tricks have been used such that you measure the concentration of the reactant and measure the enrichment of the heavier isotope closer to the end of the reactant.

So using these techniques you can actually measure very very small kinetic isotope effects and we had looked at examples where these have been used to study the mechanism for reaction. Now towards the end we had started looking at equilibrium isotope effects. So, equilibrium isotope effects can be very small. Essentially what it is is that when you do an isotopic substitution it shifts the equilibrium. So we are looking at large K instead of small *k* which is the

rate constant and we had started looking at the ring flip of cyclohexane. So we will continue with that and in the last class what we had seen is that cyclohexane ring can flip.

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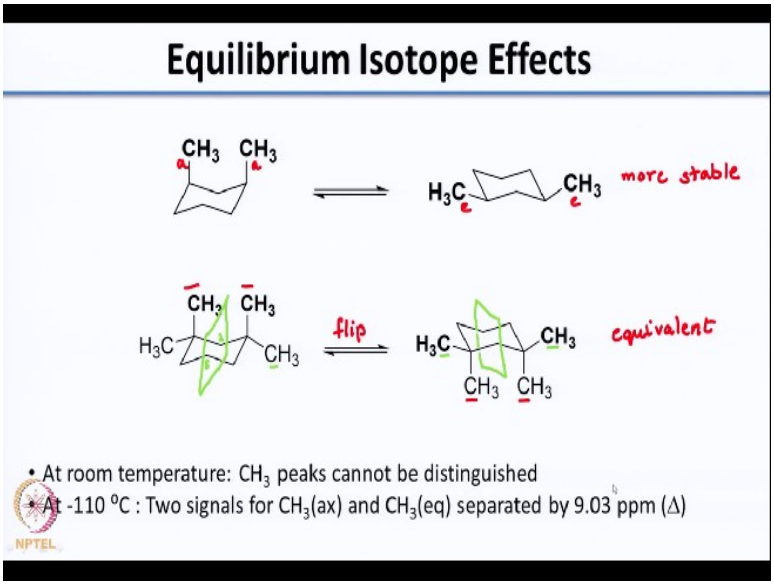

So when you have 1,3-dimethyl cyclohexane the cis dimethyl, so what you see is you can have the axial-axial and the equatorial-equatorial. So this is more stable. So then what we had seen is if you have 2 methyl groups at the 1 and 3 position, so now what happens is when you flip the ring, so when the ring flip happens you again have 2 methyls in the axial position. So what that essentially does is it makes both these structures equivalent.

And if you remember I had told you that in these cases there is a mirror plane going through this C2-C5 position. Similarly, here you have a mirror plane. So because of this mirror plane these equatorial methyls are symmetric and the axial methyls are identical. So, if you measure the NMR spectrum at room temperature all of these will come as a single line because the ring is flipping. So it is not that you are arresting the axial methyl or the equatorial methyl separately. It keeps flipping.

So what is axial here becomes equatorial here. So because of this you are not able to differentiate the axial and equatorial CH_3 peaks but when you lower the temperature this ring flip does not happen because of which you see separate peaks for the axial and equatorial and the peaks are separated by 9.03 ppm. So what I had asked you to think about before I left you is that if I make a substitution now, so I am substituting one of the methyls with CD_3,

again are these 2 structures equivalent in terms of energy or will one of these conformers be more stable? So to understand this again you can use the concept of CD bond being smaller than the CH bond.

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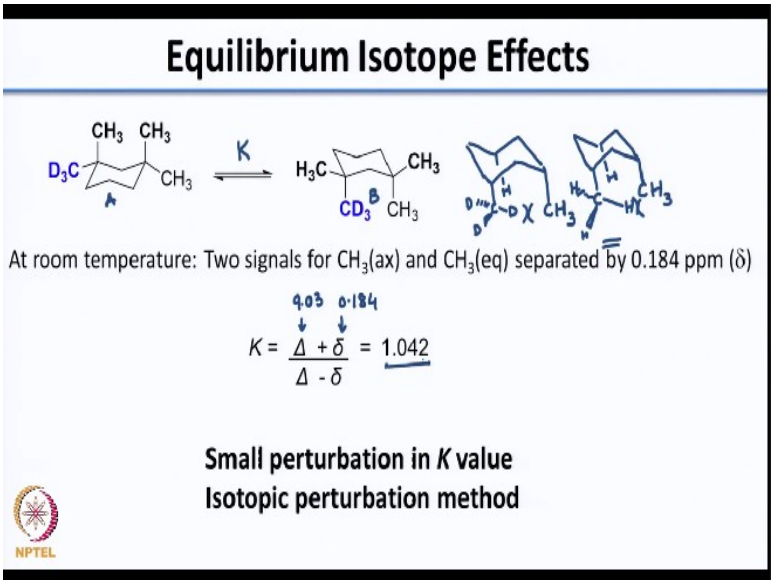

