Lecture 23B • 11/29/11

Electrophilic addition to alkenes

We'll start with a simple electrophilic addition. For the example, I'm going to use this somewhat contrived alkene. The reason I'm doing this is because if have the right kind of substituents that are going to add to the double bond, we're going to end up with both positions of that double bond having stereocenters. I'm using this example to show fully what types of products that this mechanism will end up producing. Our first reagent is HBr, a strong acid, something in which the H+ would act as the electrophile. If you have an aqueous solution, HBr would actually start out as dissociated, so if I'm showing it as a molecule here, then when I have the double bond attack the hydrogen, I also need to show the hydrogen-bromine bond dissociating. There are two potential products that we form: one of those possible products is where you could have hydrogen substituted at the position where the deuterium is in, which would end up generating a tertiary carbocation; the other other possibility is if, instead, the hydrogen adds to where the methyl and ethyl groups are, which would instead cause the formation of a secondary carbocation. Tertiary carbocations are more stable than secondary carbocations, so it's going to be the first of these two intermediates that's by far preferable in this reaction. I'll talk about how this regiochemical behavior, this trend, is known as Markovnikov addition.

Let's first complete the mechanism; instead of focusing on regiochemistry, let's focus on stereochemistry. I've showed the same initial starting step. Even once we decide that the tertiary carbocation would be more favorable, we need to recognize that the double bond is planar. You can imagine that the hydrogen, from the perspective of the way it's drawn at the moment, can add on top of the double bond, or it might add on the back side of the double bond. Those are going to produce two different stereoisomers, based on that addition. Hydrogen's going to end up where the deuterium is, so that's now going to end up becoming a stereocenter. I'll show one version wherein I leave the carbon framework in the plane of the paper and have the deuterium pointed out; the other possibility would be the hydrogen pointed out, deuterium pointed in.

That carbocation that's formed, either one of those is also planar. We stil have bromine around in solution. Bromine at this point will now act like a nucleophile. It's not exactly and Sn1 mechanism, but it has similarities to it. In the Sn1 mechanism, because you could have attack from the top or the bottom, you end up with two products; the exact same thing's going to happen here. I'll show the mechanism written on just one of these intermediates; recognize it would happen to both of those intermediates equally. Two intermediates form due to the alkene being planar. From each intermediate, two products will form because the carbocation is planar. If I write all possible products, I could represent it in this way: I'll first start out with the frame that's in the plane of the paper. Then, we have the two intermediates, so there'll be two products where we have the deuterium pointed out, and we'll have two products where hydrogen is pointed out. On the new stereocenter that's now formed, once bromine attacks the carbocation, we'll have two possibilities on each of those cases. The methyl group could be out, bromine in back for both intermediates, and then we'll have the possibility of bromine pointing out for both intermediates. The reaction potentially produces a set of four diastereomers – I say potentially, because this is a rather contrived case that does give us stereocenters both where the hydrogen adds in and the bromine adds in. But if you have had a much simple alkene, or, let's say, and alkene where the double bond was at the end of the molecule – at the end of a molecule, unless of you have deuterium or something else to somehow make a stereocenter, you won't have a stereocenter there. It's even possible, in certain cases, where you may only end up with one distinct product. That's why I'm using this particular example to show all of the different potential stereochemical outcomes.

We have four diastereomers that form, but I should point out that these are pairs of enantiomers as well: the first and the last compounds are enantiomers, as well as the two middle compounds. I could say in this case, because I started with no stereocenters and only one alkene, I'm going to end up with an optically inactive mixture, because there's equal probability of any of these cases happening. Since they would all be in equal probability, and since they're pairs of enantiomers, their optical rotations would cancel each other out.

