

CHEM 317

Ionization of Functional Groups: The Meaning and Use of the pK_a 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).

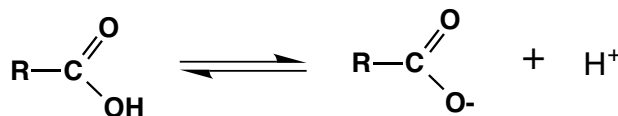
Let's review a few facts about acid-base ionization reactions. The acidity for a given functional group is described by the equilibrium shown below:



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

Defined as: $pK_a = -\log K_a$.

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:



Let's ask the medically 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 $pH = pK_a$, $[A-H] = [A^-]$ 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 LeChatlier'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:

$$K_{eq} = \frac{[H^+][RCO_2^-]}{[RCO_2H]}$$

Multiply both sides by $[H^+]$ to get:
 $K_{eq}/[H^+] = [RCO_2^-]/[RCO_2H]$

The values for K_{eq} and $[H^+]$ are known:
 $1 \times 10^{-5}/1 \times 10^{-7} = [RCO_2^-]/[RCO_2H] = 100$ (100 times more RCO_2^- than RCO_2H)!

To calculate the percent RCO_2^- we'll say that $RCO_2^- + RCO_2H = 100\%$
thus, $RCO_2H = 100 - RCO_2^-$. So $[RCO_2^-]/[100 - RCO_2^-] = K_{eq}/[H^+] = 100$ solve this to find that:

At pH 7, 99% exists as RCO_2^- and 1% exists as RCO_2H .

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