

Quiz 13
Chemical Engineering Thermodynamics
April 13, 2017

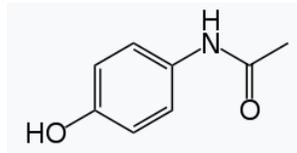
In the pharmaceutical industry drugs are often produced in an aqueous environment and must be separated to a pure product as crystals. Liquid-liquid phase separation is often undesirable and is termed oiling out because the desired drug separates as an oily phase that can be too concentrated to allow for crystallization. This oily phase can also contaminate processing equipment.

It is necessary to produce supersaturated solutions (far below the equilibrium crystallization temperature) to successfully form pure crystals of the drug.

Consider **paracetamol (1)** (Tylenol[®]) in **water (2)** at **25°C**.

a) What is the composition of the two phases that will be formed? (Assume initially that phase β is pure 1, and phase α is initially pure 2.)

Do the first initial assessment of the activity coefficients and then **three iterations** involving calculation of **3 sets of K_1 and K_2 and the resulting compositions**. Use UNIFAC (LLEa) (*and LLEb if you want*) in the ActCoeff.xlsx sheet to calculate γ 's.



Paracetamol (1)

Assume that the secondary amine can be represented as a primary amine in UNIFAC, "ACNH2". Other groups are ACOH, ACH, CH3CO.

b) For the Paracetamol (1) rich phase (β -phase) **determine the crystallization temperature** if the heat of fusion is 26.49 kJ/mol and T_f is 441.9°K. (This will require iteration of temperature beginning with 25°C to obtain γ_1 from UNIFAC. (*If you use the alpha and beta sheets you need to change T in the alpha sheet. Ignore this if you use one sheet.*) Proceed with an initial guess at T using 25°C to obtain γ and **two following iterations** obtaining γ and then obtaining T (**three total temperatures**). The two iterations after the initial guess should differ by less than 1%.

c) Explain what should happen in this separation at 25°C. That is, **do you expect to produce pure crystals of paracetamol or will the system oil out?**

$$R = 8.314 \text{ J}/(\text{mol } ^\circ\text{K})$$

1. Assume that phase β is nearly pure 1, $x_1^\alpha = 1/\gamma_1^{\alpha,\infty}$, and α is nearly pure 2, $x_2^\beta = 1/\gamma_2^{\beta,\infty}$. These represent initialization of the iteration procedure. The procedure is most stable with an initial guess of mutual solubility outside the two-phase region.
2. Calculate $K_{i,old} = \gamma_i^\beta/\gamma_i^\alpha$ where the γ_i 's are evaluated at the initial compositions.
3. Calculate $x_{1,new}^\beta = (1 - K_{2,old})/(K_{1,old} - K_{2,old})$, $x_{2,new}^\beta = 1 - x_{1,new}^\beta$.
4. Calculate $x_{i,new}^\alpha = K_{i,old}x_{i,new}^\beta$.
5. Determine $\gamma_{i,new}$ values for each liquid phase from the $x_{i,new}$ values.
6. Calculate $K_{i,new} = \gamma_i^\beta/\gamma_i^\alpha$.
7. Replace all $x_{i,old}$ and $K_{i,old}$ values with the corresponding new values.
8. Loop to step 3 until calculations converge. The calculations converge slowly.

$$\ln(x_i\gamma_i) = \frac{-\Delta H_i^{fus}}{R} \left(\frac{1}{T} - \frac{1}{T_{m,i}} \right)$$

14.24

①

Paracetamol (1)

Water (2)



1 water

- 4 AcH
- 1 AcOH
- 1 AcNH₂
- 1 CH₃CO

β - pure 1

$$\gamma_2^{\beta \infty} = 1.633$$

$$\gamma_1^{\alpha \infty} = 829.3$$

$$x_2^{\beta} = 0.6124$$

$$x_1^{\alpha} = 0.00121$$

$$x_1^{\beta} = 0.3876$$

$$x_2^{\alpha} = 0.9988$$

$$\gamma_1^{\beta} = 1.190$$

$$\gamma_1^{\alpha} = 718.8$$

$$\gamma_2^{\beta} = 1.577$$

$$\gamma_2^{\alpha} = 1.000$$

$$K_1 = \frac{\gamma_1^{\beta}}{\gamma_1^{\alpha}} = \frac{1.190}{718.8} = 1.656 e^{-3}$$

$$K_2 = \frac{\gamma_2^{\beta}}{\gamma_2^{\alpha}} = \frac{1.577}{1.000} = 1.577$$

