Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

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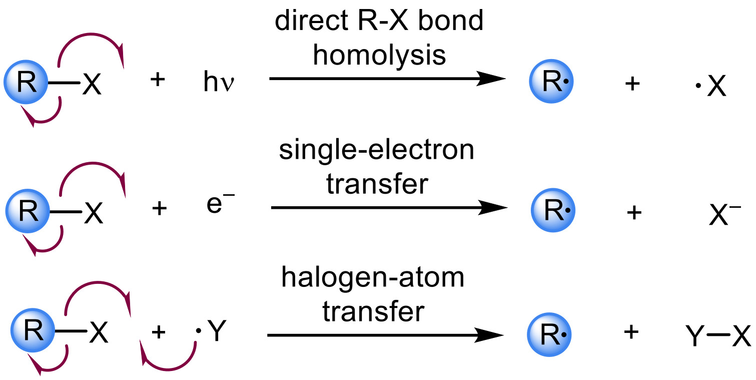
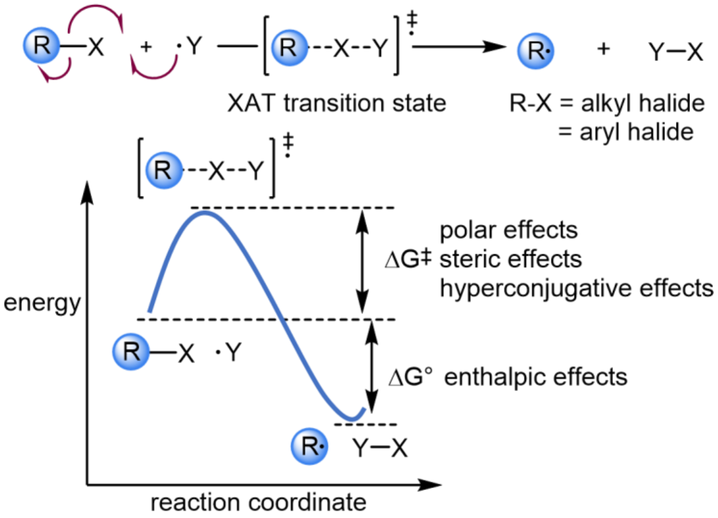
Lecture 27: Radical

Welcome back to this NPTEL online course on molecular arrangement and reactive intermediates. In the last class I talked about the hydrogen atom transfer. You have seen several reactions in which the hydrogen atom transfer occurs. So, in today's class, I am going to talk about halogen atom transfer. Finally, I am going to talk about some of the modern photoredox catalysis and how catalysts can be used in photochemistry to perform a lot of carbon bond-forming reactions. Then, most of the reaction you are going to see towards the end will be visible light in a photoredox catalysis. So, let us start with the halogen atom transfer. So, then we are going to understand the mechanism, and then we are going to learn very briefly what proton-coupled electron transfer is. I think for the rest of the time, I will talk about visible light photocatalysis.

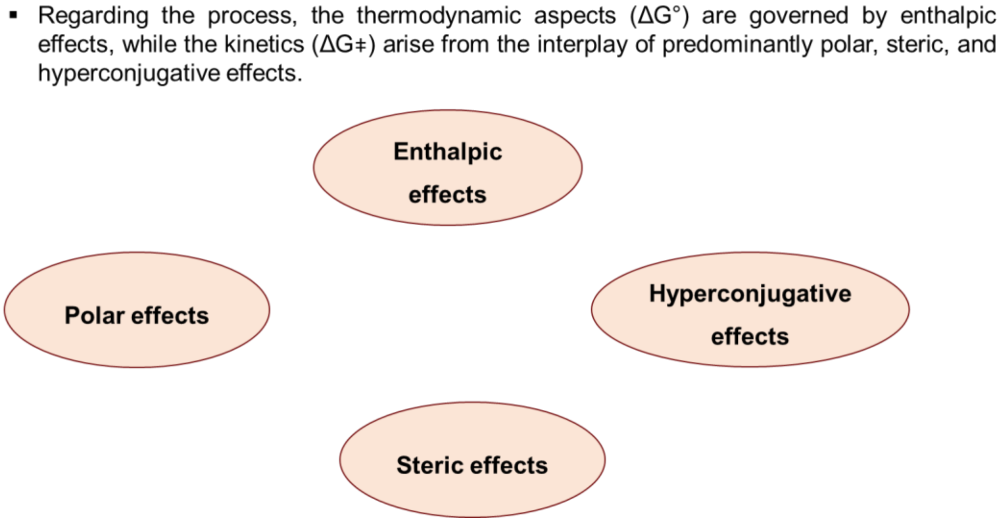
As you can see from this term from the halogen atom transfer, we have seen some of the reactions that if you have a carbon halogen bond, you have seen in the case of the samarium reaction or you have seen for the tributyltin hydride reaction. You have seen what is happening that is actually cleaving this carbon and the halogen bond to generate a radical species. So, there are three different ways I have mentioned. It could be direct homolysis of this R-X in the presence of UV light; it can form the R· or the X·. It could be a single electron transfer. I think I am going to explain some of this in the visible light photoredox catalysis. You are going to see that the catalyst can do a single electron transfer where it can cleave this bond again to form the R· and the X-. So, first, the single electron transfer is going to happen, and then it is going to form the R·, or it can happen here that there is a halogen atom transfer. So, what is happening here is you can actually think about giving another a radical, which is going to cleave this R-X bond. So, we are going to take this X as an X·, and then you are generating an R·. So, now, you are forming the Y-X; I think the most important thing is that this reaction very much depends on what type of Y· you are using and the bond energy of R-X.