I want to go back to a previous example. You gotta be careful when you make generalization of reactions like this to say that you'll always end up with an optically inactive mixture in this kind of mechanism. That's not necessarily true if you have another stereocenter on the molecule. To demonstrate what I'm talking about, let me backtrack a little and talk about an Sn1 reaction example. Let's say that I had this substituted haloalkane – a haloalkane that's also an ether. Let's say that I react that compound with water and heat. Would you think that any reaction would be possible? Yes? If we have water, what kind of nucleophile is that? It's a weak nucleophile. What kind of substrate do we have? Secondary substrate. Secondary substrates can undergo Sn1 reactions, and weak nucleophiles encourage Sn1 reactions. Because water is weak, you're not going to have Sn2 in this case, because Sn2s not that great for secondaries, possible but not great, and it's a weak enough nucleophile the carbocation can form. Let's say that, for the sake of argument, this methoxide group over here – by the way, why is methoxide not a leaving group? Why is methoxide a terrible leaving group? Br- is the conjugate base of a strong acid, methoxide is the conjugate base of an alcohol, which is not really acidic at all, in a sense, it's got a pKa value of somewhere between 16 and 18, so it's more like water in terms of its acidity. If you force methoxide to form, it's not going really going to want to be a leaving group at all.

So bromide, being the good leaving group, can undergo the reaction. If we're saying, for the moment, that methoxide has no influence on the molecule, we should, in theory, get a 50/50 mixture of two products.

Assuming, for the moment, that we do have a 50/50 mixture that is produced, will the mixture be optically active or inactive? We still do have one stereocenter present, don't we? Whenever we're talking about cancellation of optical activity, we've always talked about enantiomers in the past. But these are not enantiomers of each other, because they have two stereocenters, one of which is not inverted as we go from one compound to the other, so yes, the optical activity that might be generated by that one stereocenter might be canceled, but the optical activity of the stereocenter that remains that's the same on both molecules does not get canceled and so it's going to have an effect on the optical rotation. In all of the examples that we've done up to this point where we have substitution, there was only one stereocenter, so if we had an Sn1 occur, we said that a racemic mixture was produced. This is not a racemic mixture because it's a mixture of enantiomers. It's not a trick question; you just have to make sure that you analyze your products to see are they really enantiomers before you try to say that something is optically inactive. Even if the two products form in equal quantities, the mixture will still be optically active, since it is a mixture of diastereomers and not enantiomers. Another way to express it is that one stereocenter is not cancelled out. That was just a comment on stereochemistry.

Let's go back and cover those six aspects of the reaction [electrophilic addition]. First, the synthetic utility. This first example showed an alkene being converted into an alkyl halide. In a moment, we'll see another version, almost identical, in which we produce an alcohol instead. That same mechanism that could be used to produce an alcohol would also be able to be used to produce an ether. In terms of the reagents, you need a strong acid as the reagent, or, a weak nucleophile with a strong acid catalyst. In the first version of the mechanism we say, the reagent itself both was the acid source, the electrophile source that began the reaction, but it was also the source of the bromide that came in for the secondary attack. The mechanism that we're going to see momentarily is one which there's water present as a weak nucleophile, which won't initiate the reaction with the alkene, but we're going to have a strong acid source that that will cause the alkene to being reacting; that's the other set of reagents that are possible.

As far as conditions, this reaction occurs with fewer byproducts if it's shielded from light. Light can cause alkenes to form radicals – specifically allyl radicals. No light would encourage a more successful reaction. Mechanism, it is essentially cationic, and therefore stepwise. Of course, you could look at the last step of the reaction and say wait, how's that cationic when you've got an anion like bromi[de] attacking? Realize that the rate-limiting step, the most important step in the reaction, is the reaction of the alkene itself, which requires the use an electrophile and causes the production of a carbocation. Because you make a carbocation, we're going to have the possibility of carbocation rearrangement. The same kinds of consequences of having a cationic reaction show up here. Even despite that last step, I'm going classify overall this reaction as cationic in nature.

In terms of stereochemistry, if there's no other double bonds and no stereocenters to begin with either, you're going to get a mixture of four diastereomers. I'll also express it this way: neither syn nor anti addition. Syn addition refers to if you have a reaction of a double bond, two atoms adding to the double bond both add from the same direction. If we imagine a double bond being in the plane of the paper, so that the p orbitals are pointed our towards us or pointed back into the back of the board, syn addition would be as if both atoms substituted from one side, either the front side or the back. Anti addition would mean that you have addition on one carbon from one side versus one carbon the opposite side something would add to. In this case, we end up with both possibilities, because we have four equally-likely possibilities. We don't have specifically either syn or anti addition. Syn has to be either both from the back or both from the front.

