

## Lecture 11A • 05/07/12

### Amines – Nomenclature

[mess of a topic in textbook]

#### Types of amines

We have these terms primary, secondary, and tertiary. What do they mean in terms of amines? How many groups are on the nitrogen itself. Remember that for alcohols and other functional groups, it's how many alkyl groups are attached to the carbon that the functional group is attached to, but nitrogen's behavior is quite different than oxygen – so much so that it becomes the nitrogen that's important, not the carbon. That's why we have this difference in the way that we use the terms primary, secondary, tertiary. The designation of primary, secondary, and tertiary for amines depends on the number of alkyl groups on the nitrogen itself, and not on the type of carbon adjacent to the nitrogen. Here we have a primary, a secondary, a tertiary, and nitrogen is able to form what is called a quaternary ammonium salt.

How do we handle the nomenclature of these compounds? There's the common way to do it, which is probably the way that you'll see more of, then there's the systematic way. The common nomenclature is easy: you just list the alkyl groups attached to the nitrogen. For example, if we had a simple symmetric compound, this would just be called diethylamine, all one word, and just one alkyl group after the next. How does that change if we go into systematic nomenclature? In systematic nomenclature, we always have this idea of the main chain, which, generally, the main chain is the longest carbon chain that contains the most important functional group. There's been some revision to that, but the system is so well established that you'll still see names designed this way. In this diethylamine, that means we'll choose one ethyl group or the other, and that will be the parent chain – the longest chain with the most important functional group. That means we're going to treat the other alkyl group as a substituent. It's not going to be a substituent at a carbon anymore; it's substituent to the nitrogen. What we do is we use capital N to indicate nitrogen substitution, so this compound will be called N-ethylethylamine.

If you had an amide, this N designation shows up in amides as well. There's one very common solvent in  $S_N2$  reactions, because it is a polar, aprotic solvent. The standard name for an amide would just be to add amine to the end of a carboxylic acid name. If you have ethanoic acid, you'd have ethanamide. The one-carbon carboxylic acid, its systematic name is methanoic acid, but its common name is formic acid. So, formamide would be the name of this amide. If we then were to put two methyl groups, this becomes N,N-dimethylformamide, or DMF for short.

When we get to cyclic amines, then things get really complicated. The simple case is where the amine is not in the ring itself. This would be named just like any other amine – you look at the R group that's attached, it's cyclohexane, so this is cyclohexanamine. But what happens when you now put the nitrogen in the ring? This is one of those heterocycles – it's a cyclic molecule in which an atom other than carbon is part of the ring. Oxygen, sulfur, nitrogen, phosphorus, they're all found in compound like that. There's three ways that we can refer to this compound, one of which is known as replacement nomenclature. We use the aza- prefix; aza- means replace carbon with nitrogen. This could be azacyclobutane. There is its common name. It's five-membered ring version is pyrrolidine, then piperidine is then it's six-membered ring version – in other words, [somewhat] arbitrary names. There's one other type of name [Hans...?]. It's a heterocyclic naming system, [which] has names [for oxygen ones] like oxetane, oxepane, oxirane – oxirane means three-membered ring, oxetane means four [?], oxepane means either five, six or seven – it's which letter is in the end of the name that tells you the number of items in the ring. For nitrogen, you'd use different names; for phosphorus, it's a little different.

IUPAC nomenclature is actually divided up into several types. Mostly we've been doing what is known as substitutive nomenclature, which means the name itself means put something in. Replacement nomenclature is what it sounds like – you're taking whole sections of a structure and sticking something else in. One operation is to replace an atom; there's other operations that are more complex. Then there's additive nomenclature; there's certain situations where you have to use it. There's not just one IUPAC nomenclature, which means even under the systematic nomenclature, it is possible to generate more than one name for a structure. It's still designed in such a way, though, that one name will never refer to more than one structure.