So, there are a couple of important factors which I am going to discuss. So, the first thing we are trying to understand this reaction that once this bond is getting leaving, it is forming some sort of a transition state here where you are seeing this bond formation happening between X and Y, and there is a bond breakage happening in the transition state and then it is going to form the R· and the Y-X. So, if you try to see about this reaction then there is a transition state here. So, you start with this R-X and then with Y·; from there, you form the product. So, you can see clearly that this is an exothermic reaction. Your product is more stable than your starting material. As I mentioned, the bond dissociation energy is a very important factor here. So, this is the important factor that we call an enthalpy effect; this depends on the bond strength and the stability of this transition state. So, depending on what you can see, this energy is going to vary. So, this is the effect. So, this ΔG depends on the polar effects, steric effects, and hyperconjugation. So, these are the factors that are going to stabilize this corresponding transition state. So, based on that, we are going to see the different rates.



So, you are going to see the enthalpy effects, as I mentioned, the polar effects, hyperconjugative effects, and the steric effects. So, I will discuss things very similar to the hydrogen atom transfer and a few examples of these rates being measured.



- Regarding the process, the thermodynamic aspects (ΔG°) are governed by enthalpic effects, while the kinetics (ΔG‡) arise from the interplay of predominantly polar, steric, and hyperconjugative effects.

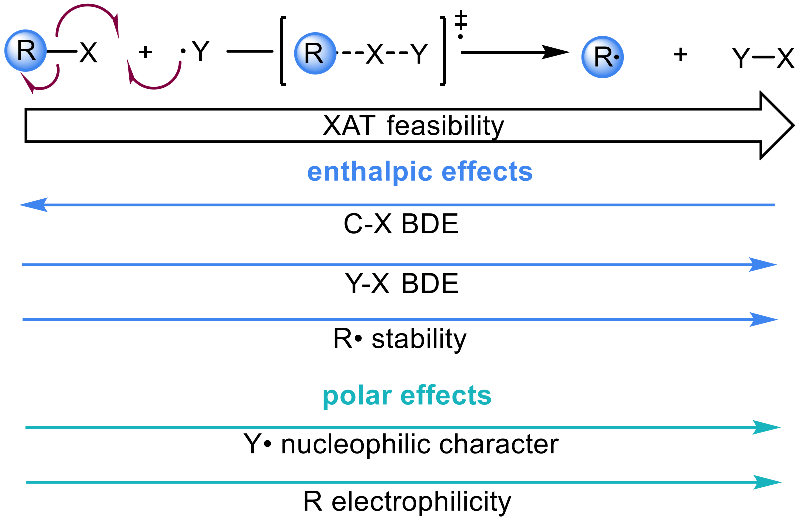
Enthalpic effects

Polar effects

Hyperconjugative effects

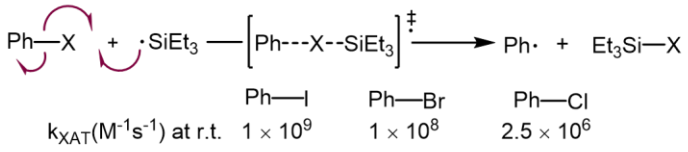
Steric effects

So, as I mentioned, there is an enthalpy effect, and the bond dissociation energy is a very important parameter. So, if you see the bond dissociation energy of the Y-X, which is forming here, and if you see once the Y-X is going to be more stable, then the reaction will be in the forward direction. The stability of the R· is also a very important factor here, and there will be a polar effect, and then there is an important thing that is the nucleophilic character of the Y·. You will see that most of the time, this Y·, which you will use for this type of XAT or the halogen atom transfer, will be a nucleophilic radical. As you can see, the X·, which is going to form here, from here it is an electrophilic radical, and which together is going to form this Y-X.

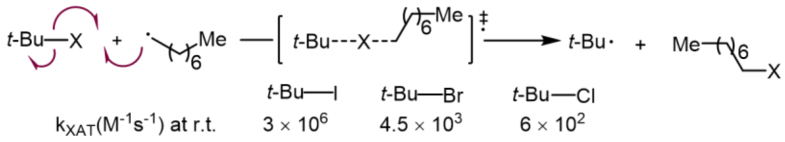


So, now you can see the cleavage of this phenyl and the X. This bond is getting cleaved here. We are using a nucleophilic radical, the triethyl silyl radical, here. So, you can see that there are different rates if you have this iodo benzene versus bromo benzene versus chloro benzene. As you can see this is completely depending on the bond energy. So, you can see once you go from the iodine to the bromo to chloro, the bond dissociation energy of this iodobenzene and chlorobenzene, you can see the bond dissociation energy getting decreased in this direction and at the same time the XAT reactivity getting increased in this direction as well. There is another example: this alkyl radical cleaves this a tert-butyl and, the halogen. So, that tert-butyl chloride versus tert-butyl iodide versus tert-butyl bromide, again, you can see the XAT is increasing in this direction.

