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

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Lecture 28

Chemistry of Radicals

Welcome back to this course on Structures, Stereochemistry and Reactivity of Organic Molecules and Reactive Intermediates. Till now, we have covered as reactive organic molecules or reactive organic functionalities like the alkynes, the arynes, the arynes including the para-benzyne diradical, and then allenes, and kittens. You have and through this course you have learned many new reactions, many new chemistries, which are not very conventionally taught at the undergraduate level.

Now, we will really go into into another entity, which is a reactive organic intermediate; namely the carbon centred radicals. Carbon centred radicals. Now, these radicals are basically single electron containing species, that we know. We will discuss its structure, the stability and the different types of radicals that are possible, and then what is the reactivity profile of radicals? What is the explanation? Why those types of reactivity profile are there? And then some examples of synthetic utility of radical chemistry.

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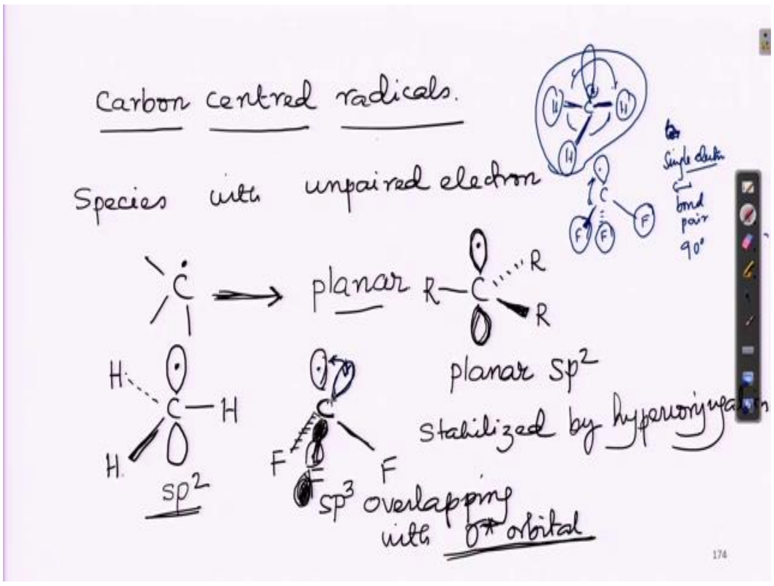

Now, the radical chemistry started towards the end of the, radical chemistry for organic chemistry as I said, radical chemistry for organic synthesis, for the benefit of organic synthesis started quite late in the 1970s. Although radicals are well known, there was gomberg reaction, some few scattered reactions were known. But generally organic chemists were a little bit sceptical in handling or generating radicals and using it for the purpose of formation of carbon carbon bonds.

There are, there are reasons for that, because you know that when you have a radical, carbon radical and if it reacts with with a system, which is diamagnetic, which does not have any unpaired electron, if it reacts with that, then after the reaction you generate another radical and then it will just continuously generating, by this reaction it will continuously generate one radical will be replaced by another radical.

So, that ultimately will lead to what? We know that that leads to polymerization. And originally the radicals are exploited in the formation of organic polymers. In synthetic organic chemistry, we do not want polymers, nor even we do not want the lower the lower oligomers also, they are also not very useful in organic synthesis, because organic molecules are small and you know that for an organic molecule to have a drug like property, the average molecular weight should be not more than 500.

So, we so, the challenge was there that the radicals are so, reactive and it actually reacts in an iterative process, continuous process and that will generate polymers. So, how to stop this polymer polymerization? That was the challenge and then how to make finally, a meaningful radical reaction useful in organic synthesis. We will go on to that.

Before that, we talk about the radical geometry a little bit. The radicals are, we are talking about carbon radicals again, the radicals are usually planar. The radicals are usually planar that means Sp2 hybridised carbon, but there are certain some radicals are they are which have got a shallow pyramidal structure, shallow pyramidal structure containing resembling Sp, Sp3 character.

However, in general radicals are mostly planar molecule. And with the radical there are single electron occupying a p orbital of the carbon. Now, why they are they adopted planar structure? Because in the planar form, there could be electron delocalization possible with adjacent substituents, with the adjacent substituents even like, even if it is hydrogen, say you have a trimethyl, you have a say T-butyl radical, then also you can have dyne hyper conjugative structures. And hyper contribution is basically a sigma bioconjugation.

