Lab 16B • 11/30/11

The first problem is where you don't know what the first substrate is, but I've told you that it's neither an alkyl halide or a sulfonate. Then, that substrate reacts with this compound and ethanol to form an ether. Part of the reason that I had indicated that this is neither an alkyl halide or a sulfonate is I was trying to steer you away from it being an Sn1 or Sn2 reaction. First, why would this be extraordinarily unlikely to be an Sn2 reaction, even if I said that you could have an alkyl halide as a starting material? What's wrong with the reagents, for Sn2? For Sn2, what kind of nucleophiles do we normally need? Strong nucleophiles, so almost always that means something that's negatively charged. We have a neutral molecule, ethanol; that would be a nucleophile much more likely to be used in an Sn1 reaction. Aside from that, we have an acid that's present; in Sn2 reactions, we generally have a base that is the nucleophile. Even if that acid didn't interfere in the sense that it didn't cause a side product, it would substantially slow down the reaction, which already is unfavorable in terms of Sn2, because we do have that weak nucleophile.

Could this, in theory, have been Sn1? It's possible; the acid may not have any kind of side effect, and, since we do have the weak nucleophile, it would be able to participate in an Sn1 reaction. But, if I now tell you it's not the starting material, that is, an alkyl halide or a sulfonate, have we gone over any other kinds of leaving groups that we would be able to use in order to be even able to have an Sn1 reaction? Is Sn1/Sn2 the only way that you could have made this product? No. What other way could we have? Addition, electrophilic addition.

If we try to analyze this, notice that we have that compound, p-toluenesulfonic acid. That is that easily manipulable, inexpensive, organic-soluble solid that is a strong acid and has a non-reactive conjugate base. [flashcards] Because we have tosic acid there, that's a big clue that, based on what we've learned so far, this is probably some kind of electrophilic addition. If this is electrophilic addition, what kind of starting material do we need? An alkene. Look at the structure of the product. There really is only one alkene that would be possible: this one. If we tried to connect from the secondary carbon where the alcohol end up, if we tried to connect it with the carbon on the other side there, that carbon already has four bonds to it. We'd have to make a fifth bond, which is not possible, so the only way that you can make an alkene is over to the right.

What would the mechanism of this reaction look like? First step would be: the double bond attacks H+; that's the point of the tosic acid. We form the carbocation, which then could be attacked by ethanol. That attack could technically occur from two different sides, but notice that the product does not show stereochemistry. There'll be a deprotonation step that occurs; once it does, we'e made the appropriate product. But this is only one form of electrophilic addition. We could also use oxymercuration-demercuration. Technically, alkoxymercuration-demercuration, which would look like this. It is possible to make this product from the same starting material using a different set of reagents. First, if we have mercury acetate with ethanol, not water, and then we react it with sodium borohydride, the following would occur: double bond attacks mercury, causing one of the acetates to be kicked off; at the same time, mercury comes back and forms a ring. We have that cyclomercurinium ion, which since we now have ethanol, not water, in the solution, that's what's going to attack and push open the ring. Once that occurs, we'll have deprotonation. We make our intermediate, which technically would be isolatable. But, we then take it and react it with sodium borohydride, which kicks off mercury and leaves us the target ether. Why would you use this mechanism or this set of reagents instead of the first set of reagents that I showed you? If we were worried about carbocation migrations.

The second problem, we have a dihalide – a molecule with both a bromine and a fluorine on it – and I had said let's imagine that that reacts with just one equivalent of sodium hydroxide. What kind of reaction's going to occur? Sn2. Why? Because we have [a] primary substrate; we have strong, basic, non-hindered nucleophile. Sn2 reaction that's going to get us, really, only one product, cause fluorine is a very poor leaving group because it's the conjugate base of a weak acid, so it really doesn't want to get kicked off. Bromine is the conjugate base of a very strong acid; it's a very good leaving group. So, given one equivalent only of sodium hydroxide, it really is only going to kick off the bromine.

