

Lecture 11A • 10/21/11

Mechanism

We need to systematically talk about how do we write mechanisms, what are the classes of mechanisms, and what's the consequence of that type of reaction mechanism on the types of products you're going to form, in terms of stereochemistry and regiochemistry.

Let's focus on writing mechanisms first, and let's focus on the types of mechanisms we're going to be seeing the most frequently – electron pair mechanisms. There are two primary events that we can talk about – forming a bond and breaking a bond. If we're talking about an electron pair mechanism, that means we're going to have a bond formation or breaking that's uneven. For example, if we break a bond, and we start out with a neutral bond, both of the electrons are going to go towards one atom, which is going to result in forming a cation and an anion. Since you formed two different types of products, breaking a bond unevenly is known as heterolysis. I'll show you two examples of this type of mechanism. As a reminder, we used a full arrow, a double-hooked arrow. The fact that you have the two lines coming off of the point of the arrow means that there's two electrons involved.

We've seen heterolysis, for example, in S_N1 reaction. Starting with a neutral molecule, the bond breaks so that the electrons, both of them in the bond, go towards bromine. We'll end up with a carbocation, and we'll also have bromine in the form of bromide, an anion. The unevenness of this is why it is referred to as heterolysis. Another example, another common step, is if we start out with an organic molecule that's positively charged, if a bond breaks on an atom that had that positive charge and if the electrons fall back to that atom, then you're going to end up with something that is now neutral. This kind of step is something that is referred to as deprotonation, which means losing H^+ . I've purposely not shown what's removing the hydrogen, because in solution it could be one of a dozen things that's removing that hydrogen, so rather than to have to get bogged down in the mechanism addressing all of those different cases, you can generalize it by focusing on the fact that that ion's going to be really acidic and just focus on the fact that hydrogen goes away. Because it's so acidic, it may not even need the assistance of another molecule to have it removed. Some textbooks take a convention where they show water [or the appropriate molecule] removing it, but I follow a convention where we don't even worry about it and don't show it. That's a bond-breaking event.

A bond-forming event would be called heterogenesis – making something, but unevenly. We've seen examples of that, such as in the S_N1 reaction. Take a carbocation and allow something neutral to react with it. In this case, because the arrow is pointing from the oxygen to the carbocation, that's trying to show a bond is going to form between the oxygen and the carbocation. Since the carbon had been positively charged, by making a new bond it will become neutral; because the oxygen had been neutral, by making a new bond it's going to become positively charged. We could, though, see an example of this where we do use oppositely charged molecules. If there was somehow a carbocation that was in the presence separately from hydroxide, the two would definitely be reactive with each other; plus and minus would react. The plus charge would go away because you form a new bond; the minus charge would go away because you formed a new bond. You start with anion and cation, but you end up with a neutral molecule.

The last case I want show you is another simple kind of electron pair mechanism: protonation, where you're adding an H^+ to something.

Now let's see the single-electron mechanisms. These mechanisms we're going to write with a hook arrow, a half arrow. That half arrow explicitly means that there's only one electron involved. Just like we could have simple bond breaking and bond formation with two electrons involved, we'll have simple bond breaking and bond formation with one electron involved. For one electron, bond breaking is known as homolysis – even breaking of a bond. A good example involves a peroxide. Peroxide – the oxygen-oxygen bond is rather weak, so in the presence of either heat or light, you can get it to break homolytically. Because there are two electrons in that bond, each arrow only shows where one electron is going, we're going to need two arrows – one that show an electron going to one oxygen, and then another arrow showing the other electron going to the other oxygen. Since this is a symmetric molecule and you're breaking it right in the middle, we'll happen in this case to form two of exactly the same product. Since we've broken this in the same way as if we were trying to calculate formal charge, giving one electron to each atom, the oxygen's going to end up neutral. So we start out with a neutral molecule, and we end up with neutral molecules – why it's called homolysis. That's bond breaking.