So, that is why say like hyper conjugation where there is a possibility or where there is a possibility of electrode donation from adjacent electron donors, or even electron acceptors because delocalisation can be in both ways. But in all the cases, it will be nice if the radical happens to occupy a p orbital. So, that is why a majority of the radicals are have planar structure with the carbon in the Sp2 hybridised form.

There is one glaring example and that is our exception that is CF3 radical. The trifluoromethyl radical, sorry the trifluoromethyl radical and the methyl radical. We know the methyl radical is planar, just like I said. However, if you have a trifluoromethyl radical then that assumes this Sp3 hybridised character of the carbon. So, now, this is mostly like this.

And, what is the reason for that? I, sorry this is radical. I said that one reason that why the radicals generally preferred planar is to allow the conjugation, resonance conjugation or hyper conjugation. So, if it happens to be the p orbital. There is another advantage of having this in planar form is that, is that the bond pair, bond pair repulsion is the least here. But that is, that is the case when these are not highly electronegative elements.

What happens that when there are these very highly electronegative elements, like fluorine which is attached attached to this carbon, then what happens? This lone pair, bond pair repulsion becomes quite high and that is why the three fluorine's now, earlier the angle between the if it is Sp2 hybridised, the angle between the lone pair, sorry between the single electron, that means the radical occupying the orbital and the bond pair is 90 degrees in the Sp2 system.

In the Sp3 system now the angle has increased 190 with 28 minutes. So, you have minimised that, minimised that repulsion in trifluoromethyl radical where that is important. However, this, there is much, there is another reason why trifluoromethyl occupies and Sp3, Sp3 carbon and why it is a pyramidal type of structure is that in this case, remember another point we should remember that these when the radical is planar them the the bond in the plane can cannot have any interaction with the radical, because they are orthogonal to each other.

The bond which is about the orbital, which is in the plane cannot have any interaction with the, with the singly occupied orbital, because they are orthogonal to each other. If they are not orthogonal, if they are not orthogonal then what happens? Like in trifluoromethyl, trifluoromethyl radical, then there is a possibility because then you do not have this 90-degree orthogonality, then what you can do, you can draw a an antibonding orbital of the CF3 which has got a bigger orbital at the back, which is weakened, that antibonding orbital of CF3 which is no longer orthogonal with the singly occupied orbital, single electron occupied orbital.

So, now there could be a conjugation possible between this radical and this anti bonding orbital of the CF bond. So, there are three CF bonds like that. So, that can give additional stability, if you, if you can have this pyramidal geometric. Again, I repeat, normally the you can say that why it is not happening in in other other systems? Because other systems have better way of stabilising the radicals through hyper conjugation or through resonance. In fluorine that is not possible.

So, in fluorine what happens? First of all, to minimise the single electron and the bond pair repulsion, the it takes a shallow shallow geometry like a pyramidal geometry and while doing so, there is an advantage that there is conjugation between the CF antibonding orbital and the lone pair because they are no longer orthogonal to each other.

So, that is some facts about the geometry of the radical. And obviously, a radical which is highly conjugated a radical adjacent to a cyanide, radical adjacent to a methoxy, where there is continuous resonance between the between the two, then it has it is much better that it adopts a complete p orbital like character, that makes the carbon Sp2.

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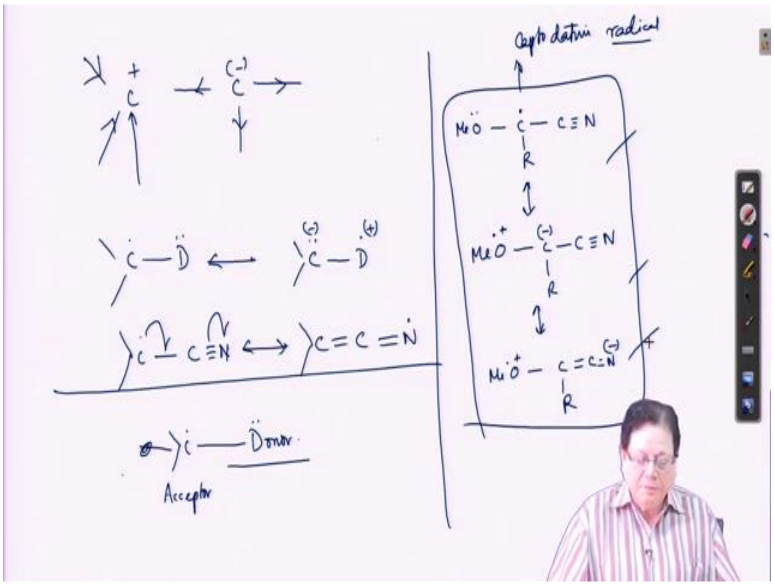

Now, let us talk about the stability of the radicals. The radicals are sorry I think, this is just a second. The radicals are stable, first look like this what is the stability of a carbocation? Or how can we increase the stability of a carbocation? We know that if electrons can be pumped towards the carbon, then the cation becomes stabilised.

