

Lecture 18A • 11/09/11

Radical reactions

I want to remind all of us the primary difference as far as representing radical mechanisms versus electron-pair mechanisms, which is that we have these half arrows that we use because each half arrow shows where only one electron is going. Let's look at the specific reaction we have today, which is free radical halogenation. This is a reaction whose overall synthetic utility is to convert alkanes into alkyl halides. [This is one of the six aspects of a reaction that we worry about]. Second is the set of reagents normally used; third are the set of conditions. Synthetic utility in this particular case is to take an alkane and make an alkyl halide. The reagents are diatomic chlorine or bromine. The conditions are that it requires light; often a shorthand used to represent light is to use $h\nu$, the same formula that we use to represent the energy of a photon. Generally, when we say light, it means, most frequently, UV light. Along with knowing these three aspects of the reaction, we're going to discuss the mechanism and what consequences that mechanism has in terms of stereochemistry, and, particularly, regiochemistry. [recommendations for flashcards; mechanism on one side, other aspects on the other][warning of workload for the quarter][why pre-meds take o-chem]

Let's tackle our first reaction. This is called [free] radical halogenation. The reason that light is required is the first step of the mechanism is for the halogen to dissociate homolytically, which means one electron goes each direction. Again, notice that I'm using these half arrows since each one represents where just one electron is going. That will produce two bromide radicals. The next step in the reaction is that that radical will react with an alkane. We should know at this point that tertiary carbocations are more stable than primary and secondary, and it turns out, for similar reasons, that tertiary radicals are more stable than primary or secondary radicals. It's going to be, in this case, more likely that this tertiary hydrogen reacts. Bromine can introduce an electron into that system, which causes the bond to break. Notice the two arrows going together; that's trying to show that hydrogen ends up with bromine. Then there's one more arrow that's needed because the bond has two electrons in it. One ends up combining with bromine to make hydrogen bromide; the other one is left behind on the carbon. The second step in this part of the process is that the radical that was just formed reacts with yet another molecule of bromine. You need as much bromine around as you do have of the alkane. At the end of that step, we'll have our alkyl halide, and we'll regenerate a bromide radical.

The first step of this process is called initiation. Later we'll talk about initiators, compounds that encourage the formation of radicals, or compounds that themselves turn into radicals. The second part of this process is called propagation. Why is it called propagation? Because this whole process, overall, is known as a chain reaction. Why? Because you start with a bromide radical, you end with a bromide radical. As long as you have more alkane around and more bromine around, this reaction keeps going and going and going and going, repeating the same process every time – that's a chain process. You initiate reaction; it'll then keep on going or propagating, while you still have enough reagents around; and then there's one of several possible termination steps. If this reaction went perfectly, if there were no by-products, you would eventually end up at the point where you might have an alkyl radical and a bromide radical, where the two of them could combine with each other, which would make the desired product, the same alkyl halide, but you don't make another radical at the same time. So although you make the same product, this reaction would stop at this point because you consumed the radical; you haven't produced a new radical. This is if things went well – there is always the chance of other termination steps. This is the problem with radical chemistry: is that radicals can do lots of side reactions. A less harmful side reaction would be if two bromide radicals happen to encounter each other in solution to remake bromine – which wouldn't be so bad if you still had light around. The bromine could re-break up and continue to react. But you also get other side products: in the same way it would be possible for two bromides to encounter each other in solution, it would be possible for two alkyl radicals to encounter each other in solution. There's one more event that could occur, which is instead of either a bromide or alkyl radical combining, you could have what's called abstraction, meaning that it pulls, in this case, a hydrogen of the molecule. But if it does, that makes a radical that can combine with the radical that's already on there. You might remember that there is this process called disproportionation, which is exactly what this is: you're taking two systems that had equivalent structural situations, they were both saturated – meaning all single bonds – with just one radical. But you end up with a set of products where in one case you have a single bond still for HBr, but then you have a double bond on what used to be the alkane. This is disproportionation – the uneven production of a single and double bond. Just this portion of it is abstraction – a radical pulling hydrogen off a molecule. All four of these termination steps can and will happen.

The reaction starts by making the halogen radical. That goes through this cyclic dance where you keep reacting it with an alkane, which then goes back and reacts with another molecule of the halogen, to remake the same bromide radical. Then, there's one of these possible termination steps that can bring the process to a halt – except for the reformation of bromine; that in the presence of light could keep on going on. Does it matter which termination step happens? Not really, we just need to know that there are these different possibilities. Even in a well-behaved reaction, you're going to have small traces of by-products.