Nature of the Halide on Aryl Derivatives

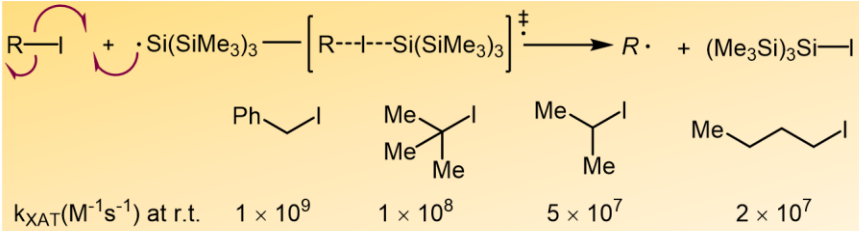


Nature of the Halide on Alkyl Derivatives



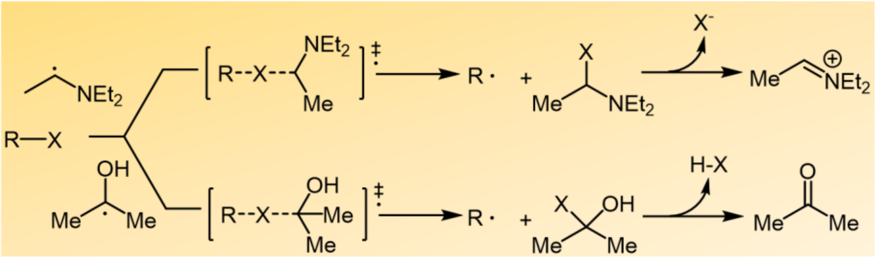
Again, there is an example here; now, I think the other important factor, as I mentioned, is the stability of this corresponding radical which is forming here. So, if you see here, there is a benzylic radical versus the tert-butyl radical, secondary radical and primary radical. So, in this direction, radical stability is increasing. That is how you can see the rate is higher in this direction. So, the XAT rate is also higher in this direction.

Alkyl Halide Substitution Pattern



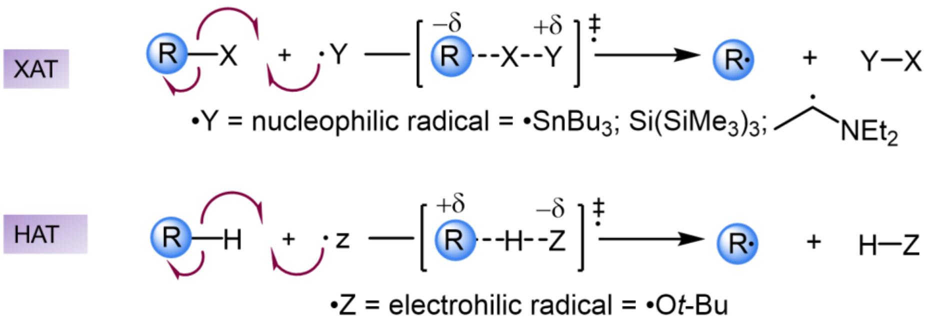
Then there is another interesting concept: if you have alpha amino radicals that can also participate in this reaction or the alpha hydroxy radical, this can also be because they are the nucleophilic radicals that can participate in the halogen atom transfer to generate this radical species here. Then, it can form this corresponding X, which can go to the corresponding iminium ion. Here is what is going to happen: it can convert to the corresponding carbonyl compound after the elimination. After you can see this comes back, get rid of the halogen to get to this carbonyl compound.

Mechanism of XAT Involving α-Aminoalkyl and α-Hydroxyalkyl Radicals



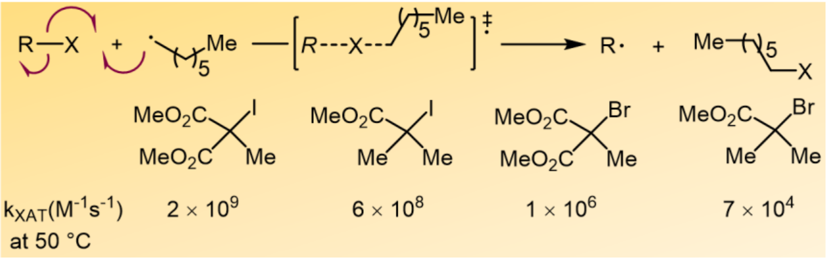
So, what we have learned is there are some polar effects. So, we have learned that there must be a nucleophilic radical like the tributyltin or the silyl, or you see this type of radical alpha amino radical. We have seen this in the case of the hydrogen atom transfer. So, this is going to be an electrophilic radical. You remember we talked about this in the last class. So, this will be an electrophilic radical, which will go for a hydrogen atom transfer. So, that can cleave the carbon and the hydrogen bond to generate this R·. And most of the time, you end up seeing that these are the radicals that are forming here. They are nucleophilic in nature.

Contrasting Charge Separation in Transition States: (A) XAT Reactions vs. (B) HAT Reactions

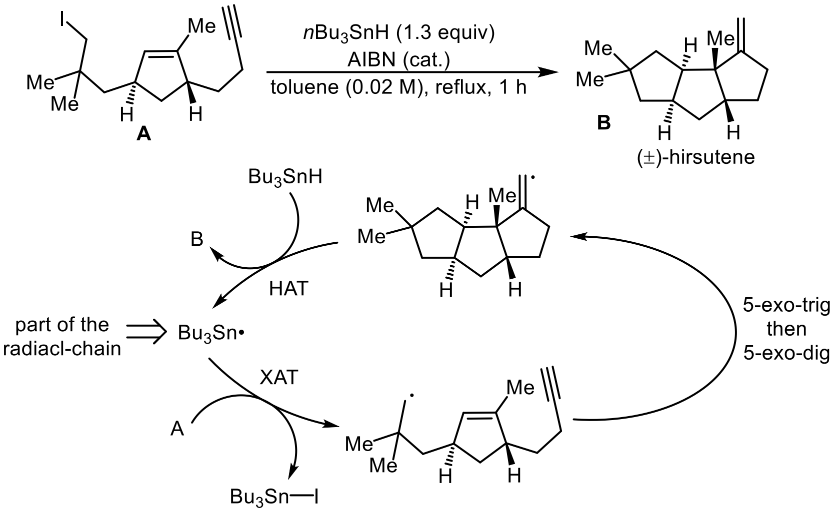


So, again, there is an alkyl halide substitution pattern you can see again once you form this corresponding R· from these species. What is happening is that stability is also going to make a difference. If you try to compare them, what is the difference between them? You have a 2-ester group, which stabilizes this radical more. So, the radical stability will be greater here than in this case. That is why it will be at least ten times higher. So, you can see here that this will be ten times higher compared to the other one, where you have only one ester with two methyl groups. A very similar thing happens if you have a bromide also.