Let's get to acid-base properties. I could see, for example, that piperidine .... Is this a primary, secondary, or tertiary amine? Secondary, because even though it's connected to itself, there are two alkyl groups on that nitrogen. The  $pK_a$  of the conjugate acid is 11.27. What does that mean? Is piperidine itself acidic or basic? Realize this is the  $pK_a$  of the conjugate. What would the conjugate of that [base] look like? With an extra proton. Amines are themselves basic, but we tend to talk about acid and bases systems using  $pK_a$  values. Have you ever heard me say: memorize this  $pK_b$ ? No, cause we don't tend to do it that way; we tend to focus on  $pK_a$  values; in water (at least) you can derive one from the other. Technically, this means, then, that dissociation governed by this dissociation constant is the one that has an extra proton and it's getting release. So, amines are weak bases, and their conjugates are weak acids.

Amines are weak bases, with base strengths comparable to the average acid strength of a carboxylic acid. In other words, the  $pK_b$  is something like 4 – 6, roughly. Remember that  $14 - pK_b$  gives you  $pK_a$ , if you're dealing with water, which means the average  $pK_a$  of the conjugate is between 9 and 11.

We're going to be comparing amines on the basis of their  $pK_a$  values. Now, if I told you that this compound, aniline, has a conjugate  $pK_a$  of 4.58. What's the significance of that? Aromaticity has something to do with it being a different value. Is aniline a stronger or weaker base than piperidine? Which is the stronger acid: piperidine's conjugate, or pyridine's conjugate? Which is a stronger base: piperidine or aniline? The follow up to that is: which is the stronger acid conjugate: the piperidinium ion or the anilinium ion? What was the  $pK_a$  of the piperidinium ion? 11.27. And then aniline is a  $pK_a$  of 4.58; it is the stronger acid. Why? Cause low  $pK_a$  means high acid strength. If anilinium is a better acid, then doesn't mean that aniline, the base, doesn't want the proton? The only reason that it would be a good acid, its conjugate, is if lets go of the proton. The only reason it lets go of the proton is if, once you make the conjugate base, the conjugate base doesn't try to take it back again. The stronger the acid, the weaker the conjugate. Anilinium is the stronger conjugate acid, which means aniline is the weaker base. Because the conjugate of aniline is the stronger acid, aniline itself is the weaker base.

Why? It's because of aromaticity. The lone pair on nitrogen in aniline is heavily conjugated with the neighboring benzene ring, so it is less able to act as a base (Lewis basicity); that's why aniline is not as basic. What if I now tell you that pyrrole has a conjugate  $pK_a$  of -3.8. What does that mean? It's not stronger or weaker; it is a strong acid. Negative  $pK_a$  means heavy dissociation. It means that pyrrole does not want to be protonated at all. The conjugate of pyrrole, pyrrolium, is a very strong acid, meaning pyrrole is a very weak base. Why? Because it doesn't want its proton back, so once it has deprotonated, it has not much reactivity, so it's a weak base. Why would it be that way? Because that lone pair is involved in aromaticity. Pyrrole is aromatic. You put a hydrogen on the nitrogen ... as I'm about to show you, it doesn't end up there. If we tried to protonate this compound, you're breaking the aromatic ring – totally unfavorable, it doesn't want to happen, so it instantly lets that proton off again. Protonating pyrrole breaks aromaticity, which is highly unfavorable, which is why the conjugate is so acidic.

Let me just show you that, in much the same way, we made this argument in Stork enamine synthesis – that we could push the lone pair of nitrogen around, even before we make an ion, to give us an idea of where electron density is really located. If I drew a resonance structure, look what we get: I push the ring around, and I end up with a positive charge on nitrogen and a negative charge on the neighboring carbon. This helps to explain why it is that if we did try to use a really strong acid and force pyrrole to be protonated, it happens in this way, conjugatively, because it is an aromatic compound. This is just like directed electrophilic aromatic substitution. [the odd, assistive behavior of heteroatoms] No one position of plain benzene is likely to react than any other; in pyrrole, there is a preference, in this particular case, for the two position, because of the interaction of the lone pair of that nitrogen. The point is, protonated pyrrole, the nitrogen does not end up protonated like we think it does. But as we can see, it still ends up with something that has  $sp^3$ -hybridization, which breaks aromaticity.

