Chemistry 131
Lecture 9: Amines - Nomenclature; Physical Properties; Heterocyclic Amines; Amine Reactivity, Amine Salts, Alkaloids
Chapter 15 in McMurry, Ballantine, et. al. 7th edition

HW #4: 15.28, 15.30, 15.32, 15.40, 15.42, 15.44, 15.50, 15.54, 15.56, 15.58, 15.62, 15.64

AMINES

Introduction

Nitrogen is common in biological systems:

- Proteins occur when amides form between the carboxylic acid functional group on one amino acid and an amino functional group on another amino acid. Additionally, 5 amino acid side chains contain N: lysine, asparagine, glutamine, arginine, and histidine

- The purine and pyrimidine bases of DNA contain nitrogen

\[
\text{Adenine} \quad \text{Thymine}
\]

The purine ring of adenine and the pyrimidine ring of thymine are examples of nitrogen heterocycles. Related to the purine ring structure, the methylxanthines comprise some highly coveted molecules

\[
\text{Caffeine} \quad \text{Theophylline} \quad \text{Theobromine}
\]
In addition to the methylxanthines above, there are many drugs - either as natural products (see below) or synthetic, containing nitrogen. A few examples

Amines are basic, which is why they were termed alkaloids when extracted from plant materials. Amongst other things, alkaloids are used in defense,
Amines are also used extensively in cellular communication (dopamine, norepinephrine and epinephrine, all of which derive from the amino acid tyrosine)

\[
\text{Tyrosine}
\]

Nicotine (bottom previous page) contains the important aromatic nitrogen heterocycle pyridine. The pyridine ring is also found in the principal biological electron transporting molecule NAD\(^+\) and is crucial for the ability of NAD\(^+\) to accept electrons (the equivalent of H:\(\equiv\)) and form NADH (ultimately delivering the electrons to the electron transport chain in order to synthesize ATP). This is due to the ability of N to be stable with either 3 bonds/neutral or 4 bonds/positive charge:

**Structure and Classification:**

Like alcohols, amines are classified as primary, secondary, and tertiary.

**UNLIKE ALCOHOLS,** the designation refers to the number of carbons **DIRECTLY ATTACHED** to the nitrogen

**Question:** Classify the following amines as primary, secondary, or tertiary:

Trimethyl amine \hspace{1cm} Aniline \hspace{1cm} N-methyl-2-butanimine
**Nomenclature:**

It is as simple as

1. Find the base chain, drop the -e, add amine

2. If there are other substitutions at the N, indicate them by N-substituent name, followed by base name

3. Other rules apply

Alternatively, the common method of indicating all groups as substituents, then crying “amine” - this is particularly useful for small amines

Trimethyl amine: Diethylamine:

If you do not wish to cite the parent compound as an amine (say there is an acid group that takes precendence) you can refer to the amine group as an amino substituent, locating it with the appropriate number of course; e.g., PABA = para-aminobenzoic acid or 4-aminobenzoic acid:

N with 4 bonds is charged. We name these compounds as the corresponding ammonium salts. As you learned in general chemistry, positive ions are named first, negative ions second

- For aromatic and heterocyclic rings, drop the e and add -ium (pyridine → pyridinium, aniline → anilinium)

- For aliphatic amines change amine to ammonium

- Again, that’s cations first, anions second.

Methylamine + HCl →

Aniline + HCl →
Nitrogen singly bonded to 4 carbon substituents (e.g. tetramethyl ammonium chloride) is permanently charged, and is referred to as a quaternary ammonium salt. This is in contrast to other amines, which will be charged at low pH values and uncharged at high pH values. Other versions of quaternary ammonium salts are typical modern cleaners (e.g. Lysol® disinfecting wipes). These are at times referred to as “quat” cleaners/sanitizers/disinfectants.

![Chemical structure of quaternary ammonium salt]

The “Benzalkonium chloride” found in these cleansers is a mixture of “alkyl” benzyl dimethyl ammonium chlorides.

An important quaternary ammonium salt in biochemistry is choline:

Name the following compounds:

1. 

2. 

3. 

4. 

5. 

