

Lab 3A • 01/23/12

First topic is the difference between formal charge and oxidation state. There's quite a bit of similarity between those two systems. Really, those are just two different systems for counting electrons. The idea is this: that you could have a collection of atoms that, individually, each would have a certain number of valence electrons in their unreacted, natural elemental states. As those atoms react to come together to form molecules, some atoms gain electrons, some atoms lose electrons, but the total number of electrons has to stay the same. That's what these two things, oxidation state and formal charge, tell us – how many electrons has an atom gained or lost as it's reacted. Why then do we have these two counting systems? Why don't we have just one? It all has to do with the way that we perceive what a bond is. We do have two diametrically opposed views of bonding. One of them is covalent bonding, in which the electrons are fully and completely shared between two different atoms. That a model that we use quantum mechanics to describe, we use orbitals to describe. A perfect covalent bond would be one in which those electrons are equally shared between the two atoms. There is also the ionic bond, which would be similar to the classical description of a bond – we view the cations and anions coming together to form that bond as just little charges. It's purely the attraction between those charges that's going to hold them together; in other words, there's no orbital description there, it's purely based on electrostatics, plus and minus attracting each other.

Reality is, no one bond is completely covalent or one bond is completely ionic. For example, sodium chloride, which we usually think of as an ionic compound, does have some orbital description to it. The behavior of the atoms in that compound, it can be somewhat described using the covalent bond. Then, if you take the case of a molecule like water, where you have oxygen and hydrogen, there's so much electronegativity [difference] between those two atoms that they, in fact, cause an intra- or intermolecular force, known as hydrogen bonding, which is not really the formation of a bond, it's just particularly strong dipole-dipole interaction. But, that means that there's this displacement of charge across the bond, so it's not really proper to call it purely covalent, so we call it polar covalent. But then, if we do get to the point where we want to know, how many electrons should really be ascribed to each of the atoms in the molecule, how do we divvy it up? Do we look at it say that we break each bond evenly, we pretend that they're covalent bonds; or do we break each bond unevenly, where we give the electrons to the more electronegative element, which would be more like an ionic bond.

The answer is that we do both. When we're drawing line structures, which are based on the idea that a molecule is held together covalently, then we use entirely formal charge. Formal charge is where, in fact, we view each bond as being evenly distributed. Not that the bonds really break in either case, it's just our way of doing an account of the electrons. But, therefore, when we encounter a bond, we give one electron from the bond to each of the atoms that are part of that bond; that's for formal charge. For oxidation state, we use that when we're doing redox reactions. In that case, we treat everything as if they're ionic bonds. Between the two atoms in the bond, we look and see which one is more electronegative, and we give both of the electrons in that bond to the more electronegative atom. That's the overview of the difference, and I also gave you a little bit of the similarity.

Formal charge and oxidation state are both counting systems for electrons, in which the number of electrons around an atom in a molecule is compared to the number of electrons that atoms would have had as an unreacted element. These are counting systems to see whether atoms gained or lost electrons. The only difference between the two systems is how the electrons in a bond are distributed. Formal charge views all bonds as purely covalent, so one electron is given to each atom in a bond, per bond – meaning if you only have one bond, one electron goes here, one electron goes there; you have a double bond, two electrons, because you have two bonds, two electrons go to one atom, two electrons go to the other. This would be the same if we approached each bond and broke it homolytically – homolysis means to evenly break a bond. Formal charge – each bond is treated as if it's covalent, meaning one electron is given to each atom in the bond, per bond; that is equivalent to undertaking homolytic cleavage.

Oxidation state is where you treat each bond as being purely ionic, which means that bond electrons in the bond are given to the more electronegative element, per bond. So if you had a carbon-oxygen bond, if you had a single bond, oxygen would receive the two electrons from that bond; if you have a double bond, the oxygen would receive the four electron in that double bond. This process would be the equivalent of heterolytic cleavage; again, it's not that bonds are being broken this way in real life, this is our way of accounting for the electrons. [There is] a situation, wherein you have a bond that has two of the same atom in it; since neither atom would therefore be more electronegative than the other, we go back to considering it a covalent bond, which means one electron goes to each atom in the bond.

