

Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

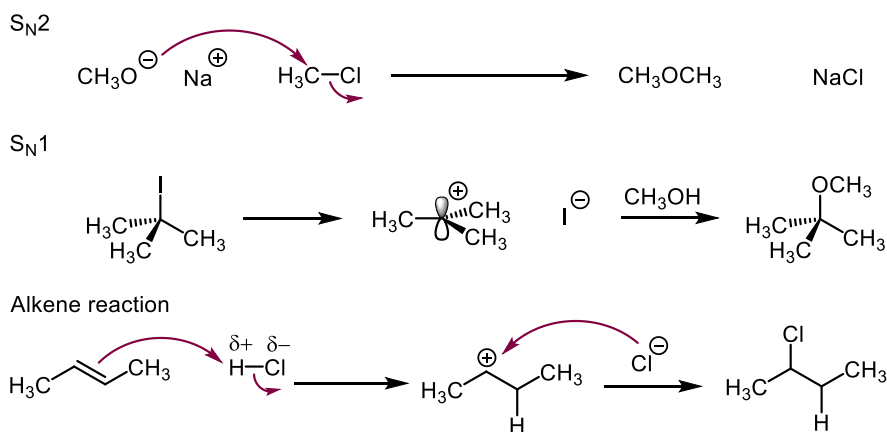
Department of Chemistry

Indian Institute of Technology, Kharagpur

Lecture 17: Radical

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last couple of classes, I talked about carbocation and carbanion, and I hope you guys have seen those lectures. In today's class, I am going to introduce you to another very important concept: radical chemistry. So, in today's lecture, I am going to introduce you to the definition of radical; what are the differences between a formation of a radical versus a formation of a carbocation and carbanion? Then, the most important concept is the different types of free radicals. So, you are going to learn today that there will be electrophilic, nucleophilic and ambiphilic free radicals. I am also going to talk about some of the cationic radicals and anionic radicals, and through the molecular orbital, I am going to discuss their stability and reactivity profile.

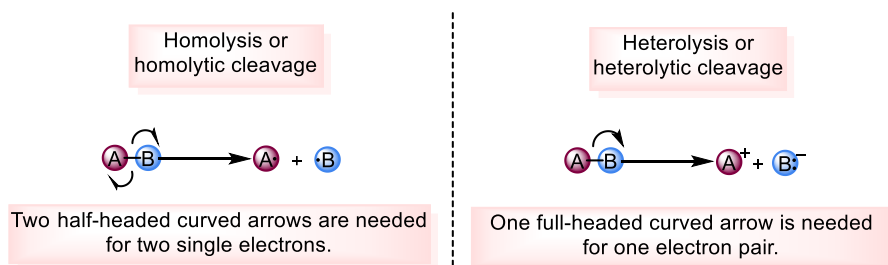
So, let us start the class. In this class, I will talk about the definition, as I mentioned, their cleavage, and then several different stability things. So, the first thing we have learned about the S_N1 S_N2 reaction. So, those are the ionic reactions. So, the first thing you can see is S_N2 reactions where a nucleophile is attacking the backside of this methyl chloride to form this ether.



Suppose you see here when this methyl chloride bond is getting cleaved. In that case, it is cleaving in a heterolytic fashion because here you can see this is you can think about like

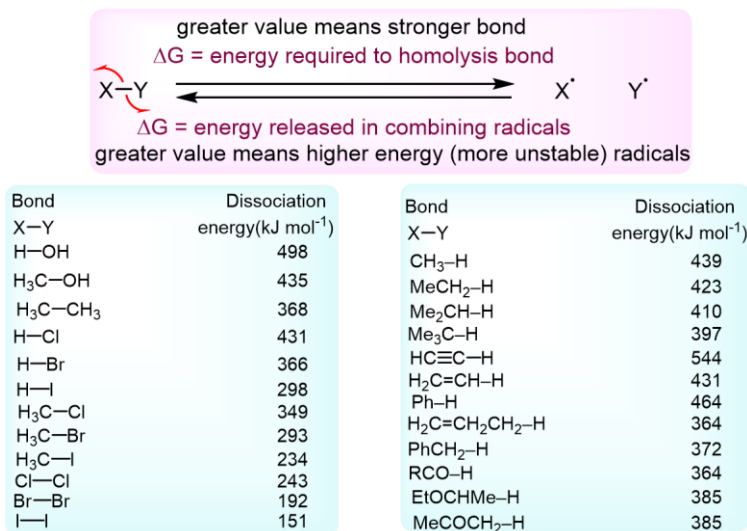
a CH_3^+ and Cl^- means these 2 electrons coming from methoxide is forming a bond with the CH_3^+ and Cl^- is getting out, which is this Cl^- and this Na^+ is actually forming this sodium chloride. The next example of $\text{S}_{\text{N}}1$ reaction in this is a first in the $\text{S}_{\text{N}}1$ reaction. The first is the ionization. The dissociation of the C-I bond will generate this carbocation here. So, this will be CH_3 , and once this carbocation is generated now, nucleophiles attack here and form the product. But the question here is that in the first step, you can clearly see that heterolytic cleavage is happening. That means this carbon-iodine bond is cleaving in a heterolytic fashion so that the two electrons of this carbon-iodine bond are getting to the iodine, forming this I^- and the carbon, which is living with a positive charge. We talk about many of these carbocation formations and their stability. And then there is another important reaction: if you have an alkene and they are reacting with HCl in the gas phase, you can also see this π -bond. So, the π -bond once gives the electron density to the H^+ , then there is a carbocation. So, the H^+ takes the two electrons and then generates a carbocation of the carbon. So, again, a heterolytic cleavage is happening. So, these are all different types of ionic reactions where we have seen the heterolytic cleavage.