6.
Physical Properties

Revenge of the Stank:

Trimethyl amine is the principal odor maker in rotting fish

1,4-butanediamine = putrescine  1,5-pentanedi diamine = cadaverine

Amines can hydrogen bond, but not as well as alcohols

\[ \text{CH}_4 \quad \text{BP} = -162 \, ^\circ\text{C} \quad \text{NH}_3 \quad \text{BP} = -33 \, ^\circ\text{C} \quad \text{H}_2\text{O} \quad \text{BP} = 100 \, ^\circ\text{C} \]

First liquid amine (next smaller for comparison):

1\textsuperscript{o}: propylamine BP = 49 \, ^\circ\text{C} (ethylamine BP = 17 \, ^\circ\text{C})

2\textsuperscript{o}: diethylamine BP = 56 \, ^\circ\text{C} (dimethylamine BP = 7 \, ^\circ\text{C})

3\textsuperscript{o}: triethylamine BP = 90 \, ^\circ\text{C} (trimethylamine BP = 2.9 \, ^\circ\text{C})

4\textsuperscript{o}: tetramethyl ammonium chloride \text{MP} = 425 \, ^\circ\text{C}

Question: Compare propylamine (3 C) to trimethylamine (3C). Why the difference in boiling points?

Answer:

Because amines do not hydrogen bond as strongly as alcohols, they have lower boiling points than alcohols of the same molecular weight. However, due to the basicity of amines, they actually are more soluble in water than alcohols of the same molecular weight:

- Triethylamine is a 6C molecule with a solubility limit of 14 g/100 mL H\textsubscript{2}O @ 25 \, ^\circ\text{C}; recall n-butanol is 4C with H\textsubscript{2}O solubility of 8 g/100 mL
• Perhaps it would be more appropriate to compare straight chain analogs: n-pentanamine is completely miscible in water while n-hexanamine has a limit of 1.2 g/100 mL H₂O. The ability of adjacent C's to "feed" electron density into a positively charged N (again with the 1°, 2°, and 3° business!) stabilizes the charged form of triethyl amine. The charged form interacts strongly with water, helping to explain the solubility difference between triethyl amine and 1-hexanamine.

• While predicting the solubility of amines is at times complex, reflecting shape/flexibility/ability of non-polar portions to be "caged" by water, the capacity to hydrogen bond with water, and relative basicities, we may establish a reasonable 1st approximation of 1 N providing marginal water solubility for 5-6 C. For comparison, an [isolated] oxygen will provide marginal solubility for 4C.

Question: At 25 °C, the solubility limit for triethylamine is 14 g for 100 g H₂O. Would you expect tetraethylammonium chloride to be completely soluble in water?

Answer:

Amine Reactivity

Basicity of Amines

Hopefully you have seen the Henderson-Hasselbalch equation in Chem& 121

\[
\log([A^-]/[AH]) = pH - pK_a \quad \text{or} \quad [A^-]/[AH] = 10^{pH-pK_a}
\]

Where

• AH is a generalized weak acid
• A⁻ is the conjugate base of the weak acid
• pH is the -log of the molar H₃O⁺ conc.
• pKₐ is the -log of the equilibrium constant for the weak acid in water

This equation may be interpreted one of 2 ways

1. It tells the ratio of weak acid (AH) to conjugate base (A⁻) necessary to generate a buffer of specific pH, given the specific pKₐ of a specific acid

2. Given an already established buffered medium (as found in the body) the equation tells us the ratio of (A⁻) ionized vs. unionized (AH) compound
While both interpretations are important, we will focus on the behavior in already buffered media. The equation may be readily extended to amines as bases, as

\[ \log([BH]/[BH^+]) = \text{pH} - \text{pK}_a \quad \text{or} \quad [BH]/[BH^+] = 10^{\text{pH}-\text{pK}_a} \]

Where

- BH\(^+\) is a generalized conjugate weak acid of an amine base
- BH\(^-\) is the weak base amine
- pH is the -log of the molar H\(_3\)O\(^+\) conc.
- \(\text{pK}_a\) is the -log of the equilibrium constant for the weak acid in water

