

Lab 1B • 01/10/12

Let me describe the types of problems we normally have on an exam, and let me give you a warning that there are no multiple choice exams in this course. Everything is short-answer, something written out, which I think most people eventually prefer, because it does give you the chance to have partial credit. So if you're used to multiple guess exams, then it might be a little rough transition, but that's partly why we're going over this today.

The four main types of problems that they had last quarter were theoretical questions, where you would have to write out a bit more of an explanation. For example, hyperconjugation was a topic from last quarter; there were a couple of different questions where they had to write out pictorial diagrams showing orbitals and then discussing hyperconjugation and linking that to why, for example, certain carbocations are more likely to be formed. Second type of problem, very simplistic, nomenclature. You do need to be able to take simple molecules... we didn't do every single rule on the planet... but you need to be able to take simple molecules and name them or potentially take a name and then draw the structure for that molecule. Third type of problem, very important for this course, mechanism. Since this is a mechanism-based course, it's not just a memorization style of o-chem, it's not just pre-med o-chem, so mechanism figures heavily into every reaction that we learn, and so there's some questions where all you're asked to do is to write out the mechanism for a reaction. And then there's what I call the fill-in-the-blank problems, where you have a substrate that's reacted upon, a set of reagents, and then the product that's generated, except one of those three things is left out, and you have to be able to come up with the substrate, the reagents, or the product.

A new type of problem that will be heavily used this quarter is the multistep synthesis problem, where you start out with some kind of original compound, you're shown the target molecule, and you're told that that target can only be made from that original compound as the source of carbon. We haven't started doing those yet; we've seen just a couple of examples in class last quarter. We had a very heavy theoretical quarter last quarter, and now we're going to shift very heavily into synthesis this quarter.

I want to start with the fill-in-the-blank type of problem first, because that's probably what for returning people they're most curious the answers were, then I'd like to step backwards and do a mechanism problem, and then do a short theory type problem.

Fill-in-the-blank problems.

First one, you had a missing substrate that reacted with mercury acetate and methanol, followed by sodium borohydride and sodium hydroxide, to form an ether. Just a reminder about the way to write reagents: you notice, there is a 1) and a 2) used in this problem, so that explicitly means that everything that's listed after the 1), those reagents react first and separately from everything that's listed under 2). Sometimes, in real life, you can directly add the second set of reagents to a reaction flask, sometime you have to isolate the intermediate first. Those kinds of details are often left out when you're just trying to write a synthesis down like this, but still it's important that you have the 1) and 2) here for this particular reaction. There are some reactions, though, where it would be inappropriate to use a 1) and a 2). For example, simple hydrogenation, you need both hydrogen gas and a catalyst present at the same time. If you put 1) Pt, 2) H₂, that would show that they're supposed to be kept separate from each other, and the reaction wouldn't work. So you have to use 1)s and 2)s where you're supposed to, but you must leave out the 1)s and 2)s where it's appropriate as well. What kind of conditions are these? What kind of reaction does this set of reagents match? You need an alkene to react with it, so an alkene's what's going to in the box there, but do you remember the name of this type of reaction? Oxymercuration-demercuration, except that this is a slight variation on that reaction since there's methanol there instead of water. That's why we end up with an ether in the product, because, if you remember, plain old oxymercuration-demercuration generates an alcohol, but by substituting the methanol there, that's how we now have that ether. This is a Markovnikov addition, which means what? That the nucleophile portion that's adding to the double bond adds to the most substituted position. Another way of saying it is that the electrophile, which in this case is going to be mercury, is going to end up at the least substituted position. So we need an alkene, and we need an alkene where the most-substituted carbon is the one where the ether group is going to show up. That means there's only one correct answer: you end up with a terminal alkene. Why? Because, if you had an alkene between this tertiary carbon and then the secondary carbon, the tertiary carbon would be the most-substituted one, so the ether's going to end up at that point instead. This is not a carbocation-based reaction. It is cationic, but it's not carbocationic, because you end up with that unusual cyclic mercury intermediate. Because of that, there's no rearrangement, and that's why it's fine that we have this terminal alkene, because the ether really is going to end up at that most substituted point.