How about bond forming? That's known as homogenesis – even formation of a bond. Let's say that we had a t-butyl radical and a methyl radical. Those could encounter each other in solution, and they could form a bond. To show bond formation with single electrons, we get the arrows to somehow point at each other, either directly or side-by-side, somehow directly showing a combination of the [electrons]. That results in a new carbon-carbon bond. Because we started with two molecules that were neutral, same number of electrons in the product, we end up with a product that is neutral.

There is one somewhat more complicated step – disproportionation. Proportion means how much; disproportion means unevenly distributed. It happens in this kind of radical step. Imagine that we had two radicals that came together. Let's say that, instead of the radicals themselves interacting, the radical causes a different bond to break. The methyl group could come in and cause the carbon-hydrogen bond that I'm showing here to break. That only involves one electron from the bond, though, so another electron is still around. What if that other electron was to combine with the radical that was next door? That would cause the formation of a double bond. So the end product in this case would be methane, for one, and then a compound that has a double bond. Since you're making both a single and double bond, you're making two different things, and you're effectively causing bond breaking and formation at the same time, that's why it's called disproportionation.

Even means that, if you have a bond that's got two electrons, one electron goes each place. Uneven breaking means if you've got the two electrons, they only go one direction together. That's exactly the difference in approach that we took to handling how to count electrons for formal charge versus oxidation state.

The two arrows are pointed at each other. There's two arrows coming together, and that's showing the formation of the bond. Once that bond breaks, the electron would otherwise end up on the carbon. In order to keep two radicals apart from each other, that bond would have to be at a 90° angle, but since we know that single bonds won't rotate, it won't stay that way, it's going to end up making the double bond. This is shown as happening in one step, since it's extraordinarily unlikely you could isolate the diradical.

Let's look at some classes of mechanisms, so types of mechanisms. There's two main kinds that we'll mostly be occupied with: cationic and anionic – mechanisms where electrons are chasing carbocations or cations versus reactions in which anions are forcing their way in and causing a reaction to happen. There are two other classes that we'll spend a little bit of time on: radical reactions, and then metal-assisted reactions. For example: catalytic converters, you have them in your automobiles, the metal interacts with the exhaust coming out to help pull out carbon monoxide, so there's some kind of interaction between the metal and what's coming out, but you can't necessarily map it out with a nice set of electron arrows like what we're going to see for our organic reactions. Sometimes, you can describe how the metal gets involved, but you can't really write it nicely on paper. I lump those reactions into this category of metal-assisted reactions.

I'll show you some examples of cation, anionic, and radical mechanisms.

First cationic. Cationic reactions often involve acids as catalysts, or, sometimes at the same time, they'll involve the formation of a carbocation as a key reaction step. A classic example: the Sn1 reaction. First step of the reaction is exactly this carbocation formation; second step of the reaction doesn't cause the formation of a carbocation, but it does cause the formation of another cation, technically something known as an oxonium ion, a positively-charged oxygen. Last step, a deprotonation step, where we lose hydrogen.

As another example of cationic mechanisms, let's look at dehydration, which does involve an acid as a catalyst. First step, oxygen reacts with an H+. This is not the most favorable reaction step. Oxygen would love to not be positively charged. If it got this hydrogen, it would like to release it again. But every once in a while, you might have, instead of the hydrogen coming off, that the oxygen disconnects from the carbon it's connected to. That would cause the formation of a carbocation. In this case, with heat, water could be driven to pull a hydrogen off of this molecule, which would end up forming, therefore, a double bond. Since we removed -OH in the second step, and we removed a hydrogen in the third step, together that makes water, which is why this is called dehydration.

Many other cationic reactions are similar to this, where you have just a bond forming or a bond breaking, occasionally with both happening at the same time. Therefore, most cationic reactions are what are known as stepwise – mechanisms that contain multiple elementary steps.

