Chapter 14. Ouellette, 2/e. Chemistry X402.

Ch 14. Amines and amides.

Skip: Sect 8.

Essays:

- *Required*. p 410, Polyamides. This discusses more condensation polymers. Proteins, Ch 15, are polyamides.
- Not required. p 399, Amphetamines.

⇒ There is a **practice quiz** for Ch 14 (Amines and amides) at the web site.

Notes

Sect 1. Ch 14 is on N-containing organic compounds. For this course, you are responsible for amines and amides, but not for imines and nitriles. (We have discussed the nitro group, Ch 5.) Loosely, the amines are to N as alcohols are to O. And amides are the N-analog of esters.

Sect 2. **Pitfall**: the "degrees" (primary, etc) are determined differently for alcohols and amines. See my web page on Primary etc for a summary of all the meanings of these terms.

p 392 introduces the resonance structures for amides, a complexity one might not expect. This complexity is yet another example of how a carbonyl group affects the properties of a nearby group. This more complex description of the amide linkage explains the lack of free rotation about the amide bond, the planarity of amides, and the lack of basicity of amides. For another discussion of this, see my web page on Amides; the level is about the same as in Ouellette.

Sect 2 & 3. You are not responsible for the special names of the heterocyclic amines.

Sect 3. **Pitfall**: Be sure to distinguish the prefixes n and N. The lower case n means "normal", an organic chemistry term for straight chain (pp 70, 74, though I don't see the abbreviation n used). That is, n-butane is C-C-C-C, to distinguish it from the branched isomer isobutane. It is not part of strict IUPAC, but is still used. There is an entry in the web site Glossary for "N- and n-".

Sect 4. The big story here is the same as discussed earlier for O-containing compounds. Look for H-bond donors and acceptors.

The structures and data at the top of p 396 might be included on my "Comparison of boiling points" handout.

The intermolecular H-bonding by amides is important in protein structure, Ch 15.

Sect 5. As usual, avoid getting bogged down in numbers here, especially if you are unfamiliar with K values.

Ouellette's statement that amines are "fairly strong" bases (p 398) needs context. They are not strong in the sense of fully ionized, like sodium hydroxide. They are about as basic as carboxylic acids are acidic.

To help you with priorities in this section…

- The top priority is that amines are basic and amides are not. For most purposes this is about all you need from this section.

- Among the amines, alkyl amines are similar in basicity to ammonia -- actually a little stronger. Aryl amines are much weaker, because the lone pair of the N, which is responsible for the basicity, is delocalized in the aromatic system.

- The lack of basicity of amides can also be explained by delocalization of the N lone pair, as discussed before. It is not critical for us that you fully understand this explanation. It is sometimes useful just to realize that there is a good explanation, even if you don't quite understand it yet.

- Details of numbers and reasons for varying basicities of different structures are "advanced".

Ouellette notes imidazole, p 401. The amino acid histidine, Ch 15, contains this ring structure. Ouellette gives a $pK_b = 7$, which means that it is half ionized at pH 7. Thus histidines are often involved in proton transfer reactions.

Be sure to distinguish basicity from hydrogen bonding. One involves a covalent bond, the other an intermolecular dipole interaction.

Sect 6. The solubility of alkyl ammonium salts, compared to amines, is consistent with the general point from introductory chemistry that ionic compounds are often soluble, especially ammonium salts.

> The product of reacting an amine (say, RNH_2) with HCl is best written as an ammonium chloride salt, $RNH_3^+Cl^-$. However, it is sometimes written as $RNH_2 \cdot HCl$, a symbolism that suggests a complex. You may see this on medicine labels, and sometimes the term amine hydrochloride is used. Ouellette does not mention this, and I do not encourage it, but you will see it.

Sect 7. Mostly "advanced", except for two points that you need:

- Sub-section "Reactions with acyl derivatives" (p 404) describes how to make amides from amines.

- Last part of section, on quaternary ammonium salts, is of some interest. The key required point is simply to see that they are quaternary N derivatives, and are substituted ammonium ions.

Reaction summary. We skipped #1, 3 & 4. One reaction is shown twice. (Which one?) For #5, he writes the simple statement that hydrolysis of an amide gives acid + amine. Depending on the pH, one or the other may be ionized. He discusses this in Sect 9. I think it is simplest to think of this in two steps. First, find the two parts of the amide, then consider the pH and write each part in its proper form.

Suggested problems

Models. Good. #3 & 4 should be thought of together.
Exercises. #1-18 are mostly on core material; a couple of them use names of heterocyclic amines, which are good homework but you aren't responsible for remembering the ring names. 19-26 are on important material, but a bit more quantitative than I would prefer; try to do at least 19, 20, 26. For #27, do b; for #28, do b,c. 29-34 are on the skipped section. 35-42 are good.