But in today's class, I am going to introduce you to the generation of radicals happening through a homolytic cleavage or homolysis. That means you have a bond between A and B, which is getting a homolytic cleavage in the presence of heat or light. So that is generating an $\text{A}\cdot$ and $\text{B}\cdot$. We call them a radical.



So, a radical can be defined as a reactive intermediate with a single unpaired electron. So that is the most important thing. And mostly you are going to see that the radicals are mostly not a charge species, but yes, you will see some of the cationic and anionic radicals as well. Then you will see that the most important thing is that once you are trying to draw this, like when trying to write the reaction mechanism, You have to understand that in the case of ionic reaction, we have already shown you that full-headed curved arrow. But once you try to show the radical, suppose you are going to show them the A and B bond is getting cleaved to generate a radical. You have to use these half-headed arrows, which means arrows like this. So, these are called half-headed arrows or

fish-hook arrows. So, you can use these to show the formation of the radical. So, the important thing is this homolytic cleavage is driven by the ability of a molecule to absorb energy from light or heat. And the bond dissociation energy or enthalpy. So, this is a very important thing. So, we will talk about the cleavage of A and B and the formation of A• and B•. But the question comes that it depends on how much energy this bond will get absorbed, which is number one, and then what their bond dissociation energy is.

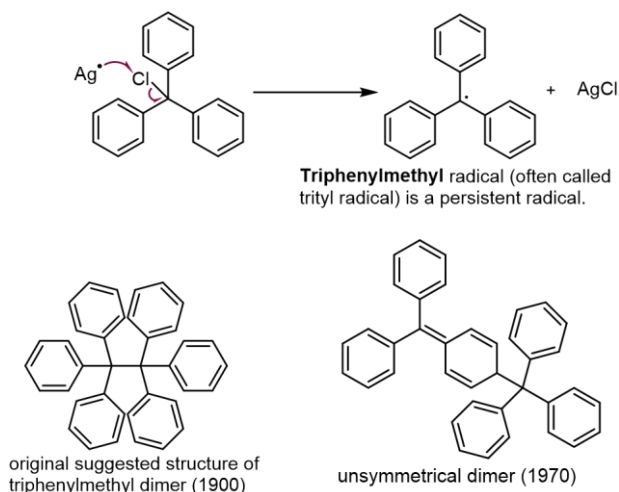


So, we are going to come back to that discussion about the bond dissociation energy being a very important parameter here. You can see if you have a bond between X and Y, which is getting cleaved to X• and Y• in the presence of light and heat, and this bond dissociation energy is a very important parameter here. So, we can compare some of the values here. So, of course, if you have these values higher, the bonds are stronger. If the values are lower, then the bonds are weaker. So, let us compare some of the examples here. These C-H bonds we are comparing have methane here. So, if it is getting cleaved, then it is going to generate a CH₃• and an H•. Now, you can have a primary radical here. If this one gets cleaved, then you are generating a primary radical, which means a MeCH₂•. If you are getting cleaved in this bond, you are generating a secondary radical. Here, you are generating a tertiary radical. So, if you see this going from methyl to primary to secondary to tertiary, what are we seeing here? We see that the C-H bond dissociation energy is decreasing.

So, that means, once the bond dissociation energy is decreased, now the radical which is forming you are going to learn soon that the radical which is going to form if the bond is weak. Now, the radical which is going to form is stable. This Me₃C• is a stable radical compared to the primary one. So, stability is also increasing in this direction. And if you

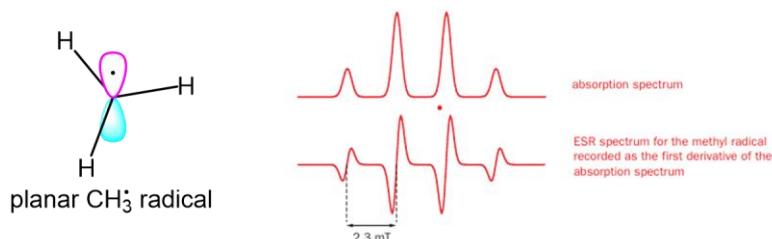
even come to the allylic one, you can see that this particular CH_1 will get cleaved and generate this CH_2 double bond CH_2 . So, this is allylic radical. You can see it is 364. So, if you compare tert-butyl radical versus an allylic radical, the allylic radical is even more stable. So, we are going to discuss all these different effects. So, here we have learned that in the case of allyl, we have learned about the resonance. In the case of methyl radical and methyl cation. If you remember, we talked about hyperconjugation. So, we are going to discuss those types of effects to explain to you the stability of this type of different type of radical and also that can explain why these bonds are weak.

So, now, we are going to come back to the discovery of free radicals. The free radical was discovered by Professor Gomberg. So, this was the first discovery that if you have a triphenylmethyl chloride. You treat it with silver; it forms this triphenylmethyl radical. You can call it a trityl radical and a silver chloride, and this is again what we are going to discuss now. This is a very stable radical if you remember when you were talking about a carbocation. I mentioned that this is a very stable carbocation in the radical, but Gomberg observed that this radical does not stay like that; it can dimerize. So, that is one of the important reactions between the radicals that they can form a dimer. So, he proposed that it could be a homodimer, that means two of these radicals come and form a dimer. However, later in the 1970s, the NMR spectra proved that it was not a homodimer. It is a heterodimer. That means what happens once you have this dot? If you try to push the arrow, you will see that you have generated a radical in this position. So, this radical is now combined with another trityl radical to form this compound. So, after that, you can see that we have already shown.

