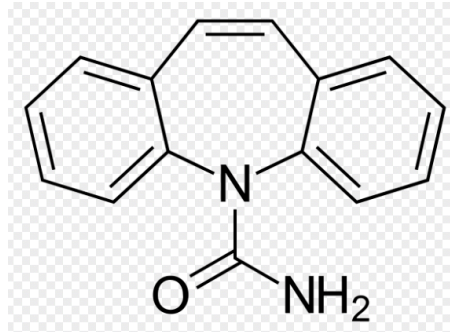


**Quiz 13**  
**Chemical Engineering Thermodynamics**  
**April 17, 2019**

Carbamazepine (CBZ), sold under the trade name Tegretol, is used to treat epilepsy, bipolar disorder, and schizophrenia. It can produce many polymorphic crystalline forms and only one crystalline form is active.



Carbamazepine (CBZ) (1)

Consider **CBZ (1)** in **water (2)** at **25°C**.

*(For this problem you can use more than 3 digits where it seems necessary. Try to round to three digits or a minimum number of digits where possible for the sake of sanity.)*

- a) What is the composition of the two liquid phases that will form? (Assume initially that phase  $\alpha$  is pure 2 and phase  $\beta$  is pure 1 (use the UNIFAC LLEa excel sheet in ActCoeff.xlsx.)

Do the first initial assessment of the activity coefficients and then **two iterations** involving calculation of **2 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 the  $\gamma$ 's.

***Assume that CBZ can be modeled with just ACH, CHO (for the carboxylic group) and ACNH2 (for the primary amine group).***

- b) The final step of synthesis, purification, and evaporation leads to an aqueous solution of  $z_1 = 0.30$ . What is the fraction of  $\alpha$  to  $\beta$  phases? (That is, are they 50:50  $\alpha/\beta$  or 20:80  $\alpha/\beta$ ? It might help to sketch  $T$  versus  $x_1$  and show the 2-phase region with your two points and a point for the input composition at 25°C.)
- c) What would happen if you evaporated to a much higher concentration,  $z_1 = 0.80$  at 25°C?
- d) Consider two of the many polymorphs (different crystalline forms) for CBZ which will be labeled I and II. For I  $T_f = 189^\circ\text{C}$  (462K) and  $\Delta H_f = 22.9$  kJ/mole. For II  $T_f = 176^\circ\text{C}$  (449 K) and  $\Delta H_f = 29.3$  kJ/mole.

For the CBZ (1) rich phase ( $\beta$ -phase) **determine the crystallization temperatures** for each of these polymorphs. (This will require iteration of temperature beginning with 25°C to obtain  $\gamma_1$  from UNIFAC. (**USE THE VLE SHEET FOR THIS QUESTION.**) Proceed with an **initial guess at T using 25°C to obtain  $\gamma$  and one following iteration** obtaining  $\gamma$  and then obtaining  $T$  (**two total temperatures**). The iteration after the initial guess should differ by less than 1%.

e) There are at least four options in this system:

- A) CBZ oils out and no crystals form.
- B) Type I crystals form.
- C) Type II crystals form.
- D) Both crystals form in a mixture.

How would you propose to manipulate the process to achieve each of these results? This is a question involving the strength of the thermodynamic driving force and the opposing kinetic constraints, so consider the rates of the three separation processes: LL phase separation; L I crystallization; L II crystallization as well as their respective thermodynamic driving forces. More complex processes are generally slower. The rate limiting step in crystallization is nucleation, so use of nucleation seeds is common. (*Please attempt to answer this question though it is pretty much beyond what you have learned. This is one of the main problems involved in the pharma industry.*)

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

1. Assume that phase  $\beta$  is nearly pure 1,  $x_1^\alpha = 1/\gamma_1^{\alpha, \infty}$ , and  $\alpha$  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  $\gamma_i$ '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

NAME:

Answer Sheet (use more pages if you want but put your numerical answers here. Show your work on other pages.)

a)  $x_1^\alpha =$   $x_1^\beta =$   
 $x_2^\alpha =$   $x_2^\beta =$

b)  $\alpha$ -fraction =  
 $\beta$ -fraction =

c)

d)  $T_I =$   
 $T_{II} =$

e)

①

a)