As far as regiochemistry, I'll go ahead and define Markovnikov addition, which is that substitution will occur the most substituted carbon. Substituted means having a tertiary versus secondary versus primary carbon involved in that position of he alkene. Substitution at that position – what I mean by that is if we review the mechanism that we've done so far, it was initiated by the double bond attacking an H+. But then, afterwards, something did come in and attack the carbocation that was formed; that object that attacked you could call a nucleophile. It ends up, therefore, substituting at that most substituted position. That's because the carbocation wants to form at the most substituted position. Another way of expressing Markovnikov addition is you end up with the product where the carbocation forms where it is most likely to form. Most electrophilic additions that we see are going to be Markovnikov additions.

There's one other aspect to regiochemistry, which is the fact that you have carbocation rearrangement possible. I'd like to show you a second alkene mechanism. Let's say that I react this alkene with water and this wonderful compound p-toluenesulfonic acid. This is a fantastic acid catalyst, because it is an easily handleable solid that is organic-soluble; it's inexpensive; it's a strong acid; and, the conjugate base that it ends up forming is non-nucleophilic, so you don't have to worry about it causing any secondary reactions once it has done its job as an acid catalyst. Let me just point out that if I circle everything except the –OH, you might remember that I had abbreviated that as Ts. p-Toluenesulfonic acid can be written as TsOH, or, in the same way that we shorten that and call the anions from these kinds of structure tosylates, we can call this tosic acid. Tosic acid is an inexpensive, easily handled organic-soluble solid that is a very strong acid and has a conjugate base that's non-nucleophilic, which makes it an excellent acid catalyst.

How does the mechanism work? It starts out the same way as the mechanism we saw first. The alkene is going to end up attacking an H+. Notice I did not write the full structure of tosic acid. That's for two reasons: one, I'm trying to simplify; we could be endlessly worried about where are all of the different H+s are coming from and going to in a reaction, but it kinda misses the point of the mechanism: what's happening to the substrate itself. In addition, since tosic acid is such a strong acid, you could even argue that's already going to be heavily dissociated in the first place, so there very likely is free H+ floating around in solution. [policy on showing H+] Since we have the acid catalyst, simplify showing H+ which, once that hydrogen adds in, it's going to end up on a carbon that already had two hydrogens on it, which means that no stereocenter is formed in this process. We do end up with a carbocation, but, that's a secondary carbocation. Since it is a carbocation, hydride shifts are possible, so we'll end up instead with a tertiary carbocation. Water is still present, so water can now attack that tertiary carbocation. It technically could do so from two different directions, but, you have two methyl groups at that position, so you're only going to end up with one unique product. Unlike the initial reaction, since we did start with a neutral nucleophile, there is going to be, as we often had in the past, a final deprotonation step to get us to our product alcohol. This will, by far, be the major product of the reaction; this is therefore one of the downfalls of this reaction: you can't, in a sense, control regiochemistry. If you knew this would happen and predicted this would happen, then it would be a beneficial reaction, if you know you were going to end up with the tertiary alcohol. But let's say that we wanted to end up with a secondary alcohol; that means we're going to have to take some other approach. This is just to show that we can have carbocation rearrangement.

Now let's see a second type of reaction where we could end up with just a secondary alcohol. This has the somewhat daunting name of oxymercuration-demercuration. As you can guess from the name, there is mercury involved, which means this is not necessarily the most environmentally friendly solution to the problem, but it is a classic reaction that is still used at least in laboratory settings, and it's in all the organic textbooks as, usually, the initial example of this second brand of mechanism. When we talked about [halogenation using bromine], we talked about these interesting cyclic intermediates that end up being formed; that was a distinct kind of mechanism. It turns out that mercury, this particular mercury reagent, also goes through the same cyclic types of intermediate. Let's see what would occur.

To again fully see the stereochemistry of all of the different products, I'm going to use that same starting alkene, the one that had two different alkyl groups on one side and then an alkyl and a deuterium. This at least sets us up so that we have a secondary versus tertiary position, and we're going to end up with stereocenters at both positions. The reagent used is mercury acetate. Ac, acyl, is an abbreviation often used for CH3CO. Acetic acid, for example, can be represented as AcOH; acetate, therefore, AcO-. The reagent involved is mercury(II) acetate. There are a number of ways of writing this mechanism. Let me describe what happens first and then we can understand why there are alternative ways to write the mechanism. Because, mercury is so big and squishy, like bromine is, that when it is attacked by a double bond, it essentially does not end up at just one carbon or the other. There's an intermediate that forms where it straddles both of the carbons, forming a cyclic intermediate. You could show the double bond attacking mercury and kicking off acetate as a leaving group. But, what's often showed also to highlight the fact that you're forming a cyclic intermediate is to show a pair of electrons from mercury attacking back in response. In other words, this is the way that it's often represented.

