Functional Groups in Drug Molecules

Most drugs currently in the market are small organic molecules that behave in aqueous solutions as weak acids or bases. We must therefore review acid-base theory in order to understand their behavior in the dilute aqueous solutions that represent physiological conditions. Upon dissolution in water, drug molecules ionize to different degrees, depending on their chemical structures. Unlike strong acids like HNO₃ or strong bases like NaOH, which ionize completely upon dissolution in water, weak acids or bases will be a mixture of an ionized species (cation or anion) and a molecular (non-ionized) species in equilibrium. Therefore, the ionization of many drugs in the aqueous solutions of body fluids is an equilibrium process.

Drug molecules are weak acids or bases in physiological fluids by virtue of the functional groups in their chemical structure, i.e., acidity or basicity of a drug molecule is dependent on it having electron-poor hydrogens (e.g., -COOH, carboxyl group) or non-bonding electrons which can be donated to hydrogen (e.g., those on amine nitrogens). A list of the functional groups most commonly found in drug molecules is given in Table 1.1. below: (click here to display this table (PDF) in a new window)
As an exercise, to familiarize yourself with the functional groups in the drugs mentioned in Table 1.1, look up their chemical structures in the internet (e.g., at ChemBioFinder.com) and decide whether the functional groups present make the drug acidic or basic in physiological fluids.

**Bronsted-Lowry Acid-Base Ionization Equilibrium of Drugs**

The acid-base theory that will work best for our purposes is that of Bronsted-Lowry:

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**Table 1.1 Some Common Functional Groups in Drug Molecules**

<table>
<thead>
<tr>
<th>Functional Groups</th>
<th>Structure</th>
<th>Drug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amine</strong> (Basic)</td>
<td>( R_1 - N(R_2 R_3) )</td>
<td>Zestril; Zithromax; Vasotec; Paxil</td>
</tr>
<tr>
<td><strong>Quaternary Amine</strong></td>
<td>( (R_2 R_3) - N^+ - (R_3 R_4) )</td>
<td>ipratropium Bromide; Cepacol; Phe-meride</td>
</tr>
<tr>
<td><strong>Azo</strong></td>
<td>( R - N == N - R' )</td>
<td>Colazal; Prontoxil</td>
</tr>
<tr>
<td><strong>Carboxylic Acid</strong> (Acidic)</td>
<td>( R - CO_2 H )</td>
<td>Tequin; Vasotec; ibuprofen; Zestril</td>
</tr>
<tr>
<td><strong>Ester</strong></td>
<td>( R - CO_2 R' )</td>
<td>Ritalin; Tricor; Vloxx Xalatan; Adalat</td>
</tr>
<tr>
<td><strong>Amide</strong></td>
<td>( R - CONH_2 )</td>
<td>Sonata; acetaminophen; Giocarol; indomethacin</td>
</tr>
<tr>
<td><strong>Imide (Acidic)</strong></td>
<td><img src="image" alt="Imide Structure" /></td>
<td>Macrobid; Avandia; phenytoin; Viagra</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>( R - OH )</td>
<td>Metroglob; Allegra; pseudoephedrine; Lescol</td>
</tr>
<tr>
<td><strong>Ether</strong></td>
<td>( R - O - R' )</td>
<td>Priosea; Serzone; Flomax Toprol; Zebeta; Skelaxin</td>
</tr>
<tr>
<td><strong>Phenol (Acidic)</strong></td>
<td>( Ar - OH )</td>
<td>Detrol; Aminox; acetaminophen; Asacol</td>
</tr>
<tr>
<td><strong>(Ar = Aromatic Rings)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aldehyde</strong></td>
<td><img src="image" alt="Aldehyde Structure" /></td>
<td>Xenical</td>
</tr>
<tr>
<td><strong>Ketone</strong></td>
<td>( R - C - R' )</td>
<td>naburnetone; Rhinocort; Percodan; Tricor; warfarin</td>
</tr>
<tr>
<td><strong>Cyano</strong></td>
<td>( R - C = N )</td>
<td>Sonata; cimetidine; milrinone</td>
</tr>
<tr>
<td><strong>Sulfonic Acid</strong> (Acidic)</td>
<td>( R - SO_3 H )</td>
<td>Cardura; Norvase</td>
</tr>
<tr>
<td><strong>Sulfonamide</strong> (Acidic if R2 and/or R3 is H)</td>
<td>( R - S - NR_2 R_3 )</td>
<td>Celebrex; Viagra; Zestoretic; Amaryl; Zarocyn; Flomax</td>
</tr>
<tr>
<td><strong>Sulfoxide</strong></td>
<td><img src="image" alt="Sulfoxide Structure" /></td>
<td>Acephene; Prilosee</td>
</tr>
<tr>
<td><strong>Sulfone</strong></td>
<td><img src="image" alt="Sulfone Structure" /></td>
<td>Vioxx</td>
</tr>
<tr>
<td><strong>Thioether</strong></td>
<td>( R - S - R' )</td>
<td>Zyprex; Axid; Ceflin</td>
</tr>
<tr>
<td><strong>Nitro</strong></td>
<td>( R - NO_2 )</td>
<td>Adalat; Macrobid; Axid Metrogel; clonazapam</td>
</tr>
<tr>
<td><strong>Carbamate</strong></td>
<td><img src="image" alt="Carbamate Structure" /></td>
<td>Claritin; Skelaxin; Ceflin</td>
</tr>
<tr>
<td><strong>Urea</strong></td>
<td>( R_1 R - N - C - O - R' )</td>
<td>Amaryl; Serzone; Glucotrol</td>
</tr>
<tr>
<td><strong>Phosphonic acid (Acidic)</strong></td>
<td><img src="image" alt="Phosphonic Acid Structure" /></td>
<td>Fosamax</td>
</tr>
</tbody>
</table>

