

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 1: INTERPRETIVE TOOLS

1-1 $k = 22.4$ liter atm, 2.27×10^{10} ergs, 2.27×10^3 joules, 5.43×10^2 cal.

1-2 $g = 32$ ft/sec; $t = 5.3$ sec.

1-3 $k = 2.65$; $n = 0.42$.

1-4 $E_a = 20,152$ cal mole⁻¹; $A = 1.13 \times 10^{13}$ sec⁻¹.

1-5 Average weight = 2.97 grains; average deviation = 0.103 grain; standard deviation = 0.13 grain.

1-6 *Partial Answers, calculated using a Casio hand calculator:*

(a) $r^2 = 0.9843$; slope = 29.46; intercept = -2272

(b) $r^2 = 0.9599$; slope = 26.14; intercept = -1255

(c) $r^2 = 0.9914$; slope = 24.65; intercept = -921.5

$r^2 = 0.9810$; slope = 24.57; intercept = -839

$r^2 = 0.9639$; slope = 27.0; intercept = -1517

1-7 $r = 0.9089$; $r^2 = 0.8262$; $RA = 2.472 + 0.5268 \log K$. For the (ethyl, ethyl) derivative, the calculated activity using the least-squares equation is 2.81, which is -0.7% different from the experimental value. Incidentally, the linear relationship found between activity and $\log K$ signifies that the more nonpolar the barbiturate derivative (as measured by the partition coefficient), the more active it is as a hypnotic agent in rats. The term r^2 has more significance than the correlation coefficient, r ; and r^2 of 0.8262 means that 82.62% of the barbiturate data are explained by the linear equation obtained in this problem. (This problem came from C. Hansch, *Biological Correlations—The Hansch Approach*, American Chemical Society, Washington, D.C., 1972, pp. 30, 33. The data are from H. A. Shonle, A. K. Keltch, and E. E. Swanson, *J. Am. Chem. Soc.* **52**, 2440, 1930. Calculated values are given by C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.* **11**, 1, 1968. The regression equation calculated here is slightly different from the result found in *Biological Correlations* because we have used only 10 of the 16 data points.)

1-8 *Partial Answer:*

(a) With use of a personal computer or a hand calculator capable of multiple linear-regression analysis,

the square of the correlation coefficient is found to be $r^2 = 0.9811$, and the equation is

$$\log S = 1.3793 - 2.5201(V/100) - 0.1216\pi + 1.8148\beta \quad (1)$$

1-9 *Partial Answer:*

The cubic equation gives the density at 25°C as 0.9970524 g/cm³; the *CRC Handbook of Chemistry and Physics*, p. F5, gives the density at 25°C as 0.9970479 g/cm³.

1-10 $r = 0.9995$; $b = 0.432$. The use of a programmed hand calculator or a personal computer will provide these results. The problem may also be done by hand, following the instructions on pages 7–16.

1-11 $1 \mu\text{g} = 1.6$ units.

so,

$$250 \text{ mg} \times 10^3 \mu\text{g}/\text{mg} \times 1.6 \text{ units}/\mu\text{g} = 400 \times 10^3 \text{ units} = 400,000 \text{ units.}$$

1-12 $20 \text{ IU}/\text{capsule} \times 2 \times 10^5 \text{ capsules} = 40 \times 10^5 \text{ IU}$ total is needed.

$$40 \times 10^5 \text{ IU} \times 1 \text{ mg}/1.49 \text{ IU} \times 1 \text{ kg}/10^6 \text{ mg} = 2.68 \text{ kg.} \quad (2)$$

1-13 $2.25 \text{ liters} \times 1000 \text{ mL}/1 \text{ liter} \times 1 \text{ fluid ounce}/29.6 \text{ mL} = 76.0 \text{ fluid ounces.}$

1-14

$$\frac{18 \text{ g}}{9 \text{ mL}} = \frac{125 \text{ g}}{X}$$

$$X = \frac{125 \text{ g} \times 9 \text{ mL}}{18 \text{ g}} = 62.5 \text{ mL} \quad (3)$$

1-15 This data set has an even number of data points, so to find the median:

Arrange the data into an array of ascending values (245, 247, 248, 250, 250, 251, 257, 259, 260, 262). Find the middle two values (250 and 251) and average them $(250 + 251)/2 = 250.5$. This is the median.

The mean is calculated using equation (1–6). The sum of the values is 2529. There are 10 capsules in this set. So, $2529/10 = 252.9$. The weights of the individual tablets are reported using 3 significant figures. Even though the calculated mean (252.9) has 4 significant figures, it is common practice to report the

answer with the number of significant figures (3) plus the first uncertain digit (the “9” in this case).

You can calculate the standard deviation using the formulas provided in the book (equations 1–8 or 1–9 as appropriate). However, it is much more common to use a calculator or spreadsheet to calculate the standard deviation. So, if you are using Microsoft Excel you would go about it in this way:

Insert the 10 capsule values in column “A” rows 1 to 10. Insert the formula for standard deviation in cell A11 as “=stdev(A1:A10)” (note—do not include the quotation marks). The spreadsheet reports back the answer as “6.045200116,” so the standard deviation is 6.04. Trailing zeros are not considered significant figures, so the first uncertain digit is the “4.”

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CHAPTER 2: STATES OF MATTER

2-1 219 liters.

2-2 The volume of the bubble at the bottom of the tank is $4.19 \times 10^{-3} \text{ cm}^3$. The radius of the bubble increases from 0.1 cm to 0.11 cm as the bubble rises to the surface.

2-3 161 g/mole.

2-4 (a) 64.1 g/mole; (b) the molecular weight should provide a strong clue.

2-5 (a) 47.23 psi; gauge pressure = 32.5 psig; (b) $14.69594 \text{ lb (avoirdupois)}/\text{in.}^2 = 101,325 \text{ kg m}^{-1} \text{ s}^{-2} = 101,325 \text{ N m}^{-2} = 101,325 \text{ Pa}$; (c) check with your local service station attendant.

2-6 (a) 0.256 atm or 194.3 torr; (b) 0.254 atm or 193.3 torr.

2-7 (a) 0.0177 kg; (b) 9.84 liter; (c) 9.64 liter.

2-8 55.2 mm Hg.

2-9 From the graph, the vapor pressure, P , is 43.7 torr; $\Delta H_V = 10,282 \text{ cal/mole}$. Using linear regression, we find $\Delta H_V = 10,267 \text{ cal/mole}$ and $P = 43.9 \text{ mm}$. The heat of vaporization, ΔH_V , of ethyl alcohol given in the *CRC Handbook of Chemistry and Physics*, 67th Ed., is 9673.9 cal/mole.

2-10 *Partial Answer:* (a) Butane, -11.30°C ; propane, -50.73°C ; (c) Water boiling point is about 89°C at the mountain top.

2-11 (a) $p' = 329.3 \text{ torr}$; (b) $\Delta H_V' = 7112 \text{ cal/mole}$.

2-12 (a) $\Delta T = -0.470 \text{ K}$; (b) $\Delta T = -0.468 \text{ K}$.

2-13 (a) Using equation (2-17), we obtain $\Delta T/\Delta P = -0.041 \text{ K/atm}$; (b) 49.4°C . If the temperature during processing were greater than 50°C , form I might change to form II.

2-14 (a) 30 g; 105 g; (b) 9.00 g; 97.65 g.

2-15 (a) There is a single liquid phase up to 31% w/w of A present, at which point two liquids are formed (compositions are 31% w/w A and 78% w/w A). As more A is added, the amount of the second phase, B , decreases while that of the first phase A increases. When the system exceeds 78% w/w A at 25°C the two phases disappear and the system again becomes one phase. (b) At 45°C , we are above the region of immiscibility, and hence a single phase exists for all combinations of A and B .

2-16 (a) 30% w/w A and 70% w/w B ; 80% w/w A and 20% w/w B . These are conjugate phases; (b) 40 g of A and 10 of B g.

2-17 (a) 39°C ; (b) 15 g of B (to produce a system containing 20% w/w A and 80% w/w B); (c) 40 g of A (to produce a system containing 90% w/w A and 10% B).

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 2: STATES OF MATTER

- 2-1** A weather balloon rises 2 miles into the upper atmosphere. Its volume at ground level is 2.50 liters at 1 atm pressure and 24°C. What is its final volume if the atmospheric pressure is 8.77×10^{-3} atm and the temperature is -44.7°C at the 2-mile position?
- 2-2** An air bubble is blown by a fish at the bottom of an aquarium tank and it rises to the surface. As in the case of the weather balloon in *Problem 2-1*, its volume increases as the pressure on the bubble decreases. The bubble has a radius of 0.1 cm at the bottom of the tank, where the pressure is 1.3 atm and the temperature is 14°C. At the surface of the tank the pressure is 750 torr and the temperature is 27°C. What is the radius of the bubble when it comes to the surface of the tank? For the equation for the volume of a sphere, see the inside front cover of the book.
- 2-3** If 0.50 g of a drug in the vapor state occupies 100 mL at 120°C and 1 atm pressure, what is its approximate molecular weight?
- 2-4** The Air Protection Laboratory in a large city isolated a new gaseous pollutant that was found to exert a pressure of 1.17 atm when 6.07 g of the substance was confined in a 2.0-liter vessel at 28°C. (a) What is the molecular weight of the pollutant? (b) If the pollutant is known by chemical test to be a sulfur compound, what do you suppose the compound might be?
- 2-5** An auto tire is inflated to 30 psi gauge pressure (1 atm = 14.7 pounds per square inch, and the total air pressure is the tire gauge pressure plus 14.7 psi) on a day when the outside temperature is 10°C. After the car has been running on the highway for several hours, the temperature of the air in the tire has risen to 26°C. (a) What is the pressure in the tire at this time, assuming that the volume of the tire does not change appreciably with temperature? (b) Refer to a table of conversion factors in a handbook of chemistry to assure yourself that 1 atm = 14.7 lb/in.² (actually, 14.6959 lb/in.²). Express the value 14.7 lb/in.² in the SI units of Pascals. (c) Would it be wise to release some air from the car tires after traveling for hours during August in the Southwest? How high can the pressure in a tire become before it is in danger of blowing out?
- 2-6** An experimenter wishes to determine the partial pressure of chloroform required to anesthetize a 28.0-g mouse in a 2.37-liter container at 20°C. If 2.00 cm³ of CHCl₃ is introduced into the closed vessel through a valve, what is the partial pressure of the CHCl₃ in the container? Assume complete evaporation of the chloroform. Calculate the partial pressure using both (a) the ideal gas equation and (b) the van der Waals equation. Assuming the density of the mouse to be about 1 g/cm³, calculate its volume in liters and subtract this from the volume of the vessel to obtain the volume available to the chloroform vapor. The density of liquid chloroform at 20°C is 1.484 g/cm³, so $2.00 \text{ cm}^3 \times 1.484 \text{ g/cm}^3 = 2.968 \text{ g}$ and because the molecular weight of chloroform is 119.4 g/mole, $2.968 \text{ g} \div 119.4 \text{ g/mole} = 0.0249$ mole of chloroform in the vessel. The van der Waals *a* and *b* values for CHCl₃ are given in Table 2-3.
- 2-7** A small household fire extinguisher of 0.80-liter capacity contains CO₂ at a pressure of 12.3 atm and 25°C. (a) What is the weight of the CO₂ in kg in the extinguisher? (b) What is the volume of this mass of CO₂ at 25°C when the pressure is reduced to 1 atm? (c) Compare your result with that obtained from the density of gaseous CO₂ at 25°C (density = 0.001836 g/cm³). CO₂ is a gas, not a liquid, at atmospheric pressure. The molecular weight of CO₂ is 44.01 g/mole.
- 2-8** The vapor pressure of water at 25°C is 23.8 mm Hg. The average heat of vaporization between 25°C and 40°C is about 10,400 cal/mole. Using the Clausius–Clapeyron equation, calculate the vapor pressure at 40°C. The experimentally determined value is 55.3 mm Hg.
- 2-9** The vapor pressure of ethyl alcohol is 23.6 torr at 10°C, 78.8 torr (mm Hg) at 30°C, and 135 torr at 40°C. Using equation (2-16), plot log *P* versus 1/*T* [ln *P* of equation (2-17) may be used instead of log *P* and the factor 2.303 will then not be needed] and obtain the vapor pressure of ethyl alcohol at 20°C. What is the heat of vaporization, ΔH_V , at this temperature?

2-10 A group of hikers decides to climb a mountain and heat cans of beans and some sausages when they reach the summit, using backpacker stoves. The mountain is 3500 meters high (11,500 ft), at which height the atmospheric pressure is 506 mm Hg. The temperature at this time of year is -15°C (5°F) at the mountain top.

The heat of vaporization of butane and propane, two volatile compounds used as fuel for backpacker stoves, are 5318 and 4812 cal/mol, respectively; and their normal boiling points (at sea level) are -0.50°C and -42.1°C , respectively.

It may be noted that flammable liquids such as butane and propane will not vaporize and ignite at temperatures below their boiling points and cannot serve in cooking stoves at lower temperatures.

- Compute the boiling point of butane and propane at the top of the mountain. Changes in temperature with vapor pressure are dealt with using the Clausius–Clapeyron equation.
- Could either the butane or the propane stove be used at the top of this mountain?
- Can water be “boiled” on the mountain top to prepare coffee for the hikers? The heat of vaporization of water is 9717 cal/mole and its boiling temperature is 100°C at 1 atm.

2-11 Isoflurane and halothane are nonflammable volatile liquids used for general anesthesia.

- What is the vapor pressure, p' , of isoflurane at room temperature, 25°C ? The heat of vaporization, $\Delta H_V'$, of isoflurane is 6782 cal/mole at its boiling point. The vapor pressure, p' , for isoflurane at its normal boiling point, 48.5°C , is 1 atm according to the definition of the normal boiling point.
- What is the heat of vaporization, $\Delta H_V'$, of halothane within the temperature range 20°C to its boiling point, 50.2°C ? The vapor pressure, p' , of halothane at 20°C is 243 mm Hg. These two general anesthetics are slightly greater in vapor pressure than ether (ether, $p = 217$ torr at 20°C). Of much greater importance, they are nonflammable, whereas ether is highly flammable.
- What other advantages does halothane have over ether as a general anesthetic? Consult a book on pharmacology.

2-12 If the skate blade of a 175-lb man on ice is 12 in. long and $1/64$ in. thick and the heat of fusion of water (ice) is 6025 J/mole, what is the melting point change that produces liquid water under the skate allowing the liquid to lubricate the skate? The molar volume of liquid water (its molecular weight divided by its density) is 0.018 liter and the molar volume of ice is 0.01963 liter.

- Carry out the calculations using SI units and the integrated form of the Clausius–Clapeyron equation,

$$\int_{273.15^{\circ}\text{K}}^T \frac{1}{T} dT = \frac{\Delta V}{\Delta H_f} \int_{P_1}^{P_2} dP \quad (1)$$

- Repeat, using the approximation

$$\frac{\Delta T}{\Delta P} = T \frac{\Delta V}{\Delta H_f} \quad (2)$$

2-13 When a solid that exists in more than one crystalline form is subjected to the relatively high pressure of a tablet machine it might favor transformation to a denser polymorphic form.

Sulfathiazole can be obtained in at least two polymorphic forms, I and II, with I being the lower-energy state at room temperature. The densities are 1.50 g/cm^3 for form I and 1.55 g/cm^3 for form II. The transition temperature I \rightarrow II is 161°C and the heat of transition, ΔH_t , is 1420 cal/mole.³

- What is the effect of a normal pressure of 1 atm on the transition temperature of sulfathiazole from form I to form II? The molecular weight is 255.32 g/mole. Use equation (2-17), substituting ΔH_f , V_t , and V_s with ΔH_t and the molar volumes of the two polymorphs.
- What is the transition temperature when form I is compressed in the tablet machine at 2812 kg/cm^2 (2757.6 bar)? Would form I be stable during the tableting process? ($1 \text{ bar} = 14.5038 \text{ pounds/in.}^2$ and $1 \text{ kg/cm}^2 = 14.223343 \text{ pounds/in.}^2$)

2-14 A mixture containing 21% by weight of phenol in water (see Figure 2-22) is prepared and allowed to come to equilibrium at 30°C . The two liquid phases that separate contain 7% and 70% of phenol, respectively. If the total weight of the original mixture was 135 g, calculate (a) the weight of each phase at equilibrium and (b) the actual weight of water, in grams, in each phase.

2-15 A and B are two partially miscible liquids. The following mixtures (percent by weight) all formed two liquid phases below, and one liquid phase at the temperature noted (in other words, these are temperatures at which two-phase systems became one-phase systems).

Plot these results on rectangular coordinate paper and describe the phase changes observed as A is continually added to B at a temperature of (a) 25°C and (b) 45°C .

Data for Problems 2–15 and 2–17

A (%w/w)	B (%w/w)	Temperature (°C)
20	80	10
30	70	22
40	60	34
50	50	39
60	40	38
70	30	32
80	20	22
90	10	10

2–16 If a liquid mixture containing *A* (20 g) and *B* (30 g) is prepared and allowed to come to equilibrium at 22°C, (a) what are the compositions of the two phases present and (b) what is the weight of each phase? See *Problem 2–15*.

2–17 Using the table of data in *Problem 2–15*, plot % *A* on the horizontal axis versus temperature (°C). Ten grams of a mixture containing equal weights of *A* and *B* at 50°C is cooled to 10°C. (a) At what temperature will a phase change be observed; (b) at 10°C, how much *B* must be added to produce a single phase; (c) at 10°C, how much *A* must be added to produce a single-phase system? See *Problem 2–15*.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 3: THERMODYNAMICS

3-1 Why is alcohol used in thermometers for measuring very low temperatures, whereas mercury is used for high temperatures? *Hint:* Look up in a handbook of chemistry and physics the melting points of alcohol and mercury.

3-2 Calculate the work required to vaporize 1.73 moles of water at 0.68 atm pressure and a temperature of 373 K. Assume that the vapor behaves as an ideal gas. *Hint:* The volume can be calculated by using the ideal gas equation, and the work can be calculated using $W = P\Delta V$, where ΔV is the difference in volume between liquid water at 373 K, that is, $18.795 \text{ cm}^3/\text{mole} \times 1.73 \text{ mole}$, and its vapor at 373 K.

3-3 By the use of thermodynamic calculations, we can relate work done and heat produced in various processes regardless of how seemingly unrelated the processes might be. Consider the following: A 30-year-old man weighing 70 kg (154 lb) produces 3600 kcal of heat per 24 hr by working 8 hr as a brick layer and bowling in the evenings. If this heat were used to raise the temperature of 200 kg of water (specific heat of water = $1 \text{ cal g}^{-1} \text{ deg}^{-1}$) that was originally at 25°C , how hot would the water become?

3-4 An athlete resting on his back on the floor lifts an 80-lb dumbbell 2 ft above his head. From physics we know that force = mass \times acceleration of gravity, and the force multiplied by the distance the mass is lifted yields the work done or energy used.

- How much work is done when the dumbbell is lifted 500 times?
- If we assume that the energy expended is obtained totally from burning body fat, how many pounds will the athlete lose in this exercise? Approximately 9.0 kcal of metabolic energy is obtained per gram of fat burned.
- How many lifts of the 80-lb weight would be required for the person to lose 1 lb of fat?
- It is agreed that exercise such as weight lifting is excellent for toning the muscles of the body. From your calculations, do you find that it also contributes significantly to weight reduction as part of a diet regimen?

3-5 At the beginning of the 19th century, Dulong and Petit determined the heat capacity, C_V , of solid elements to be approximately $6 \text{ cal mole}^{-1} \text{ K}^{-1}$.

A bar of iron, atomic weight = 55.847 g, falls accidentally from the top of a building 93-m high. Taking the molar heat capacity, C_V , of iron as approximately $6 \text{ cal mole}^{-1} \text{ K}^{-1}$, compute the increase in the temperature of the bar as it falls from the top of the building to the street. Use SI units in your calculations.

We actually desire the heat capacity per gram (i.e., the specific heat), or, because we are using SI units, we want the heat capacity per kilogram. To convert from calories/mole to calories/gram, we divide the molar heat capacity of iron by its “molecular” or atomic weight, 55.847 g. Thus,

Hint: Express C_V in J/(kg K).

3-6 The molar heat capacity at constant pressure, C_p , varies with temperature. The changes in the heat capacity, ΔC_p , for a reaction at a fixed temperature is given by the expression

$$\Delta C_p = \sum (nC_p)_{\text{products}} - \sum (nC_p)_{\text{reactants}} \quad (1)$$

where Σ stands for “the sum of” and n is the number of moles of the compound.

C_p can be calculated at different temperatures using the empirical equation

$$C_p = \alpha + \beta T + \gamma T^2 + \dots \quad (2)$$

where α , β , and γ are constant coefficients. C_p and ΔC_p are given here in $\text{cal K}^{-1} \text{ mole}^{-1}$.

Calculate C_p for $\text{CO}_{(\text{g})}$, $\text{H}_{2(\text{g})}$, and $\text{CH}_3\text{OH}_{(\text{g})}$ at 25°C and compute the change in heat capacity, ΔC_p , for the reaction:

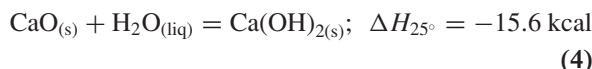


Data for Problem 3-6*

	$\text{CO}_{(\text{g})}$	$\text{H}_{2(\text{g})}$	$\text{CH}_3\text{OH}_{(\text{g})}$
α	6.342	6.947	4.398
$\beta \times 10^3$	1.836	-0.20	24.274
$\gamma \times 10^6$	-0.2801	0.4808	-6.855

*Data in this chart is from S. Glasstone, *Thermodynamics for Chemists*, Van Nostrand, New York, 1947, pp. 53, 503.

3-7 The heat of reaction associated with the preparation of calcium hydroxide is represented as



What is the standard heat of formation, ΔH° , of $\text{Ca}(\text{OH})_2$ at 25°C ? The standard heat of formation of water is $\Delta H^\circ(\text{H}_2\text{O}_{(\text{liq})}) = -68.3$ kcal/mole and the standard heat of formation of calcium oxide is $\Delta H^\circ(\text{CaO}_{(\text{s})}) = -151.9$ kcal/mole.

- 3-8** The synthesis of methanol involves the reaction of carbon monoxide and hydrogen gas. The reaction, together with values at 25°C for S^0 cal deg $^{-1}$ mole $^{-1}$, ΔH_f° in kcal mole $^{-1}$, and ΔG_f° in kcal mole $^{-1}$, is given as follows¹:



Data for Problem 3-8

	$\text{CO}_{(\text{g})}$	$\text{H}_{2(\text{g})}$	$\text{CH}_3\text{OH}_{(\text{g})}$
S^0	47.219	31.208	56.63
ΔH_f°	-26.416	0	-48.10
ΔG_f°	-32.78	0	-38.90

- (a) Calculate ΔH° for the synthesis of methanol under standard conditions.
 (b) Calculate ΔG° , using the foregoing data.
 (c) From ΔG° and ΔH° , compute ΔS° at 25°C . Compare this value with ΔS° obtained directly from S^0 in the foregoing table.

