

## Lecture 6B • 04/24/12

### Alpha halogenation of aldehydes and ketones

We'll start with acetone, a very simple ketone. We're going to react it with bromine and acetic acid. If I tell you that there's not going to be any specific reaction between the bromine and the acetic acid, and if further tell you that carbonyls normally aren't reactive towards bromine itself, then what's about the only thing that's probably gonna happen with acetone, given these conditions? Knowing that we're talking about alpha chemistry, what do you think the only thing that's going to happen will be? When we did aldol condensations, we saw at that point both a base and an acid way in order to make, respectively, an enolate and an enol – in other words, to move the position of that carbon-oxygen double bond to being a carbon-carbon double bond. That's what's going to happen first in this case: the carbonyl will be protonated, which means we generate a carbonyl that we can show opening. In this case, we don't have bromide, we have bromine, which is not a nucleophile, it's an electrophile, so nothing's going to attack the carbocation at this point; instead, what could happen is acetate or something else in solution that could be called a base could pull off a proton alpha to the carbocation, which lets us form an enol.

The first part of this mechanism is reversible; in fact, this is not a favorable process, but – this is a phrase that I've already used and probably use a great deal more – if equilibrium can happen, it will happen, meaning that this process may not be favorable, but small concentrations of the enol form at one time or another. The point is that, if you do form a little bit of that enol, we do have bromine here that's going to react with it. This is similar to the reaction of an alkene with bromine, but with one crucial difference – it does not go through the same cyclobromonium intermediate, because we have the presence of that -OH group there. In fact, as soon as we do this reaction, it brings us to an interesting point. Look at the way I'm drawing this mechanism – because resonance isn't a step, I can always combine resonance with a real reaction step, and it would be proper to do so. The alkene is what's going to attack the bromine; you would form a carbocation at the same time, but I'm going to go ahead and show the resonance closing up that carbocation. We've added a bromine at the alpha position; we'll have deprotonation of the carbonyl; and we have our alpha-halogenated compound.

I'm going to star two positions, and I'm going to write in hydrogens at those positions. In a starting material, I circled the alpha proton purple, in the product, I circled one of the alpha protons, the one that's by the bromine (in green). What [would you imagine] the pKa of the green proton will be, relative to the purple one – is it going to be higher pKa, lower pKa, [or the] same pKa? The green one down below, is that going to have a higher, lower, or equal pKa to the original compound? Lower; is that going to mean it's more or less acidic? If we're agreeing that it's got lower pKa, does that mean it's more or less acidic? More, because pKa is the negative log of the acid dissociation constant, so a strong acid has a tiny pKa. If you're telling me that the circled proton in green has a lower pKa, it's going to mean it's more acidic.

It is more acidic, which is going to mean something once we're in basic conditions, cause right now I'm setting up to do a cationic version of this, but this whole reaction can occur under basic conditions instead. Since I've pointed out that we're going to have these two mechanisms, we're I'm eventually going to argue to is that, in acidic conditions, this is only going to occur once, this reaction, whereas in basic conditions, we're going to see that it's going to happen multiple times. The reason I'm pointing this out is because it's a continuation of this trend that, when a reaction has a cationic mechanism, whatever it does tends to be opposite the behavior you would have if you had a basic mechanism. For example, even right here, we can see that in the acid mechanism, the carbonyl doesn't get attacked first; you protonate the carbonyl to encourage it to react. When we see the basic mechanism, the carbonyl is what gets attacked first, and it's only afterwards that protonation occurs, so things are reverse.

Along with this opposition in behavior, let's now focus on why this reaction's only going to occur once, because it isn't the alpha proton that matters in this case; it's the ability to form a carbocation. Let me go back and circle some other things here. We have the carbocation I just put a box around, and there's no carbocation here, but I'm going to put a box around that carbonyl position anyways. Do you think that that carbonyl will form a carbocation that is more or less stable than the actual carbocation I have boxed up at top? Less stable? Why? When we have things that pull electron density away, that made it so you wouldn't want to put a positive charge next to it. We have a bromine on here that's going to put a delta positive right next to the carbonyl; that means that the carbonyl's even less likely that before to open up a make a true positive charge, cause you already have a positive charge next door. If anything, having the bromine there makes the carbonyl less reactive, so this reaction will not occur a second time. The product that forms is unlikely to react further, since the halogen creates a delta positive center immediately next to the carbonyl [blue box]. That will have the effect of making the carbonyl less likely to react, to open, which is why the reaction only happens once.

