ChE **class and home problems**

MATERIAL AND ENERGY BALANCES: FLOW CHEMISTRY CASE STUDY

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Undergraduate students taking the Material and Energy Balance course often comment on (a) having a desire to know more about what kinds of problems chemical engineers working in industry address; and (b) feeling that in-class examples and homework problems do not address real-world problems. This case study, used in the Material and Energy Balance course in spring 2018, aims to help students gain a better understanding of the chemical engineering profession and to closely study a new, high-impact production process. Relating the various concepts introduced throughout the semester to a single production process helps students integrate these concepts. Finally, by demonstrating the application of course concepts to the safe and lower-cost production of a potential anti-cancer compound, this case study may provide some of the benefits previously attributed to service-learning.[1]

PROCESS OVERVIEW

In 2017 researchers from Eli Lilly and Company described the design and implementation of a continuous process for the production of approximately 3 kg per day of the pharmaceutical compound prexasertib monolactate monohydrate.[2] This process complies with current good manufacturing practices (cGMP) and was deemed to have improved performance and safety compared to batch processing.[2] The continuous operation mode ("flow chemistry") helps to decrease the risk associated with the use of hydrazine.[3]

The original process flow diagram[2] (Figure 1) and the alternate diagram (Figure 2) were provided to students at the beginning of the course. This publication[2] and its supplementary material include process equipment photographs. In addition, the *Chemical & Engineering News*[3] process summary can be provided to students.

A summary of all chemical species used in the case study is given in Table 1. The process consists of four distinct reactions, with each reaction being followed by at least one purification step. Various separation processes are employed, including liquid-liquid extraction, evaporation, crystallization and filtration. Most students who are enrolled in the sophomore-level Material and Energy Balance course will have already encountered these processes in the general chemistry lab courses and may also be covering related material in the organic chemistry lecture and lab courses.

While the flow chemistry aspect is a substantial part of the novelty of this process, none of the assigned homework problems address this aspect. Instead, process units are modeled as operating either entirely in batch mode or entirely in steady-state continuous mode. The distinction of flow chemistry from standard industrial processes may be suitable in junior- or senior-level curriculum.

HOMEWORK PROBLEMS

The problems given below were assigned as part of the approximately-weekly homework sets. Other homework problems not related to the case study were also assigned as part of these homework sets. Each homework problem was divided into a part to be completed individually and then a more difficult part to be worked within their homework group. These divisions are not specified here. Solutions to these problems are available from the author upon request (ljarboe@iastate.edu).