There is a shorthand I haven't really discussed before, but it does make it a lot more convenient that having to redraw the molecule every single time. If you think of it this way: carbon is tetravalent, meaning it wants to have four bonds naturally. If you think about carbon in almost all of the molecules we ever see, it's got four bonds of some sort. Just like pnictogens like nitrogen are usually trivalent; think of ammonia. Chalcogens like oxygen, they're usually divalent, something like water. Halogens, they're monovalent.

So if we got a carbon that's tetravalent, wants to have four bonds, then in this counting system, under oxidation state, if we identify a bond as belonging to the atom that's attached, if you have something that's more electronegative like oxygen, chlorine, nitrogen, then that means there's an effective loss of an electron from carbon, and so that means it's going to increase the oxidation state of carbon. For each atom attached that's more electronegative, it causes a +1 oxidation state on carbon, per bond. Each atom that is more electronegative than carbon will cause a +1 oxidation state on the carbon it's attached to, per bond; so, if I have a single oxygen attached, you increase the oxidation state of carbon by 1; if you have a double bond to carbon, increase it by two. The reverse is true. If you have something that is less electronegative than carbon, then in that tug-of-war that we imagine that happens for the purposes of oxidation state, carbon would effectively end up with an extra electron, which means it would count as a -1 towards the oxidation state of carbon. Two good examples are hydrogen and boron – if we had either of those, it would cause a -1 oxidation state on the carbon to which it is attached. If you had another carbon, then you treat it as a covalent bond, which means you end up with exactly as many electrons as you should have. If you have carbon connected to four other carbons, the oxidation state is zero. Each carbon attached to a carbon has no effect on that carbon's oxidation state. If one carbon is attached to another, then neither carbon causes any effect change on the oxidation state of the other.

Let's do an example, where first we'll use these nice shorthand rules to tackle the molecule, and then we'll go back and do the drawing it out and manually breaking the bonds to find out it's really the same thing, because every time we break the bond with oxygen, oxygen is going to get the electrons (if we're talking about focusing on carbon). Let's look at the molecule butanal. We can see that we've got a double bond to oxygen, we have a single bond to carbon, we have a single bond to hydrogen. Starting on the left, the carbon that's attached – we're only going to focus on the carbon that's part of the carbonyl – the carbon that's attached to that carbonyl, what effect on oxidation state will that carbon have? None, because it's the same, so it's zero effect. Because of the oxygen having a double bond, it would cause the carbon to be +2. What about the hydrogen, what would that cause on the carbon? -1. So we have zero over here, then we have +2 because of the oxygen and -1 because of the hydrogen, zero plus 2 minus 1 gives us an overall +1 oxidation state on that carbonyl carbon. We [can] manually disconnect bonds to more formally count electrons. What I want to demonstrate is that's the long way of doing what these rules summarize. If you're talking about carbon, every time you have something more electronegative, then the response is the same. Instead of doing the pictures over and over again, I now comfortable using this set of rules. If I did want to rewrite that molecule, focusing just on the carbonyl carbon, there's oxygen around it, a hydrogen around it, and then another carbon. With the carbon-carbon bond, each atom of that bond receives one electron, because it's treated covalently. For the oxygen-carbon double bond, oxygen would get both pairs of electrons, leaving carbon with nothing. As far as the carbon-hydrogen bond, both of the electrons that are in that bond would be ascribed to the carbon, because it is more electronegative than hydrogen. Notice that that means that the carbon effectively has three electrons. Unreacted carbon, though, has four. If it's supposed to have four and it's missing one, that means it's charged, and that's how we get the same +1 oxidation state.

This is the difference between oxidation state and formal charge and it stems from the fact that usually, one bond in itself cannot be described purely as ionic or covalent. So we carry both numbers to give a fuller picture of how that bond will react.

In the other section, someone made the comment that methane's gonna be polar because it has an oxidation state of minus four. Yes, it has an oxidation state of -4, but you can't forget the geometry. What's really going on there is each bond individually, yes, is going to be polar, and yes, the way that we do oxidation state, you're going to end up with a large displacement of charge, per bond. Remember that methane is tetrahedral, so these dipoles that form are all symmetrically arranged. So yes, if you're sitting there at carbon, you're going to think I'm getting electrons from that one, from that one, from that one, and from that one. But since it's equally getting it from all directions, from the outside, the molecule appears non-polar.

