Mechanisms in Organic Chemistry
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Lecture-29
Trapping Intermediates: Part B

So, welcome back. In the last class we were looking at how you can get an idea of what an intermediate is by trapping it. So, we had looked at what properties a trap should have. A trap should not interfere with the reaction. A trap should be such that it will react with the intermediate and typically trap is added in an excess concentration. So, that there is a greater probability of it reacting with the intermediate. We had also seen as to how you can have trap being part of the reactants. So, that it can quickly grab the intermediate.

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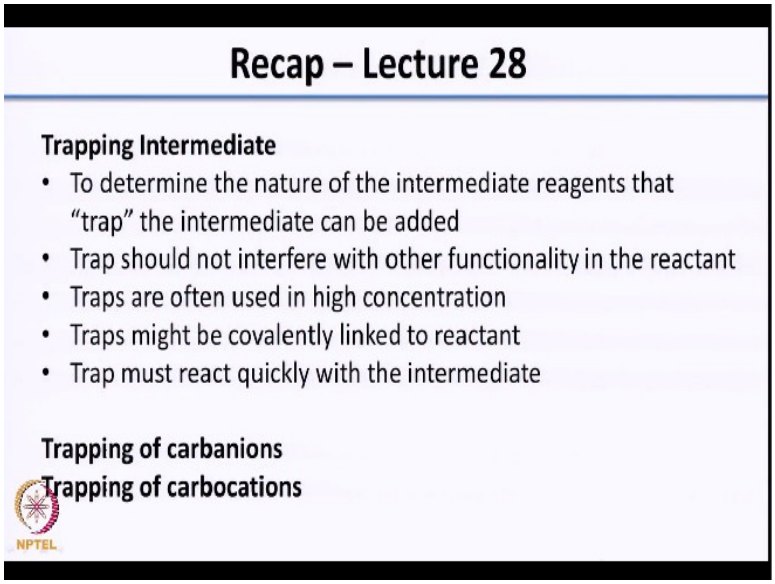

And we had looked at specific examples of how traps can be used for intermediate such as carbanions and carbocations.

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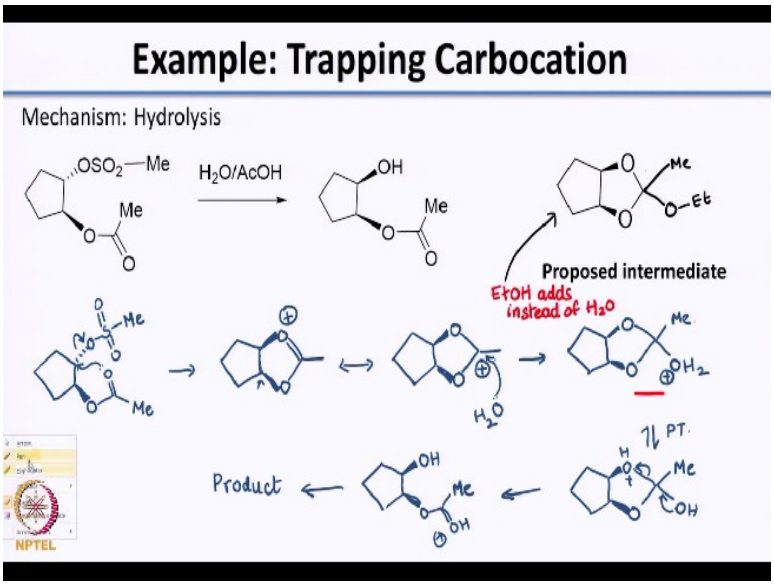

So, before I had left, I had given you a question where I had asked you to write the mechanism for this hydrolysis. Now you might be tempted just to write an S_N2 replacement looking at the stereochemistry which is why I had also given you a hint that the neighboring group has a role to play. Now, what has been proposed as an intermediate for this reaction is, this particular carbocation.

So, now that I have shown you what the intermediate is, I want you to write the mechanism for this reaction if you have not used this intermediate, or if your mechanism does not have this intermediate. So, if you do not have it go ahead press the pause button and write the mechanism. So, now let us see if your mechanism is correct. So what is happening here is, I will write out the structure.

So, you have and then here I am going to write it like this, to just give you a hint as to what might be taking place. So, what happens is because you have an nucleophilic group close to your living group, it can attack here and what you would end up generating would be the intermediate that is shown above and why the stereochemistry? The stereochemistry would be dictated by this position here.

