Acid-Base Properties of Drugs

Strength of Acids and Bases

Bronsted-Lowry acids vary in their ability to transfer a proton to water upon dissolution, i.e., they vary in their ability to "ionize" in aqueous solutions.

A strong acid is one that can transfer 100% or close to 100% of its acidic hydrogen atoms to water upon dissolution. This process generates many hydronium ($H_3O^+$) ions in solution, and the equilibrium in equation Eq.2.1 lies far to the right. The actual concentration of unionized species $HA$ present in solution may be so small that cannot be measured, and the resulting $K_a$ (Eq.2.5.) is a very large number.

A weak acid is one that transfers only a small portion of its acidic hydrogen atoms to water upon dissolution. The amount of hydronium ions thus generated are much less than in the case of strong acids. The actual percentage of proton transfer for weak acids depends on the molecular structure, the molecular polarity, and the strength and polarity of individual bonds in the molecule. A weak acid generates a small amount of hydronium ions, and the equilibrium in equation 1 is far to the left, towards the non-ionized species $HA$. The resulting $K_a$ is a small number.

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

When comparing two acids for their relative strength it is usually the magnitude of the difference (as a power of 10) in their $K_a$ that is most informative. For example,

if acid A1 has a $K_a$ of $5.1 \times 10^5$ and acid A2 has a $K_a$ of $3.4 \times 10^2$, we can say that acid A1 is approximately 1000 times stronger than acid A2.

This approximation is all we need in many cases. It is also more convenient for our purposes to use the logarithm of $K_a$ rather than $K_a$ itself when comparing acid strengths.

The logarithm of a number is the exponent to which 10 is raised to generate the number:

$$\log_{10}x = x \quad \text{and} \quad \log_{10}10^x = x$$

The equilibrium constant for strong acids is a large number, and logarithms of numbers greater than 1 are positive numbers. Strong acids therefore have positive values of $\log K_a$.

Weak acids on the other hands, such as many drug molecules, have $K_a$ values in the range between 0 and 1. Logarithm of $K_a$'s in this range are negative numbers.
For example, if acid HA1 donates 1 in 1000 of its acidic hydrogen atoms to water, its $K_a$ will be $1 \times 10^{-3}$, and the log $K_a$ will equal -3. An even weaker acid may donate only one in a million of its acidic hydrogen atoms to water, its $K_a$ will be $1 \times 10^{-6}$ and its log $K_a$ will equal -6.

Scientists have found it more convenient to compare different acids strengths in term of positive numbers, and therefore it is the -log$K_a$ that is used to compare different acids. In analogy with pH, which is the -log[H$^+$], the -log$K_a$ is called the pKa of the acid. A small pKa means a large $K_a$ (strong acid), just like a small pH means a large [H$^+$].

In the example of the two acids above, the pKa’s will be 3 and 6 respectively, and the acid with the smaller pKa (3) is stronger than the acid with the larger pKa (6).

Many published Tables in the literature list acids and their pKa as a means of comparing their relative strength. Table 2.1 gives some examples of strong acids (large $K_a$, small pKa) and weak acids (small $K_a$, large pKa).

Just like there are strong acids and weak acids, there are also strong bases and weak bases. Strong bases are limited to the hydroxides of group IA and IIA in the periodic Table. Weak bases are many of the drug molecules that possess an amine functional group: -NH$_2$. When comparing two bases, the one with a smaller pKb is the stronger of the two. We will not, however, find many Tables published with pKb values to compare base strengths. Instead, scientists have found it more convenient to compare relative acid strengths for all proton-donating species, HA in case of acids and BH$^+$ in case of bases. We will use four common drugs to illustrate:
The comparison of aspirin and acetaminophen is straightforward, as explained before, aspirin with the smaller pKa is stronger than acetaminophen as acid.

In order to compare the two bases we must remember that it is their conjugate acids that we are dealing with, when we use their pKa. The conjugate acid of diazepam, with the small pKa, is stronger than the conjugate acid of amphetamine, which means that diazepam is the weaker base of the two.

In order to make a judicious use of the many pKa tables in the literature one must know the chemical structure of the acidic species listed, and by inspecting the nature of the functional groups present decide whether the pKa refers to an acid or to the conjugate acid of a base. We must know this because for bases, as we saw in the example above, the larger the pKa the stronger the base. This is contrary to acids: the larger the pKa the weaker the acid.

In summary, for calculation purposes, we can view all acid-base reactions in aqueous solutions from the standpoint of the conjugate acid form losing a proton to form the conjugate base. When we do this we can always use the pKa’s in our calculations and do not need to deal with Kb’s or pKb’s at all. Just remember:

<table>
<thead>
<tr>
<th>Weak acids: acetaminophen, aspirin</th>
<th>Aspirin pKa = 3.5</th>
<th>Acetaminophen pKa = 9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak bases: amphetamine, diazepam</td>
<td>Amphetamine pKa = 9.8</td>
<td>Diazepam pKa = 3.3</td>
</tr>
</tbody>
</table>

For acids: the stronger the acid, the smaller the pKa
For bases: the stronger the base, the larger the pKa