- 3-9** What is the theoretical efficiency of a steam engine operating between the boiler at 20 atm, where the boiling point of water T_{hot} is 209°C (482 K), and the low-temperature reservoir or sink, where the temperature T_{cold} is 30°C (303 K).²

- 3-10** What is the minimum work in joules that must be done by a refrigerator to freeze 1 avoirdupois pound (453.6 g) of water at 0°C with the surroundings at 23°C ? How much heat is discharged into the room at room temperature (23°C)? The heat of fusion of ice is 1438 cal/mole or 1438/18.016 g/mole = 79.8 cal/g (in the range of 0°C – 100°C). Thus, 79.8 cal/g \times 453.6 g of heat must be removed from the water to form ice [from 23°C (296 K, T_2) to 0°C (273 K, T_1)].

The principle of a refrigerator (or air conditioner) is the opposite to that of a heat engine.² The refrigerator fluid takes up heat at the low temperature of the refrigerator and discharges it at the higher temperature of the surroundings (see pages 62–63 for an explanation of a heat engine).

Because heat is discharged in a refrigerator (or air conditioner) rather than taken up, as in a heat engine, the work has the opposite sign to that given in equation (3–34):

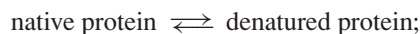
$$-\frac{W}{Q_1} = \frac{T_2 - T_1}{T_1}$$

$$-W = \left(\frac{T_2 - T_1}{T_1} \right) Q_1 \quad (6)$$

What is the efficiency, $(T_{\text{hot}} - T_{\text{cold}})/T_{\text{cold}}$, or, as it is called, the *coefficient of performance* of this refrigerator?

- 3-11** What is the entropy change involved in the fusion of 1 mole of ice at 0°C ? What is the entropy change in the surroundings? The heat of fusion of ice is 79.67 cal/g.

- 3-12** At 50°C , a certain protein denatures reversibly with a heat of reaction of 29,288 J mole $^{-1}$:

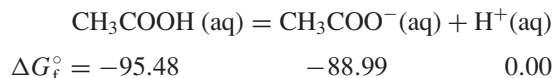


$$\Delta H_{50^\circ} = 29,288 \text{ J mole}^{-1}$$

The system is at equilibrium and $\Delta G = 0$. Compute the entropy change for the reaction.

- 3-13** According to Hill,³ the stomach excretes HCl in the concentration of 0.14 M from the blood, where the concentration is 5.0×10^{-8} M. Calculate the work done by the body in the transport (excretion) of 1 mole of HCl at a temperature of 37°C .

- 3-14** For the ionization of acetic acid in aqueous solution,



The *standard free energies of formation*, G_f° , at 25°C are given immediately under each species in kcal/mole. Calculate the standard free energy change, ΔG° , for this reaction; from the thermodynamic equation giving the equilibrium constant (ionization constant), $\Delta G^\circ = -RT \ln K$, calculate K for acetic acid.

- 3-15** Given the standard free energy of formation, ΔG° , and the standard enthalpy of formation, ΔH° , calculate the standard entropy change, ΔS° , and the equilibrium constant, K , for the reaction



The values for ΔG° and ΔH° are obtained from tables of standard thermochemical data (Wagman et al.⁴) for 1 mole at 1 atm pressure and 25°C , where (aq) refers to a hypothetical ideal aqueous solution. The values of ΔG° and ΔH° for $\text{H}^+(\text{aq})$ are taken as 0.00.

For the various species in solution, the values of ΔG° and ΔH° in kcal/mole are as follows:

	$\text{CO}_2(\text{g})$	$\text{H}_2\text{O}(\text{liq})$	$\text{HCO}_3^-(\text{aq})$	$\text{H}^+(\text{aq})$
ΔG° (kcal/mole)	-94.254	-56.687	-140.3	0.0
ΔH° (kcal/mole)	-94.051	-68.315	-164.8	0.0

- 3-16** For one of the steps in the citric acid (Krebs) cycle,⁵
- (a)
- | | | | | | | |
|-----------------------------|---|------------------|---|----------|---|-------------------------------|
| oxaloacetate ²⁻ | + | H ₂ O | → | pyruvate | + | HCO ₃ ⁻ |
| ΔG° (kcal/mol) | | -190.53 | | -56.69 | | -113.32 - 140.29 |

and for another step in this complex series of chemical reactions required for energy production in the body,

- (b)
- | | | | | |
|-----------------------------|---|---------|---|-----------------------|
| oxaloacetate ²⁻ | + | acetate | → | citrate ³⁻ |
| ΔG° (kcal/mol) | | -190.53 | | -88.99 - 273.90 |

Calculate ΔG° and K at 37°C for these two reactions.

- 3-17** Diluted hydriodic acid (HI) is a pharmaceutical product containing 10% of HI and about 0.8% of hypophosphorous acid (H₃PO₂) to prevent discoloration of the aqueous preparation in the presence of light and air.

Hydriodic acid is prepared on a large scale by several processes, principally by the interaction of I₂ and H₂S. Diluted hydriodic acid may be made into a syrup with dextrose and used for the therapeutic properties of the iodides and as a vehicle for expectorant drugs.

Taylor and Crist⁶ investigated the reaction of hydrogen and iodine to form hydrogen iodide at a temperature of 457.6°C (730.75 K),



They obtained the following results, where K is the equilibrium constant:

Data for Problem 3-17

$K = \frac{[\text{HI}]^2}{[\text{H}_2][\text{I}_2]}$		
H₂ mole/liter	I₂ mole/liter	HI mole/liter
3.841×10^{-3}	1.524×10^{-3}	1.687×10^{-2}
1.696×10^{-3}	1.696×10^{-3}	1.181×10^{-2}
5.617×10^{-3}	0.5936×10^{-3}	1.270×10^{-2}

- (a) Calculate the equilibrium constants for the three experiments shown and obtain the average of these K values at 730.75 K.
- (b) At 666.8 K the average equilibrium constant, K_{av} , for the reaction of I₂ and H₂ to form hydrogen iodide (hydriodic acid) is 60.80.⁷ Calculate the enthalpy change, ΔH° , for the reaction over the temperature range of 666.8 to 730.75 K.
- (c) Does the constant K increase or decrease as the temperature is elevated? What does this say about an increased or decreased production of hydrogen iodide from its elements as the temperature is elevated? Do these results suggest that the reaction would be exothermic or endothermic? What quantitative result do you have to answer this last question? How does the van't Hoff equation [equation (3-138)] help to answer this question?

- 3-18** Equation (3-135) allows you to calculate the free energy change at the three separate temperatures for the reaction of hydrogen and iodine to yield hydrogen iodide. Given the experimentally determined K values and corresponding absolute temperatures, calculate the standard free energy change at these three temperatures.

- 3-19** A student cannot find the heat of vaporization, the heat of sublimation, or the heat of fusion of water in her handbook of chemical properties, but she is able to find a table of vapor pressures (in mm Hg) for liquid water in equilibrium with its vapor at temperatures from -15°C to +20°C and for ice in equilibrium with its vapor from -50°C to 0°C.

For ice passing directly to water vapor (sublimation), and for the conversion of liquid water to vapor (vaporization), the following values are found as the table below:

Data for Problem 3-19:

Vapor Pressures for the Sublimation and Vaporization of Water

Ice → Vapor (Sublimation)		Liquid Water → Vapor (Vaporization)	
Vapor Pressure (mm Hg)	t (°C)	Vapor Pressure (mm Hg)	t (°C)
0.0296	-50	1.436	-15
0.0966	-40	1.691	-13
0.2859	-30	2.149	-10
0.476	-25	2.715	-7
0.776	-20	3.163	-5
1.241	-15	3.673	-3
1.950	-10	4.579	0
3.013	-5	6.593	5
4.579	0	9.209	10
—	—	12.788	15
—	—	17.535	20

- (a) Plot the sublimation and vaporization curves in the form of $\ln(\text{vapor pressure})$ versus $1/T$ (K⁻¹).
- (b) Using the indefinite integrated form of the Clausius–Clapeyron equation,

$$\ln P = -\frac{\Delta H}{R} \frac{1}{T} + \text{constant} \quad (9)$$

calculate the heat of vaporization and the heat of sublimation for water within the temperature ranges found in Table 3-1. ΔH is the heat of vaporization or the heat of sublimation. Linear regression on the data in Table 3-X, $\ln(\text{vapor pressure})$ versus $1/T$, yields $(-\Delta H/R)$ as the slope from which ΔH_{v} or ΔH_{s} is obtained. An estimate of the slope,

$$\frac{\ln P_2 - \ln P_1}{\left(\frac{1}{T_2} - \frac{1}{T_1}\right)} \quad (10)$$

can also be obtained from a plot of $\ln P$ versus $1/T$ on rectangular coordinate graph paper. Use least-squares linear regression, or the slope of the line obtained from a plot of the data, to calculate ΔH_V and ΔH_S .

- (c) For conversion of a solid to a vapor at constant temperature the process should be independent of the path: solid \rightarrow liquid \rightarrow vapor; therefore, $\Delta H_S = \Delta H_V + \Delta H_f$, where ΔH_f is the enthalpy change involved in the fusion (melting) process.

Compute ΔH_f (for the transition water \rightarrow ice) from ΔH_V and ΔH_S obtained in part (b).

References

1. S. Glasstone, *Thermodynamics for Chemists*, Van Nostrand, New York, 1947, pp. 53, 503.
2. S. Glasstone, *Thermodynamics for Chemists*, Van Nostrand, New York, 1947, pp. 138, 139.
3. A. V. Hill, *Adventures in Biophysics*, Oxford University Press, Oxford, 1931.
4. D. D. Wagman et al., *Selected Values of Chemical Thermodynamic Properties*, National Bureau of Standards, Washington, D. C., 1968.
5. J. W. Moncrief and W. H. Jones, *Essentials of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, pp. 69, 119.
6. A. H. Taylor and R. H. Crist, *J. Am. Chem. Soc.* **63**, 1377, 1941.
7. S. Glasstone, *Textbook of Physical Chemistry*, Van Nostrand, New York, 1946, p. 834.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 4: DETERMINATION OF THE PHYSICAL PROPERTIES OF MOLECULES

4-1 2.93×10^{-19} J.

4-2 797 μg per 24-hr sample. This is an unusually high copper level in urine and indicates a pathologic condition.

4-3 At 285 nm, $c = 2.6 \times 10^{-6}$ mole/liter; at 276 nm, $c = 2.1 \times 10^{-6}$ mole/liter; and at 226 nm, $c = 2.3 \times 10^{-7}$ mole/liter. The 1/4-grain sodium saccharin tablet in a 50-mL solution provides a concentration of 1.58×10^{-3} mole/liter, which is larger than the minimum detectable concentrations at 285, 276, and 226 nm. Any of these three wavelengths is suitable for the analysis.

4-4 *Partial Answer:* When at high concentration, the molecule interaction interferes with the absorptivity.

4-5 $P_i = 54.73 \text{ cm}^3/\text{mole}$; $\alpha_p = 2.17 \times 10^{-23} \text{ cm}^3$.

4-6 The average molar absorptivity is $\epsilon = 4.29 \times 10^4$ liter mole $^{-1}$ cm $^{-1}$.

4-7 $\epsilon = 6512$ liter mole $^{-1}$ cm $^{-1}$.

4-8 The standard isoniazid sample of 0.80 $\mu\text{g}/\text{mL}$ yields a fluorescence emission intensity of $60.5 - 1.2$, or 59.3, where 1.2 is a correction for the blank. The isoniazid in the serum sample produces a fluorescence intensity of $38.4 - 1.2$. Thus, by the method of proportions, one directly obtains the isoniazid concentration, 0.50 $\mu\text{g}/\text{mL}$.

4-9 $\{\alpha\}_D^{25^\circ} = 131$ deg.

4-10 Look up the structure of codeine and cocaine, and consult an infrared spectrum absorption table from an organic chemistry textbook or spectroscopy handbook.

4-11 25 mg of diphenhydramine hydrochloride per capsule.

4-12 (a) The values in Table 4-1 yield R_m for methanol as $8.343 \text{ cm}^3/\text{mole}$; and with the density of methanol as $0.7866 \text{ g}/\text{cm}^3$ at 25°C , equation (4-24) yields the value $R_m = 8.218$; (b) As (a), the unit (cm^3/mole) should be readily attached to R_m .

4-13 From equation (4-28), the molar ellipticity, $[\Theta]$, is 364 deg liter mole $^{-1}$ dm $^{-1}$.

4-14 25 deg 45 min.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 4: DETERMINATION OF THE PHYSICAL PROPERTIES OF MOLECULES

4-1 The wavelength for the detection of lithium by its atomic emission spectrum is 670.8 nm. What is the energy of the photon of radiation that corresponds to this emission line for lithium?

4-2 A urine sample is being analyzed for trace levels of copper by atomic emission. The following flame emission intensities (EI) were obtained at a wavelength of 324.8 nm for the 24-hr urine sample, which had a total volume of 980 mL. A set of copper samples (CS) yielded EI values as shown in the table.

Data for Problem 4-2

Copper Samples (CS)	Emission Intensity (EI)
Cu standard, 0.5 $\mu\text{g/mL}$	20
Cu standard, 1.0 $\mu\text{g/mL}$	38
Cu standard, 1.5 $\mu\text{g/mL}$	61
Cu standard, 2.0 $\mu\text{g/mL}$	80
Urine sample	32

What is the concentration of copper in the 24-hr urine sample? If the normal copper level in urine is approximately 20 μg per 24-hr sample, does this calculated copper concentration indicate an unusually high pathologic condition?

Hint: Regress CS in $\mu\text{g/mL}$ against EI: $\text{CS} = a + b \times \text{EI}$. From the equation, if the relationship is linear, obtain the concentration in $\mu\text{g/mL}$ for copper in the urine sample having an EI of 32. This is the result per milliliter; but the volume of the 24-hr urine sample is 980 mL. Calculate the micrograms of copper in the urine over a 24-hr period.

4-3 The ultraviolet spectrum of saccharin has absorption maxima in methanol at 285, 276, and 226 nm and molar absorptivities, ϵ , of 775, 951, and 8570 liter $\text{mole}^{-1} \text{cm}^{-1}$, respectively. Assuming a minimum absorbance level of $A = 0.002$, find the minimum detectable concentration of saccharin at each of its absorption maxima wavelengths. Which of these wavelengths would be suitable for the analysis of the amount of saccharin in a tablet with a label claim of 1/4 grain of sodium saccharin when the tablet is dissolved in 50 mL of methanol? The molecular weight

of sodium saccharin is 205.16 g/mole. Assume that the path length of the cell is 1 cm.

4-4 The Beer's law plot, as shown in Figure 4-10, is a straight line relating absorbance to concentration. Describe an experimental condition in which the Beer's law plot might be a curved line, with the slope of the curve decreasing at higher concentrations. From a molecular point of view, what is the cause of deviations from ideal solution behavior at high concentrations?

4-5 The molecular weight of diethyl ether is 74.12 g/mole and its density is 0.7134 g/cm^3 at 20°C. What is the induced molar polarization, P_1 , of diethyl ether? See Table 4-2 for the dielectric constant of diethyl ether. What is the calculated induced polarizability, α_p , for diethyl ether at 20°C?

4-6 The following table of concentrations and absorbance values, A , was produced for solutions of nitrazepam in 0.1 N sulfuric acid. The absorbance, A , was measured at 277.5 nm. What is the average molar absorptivity, ϵ , of nitrazepam in 0.1 N sulfuric acid calculated from the three sets of data in the table? A cell of 1-cm path length was used for the experiment. Draw the Beer's law plot associated with the data given in the table. The molecular weight of nitrazepam is 281.3 g/mole.

Data for Problem 4-6

Concentration (C)(mg/L)	Absorbance (A)
0.394	0.06
0.844	0.13
1.160	0.25

4-7 A traditional convention to describe the absorbance through a 1-cm path length containing 1 gm of solute per 100 mL of solution was termed the $E_{1\text{cm}}^{1\%}$ value. The $E_{1\text{cm}}^{1\%}$ value for the ultraviolet absorbance of indomethacin at 318 nm is 182 per 100 mL $\text{g}^{-1} \text{cm}^{-1}$. What is the molar absorptivity, ϵ , corresponding to this $E_{1\text{cm}}^{1\%}$ value? The molecular weight of indomethacin is 357.81 g/mole.

4-8 A blood serum sample is being analyzed for isoniazid by fluorescence induced with salicylaldehyde. The following relative fluorescence emission intensities

are obtained for a blank sample with no drug, a standard of $0.80 \mu\text{g/mL}$, and the serum sample: 1.2, 60.5, and 38.4, respectively. Assuming that the emission intensity is proportional to the isoniazid concentration, determine the isoniazid concentration in $\mu\text{g/mL}$ in the serum.

4-9 An aqueous solution of maltose containing 15.3 g per 100 mL was observed in a polarimeter to have a rotation of 20 deg at 25°C using the sodium D line. The polarimeter cell was 10-cm long. What is the specific rotation, $\{\alpha\}_D^{25^\circ}$, of maltose? *Note:* Cell length must be expressed in decimeters.

4-10 A forensic scientist is attempting to identify a sample as either a codeine or cocaine salt by infrared spectroscopy. The infrared spectrum shows no strong bands between 1600 and 2000 cm^{-1} , some strong bands in the region of 1400 to 1500 cm^{-1} , and some broad bands in the region of 3200 to 3700 cm^{-1} . Based on these data, which compound is associated with the spectrum?

4-11 The diphenhydramine hydrochloride content of a capsule formulation can be determined by proton NMR using t -butyl alcohol as an internal standard.¹¹ The integral, I_u , of the six N -methyl protons in the diphenhydramine band at 2.85 ppm is divided by the integral, I_s , of the nine methyl protons of t -butyl alcohol in the band at 1.27 ppm using equation (4-22). If a single

capsule's contents, v , are assayed, using $W = 25 \text{ mg}$ of t -butyl alcohol as the internal standard, and the average integrals of the bands at 2.85 and 1.27 ppm are 1200 and 7059 units, respectively, what is the amount, C (in mg per capsule), of diphenhydramine hydrochloride in the capsule? The formula weights (molecular weights) for diphenhydramine hydrochloride, EW_u , and t -butyl alcohol, EW_s , are 291.9 and 74.1 g/mole, respectively.

4-12 (a) Calculate the molar refraction, R_m , of methanol using Table 4-1 for the molar refraction of contributing atoms and groups. Compare the result with that obtained by using equation (4-24). The refractive index, n , of methanol is 1.326, its molecular weight is 32.04 g/mole, and its density is 0.7866 g/cm^3 at 25°C .
(b) What are the units on R_m ?

4-13 What is the molar ellipticity, $[\Theta]$, for a penicillin V solution with a specific ellipticity, $[\Psi]$, of $1.04 \times 10^5 \text{ deg mL/g dm}$ at 230 nm? Penicillin has a molecular weight of 350 g/mole.

4-14 The refractive index, n , for quinoline, an antimalarial drug, is 1.627 at 20°C using light from the D -line emission of sodium. If the incident light, passing through air, is at an angle of 45 deg from the perpendicular to the surface of the quinoline liquid, what is the angle of its direction inside the quinoline?

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 5: NONELECTROLYTES

5-1 A solution of sucrose (molecular weight 342) is prepared by dissolving 0.5 g in 100 g of water. Compute (a) the weight percent, (b) the molal concentration, and (c) the mole fraction of sucrose and of water in the solution.

5-2 What is the normality of a 25.0-mL solution of hydrochloric acid that neutralizes 20.0 mL of a 0.50 *N* sodium hydroxide solution?

5-3 (a) Give the number of equivalents per mole of HCl, H₃PO₄, and Ba(OH)₂.
(b) What is the equivalent weight of each of these compounds?

5-4 What is the equivalent weight of anhydrous NaAl(SO₄)₂ (molecular weight 242) when used for its sodium, aluminum, and sulfate content, respectively?

5-5 How many grams of Ca₃(PO₄)₂ are required to prepare 170 mL of a 0.67 *N* solution? The molecular weight of Ca₃(PO₄)₂ is 310.

5-6 The vapor pressure, p_B° , of pure butane is 2.3966 atm at 25°C and that of *n*-pentane, p_P° , is 0.6999 atm at 25°C. Using Raoult's law, calculate the partial vapor pressure of *n*-butane (molecular weight 58.12) and *n*-pentane (molecular weight 72.15) in a mixture of 50 g of each of these two vapors at 25°C in atm and in pounds/in.².

5-7 The vapor pressures of pure Freon 11 and pure Freon 12 at 25°C are 15 and 85 lb/in.², respectively. In the preparation of a pharmaceutical aerosol these two propellants were mixed together in the mole ratio of 0.6 to 0.4.

- (a) What are the partial vapor pressures of Freon 11 and Freon 12 in a mixture having a mole ratio of 0.6 to 0.4, assuming that the mixture follows Raoult's law?
- (b) What is the total vapor pressure of this mixture at 25°C?
- (c) An aerosol can safely be packaged in a glass container protected with a plastic coating as long as the pressure does not exceed about 35 lb/in.² (20 lb/in.² in gauge pressure) at room temperature. Can such a container be used for the preparation

described in this example? Can freons be used today in pharmaceutical aerosols?

5-8 (a) State Henry's law and discuss its relationship to Raoult's law.
(b) How is Henry's law used in the study of gases in solution?

5-9* One may wonder how a fish breathes oxygen when the oxygen is dissolved in water. It is the peculiar gill system of a fish that allows it to take up the oxygen into its body directly from water. The solubility of oxygen in the air dissolved in water is calculated using Henry's law, $p_{O_2} = kX_{O_2}$. The partial pressure, p_{O_2} , of O₂ in the air at 25°C is 0.20 atm and that of N₂ is 0.80 atm. The Henry law constants at 25°C are given in the following table:

Data for Problem 5-9

Gas	mm Hg Per Mole Fraction of Gas	Atmospheres Per Mole Fraction of Gas
O ₂	3.30×10^7	4.34×10^4
N ₂	6.51×10^7	8.57×10^4

- (a) Calculate X_{O_2} , the mole fraction of oxygen, and X_{N_2} , the mole fraction of nitrogen gas, in air at 25°C.
- (b) What is the total mole fraction concentration of these two gases in water at 25°C?
- (c) In air, oxygen constitutes 20%, or one fifth, of the total pressure (see prior comment). What fractional contribution does oxygen make to the concentration of the two gases *in water*?
- (d) Is the dissolved air a fish breathes in water proportionately greater in oxygen than the air we land animals breathe?