Oxidation

There are two main classes of reagents that we're going to discuss; the one that we'll do today is the chromium-based reagents. With chromium reagents, there's two types of behavior you can have in the case of primary alcohols; that's where I'm going to start this discussion, is the selective oxidation of primary alcohols. What we're going to find is in these different chromium oxidations, there are two main reagents that you're going to learn. One of them is normally used in anhydrous conditions; for the selective oxidation, it is key that we have anhydrous conditions. With anhydrous environments, there's a particular reagent that's used: pyridium chlorochromate (PCC). That same reagent can be used in aqueous environments, but it's kinda a waste; the only reason we use PCC is because it's a reagent that, in the absence of water, is able to do this selective oxidation. It's not PCC itself, per se, that's magical, it's the combination of it and the fact that you have no water that gets the result I show you.

A little nomenclature. This nitrogenous analog of benzene, where we've taken on of the carbons of benzene and substituted it with nitrogen, is called pyridine. Most nitrogen-containing compounds are bases; the lone pair of a nitrogen is weakly basic. If pyridine is the neutral compound, then you can have its charged conjugate acid, which is called pyridium; that -ium ending is an ending very frequently used to mean cation. The reagent is PCC. Pyridinium chlorochromate. What is chromate? CrO_4^{2-} . Chlorochromate means replace one of the oxygens with a chlorine instead, so it turns out it's only going to be a -1 ion. You must know the name and the abbreviation and the structure of this reagent.

Any reagent or solvent that I ever use abbreviations for, you need to know the name, the structure, and the abbreviation – particularly because you might have a mechanism problem where you have to write where the electrons are going. In these kinds of problems, if there's any portion of the structure where you're able to abbreviate, then you must show the full structure once, and then you may use the abbreviation afterwards; that's exactly what I'm going to do when I show you this example. I'm going to take an alcohol, I'm going to set it up so we start the oxidation, write the full reagent out once, and then the next step I'll show you how I abbreviate it.

For my example, I'm going to use butan-1-ol. Here is the pyridinium chlorochromate. [Make sure that you keep your] Cr and Cl clearly identifiable from each other. It is chromium, not chlorine, that makes the center of this molecule – although it's not impossible to have a chlorine-centered molecule. Just point out it is chromium here. What is the oxidation state of chromium in this case? Remember that oxygen's the second most electronegative element and fluorine's the most. You could easily figure out between oxygen and chromium, and I'll just tell you that chlorine is more electronegative than chromium. +6, because in each of the cases here, each bond, the outside electron is more electronegative, so if you have six bonds that pull away six electrons, that effectively makes a +6 oxidation state. [commentary on erin brokavich] Reason for showing you that +6 oxidation state is it means chromium really likes to get electrons. Chromium makes a good oxidizing agent, but good oxidizing agents are ones that therefore, in turn, get reduced. That which oxidizes and pulls electrons away is itself gaining those electrons and becoming reduced. There will be one key reaction step coming where chromium gets electrons and its the driving force for this reaction. [commentary on whether reversibility of individual steps needs to be known]