Problems were written with the intention that students

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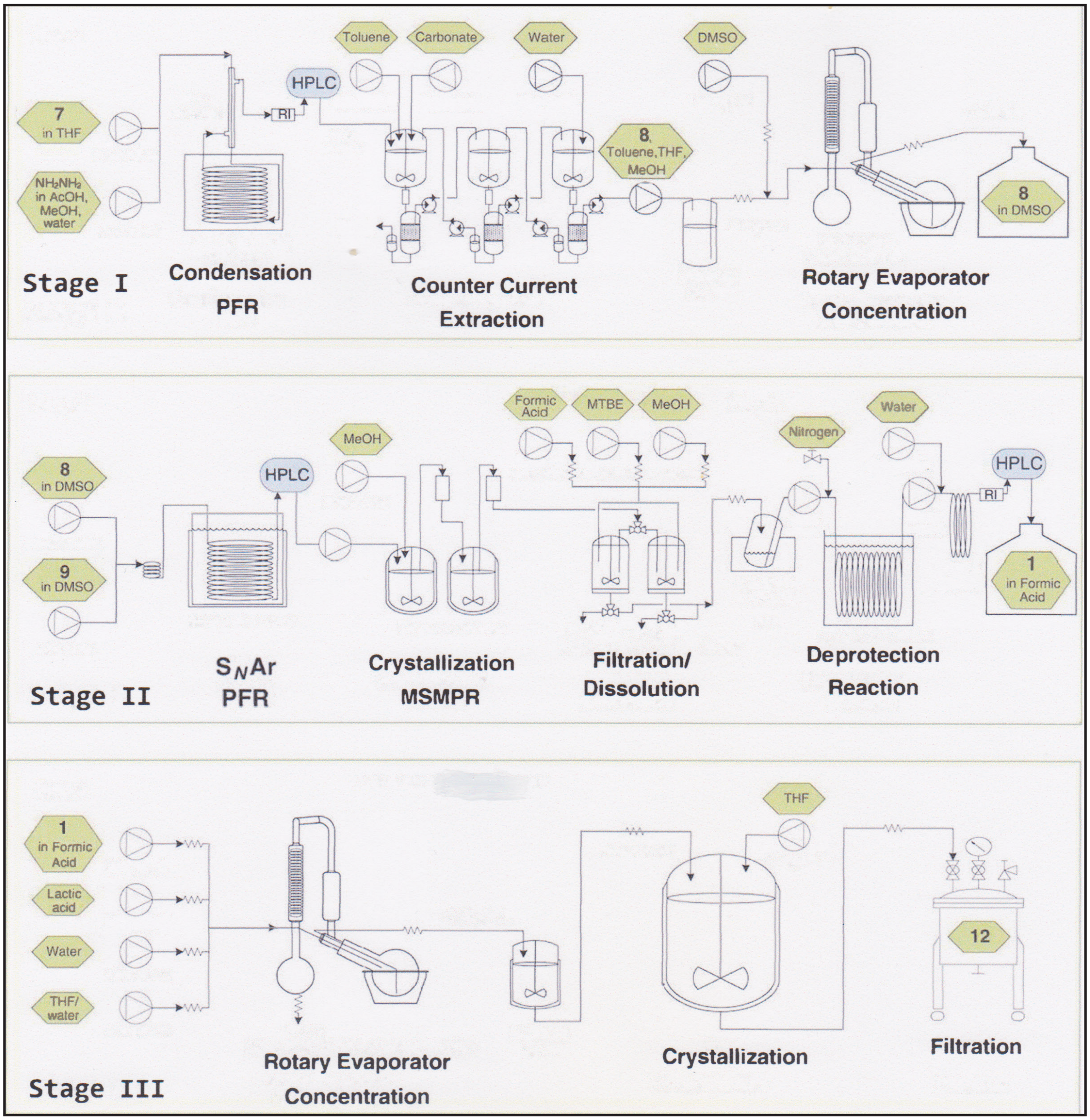

Figure 1. *Process flow diagram,[2] with some text removed or enlarged to improve legibility. Reprinted with permission from AAAS.*

would not have to access the case study materials in order to solve the assigned problem. As part of the first homework assignment, students were asked to look over the case study materials and write a few sentences summarizing their initial thoughts about the case study, such as which steps they were already familiar with, which they found to be the most confusing, and whether or not this process was of interest to them and consistent with their understanding of the type of work a chemical engineer does. During the final lecture of the semester, the process flow diagram (Figure 2) was shown and discussed, with a review of which course topics were applied to which steps in the process.

Problem 1: A storage tank contains 0.36 kg of species E, 6.04 kg FA, 0.72 kg LA, and 1.68 kg W. Calculate the composition of this mixture (stream 40) on both mass and mole bases.

Problem 2: Two streams are combined at a mixing point in a continuous steady-state process to form stream 3.

- *Stream 1 contains 5.4 mol% A and 94.6 mol% THF.*
- *Stream 2 contains 30.8 mol% MeOH, 1.8 mol% AA, 59.8 mol% W, and 7.6 mol% H.*

a. Draw and completely label a flowchart and then perform a degrees of freedom analysis on this process.

b. Assume streams 1 and 2 each have a flowrate of 1.0 mol/s. Update your degrees of freedom analysis to include this *information. You should find that the system is solvable; find the composition (mol%) and flowrate (mol/s) of stream 3.*

c. *Assume stream 1 has a flowrate of 1.0 mol/s but the flowrate of stream 2 is not specified. Instead, the mol% of A and H in stream 3 are specified to be equal. Update your DoF analysis from (a) to include this information. You should find that the system is solvable; find the required flowrate (mol/s) of stream 2 and the flowrate (mol/s) and composition (mol%) of stream 3.*

Problem 3: The outgoing stream from a Reactor contains species B, which is needed for stage II of the process. But this stream also contains undesired species, such as unreacted species A and H. Liquid/liquid extraction (covered later in the course) is used to separate the desired and undesired species.

Four liquid streams enter this process unit.