Using ethanoic acid (acetic acid) and ethyl amine as examples will help

\[
\begin{align*}
\text{AH} & \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{OH} + \text{H}_2\text{O} & \quad \rightarrow \quad \text{A} \quad \text{O} \quad - + \text{H}_3\text{O}^+ \\
\text{BH}^+ & \\
\text{O} \quad \text{+} \quad \text{NH}_3^+ + \text{H}_2\text{O} & \quad \rightarrow \quad \text{A}^+ \quad \text{NH}_2 + \text{H}_3\text{O}^+ \\
\end{align*}
\]

To develop a feeling for this \(\text{pK}_a\) business, recall the equilibrium constant from Chem\& 121, where

\[ K = \text{conc. products} \div \text{conc. reactants} \quad \text{or more specifically} \]

\[ K = \frac{[A^-][H_3O^+]}{[AH][H_2O]} \quad \text{or} \quad \text{pK}_a = \frac{[A^-][H_3O^+]}{[AH]} \]

- With products in the numerator, large values (> 100) for \(K\) or \(\text{pK}_a\) mean a strong acid has been placed in water (recall strong acids generate essentially 100% H\(_3\)O\(^+\) in water. Small values (< 0.01 or 10\(^{-2}\)) mean weak acids placed in water
- Since we are dealing with weak acids (or weak conjugate acids of weak bases) the K values will be very small. As such, [H\(_2\)O] is written into the "Konstant" side of the expression in the \(\text{pK}_a\) form
- Recall the brackets refer to the molar concentration
Acetic acid $pK_a = 4.75$  
Ethyl Ammonium $pK_a = 10.8$

If we say for simplicity the $pK_a$ of acetic acid = 5 and blood pH = 7, then

$$\frac{[A^-]}{[AH]} = 10^{pH-pK_a} = 10^{7-5} = 10^2 = 100 = 100/1$$

:. The ratio of ionized carboxylic acid to unionized carboxylic acid is about 100:1

If we say for simplicity the $pK_a$ of the ethyl ammonium ion = 10.4 and blood pH = 7.4 (it is) then

$$\frac{[BH]}{[BH^+]} = 10^{pH-pK_a} = 10^{7.4-10.4} = 10^{-3} = 1/1000$$

But noticed the conjugate acid of an amine is ionized, and so

:. The ratio of ionized amine to unionized amine is about 1000:1

Thus in the body, both carboxylic acids and amines are almost completely ionized.

Bear in mind however these acid-base reactions establish an equilibrium, and so a few molecules will exist in the unionized form. Nonpolar molecules that have ionizable functional groups make for good drug candidates, since the ionized form can dissolve well in water, and the unionized form can penetrate non-polar cellular membranes. Since the ratio of ionized to unionized form is pH dependent, drugs may be trapped in their ionized forms in various places of the body as a function of pH. This can be used to hasten the elimination of basic (mostly amine containing) drugs by acidification of urine:

![Diagram](image)

**FIGURE 1-6** Trapping of a weak base (methamphetamine) in the urine when the urine is more acidic than the blood. In the hypothetical case illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane, but the total concentration (charged plus uncharged) in the urine (more than 10 mg) is 25 times higher than in the blood (0.4 mg).
Please complete the following acid-base reactions

\[ \text{CH}_3\text{CH}_2\text{NH}_2 + \text{HCl} \to \]

\[ \text{CH}_3\text{CH}_2\text{NH}_3\text{Cl} + \text{NaOH} \to \]

Question: Given that ionized compounds have much greater water solubility than unionized compounds, how might you go about removing nicotine from tobacco leaves into water? What would be a potential source of contamination?

Answer:

**Amines as Nucleophiles**

*Condensation of Amines with Carboxylic Acids to Form Amides:*

In the lab, often times a carboxylic acid derivative takes the place of the carboxylic acid. Let's examine the reaction in acid-base terms to see why this is the case:
Alternatives:

- Acetic anhydride + Isopropyl amine → N-isopropylacetamine
- Ethyl acetate + Isopropyl amine → N-isopropylacetamine

- While an amine displacing an alcohol (converting an ester to an amide) is fairly common (e.g. amino acids linking together while bound to tRNA in the ribosome) the reverse reaction does not readily take place