Lecture 11B • 05/08/12

Amines

This is the first time we're focusing on nitrogen, which does have a very different reactivity – partly because, given equivalent carbon structures, an oxygen is not basic, while a nitrogen is; that's one huge difference right there. Then, oxygen is divalent, meaning it only has two bonds normally, whereas nitrogen is usually trivalent, again changing the type of reactivity that we have. Even how refer to compounds ... what do the terms primary, secondary, tertiary, quaternary mean for amines versus alcohols or other functional groups. [preview of content]

Let me draw a series of very simple amines. The primary structural feature of an amine is that it has a carbon-nitrogen single bond. We do have these terms primary, secondary, tertiary, quaternary, which differ for these amines. How is the term, for example, secondary used differently for an amine than it would for an alcohol? For the other functional groups that we had in the past, if we called it secondary, what that meant is the functional group was on a carbon that itself was secondary, meaning it had two alkyl groups attached. Because the reactivity of amine focuses largely on the nitrogen and not what kind of carbon you have, that's why the terms refer to how many alkyl groups are on the nitrogen itself. So, from left to right, these are examples of a primary, secondary, tertiary, and then quaternary – technically, ammonium salt, because it is charged, but it is possible – in fact, sometimes it's easy – to make these tetra-substituted amines. The designation of primary, secondary, whatever, for amines depends on the number of alkyl groups on the nitrogen itself, and not on the type of carbon that's next to that nitrogen.

Let's move on to nomenclature. For non-cyclic amines, there's generally two forms of nomenclature used: one is common nomenclature, which you'll see quite a bit, and then there's a more systematic, the substitutive, the IUPAC nomenclature. For common nomenclature, you just list the alkyl groups attached to the nitrogen itself. In this example, we have two ethyl groups, so this is called diethylamine – very similar to the way that common names for ethers are generated: we have diethyl ether, our common lab solvent, where you just name the fact that there's two alkyl groups. But, recall that systematic name for an ether treats an ether as an alkoxide. It's not exactly the same thing that's done here, but we do identify one main parent chain, cause that's how substitutive nomenclature always works – you try to find the longest carbon chain that contains the most important functional group. We'll take that same compound and, since it's symmetric – you have two ethyl groups attached – it doesn't matter which one we select as the name chain, but one of them we'll just declare as such. Again, that parent chain is the longest carbon chain with the most important functional group. Once we've got that parent chain, then we treat the other alkyl group as a substituent to nitrogen. The carbon chain, you would still number it 1, 2, 3, 4, 5, as you normally would. Since we have a substituent on the nitrogen, we use this N designation. So, this is N-ethylethanamine. Notice that the systematic name, the last part of that compound, is not an -yl ending – ethanamine, not ethyl amine. If you say ethyl amine, that's a common name.

You've seen this N before, if only briefly. Where it showed up is with one of the solvents we used in Sn2 reactions. [For amides,] just like we add 'amine' to the end of a name, we would just amide to the end of the name. If we had the two carbon amide, it would be ethanamide. This is a one-carbon amide, so its systematic name would be methanamide. [What is the common name] for the one-carbon carboxylic acid? Formic [acid]. Formic acid turns into formamide for the amide. But this amide has two alkyl groups on it as well. Since they're both on the same nitrogen, even though they're on the same nitrogen, we can't just say N-dimethyl; you have to say where each substituent is, just like we would even if there were no nitrogens there. Any compound, we put two methyl groups on it, we say where the position of each one is. This compound is N,N-dimethylformamide, or DMF for short. This is often used in Sn2 reactions because it's polar, but it's aprotic. It's also just a chance for me to show you where you have seen this N designation.

What if you have two nitrogens, a diamine? What if you have substituents on both of them? The common way is to use what is called prime notation. We write N to mean substitution on one nitrogen, then N' to show that it's the other nitrogen.

Cyclic amine nomenclature gets tricky. Let me show you the very limited number of examples that we're going to tackle. There's two types of cyclic amines. There's one type where the nitrogen is not in the ring, meaning that the compound is cyclic, but has an amino group dangling off of it. This is named like any other amine, because you just have an R group attached. You'd name that R group and then name the amine, so this is cyclohexanamine. That's not too bad. Where things get bad is the next case, where the nitrogen is in the ring. That becomes what is known as a heterocycle, which is a cyclic molecule in which one or more atoms of the ring have been replaced by something other than carbon. Why are these heterocycles important? There's certain hetercycles that we can make polymers out of. There's other heterocycles that you find as, for example, the base pairs in DNA. As far as nomenclature, here's the complication. There's what's known as replacement nomenclature. We're going to have a prefix that we can use to mean: take out a carbon, put something else in. There's also common nomenclature. Many of the cyclic amines have their own common names. I saw a chart once of the common 100s, and it's amazing cause you get things like pyridine, piperidine, pyrrolidine, or very close-sounding combinations.

