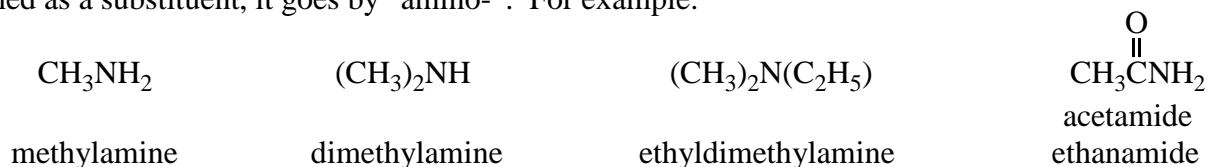


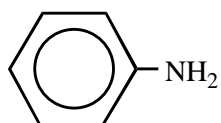
## Chapter 16 – Amines and Amides

### 16.1 Occurrence, Names, and Physical Properties of Amines

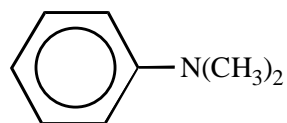
An amine is basically an ammonia molecule with one or more aliphatic and/or aromatic organic groups attached. Thus they have the generic formulas  $\text{NH}_2\text{R}$ ,  $\text{NHR}_2$ , and  $\text{NR}_3$ . If a carbonyl group lies between the nitrogen and R the compound is called an amide. Amines are typically named by naming the organic group as a substituent and using the suffix “-amine.” This is the old common system and we will use it for the rest of the course. If an  $-\text{NH}_2$  group is named as a substituent, it goes by “amino-”. For example:



Aromatic amines are called anilines. When other groups are also attached to the nitrogen in aniline, they are named as for amines, except that a capital “N” is placed in front to indicate the substituent group is bound to the nitrogen, rather than the aromatic ring. A couple of examples include:

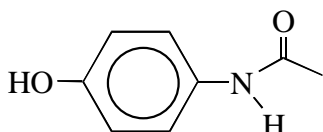


aniline



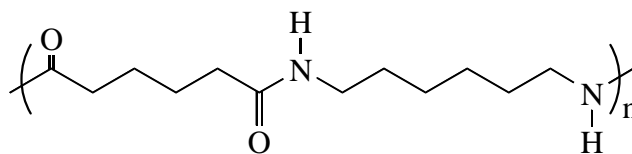
*N,N*-dimethylaniline

Aromatic amides are analogous to their aliphatic counterparts. Two amines/amides that you have heard of are:



Acetaminophen

*N*-*aceto*-4-*aminophenol*



Nylon-66

poly(hexamethylene adipamide)

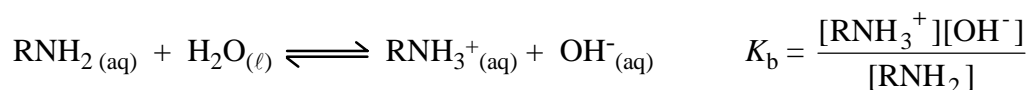
Many natural products chemicals (these are species extracted from living systems) contain amino groups. The alkaloids are a class of these materials. If you see a drug end in “-ine” there is a good chance of it containing an amino group. Examples include: codeine, morphine, and quinine (all have pictures in your book on p. 486).

Amines generally have an odor that is ammonia-like to fishy and mildly unpleasant, although apparently some smell quite bad. A couple of examples of the latter (I assuming here, never having checked this out for myself) include putrescine (1,3-propanediamine) and cadaverine (1,5-pentanediamine). Amines are weak bases like ammonia, but are frequently little stronger. Anilines are very weak bases, while amides are not at all basic. Table 16.1 (p. 480) lists the  $K_b$ s of some amines and aniline. For comparison purposes, ammonia has a  $K_b$  of  $1.8 \times 10^{-5}$ .

Amines tend to form hydrogen bonds like alcohols, but they are weaker. This is because nitrogen is less electronegative than oxygen, resulting in a decreased attraction between the N and H on different molecules. Like alcohols their boiling points are higher than is expected from their molecular size, but because the hydrogen bonding is weaker than in alcohols, the boiling point increase isn't as large. A table in the right margin on p. 481 of your textbook shows that the boiling point of methylamine is roughly halfway between those of ethane and methanol. Likewise, they are much more soluble than comparable hydrocarbons. Also like alcohols, the effect of the amino group decreases as the size of the molecule increases.

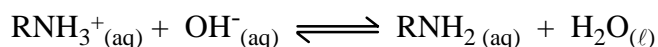
## 16.2 Chemical Properties of Amines

Since amines are weak bases much like ammonia they react with water much like ammonia.

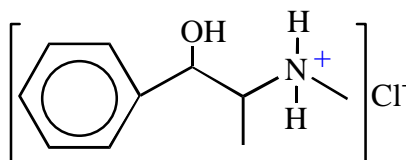


Anilines engage in the same types of reaction, but since their  $K_b$ s are about a million times smaller than for aliphatic amines, they barely ionize in water. Indeed, the only acid/base reaction they usually engage in is with strong acids.