I've given you three prime examples of amines: a plain old alkanamine – yes, it's cyclic, but there's nothing special about it being cyclic, it's just a secondary amine. [It has a  $pK_a$  of about 11,] which is right in the average range. Ammonium itself is right at 9.25 – which brings up an interesting point about those alkyl groups. Having alkyl groups can affect basicity. I then compared it to aniline – an aromatic amine; and then I compared it to pyrrole, a heterocyclic amine. We saw three very different  $pK_a$  values, which can be very easily explained.

I have a question. This is piperidine, and it has a conjugate  $pK_a$  of 11.27. Here is pyrrolidine, and it has a conjugate  $pK_a$  of 11.12. Why, just by removing one carbon, have we changed the  $pK_a$  value.

I have three compounds we're going to compare: ammonia, ethanamine, and N-ethylethanamine. The conjugate  $pK_a$  of ammonium is 9.25; ethanamine has a  $pK_a$  of 10.81; and, the diethyl amine has a  $pK_a$  of 11.02. From left to right, are these bases getting stronger or weaker. Here's that same confusing thing that's going to come up: this is the conjugate  $pK_a$  that I'm giving you for the values. That means what I'm really comparing are these three things: the ammonium ion, the ethan ammonium ion, and the N-ethylethan ammonium ion. Of these three compounds, which way is the increasing acid strength: from left to right or right to left? From right to left, because higher  $pK_a$ , weaker acid, lower  $pK_a$ , stronger acid. The highest  $pK_a$ , the [weakest] of this group. That means that the bases themselves have the opposite strength; remember that the strengths of the bases and acids are complimentary to each other, opposite. Why does this matter? What's the product of this  $S_N2$  reaction? What would be the name? Ethanamine.  $S_N2$  means that the nucleophile attacks the substrate, kicking out the leaving group; in this case, that means we initially get an ammonium ion, but since it is acidic (slightly), it can deprotonate and make ethanamine. But, we just discussed up above how ammonia is the weaker base, and you make a product that is a stronger base. Although nucleophilicity and basicity are not the same thing, but they're related, so if you have something that's now a strong base, that means it's a stronger nucleophile, which means the reaction doesn't stop. You'll make the secondary, then, if you have enough material around, you'll make the tertiary. It'll react one more time, and, for it's common name, we've made the tetraethylammonium chloride salt.

$S_N2$  synthesis of primary amines is generally difficult, because it is generally difficult to stop the process at the primary amine.

In general,  $S_N2$  reactions are problematic because the product is often more basic – and therefore more reactive – than the starting material. In fact, because of this property, if we wanted to make an ammonium salt, we'll do what's called exhaustive alkylation – exhaustive means do it over and over and over and over again until you've run out.

Nitrogen chemistry is different. If you think about oxygen chemistry, so much of it involved alcohols or carbonyls. [first non-oxygen functional group in a while] Nitrogen has a different reactivity, partly because nitrogen is basic and oxygen is not, partly because nitrogen is trivalent and oxygen is divalent – meaning nitrogen is neutral having three bonds, oxygen is not; that right there changes the reactivity. [list of amine synthesis reactions]

Gabriel amine synthesis – uses phthalimide

[KHP] Phthalic acid is ortho-benzoic dioic acid. What's an imide? Two carbonyls on the nitrogen; it's like a twin amide. Phthalimide, then, is this compound. The hydrogen that's shown here, what would you guess its  $pK_a$  value to be? Above 20 or below 20? Below 20. If you have enough resonance to support a negative charge, then yes, you can deprotonate a nitrogen. Sodium hydroxide is, in fact, a strong enough base to pull this hydrogen off. We make this anion that can now undergo an  $S_N2$  reaction. We still end up with a nitrogen with a lone pair, but that lone pair is so involved in conjugation that no further alkylation will occur. If we then saponify, this is a way to make a primary amine.

