Lecture 18B • 11/10/11

Six aspects of a reaction

Free radical halogenation is a reaction that allows you to convert a plain old alkane into an alkyl halide. [The first of the six aspects of a reaction] was the synthetic utility – what's the use for that reaction. For this reaction it would be to convert an alkane to an alkyl halide. Each of the different reactions that we're going to learn generally has a characteristic reagent or set of reagents. The reagents that could be used in this reaction are either diatomic chlorine or diatomic bromine. Conditions: sometimes reactions have to be done under certain specific conditions like certain temperatures, maybe even a sequence of temperature changes. In free radical halogenation, that's frequently done in light. Often light is abbreviated using the same symbol to represent the energy of a photon. Generally, if you're using this symbol, you're implying just that it's light but it's UV light. Why? Because that happens to be right in the right energy range to cause compounds like chlorine and bromine to dissociate. One of the main features of a reaction is mechanism. By knowing the mechanism, we can then talk about what are the stereochemical consequences of the reaction and, even more in this case, we're going to talk about the regiochemical consequences – the fact that there can be a whole multitude of products that can form, and we need to discuss which one's going to be the more likely one. For each reaction we're going to learn, we're going to hit these six items. [flashcards]

Let's look at the mechanism for this free-radical halogenation. It can be a really useful reaction, because alkanes really aren't reactive, generally. There's no good polarity difference on the molecule or on the bonds, so there's no place for other molecules to get a grip on, you could say. The way that this reaction starts is by either chlorine or bromine dissociating; I'll start out with bromine as my example reactant. In the presence of light, bromine can break homolytically. Everything we see today is going to be the exception for the quarter; it's going to be a single-electron mechanism. Notice I'm using the half arrows. Because the bond contains two electrons, that means we're going to need two arrows, since each arrow only shows where one electron goes. I'll form two bromine radicals. The next step is for that bromine radical to then react with an alkane; a good example molecule I'll use for that is 2-methylbutane. Let's just say that I'm going to show the removal – or what's called the abstraction – of this hydrogen from a tertiary position. The bond has two electrons, so I'm going to need two arrows coming from that bond. I'm going to draw one of them pointing towards the bromine, so it's going to imply that that electron, with the hydrogen, is going to connect to bromine, which means we're going to produce hydrogen bromide as a by-product; then, we'll have an alkyl radical. That alkyl radical will turn right around and react with another molecule of bromine. When it does that, we'll get our product – a haloalkane – and then we'll make a bromine radical, which is exactly the first thing that we started with to attack the alkane. In fact, this process of free-radical halogenation is classified as a chain reaction, cause once the reaction starts, as long as you don't run out of reagents, you keep generating the exact same reactive species, so it keeps on reacting, forming, reacting, forming, over and over again. A chain reaction is a mechanism that repeats continuously until reagents run out, since one of the products produced is itself a reactant.

Let's put some names to the different phases of this mechanism. The top step happens all by itself; that is known as the initiation step. The next two steps together, since it's the pair of them that repeats and you keep the reaction going and going, the couple is called the propagation step. Then, there are one or more termination steps that can occur. I used this term abstraction earlier – in this case, the abstraction refers to the removal of a hydrogen. One of the possible termination steps is that two bromide radicals might happen to find each other again in solution to remake Br2; fortunately, that termination step leads to one of the reagents, so the reaction wouldn't necessarily end overall if this occurred if there was still light being used to reform radicals. Another possible termination step would be if a bromide radical reacted with an alkyl radical. That would make the desired product, but that reaction, at least that branch of the reaction, would end, because you haven't regenerated radicals; you made the product without making another radical because you combined radicals. Of course, if a bromide and an alkyl radical could react with each other, maybe an alkyl radical would happen to interact with another alkyl radical. That, of course, would be an unwanted reaction because you'd get a by-product. One of the unfortunate things about radical reactions, though, is that it's very difficult to control. There's one other common by-product that could form, where instead of two alkyl radicals combining, you could have one radical abstract a hydrogen from the other. If that was to occur, you'd make another radical, which since in this case they're radicals that are right next door to each other, they could combine to make a pi bond. You end up with two products that have similar backbone, but one is a saturated, fully singly-bound compound, the other one, you produce an alkene; that unequal distribution is called disproportionation. For our purposes, we don't care which of these happen, it's just the fact that they all can happen. Since you have a molar molar equivalent of your alkane and bromine, other than the regiochemical effect that we're going to talk about in a moment, there is a good chance that you're going to get the alkyl halide product. However, it is possible that you might have one alkane that reacts twice, so it is kinda a messy reaction. This is sequence: initiation – again either chlorine or bromine splitting up; we have this two step back-and-forth reaction of the halide making an alkyl radical and an alkyl radical reacting with a halogen to make a halide radical; and then we have one of several possible termination steps.

