Structure, Stereochemistry and Reactivity of Organic Compounds and Intermediates: A Problem-solving Approach

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Lecture 29

Reactivity of Radicals Frontier Orbital Approach

Welcome back to this course on Structures, Stereochemistry and Reactivity in Organic Chemistry in Organic Molecules and Intermediates: A Problem-solving Approach. In the last lecture, we have been discussing the chemistry of radicals. We have discussed first the geometry, what type of geometry radicals adopt. Then some special geometry and trifluoromethyl radical, thirdly the classification of radicals, sigma pi radicals, then we have nucleophilic, electrophilic radicals.

And we also know the stability, how they are stabilised? We have been, we have introduced to you the capitalism radicals and finally, the type of reactivity that the radicals can have. And it was found ultimately, that the radicals usually are they very fluently add to carbon carbon double bonds. And when they add to carbon double bonds, if it is a carbon centred radical, you make a new carbon carbon bond. And that is the major emphasis of organic synthesis. The advantage of using radical is this, basically the neutral condition and the orthogonality with several other functionalities.

However, there are major challenges, major challenges is basically number one is how to make radicals under ambient, under very mild condition, that is number one, because we have not said how to make radicals under mild conditions that is number one. Number two is the how to stop the polymerization or how to stop the oligomerization that always expected that is expected when radicals start adding to double bonds. So, we will discuss that.

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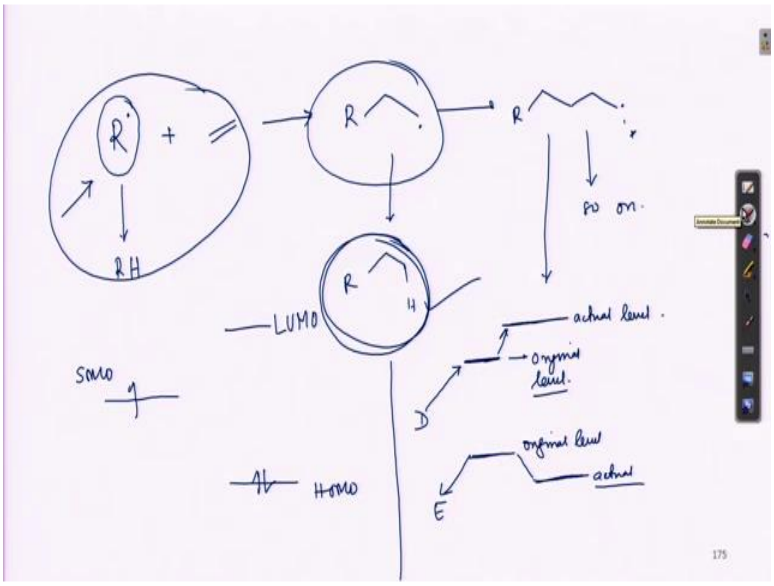

Now, so, the reaction that we are talking about is R dot plus a double bond. And how the reaction should go? The reaction should go in this fashion, it forms a new radical at the centre and then that adds to another one and so on, and so on. Now, in the meantime, also, the question is actually how the radical is generated?

The radical is generated by, there are methods we will discuss that, but, when I am talking about addition to the double bonds, you always remember there may be some species inside the reaction medium which are hydrogen donors. So, at each stage, there is a possibility that the radical gets quenched by the hydrogen donor. So, rather than attacking the double bond, it can be quenched by the hydrogen donor or it adds to one double bond and then gets quenched by the hydrogen donor.

So, you see the complicacy of this process, one is polymerization that is going on and another is this donation of the hydrogen atom, that is also possible at every step. And if you want that, I want only this product as the major product, you see the challenge. First of all, if you want to, that means you want to add to only one of the double bonds only one double bond one time, number one that means when this reaction has taken place or you want to do this reaction, that the radical should not abstract hydrogen instead it should add to the double bond.

This can only happen, this can happen on two, on two accounts. One is if the double bond has a very good affinity for the radical then the radical is going to add faster to the double bond, that is number one. And number two is that if the double bond, the alkyne is present in higher concentration in the medium as compared to the hydrogen donor, hydrogen atoms donor. So, there are two, two ways to induce the first reaction that means the radical adding to the double bond and not being quenched by the hydrogen.

One is that you employ an alkyne which has got, which has got more felicity towards the radical. And means which has got a more preference for reacting with the radical rather than the radical reacting with the hydrogen, that is number one. And the number two is that you can use excess of the alkene and just by concentration effect the radical will now react with the double bond. So, these are the two possibilities.