- *Stream 6 is 21.5 mL/min with unspecified amounts of A, B, H, AA, MeOH, THF and W. The density is unknown.*
- *Stream 7 is 10.3 mL/min of pure TOL.*
- *Stream 8 is 8.2 mL/min of 9.2 wt% sodium carbonate, in water. The density is unknown.*
- *Stream 14 is 2.6 mL/min of pure water.*

Two liquid streams exit this process unit.

- *Stream 15 (organic) moves forward to the next step of this process. For now, assume this stream contains only B, TOL, THF and MeOH.*
- *Stream 10 (aqueous) is waste. This stream contains A, B, H, AA, MeOH, THF, W, and sodium carbonate.*

Other information:

- *99% of the B that enters the extraction process will be recovered in the organic stream.*

a. *Draw and completely label a flowchart.*

b. *Perform a degrees of freedom analysis.*

c. *Do not do any calculations, but write out each of the equations specified in your degrees of freedom analysis.*

Problem 4: The conversion of species A to species G involves four distinct reactions. Each of these is carried out in a different reactor, with at least one separation step between each set of reactors. Stage I involves the first reaction and processing of that reaction product in preparation for the second reaction. Stage I can be represented in a simplified model consisting of two process units:

- *A reactor with feed stream 3 and product stream 6. The balanced equation associated with this reactor is (A + H ➔ B + W). Do not assume that the reaction goes to completion.*
- *Stream 3 is produced from the mixing of streams 1 and 2. Since we previously modeled the mixing in problem 1, you can start your process diagram with stream 3. Stream 3 consists of: 0.51 mol/h of species A, 1.64 mol/h of H, 6.65 mol/h of MeOH, 8.91 mol/h of THF,*