So when you try to visualize this you can think of the case, so I am drawing out the CD part. This is the CD bond, this is the methyl, so this is a destabilizing 1,3-diaxial interaction, you also have a hydrogen which also leads to a destabilizing methyl-hydrogen and CD_3-hydrogen interaction. So when you compare this with another structure where you have CH_3, remember the CH bond is longer than the CD bond.

So, in which case do you think you will have greater problem because of sterics? It will be this case, because the CH bond is longer. So having CD_3 at the axial position is better than having CH_3 at the axial position. So if I were to call this A and B, B would be slightly more stable than A because it has CD_3 in the axial position but the shift in equilibrium will be very very small, it will not be like a large shift in equilibrium.

Let us say this K is the equilibrium constant for this. So what you see here is now at room temperature you get 2 signals for the CH_3 axial and CH_3 equatorial because now what is happening is you have a slight preference for one of these geometries and the value that it is shifted by is actually very small. It is 0.184 ppm. So the value is pretty small but because of the

small perturbation in equilibrium you see at least a small difference between the axial and equatorial methyl groups.

Now using an equation given by $K = \Delta + \delta / \Delta - \delta$, so here Δ is given by low temperature difference between the 2, so this is 9.03 ppm and δ is once you make the substitution you have a shift in the equilibrium that shift is what we are trying to see. So that shift is given by 0.184, so if you substitute this value in this equation what you see is the equilibrium constant you get is 1.042.

So what you are seeing is a very small shift in equilibrium 1.042 but which is also measurable. So there can be a very small perturbation in K value due to substitution within isotope. So this is a classic example for that where you have made the substitution and because of this very small perturbation which you are experimentally able to measure you can determine the equilibrium constant change.

So this gives you one example where we have seen a small perturbation. We will look at how this can be useful for you to determine the mechanism or the nature of the intermediate.

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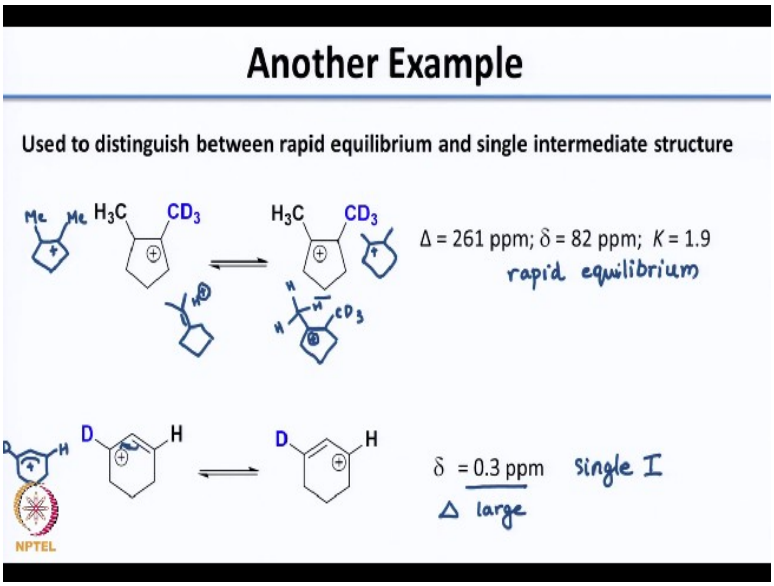

Shown on your screen are 2 structures. The structure on the left you have a carbocation next to CD_3. A structure on the right you have a carbocation next to CH_3. So, if you compare this with an example where you have both methyls, so you have a + sign here and then so in the other case

you will have a + sign here, but again both are methyl. So both these structures would be equivalent.