Next. You're given the substrate, but not the reagents, and you form this difunctional molecule. Does anybody remember what the name of this type of functional group is? Part of it looks like it's had water added to it, and it's got a halogen, so if you can remember that, this is a halohydrin. More specifically, it's a bromohydrin, because you have bromine on there. Today, we want to remember the set of reagents to make a halohydrin: bromine and water. You have to specify that water is there. If you had just bromine by itself, you would end up with a vicinal dibromide, two bromines right next door to each other.

Because of water being there, water ends up being the thing that attacks... remember that this reaction forms a cyclic intermediate as well, just like in the first reaction, the mercury one, and water is the thing that pushes that intermediate open in this case. It is important that you list both reagents simultaneously, and, light should not be listed as a condition for this reaction. This is an electron-pair mechanism, so no light is involved.

Next. We start off with a cyclic alkene that reacts with meta-chloroperoxybenzoic acid (MCPBA). For the new ones of you, you might have instead learned the reagent magnesium monoperoxyphthalate (MMPP), which does the same job. I'll write the structure of the first reagent out. We are, in fact, going to be covering benzene and its derivatives this quarter. This is a derivative of benzene. Benzoic acid is just sticking a carboxylic acid group on here. Peroxybenzoic acid means there's an extra oxygen in it, which is what gives this reagent its unusual reactivity. The MC part of the name, meta-chloro, meta is a position two positions away from the first substituent. We're going to be learning about ortho, meta, and para again this quarter. Chloro- means chlorine, so that is meta-chloroperoxybenzoic acid, which is a reagent that creates what? Epoxides. An epoxide is a three-member ring where you have two carbons and one oxygen. It's a cyclic ether, and ethers and epoxides are one of our topics in just a few weeks from now. However, this is a flat alkene, the carbons are sp^2 -hybridized, which means this MCPBA could attack from the top or the bottom, and since you would end up with something that's not totally symmetric, you do end up with two products; you end up with a mixture of enantiomers. It's physically impossible for that ring to be formed where one carbon is pointing up to the oxygen, the other is pointing down; so in other words, this reaction occurs as syn addition. So, the ring is either going to be written both with wedges or both with dashes.

Next. Unknown substrate, reacting with three equivalents of hydrogen and platinum to form an alkane. This will probably be the most frustrating one for those of you who didn't get it right when you see what the right answer is. Hydrogen and platinum, those are the conditions for hydrogenations. Three equivalents of hydrogen would mean that there are three pi bonds that react. But, we've got to think about how could we stuff three different pi bonds onto this structure, because if we look at the middle of the molecule, that is a quaternary carbon, and you can't make a double bond to a quaternary position. So that means that none of these three carbons at the bottom could have been involved in making pi bonds. That leaves only the ethyl group on the left and then the ethyl group on the right as where we could put the unsaturation. Well, if we put one double bond on either side, that leads us to only having two degrees of unsaturation, which means only two hydrogens would have been consumed. So, what's the way we could get three? Put a triple bond in. So, a triple bond on one side, a double bond on the other, that would give you exactly three degrees of unsaturation. That's what the correct answer was. If you had two triple bonds, that would be too many hydrogens that would be needed. If you only had double bonds, you weren't using enough hydrogens.

Next problem, involving hydrogenation still. This time, starting with just an alkyne reacting with something to make an alkene: specifically, with cis configuration. You hopefully remembered, to stop at the alkene, but to make a cis double bond, that would be still plain hydrogenation but using a poisoned catalyst, Lindlar's catalyst, which is a palladium or platinum which has been poisoned with lead, usually something like lead carbonate, might be a base in there like quinoline, which is a compound that we'll cover this quarter. It reduces the reactivity of the catalyst, makes it where it can start here, but with the catalyst you do have to have the reagent itself that's reacting. Since in this case it's D that got added, deuterium, D2 would be the other reagent.