What will be the charge on mercury that results? It's effectively now made two bonds with two different carbons, but it's only lost one bond when acetate is kicked off; so, in the intermediate, mercury's going to end up being positively charged, with acetate being around as a counterion. We have the same kind of problem writing these cyclic intermediates that we would have run into with the bromine reaction, which is: how are we going to properly show stereochemistry? Cause we're starting out with something that's flat. We have this idea that yes, mercury can sit down on the front or the back of the alkene, but then how are we going to represent this properly with dashes and wedges on paper? What I'm going to do is I'm going to say that the methyl group and ethyl group, we're going to pretend that they're immobile8 somehow. If the mercury was to come from the front, it's going to end up pushing the methyl and deuterium in back, so that the mercury itself would be in front with a wedge. Or, you can imagine that it's going to come from the back, which means we'll write mercury with a dash, it'll end up pushing the methyl and deuterium towards us in the front. That will allow me to write the ring itself as either wedges or dashes while keeping the long chain, the main chain of the compound, in the plane of the paper. In other words, we get the following. For just this portion of the mechanism, this much of it would be considered syn addition, because notice that mercury is pointed the same direction from either carbon in either of the two intermediates that could form. It is, in fact, physically impossible to have a three-membered ring in which one bond is pointed one direction, a second bond is pointed the opposite direction, and somehow those two bonds connect to the same atom. The bond itself would have to twist in space for that to be possible, which it's not. You can't end up with a three-membered ring where one is wedge and one is dash; not physically possible. The initial step of this reaction occurs as syn addition. Both new connections to where the double bond had been located point the same way.

What happens next is, in some ways simple, in some ways kinda a complicated story, cause there's both a stereochemical consequence of this reaction and a regiochemical consequence. The regiochemical consequence is that this still ends up being Markovnikov addition. One of the reagents I have not yet shown is water. This is a reaction that, overall, is going to produce an alcohol. Water's going to be involved; water's going to attack this three-membered ring. If I'm telling you that this ends up being Markovnikov addition, then that means that water's going to end up attacking the tertiary position. In fact, it will only attack at the same time the mercury ring is opened.

Given that behavior that it's attacking at the tertiary position and that it's a simultaneous attack ofthat nucleophile on the mercury that, in a sense, ends up being a leaving group, why would that be unusual? Why would that seem strange, with what we've just recently learned? That, in this reaction, let me just show you the mechanism what occurs. In fact, before I show you the mechanism, let me write down this intermediate has the name cyclomercurinium ion. Which is just a technical way of saying a cyclic, positively-charged mercury ion: mercury; mercurinium; cyclomercurinium. The reaction step that happens next is that water attacks the ring at the more substituted position, simultaneously kicking open the ring. Of course, this happens with the enantiomer as well. [ok to say "plus enantiomer" when writing a mechanism].

The product that we end up with – I'll show both products at least – is where mercury ends up at the less-substituted position, and the attacking nucleophile – water – end up at the more substituted position. [There is one last step:] to allow the hydrogen on water to come off, so that we can at least end up with a neutral intermediate. [The two products] are enantiomeric. To be complete about it, let me show you that the two things added in – the -OH group and the mercury, overall, this addition occurred as an anti addition, because of the fact that the ring does not open until water comes to attack. If the ring opened by itself, then we should, in theory, get four different products, because each of the two possibilities: mercury pointed towards us or away from us on one stereo, would then be accompanied by water, in either of those cases, being pointed towards us or away from us, so we should end up with four possibilities. But, we don't, and the explanation for that is the ring does not open until attack occurs. Overall, this reaction occurs with anti addition. The ring does not open until the nucleophile attacks the ring. There's also no carbocation rearrangement, because a carbocation never forms.

