Mechanisms in Organic Chemistry
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Lecture-27
Trapping Intermediates: Part A

Welcome back. In the last class we had looked at how you can use isotopes to put labels on molecules. So you can label specific positions of molecules using isotopes. Then you can observe how the isotope changes its position from the reactant to the product. So this is a good way for you to figure out if the mechanism involves a rearrangement or not. It also gives you tremendous insight into the nature of the intermediate.

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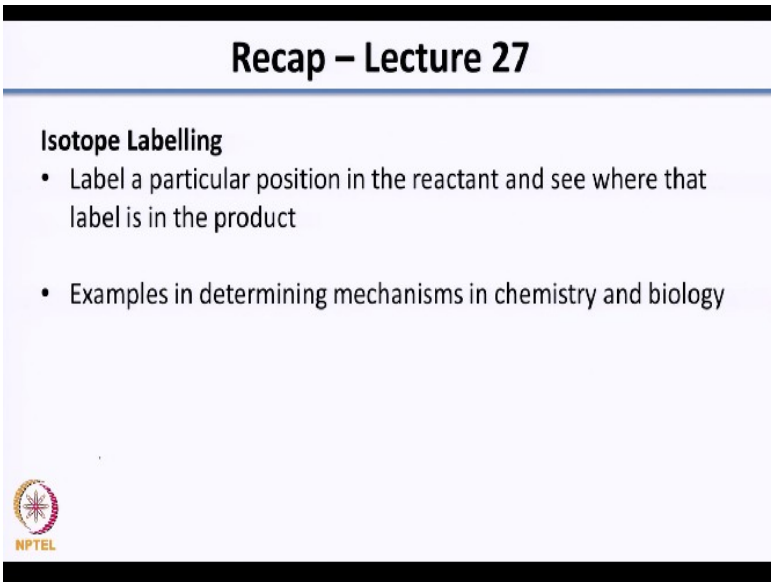

So we had looked at several examples on how labeling can be used to determine the mechanism and towards the end we had also looked at an example as to how isotope labeling was used to determine the mechanism of the particular enzyme and before leaving I had just started discussing another experiment that is used to determine the mechanism and this is trapping the intermediate.

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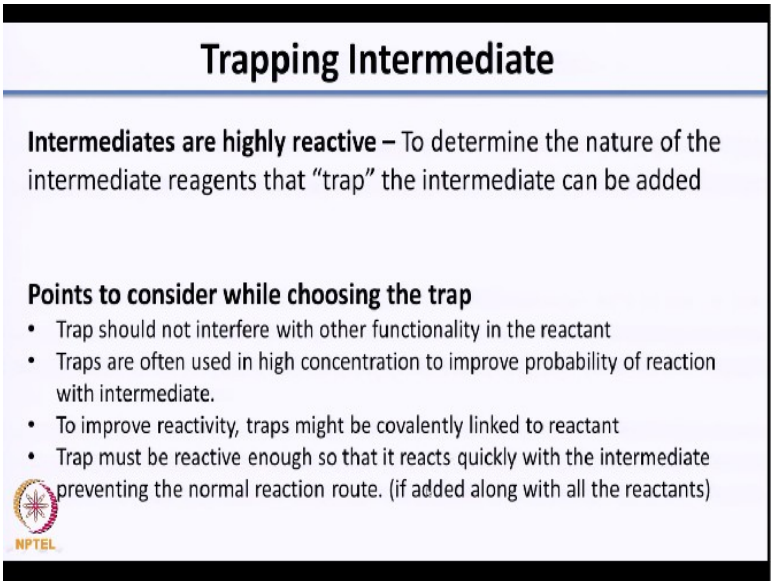

So just a quick recap. Intermediates are very very reactive right? So it is very difficult for you to see the intermediate. So what is done is you add an external reagent or change your reactant such that you can trap the intermediate. So by trapping the intermediate into a very stable state you can actually observe the intermediate. So this is a very clever trick that has been used to identify what the nature of the intermediate is.

And there are certain points that one needs to keep in mind when one designs traps for a particular intermediate. So points you should consider is the trap should not interfere with other functionality in the reactant. So the trap should just be in the flask and should not interfere in the reaction. It should only react with the intermediate once it is formed. A lot of times to improve reactivity traps are covalently link to the reactant or high concentration of the trap is used.