Since aliphatic amines are weak bases, their protonation products,  $R_nNH_{4-n}^+$  ( $n = 1-3$ ), are also weak acids. Strong bases react with these ammonium ions to regenerate the parent amines.



When an amine forms an ammonium-type ion, the product is a solid. It is frequently water soluble even if the parent amine isn't. Unless the parent amine is miscible with water, the corresponding ammonium ion will be more water-soluble. These features explain why many drugs come as the "hydrochloride" salt. For example, the active ingredient in Sudafed® is pseudoephedrine hydrochloride (see below). Do you see where the product name comes from?:



As a salt it is easier to package, store, and deliver to the patient. Many pharmaceuticals contain amino groups and a very large percentage of them are sold as ammonium salts. In fact, any time you see the phrase "hydrochloride" following a drug's name, it's a good bet that the active form of the medication is an amine.

As an aside, amines are rarely found free in nature. This is because naturally occurring water is slightly acidic because of the  $CO_2$  that dissolves in it. (Remember that  $CO_2$  dissolves in water to form  $H_2CO_3$  (carbonic acid which is a weak acid)). Therefore amines that are exposed to environmental water are usually protonated. Amines are found free in restricted environments.

As was just noted, the solubilities of amines in water can be greatly enhanced by converting

them to ammonium salts (your book calls them amine salts). In this they are much like the carboxylic acids we learned about in the last chapter (which become more soluble when deprotonated). In fact, we will see shortly that molecules containing both amine and carboxylic acid functional groups are quite soluble in water because the latter transfers a proton to the former yielding an internal double salt.

### 16.3 Amides of Carboxylic Acids

The bond between the carbonyl carbon and the nitrogen in an amide is called the amide bond. This bond is a major site of reactivity in the molecule as we shall soon see. Amides with two hydrogen atoms bound to the nitrogen are called simple amides. Those with one or two aliphatic or aromatic groups are called amides of amines.

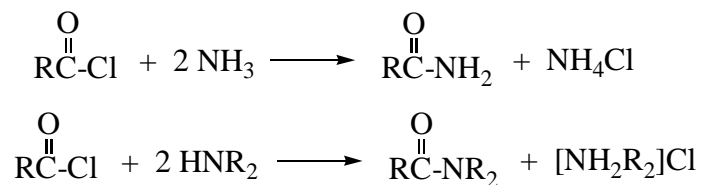
The hydrogen bonding in these molecules is amongst the strongest observed. (See the table in the margin of p. 487 of your textbook.) A result is that they almost always exist as solids when pure (as a result of bonding to each other). They are also generally quite water-soluble. Unlike amines, amides show no measurable basicity. Two factors account for this. Most importantly, the lone pair of electrons on nitrogen interacts with the carbonyl  $\pi$ -bond much like the  $\pi$ -bonds in benzene interact with each other. Also, the electronegative oxygen pulls the lone pair of electrons towards itself. The effect is to render these electrons unavailable for acid/base reactions.

Amides are named using the following rule:

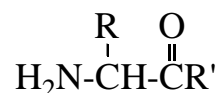
Name the corresponding carboxylic acid (i.e. pretend the  $-\text{NH}_2$  is an  $-\text{OH}$ ). Now replace “-ic acid” with “amide” from the common name or replace “-oic acid” with amide from the IUPAC name. Thus  $\text{CH}_3\text{C}(\text{O})\text{NH}_2$  is acetamide or ethanamide, respectively.

### Preparation

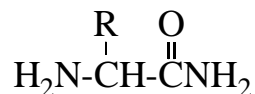
In a chemistry lab, the easiest way to make amides is the reaction of an acid chloride with ammonia or either a primary or secondary amine. For example:



Your book also points out that amides can be prepared from anhydrides but this method is more difficult and is less commonly used. Since acyl chlorides and anhydrides are far too reactive to exist in the body, the biochemical production of amides follows a different route. The molecule transferring the acyl group has the general form:



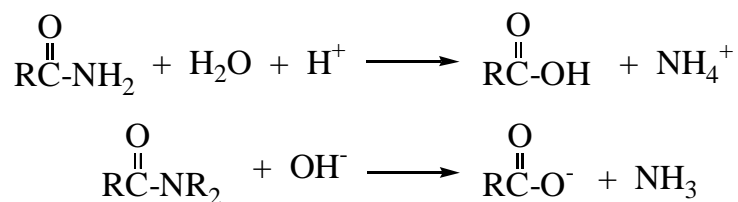
In the reaction the  $-\text{R}'$  group is replaced by an  $-\text{NH}_2$  group. The product molecule



is called a peptide. We'll return to this type of molecule in Chapter 20.

### Hydrolysis

In the presence of strong acids or bases amides hydrolyze to carboxylic acids or their salts respectively.



Since strong acids and bases don't exist in the body, enzymes catalyze the hydrolysis

reaction and permit it to happen *in vivo*. This enzyme reaction is how your body breaks down proteins.

January 20, 2002