Now with the isotopic substitution of CD_3 what I want to ask you is do you think there will be a perturbation or a change in the equilibrium or in other words are one of these structures more stable? So if I have the carbocation next to a CD_3 versus a carbocation next to CH_3 will one of these structures be more stable? You can press the pause button and think about this and try to rationalize your answer in your notebook.

So if you are still thinking I will give you a hint think of hyperconjugation. So when you think of hyperconjugation in which case would you have greater stabilization? Remember it is easier to break a CH bond as compared to a CD bond. So when we were studying kinetic isotope effects that was the very first thing we had looked at because the zero-point energy of CH bond is higher than the CD bond.

So it is easier to break the CH bond. So keeping this in mind can you now say which of these would be stabilized more due to hyperconjugation? It will be the structure on the right because essentially when you think of hyperconjugation, so when you are looking at hyperconjugation as I told you it is a type of no bond resonance. So you have CH, CH and then CH. So you are thinking of almost as if this bond is breaking to give you a structure where you get.

So, you are looking at a structure like this, so when you compare CH versus CD, CH would be easier to think of I mean the no bonded resonance would be greater for the CH_3 case. So which is why the structure on the right is more stable. So now when you try to study the NMR of these species what is seen is that the Δ value, big delta will obviously be very very large here because you are looking at a charged center versus and uncharged center.

So the Δ value would be very large, now when you make the isotopic substitution what you see is the small δ value you get is 82 ppm, remember in the earlier case it was 0.185 because the delta value was also very small 9.03. But in this case the Δ value is very high, big delta so that is why the small δ value is also pretty significant. So what this gives you is that the perturbation of

equilibrium in this case is 1.9 which is much larger than what we had seen in the case of the ring flip for cyclohexane.

So now let us look at another example. Now in this example this is essentially again a carbocation rearrangement. So you can also think about it in terms of resonance where when you write the resonance structure you get the other carbocations. So is it a rapid equilibrium that you have here or is it a resonance structure? So, the actual structure is a hybrid of both of these structures, if that were the case what you would see is you will not see any great perturbation in the equilibrium constant.

So that is essentially what you observe, you observe a small δ value of 0.3 ppm. So this is very small considering the fact that the large Δ value in this case would be very large. So what this isotopic substitution experiment tells you is that in this case you have a single intermediate structure, whereas in the case that we saw first you have a rapid equilibrium. So this method is actually very nice for you to get mechanistic insights into what is the nature of the intermediate.

So to summarize we have looked at kinetic isotope effects where based on the difference in reaction rates of CH versus CD you get a rich information about the mechanism for a reaction and we looked at several different types of kinetic isotope effects. We also looked at equilibrium isotope effects where they are not looking at kinetics, but the perturbation of the equilibrium due to isotopic substitution.

Now isotopes play a very important role in determining mechanisms by what is called as isotopic labelling. Now just like the name suggests whenever you have a book you put a label on it to tell you what book it is. Right? A label essentially helps you identify something.

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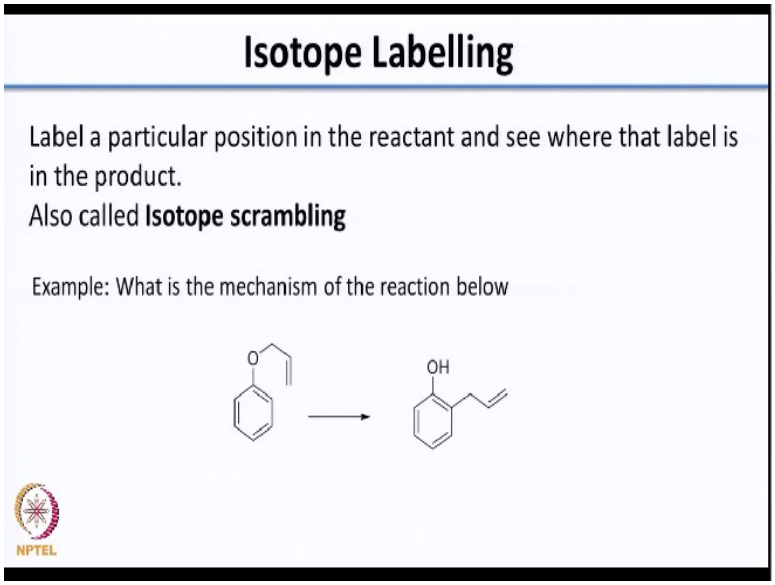

