Molecular Rearrangements and Reactive Intermediates in Organic Synthesis

Prof. Santanu Panda

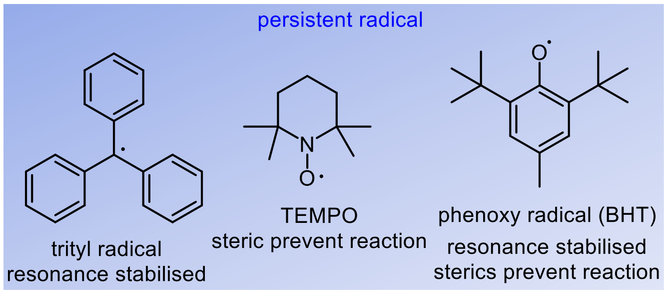
Department of Chemistry

Indian Institute of Technology, Kharagpur

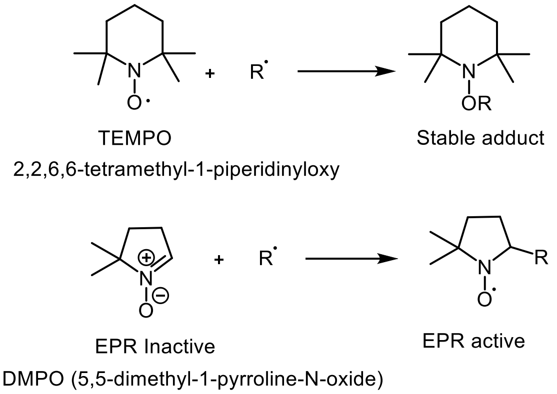
Lecture 21: Radical

Welcome back to this NPTEL online certification course in molecular rearrangement and reactive intermediates. In the last four classes, I started talking about radical chemistry. In today's class, I will talk about some of the radical halogenation reactions, which are well-studied at the undergraduate level. I am also going to talk about some of the persistent radicals, why they are persistent, and how you detect radicals if you do a reaction.

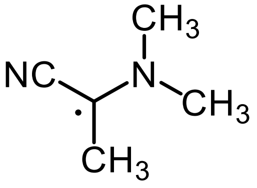
So, let us start with this: which radicals are persistent? So, I talk about how some radical species are very reactive. They form, and they react. They do not have many lifetimes, but some stable radicals can be stored, like TEMPO, as they can be stored in the fridge and used to detect any radicals. Then there are triphenylmethyl radicals, which are also stable radicals because there is resonance stabilization. Also, what is happening with this radical? Although we say this is a resonance stabilized radical, but in the actually, you can see here and there that the final ring is not actually in a plane; they still have a 30 to 40° angle. So, that means it is not always the only factor that the resonance is making them stabilize. There is also a steric factor. That is very similar to the case of TEMPO and in the case of BHT because these radicals are also stable radicals, and the reason is because of the steric effect; because of the steric effect, they cannot have the chance to dimerize.

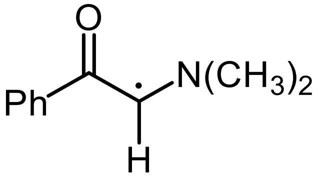


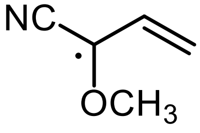
So, these are the radicals that are very stable, and now I will talk about some of the radical traps that mean if you have made a radical, what do you in the generally common practice that radical can be combined with TEMPO? So, if you add TEMPO into the reaction where the radical forms, it can form a stable adduct. This stable adduct can be detected by HRMS. Sometimes, it is possible to isolate and characterize it using NMR spectroscopy. There is another way: It is called a radical trap in this compound, like DMPO. So, the DMPO is EPR inactive. So, again, I told you at the beginning of class that if you are forming a radical, then you can detect it by using EPR spectroscopy. So, here in this compound do not have a radical. So, it is EPR inactive, but once you are forming a radical, it can add to this corresponding carbon-nitrogen double bond here. So, you can see here that radicals can add and generate a new radical species. So, now, this compound is EPR active. So, from the EPR signal, you can also say that you are generating a radical.



Now, I am going to talk about another effect. I think I talked about the electrophilic radical and nucleophilic radical at the time I told you that if you have an electron-withdrawing group, how it is a stabilizing radical, or if you have an electron-donating group, you have non-bonding electron pair, then how that is stabilizing a radical. But here I am going to talk about a captodative stabilization where you are generating a radical with both electrons withdrawing and an electron-donating group. So this type of effect is called a captodative effect, which refers to a phenomenon where organic radicals are stabilized by the substitution, which is an electron-donating as well as an electron-withdrawing group.

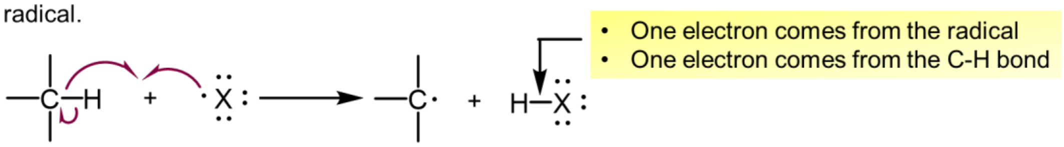






So, now I am going to talk about some of the radical reactions. So, I have talked about already some of the radical reactions like this Barton decarboxylation reaction like the Minisci reaction where you have seen generation of different radicals, and it is going to add to it can either go for hydrogen abstraction, or it can add to a hetero aromatic. But today, I am going to talk about another thing: if you are generating a radical species that is forming from a halogen, then that can abstract a C-H bond here. To form a H-X and a carbon center radical. So, what is happening here is cleaving this carbon-hydrogen bond, and then it gives one and one electron to form this compound, which is a radical species. Knowing this type of radical can also add to an olefin. If the radical adds to an olefin, what is going to happen again? The olefin can be thought of as two electrons. Now, one electron can form a bond with the X to generate a new radical species and form a new bond here.

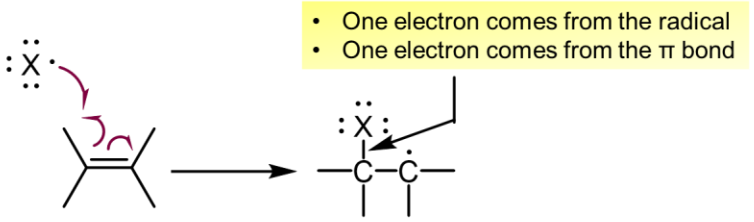
- A radical X• abstracts a hydrogen atom from a C –H σ bond to form H –X and a carbon radical.