The third problem, we have mesylate, a methanesulfonate, that reacts with some kind of material to form a functional group that we've never discussed before. This N3- ion is known as the azide [ion], so this is an alkyl azide. What kind of reaction appears to have occurred here? Sn2. It's a primary substrate, which means we're going to want something that's negatively-charged as our nucleophile. Notice also that this is substitution – we go from having a mesylate to an azide – and it occurs with inversion of configuration. Primary substrate with inversion, and it's substitution, so that means it's Sn2, which means we need a good nucleophile. The nucleophile in this case is the azide ion itself. Let me write out two Lewis dot structures for that. The structure on the right is useful for demonstrating why is it that these types of compounds can be explosive, because if you were to break the left nitrogen-nitrogen single bond, you would be able to spit off diatomic nitrogen; it's generally very, very thermodynamically favorable to produce nitrogen in this way. That structure explains some of the reactivity of azide compounds. The first structure is a bit more correct, because that has charge evenly balanced across the molecule; by having this symmetry like that, it more closely matches what you would observe in real life. I'll use that first version of the Lewis dot structure to show the mechanism of what would occur here.

Either side of the azide ion simply attacks the mesylate and kicks it off, simple Sn2 substitution that causes the inversion and gets us in one step to our product. [need to show a counterion as well; sodium used since more common]

[Skip 4th one. 5th one – alkene connected to a cyclohexane ring]

We had some unknown substrate reacting with this compound to form an alkene. What kind of reaction is occurring here? It's definitely elimination, because that's the only reaction we've learned so far that makes alkenes. Is this E1 or E2? It's E2. Why? Not because of the substrate. The substrate could determine whether E1 would be possible or not, but it's E2 because of the nucleophile used; this is a strong, hindered, basic nucleophile. I've written it as KO without a bond being shown between them and without charges being shown, but recognize that potassium is an ion, so if I write KO, that's really the same thing as saying K+ attached to a negatively-charged oxygen. Having shown you that, though, let me restate a pervious warning: if I have a hydrogen attached, that it is not the same thing as saying that the hydrogen dissociates to form an oxygen minus, because that hydrogen is not very acidic; it's got a pKa of maybe 18 in solution, which means it's less acidic that water. It does not want to dissociate on its own; very unfavorable to do so. If I had used a neutral molecule or a non-charged molecule like t-butanol, 1,1-dimethylethanol, that would have to have undergone an E1 reaction. We didn't have that; we did have the ionic version. A strong, basic, hindered nucleophile means E2.

If we had E2, what does that mean our starting material had to have in it? Some kind of leaving group, cause that's the only way elimination can happen; lit can't just be a hydrogen; hydrogens do not normally eliminate. A hydrogen, of course, is pulled off during an elimination reaction, but because next door there's a leaving group. If all you had was hydrogens, period, nothing would happen. We need a halide or a sulfonate somewhere in my answer. For simplicity, I'll just choose bromide. Part of the reason I keep choosing bromide for so many of my examples is because bromine is a good leaving group, but it is relatively easy to synthesis alkyl bromides. Iodide is a better leaving group, but it can be trickier to make iodides, because they often, at least in light, decompose. So you can use chloride, bromide, iodide, or mesylate or tosylate. I'm just going to arbitrarily choose bromide.

Let's think now: where would the bromine need to be located? Because, if we're going to form a double bond between these two positions, and if this kind of anionic reaction occurs without any kind of rearrangements, that means that the leaving group needs to start out at one of the carbons of this compound. Let's figure out whether or not it matters which one of those positions we put it at. Could [E2] elimination occur to give us the correct product if we had the bromine on the primary position? Yes; in fact, it's the only possible product of elimination, because there's only one neighbor that has hydrogens on this compound. In other words, in elimination, you would be extraordinarily unlikely to have any kind of side products in this case. The mechanism would look like the this: the t-butoxide ion would pull off the hydrogen; the pair of electrons that had been in that carbon-hydrogen bond could fall back to attack the leaving group bromine, kicking it off, making the correct alkene. That's a valid starting material.

