Lab 16A • 11/30/11

Let's start with the first example, where we had some kind of unknown substrate that we react with ethanol and TsOH. What is TsOH? Tosic acid, exactly that strong, organic-soluble, inexpensive, easily manipulable, solid acid catalyst that we talked about. Unknown substrate reacting with TsOH and ethanol to make an ether as a product. I told you that the starting material was not an alkyl halide or a sulfonate. Essentially what I was trying to say is: what if this is not an Sn1 reaction? [Otherwise, you could look at that] and say: secondary position, weak nucleophile, what if it's Sn1? If it wasn't an alkyl halide and it's not a sulfonate, you don't really know much else in the way of leaving groups, so it probably forced you to try to figure out another reaction that might work. What other reaction might work? Electrophilic addition. How? Electrophilic addition, that would be to an alkene. [This] alkene is the only posible alkene, because if you had the two methyl groups here in the middle, there were already four bonds to that carbon, so you can't have a double bond to that direction because it would give you five bonds total, which is not possible. If you took that alkene and reacted it with an acid catalyst, you could make a carbocation that could then be attacked by the ethanol. When the attack occurs, it does occur from two different positions. Notice in the way that I wrote the problem, I didn't even address stereochemistry; I used just a plain line. There'll be a deprotonation step, and we'd end up with the [neutral compound].

What was the logic behind how I came up with the starting material? If it's not an alkyl halide, or if it's not a sulfonate, you probably couldn't think of any other good leaving group to throw in there. The other clue about what kind of reaction it could have been is that tosic acid, cause you haven't seen tosic acid used anywhere except in electrophilic additions. The variation of plain electrophilic addition, where you have the acid catalyst, that's the only time we had talked about tosic acid. If you then guessed it was electrophilic addition, you'd have to look at that and say: wherever the ether ended up, that's where one of the two carbons of the double bond had to be. But, the other carbon of the double bond could not be the middle carbon because that already has four bonds, so you had to draw it to the end of the molecule. [flashcards]

Look at the product and see what we've got. We have an ether. Have we learned any ways to make ethers? I had [mentioned] that simple electrophilic addition could be used to make ethers, but I hadn't actually showed you any in class yet. [need to read the text] You had to think: what reactions had you learned? Sn1, Sn2, E1, E2, radical halogenation, and electophilic addition. This can't have been an elimination reaction, because elimination reactions make alkenes. So then you might have thought: is this a substitution reaction? This can't be Sn2; why not? Cause you have ethanol, which is a weak nucleophile. On top of that, you have an acid; Sn2 prefers to have bases. On top of the fact that we don't have a base, we also have an acid, so this is Sn2. Could it have been Sn1? Possibly, but I was trying to steer you away from Sn1 by saying no alkyl halides or sulfonates. So, that only leaves electrophilic addition and radical halogenation. Is the product a halogen or an alkyl halide? So the only reaction possible is electrophilic addition. At the end, what's another piece of evidence that it's electrophilic addition? The fact that you've got the tosic acid. If you decide it is electrophilic addition, then what's the starting material have to be? An alkene. Once you decide it's an alkene, there is only one possible product, because there is only one type of alkene that would include the carbon where you ended up with the product.

The second one, you had a dihalide – bromine and fluorine on the same molecule – and you were told one equivalent sodium hydroxide. What type of reaction will happen here? Sn2. Why Sn2 instead of Sn1? Strong base; basic nucleophiles make it where Sn2 is preferable. Why else can this not be Sn1? Primary substrate. Strong, basic, but small nucleophile. That makes it Sn2. If this is an Sn2 reaction, but I only have one equivalent of the sodium hydroxide, what really is going to be the only product that forms? You're going to form an alcohol, correct? An alcohol that still has the fluorine. Why? Because fluorine's really not a leaving group, or it's so poor of a leaving group compared to bromine that it just really is not going to react at all. [The] mechanism for this reaction is, in fact, quite simple: it is hydroxide kicking out the bromine to make the product.