- One electron comes from the radical
- One electron comes from the C-H bond

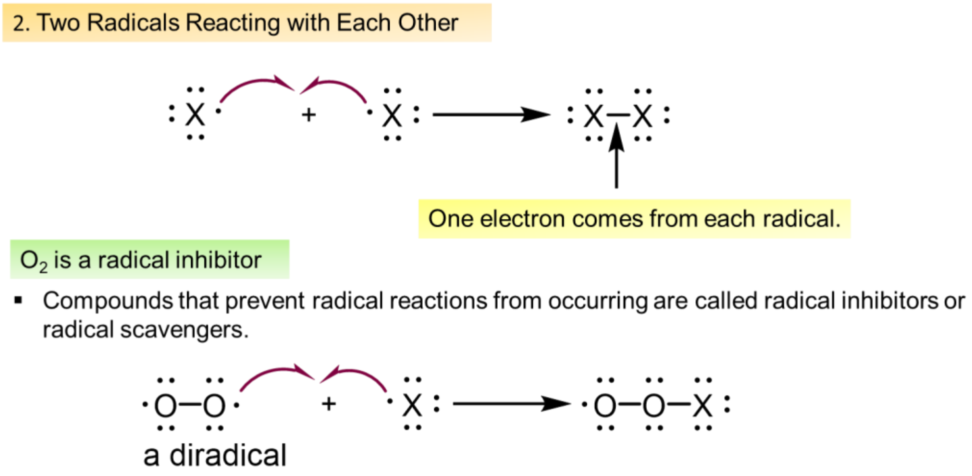
2. Reaction of a Radical X• with a C=C

- A radical X• also adds to the π bond of a carbon–carbon double bond.



- One electron comes from the radical
- One electron comes from the π bond

Then, there are other types of reactions. I think I mentioned at the beginning that they can dimerize one the radical going to form. They can combine to form a dimer. We have also learned that oxygen is a radical inhibitor. Sometimes, we use it if we want to make from an R· to the corresponding alcohol. Then, you can add some oxygen. What is going to happen is if you have a radical species, it can add to the oxygen now; we can say this is a radical scavenger species, but this compound can also convert to the corresponding alcohol as well. We have shown you the type of Barton decarboxylation reaction. Sometimes, you are making the R·, which can also form the corresponding alcohol in the presence of oxygen.



2. Two Radicals Reacting with Each Other

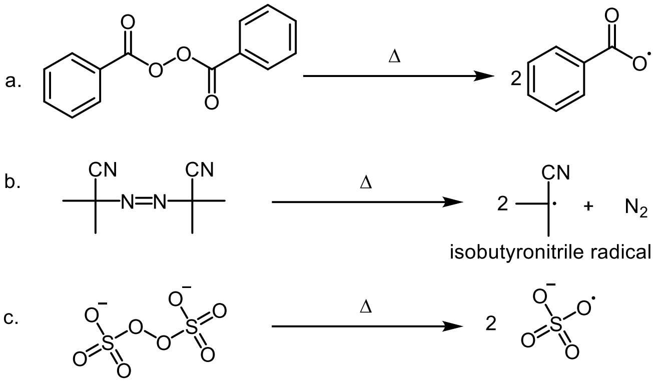
One electron comes from each radical.

O_2 is a radical inhibitor

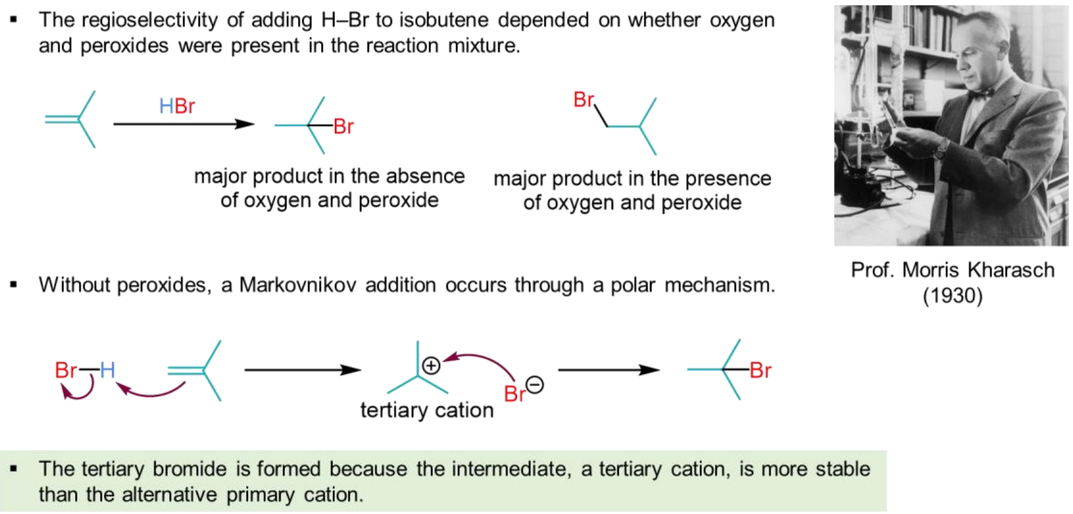
- Compounds that prevent radical reactions from occurring are called radical inhibitors or radical scavengers.

a diradical

So, I talk about the different types of reactions of the radical species. Now, the question comes: you have learned about the formation of the X·. Now, the question comes, how do you generate the X·? So, there are some radical initiators because these types of radical initiators are compounds that have weak bonds like this type of oxygen-oxygen bond. Or you have a compound where the nitrogen can easily get out from here to generate a radical species, or you have this weak oxygen-oxygen bond in this type of radical initiator. Once you put heat into it under heat, this bond is going to get cleaved. The weak bond is going to get cleaved here, or the N_2 is getting out from here. It is going to generate a stable radical. I have already mentioned that if you have a radical species next to the electron-withdrawing group, this type of radical species is stable. So, because this type of species is stable, this type of radical species can participate in different types of radicals. It can abstract hydrogen from other species. As you guys have seen, we have already discussed some of the reactions of AIBN. I think I have already discussed the reaction of AIBN. In this case, it is Barton's decarboxylation reaction. So, you have seen this can abstract hydrogen from the tributyltin hydride to generate the reaction.