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When an acid or base is dissolved in water, the following acid-base reaction takes place and equilibrium is established:

For Acid HA:

\[
\text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{A}^- \tag{Eq.2.1.}
\]

For Base B:

\[
\text{B}^- + \text{H}_2\text{O} \rightleftharpoons \text{BH}^+ + \text{OH}^- \tag{Eq.2.2.}
\]

The equations above indicate that water can act as either proton acceptor or donor, depending on the other reaction component. Equilibrium is established when the rate of the forward reaction equals the rate of the reverse reaction. The corresponding equilibrium constants are:

For Acids:

\[
K_{eq} = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}][\text{H}_2\text{O}]} \tag{Eq.2.3.}
\]

For Bases:

\[
K_{eq} = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}^-][\text{H}_2\text{O}]} \tag{Eq.2.4.}
\]

The concentration of water in any given physiological fluid is not affected by the solutes present, since they are all very dilute conditions. Water concentration remains constant at 55 M, based on a density of 1 g/mL and a molecular weight of 18 g/mole of water. Substituting this water concentration in equations 2.3 and 2.4 above yields expressions that will be more useful for our analysis of drugs in physiological fluids. The acid dissociation constant, $K_a$, is defined as follows:

\[
K_a = 55K_{eq} = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \tag{Eq.2.5.}
\]

Likewise, the base association constant, $K_b$, is defined as follows:

\[
K_b = 55K_{eq} = \frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}^-]} \tag{Eq.2.6.}
\]

Clearly, the more that the above equilibriums (Eq.2.1. & Eq.2.2.) lie to the right hand side, the larger $K_a$ and $K_b$ will be, the stronger the acid or base, and the more ionized they will be.

**Hydrolysis of Salts**

Many drugs are formulated as salts, a process that involves taking the weak acid or base and reacting it with base or acid, respectively, in order to generate an ionic compound, or salt. When salts are dissolved in water, the ions dissociate completely and associate with water molecules to form solvated anions and cations. One common error is to confuse low solubility with low percent dissociation, but these two processes are totally different. Barium sulfate, for example, has very low water solubility, but whatever amount does dissolve is 100% ionized into Ba$^{+2}$ and SO$_4^{-2}$. The same applies to many drugs formulated as salts. They may have varying degrees of water solubility, but whatever amount is dissolved in water is 100% ionized into the component ions. Indeed, the decision to formulate a drug as a salt, usually adding one more step in the manufacturing process, comes from the need to obtain greater solubility in body fluids. The salt is invariably more soluble than the parent compound, although some exceptions will be discussed in a later chapter.