Third one, the reagent was missing, and you were given the product. What kind of reaction occurred here, then? Sn2 again. Why can we say that it's Sn2? Because substitution occurred, so it has to be Sn1 or Sn2. What kind of stereochemical change occurs? Inversion. Does inversion happen with Sn1? Yes, but so does retention; both happen, not just one, so it can't be Sn1. Why else can it not be Sn1? Primary substrate. So we have primary substrate, and we have substitution with inversion; that means Sn2. If we have Sn2, then that's going to influence what kind of nucleophile we say could exist. It should be something that's either negatively charged, basic, or both. We could come up with that in that case. What is the that N3- ion called? Axide. There are two ways to write structures for the azide ion: one of those structures is reflective of the fact that nitrogen does like to form triple bonds with itself. In fact, that second structure where I show that nitrogen triple bond can be used to explain why is it that these compounds are often explosive, because forming nitrogen is such a thermodynamically favorable event that it can just pop off this molecule. But the better resonance structure, in a way, is the first one, because it's a balanced structure, and it makes more sense that charge would be even distributed across the molecule instead of concentrated. I'll use the first structure when I show the mechanism. That azide ion is fairly nucleophilic. What happens is just, in fact, a standard Sn2 mechanism. One of the ends of the molecule azide, one or the other, attacks the carbon with the sulfonate; it gets pushed off. That forms the new carbon-nitrogen bond, and, since it's Sn2, it is inversion, which is why the deuterium flips around.

The next one had two boxes for reagents. I'm going to save that for last. Let's skip instead to what's going to be a very interesting problem. We had a box, and then we had this particular reagent, and we formed an alkene. What kind of reaction is this? It has to be elimination, because we formed an alkene. What kind of reagent do we have? Hindered, strong, basic nucleophile. Which kind of elimination is the only one possible here? E2, cause E1 requires a non-basic nucleophile; it requires a nucleophile that gives the carbocation a chance for form. Potassium t-butoxide – this might be deceptive because I didn't write this a O minus, K plus, but you do need to recognize that an oxygen-potassium bond is going to be largely ionic in character. You need to recognize that is O minus.

If I showed you the alcohol, that is absolutely not the same thing as saying that you have any appreciable quantity of that alkoxide around. The alcohol is neutral; it is acidic under certain circumstances, but with a pKa of about 18, it's less acidic than water, so in solution all by itself, you would never form the negative ion.

We have formation of an alkene, and we have a strong, hindered, basic nucleophile. That means, E2. It doesn't actually matter if that original [leaving group] was on a primary, secondary, or tertiary position, because in eliminations, the only reaction in which the position of the [leaving group] matters is E1, cause in E1 you have to form a carbocation, so you can't have a primary substrate. For E2, it could primary, secondary, or tertiary. If this was E2, what does that mean have to have been on that starting molecule? A leaving group, right? In elimination reactions, you get rid of the leaving group; that means the original molecule had to have a leaving group. So that, in fact, means there's more than one right answer, because it could have a been chloride, a bromide, an iodide, a tosylate, [or] a mesylate – at least five different choices. Where should the leaving group be? Because, if we get rid of the alkene, the carbon structure of the starting material will be this, plus the leaving group. Where does the leaving group go? Where would be the best choice? On the methyl group? If we did that, it would ensure that we only have one type of elimination possible, because there's only one neighbor, period, and yes that neighbor has a hydrogen on it. So the hydrogen's pulled off; at the same time, the paid of electrons that was in that carbon-hydrogen bond falls over and kicks out the leaving group.

That works, but what about that one, putting the leaving group at the tertiary position instead? How many products could form from that material? Two. If I were to generalize this argument, I could say some kind of base could come along, pull off a hydrogen from the primary position, which would make the same kind of product that we'd seen already. But, wouldn't it also be possible that a hydrogen from the ring could be pulled off instead? Which one of these is more favorable? If we didn't know that identity of the base, then, on the basis of thermodynamics, which of these would be more favorable? What dos Zaitsev's rule say? What is Zaitsev's rule? That more substituted alkenes would form during elimination. Let's try to understand where that rule comes from. Zaitsev's rule: during eliminations, the more substituted alkene will normally form in greater quantity.

Let's take a different example, just for the sake of argument. Let's take 2-bromobutane; don't worry about stereochemistry, because it's going to disappear as soon as elimination happens anyways. If I use sodium hydroxide, yes, substitution could occur, but let's say we do this at high heat, a way that might favor elimination. There are two products that can form, or really, three: there's what's called a terminal alkene, and then we have internal alkenes. Terminal means the double bond's at the end of the molecule; internal means it's not. Which one of these three do you think is the most favorable product, #1, #2, #3? Why do you think it's not #1? What's different between #1 and #2 or #1 and #3? If we wanted to take compound 1 and draw a very simplified SMOG where I show the p orbitals only, and let's say that I showed the sp3 orbitals on only its neighbor. Notice that there's hyperconjugation that's possible. We don't have a p orbital that's empty, we don't have a plus charge, but we do have a pi bond that's kinda like a p orbital. It could have hyperconjugation with that one alkyl neighbor, but the other hydrogens that are on there, there's a 90° angle, so there's only one neighbor that hyperconjugation could occur with. In other of the other products, I have two alkyl groups on there. If I draw the sp3 orbitals just for the one neighbor. Please recognize these are not proper SMOGs, they're incomplete, but they do show that two interactions are possible. So, the more alkyl groups present on an alkene, the more stable the alkene is due to hyperconjugation with those neighboring groups. So, that's original of Zaitsev's rule: that more substituted bonds form because they're more thermodynamically favorable, because you have a greater amount of hyperconjugation.