So, now I am going to talk about some of the chemistry using benzoyl peroxide and how you generate radicals. So, the first thing we are going to talk about is the regioselectivity of adding the HBr to isobutene. So, I think if you remember the topic that I taught you at the beginning called carbocation, here I talk about how if you take HBr and if you add to an olefin, what is going to happen? We end up getting to this type of product here, forming this type of stable carbocation. So, it is going to form this tertiary carbocation where this Br- going to add to form this product. Now, if you want to get this product as a major product where the bromine will be in the terminal process, how do you get it? To achieve that, you have to use this benzoyl peroxide, which means you have to go for a reaction that goes by a radical pathway, not via an ionic pathway.



- The regioselectivity of adding H–Br to isobutene depended on whether oxygen and peroxides were present in the reaction mixture.

major product in the absence of oxygen and peroxide

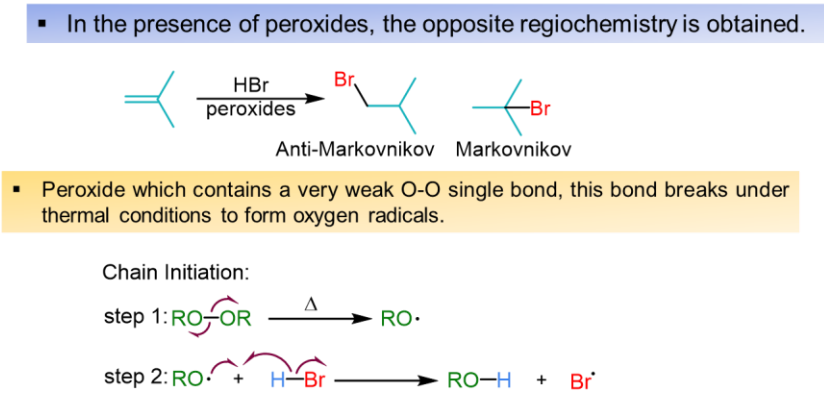
major product in the presence of oxygen and peroxide

Prof. Morris Kharasch (1930)

- Without peroxides, a Markovnikov addition occurs through a polar mechanism.
- The tertiary bromide is formed because the intermediate, a tertiary cation, is more stable than the alternative primary cation.

So, now, we are going to learn that if you take HBr and peroxide and take the isoprene. Now, you end up getting this anti-Markovnikov product as a major product, not the

Markovnikov product that you have seen in the case of the ionic mechanism. Again, how does this reaction happen? As I mentioned, benzoyl peroxide has this weak oxygen-oxygen bond, which is going to get cleaved to generate this type of radical species that can able to go for a hydrogen atom abstraction to generate this Br radical. Now, once you have the Br· it can able to start the reaction. So, what is happening here? I am trying to write that we are forming an H-O bond, which has a bond dissociation energy of 102 kcal/mol. That means you are forming a stable bond at the expense of a weaker bond between this H and Br. So, this reaction will be favorable. So, actually, this bond dissociation energy makes this reaction essentially irreversible.



- In the presence of peroxides, the opposite regiochemistry is obtained.

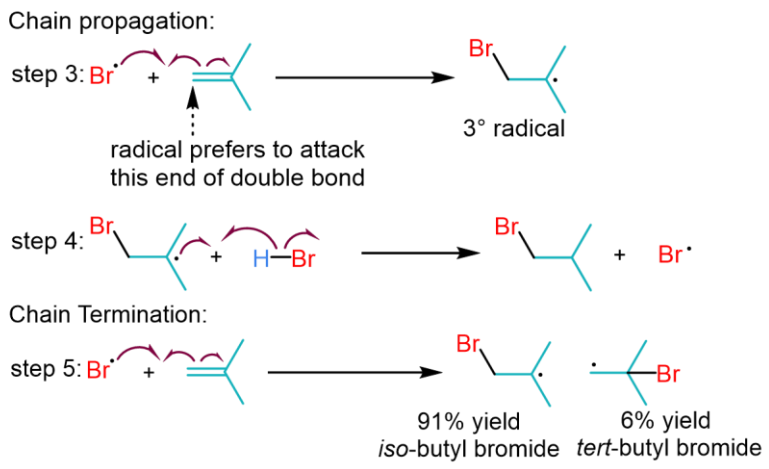
- Peroxide which contains a very weak O-O single bond, this bond breaks under thermal conditions to form oxygen radicals.

Chain Initiation:

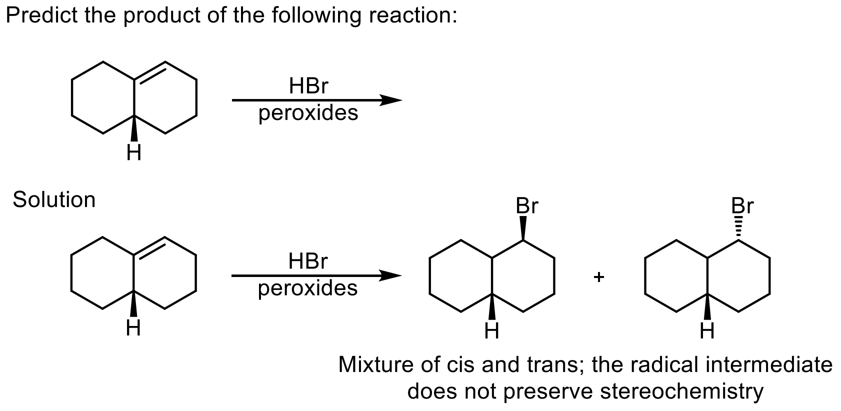
step 1: $RO{-}OR \xrightarrow{\Delta} RO\cdot$

step 2: $RO\cdot + H{-}Br \longrightarrow RO{-}H + Br^{\cdot}$

So, now what is happening this Br· now can add to this olefin here you can see it can add here to generate this type of 3 degree radical which is stable in a radical species. Now, what is going to happen? This radical that is forming here goes for a hydrogen atom abstraction from HBr to get to this corresponding product. And once you have this Br· which is coming out of it, it can take one more equivalent of alkene to continue this reaction.