Regiochemistry and chemical equivalency [reworded]

If I threw one chloride radical at that molecule, how many unique products could form? Four or five, depending on whether or not we're worried about stereochemistry. To keep things simple for the moment because I want to focus on regiochemistry first, let's say I ignore stereochemistry. If I ignore stereochemistry, how many unique products are there? Four. Why? I could have substitution at that same tertiary position I showed in my first example. Or, I could have substitution at the secondary position; this is the one that does have a stereocenter. Now we have two other products, though: one where the chlorine substitutes at this primary position, versus having substitution at the other primary position. One common mistake is to lump all primary hydrogens together and call them equivalent. But, as we can see, we have two very distinct products that would form. In one case, we would have 1-chloro-3-methylbutane, and in the other case we have 1-chloro-2-methylbutane. So four unique products.

In terms of regiochemistry, we can answer: which one of these is more likely to form, but we have to discuss a little bit of a reaction coordinate diagram first. Why? Because, it turns out, for halogenation with a chloride, the first step of the reaction, the first propagation step of a chloride reacting with an alkane form HCl plus the alkyl radical, ΔH is normally less than zero, so it's exothermic. Now we're going to have our first chance for me to talk formally about the words stable. Because, really, to talk about things that are stable means you have to compare two equivalent chemical systems. If I have butane versus dodecane, twelve carbons versus four, those are not equivalent molecules. Even if I have the same reaction going on for both of those molecules and I might be able to make some statement about how much energy it takes in this molecule versus another one, since they're not the same molecule, I can't really say this one's more stable than the other, cause it's comparing two completely different systems. In this reaction coordinate diagram I'm just about to show you, I'm going to take the same starting reagents – the alkane and the chloride radical, and I'm going to show you different outcomes. But because they all start at the same point, it is perfectly valid for me to put all of them on the same reaction coordinate diagram. Because of this, these different outcomes, which will have different energy levels, the lower the energy, the more stable. I can now use that word properly because now I'm comparing different results from the same starting point. [story about stable] If I say that there's two completely different molecules, then you might have a molecule that in that particular case it's a secondary carbocation that forms but that might not require as much energy as a tertiary carbocation in some other rare case. In terms of raw energy, you might have a secondary carbocation that, everything being equal, forms more easily than a tertiary. But if on that same molecule you had the ability of a tertiary carbocation to form, it's going to be lower in energy than the secondary. So within that molecules, it's always correct to say tertiaries are more stable than secondaries, but from one molecule to the next, in terms of just the numerical value of energy, it might not be a correct statement.

With all that preamble, let's just say a tertiary radical is more stable than a secondary, which is more stable than a primary, and if this is an exothermic process, that means I'm gonna have these three different energy possibilities occur: tertiary, secondary, and either one of the primaries, in this case. That means that there's going to be three different curves I could draw. If this is a one-step process, in all cases I'll have just one transition state, and the transition states, in fact, will be very similar in energy. The secondary's transition state will be a little lower; the tertiary's will be a little lower still. Lower activation energy means higher rate of reaction. Because that activation energy is smaller than the primary's, that explains why the tertiary radical forms more easily. On top of this graph, there is one principle behind it that you need to know, which is the Hammond postulate. The Hammond postulate says this: that in a transition state, the structure of that transition state will more closely match either the product or reactant or intermediate that is closer in energy to that transition state. The structure of transition state more closely matches the structure of the product, reactant, or intermediate that is closer in energy to the transition state. The point of this Hammond postulate is so that I can look at the reactant, the alkane, and say: the transition states for the three possibilities – making the primary versus the secondary versus the tertiary radical – those transition states are going to be close in energy, cause they're all close to the original starting material, so there's not a lot of differentiation between these. In this case, since the transition state more closely resembles the reactant, there's not a huge difference in the activation energies for forming the primary versus secondary versus tertiary carbocations. [double dagger for transition state]

The relative rates of reactivities of a primary versus a secondary versus a tertiary hydrogen with the chloride radical is 1:4:5; it's more like 1:3.8:5, but I like round numbers. Five times more quickly the tertiary will form more than the primary. Let's go back up to the example we working on, where we made these four different products. Based on that idea that the tertiary forms five times more quickly than the secondary than the primary, which of these products is going to be the major one? First? Wrong. I know you're going to look at me and say: you just told us tertiary is more reactive. How many tertiary hydrogens are there? One. How many of this kind of primary hydrogen are there on this molecule? Six, because this position is the same as this position, but not the same as the other primary position, because it makes a different molecule if it reacts at that particular carbon; there are six hydrogens that are all the same. So if you have six hydrogens, times relative reaction rate of one, then you get a relative distribution of that product of six. For this other primary, there's three hydrogens times one, which gives you three; for the secondary, there's only two hydrogens, but they react four times as quickly, so it has a distribution of eight; and then the tertiary, there's only one hydrogen, so even though it reacts five times as quickly, it only has a relative distribution of 5. This is the main product of the reaction. This is regiochemistry; regiochemistry means where does the functional group end up. One thing you need to know about the radical reaction is that every possible product will form; every possible position that a hydrogen can be removed, we'll make a product. But then which is the most likely product depends on the combination of how many hydrogens there are – what's the probability that it's going to be reactive – multiplied by its relative rate of reaction, how hot is the hydrogen to react.