And then suppose you have bypassed the first one, you went to the second one and now, you want to stop the reaction at this stage, stop means you want that these pieces should abstract the hydrogen and should not undergo any further addition to the double bond. So, that is where you have another challenge here.

Here you because you have already started the reaction, your concentration is fixed, your hydrogen atom donor concentration is fixed, the character of your alkene you have already taken an alkene which is basically has more felicity towards the radical that you are using. So, at this point you cannot change anything.

However, interestingly by logic, I will show you that this preformed that this the radical that is formed after first edition is will have a less propensity to attack the second molecule provided you have the right type of functionality present in your alkene. So, we will discuss that. So, I just introduced you the challenge, we want a decent amount of this product that means first addition to the double bond and then abstraction by the hydrogen. Now, how to do that.

In order to go into that, discuss into that, let us talk about that what about the orbital interactions that take place when a radical reacts with an alkene. What type of radical, orbital interactions take place, like when you have these two alkenes adding on together. So, we have what? A LUMO of the alkene and the HOMO of the other parts they combine with each other.

So, we considered the HOMO LUMO and that is popularly known as the frontier molecular orbital theory. So, according to frontier orbital theory, it is basically the radical now, the radical will react with either the, either the LUMO of the because radical is in between a HOMO and the LUMO. So, it has got dual character. So, radical is one component.

Suppose you see, so, if that acts as a HOMO then it has to react with the LUMO of the other component that means the alkene. If the radical you think that it is acting as a HOMO then it should acting as a LUMO sorry acting as a LUMO then it should only interact with the HOMO of the other alkene.

So, you should remember that again I repeat first of all according to the frontier orbital theory the radical has to react with the HOMO or SOMO of the, sorry HOMO or LUMO of the double bond. Now, which one it will react? All depends on the relative energies. If the by the way the singly occupied orbital, a singly occupied orbital is called SOMO. So, you have a HOMO which is filled, doubly filled; LUMO unfilled, vacant and then you have SOMO where the orbital is filled by one electron.

So, now, the interactions that can happen during the reaction when the radical adds to the double bond is either SOMO HOMO, or SOMO LUMO, which one will happen depends on the energy gap, that we know. The closer the energy between the two orbital levels, the better is their interaction. So, let us draw the the picture that we are talking about. Suppose you have this, this is the SOMO of the radical. And suppose this is the HOMO of the alkene and this is the LUMO of the alkene, here there are two electrons.

Now, certain things you should know one is that, how to part up the energy level of an orbital? If you simple thumb rule is without going into the any any reasoning that if you have an orbital at this energy level and if you try to donate electrons, if there are groups which are donating electrons towards the towards that orbital, then what happens, its energy level goes up.

So, this is the donor, this is the original level, but as soon as you are attaching D it goes up. So, this is the actual level now, actual level. On the other hand, if you do the reverse this is the original level and you are trying to withdraw electrons from the orbital by groups surrounding it, then what will happen? Then there will be, this will go down in energy. So, this was the original level and this is the now actual level. So, very simple that electron donation raises the level of the energy orbital and electron withdrawal lowers the lowers the energy level.

So, now we see that when a radical reacts with a double bond, first we have to see what type of radicals we are using whether it is a nucleophilic radical that means, whether electron donation is going on to the radical or electron withdrawal is going on to the radical that will decide whether it is nucleophilic or electrophilic. And then the third one and the second one is what type of alkene you are using. Is the alkene having an electron donor with it or an electron withdrawal with it, because that will decide where is the LUMO where is the HOMO.

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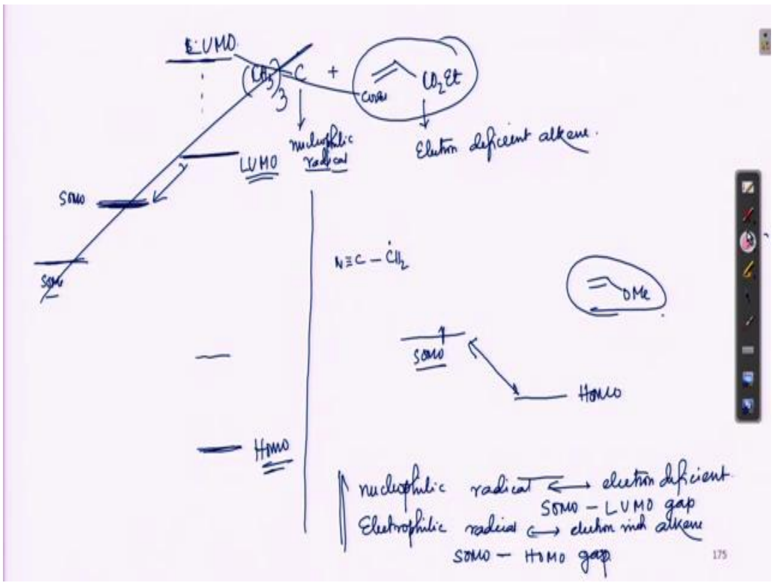