What about the other position? If we had the bromine at the tertiary position instead, would that undergo E2? It's be the only thing possible. You might try to make some argument that in the first case, you could say, couldn't [Sn2] happen because that's a primary substituent? My response would be no, because you've got enough steric hindrance around that position that it would probably be unlikely to substitute; that's the whole point of using one of these bulky bases. Down here, because this is tertiary, it can't do Sn2 period. It won't do Sn1 because the this a strong bulky nucleophile, so it wouldn't even give Sn1 a chance to occur. E2 is going to be the only thing that happens in this case. But, which E2? Because, we do have two different neighbors now: we have the one that would give us the product that we want, so if we had t-butoxide pull off a primary hydrogen, which again would cause this cascade, we'd get the product we want. But, from that same starting material, there's another possibility, in theory at least: what if instead, a hydrogen is pulled off from the ring. Same type of thing could occur. Since there's two hydrogens on that position, we'd be guaranteed that one of them would be able to achieve the antiperiplanar configuration that is required to have elimination occur. But this gives us a different product, not the one we want.

Which one of these two products is thermodynamically more favorable? Turns out, it is the one on the right. Look at how many substituents are connected to double bond. In this first case, we have two alkyl substituents connected; in the second case, we have three alkyl substituents connected. Why does it matter how many substituents we have? For just a moment, let's look at another example of the same type of thing, then we'll come back and answer this question of what's really going to happen.

The short side story is the following: let's say we have some arbitrary base, and let's say for the sake of argument that we're not worried substitution, that for whatever magic reason, only elimination's going to occur. If elimination occurs, we theoretically have three products that could form: one where elimination occurs to the primary position; and then a second case is where it eliminates to the secondary position. But if it eliminates to the secondary position, then we have both cis and trans that can form. The case of what is called this terminal alkene – terminal because one of the carbon's that's involved in the double bond is at the end of the molecule; the other pair of molecules, those would both be called internal alkenes. If we look at the terminal alkene, and if we did a highly simplified SMOG, where I show only the p orbitals that are part of the pi bond and the sp3 hybrids on just the carbon immediately neighboring on the alkyl group. There are of course hydrogens not being shown here, [a] very, very incomplete diagram.

[The] point of the diagram is just to draw enough to show that we're going to have the same type of hyperconjugation interaction possible as we would if this was a carbocation. Similar to the type of situation that we discussed previously, the hydrogens that are otherwise attached to the double bond, they are 90° to the pi bond, so there is hyperconjugation in those directions; there's just a hydrogen there. There's hyperconjugation only to where the alkyl substituent is. We have one R group, which means one hyperconjugation interaction.

Let's take the cis alkene, the internal double bond, and see how it differs. Looking at the internal case, we have two alkyl groups; again, highly simplified, I'm just going to draw the sp3 orbitals that would be on that carbon of the neighboring groups. Now, because we have two alkyl groups, we have two places where that overlap occurs. If I were to draw the other two hydrogens attache to the double bond in, those hydrogens again are going to be 90° to the double bond itself, which means they're not going to have any hyperconjugation. So, two R groups means two hyperconjugation interactions. Those hypercojugation interactions act to stabilize the pi bond – same type of reasoning we had before with carbocations. In that case, we said the carbocations were more stabilized by having this hyperconjugation. For alkenes, alkenes end up more stable the more alkyl groups that you have attached to it. When comparing a series of isomeric alkenes – technically, we can only compare things that are isomers if we really want to say this word 'stable'. But we are comparing isomers here, they're all one degree of unsaturation; one degree of unsaturation for four carbons means take two away from the number of [hydrogens] you'd normally count. Four carbons: 2 x 4 + 2 = 10, subtract two would give us eight hydrogens. These three compounds are all C4H8, and we can, therefore, directly compare energies. When comparing a series of isomeric alkenes, the more substituted alkene will generally be the thermodynamically most favored alkene.

