Ionization of Functional Groups: The Meaning and Use of the pK<sub>a</sub> Values

Following our discussion of “weak binding forces”, solubility, and LogP, we can see that the ionization state of functional groups can be extremely important in drug-receptor interactions and in pharmacokinetics. Ionization is a simple chemical property that can potentially be quantitatively related to drug activity (QSAR).

Let’s review a few facts about acid-base ionization reactions. The acidity for a given functional group is described by the equilibrium shown below:

\[ \text{A}-\text{H} \rightleftharpoons \text{A}^- + \text{H}^+ \]

The equilibrium constant for this reaction is \( K_a \). A useful value related to the \( K_a \) is \( pK_a \):

\[ pK_a = -\log(K_a) \]

Consider the acid-base ionization of a common functional group found in drugs, the carboxylic acid group. The carboxylic acid group can exist in the protonated (neutral) state or in an ionized (charged) form, as shown:

\[ \text{RCO}_2\text{OH} \rightleftharpoons \text{RCO}_2^- + \text{H}^+ \]

Let’s ask the medicinally relevant question: “at physiological pH (7), does the carboxylic acid group exist as the neutral protonated form or in the ionized, negatively charged form?”

For an average carboxylic acid group \( K_a = 1 \times 10^{-5} \); thus, the \( pK_a = 5 \) (Such values are found in tables and on your table of amino acids)

Useful Rule: When the \( \text{pH} = pK_a \), \([\text{A-H}] = [\text{A}^-] \) i.e. the concentration of the protonated and ionized forms are equal.

**Without doing any calculations** we can reason: pH 7 is more basic than pH 5. At pH 7 there is a lower concentration of protons than at pH 5 (two log units means 100 fold lower concentration). Thus, with the lower proton concentrations at pH 7 (relative to pH 5) the equilibrium will “lean” (or be “pulled”) toward the right (according to LeChatelier’s Principle). At pH 5 there are equal amounts of the neutral and charged forms of the carboxylic acid group; whereas at pH 7 there will be more (about 100 times more) of the ionized, negatively charged form.

**We can use calculations** to arrive at an exact answer to the question “at pH 7, what fraction of carboxylic acid exists in the ionized form?” Remember that:

\[ K_{eq} = \frac{[\text{H}^+][\text{RCO}_2^-]}{[\text{RCO}_2\text{H}]} \]

Multiply both sides by \([\text{H}^+]\) to get:

\[ K_{eq}/[\text{H}^+] = [\text{RCO}_2^-]/[\text{RCO}_2\text{H}] \]

The values for \( K_{eq} \) and \([\text{H}^+]\) are known:

\[ 1 \times 10^{-5}/1 \times 10^{-7} = [\text{RCO}_2^-]/[\text{RCO}_2\text{H}] = 100 \] (100 times more \( \text{RCO}_2^- \) than \( \text{RCO}_2\text{H} \)!

To calculate the percent \( \text{RCO}_2^- \) we’ll say that \( \text{RCO}_2^- + \text{RCO}_2\text{H} = 100\% \)

thus, \( \text{RCO}_2\text{H} = 100 - \text{RCO}_2^- \). So \([\text{RCO}_2^-]/[100 - \text{RCO}_2^-] = K_{eq}/[\text{H}^+] = 100 \) solve this to find that:

**At pH 7, 99% exists as \( \text{RCO}_2^- \) and 1% exists as \( \text{RCO}_2\text{H} \).**

Note: these calculations are just a reworking of the Henderson-Hasselbach Eqn that you’ve seen before in Chemistry and Biochemistry courses.