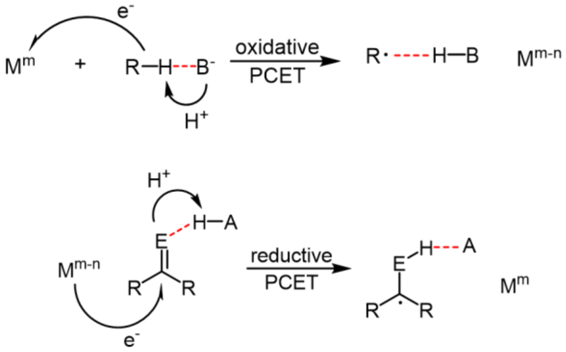
Alkyl Halide Substitution Pattern



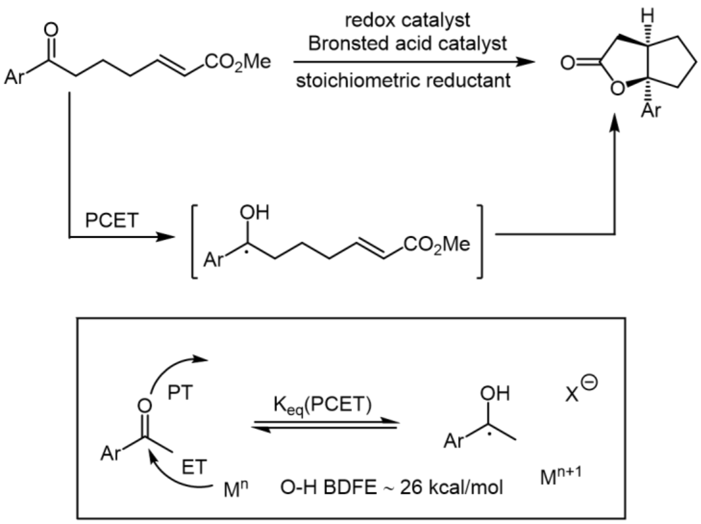
So, now we are going to talk about some of the applications that I think we have already talked about in this reaction when I was talking about the intermolecular radical cyclization, but again, you can see these are very similar concepts here. So, in this particular reaction, you will see the halogen atom transfer and the hydrogen atom transfer, both happening here. So, now I think the first thing is if you have the AIBN. If you remember, I have already talked about AIBN, and once you heat up, it is going to generate a more stable radical here if you forget about it. We generate this radical from AIBN. Now, what is going to happen? That can go for a hydrogen atom transfer from this. So, that can go for a hydrogen atom transfer to generate this tin radical here, and once you have a tin radical, it goes for the halogen atom transfer first. To form this radical species, it can go for an intermolecular radical cyclization, and then it will form this radical here, which will go for another intermolecular radical cyclization. So, there is a 5-exo-trig and 5-exo-dig to end up here, which can finally go for a. So, you can see I already talk about the vinyl radical as a more reactive radical. So, it will go for immediate hydrogen transfer to get to the product.



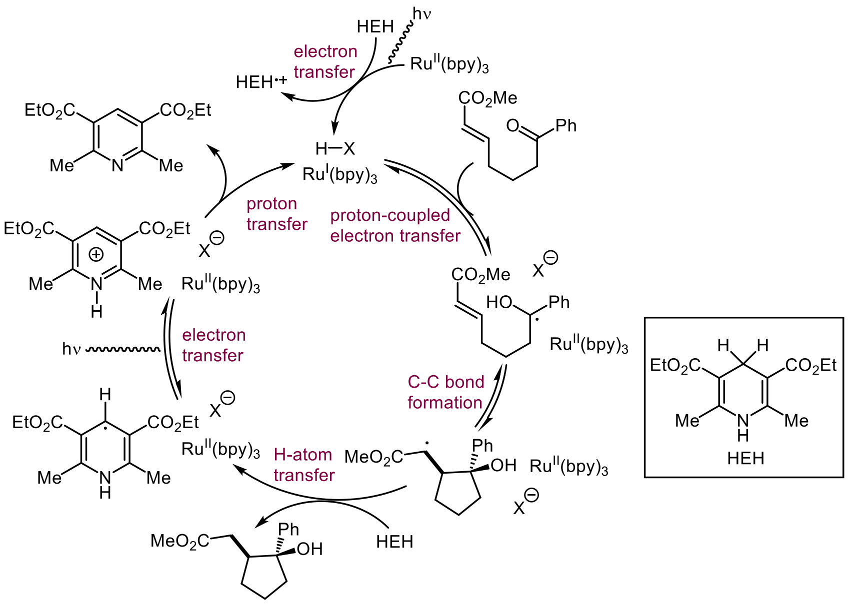
So, that is all about XAT. I think we can also practice some of the reactions during the assignment. Now, I think I will briefly talk about proton-coupled electron transfer, and I will just talk about one example of that. So, you can see what we are talking about here. So, we know about the electron transfer going to happen. We know about the electron going to transfer from the metal, or I think we are mostly going to see it here. We are going to learn them there. In the case of the transition metal photoredox catalysis, electron transfer will happen. But here we are learning that there will be a proton-coupled electron transfer. So, what is going to happen if you see this particular example of carbon H or if you have a carbonyl group here, especially when we are talking about E equal to oxygen? So, in a carbonyl group, what is happening in the presence of a proton source if you think about E equal to oxygen? This oxygen is going to get protonated. So, now you can if you have seen that this reaction what you have learned the reduction of this carbonyl group is highly dependent on whether you have the protonated form or a non-protonated one. Once you have a protonated form of the transition metal, the photocatalyst can go for electron transfer to form these species. So, now you can reduce the carbonyl group to make this radical species here. So, what is happening is that this proton, which is getting coupled here, allows the electron transfer. So, that is called the proton-coupled electron transfer.