That would make us think that one of the internal alkenes should form in preference to the internal one. But, we have two different cases for the internal, cis and trans. So there, which one of those two compounds would be most favorable? The trans alkene. Why? Because it avoids steric hindrance. This cis alkene, those two substituents, although they're kinda pointed away from each other, they're still close enough, because don't think of it as the little sticks that we draw it, think that there's three hydrogens attached to the methyl groups as well. That branching brings those groups close enough that you have steric hindrance in the cis case that is avoided in the trans. Also, trans alkenes are more stable that the related cis alkenes, due to lower steric hindrance between substituents.

What I had said initially that here's this hydrogen that could be removed that should give us this product. I then said here's this other hydrogen that could be removed to give us another product. I then took us on this detour just for a moment to talk about what should be the more thermodynamically stable alkene. Between the two possibilities, which is these two is the thermodynamically more stable alkene, the one on the left or the one on the right? The one on the right, because it's got three alkyl substituents on it instead of two. But, when you get a hindered enough base, that base then has difficulty accessing that hydrogen; it becomes a kinetic effect. Although thermodynamically one of the products may be more favorable, if physically the reaction is difficult to occur, that will slow it down. By using a bulky enough base, it slows down that reaction enough that removal of a primal hydrogen becomes enough easier that it will lead to the formation of an unfavorable product. That's exactly what occurs with this kind of base. What that means, as far as the answer to this problem, is that either of these two positions for the leaving group, in this case alone, would have been acceptable, because in both cases, elimination would only occur one way. It causes what is known as anti-Zaitsev elimination. Zaitsev elimination is the tendency for the thermodynamically stable alkene to form, but if you throw a kinetic factor in there, that can cause the exact opposite behavior.

Zaitsev elimination means during elimination, the thermodynamically more stable alkene tends to form. Why? Because the most energy would be released, forming that most stable alkene. But then, here's where t-butoxide's role comes in. If the base used in elimination is very bulky – more specifically, has a great amount of steric hindrance – it is possible to form, to cause anti-Zaitsev elimination, which means means formation of a less-substituted, less-favorable thermodynamic product. The reason this occurs is because physically that bulk prevents the easy removal of a hydrogen. I want to again put up this reaction coordinate diagram that I might have shown [previously] to graphically show this situation. Imagine that we had our substrate and that we had the possibility of forming our internal versus terminal alkenes. The internal alkene is more thermodynamically stable because it's got more substitution, so it's going to be lower in energy. But what if the proton to get to that product is more difficult to remove? Then by using a bulky base, you may end up causing it to have a high activation energy, even though it would then form the more favorable product. That could be in comparison to making a terminal alkene, which may end up having an easier transition state to reach – easier meaning lower energy. In this situation, if you had low temperature, and the reaction was looking at geting over one of these two activation barriers, the smaller activation barrier is going to be far more easily crossed. If you're at low energy, which means you have a distribution of molecular energies so that you don't have very many fast-moving molecules, the lower the reaction barrier, the faster the reaction's going to go. So, particularly at low temperatures in these kinds of situations, whatever happens first is the product you're going to get. In this case, because of the lower activation barrier, the terminal, or less substituted alkene, would be formed. Conversely, if you were to raise the temperature, where you had more molecules that maybe could get over that higher activation barrier, [particularly if you had] a reversible reaction that could go back and forth and back and forth and back and forth across these hills, making the most stable product would make the product that would least likely want to react in reverse, because that reverse reaction activation energy would be the tallest of any of the reactions possible. This is called thermodynamic versus kinetic control.

Most eliminations occur thermodynamically, but by having that bulky base, it could cause the kinetic product, the less favorable product, to form.

Wrapping this up and going back to [what was] originally asked, that something reacts with the potassium t-butoxide in order to form this specific alkene. Because it is a strong, hindered base, the two answers allowable are this or this.

