

Lecture 5B • 01/24/12

We're going to be talking about epoxides today. As a reminder, an epoxide is a functional group that's essentially a type of ether; it's an ether in which we have a three-membered ring, two members of which are carbon, one of which is oxygen that's bridging the two. Last quarter, we learned two different methods for synthesizing epoxides. One of them was to use the reagent MCPBA. MMPP is another reagent sometimes used. The acronym MCPBA stands for meta-chloroperoxybenzoic acid. Benzoic acid is benzene with a carboxylic acid group attached to it; peroxybenzoic acid means you've got an additional oxygen; meta is a position two away from where the carboxylic acid group is. I'll put parentheses here that we can more generally use, in theory, any peroxy acid to cause this reaction, but there's only one small problem, in that many, many peroxyacids are explosive – shock hazards where often you just shake the flask and it causes it to, well.... This MCPBA is used because it is a much more stable reagent, not really as prone to that kind of sudden decomposition. MMPP, magnesium monoperoxyphthalate, that's also one of these more stable reagents. How does it react/ It's the oxygen-oxygen bond that's weak here, so the oxygen furthest from the carbonyl is the one that's more reactive; the oxygen directly connected to the carbonyl has the potential to enter resonances, which is why it is not as reactive an oxygen.

What's the mechanism for this reaction? This is what's known as a pericyclic reaction, meaning that there's going to be effectively a circle that goes on as far as transfer of electrons. It's got two circles, you could say, connected to each other, because effectively what happens is that the end oxygen sits down and reacts with that double bond, forming the three-membered ring. I'll show the reaction occurring in this way: let's say that the double bond does attack that oxygen, because the oxygen-oxygen bond is weak. What would be the oxidation state of either of those two oxygens? -1, which is not the -2 oxidation state that oxygen would normally have; that's because of the oxygen-oxygen bond. If we were to do an analysis of this, oxygen, when it's connected to another oxygen, we treat that bond as if it were covalent, even if we're trying to determine oxidation state. If we look at the oxygen as connected to a hydrogen versus an oxygen, from the hydrogen, it would get both electrons; from the oxygen, you would only get one electron under this counting system. The atom effectively has seven valence electrons by this counting system, versus the six it would have if it was an unreacted oxygen. Seven versus six, that's why it just has a -1 oxidation state, and therefore would like to be reduced – which happens when it gets the electrons from carbon. When oxygen's attacked, the oxygen-oxygen bond breaks, which I'm going to show swinging over and attacking the carbonyl, because once you've broken that bond, you do have something that could undergo resonance. So by that pair of electrons attacking the carbonyl, that pushes the carbonyl open. Except, it turns out that the hydrogen in real life is close enough that, when the carbonyl opens, it can just reach out and grab that proton, because effectively what we have is benzoate, which is a base, and then we had an acid, so it would have been acidic. Well, if it takes that hydrogen, the oxygen-hydrogen bond breaks and that pair of electrons collapses towards the alkene, to finish forming the epoxide. You can see that there's three arrows – the oxygen-oxygen bond breaking, the carbonyl opening, and then hydrogen being grabbed like it's in a circle, and then we have this other pair of arrows as well. Since the alkene was planar to begin with, then we're going to end up with (potentially) two products, that would be enantiomers of each other. If we had a symmetric alkene, something that has the same groups on either side of the double bond, then we'd only end up with one product, because we wouldn't have chirality.

That's just one way of making the epoxide. Intramolecular S_N2 [is another]. Which functional group is it that we used to do that? A bromohydrin. So we use bromine and water to make the bromohydrin, and then you can do a deprotonation. Let me show you an example. I'm going to throw a deuterium on here so I can better show stereochemistry. Bromine and water, the bromine goes to the less substituted position, because bromine first forms a ring, and then water comes and pushes it open. Water ends up attacking at the more substituted position, which would push the halogen to the less-substituted position. Water ends up at the more substituted position. Remember that this is an anti addition, because water attacks from the opposite face of where the bromine originally ends up. Remember that the alkene was planar, so can get this product but we will also get the enantiomer. What you would use next is something like sodium hydride, which could deprotonate that oxygen. These groups, the oxygen and the leaving group, are now opposite of each other, even if this have been down with a ring, a cyclic alkene, the groups would be opposite each other, which means they would be able to get into that antiperiplanar configuration, which means you're going to have an intramolecular S_N2 reaction.

