Lecture 23A • 11/28/11

Electrophilic additions to alkenes

I'd like to go over a very specific case. The reason I'm doing this case I'm about to do is because it will generate stereocenters at both of the positions where the double bond used to be before the reaction occurs. This is going to be a deuterated alkene. We'll have a secondary – or what could become a secondary carbon – versus what could become a tertiary carbon. Alkenes do have pi bonds that have electron density that's not right directly in between the two atoms, so it's a bit more accessible to other things from the outside. Carbon-carbon pi bonds certainly break more easily than carbon-carbon single bonds. I'm going to [react] an alkene and HBr. The hydrogen in HBr is an electrophile – something that is electron deficient would not mind being attacked by something that has electrons: that's going to be the alkene. Hydrogen can only have one bond at a time, so if something is reaching out to attack the hydrogen, then hydrogen's bond with bromine has to dissociate. If we had an aqueous solution of HBr, we'd already be dissociated, but if I'm writing it as a compound, then formally I need to write that it's dissociating. You do need, for this mechanism, a strong acid or acid catalyst. This first mechanism we're seeing is where the acid itself is the reagent. There's a small number of reagents that will have exactly the same mechanism. This is the easiest case, so that's why we're tackling it first.

There's two regiochemical possibilities; we'll get to the stereochemical complications in a moment. If we just deal with the regiochemical possibilities. There's one of two carbocations that could be made: the hydrogen that just came from HBr could end up on what now is the secondary carbon, generating a tertiary carbocation; or, we could have that hydrogen end up at the now tertiary position, generating instead a secondary carbocation. Which of the two possibilities is far more likely to occur? The first possibility. Why? Because it makes a tertiary carbocation. If the secondary carbocation is so much less favorable than the tertiary, then it really just is not, in appreciable quantities, going to form. That first step of the reaction, when you have addition so that whatever comes next to attack ends up at the most substituted position, that's called Markovnikov addition. This is the regiochemical consequence – one of them. Later, we'll talk about carbocation migration.

This is the regiochemically preferred intermediate. Tertiary carbocation – more favorable than secondary. Why I chose to use a deuterated starting material will now become clear. When that double bond attacks the hydrogen, it could happen from above or below the position of the double bond, which means, in terms of dashes and wedges, the hydrogen might be pointed towards us or away from us. In other words, at that one position, because the double bond is planar, then, using the same logic that we used in Sn1 reactions, we can say that we're going to end up with two intermediates. [pondering benefits of having already covered fundamentals so heavily; potentially allows new reactions to be presented rapidly] The double bond can attack from the top or bottom, so we end up with two intermediates. Tertiary carbocation more favorable than secondary, so these are the two intermediates that will result. It's arbitrary how I draw this righthand stereocenter, so whether you want the methyl group in the plane as I've done, or whether you want the hydrogen or the deuterium, it doesn't matter. What matters is you can get attack from either side, and so you will form two intermediates.

What is the stereoconfiguration where my pen is, R or S? R. Two intermediates form due to the alkene being planar. Each one of these intermediates can be attacked by the bromide that's still in solution. In fact, if HBr is your only reagent, that's exactly what's going to happen. But, the carbocation is itself planar, is it not? Let's presume, for the moment, that the methyl group does not have a large steric influence on this reaction, because we have a sigma bond that, at room temperature at least, freely rotates, so at any one moment, there's equal likelihood that the carbocation can be attacked from either side. I'll show only one arrow; it gets confusing if you try to show with multiple arrows the multiple possibilities. Someone reading the mechanism, knowing the mechanism, it would be clear enough just by seeing this.... a person that knows about mechanism would already known that this should be planar and get attacked from both sides so we're going to end up with four products, which will be the following. The first two products will have the same kind of configuration on the righthand carbon; the lefthand carbon, in one case we could write the methyl group with a wedge or the bromine I could write with a wedge instead. That would be from the first intermediate; then we have two more possibilities of two more intermediates. So hydrogen on the right will be the wedge; the last possibility is .... So we get a mixture of diastereomers; but, they're also in the form of pairs of enantiomers, so if you notice, these first and last compounds, and so are the middle two. We will end up, in this case, with a racemic mixture.