Next one is the trickiest one we had. It is something that came up in our discussion of the reaction of alkynes. For example, if you wanted to use borane with an alkyne, in principle, if we ignored any other considerations, we could try to generate something like this, where an -OH group ends up at the same position as an alkene. But what's the name that we often use for this kind of compound, where there's an alcohol and an alkene joined at the same carbon? An enol, which you can remember because it's an alkene, and alkenes are named with the functional group ending -ene, and an alcohol, which are named with the functional group ending -ol. So an enol is almost always thermodynamically unstable. We're going to learn one major exception later in the quarter. But a plain, non-cyclic, particularly, enol is usually not favorable. This undergoes a type of reaction known as tautomerization. Tautomerization looks a little bit like resonance, but it's not resonance, it is two separate molecules, what you start with and what you end up with. So what this involves is the exchange of a single and double bond. So the carbon-carbon double bond turns into a single bond; the carbon-oxygen single bond turns into a double bond. So, in other words, what we end up with is a ketone.

The last question. The one multistep synthesis we did see last quarter. So, two separate reagents that were used to convert an alkene into an alkyne. This was the two-step process of using bromine and then a strong base. Br₂ adds to the double bond, putting a bromine at neighboring positions. If you use a strong base like sodium amide, it can do a double-elimination reaction. Technically, it would be best to say bromine like this, then 2) two equivalents of sodium amide. If you didn't put the two equivalents in, technically it should be two equivalents, because two eliminations do occur.

Let's back up one problem to the mechanism problem. I'll start with the first set of mechanisms. First was a terminal alkyne reacting first with sodium amide, followed by iodomethane, or methyl iodide, followed by sodium metal in liquid ammonia. The first reaction is connected to the fact that alkynes are, for plain hydrocarbons, somewhat unusually acidic. There were three factors we discussed last quarter as to why a compound might be more acidic.

One of them was, what is the the case here, hybridization, which I'll return to that in just a second. Second was the inductive effect; if you had some kind of electronegative element, it could pull electron density towards itself, making it easier for a bond that had been connected to it easier to break. Then there's resonance. Acetic acid is, for example, as acidic as it is because once the hydrogen comes off, the resulting anion is stabilized by resonance.

Back to the case of hybridization. If this hydrogen on the terminal alkyne was removed, you'd end up with a lone pair on a carbon that's sp-hybridized, versus if we had an alkene which would be sp²-hybridized, or an alkane that would be sp³-hybridized. For polyelectronic systems, sp³-hybridized orbitals are lower in energy than sp² than sp³. Putting the lone pair into that lower-energy orbital means it's easier for the hydrogen of an alkyne to come off than it would be for the less energetically-favorable alkene, than it would be for an alkane. That's why alkynes have a pK_a of about 25, versus alkenes of about 34, versus alkanes that can be up in the 50s and 60s. So, first step here is an acid-base neutralization. I'm fussy about lone pairs, so if you're used to a textbook that doesn't show lone pairs, or if you had an instructor who didn't care, you're going to have a little transition, because I want to know that you know what the proper oxidation state for all of these atoms is.

Once we've deprotonated, we've formed an intermediate known as the acetylide ion. Second step here is an S_N2 reaction. Acetylide ions can be used for S_N2, as long as you're using primary substrates or, even better, something like this – a methyl substrate where there's zero chance of elimination occurring. Very easy S_N2 reaction would occur; methyl iodide is very reactive. We end up with now an internal alkyl, which now reacts with sodium metal in ammonia liquid – that's the set of conditions for reduction to form a trans alkene. Last quarter, there were two reactions that involved radicals: this was one of them, this radical reduction; the other one was free-radical halogenation. I'm pointing this out because this is one of the few places that we would use single arrows; everything else, all these other arrows so far have been double-headed arrows, meaning that they showed the flow of two electrons at a time. But, because this is a radical process, some of the arrows here are going to be single-headed arrows.