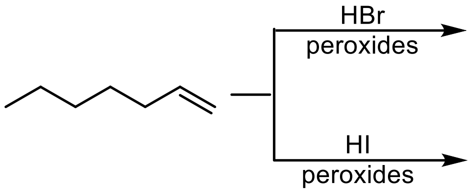


So, now the question comes that if you take this compound, you have a particular stereochemistry here, and then if you try to add HBr with the peroxide, what will be your product? Again, here you have to understand that Br· can add either from this top face or can be add from the down face. So, that way you will end up. So, once it is added here, it is going to form this radical species that is going to go for a hydrogen atom abstraction to form this product. So, you will end up getting a mixture of cis and trans.



So, predict the major product in the following reaction again. If you have HBr peroxide, what is going to happen? I think there will be Br·, which is going to add here to this position. So, you will end up getting a compound where bromine will be added here. So, this will be your major product here.

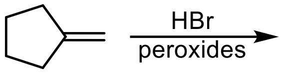
Predict the major product of the following reaction:



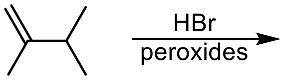
So, what will be the major product in the following reactions? Again, you can see you have an HBr and peroxide, which means you will generate this Br·, which is going to add here and generate a radical species, which can go for a hydrogen atom abstraction. So, it will end up making this compound. A very similar thing is going to happen here: you have a Br·, which is going to add to this type of olefin to get to the corresponding product very similar to the previous example.

Give the major product of the following reactions.

a.

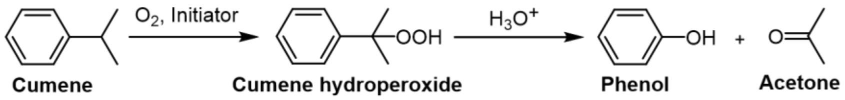


b.

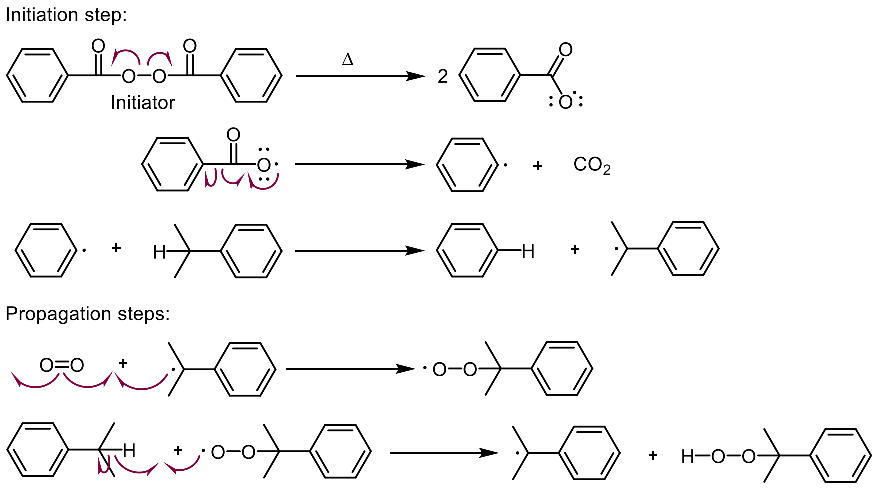


So, moving further, I am going to talk about autoxidation. So, that means autoxidation is the process if you have oxygen and an initiator; if the initiator is able to generate a radical, then radical species can trap oxygen to generate this type of hydroperoxide species. From the hydroperoxide, if you give H_3O^+, it can convert to the corresponding phenol. As I mentioned initially, I think you try to convert the cumene to the corresponding phenol. So, this is a very important process, and that is how people generate tons of phenol, starting from cumene using oxygen and an initiator. It can directly convert from cumene to the phenol.

- Autoxidation refers to oxidations brought about by reactions with oxygen at normal temperatures, without the intervention of flame or electric spark.
- The term is usually used to describe the gradual degradation of organic compounds in air at ambient temperatures.
- A major use of the compound cumene is in the industrial preparation of phenol and acetone in the two-step synthesis, shown below.

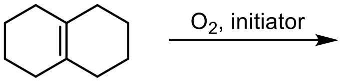


So, what is happening here? We are trying to learn about this autooxidation process. The first thing that is going to happen, as I said, is this benzoyl peroxide is going to cleave this oxygen-oxygen bond. In the presence of heat, this radical species can get rid of CO_2 to generate the aryl radical species that can get this hydrogen atom abstraction to form this radical species here. So, here is what is going to happen after that: this radical species can add to the oxygen, as I mentioned, to generate this type of hydroperoxide, which is going to happen which going to take another hydrogen abstraction going to happen to form this finally to hydroperoxide, which is finally going to convert to the corresponding phenol.



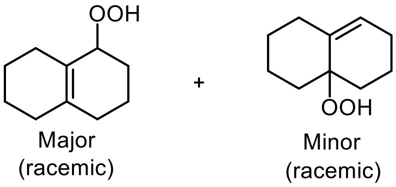
So, many different transformations actually happen through autooxidations. Again, I think there is a question here: if you use this O_2 and the initiator for this particular compound, do you know what is going to happen here? Again, you can see the product is going to form through the process, so this will be a major product that will be your minor product. Now, you can see clearly what is going to happen here in place of the initiator. We are going to generate a radical, which is going to be allylic radical here, and then it can go to take the O_2 to generate, you know, this type of hydroperoxide species. And again, you have a chance of getting to the minor isomer again, the more substituted double bond that is forming here, which is going to give you a major product compared to the other one.

What products would you expect from the following reaction? Indicate the major one and specify stereochemistry if relevant.



