Key for Take-Home Assignment 04

Benzocaine, $C_9H_{11}NO_2$, is an anesthetic used to provide topical pain relief. It has a mass solubility of 1.310 g/L in water and a partition coefficient, K_D, of 72 between water and octanol.[1] Pentobarbital, $C_{11}H_{18}N_2O_3$, is a sedative. It has a mass solubility of 0.679 g/L in water and a partition coefficient of 126 between water and octanol. For the following questions, assume you have an aqueous solution that is saturated with respect to both drugs and that you are interested in determining the concentration of benzocaine (the analyte) in the presence of pentobarbital (the interferent). Assume, as well, that your analytical method is 2× more sensitive for benzocaine than it is for pentobarbital: that is, $K_{A,I} = 0.5$ in both water and in octanol.

Question 1. If you try to analyze the sample as originally provided, what is the expected error for the reported concentration of benzocaine?

Answer. First, we need to determine the initial concentrations of benzocaine and of pentobarbital in the saturated aqueous solution; these are

$$[\text{benzocaine}]_o = \frac{1.310 \text{ g/L}}{165.08 \text{ g/mol}} = 0.007936 \text{ M}$$

$$[\text{pentobarbital}]_o = \frac{0.679 \text{ g/L}}{226.27 \text{ g/mol}} = 0.003001 \text{ M}$$

Next, we calculate the error by setting the recoveries for the analyte and the interferent to 1; thus

$$\text{error} = (R_B - 1) + K_{A,I} \times \frac{[\text{pentobarbital}]_o}{[\text{benzocaine}]_o} \times R_P = (1 - 1) + 0.5 \times \frac{0.003001}{0.007936} \times 1 = 0.189$$

or 18.9%.

Question 2. If you extract 25.0 mL of the aqueous solution using 25.0 mL of octanol, what is the concentration of each species in each phase after a single extraction? What is your anticipated error if you analyze the octanol phase for benzocaine?

Answer. Using the equation

$$q_{aq} = \frac{V_{aq}}{DV_{org} + V_{aq}}$$

where $D = K_D$, gives the fraction of benzocaine as 0.014 in the aqueous phase and as 0.986 in the octanol phase. The fractions for pentobarbital are 0.008 and 0.992 in the aqueous phase and the octanol phrase, respectively. To find their respective concentrations, we multiply the initial concentrations by the fractions; thus

- $[\text{benzocaine}_{aq}] = 0.007936 \times 0.014 = 0.000109$ M
- $[\text{benzocaine}_{org}] = 0.007936 \times 0.986 = 0.007827$ M
- $[\text{pentobarbital}_{aq}] = 0.003001 \times 0.008 = 0.000024$ M
- $[\text{pentobarbital}_{org}] = 0.003001 \times 0.992 = 0.002977$ M

The anticipated error for benzocaine when analyzing the octanol phase is

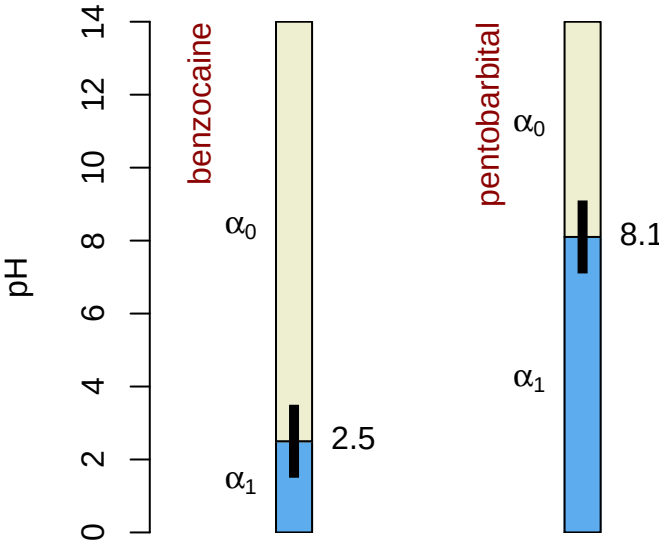
$$\text{error} = (0.986 - 1) + 0.5 \times \frac{0.003001}{0.007936} \times 0.992 = 0.174$$

or 17.4%. Note that there is little improvement in the error because both the analyte, benzocaine, and the interferent, pentobarbital, are preferentially extracted into the organic phase.