In fact, it starts with a single-electrons transfer of an electron. Where does that electron come from? Sodium, because sodium's a good reducing agent because sodium has a low ionization energy. The electrons are just floating around in solution. Why does this cause this bond to break? If we think back to molecular orbital theory, this triple bond is composed of a sigma bond and two pi bond. If we bond, there are antibonding orbitals as well, so this electron ends up going into an antibonding orbital. An electron adds in; that does cause one of the the pi bonds to break, and we end up with an intermediate known as a radical anion. Since both positions eventually end up reacting, it doesn't matter which one we draw the radical or the lone pair on – the point is, you end up with both. We've gone from an alkyne to an alkene, that alkene having a lone pair, much more basic than the alkyne was – in fact, basic enough to do something unusual, which is to force ammonia, which is normally a base, to instead act as an acid, a source of hydrogen. Since that is an acid-base neutralization, we're back to using the double-headed arrows, an electron pair process. That gets us to a radical, which will react with another electron. So, two reductions end up happening. This is the key point of this reaction mechanism, because that radical, that position where the radical was, had been sp³-hybridized. Single electrons don't have the repulse force that electron pairs do; because of that, they don't affect geometry. In terms of VSEPR theory, we would still call that geometry linear, since there's only atom on either side that carbon's bound to. Hybridization is a framework whose purpose is to try to match the predictions of VSEPR. Since a single electron doesn't affect geometry, it also doesn't affect hybridization, so that's sp-hybridized – until it does get that extra electron, which means it now turns into a lone pair, which means it is sp-hybridized, which means it matters which way we put the lone pair. Thermodynamically, the methyl groups wants to be pointed away from the first one to avoid steric interaction, so the lone pair is going to end up in the position where I've written. Of course, since this is still in ammonia, that means one more neutralization can occur. The product of this first reaction is trans-but-2-ene.

Let's do the second mechanism; considerably easier than the first one. Here we have an alkene reacting first with HBr, followed by sodium methoxide. HBr, those are the conditions for plain old simple electrophilic addition. Alkene first attacks the H⁺ from HBr, and then the counterion turns back and attacks the carbocation that forms. Here's the attack on hydrogen. This occurs with Markovnikov addition, which means that hydrogen ends up at the less-substituted position, so that the carbocation ends up at the most stable, the tertiary position, of this molecule. Bromine now can come back to attack, which forms only one product. Realize that, since the ring is symmetric, there is not a stereocenter formed here. Even though you might use wedges and dashes, it didn't matter in this case, because there is no stereocenter. I am going to use wedges and dashes to show this, because if I'm being really careful, I need to show the stereochemistry of the next step. Consider this: what kind of alkyl halide did I just synthesize, in terms of its substitutiveness: is it a primary, secondary, or tertiary alkyl halide? Tertiary. Why? Because there's three carbons connected to the carbon that the bromine's connected to. Tertiary alkyl halide – what kind of nucleophilic reactions can a tertiary undergo: S_N1, S_N2, E1, or E2, or some combination of those? S_N1, cause it's good at forming a carbocation; if S_N1's possible, what automatically else is possible? E1. What else can a tertiary substrate do? E2. Why can't it do S_N2? Too hindered; too much steric hinderance. What kind of nucleophile are we throwing at it; is it ionic or non-ionic. Ionic, meaning we're going to have an oxygen negatively-charged. So is this a strong or a weak nucleophile? [Strong] Is it a basic or non-basic nucleophile? Basic. So we have a strong, basic nucleophile and a tertiary substrate; what reaction does that automatically mean is going to happen? E2. If it's E2, we have to wonder if it's going to be Zaitsev elimination or Hoffmann elimination – Zaitsev meaning the most thermodynamically-stable, the most substitute alkene will form; Hoffmann (or anti-Zaitsev), that when a less thermodynamically-stable alkene forms. Why would a less favored alkene form?

