Lecture 11B • 10/21/11

[lab reports][quiz review]

Mechanism

First, I want to show you properly, how you show the formation of a bond and the breaking of a bond, both for an electron-pair and single-electron process. The vast majority of reactions that you're going to learn are electron-pair mechanism. In fact, a lot of the time we'll be looking at it as if it was a Lewis acid-base reaction. For electron pair mechanisms, there are two mains steps that we can talk about: heterolysis, which is the uneven breaking of a bond; and heterogenesis, the uneven formation of a bond. Let's see some example mechanistic steps for each of these.

One very common type of step is if we had some kind of neutral compound in which a bond breaks. Remember that the tail of the arrow shows where the electrons come from, the head of the arrow shows where the electrons go to. The fact that I have the double-headed arrow, were I have a little hook that's on the left and the right, that indicates that you have two electrons involved. Since we have both of the electrons that are going to be moving, then what we'll produce is a set of ions: in this case, we would have hydroxide and a carbocation that are formed. That's the point. That's why this is called heterolysis – we're making two unequal things – one plus charge, one minus charge. This is one example mechanistic step. If we started with something that was already positively charged, if a hydrogen was to come off of this positively charged oxygen, the oxygen now becomes neutral, and we'll just have an H+ floating around in solution.

Heterogenesis would be the exact opposite, where you're bringing two things together to form a bond. For example, if we had a carbocation, and we had a molecule like ethanol, ethanol can attack – by that lone pair pointing at the carbocation, you're saying a new bond is going to form there. Since carbon started out positively charged, it's going to end up neutral. Since the oxygen started neutral, it's going to end up positively charged; there is conservation of charge in this reaction step. What happens, though, if you started with a neutral oxygen and just saw it getting protonated, meaning that it's going to get an H+. You should be familiar with that term protonation. Just to be symmetric about this, since I showed you a bond-breaking event that made ions and a bond-breaking even that produced something that was neutral, let's just see that if we did take oppositely-charged molecules and allowed bond formation to occur, we would end up with something that is neutral.

Let's move on to single-electron processes, single-electron mechanisms. In this case, we use hook arrows or half-arrows – arrows that only have one part of the arrow head. For each arrow, there's only going to be one electron involved. Now let's see what the two processes would be here – bond breaking and formation. If we start out with a neutral molecule and broke a single bond, if we were to do it evenly, that means one electron goes to each atom, which means we're going to end up forming a pair of radicals. This is called homolysis – even breaking of a bond. If we started out with something that had no charge on it .... what functional group is this that I just wrote up? A peroxide. Peroxides – the oxygen-oxygen bond is weak, and very often, under the influence of either heat or light, that bond will break homolytically. The way that we write it is using two arrows. Each arrow involves only one electron. Since a bond has two electrons in it, that's why we need two arrows. Since this was a symmetric molecule, we'll end up making two of the same product, two radicals. I'll point out that the products are uncharged; this is an even breaking of the bond.

Along with homolysis, we have homogenesis, the even formation of a bond. We could imagine that we have two alkyl radicals, for example, both of which start out uncharged. They can form a bond. To show that bond formation, we write arrows that are pointing at each other, like this. Again, each arrow only has one part of the hook on it, which is showing that it's only one electron. Since one electron interacts with one electron, that makes a new bond. We started out with two molecules that are uncharged; we're going to end up with a molecule that's uncharged.

There's one combo step reaction that can occur – disproportionation. What this means is we're going to end up with something that's got a single bond, and we're going to end up with something that's got a double bond on it. Let's say that we had this radical, and we had yet another radical come and interact with it. We saw just previously that I could do a simple bond formation. But what if, for whatever reason, instead of one radical interacting with another, a second radical comes in and does what is called abstraction – takes a proton away. It can try to add into this carbon-hydrogen bond. That carbon-hydrogen bond, that bond should only have two electrons. What that's going to indirectly cause is the bond to break. One electron can come to that radical to form a new bond; hydrogen is pulled away. That leaves a radical on the carbon that the hydrogen used to be attached to. That electron has to go somewhere, and it could react with the radical that's right next door. What you'll end up producing, then, is something that has a single bond and something that has a double bond. It's a combination of bond forming and bond breaking. Since you're taking something that used to be plain alkyl radicals and you're making something that's an alkane but also something that's an alkene, that's why it's called disproportionation.

Again, we will see almost exclusively electron pair mechanisms. This is how to write mechanisms.