Now back to the issue [of] the acidity of these protons. Let's see why that matter's, cause let's now see the basic mechanism. Here I'll show an alpha protone cause I have to, because under basic conditions, the first step is deprotonation. I'm again trying to condense the mechanism a bit by combining resonance with deprotonation. Why did I use a reversible arrow here, because it's not resonance alone that's occurring? But yet, it's still appropriate to write a reversible arrow: why? The basicity of the enolate and the hydroxide are close enough together that you don't fully convert one direction or the other in this reaction. It is

true that the ketone has a pKa of 19, and water has a pKa of about 16, so we're trying to make a stronger base out of a weaker one, so this reaction is going to be very off-balanced, very reactant-favored – but, if equilibrium can occur, it will occur. Some of this enolate will form and, once it has, it can react with bromine, or, one of the other halogens. Let me again circle those protons, cause this is the correct place to talk about it. If the original compound has a pKa of maybe about 19, you already agreed that this second compound's going to have a lower pKa – maybe we'll guesstimate about 17. If you have more hydroxide in solution, which normally if you did this reaction and you know what's going to happen, you would use an excess of hydroxide. You can't stop the reaction from happening a second time; that means you're going to end up with yet another halogenation.

The circled alpha proton of the product (the one in green) has a lower pKa – which means it's more acidic – than the alpha proton of the starting compound (purple). Because the reaction's in the same reaction conditions as the original material, it will react further. Same type of mechanism: start out with an alpha proton that gets deprotonated. You'll again have an attack on bromine, which will give us a dihalogenated product. But, what is the acidity of this alpha hydrogen compared to either of the other ones? Higher acidic, because if one bromine causes an inductive effect to make the hydrogen more acidic; two bromines has even more effect. It happens one more time; we'll have one more attack on bromine. What would be the acidity of the alpha proton now? There is no more alpha proton at that position; we've replaced all three of them with bromine. If deprotonation was going to happen, the only thing that could be deprotonated is the other alpha proton. But, there's something else that's going to happen, though. What does it matter about the base that you choose to avoid [transesterification]? A similar issue comes up here, because yes hydroxide can do acid-base reactions, but it can also attack the carbonyl, which we can argue is reversible. If it was reversible, then when the carbonyl collapses, it's going to kick hydroxide back off – but it's not, because hydroxide is more basic than this carbon. We're not used to this idea, but because we put three bromines on the same carbon, you've got enough electron withdrawing going on that the carbon becomes mildly – and I use the term liberally – acidic, more acidic at least than water, which if it's more acidic than water, it's a better leaving group than hydroxide, so it gets kicked out. We're back to the saponification argument: the act of it being kicked out is itself reversible, but because it is itself a base, it turns right back around and neutralizes again, so we end up with acetate plus  $\text{HCOBr}_3$ ; this is the molecule bromoform. If you put chlorine on it instead, it would be the molecule chloroform. In general, when you have a methyl ketone, which acetone is classified as that, methyl ketones will undergo this multiple reaction to convert them to carboxylic acids. It can actually be used as a qualitative test to identify if you have a methyl ketone. If you used it that way, this is called the haloform reaction, because it produces chloroform, bromoform, or iodoform as its product.

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alpha-halogenation of aldehydes and ketones

The product that forms is unlikely to react further, since the halogen creates a  $\delta^+$  center immediately next to the carbonyl, making the  $\text{C}=\text{O}$  less likely to open/react.

The circled alpha-proton of the product has a lower pKa (more acidic) than the alpha-proton of the starting compound. Because the product is in the same rxn conditions as the original starting material, it will react further.

Haloform reaction

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Structures – Identical to those from lecture 6A (04/23/12)