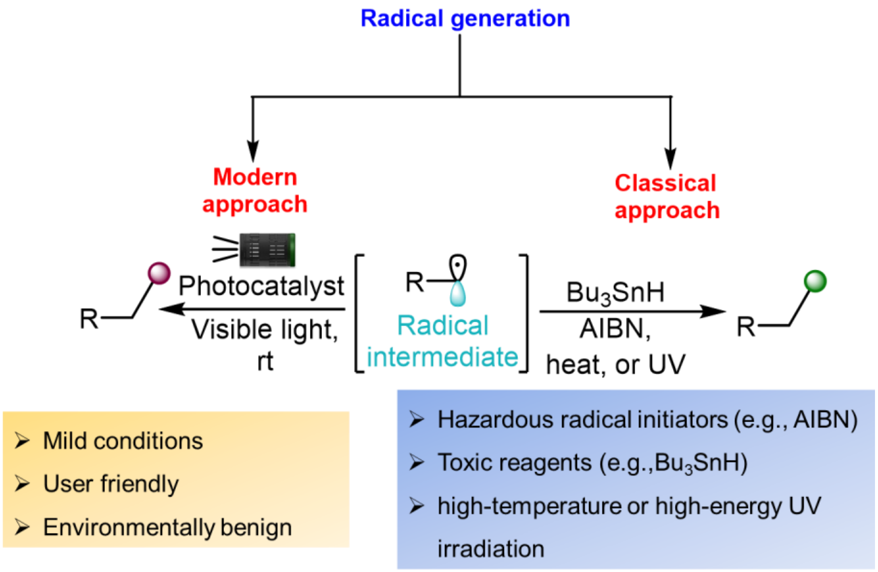
So, you can see a mechanism here: what is happening? So, you actually form this carbonyl group under the photoredox catalyst, the bronsted acid catalyst, and the stoichiometric reductant. What are they doing? They generate this ketal radical after the proton-coupled electron transfer. Here, this ketal radical can take part in a cycloaddition with the sorry. It can take part in a 1,4 addition with these alpha,beta-unsaturated carbonyl compounds, and at the end, after the addition, it is going to happen. It can generate this radical here, and then at the end, it will be finally it can able to go for a hydrogen abstraction, and finally, this OH and the ester going to get form this corresponding lactone. So, this work was done by Noel's group from Princeton; they have shown that you can do this proton-coupled electron transfer using a proton source. As I mentioned, a bronsted and photoredox catalyst can do this radical species.



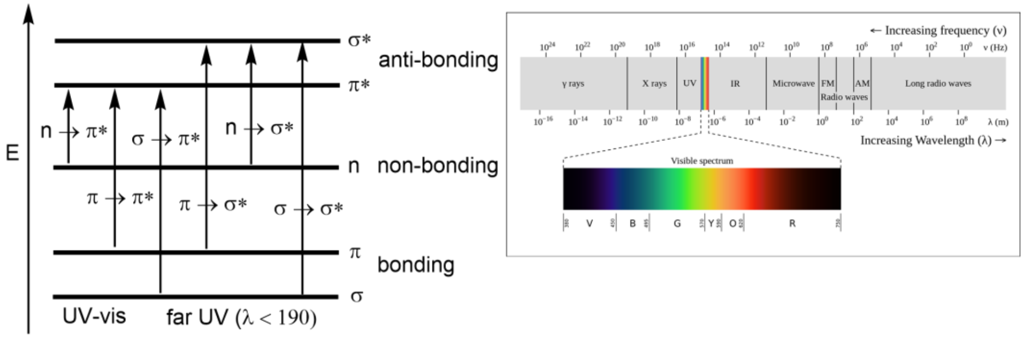
So, in this reaction, they used this ruthenium bipyridyl complex, which we will explain in a minute what their structure is and how the reaction happen from there. They use a HEH source. So, what is happening here? That the ruthenium is going to the excited state. We will talk about this mechanism after a few slides, and it will go for the first. So, an electron transfer will happen, and you can end up forming the Ru(I). In that stage, it is going to go for a proton-coupled electron transfer here. We can convert Ru(I) to Ru(II) to generate this species here. Now, you can go for this. The ketal radical cyclization is going to happen first, and then there will be a hydrogen atom transfer, and then you can see that you have this Ru(II). So, then there will be the Ru(II) again. What is going to happen? It can go to the corresponding excited states and start the process. So, electron transfer will happen from here, and it is going to start.