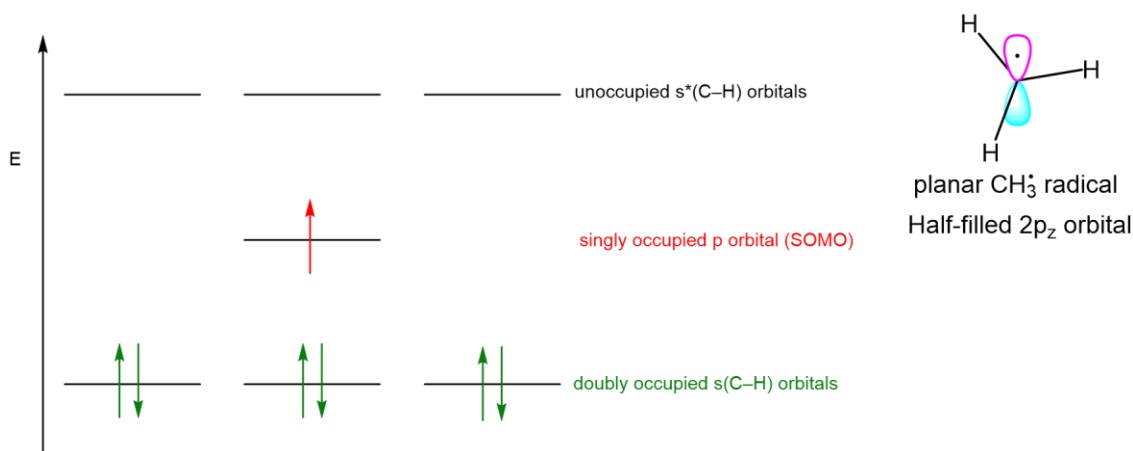


So, the radical was discovered, but then there was the instrument technique, which was also developed, called electron spin resonance (ESR), or EPR (electron paramagnetic

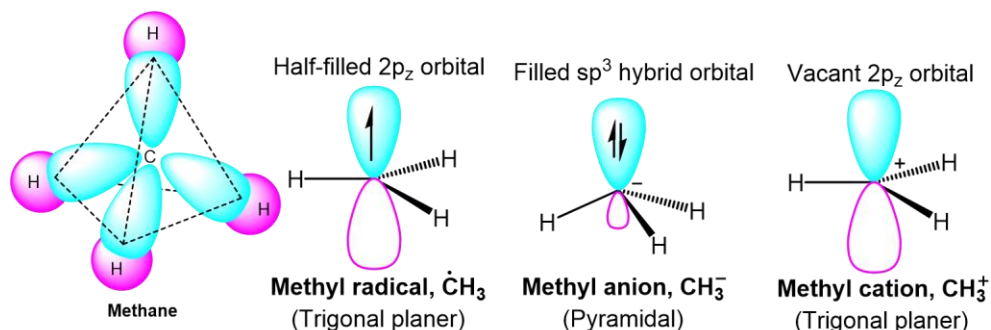
resonance). So, what you see is that we can detect the free radicals using these two spectroscopy techniques. You can find the characteristic peaks here, and from there, you can confirm not only the presence of the radical but also get some information about the structure. So, you can get some specific information about the structure of the radical.



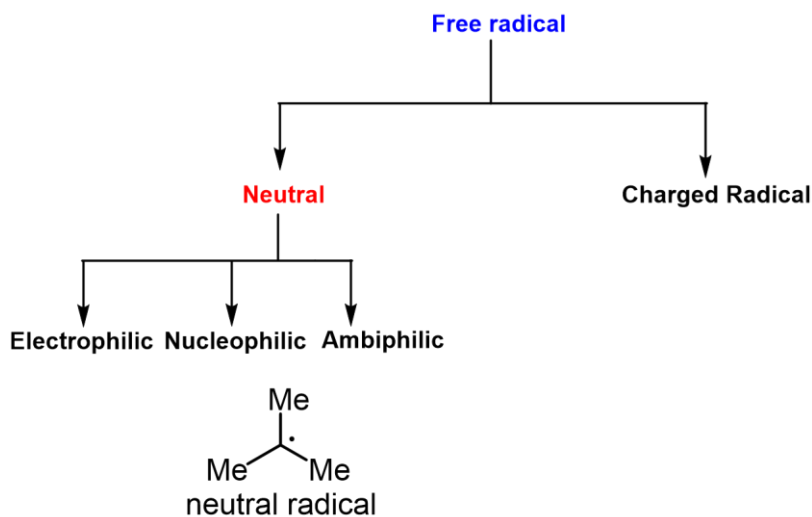
So, moving further now, we are going to learn about the MO of a methyl radical. So, that is the simplest radical here. So, this is a CH₃•, and if you see this CH₃•, the carbon will be sp² hybridized. We are going to come back in a minute about the hybridization, and of course, that is only for methyl radicals. I am going to come back; that is not always true for all the radicals. So, now, if you look at this one, you have a three C-H bond, the carbon will have a sp² hybridization, and the hydrogen will have a 1s orbital. So, that is forming this doubly occupied s(C-H) orbitals will be there. So, there will be three of these orbital. So, these are the three C-H bonds. Then you have one p orbital, which is the p_z orbital, which will be singly occupied. Now, that is the radical here, which is a single occupied p orbital or single occupied molecular orbital. We call it SOMO, and then there will be a σ* orbital here. So, that will be LUMO. So, first, there will be HOMO, then there will be SOMO, and then there will be LUMO. As I mentioned, that does not always have to be a sp² hybridize. You are going to learn that the case of CF₃ radical is pyramidal. So, again, in the case of CF₃ radicals, because of this fluorine, then once it has achieved planarity, there will be a huge repulsion. That is why it is going to be preferred in this pyramidal geometry.



