Key for Take-Home Assigment 05

The biopharmaceutical properties of a drug depend on the particular form it takes in the body. This is particularly important for a drug that is a weak acid or a weak base as, depending on the pH, it can exist in a molecular or an ionic form that differ in their ability to diffuse across membranes. For this reason, determining a drug's pK_a value(s) is important.

One method for determining the pK_a of a drug is to prepare a saturated solution of the drug in water and measure the solution's pH when equilibrium is established, as shown here for a drug that is a molecular, monoprotic weak acid, HA

$$HA(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + A^-(aq)$$

or a molecular, monoprotic weak base, B

$$B(aq) + H_2O(l) \rightleftharpoons OH^-(aq) + HB^+(aq)$$

In a typical analysis for the drug pentobarbital, the pH is measured as 5.312. The drug's formula is $C_{11}H_{18}N_2O_3$ and its mass solubility—the grams of the drug needed to prepare a 1.0 liter saturated solution—is 0.679 g/L. Using this information, determine if pentobarbital is a weak acid or a weak base, and report its pK_a if it is a weak acid and its pK_b if it is a weak base.

This assignment is due in class on Friday.

Answer. The first thing you must do is determine if the drug is a weak acid or a weak base. If the saturated solution is acidic (pH < 7), then the compound is a weak acid; if the saturated solution is basic (pH > 7), then the compound is a weak base. If the compound is a weak acid, then the equilibrium reaction and the equilibrium constant of interest are

$$HA(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + A^-(aq) \qquad K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

and if the compound is a weak base, then the equilibrium reaction and the equilibrium constant of interest are

$$B(aq) + H_2O(l) \rightleftharpoons OH^-(aq) + HB^+(aq) \qquad K_b = \frac{[OH^-][HB^+]}{[B]}$$

Once you decide on the correct equilibrium constant expression, you use the pH to determine either the equilibrium concentration of H_3O^+ if the compound is a weak acid or the equilibrium concentration of OH^- if the compound is a weak base; let's call this value x. The equilibrium concentration of the drug is $[\text{drug}]_o - x$, where $[\text{drug}]_o$ is the drug's initial concentration, which is equivalent to

$$[\text{drug}]_o = \frac{\text{solubility in g/L}}{\text{molar mass in g/mol}}$$

Substituting back gives either

$$K_a = \frac{(x)(x)}{[\text{drug}]_o - x} \qquad K_b = \frac{(x)(x)}{[\text{drug}]_o - x}$$

which you can now solve to give K_a if your drug is a weak acid, or to give K_b if your drug is a weak base.

Note. You cannot use a compound's K_a or its K_b to determine if it is a weak acid. If a compound is a weak acid, then its K_a value tells you about its strength as an acid; if a compound is a weak base, then its K_b value tells you about its strength as base.