In case of an anion, it is the other way around. If electrons can be driven away from the carbon that means the more delocalise, the more delocalise you have or you make to the charge, the more stable is the system. It does not matter what charge it is, if it is positive charge, try to de localise it, spread it as much as possible or negative charge try to spread it as much as possible, that gives the stability.

So, if it is negative then electron withdrawing groups stabilise the carbocation. In case of radicals, radicals are first of all, they are stabilised by both donor. If you talk about the resonance, if you invoke resonance then what happens? You can draw a resonating structure which will be like this, this is minus that is plus. So, because of this resonance, when you add a donor to a radical that stabilises the radical.

What happens when you have an acceptor like cyanide, then you know that you have a system like this, a resonance like this C double bond C double bond in N. So, because of this resonance the radical is stabilised. So, radical is stabilised by both donor as well as acceptor. That is interesting.

And the best way to stabilise the radical is that when both are present, that means the radical where which is connected to a donor and which is connected, sorry which is connected to an acceptor. So, this is an acceptor and this is a donor. Why is that? You can see that there are more number of resonance structures possible and there is more delocalisation as I said spreading of charge is more, if you have both donor and acceptor.

Let me give an example donor and acceptor. Suppose I have a radical which is attached to a cyanide. And this is attached to a methoxy. Now, as per, as per our assertion that this is, this is the case where it will be highly stabilised, much better stabilised then isolated cases that were only donor present or only acceptor present, when both complimentary groups are present the radical gets exceptional stability. By the way, this radical is what is called a captodative radical.

Maybe I mentioned it earlier also, captodative radical and their stability comes from resonance like this, first of all there will be a resonance with the donor that makes the carbon negative and then the carbon negative can be delocalised with the cyanide, with the cyanide. So, you get a much-delocalised charges.

So, these three resonating structures are the reason why captodative radicals are very stable. So, that is all about the stability. So, this to summarise, that radicals are stabilised by donors, they are stabilised by acceptors. However, the best stability comes from when both acceptor and donor are present and these radicals are called captodative radicals.

Now, let us talk about the classification of radicals. One we have seen a captodative radical. That is classification based on stability. The other is based on reactivity, whether there is any classification that is one type of classification and the other is based on the type of orbital that it is occupying whether we can have also a classification.

First of all, radicals depending on whether they are present in a, in a sigma orbital or whether they are present in a, in a if they are present in a pi system where their contribution is in the form of a p orbital. So, these type of orbitals are are known and they are called sigma orbitals or pi orbitals.

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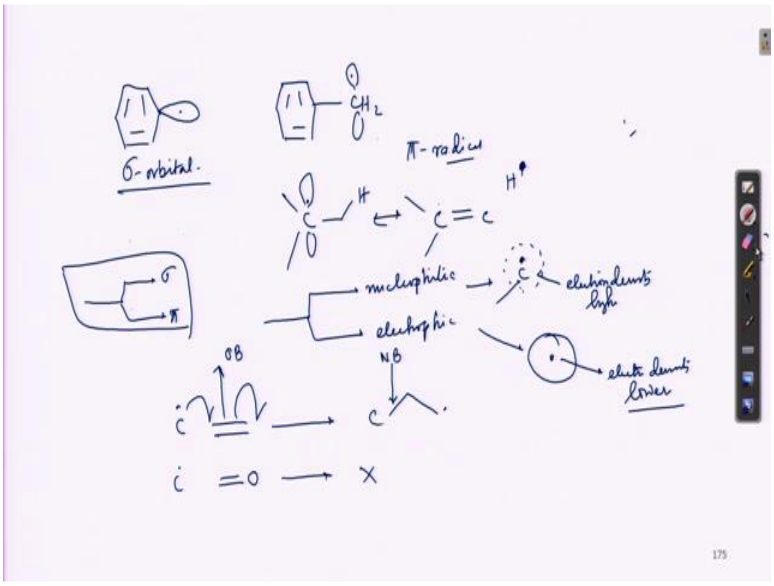

Like if I have, this is one classification depending on the type of radical the orbitals that it is it is occupied, like this is a sigma orbital. Here there is no conjugation possible to this to this sigma orbital. On the other hand, if you have this, this is a pi radical, because this radical belongs to an extended pi system involving this benzene ring and that is why this is called a pi radical.