5-10 The freezing point lowering of a solution containing 1.00 g of a new drug and 100 g of water is 0.573°C at 25°C.

- (a) What is the molecular weight of the compound?
(b) What is the boiling point of the solution?
(c) What is the osmotic pressure of the solution?

5-11 A 105-g sample of polyethylene glycol 400 (PEG 400) was dissolved in 500 g of water, and the vapor pressure of the solution was found to be 122.6 torr at 56.0°C. The boiling point elevation of this solution

*Problem 5-9 is modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, p. 115.

over that of pure water (100°C at 1 atm) was determined to be 0.271°C . The vapor pressure of pure water, p_1° , at 56°C is 123.80 torr. Calculate the molecular weight of this sample of PEG 400 using vapor pressure lowering, boiling point elevation, and osmotic pressure. The “400” attached to PEG means that the molecular weight of this polymer is approximately 400 g/mole. The density of water at 56°C is 0.985 g/cm^3 . Experimentally, π was obtained as 0.0138 atm.

5-12 A solution of drug is prepared by dissolving 15.0 g in 100 g of water and is subjected to ebullioscopic analysis. The boiling point elevation is 0.28°C . Compute the molecular weight of the drug.

5-13 A solution containing 0.2223 g of benzanthine penicillin G in 1000 g of benzene has a freezing point of 0.00124°C below that of the pure solvent (5.5°C for benzene). What is the molecular weight of benzanthine penicillin G?

5-14 (a) Compute the freezing point depression of 1 g of methylcellulose (molecular weight 26,000 g/mole) dissolved in 100 g of water.

(b) Using the Morse equation, compute the osmotic pressure of this solution at 20°C . Express the result in cm of solution. To convert mm of mercury to mm of solution, use $\text{mm solution} = \text{mm Hg} \times \rho_{\text{Hg}}/\rho_{\text{solution}}$. The density of mercury at 20°C is 13.5462 g/mL . Assume that the density of the solution is 1 g/mL .

(c) Assume that you have a thermometer in which you are able to accurately read 0.05°C and estimate the value to 0.005°C . Can you use freezing point depression of the methylcellulose solution to determine the molecular weight of this polymer? Can you use osmotic pressure to obtain the molecular weight?

5-15 (a) Calculate the cryoscopic constant of benzene. The heat of fusion, ΔH_f , is 2360 cal/mole , and the melting point of benzene is 5.5°C . Its molecular weight is 78.11 g/mole .

(b) Calculate the ebullioscopic constant of phenol. Its heat of vaporization is 9730 cal/mole and its boiling temperature is 181.4°C . The molecular weight of phenol is 94.11 g/mole . Compare your results with those found in Table 5-4.

5-16 Compute the freezing point depression of a 0.20% w/v glucose solution. The molecular weight of glucose is 180 g/mole .

5-17 What concentration of ethylene glycol is required to protect a car’s cooling system from freezing down

to -20°F ? Express the concentration in grams of antifreeze per 100 g of fluid in the system. The molecular weight of ethylene glycol is 62.07 g/mole .

5-18 It is winter and you are caught in your home at night in a severe winter storm of snow and ice; the temperature is -20°F . Your child is sick and you must get to the village pharmacy 10 miles away in the morning to have your child’s prescription filled. You just brought home a new car but you forgot to have it serviced with antifreeze. You have a 5-lb bag of sucrose in the house and you know that the volume of the car’s coolant system is 9 quarts (1 quart = 0.9463 liters).

(a) How far can the temperature drop overnight in your driveway (no garage) before the coolant system would freeze if you added 5 lb of sugar to the water in the radiator and were sure that it dissolved completely? The molecular weight of sucrose is 342 g/mole , and 1 lb (avoirdupois) = 0.4536 kg .

(b) All means of transportation, including taxis, buses, and emergency vehicles, are tied up because of the storm. The demands on the pharmacy, grocery, and other stores are such that they cannot deliver. What other solutions might you arrive at to handle this emergency, should the addition of sucrose not protect the car’s coolant system?

5-19 What is the osmotic pressure of a solution of urea (molecular weight 60) containing 0.30 g of the drug in 50 mL of water at 20°C ? Use the van’t Hoff equation.

5-20 If the freezing point of blood is -0.52°C , what is its osmotic pressure at 25°C ? What is the vapor pressure lowering of blood at this temperature?

5-21 A new alkaloid, guayusine, was isolated from a South American plant, *Guayusa multiflora*. A solution containing 0.473 g of the alkaloid per 500 mL of aqueous solution produced an osmotic pressure of 0.060 atm (i.e., 45.6 mm of Hg or 619 mm of solution) at 25°C . The drug does not associate or dissociate in aqueous solution. Calculate the approximate molecular weight of guayusine.

5-22 A new polypeptide drug has been synthesized and its molecular weight is estimated to be in the range of 10,000 daltons (1 dalton = 1 g/mole). Which colligative property method would be best for accurately determining its molecular weight? The question is answered by calculating ΔT_b , ΔT_f , Δp , and π at 20°C for a 1% solution of the drug in water. The vapor pressure, p_1° , of water at 20°C is 17.54 mm Hg. The density of the solution is 1.015 g/mL , and the density of mercury needed to convert mm Hg to mm solution is 13.5462 g/mL at 20°C .

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 6: ELECTROLYTE SOLUTIONS

6-1 400 mho cm²/Eq.

6-2 (a) The equation of the line is $\Gamma_c = 126.45 - 43.70\sqrt{c}$; $r^2 = 0.9999$. The intercept is $\Gamma_0 = 126.45 \text{ ohm}^{-1} \text{ cm}^2/\text{Eq}$.

(b) From the definition of transference number and the Kohlrausch law, equation (6-23), we can use the transference numbers to calculate the ionic equivalent conductances, l_c° and l_a° , where $l_c^\circ = \Gamma_0 t_{c+}^\circ$, $l_a^\circ = \Gamma_0 t_{a-}^\circ$; and $\Gamma_0 = l_a^\circ + l_c^\circ$; $t_{a-}^\circ = 0.604$.

In the literature we find $l_a^\circ = 76.34$ and $l_c^\circ = 50.07$ mho cm²/Eq.

6-3 $i = 1.11$ (a dimensionless number).

6-4 145 lb (66 kg). Some ice will sublime and pass directly from the solid into the vapor state. This and other factors such as heating by the sun will render the answer given here a rough approximation. However, the calculation will give the city winter emergency crews an estimate of the amount of CaCl₂ needed for clearing sidewalks and streets. (Note: Some cities no longer use "salt" on streets and sidewalks because of its pollution problems.)

6-5 *Partial Answer:* **(b)** Concentration of NaCl solution = 4.9 m or 286 g salt/kg water; **(c)** Check with a good cook about the saltiness of the food in this concentration of salt solution.

6-6 0.00276, or 0.28%.

6-7 (a) $a = 0.949$; **(b)** $a = 0.925$; **(c)** $a = 0.930$; **(d)** $a = 0.805$.

6-8 (a) The vapor pressure is lowered from 23.8 torr to 20.91 torr, or $\Delta p_1 = 2.89$ torr; **(b)** $a_1 = 0.879$; $\gamma_1 = 0.915$ (you will need to calculate X_1 , the mole fraction

of water, to obtain this activity coefficient, 0.915, for water).

6-9 $a_1 = 0.990$; $\gamma_1 = 1.000$. Thus, in a 100-g/kg H₂O solution of glucose (fairly concentrated, 0.56 m), both the activity and the activity coefficient of water may be taken as approximately equal to 1.0. This is not so for a solution of an electrolyte, as seen in *Problems 6-8*.

6-10 $\gamma_{\pm} = 0.85$.

6-11 $\gamma_{\pm} = 0.75$.

6-12 (a) 0.01 M CaCl₂; **(b)** From equation (6-58), $\gamma_{\pm} = 0.494$ and $a_{\pm} = 0.0157$. From equation (6-60), $\gamma_{\pm} = 0.582$ and $a_{\pm} = 0.0185$. The results from the two equations are different. The ionic strength of the solution is 0.02 M, so equation (6-60) is required.

6-13 $\mu = 0.205$.

6-14 0.90.

6-15 $\mu = 0.16$.

6-16 (a) $i = 1.69$; **(b)** $g = 0.85$; **(c)** $L = 3.16$.

6-17 $i = 1.02$; $\Delta T_f = 0.11^\circ$; $\alpha = 0.02$, or 2% dissociated.

6-18 214.8 mOsm/(liter solution).

6-19 (a) *Partial Answer:*

X_1	1.0	0.878	0.575
a_1	1.0	0.870	0.504
γ_1	1.0	0.991	0.877

This tabular answer states that when $X_1 = 1.0$, $a_1 = 1.0$ and $\gamma_1 = 1.0$, and so on. **(b)** *Partial Answer:* the plot indicate the intra molecular forces between acetone and chloroform is greater than that in an ideal solution.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 6: ELECTROLYTE SOLUTIONS

6-1 The equivalent conductance, Λ_0 , of the sodium salt of a sulfonamide at infinite dilution was found by experiment to be $100.3 \text{ mho cm}^2/\text{Eq}$. The Λ_0 for HCl is 426.16; for NaCl, it is 126.45. What is Λ_0 for the free acid (the free sulfonamide)?

6-2 The equivalent conductances, Λ_c ($\text{mho cm}^2/\text{Eq}$), of NaCl at several molar concentrations, c , are

Data for Problem 6-2

c	0.09	0.04	0.01
Λ_c	113.34	117.70	122.08

(a) Plot Γ_c against \sqrt{c} as in Figure 6-4. Compute Γ_0 and the equation of the line (use least squares).

(b) The transference number, t_c , of Na^+ at infinite dilution is 0.396. Compute the ionic equivalent conductance of Na^+ , Cl^- , and the transference number of Cl^- at infinite dilution.

6-3 A 1.0 m solution of sucrose had an observed osmotic pressure of 24.8 atm at 0°C . Calculate the van't Hoff i factor for sucrose at this concentration.

6-4* Calcium chloride may be used to melt the ice from sidewalks. How many pounds (avoirdupois) of CaCl_2 is required to melt a layer of ice 0.5 in. thick on a sidewalk 50 ft long and 4 ft wide if the temperature of ice is 10°F ? The molecular weight of CaCl_2 is 110.99 g/mole. The density of the ice at 10°F is 0.9973 g/mL, and the degree of ionization, α , of CaCl_2 is 0.8.

6-5 Some cooks add salt to a kettle of water in which they are boiling peeled corn or unpeeled potatoes. In addition to improving the flavor, this practice is reputed to cook and soften the food better.

- (a) Is there any scientific justification for this? Explain.
- (b) What is the concentration of NaCl in grams of salt per kilogram of water needed to obtain a significant rise in the boiling point, say 5°C ?
- (c) Would this concentration of NaCl render the food too salty to the taste?

6-6 The equivalent conductance of a sulfonamide at 0.01 M concentration was found by experiment to be 1.104. The equivalent conductance of the drug at infinite dilution is 400.0. What is the degree of dissociation of the weak electrolyte at this concentration?

6-7 (a) The vapor pressure of water over an aqueous solution of a drug is 721 mm Hg at 100°C . (a) What is the activity of water in this solution?

(b) Methanol has a boiling point of 64.7°C . The vapor pressure of methanol in a methanolic solution of a sulfonamide is 703 mm Hg. What is the activity of methanol in this solution at 64.7°C ?

(c) Chlorine has a vapor pressure of 10.0 atm at 35.6°C . In a mixture of chlorine and carbon tetrachloride the vapor pressure of chlorine is 9.30 atm at 35.6°C . What is the activity of chlorine in the mixture?

(d) Formic acid has a vapor pressure of 40.0 mm Hg at 24°C . In a mixture of formic acid and acetic acid, formic acid has a vapor pressure of 32.2 mm at 24°C . What is the activity of formic acid in the mixture?

6-8* The vapor pressure, p_1° , of water at 25°C is 23.8 torr.

(a) Compute the lowering of the vapor pressure of water when 25 g of CaCl_2 is added to 100 g of water. The molecular weight of CaCl_2 is 110.99 g/mole.

(b) Compute the activity and the activity coefficient of water in the solution.

6-9 The vapor pressure of pure water (23.8 torr) at 25°C is lowered when 100 g of the nonelectrolyte glucose is added to 1000 g of the water. The molecular weight of glucose is 180.16 g/mole. What are the activity and the activity coefficient of water at this temperature and concentration of glucose?

6-10 Compute the mean ionic activity coefficient of a 0.01 M aqueous solution of diphenylhydantoin sodium containing 0.01 M KCl at 25°C . Use the limiting Debye-Hückel equation.

6-11 Using the extended Debye-Hückel equation, compute the mean ionic activity coefficient of a 0.05 M solution of epinephrine hydrochloride containing 0.05 M potassium chloride.

*Problems 6-4 and 6-8 are modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, pp. 146 and 124, respectively.

6-12 (a) What amount of CaCl_2 (in moles/liter) should be added to a 0.02 M solution of neomycin sulfate to produce an ionic strength of 0.09 ?

(b) Calculate the mean ionic activity and the mean ionic activity coefficient for the 0.02 M solution of neomycin sulfate at an ionic strength of 0.09 and a temperature of 25°C . Use both equations (6-58) and (6-60) (pages 140 and 141) and compare the results.

6-13 A solution contains 0.003 M of sodium phenobarbital together with a buffer consisting of 0.20 M sodium acetate and 0.30 M acetic acid. Acetic acid is a weak electrolyte; its degree, or fraction, of dissociation, α , at this concentration is 0.008 and the undissociated species do not contribute to the ionic strength. What is the ionic strength of the solution?

6-14 A solution contains 0.05 M AlCl_3 and 0.2 M Na_2HPO_4 . What is the ionic strength of this solution?

6-15 Ringer's solution USP has been designed to have approximately the same ionic strength as that of normal blood. Calculate the ionic strength of blood from the concentration of the constituents of Ringer's solution.

6-16 The freezing point depression of a solution containing 4 g of methapyrilene hydrochloride in 100 mL of solution was 0.423° . Methapyrilene hydrochloride dissociates into two ions and has a molecular weight of 297.85 . Calculate **(a)** the van't Hoff factor, i , **(b)** the osmotic coefficient, g , and **(c)** the L value for the drug at this concentration.

6-17 The L_{iso} value of an aqueous solution of ascorbic acid is 1.90 and its osmotic pressure at 37°C is $\pi = 1182\text{ mm Hg}$. Compute i , ΔT_f , and the degree of dissociation, α .

6-18 A 0.120 m solution of potassium bromide has a milliosmolality of $1.86 \times 120\text{ mm} = 223\text{ mOsm/kg}$ (see *Example 6-16*, page 144). The density of water at 25°C is 0.997 g/cm^3 , and the partial molar volume of KBr is $\bar{v}_2^\circ = 33.97\text{ cm}^3/\text{mole}$. Calculate the milliosmolarity, $\text{mOsm}/(\text{liter solution})$, of this KBr solution using equation (6-66).

6-19 Partial pressures (in mm Hg), p_1 , of acetone at various mole fractions, X_1 , are given in the following table for a mixture of acetone and chloroform:

Data for Problem 6-19

X_1	1.000	0.950	0.925	0.878	0.710	0.575
$p_1(\text{mm})$	344.5	327.5*	317.0*	299.7	230.7	173.7

*These points have been added to the data.

Source: Data from J. von Zawidzki as reported by I. M. Klotz and R. M. Rosenberg, *Chemical Thermodynamics*, W. A. Benjamin, Menlo Park, Cal., 1972, pp. 355, 356. Some points are omitted and two points have been added near $X_1 = 1.000$.

(a) Compute the activity and activity coefficient for acetone at various X_1 values in these solutions.

(b) Plot both the experimental p_1 values and the Raoult's law pressures versus X_1 . Discuss the deviations from Raoult's law and its implications regarding possible intermolecular interaction between chloroform and acetone.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 7: IONIC EQUILIBRIA

7-1 (a) $[\text{H}_3\text{O}^+] = 2.88 \times 10^{-3}$; (b) $\text{pH} = 3.10$; (c) $[\text{OH}^-] = 5.62 \times 10^{-6}$, $[\text{H}_3\text{O}^+] = 1.78 \times 10^{-9}$; (d) $\text{pH} = 2.42$, $\text{pOH} = 11.58$; (e) $\text{pH} = 11.96$; (f) $\text{pH} = 2.32$; (g) $\text{pH} = 7.07$; (h) $\text{pH} = 7.08$; (i) $\text{pH} = 4.81$; (j) $\text{pH} = 8.53$, $[\text{H}_3\text{O}^+] = 2.95 \times 10^{-9}$; (k) $\text{pH} = 7.18$, $[\text{OH}^-] = 1.51 \times 10^{-7}$; (l) $\text{pH} = 6.89$, $\text{pOH} = 7.11$; (m) $\text{pH} = 2.49$.

7-2 $\text{pH} = 6.84$, $\text{pOH} = 7.16$.

7-3 (a) 23%; (b) 28%.

7-4 (a) $\text{pH} = 5.14$; (b) $[\text{OH}^-] = 1.38 \times 10^{-9}$.

7-5 $\text{pH} = 4.70$.

7-6 $\text{pH} = 10.92$.

7-7 $\text{pH} = 2.58$.

7-8 $\text{pH} = 9.94$.

7-9 $\text{pH} = 2.36$.

7-10 (a) $[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{NH}_3]$; (b) $[\text{H}_3\text{O}^+] + 2[\text{H}_3\text{PO}_4] + [\text{H}_2\text{PO}_4^-] = [\text{OH}^-] + [\text{NH}_3] + [\text{PO}_4^{3-}]$.

7-11 $\text{pH} = 4.3$.

7-12 $\text{pH} = 4.06$.

7-13 (a) $\text{pH} = 9.24$; (b) $\text{pH} = 7.06$.

7-14 $\text{pH} = 10.72$.

7-15 $\text{pH} = 5.20$.

7-16 $\text{pH} = 10.09$.

7-17 $\text{p}K_b = 4.68$.

7-18 0.0087, or 0.87%.

7-19 (a) $\text{pH} = 7.84$; (b) $\text{pH} = 7.68$.

7-20 *Partial Answer:* (b) The equation obtained using the nine oximes from the work of Kurtz and D'Silva is

$$\text{p}K_a = 29.92 - 1.71 \delta_{\text{OH}}; r^2 = 0.967, n = 9 \quad (1)$$

(n stands for the number of compounds involved in the regression as independent variables)

(c) The $\text{p}K_a$ of acetophenone oxime calculated from the equation under part (b) is 10.85. The literature value is 11.41.

7-21

Compound	$\text{p}K_a$	
	Calculated	Literature
Benzaldehyde oxime	10.81	10.78
2,3-Butanedione monooxime	9.13	9.34
Phenol	9.88	9.97
2-Nitrophenol	7.42	7.14

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 7: IONIC EQUILIBRIA

7-1 Practice calculations involving pH, pOH, and ionic concentration in aqueous solutions.

- Convert $\text{pH} = 2.54$ to hydrogen ion concentration, $[\text{H}^+]$.
- What is the pH of a 7.93×10^{-4} molar solution of a strong acid?
- If the pH of a solution of a strong base is 8.75, what is its hydroxyl ion concentration? What is its hydrogen ion concentration?
- What is the pH of a 0.00379 *M* solution of HNO_3 ? What is its pOH?
- Convert the hydroxyl ion concentration 0.00915 *M* to pH.
- Calculate the pH of a 2.37×10^{-3} *M* solution of sulfuric acid. H_2SO_4 dissociates completely as a strong electrolyte in a dilute solution, as found in the present problem.
- A 0.017 *M* solution of HCl is mixed with a 0.017 *M* solution of NaOH. What is the pH of the final mixture?
- What is the pH of a 0.034 *M* solution of NaCl?
- The solubility of phenobarbital in water at 25°C is 0.14% (w/v). What is the pH of the saturated solution?
- If 15 mL of 0.02 *M* NaOH is added to 15 mL of 0.02 *M* acetic acid, what is the pH of the solution? Convert the pH to hydrogen ion concentration.
- The pOH of a drug solution is 6.82; what is the pH of the solution? What is the hydroxyl ion concentration if the solution is a strong base?
- What are the pH and pOH of a 5×10^{-8} *M* solution of HCl at 25°C?
- Calculate the pH of a 0.06 *M* solution of formic acid.

7-2 If 100 mL of 0.005 *M* sulfathiazole is mixed with 57 mL of 0.003 *M* sodium hydroxide, what is the pH of the mixture? What is the pOH of the solution? Sulfathiazole reacts in part with NaOH to give sodium sulfathiazole. *Hint*: Use the Henderson–Hasselbalch equation. The $\text{p}K_a$ of sulfathiazole is 7.12.

- What is the mole percent of free phenobarbital in solution at pH 8.00?
- What is the mole percent of free cocaine in solution at pH 8.00?

- What is the pH of a 5 g per 100 mL solution of phenol?
- What is the hydroxyl ion concentration of the solution?

7-5 Calculate the pH of a 1% (w/v) solution of morphine sulfate. The molecular weight of this salt is 668.76.

7-6 What is the pH of a 1:200 aqueous solution of ephedrine at 25°?

7-7 Calculate the pH of a 0.01 *M* solution of tartaric acid.

7-8 Calculate the pH of a 0.01 *M* solution of physostigmine at 25°C.

7-9 Calculate the pH of a solution containing 0.1 *M* acetic acid and 0.1 *M* formic acid.

- What is the PBE for a solution of ammonium chloride?
- What is the PBE for a solution containing equimolar amounts of Na_2HPO_4 and ammonium chloride?

7-11 The sulfonamides can exist in the form of an ampholyte $^+\text{NH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NR}^-$ in aqueous solution. The two acidity constants of sulfadiazine are $\text{p}K_1 = 2.1$ and $\text{p}K_2 = 6.5$. Calculate the isoionic point for this drug.

7-12 What is the pH of a solution containing acetic acid 0.1 *M* and sodium acetate 0.02 *M*?

- Calculate the pH of a 0.1 *M* solution of ammonium borate.
- Calculate the pH of a 0.1 *M* solution of ammonium propionate.

7-14 What is the pH of a 0.01 *M* solution of $(\text{NH}_4)_3\text{PO}_4$?

7-15 What is the pH of a solution containing equimolar amounts of succinic acid and tribasic sodium citrate?

7-16 What is the pH of a sulfadiazine sodium solution containing 0.5 mole of drug in 1000 mL of solution?

7-17 The pH of a 1:500 aqueous solution of ephedrine was determined with a pH meter and was found to be 10.70. Calculate the pK_b for ephedrine.

7-18 Calculate α , the degree of dissociation of 0.01 M physostigmine, disregarding the secondary ionization. α is the concentration of the ionized form, $[\text{physostigmine}^+] = [\text{OH}^-]/C_b$, where C_b is the concentration of the compound.