So, let us see that suppose we start with an alkene we are doing a reaction like this CH3 thrice C radical plus a double bond with an electron acceptor say CO2ET. So, if you do this reaction you are now using a nucleophilic radical because of these three methyl's present nucleophilic radical and this is an electron deficient alkyl.

So, compared to a free carbon radical now you are trying to push electrons towards the radical. It is a pi radical. So, the energy if it was originally the energy here of the SOMO, now, by the presence of these three methyl groups the energy will go up. That means it is now going closer to the to the LUMO of the alkene, because the LUMO is further up.

However, an additional point is that in the alkene you have an electron withdrawing group. What electron withdrawing groups does? Electron withdrawing group brings down the energy level of the orbital. So, earlier if the SUMO was here, sorry the LUMO I am very sorry LUMO was here. Now, by putting the CO2ET group CO2ET group you are bringing down this and it will come down here.

What about the HOMO? The HOMO was suppose earlier here, but by putting the electron withdrawing group the HOMO goes farther down. So, by a combination of two that means using a nucleophilic radical and an electron deficient alkene, what you are doing? You are basically bringing the, you are basically lowering the gap between the SOMO and the LUMO and you are increasing the gap between the SOMO and the HOMO.

So, that means there will be reaction between the the SOMO HOMO. SOMO will be from the radical and LUMO from the alkene. It is not SOMO, HOMO, HOMO. So, that part is clear. That means, if you want to have a reaction between a radical, a nucleophilic radical the best way is to employ an electron deficient alkene.

And if you want to have the reaction between an electrophilic radical now, we have not discussed electrophilic radical. Suppose if we want to have an electrophilic radical, suppose C, put a nitro or cyanide group. So that is an electrophilic radical because you have an electron withdrawing group, electrophilic radical what it will do? It will withdraw electron from the radical. So, the SOMO energy will go down now, this is the SOMO.

Any withdrawal will lower the energy of the orbital. So, SOMO will be here. And now see if you use an electron deficient alkene SOMO goes down. So, also LUMO, but you are not basically you are not encashing on the fact that the SOMO has go down. So, either you make the LUMO go down farther and farther, which is extremely difficult.

The other option is that you raise the energy level of the HOMO and that is in your hand because you know that by electron donation to the double bond, you can raise the energy level of the HOMO. So, if you now use an alkene, which is suppose the methoxy ethylene, which is a donor now. So, this will now earlier HOMO was there only alkene, Ethylene now methoxy, methoxy as you put that goes up, because as I said, electron donation raises the energy level.

So, this is now HOMO and now, there will be a much better interaction between the SOMO and the HOMO and the reaction will be will be feasible. At least the first reaction, first addition reaction. So, the bottom line is that what we are saying that if you want to do a meaningful radical reaction, what you have to do? For nucleophilic radical, for nucleophilic radical you have to employ an electron deficient alkene and you now know what is the reason that is to decrease the SOMO LUMO gap.

And if you have an electrophilic radical then what you have? Then you have to employ an electron rich alkene and that will lower the SOMO HOMO gap. So, this is the gap. This is the summary and this is the the important thing that one has to remember. Now, let us talk about how to stop the reaction at the second stage when one double bond has been has added but then the further addition of the double bond how can we, how can we stop? Sorry, that means formation of the telomere. These are called actually telomere as more and more monomers are added, alkenes are added the products are called telomere.

