

Lecture 6A • 04/23/12

Alpha halogenation of aldehydes and ketones

There is a ketone, and we're reacting it with bromine and acetic acid. Bromine is not going to do anything directly with the carbonyl, so let's say that means that the acetic acid is going to do something. What could happen between a ketone and acetic acid? What is the only thing that's logical to happen with this combination, a ketone and an acid? Protonation. After protonation, what is possible? Tautomerization. First step, ketone gets protonated; we'll open up the carbonyl as a result; we end up with a carbocation that, if we used acetic acid, we can assume that acetate is around, so acetate can be our base in order to do a deprotonation. Protonation is always technically a reversible event (deprotonation as well). Now that we have bromine around, once we form the enol, then we have a second step possible instead of the simple decomposition of that enol. Instead, we could have the double bond attack bromine. This is a slightly special case, so this is not the same mechanism as [electrophilic addition of a halogen to an alkene], we're not going to go through the cyclobromonium ion. At this point, it's going to be a forward reaction.

What do you think about the stability of the carbocation I just drew, versus the first carbocation that we formed? The second one won't be as stable because bromine's electronegative and it's pulling electron density away from something that's already trying to be positively-charged, so if you've got something that wants to be a positive charge but it's already partially positive, it makes it even less likely to become even more positively-charged, so the more electron-withdrawing groups we put around this carbocation, the less likely that that carbocation is going to form. For that reason, what happens next is that delocalized ion deprotonates and doesn't go any further in reaction. After bromination, the resulting carbocation is less favorable than the initial carbocation [or the carbonyl is less basic]. Because of the difference in stabilities of the carbocations, an enol does not form a second time, so halogenation only occurs once.

What we've seen for acid mechanism has often had some kind of reverse behavior when we switched to using a base. For example, when we saw the hydrolysis of nitriles, in the acid mechanism, protonation occurs to coax the carbon-nitrogen bond into opening and then the water attacks; in base, it happens in reverse order: something attacks first, and then there is a protonation step afterwards. There's going to be that same kind of inversion of mechanism here, where, at first, we had protonation of that carbonyl and then formation of the enol. [Formation of an enolate occurs] by an active deprotonation first. But along with this reversal of mechanism pattern as we go from acid to base, there's going to be a difference in reactivity, because in this acid case, because it does depend on the formation of the carbocation, and because after adding a halogen that carbocation is less favorable than what you started with, the reaction doesn't proceed further. If acid and base [mechanisms] have contrasting behavior, one might wonder if we switched to the mechanism whether this reaction occurs multiple times. Let's find out.

We're going to deprotonate first. I'm going to use hydroxide. What is the approximate pKa of water? 15.7. And what is the approximate pKa of a ketone? 19. So is the hydroxide going to easily deprotonate the ketone? No. It's going to be formed only a little bit at a time, whatever enolate results. [From an ICE problem there'd roughly be 1% of the enolate versus the ketone.] But, if that enolate forms, it's going to react. For this first step, because the pKa values are similar, we have a reversibility of reaction. I'll show resonance combined with deprotonation because resonance is not a step, so if you combine resonance with anything, that's fine. The reason I'm doing it is because it allows me in one reaction step to make this enolate, which is the main reactive intermediate. We have bromine in solution, so the next thing that happens is bromine gets attacked. The carbonyl reforms, we have an attack on bromine; it's non-reversible.