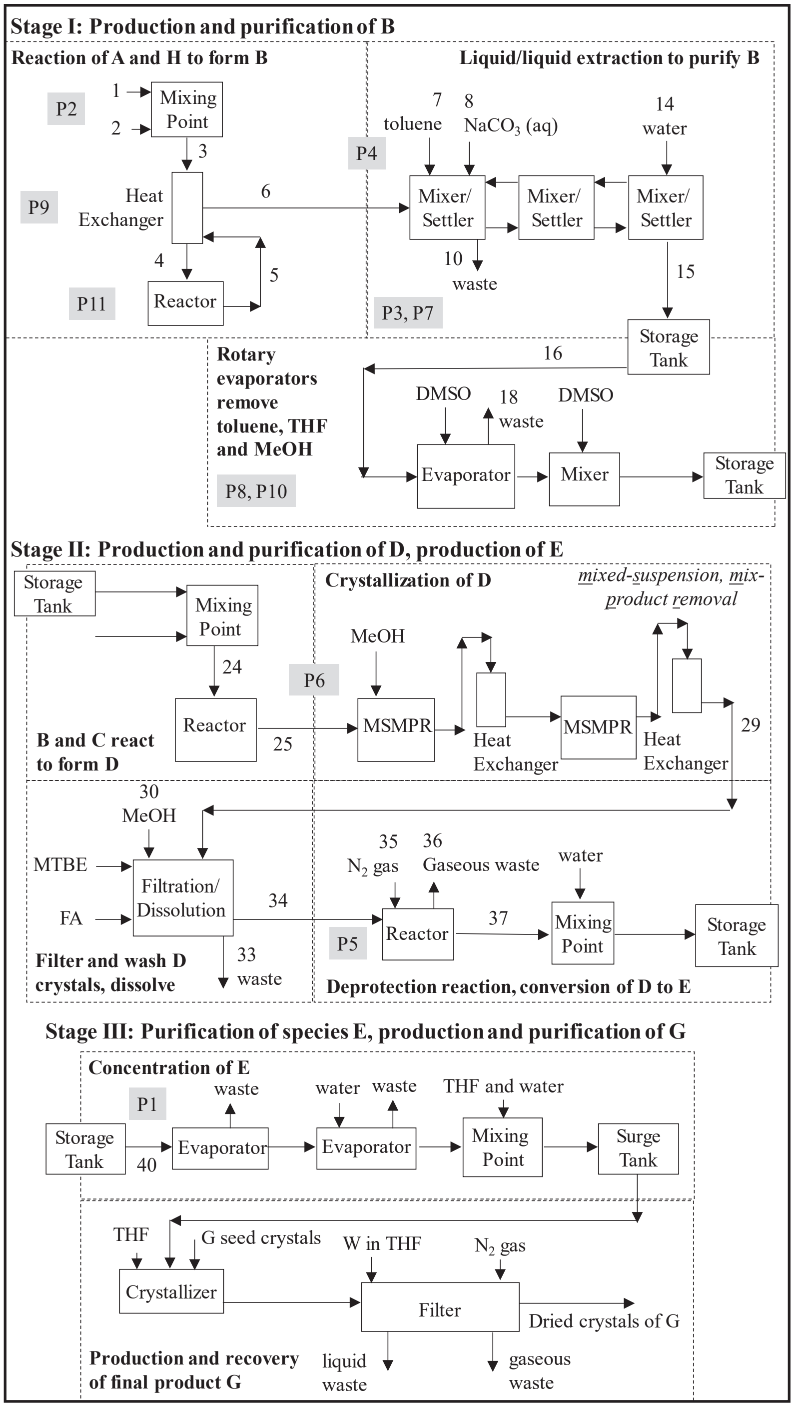

Figure 2. *Process flow diagram provided to students. Not all stream numbers are shown; associated problems are indicated. Gray boxes indicate homework problems.*

and 12.9 mol/h of W.

- *A liquid-liquid extraction unit with feed streams 6, 7 (5.83 mol/h TOL), and 14 (33.3 mol/h W). Two streams leave the simplified liquid-liquid extraction unit: stream 15, which moves on to the next part of the process, and stream 10, a waste stream. As in problem 3:*
  - *Stream 15 contains only species B, TOL, THF and MeOH*
  - *Stream 10 contains species A, B, H, MeOH, THF, and W*
  - *99% of the species B that enters the extraction unit is recovered in the organic stream.*

Note that we are currently ignoring the presence of AA and $NaCO_3$ in this system.

a. *Which reactant is fed in excess, and at what percent?*

b. *Write the extent of reaction equations for species A, H, B, and W.*

c. *Draw and completely label a flowchart of this process.*

d. *Perform a degrees of freedom analysis on the reactor, on the extraction unit, and on the overall system. Use the extent of reaction method.*

e. *Write out the equations that you intend to use to solve for all unknowns. Where possible, solve for the unknowns.*

f. *You have been told to expect 95% conversion of species A in the reactor. Update your degrees of freedom analysis on the reactor, extraction unit and overall process and then solve for all possible unknowns. Hint: you should still have some unknowns even after incorporating this information.*

TABLE 1
Chemical species used in the case study

Case Study Name	Chemical Name	Formula	Name in Cole et al[2]
A	tert-butyl (3-(2-(2-cyanoacetyl)-3-methoxyphenoxy)propyl)carbamate	$C_{18}H_{25}N_2O_5$	7
B	tert-butyl (3-(2-(3-amino-1H-pyrazol-5-yl)-3-methoxyphenoxy)propyl)carbamate	$C_{18}H_{27}N_4O_4$	8
C	5-chloropyrazine-2-carbonitrile	$C_5H_2N_3Cl$	9
D	tert-butyl (3-(2-(3-((5-cyanopyrazin-2-yl)amino)-1H-pyrazol-5-yl)-3-methoxyphenoxy)propyl)carbamate	$C_{23}H_{28}N_7O_4$	10
E	--	$C_{17}H_{18}N_7O_3$	1
F	prexasertib monomesylate monohydrate	--	11
G	prexasertib monolactate monohydrate = (2S)-2-hydroxypropionic acid-5-({3-[2-(3-aminopropoxy)-6-methoxyphenyl]-1H-pyrazol-5-yl}hamino)pyrazine-2-carbonitrile monohydrate	$C_{18}H_{20}N_7O_2$	12
H	hydrazine	N_2H_4	--
AA	acetic acid	$C_2H_4O_2$	--
CO_2	carbon dioxide	CO_2	--
DMSO	dimethyl sulfoxide	$(CH_3)_2SO$	--
FA	formic acid	CH_2O_2	--
HCl	hydrochloric acid	HCl	--
iB	isobutylene	C_4H_8	--
LA	lactic acid	$C_3H_6O_3$	--
MeOH	methanol	CH_3OH	--
MTBE	methyl tert-butyl ether	$C_5H_{12}O$	--
$NaCO_3$	sodium carbonate	Na_2CO_3	--
NEM	N-ethylmorpholine	$C_5H_{11}NO$	--
N_2	nitrogen gas	N_2	--
TOL	toluene	C_7H_8	--
THF	tetrahydrofuran (oxolane)	C_4H_8O	--
W	water	H_2O	--