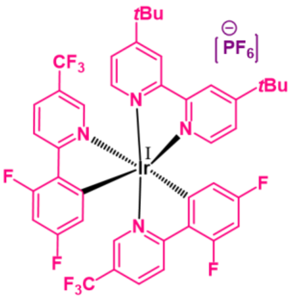
So, now I am going to talk about I think till now I think what I have talked about in most of the reactions talking about UV light; you need UV light starting from this several different types of reactions in tributyltin hydride using AIBN under heat, or you have seen in a lot of reactions like Paterno-Buechi reaction or some other chemistry I talked about I think the Di-π methane rearrangement. Most of the time, I was talking about the UV light because you have to understand to go for this n-π* transition, you have to use a like somewhere in the 280 nm. If you want to π-π* for an olefin, it will be around 200 or 180 nm, but now we are talking about a photoredox catalyst. So, how can you generate a radical species using organoboron or a transition metal with photocatalyst. So, this will be mild conditions, user-friendly, and environmentally benign.



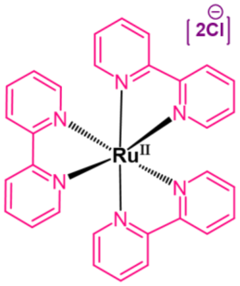
So, again, I think we have already learned about this. I have already shown you this diagram. I think you have seen there this n-π*, π-π transition mostly with the UV light. Now, we are going to talk about visible light here, which starts from 380 nm to 750 nm.



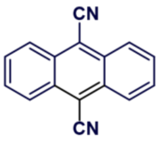
So, we are talking about the catalysis which is happening in this range. So, there are different types of photoredox catalysts. We use ruthenium or iridium. So, there are some organophotocatalysts; we have shown some examples here, and there are more examples of organophotocatalysts. So, I think the example you have shown is that they are the donor-acceptor photocatalyst. Again, I will not talk more about these things in this class.



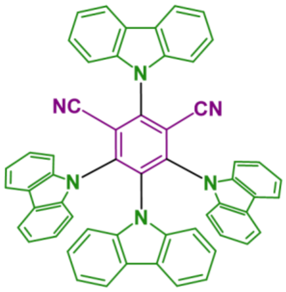
Ir[dF(CF$_3$)ppy]$_2$(dtbbpy) PF$_6$



Ru(bpy)$_3$$^{+2}$

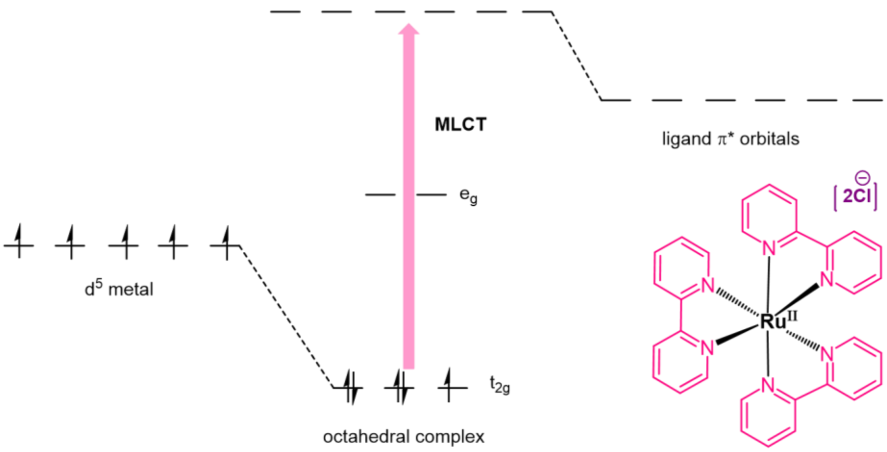


DCA

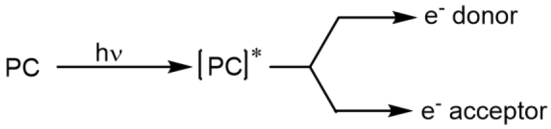


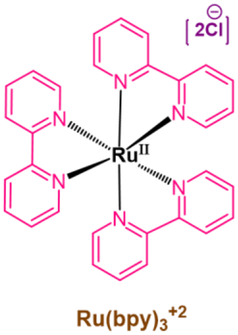
4CzIPN

So, briefly, I am going to talk about some of the important facts. So, now, if you try to understand this particular complex, it is a low spin complex here. So, you can see here it has this $t_{2}g$ with the d^5 octahedral complex. So, here you can see there will be a metal to ligand charge transfer going to happen. So, once you shine a light here, what will happen under it will absorb the visible light, and there will be a metal to ligand charge transfer.