Now, in this case, this is resonance. If you take tertiary butyl radical that is also a pi radical because in this case, what you have is a hyper conjugation with adjacent beta hydrogens. So, that is the, so you have H plus you have a double bond here and not H plus H dot sorry, H dot and a double bond.

So, these type of hyper conjugation is there and that will, that will stabilise this molecule, not only that, that will allow the carbon radical to stay in a p orbital. And that is why they are called pi radical not p radical, because pi radical because they actually form a large form a network of a larger pi system. They belong to a network of a larger pi system.

So, this is one type of classification, a sigma radical, which is not conjugated at all and a pi radical. Pi radicals obviously, which one will be most reactive, it must be the sigma radical. Sigma radical will be much more reactive than the, than the pi radical. One simple argument is that, when the radical reacts with a suppose a hydrogen donor the CH bond that is formed out of a sigma radical is much stronger than the CH bond which is formed from the reaction of a pi radical with the hydrogen. So, that is the rule of thumb, sigma radical is much more reactive than the pi radical.

Now, apart from this the which type of orbital, which type of system it belongs too that classification is there. But there is another one depending on the the reactivity profile, depending on the reactivity profile and the kind of charge density that is surrounding the radical centre, we have another type of classification. And that classification is what is called nucleophilic radical or electrophilic radical.

As I said, that if there is some perturbation of charge density if there is some donation coming to the to that carbon radical from adjacent atoms, then the electron density although it is a radical it is a neutral species, but the electron density around the radical will be more and that radical will be called nucleophilic radical.

On the other hand, if the electron is pumping out is is the there are groups which are drawing the electrons, electron density towards itself, then that radical will have some electron deficient character surrounding it. So, that will be called an electrophilic radical. So, now, what we are saying, that first of all this sigma and pi radical, that is one type of classification.

Then now, we are saying that nucleophilic and electrophilic, what is a nucleophilic radical? That means, a radical having a surrounding the nuclear charges charge is more, electron density is more that is a nucleophilic radical. Electron density higher and then sorry this is radical and electrophilic is electron density lower.

Now, this word this higher or lower is basically in competition with when there is no perturbation, when there is no donation coming or accept donation or withdrawal coming from the adjacent atom. So, that is by that is by reference. So, if some electron density now comes towards the nuclear, towards the radical that becomes nucleophilic radical and the other one becomes electrophilic radical. So, when in terms of defining the reactivity of these radicals, this concept is very important that you have to keep, you have to be careful whether your radical is nucleophilic or electrophilic.

Now, if you talk about the the major chemistry of radicals, we know that the radicals can have two very important reactions. And one is the radical if it is surrounded by atoms by species which can donate atoms very readily, then it will abstract that atom, like we have seen the benzyne 1, 4 diradical, if it is surrounded by 1, 4 CHD it abstracts the hydrogen. If it is surrounded by DNA nucleic acids it will abstract hydrogen from the nucleic acid. So, that is one type of reaction. And suppose those type of donors are not, maybe their concentration is much less, but on the other hand you have some other functionality which is which can be also very reactive to radicals.

And that is one thing you must also notice that when a reaction happens, suppose, you are having a carbon radical and you are now attached, you are taking abstracting a hydrogen from another substrate. The question is why that other substrate will donate the hydrogen? There must be some energy gained somewhere that means, the new CH bond that you are forming must be more stable than the old CH bond which you are breaking. So, that is one basic principle.

Similarly, if you take a radical which is basically an in between a cation and an anion, a radical and if it adds to a multiple bond like a double bond. So, it can add to a double bond and we know radicals add to a double bond and the double bond becomes a radical. Now, the question is, is this reaction very feasible? Yes, this is feasible because, by doing this you are forming a carbon carbon single bond and which is replacing a carbon carbon double bond and you know, carbon carbon single bonds are very strong bonds.

So, what I am saying that when the radical adds to a double bond, so, this is the type of chemistry that you are seeing. It forms a new radical. However, this is a new bond. And this is the old bond. Old bond is much weaker, you know, the double bond, double bond conversion to single bond the kind of energy that is liberated, but if you form a single bond much more energy is liberated. So single bond are stronger. So, that is why this reaction takes place.