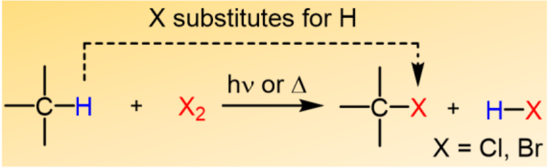
Solution

The major product has the more substituted double bond. (Both are racemic)

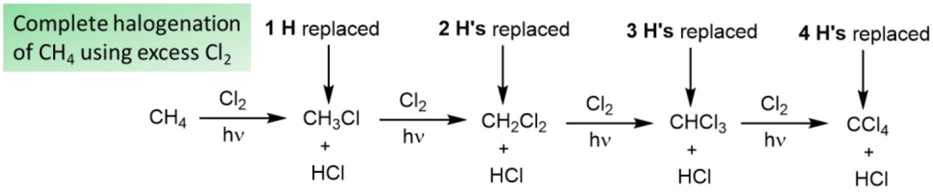


Then, I am going to move to the halogenation of alkanes. So, what is happening here? Now, we are going to learn about the radical halogenation of alkane. What is happening? Starting from an alkane using the halogen source in the presence of light or heat can replace one carbon-hydrogen bond with the carbon-halogen bond. So, the halogenation of alkane is only useful for chlorine and bromine. Of course, the reaction with fluorine is too violent, and it is too slow with iodine. Now, what is shown here starts from the methane. First, there will be replaced one hydrogen with one chlorine CH_3Cl, which can go for CH_2Cl_2, then $CHCl_3$, and then finally, to the carbon tetrachloride. So, you can see a huge change in oxidation number from going from CH_4 to CCl_4. So, this reaction takes place very slowly in a week; you can convert this methane to the corresponding carbon tetrachloride.

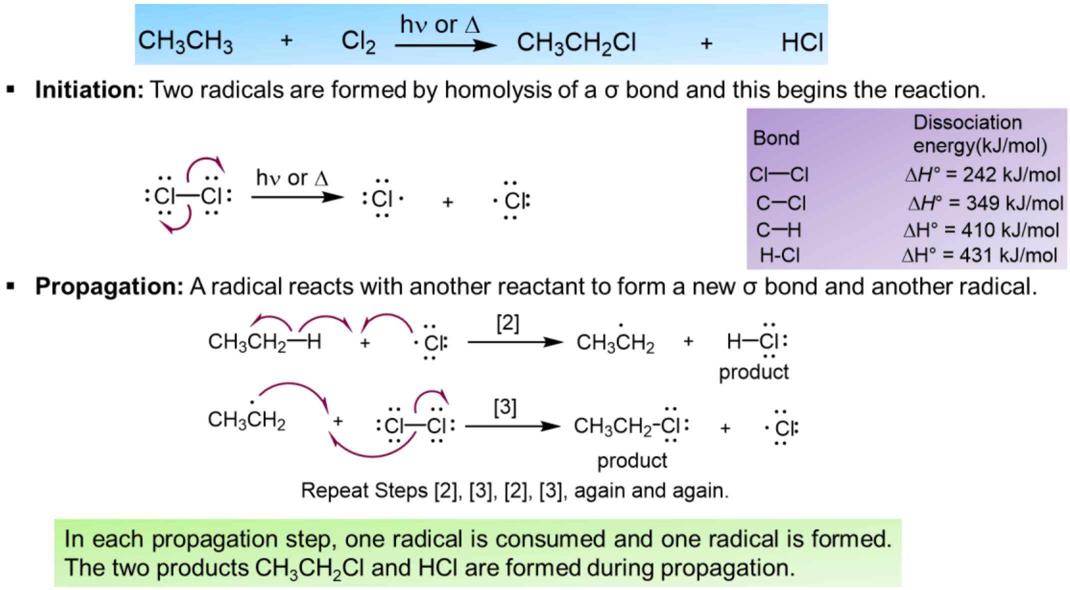
- Halogenation is a **radical substitution reaction**, because a halogen atom X replaces a hydrogen via a mechanism that involves radical intermediates.



- Halogenation of alkanes is useful only with Cl_2 and Br_2. Reaction with F_2 is too violent and reaction with I_2 is too slow to be useful.



So, now I am going to talk about some of the different examples here and some of the elementary steps of this halogenation reaction that is happening here. So, starting from this corresponding ethane in the presence of the chlorine and the radical initiator, it can form this compound CH_3CH_2Cl. So, what is happening in this reaction? You can see you are cleaving a chlorine-chlorine bond, which is a weak bond. Again, you can see the ΔH^{o}. So, the bond dissonance is 242 kJ/mol, and at the same time, you are actually what is happening. You are forming a carbon-chlorine bond at the product with a higher bond energy of 349 kJ/mol. Also, you are forming an HCl, you have to think about the other one, which has a bond dissociation energy of 431 kJ/mol. You are cleaving one carbon-hydrogen bond here, which has a of 10 kJ/mol. So, we are quickly going to learn that. So, these types of halogenation of alkane using chlorine are actually exothermic reactions, which you can clearly see from this bond dissociation energy. So, here is what is happening: the first thing is the propagation. We have already learned about the initiation steps here in this part where the chlorine is going to break to generate this chlorine radical. The chlorine radical can able to go for a hydrogen atom transfer to generate this radical species. Now, this radical species can get chlorine from here to form this corresponding product and the chlorine radical, which can take part in the reaction again.



$CH_3CH_3 + Cl_2 \xrightarrow{h\nu \text{ or } \Delta} CH_3CH_2Cl + HCl$

- **Initiation:** Two radicals are formed by homolysis of a σ bond and this begins the reaction.

$:\ddot{Cl}-\ddot{Cl}: \xrightarrow{h\nu \text{ or } \Delta} :\ddot{Cl}\cdot + \cdot\ddot{Cl}:$

Bond	Dissociation energy(kJ/mol)
Cl—Cl	ΔH° = 242 kJ/mol
C—Cl	ΔH° = 349 kJ/mol
C—H	ΔH° = 410 kJ/mol
H-Cl	ΔH° = 431 kJ/mol

- **Propagation:** A radical reacts with another reactant to form a new σ bond and another radical.