So, now we are going to try to compare what we have learned about methyl radicals. We have learned previously that there will be methyl cation and methyl anion. So, let us try to compare them. If you look at the case of methyl radicals, as I mentioned, sp^2 hybridized, there will be one electron in the p_z orbital. And then, in the case of sp^3 , like in the case of CH_3^- you will have two electrons, which will be in that you have a sp^3 hybridization here. We have already talked about how it will be pyramidal. And now, I am going to talk about CH_3^+ ; you have already learned that because of CH_3^+ , you will see there will be a vacant p_z orbital here and the hybridization will be sp^2 . So, try to compare them in the case of the radical and the carbocation and what the things happening in the case of the carbocation. You will see that there will be 6 electrons, that is, the 3 bonding electrons with the CH, but here you will have a 7 because you have a free radical in the case of the CH_3^\bullet . So, that means what generally happens in the case of free radicals and carbocation is not an octet. It does not have 8 electrons. It will still have some deficiencies, that is why you will see there will be some characteristics. So, the radical will have some characteristics of a carbocation. And then again, as I mentioned, it is not always sp^2 hybridization. In the case of this radical, it could also be shallow pyramidal geometry. So, depending on the substitution, it could have a pyramidal geometry, or it could have a pseudo pyramidal geometry, or it could be a planar geometry.

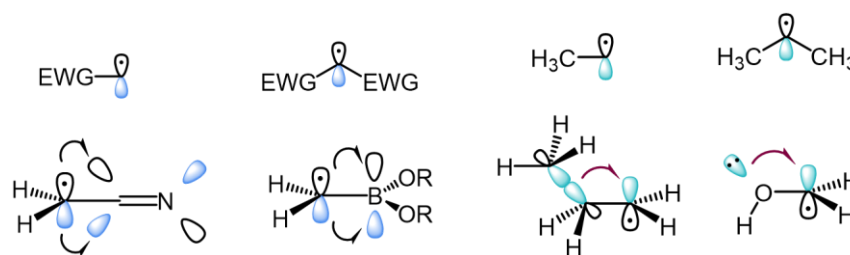


Now, we are going to classify the radical. So, the free radical can be classified as a charge or neutral radical. So, most of the time, you will see the radicals are neutral, but again, you will see some cases where there will be charged radicals. The neutral radicals can now be classified as electrophilic, nucleophilic, and ambiphilic. So, we will return to each of these different classes.



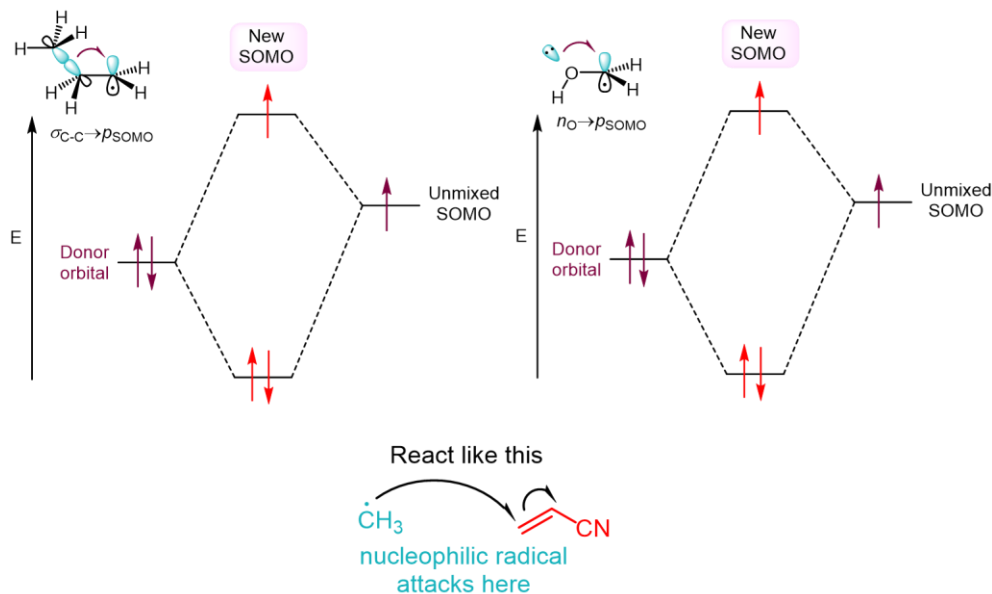
And then for charge radical, there will be a cationic, and there will be an anionic, or you can talk about the radical cation, and you know radical anion. You must have heard about this reaction when you take naphthalene and sodium metal, it will generate this anion here, which is a very good reducing agent. It generates this type of radical anion here, and we will talk about some of this chemistry later. Then there is a radical cation where you can see if you have an amine or a methoxy group, and sometimes, they can do a single electron transfer. That can generate a plus as well as a radical dot. So, we can call them a

isopropyl here like CH_3CH_2 or if you have a three CH_3 group (tert-butyl radical). So, in every case you see here, you get electron density. So, these are nucleophilic radicals or electron-rich radicals. We going to learn. So, now the important thing is to understand what the stability will be and how both the radicals are stable. So, both nucleophilic radicals and electrophilic radicals are stable. We are going to learn why they are stable and how they are getting stabilized. You can see what we are showing here in this diagram. If you have an electron-withdrawing group here, like a cyano, then the radical is interacting with the corresponding π^* orbital to get stabilized. Also, if you have a boron atom, the vacant p orbital interacts with it.