And also the trap must be reactive enough to grab the intermediate. So with this idea in mind I had asked you to think about this example.

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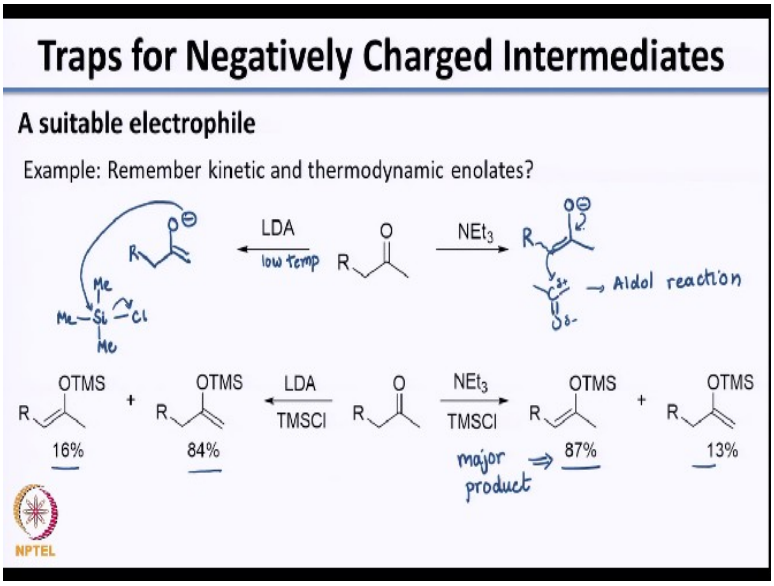

So when you think of trapping negatively charged intermediates, obviously what likes negative charge? Positive charge. So if you are looking at trapping a negatively charged intermediate such as a carbanion or an enolate you would look at an electrophilic species to trap it. So shown on your screen are 2 bases that can be used to deprotonate the given ketone. So if you remember what you had studied about kinetic and thermodynamic enolates.

So in which case do you get the kinetic enolate? And remember I had asked you to look at the situation where you use a low temperature? So when you use a low temperature what you get would be the kinetic enolate and with another base like triethylamine you would end up getting the thermodynamic enolate. So the let us go ahead and write the structure of both the enolates. So the kinetic enolate will deprotonate at the less hindered site.

So what you would get would be and the thermodynamic enolate would be, so I am drawing the squiggly line because the stereochemistry will not be clear of the double bond that is formed. So now that you have these 2 enolates, what is a good way for you to actually say yes that you have the enolates that is formed or is there a way to trap the enolate? Further it will be interesting to see if you can trap it in the form of the enol form and not the keto form.

So to understand that let us look at one reagent which is used and that reagent is TMSCl. So the structure of TMSCl is, now what is the electrophilic position in TMSCl? You can look at the

structure and write it down in your notebooks. So if you generate an enolate where will it react? So let us look at what happens in the case of LDA. So you will have this enolate. So what you generate is the OTMS.

So this is OTMS form of the enolate. So this is one way for you to tell clearly that you are forming the kinetically favored enolate because if you see you have 84% of the kinetically favored enolate and only 16% of the thermodynamically favored enolate. So, adding TMS chloride is a very good way for you to trap the enolate. So similarly when you add triethylamine and TMS chloride now what you are doing is what you trap is both the kinetic and the thermodynamic enolate.

But you see that the thermodynamic enolate is the major product. So in this way you are able to visualize the intermediate by adding a reagent, such as TMS chloride. Now I have a question for you, when you add TMS chloride why do you have the oxygen center actually interacting with TMS chloride. Remember when we had looked at mechanism of the aldol reaction? Once you draw the enolate you again push the arrow and you show

so you show the electrons coming here and then you have the reaction to a carbonyl right to give you aldol etc., whereas in this case what you see is you have the oxygen actually interacting with the silicon because you see that here you have 2 nucleophilic centers, oxygen and carbon. So why do you have carbon interacting in this side and oxygen interacting in the other side? I want you to think about this question you can press the pause button if you need more time to think.