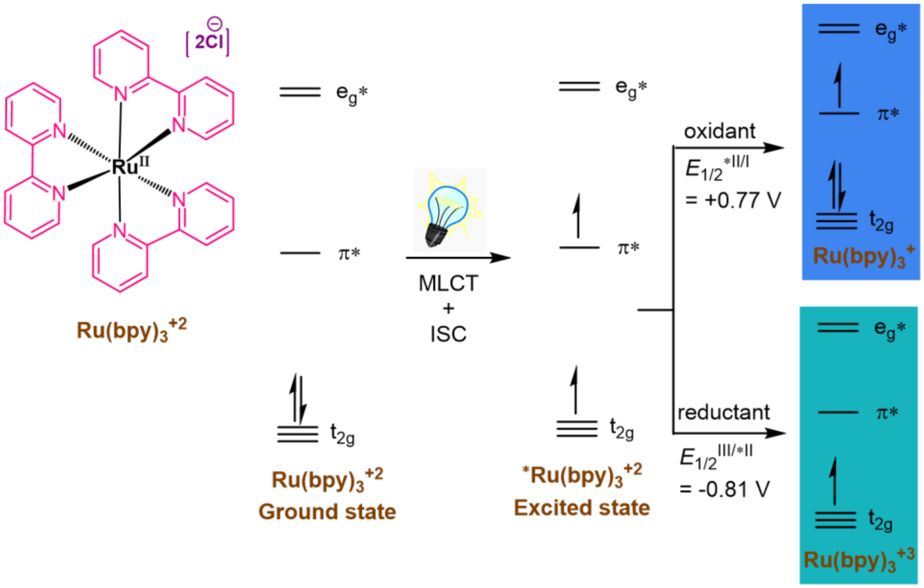
So, once it is going to the excited states, it is going to be excited singlet. From there, it is going to be an excited state triplet. So, now, once it is in the excited state, it could be a reductant or an oxidant. So, it is absorbing in the 450 nanometers. Now you can see it is absorbing the visible light. There is a long-lived triplet state here, which means it will go to the singlet to the triplet state, and from there, it can go for electron transfer or it can go for energy transfer. So, then it can go for the single electron transfer, and again, as I mentioned, it could be an effective oxidant or reductant.



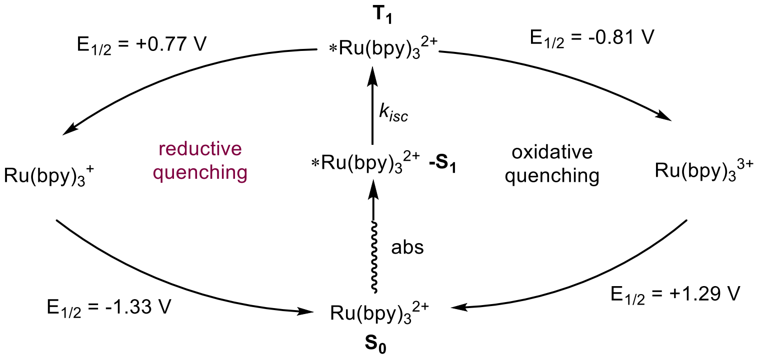


- Absorption at 452 nm (visible light)
- Stable, long-lived excited triplet state = 1100 ns
- Single electron transfer (SET) catalyst
- Effective excited state oxidant and reductant

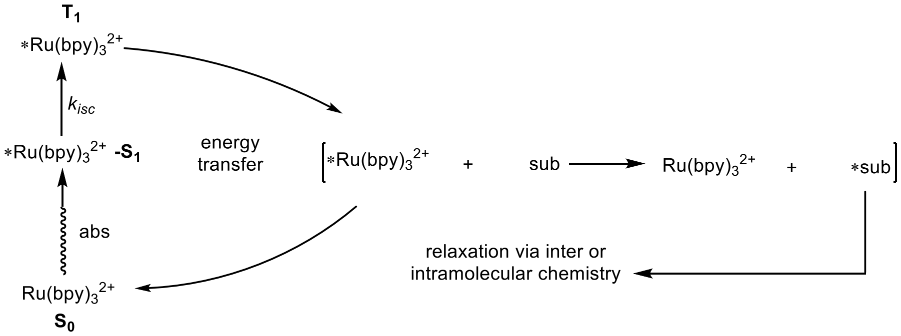
Now, if you see this diagram, you are trying to show the metal t₂g from here once you shine a light. You know, what is going to happen through metal to ligand transfer? It is going to go to the π* orbital of the ligand. So, metal to ligand transfer will happen in the excited states. So, first, there will be metal to ligand transfer, followed by an inter-system crossing. So, it is going to generate a triplet state. Now, it can be a very good oxidant or very good reductant. So, based on this redox potential, you can see it can go for oxidation of some bonds, or it can go for it to act as an oxidant. So, that means it can take an electron from somewhere or act as a reductant.



So, now you can see here we are trying to show you it is going to absorb the visible light and go to the singlet excited states. There will be an inter-system crossing to the triplet excited state from there. It can be a very good oxidant or very good reductant, and that also depends on what type of things you have that you have to match with the redox potential, which is the important factor here. So, depending on the redox potential of your excited photocatalyst, it can be an oxidant and reductant, and, of course, it depends on the substrates.