Iteration 1

$$x_1^{\beta} = \frac{1 - K_2}{K_1 - K_2} = \frac{1 - 1.577}{1.656e^{-3} - 1.577} = 0.3663$$

$$x_2^{\beta} = 0.6337$$

$$x_1^{\alpha} = K_1 x_1^{\beta} = 0.000604 \quad x_2^{\alpha} = 0.99940$$

②

$$\gamma_1^B = 1.610$$

$$\gamma_2^B = 1.478$$

$$\gamma_1^A = 776.5$$

$$\gamma_2^A = 1.000$$

$$K_1 = \frac{\gamma_1^B}{\gamma_1^A} = \frac{1.610}{776.5} = 2.073 e^{-3}$$

$$K_2 = \frac{\gamma_2^B}{\gamma_2^A} = \frac{1.478}{1} = 1.478$$

Iteration
2

$$\begin{aligned}
 x_1^B &= \frac{1 - K_2}{K_1 - K_2} = \frac{1 - 1.478}{2.073 e^{-3} - 1.478} = 0.3239 \\
 x_2^B &= 0.6761 \\
 x_1^A &= (0.3239) \left(\frac{2.073 e^{-3}}{K_1} \right) = 1.402 e^{-3} \\
 x_2^A &= 0.9986
 \end{aligned}$$

$$\gamma_1^A = 701.7 \quad \gamma_2^A = 1.000$$

$$\gamma_1^B = 1.793 \quad \gamma_2^B = 1.443$$

$$K_1 = \frac{1.793}{701.7} = 0.002555$$

$$K_2 = \frac{1.443}{1} = 1.443$$

iteration
3

$$x_1^B = \frac{1-k_2}{k_1-k_2} = \frac{1-\overset{1.443}{\cancel{2.002}}}{0.002577-1.443} = 0.3075$$
$$x_2^B = 1-x_1^B = 0.6925$$
$$x_1^\alpha = k_1 x_1^B = 0.001769$$
$$x_2^\alpha = 1-x_1^\alpha = 0.9823$$

3

$$y_1^\alpha = 614.2 \quad y_2^\alpha = 1.000$$

$$y_1^B = 1.886 \quad y_2^B = 1.427$$

$$K_1 = \frac{y_1^B}{y_1^\alpha} = 3.071e^{-3} \quad K_2 = \frac{y_2^B}{y_2^\alpha} = 1.427$$

iteration
4

$$x_1^B = \frac{1-k_2}{k_1-k_2} = 0.2999$$
$$x_2^B = 0.7001$$
$$x_1^\alpha = x_1^B k_1 = 0.0009210$$
$$x_2^\alpha = 0.9991$$

④

$$(x_1, \gamma_1) = \exp\left(-\frac{\Delta H^f}{R} \left(\frac{1}{T} - \frac{1}{T_f}\right)\right)$$

$$x_{1, \text{initial}} = 0.3075$$

$$\gamma_1 = 1.886$$

$$\Delta H^f = 26,490 \text{ J/mol}$$

$$T_f = 441.9 \text{ K}$$

$$T = \frac{1}{\frac{1}{T_f} - \frac{R \ln(x_1, \gamma_1)}{\Delta H^f}}$$

$$= \frac{1}{\frac{1}{441.9 \text{ K}} - \frac{8.314 \text{ J/mol K} \ln((0.3075) \cdot 1.886)}{26,490 \text{ J/mol}}}$$

$$= 410.9 \text{ K} (137.9 \text{ }^\circ\text{C})$$

Re calculate γ_1 at $137.9 \text{ }^\circ\text{C}$

$$\gamma_1 = \frac{1.886}{2.370}$$

1st iteration

$$T = \frac{T_f}{1 - \frac{RT_f}{\Delta H^f} \ln(x_1, \gamma_1)} = \frac{441.9 \text{ K}}{1 - \frac{8.314 \text{ J/mol K} \cdot 441.9 \text{ K}}{26,490 \text{ J/mol}} \ln(0.3075 \cdot \frac{1.886}{2.370})} = 424.7 \text{ K} (151.0 \text{ }^\circ\text{C})$$

2nd iteration

$$\gamma_1 = 2.398$$

$$T = 423.8 \text{ K} (150.9 \text{ }^\circ\text{C})$$

It is difficult to determine the exact outcome of this separation. It depends largely on the kinetics of the phase separation and crystallization and the degree of seeding of the crystals. In the pharmaceutical industry crystallization or products is the most difficult stage of production and there are many trade secrets involved in the process. In this case it would seem that the large degree of undercooling would lead to rapid crystallization of paracetamol prior to oiling out.