Lecture 22A • 03/21/12

Question 1 – You had four different functional groups. Hydrazine is the molecule NH2NH2, so if you put that as an answer, that was correct. What I had meant to put was hydrazone. Oxime, cyanohydrin, carbinolamine.

Question 2 – Imines and enamines. The first part of the question asked you to write a mechanism for the formation of an imine from cyclohexanone and a primary amine of your choice. [identical mechanisms for formation of a semicarbazide] This is one of those mechanisms that it is acceptable to show nitrogen attacking the carbonyl first. If you have water as a nucleophile, that would not be appropriate, because water is not basic. Technically, it's amphoteric, but it's not a strong base at all. Nitrogen is actively somewhat more basic, which is why it's justifiable doing the mechanism in this way. All the other POAD-style mechanisms – we saw those in the formation of a cyanohydrin, in formation of hydrates, acetals, ketals, hemiacetals, hemiketals, all those other mechanisms – the cabonyl gets protonated first. Here, we can show the attack first. The optimal pH level is pH 5, because too acid, and you would just protonate the amine. That's the first step. I supposed it may be theoretically possible for the oxygen to grab a hydrogen off of the positively-charged nitrogen right next door, but that would equivalently be a four-membered ring; those aren't impossible formations, borane goes through a four-centered transition state when it reacts. It's probably more likely that the ammonium portion of this will simply lose a proton and then the alkoxide of it will gain a proton from somewhere. If you do show these as different events, you can't show them simultaneous, because if the oxygen does not grab the hydrogen from right next door, it's unlikely that two different processes – the dissociation and the bond formation – would happen exactly simultaneously. It doesn't really matter which one you show happening first, although since the oxygen is more basic than the ammonium is acidic, I'll show this getting protonated first, and then the nitrogen becoming deprotonated. This is, in fact, a carbinolamine, because it's halfway towards making an imine.

To continue, the oxygen would get protonated again, making water. Water [can] leave and nitrogen [can] donate its lone pair over in the form of resonance. Recognize that resonance structures are just two ways of writing the same molecule. You [can] show the nitrogen lone pair moving over and water leaving simultaneously. Because the nitrogen lone pair moving over is just resonance, this is an acceptable way to write a slightly more compact mechanism. I've done the open and attack in one step. Once I've done that, the last step is for nitrogen to be deprotonated. That's the mechanism for imine formation, but it's identical to the mechanism for oximes, hydrazones, and semicarbazones.

Part two of that same problem was asking you to use the mechanism to explain why an imine like this cannot be formed from a secondary amine. [need to explain more carefully why] If you notice, a primary amine has two hydrogens on the nitrogen. One of the hydrogens comes off after the addition of the amine to the carbonyl, and the other hydrogen comes off at the end step here in order to relieve that positive charge and make a neutral molecule. If you have a secondary amine, you only have one hydrogen, which would be able to deprotonate to make the carbinolamine, but you wouldn't be able to do the second deprotonation to isolate a neutral, doubly-bound nitrogen, so it just doesn't happen. That's the real answer.

The third part of the question was asking you to draw an enamine made from a primary amine and to show its tautomerization. I'll use the same amine. This is a tautomer of what I had already drawn. Because I used the same amine, at the end of the second mechanism I'm going to have the same imine. The mechanism is for the double bond to attack hydrogen; the lone pair can delocalize. This time I'm showing it in a separate step. Just like up above, since we've now formed a positively charged nitrogen, it deprotonates to become neutral.

Mechanisms. The first one involved the hydrazone of butanal reacting with sodium hydroxide and heat. This is the Wolff-Kishner reduction. It's initiated by the amine portion of the hydrazone being deprotonated, which, in fact, initiates a tautomerization. Once you deprotonate, you have a delocalized ion, which we could show ending up with the negative charge on carbon instead of nitrogen. Since we have hydroxide as a reagent, we could show now this attacking water, which is a key point in this mechanism: there is no H+ in solution if we have hydroxide, so to show the protonation here, you must show water being attacked. Now we have a similar process again, where again hydroxide deprotonates from the nitrogen – only this time, delocalization is not possible, cause there's no place for the electrons to go. In fact, though, if the electrons did try to move over, what ends up happening is nitrogen gas is kicked off as as result. That makes a carbanion that's enormously basic, so it'll get instantly neutralized by water to become butane.

Last mechanism problem. This was a hydroxyketone that reacted first with tosic acid and DHP. Tosic acid, what is the whole point of it? [tosic acid on birthday cake] Because, once it dissociates, once the acid part of it is consumed, the leftover, the tosylate ion, is not nucleophilic, it does not want to react with things. If you have tosylate involved in the mechanism at all, you're missing the point of what tosic acid is for. It is there because it only serves to give H+. The only way, in fact, that you can get tosylate active in a reaction is if you make a tosylate using tosyl chloride, but that's a different process that wasn't involved in this question. Tosylate will do nothing; it's just an acid source. What happens with that acid source is the alkene from DHP reacts. You make a carbocation that's somewhat supported by that oxygen lone pair next door. The oxygen from the hydroxyketone attacks next. This is, of course, the process of forming a THP ether, which is one of our protecting groups.

After that attack of the oxygen, we have a deprotonation, which will get us the THP ether. This was only the first of three reagents that you were shown.

The second reagent was methylmagnesium bromide, so a Grignard reaction happens next. The short-hand way for writing that was to go ahead and write the full structure of methylmagnesium bromide, or whatever Grignad reagent you have, and then show the bond from that attacking the carbonyl; it would be understood by a chemist that it's the carbon that's going to react, not the magnesium. That will force the carbonyl open. We have another methyl group, and we have an alkoxide. At this point, you're shown acid, water, and heat. There was only one intended answer. First thing that's going to happen in acid is this alkoxide's going to get protonated to make an alcohol. Then, since there's still acid and water around, those are the conditions for decomposing a THP ether to release that protecting group. From the perspective of the target molecule, not even a complete cycle of protonate-open-attack-deprotonate, cause oxygen gets protonated, which then allows that core part of the product to leave the THP ring. The question did ask for you to show what happens with any byproducts that form, so you needed to show what happened after this part.

We make our product, which is a diol, plus we now have the rest of the THP ring that we need to show its decomposition. The way it works is water would attack at this point. Water then deprotonates once it attacks, and then there's one more round of protonate-open-attack-deprotonate. The ring oxygen gets protonated, which, in theory, means the ring could open two ways, but there only one way that makes sense, because there's only one way that generates a carbocation that would be supported by resonance; that why the ring open[s] this way, leaving a plus charge right next to the –OH group. The whole point of that being the more favorable route is because we can have resonance, which will make a carbonyl, an initially protonated carbonyl, which upon deprotonation leaves us with this omega-hydroxyaldehyde. Relative to the carbonyl, there's a common nomenclature system where you can name the position right next door alpha, the one beta, gamma, delta, down the list. [I earned my geek badge] The last letter of the Greek alphabet is omega, so if you have the end of a molecule that you want to refer to, instead of counting how many positions, you can just say it's omega substituted, so this is an omega-hydroxyaldehyde.

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Structures – Identical to those from lecture 24B (03/20/12)