Let's see a couple of anion examples. Aside from the fact that we're now going to be dealing with positive charge, because of the way that anions react, we're going to find that there's this opposition in reactivity. What I means is: in cationic reactions, you're going from step to step to step to step because you're chasing around a carbocation or a cation. In an anionic reaction, like Sn2, that nucleophile pushes its way into a molecule; it doesn't wait for a carbocation. Because it pushes its way in, simultaneously something else gets kicked out. Most anionic reactions are going to be concerted – they're simultaneous reactions.

Anionic mechanisms usually involve strong bases, but not always. There is a distinction between base and nucleophile. A base is something that wants H+; a nucleophile is something that wants positive charge. They're not exactly the same thing. Anionic reactions usually involve strong bases and occur in a small number of steps. Sn2 is a good example of an anionic reaction. To demonstrate that it's not always oxygen that involved; we could have a negatively charged sulfur that might attack a bromine. This molecule is less basic than hydroxide, but it performs this reaction much better than hydroxide, because of the difference between what's a nucleophile and what's a base.

One molecule attacks and pushes out a part of another at the same time, making, in this case, a thiol. This is a concerted reaction; just like going to a concert, things happening at the same. It's a mechanism with simultaneous steps.

The other example I want to show you is very important reaction known as a Grignard reaction. This is a reaction involving carbanions. To make sure that we are reading this notation correctly, how many carbons are in this molecule? 2? The negative charged does not need its own bond symbol, so the fact that you have a line to that negative charge means there's a carbon where that negative charge is, so that molecule has three carbons. Carbanions are extraordinarily basic. pKa of an alkane ranges generally somewhere between 50 and 60, closer to 60. Water has a pKa of 15.7. That means that alkanes, when you take a proton off, they're really, really super basic – so basic that some of them combust if you squirt them out into open atmosphere. That very basic molecule is very likely to very attracted to the delta positive center of that carbon-oxygen [double] bond or carbonyl. Carbon can only have four bonds at the same time, so if you attack that carbon-oxygen double bond, something has to give, which ends up being the double bond itself. The result will be that we have a negatively-charged oxygen, but the crucial thing is that we made a new carbon-carbon bond. Any time that we can expand the carbon framework, that's an incredibly important synthetic reaction.

This is not really a complete reaction, what I've shown you. You could isolate that product with some kind of metal counterion. You can't just have a negative charge in solution; something's gotta go with it. We could isolate this product as a salt, but generally, that's not what we want. When we're using Grignard reactions, if we just put a proton on there, we've made an alcohol. There's usually some kind of follow-up step where we do something just for the purposes of getting out the final product from the solution. This is generally referred to as work-up. Work-up is a secondary reaction or sequence of reactions used to isolate a product. So, first, we could do the Grignard reaction itself. Magnesium bromide is the most common counterion in this kind of reaction. To get the alcohol out, as a second step, we follow that up with some kind of acid – hydrochloric is usually a good choice (dilute). Notice the 1 and 2 I've used to show this reaction. This is not a mechanism; this is how we write things synthetically. If you want to focus on the transformation involved, if you want to just focus on what the product is, you leave all of the mechanism out, but we still have to say, if it's important, that one reagent reacts, then, entirely separately from that, in another reaction step, sometimes physically in a different reaction pot, there's a different reagent that's later on added, and that's what the 1 and the 2 here mean. These numbers indicate reaction order. For example, the reagents in step 2 are not introduced until the reaction shown in step 1 is fully completed.

Generally it's not notated when you continue on and add stuff to the same reaction pot or whether you have to isolate, separate. That would be in the procedure that you write up, but to keep things a little more compact, we don't often put all of those details when we write a reaction out.