But now, between the two internal alkenes, which of the two do you think is more likely? Why trans? Less steric hindrance in the product. The cis product, the two alkyl groups are close enough to each other you're going to have some interaction; in the trans version, you avoid that interaction. Normally, trans alkenes normally form more easily than cis alkenes due to decreased steric hindrance.

We were looking at these two possibilities of cyclohexene forming, where the double bond is in the ring itself, versus the exterior, the terminal version. Thermodynamically, which one of these two would probably be more favorable? The lower one, because there's three alkyl groups substituted on it, versus just the two alkyl substituents up above. But this is a double trick question, because Zaitsev's rule says that this position might be a poor choice because I'd get the more substituted alkene, but, thermodynamics is not the only consideration. You can have a product that might be favorable to form, but what if forming it's difficult. Look at the base that was involved in this initial reaction – potassium t-butoxide, a big, bulky base. What if, because of its bulk, it has enough difficulty getting to this more crowded secondary position than the primary position? It turns out that is the case: that if you throw in a big, bulky base like this, anti-Zaitsev elimination can occur because of kinetic effects.

You have two products that can form, one of which is going to be thermodynamically more favorable; that's where the double bond is part of the ring. Normally, in eliminations, that's the one that would form. If I used sodium hydroxide, we're going to get elimination ... if we have this tertiary alkyl halide, small, basic nucleophile like hydroxide, you can't do Sn2 because we have a tertiary substrates, elimination's going to happen, and because this product has three alkyl groups on the double bond, it's going to be the more favorable one. But, when we have the same starting molecule – that's the thermodynamic product – but when you have a big, bulky base like this, it will encourage anti-Zaitsev elimination. Potassium t-butoxide is sterically hindered, so it is less favorable in terms of kinetics for it to remove a secondary hydrogen versus a primary hydrogen. These kinds of big, bulky bases can cause anti-Zaitsev elimination.

Going back to the original question of something reacting with t-butoxide to form this alkene, the answer is either of these, or replace bromine with your preferred leaving group.

Let's do the last one, and then we'll come back to the one we skipped. Last one was this: cyclohexene reacting with Br2 to make what. Let's write the mechanism for review. First, you form that cyclic intermediate, and then bromide comes back to attack again. Since this molecule is symmetric, the bromine can attack either the top or bottom carbon of the ring; I'll do it on the top. We'll get two products. Notice that the two products are enantiomers; that matches what we expect based on the mechanism for this reaction, because the initial attack by the alkene can happen on either side; that's why we have two possibilities. We have not more than two possibilities because the ring only gets attacked from behind the ring. In this case, you might look at it and say: wait a minute, since it's equal, the two carbons that are part of the ring, couldn't you have attack at either carbon? Yes, but you'd just end up making the same two products. Those are the products of the reaction.

If I had a single bond here, cyclohexane to the methyl group, can elimination happen? No, because unless you have a halogen or a sulfonate or something, you can't kick hydrogen off.

The last problem is a multi-step synthesis. You have to figure out first some reagent that's going to make some new product that, when you throw yet one more reagent at it, you're going to be able to make the target molecule. This reaction is not going to be Sn1, nothing simple like that, because the chloride on the starting material's on the primary position. You might think, if that just came off, you made a carbocation, the carbocation moves next door and you make the product – not possible in this case. So you have to think: what reactions of primary alkyl halides do you know? You could do Sn2, or you could do elimination; those are the only reactions that you currently know. Does Sn2 get us anywhere useful? Not really, because we'll still have something at the primary carbon instead of the secondary. If you made an alcohol, you don't even know how to react alcohols yet. Here's something for you to consider: if somehow you were going to make an alkene here, that alkene could react to make the product. In fact, let's step backwards from the product and figure out what would that alkene be, what would the reagent necessary be. If I had an alkene, what reagent would get us to this final product? HCl, simple electrophilic addition. What alkene would work? Two of them would work; the one that's better in this case is the one I've just drawn. That would attack hydrogen, form a carbocation on the tertiary position; chloride would attack the tertiary position; you'd end up with the product. Great. Can we make that alkene from the starting material that we have? Yes, by just doing an E2 reaction. We could ensure the E2 reaction by using a strong, bulky base. Since only one form of elimination is possible, we don't have to worry about anti-Zaitsev elimination. We take this starting material, turn it into an alkene; that alkene bridges the two different carbons; it gives us access to that tertiary carbon, because we've created the functional group starting from the primary carbon. Once we have that alkene, we simply react it with HCl, and we've got our product.