There's also this naming system [name?] – this complicated system has endings that the ending doesn't just mean a functional group – it's not as simple as just -one, -ane, -ene, -ol. The name means both the functional group and how many atoms are in the ring, and how many of them are heteroatoms. You might remember the name oxephosphetane. [It's was an intermediate in the Wittig reaction] with a four-membered ring, and you had a carbon, an oxygen, a carbon, and a phosphorus? Phosphorus and oxygen – oxephoph; etane, the -etane means four-membered ring. Oxephosphetane literally means: four-membered ring with oxygen and phopshorus in it. Our default is going to be replacement nomenclature, so let me show you that. [Amines are named with the 'aza' prefix.] That means, replace carbon with nitrogen. For example, if I had this four-[member] nitrogen[-containing ring], this is azacyclobutane. [Common nomenclature of piperidine and pyrrolidine, -idine ending]

Acid-base properties of amines

For compounds like piperidine, you could look this up and find out that the pKa of the conjugate is equal to 11.27. Does this mean piperidine is basic or acidic to start with, and does it mean it is a strong acid or base? First, is piperidine an acid or a base? [The pKa given is the] pKa of the conjugate. What does that mean? That means for most amines, when you go to a table and you're looking up pKa values, you're getting them in the protonated form (that is the conjugate form), so the pKa value describes this dissociation, remaking the neutral amine. The pKa of an average amine is something like 35-40. That nitrogen doesn't wan to be negative; it is less electronegative than oxygen, so there's no good driving force for a hydrogen to come off. This pKa of 11.27 I gave you is for the conjugate, which means that the amine itself is basic. Is this conjugate a strong or a weak acid? A weak acid. So does that mean the amine itself is a strong or a weak base? It is weak. You [might have learned] that when you have a weak acid, it has a strong conjugate; [in absolute terms, that's] not always true. What if you had something that has a pKa of 7? In water, what would be the pKb of its conjugate? Also 7. Seven's right in the middle of strength, but both the acid and the base have that same pKa or pKb value, so the acid is weak and the base is weak. If the acid got weaker, the conjugate base would be stronger, so you're allowed to say 'weaker base/stronger base', but if I say something is a weak base, that doesn't mean its conjugate is a strong acid. This is a pKa of 11.27, in water, the [pkb] of the conjugate would be 3.73, which is not that much higher than the [pKa value] of acetic acid, which we classify as a weak acid. Both the conjugate and the base are weak. In this discussion, we're going to be talking about weaker and strong, because those terms we can always use.

Having said that, let me make this observation. The pKa of ammonium is 9.25, which means the pKb of ammonia is 4.75; 4.75 happens to be exactly the value of the pKa of acetic acid. In other words, the acid strength of a carboxylic acid is roughly equivalent to the base strength of an average amine. In general, amines are weak bases, with base strengths measured by pKb that are comparable to the average acid strength of a carboxylic acid – generally, roughly in the range of 4 - 6. That means the average pKa of the conjugate is somewhere between 9 and 11. What I've shown you is an alkyl amine; I want to show you aromatic amines next, because we need to talk about how it being part of an aromatic system is affecting its basicity. Aniline has a conjugate pKa of 4.58. Which is the stronger base: piperidine, or aniline? The pKa of pyridinium ion is 11.27 and the pKa of anilinium ion is 4.58, so which is the stronger base, pyridine or aniline? Which is the stronger acid conjugate? The [anilinium ion], because the lower the pKa, the stronger an acid is. To make an ion out of [amine, for purposes of nomenclature], you just add the -ium ending: piperidine, piperidinium. Yes, the [anilinium ion] is the stronger acid; we're still not going to say strong, because it's got a pKa above 4, but it's stronger than [the] pyridinium [ion]. Lower pKa is the same thing as saying stronger acid. Because the anilinium [ion] is the strong acid, the conjugate – aniline itself – is the weaker base. Piperidine is the stronger base. If you have something that really likes letting go of a proton, that means it doesn't the proton back. If you have a strong acid, it means it gives away the proton; the conjugate base doesn't want to get that proton back. Other way around: if you have a weak acid that's holding on to that proton, then that means if you have the base, it's going to try to get that proton cause it wants it. Here, we're saying that aniline doesn't want the proton; the question is: why?

Because nitrogen has the ability to delocalize very easily, as we can see in the mechanisms such as the reduction of amides. The lone pair in that nitrogen is heavily involved with the benzene ring, which means if you protonate the nitrogen, you'll lose the ability to delocalize. That delocalization ends up being favorable, so to break it is unfavorable, so it doesn't want the proton, so it's not as basic. The why in this case is: the lone pair on nitrogen is heavily conjugated with the neighboring aromatic ring. To say it simply, that means it's less able to act as a base. Let me throw up a comparison example. Aniline [is] an aromatic amine in which the nitrogen was still not actually in the ring. Here is a heterocycle pyrrole. It has a conjugate pKa of the pyrrolium ion of -3.8 [???]. What does that mean? [It] means that if you put a proton on pyrrole, it wants right back off again. -3.8 is strongly, strongly acidic, in excess of 99% dissociation. Since the pyrrolium ion is so strong, that means pyrrole itself is a weak base. Since we did identify the acid as being that strong, automatically the conjugate now is weak. Why? Why does pyrrole not want a hydrogen, cause that's what this means? Is pyrrole aromatic? Why? Because the H is orthogonal to the pi system – which means what's happening to the lone pair? It's in conjugation with the pi system. This is aromatic, which means that lone pair is formally delocalized. It wouldn't be, though, if you protonate it, cause if you protonate it, you end up with an sp3-hybridized center that blocks aromaticity. Aromaticity, we know, is a big stabilization force. So, pyrrole is not a base because gaining a proton would break aromaticity, which is highly unfavorable.