What would we normally have to use to force that to happen? Use a hindered base, use a hindered nucleophile. But is this a big, bulky nucleophile? Not particularly. So this should go by standard Zaitsev elimination, meaning that choosing to pull a hydrogen off of the ring versus the methyl group, it's going to pull it off the ring. Since it is a cyclohexane ring, what does that mean about the relative position of the hydrogen being removed and the leaving group, the bromine? They have to be trans from each other because that's the only way you could get both of them into an axial position, which is what would give us the antiperiplanar geometry necessary for an E2 reaction. If I was being really, really technical, that would mean that for this particular structure, I have to show the structure with a dash being pulled off, not a wedge. So methoxide pulls the hydrogen off; simultaneously, cause it's an E2 reaction, the pair of electrons falls back and kicks bromine off, and the one and only product we end up with is 1-methylcyclohexene. Here you should not have used wedges and dashes at all, because that part of the molecule is flat. Those sigma bonds transform into a pi bond. If you have the sigma bond parallel like this, or parallel like this, so one side or the other, then it more easily forms the pi bond. If you have periplanar geometry – that's also possible, but not in this case, what's possible in this case is antiperiplanar.

Let's do the third mechanism, which was its own separate problem, because this one was the toughest in terms of memory work. This was a reaction involving an alkyne. Although the reagent itself looks scary, it actually makes the mechanism quicker to write, because – well, let's see why. You had terminal alkyne that reacted with this substituted borane. If you're not familiar with this reagent, it does the same thing as BH₃. If you look at it, it's just been modified to have two alkyl groups on it instead. There is a shorthand way to write that compound – make what looks like the letter 'pi', really it's the same alkyl groups just drawn more stylistically, in a little more compact way. The alkyl groups do two things: one, it makes it where the boron only has one reactable hydrogen, which is we're reacting with an alkyne, one potential issue with doing hydroboration of alkynes is the formation of a network product. That's because borane normally has three reactable hydrogens, which means if it reacted with one alkyne, then it has two more hydrogens that could continue reacting. This helps prevent that. Along with the fact that the alkyl groups are bulky, so just on the basis of sterics, it helps prevent any further reaction, because even once you add to an alkyne, there's still another pi bond there that could react. So short story, this makes addition happen only once. You still have the same work-up conditions that you'd have for any kind of hydroboration, which is hydrogen peroxide and sodium hydroxide.

Remember that in borane, boron is the less electronegative atom; that's why it has the appearance of doing a backwards reaction, because the hydrogen, which normally goes to the least-substituted position, instead goes to the most-substituted position. This is what I meant by the use of R notation. R is just a variable name. It makes it where you don't have to write that 1,2-dimethylpropyl group over and over and over and over again. This was one of the most common errors that some of you made: it really didn't matter what happened to the R group in this reaction. That R group is just there to be something sterically bulky on the borane. You need to focus instead just on what happened to the alkyne, which is what I'm going to show you now. First step of the reaction: simultaneous attack of the pi bond on boron and then hydride attack back to the pi bond. This forms a four-center transition state, which is part of the reason this is a syn addition. Since it's syn addition, we're going to end up with the new hydrogen and the boron on the same face of the alkene. There are no more hydrogens, so that boron doesn't react further; the substituents are bulky enough that the alkene doesn't react further. The next step is to do the hydrogen peroxide and hydroxide oxidation. In solution, hydrogen peroxide is more acidic than water, so hydroxide will deprotonate hydrogen peroxide, to make the peroxide ion, which then will attack boron, because boron lacks an octet; that's what gives boron a lot of its unusual reactivity, including the next step of this reaction. Notice that, with the addition of the hydrogen peroxide, boron has now become negatively-charged. Notice the sequence of bonds we have here: from the alkene, we have a carbon, connected to boron, connected to oxygen, connected to oxygen. That oxygen-oxygen peroxide bond is weak, and a carbon-boron bond is not anywhere near as favorable as an oxygen-boron bond. So, what happens is that group will shift over. That shift is very unusual because hydroxide, in sense, becomes a leaving group; it's not an S_N1/S_N2 reaction, but, robbing that terminology, that's what looks like that's going on here. What we now have is an oxygen between what used to be the alkyne and the boron. What happens next is this decomposes. Hydroxide can now attack the boron, which again makes boron negatively charged. That negative charge could be relieved by hydroxide just popping back off, or it could be this product that pops off, which if it did, there would be a rapid neutralization that occurs.