So what happens is in the case of the aldol reaction since your carbon electrophilic center is softer what you see is instead of oxygen interacting with this softer electrophilic center you have the softer carbon nucleophilic center interacting with the electrophilic carbonyl carbon. Here what happens is your OSi bond is very strong. So that is a huge driving force for interaction of the oxygen center with silicon which is why you are able to capture the enolate in the TMS form.

So this is one example where we have trapped enolate using a trapping agent which is TMS chloride. Let us look at another example. Now you have studied probably several carbocation rearrangements. A carbanion rearrangements are not as common.

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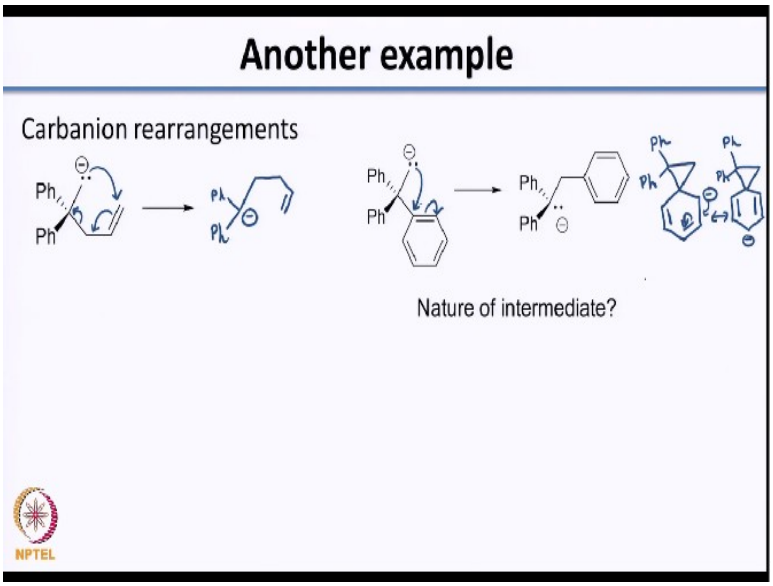

So suppose you have a carbanion like this and can you push arrows to think of what could be a rearranged product for this? So again you can press the pause button if you want and try to work out this problem yourself. So let us see if you have the answer correct. So you have a carbanion here. So you can push the arrows obviously that would be your source. So this pi bond would migrate and then you will have the electrons residing here.

So what you end up generating would be this intermediate. So you have I am just following the arrows. So you have formed this new bond and then once you have formed this new bond you have migration of the pi electrons. And then here you have generated a new carbanion alright? So this is how the rearrangement would take place. Now what is the driving force for this rearrangement? You have this anion which is formed here which is right next to 2 aromatic rings.

So that is your driving force for the rearrangement because you are stabilizing the carbanion. Similar to what you had studied in the case of carbocations right whenever you have a rearrangement there should be some reason for the molecule to do it. So it would do it if it finds some advantage in migration. So now here is another example where you have instead of an allylic group now you have a phenyl group.

So what you see is again you have a carbanion and you see a migration of the phenyl group to actually generate the new carbanion. So again you have to think of the mechanism for this. Now one possible intermediate for this could be. So if I think about this. So one mechanism could be where I push the electrons like this and then I have and then you can write multiple resonance structures for this. So if I follow this mechanism,

So now the intermediate that you have would be, right you generate a 3 membered ring and then way I have drawn it this would be the intermediate. But you can also write the resonance structure for this where you show the charge at this position, if you want to see the arrows. So this is another intermediate that you can write. So this negative charge is resonance stabilized. So now the question is, is there a way for you to actually prove that this exists? As I told you all of these happen there is some driving force for it to take place.