If you have light hitting a sample of this reaction, you'd have multiple molecules of bromine falling apart at once. Those individual radicals could start their own chains – chain reaction. Some may terminate; if you're continuously bombarding it with light, others are starting because you're making more bromide radical. Some are starting and stopping all during the reaction. [radical scavengers]

Let's get into the regiochemical effect of this mechanism. I've shown one possible product of this reaction. [There is this concept of chemical equivalency] – when is it that two hydrogens, for example, on the same molecule could be called the same hydrogen. If I had 2-methylbutane, and let's say for the moment I don't worry about stereochemistry, I don't worry about whether a stereocenter is generated or not. If I put aside that worry, how many unique products could be formed in this reaction? Instead of talking about bromine first, I want to talk about chlorine. Same mechanism, same results, in terms of same type of product – but how many [different] products would we get if only one chlorine reacted? We have the tertiary center I've already showed reacting, so there's one type of product. What other unique kind of product could we get if we just put a chlorine somewhere on this molecule? We could put it here; would I generate a different product if I put it on the bottom one versus the top? No, you would not get a different product since both methyl groups are hooked up to the same positions, and since from that junction point the rest of the molecule from the perspective of these two methyl groups, the two methyl groups are equivalent. But they're not the same as this other terminus of the molecule, because over here on the righthand side, that's a CH3 group attached to a secondary carbon, versus where we had initially, which those methyl groups are attached to a tertiary carbon. The two ends are not the same as each other, even though they are both primary carbons; they're different primary carbons. If we ignored stereochemistry, then, the only other product we're going to get is if we substituted the secondary position. So four types of products.

Which one is going to be the most likely to form in this reaction? Our instinct might tell us that first molecule's going to react, because in the process of this reaction, we make a tertiary radical. Tertiary radicals are more favorable, generally, than secondary than primary – same way that tertiary carbocations are more favorable than secondary than primary. Since we could say that tertiary radicals are more favorable than secondary than primary, we can now make a very firm energetic comparison. Let's examine again the first step of this reaction – the chlorine pulling off a hydrogen to make a radical. If I have a primary versus secondary versus tertiary radical forming from the same molecule, that means on a reaction coordinate diagram I'd be starting from the same energy level each time – in other words, if I start with this alkane and look at making either of the primaries versus a secondary radical versus a tertiary radical, which hydrogen chloride being the same by-product each time, and chloride being the same reactant each time, this is one of those cases where we can truly use the word stable. [story of coursework at berkeley] Let's say I had something like butane versus decane, something with four carbons versus something with ten carbons. They're not the same molecule, so if you make a radical from butane versus making a radical from decane, you can't make a direct comparison between those processes, cause you're not comparing from the same starting point. Think of Hess's law – the energy in chemical reactions depends on just the reactant and just the product. We have different reactants; how can you make a direct comparison? So even though we say things like "tertiary carbocations are more stable than secondary", there's probably some case out there where the amount of energy to form a tertiary carbocation on one particular molecule might happen to be more energy than to make a secondary in some other case. In that case, you'd have to say the secondary's more stable because less energy was used to make it. But, if within the same molecule – which is what we're doing here – we're comparing tertiary versus secondary versus primary, then you're referring back to one firm starting point, so you really can compare the energy differences. That's when you can really use the word stable.