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Amines

The designation of 1°, 2°, & 3° for amines depends on the number of alkyl groups on the nitrogen itself, and not on the type of carbon adjacent to the N.

Common nomenclature – List the alkyl groups attached to the N.

Systematic IUPAC nomenclature

Cyclic amines

Heterocycle – a cyclic molecule in which an atom other than carbon is part of the ring  
replacement: "aza" = replace C w/ N

Acid/base properties – Amines are weak bases with base strengths ( $pK_b$ ) that are comparable to the average acid strength ( $pK_a$ ) of a carboxylic acid: 4 – 6  
→ Average  $pK_a$  of conjugate: 9 - 11

Question: Which is a stronger base: piperidine or aniline?

Follow-up: Which is the stronger acid conjugate?

Since the anilinium ion is the stronger acid, its conjugate (aniline) is the weaker base. Why? The lone pair on N is heavily conjugated with the neighboring aromatic ring, so it is less able [to] act as a base.

Since the pyrrol[ium] ion is a very strong acid, pyrrole itself is a weak base. Protonating pyrrole breaks its aromaticity, which is highly unfavorable, which is why the pyrrol[ium] ion is so acidic.

Directed electrophilic aromatic substitution

$S_N2$  rxns involving amines are generally problematic since the product is usually more basic than the reactant so it can be difficult to prevent multiple rxns.

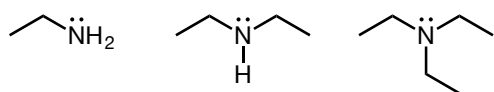
Exhaustive alkylation – add as many alkyl groups as possible.

Gabriel amine synthesis

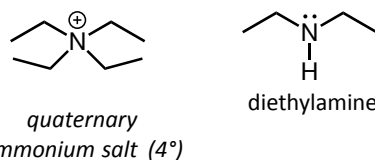
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Structures

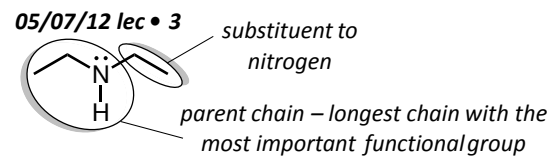
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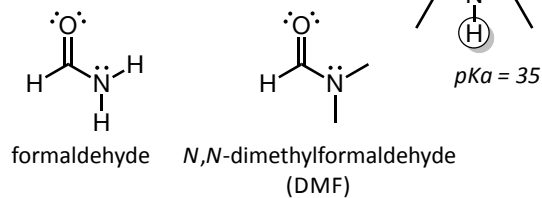


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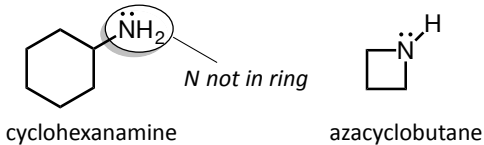
N-ethylethanamine  
diethylamine

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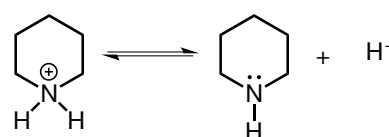