If you protonate pyrrole, it doesn't go to the nitrogen. We see that lone pair on nitrogen and think: oh, it's going to protonate there. Why? If it's aromatic, the lone pair is everywhere. Where would it make more sense for the lone pair to be when protonation occurs? We can get an idea of that by looking at some resonance structures of pyrrole.

When we did the Stork enamine synthesis, even before we let the compound react, we could still push the lone pair around and see what kind of structure we would end up with. We'd end up with a positive charge on nitrogen, which we'd expect, but we also end up with a negative charge at the position right next to the hydrogen. This resonance structure is favorable enough that it shows that there is electron density not on the nitrogen – and in fact, this is how it gets protonated. In real life [whatever that is] when protonation occurs, it happens on that side addition. This is related to other forms of electrophilic aromatic substitution, which this effectively is. Since this nitrogen has an effect on where electron density ends up, this is a directed electrophilic aromatic substitution. We have one carbon that now would have two hydrogens, which means we have an sp3-hybridized center which blocks aromaticity.

We saw three types of amines: a linear amine, a cyclic amine (one that was aromatic), and then a third amine that was also aromatic but with the nitrogen being part of the ring itself.

I want to leave you with a question: the six-membered ring cyclic amine, pipiridine, has a conjugate pKa of 11.27. If we look at its five-membered ring equivalent, pyrrolidine, it turns out that the conjugate pKa is only 11.12. All we've done is change the number of atoms in the ring, but it's changed its basicity.

The following set of compounds: ammonia, ethanamine, and N-ethylethylamine. Turns out those conjugates have strengths of 9.25, 10.81, and 11.02; let me write out the conjugates, just so I can name this one to show you that -ium ending. This is the ethanammonium. Which one of these conjugates – ammonium, ethanammonium, or N-ethylethanammonium – is the stronger acid? Left, because a lower pKa value means a higher strength of the acid, so these are the stronger acid conjugates. Now separate those out and look back at the bases themselves. From left to right, are we going up or down in base strength? If we have a weaker acid on the right, that means it's conjugate is the stronger base. As we go from left to right, now we have stronger bases. Why am I pointing this out? To show you that we do need to know these different routes for synthesizing amines. The first step in an Sn2 reaction involving an amine ... after we do Sn2, which will be followed up with a deprotonation – if I use exactly this example here of ethyl chloride an ammonia, the two of them will make ethanamine – but that means I started with something that was a weaker base, and because of the alkyl group, that alkyl groups has made this a stronger base. In this case, although they're not the same thing, this also means it's a stronger nucleophile. If it reacts again to make the ethanamine, which, from the numbers above, is an even stronger base, so it reacts again and again, until you end up with the tetraethylammonium ion.

Sn2 reactions involving amines are generally problematic, since the product is usually more basic than the reactant, so it can be difficult to prevent multiple alkylation.

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Amines – The designation of 1°, 2°, etc. depends on the # of alkyl groups attached to the nitrogen itself, and not on the type of carbon adjacent to the nitrogen.

Common nomenclature – List the alkyl groups attached to N.
Systematic (IUPAC) nomenclature
Cyclic amines
– N not in the ring
– N in the ring – Heterocycle – a cyclic molecule in which the ring itself contains an atom other than carbon
– replacement nomenclature: "aza" –> replace C w/ N
– common
Acid/base properties of amines – Amines are weak bases with base strengths comparable [to] the average acid strength of a carboxylic acid (pKb ~4-6) –> average pKa of the conjugate: 9-11
Question: Which is a stronger base: piperidine or aniline?
Follow-up: Which is the stronger aci conjugate: piperidinium ion or anilinium ion? lower pKa = stronger acid
Because the conjugate of aniline is the stronger acid, aniline is the weaker base. Why? THe lone pair on N is aniline is heavily conjugated w/ the neighboring benzene ring, so it is less able to act as a base (Lewis).
Conj. pKa [pyrrole] = -3.8
Conj. of pyrrole is a very strong acid, meaning pyrrole is a very weak base. Protonating pyrrole breaks aromaticity, which is highly unfavorable, which is why the conj. is so acidic.

Directed electrophilic aromatic substitution
Sn2 rxns involving amines are generally problematic since the amine produced is usually more basic than the reactant, so it can be difficult to prevent multiple alkylation.

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Structures – Identical to those from lecture 11A (05/07/12)

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