Since I can put all of these things confidently on one energy diagram, I can then talk about the energy of the transition states. This is going to bring up something known as the Hammond postulate. The Hammond postulate says this: whichever of the reactants or products that a transition state is closer in energy to, the structure of that transition state will also more closely match either that product or reactant. For example, in this case, the alkane is higher in energy than the alkyl halide; for just this portion of the reaction, the chlorine abstracting a hydrogen, it's exothermic. Since the alkane is higher in energy than the alkyl alkyl radical that's formed, and the transition state is above either of those in energy, the transition state energy is going to be closer to the alkane's than the alkyl radical's, and so the structure of the transition state is going to look more like the reactant, in this case, than the product. The Hammond postulate says the structure of the transition state [double dagger] more closely matches the structure of the product or reactant or intermediate that is closest to the transition state in energy. In this particular case, a chloride radical reacting with an alkane to make HCl plus the radical, that's a process where the energy change is exothermic. Because that puts the alkane higher in energy, the transition state's going to look more like the alkane. That means for the three different possible reactions, there's not an enormous difference between the activation energies of these reactions. There is a difference, though; I'm exaggerating it in the way that I'm drawing it so you can see the different activation energies. We can see that the activation energy for making a primary radical is going to be larger than the activation energy for a second which is larger than the activation energy for the third; consequentially, forming a tertiary radical is going to happen more quickly than a secondary than a primary. In this case, the transition state more closely resembles the reactant, so there is not a huge difference in the activation energies for forming a primary versus secondary versus tertiary radical. As a consequence of this, there is a generalized relative reactivity of a [chlorine] to primary, secondary, and tertiary [hydrogens]. It turns out that that ratio, if you round the numbers, is 1:4:5. That means that the tertiary radical is five times more likely to form, which means that you're going to get five times greater amount of tertiary product than you would for primary.

Let's go back to the set of products. GIven what we've just discussed, let me ask again: which of these four products should be the most likely, statistically. You might be tempted to .... These relative reactivities – 1:4:5 – those are relative reactivities per hydrogen. But how many total hydrogens that look like the one that got substituted here? How many hydrogens are there in the two methyl groups combined? Six hydrogens. If we take the fact that there's six hydrogens and we multiply by its relative reactivity of one, then on a ratio basis we'll make 6 molecules of this particular product. Let's look at the other primary product; there's only three of that same kind of hydrogen there. It would have the same reactivity, basically, as the other primary position, so if you form six of the second product, you'd only form three of the third one. What about the first one, the more reactive tertiary center? It may be more reactive, but there's only one hydrogen at that place, so even though it's five times more likely to react, that means it's going to be a minor product compared to the primary position. Look at the last product – it has two hydrogens at that position that, ignoring stereochemistry, would give us the same product. Secondaries are four times more reactive than primaries, so on a ratio basis, you'd get 8 of this molecule, which means this is, statistically, the product formed in greatest quantity. This is the regiochemical consequence of this reaction – that the most likely product depends on both the reactivity the hydrogen and statistically how many hydrogens are present. On top of that, we're going to have every possible monohalogenated product formed, along with some side reactions where you could get multiple halogenation. Let's focus just on the monohalogenation. Every possible monohalogenated product would form, and the most likely product depends on the reactivity of the hydrogen along with how many hydrogens are present. This for chlorine.

Let's go back and look at bromine. Turns out the relative reactivity of bromide towards a primary, secondary, or tertiary alkane position, if you round the numbers off, it ends up being 1:80:1600 – quite a bit more selectivity, far more likely to get the tertiary product out. Why is this so? It turns out it's because the first step of that propagation reaction, that portion of the mechanism where bromide would abstract a hydrogen, that step is endothermic. What does that mean as far as the reaction coordinate diagram that we would draw in this case? Similar to what we did before (but of course with one big difference), the reactants would now lie lower in energy than any of the radicals formed. From the Hammond postulate, we would say the energy of the transition state more closely matches the energy of product or reactant it is closer in energy to. Since the radicals are higher in energy than the reactant, then the transition states will all look more like the radicals, so those energies are going to be closer to the radicals. That causes a much bigger difference between the activation energies for these three possible outcomes. Since the transition state in this step more closely resembles the product, there's a greater difference in the activation energies for forming a primary versus secondary versus tertiary radical.