$CH_3CH_2-H + \cdot\ddot{Cl}: \xrightarrow{[2]} CH_3\dot{C}H_2 + H-\ddot{Cl}:$

product

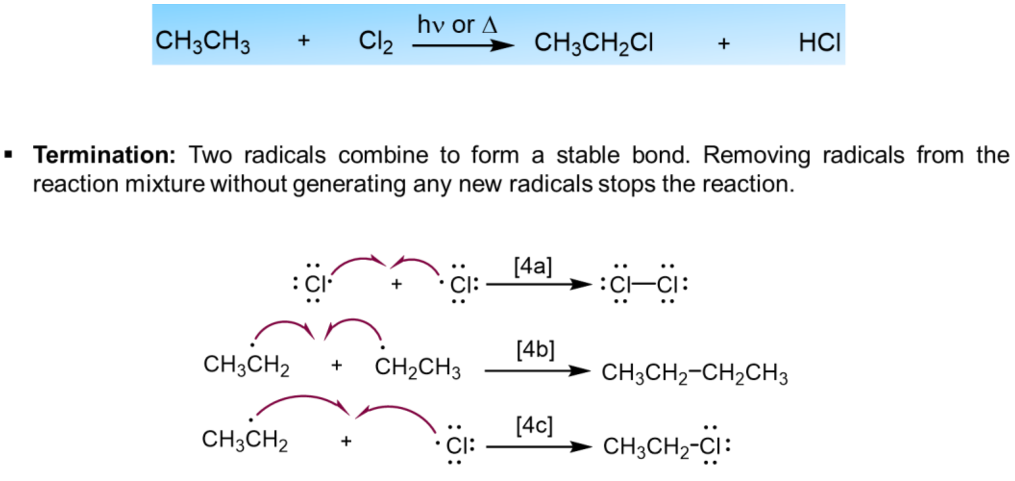
$CH_3\dot{C}H_2 + :\ddot{Cl}-\ddot{Cl}: \xrightarrow{[3]} CH_3CH_2-\ddot{Cl}: + \cdot\ddot{Cl}:$

product

Repeat Steps [2], [3], [2], [3], again and again.

In each propagation step, one radical is consumed and one radical is formed.
The two products CH_3CH_2Cl and HCl are formed during propagation.

Now, you can see what is going to happen in the termination step. As I mentioned, you have this chlorine radical that can go for another reaction, or it can form a dimer, and this type of methane radical also can form a dimer, and this CH_3CH_2 radical can form the corresponding product.



$CH_3CH_3 + Cl_2 \xrightarrow{h\nu \text{ or } \Delta} CH_3CH_2Cl + HCl$

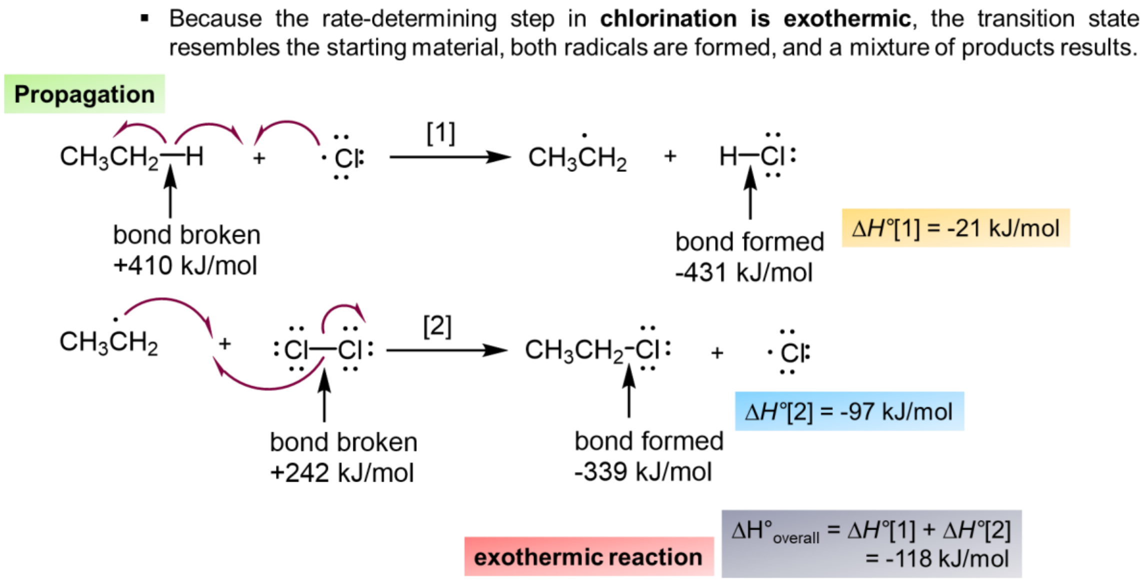
- **Termination:** Two radicals combine to form a stable bond. Removing radicals from the reaction mixture without generating any new radicals stops the reaction.

$:\ddot{Cl}\cdot + \cdot\ddot{Cl}: \xrightarrow{[4a]} :\ddot{Cl}-\ddot{Cl}:$

$CH_3\dot{C}H_2 + \dot{C}H_2CH_3 \xrightarrow{[4b]} CH_3CH_2-CH_2CH_3$

$CH_3\dot{C}H_2 + \cdot\ddot{Cl}: \xrightarrow{[4c]} CH_3CH_2-\ddot{Cl}:$

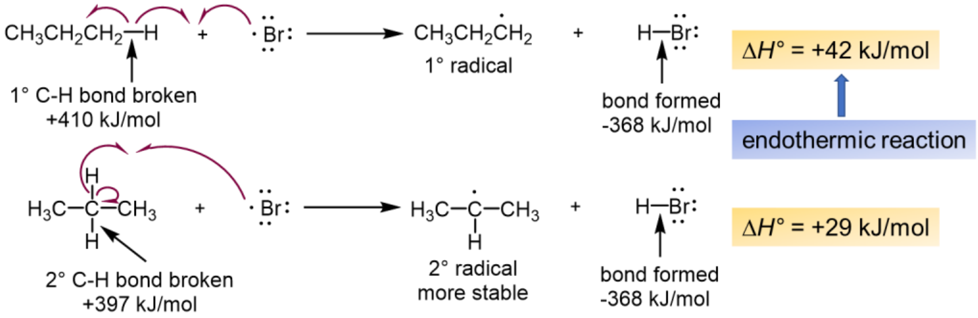
So, now, as I mentioned, the chlorination is exothermic. You can see from the bond dissociation energy of these different elementary steps. Also, you can clearly see here you are breaking a carbon-hydrogen bond of 410 kJ/mol, where you are forming a bond of 431 kJ/mol. At the same time, you are breaking a chlorine-chlorine bond, which is a weak bond of 242 kJ/mol. You are forming a bond of 339 kJ/mol. So, you can see this reaction is actually exothermic.