We are going to come back to that in the next slides. So, let us come back to first with the electron-rich radical or nucleophilic radical. We are going to talk about that there, we can understand clearly that if you have an electron-withdrawing group, then the radical is interacting and getting stabilized. But now, if you ask me if you have an electron donating group, we have learned that in the case of carbanion, once you have a 3 CH_3 group, it means once you have a tert-butyl carbanion versus methyl carbanion. We have always known that methyl carbanion will be more stable than tert-butyl carbanion, but when it comes to a radical, the student often gets confused and might think, why, sir, will this radical be more stable? So, why will this be more stable compared to the CH_3 ? So, to understand that, you have to understand this diagram, which means one, so you have this single electron here. So, let us talk about how carbon will have an unmixed single electron molecular orbital SOMO, and you have these three CH_3 groups. So, they can give the sigma electron through the hyperconjugation you have learned before, or this carbon-carbon bond can also give electron density to the inductive effect. So, now that you have this type of donor orbitals, what will happen once they mix up? Once this single electron in the singly occupied molecular orbital interacts with the donor orbital, it actually generates one more stable, and the new singly occupied molecular orbital will be higher in energy. So, previously, the singly occupied molecular orbital is here. By interacting with this, the donor orbital's energy increases. But at the same time, it stabilizes the donor orbital. So, overall, you are stabilizing 2 electrons and unstabilizing

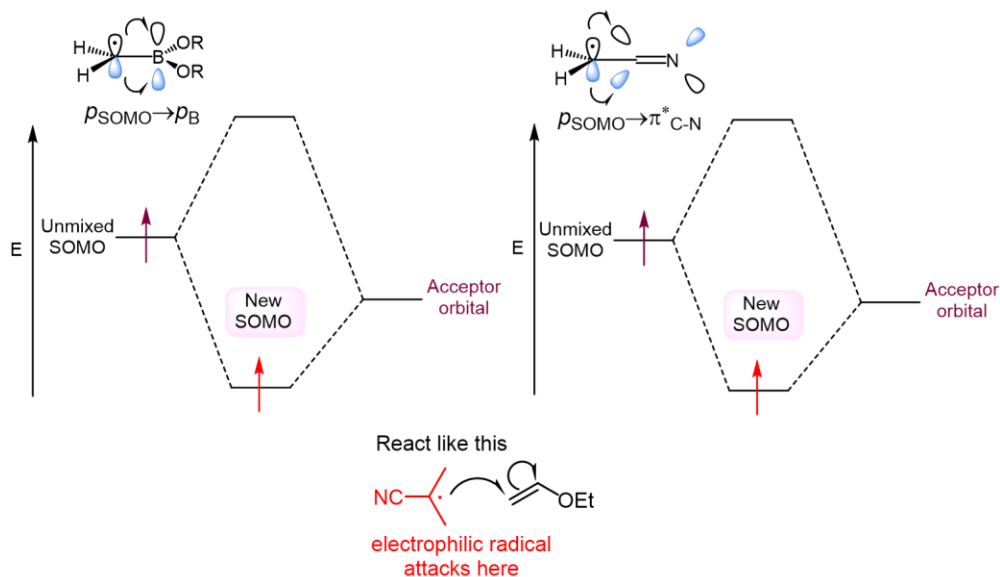
1, giving you overall molecule stabilization. Because of this overall stabilization, the molecule getting this radical is getting stabilized as well.



Again, it is a very similar thing. If you have oxygen or nitrogen, that means if you have a radical next to oxygen, then these radicals will also be nucleophilic. So, again, these cases are also getting stabilized. How are they getting stabilized? The oxygen lone pair can now interact with this singly occupied molecular orbital of the radical, and if it is interacting, it is generating this more stabilized HOMO is getting generated here. Once it generates a more stabilized one, of course, it generates this new SOMO that will be higher in energy, but it is stabilizing 2 electrons and unstabilizing one. So, that is giving overall stabilization to the system. So, that is why if you have a case of nucleophilic radical, it is also getting stabilized.

As I mentioned in the case of electrophilic radicals, you remember that at the beginning, this radical is a singly occupied molecular orbital at the unmixed. When you have an acceptor orbital, it is a vacant p orbital; it interacts with that and forms the new singly occupied molecular orbital. So, that is more stable than this unmixed SOMO. So, that is generating more stability in the system. Similarly, if you have a cyano here with a corresponding π^* orbital, it interacts with this unmixed SOMO. So, once this acceptor orbital interacts, it generates a new SOMO, which is more stable than the starting SOMO, the unmixed SOMO. That means it is generating stability in the system by interacting with this type of π^* orbital and the p orbital of the boron. We are going to come back to

this discussion about why these radicals we are going to prefer to react with an electron-rich olefin.



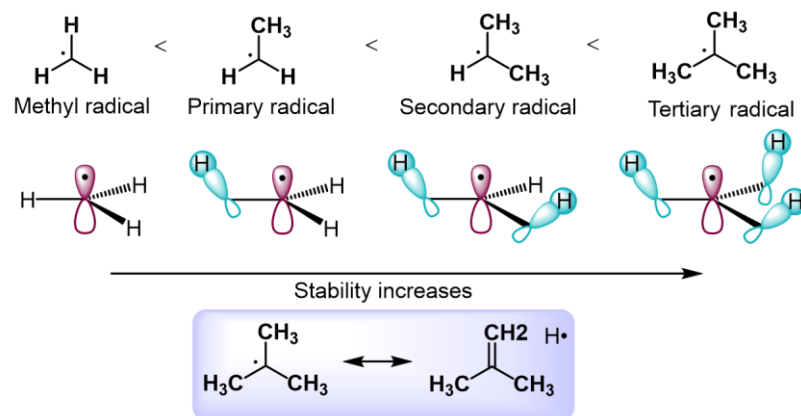
We are going to come back to that explanation later, but first, we have learned about stability, so let us solve some of the problems based on stability. So, radical stability increases in the order of these, as I mentioned, because of this inductive effect. I think I have mentioned that is why the tertiary radical will be more stable compared to secondary, primary, and methyl. You have seen the very similarity; because of that stability, the bond energy gets the C-H bond energy, which decreases.