Problem 5: A reactor is used for the conversion of species D to species E. CO_2 and iB are formed as co-products (D ➔ E + CO_2 + iB). N_2 gas (stream 35) is bubbled through the reactor to remove some of the CO_2 and iB from the liquid phase. For each of the scenarios described below, draw and completely label a flowchart, perform a degrees of freedom analysis and define a strategy for solving for all unknowns. You can assume ideal gas behavior, but think about how your solution strategy would change if you did not assume ideal gas behavior. Assume that the Antoine Equation coefficients for FA are valid at 25°C and ignore the presence of any dissolved N_2 gas in the liquid phase. 1.5 L of pure liquid FA is placed in a rigid container with a volume of 6.0 L.

a. *4.0 L of N_2 gas at 25°C, 45 psia is added to the container. The container is sealed and allowed to reach equilibrium at 25°C.*

b. *4.0 L of N_2 gas containing 1.0 mol% CO_2 at 25°C, 45 psia is added to the container. The container is sealed and allowed to reach equilibrium at 25°C. Ignoring the evaporation of the FA, find the mole fraction of CO_2 in both the liquid phase and the gas phase at equilibrium. Ignore the contribution of the CO_2 to the density of the liquid phase. The Henry's Law constant for CO_2 at 25°C is 0.163×10^4 atm/mole fraction.*

c. *4.0 L of N_2 gas containing 1.0 mol% iB at 25°C, 45 psia is added to the container. The container is sealed and allowed to reach equilibrium at 25°C. Ignoring the evaporation of the formic acid, find the mole fraction of isobutylene in both the liquid phase and the gas phase at equilibrium. Ignore the contribution of the isobutylene to the density of the liquid phase. The Henry's Law constant for isobutylene at 25°C is 1.19×10^4 atm/mole fraction.*

Problem 6: Species D is produced from species B and C in a reactor and then purified by crystallization and filtration. Model this as a three unit process.

- *Reactor: 25.9 kg of species B, 85.5 kg of DMSO, 10.1 kg of NEM, 12.3 kg of species C, and 60.9 kg of DMSO are fed to the reactor (stream 24). The balanced reaction is B + C ➔ D + HCl. Assume that the reactor is operated so that there is 99% conversion of the limiting reactant.*
- *Crystallizer: The reaction product (stream 25) is fed to a crystallizer. 3.0 L of liquid methanol is also added to the crystallizer. The slurry leaving the crystallizer (stream 29) is saturated with crystals of species D. None of the other species crystallize. Assume that the solubility of species D in this system is known.*

- *Filter: The slurry is fed to a filtration unit. The liquid component of the slurry leaves the filtration unit as waste (stream 33). The solid component of the slurry leaves as pure crystals of species D (stream 34).*

Not modeled: The crystals are washed with FA and MTBE and dissolved into fresh FA in preparation for the deprotection reaction.

a. Draw and completely label a flowchart of this process.

b. Break the process down into subsystems, perform a degrees of freedom analysis and identify the order in which you would solve the subsystems.

c. Write the equations that you would use to solve for all unknowns, and indicate the order in which you would solve for the unknowns.

d. If the solubility of species D in the crystallizer is 1 g/L, find the mass of crystals recovered and the percent of the incoming mass of species D that is recovered in crystalline form.

e. If the solubility of species D in the crystallizer is 10 g/L, find the mass of crystals recovered and the percent of the incoming mass of species D that is recovered in crystalline form.

f. Propose at least two changes in the way that the reactor, crystallizer and/or filtration unit are operated in order to increase the mass of crystals recovered.