I showed you a trick question related to Sn2 where I had two stereocenters, one of which reacted, one of which couldn't. If we had something like an ether, that does have a leaving group on it, is that ether going to want to be a leaving group? Will the ether itself want to be a leaving group? If I'd made –OH instead of an ether and asked the same question, would –OH want to be a leaving group? No. Hydroxide's a strong base, and strong bases don't want to be leaving groups. Leaving groups are conjugate bases of strong acids, which means the leaving groups themselves should be not basic. If you tried to kick the oxygen off with the methyl group that's attached, you'd end up with O minus; that's even more basic than hydroxide, so it's an even poorer base than hydroxide. This is not a leaving group because methoxide is a strong base. Let's say that, for the sake of argument, when I put it in water, this compound, I get a reaction in which that methoxide has no steric effect. Let's assume further that we do not form ion pairs. The ion pair formation is what explains why, even when you have a 50/50 chance of making products, it may not end up 50/50. Let's say that that doesn't happen; let's say the ethoxide has no effect.

So I end up, in theory, with the possibility of having equal proportions of these two products. Would this mixture be optically active, then? Yes, because even though the one stereocenter cancels out from one molecule to another, you still have one stereocenter that doesn't, so it doesn't matter that you've got 50/50 quantity, this is not 50/50 quantities of enantiomers, this is 50/50 quantities of diastereomers. Only if you have 50/50 proportion of enantiomers do you form a racemic mixture. Even if these two products form in equal quantities, the mixture will still be optically active, since it is a mixture of diastereomers, not enantiomers. One stereocenter is not cancelled out. In this case, because we only started with the double bond, there were no other stereocenters, and because the only stereocenters that formed were because of the reaction, that's why I say in this case we're going to end up with an optically inactive mixture, cause we'll end up with 25/25/25/25 proportions of the four major products.

[six aspects of the reaction] Alkene to alkyl halide. Or, you could also use the same mechanism to make an alcohol or an ether. What are the reagents? A strong acid, or a weak nucleophile with a strong acid catalyst; that's the variation that will let us make alcohols and ethers. What are the conditions? To really get it to perform correctly, no light, because alkenes, under light, specifically UV light, can undergo side reactions. The mechanism you have up above. In terms of stereochemistry, you have loss – actually, it's not loss of configuration, cause you didn't start out with any configuration, you could just say no configuration, no particular configuration, cause you potentially have a mixture of four diastereomers. There's another term that we haven't used yet. What is the relative position of the two new things that just added to the double bond? Imagine this piece of paper as the alkene. One position, something added to the top or bottom; the other carbon, independent of what happened with the first one, you still have the potential addition to the top or the bottom. You have one product like this, one product like this, one product like this, and one product like this. That means there's no fixed orientation due to the mechanism itself. There's what is known as syn addition to double bond, where both things add to the same face, the same whatever of the double. Then there's going to be anti addition, where on one carbon, one group points one way and one carbon, the group points the other way. That doesn't happen in this case. Neither nor syn or anti, in terms of the stereochemistry of addition.

In terms of regiochemisty, what do we have there? We have Markovnikov addition, which means that substitution will occur at the most substituted carbon. If you look at the products of the reaction, we stated out with an alkene that we effectively added bromine to; yes, we added a hydrogen in there as well, but in Markovnikov, we're discussing where addition occurs. Since so often hydrogen is the first thing added, we're usually talking about what comes afterwards; in this case, it was bromide. Bromide substituted at the more substituted position. Why? Because that's where the carbocation was more favorable to be formed. That's what Markovnikov addition's really about: the fact that if you had this choice between carbocations, the more favorable one is going to be the one that occurs. Most of the time, you really are going to get far more preferential formation of this Markovnikov product. Carbocation rearrangement is also possible. If we wanted to summarize this mechanism, it is cationic and stepwise. Cationic? But there's Br- minus involved? Yes, but that's kinda an afterthought, in the sense that the main part of the reaction, the rate-limiting step of the reaction, is the reaction of the alkene with the electrophile, which causes the formation of a cationic intermediate. It's because it's cationic, the intermediate, and specifically carbocationic intermediate that we have these carbocation shifts that can occur. When we say most substituted, we mean most [attached] carbons; tertiary versus secondary versus primary. Heat is not automatically a necessary condition for this reaction.