Like the reaction of thionyl chloride and tosyl chloride, what do you think the first step in this reaction will be? Oxygen from the alcohol attacks the chromium, pushing one of the double bonds to chromium open, because chromium is in the +6 oxidation state, it's got all of this electronegative stuff around it to make it really delta positive. Just like thionyl chloride and sulfonyl chloride, oxygen is going to attack it. [I'm going alternate version for the opening and closing of the chromium-oxygen double bond.] Oxygen attacks chromium; chromium-oxygen bond opens up. I'll show the subsequent reformation of that [chromium-oxygen double bond] separately this time. Notice the abbreviation: since you've been shown the pyridium once, I'm just going to abbreviate it thereafter. What happens next? You have a negative charge on two different oxygens; you've gotta think many one or the other of them is going to want to attack chromium again because chromium doesn't mind having electrons. When it does, chlorine is a good leaving group, so chloride can get kicked off. We still have an excess charge, because oxygen had been neutral, so we'll have protonation. All protonations or deprotonations are – in theory – reversible, so when you show hydrogen falling off like this, you should be using a reversible arrow. Why am I showing a forward arrow then? Because it's extremely acidic, so it's going to be at equilibrium, but it's going to be 99.99% shifted to the right; that is my justification for using the forward arrow, to simplify our lives a little bit. Once it falls off, we have this intermediate. Allow me to show you another kind of [molecule]. First, I'll start off with a carboxylic acid; notice that that has a carbonyl to which is attached an –OH group. There is a type of reaction where we can convert that into this kind of molecule, where the –OH has been replaced by an –OR. This second type of molecule is an ester. That's a carbon ester. Notice the similarity between that and what we just generated up above; here we also have that –OR attached not to a carbonyl, but a chromium oxygen [double bond]. This thing is called a chromate ester. Similar, when we used a sulfonyl chloride, tosyl chloride, to make a leaving group, that was making a sulfonate ester. It is at this point that the unusual activity occurs, where the oxidation step itself happens. The [hydrogen] that is attached to the same carbon as what had been the alcohol will now get attacked by a base. Some kind of base comes along and pull a hydrogen off. The carbon-hydrogen bond that had been there goes to the oxygen. Do write it to the bond in between the carbon and the oxygen, or do I write it to the oxygen itself? In my mind, it's the same thing, you're making a new connection, so whether you're showing it to the bond or to the atom, you are making it to the bond. But, oxygen is normally divalent, so something gives. It would be the chromium oxygen. Formally, those two electrons are explicitly coming to chromium now, therefore chromium is gaining more electrons, it is reduced in its oxidation state. Chromium's reduced, carbon is oxidized. What's the end result? An aldehyde – plus, things happen to the chromium reagent afterwards. What I've just shown you is a reaction to convert a primary alcohol into an aldehyde. [will hydrogen come off first, or will chloride be eliminated first?]

Continuing our story of chromium oxidation, we have just seen has PCC can be used to selectively oxidize a primary alcohol up to an aldehyde. Now let's see what would happen if we did have aqueous conditions. PCC in and of itself is not just the key part of it, it is we have anhydrous conditions. If we have water, we could still use PCC, but it would not have the selectivity of what I have just shown you. Before I show you the mechanism itself, let me make a comment about equilibrium. If an equilibrium can occur, it will occur, even if the products that are formed are not favorable. Equilibrium one of its definitions, is that it's a dynamic process in which the forward and reverse rates of that process are equal to each other. In a chemical reaction, you can't have a reverse reaction unless you have product, and if you only have a forward reaction, that means you're going to make product. So if you have the environment in which a reversible reaction can be established, it will establish equilibrium, which means you're going to make a little tiny bit of the product, even if it's just a handful of molecules. The key here is: imagine that we had this aldehyde. An aldehyde in the presence of water can form something called a hydrate. Hydrates have –OH group, so what if we have this chromium reagent; you made the aldehyde, but you have water. The water can cause the formation of a hydrate, which makes an –OH group, which can react with the chromium again. That's exactly what happens. If an equilibrium can be established, it will be established, meaning there will always be some non-zero quantity of products, even if the formation of products is not favorable. What is going to occur? We're going to form a hydrate.

Let's remind ourselves how this mechanism works. This is this mnemonic that I came up with: protonate, open, attack, deprotonate. So the first step of that is for the carbonyl to become protonated reversibly, that is key. Then you end up with a delocalized ion that we can show formally using resonance structures, so in this case we'll have the carbonyl open; generates a carbocation that then can be attacked by water, so that's the attack; again reversible formation. After the addition of water, we'll have a deprotonation step. We have the hydrate, which is a geminal [diol], geminal meaning twin, meaning the two -OH groups are located on the same carbon. More importantly we have -OH groups, which this means it can react with the chromium, and another round of oxidation could occur.