That's the reagent that's going to react with acetone first. Magnesium bromide would be the counterion. The first step would just be that carbon attacking. Separate from that, we've got this negatively charged oxygen which, like hydroxide, is pretty basic, so we throw an acid in. But, the acid would destroy the first reagent, so if we mixed everything together in one pot, nothing [useful] happens. So, first, you add reagent one, let it do its thing, then you add the acid afterwards.

Let me briefly show you an example of radical reactions. If you have bromine or chlorine diatomic, elemental bromine or chlorine, if you expose it to light, you can get the molecules to break up so that you make radicals, so I'm starting off here with a bromine radical. It is able to undergo abstraction, where we steal a hydrogen from this molecule. Bromine reacts, bond breaks, one electron goes towards bromine to make a new bond; the other electron goes somewhere, it's going to wind up falling back to carbon. It's not just one molecule of bromine that's floating around; we throw it in as a reagent, we use one mole for one mole. Since there's bromine floating around in solution, the radical that formed can turn right back around and react with bromine. Notice that I've got two arrows pointing towards each other, one coming from the bromine, indicating it's going to form a bond with the carbon radical. Since a bond has two electrons, though, there's another arrow showing that the electron falls back to bromine. I end up with an alkyl halide plus a bromine radical.

One special feature of this reaction is that it is a chain mechanism. Notice that we start with a bromine radical, we end with a bromine radical – which can then undergo exactly the same kind of reaction, again making bromine radical, which reacts, which makes a bromine radical, and so on and so on and so on.

Now let's talk about how mechanism affects the types of products that you're going to end up with. Sn2, because it involves this simultaneous reaction, nucleophile coming in and pushing something off, that geometry at that stereocenter flips; we call that inversion of configuration. Turns out that there are three different stereochemical consequences. I'll start with retention of configuration (geometry). We're going to find out that just because a stereocenter stays a wedge or stays a dash or flip-flops between the two, that can be something independent of what the priority order of the substituents on that molecule is. Imagine that Sn2 case: molecule's coming in, something else is leaving. What if the part of the molecule that's leaving was priority number 4 and that what comes in is priority number 1 now. [bad example given] You could have a complete flip-flop of you priorities. That means that, even though you invert the stereocenter, the wedge goes to a dash, it may go from S to S, just because of the technical way in which we determine what R and S is. When I say retention of configuration, that doesn't mean R stays R, it doesn't mean S stays S; it means the geometry at that place stays the same.

It stays a wedge or stays a dash. An easy example of this is protonation. Imagine we had an alcohol that happened to be at a stereocenter. You put a proton on it, sure the oxygen changes, but the carbon that the oxygen is attached to, it doesn't change at all. Therefore, that stereocenter's geometry is the same, so we call it retention of configuration; a wedge stayed a wedge.

It's opposite is inversion of configuration; that's the S_N2 example. Starting out with a chiral alkyl halide..... what does chiral mean? That it has handedness. If a molecule has a stereocenter, does that mean it's chiral? No. Why not? Cause you could have a meso compound. Is this meso? Why not? Cause you don't have an oppositely-configured stereocenter. You have to have some kind of mirror plane in the molecule. We've only got one stereocenter; it's not symmetric its own self. If it was only one stereocenter and it was symmetric, it wouldn't really be a stereocenter, so this is chiral. Hydroxide attacks, and because it attacks from behind where the bromine is located, then when the $-OH$ group ends up in there, it's going to be the opposite geometry.

The third case we've seen in S_N1 reactions; that's loss of configuration. Let's say we had the following: a chiral alkyl halide. Let's see one that'll react with water instead of hydroxide. That means that the chlorine's going to come off first before water attacks. When that happens, the geometry becomes planar, trigonal planar, so the water can attack from either side. Once water deprotonates, that means we're going to end up with two different products – one in which the $-OH$ group appears to have retained its configuration, and one in which it appears opposite. There's multiple ways that we could show the fact that we get multiple products. One is to just explicitly write them all out. But if you're writing a mechanism, we may not want to have to write those over and over and over again. Sometimes, as a shortcut is done, you'll see, here's a product, and just write in in words "plus enantiomer" – it's the flag that yes, there's really multiple products. Another way that it's sometimes done is if you know you made multiple products, but you can't specify which one you're going to get, you can use a squiggly line. Squiggly line means it's got a configuration, and you either can't tell or don't care what it is. If you really, truly don't care at all, sometimes, it'll be shown just with a plain line. Normally I won't let you do that for mechanisms, cause I want to know that you know that it makes multiple products. Using a plain line does not broadcast that you know that multiple products are there.