Problem 7: In problem #3, we modeled the first reactor in the case study and the associated liquid-liquid extraction unit. However, the calculations for the liquid-liquid extraction unit were incomplete. As a reminder, we had two streams leaving the extraction unit. The aqueous waste stream (10) contained 0.0255 mol A/h, 0.005 mol B/h, 46.68 mol W/h, and 1.1555 mol H/hr. The organic stream (15) contained 0.480 mol B/h and 5.83 mol TOL/h. We also know that 6.65 mol MeOH/h and 8.91 mol THF/h leave the extractor, but the distribution of these two species between the aqueous stream and the organic stream is unknown.

a. Assume that the partition coefficient of methanol is 0.05 mole fraction in toluene/mole fraction in water.[4] Ignoring species A, B, H and THF, solve for the amount of MeOH in both streams leaving the liquid-liquid extraction unit.

b. Ignoring species A, B, H and MeOH, solve for the amount of THF in both streams leaving the liquid-liquid extraction unit. Use the graph provided in Figure 3, where the black squares indicate a mixture of THF, W and TOL.[5] This will require an iterative solution approach.

Problem 8: A rotary evaporator is used at the end of stage I to remove TOL, THF and MeOH from the organic extract from the first reaction (stream 16). Species D does not evaporate, it is dissolved in DMSO and sent to reactor #2. The gaseous waste stream (18) containing TOL, THF and MeOH cannot simply be vented to the atmosphere. One way of removing these compounds from the gas phase is adsorption onto a solid, which can then be disposed of properly.

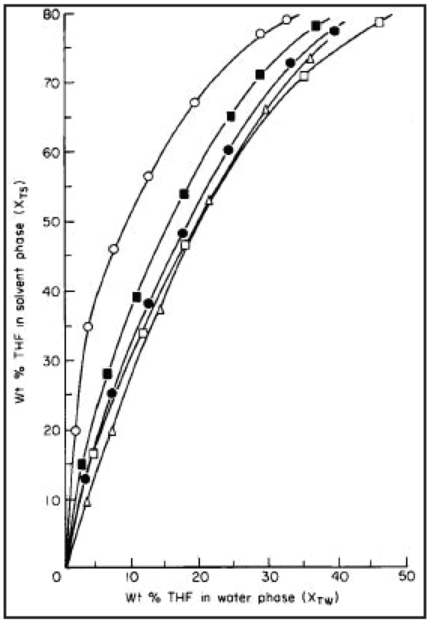

Figure 3. *Room temperature equilibrium data for THF-water-hydrocarbon systems for use in problem #7, with toluene indicated in black squares. Other hydrocarbons include: benzene (white circles), chlorobenzene (black circles), nitrobenzene (white triangles), and cyclohexane (white squares). Reproduced with permission from Patel.[5]*

A sealed vessel is loaded with 10 L of N_2 gas containing 10 mol% MeOH at 25°C and 2.0 atm. The vessel has a volume of 25 L and is maintained at 25°C. According to the data reported by Innes and Rowley[6] (Figure 4), what mass of activated charcoal is needed to adsorb 99% of the MeOH? Use the top line ($n^s_a = 0$).

Problem 9: To recover some of the energy from the liquid product stream leaving the first reactor, this stream and the liquid stream entering the reactor pass through the same heat exchanger. The liquid stream fed to reactor (stream 4) contains 0.51 mol/h of species A, 1.64 mol/h of species H, 6.65 mol/h of MeOH, 8.91 mol/h of THF, and 12.9 mol/h of W. The liquid stream leaving the reactor (stream 5) contains 0.026 mol/h of species A, 0.48 mol/h of species B, 1.64 mol/h of species H, 6.65 mol/h of MeOH, 8.91 mol/h of THF, and 13.4 mol/h of W.

a. Express the heat capacity of the feed stream as an equation, $C_p(T)$. The only non-numerical value in your equation should be T. Use Kopp's Rule when necessary to estimate heat capacity values.

b. Repeat (a) for the product stream.

c. Assume that the reactor feed stream has a temperature of 22°C when it enters the heat exchanger. Assume that the reactor product stream has a temperature of 130°C when it enters the heat exchanger. The temperatures of both streams are unknown when they leave the heat exchanger. Draw and completely label a flowchart for the heat exchanger and simplify the corresponding energy balance.

d. The heat exchanger is well-insulated and of sufficient surface area that the two streams leaving the heat exchanger are assumed to have the same temperature. Find this temperature.