Let me go back to the question I was asking earlier, which if this is the mechanism, if this is a concerted step, water's attacking at the same time that mercury is opening up, what reaction that we've seen would closest resemble this? Sn2. But Sn2 does not occur for tertiary substrates, and yet it is the tertiary position at which attack most occurs. What could be going on here? What happens is this cyclomercurinium ion is not balanced. The two bonds from mercury are not the same length, because if the bond going to the tertiary position were to break, you'd form a tertiary carbocation, which is more favorable. Since it's more favorable, that bond would more easily break. Versus the other bond, which is to the secondary position. Because it's to the secondary position, it doesn't want to break as much, because you'd form a secondary carbocation, which is not as favorable. So the tertiary position, because it's more favorable, the bond to it is weaker and longer and more ready to break. The secondary position, because it's not as favorable to form a carbocation, that bond is stronger and shorter and not as likely to break. This is why the ring preferentially opens on one place versus the other. The bond to the tertiary position is longer and weaker than a bond to the secondary position because the potential formation of a carbocation is more favorable at the tertiary versus secondary position. Realize also it's a three-membered ring, so it's strained, and it's positively charged, so it's even more strained. So, the ring does want to open, but one side is weaker than the other, and it's the weak side that ends up getting attacked, which explains why it looks like Sn2, and it still has, in fact, inversion of stereochemistry at that position, but it's not truly Sn2. The fact that the ring is strained is why it is occurring at a tertiary position.

There's one last step of this reaction. [This is a radical mechainsm, so] it's going to end up potentially scrambling the stereocenter at which the mercury is located. What happens – I'll show it with just one of the enantiomers – if we used the compound sodium borohydride – it is a source of H- which easily attacks carbonyl bonds (C=O double bonds). It will aslo, however, displace the mercury. This is the demercuration step of the reaction. Hydride, in some way, effectively displaces mercury, totally knocking it off the molecule, which means the overall transformation we were able to accomplish is we made an alcohol at the secondary position like I wanted to.

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Electrophilic additions to alkenes

Even if the two products form in equal quantities, the mixture will still be optically active since it is a mixture of diastereomers and not enantiomers (one stereocenter is not cancelled out).

1) utility – alkene -> alkyl halide, alcohol, ether
2) reagents – strong acid or weak nucleophile w/ strong acid catalyst
3) conditions – no light
4) mechanism – cationic + stepwise
5) stereochemistry – mixture of 4 diastereomers, neither syn nor anti addition
6) regiochemistry – Markovnikov addition* – substitution will occur @ the most substituted carbon (3° vs 2° vs 1°) –> carbocation rearrangement possible

Tosic acid is an inexpensive, easily-handled organic-soluble solid that is a strong acid and has a conjugate base that is non-nucleophilic, which makes it an excellent acid catalyst.
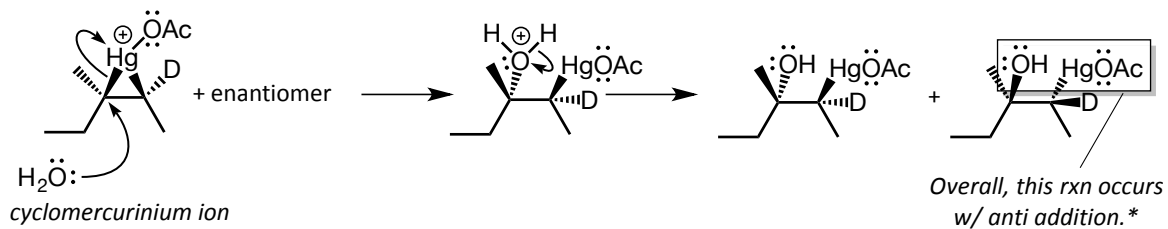
Oxymercuration-Demercuration

The initial step of this reaction occurs as syn addition (both new connections to where the double bond had been located point the same way).

*The ring does not open until the nucleophile attacks the ring. Additionally, there is no carbocation rearrangement since a carbocation never forms.
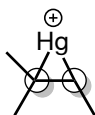
The bond to the 3° position is longer and weaker than the bond to the secondary position because the potential formation of a carbocation is more favorable at the 3° vs 2° position.

Structures *(remaining structures identical to lecture 23A)*

11/29/11 lec • 1

cyclomercurinium ion

+ enantiomer

+

Overall, this rxn occurs w/ anti addition.*

11/29/11 lec • 2   *11/29/11 lec • 3*

NaBH₄

sodium borohydride