The way that I've written that molecule – can you determine from the way I've written it whether it's R or S? No, because everything is being drawn with a plain line. To name that molecule, you just leave the R and S out. If you have a bottle that is labeled 2-chlorobutane, if it doesn't have R or S on it, it means the way it was synthesized, you have both. Because you didn't care about stereochemistry, or because it was synthesized in a way to isolate the two, it's just sold as the mixture. That's why it was labeled without R and S on it.

These are stereochemical consequences. Now regiochemistry. Regiochemistry is defined as where on a molecule you might have a substituent. To revisit that topic, let me draw these three forms of pentanol: pentan-1-ol, pentan-2-ol, and pentane-3-ol. These are a series of what are called regioisomers – molecules that have very similar structure, except for the position of a key functional group. With one starting molecule, we could make all three of these products at the same time. Maybe in some cases that's what you want, but in most cases you don't want that. You at least want to be able to predict what form of product you're going to get. I'll show you a case in which regiochemistry is specific – meaning, it only happens at one location. This is something that is most commonly found in anionic reactions. Why? Because it's the anion that's forcing its way along and causing the reaction to occur. I am using S_N2 as my example since it is a relatively simple reaction. The negative charge attacks the location where bromine is, because that's where the bromine is, because bromine, being there, makes the carbon delta positive, which is the only reason it would want to be attacked in the first place. In an S_N2 reaction, you're guaranteed, pretty much, that where the function group started is where the functional group is going to end.

There are other cases where it is non-specific. When we discuss alkenes reacting, we'll going to go heavily into whether they make one product, two products, multiple products. One small example, one piece of an example I want to show you, is what happens with S_N1 reactions. Let's say that we have a secondary alkyl halide. What we'll see is that there is much more hyperconjugation that occurs in a tertiary carbocation than a secondary than a primary. The first step in this reaction would be for bromine to come off; and it will, it can. You can make a secondary carbocation, but the molecule would be at lower energy is somehow it could become a tertiary carbocation, which is exactly what it does. We'll learn that the hydrogen can hop right next door. This is a process called two things: one, since you move the position of the carbocation, it's called carbocation rearrangement. You focus on the hydrogen, it's also called a hydride shift, because the hydrogen – along with the pair of electrons in that bond – moves. Hydrogen with a pair of electrons is H^- , hydride, that's why it's called a hydride shift.

Why is this so critical? Because it frequently happens for cationic reactions. Before, we say this dichotomy, where cationic reactions are generally stepwise, anionic reactions are generally concerted. What we'll find out also is that anionic reactions tend to be specific; you don't tend to get multiple products. Cationic reactions, depending on the flavor, you can. [information about quiz]

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: S_N1

Dehydration

Stepwise – mechanisms that contain multiple elementary steps

Anionic – usually involve strong bases and occur in a small number of steps

Examples: S_N2

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

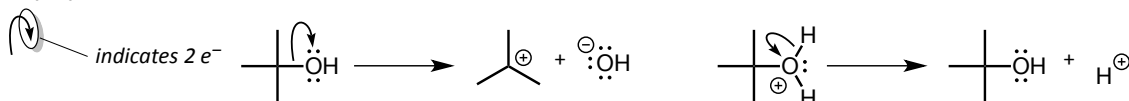
specific – happens often in anionic reactions