Now, let's talk about classes of mechanisms, types of mechanisms. We saw two main sorts of mechanisms in Sn1 and Sn2. There's four classes of mechanisms – cationic, anionic, radical, and metal-assisted or organometallic. Cationic – those are mechanisms where the main point of the mechanism is that you have to form a carbocation somewhere; that would be much like the Sn1 mechanism. Anionic mechanisms would be mechanisms that are primarily driven by bases, primarily driven by things that are negatively charged; that would be like the Sn2 mechanism. Radical mechanisms, you haven't seen yet. And then metals – we'll see that there are a couple of reactions – principally involving hydrogen – where, in order to make hydrogen more reactive – we use a catalyst. The interaction of a catalyst with something like hydrogen doesn't have a nice set of arrow associated with it, like this types of mechanisms that you've see so far. I lump those into this fourth class of metal-assisted mechanism.

Let's look at the first three types of mechanisms – cationic, anionic, and radical.

Cationic mechanisms either involve a carbocation as an important step on the mechanism, or, often they involve acids. One example would be Sn1. In Sn1, the reaction does not begin until a halogen leaves, forming a carbocation. At that point, you could have another molecule come in to attack, which doesn't produce another carbocation, but still has a cationic intermediate. Then we have a deprotonation – hydrogen leaving – which finally gets us to the neutral molecule. Notice how each intermediate here had something that was positively charged. Another example of cationic mechanism would be dehydration. In dehydration, something like the following can happen. An alcohol is not particularly basic – it's kinda like water, if you force a proton on it, it'll accept it, but otherwise it will release that proton right away again. If you put a strong acid source, you can get oxygen to become protonated, but oxygen doesn't particularly like to be positively charged. One aspect of this reaction is that it is an equilibrium process, where that proton hops off and on and off and on. But, to relive the positive charge on oxygen, instead of the hydrogen coming off, what if the carbon-oxygen bond broke, forming a carbocation? If there's heat present, what can happen is then a neighboring hydrogen gets pulled off, and that pair of electrons that used to be in the bond would go back to satisfy the carbocation, eventually forming a double bond. This is called a dehydration reaction because we removed this –OH group and we removed the neighboring hydrogen, so together that means we removed water. The rate-limiting step in this reaction will turn out to be the second step, making that carbocation. Back to this definition I gave you, that cationic mechanism generally involve forming a carbocation as one of the prime steps. This is also an example where acids are involve. We need an acid catalyst in order to get this reaction to progress.

One bit of terminology. Notice that, because there's a carbocation, there generally tends to be this cascade of steps that occurs. There might be portions of the reaction where's there's a simultaneous reaction – specifically, this last step, water coming in to remove this proton and at the same time a bond then forms between the two carbons. But many of the steps will be individual steps – proton hopping on, a bond breaking, a bond forming, a proton hopping back off again. These are what are known as stepwise mechanisms, which are mechanisms that contain multiple elementary steps.

Let's see the anionic mechanisms. Cationic, anionic, they're opposite charge. What that translates into, though, is opposite behavior in mechanisms. Cationic mechanisms, they tend to be stepwise. Because an anionic mechanism, it's the power of the negative charge that's in operation, they often tend to be simultaneous reactions, what are known as concerted mechanisms. There's an opposition in behavior as well as charge. Anionic mechanisms usually involve strong bases and occur in a small number of steps. Our examples here: Sn2 would be a good one. If you have an alkyl halide, you can have something come in, a nucleophile, where the bromine gets attacked, and comes off in the same reaction step. Instead of showing hydroxide making an alcohol, this time I showed sulfur making a thiol.

What would be another anionic type of reaction? A Grignard reaction. It's a reaction involving a carbon-oxygen double bond – the common name for which is carbonyl – and then a carbanion. Carbanions are incredibly basic. The pKa of an alkane is somewhere between 50 and 60; the pKa of water is 15.7. From 15 to 60, that's 45 orders of magnitude difference in the equilibrium constants. Alkanes, when we pull protons off of them, sometimes that makes them so basic that if you were to put them into a syringe, squeeze them out into open atmosphere, you'd end up with a flame thrower because they're that reactive. It's something so incredibly basic it ends up being attracted to the delta positive center of the carbon-oxygen double bond. The same type of story that we had with Sn2: carbon can only have four bonds at once, so the carbon-oxygen bond will be forced open. This is a good example mechanism, because this portion of it is anionic, this portion is concerted, meaning it's a mechanism with simultaneous steps.