Because this is above the plane, so, it will attack from above the plane and anti to the leaving group. So, this is of course, a resonance structure of the intermediate that I had shown you above.

So, now that you form this intermediate, what is remaining is just for you to generate the final product. So, as you have seen the stereochemistry here is set. So, you can go ahead and draw the water. The water will come in you can draw it to each of these structures does not matter.

So, now what you get would be now this stereochemistry will not be disturbed. Then you can think of proton transfer and then you can have these lone pairs come in to give you the protonated form of the product which will give you the product. So, now what you see is the stereochemistry here is dictated by the neighboring group. Now, you can always argue with me that I wrote a direct displacement by an S_N2 like mechanism.

And I would say no, no, it has to go through this intermediate. So, to solve this fight, we would need some experiment to prove either of these mechanisms. So we have done several experiments so far, which could be useful in proving these mechanisms. And you can think about it. So you think about what experiments you can use for proving which mechanism it is. But now, what I am going to suggest now is since we are looking at the concept of trapping the intermediate, is it possible for us to trap this intermediate shown here.

So is there some way for us to trap this intermediate? So now I have a carbocation. So what can it react with, so that it is trapped? It can react with the nucleophile. And a good nucleophile would be, say ethanol. So imagine that you are doing this reaction in ethanol. So, what will happen is that once you generate this intermediate, instead of water, what you would have is you would have ethanol added.

So at this point, you would have ethanol adding in. So then what is the structure you get here? So here the structure that you would get would have what I am going to do is I am going to erase this so that we have some room on the slide. So, what you would get here is you would get so, once you get this intermediate, so this is what you get is ethanol adds instead of water.

So, once you get this intermediate, there is not much that can happen here other than this losing the proton. So what you end up getting is the trapped intermediate. So if you see this formed in your reaction then you know for sure that you are generating this carbocation intermediate shown

on your screen. So this is an illustration of how you can trap a carbocation using a solvent and this will directly tell you that it is not an S_N2, but going via neighboring group participation.

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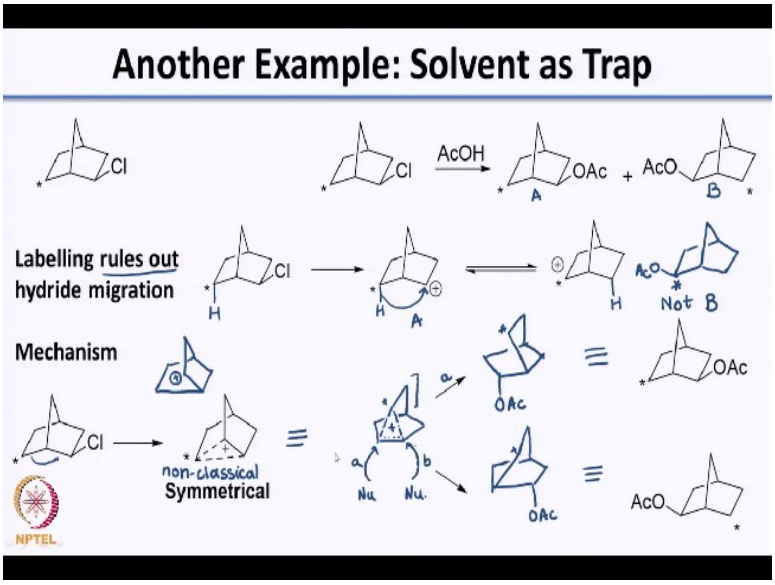

So, now we will look at another example where solvent has been used as a trap. So shown here is another alkyl chloride. So here if you were to do a solvolysis, solvolysis means instead of adding an additional nucleophile, your solvent itself adds as a nucleophile. So say you are doing this reaction in acetic acid, what is the product that you will get? So, just imagine you are doing this reaction. Now S_N2 kind of reaction would be difficult because you do not have much free space here.

So if you would imagine an S_N1 like reaction, what are the products theoretically that one might assume? Now I will show you what are the products that were actually observed. So the products formed for this reaction were these 2 enantiomers alright? So if you had written an S_N1 reaction by generating a carbocation here, one would not assume that you would still get only the exo product or the product coming from the top side.