Let me summarize that: in radical halogenation, every possible product being generated from every type of removable hydrogen will form; the distribution of products depends on the number of hydrogens involved, multiplied by the relative reactivity of that hydrogen. This is for chloride; how does it change when we go to bromide?

It turns out that primary versus secondary versus tertiary reactivity is 1:80:1600, if you round the numbers up. Why this huge differentiation now? Chloride, primary versus secondary versus tertiary wasn't that much different, which makes free radical chlorination not the best reaction. Bromide works much better, although overall the process is slower. Why? The reaction step of going from a bromide reacting with an alkane to halating that hydrogen bromide form and then the radical is endothermic. That means the alkyl radical that forms is higher in energy. Since the transition will now be closer in energy to the product, there's more differentiation between the different activation energies. If we want a combined reaction coordinate diagram from this case, it would look like the following.

Since transition state this reaction step more closely resemble the product; there's a greater difference in the activation energies for the formation of the primary versus secondary versus tertiary radical, which is why we have 1:80:1600 being that difference between relative rate. If we had the same reaction, if we use the same alkane, reacted it with bromine and light, then we'll get the same four types of products: substitution at the primary, substitution at the secondary; substitution at two different primaries. Now if we look at the relative distribution, there may only be one hydrogen, but it reacts 1600 times as quickly, so we get a relative product distribution of 1600. For secondary, there's only two hydrogens; it's got a relative rate of 80, so you'd get 160 relative distribution. For the primaries, we have six times one and three times one. The amount of primary product will almost be non-existent in this case. When possible, if halogenation is going to be done, bromine is used instead of chlorine, because of its much greater regiochemical selectivity. Tertiary is more reactive than secondary and more reactive than primary, and bromine, much better than chlorine [memorization] It's not that those radicals are more reactive; forming the radical is more reactive, which is the same way of saying it's more stable.

Chlorination, because it's not as selective, is usually used only when you have symmetric molecules. An example your book gives of using chlorination is cyclohexane, because no matter which of the hydrogens gets removed, you're going to make chlorocyclohexane. Iodine is not used because the reaction, overall, is endothermic, which means in light alkyl iodide decompose – means the reverse reaction, the iodine actually comes off, and you'll form either an alkane or, by disproportion, and alkene. [If] you take an alkyl iodide, put it in light, and you'll see, if it's a clear solution to begin with, it starts turning yellow, because iodine gets released. [The reaction] is more exothermic for chlorine than bromine, which is why chlorination, even though it's less selective, because of it, it's also a faster reaction. Fluorine is not used because the overall reaction is too exothermic, which results in there being almost no difference in the activation energies for forming different kinds of radicals. For fluorine, the differentiation between primary, secondary, and tertiary is roughly 1:1.2:1.4. Fluorine just reacts with anything, it's so darn reactive. Think about fluoride dot, fluoride radical; it just gets that one electron from somewhere and it's fluoride. It's the most electronegative element on the periodic table; it has the highest electron affinity, so it just pulls electrons from anywhere it can get it. In this case, it means it has such poor selectivity that it's just not used – not at least if you want to make a monohalogenated product. A side product that can form is that if multiple halogenation occurs. For fluorine, that's done on purpose; that's how we get things like teflon.

Radical halogenation

1) Synthetic utility : alkane \rightarrow alkyl halide; 2) Reagents : Cl_2 or Br_2 ; 3) Conditions: $h\nu$ (UV light); 4) Mechanism; 5) Stereochemistry; 6) Regiochemistry

Hammond postulate – The structure of the transition state more closely matches the structure of the product/reactant/intermediate that is closer in energy to the transition state. In this case, since the transition state more closely resembles the reactant, there is not a huge difference in the activation energies for forming the 1° vs 2° vs 3° carbocations. Relative reactivity with $\text{Cl}\cdot$ – $1^\circ : 2^\circ : 3^\circ$ hydrogen $\rightarrow 1 : 4 : 5$

Regiochemistry – In radical halogenation, every possible product (generated from every type of removable hydrogen) will form. The product distribution that forms depends on the number of hydrogens involved multiplied by the relative reactivity of that hydrogen.

Relative reactivity w/ $\text{Br}\cdot$ – $1^\circ : 2^\circ : 3^\circ$ hydrogen $\rightarrow 1 : 80 : 1600$. Since the transition state in this rxn step more closely resembles the product, there is a greater difference in the activation energies for the formation of the 1° vs 2° vs 3° radical.