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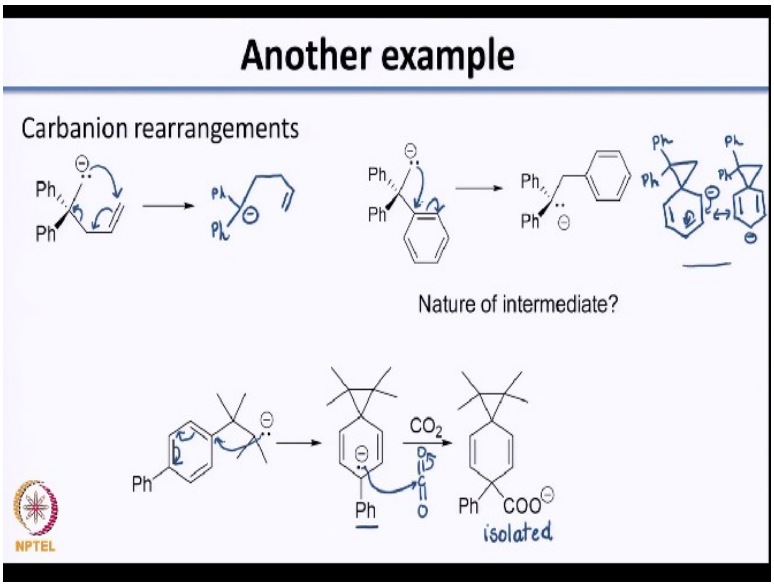

So a very clever design here is where what is chosen is now instead of having 3 phenyl rings you have a methyl group. So you have 2 methyl groups and then you have an aromatic ring and in the aromatic ring you have a phenyl group at the 4 position okay? With respect to this substituent. So now this is very interesting. So what is done is I had told you earlier that the driving force for this kind of rearrangement is generation of this stabilized carbanion.

Now what happens here is if you have the complete migration taking place you have the carbanion next to 2 methyl groups. So this is a very clever design where you are increasing the stability of this intermediate because now what happens is if again I push arrows like I had shown you earlier, so if I push arrows, so I can show again formation of this 3 membered ring. So when I form this 3 membered ring I now have a negative charge that is generated and this is right next to an aromatic ring.

So now you have the driving force for actually this intermediate to be around in your reaction flask for some time. So now that you have this intermediate you can use a reagent to trap it and here what is used to trap it? CO_2. So the structure of CO_2 as you know is right. So if you have your nucleophilic centre here what you would have is you would end up putting a carboxylate at the 4 position with respect to this 3 membered ring.

So this could be isolated and based on this you could say that the reaction goes via the intermediate that I have drawn here. So this is a nice example of how you could trap the intermediate using CO_2. So this way you know that how the reaction is actually going through this 3 membered ring formation and then stabilization of this carbanion by the aromatic ring was another trick that was used

so that it could be trapped by the CO_2. So now let us look at traps for positively charged intermediates such as carbocations. So just like we had electrophilic traps for carbanion and other negatively charged intermediates for positively charged intermediates you would use something which is nucleophilic and solvents are very attractive. So if you have solvents like acetic acid, ethanol they are also nucleophilic and if it is a solvent obviously it is in excess.

Remember I told you in the very first slide on trapping reagents that the trap sometimes is used in excess or large concentration. So that there is enough chance for it to interact with an intermediate and I had also given you the example of your class reunion where if you have a batch reunion there is a greater probability for you to shake hands with your batch mates. So now we will look at some examples of traps that are used for carbocations.

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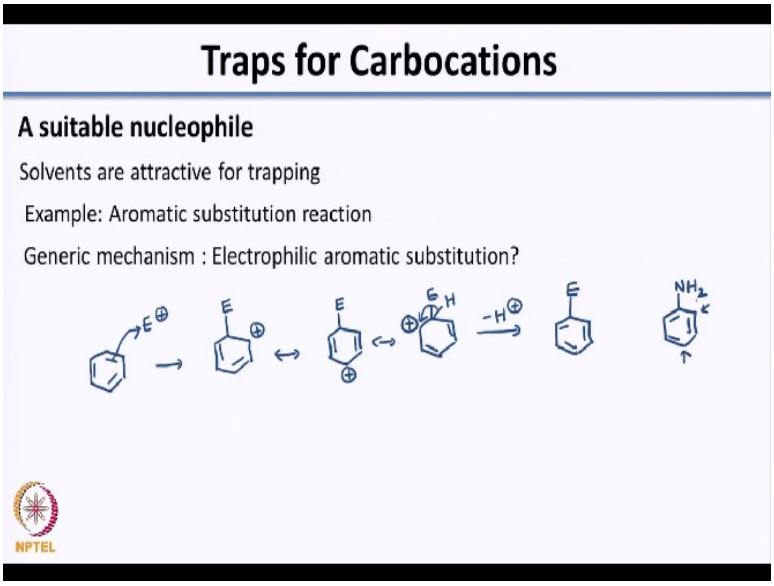

So, one example that I will start off with is the electrophilic aromatic substitution reaction because that is something that you study right since 11th standard. So what is the mechanism of the electrophilic aromatic substitution? Can you go ahead and quickly write that in your notebooks? You can press the pause button on the screen. So let us see if your mechanism is correct. So if you have this is your benzene.