Overview of skipped section

Sect 8. Reactions to make amines. Some have come up before, but I just don't want too many new reactions at this point.

Are amines chiral?

The book doesn't mention this point, but students sometimes do. So let's look at it.

It's only a possible issue for some tertiary amines. If an amine has three different R groups, plus a lone pair on the N, does this give us the asymmetry that is needed for chirality?

Maybe. Or, better: yes, but.

If you make a model of such an amine, it will certainly look chiral. You can make a mirror image, and the two are not superimposable.

However, if you measure the optical activity of such a tertiary amine, you will (probably) find none. Why? Because the molecule inverts so rapidly that, as a practical matter, a real sample is almost always racemic. That is, the molecules indeed are chiral, but it is not possible to separate the two enantiomers, because they interconvert so fast. (The interconversion is sometimes referred to as an "umbrella flip" -- a term that should convey a good image of the process.)

There are some special cases. One would be very low temperature. At low T, the inversion rate may be slow enough that the enantiomers do not interconvert. Perhaps more importantly, if the overall structure of the molecule constrains the interconversion, then it may not happen. A good example of this would be a tertiary amine with the N in a ring system that constrains the three R groups. Finally, it should be simple enough that quaternary ammonium ions can be chiral.

For beginning students, this may be more than you want to know. If it comes up, the most important thing is to follow the logic of each point. It all follows the basics of what you know about chirality.

Errata

p 396, in section on "Hydrogen bonding…" (near bottom of page). End of first sentence of that section refers to intramolecular hydrogen bonding. That should be intermolecular -- consistent with the sketch that follows immediately.

p 406, Problem 14.6. Answer given is rather weak. Not only is it not a particularly good reaction, but the only reaction for making amides introduced in the chapter before this point uses the acyl chloride (p 404).

p 414, #8a. Answering this correctly requires knowing that -OH takes precedence in the name. Not sure this was ever presented.

p 418, #41. Answer given violates Fig 12.3.

Further reading (See Old Articles page at web site for more.)

J A Klun et al, Synthesis and repellent efficacy of a new chiral piperidine analog: Comparison with Deet and Bayrepel activity in human-volunteer laboratory assays against Aedes aegypti and Anopheles stephensi. J Med Entomol 40(3):293-299, 5/03. The popular insect repellent Deet is an amide (p 414, #4a). Here they compare a new candidate repellent, and show that it has considerable promise. A key part of developing this, after encouraging initial leads, was synthesizing the four stereoisomers of the new compound; one of those (SS-220, also an amide, with a similar overall structure) is definitely best. Deet has one serious limitation in field use: it attacks some plastics. The new repellent is gentler. Interestingly, different mosquito species respond differently to the various repellents tested, thus showing that they do not all work exactly the same way. From the USDA, in collaboration with the US Army.

G Sun & S D Worley, Chemistry of durable and regenerable biocidal textiles. J Chem Educ 82:60, 1/05. General interest, but some of the biocides discussed here are amines or ammonium salts.

K L Mueller et al, The receptors and coding logic for bitter taste. Nature 434:225, 3/10/05. Bitter is one of the five fundamental tastes -- and is often due to amines. The bitter substances are detected by special receptor proteins, but the perception of bitterness is due to how the cells are connected to the brain. Mice with a receptor for bitter substances expressed in "sweet" cells are attracted to the normally-repellent bitter substances. Also see Wooding et al (2006).

M Rodríguez-Sáiz et al, Why did the Fleming strain fail in penicillin industry? Fungal Genetics and Biology 42:464-470, 5/05. Some history here, with an update. The original penicillin-producing strain that Fleming discovered was soon replaced by others, which produced much higher levels, for commercial production. Now, modern genetic research reveals why the replacement strains were better: they lack an enzyme that destroys one of the precursors to penicillin.

M Petracco, Our everyday cup of coffee: The chemistry behind its magic. J Chem Educ 82:1161, 8/05. Good overview of coffee, from a range of perspectives. This set includes other articles on coffee and caffeine; more are on the Old Article web page.

R Mokaya & M Poliakoff, Chemistry: A cleaner way to nylon? Nature 437:1243, 10/27/05. News. "The polymer nylon-6 is much in demand. An innovation in producing the precursor molecule, ε-caprolactam, involves a one-step process that is environmentally benign and may be scaled up for bulk production."

S Wooding et al, Independent evolution of bitter-taste sensitivity in humans and chimpanzees. Nature 440:930, 4/13/06. Bitter taste is commonly due to amines -- though not in the particular case here. But this is fun: They show that chimpanzees, like humans, can be divided into tasters and non-tasters for the bitter substance phenylthiocarbamate (PTC). The taste receptor gene involved is well characterized. Analysis shows that the alleles for tasting and non-tasting are different in the two organisms, showing that they arose independently. Also see Mueller et al (2005).