Now let's look at the product distribution again, just like we did for the chloride – same example alkane reacting now with bromine and light. We'll form the same four types of monohalogenated products – tertiary, secondary, and the two different primaries. We would again have one hydrogen versus two hydrogens versus three versus six – times now the relative reactivities of 1600 versus 80 versus 1. That would give us a ratio of 1600:160:3:6 for these different products. So you'd still get a significant quantity of the secondary product, but far greater amount of the tertiary. If it's possible to be used, bromine is usually chosen instead of chlorine in this kind of radical reaction. The overall process is not as energetically favorable with bromine, so overall it is a slower reaction. When possible, bromine is used instead of chlorine due to bromine's greater selectivity. Chlorination is most frequently used in molecules that have some sort of symmetry, where there's maybe only one possible product that's formed – [on example] is the chlorination of cyclohexane. If you only have monohalogenation, it doesn't really matter if you're attacking an equatorial versus axial hydrogen, you're gonna get the same product. Since all the carbons are equivalent, ignoring by-products from polyhalogenation, you're only going to get one major product.

Iodide is not use [in this reaction] because the overall reaction is endothermic. If I tried to represent it this way, the magnitude of the heat of reaction using fluorine is much greater than the magnitude for chlorine is much greater than the magnitude for bromine. All of these are [exotermic] processes, so the larger the magnitude, that means the more favorable the reaction is. Let me highlight this and say the energy released by fluornation is a lot greater. Fluorine is generally not used because it's so reactive that there's very little differentiation between primary, secondary, and tertiary. The reaction with fluorine is so exothermic that there is almost no difference in the activation energies for forming different radicals – for primary versus secondary versus tertiary, that ratio is 1:1.2:1.4. It essentially means, the more hydrogens there are, the more of that product there'll be, regardless of if it's primary, secondary, or tertiary. Back to iodine. Iodine, it's reaction is endothermic, which means the reverse reaction of getting rid of iodine is more favorable. If you tried to do this reaction to form alkyl iodides, those alkyl iodides, under light, would just decompose. You could see evidence of alkyl iodides decomposing by the solutions containing them turning yellow. Halogenation using iodine is not possible since the reaction is endothermic; that means the alkyl iodides would decompose under light.

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Radical halogenation

1) Synthetic utility : alkane –> alkyl halide; 2) Reagents : Cl2 or Br 2; 3) Conditions: hv (light, usually UV); 4) Mechanism; 5) Stereochemistry; 6) Regiochemistry

chain reaction – a mechanism that repeats continuously (until reagents run out) since one of the products produced is itself a reactant.

Hammond postulate – The structure of the transition state more closely matches the structure of the product/reactant/intermediate that is closer to the transition state in energy.
In this case, the transition state more closely resembles the reactant, so there is not a huge difference in the Ea for forming a 1° vs 2° vs 3° radical.

Relative reactivity of Cl• to 1° : 2° : 3° –> 1 : 4 : 5

Regiochemistry – Every possible monohalogenated product would form, and the most likely product depends on both the reactivity of the hydrogen involved along with the number of hydrogens.

Relative reactivity of Br• – 1° : 2° : 3° hydrogen –> 1 : 80 : 1600

Since the transition state in this 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 due to bromine's greater selectivity.
Chlorination is more frequently used when only one major product forms.
The reaction with F2 is so exothermic that there is almost no difference in the Ea for forming different radicals. 1° : 2° : 3° –> 1 : 1.2 : 1.4
delta HI> 0
Halogenation using I2 is not possible since the reaction is endothermic (alkyl iodides would decompose under light).

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Structures

Identical to those from lecture 18A (11/09/11)