7-19 The weak acid corresponding to the salt benzylpenicillin sodium, molecular weight 356.38, has a pK_a of 2.76, and the drug is dissolved in isotonic sodium chloride solution (0.9 g NaCl per 100 mL) to make a 3% w/v solution of the antibiotic.

- (a) What is the pH of this solution, disregarding activity coefficients?
 (b) What is the result using ionic activity coefficients? (Use the Debye–Hückel equation.)

7-20 In a study of insecticidal oximes ($R_2C=NOH$) Kurtz and D'Silva (A.P. Kurtz and T.D.J. D'Silva, J. Pharm. Sci **76**, 599, 1987.) postulated a relationship between the pK_a value of an oxime and its proton chemical shift, δ_{OH} (see pages 99 and 100 for a description of chemical shift). To learn whether pK_a values could be obtained from NMR data, the authors determined chemical shifts of the hydroxyl proton, δ_{OH} , of selected oximes with known pK_a values. pK_a and δ_{OH} values are listed in the table that accompanies this problem.

- (a) Plot pK_a on the vertical axis versus the experimentally determined δ_{OH} values on the horizontal axis.

Data for Problem 7-20

Known pK_a and Experimental δ_{OH} Values		
Compound	δ_{OH}	pK_a
2-Propanone oxime	10.12	12.42
2-Butanone oxime	10.14	12.45
3-Pentanone oxime	10.18	12.60
Acetophenone oxime	11.15	11.41
Benzaldehyde oxime	11.19	10.78
4-Nitrobenzaldehyde oxime	11.84	9.88
2,3-Butanedione monooxime	12.27	9.34
3-Oximinopentane-2,4-dione	12.92	7.38
2-Oximino-1,3-dithiolane	11.15	10.70

- (b) Use least-squares linear regression analysis, regressing pK_a versus δ_{OH} , to obtain an equation relating these two variables. How well do the coef-

ficients of your equation correspond to those of Kurtz and D'Silva?

- (c) Use your equation of the least-squares regression line to calculate the pK_a from $\delta_{OH} = 11.15$ for acetophenone oxime. Compare your calculated pK_a with the literature value, $pK_a = 11.41$, for acetophenone oxime.

7-21 Kurtz and D'Silva (A.P. Kurtz and T.D.J. D'Silva, J. Pharm. Sci **76**, 599, 1987.) used NMR chemical shift data to obtain the pK_a of a number of oximes, as described in *Problem 7-20*. Furthermore, these workers observed that the sensitivity of phenol pK_a values was similar to that of oxime pK_a values for changes in proton chemical shift, δ_{OH} . That is, the slope of the plot of pK_a versus δ_{OH} for oximes was nearly the same as that for phenols. Thus, it should be possible to use a single equation to express the pK_a versus δ_{OH} values for both oximes and phenols. To test this possibility, the authors used 20 oxime pK_a values and 51 phenol pK_a values and regressed these against measured δ_{OH} values. Kurtz and D'Silva added an *indicator variable** to account for the difference in these two classes of chemicals. The indicator variable, I , is taken as equal to unity for each phenol in the equation and as zero for each compound that is an oxime, giving the expression

$$pK_a = a + b(\delta_{OH}) + c(I) \quad (1)$$

The 20 pK_a and δ_{OH} values for the oximes and the 51 pK_a and δ_{OH} values for the phenols are entered into a computer program designed to handle linear regression with indicator variables. As the oxime and phenol data are entered, I is given a value of 0 for each oxime and a value of 1 for each phenol. The computer-generated results (N. H. Nie, C. H. Hill, J. G. Jenkins, K. Steinbrenner, and D. H. Bent, *SPSS: Statistical Package for the Social Sciences*, 2nd Ed., McGraw-Hill, New York, 1975, pp. 373–375) provide values for a , b , and c in the foregoing equation.

In essence, the indicator variable produces different intercepts and thus divides the results into two separate lines having the same slope. The lines in this case represent the two classes of compounds, oximes and phenols; and the single equation relating pK_a and δ_{OH} for these two classes is, according to Kurtz and D'Silva,

$$pK_a = 28.15 - 1.55 \delta_{OH} - 3.96I, r^2 = 0.97 \quad (2)$$

*Indicator variables, also called *dummy variables*, are described in N. H. Nie, C. H. Hill, J. G. Jenkins, K. Steinbrenner, and D. H. Bent, *SPSS: Statistical Package for the Social Sciences*, 2nd Ed., McGraw-Hill, New York, 1975, p. 373.

Plot the two lines on a graph of pK_a against δ_{OH} . Locate the points for benzaldehyde oxime and 2-3 butanedione monooxime on the one line and phenol and 2-nitrophenol on the other line. Use the observed (measured) δ_{OH} values for these four compounds:

Data for Problem 7-21

Compound	Measured δ_{OH}
Benzaldehyde oxime	11.19
2,3-Butanedione monooxime	12.27
Phenol	9.23*
2-Nitrophenol	10.82*

*From G. Socrates, Trans. Faraday Soc. **66**, 1052, 1966.

and the foregoing equation to calculate the pK_a values.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 8: BUFFERED AND ISOTONIC SOLUTIONS

- 8-1** The acid:salt ratio is 1:0.36.
- 8-2** pH = 10.36.
- 8-3** (a) pH = 7.03; (b) pH = 6.46.
- 8-4** (a) pH = 2.40; (b) a 25.1:1 ratio of sodium ascorbate to ascorbic acid, or 96.2 mole % sodium ascorbate and 3.8% of ascorbic acid.
- 8-5** $pK_1 = 6.13$.
- 8-6** $\beta_{\max} = 0.115$ and it occurs at pH 3.98.
- 8-7** $\beta = 0.15$.
- 8-8** *One Possible Answer:*
- $$\begin{aligned} \text{Na}_2\text{HPO}_4 \text{ (salt)} &= 0.052 \text{ M} \\ \text{NaH}_2\text{PO}_4 \text{ (acid)} &= 0.265 \text{ M} \end{aligned} \quad (1)$$
- 8-9** *Partial Answer:* β at pH 7.0 is 0.0048; β at pH 8.2 is 0.064; β at pH 9.24 is 0.21; β at pH 10.8 is 0.021, β_{\max} is found at pH 9.24, where $\text{pH} = \text{p}K_a$; $\beta_{\max} = 0.576C = 0.21$.
- 8-10** (a) pH disregarding ionic strength is 7.87; (b) including ionic strength, pH = 7.79.
- 8-11** $\beta = 0.0069$.
- 8-12** $\beta_{\max} = 0.015$ at pH 6.1 (see pages 218–219).
- 8-13** A mixture of 0.044 Na_2HPO_4 and 0.0105 NaH_2PO_4 has a buffer capacity of 0.03 and provides a pH of 7.4. The ionic strength of this mixture is 0.14. The ionic strength may be raised to 0.16 by the addition of 0.02 M NaCl or KCl.
- 8-14** pH = 8.34.
- 8-15** 3.83 grains = 248 mg.
- 8-16** $V \div 6.7 \text{ mL}$, $E \div 0.20$, $\Delta T_f = 0.12$.
- 8-17** *Partial Answer:* From the Sprowls valve you can calculate the concentration of the isotonic solution, which is lower than 25%.
- 8-18** Check your results against Table 8–4.
- 8-19** (a) $E = 0.84, 0.60, 1.31, \text{ and } 0.25$; (b) $\Delta T_f^{1\%} = 0.49^\circ\text{C}, 0.35^\circ\text{C}, 0.76^\circ\text{C}, \text{ and } 0.15^\circ\text{C}$.
- 8-20** (a) Add 7.2 g of NaCl; (b) add 0.14 g of boric acid.
- 8-21** Dissolve the drugs in 66.44 mL of water. This solution is isotonic. Add 0.3 g of NaCl and bring to a volume of 100 mL.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 8: BUFFERED AND ISOTONIC SOLUTIONS

8-1 One desires to adjust a solution to pH 8.8 by the use of a boric acid–sodium borate buffer. What approximate ratio of acid and salt is required?

8-2 What is the pH of a solution containing 0.1 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution?

8-3 (a) What is the pH of a buffer consisting of 0.12 M NaH_2PO_4 and 0.08 M Na_2HPO_4 , the former acting as the acid and the latter as the salt or conjugate base (see E. J. Cohen, F. F. Heyroth, and M. F. Menkin, *J. Am. Chem. Soc.* **49**, 173, 1927; **50**, 696, 1928).

(b) What is the value when the ionic strength corrections are made using the Debye–Hückel law? *Hint:* Use equation (8–15). The value for n in the terms pK_n and $(2n - 1)$ is 2 in this problem because the second stage of ionization of phosphoric acid is involved. Thus, the equation becomes

$$\text{pH} = 7.21 + \log \frac{[\text{Na}_2\text{HPO}_4]}{[\text{NaH}_2\text{PO}_4]} - \frac{0.51 \times 3\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (1)$$

8-4 Ascorbic acid (molecular weight 176.12) is too acidic to administer by the parenteral route. The acidity of ascorbic acid is partially neutralized by adding a basic compound, usually sodium carbonate or sodium bicarbonate. Thus, the injectable product contains sodium ascorbate, ascorbic acid, and the neutralizing agent.

(a) What is the pH of an injectable solution containing only ascorbic acid in the concentration of 55 g per liter of solution? $K_1 = 5 \times 10^{-5}$ and $K_2 = 1.6 \times 10^{-12}$.

(b) What is the molar ratio of sodium ascorbate to ascorbic acid, and the percentage of each compound required to prepare an injectable solution with a pH of 5.7?

8-5 The thermodynamic dissociation exponent, pK_1 , for carbonic acid at 30°C is 6.33. According to Van Slyke et al.,¹ the ionic strength of the blood is roughly 0.16. Compute the apparent dissociation exponent, pK_1 , to

be used for the carbonic acid of blood at 30°C. Notice that the pH or $-\log a_{\text{H}^+}$ is given by the expression

$$\begin{aligned} \text{pH} &= pK_1' + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \\ &= pK_1 + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} + \log \gamma_{\text{HCO}_3^-} \quad (2) \end{aligned}$$

Therefore,

$$pK_1' = pK_1 + \log \gamma_{(\text{HCO}_3^-)} \cong pK_1 - 0.5\sqrt{\gamma} \quad (3)$$

8-6 Plot the buffer capacity–pH curve for a barbituric acid–sodium barbiturate buffer of total concentration 0.2 M over the range of pH 1 to 7. What is the maximum buffer capacity and at what pH does β_{max} occur?

8-7 What is the buffer capacity of a solution containing 0.20 M acetic acid and 0.10 M sodium acetate?

8-8 Your product research director asks you to prepare a buffer solution of pH 6.5 having a buffer capacity of 0.10. Choose a suitable combination of buffer species and compute the concentrations needed.

8-9 What is the buffer capacity of a solution containing 0.36 M boric acid at a pH of 7.0? What is the buffer capacity at pH 9.24, that is, where is $\text{pH} = pK_a$? At what pH is β a maximum and what is the value of β_{max} ? What is the buffer capacity at pH 10.8? Using the calculated values of β , plot the buffer capacity versus pH. If the student wishes to smooth the buffer curve a little better, he or she may also calculate β at pH 8.20 and at 10.0. When these six points are plotted on the graph and a smooth line is drawn through them, a bell-shaped buffer curve is obtained. See Figure 8–4 for the shapes of several buffer curves.

8-10 A borate buffer contains 2.5 g of sodium chloride (molecular weight 58.5 g/mole); 2.8 g of sodium borate decahydrate (molecular weight 381.43); 10.5 g of boric acid (molecular weight 61.84); and sufficient water to make 1000 mL of solution. Compute the pH of the solution **(a)** disregarding the ionic strength, and **(b)** taking into account the ionic strength.

8-11 Calculate the buffer capacity of an aqueous solution of the strong base sodium hydroxide having a hydroxyl ion concentration of $3.0 \times 10^{-3} M$.

8-12 Assuming that the total bicarbonate buffer concentration in normal blood is about 0.026 mole/liter, what would be the maximum buffer capacity of this buffer and at what pH would β_{\max} occur?

8-13 Describe in detail how you would formulate a buffer having approximately the same pH, ionic strength, and buffer capacity as that of blood. The ionic strength of the blood plasma is about 0.16 and the buffer capacity in the physiologic pH range is approximately 0.03. Use the $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ buffer and $\text{p}K_2$ of phosphoric acid. Activity coefficients must be considered, and the thermodynamic $\text{p}K_2$ of phosphoric acid must be used to obtain the answer.

8-14 Plot the pH titration curve for the neutralization of 0.1 *N* barbituric acid by 0.1 *N* NaOH. What is the pH of the solution at the equivalence point?

8-15 A 1-fluid ounce (29.573 mL) solution contains 4.5 grains (291.60 mg) of silver nitrate. How much sodium nitrate must be added to this solution to make it isotonic with nasal fluid? Assume that nasal fluid has an isotonicity value of 0.9% NaCl.

8-16 Compute the Sprowls *V* value, the *E* value, and the freezing point depression of a 1% solution of diphenhydramine hydrochloride.

8-17 A 25% solution of phenylpropanolamine hydrochloride is prepared. The physician desires that 0.25 fluid ounce (7.393 mL) of this solution be made isotonic and adjusted to a pH of 6.8. The Sprowls *V* value is 12.7. Discuss the difficulties that are encountered in filling the physician's request. How might these difficulties be overcome?

8-18 Compute the freezing point depression of 1% solutions of the following drugs: (a) ascorbic acid, (b) calcium chloride, (c) ephedrine sulfate, and (d) methacholine chloride. The percentages of sodium chloride required to make 100 mL of 1% solutions of these drugs isotonic are 0.81%, 0.48%, 0.76%, and 0.67%, respectively. *Hint*: Refer to *Example 8-11*.

8-19 (a) Compute the approximate sodium chloride equivalent of MgO (molecular weight = 40.3 g/mole),

ZnCl_2 (molecular weight = 136.3 g/mole), $\text{Al}(\text{OH})_3$ (molecular weight = 77.98 g/mole), and isoniazid (a tuberculostatic drug, weak electrolyte, molecular weight = 137.2 g/mole), using the average L_{iso} values given in Table 8-3.

(b) From the *E* value you calculated in part (a), compute the freezing point depression of a 1% solution of these drugs.

(c) Can one actually obtain a 1% aqueous solution of MgO or $\text{Al}(\text{OH})_3$?

8-20 Using the sodium chloride equivalent method, make the following solutions isotonic with respect to the mucous lining of the eye (ocular membrane).

(a) Tetracaine hydrochloride: 10 g

NaCl: x g

Sterile distilled water, enough to make 1000 mL

(b) Tetracaine hydrochloride: 0.10 g

Boric acid: x g

Sterile distilled water, enough to make 10 mL

8-21 Make the following solution isotonic with respect to blood:

Chlorpromazine hydrochloride	2.5 g
Ascorbic acid	0.2 g
Sodium bisulfite	0.1 g
Sodium sulfate, anhydrous	0.1 g
Sterile distilled water, enough to make	100 mL

Hint: First, compute the *E* values of chlorpromazine HCl and sodium sulfate, not given in Table 8-4, from the approximate L_{iso} values given in Table 8-3. The molecular weight of chlorpromazine hydrochloride is 318.9 daltons* and the molecular weight of sodium sulfate is 142.06 daltons.

Reference

1. D. D. Van Slyke, A. B. Hastings, C. D. Murray, and J. Sendtoy, *J. Biol. Chem.* **65**, 701, 1975.

*The word *dalton* is used in connection with molecular weight: 1 dalton = 1 g/mole.

TABLE 8-4
ISOTONIC VALUES

Substance	MW	E	V	$\Delta T_f^{1\%}$	L_{iso}
Alcohol, dehydrated	46.07	0.70	23.3	0.41	1.9
Aminophylline	456.46	0.17	5.7	0.10	4.6
Ammonium chloride	53.50	1.08	36	0.64	3.4
Amphetamine sulfate (benzedrine sulfate)	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Antistine hydrochloride (antazoline hydrochloride)	301.81	0.18	6.0	0.11	3.2
Apomorphine hydrochloride	312.79	0.14	4.7	0.08	2.6
Ascorbic acid	176.12	0.18	6.0	0.11	1.9
Atropine sulfate	694.82	0.13	4.3	0.07	5.3
Aureomycin hydrochloride	544	0.11	3.7	0.06	3.5
Barbital sodium	206.18	0.29	10.0	0.29	3.5
Benadryl hydrochloride (diphenhydramine hydrochloride)	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Butacaine sulfate (butyn sulfate)	710.95	0.20	6.7	0.12	8.4
Caffeine	194.19	0.08	2.7	0.05	0.9
Caffeine and sodium benzoate	—	0.25	8.7	0.28	—
Calcium chloride 2H ₂ O	147.03	0.51	17.0	0.30	4.4
Calcium gluconate	448.39	0.16	5.3	0.09	4.2
Calcium lactate	308.30	0.23	7.7	0.14	4.2
Camphor	152.23	0.20	6.7	0.12	1.8
Chloramphenicol (chloromycetin)	323.14	0.10	3.3	0.06	1.9
Chlorobutanol (chloretone)	177.47	0.24	8.0	0.14	2.5
Cocaine hydrochloride	339.81	0.16	5.3	0.09	3.2
Cupric sulfate · 5H ₂ O	249.69	0.18	6.0	0.11	2.6
Dextrose · H ₂ O	198.17	0.16	5.3	0.09	1.9
Dibucaine hydrochloride (nupercaine hydrochloride)	379.92	0.13	4.3	0.08	2.9
Emetine hydrochloride	553.56	0.10	3.3	0.06	3.3
Ephedrine hydrochloride	201.69	0.30	10.0	0.18	3.6
Ephedrine sulfate	428.54	0.23	7.7	0.14	5.8
Epinephrine bitartrate	333.29	0.18	6.0	0.11	3.5
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Ethylhydrocupreine hydrochloride (optochin)	376.92	0.17	5.7	0.10	3.8
Ethylmorphine hydrochloride (dionin)	385.88	0.16	5.3	0.09	3.6
Eucatropine hydrochloride (euphthalmine hydrochloride)	327.84	0.18	6.0	0.11	3.5
Fluorescein sodium	376	0.31	10.3	0.18	6.9
Glycerin	92.09	0.34	11.3	0.20	1.8
Homatropine hydrobromide	356.26	0.17	5.7	0.10	3.6
Lactose	360.31	0.07	2.3	0.04	1.7
Magnesium sulfate (optochin) · 7H ₂ O	246.50	0.17	5.7	0.10	2.5
Menthol	156.26	0.20	6.7	0.12	1.8
Meperidine hydrochloride (demerol hydrochloride)	283.79	0.22	7.3	0.12	3.7
Mercuric chloride (mercury bichloride)	271.52	0.13	4.3	0.08	2.1
Mercuric cyanide	252.65	0.15	5.0	0.09	2.2
Mercuric succinimide	396.77	0.14	4.8	0.08	3.3
Methacholine chloride (mecholy chloride)	195.69	0.32	10.7	0.19	3.7
Methamphetamine hydrochloride (desoxyephedrine hydrochloride)	185.69	0.37	12.3	0.22	4.0
Metycaine hydrochloride	292.82	0.20	6.7	0.12	3.4
Mild silver protein	—	0.18	6.0	0.11	—
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Naphazoline hydrochloride (privine hydrochloride)	246.73	0.27	7.7	0.16	3.3
Neomycin sulfate	—	0.11	3.7	0.06	—
Neostigmine bromide (prosgimine bromide)	303.20	0.22	6.0	0.11	3.2
Nicotinamide	122.13	0.26	8.7	0.15	1.9
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9

(Continued)

TABLE 8-4
ISOTONIC VALUES (Continued)

Substance	MW	E	V	$\Delta T_f^{1\%}$	L_{iso}
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5
Penicillin G sodium	356.38	0.18	6.0	0.11	3.8
Phenacaine hydrochloride (holocaine hydrochloride)	352.85	0.20	5.3	0.11	3.3
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Phenylephrine hydrochloride (neosynephrine hydrochloride)	203.67	0.32	9.7	0.18	3.5
Physostigmine salicylate	413.46	0.16	5.3	0.09	3.9
Physostigmine sulfate	648.45	0.13	4.3	0.08	5.0
Pilocarpine nitrate	271.27	0.23	7.7	0.14	3.7
Potassium acid phosphate (KH ₂ PO ₄)	136.13	0.43	14.2	0.25	3.4
Potassium chloride	74.55	0.76	25.3	0.45	3.3
Potassium iodide	166.02	0.34	11.3	0.20	3.3
Procaine hydrochloride	272.77	0.21	7.0	0.12	3.4
Quinine hydrochloride	396.91	0.14	4.7	0.08	3.3
Quinine and urea hydrochloride	547.48	0.23	7.7	0.14	7.4
Scopolamine hydrobromide (hyoscine hydrobromide)	438.32	0.12	4.0	0.07	3.1
Silver nitrate	169.89	0.33	11.0	0.19	3.3
Sodium acid phosphate (NaH ₂ PO ₄ (optochin) · H ₂ O)	138.00	0.40	13.3	0.24	3.2
Sodium benzoate	144.11	0.40	13.3	0.24	3.4
Sodium bicarbonate	84.00	0.65	21.7	0.38	3.2
Sodium bisulfite	104.07	0.61	20.3	0.36	3.7
Sodium borate · 10H ₂ O	381.43	0.42	14.0	0.25	9.4
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Sodium iodide	149.92	0.39	13.0	0.23	3.4
Sodium nitrate	85.01	0.68	22.7	0.39	3.4
Sodium phosphate, anhydrous	141.98	0.53	17.7	0.31	4.4
Sodium phosphate · 2H ₂ O	178.05	0.42	14.0	0.25	4.4
Sodium phosphate · 7H ₂ O	268.08	0.29	9.7	0.17	4.6
Sodium phosphate · 12H ₂ O	358.21	0.22	7.3	0.13	4.6
Sodium propionate	96.07	0.61	20.3	0.36	3.4
Sodium sulfite, exsiccated	126.06	0.65	21.7	0.38	4.8
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Strong silver protein	—	0.08	2.7	0.05	—
Sucrose	342.30	0.08	2.7	0.05	1.6
Sulfacetamide sodium	254.25	0.23	7.7	0.14	3.4
Sulfadiazine sodium	272.27	0.24	8.0	0.14	3.8
Sulfamerazine sodium	286.29	0.23	7.7	0.14	3.9
Sulfanilamide	172.21	0.22	7.3	0.13	2.2
Sulfathiazole sodium	304.33	0.22	7.3	0.13	3.9
Tannic acid	—	0.03	1.0	0.02	—
Tetracaine hydrochloride (pontocaine hydrochloride)	300.82	0.18	6.0	0.11	3.2
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0
Tripeleminamine hydrochloride (pyribenzamine hydrochloride)	291.83	0.30	7.3	0.17	3.8
Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1
Zinc phenolsulfonate	555.84	0.18	6.0	0.11	5.9
Zinc sulfate · 7H ₂ O	287.56	0.15	5.0	0.09	2.5

The values were obtained from the data of E. R. Hammarlund and K. Pedersen-Bjergaard, *J. Am. Pharm. Assoc. Pract. Ed.* **19**, 39, 1958; *J. Am. Pharm. Assoc. Sci. Ed.* **47**, 107, 1958; and other sources. The values vary somewhat with concentration, and those in the table are for 1% to 3% solutions of the drugs in most instances. A complete table of E and ΔT_f values is found in the *Merck Index*, 11th Ed., Merck, Rahway, N. J., 1989, pp. MISC-79 to MISC-103. For the most recent results of Hammarlund, see *J. Pharm. Sci.* **70**, 1161, 1981; **78**, 519, 1989.