Imagine that you did the oxidation you saw previously, where you have PCC, primary alcohol, you end up with an aldehyde. Let's say that we have water around, which means that we still have PCC around. The same cycle occurs. Oxygen from one of the alcohols, it doesn't matter which, attacks the chromium. Notice that I'm remembering my pyridinium. After that initial attack, we have lots of stuff hooked up to that chromium. [There is a separate step of the oxonium ion deprotonating]. One of the other oxygens attacks the chromium, kicking the chlorine off. Now we end up with the chromate ester. Here's why I wrote that hydrogen in. If we didn't have that hydrogen, no elimination could occur; you would not be able to further unsaturate the molecule. Because we have that removable hydrogen, it will get removed, which will come back and force the oxygen-chromium bond to break towards the chromium, causing the reduction of the chromium, the oxidation of the carbon, and resulting in a carboxylic acid. So, in the presence of water, a primary alcohol will over-oxidize to a carboxylic acid, which under normal conditions won't react any further. Using the normal chromium reagents, nothing else happens here, for two reasons: one, there is no more hydrogen at that position to be able to eliminate to cause a double bond to form. So even if we could somehow attack that carbon and somehow put more water on there - cause you can make what's called an ortho acid, meaning you have three -OH groups on one carbon - [it] won't get oxidized. Why? Because if we had some regular oxidation reagent, and let's say that we got another carbonyl somehow, notice that that means five bonds to carbon, which means it's not going to react any further.

So, PCC, no water, a primary alcohol can go to an aldehyde. PCC or any chromium reagent with water, overoxidation is going to occur to make a carboxylic acid. When you do want to oxidize like this, we don't use PCC, we use a form of chromium trioxide. When aqueous conditions are used, aqueous chromium trioxide is used instead of PCC. PCC we'd only use when you have anhydrous conditions, because that's the advantage that no water and PCC gives you. You can stop at the aldehyde. A mixture of a trace amount of sulfuric acid, water, and then chromium trioxide, mix that together, that's called the Jones reagent.

Let's move on to secondary alcohols, if we've got primary alcohols under control. Secondary alcohols can only be oxidized to ketones; this is presuming that we're using an oxidizing agent that's specific to oxidizing alcohols and won't just rip the entire molecule apart. Why is true? Let's take something like isopropanol. Notice, it only has one hydrogen attached to the same carbon that the -OH group is attached to. That means if we use oxidative conditions, we're able to pull that hydrogen off to make a carbonyl. But, if we then try oxidize at that point, there's no hydrogen on that carbon to remove, and even if somehow we forced an -OH group on there to make it look like a carboxylic acid, it won't happen, because we have five bonds to carbon. So you can use PCC but there's no reason to; use the cheaper reagent cause you can't go past the ketone anyways.

With that in mind, let's go ahead and go on to tertiary alcohols. If you use something like chromium trioxide in water, no reaction, for exactly the same two reasons: there's no hydrogen, and if we tried to make the product, we'd have five bonds to carbon.

Our next topic is going to be on epoxides, because they have a different reactivity than other ethers. An epoxide is nothing more than a specific kind of cyclic ether, where you have two carbons that are both spanned by the same oxygen; that's a three-membered ring that's strained; it can be formed, they are common functional groups, but they're just reactive functional groups. We've learned two methods to synthesize these. MCPBA and MMPP are the two acronyms for the two reagents that are most commonly presented. We'll start with MCPBA - meta-chloroperoxybenzoic acid. Benzoic acid would be a benzene ring with just a COOH group; peroxy means you throw an additional oxygen in there. Meta is two positions away. In general, it does not actually matter that we have the benzene ring; what you have to have is this peroxyacid. The reason that we do have these two specific reagents that are normally used is that peroxyacids have this bad habit of exploding, because of the oxygen-oxygen single bond; it is a weak bond, and these compounds decompose - my recollection is that these are shock hazard, so give a good sharp jolt to the reaction flask and, well, boom. This is somewhat more stable, so we use it.

How does it react? It's essentially the oxygen adding into the double bond and forming one of those ring-type structures like we did with mercury and bromine last quarter. When I show you how this epoxide behaves, how it reacts, there's going to be some very direct parallels and the cyclobromonium and cyclomercurinium ions that we saw last quarter. What is the reaction mechanism that occurs? Complicated. This is what is known as a pericyclic reaction, meaning that in some sense, there's electrons that are going to be travelling around as if they were travelling in a circle. That's one thing that's going on; at the same time, you've got oxygen interacting with this double bond. Whether you express it as the double bond attacking oxygen - because that oxygen-oxygen bond easily breaks - or if you have oxygen attacking the double bond, it kinda doesn't matter. Let's have that alkene attack the oxygen first, causing the oxygen-oxygen bond to break.