On the other hand, if you have a carbonyl, if you try to add a radical to a carbonyl it is much more difficult, because carbon oxygen bond is very strong, even if it is a double bond. You know that here a single bond is not multiplied by two to generate the strength of a double bond actually it is much less strength of a double bond. And if you go to triple bond it becomes even more or less.

But for oxygen carbonyl what happens, the single bond energy is virtually doubled, there is no reduction in the energy while forming the pi bond. So, this that means the double bond pi the pi one the pi double bond is much weaker than a sigma single bond. So, that is why this reaction takes place. However, this is difficult reaction. So, that is why you do not see much reactions where carbon radical like a nucleophile is adding on to a carbonyl.

So, now, let us see that so, there are two types of reactions, one is that quenching with the atom which is a donor atom or addition to a double bond. So, let us see what is the, what is the consequence of adding to the double bond. I already told you that the problem of radical chemistry earlier was basically that how to stop the reaction at a particular stage? Because, as soon as it adds to a double bond, it forms a new radical. And that new radical will also add to another double bond. And that will continue.

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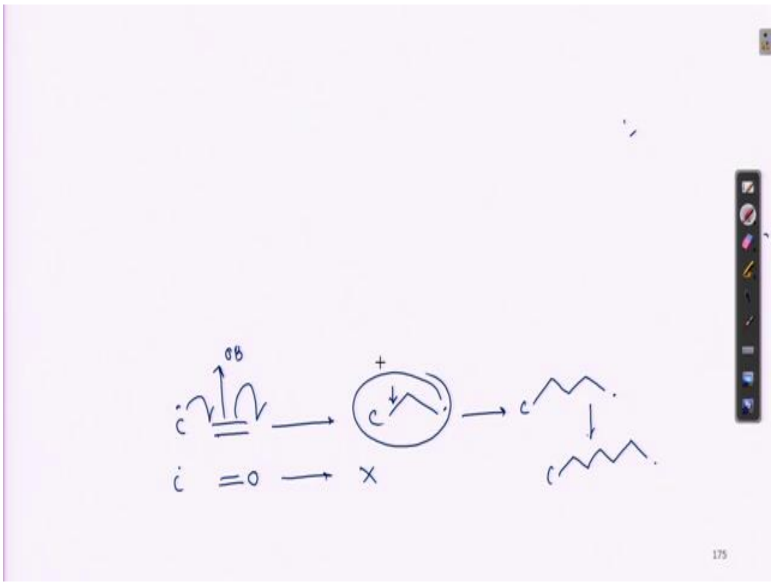

So, C, then it will add to another double bond. So, now, that will form another radical, and that is how the chain grows. And this process will continue until there is a disproportionation reaction where the chain is very large, and this is the basis of polymerization. But synthetic organic chemists are interested what, are interested only up to this say they want to form a one single carbon carbon bond in high yield.

And so, we will talk about that, that how to make these reactions synthetically useful. But before that, let me also point out that you might ask that there are many carbon carbon bond forming reactions, which involve carbocation carbon ion like the aldol condensation. So, most of the reactions carbon carbon bond forming reactions that we have, Claisen condensation, aldol condensation, Perkin condensation lot of these reactions are basically reaction between a positive and negative, that means cation anion chemistry.

And they give very good yield that we know, but they have a problem. Cation anion has a problem in the sense that you have to have it either acid catalysed or you have to have it as a base catalysed. These two are the possibilities. Acid and base may not be, may not be friendly to various other functionalities that are present in a molecule.

Basically, again I repeat, suppose, you want to do an aldol condensation in a molecule where there are the two requisite functionalities, the carbonyl functionalities that are required for aldol condensation. However, there are other functionalities such as ester functionality, a cyanide functionality and isonitrile functionality or a double bond some or acetylene. So, many functionalities or an amide or a strained amide bond, strained ester bond. So, which are very susceptible during opening by acid or base.

So, in those cases for molecules where there are other functional groups, this use of acid and base could be very, is not possible because then you will rupture the molecule as a whole other reactions will take place. So, the reaction will not be selective at all. So, that is why people looked at the radicals because radical reactions have to be performed under neutral conditions. And under neutral condition, you do not have those type of problems, side reactions. That is the advantage of radical reactions. That is one advantage that it is done in neutral condition, no acid, no base.

Number two, another advantage is most of the functional groups are orthogonal to the radical reactivity. That means radicals generally react with double ones or triple ones, but they do not react with carbonyl. And we have so many galaxy of functional groups involved in carbonyl. So, they are all safe. So, two advantages of radical chemistry, neutral condition and the orthogonality with the major types of functionality. Thank you.