And how do you account for formation of this other product? So, now this led scientists to think of what could be actually the mechanism of the reaction. Now, here again is an illustration of how labeling can also come in very useful. Normally whenever you see migrations like this, you assume that okay there might be a hydride transfer taking place, which is why you have the rearrangement, but if you had hydride transfer what would be the products that you get?

So, if you had hydride transfer, so, let us imagine, I am going to show you the hydrogen here and here. So, now if I have transfer of this hydride to this position, I will generate a new carbocation and now I have moved this hydride here. So now what would be the products that I would get? One would be product A, let us call it product A, but then the second product I would get would not be product B. So what I get would be this product where I have the label on the carbon. which has the nucleophile attached to it. Right? I would not get B.

So based on the fact that hydride transfer will not form B, this mechanism is ruled out. So now I will tell you what was proposed for this. What was proposed is, it goes via what is called as a non classical carbocation intermediate. So non classical carbocation is a carbocation where you talk about the charge being actually shared by these 3 carbon atoms. So, what it tells you is that because you have this bond, which is antiperiplanar to this bond

you have seen it before a dihedral angle of 180 degree, you can think about this being involved in this displacement of the chloride. So when the chloride leaving group goes, this single bond is probably assisting the chloride group to leave. Now, if it assists this instead of just forming a carbocation at this center, what is proposed is a more stable carbocation, the charge is shared by all these atoms.

So this is more stable than just the structure where you have say this carbocation. So, this would be more stable than this structure. So, again we are talking about, so this group we are saying is helping in pushing out the Cl. So, what you would generate would be a structure like this. So, this is a new bond that is formed and a carbocation like this. So this is one extreme of seeing this structure. So what is proposed is that the non classical carbocation is what is formed

because it is more stabilized here. So now this is symmetrical, I hope you are able to see the symmetry here, because you have these 3 carbon atoms, and on either side, you have 1 carbon atom. So to make it easier for you to visualize this, what I am going to do is I am going to show you the same structure in another form. So imagine that I am rotating this structure a little. So I have and again having the label will help you visualize it.

So I have, so this is where my label is. So I am here. So behind the label, I have 1 carbon atom, which is this carbon atom, and then I have that coming down. Correct? And then I have and my positive charge is here. So I hope you are able to see the structure that I have drawn here. So I am showing the broken bond here is just to show that this is in front. So I have a 5 membered ring at the back and this is my non classical carbocation in the front.

So now that I formed this non classical carbocation, I can now attack the nucleophile. So this is symmetric, you can imagine a plane of symmetry here. Now I can imagine the nucleophile attack at either of these positions. Right? Now, if I have the nucleophile attack at position A, what is the product that I get? So if I have the nucleophile attack at position A, the structure I get would be. I am going to write it out exactly like how this is, so that you are not confused.

So I attack it here, these electrons will now move here. So what I will get would be so let us call this I will put it instead of a Nu I can put OAc directly. So I put OAc here, I have, again the label will help you see what is going on, hopefully. So this is where the label is. Alright? And because you have the structure on top, the nucleophile will attack from below. So this is what you get, if it goes via pathway A.

Now if it goes via pathway B, so let us write the structure if it goes via pathway B. So what you get would be, so you will have the nucleophile attack here and you will have this bond break, so you will have. So this will be the structure that would be formed. And of course your label is at this carbon. Now the relationship between these 2 are they are enantiomers. So this structure if you see you have the OAc close to this bridgehead.

So this is what this is equivalent to. And this structure is equivalent to the product shown here. So all you need to do is whatever structure I have written here, just imagine that you are flipping it to one side, so when you flip it to one side, what you would have is, so imagine, if you have this OAc you have the bridgehead here. So bridgehead is right here.

So this is the OAc, this is the bridgehead, they are on the same side, which is exo and then this label is coming here. So I am rotating it, imagine that I am rotating it in a counter clockwise fashion. Alright? Same thing here, you can imagine that you are rotating this in a clockwise direction. So again, you have the bridgehead at OAc on the same side. So exo and this is where your label is.

So this labelling as well as trapping of this non classical carbocation using solvent is a beautiful way to prove this mechanism. So you know that it is not hydride transfer, but here you have used the solvent as a trap to prove the mechanism for this reaction. And what is interesting is if you see the intermediate here, the intermediate carbocation, it is symmetric, it has a mirror plane. So obviously, since it is symmetric, the products that you get from it would be enantiomers.