And if you have an electrophile, then you generate a carbocation here and now this is again resonance stabilized. So you can write multiple resonance structures. You can also write the resonance structure. So these are the multiple resonance structures that you can write and once you have written this the next thing you have is you have loss of the proton to give you a product. Now you have studied that depending on the groups for example if you have aniline, this is highly activating at the ortho and para position.

And that is because you have a greater electron density at these positions or in other words suppose you put aniline here what you would see is you would have greater stabilization for the intermediate that is formed, because the intermediate if this is your electrophile your positive charge is right next to the electrophile. So when you add the electrophile here it will be right next to this aniline which is releasing.

So you would be able to write resonance structures to stabilize the intermediate. So you remember that this similarly if you have electron withdrawing groups you have studied that this deactivates the ring. Now all this you know about electrophilic aromatic substitution. But how do I know that it actually goes through this sort of an intermediate right? Where it actually has the electrophile coming in generating a positive charge and then one can argue it is disrupting aromaticity.

So why is this forming? So is there some way for you to characterize the intermediate? Because the intermediate as I said is not very long-lived. So you have to use special tricks to characterize the intermediate. So I will show you 2 examples, one is where you use intramolecular trapping.

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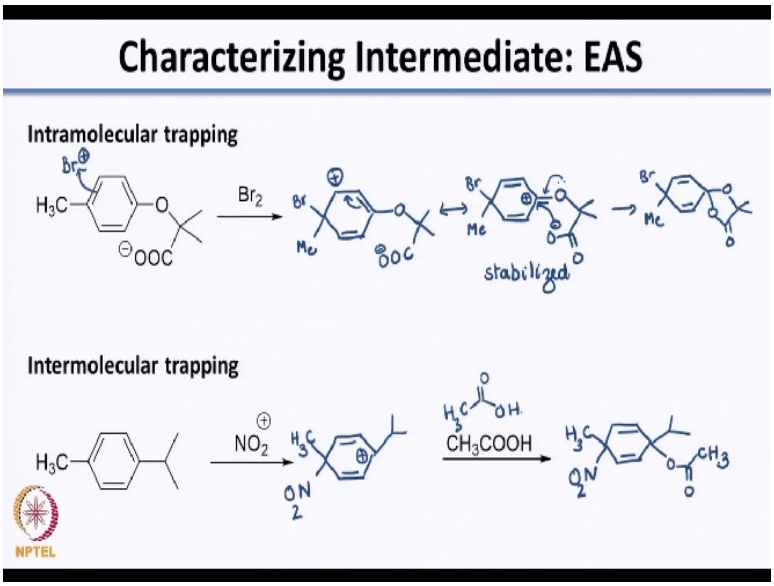

So intramolecular trapping means now your reactant itself is modified. So, that the trap is part of your reactant. So again in the very first slide I told you to increase the probability of the intermediate and the trap reacting with each other what you do is you modify the reactant. So that it keeps the trap in close proximity to your intermediate. So now again I want you to write the mechanism for this.

Now based on whatever I had shown you in the previous slide what you need to figure out is now if you add an electrophile, so in this case you are adding Br^+. So imagine you are adding Br^+ where will the electrophile go? So you have multiple positions on the aromatic ring where the

electrophile can go and now you have 2 substituents here you have let us take this as OR and then you have Me alright?

So where will the electrophile go? So I want you to think about this very, very carefully. Do not be tempted to just put ortho para like you have studied before, think a little more to see where the Br will go. I suggest you press the pause button and think about all possibilities and see which would be very stabilized. So one hint, in this case you have a very large group here. So these two positions will be very difficult for the electrophile to access.