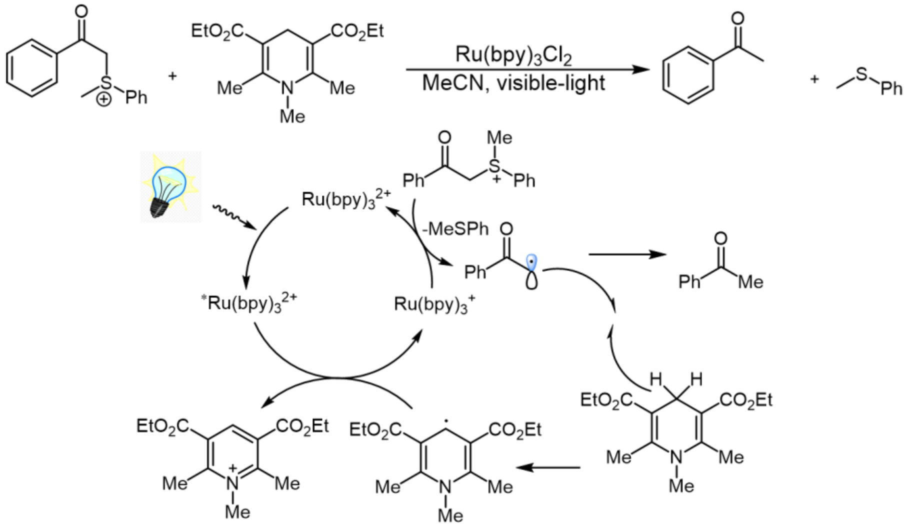


So, that is all about the electron transfer, and there is another thing happening called energy transfer that means, in the excited state, it can also act as an energy transfer agent. So, it can transfer the energy and come back to the ground state from the excited triplet state. So, there, it can transfer the energy to the substrates, which cannot be excited, and then the substrates can go to the excited state, and from there, it can participate in different types of reactions. It can go for isomerization, and it can go for some sort of other chemistry that can happen from there. So, again, there is this energy transfer that can be a Förster and Dexter. Again, I think we do not have to discuss more details here. So, this is a very general thing I just want to tell you about this visible light photocatalyst.



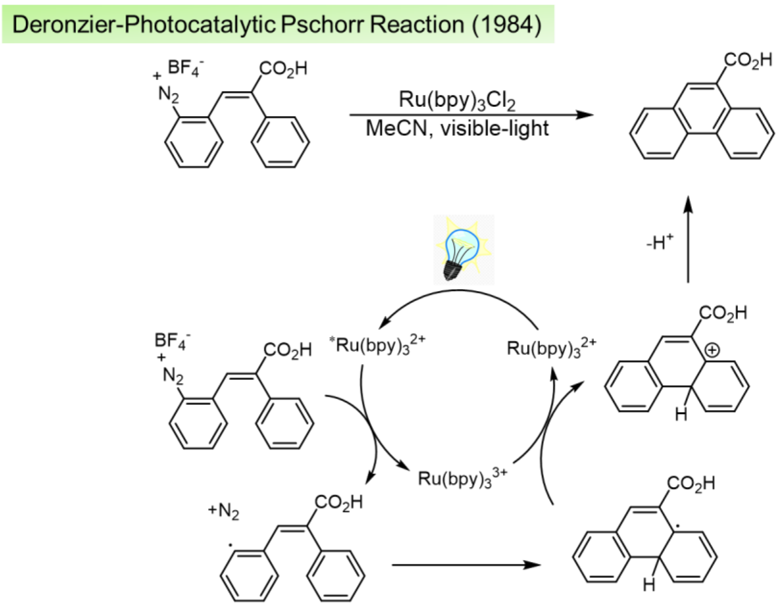
I just want to show two important reactions that were discovered in the 1970s. One of the reactions about this Kellogg-Reductive desulfuration is what is happening here. If you see, we have learned about some of the reactions here under the UV light, while if you have this carbon bromine bond here instead of the sulfur under UV light, you have seen that it is going to form the radical, and then it is going to get a hydrogen atom abstraction. But now we are using a visible light using this ruthenium catalyst. So, what is going to happen once we excite the ruthenium catalyst? It is going to go into an excited state. So, the first thing you can see here is going to go for an electron transfer going to happen from here. From there, it will form the Ru(I), and now, what will happen? Now, at this stage, the Ru(I) wants to go to the Ru(II). So, it is going to transfer one electron here. Once it transfers one electron here, this bond will get cleaved, and you see this is getting out. It generates this radical when alpha-keto radical generating happens, and once it is generated, this radical is just a stable radical. We know we have learned it can go for a hydrogen atom abstraction. So, this hydrogen atom abstraction is going to happen and form the product.

Kellogg-Reductive Desulfuration (1978)



Another important reaction was discovered in the 1980s. So, here you have a diazo compound. We have already talked about how you make this compound from aniline. Now, using the ruthenium photocatalyst, you can convert this to the corresponding H here, and at the same time, you can see where you end up making phenanthrene. So, starting from this isolated phenyl ring, you are making some sort of a cyclic product at the end. So, we will quickly learn about the mechanism of what is happening again, that is, ruthenium in the excited states what is happening. First, it is going to as you see the

Ru(II) to the Ru(III) happening. So, as you have learned, I think we have already talked about the Sandmeyer reaction in copper chemistry. You can see how it generates aryl radicals here. A very similar thing is happening here. So, ruthenium is giving one electron here. That way, it is going to get an N_2 out, and a phenyl radical formation happens. Now, this phenyl radical is coming in, and it is going to add to this aromatic ring here. The generation of this radical further, the ruthenium will now take back the electron that will generate a positive charge here, which will go for a hydrogen abstract, which will go for a proton going to take from here, and that is going to form the corresponding phenanthrene.



So, in this particular topic, I talk about the halogen atom transfer reaction, and it is reactivity. I will talk about the different factors and their importance in the halogen atom transfer reaction. I also talk about how the bond dissociation energy is very important. Also, you have seen other factors, such as the need to use a nucleophilic radical for this reaction. And, then, you have seen how this reaction is important once you are using the alpha-amino radical for this reaction. Then, in the end, I will talk about the definition of proton-coupled electron transfer. I think I have shown you one mechanism of how the proton binds with the oxygen. So, that is allowing the reduction of the carbonyl group to generate a ketal radical. Then, I will talk about visible light photocatalysts and how different they are from UV light. So, now you are using photocatalysis, which can act as a catalyst in the reaction; it can absorb light in the visible range, it can go to the excited singlet through intersystem crossing to the triplet, and from there, it can go for a single electron transfer, or it can go for energy transfer. We have seen some examples of this reaction as well. Again, these are the references here. Thank you for coming to the class, and I am going to see you guys in the next class. Thank you.