non-specific – cationic mechanisms

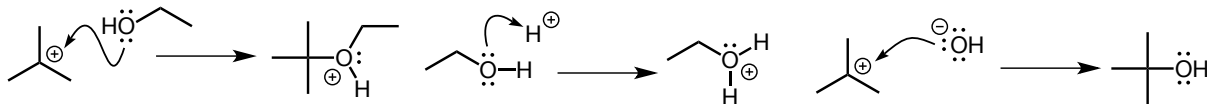
Structures

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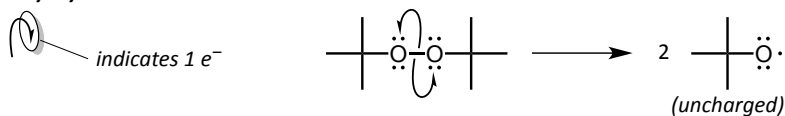


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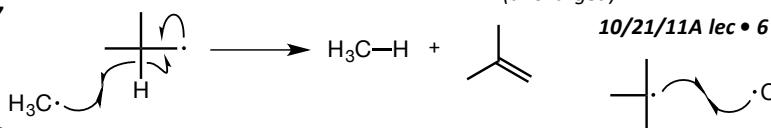


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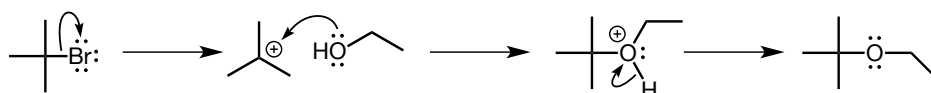


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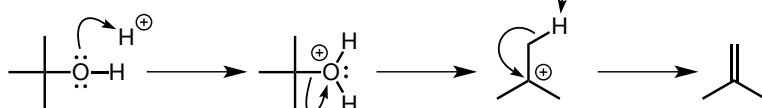


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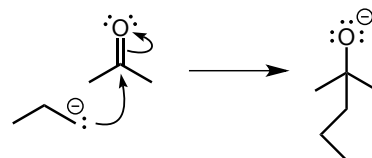
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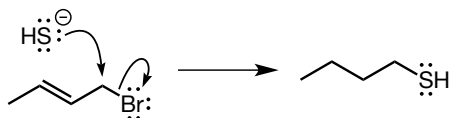
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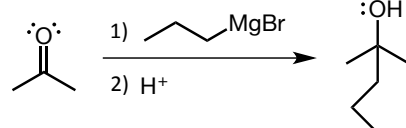
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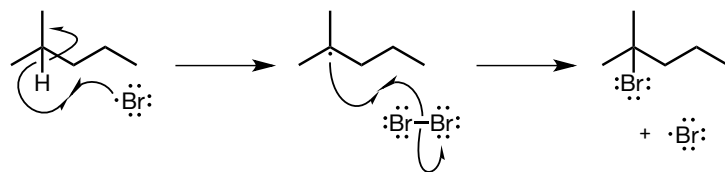
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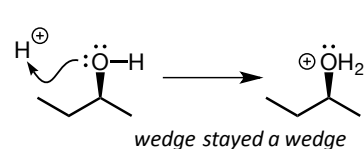
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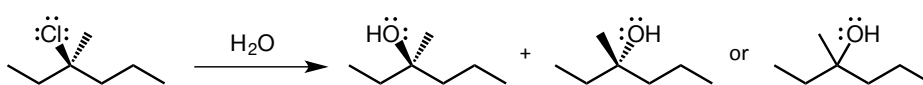
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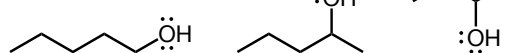
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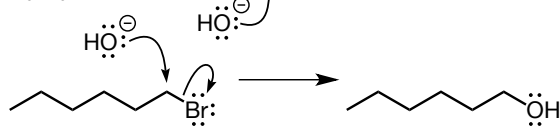
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