The electrons could simply settle on the oxygen, but that's a delocalized ion. If you have a negatively-charged oxygen right next to a carbonyl, you're going to have resonance that occurs. Instead of just showing you electrons arriving at and staying on the oxygen, I'm going to show them delocalizing by pushing open that carbonyl. When that carbonyl opens, we have a negatively-charged oxygen. This had been a peroxyacid, meaning that the hydrogen at the end can come off, so imagine that that carbonyl grabs a hydrogen. That pair of electrons has to go somewhere; it falls back to the oxygen, which in turn can attack back towards the alkene. Notice that there's this cyclic portion of this mechanism, and then there's the fact that oxygen sits down on that alkene.

What you get are three things – you get two epoxides, at least in this case, because the double bond had been flat, so that means that the reagent could have attacked from either face of the double bond, which means in cases like this where you have asymmetric products, you're going to end up with enantiomers. The other thing that you end up with is the by-product meta-chlorobenzoic acid. That's one way to make an epoxide.

We learned a second way last quarter. To do so, I'm going to do one of my common, favorite tricks, which is to add a deuterium. Recognize, deuterium's just a form of hydrogen, so once that becomes unsaturated, this is going to be a primary carbon – don't count the D as an R group, cause it's not; it's just a special form of hydrogen. I'm doing this so we ensure that we end up with stereocenters on both carbons, once we have our product, to help show what happens stereochemically in this reaction. What is the first set of reagents that we use here? What we make is a halohydrin – bromine and water. The result is going to be a bromohydrin, meaning that we have a bromine and a –OH group right next door to each other. One of the key aspects of this reaction is addition to the double bond occurs with anti addition. The –OH group that results – the –OH group does go to the more substituted positions, that's the Markovnikov product – it's going to be pointed the opposite way of the halogen that ends up on there. Notice that means that these two groups could be, even in a ring situation, in the antiperiplanar configuration that we need for elimination to occur. The second step of this reaction is for sodium hydride to be used to make an alkoxide. If you have the alkoxide pointed one way and the leaving group the other, S_N2 can happen, just happens to be intramolecular S_N2. In both of these cases, we're going to end up with enantiomers, because the original double bond was flat. So product's going to be a pair of epoxides. This just review – how do we synthesize.

I want to show you two examples of the way that epoxides react. We're going to explore the fact that, because this is a strained three-membered ring, it can be opened. It can be opened under two different sets of conditions – cationic, which is generally acidic conditions, or anionic, which means generally basic conditions. First, we're going to do cationic, acid catalyzed ring opening. We could, for example, do something like this. I'm going to take the same generalized chiral epoxide that I just generated, the one that has the deuterium, and let's say that I react it with ethanol and TsOH. What does TsOH stand for? Tosic acid. Is any portion of the tosic acid going to remain on this molecule after the reaction is over? Specifically, is the tosylate portion of the molecule in any way going to end up on our product molecule? No. That is one of the most common wrong answers I see when I put tosic acid down, because if you don't remember what the structure is, you think it has to go somewhere, so in the answers, people try to stuff that into the product. Doesn't work that way. Remember that tosic acid is this organic-soluble, easily-handleable cheap solid that's a strong acid that has a conjugate that's not nucleophilic. If it's not nucleophilic, it's not going to react. It is only here as a source of H⁺. What does happen? The alcohol is not a good nucleophile; it's a weak nucleophile. So even though the ring is strained, an alcohol alone won't do it; that's why we have the acid catalyst.