[1] In the pharmaceutical industry, a drug's partition coefficient, K_D, between water and and octanol is reported as $\log P$, where P stands for partition coefficient. Octanol is intended to serve as a simple model of a phospholipid membrane; thus, the partition coefficient distinguishes between hydrophilic drugs with smaller values of K_D, and lipophilic drugs with larger values of K_D.

Question 3. Benzocaine is a weak base with a pK_b of 11.5, and pentobarbital is a weak acid with a pK_a of 8.1. Draw ladder diagrams for both compounds and identify the range of pH levels where (a) benzocaine is present in its neutral weak base form and pentobarbital is present in its anionic weak base form, and where (b) benzocaine is present in its cationic weak acid form and pentobarbital is present in its neutral weak acid form. These are pH ranges where a separation is possible.

Answer. The ladder diagrams appear below, where α_1 is a drug's weak acid form (HB^+ for benzocaine and HP for pentobarbital) and α_0 is a drug's weak base form (B for benzocaine and P^- for pentobarbital). From the ladder diagram, we see that (a) at any pH greater than 9.1, benzocaine is present as its neutral weak base and pentobarbital is present as its anionic weak base, and that (b) at any pH less than 1.5, benzocaine is present as its cationic weak acid and pentobarbital is present as its neutral weak acid. From this, we expect that as the pH level becomes greater than 8.1, we will extract increasingly more benzocaine into the octanol phase and that at pH levels less than 1.5, we will retain increasingly more benzocaine in the aqueous phase.



Question 4. For each of (a) and (b) in Question 3, if you extract 25.0 mL of the aqueous solution using 25.0 mL of octanol, what is the concentration of each species in each phase after a single extraction? What is your anticipated error for a quantitative analysis for benzocaine if you analyze the phases enriched in the analyte?

Answer. We have to choose a specific pH level for both (a) and for (b); let's use a pH of 12 for (a) and a pH of 1 for (b). At a pH of 12, the concentrations are

- $[\text{benzocaine}_{aq}] = 0.007936 \times 0.014 = 0.000109$ M
- $[\text{benzocaine}_{org}] = 0.007936 \times 0.986 = 0.007827$ M
- $[\text{pentobarbital}_{aq}] = 0.003001 \times 0.984 = 0.002954$ M
- $[\text{pentobarbital}_{org}] = 0.003001 \times 0.016 = 0.000047$ M

and the anticipated error for the analysis of benzocaine in the octanol phase is

$$\text{error} = (0.986 - 1) + 0.5 \times \frac{0.003001}{0.007936} \times 0.016 = -0.011$$

or -1.1%. At a pH of 1, the concentrations are

- $[\text{benzocaine}_{aq}] = 0.007936 \times 0.312 = 0.002474$ M
- $[\text{benzocaine}_{org}] = 0.007936 \times 0.688 = 0.005461$ M
- $[\text{pentobarbital}_{aq}] = 0.003001 \times 0.008 = 0.000024$ M
- $[\text{pentobarbital}_{org}] = 0.003001 \times 0.992 = 0.002977$ M

and the anticipated error for the analysis of benzocaine in the aqueous phase is

$$\text{error} = (0.312 - 1) + 0.5 \times \frac{0.003001}{0.007936} \times 0.008 = -0.687$$

or -68.7%. Note that even though the pH is more than one pH unit below benzocaine's pK_a value—a pH level where the predominate form of benzocaine is HB^+, the majority of the benzocaine continues to extract into the organic phase because its K_D value is so large; the error in the octanol phase, however, also is large because pentobarbital also extracts preferentially into octanol

$$\text{error} = (0.688 - 1) + 0.5 \times \frac{0.003001}{0.007936} \times 0.992 = -0.124$$

or -12.4%.

Question 5. Prepare a single plot that shows the fraction of benzocaine and the fraction of pentobarbital in the aqueous phase as a function of pH when extracting 25.0 mL of the aqueous solution with a single 25.0 mL portion of octanol.

Answer. A plot of q_{aq} for both benzocaine and for pentobarbital is shown below. Note that this plot is consistent with our observations in the previous question; that is, we cannot achieve an effective separation at any acidic pH because q_{aq} for benzocaine does not reach a value of 1 even at a pH of 0. We can, however, achieve an effective separation at a pH of 12 or greater because q_{aq} for benzocaine essentially is 0 and q_{aq} for phenolbarbital essentially is 1.