Let's see our second version of this. Recognize the incredible similarity and learn one general mechanism. The second reaction we're going to see is of this alkene with water and a favorite compound of mine – this is the compound p-toluenesulfonic acid. You might notice it bears a very striking resemblance to a particular leaving group that we've already discussed – tosyl groups. So although this is called p-toluenesulfonic acid, it is sometimes called tosic acid for short. We can even abbreviate tosic acid TsOH. Remember when we abbreviated tosylate, we did not include the oxygen as part of that Ts group. Tosyl doesn't have the oxygen in it. Tosyl hydroxide, there's no such compound, [it's] tosic acid. Why am I so enamored by this compound? Because it's a solid, it's cheap, it's a strong acid, it's organic soluble, and, the counterion is non-nucleophilic. Tosic acid is an inexpensive, easily handed organic-soluble solid that is a very strong acid which has a conjugate that is non-nucleophilic. In other words, it gives up its little H+, and that's all it's going to do. SInce it's a solid, trivial to measure out. Cheap. It's a catalyst, so we don't even use large quantities of it to begin with; it's organic soluble, so you know it's going to be in the mixture. Most importantly, it's a strong acid.

The first step of reaction will be that the alkene attacks H+, coming from the tosic acid. In this case, water would not be the proton source because water is not a strong acid; it would be coming form tosic acid. Once that reacts, there is only one intermediate that initially forms, because there are already two hydrogens at the end of the molecule; putting a third one one there, we definitely are not creating a stereocenter. Although in the first example I showed you we, at this point, had two intermediates, not always going to happen; it's going to be the exception for the examples that you see rather than the rule. At this point, there's this much more preferable tertiary position that the carbocation would be much more satisfied on than the secondary, so, you can and will get a carbocation shift. At this point, we have water left in solution. Water is able to attack that carbocation, and because we have two methyl groups at that point, we generate no stereocenter, so we still only have one intermediate which, unlike the previous case, has yet one more step, because water started out neutral, so once it attacks, it must first deprotonate before we get our product. Notice that we started out with a double bond between the primary and secondary positions, but we ended up with the alcohol, which is our product, at the tertiary position. They're positions which would become primary or secondary, but it doesn't happen because of the carbocation shift.

Can the carbocation move up and down the chain? Yes it can, so that ends up being a complicating factor in these reaction. That's exactly why reactions with carbocation intermediates can be a problem, which exactly why there are alternate reactions.

What if we really wanted to put an alcohol just at that position? What if you really wanted to have some kind of reaction that would carbocation migration and would give us the kind of alcohol that we want. This reaction I'm about to show you is a distinct mechanism from what we did before. This is called oxymercuration-demercuration. It is actually not the best alternative in terms of environmental friendliness, because it does use mercury-containing compounds as the reagent; specifically, it contains mercury acetate. Mercury is a big, squishy atom, like bromine is a big, squishy atom. I showed you a mechanism and said, here's normal electrophilic addition, which is what we've been reviewing so far. Then, there are these other mechanism, bromine reacting of which is one, that you have a cyclic intermediate that forms instead. There were several very important things related to that cyclic intermediate formation: specifically, what does it mean for stereochemistry, and what does it mean for regiochemistry. How do regiochemical differences manifest themselves in this reaction?

Let's use the same kind of contrived starting material so that we can again investigate all of the stereochemical possibilities. There's several ways of writing this first reaction step. I'm going to show you a hybrid of what I've learned and what I've seen in different textbooks. First of all, we're going to use the Ac abbreviation for acyl. The Ac group refers to the two carbons I've circled, plus the carbonyl. If you put an O on there, it becomes acetate, which is what the OAc abbreviation really means. Acetate will get kicked off when mercury gets attacked by the alkene. At the same time, there's effectively a pair of electrons on mercury that back attacks; that's one way of showing it. Some people will show just one arrow coming from the alkene itself. What both of these versions are trying to show is the fact that because mercury is a big, squishy atom, it will form a ring. We're also going to end up, because it's now made two connections to carbon, not just one, it's going to be positively charged in the intermediate. Let me write the two rings first, then I'll attach my substituents. The reason I've drawn it this way is to show the two possible configurations of the ring. Let's figure out where, relative to that ring, the substituents are going to be. Imagine that we're looking at the compound from down here, below the compound looking up at the plane of the paper. We could imagine mercury being on top here, in front of the board, or mercury can be behind here, behind the board. In either case, this ethyl group and the methyl group would be closer to you. The back methyl group and deuterium would be away from us. I've already got a wedge or a dash, so let's just choose that in this reaction, the ethyl and methyl groups will stay in the plane of the board, and then the methyl and the deuterium will either get pushed back or pushed forward by the mercury reacting. We'll keep the ethyl and methyl the same, but then the other groups will be pushed either backwards or forwards.