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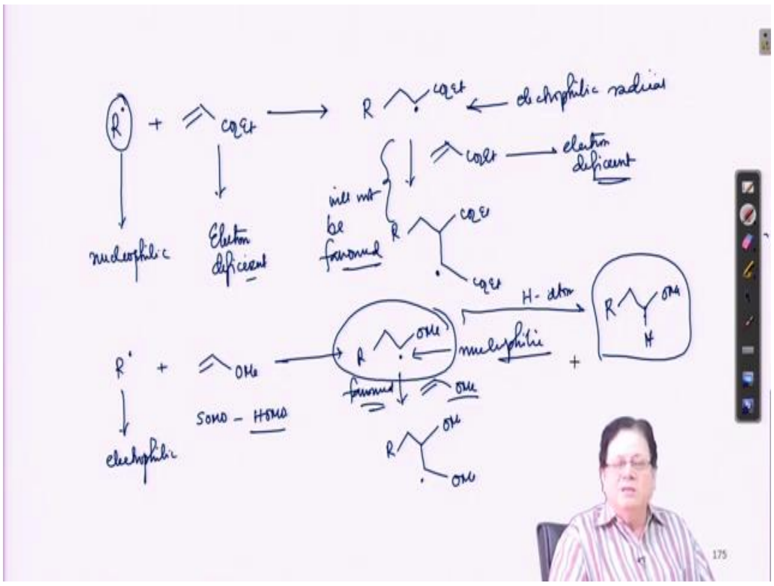

So, how to stop the telomerization process? Not much difficult, if you look at the characteristic of the newly formed radicals, suppose I started with an nucleophilic radical and I added it to an electron deficient alkene, which is good, because this partner I want nucleophilic radical and electro deficient alkene. So, they add R CO2ET and you form a radical here.

Next question is, this how to stop the next addition reaction? So, if it adds then you will get this type of species. However, one interesting point to note here that you are starting radical is nucleophilic. This is electron deficient very good, good partner deficient. Now, this radical is adjacent to an electron deficient group. So, if that happens, this radical is now electrophilic radical.

And this radical is, this radical is electrophilic and however alkene is still electron deficient, alkene is still electron deficient. So, this reaction will automatically will not be favoured. Because for electrophilic radical one should employ electron rich alkene. So, you have automatically by choice proper choice of the partners nucleophilic radical plus electrophilic electron deficient alkene, your second oligomerization but telomerisation is automatically slowed down because of the mismatch of the radical character and the alkene.

The same will be true if you have R dot as electrophilic and then you have a now electrophilic radical one should use electron rich alkene. So, that will give this type of product the first addition, this is good here here the interaction will be SOMO and HOMO and that will give this, this is a good proper partner between them electrophilic versus electron rich.

And then the next reaction you want to stop. But what is the next reaction? OMe and then OMe here. Again, you see, there is a complete inversion of the character of the radical. Now, this is what is called in organic chemistry there is a term to describe that the complete change of the character of a carbon, like if a carbon is expected to be electrophilic, but if it is reacting as a nucleophile or if the vice versa. It is called umpolung activity of the carbon.

So, here also the radical becomes umpolung. Of course, it is not the same radical, the first radical is this one R dot, the second radical is a, is that one and this is the third one. Although the radical positions are different, but what you are doing as a substrate point of view you are changing the character of the radical centre.

Initially it was electrophilic. Now, what happens? There is a donor. So, this is now nucleophilic. Now, you are trying to add a nucleophilic radical on to an electron rich alkene which is not, which is not favoured because the gap is not amenable, the gap between the SOMO HOMO SOMO LUMO are much wider. So, the reaction is not favoured. So, automatically you will get a stoppage at this time.

However, the only way now, it can have is to abstract the hydrogen atom from the donor. And then you will get OMe. So, this is the way how people solve the problem of oligomerization, they have solved the problem of initial reduction of the R dot. So, a lot of, lot of manipulations, good thinking, brilliant thinking that has gone into it and today the radical chemistry has become a very strong, very useful synthetic methodology. Lot of complicated molecules have been made by this method. So, I think this is, this part is clear, that how to do this reaction. Now, the question is that, who is the hydrogen donor? And how the radical is created? So, some examples of the radical reactions.