But often, in reactions, you might have a combination of both anionic and cationic mechanisms. For example, this Grignard reaction, you could stop right here, and it is possible to isolate this negatively-charged product, because if somewhere in solution there's going to be a metal cation that's going to counter the anion that's being shown here, so you can isolate a salt from solution. But, often what we do is go ahead and neutralize that molecule, to get that alcohol that would probably be more likely what we want. To do that, that means we're going to need a second step, a follow-up step where we add acid in. As soon as we add acid in, we're not going to have bases anymore, we're not going to have anions any more, so it changes the style of mechanism that's going to occur. When you're learning reactions, I'm going to generally classify them as anionic or cationic. This Grignard reaction is an anionic reaction, but what you do in real life, what's called work-up, getting that product isolated, is going to involve a secondary acidic step. So work-up is some form of secondary reaction used to isolate the product material.

This is a good place for me to show you how to show the sequence of reactions steps you use. If you had a ketone that you reacted with a Grignard reagent, a magnesium-containing reagent – the one in front of that means it reacts first, and it reacts with nothing else around, except what's in that same line with that compound. As a second step, I'll add acid, I'll add a source of H+. In this case, the oxygen negative I would have ended up with will react; it will become an alcohol. The fact that I have a 1 and a 2 means that these steps happen entirely independently from each other, and that there's a very specific reaction order. These numbers show you reaction order and the reagents in step two are not introduced into this reaction until whatever what step one is doing is completely finished. Sometimes [in other reactions], you do just pile reagents on top of each other, sometimes, though, you do have to isolate them. This particular reaction, you just carefully add the H+ directly to the reaction mixture after step 1 is complete; we'll see other cases where, no, you need to distill it, filter it, whatever you're going to do to it.

The last kind of reaction class will be radical mechanisms. I'll show you one example. For radical mechanisms, the only definition is that it involves radicals. One prime example is reaction of an alkane, a plain old alkane, with halide radicals. For example, with light, you can cause diatomic bromine, Br2, to split apart and form a bromine radical. That bromine radical can react with an alkane to pull a hydrogen off. What does this mean that I just wrote? The arrows are facing each other which shows a bond is going to form. One of them is coming from the bond with hydrogen, so what that's showing is the hydrogen is going to end up attached to the bromine. Remember that arrows don't show you which way atoms go, but since the atom is following the electron in this case, it does coincidentally happen to show where the hydrogen's going. Since a bond contains two electrons, we need to show where that second electron goes, and it's going back to the carbon. That's one reaction step. In this sort of reaction, there would be more bromine that's floating around in solution. What can happen is that molecular bromine can be attacked by the radical that was just formed. In this case, what I'm showing is the formation of a carbon bromine bond, then there is one electron left over from the bond that ends up on another bromine radical. This is an example of something known as a chain mechanism, cause I start with a bromine radical and I end with a bromine radical, which would then react with another alkane to do the same reaction, which makes a radical, which does the same reaction, and so on and so on and so on.

Those are our three main classes.

Now let's talk about the consequences of reactions. If you have stereocenters, there's three possible results that could happen in a reaction; this is all assuming that a reaction is going on [at or] near the stereocenter. One possibility is nothing changes; the configuration remains the same as it is. Another possibility is that the configuration inverts. Since there's only R and S, that's why there's those two possibilities: it stays the same, it changes – or, you scramble the stereocenter, you lose any specificity. The reaction mechanism is going to dictate what's going to happen stereochemically. The three consequences I just mentioned are: retention of configuration, in which the configuration remains unchanged. For example, in protonation of an alcohol that exists on a stereocenter, since it's just the oxygen that's getting involved, nothing changes with the carbon. We can operate on that oxygen all day long; carbon's stereocenter is not going to change. It starts S, it ends S; retention of configuration.

Having just said that, I've got to warn you, you can't automatically say that in this reaction mechanism, S is going to stay S and R is going to stay R. If you had an Sn2 reaction where you kicked off what happened to be the lowest-priority group, and what you attach is a high-priority group, then not only are you going to have that stereocenter invert, but your 1s, 2s, 3s, and 4s are also going to change. You can sometimes have a reaction in which the stereocenter is unaffected but it does change R & S because of a technicality in how we determine priority. Or you might have a stereocenter change but it doesn't change from R to S, again because you're messing with priority order. It's best just to think of this in terms of geometry. For configuration, I really mean geometry, not R or S. It starts out as a wedge, it ends up as a wedge; that's what I'm trying to say.