So, that is also seen beautifully in both the products that are obtained. So, now we will move to studying radicals.

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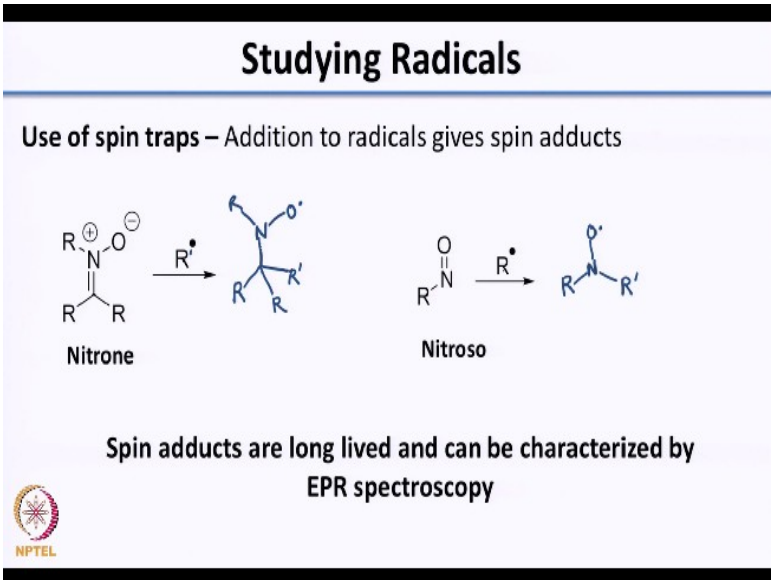

So, when you study radicals, there are 2 types of traps that are used. One is a type of trap, where it still maintains the radical behavior. So, these are called us spin traps, because you get a more stable radical. So, the spin is still trapped in a way, you are not, the radical is not quenched or combined with another radical you are generating a new more stable radical and why more stable radical? With the more stable radical you can study it using techniques such as EPR spectroscopy.

So, EPR is a type of spectroscopy, which is used to study radicals. Now, obviously, you need to choose appropriate traps which would retain the spin or the free radical character. So 2 such traps are shown, one is the nitrone and the other is the nitroso. So when you react a nitrone with the radical the product that you get is, so, you generate a new radical and this new radical is stabilized because it is next to a nitrogen.

So, because of having the nitrogen proximal to it, this radical is much more stabilized as compared to R ·, which can easily recombine. The other example is a nitroso radical. So, here again the new radical that you generate would be. So these 2 radicals are long lived. So they are called a spin adducts, the adducts that you get and differentiating between these 2, we can call this R prime. So you have R prime adding in.

So, this is one way for you to convert a reactive R radical so you converting a reactive R radical to a new radical, which can be studied by EPR spectroscopy. There are other methods that are also used, in this case you are trapping the radical, where the radical nature is actually lost.

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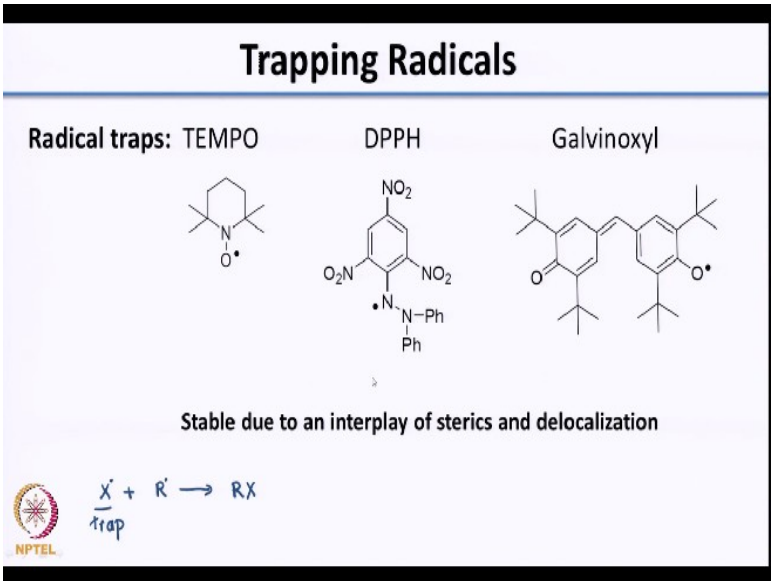

So, here what happens is you are reacting it with a radical in itself. So in the earlier example, what we had seen is we had reacted it with the nitrone and the nitroso group to generate a stable radical. So you already had the alkyl radical, and you had the spin traps which were used to

generate a new radical. In this case what you are doing is the trap itself that you are using is a radical.