We still have sodium hydroxide around; will the reaction happen a second time? Will an alpha proton want to be deprotonated? I suggested that if the reaction only happens once in acidic conditions because of some kind of destabilization, does that mean that when we flip everything around, play around with minuses instead of pluses, does that mean we're going to have contrasting behavior? Does somehow a stabilization occur? The answer is yes. If the pKa in the first ketone is about 19, guesstimate the pKa of this new ketone. Will the pKa of the green proton be higher or lower than the purple? Is the green proton going to be more acidic or less acidic? More acidic. If this is more acidic, is it a lower or higher pKa? Lower. It is a lower pKa. Why? Induction. Bromine is still pulling electron density away. Before, that was bad because we were trying to make a positive charge. Here, if we deprotonate, we're making a negative charge. Negative charges can be pulled by induction to delocalize a bit, not by resonance, but just to distribute that electron density. That's favorable. After bromination, the alpha proton is more acidic [green] than the original alpha proton [purple] due to induction; the negative charge is stabilized by electron density being pulled away by the halogen. If it's more acidic, doesn't that mean the reaction's going to happen a second time? If we're got excess hydroxide around, that means the reaction continues. We get a second deprotonation; to emphasize this is a delocalized ion, I'm going to built resonance into the same step. Since they're still comparable in pKas, water that's formed by this alpha proton that's getting pulled off, that step is reversible. We make an enolate that will again react with bromine. That gets us a dibrominated intermediate.

Compared to the first two alpha protons, what do you think the pKa of this one is: lower or higher or equal to the previous ones? Lower, because if you put one bromine on and it make it more acidic, then two bromines is going to be that much more acidic – so, another round [occurs]. We made the enolate one more time; the enolate reacts one more time. What do you think that's going to [cause] in terms of alpha acidity now? Nothing, because on this carbon that we've been working on, there are no more alpha protons. What's going to happen now? If you have a methyl ketone, here's what happens next. When you have three halogens on one carbon, at least that makes carbon have a pKa (with a hydrogen on it) of 13.3. That means it's more acidic than water, so if we had a hydrogen there, we'd be able to easily deprotonate it. But we don't have a hydrogen there, so the whole thing gets kicked off. This is one of those rare times we're breaking a carbon-carbon bond; that's because of this trick of pKas. This is technically reversible, except because we just made an acid in the presence of a base, we get neutralization instead. This thing is called bromoform. If you had chlorine, it would be called chloroform; if you had iodine, it would be called iodoform. In general, this is known as the haloform reaction.

alpha-halogenation of aldehydes and ketones

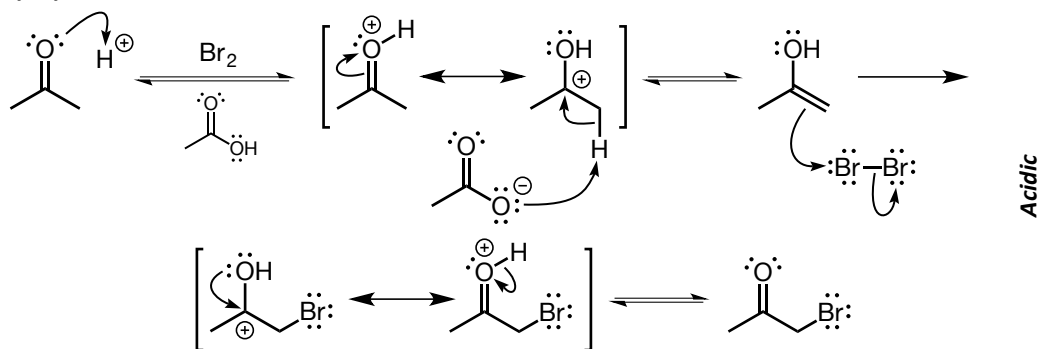
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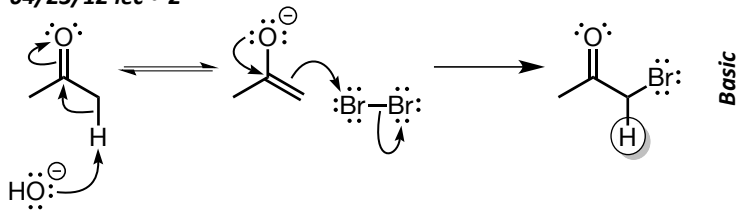
Haloform reaction

Structures

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