Problem 10: In Stage I of the case study, an evaporator is used to remove the TOL and THF from the organic extract of the first reaction (stream 16). We will model this process as a continuous, steady-state evaporator that operates at 60°C and 80 torr. Assume that the stream entering the evaporator is at 25°C and contains 0.48 mol B/h, 5.83 mol TOL/h and 9.0 mol THF/h. We are ignoring the small amount of MeOH. Assume that species B does not evaporate.

a. *Complete the material balance for this process.*
b. *Simplify the energy balance for this process.*
c. *Set up an enthalpy table for this process.*
d. *Find the energy demand for this operation.*

Problem 11: We previously modeled operation of the reactor in Stage I of the case study with 95% conversion of species A. The reactor has a liquid feed stream (3) containing: 0.51 mol/h A, 1.64 mol/h H, 6.65 mol/h MeOH, 8.91 mol/h THF, and 12.9 mol/h W. The liquid stream leaving this reactor (5) contains: 0.0255 mol/h A, 1.1555 mol/h H, 0.4845 mol/h B, 6.65 mol/h MeOH, 8.91 mol/h THF, and 13.38 mol/h W. We previously estimated that the temperature of stream 4 is 75.8°C. This reactor is maintained at 130°C.

a. *Find the standard heat of reaction for this reaction (A + H ➔ B + W). Estimated values for the standard heat of formation for species A in the dissolved state (aq) are 19.45 kJ/mol and for species B in the dissolved state (aq) are 55.14 kJ/mol. These values were estimated using the Domalski-Hearing method, which is not covered in this course. You may need to use an outside source for some of the enthalpy of formation values. Cite your sources.*
b. *Set up an enthalpy table for this process.*
c. *Solve for the energy demand of this process, using the heat of reaction method.*
d. *Solve for the energy demand of this process, using the heat of formation method.*

STUDENT FEEDBACK

At the beginning of the semester, students expressed enthusiasm for the case study, though with some trepidation regarding the complexity of the process. Some students also commented on their familiarity with some process steps due to previous chemistry lab experiments. Approximately 75% of the students who completed the course provided a non-anonymous summary of how the case study impacted their learning of course concepts. Among these students, 39% provided only positive feedback, 39% provided mixed feedback and 22% provided only negative feedback. Positive feedback commented on the benefit of a real-life example and the "big picture" coverage of course material. Many students also commented on the sense of satisfaction in seeing how much of the process they understood relative to their confusion at the beginning of the semester. Negative feedback addressed lingering confusion about the process and a lack of connection of the homework problems to the actual process. This negative feedback could possibly be addressed by spending more time discussing the case study in class.

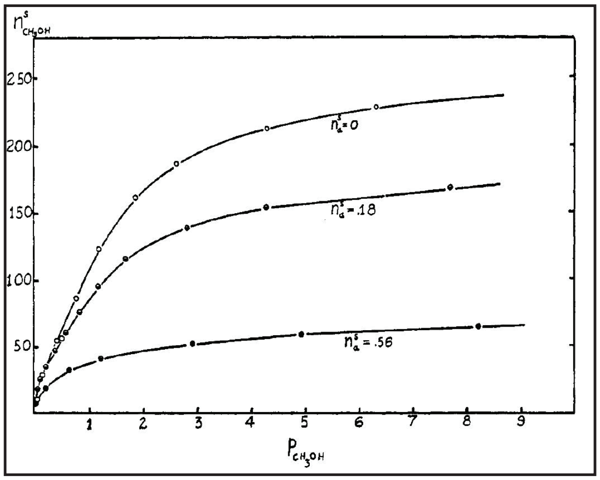

Figure 4. *Equilibrium data for adsorption of methanol by activated carbon at 25°C. Reprinted with permission from Innes and Rowley.*[6] *Partial pressure of methanol (x-axis) is given in cm of Hg, moles of adsorbed methanol (y-axis) is given in cm^3 at normal temperature and pressure (101.3 kPa and 20°C) per gram of charcoal. The n^s_a metric indicates the presence of carbon tetrachloride on the adsorbent (moles adsorbed per g of adsorbent). Copyright 1947 American Chemical Society.*

ACKNOWLEDGMENTS

Liyang Shen (ISU) estimated the enthalpy of formation values given in problem 11 and provided helpful feedback on the problems.

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