So now what this does is when you use a trap like this, which is a radical, it will react with another radical to generate a species where now you do not have the spin. So you will have essentially like similar to a termination reaction. So you have 2 radicals coming together. So you can imagine each of these reacting within an R group to generate, so each of these let us call these $X^{\cdot}$, will react with $R^{\cdot}$ to generate RX.

So where X is your trap, so this you cannot study by EPR anymore, because the spin is low. So that's why I want to differentiate between radical traps and spin traps. In the spin trap, you are generating a long lived radical, whereas in a radical trap, you are reacting it with a radical, so that you generate a molecule which can be studied. It is stable and 3 radical traps are shown in front of your screen.

Now, the structure of these are very interesting one is tempo, where you have the NO radical. So here you have the NO radical. Now, one problem with radicals is that they have the tendency to dimerise. So you have $R^{\cdot}$ $R^{\cdot}$dimerizing to give you RR. Now what you see is when you have tempo, for example, any of these molecules, you have these bulky groups next to it. So tempo, the other one which is DPPH, again here you have 2 phenyl rings.

So, you have another 3 aromatic rings and this aromatic ring has nitro groups on it. Similarly, here you have 2 t-butyl groups on. on the side of the radical. And these bulky groups prevent dimerisation of the radical due to sterics. So, that is one path of reactivity of these radicals. That pathway can be ignored in these cases because the dimerisation is not possible. So actually, these radicals can be stored as this.

So, these are very stable, they are very very long lived, they can be bought, they can be stored, and whenever you need to check a reaction, they can be added, they are very very convenient. The other thing is they are stable due to the delocalization. So you have a nitrogen here next to

the oxygen here, in this case also you have nitrogen, and in this case, you have the aromatic ring. So that is why TEMPO DPPH and Galvinoxyl are commonly used radical traps.

And again, the stability is due to an interplay of sterics and delocalization and some of these, so, all of these are, they have very nice colors in what you can see is as the radical interacts with another radical to form the unreactive finals species, you see a change in the color. So, you can also use absorbence to figure out whether the reaction is taking place or even visual clues. So, you can look at the color of your reaction flask and get an idea as to whether the radical is being quenched, whether these radicals are being quenched.

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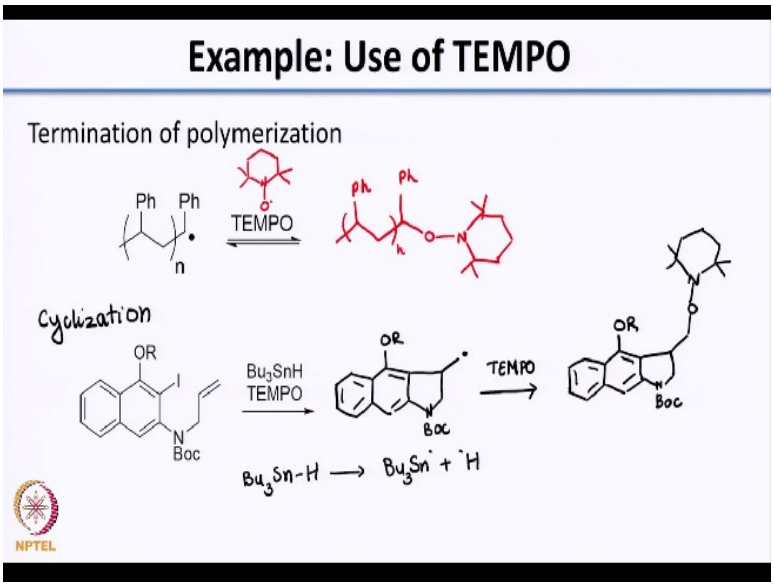

So, let us look at specific examples in the use of TEMPO. Now TEMPO has been used for termination of polymerization and this is an example shown here. So it is a polymerization reaction, radical polymerization. Now with the radical polymerization, what happens is at the end each propagation step will generate a new radical. So here, if you add TEMPO, what would be the product that would be formed?

