Key for Take-Home Assigment 06

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

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

or a molecular, monoprotic weak base, B

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

In a typical analysis for the drug naphazoline, the pH is measured as 10.182. The drug's formula is $C_{14}H_{14}N_2$ and its mass solubility—the grams of the drug needed to prepare a 1.0 liter saturated solution—is 0.0381 g/L. Using this information

- determine if naphazoline is a weak acid or a weak base and explain how you arrived at your decision
- write the reaction that shows naphazoline behaving as a weak acid or as a weak base (whichever is appropriate for naphazoline)
- determine the pK_a or the pK_b for naphazoline (whichever is appropriate for naphazoline)

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

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

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

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

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 $[\mathrm{drug}]_\mathrm{o} - x$, where $[\mathrm{drug}]_\mathrm{o}$ is the drug's initial concentration, which is equivalent to

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

Substituting back gives either

$$K_\mathrm{a} = \frac{(x)(x)}{[\mathrm{drug}]_\mathrm{o} - x} \qquad K_\mathrm{b} = \frac{(x)(x)}{[\mathrm{drug}]_\mathrm{o} - x}$$

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.