So in this case what is done is a position of the reactant is labelled with an isotope. So a particular position of the reactant is labelled and then what are seen is how that label moves when you go from reactant to product. This is also called as isotopic scrambling sometimes. So do not get confused when you hear both of these terms. So when I discuss some of these examples with you the concept of isotopic labelling would be clearer to you.

So shown below is a reaction. You must have seen this reaction before. Do you know the name of this reaction? Think about it I will give you a second. Does the name Claisen ring a bell? So this is actually an example of a [3,3] sigmatropic shift. Alright? and this is the aromatic Claisen variant of that. So what I want you to do first is I want you to write the mechanism for this reaction based on whatever you have studied in your textbook.

And also think of other probable mechanisms that could be possible for this reaction. So press the pause button and go ahead and write all these mechanisms.

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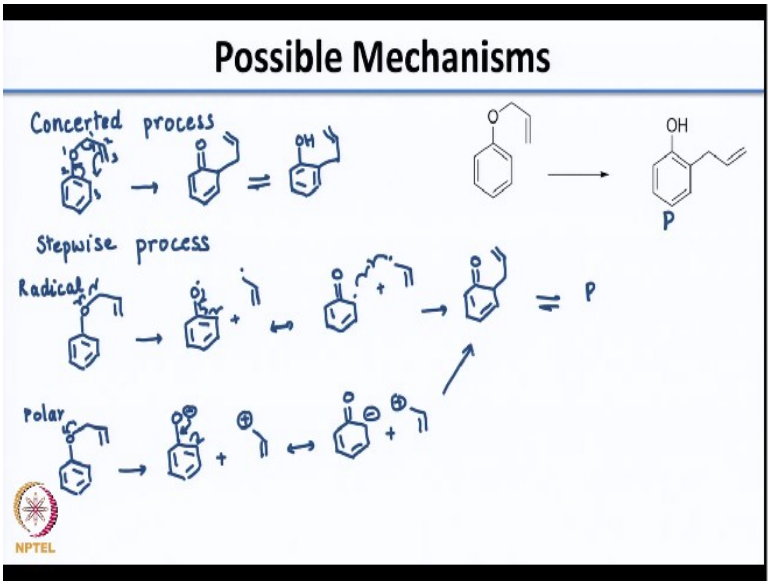

So let us see. So one is the concerted mechanism. So this is the textbook mechanism which you must have studied. So in the concerted process essentially what you have is you have and as I told you it is a [3,3] sigmatropic shift. You can number this as 1,2,3. So you have a new bond forming here and then you have this to give you the intermediate. Nothing happens to these bonds. So I am just leaving it as it is and then this new bond is formed between the 2,3 positions and then you have this double bond.

And then this tautomerises to give you the final product which is shown. Now this is the concerted process. Now what if it is a stepwise process? I can also argue that maybe it is not a concerted process maybe it is a stepwise process. So if it is a stepwise process you can think of a radical process, so you can think of again I am using the fish hook arrows to give you and then once you have that radical you can also imagine this coming together.

So you can think of the resonance structure for this where you have again nothing is happening to this. So I have this double bond O, I am generating this radical, this can combine with the allyl radical, the allyl radical can also rearrange to its other resonance form and you will get, so you will get this product which again will tautomerize to give you the product, let us call it P. You can think of a polar mechanism, again a step wise mechanism. Right?

Theoretically you can think of all of these pathways. So obviously when you are breaking this bond you will break it such that you put the negative charge on the electronegative oxygen plus you have and of course again you can write the resonance structure for this and then and once you write this resonance structure it can combine with the allylic cation to give you this product. So all these mechanisms you can technically write.