For most hydroboration reactions, this would be the end. But, we just made an enol, which is not thermodynamically stable, so this can't be isolated. It's going to turn right back around and react again. Hydroxide is going to again pull a hydrogen off. Technically, one could argue that maybe the hydrogen never hopped on in the first place. The point is, when we have a negative charge on that oxygen, it's a delocalized system: we could show the negative charge instead being on carbon, which could then be protonated. Realize that this whole process has been taking place in basic conditions, so at the very end here you can't suddenly switch and say H⁺ as a way of putting hydrogen on there, you have to show water, which we can assume water's there because we had hydroxide pulling a hydrogen off somewhere else. The final product in this case is an aldehyde.

I'd like to do a theory-based problem, in which you were presented a series of pairs of reactions, a comparison between different type of S_N1 and S_N2 reactions. The question was being asked: which the pair of reactions would be the faster reaction, and why. Let's see the first pair. In that first pair, it was the same substrate, reacting with the same nucleophile both times. Bromoethane reacting with sodium fluoride to make fluoroethane. Same reaction twice, but in the first case, methanol was used as a solvent. The other reaction, I wrote out the structure, but this is the solvent DMF, N,N-dimethylformamide, which is a great polar aprotic solvent.

That was the point of the question: methanol is a protic solvent, so yes, protic versus aprotic will change the order of reactivity of halogens, but also it also slows all of the halogens down to be in a protic solvent. So, methanol, being protic, will slow the reaction down versus DMF, which would encourage the reaction because it's not going to interfere with the nucleophile. It's going to be the second of these that's the faster reaction, because it's an aprotic solvent.

Second pair, we had two different substrates that were being used, with the same nucleophile. Fluoroethane reacting with sodium hydroxide to make ethanol, versus bromoethane reacting with sodium hydroxide to make ethanol. I would like to direct your attention to the directions for that question. It very clearly says: be sure to explain the underlying reason for the greater reaction rate. An answer in the form of: 'the molecule has a better (whatever)' is inadequate. So if you looked at this and say bromine's the better leaving group, the directions say that is not a good enough answer. Why is it the better leaving group. It is because it is the conjugate base of a stronger acid. HBr is a strong acid, which makes bromine a good leaving group; HF is a weak acid, which means its conjugate, fluoride, is basic, which is why it's a poor leaving group. It is the second reaction that is faster, and that's Br is the conjugate of a stronger acid; HBr versus HF.

Next pair, we have the same reagent, two different substrates again. One was bromoethane reacting with this sulfur nucleophile, and then the other was 2-bromo-2-methylpropane reacting with that same nucleophile, in both cases forming thiols. What kind of nucleophile is this, strong or weak? It's quite a strong nucleophile, because it is charged, it's ionic, and it has sulfur; remember that sulfur, being squishier, being more polarizable than oxygen, more easily forms bonds in substitution reactions. So it's not as basic as hydroxide, but it's much more nucleophilic. If this is a strong nucleophile, what kind of reaction is it going to favor? Sn2, and Sn2 would be more favorable with that first primary substrate or that second tertiary substrate? Why the primary? Less steric hinderance. So the first reaction is faster; it's Sn2; and there's less steric hinderance.

Last pair; similar situation. A primary substrate reacting with water to form ethanol, and a tertiary substrate reacting with water to form t-butanol. Water, is that a strong or a weak nucleophile? Weak, non-charged. Weak nucleophile, do they favor Sn1 or Sn2? Sn1. Primary versus tertiary substrate: which is better for Sn1? Tertiary, incredibly better, because it's nearly impossible to favorably generate a carbocation on a primary carbon; a carbocation is the primary intermediate in an Sn1 reaction, and so that's why this tertiary substrate works so much better. So Sn1 and a tertiary carbocation is a much more favorable intermediate.

[safety review]

[pre-lab]

Structures

Identical to those from lab 1A (01/09/12)