Notice that the two connections to the mercury are pointed the same way; it's not possible to have a three-membered ring where one group is pointed one way and one group is pointed the other, because you can't have a bond that twists 180° around in space, or 360° or whatever that would end up being. This one step occurs with what is called syn addition, because it adds to just one face of the double bond. At the same time that the wrap around mechanism's occurring, one of the acetates gets kicked off as well. That's why it's not double plus, because you do lose a minus during this process. This portion of the mechanism occurs with syn stereochemistry, occurs as a syn addition; both new connections to where the alkene was located are pointed the same way. It's not physically possible for just this much of it to be anti; you can't have the ring point one direction, wrap around in space, then magically end up pointing the other direction.

Here's the part that confuses people most about this mechanism. This is a cyclomercurinium ion; cyclo means cyclic, mercury, you put a plus charge, mercurinium – cyclic positively charged mercury ion. It's not a carbocation, so there's not going to be any carbocation rearrangement, because there isn't one. That's the regiochemical importance of this reaction, that you don't have carbocation shifts. But, what's going to happen next, because you have a ring. Water or something else might be able to attack on the lefthand side of that ring or the righthand side. Which side do you think it would make more sense for it to attack, if this was an Sn2-style attack? We have a secondary versus tertiary position, so if this was Sn2, we would expect that the secondary position should be the one that's more prevalent to attack. If we had an Sn2-style attack, what should happen to the stereochemistry at that position? It gets inverted, or should, right? What if I tell you that inversion occurs, but that the tertiary center instead. Why would it attack the tertiary position instead? It can't be sterics, because sterics would tell us to attack the secondary. This is really a kind of strained structure, having one atom that's bridging two others. One of these bonds is weaker than the other; which one? It might make sense, based on the answer that I gave you, that it's to the lefthand carbon. Why? Because, if you were to form a carbocation at that position, that would be the more favorable carbocation to form. That means, effectively, less energy would be needed to break that bond, because the carbocation that results is more favorable. At the same time that bond would take less energy to break, that means it's a weak bond. If it's a weaker bond, it is longer and more stretched and ready to break in comparison to the bond that is going instead to the secondary position, which if it were to break would produce a less favorable carbocation. This is not a symmetric ring; one bond is longer than the other – that's the one that break, and that's why attack occurs at the tertiary position. This reaction still occurs with Markovnikov regiochemistry; the eventual thing that gets added in, which gonna be water, is still going to occur at the more substituted position, because that's position the bond would prefer to break first.

Let me just show you the overall process that happens. Notice this is the first formal use of these 1s and 2s in class. What this means is the first reagent, including water, happens before you do anything with the second set of reagents. What you'll form first is a mercury intermediate that gets decomposed by this compound sodium borohydride.

The end result is going to be a mixture of two alcohols; it’s still a mixture because we still have the double bon that can be attacked from one of two different directions, that why we end up with the two different products.

____

Electrophilic additions to alkenes

Even if these two products form in equal quantities, the mixture will still be optically active since it is a mixture of diastereomers, not enantiomers (one stereocenter still 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
5) stereochemistry – no configuration (mixture of 4 diastereomers), neither syn nor anti
6) regiochemistry – Markovnikov addition* – substitution will occur @ the most substituted carbon.
* Carbocation rearrangement is possible.
4) mechanism – cation + stepwise

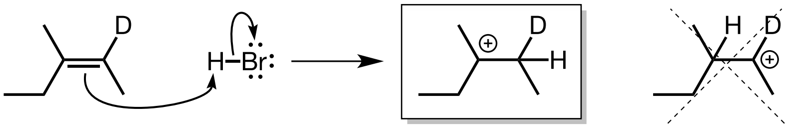
Tosic acid is an inexpensive, easily handled organic-soluble solid that is a very strong acid which has a conjugate that is non-nucleophilic

Oxymercuration-Demercuration

This portion of the mechanism occurs as a syn addition (both new connection[s] to where the alkene was located are pointed the same way).