pKa = 35

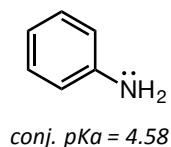
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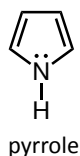
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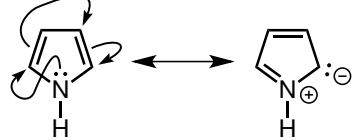
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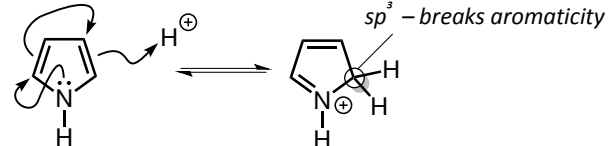
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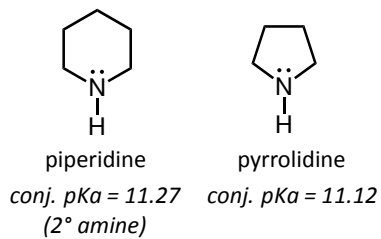
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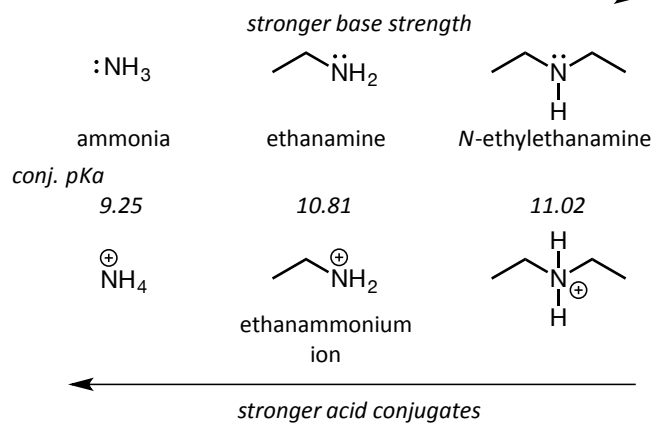
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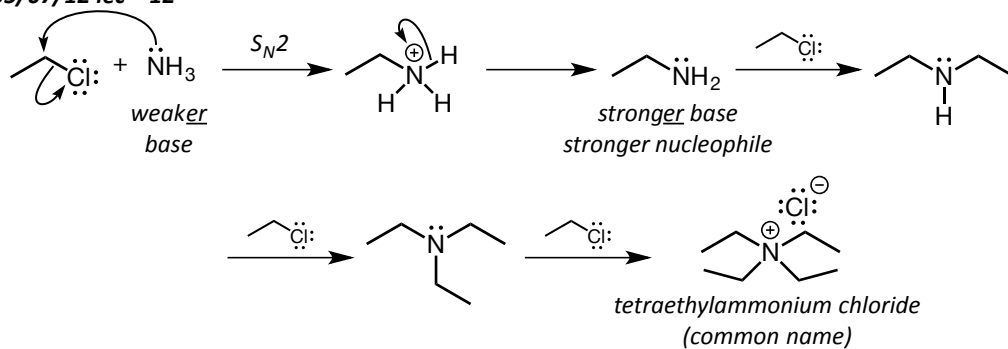
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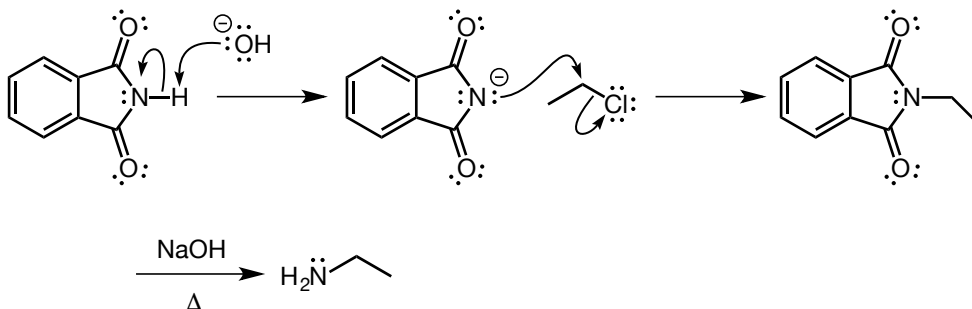
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