- Radical Stability increases in the order methyl < primary < secondary < tertiary



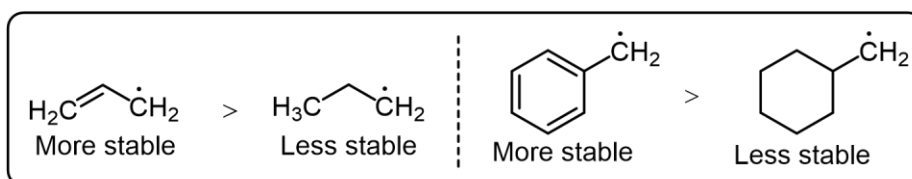
Again, you can also explain them through hyperconjugation, as I mentioned. So, you can see here that the stability increases in this direction very similarly because more hydrogen atoms can participate in the hyperconjugation. It is similar to what we discussed during the carbocation stability, hyperconjugation, and inductive effect.

- More the number of α - hydrogens more will be the stability of the free radical via hyperconjugation.

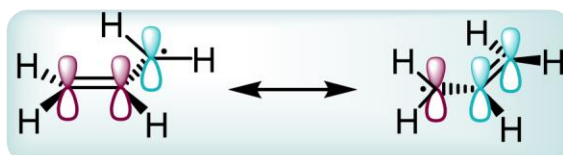


I think one more thing we have also mentioned, if you remember, called a resonance if the radical got a resonance stabilization. If you have this radical here, this allylic radical will be more stable than the corresponding propyl one because this radical can draw a resonance structure like this. So, that means if you can draw a resonance structure, that is why this radical is this allylic radical is more stable. Again, the geometry of free radicals is shallow pyramidal, so they can partially overlap with the adjacent p orbital of the pi bonds, resulting in delocalization. What is saying is that because of this shallow pyramidal geometry, this radical here can interact with these adjacent π bonds to form this resonance structure. Again, the benzylic will be more stable compared to the corresponding primary radicals. Again, because of this, the resonance stabilization of this radical.

- Charge delocalization also stabilizes electron deficient species.

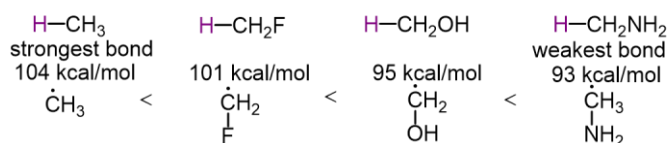


- Geometry of free radicals is shallow pyramidal such that the partially filled p-orbital can overlap with adjacent p-orbitals of the π -bonds resulting in delocalization.



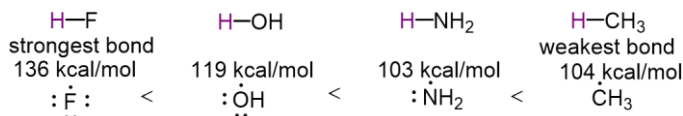
So, the radical stability increases with adjacent lone pair donors. If you have a lone pair donor, the bond energy is 93 kcal/mol; this is the weakest bond once you have this with an NH₂ versus OH versus fluorine. So, what is happening here, you can see it is 93, 95, 101. So, in this direction, you see that the bond energy is increased, and the stability is decreased. So, that means this is more stable than oxygen than fluorine, and you can also see across the stable the increasing electronegativity of decreased stability.

▪ Radical stability increases with adjacent lone pair donors



So, that means, if you go in this direction, you are going to see that you are in the fluorine. So, I think we can explain the same result from this chart here. Also, if you compare nitrogen, oxygen, and fluorine, which one is more electronegative? Fluorine will be the highest compared to oxygen and nitrogen. So, as the electronegativity decreases, the stability also increases because you can understand that the radicals. As I mentioned, the radicals are not in the octet. So, it is still a 7 electron, which means it is not an electron-rich species. So, if you increase the electronegativity, the s-character will increase. So, that can stabilize the radical more that is why the radical next to fluorine will be less stable compared to the nitrogen one.

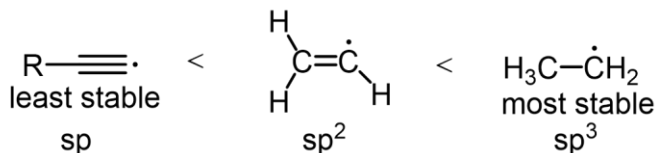
▪ Radical stability increases from left to right along the periodic table



Again, I think I have explained that once you have a methyl radical in the sp³ versus sp² versus sp. So, you can see the percentage of s-character is getting increased. As I mentioned, what is going to happen once the percentage of s-characters increases? Now, it is going to abstract more electrons toward the nucleus, but you see, the radicals are already electron-deficient species. That is why the increase in the s-character will

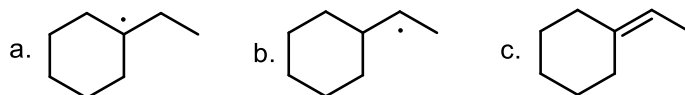
destabilize the system. That is why the stability is going to decrease once you have a sp radical versus a sp³ radical.