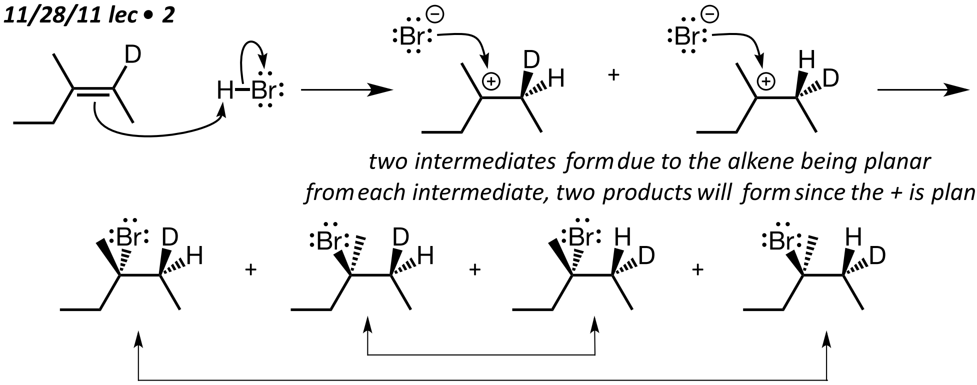
Structures

11/28/11 lec • 1



3° carbocations more favorable than 2° carbocations

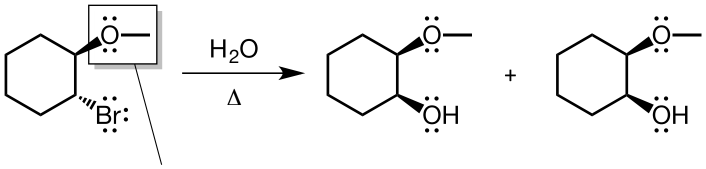
11/28/11 lec • 2



two intermediates form due to the alkene being planar
from each intermediate, two products will form since the + is planar

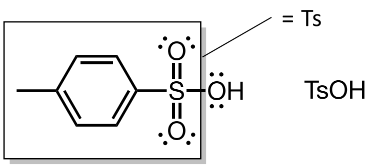
enantiomers

11/28/11 lec • 3



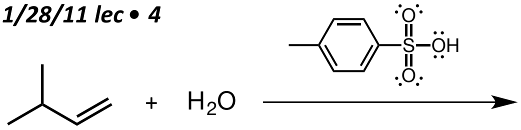
not a leaving group
(methoxide is a strong base)

11/28/11 lec • 5

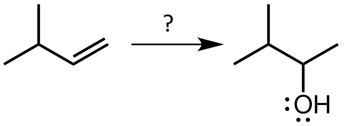


p-toluenesulfonic acid
tosic acid

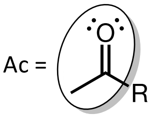
11/28/11 lec • 4



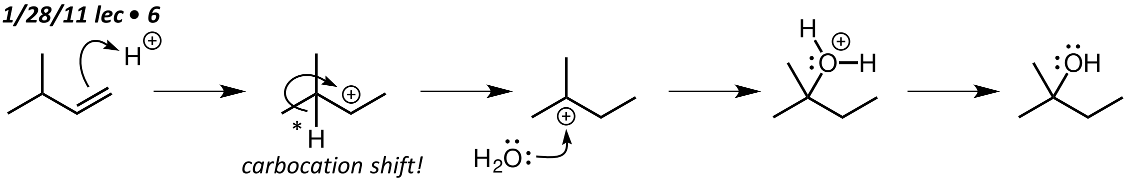
11/28/11 lec • 7



11/28/11 lec • 8

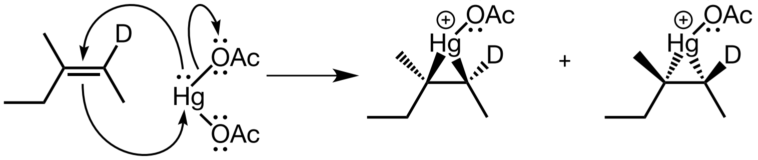


11/28/11 lec • 6



carbocation shift!

11/28/11 lec • 9



11/28/11 lec • 10