H H Wasserman, Chemistry: Synthesis with a twist. Nature 441:699, 6/8/06. News. We talk about how amides are stabilized by resonance between the simple structure we usually draw and a di-ionic structure. Of course, that resonance is not possible if the amide is constrained so that it cannot be planar. Penicillin is actually an example of a twisted amide. Here, they discuss a recent report of a simple model twisted amide.

R C Ladenson et al, Isolation and characterization of a thermally stable recombinant anti-caffeine heavy-chain antibody fragment. Analyt Chem 78:4501-8, 7/1/06. This can be used for a dipstick test for caffeine -- in hot and cold beverages; a consumer product is under development. Interestingly, the antibody is from llamas or camels -- animals known to make heat-stable antibodies. This set includes other articles on coffee and caffeine; more are on the Old Article web page.

Y Liu et al, Switchable surfactants. Science 313:958, 8/18/06. Can one functional group be both polar and nonpolar? Well, sort of. What they do is to take a large, fairly nonpolar amine, and add CO_2. The result is an ammonium carbonate salt -- very polar. The change is reversible, by changing the atmosphere. Now, attach this group to a large alkyl chain, and you have a substance that is or is not a detergent (surfactant), depending on the atmosphere. They suggest such a substance may have practical applications, as an emulsifier that can be turned on and off.

1) J L Mynar & T Aida, Materials science: The gift of healing. Nature 451:895, 2/21/08. News.
2) T F A de Greef & E W Meijer, Materials science: Supramolecular polymers. Nature 453:171, 5/8/08. News.
These two news stories are related: they deal with "supramolecular" polymers; one feature of some of them is self-healing. Supramolecular polymers are based on small subunits

interacting with each other through hydrogen bonding; this opens up the possibility of new types of behavior, since hydrogen bonds -- individually -- can be easily broken and reformed. #1 focuses on the self-healing aspect; #2 is a more general discussion of such polymers. The polymers are based on urea derivatives, hence relevant to this chapter. Also see the course web site, under alkenes, where another approach to self-healing polymers is presented; that was a pioneering effort, but perhaps superseded in some ways by the more recent work here.

R A Raguso, Plant science: The “invisible hand” of floral chemistry. Science 321:1163, 8/29/08. News. We know that flowers attract pollinators. The work discussed here suggests that they may also repel pollinators. Why? To make sure the pollinators visit multiple plants, rather than only one. The repellent is nicotine -- in the tobacco plant.

Z-G Qian et al, Metabolic engineering of Escherichia coli for the production of putrescine: A four carbon diamine. Biotechnology and Bioengineering 104:651, 11/1/09. Microbes are used for the commercial production of numerous chemicals. Examples include ethanol and drugs such as penicillin. Traditionally, one finds a promising organism in nature, and improves the production of the desired chemical by mutagenesis and screening for the desired characteristics. This report is an example of improving an organism by design. They understand much of the pathway of how the chemical is made, and they modify it by making specific changes that should improve production.

K Scheidt, Organic chemistry: Amide bonds made in reverse. Nature 465:1020, 6/24/10. News. “Amide bonds connect the amino acids in proteins and occur in many other useful molecules. An amide-forming reaction that turns the conventional approach on its head offers a practical way of making these bonds.” The new work presents a different way to activate the reactants, so that the amine ends up being the electron-deficient reactant -- rather than the electron-rich reactant. As usual, different procedures for carrying out a reaction have different pro and con features, so this novel approach will make some couplings easier. This news story is a nice readable introduction to the issues, as well as to the new development.

B Borrell, Make it a decaf -- The enduring quest for a coffee bean without the buzz. Nature 483:264, 3/15/12. News feature. Since the “poor taste” of ordinary decaffeinated coffee is probably due to removal of other flavor components during processing, the idea of having a coffee plant that simply does not make the caffeine has appeal. This news feature is an overview of various approaches to making a coffee bean without caffeine. They include making use of occasional natural coffee strains with low caffeine, and a range of breeding approaches, including genetic engineering. The bottom line is that there is no clear success. This set includes other articles on coffee and caffeine; more are on the Old Article web page.

Computer resources

Spring 2007 brought stories of pets dying from contaminated pet food. It now seems likely that a combination of two heterocyclic amines, melamine and cyanuric acid, was responsible. The web page tells more, shows the structures, and links to some news stories.

My web pages on Primary (etc.), Amides, and Glossary were mentioned above.

For more on the heterocyclic aromatic amines, see my page on Aromaticity.

There is nothing in any of these that is required. The coverage in Ouellette is fine.

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