- Free radicals decrease in stability as the % of s-character in the orbital increases [i.e. as the half-empty orbital becomes closer to the nucleus].



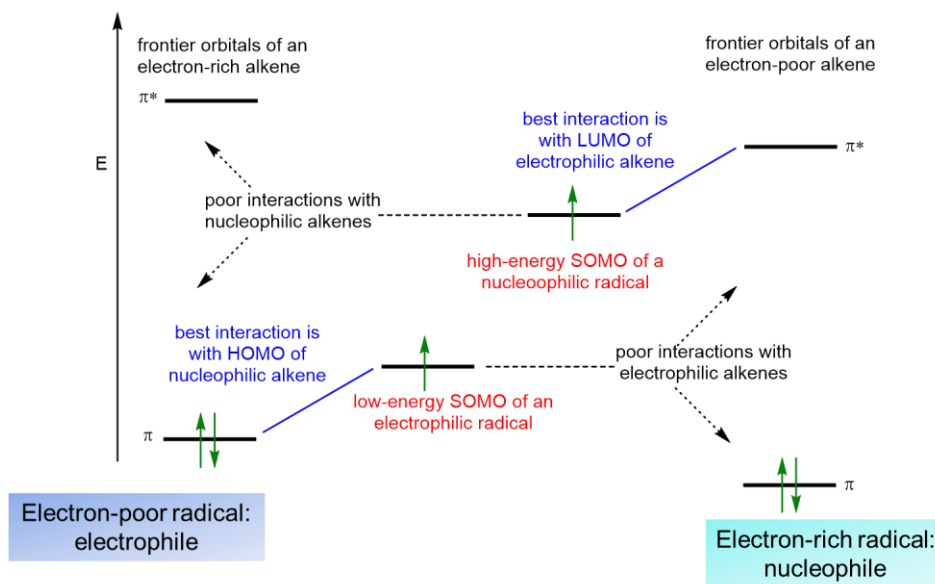
So, can we rank them? You have these three different radicals here. You have a tertiary here. You can clearly see a secondary and an allylic one here. So, which one do you think will be more stable? So, think about it. I have already shown you the bond energy at the beginning. So, if you remember the allylic one, it will be the most stable. So, the C will be more stable than the A and the B.

Rank each group of radicals in order of increasing stability.



So, now I will explain one of the important concepts to you at the beginning. As I mentioned, we are going to learn slowly that once you have an electrophilic radical, suppose you have a radical with a; let us consider this one: you have two different electron-withdrawing groups. Now, you will see that if you have a two-electron withdrawing group, this will be an electrophilic radical, and the electrophilic radical will try to add the olefin, which is electron-rich. Suppose this one; so, this will prefer to add these olefins, which are electron rich because the oxygen can give electron density. On the other side, if you have a radical like this, then they will prefer to add to an olefin, which is electron deficient. So, they will prefer to add to an olefin, which is an electron-deficient olefin. Now the question is why there is a preference for that so that can also be explained through the molecular orbital again; I think if you understand this molecular orbital, it will be easy for you to predict the product, as I mentioned at the beginning, so let us try to understand this diagram. So, if you remember, when I was talking about the stability of the nucleophilic radical if you remember the stability of nucleophilic radicals when I was talking about it, you saw that in the case of nucleophilic radicals. I have

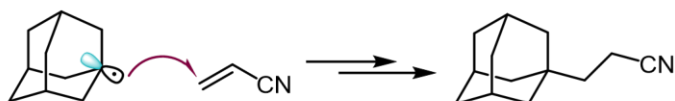
shown this diagram when an interaction happens with the acceptor orbital, which gives the electron density we generate. So, this is your SOMO, and it was at the beginning. So, what happened? If you remember, after this interaction. So, this was the earlier SOMO before the interaction. After the interaction, this is the new SOMO, which is higher energy. That means the SOMO of the nucleophilic radical will be higher in energy because it is the higher in energy it cannot able to interact with the π orbital. It will only interact with a π^* orbital, which means I was trying to talk about that here, this radical SOMO radical and your olefin. So, let us consider this is the electron-poor olefin. Once you have electron-poor olefin, suppose consider this one. In the case of electron-poor olefin, the π orbital will be because the electron-withdrawing group can take electron density towards it. So, that can stabilize the HOMO. That is why the π will be more stabilized. This singly occupied molecular orbital can only interact with the π^* orbital. That means it can interact with the π^* orbital of this π bond. And so, it can react with the olefin, which is attached to the electron-withdrawing, by interacting with this π^* orbital.



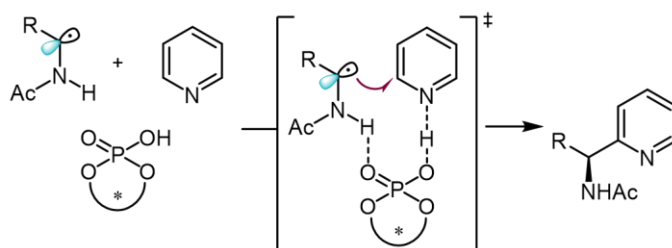
But once you come back to an electrophilic radical, if you remember, in the case of electrophilic radicals, we have shown the earlier this is your SOMO, after interacting with the acceptor orbital, what you have learned, the new SOMO will be more stabilized, we have I have shown this diagram guys in the beginning. So, this will be more stabilized. So, this one will now interact if you see this is electron-rich olefin here. So, we are talking about a frontier orbital of an electron-rich alkene. In the case of electron-rich alkene, the π orbital will be higher in energy compared to the electron-deficient one. So, that is why this π now comfortably interacts with the low-energy SOMO of an

become electrophile. Now, this olefin is where the radical is adding here. Now, you can think about this as a C=N with a plus charge here. So now the radical is adding here to form this corresponding product. This is a very interesting reaction here. You can achieve asymmetric so this can react through a network of hydrogen bonding, and if you have a chirality in this chiral phosphoric acid, then this product will be chiral. So, we are going to discuss some of this in radical asymmetric catalysis.