Key: MW is the molecular weight of the drug; E is the sodium chloride equivalent of the drug; V is the volume in mL of isotonic solution that can be prepared by adding water to 0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution); $\Delta T_f^{1\%}$ is the freezing point depression of a 1% solution of the drug; and L_{iso} is the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 9: SOLUBILITY AND DISTRIBUTION PHENOMENA

9-1 (a) $6.421 \times 10^{-3} M$; (b) $6.378 \times 10^{-3} m$; (c) $X_2 = 1.251 \times 10^{-4}$.

The eutectic point, obtained from the intersection of the two lines, corresponds to a mixture of 0.30 griseofulvin and 0.70 succinic acid on the mole fraction scale. The melting point of the eutectic mixture is $173^\circ C$.

9-2 660 g.

9-3 The aqueous layer weighs 170.2 g and contains 22.1 g of phenol; the phenol layer weighs 29.8 g and contains 17.9 g of phenol.

9-4 (a) 1.5×10^{-4} mole/liter; (b) 8.8×10^{-4} g/dL. The symbol dL stands for deciliter = 100 mL.

9-5 (a) 0.274 mole/liter; (b) $K_{sp} = 0.0335$; (c) 0.280 mole/liter.

9-6 4.3×10^{-5} mole/liter.

9-7 $pH_p = 9.03$.

9-8 $pH_p = 8.5$.

% Alcohol	10	20	30	40	50
pH_p	8.73	8.63	8.55	8.02	*

*At about 50% alcohol and above, phenobarbital in a 3 g/100 mL solution of the drug will not precipitate no matter how low the pH.

9-10 13.3 mL.

9-11 $pH = 5.7$.

9-12 $\Delta S_f = 16.0$ eu, $\log K_{calc} = 2.71$, $\log S = -2.73$, $S_{calc} = 1.86 \times 10^{-3} M$, $S_{obs} = 1.29 \times 10^{-3} M$.

9-13 0.083 g after first extraction; 0.046 g after second extraction.

9-14 $C = 1.0$ mg/mL.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 9: SOLUBILITY AND DISTRIBUTION PHENOMENA

- 9-1** The solubility of sulfamethoxypyridazine (SMP) in a 10% by volume mixture of dioxane and 90% by volume of water is 1.8 mg/mL at 25°C. Calculate (a) molarity, (b) molality, and (c) mole fraction of SMP. The density of the liquid, dioxane, is 1.0313 g/mL; of the solution is 1.0086 g/mL; of water is 0.9970 g/mL; and of the solvent mixture is 1.0082 g/mL. The molecular weight of SMP is 280.32 g/mole, that of dioxane is 88.10, and that of water is 18.015.
- 9-2** At the critical solution temperature of 65.85°C for the phenol–water system (page 45), the critical composition is 34% by weight of phenol. How many grams of water are dissolved in 1000 g of the solution at this temperature?
- 9-3** A 200-g mixture of phenol and water at 55°C has a total composition of 20% by weight of phenol. The two liquids have the respective compositions of 13% and 60% phenol. What is the weight in grams of the aqueous layer and of the phenol layer and how many grams of phenol are present in each layer?
- 9-4** What is the solubility of the electrolyte magnesium hydroxide (a) in moles/liter and (b) in g/100 mL if the solubility product is 1.4×10^{-11} ? The molecular weight of $\text{Mg}(\text{OH})_2$ is 58.34.
- 9-5** Brequinar sodium dissociates as brequinar⁻ and Na⁺. Its apparent solubility product is $K_{\text{sp}} = 0.0751$. (a) Compute the solubility of this compound.¹ (b) Compute the solubility product, K_{sp} , using the mean activity coefficient, γ_{\pm} . (c) Compute the solubility after addition of a 0.05 M solution of KCl.
- 9-6** What is the solubility of barium sulfate in a solution having an ionic strength, μ , of 0.25 and $K_{\text{sp}} = 1 \times 10^{-10}$ at 25°C? The activity coefficient for a bivalent salt at this ionic strength is 0.23.
- 9-7** The molar solubility of sulfathiazole in water is 0.002, the $\text{p}K_{\text{a}}$ is 7.12, and the molecular weight of sodium sulfathiazole is 304. What is the lowest pH allowable for complete solubility in a 5% solution of the salt?
- 9-8** What is the pH_p of a 2% w/v solution of sodium phenobarbital in a hydroalcoholic solution containing 15% by volume of alcohol? The solubility of phenobarbital in 15% alcohol is 0.22% w/v. The $\text{p}K_{\text{a}}$ of phenobarbital in this solution is 7.6. The molecular weight of sodium phenobarbital is 254.22 g/mole and that of phenobarbital is 232.23 g/mole.
- 9-9** Using data in Figures 9-4 and 9-5, calculate the minimum pH required for complete solubility of sodium phenobarbital in a solution containing 3 g of the drug in 100 mL of a mixed alcohol–water solvent. (a) Calculate pH_p , the minimum pH for the drug, in each aqueous solvent consisting of 10%, 20%, 30%, 40%, and 50% by volume of ethanol. (b) Plot pH_p versus percent by volume of alcohol in the solvent. The molecular weight of phenobarbital is 232.23 g/mole and that of sodium phenobarbital is 254.22.
- 9-10** A prescription calls for seven grains (1 g = 15.432 grains) of phenobarbital in 60 mL of solution. The vehicle consists of 20% by volume of glycerin, 5% by volume of alcohol, and the balance water. From Figure 9-4 it is observed that about 25% by volume of alcohol is required in the solution to dissolve this quantity of phenobarbital. How much USP alcohol (95% by volume) must be added?
- 9-11** If a container of pure water is shaken in the air, the water will dissolve atmospheric carbon dioxide until the dissolved gas is in equilibrium with that in the air. At atmospheric pressure the solubility of CO_2 is found to be 1×10^{-5} mole/liter. The dissociation constant, K_1 , of carbonic acid is approximately equal to 4×10^{-7} . Compute the pH of water saturated with CO_2 . *Hint:* $[\text{H}_3\text{O}^+] =$ in which c is the equilibrium concentration of the gas in water.
- 9-12** Calculate the molar solubility of butyl *p*-hydroxybenzoate (mp 68°C) in water at 25°C using equation (9-27). The $\log K$ for benzoic acid is 1.87; the contribution by an OH group is -1.16 and by a CH_2 group is 0.50, according to Leo et al.²
- 9-13** If 0.15 g of succinic acid in 100 mL of ether is shaken with a 10-mL portion of water, how much succinic acid is left in the ether layer? The distribution coefficient $K = (\text{concentration in ether})/(\text{concentration in water}) = 0.125$ at 25°C. How much succinic acid is

left in the ether when the phase is extracted with an additional 10 mL of water?

9-14 Propionic acid is added to the aqueous phase of a 20% oil–water emulsion, and 0.65 mg/mL of free acid remains in the aqueous phase after equilibrium has been attained between the two phases. In a 20% emulsion, $q = V_o/V_w = 20/80 = 0.25$. The aqueous phase is buffered at pH 3.5. Propionic acid is found to dimerize in the oil phase, and the distribution constant, $K'' = [HA_w]$, is equal to 15.0. The K_a

of propionic acid is 1.4×10^{-5} . Compute the initial concentration, C , of propionic acid to be introduced into the aqueous phase. The molecular weight of propionic acid is 74.08 g/mole.

References

1. S. Y. P. King, A. M. Basista, and G. Torosian, *J. Pharm. Sci.* **78**, 95, 1989.
2. C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.* **33**, 347, 1968; A. J. Leo, C. Hansch, and D. Elkin, *Chem. Rev.* **71**, 525, 1971; C. Hansch and A. J. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 10: COMPLEXATION AND PROTEIN BINDING

10-1 $\log K_1 = 3.9$, $\log K_2 = 2.97$, $\log \beta = 6.87$.

10-2 $K = 38.5$.

10-3 2:1 complex.

10-4 (a) The phase diagram should look similar to Figure 10-12; (b) $S_0 = 1.7 \times 10^{-6} M$ (the solubility in water reported by the authors is about $1 \times 10^{-6} M$); (c) $K = 479 M^{-1}$.

10-5 (a) $m = 3.39$ (number of hexanoic acid molecules per griseofulvin molecule in the complex); (b) $K_m = 1248 M^{-1}$, the stability constant of the complex of the formula, AD_3 . The number 3.39 is obtained by regression analysis and is therefore an average. It is assumed to be an integer value, $m = 3$, for the complex.

10-6 See Table 1 in Al-Obeidi and Borazan. (F. A. Al-Obeidi and H. N. Borazan, *J. Pharm. Sci.* **65**, 982, 1976.)

10-7 $K = 12.8$, $(\delta_c^A - \delta_m^A) = 0.50$.

10-8 (a) $K = 0.0552 \text{ liter}/\mu \text{ mole} = 55,200 \text{ liters/mole}$; $v = 2.75$; (b) $K = 0.0602 \text{ liter}/\mu \text{ mole} = 60,200 \text{ liters/mole}$; using $v = 2.75$ from part (a), $[P_t] = 22.2 \mu \text{ mole/liter}$.

10-9 $r = 0.14$; $\beta = 0.571$.

10-10 *Partial Answer:* for $[D_f] = 1.43 \times 10^{-3} \text{ mmole/liter}$ ($1.43 \times 10^{-6} \text{ mole/liter}$), $r = 0.41$; $r/[D_f] = 289 \text{ (liters/mmole)}$.

10-11 *Partial Answer:* In case I (see the table for this problem), the concentration, $[D_t]$ ($= A/\epsilon b$), of unbound acetaminophen in the absence of phenylbutazone, $[D_t'] = 0$, is $2.97 \times 10^{-4} \text{ mole/liter}$. The concentration, $[D_b]$, of bound acetaminophen is $1.00 \times 10^{-4} \text{ mole/liter}$. The r value is given by $[D_b]/[P_t] = 0.17$, and the percent bound is $([D_b]/[D_t]) \times 100 = 25\%$.

In case II (in the presence of phenylbutazone $[D_t] = 0.65 \times 10^{-4} \text{ mole/liter}$), the concentration of unbound acetaminophen is $[D_f] = A/(\epsilon b) = 0.782/(2.03 \times 10^3)(1) = 3.4 \times 10^{-4} \text{ mole/liter}$. $[D_b]$ is $(3.97 \times 10^{-4}) - (3.4 \times 10^{-4}) = 0.57 \times 10^{-4} \text{ mole/liter}$ and $r = (0.57 \times 10^{-4})/(5.8 \times 10^{-4}) = 0.10$.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 10: COMPLEXATION AND PROTEIN BINDING

10-1 Albert¹ studied the chelation of cadmium ion by asparagine. Potentiometric titration of 0.01 *M* asparagine, $pK_a = 8.85$, and 0.005 *M* cadmium sulfate was conducted in 50-mL samples by adding successive quantities of 0.1 *N* KOH. Plot the data of \bar{n} versus $p[A]$ and compute $\log K_1$, $\log K_2$, and $\log \beta$. The data table is below (\bar{n} , $p[A]$, and β are defined on pages 208–209).

Data for Problem 10-1

mL of 0.1 <i>N</i> NaOH	pH	\bar{n}	$p[A]$
0	4.81	—	—
0.25	6.12	0.10	4.75
0.50	6.50	0.20	4.40
1.0	6.85	0.40	4.10
1.5	7.20	0.57	3.80
2.0	7.45	0.74	3.62
2.5	7.70	0.93	3.45
3.0	7.95	1.11	3.30
3.5	8.21	1.26	3.16
4.0	8.50	1.42	3.05
4.5	8.93	1.56	2.92

10-2 The following results were obtained by Higuchi and Zuck² for the complex formed between caffeine and benzoic acid. In the analytic procedure, benzoic acid was distributed between water and a hydrocarbon solvent, Skellysolve-C.

Molar concentration of free benzoic acid in aqueous solution of caffeine obtained by partition study	11.94×10^{-3} mole/liter
Experimentally determined molar concentration of total undissociated benzoic acid in the aqueous phase, corrected for partial dissociation (free + complexed benzoic acid)	20.4×10^{-3} mole/liter
Original concentration of caffeine added (free + complexed caffeine)	2.69×10^{-2} mole/liter

Assuming that the stoichiometric ratio of the two species in the complex is 1:1, compute the association constant, K .

10-3 Using the solubility method, Higuchi and Lach³ studied the complexation between a polyethylene glycol and phenobarbital. The findings obtained at 30°C are as follows:

Polyethylene glycol content of the complex formed in the plateau region of the solubility diagram	30×10^{-3} mole/liter
Total phenobarbital added	21.5×10^{-3} mole/liter
Phenobarbital dissolved at point B in the solubility diagram, Figure 10-12	6.5×10^{-3} mole/liter

Compute the stoichiometric ratio [PGE]/[phenobarbital].

10-4 The formation of an inclusion complex of 1,8-dihydroxy-anthraquinone with γ -cyclodextrin in aqueous solution was studied using the solubility technique⁴ (see page 211). The concentrations of anthraquinone derivative found after addition of several increments of γ -cyclodextrin to 10 mL of buffer containing an excess of the anthraquinone (1×10^{-3} *M*) are

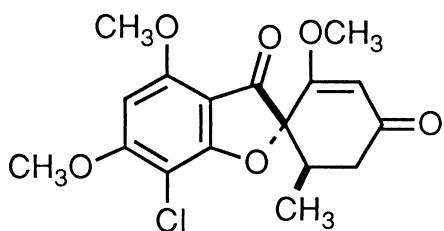
Data for Problem 10-4

Cyclodextrin Added ($\times 10^3$ <i>M</i>)	Anthraquinone Found ($\times 10^6$ <i>M</i>)
2.37	2.56
7.89	8.72
11.58	12.56
15.79	15.60
18.95	15.81
22.63	16.41
30.0	16.41
38.0	13.84

- Obtain the phase diagram by plotting the concentration of the anthraquinone found (vertical axis) against the concentration of γ -cyclodextrin added (see Fig. 10-12 for a similar diagram).
- Compute the solubility of 1,8-dihydroxyanthraquinone.

- (c) Compute the apparent stability constant, K , of the complex from the slope of the initial linear portion of the plot obtained in part (a). (Use the first five points.) K is obtained from the expression J. A. Plaizier-Vercammen and R. E. De Nève, *J. Pharm. Sci.* **71**, 552, 1982. $K = \text{slope}/[\text{intercept}(1 - \text{slope})]$.

10-5 Griseofulvin contains two keto groups, four ether oxygen atoms, and an aromatic ring, all capable of accepting protons to form hydrogen bonds. Griseofulvin has no proton-donating groups, so it acts only as a proton acceptor, A . The molar solubility of griseofulvin in isooctane, $[A_o] = 0.9358 \times 10^{-5}$ mole/liter, increases rapidly with increasing molar concentrations of hexanoic acid, $[D_1]$, an acidic donor, owing to the formation of a donor-acceptor complex, AD_m :



Griseofulvin

where m is the stoichiometric number of D molecules interacting with one A molecule. Mehdizadeh and Grant⁵ determined the experimental solubilities of griseofulvin in isooctane with increasing concentrations of hexanoic acid, $[D_1]$; the data are shown in the following table:

Data for Problem 10-5*

$[D_1]$, Molar Concentration of Hexanoic Acid (Donor)	$[A_1]$ ($M \times 10^5$), Concentration of Griseofulvin (Acceptor)
0.1632	2.317
0.465	4.178
0.784	7.762
1.560	20.902
3.118	77.581
4.693	207.16
6.316	435.18
7.855	858.98

*The concentrations given here are selected from among the 15 concentrations each of hexanoic acid and griseofulvin given in the original article.

The authors show that if only one complex species, AD_m , is considered, say $m = 2$, the increase in solubility, $[A_1] - [A_o]$, of the acceptor (griseofulvin) in

isooctane is proportional to the $m/2$ power of the total concentration of the donor (hexanoic acid), $[D_1]^{m/2}$, according to the following expression:

$$[A_1] - [A_o] = [AD_m] = K[D_1]^{m/2} \quad (2)$$

where K includes K_m , the stability constant of the complex, K_d , the dimerization constant of hexanoic acid raised to the power $(-m/2)$, and an additional term, $2^{-m/2}$:

$$K = K_m K_d^{-m/2} 2^{-m/2} \quad (3)$$

- (a) Take the log of both sides of equation $[A_1] - [A_o] = [AD_m] = K[D_1]^{m/2}$ and regress $\log([A_1] - [A_o])$, the dependent variable, against $\log [D_1]$, the independent variable. Compute the stoichiometric number, m , of the complex from the slope.
- (b) Obtain the stability constant of the complex, K_m , using the intercept you got in part (a) and the second equation above. The dimerization constant of hexanoic acid from a separate experiment is $K_d = 6000 M^{-1}$.

10-6 Al-Obeidi and Borazan⁶ investigated the charge transfer complex formation between epinephrine and the nucleic acid bases adenine, thymine, and uracil by ultraviolet absorption spectrometry. Epinephrine is an electron donor, and the nucleic acid bases are assumed to act as electron acceptors.

Obtain the molar absorptivity, ϵ , and the equilibrium constant, K (1/molarity), of the Benesi-Hildebrand equation [equation (10-28)] by plotting A_o/A versus $1/D_o$. Here A_o and D_o are the total concentrations of adenine and epinephrine, respectively; A is the absorbance of the complex at a definite wavelength. It is assumed that epinephrine forms 1:1 charge transfer complexes with these nucleic acid bases in acidified aqueous solution.

The accompanying table shows the values for A_o/A and $1/D_o$ for the adenine-epinephrine complex at four temperatures, as back-calculated from the K and ϵ values of Al-Obeidi and Borazan.⁶

Data for Problem 10-6

$1/D_o$ (liter/mole)	1.0	2.0	3.0
A_o/A at, 2°C	0.022	0.034	0.047
A_o/A 18°C	0.029	0.047	0.066
A_o/A , at 25°C	0.031	0.053	0.075
A_o/A at, 37°C	0.037	0.065	0.093

10-7 Hanna and Askbaugh⁷ derived an expression for computing the apparent equilibrium constant of 1:1 π -molecular complexes from nuclear magnetic resonance data:

$$\frac{1}{\Delta_{\text{obs}}^A} = \frac{1}{K(\delta_c^A - \delta_m^A)} \frac{1}{C_D} + \frac{1}{\delta_c^A - \delta_m^A} \quad (4)$$

where C_D is the concentration of the donor on the molality scale, δ_c^A is the chemical shift (see Chapter 4, page 99.) of the acceptor in the pure complex form, and δ_m^A is the chemical shift of the acceptor in the uncomplexed form. Therefore, $\delta_c^A - \delta_m^A$ is the shift due to complexation. Δ_{obs}^A is the difference between the observed chemical shift and δ_m^A .

The equation requires that the concentration of the donor be much larger than that of the acceptor and is analogous to the Benesi–Hildebrand equation except that the shift of acceptor protons on the pure complex replaces the molar absorptivity of the complex, and the concentration of acceptor does not appear.

Nishijo et al.⁸ studied the complexation of theophylline with an aromatic amino acid, L-tryptophan, in aqueous solution using proton nuclear magnetic resonance. L-Tryptophan is a constituent of serum albumin and was suggested to be the binding site on serum albumin for certain drugs. The authors added L-tryptophan to a fixed concentration of theophylline at 25°C.

Data for Problem 10–7

(Tryp), $1/C_D$ (M^{-1})	25	50	75	100
$1/\Delta_{\text{obs}}^A$	5.9	9.8	13.7	17.6

Compute the apparent equilibrium constant, K , and the complexation shift, $(\delta_c^A - \delta_m^A)$, using equation above. $\frac{1}{\Delta_{\text{obs}}^A} = \frac{1}{K(\delta_c^A - \delta_m^A)} \frac{1}{C_D} + \frac{1}{\delta_c^A - \delta_m^A}$

- 10–8** The binding of warfarin to human serum albumin was studied at pH 6, ionic strength 0.170. The following values were found by O'Reilly.⁹

Data for Problem 10–8

[PD] μ mole/L	[D _f] μ mole/L	$r/[D_f]$ L/ μ mole	r
9.1	3.0	0.13	0.40
17.8	6.4	0.11	0.72
30.2	17.2	0.08	1.35
46.1	50.8	0.04	2.00

- (a) Obtain the Scatchard plot, equation (10–40), using these data and compute K and ν using linear regression; ν is the number of independent binding sites. Express K in liters/mole.
- (b) Assume that the concentration of protein is unknown, and compute K from $[PD]$ and $[D_f]$ [equation (10–41)]. Compare the constant K obtained in parts (a) and (b). Compute $[P_t]$, the total concentration of protein, using the number of binding sites obtained in part (a). See equation (10–41).

- 10–9** In a study by Meyer and Guttman¹⁰ of the binding of caffeine to bovine serum albumin by the equilibrium dialysis method, $2.8 \times 10^{-4} M$ of albumin was allowed to equilibrate with $1 \times 10^{-4} M$ of caffeine. After equilibrium was established, $0.7 \times 10^{-4} M$ of caffeine was contained in the dialysis bag, and $0.3 \times 10^{-4} M$ of caffeine was found in the external solution. Calculate r , the ratio of bound to total protein. What is the fraction bound, β , of caffeine?

- 10–10** Chan and his associates¹¹ investigated the in vitro protein binding of diclofenac sodium, a nonsteroidal anti-inflammatory drug, by equilibrium dialysis and plotted the results according to the Scatchard equation (10–44) used to describe two classes of sites:

$$r = \frac{\nu_1 K_1 [D_f]}{1 + K_1 [D_f]} + \frac{\nu_2 K_2 [D_f]}{1 + K_2 [D_f]} \quad (5)$$

These workers used a statistical method known as *nonlinear regression* on the following data to calculate the parameters ν_1 , ν_2 , K_1 , and K_2 . The numbers of binding sites, ν_1 and ν_2 , found for the two classes of sites are 2.26 and 10.20, respectively. The corresponding association constants are $K_1 = 1.32 \times 10^5 M^{-1}$ and $K_2 = 3.71 \times 10^3 M^{-1}$.