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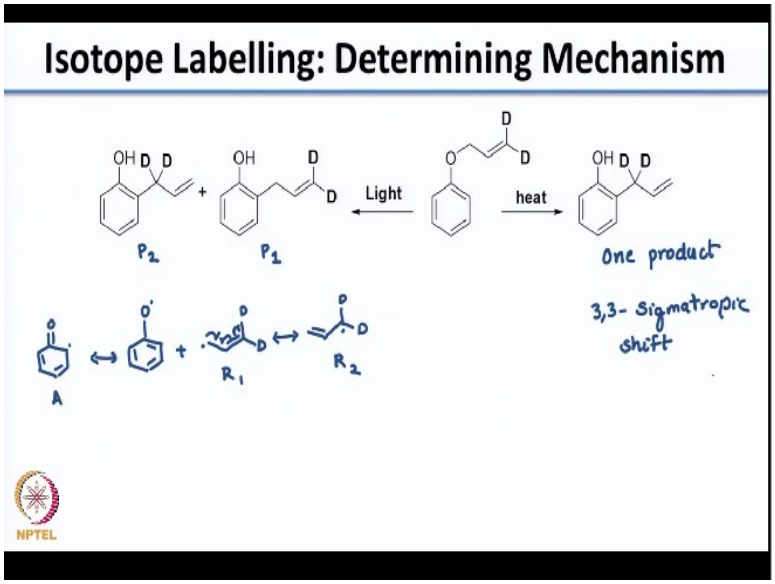

Now how will you distinguish which is which mechanism? So to do that this is the experiment that was done. So you have now done isotopic labelling, so what is done is you have labelled these 2 positions here with deuterium. So why you do that is you can follow where the deuterium goes. So this reaction is carried out under 2 different conditions heat and light. In the case of heat you get one product whereas in the case of light you get 2 products.

So in the previous slide we had gone through all the possible mechanisms. So now can you tell me based on the labelling of deuterium that when the reaction is carried out under heat which is the mechanism that takes place and when it is carried out under light which is the mechanism the takes place? So you can press the pause button and work out the mechanism. So let us first look at the light.

So in the case of light there is a greater chance of homolytic cleavage. So radical generation is highly probable in when you do this reaction in the presence of light. So in the presence of light the homolytic bond cleavage occurs readily. So you will generate this radical as well as this other

radical if you have doubts you can see the earlier slide where we do the arrow pushing. Now this has the following resonance structure.

Again, we had written the arrow push in the previous slide. Now I can also push arrows here to generate another intermediate. So if this is A, intermediate A can interact with so that is a radical here, either this radical I will call it as R_1 or the second radical R_2. So if intermediate A reacts with radical R_1 the product that you get is one where you have no rearrangement. So let us call this product 1. If it interacts with the radical after rearrangement you get the product 2.

So this tells you there has to be a CO bond cleavage in order for this kind of mechanism to take place, because had the CO bond not cleaved to generate these radicals you would not get the rearrangement and you would not get the rearranged products. Now let us look at the second case. So in heat since you are getting only one product it indicates that you do not have formation of a radical or a polar intermediate at all, it indicates that the process is concerted.

So what you have is essentially a concerted process like I had shown you where it is a [3,3] sigmatropic shift. So this is a very nice example. By labelling you can actually figure out what is the product that is formed, specifically what is the nature of the intermediate to form that particular product.

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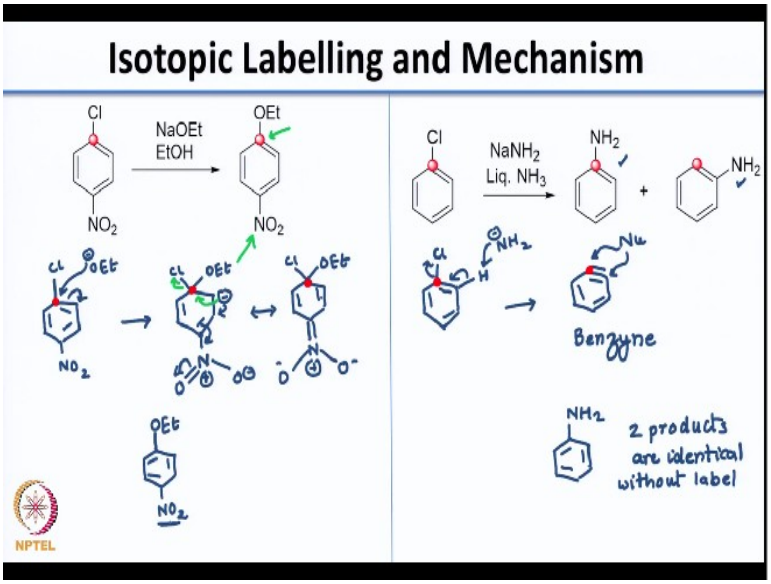