Another caveat to add at this point is that whether the drug is administered as a free acid or base, or as its salt, dissolution in water will bring about the corresponding acid-base equilibrium. The equilibrium constant will be satisfied, regardless of whether we begin with the parent compound or one of its salts. The reaction of potassium acetylsalicylate (aspirin, potassium salt) and water is shown below, abbreviating the acid as HA, the salt as KA.

\[
\text{KA} + \text{H}_2\text{O} \rightleftharpoons \text{K}^\text{hydrated} + \text{A}^-\text{hydrated} \tag{Eq.2.7.}
\]
Once in solution, A\textsuperscript{−} will pick up H\textsuperscript{+} (from water dissociation) to form HA. We can write this reaction as:

\[ A^- + H^+ \rightarrow HA \]  \hspace{1cm} \text{Eq.2.8.}

But as soon as H\textsuperscript{+} is withdrawn from the solution this way, the H\textsubscript{2}O dissociates some more to replace that H\textsuperscript{+}. This reaction we have seen before:

\[ H_2O \rightarrow H^+ + OH^- \hspace{1cm} K_w = \frac{[H^+][OH^-]}{[H_2O]} \]  \hspace{1cm} \text{Eq.2.9.}

Adding both these reactions gives us the net reaction for the hydrolysis of A\textsuperscript{−}:

\[ A^- + H_2O \rightarrow HA + OH^- \]  \hspace{1cm} \text{Eq.2.10.}

This is the so-called hydrolysis reaction, and its equilibrium constant, commonly designated by \( K_h \) (hydrolysis constant), can be written as follows:

\[ K_h = \frac{[HA][OH^-]}{[A^-]} = \frac{s}{K_w} \]  \hspace{1cm} \text{Eq.2.11.}

We leave out the water from the denominator because as usual its activity stays constant. Multiplying the numerator and denominator by [H\textsuperscript{+}] yields a value for \( K_h \) equal to \( K_w/K_a \).

The hydrolysis reaction above will be similar for all salts of drugs that are weak acids and have been reacted with a strong base (i.e. KOH) to form a salt. It also explains why an aqueous solution of the salt of a weak acid is slightly basic, i.e., OH\textsuperscript{−} is generated upon hydrolysis. This last point is not significant in physiological fluids since the latter are commonly buffered, so that they can resist pH changes.

A similar situation arises when the salt we are considering is formed from a parent drug which is a weak base (i.e. epinephrine), and a strong acid (HCl).

Let’s abbreviate epinephrine as RN\textsubscript{H}\textsubscript{2} and its chloride salt as RN\textsubscript{H}\textsubscript{3}\textsuperscript{+}\textsubscript{Cl}\textsuperscript{−} or RN\textsubscript{H}\textsubscript{2}\textsuperscript{+}H\textsubscript{Cl}. Upon dissolution of this salt in water there is complete ionization of the salt, as follows:

\[ RNH_3^+Cl^- + H_2O \rightarrow RNH_2^+ + Cl^- \]  \hspace{1cm} \text{Eq.2.12.}

The Cl\textsuperscript{−} does not affect the water dissociation equilibrium (Eq.2.9), but the RNH\textsuperscript{3}\textsuperscript{+} can because some of it can combine with OH\textsuperscript{−} to produce RNH\textsubscript{2} and H\textsubscript{2}O by the reaction:

\[ RNH_3^+ + OH^- \rightarrow RNH_2 + H_2O \]  \hspace{1cm} \text{Eq.2.13.}

Adding this equation and the water dissociation we get the following net reaction:

\[ RNH_3^+ \rightarrow RNH_2 + H^+ \]  \hspace{1cm} \text{Eq.2.14.}

This last equation looks like a simple dissociation of a protonic acid, and this is the way we will consider the ionization equilibrium of basic drugs in physiological fluids. In this manner, we can view acids and bases on a similar framework of ionization equilibrium, a perspective which will be convenient for our purposes.

The equilibrium expression for Eq.2.14. has the form:
Multiplying numerator and denominator by $[\text{OH}^-]$ we get:

$$K = \frac{[\text{RNH}_2][\text{H}^+]}{[\text{RNH}_2^+]}$$

Although it would be most proper to call $K$ the hydrolysis constant for the amine $\text{RNH}_2$, for the purposes of our discussion we will call it the dissociation constant ($K_a$) of the cationic form of the amine, or $\text{RNH}_3^+$.  

Equation 2.16 expresses the inverse relationship between the base strength ($K_b$) of the parent compound, and the acid strength of its protonated, cationic form:

A strong base (large $K_b$) has a protonated, cationic form which is a weak acid (low $K_a$)  
A weak base (small $K_b$) has a protonated, cationic form which is a strong acid (high $K_a$)