Using the equation just given, calculate the values of r (dimensionless) for the following free drug concentrations: $[D_f]$ in millimole/liter ($\times 10^3$) = 1.43, 4.7, 16, 63, 132.4, 303.4, and 533.2.

Plot $r/[D_f]$ (liter/millimole) versus r to obtain what is called a *Scatchard plot*. Compare your results with those of Chan et al. To obtain an answer to this problem, you may compare your calculated $r/[D_f]$ values with the $r/[D_f]$ abscissa values read from the graph of Chan et al.

Hint: Use the same units on K_1 , K_2 , and $[D_f]$ to calculate r .

- 10–11** The effect of phenylbutazone in displacing acetaminophen from its binding sites on human serum albumin (HSA) was studied by the ultrafiltration method at 37°C and pH 7.4, with a constant concentration of acetaminophen of $[D_t] = 3.97 \times 10^{-4}$ mole/liter and with increasing concentrations of phenylbutazone, $[D'_t]$. After ultrafiltration the absorbance, A , of the free fraction of acetaminophen corresponding to several concentrations of phenylbutazone is

Data for Problem 10–11

Case	I	II	III	IV
$[D'_t] \times 10^4$ mole/liter	0	0.65	3.89	6.48
A	0.683	0.782	0.809	0.814

The table also shows the absorbance of acetaminophen in the absence of phenylbutazone, $[D'_1] = 0$. The molar absorptivity, ϵ , of acetaminophen at 420-nm wavelength in a cell of path length $b = 1$ cm is 2.3×10^3 liter mole $^{-1}$ cm $^{-1}$. The HSA concentration, $[P_1]$, is 5.8×10^{-4} mole/liter.

Calculate the percent decrease in the Scatchard r values for acetaminophen and the percent bound at different concentrations of phenylbutazone, $[D'_1]$, shown in the table.

References

1. A. Albert, *Biochem. J.* **47**, 531, 1950.
2. T. Higuchi and A. A. Zuck, *J. Am. Pharm. Assoc. Sci. Ed.* **41**, 10, 1952.
3. T. Higuchi and J. L. Lach, *J. Am. Pharm. Assoc. Sci. Ed.* **43**, 465, 1954.
4. G. Smulevich, A. Feis, G. Mazzi, and F. F. Vincieri, *J. Pharm. Sci.* **77**, 523, 1988.
5. M. Mehdizadeh and D. J. W. Grant, *J. Pharm. Sci.* **73**, 1195, 1984.
6. F. A. Al-Obeidi and H. N. Borazan, *J. Pharm. Sci.* **65**, 982, 1976.
7. M. W. Hanna and A. L. Askbaugh, *J. Phys. Chem.* **68**, 811, 1964.
8. J. Nishijo, E. Iwamoto, I. Yonetani, S. Tokura, and M. Sugiura, *Chem. Pharm. Bull.* **36**, 2735, 1988.
9. R. A. O'Reilly, *J. Clin. Invest.* **48**, 193, 1969.
10. M. C. Meyer and D. E. Guttman, *J. Pharm. Sci.* **57**, 895, 1968.
11. K. K. H. Chan, K. H. Vyas, and K. D. Brandt, *J. Pharm. Sci.* **76**, 105, 1987.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 11: DIFFUSION

11-1 $Q/t = 6.71 \mu\text{g cm}^{-2} \text{ day}^{-1}$.

11-2 *Partial Answer:* (a) The equation of the linear regression line is $\log R = -7.569 + 1.646 \log r$. The slope, 1.646, and intercept, -7.569 , compare well with the values 1.667 and -7.4739 , respectively, predicted by the convective diffusion (CD) equation (1).

(b) For $r = 1.25$ cm substituted into equation (1) for the linear regression line,

$$\log R = -7.569 + 1.646 \log(1.25) = -7.4095$$

$R = 3.90 \times 10^{-8}$ mole/min. From the CD equation, $R = 4.87 \times 10^{-8}$ mole/min. The regression equation (2) has an error of about 0.5% and the CD equation, (1), an error of about 26% in relation to the experimental value of $R = 3.881 \times 10^{-8}$ mole/min.

(c) Under aqueous diffusion layer control, page 234, equation (11-33),

$$j = \frac{dM}{dt} \frac{1}{S} = \left(\frac{D_a}{2h_a} \right) C_s; R = \frac{dM}{dt} = \left(\frac{SD_a}{2h_a} \right) C_s = \left(\frac{\pi r^2 D_a}{2h_a} \right) C_s \quad (1)$$

$h_a = 0.0214$ cm. The actual dimethicone membrane thickness is about 0.025 cm.

11-3 $3.182 \text{ g}/(10^3 \text{ cm}^2) \text{ per day}^{1/2}$.

11-4 $3.194 \text{ g}/(10^3 \text{ cm}^2) \text{ per day}^{1/2}$. A value of about $3.1 \text{ g}/(10^3 \text{ cm}^2) \text{ per day}^{1/2}$ is obtained experimentally. Y. W. Chien et al., *J. Pharm. Sci.* **63**, 365, 1974.

11-5 $J = 9.55 \times 10^{-4} \text{ mmole}/(\text{cm}^2 \text{ hr})$.

11-6 *Partial Answer:* (b) $k_o = D_m C_p / h_m = 0.530 \text{ mg cm}^{-2} \text{ hr}^{-1}$; $t_{\text{lag}} = 0.0539 \text{ hr}$ or 3.23 min; (c) $D_m = 2.31 \times 10^{-7} \text{ cm}^2 \text{ sec}^{-1}$ using $h_m = 0.0164 \text{ cm}$; (d) $C_p = 10.46 \text{ mg cm}^{-3}$.

11-7 $P_{\text{calc}} = 2.08 \times 10^{-4} \text{ cm/sec}$.

11-8 *Partial Answer:* percent dissociation at pH 4 is 0.32%; at pH 8, it is 96.93%.

11-9 *Partial Answer:*

(b) at pH 4.67, $P(\text{theoretical}) = 4.885 \times 10^{-6} \text{ cm/sec}$, and at pH 6.67, $P(\text{theoretical}) = 7.285 \times 10^{-6} \text{ cm/sec}$.

(c) The Henderson–Hasselbalch equation is used to arrive at the relationship $\text{pH} = \text{p}K_a$ at the half neutralization point, and the Henderson–Hasselbalch equation is also used in this chapter (page 237) to obtain an equation for the percent ionization of a weak acid at various pH values. These remarks should assist you in arriving at your answer.

11-10 *Partial Answer:* (b) $y = 0.111x^{1.005}$; (c) $y = 0.0724x + 0.2355$.

11-11 15,945 cal/mole, or 16 kcal/mole. The answer varies depending on the number of significant figures retained.

11-12 *Partial Answer:* 36.63 mg released in 15 days.

11-13 $D = 12.4 \times 10^{-5} \text{ cm}^2/\text{sec}$.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 11: DIFFUSION

11-1 The diffusion coefficient of tetracycline in a hydrox-ethyl methacrylate–methyl methacrylate copolymer film in a mole ratio of 2:98 is $D = 8.0 (\pm 4.7)^* \times 10^{-9}$ cm²/sec and the partition coefficient, K , for tetracycline between the membrane and the reservoir is $6.8 (\pm 5.9) \times 10^{-3}$. The membrane thickness, h , of the trilaminar device is 1.40×10^{-2} cm, and the concentration of tetracycline in the core, C_o , is 0.02 g/cm³ of the core material. Using equation (11-103), calculate the release rate, Q/t , in units of $\mu\text{g cm}^{-2}$ of tetracycline per day.

11-2 Nelson and Shah¹ applied their convective diffusion model (see *Example 13-3*, Chapter 13, page 305) to the permeation rate (rate of diffusion), R , of butamben through a dimethicone membrane under conditions of aqueous diffusion layer control. For a circular membrane, the permeation rate is given by the convective diffusion (CD) equation:

$$R = 2.157 D_a^{2/3} C_s \alpha^{1/3} r^{5/3} \quad (1)$$

where D_a is the diffusivity (diffusion coefficient) of the solute in the aqueous layer, C_s is the solubility, α is the rate of shear over the membrane, and r is the radius of the circular membrane. The rate of permeation, R , written as dM/dt elsewhere in this chapter was considered the dependent variable, using the radius of the membrane as the independent variable. The equation obtained by least-squares regression predicts a straight line in a plot of $\log R$ versus $\log r$, holding the other parameters constant.

(a) Prepare the graph of $\log R$ versus $\log r$, compute the slope and intercept, and determine how well they compare with comparable quantities predicted by equation (1) as above. The values of the known parameters are $D_a = 6 \times 10^{-6}$ cm² sec⁻¹ = 3.60×10^{-4} cm² min⁻¹; $C_s = 9.4 \times 10^{-4}$ mole/liter = 9.4×10^{-7} mole cm⁻³; and $\alpha = 35.006$ min⁻¹; the experimental R and r values for the plot are as follows:

Data for Problem 11-2

R (mole/min)	1.325×10^{-8}	2.712×10^{-8}	3.881×10^{-8}
r (cm)	0.65	1	1.25

*The quantities in parentheses are standard deviations. That is the diffusion coefficients ranges from $8.0 (-4.7) \times 10^{-9}$ to $8.0 (+4.7) \times 10^{-9}$, based on a variability of ± 1 standard deviation (4.7) from the mean D value 8.

(b) Choose one of the three values of r from the table and the known parameters given here; substitute these into the least-squares regression equation and into the CD equation [equation (1)]. Compare your results from these two methods for calculating R . What is the percentage error in these two methods relative to the experimental value of R ?

(c) This system is under aqueous diffusion layer control. Compute the thickness, h_a , of the static aqueous layer using $r = 1.25$ cm and $R = 3.881 \times 10^{-8}$ mole min⁻¹ = 6.47×10^{-10} mole sec⁻¹.

Note: In preparation for graphing, be sure to first convert R and r to logarithms. Recall that when converted to logarithmic form in equation (1), quantities multiplied together are added. Therefore, equation (1), written as $\log R$ versus r , becomes $\log(2.157) + 2/3 \log D_a + \log C_s + 1/3 \log \alpha + 5/3 \log r$, and for D_a , C_s , and α held constant, we have

$$\log R = \log (2.157 D_a^{2/3} C_s \alpha^{1/3}) + 5/3 \log r \quad (2)$$

with the first log term on the right side as the intercept and $5/3 = 1.667$ in the second log term as the slope.

11-3 The release of ethynodiol diacetate through a silicone dosage form may be calculated using the Higuchi equation,

$$Q/t^{1/2} = [D(2A - C_s)C_s]^{1/2} \quad (3)$$

because diffusion is found in this case to be the rate-limiting factor for drug release. A , the amount of drug per unit volume of the silicone matrix, is 100 g/(10³ cm³); the solubility, C_s , of the drug in the silicone polymer is 1.50 g/(10³ cm³); and D , the diffusivity of the drug in the silicone matrix, is 3.4×10^{-2} cm²/day. Calculate the rate of drug release from the silicone dosage form in units of g/(10³ cm²) per day^{1/2}.

11-4 When C_s is small relative to A , as found in *Problem 11-3*, the Higuchi equation reduces to $Q/t^{1/2} = \sqrt{2DAC_s}$. Recalculate the results of *Problem 11-3* using this abbreviated equation.

11-5 A cell contains a silastic membrane with diffusion layers of identical thickness on either side and butyl-aminobenzoate at a concentration $C = 1.72$ mmole/liter or 1.72×10^{-3} mmole/cm³ in the donor compartment. Calculate the steady-state flux, J , through the membrane in millimoles per cm² per hour.

The equation that represents the process in which both membrane and diffusion-layer control obtain is

$$J = \left[\frac{D_m K D_a}{h_m D_a + 2h_a K D_m} \right] C \quad (4)$$

The data obtained from an experiment at 37°C are as follows: $D_m = 2.7 \times 10^{-6} \text{ cm}^2/\text{sec} = 0.00972 \text{ cm}^2/\text{hr}$, $D_a = 6.0 \times 10^{-6} \text{ cm}^2/\text{sec} = 0.02160 \text{ cm}^2/\text{hr}$, $h_m = 0.006 \text{ cm}$, $h_a = 0.0188 \text{ cm}$, and $K = 10.3$.

- 11-6** Borodkin and Tucker² studied the diffusion of salicylic acid from a polymer film containing dispersed drug. The kinetics was made linear with time, that is, zero order, by laminating a second film, consisting of a hydroxypropylcellulose-polyvinyl acetate membrane of thickness $h_m = 0.0164 \text{ cm}$, to the releasing side of the film with the drug as a reservoir layer.

The drug layer controlled the duration of release, whereas the nondrug layer consisting of the cellulose membrane served as a rate-controlling membrane. Diffusion through the film is the limiting factor in a drug release, so that equation (11-72) applies. Q , the amount of drug released per unit surface area, is given for various times:

Data for Problem 11-6

$Q(\text{mg}/\text{cm}^2)$	0.46	1.00	1.54	2.19	2.69	3.23	3.54
Time (hr)	1	2	3	4	5	6	7

Equation (11-72) can also be written as

$$\frac{dQ}{dt} = \frac{D_m C_p}{h_m} \quad (5)$$

which represents the instantaneous rate of release of drug at time t . Integration of this equation and evaluation of the integration constants yields a term for the lag time, t_{lag} :

$$Q = \frac{D_m C_p}{h_m} t - \frac{D_m C_p}{h_m} t_{\text{lag}} \quad (6)$$

Equation (6) shows that a plot of Q against t yields a straight line of slope $D_m C_p / h_m = k_o$, the apparent zero-order rate constant. The intercept of equation (6) is $(D_m C_p / h_m) t_{\text{lag}} = k_o t_{\text{lag}}$, from which t_{lag} can be computed.

- (a) Plot Q versus time, t , from the data given in the table.
 (b) Regress Q against t and obtain $k_o = D_m C_p / h_m$ (mg cm^{-2}) from the slope and t_{lag} from the intercept.
 (c) Knowing the lag time and the thickness h_m of the nondrug layer, compute the diffusion coefficient, D_m . You will need the lag time equation.
 (d) From the slope obtained in part (b) and the diffusion coefficient, D_m , calculated in part (c), compute the value of C_p , the concentration of the drug, salicylic acid, in the reservoir layer of the base film.

- 11-7** Farnig and Nelson³ studied the effect of polyelectrolytes, such as carboxymethylcellulose (CMC), on the permeation rate of sodium salicylate across a cellulose membrane at 37°C. Fick's law can be written to cover this case, assuming the existence of three barriers in series: the membrane and an unstirred liquid diffusion layer on either side. The reciprocal of the permeation coefficient for the three layers is

$$1/P = h_1/D_1 + h_m/\phi D_m K + h_2/D_2 K \quad (7)$$

where $h_1 = h_2 = 82 \times 10^{-4} \text{ cm}$ for the two static diffusion layers; $h_m = 46.6 \times 10^{-4} \text{ cm}$ for the cellulose membrane thickness, $D_1 = 1.33 \times 10^{-5} \text{ cm}^2/\text{sec}$, $D_2 = 1.11 \times 10^{-5} \text{ cm}^2/\text{sec}$, and $D_m = 1.69 \times 10^{-6} \text{ cm}^2/\text{sec}$ for the three diffusion coefficients. The partition coefficient, K , for the salicylate between the solution in compartment 1 (left-hand reservoir) and water in the membrane is 1.16. The volume fraction, ϕ , of water in the membrane is 0.667. Calculate the permeability, P , for the salicylate and compare it with $P_{\text{obs}} = 1.86 \times 10^{-4} \text{ cm}/\text{sec}$.

- 11-8** Sulfadiazine, $\text{p}K_a = 6.50$ at 25°C, as with all weak acids shows a variable-percent dissociation as a function of pH.

- (a) Prepare a table showing the percent dissociated and percent undissociated sulfadiazine at pH 2, 4, 6.5, 7, 8, 10, and 12.
 (b) Plot the results on rectangular graph paper.
 (c) Predict the absorption of sulfadiazine from the gut and from the small intestine in terms of the pH-partition hypothesis and from the results obtained in parts (a) and (b).

- 11-9** (a) As a continuation of work on transcorneal permeation of pilocarpine (see *Example 11-7*), you are asked to plot the experimentally determined corneal membrane permeability, P , versus pH (Table 11-5) on ordinary rectangular graph paper.
 (b) Calculate $P(\text{theoretical})$ [see *Example 11-7*, equation (11-62)] using the values $P_B = 9.733 \times 10^{-6} \text{ cm}/\text{sec}$ and $P_{BH^+} = 4.836 \times 10^{-6} \text{ cm}/\text{sec}$. The nonionized fraction, f_B , of pilocarpine at each pH value is calculated from equation (11-96). Plot $P(\text{theoretical})$ versus pH on the graph prepared under (a). Note that the pH at the inflection point of the sigmoidal line is equal roughly to $\text{p}K_a = 6.67$ for the conjugate acid of pilocarpine at 34°C.
 (c) Does this sigmoidal curve suggest any relationship to the titration curve of a weak acid, Figure 8-1, where, at half-neutralization, $\text{pH} = \text{p}K_a$?

- 11-10** The steady-state penetration of progesterone and its hydroxyl derivatives across the intact skin was found to be related to the solubility of the drug in the stratum corneum. The solubility in the stratum corneum and

the rate of permeation decrease as the hydrophilicity of the progesterone derivatives increases.⁴ The data are found in the following table for the progesterone derivatives numbered 1 through 7:

Data for Problem 11-11

Drug no.	1	2	3	4	5	6	7
Solubility (mg/mL)	1.09	2.46	7.97	2.82	12.5	32.4	47.7
Permeability rate ($\mu\text{g}/(\text{cm}^2 \text{ hr})$)	0.15	0.31	0.97	0.29	0.57	4.73	2.37

- (a) Plot the permeability rates, dQ/dt , in $\mu\text{g}/(\text{cm}^2 \text{ hr})$, on the vertical axis against the solubility of the progesterone derivatives on the horizontal axis of three-cycle log-log paper. One may postulate a linear relationship between the steady-state rates of permeation of progesterone and its solubility in the stratum corneum. However, it is found that a linear relationship is obtained only when the data are plotted on a log-log graph, which suggests that the true relationship is a power curve. Let permeability rate, dQ/dt , be y and the solubility in the stratum corneum be x , and write the power curve relationship:

$$y = ax^b \quad (8)$$

where a and b are arbitrary constants.

- (b) Use a handheld calculator or a personal computer to obtain the values of a and b using the data given.
 (c) Now assume a relationship between y and x in the linear form

$$y = a'x + b' \quad (9)$$

and compute a' and b' . Does equation (8) or equation (9) better fit the data?

- (d) Why did a log-log fit of the data suggest using the power equation $y = ax^b$?
 (e) Would it be possible to extrapolate results such as these to the transdermal absorption of progesterone derivatives from various ointment bases into intact and damaged or diseased human skin? What factors would need to be taken into consideration?

- 11-11** The percutaneous absorption of chloramphenicol through mouse skin was investigated at various temperatures. Permeability coefficients were recorded together with temperatures as follows:

Data for Problem 11-12

Temperature, °C	25	31	37	45
P (cm/min) $\times 10^4$	1.12	1.87	3.01	6.20

Plot the Arrhenius curve and calculate the energy of activation for permeation. Compare your results with those of Aguiar and Weiner,⁵ who, in a similar study, found E_a to be 15,000 cal/mole.

- 11-12** Hydrocortisone was released from a silicone matrix implanted in the vaginal tract of a rabbit (see Table 11-6, page 247). Calculate the amount of hydrocortisone (mg) released from the vaginal implant in 2.5, 5, 10, 15, 20, 25, 30, and 40 days. Plot the amount released, m (mg), versus time in days. The following data are taken from the work of Ho et al.⁶ The solubility of the drug in the polymer matrix, C_s , was 0.014 mg/cm³; the diffusion coefficient in the matrix, D_e , was 4.5×10^{-7} cm²/sec; the partition coefficient for silicone/water, K_s , was 0.05; the permeability coefficient of the rabbit vaginal membrane, P_m , was 5.8×10^{-5} cm/sec; P_{aq} was 7×10^{-4} cm/sec; the loading concentration (initial amount of drug per unit volume of plastic cylinder), A , was 100 mg/cm³; the length, h , of the silicone cylinder was 6.0 cm; and its radius, a_0 , was 1.1 cm.

- 11-13** A new drug is placed in a Graham closed-boundary diffusion cell (see Fig. 11-27) to determine the drug's diffusion coefficient, D . The initial concentration of the drug, u_0 , is 0.0273 g/cm³ in water at 25°C. The total height of the cell is $H = 3.86$ cm and the height of the drug solution in the cell is $h = 1.93$ cm. A sample is taken at a depth of $x = H/6$ at time $t = 10,523$ sec (2.923 hr) and analyzed for the drug; its concentration, u , is found to be 0.0173 g/cm³. Rearrange equation (11-108) so as to calculate D , the drug's diffusion coefficient. (See Example 11-13.)

References

1. K. G. Nelson and A. C. Shah, *J. Pharm. Sci.* **66**, 137, 1977.
2. S. Borodkin and F. E. Tucker, *J. Pharm. Sci.* **64**, 1289, 1975.
3. K. F. Farnig and K. G. Nelson, *J. Pharm. Sci.* **66**, 1611, 1977.
4. G. B. Smith and E. F. Schoenewaldt, *J. Pharm. Sci.* **70**, 272, 1981.
5. A. J. Aguiar and M. A. Weiner, *J. Pharm. Sci.* **58**, 210, 1969.
6. N. F. H. Ho et al., *J. Pharm. Sci.* **65**, 1578, 1976.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 14: CHEMICAL KINETICS AND STABILITY

14-1 If first order, $k = 0.026 \text{ hr}^{-1}$, $t_{1/2} = 26.8 \text{ hr}$.

14-2 (a) $k_0 = (2.2 \times 10^{-7} \text{ g dL}^{-1} \text{ sec}^{-1})$; (b) $t_{90} = 13.2$ days at 35°C (zero-order breakdown); (c) $t_{90} = 6.1$ days at 35°C (first-order breakdown).

14-3 (a) $t_{1/2} = 142.5 \text{ min}$ or 2 hr 22 min; (b) $k = 7.87 \times 10^{-4} \text{ min}^{-1}$, $t_{1/2} = 880.56 \text{ min}$ or 14 hr 41 min; k decreases by 84%, and $t_{1/2}$ increases by 518%; (c) without (I), $1.2 \times 10^{-5} \text{ M}$; with addition of (I), $4.10 \times 10^{-5} \text{ M}$.

14-4 (a) $E_a = 20.8 \text{ kcal/mole}$; (b) k at 25°C is 1.99×10^{-5} absorbance unit per hour (using regression analysis); (c) predicted life = 513 days (ca. 1.4 years).