We've got two more. This next problem, we start out with cyclohexene and react it with bromine – no light, no water, just plain bromine. What are we going to get? Alkene attacks bromine, bromine attacks back; bromide is kicked off at the same time. We make a cyclic intermediate that is achiral. Even though I'm using wedges, recognize that that is, currently, a meso structure, because you can write a mirror plane all the way through it. But, from this structure, because it's symmetric, either position could be attacked. Depending on which of the two positions get attacked, you're going to end up with two distinct products. It's not that the two can occur simultaneously on the same molecule, I'm just saying two different approaches are possible. What you'll end up with is a set of enantiomers, because when that second bromine comes in to attack, we end up with a trans substitution pattern, which is not meso. Because attack is possible at either position, that's why we end up with the enantiomers. The two of those products would be the answer for this problem.

The last one I saved for last because it's our first example problem of a multistep synthesis, where you produce some material that then reacts in some secondary reaction to make the eventual product. [lab directions] There some reagent that makes some kind of stopping-off point, some intermediate structure that then undergoes a second reaction to make this product. You might be tempted to look at this and say: ooh, maybe there's some kind of Sn1 possible here. You know that Sn1 occurs with the possibility of carbocation rearrangement. But, this starting molecule can't do Sn1 because that's a primary position. What other approach might we be able to take? What if we could somehow get both of these carbons where the functional groups starts out with and where the product ends up at, what if we can get them boh involved at the same time? We do know a way of doing that: an alkene. What if we had an alkene at this position, between the tertiary carbon and the methyl group? If so, couldn't we just take that alkene, react it with HCl, and we'd get the correct product? Yes, because that would be simple electrophilic addition, the very first type of mechanism I showed you [for alkenes]. It would also be the correct type of regiocheimstry; that would be the Markovnikov product, by far the more likely product to form.

Are we able to form this alkene somehow? Absolutely, using exactly the same kind of bulky, hindered base that we saw just a few moments ago. Only one type of elimination is possible, because there's only one neighbor to the functional group. So, this series of reactions would be exactly the right answer: first, do an elimination to make the alkene, and then react the alkene to make an alkyl halide.

You'll be given some form of substrate; you'll be given the product; but, you won't be told how many steps go in between, because that's exactly what happens in true-life organic synthesis. You have a target you want to make, you have a selection of starting materials you can buy, and you yourself have to figure out the best way to get between the two. That's the goal of organic chemistry; that's what we are working towards.

First of these [examples] involves a problem from the book, where you had a leaving group that was trans to a methyl group, and you were give, yet again, that same bulky, strong base. What will be the product of this reaction? This is going to be an E2 reaction, because it's a secondary substrate and it is a strong, hindered base. You might think: he's trying to catch us on that synperiplanar/antiperiplanar geometric consideration. What's the only product going to be in this reaction? This, not just because it's the thermodynamically less-favored product, which is what you should get from this kind of bulky base; it is also because if we were to draw a chair structure for this and we look at the position of the chlorine, versus the methyl group, the methyl group can be come antiperiplanar to that chlorine, but the hydrogen cannot; in this example, we would have a 60° dihedral angle between the chlorine and the hydrogen. Even if we did a ring flip, we're still not going to end up with antiperiplanar geometry, so elimination cannot happen from that position where the methyl group is, even ignoring this idea of kinetic versus themodynamic control.

The other [example's] the following: predict the possible products of this reaction; for this one, don't even worry about synperiplanar or antiperiplanar. If we're ignoring configuration, it looks like there would be two products we'd be able to form. But, one of them is a physically impossible molecule. This is our first example of a bicyclic compound. In polycyclic compounds like this, there are what are known as bridgehead positions. If you imagine that little peak that I've got in the molecule as being, metaphorically, a type of bridge, the bridgehead is the entry onto the bridge. That bridgehead position on rings that are small in size cannot become planar, because you would force such angle strain on everything attached to them it just simply would never get there. It has to become planar if it's going to be come an alkene. It just won't happen. This is a phenomenon known as Bredt's rule. A bridgehead carbon is a carbon at the junction of two what are called fused ring. It's no just one ring that happens to have just one contact point with another; these are rings that are effectively squished together. Bredt's rule says that elimination is not possible to a bridgehead position unless the rings involved are large.
[lab directions]