The first step of the reaction is, in fact, for the oxygen of the epoxide to get protonated. Quite technically, I could call this a cyclooxonium ion; what other intermediates from what reactions last quarter does this look an awful lot like then? Where have you seen reactions before that had some three-atom ring with a positive charge on one of the atoms of that ring? Oxymercuration, where we had the mercury that was positively-charged; that's the cyclomercurinium ion. What other reaction? The cyclobromonium ion, where we had Br₂. That's what you form in the first step of Br₂ and water, you form a cyclobromonium ion. The reason I'm bringing this up is if you had something like this, where you have a primary versus secondary carbon, the bond from oxygen is weaker to which of those two positions, the primary or the secondary? If one of the two bonds on that ring's going to break, which one is going to break more easily? The bond to secondary carbon. Why? Because if we formed a carbocation – which we don't in this reaction – but if the ring popped open by itself, it would make sense that it would form the positive charge on the secondary position instead of the primary. That's because of hyperconjugation. If that's true, if it's easier to form the carbocation on the secondary position, that means that the bond to the secondary position is weaker and longer, and therefore that's what breaks, breaks. This bond, going to the secondary position, is longer and weaker because if it broke on its own, a more stabilized carbocation would form. If it broke on its own; it doesn't. It's exactly the same as in those mercury and bromine intermediates. Something comes along and pops the ring open. The reason that's important is because stereochemistry is specific. You're going to have inversion of configuration occur wherever the alcohol attacks. Now let's show the alcohol attacking, which pushes the ring open. The acid catalyst helps destabilize it more, makes the three-membered ring even less favored. It allows something to attack it and push it open, therefore, but that attack and opening is concerted, which is why you end up with inversion of configuration at that point. So initially, you have a positively-charged intermediate, which deprotonates, and we end up with a molecule that has both alcohol and ether functionality. Notice that the reaction under cationic conditions ends up putting the ether at the more-substituted position.

Now for the anionic base-promoted ring opening. I really want to drive in this difference in regiochemistry that occurs whether you use cationic or anionic reagents. This is going to be anionic. It's not base-catalyzed. It's called acid-catalyzed because notice that the last step, we get the H⁺ back. Technically, it's a different H⁺ than what we started with. Base-promoted, that's a phrase that we use because the base is going to end up a part of the product. Starting with that same chiral alcohol... For the cationic version, we used a weak nucleophile, a neutral one; for the anionic, the basic one, we're going to use an ionic nucleophile, an alkoxide. A strong enough base is able to open up the epoxide all by itself. Where do you think the attack is going to occur this time, on the more the less substituted position? Less, because since there is nothing else further destabilizing the ring, this really turns into a question of kinetics. This is very much like a plain old S_N2 reaction; we're just using an unusual form of leaving group – oxygen's being the leaving group, but only because of the three-membered ring. The primary position is less sterically hindered, and so the attack is going to occur at the primary position. This is concerted, meaning the ring opens the same time the attack occurs. It's not that this is S_N2 and the first one is S_N1, but that would be a reasonable parallel to expect because S_N1 is a cationic process, S_N2 is an anionic process. If I said S_N2 here, it would have made sense you thought S_N1 previously. But, the stereochemistry is inverted with cationic conditions. Make sure you don't automatically one as S_N2/S_N1. Here because the attack is simultaneous, we have inversion of configuration, but because the primary position is less sterically hindered, it's the one that gets attacked, which means it's two things: that's the one where the inversion of stereochemistry occurs, but that means that the ether that forms is going to be at the less substituted position. Now if we had no further reagents, this is where we would end up potentially, so there is a second step when we write this out synthetically that we must include. Normally I wouldn't write anything that looks like synthesis while writing a mechanism, but I want to highlight the fact that I'm going to switch to acidic conditions – I'm going to switch to acidic conditions. [Remember that you can't mix acid and bases because they'll just neutralize each other.] So in the process of writing a mechanism, if you start with H⁺, you never can write an OH⁻; if you start with OH⁻, you can never write an H⁺. You have to put a 2 here to show you're going from basic ... recognize that that's an alkoxide, that's base, so there's no H⁺ around, no appreciable, useable quantity of H⁺ in solution. So if I want to write H⁺, I have to put the 2 there. Since I did put the 2 there, that means it's ok for me to write H⁺ to get us to our product, which has both alcohol and ether functionality. The regiochemistry has been inverted.

Formal charge and oxidation state and both counting systems in which the number of electrons around an atom in a molecule [is] compared to the number of electrons that atom would have in its unreacted elemental state. The only difference between the systems is how the electrons in bonds are distributed.

Formal charge: Each bond is treated as if it is purely covalent, meaning one electron is given to each [atom] in the bond (per bond). → homolytic cleavage

Oxidation state: Each bond is treated as if it is purely ionic, meaning the both electrons in the bond are give the more electronegative element.* → heterolytic cleavage. *If a bond is composed of two of the same atom, it is treated as a covalent bond, since neither atom is more electronegative than the other.

- Each atom that is more electronegative than carbon (N, O, Cl, Br) will cause a +1 O.S. on the carbon it is attached to (per bond).
- Each atom less electronegative than carbon (H, B) will cause a -1 O.S. on the carbon it is attached to(per bond).
- If a carbon is attached to another carbon, neither carbon causes a change in O.S. on the other.