Can you write the product? It is pretty straightforward, you are just combining 2 radicals. So go ahead and write the product. You can take your answers with me. So, this would be the product and what is nice about this is, now you have trapped this radical with TEMPO, if you need to regenerate it, you can do that again by the homolytic cleavage of this bond. So, this is a nice way for you to trap radicals. Ok?

Let us look at another example. So, this is an intramolecular cyclization reaction. So, here we are looking at cyclization. So the reagent here is known to generate radicals. So if you have, so, once you generate this radical, you can imagine generation of a radical here and it undergoing the cyclization to generate this intermediate. So, this radical intermediate would be generated. And this radical intermediate, when it reacts with TEMPO will give you the trapped radical.

Here. So, this way, you can actually trap the radical and say that the reaction goes via a radical pathway. People also use another trick to figure out whether the reaction proceeds via an ionic pathway or a radical pathway when it is unknown is they will add a small amount of TEMPO in the reaction. If it has shown that TEMPO is slowing down the rate of the reaction or addition of TEMPO is not leading to formation of the product that was observed earlier, it indicates that the reaction goes via a radical pathway.

But if that is not happening, it indicates that the reaction goes via an ionic pathway. So, this is another trick that people use to determine whether the nature of the reactant is a radical, or it is not radical. So I will stop here with the last example for radical traps.

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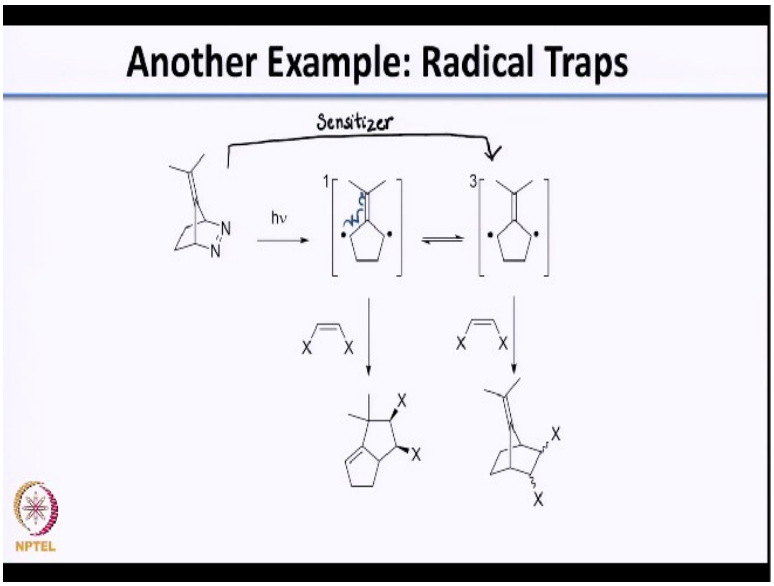

So, shown here is a reactant and this bond is highly labile and why is that? Because you can easily lose nitrogen to generate this biradical. So, you can generate this biradical, this 1 and 3 here correspond to a singlet or triplet state of the radical. So, you can access the singlet state by

shining light on to this molecule and from the singlet you can go to the triplet state. You can also directly access the triplets state, where you do the reaction in the presence of what is called as a sensitizer.

Now, how do you know that all these are being formed? So that you are forming this biradical whether it is in the singlet state or the triplet state? So a very clever trick that scientists have used is they use this alkene where the stereochemistry is fixed. So, it is the cis alkene. So, when you add the cis alkene what is found is that in the case of the triplet biradical, you get the adduct shown here, whereas in the case of the singlet biradical, you have the adduct shown here.

So, this adduct you get by imagining a, so, you can think of you have this radical here, and these 2 radicals can combined with the double bond to give you a 5 membered ring. So, how do you know this a singlet and how do you know this is triplet? This you can figure out based on the double bonds stereochemistry. So, in this case, the stereo chemistry of the double bond is retained where you have both the groups syn to each other.

Whereas in this case, the double bonds to chemistry is jumbled up. So it indicates that it is a triplet intermediate and not the singlet intermediate. So, this is a lovely illustration as to how the trap is used to actually determine the presence of the biradical. Further, the trap also shows you a difference in reactivity between the singlet and the triplet biradical.

So, we will stop here. In the next class, we will look at some other traps which are used for reactions that do not involve radicals, carbocations and carbanions. And we will also look at the use of traps in biology to understand the mechanism of action of a particular enzyme. So, thank you and see you in the next class.