(1)	(2)	
CBZ	H <sub>2</sub> O	AcH 10
$\alpha$	$\beta$	CKO 1

ACNH<sub>2</sub> 1

$$\gamma_2^\alpha = 2.337 \quad \gamma_1^\beta = 72609$$

$$x_2^\alpha = \frac{1}{\gamma_2^\alpha} = 0.428 \quad x_1^\beta = 1.38e^{-r}$$

$$x_1^\alpha = 0.572 \quad x_2^\beta = 0.99999$$

$$\gamma_1^\alpha = 1.519 \quad \gamma_1^\beta = 72451$$

$$\gamma_2^\alpha = -2.892 \quad \gamma_2^\beta = 1.00$$

$$K_1 = 47697 \quad K_2 = 0.3458$$

$$x_1^\beta = \frac{1-k_2}{a_1 \cdot b_2} = 1.37e^{-r} \quad x_1^\alpha = K_1 x_1^\beta = 0.654$$

$$x_2^\beta = 0.99999 \quad x_2^\alpha = 0.346$$

$$\gamma_1^\alpha = 1.361 \quad \gamma_1^\beta = 72412$$

$$\gamma_2^\alpha = 2.921 \quad \gamma_2^\beta = 1$$

$$K_1 = 53236 \quad K_2 = 0.3423$$

(2)

$$x_1^B = \frac{1-k_2}{k_1-k_2} = 1.24e^{-r} \quad x_1^\alpha = k_1 x_1^B = 0.660$$

$$x_2^B = 0.99999 \quad x_1^\alpha = 0.340$$

$$y_1^\alpha = 1.351 \quad y_1^B = 72466$$

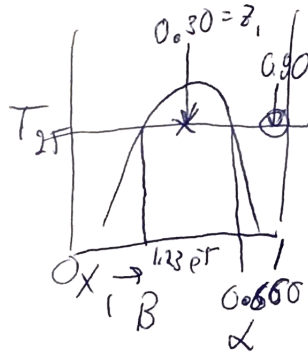
$$y_2^\alpha = 2.920 \quad y_2^B = 1$$

$$k_1 = 53639 \quad k_2 = 0.3425$$

$$k_2 \Rightarrow x_1^B = \frac{1-k_2}{k_1-k_2} = 1.23e^{-r} \quad x_1^\alpha = k_1 x_1^B = 0.660$$

$$x_2^B = 0.99999 \quad x_2^\alpha = 0.340$$

(b)



$$f_{\text{fracn}} = \frac{0.30 - 1.23e^{-r}}{0.660 - 1.23e^{-r}}$$

$$= 0.455$$

$$f_{\text{fracn}} = 0.545$$

c) The circle above shows that it would be a single CB + Rich phase. No phase separation.

3

d)

$$T = \frac{1}{\frac{1}{T_f} - \frac{R \ln(x_1 \gamma_1)}{\Delta H_f}}$$

Start at 25°C

$$I \quad T_I = \frac{1}{\frac{1}{462K} - \frac{8.31 \frac{J}{mol \cdot K} \ln(0.660 \cdot 0.961)}{22,900 \frac{J}{mol}}} = 429 K (156^\circ C)$$

$1.652 \cdot 10^{-4}$

$$II \quad T_{II} = \frac{1}{\frac{1}{449K} + 1.291 \cdot 10^{-9} K^{-1}} = 424 K (151^\circ C)$$

$$I \quad \gamma_1(156^\circ C) = 0.976$$

$$II \quad \gamma_1(151^\circ C) = 0.975$$

$$T_I = \frac{1}{\frac{1}{462K} - \frac{8.31 \frac{J}{mol \cdot K} \ln(0.660 \cdot 0.976)}{22,900 \frac{J}{mol}}} = 430 K (157^\circ C)$$

$$T_{II} = \frac{1}{\frac{1}{449K} + \frac{8.31 \frac{J}{mol \cdot K} \ln(0.660 \cdot 0.975)}{29,300 \frac{J}{mol}}} = 425 (152^\circ C)$$

e) The LL phase separation occurs much faster than crystallization since in crystallization the molecules must diffuse to a growing crystal front then rearrange and form associations which

takes time. The two crystallization processes are similar and have similar heats of fusion and melting temperatures so it will be almost impossible to produce a single polymorph, unless seeds of one of the two polymorphs can be introduced. (The slowest step in crystallization might be the formation of the initial nucleus for the crystal.) So seeding is a primary way to control the process. If one wanted the oil phase then a rapid quench to a low temperature would produce an oil phase for type A phase separation. A more gradual process with cooling from a high temperature might favor B, C, and D.