So that leaves these 3 positions alright. So now you think of the nature of the intermediate you get if Br^+ comes here, here or here. Okay? So I want you to write the intermediates and see which will be very very stabilized, because remember compared to O and C, here you have the lone pair O provides you greater stabilization. So let us see if you are able to figure out the intermediate. So in this case when I add my Br^+ what happens is,

so if I push the arrow what the intermediate I get would be nothing is happening here. So for now I am just going to write it like this. So I have Me, Br and now I have generated the positive charge here. Right? Now this is very stable because this is in conjugation. Now I will write this out okay? So this positive charge is in conjugation with this double bond which is attached to an oxygen. So what is happening is you have tremendous stabilization here.

This particular resonance structure is stabilized more as compared to the resonance structure I had written earlier. So what happens is when you form this stable resonance structure and in its proximity you have a nucleophilic species what you end up doing is you end up trapping the so you end up trapping this intermediate. So the product that you get is, so nothing is happening here. So you can isolate this product alright?

So this is a direct evidence for you that it is forming a carbocation. Alright? Now let us look at whether this can also be done in an intermolecular fashion. So here is another example. So here what is done is you do the electrophilic aromatic substitution. So here you are doing a nitration reaction. So you have the aromatic system here. So you have methyl versus isopropyl. So again

you have to figure out which position will your electrophile go-will it go at this position or will it go at this position?

So I want you to think about which position your electrophile will go. So again press the pause button and try to write out this complete series that I have shown you here. So let us check if your answer is correct. So as in the earlier case I am not going to write it again. So I am going to directly write the structure of the stable intermediate. So I have CH_3NO_2 and then, so I have this and now I am reacting that with acetic acid. So I have so then the product that I will get would be, so this would be the product that I would get.

So here we have seen 2 examples where we have used a trap to trap a carbocation or a positively charged intermediate intra-molecularly as well as intermolecularly and if you see in all these cases the model reactant chosen has been chosen very, very carefully. So, that you actually get a stabilized intermediate which can be trapped. If the intermediate is too reactive it is often very difficult to trap it.

So before we end this lecture I am going to leave you with a question as usual. So shown here is the mechanism for hydrolysis of this ester and what is seen is that you have a substituent right next to it.

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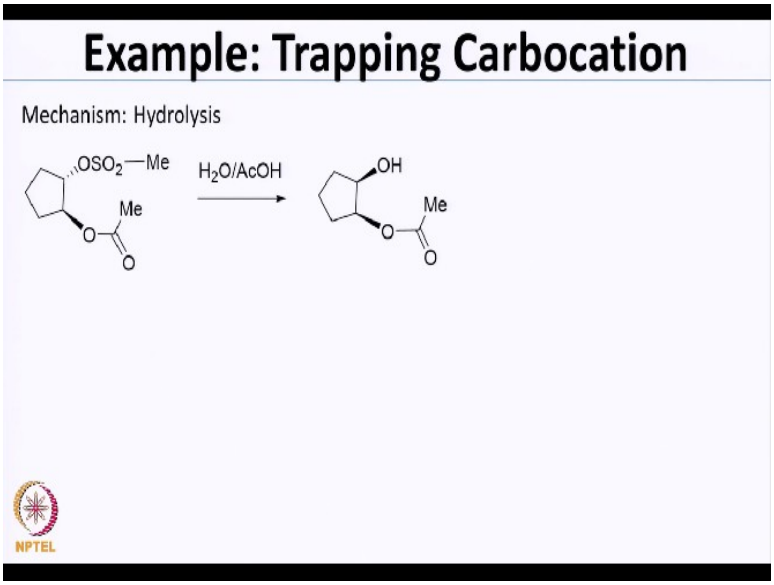

And the reaction is carried out in water/acetic acid. So it is a slightly acidic medium and you are hydrolyzing this bond and what I want you to pay attention to here is that when you hydrolyze this bond you generate this product. So carefully observe the stereochemistry at this position. So you get complete inversion at this position. So I want you to think of possible mechanisms of what is going on and again as a hint I can tell you that there might be a role of this neighbouring substituent.

So, I leave you with this question. Think about it and try to write the mechanism and then we will see as to how we can prove the mechanism by trapping the carbocation. So thank you and see you in the next lecture.