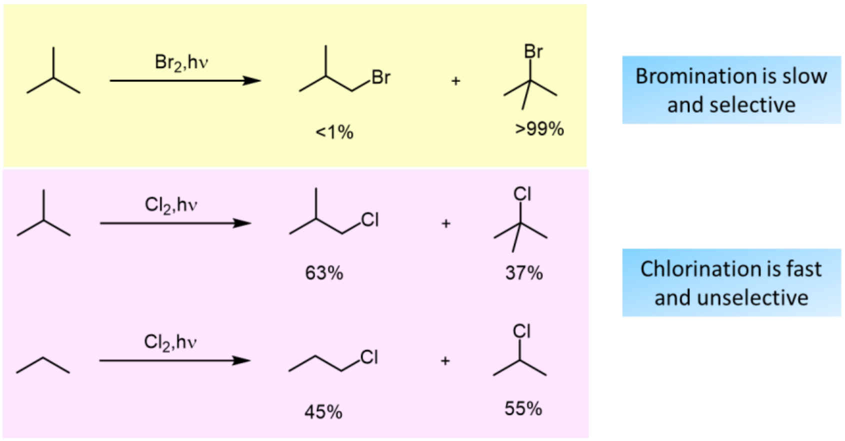
- Because the rate-determining step in **chlorination is exothermic**, the transition state resembles the starting material, both radicals are formed, and a mixture of products results.

So, now we are going to see that if you go for bromination, then things are a little different. What is happening here? In the case of bromination, your C-H bond is 410 kJ/mol, but the hydrogen of the H-Br bond is actually weak. It is only 368 kJ/mol. So, now you can see that the reaction is actually an endothermic reaction happening here. Now, the question comes that two different scenarios can happen:. It can either abstract this from the terminal in a position where it can go for hydrogen abstraction, or it can go for hydrogen abstraction from this internal hydrogen. So, now, if you see that the internal C-H bond is even weaker. At the internal C-H bond is weaker than the terminal one, what is going to happen is you end up generating this more stable radical, which is going to give you the corresponding product as a major product.

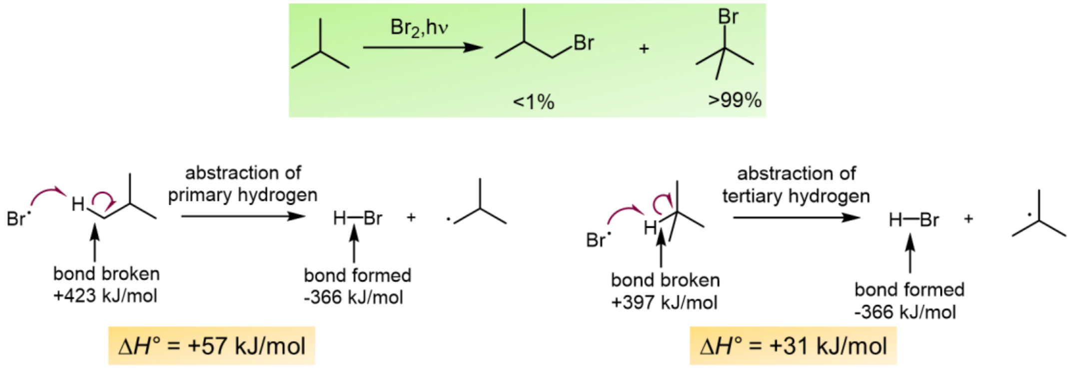
- Because the rate-determining step in **bromination is endothermic**, the more stable radical is formed faster, and often a single radical halogenation product predominates.



That is why once you go for bromination, you end up this product as a major product instead of this one as a minor product. However, when you go for chlorination of this same compound, you get a 63% yield of this primary and 37% of this tertiary. So, chlorination is fast and unselective, but bromination is slow and selective.

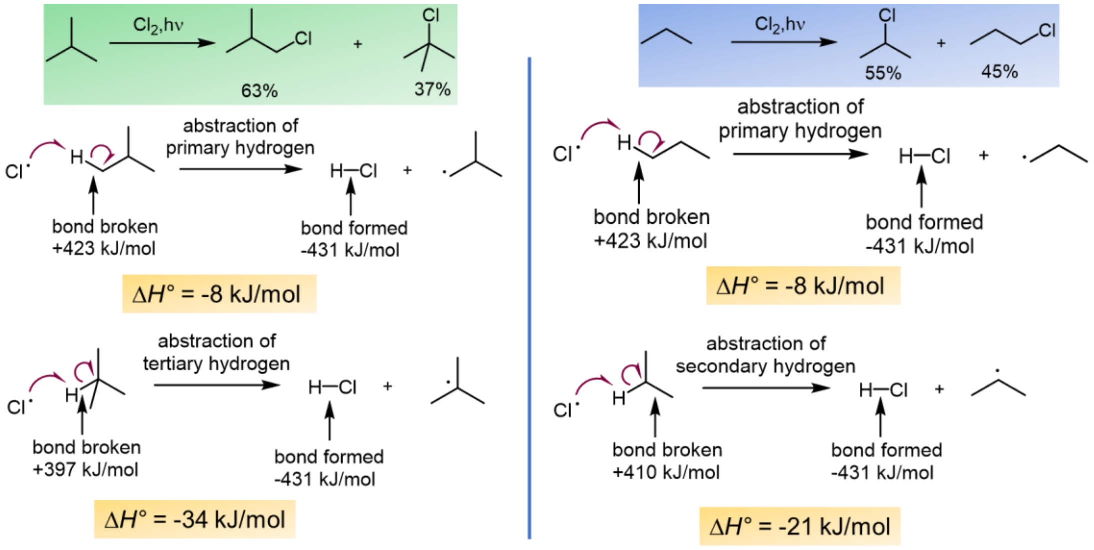


So, we will try to understand what is happening here very quickly. As I mentioned, one of the important things about bromination is that it is an endothermic reaction. So, because of that, and as you have seen, the bond dissociation energy of this internal bond's C-H bond is less than the terminal one. Because the rate-determining step of the bromination is endothermic, the more stable radical forms often lead to the product. That is why you ended up making this product a major product here.