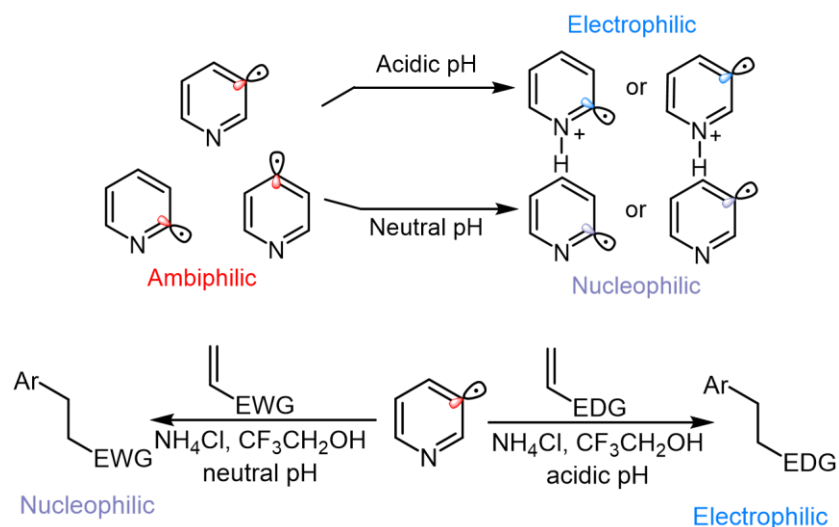
- Tertiary alkyl radicals: Nucleophilic



- α -Amino radicals: nucleophilic

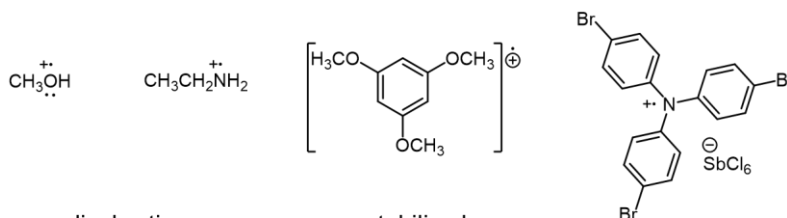


Then, I am going to talk about the ambiphilic radical. So, what is this radical? Now, you can see these are the radicals we are talking about here: pyridine in the 2 positions, 3 positions, and 4 positions, depending on the pH. If in the acidic pH, these radicals become electrophilic because your nitrogen is protonated. So that is why this radical next to the nitrogen is becoming electrophilic, but in the neutral condition, this is becoming a nucleophilic radical. So, you can see here we are starting from this condition, which means if you have a 3-bromo pyridine, you can generate this radical. And now, if you are in the acidic pH, it can add to an olefin with an electron-donating group here because, in the acidic pH, it is becoming an electrophilic radical, that is why it is going to form this product. In the neutral pH, it adds to an olefin with an electron-withdrawing group to get to this product. So, depending on the pH it is forming, it is reacting in the case of an electron-donating group and an electron-withdrawing group. So that is why this type of radical is called an ambiphilic radical, and then there is a radical cation and the radical anion.

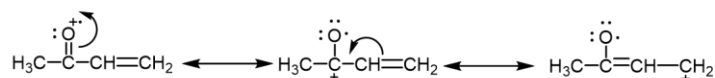


So, radical cation, as I mentioned, if you have this nitrogen and oxygen, if there is a single electron transfer happening, you will be generating a plus and the dot. You can see here we are going to talk about some of this chemistry. You can see there is an example of some radical cations that are even resonance stabilized. If you have this oxygen dot with this double bond attached here, that can also get stabilized through the resonance.

- A radical cation is a positively charged species that has an atom bearing an unpaired electron.



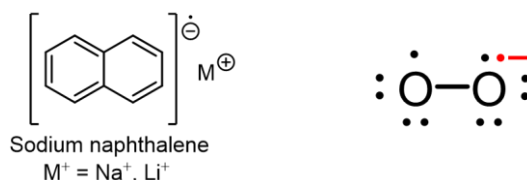
- Some radical cations are resonance stabilized.



- Radical cations are common intermediates in reactions occurring in the mass spectrometer.

Then the other class is radical anion. So, again, the radical anion is a free radical species with a negative charge. So, radical anions are encountered in organic chemistry as reduced derivatives of polycyclic aromatic compounds, e.g., sodium naphthenide. So, suppose you take naphthalene and sodium and stir it. In that case, you will be generating

this sodium naphthenide, a very good reducing agent with a reduction potential of around 2.5 volts. So, you can see that there is another example here, which is called a superoxide anion. If you have an oxygen molecule and one electron getting transferred, that generates a superoxide anion. In future classes, We will discuss some of the chemistry using this radical cation and radical anion.



In this class, I talk about the formation of radicals through the homolytic cleavage of the carbon-hydrogen bond. So, you can generate this type of radical depending on the different types of atoms. We talk about their hybridization, we talk about the ESR and the EPR technique, the different types of radicals I have introduced to you, and also I talk about their stability.

Again, these are important textbooks. You can find the radical chapter in all these books, and thank you so much for coming to the class. I hope you want to come back to the next class, where we are going to talk more about radical chemistry. Thank you so much