Oxidation – Selective oxidation of primary alcohols – *anhydrous conditions

PCC – pyridinium chlorochromate

1° alcohol can be selectively oxidized to an aldehyde.

If an equilibrium can be established, it will be established, meaning there will always be some non-zero quantity of products present, even if the formation of products is unfavorable.

In the presence of water, a 1° alcohol will over-oxidize to a carboxylic acid.

When aqueous conditions are used, aqueous CrO₃ is used instead of PCC (cheaper).

Jones – CrO₃, H₂O, trace H₂SO₄

2° alcohols can only be oxidized to ketones

Epoxides

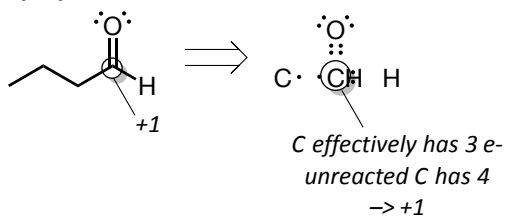
MCPBA – m-chloroperoxybenzoic acid

Cationic, acid-catalyzed ring opening

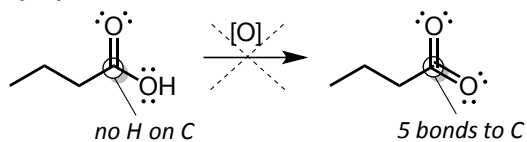
Anionic, base-promoted ring opening

Structures (remaining structures identical to lecture 4B)

01/23/12 lec • 1

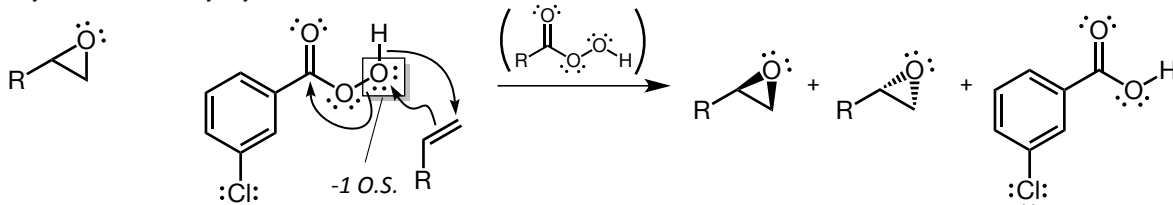


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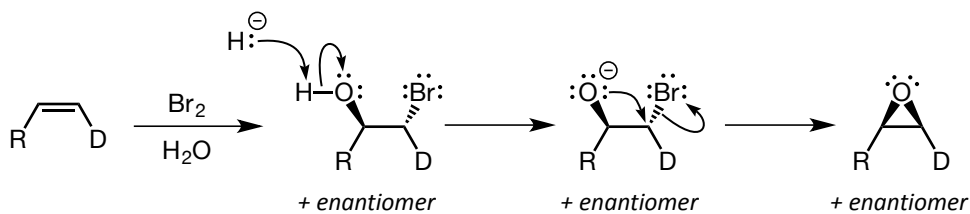


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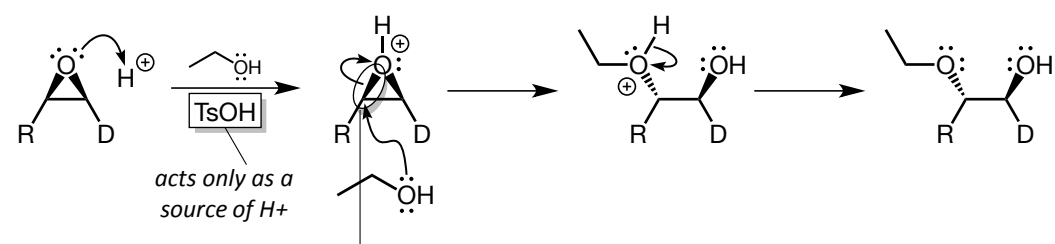
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01/23/12 lec • 5



01/23/12 lec • 6



This bond is longer and weaker than the bond to the 1° carbon because if the bond broke on its own, a more stabilized carbocation would form.

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