Another example is in nucleophilic aromatic substitution reactions. So there are 2 reactions shown in the screen in front of you. Shown in red is actually a labelling of carbon here. So you have isotopically labelled the carbon atoms which are shown in red. In the first reaction what you see is, when you add sodium ethoxide in ethanol, so you are essentially displacing the Cl at the same carbons.

So whichever carbon was labelled you have displaced the ethoxide. Now in the second case what you see is you have again the labeling on the carbon, you treat it with a base and liquid ammonia so your nucleophile here is your NH_2 and what you see is the NH_2 can be at the position with the labelled carbon or right next to it. So now what you need to think about is the mechanism for each of these reactions.

So obviously the mechanism is not the same because you are getting a different product distribution in each of these cases and the starting material, the big difference here is you have a nitro group here. So now I want you to think about what could be the mechanisms for both of these reactions and write them in your notebook. So in the first case since there is no displacement or no scrambling of that carbon which is labelled,

what you can say is, you can say that you have OEt^- adding directly to this position. So this will generate an intermediate. So this intermediate is highly stabilized because you have this nitro group next to it. So if I were to draw out the structure of the nitro group you can have resonance stabilization because of this nitro group. So you have this additional stabilization because of the nitro group that is why this reaction goes via direct nucleophilic attack at the labelled position.

So your labelled position here is this carbon. So once you have the direct nucleophilic attack, so then you can think of this coming back in and this leaving to give you the product. So this mechanism is proved by the fact that the label does not change. So your product also has the label at the same position. Now what is happening in the second reaction? In the second reaction the mechanism has changed.

So what is happening here is since you do not have the nitro group to stabilize this negative charge which is generated in the intermediate and you have a very strong base in the form of sodamide, so you can think of a different mechanism where elimination takes place first followed by addition of the nucleophile. So when you have your base here, will abstract a proton to give you a product, sorry not a product it will give you an intermediate,

and this intermediate is called a benzyne intermediate. So as you know the benzyne is not very stable. Now let us put the labels back. So that you know so see labelling helps so much to keep track of the carbon atom. So this is where the label was and in the benzyne you have the label here. Now once your nucleophile comes in your nucleophile can actually add an add either of these positions because both of these positions are identical in terms of reactivity.

You just have a carbon isotope label. So what you have is your nucleophile can either come here or it can come here. So then what you get is you get the 2 products which you see. So in one product where the nucleophile directly attacks at the position which has the isotopic label you get this product whereas in the other case you get the label next to the position where the nucleophile attacks.

So using isotope label you can actually get lot of insight into the reaction mechanism. So shown here are very similar substrates, the main difference being and one you had an electron withdrawing group and what you see is the mechanism differs and this difference in mechanism is evident when you have isotope labelling. If you had not put the label then what would have happened? Both of these would have become identical.

Because you would have just, without the label both of it would have just given you aniline. 2 products are identical without labelling and even in this case the first case without label, so the first case because you have the nitro group you can still figure out the mechanism without the label because the nitro group essentially acts as a place for you to determine what is going on. Okay?

So shown here is an example of how you can use isotopic labelling to determine the mechanism of the reaction. So now before we finish this lecture, I will leave you with a question. So shown here is hydrolysis of this amide. So what I want you to do is before the next class I want you to think about the possible mechanism for hydrolysis of this amide. Okay? So write all possible mechanisms for hydrolysis of this amide.

So one hint I can give you is it need not always be direct addition of water. So I want you to think of all possible mechanisms for hydrolysis of this amide and we will discuss how isotopic labelling can be used to distinguish or determine the mechanism for this reaction. So thank you and see you in the next lecture.