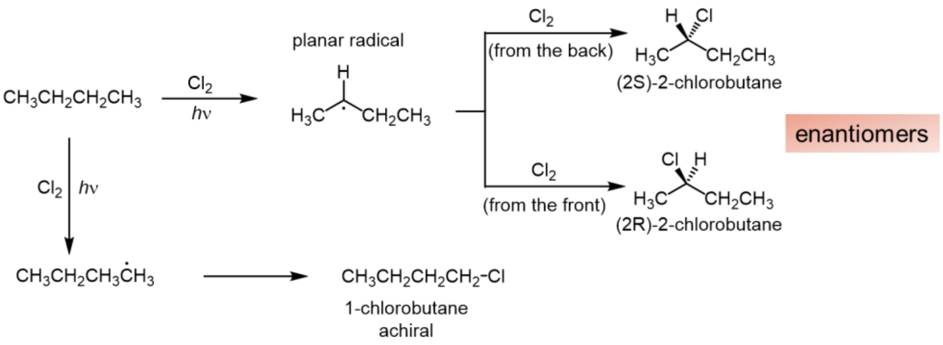
- Because the rate-determining step in bromination is endothermic, the more stable radical forms faster, often leading to a predominant single radical halogenation product.

However, in the case of chlorination, as I mentioned, chlorination is an exothermic reaction. So, because of that reason, the formation is an exothermic reaction. You will see that your transition will be mostly your starting material. So, that is how, because the formation of you can see this reaction is not very selective, you end up getting to the mixture of products where this one is going to give you the major and this one is going to give you as a minor.



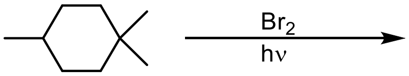
So, there is another example: if you start with this compound, if you can abstract a radical from this corresponding CH_2 from the internal one, then it can form this corresponding planar radical. If chlorine attacks from the front and back, it can generate an enantiomer.

This does not happen if you take a terminal position, and then it will end up making a corresponding 1-chlorobutane. So, if it is an internal one, it can form the enantiomer, and here, it can form just a linear compound.

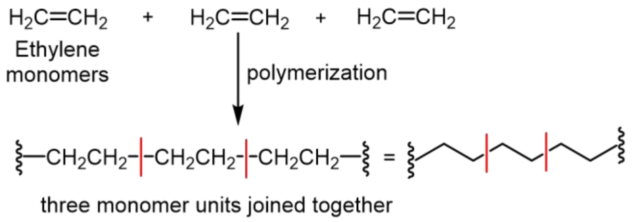


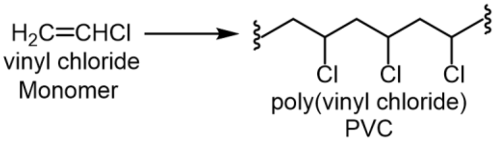
So, for example, of bromination, you predict the major in the following reaction; you can see you have this. So, this is the internal one. Here, you have a terminal. So, it will be the bromination as I mentioned, it is going to prefer the internal one. So, you will end up making a product where you have a bromine in this position. So, I talked about chlorination and bromination in the previous case, and you can see that one is exothermic, and the other is endothermic.

Predict the major product of the following reaction:



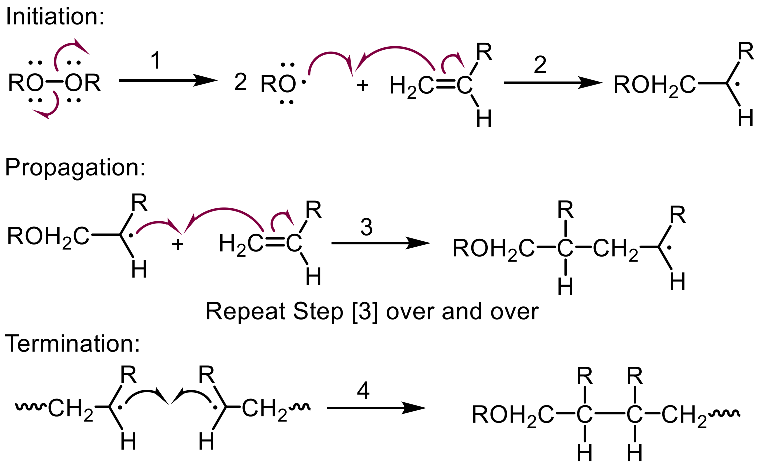
So, now I am going to talk about the polymerization. So, what happens if you have this ethylene as a monomer, and now this can form a polyethylene? So, after the polymerization, what is happening here is that you can also introduce the corresponding chlorine. Starting from the vinyl chloride monomer, it can form a poly(vinyl chloride) PVC, a very useful polymer.





PVC blood bags and tubing

So, now you can see how this type of polymerization is happening, again the very similar type of reactivity we have learned. So, this benzoyl peroxide reactivity is very important because once the initiation is done and this oxygen-oxygen bond is cleaved, it can generate this corresponding radical here. Once this radical is forming, you can see it will act to this corresponding olefin here. Once it acts on the corresponding olefin, it can generate this radical species here. So, now you can see how this radical species is going to act. So, first, this is an initiation process to generate this radical. Once you are forming this radical, it is just this secondary radical. So, this can add to another olefin, and now it is forming another radical species here. So, this can happen again and again and again. As soon as you use this type of radical initiator in this reaction, you can end up making a polymer here. A very similar thing can happen here, and then at the end, what is going to happen after this propagation happens is it can finally form a dimer, which means two of these radicals are going to form, which will form a dimer to form this finally a polymer in it here. Again, you will see that this process is called head-to-tail polymerization. So, this is the head, and that is the tail, so that is finally combined to terminate the process.



So, in this class, what is happening? I have already started with the radical initiator. I talked about the persistent radical, the TEMPO, and then the DMPO and how they can be useful in finding a radical trap. I talk about persistent radicals; I talk about the triphenylmethyl radical. Then, I talked about the different types of radical initiators, how they form in case of heat, and how they are very useful. First, I have already shown them that they have a weak bond that is getting cleaved to generate the radical initiation step for several different transformations. And we also end up talking about the polymerization using peroxide. I also talk about chlorination and bromination. It is very important. You have seen that chlorination is not selective, but bromination is very selective. One is exothermic, and the other is the endothermic reaction. So, again, I think you can follow these books for this discussion about radical chemistry, and I hope you guys like this course. Thank you for coming to the class. I will see you guys in the next class.