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When comparing a series of isomeric alkenes, the more substituted alkene will generally be the thermodynamically most favored alkene. Also, trans alkenes are more stable than the related cis alkenes due to lower steric hinderance between substituents.
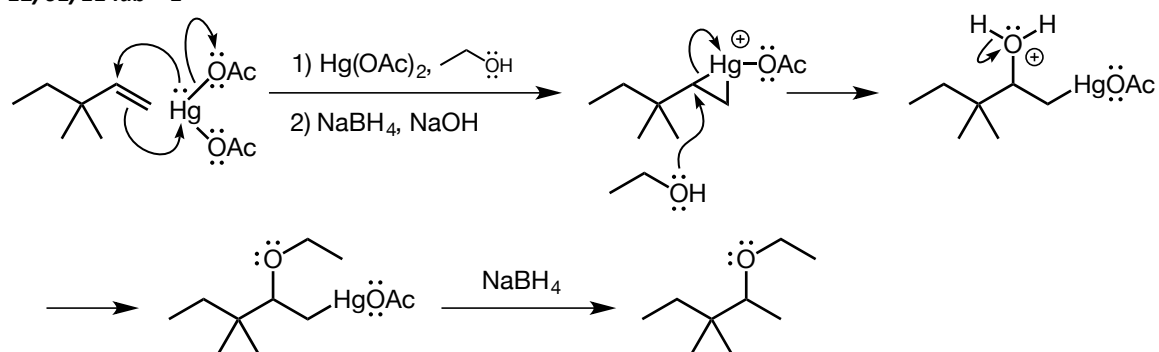
Zaitsev elimination – during elimination, the thermodynamically more stable alkene tends to form.

If the base used in elimination is very bulky (has a great amount of steric hinderance), it is possible to cause anti-Zaitsev elimination (less substituted, less thermodynamically favorable product). This occurs because the steric hinderance of the base could cause the elimination of a hydrogen from a less substituted position to occur due to it being easier kinetically.
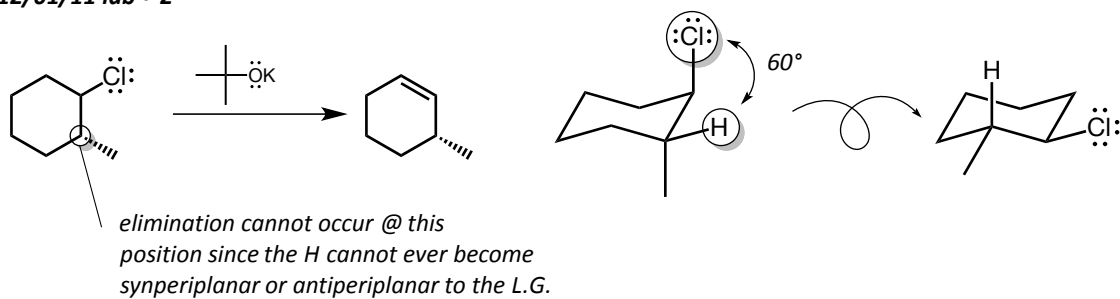
Bredt's rule – elimination is not possible to a bridgehead position unless the rings involved are large.

Structures *(remaining structures identical to lab 16A and lecture 25A)*

12/01/11 lab • 1

1) Hg(OAc)$_2$, ⁀ÖH

2) NaBH$_4$, NaOH

NaBH$_4$

12/01/11 lab • 2

+ÖK

60°

elimination cannot occur @ this position since the H cannot ever become synperiplanar or antiperiplanar to the L.G.

12/01/11 lab • 3

+ÖK

or

bridgehead carbon – a carbon at the junction of two fused rings.