Let's talk about reactions of epoxides. We're going to talk about mainly two types of reactions today: one in which that ring is going to open in a cationic method, so we're going to use an acid catalyst. Cationic, acid-catalyzed ring opening. A three-membered ring is definitely strained, but it can be formed. But even though it's strained, it won't automatically fall apart, necessarily; you have to sorta help it along one way or another. In the anionic reaction, we have something pushes the ring open; for the cationic reaction, the reason the reaction is acid-catalyzed is in order to encourage that ring to be more reactive, it's going to get protonated first. Let me take on of the enantiomers from the synthesis above to show this reaction on. We have acid catalyst; the only thing that makes sense to react first is the oxygen. [commentary on reversible arrows] We do put a proton on, which is going to destabilize the ring. What kind of intermediate does this look like? What reactions from last quarter does that structure look an awful lot like? Like the cyclomercurinium ion? What about the cyclobromonium ion? The logic of what happens next is exactly identical to the logic that we used last quarter to talk about which one of the bonds in this ring is going to break. You might look at this and say, oh, if something's going to come attack the ring, then maybe kinetics is the more important consideration – how hard is it physically for the thing attacking to get to the molecule.

That's not when ended being the case in either the bromonium or the mercurinium ion cases. In that case, we looked that the two bonds and said one of the two bonds is going to be weaker than the other. Which is the weaker bond (the way that I have written it), the one on the left or the one on the right? Is this a primary, secondary, or tertiary position? Is deuterium a carbon? No, this is a primary position; there's only one other carbon attached to where my finger is. Is this primary, secondary, or tertiary? Secondary, so where would a more favorable carbocation form, on a primary? On a secondary, right? There is not a carbocation that forms in this mechanism, but you could imagine that it could form carbocation. Because it turns out to be easier to form a carbocation on a secondary position, that means the bond is weaker to that position because what you make would be more favorable. The bond to the primary position, therefore, is stronger, because it wouldn't want to break at all because you'd end up with a primary carbocation. So the bond on the left is weaker and longer because of the potential to make a carbocation. To the bond on the left is longer and weaker than the bond to the primary carbon, because if the bond broke on its own, a more stable carbocation would form. The positive charge that may form during the reaction is more favorable on the secondary than the primary.

Generally, there's an alcohol or water that's used as the reagent; I'm just going to use an alcohol as my first example. Now that the ring is protonated and it's destabilized, now an alcohol would be able to attack. Why wouldn't it have been able to attack before? Because it's a weak nucleophile – remember if we have something neutral like this, it's neither basic nor acidic, really. If we wanted to force the ring open, we need to use a base, an alkoxide. But since we just have an alcohol, it had to wait for this protonation to occur. Now that it's occurred, it can push the ring open. Notice that it's a concerted mechanism, so it has some of the feel of S_N1 , in the sense that we're worried about the potential to make a carbocation, but notice that you never do make a carbocation, and there's stereochemical evidence for that, because we're going to end up with a very specific configuration to our stereocenters. The important thing is that we're going to have inversion of configuration, where the ether attacks. Notice that the alcohol that's formed is at the less substituted position, and the ether forms at the more-substituted positions, and we have one final deprotonation step before we get to our product.

Let me briefly introduce to you the anion version of this. This is not base-catalyzed. The previous reaction was called acid-catalyzed because you get the proton back after the end of the reaction. Here, the base is going to be incorporated into the product. We can use the same starting material. The key difference in this reaction is, before, we had a weak nucleophile that could not directly force the ring open. But now, we're going to use a basic alkoxide. Because this a base that's going to approach and force the ring open, it's no longer carbocations that matter – we're not going to form one at all – it's sterics that are going to matter. Wherever the less sterically-hindered side is, that's where the attack is going to occur. The alkoxide attacks that position, pushes the ring open, and because sterics matter more, notice that ether is at the less substituted position. In these types of reactions, nothing further would normally happen, unless we switch reaction conditions. We've used the base up, we've pushed the ring open, we've made another base that has nowhere else it can go. We [must formally] switch reaction conditions. In this case, you would list the alkoxide, and then as a second step – a work-up step – you would show H^+ , which would finally protonate the alkoxide that was formed, and we'd end up with our product.

Epoxides

MCPBA – m-chloroperoxybenzoic acid

Cationic, acid-catalyzed ring opening

Anionic, base-promoted ring opening

Structures

Identical to those from lab 3A (01/23/12)