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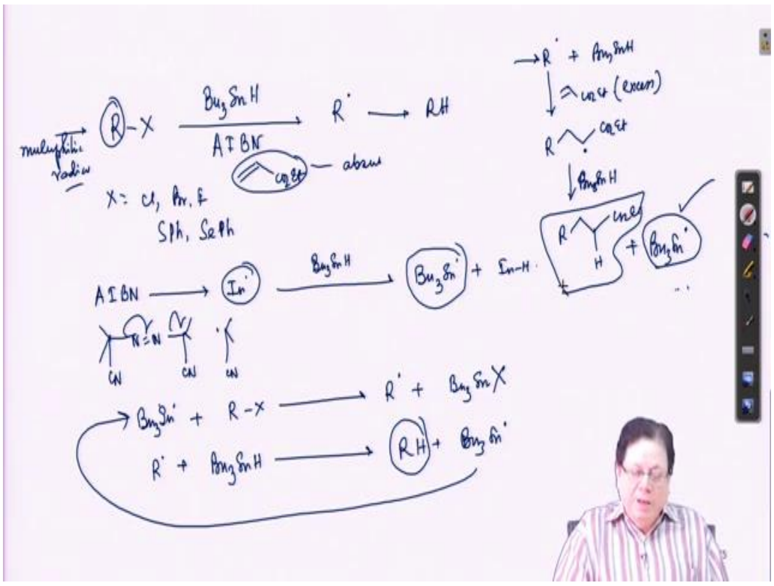

Now, one very typical reaction is that, if you have RX and if you add tributyltin hydride with some initiator, radical initiator like I gave you that azobisisobutyronitrile, that is a good you can have dibenzoyl peroxide also in Kharasch effect that when you have the peroxyl, when you know the anti-markovnikov's rule, the peracids were used there at that time, in the peracid we have the vulnerable O-O bond, in azobisisobutyronitrile you have a vulnerable N double bond N bond which can come out as the nitrogen and generate the radical.

So, you need a little radical initiator, if you do not add radical initiator, maybe you have to shine some light and that can generate the very small amount of initial radical that you need to start this reaction. So, one way of making radical is take RX, where X is equal to chlorine, bromine, iodine, or Sph or Seph. So, it could be a selenium compound or even tellurium compounds also, sulphur, thiophenol, selenophenyl, tellurophenyl, all these are possible.

The most common is basically the the chlorine, bromine, iodine. Now these, this will form an R dot. So, if you do this reaction in presence of an alkene, suppose this R is nucleophilic radical, nucleophilic radical then this will add to this, you need an electron deficient alkene. So, R dot is formed. How?

First AIBN will generate the initiator radical, initial AIBN again I write the structure CN N double bond N, it usually decomposes around after you heat it to be on 70 degree and then what you need is a very extremely small amount of AIBN. So, that breaks and forms this, this radical that isobutyronitrile radical, that is the initiator radical. And now this initiator radical will react with tributyltin hydride and forms the Bu3Sn radical plus that will take the hydrogen.

Now, this Bu3Sn dot, Bu3Sn dot will abstract the pick up the hydrogen from the X, from the R and that will form R dot plus Bu3SnX. That is a stable molecule. And then now R dot in absence of any alkene. Suppose you do not have the alkene, then the final product will be RH. If this is not present, absent then the final product will be RH. But it is a radical chain process.

Radical chain process means that you have to always have the initiator kind of molecule, means what is making the original radical you can, that is again formed at the end of the reaction, each reaction, each step. So, here this is the radical that is formed. And that started the cascade, that took the hydrogen, the X from the R generating R dot.

Now, R dot reacts with another tinhydride molecule and forms RH plus Bu3Sn dot. Now, this Bu3Sn dot will continuously do this thing because that is what is the, that is the what do you, what will help to propagate the chain, and propagate the chain. So, ultimate product is what? The ultimate product is RH. Now, instead of now you add this alkene.

So, what will happen? We have a competing reaction, this R dot adding to Bu3SnH or R dot adding to double bond. Because you have a nucleophilic radical and because you have the correct partner that the electron deficient alkene, so, you can expect that there will be a good reaction, the rate of this addition will be high as compared to the rate of hydrogen abstraction.

However, just to make sure that R dot reacts with the alkene in a semi quantitative manner. So, what exactly usually done that it is used in excess. If it is used in excess, then you actually are taking advantages up to one is this relative character of this two, another also the reagent in excess. So, you take the advantage of the concentration. So then mostly it is going to add to CO2ET.

And then as I said, the next reaction will be difficult to add to the double bond because of the mismatch between the electrophilic radical and the electron electron deficient alkene. So, at that time now, the tributyltin hydride we supply the hydrogen and you get the quenched product. And in the process the one which will propagate the the radical reaction that has been again generated. So, this way the reaction continues and ultimately, one can end up with a very good yield of this. In the next lecture will show some of the examples of utility of these type of reaction, in organic synthesis. Thank you.