Substitution can happen with primaries, more quickly that secondaries or tertiaries. If you have something that's a very small nucleophile, substitution might be preferred, unless you can a tertiary substrate, and then only elimination's possible. Eliminations are preferred in tertiary substrates, but not impossible in others.

Instead of being given a series of boxes, you'll be given this product, and you won't be told how many steps go in between. It'll be your job to figure out the 1), 2), 3, 4), 5), 6), 7), however many it happens to be – reactions that go from the starting material to the product.

[lab directions]

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formation of an alkene, strong hindered basic nucleophile –> E2
∴ substrate must have a leaving group

Zaitsev's rule – during eliminations, the more substituted alkene will normally form in greater quantity.
The more substituents located on an alkene, the more stabilized the pi bond is due to hyperconjugation.
Trans alkenes are normally formed more easily than cis alkenes due to decreased steric hindrance.
[Potassium t-butoxide] is sterically hindered, so it is less favorable in terms of kinetics for it to remove a 2° hydrogen vs 1° hydrogen.
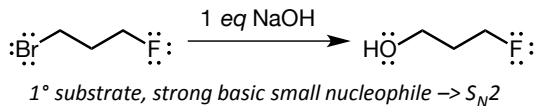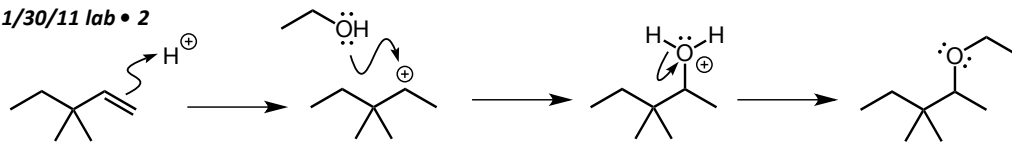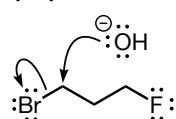
Structures

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[structure] ⟶ TsOH / EtOH ⟶ [ether product]

not an alkyl halide
or sulfonate

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:Br⟋⟍⟋F: ⟶ 1 *eq* NaOH ⟶ HO⟋⟍⟋F:

1° substrate, strong basic small nucleophile –> S_N2

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[alkene] + H⊕ ⟶ [carbocation] ⟶ [oxonium, with H–O–H] ⟶ [ether product]

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[⁻OH attacking Br-substituted substrate with F]

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[mesylate with D] ⟶ [alkyl azide, D] N=N⊕=N:⁻

alkyl azide

1° substrate, substitution w/ inversion –> S_N2

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[cyclohexene] ⟶ Br₂ ⟶ [box]

[product with D] N=N⊕=N:⁻

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[⁻:N=N⊕=N:⁻ ⟷ ⁻²:N–N≡N:⊕]

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[mesylate with D and azide attack] ⟶ [product with D] N=N⊕=N:⁻

⁻:N=N⊕=N:⁻

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[t-BuOK in box] — *same as* — [methylenecyclohexane]

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[t-Bu-O:⁻ ⊕K] [t-Bu-O:⁻] ≠ [t-Bu-O:⁻] + H⊕

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[cyclohexyl with Br, H and ⁻O-t-Bu] ⟶ [methylenecyclohexane]

[B:⁻ abstracting H, Br leaving] ⟶ [methylenecyclohexane]

[cyclohexene Br H with :B⁻] ⟶ [methylcyclohexene]

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[sec-butyl bromide] ⟶ NaOH / Δ ⟶ [terminal alkene] + [cis internal] + [trans internal]

        terminal   *internal alkenes*
        alkene

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[1-methyl-1-bromocyclohexane] ⟶ NaOH ⟶ [1-methylcyclohexene]

major product
(3 alkyl groups on C=C versus 2)

[1-methyl-1-bromocyclohexane] ⟶ t-BuOK ⟶ [methylenecyclohexane]

anti-Zaitsev elimination

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⟋⟍⟋Cl: ⟶ t-BuOK ⟶ [isopropenyl alkene] ⟶ HCl ⟶ ⟋⟍⟋Cl:

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[box] ⟶ t-BuOK ⟶ [methylenecyclohexane]

[cyclohexylmethyl bromide] *or* [1-methyl-1-bromocyclohexane]

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[cyclohexene + Br–Br] ⟶ [bromonium ion] :Br:⁻ + [bromonium ion] :Br:⁻

⟶ [trans-1,2-dibromocyclohexane] + [trans-1,2-dibromocyclohexane enantiomer]

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