14-5 $k = 1.082 \text{ (liters/mole) min}^{-1}$; $t_{1/2} = 92.4 \text{ min}$.

14-6 (a)
$$B_{ss} = \frac{k_3}{k_4} [AH^+] \quad (1)$$

(b)
$$[AH^+]_{ss} = \frac{k_1[A][H_T^+]}{k_1[A] + (k_2 + k_3)} \quad (2)$$

(c)
$$\text{rate} = \frac{d[P]}{dt} = \left(\frac{k_1 k_3}{k_2 + k_3} \right) [A][H^+] \quad (3)$$

14-7 *Partial Answer:* (a) $k_1 = 0.0383 \text{ hr}^{-1}$; (b) at $t = 5 \text{ hr}$, $B = 0.046 \text{ mM}$ and $C = 0.004 \text{ mM}$; at $t = 10 \text{ hr}$, $B = 0.079 \text{ mM}$ and $C = 0.011 \text{ mM}$; (c) $t_{1/2}$ for $A = 18.1 \text{ hr}$; the concentrations of B and C at 18.1 hr are 0.110 and 0.03 mM , respectively.

14-8 $A = 3.8 \times 10^3 \text{ sec}^{-1}$.

14-9 $E_a = 20.3 \text{ kcal/mole}$, $A = 1.2 \times 10^9 \text{ sec}^{-1}$ (using regression analysis).

14-10 $E_a = 29.8 \text{ kcal/mole}$, $A = 3.71 \times 10^{14} \text{ hr}^{-1}$

14-11 (a) $\Delta S^\ddagger = -41.5 \text{ cal/mole}$, $k = 0.072 \text{ hr}^{-1}$; $\Delta G^\ddagger = 24.9 \text{ kcal/mole}$; (b) 0.26 mg/mL ; (c) 22.5 min .

14-12 $E_a = 61.6 \text{ kcal/mole}$.

14-13 *Partial Answer:* $\log k_{obs} = 0.111\delta_1 - 4.504$. A plot of $\log k_{obs}$ against δ_1 results in a straight line. Dioxane

is toxic and cannot be used in pharmaceutical preparations. See *Merck Index*, 11th Ed., 1989, p. 3297.

14-14 (a) $k_o = 0.019 \text{ hr}^{-1}$; (b) check your answer with equation (14-113) and *Example 6-14*. The rate constant, k_o , changes to 0.0156 hr^{-1} when $\sqrt{\mu}/(1 - \sqrt{\mu})$ replace $\sqrt{\mu}$ on the x axis and the slope A becomes 0.5295 , similar to the theoretical A value.

14-15 $k_H = 0.229 \text{ M}^{-1} \text{ hr}^{-1}$ or liter mole $^{-1} \text{ hr}^{-1}$; $k_o = 0.00135 \text{ hr}^{-1}$ by linear regression analysis; extrapolation by eye yields 0.0013 hr^{-1} .

14-16 From the figure in *Problem 14-16*, $\log k = -3.75$; $k = 1.78 \times 10^{-4} \text{ min}^{-1}$. From the calculation using the given equation, $k = 1.95 \times 10^{-4} \text{ min}^{-1}$ for compound 7 at pH 4.

14-17 *Partial Answer:* At pH = 2.0, $[H^+] = 0.01 \text{ M}$, $[OH^-] = 1.0 \times 10^{-12} \text{ M}$, $k_{obs} = 7.62 \times 10^{-11} \text{ sec}^{-1}$, $\log k_{obs} = -10.12$. At pH = 8.0, $[H^+] = 10^{-8} \text{ M}$, $[OH^-] = 10^{-6} \text{ M}$, $k_{obs} = 7.60 \times 10^{-11} \text{ sec}^{-1}$, $\log k_{obs} = -10.12$.

14-18 *Partial Answer:* (b) The regression equation is $\log k_{obs} = 0.8689 \text{ pH} - 11.150$. The value of k_{OH^-} is $7.08 \times 10^2 \text{ sec}^{-1}$.

14-19 *Partial Answer:* $k_{25^\circ\text{C}} = 0.0315 \text{ hr}^{-1}$ at pH 5, $k_{25^\circ\text{C}} = 0.0083$ at pH 8, $k_{40^\circ\text{C}} = 0.111$ at pH 5.

14-20 The H_2PO_4^- ion is acting as a catalyst.

14-21 *Partial Answer:* (a) At pH 6, $k_{obs} = 0.0547 \text{ hr}^{-1}$; at pH 6.5, $k_{obs} = 0.162 \text{ hr}^{-1}$.

See equations (14-138) and (14-139). To compute $[\text{H}_2\text{PO}_4^-]$ and $[\text{HPO}_4^{2-}]$ at each pH one uses the buffer equation

$$\text{pH} = \text{p}K_a + \log \left(\frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]} \right) \quad (4)$$

where $\text{p}K_a$ is the second dissociation constant of H_3PO_4 . At pH 6, one obtains $[\text{HPO}_4^{2-}]/[\text{H}_2\text{PO}_4^-] = 0.062/1$. Thus, for 1 mole of buffer mixture, one has $0.062/(1 + 0.062) = 0.058$ mole HPO_4^{2-} and $(1 - 0.058) = 0.942$ mole H_2PO_4^- . Calculate the $[\text{H}_2\text{PO}_4^-]$ and $[\text{HPO}_4^{2-}]$ values at pH 6.0, 6.5, 7.0, and 7.2 for 0.1 mole/liter of buffer. The total rate constant at pH, say, 6, where $[\text{OH}^-] = 10^{-8}$, is $k_{\text{pH}6} = (4.28 \times 10^6 \times 10^{-8}) + (0.036 \times 0.0942) + (1.470 \times$

0.0058) = 0.0547 hr⁻¹. Then, calculate the k_{obs} values at pH 6.5, 7.0, and 7.2.

(b) Finally, plot the log k_{obs} values versus pH.

14-22 (a) $k_{\text{M}} = 0.169 \text{ M}^{-1} \text{ sec}^{-1}$; (b) $k'_{\text{M}} = 9.03 \times 10^5 \text{ M}^{-2} \text{ sec}^{-1}$.

14-23 $k_{\text{o}} = 0.056 \text{ day}^{-1}$; $k_{\text{H}^+} = 18.0 \text{ M}^{-1} \text{ day}^{-1}$; and $k_{\text{OH}^-} = 3.3 \times 10^4 \text{ M}^{-1} \text{ day}^{-1}$.

14-24 $t_{95\%} = 10.4 \text{ min}$. Degradation has occurred to the extent of 5% in 10.4 min, so heating at 70°C for a full 15 min would not be advisable. Brooke et al. (D. Brooke, J. A. Scott, and R. J. Bequette, *Am. J. Hosp. Pharm.* **32**, 44, 1975.) found by actual assay that heating at 50°C or 60°C produced less than 5% decomposition.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 14: CHEMICAL KINETICS AND STABILITY

- 14-1** The time and amount of decomposition of 0.056 M glucose at 140°C in an aqueous solution containing 0.35 N HCl were found to be

Data for Problem 14-1

Time (hr)	Glucose, Remaining (mole/liter $\times 10^2$)
0.5	5.52
2	5.31
3	5.18
4	5.02
6	4.78
8	4.52
10	4.31
12	4.11

What are the order, the half-life, and the specific reaction rate of this decomposition? Can one unquestionably determine the order from the data given?

- 14-2** According to Connors et al.,¹ the first-order rate constant, k_1 , for the decomposition of ampicillin at pH 5.8 and 35°C is $k_1 = 2 \times 10^{-7} \text{ sec}^{-1}$. The solubility of ampicillin is 1.1 g/100 mL. If it is desired to prepare a suspension of the drug containing 2.5 g/100 mL, calculate (a) the zero-order rate constant, k_0 , and (b) the shelf-life, that is, the time in days required for the drug to decompose to 90% of its original concentration (at 35°C) in solution. (c) If the drug is formulated in solution rather than a suspension at this pH and temperature, what is its shelf-life? Note: 100 mL = 1 deciliter = 1 dL.

- 14-3** (a) Menadione (vitamin K₃) is degraded by exposure to light, a process called *photodegradation* or *photolysis*. The rate constant of decomposition is $k = 4.863 \times 10^{-3} \text{ min}^{-1}$. Compute the half-life. (b) The formation of a complex of menadione with the quaternary ammonium compound cetylmethylmorpholinium ethosulfate (I) in aqueous solution slows the rate of photodegradation by ultraviolet light. The rate of decomposition of $5.19 \times 10^{-5} \text{ M}$ of menadione containing 5% (w/v) of the complexing agent (I) is as follows (the data are based on the paper by Kowarski and Ghandi²):

Time (min)	10	20	30	40
Menadione remaining (mole/liter $\times 10^5$)	5.15	5.11	5.07	5.03

Compute the k value, $t_{1/2}$, and the percent decrease of k and increase of $t_{1/2}$ in the presence of the complexing agent.

- (c) What is the concentration after 5 hr with and without complexing agent? Use \ln rather than \log throughout the problem.

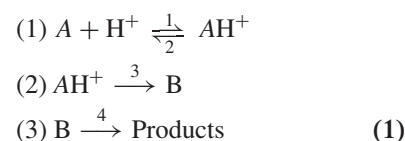
- 14-4** Garrett and Carper³ determined the zero-order rate constant for the degradation of the colorants in a multisulfate preparation. The results obtained at various temperatures are as follows:

°C	40	50	60	70
k	0.00011	0.00028	0.00082	0.00196

- (a) Plot these results according to the Arrhenius relationship and compute the activation energy, E_a . (b) Extrapolate the results to 25°C to obtain k at room temperature. You can also use regression analysis to answer (a) and (b). (c) The rate of decrease of absorbance of the colored preparation at a wavelength of 500 nm was found to be zero order and the initial absorbance, A_0 , was 0.470. This preparation should be rejected when the spectrophotometric absorbance, A , falls to a value of 0.225. Therefore, to predict the absorbance of the preparation at any time t hours after preparation, one uses the zero-order equation $A = A_0 - kt$. Calculate the predicted life of the preparation at 25°C.

- 14-5** In the saponification of methyl acetate at 25°C, the molar concentration of sodium hydroxide remaining after 75 min was 0.00552 M. The initial concentrations of ester and of base were each 0.01 M. Calculate the second-order rate constant and the half-life of the reaction.

- 14-6** Assume that under acidic conditions a compound undergoes reaction according to the following mechanism:

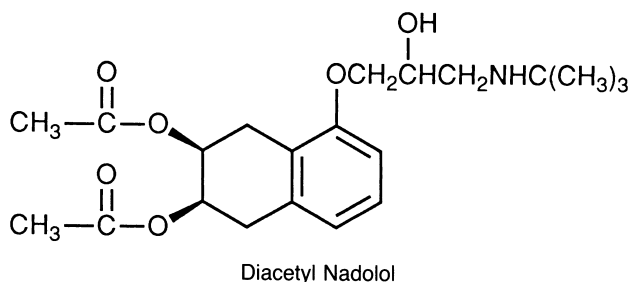


- (a) What is the expression giving the steady-state concentration of B ?
- (b) What is the expression giving the steady-state concentration of AH^+ if the total concentration of acid added to the reaction mixture, $[H_T^+]$, is related to the acid present during the reaction, both free, $[H^+]$, and bound, $[AH^+]$, by the equation

$$[H_T^+] = [H^+] + [AH^+] \quad (2)$$

- (c) Give the rate law expressing the rate of formation of products if, instead of measuring the total concentration of acid added to the reaction mixture, one uses a pH meter to measure the concentration of "free" acid, $[H^+]$. Use the results of parts (a) and (b). See under Rate Determining Step, page 329, for help in solving this problem.

- 14-7** Diacetyl nadolol, used in ophthalmic preparations for glaucoma therapy, hydrolyzes in a series of consecutive reactions represented as $A \xrightarrow{k_1} B \xrightarrow{k_2} C$, where B and C are the intermediate and final products, acetyl nadolol and nadolol, respectively.



The apparent rate constants, k_1 and k_2 , are first-order constants. The rate of decomposition $A \rightarrow B$ is given at pH 7.55 and 55°C by Chiang et al.⁴ as

Data for Problem 14-7

A (mM)	0.23	0.19	0.16	0.13	0.09	0.06
t (hr)	5	10	15	20	30	40

where mM stands for millimolar.

- (a) Compute k_1 using least squares.
- (b) The rate constant in the second step, k_2 , was found by nonlinear regression analysis to be 0.0243 hr^{-1} . On the same graph plot the concentration of A remaining and the concentrations of B and C appearing as A hydrolyzes, versus the time in hours as given in the table. Prepare a table of concentrations of A , B , and C at various times, t , using the appropriate equations in the section on the complex reactions in this chapter, pages 324–328.
- (c) Compute $t_{1/2}$ for A . What are the concentrations of B and C at this time?

- 14-8** The hydrolysis of atropine base was found by Zvirblis et al.⁵ to be first order with respect to the base. The degradation constant, k , at 40°C was 0.016 sec^{-1} . If the energy of activation, E_a , is 7.7 kcal/mole, what is the Arrhenius factor, A ? What does the value of E_a suggest about the stability of atropine base at 40°C?

- 14-9** The following data for the first-order decomposition of penicillin are obtained from Swintosky et al.⁶:

Data for Problem 14-9

First-order rate constant, k , hr^{-1}	0.0216	0.0403	0.119
Temperature (°C)	37	43	54

Plot the results and compute the activation energy. What is the Arrhenius factor, A ?

- 14-10** The first-order degradation of glucose in acid solution results in the formation of 5-hydroxymethylfurfural (5-HMF), and 5-HMF yields additional breakdown products that give the straw color to glucose solutions stored for long periods of time at high temperatures. These conditions exist, for example, in military warehouses and medical units.

The values of the rate constant for the breakdown of glucose in 0.35 N HCl solution at 110°C to 150°C are given in the following table:

Data for Problem 14-10*

°C	°K	$1/T$ (°K ⁻¹)	k (hr ⁻¹)	$\ln k$
110	383	0.00261	0.0040	-5.521
130	403	0.00248	0.0267	-3.623
150	423	0.00236	0.1693	-1.776

*Data are from K. R. Heimlich and A. Martin, *J. Am. Pharm. Assoc., Sci. Ed.* **49**, 592, 1960.

Calculate the activation energy and the Arrhenius factor, A , for glucose in acid solution tested experimentally for accelerated breakdown over the temperature range of 110°C to 150°C.

- 14-11** Methenamine is used to treat urinary tract infections, its antibacterial activity being derived from formaldehyde, which is produced on hydrolysis in acidic media. About 0.75 mg/mL is the physiologic concentration of methenamine following a normal dose in humans. Methenamine circulates in the blood (pH 7.4) as the intact drug without degradation but is rapidly converted to formaldehyde when it reaches the acidic urine.

The Arrhenius activation energy, $E_a = \Delta E^\ddagger$ at pH 5.1, obtained in vitro at several temperatures is 12 kcal/mole and the Arrhenius factor, A , at 37.5°C is 2×10^7 hr^{-1} (Strom and Jun⁷).

- (a) Compute the entropy of activation, ΔS^\ddagger , and the first-order rate of the reaction, k . Compute the free energy of activation, ΔG^\ddagger , from equation (14-91). Assume that $E_a = \Delta H^\ddagger = \Delta E^\ddagger$.
- (b) The drug remains in the bladder for about 6 hr and the effective concentration of formaldehyde is about $20 \mu\text{g/mL}$. Compute the concentration of formaldehyde in the bladder after 6 hr assuming that the concentration of methenamine in the urine is that of the drug in plasma (0.75 mg/mL).
- (c) When does formaldehyde reach the effective concentration, $20 \mu\text{g/mL}$, in urine?
- (d) Note that ΔH^\ddagger is a large positive value, ΔS^\ddagger is a relatively large negative value, ΔG^\ddagger is therefore positive, and the Arrhenius factor is small relative to A values normally found. Rationalize these factors in terms of the conversion of methenamine in the body to formaldehyde. See *Example 14-11* and the paragraph following it to assist you in your reasoning.

14-12* In a differential scanning calorimetric experiment on the thermal degradation of cefamandole naftate, Zheng and Zhang⁸ obtained the following data:

Data for Problem 14-12

Heating rate, β ($^\circ\text{C}/\text{min}$)	5	2	1	0.5
Degradation peak temp., T_m ($^\circ\text{K}$)	472	466	460	475

Let $x' = 1/T_m$ and $y' = \ln \beta/T_m^2$. One then casts the data into the following transposed form:

Data for Problem 14-12

$x = x' \times 10^3$	2.119	2.146	2.174	2.188
$y = y' + 13$	2.2955	1.4048	0.7375	0.0575

Now one carries out regression analysis of y against x where the slope is $-E_a/R$, and solve for E_a . The degradation peak temperature, T_m , of a drug molecule depends on the rate of heating, β , in a differential scanning calorimeter; thus the slope is

$$-\frac{E_a}{R} = \frac{dy}{dx} = \frac{d \ln(\beta/T_m^2)}{d(1/T_m)} \quad (3)$$

In this way one can obtain E_a values and rapidly scan a series of drug analogues for their stability or breakdown. This method is known as the Kissinger approach.⁹

*Problem 14-12 was provided by Professor Z. Zheng, Shanghai Medical University, Shanghai, China.

14-13* The observed alkaline hydrolysis rate constants, k_{obs} , of maleimide¹⁰ in dioxane-water mixtures (v/v %) at 30°C containing 0.03 M NaOH are given, in chart below, together with the solubility parameters¹¹ of the solvent mixtures, δ_1 (dioxane-water). Plot k_{obs} (vertical axis) against the delta value, δ_1 . Then plot the log of k_{obs} versus δ_1 on the same graph and find a simple linear relationship between the two variables. Does the addition of dioxane protect maleimide against hydrolysis? Explain. (The solubility parameter is related to polarity, as explained on pages 334-335; the larger is δ_1 , the greater is the polarity of the dioxane-water mixture).

Data for Problem 14-13

% (v/v) Dioxane	$\delta_1(\text{cal}/\text{cm}^3)^{1/2}$	$k_{\text{obs}} \times 10^3 \text{ s}^{-1}$	$\log k_{\text{obs}}$
5	22.78	10.68	-1.971
10	22.11	9.219	-2.035
15	21.43	7.612	-2.1185
20	20.76	6.572	-2.182
25	20.09	5.476	-2.262
30	19.42	4.580	-2.339
40	18.07	3.217	-2.493
50	16.73	2.223	-2.653
60	15.39	1.573	-2.803
70	14.04	1.199	-2.921

Would the toxicity of dioxane[†] prevent its use in pharmaceutical products? See *Merck Index*, 11th Ed., 1989, p. 521.

14-14 The effect of ionic strength, μ , on the observed degradation rates of cefotaxime sodium, a potent third-generation cephalosporin, was studied in aqueous solution at several pH values, with the following results¹²:

Data for Problem 14-14*

Ionic Strength μ	$k_{\text{obs}} \times 10^3 \text{ hr}^{-1} (25^\circ\text{C})$		
	pH 2.23	pH 5.52	pH 8.94
0.2	7.99	3.28	22.6
0.4	7.82	3.30	25.6
0.5	7.82	3.24	25.5
0.7	8.07	3.25	27.1
0.9	7.79	3.17	28.3

*Data in this chart are from S. M. Berge, N. L. Henderson, and M. J. Frank, *J. Pharm. Sci.* **72**, 59, 1983.

*Maleimide reacts with the sulfhydryl group of proteins and may one day become a useful drug. This problem deals with the chemical kinetics of the alkaline hydrolysis of an imide in an aqueous solvent, the dielectric constant of which is altered by the addition of dioxane.

†Dioxane is toxic and cannot be used in pharmaceutical preparations. See *Merck Index*, 11th Ed., 1989, p. 3297.

- (a) Does a primary salt effect exist at any of the pH values under study? If so, compute the rate constant, k_o , by plotting $\log k_{\text{obs}}$ versus $\sqrt{\mu}$ and extrapolating to $\mu = 0$.
- (b) When you regress $\log k_{\text{obs}}$ versus $[(\sqrt{\mu}/(1 + \sqrt{\mu}))]$ instead of $\sqrt{\mu}$ at pH 8.94, the slope agrees better with the theoretical value, $A_{Z_A Z_B}$, where $A_{\text{theor}} = 0.51$ at 29°C. Why? See Carstensen.¹³

14–15 The following data were obtained for the decomposition of 0.056 M glucose at 140°C at various concentrations of the catalysts, HCl:

Data for Problem 14–15

k_{obs} (hr ⁻¹)	Normality, [H ₃ O ⁺]
0.00366	0.0108
0.00580	0.0197
0.00818	0.0295
0.01076	0.0394
0.01217	0.0492

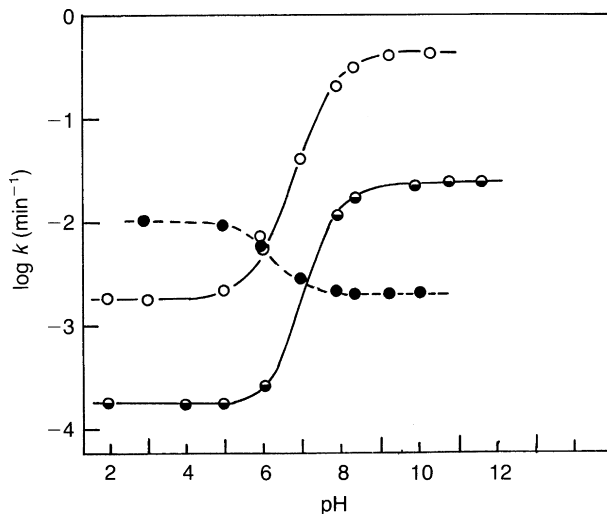
Plot the results and, from the graph, obtain k_o and the catalytic constant, k_H . It may be assumed that hydroxyl ion catalysis is negligible in this acidic solution.

14–16 The moieties $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}$, and $-\text{CH}_2\text{NO}$ were attached to a model peptide to form a prodrug known as a Mannich base (compounds 7, 8, and 9, respectively, of Bundgaard and Møss¹⁴). The pH–rate profile for the hydrolysis of the Mannich bases (see Fig. 3 in reference 12) exhibits sigmoidal shapes. The points of the three curves can be calculated using the equation

$$k' = \frac{k_1 K_a}{[H^+] + K_a} + \frac{k_2 [H^+]}{[H^+] + K_a} \quad (4)$$

where k_1 and k_2 are the first-order rate constants for degradation of the Mannich base, B , and the conjugate acid, BH^+ , respectively. K_a is the ionization constant of the protonated Mannich base. The values at 37°C given by the authors for compound 9 are k_1 (min⁻¹) = 2.5×10^{-3} , k_2 (min⁻¹) = 1.0×10^{-2} , and $\text{p}K_a = 5.1$; $K_a = 7.94 \times 10^{-6}$.