We have seen an example of inversion, this second case. That was for the Sn2 reaction. If a nucleophile comes in a pushes off a halide, it has to do it from the opposite way the halide is pointed, which will make the product have opposite configuration, opposite geometry. The third possibility, we saw that with the Sn1 reaction, which would be loss of configuration. A tertiary alkyl halide, if it reacts in water, you're going to end up with two products, one in which the geometry appears to be maintained, and one in which the geometry appears to be inverted. Sometimes, if we want to show that you're going to end up with multiple products, but you don't want to have to keep writing all of the products over and over again, but you want to know that someone knows that you mean that there's multiple products, you can do this: use a squiggly line, to show the configuration is unknown. Or, if you really don't care, you just use plain lines. If I gave you a molecule like that, and I wrote it with plain lines, can you tell if it's R or S? So then you don't even worry about naming whether it's R or S. Think about a bottle labeled 2-bromobutane. If the bottle doesn't state whether it's R or S on it, that's because it was a mixture of both. However that compound was synthesized, it was synthesized likely in a manner that was 50/50. Since you can't figure out which one it is, or if the way it was synthesized it was not specific, it's not even labeled.

There are enantiomers, so to not have to rewrite structure after structure after structure, we'll shorthand it and say: here's the answer, plus enantiomer.

This is stereochemistry. Now let's come back to the topic of regiochemistry. The term regioisomer is sometimes used to denote structural isomers that are virtually identical, except for the position of an important functional group. As an easy example, imagine these forms of pentanol: pentan-1-ol, pentan-2-ol, pentan-3-ol. They're all isomers, they're structural isomers, but they can be referred to as regioisomers; the region where the –OH is is different between them. What do I mean by regiochemical consequences? There's not good labels I can put on these, so I'll give you a case where then regiochemistry is specific: the Sn2 reaction. You can throw hydroxide at this molecule, and it's not going to react with anything, really, except the carbon where the bromine is located. In other words, we can predict in this reaction, if we're trying to make an alcohol, we're going to make one where the bromine started.

But [in other reactions] that's not always true. This happens most frequently for cationic reactions. This dichotomy – specificity of reactions, in terms of regiochemistry, is generally found for anionic reactions. Non-specificity, or the potential to form multiple products, happens most often for cationic mechanisms. Let me show you the mechanism. Imagine that you have an Sn1 style reaction where the first critical step is forming a carbocation. We can use to say that tertiary carbocations are more favorable than secondary. Wouldn't it be great, then, if we could make a tertiary carbocation out of this, energetically at least. It turns out, it can happen – a hydrogen can hop from one position to the next. This is a process known as carbocation rearrangement, and it's also called a hydride shift, because a hydrogen with its bond moves over. What this means is if you do a reaction where you have a functional group that starts in one place, when you get to the product, it might be somewhere else. That's a huge consequence from the mechanism of a reaction.

[quiz information]

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single versus electron pair mechanisms
stepwise versus concerted; anionic vs. cationic
stereochemical and regiochemical consequences

Electron Pair Mechanisms

Heterolysis – Uneven breaking of a bond
Heterogenesis – Uneven formation of a bond
protonation – add H+ to a molecule

Single Electron mechanisms

Homolysis – Even breaking of a bond
Homogenesis – Even formation of a bond
Disproportionation

Types of mechanisms

Cationic – often involve acids and/or the formation of a carbocation as a key reaction step
Examples: Sn1
Dehydration
Stepwise – mechanisms that contain multiple elementary steps

Anionic – usually involve strong bases and occur in a small number of steps
Examples: Sn2
Grignard
Concerted – mechanism with simultaneous steps

Work-up – A secondary rxn or sequence of rxns used to isolate a product
These numbers indicate reaction order. The reagents for step 2 are not introduced until the reaction in step 1 is fully completed.

Radical

Stereochemical consequences
retention of configuration – configuration (geometry) remains unchanged
inversion of configuration
loss of configuration

Regiochemical consequences

regioisomers – isomers that are structurally very similar except for the position of a key functional group

specific – happens often in anionic reactions

non-specific – cationic mechanisms

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Structures

Identical to those from lecture 11A (10/21/11)