When possible, bromine is used instead of chlorine because of its much greater regiochemical selectivity.

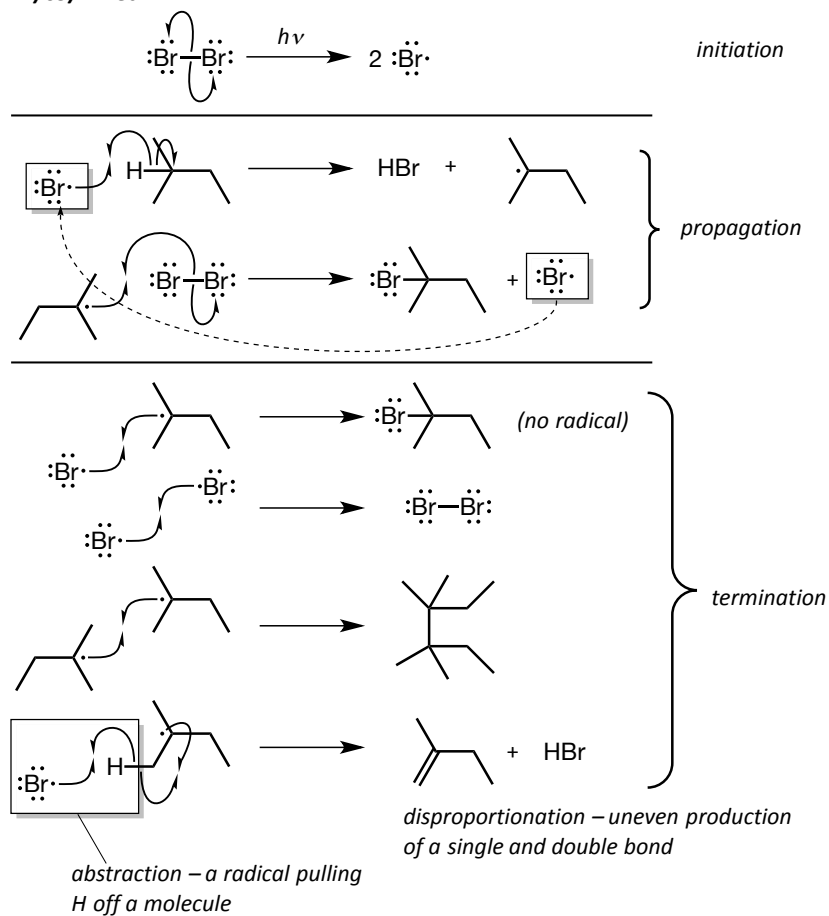
Chlorination is normally not used because of poorer selectivity, or if it is used, it is used on symmetric molecules.

Iodine is not used because the rxn overall is endothermic \rightarrow in light, alkyl iodides decompose.

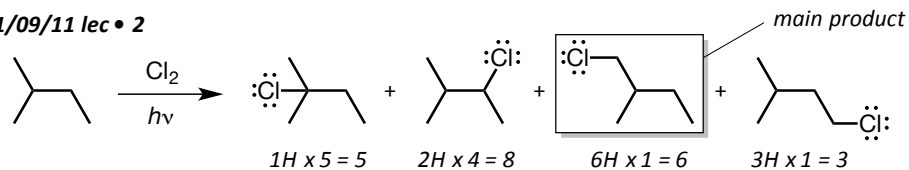
Fluorine is not used because the overall rxn is too exothermic, which results in there being almost no difference in the activation energies for forming different kinds of radicals. $1^\circ : 2^\circ : 3^\circ \rightarrow 1 : 1.2 : 1.4$

Structures

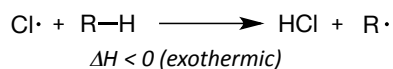
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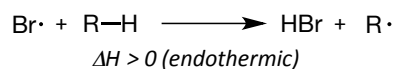
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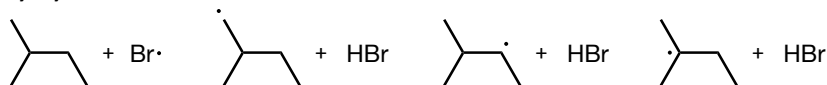
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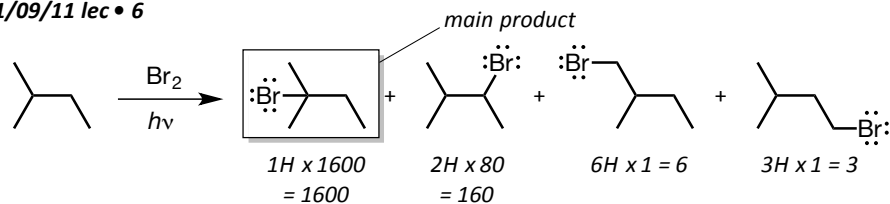
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