Calculate k , the first-order rate constant for the degradation of the Mannich base, compound 9, at pH 4. Check your answer at pH 4 by reading the $\log k$ value from the accompanying figure and converting it to the rate constant, k (min⁻¹), for hydrolysis. You may want to calculate the k values for compounds 7 and 8. The rate data for the breakdown of compound 7 are as follows: $k_1 = 0.024$ (min⁻¹), $k_2 = 1.8 \times 10^{-4}$ (min⁻¹), and $\text{p}K_a = 7.2$. The values for compound 8 are $k_1 = 0.42$ (min⁻¹), $k_2 = 1.7 \times 10^{-3}$ (min⁻¹), and $\text{p}K_a = 7.2$.



pH profile for the Mannich base derivatives 7 (●), 8 (○), and 9 (●) in aqueous solution at 37°C. (Figure 3 of H. Bundgaard and J. Moss, *J. Pharm. Sci.* **78**, 122, 1989. Reproduced with permission of the copyright owner and altered according to the authors.)

14–17 The degradation constant, k_{obs} (sec⁻¹), for codeine sulfate can be calculated at 25°C using the expression

$$k_{\text{obs}} \text{ (sec}^{-1}\text{)} = k_{\text{H}^+} [\text{H}^+] + k_{\text{OH}^-} [\text{OH}^-] + k_o \\ = 2.46 \times 10^{-11} [\text{H}^+] + 3.22 \times 10^{-9} [\text{OH}^-] \\ + 7.60 \times 10^{-11} \quad (5)$$

The constants k_{H^+} and k_{OH^-} associated with the concentrations of $[\text{H}^+]$ and $[\text{OH}^-]$, respectively, are expressed in $M^{-1} \text{sec}^{-1}$, where M^{-1} stands for reciprocal moles per liter and k_o is in sec^{-1} . Calculate the observed rate constant, k_{obs} (sec⁻¹), for the decomposition of codeine at 25°C in codeine sulfate solutions at pH 0.0, 2.0, 8.0, and 10. Powell¹⁵ showed that codeine sulfate solutions are subjected to general acid–base catalysis due to a buffer consisting of the phosphate ions, Na_2HPO_4 and NaH_2PO_4 . Plot $\log k_{\text{obs}}$ versus pH and compare with Figure 1, page 902, in the report by Powell. *Note:* At pH = 0.0, $[\text{H}^+] = 1 \text{ M}$. Above this concentration ($>1 \text{ M}$), pH values become negative. However, below pH = 0 we do not use minus pH values but rather an acidity function known as H_o (see Albert and Serjeant¹⁶).

14–18 Equation (14–132) can be written in logarithmic form to produce equation (14–134),

$$\log k_{\text{obs}} = \text{pH} + \log (k_w k_{\text{OH}^-}) \quad (6)$$

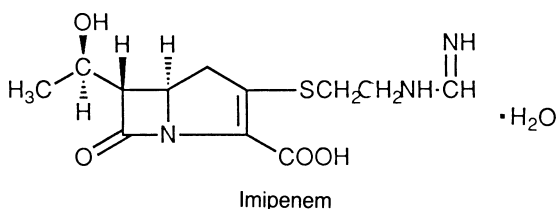
This equation allows one to compute k_{OH^-} from the intercept of a regression of $\log k_{\text{obs}}$ against pH. Use the data of Khan¹⁰ for the effect of pH on the alkaline hydrolysis rate constant of a new drug, maleimide, given in the following table:

Data for Problem 14–18

pH	8.39	8.51	8.84	8.88	9.13	9.36	9.68	9.89	10.08
$k_{\text{obs}} \times 10^3$	0.1514	0.1750	0.330	0.3124	0.6510	0.9310	2.059	2.633	4.057

- (a) Plot $\log k_{\text{obs}}$ (vertical axis) against pH.
 (b) Using least squares, compute the specific catalytic constant k_{OH^-} from the intercept.

14-19 Thienamycin is an antibiotic with a structure somewhat related to the penicillins. Its decomposition accelerates as the concentration is increased, and a derivative, *N*-formimidoylthienamycin (imipenem, imipenem), has been introduced to improve the stability and broad spectrum of activity.



Smith and Schoenewaldt¹⁷ studied the stability of imipenem in aqueous solution at 25°C and 40°C. A first-order reaction of ring opening occurred in dilute solution (1 or 2 mg/mL) and a second-order reaction became evident at higher concentrations. The pseudo-first-order rate constants, k , hr^{-1} , at 25°C and 40°C are given in the following table at buffer pH from 5.0 to 8.0. The reaction rates were independent of general acid–base buffer effects, and the effect of ionic strength on rate was insignificant.

Data for Problem 14-19

Buffer pH	5.0	6.0	7.0	8.0
k (hr^{-1}), 25°C	0.0315	0.0069	0.0040	0.0083
k (hr^{-1}), 40°C	0.111	0.0257	0.0169	0.0462

The equation describing the rate–pH profiles of the drug at 25°C and 40°C is

$$k_{\text{obs}} = k_1[\text{H}^+] + k_2K_w/[\text{H}^+] + k_0 \quad (7)$$

where k_{obs} is the experimentally determined first-order rate constant, k , at a definite pH; k_1 and k_2 are the second-order rate constants for hydrogen ion and hydroxyl ion catalysis, respectively, and k_0 is the first-order rate constant for water or “spontaneous” decomposition. $K_w/[\text{H}^+]$ is written in place of $[\text{OH}^-]$, where K_w is the ionization constant of water. Knowing the pH, one has by experiment both $[\text{H}^+]$ and $[\text{OH}^-] = K_w/[\text{H}^+]$. At 25°C, $K_w \cong 10^{-14.00}$ and at 40°C, $K_w = 10^{-13.54}$.

Plot the experimentally obtained points on the pH profiles for the pseudo-first-order rate constants at 25°C and 40°C using the data from the table. Draw the line obtained by use of equation (14-150) to determine how well the theory fits the experimental results. Using multiple least-squares regression, compute the

values of k_0 , k_1 , and k_2 at both 25°C and 40°C. The researchers obtained the following results using a statistical method known as nonlinear regression:

Data for Problem 14-19

Temperature	k_0 (hr^{-1})	k_1 ($M^{-1} \text{hr}^{-1}$)	k_2 ($M^{-1} \text{hr}^{-1}$)
40°C	0.01565	9730	10300
25°C	0.00403	2780	4150

Use the coefficients k_0 , k_1 , and k_2 to back-calculate $k_{25^\circ\text{C}}$ and $k_{40^\circ\text{C}}$.

14-20 Notari¹⁸ studied the hydrolytic deamination of cytosine arabinoside in buffer solutions of varying composition prepared so as to maintain the pH and the ionic strength constant. He reported the following data for the hydrolysis at 70°C:

Data for Problem 14-20

pH	Buffer Composition			k , hr^{-1}
	$\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$	Na_2HPO_4	NaCl	
6.15	0.120	0.012	0.000	0.00311
	0.048	0.0048	0.094	0.00171
	0.024	0.0024	0.125	0.00118
6.90	0.040	0.040	0.000	0.00113
	0.029	0.029	0.043	0.000872
	0.016	0.016	0.092	0.000619

Using these data, determine which species in the buffer solution is functioning as a catalytic agent. Give your reasoning for choosing this agent. *Hint:* Plot k versus $[\text{NaH}_2\text{PO}_4]$ and versus $[\text{Na}_2\text{HPO}_4]$ on the same graph. If one or the other of these catalytic species produces parallel lines at the two pH values, catalysis by this species is occurring.*

14-21 The degradation of phentolamine hydrochloride in phosphate buffer at pH 5.9 to 7.2 and 90°C is attributed to both the buffer species $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$ and specific base catalysis. The value of the specific base catalysis constant k_{OH^-} was found to be 4.28×10^6 liters mole⁻¹ hr⁻¹. The catalytic coefficients of the species H_2PO_4^- and HPO_4^{2-} are $k_1 = 0.036$ and $k_2 = 1.470$ liters mole⁻¹ hr⁻¹, respectively, and the total buffer concentration is 0.1 mole/liter. The equation for the overall rate constant is

$$k_{\text{obs}} = k_{\text{OH}^-}[\text{OH}^-] + k_1[\text{H}_2\text{PO}_4^-] + k_2[\text{HPO}_4^{2-}] \quad (8)$$

The solvent effect is negligible and $k_0 = 0$ (based in part on Wang et al.¹⁹).

*Dr. Keith Guillory, University of Iowa, suggested the test in *Problem 14-20* to determine what species is acting as the catalyst.

- (a) Compute the overall hydrolysis rate constant, k , at the pH values of 6, 6.5, 7, and 7.2 using the appropriate expression. At the pH range of 5.9 to 7 you can use the second dissociation constant of phosphoric acid, $pK_{a2} = 7.21$, to obtain the concentration of $H_2PO_4^-$ and HPO_4^{2-} at each pH value. Disregard the effect of the solvent alone. Then calculate the k_{obs} values at pH 6.5, 7.0, and 7.2. Finally, convert the k values into $\log k$ and plot them versus pH.
- (b) Plot the logarithm of the calculated k values against pH.

14-22 The degradation in methanol of chlorthalidone, an oral diuretic sulfonamide, is catalyzed by ferric ions. The observed rate constants in methanol as solvent vary with the $FeCl_3$ concentration as follows:

Data (a) for Problem 14-22*

$[FeCl_3] \times 10^4$ M	0.64	1.93	3.78	4.96	6.22
k_{obs} , hr^{-1}	0.019	0.081	0.21	0.26	0.36

*Data in this chart are from N. K. Pandit and J. S. Hinderliter, *J. Pharm. Sci.* **74**, 857, 1985.

The addition of acetic acid to a chlorthalidone–methanol solution containing 6.15×10^{-4} mole/liter of $FeCl_3$ also influences hydrolysis. The variation of the observed rate constants with increasing concentrations of acetic acid, expressed as $[H^+]$, are as follows:

Data (b) for Problem 14-22

$[H^+] \times 10^7$	0.52	1.60	1.98	2.30
k_{obs} , hr^{-1}	0.436	0.672	0.764	0.772

The total k_{obs} , when both $[H^+]$ and $[FeCl_3]$ vary, can therefore be represented as

$$k_{total} = k_o + k_M[M] + k'_M[M][H^+] \quad (9)$$

where k_o is the first-order rate constant due to the catalytic effect of the solvent alone (methanol), k_M ($M^{-1} \text{ sec}^{-1}$) is the pseudo-second-order constant for the metal ion catalyzed reaction, $[M]$ is the concentration in mole/liter of $FeCl_3$, and k'_M ($M^{-2} \text{ sec}^{-1}$) is the pseudo-third-order constant for the metal ion and acid-catalyzed reaction.

- (a) Plot k_{obs} (vertical axis) against $[FeCl_3]$ from the first table of this problem and compute the equation of the line from which k_M is obtained.
- (b) Plot k_{obs} versus $[H^+]$ from the second table, and compute k'_M . *Hint:* Apply the general equation (9) to each part of the problem. That is, include the appropriate terms in the slope and intercept you get in parts (a) and (b).

14-23 The hydrolysis of cefotaxime sodium at 25°C is first order,²⁰ and $k_{obs} = k_o + k_{H^+}[H^+] + k_{OH^-}[OH^-]$. The pH has very little effect in the range of 4.3 to 6.2, and k_{obs} in this pH range has the value 0.056 day^{-1} . The ionic strength and the phosphate buffer used have no effect on the decomposition constant. The k_{obs} values at pH 1.5 and 8.5 are 0.625 and 0.16 day^{-1} , respectively. Compute k_o , k_{H^+} , and k_{OH^-} values.

14-24* Cyclophosphamide monohydrate is available as a sterile blend of dry drug and sodium chloride packaged in vials. A suitable aqueous vehicle is added and the sterile powder dissolved with agitation before the product is used parenterally. However, cyclophosphamide monohydrate is only slowly soluble in water, and a hospital pharmacist inquires concerning the advisability of briefly (for 15 min) warming the solution to 70°C to facilitate dissolution. Brooke et al.²¹ addressed this problem. Assuming that degradation to 95% of the labeled amount is permitted for this compound, and given k at $25^\circ\text{C} = 0.028 \text{ day}^{-1}$, $E_a = 25.00 \text{ kcal/mole}$, what answer would you give?

References

1. K. A. Connors, G. L. Amidon, and L. Kennon, *Chemical Stability of Pharmaceuticals*, 2nd Ed., Wiley, New York, 1986, p. 201.
2. C. R. Kowarski and H. I. Ghandi, *J. Pharm. Sci.* **64**, 696, 1975.
3. E. R. Garrett and R. F. Carper, *J. Am. Pharm. Assoc. Sci. Ed.* **44**, 515, 1955.
4. C.-H. Chiang, C.-Y. Wu, and H.-S. Huang, *J. Pharm. Sci.* **76**, 914, 1987.
5. P. Zvirblis, I. Socholitsky, and A. A. Kondrizer, *J. Am. Pharm. Assoc. Sci. Ed.* **45**, 450, 1956; *ibid.* **46**, 531, 1957.
6. J. V. Swintosky et al., *J. Am. Pharm. Assoc. Sci. Ed.* **45**, 34, 37, 1956.
7. J. G. Strom Jr. and H. W. Jun, *J. Pharm. Sci.* **69**, 1261, 1980.
8. J. Zheng and J.-F. Zhang, *Acta Pharm. Sin.* **22**, 278, 1987.
9. H. E. Kissinger, *Anal. Chem.* **29**, 1702, 1957.
10. M. N. Khan, *J. Pharm. Sci.* **73**, 1767, 1984.
11. A. Sharma and E. Ruckenstein, *J. Colloid Interface Sci.* **133**, 358, 1989.
12. S. M. Berge, N. L. Henderson, and M. J. Frank, *J. Pharm. Sci.* **72**, 59, 1983.
13. J. T. Carstensen, *J. Pharm. Sci.* **59**, 1141, 1970.
14. H. Bundgaard and J. Møss, *J. Pharm. Sci.* **78**, 122, 1989.
15. M. F. Powell, *J. Pharm. Sci.* **75**, 901, 1986.
16. A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, 3rd Ed., Chapman and Hall, New York, 1984, p. 75.
17. G. B. Smith and E. F. Schoenewaldt, *J. Pharm. Sci.* **70**, 272, 1981.
18. R. E. Notari, *J. Pharm. Sci.* **56**, 804, 1967.
19. D.-P. Wang, Y.-H. Tu, and L. V. Allen Jr., *J. Pharm. Sci.* **77**, 972, 1988.
20. V. D. Gupta, *J. Pharm. Sci.* **73**, 565, 1984.
21. D. Brooke, J. A. Scoppit, and R. J. Bequette, *Am. J. Hosp. Pharm.* **32**, 44, 1975.

*Problem 14-24 was suggested by J. K. Guillory, University of Iowa.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 15: INTERFACIAL PHENOMENA

- 15-1** *Hint:* What kind of intermolecular forces do you believe might contribute to these observations? *Partial Answer:* increasing temperature decreases molecular interaction.
- 15-2** *Partial Answer:* (a) $\gamma = 73.37$ dynes/cm.
- 15-3** Check your answer with Hiemenz.¹
- 15-4** 39.2 dynes/cm².
- 15-5** 65.2 dynes/cm.
- 15-6** (a) 64.0 cm.
(b) The important process is not capillary action, but rather appears to be osmosis.
- 15-7** *Partial Answer:* (a) 2.30 cm.
- 15-8** *Partial Answer:* (a) the spreading coefficient is $S_{\text{initial}} = 35.10$ dynes/cm. (b) The positive spreading coefficient means the test lotion spread on water. To understand it spreading on the skin, the literature used a substrate to mimic the skin condition. Please refer to the original literature.
- 15-9** $W_c = 54$ ergs/cm²; $W_a = 91.8$ ergs/cm²; $S_{\text{initial}} = 37.8$ ergs/cm².
- 15-10** $W_{\text{SL}} = 48.98$ ergs/cm² or 0.049 N/m; $S_{\text{initial}} = -77.42$ ergs/cm² or -0.077 N/m.
- 15-11** *Partial Answer:* (a) Magnesium stearate: $\gamma_{\text{SL}} = 109.8$ dynes/cm; lactose: $\gamma_{\text{SL}} = 8.55$ dynes/cm; (b) for magnesium stearate, $S_{\text{initial}} = -110.3$ dynes/cm; for lactose, $S_{\text{initial}} = -9.76$ dynes/cm.
- 15-12** $\Gamma = 6.6 \times 10^{-9}$ mole/cm²; 7.1×10^{-7} g/cm².
- 15-13** (a) $\partial\gamma/\partial(\text{wt}\%) = -0.06015$ ergs cm⁻² (wt%)⁻¹;
(b) $\Gamma = 1.2 \times 10^{-11}$, 2.27×10^{-11} , and 3.26×10^{-11} mole cm⁻²;
(c) the areas per molecule are 1383, 730, and 510 Å²;
(d) Does aminobutyric acid significantly lower the surface tension of water?
- 15-14** At pH 5, $(d\gamma/d \ln c) = 9.28 \times 10^{-5}$ N/m; $A = 45$ (nm)²/molecule. At pH 4, $(d\gamma/d \ln c) = 2.5 \times 10^{-5}$ N/m; $A = 160$ (nm)²/molecule = 16,400 Å²/molecule. Tanford et al.² calculated the area of bovine serum albumin at pH 4 using intrinsic viscosity and obtained 16,286 Å²/molecule.
- 15-15** Check your answers against Figure 1 of the article by Korzacz et al.³ Extrapolating to the lower end of the curve yields an area/molecule of $A \cong 52 \times 10^{-20}$ m² = 52 Å². Extrapolating to the end of the curve yields $A \cong 96 \times 10^{20}$ m² = 96 Å².
- 15-16** 25 Å.
- 15-17** 22 Å.
- 15-18** $M = 10,121$ g/mole.
- 15-19** 6042 g/mole.
- 15-20** (a) $n = 1.1$, $k = 1.76$ liters/g; (b) $n = 1.1$, $k = 1.76$ liters/g.
- 15-21** (a) Using the two-point formula and the Freundlich isotherm for slope, $1/n$, and reading directly from the y intercept on the log–log plot for k , one obtains $1/n = 0.688$ (dimensionless) and $k = 0.4$ mg/g.
The units on k are taken as mg/g because at the intercept the Freundlich equation requires that $c = 1$ mg/mL, or in logarithmic form, $\log c = \log 1 = 0$. Then, $\log(x/m) = \log k + (1/n) \log c = \log k + 0$ and $\log(x/m) = \log k$. Therefore, $(x/m) = k$ and k has the same units, mg/g, as has x/m .
Using regression analysis on the Freundlich log–log equation, $\log(x/m) = -0.4048 + 0.6906 \log c$; $r^2 = 0.9999$. The slope = $1/n = 0.6906$ (dimensionless) and from the intercept, $\log k = -0.4048$; $k = \text{antilog}(-0.4048) = 0.394$ mg/g.
(b) Using the two-point formula and the Langmuir isotherm for $1/y_m$, we obtain the slope:
- $$\begin{aligned} 1/y_m &= \frac{(c/y)_1 - (c/y)_2}{(c)_1 - (c)_2} = \frac{6.45 - 3.57}{20 - 3} \\ &= 0.1694 \text{ g/mg} \\ y_m &= 1/0.1694 = 5.903 \text{ mg/g} \end{aligned} \quad (1)$$
- For the intercept, one reads directly from the graph to obtain $1/(by_m) = 3.35$ g/dL; $1/b = \text{intercept} \times y_m = (3.35 \text{ g/dL}) \times (5.903 \text{ mg/g})(1/b) = 19.78 \text{ mg/dL}$; $b = 0.051$ dL/mg.

Using regression analysis on the Langmuir equation,

$$c/y = 1/(by_m) + (1/y_m)c;$$

$$c/y = 3.247 + 0.1653c; r^2 = 0.978$$

$$\text{Slope} = 0.1653 \text{ g/mg} = 1/y_m; y_m = 6.0496 \text{ mg/g}$$

$$\text{Intercept} = 1/(by_m) = 3.247 \text{ g/dL}$$

$$1/b = 3.247 \times 6.0496 = 19.643 \text{ mg/dL}$$

$$b = 0.051 \text{ dL/mg} \quad (2)$$

15-22 Aspirin, 63 tablets; chlordiazepoxide, 452 tablets; and diazepam, 1958 tablets.

15-23 (a) $\Delta G^\circ = -2.9$ kcal/mole at 37°C and -3.0 kcal/mole at 50°C ; (b) $\Delta H^\circ = 490$ cal/mole; (c) $\Delta S^\circ(37^\circ\text{C}) = 10.8$ ue and $\Delta S^\circ(50^\circ\text{C}) = 10.8$ ue; (d) at 37°C , $x/m = 8.3$ mg/g; at 50°C , $x/m = 7.9$ mg/g at c (mg/100 mL) = 0.5.

15-24 *Partial Answer:* (b) $S^s = 0.0879$ erg cm^{-2} deg^{-1} ; $H^s = 89.17, 90.52,$ and 89.09 ergs cm^{-2} at $20^\circ\text{C}, 90^\circ\text{C},$ and $150^\circ\text{C},$ respectively; (c) See Harkins⁴ for an interpretation of H^s and S^s .

15-25 *Partial Answer:* $S^s = 0.113$ erg cm^2 deg^{-1} ; at $20^\circ\text{C}, H^s = 60.08$ ergs cm^2 .

15-26 *Partial Answer:* (a) θ (water) = 115.7° , θ (ethylene glycol) = 92° , θ (benzene) = 50.2° .

15-27 35.6 mJ/m^2 . (Note that the numerical value 35.6 for the surface tension in the SI units of mJ/m^2 is the same

as the numerical value for surface tension in the cgs system, namely 35.6 ergs/ cm^2 .)

15-28 *Partial Answer:* A sphere has the minimum surface area.

15-29 The film converts into a small spherical drop, which has very small diameter because of the very thin thickness of the film.

15-30 11.8×10^{-6} joules.

15-31 *Hint:* Apply equation (15-11). *Partial Answer:* The small become smaller and the big become bigger.

15-32 The surface tension of hot water is less than that of cold water. This could lead to the decrease in the capillary rise. On the other hand, the density of hot water is less than that of cold water. This in turn should lead to an increase in the capillary rise. The decrease in the capillary rise that was found in the experiment indicates that the change in surface tension with temperature is higher than the change in density.

References

1. P. C. Hiemenz, *Principles of Colloid and Surface Chemistry*, 2nd Ed., Marcel Dekker, New York, 1986, p. 296; 1st Ed., 1977, p. 213.
2. C. Tanford, J. G. Buzzell, D.G. Rands, and S. A. Swansaw, *J. Am. Chem. Soc.* **77**, 6421, 1955.
3. Z. Korazac, A. Dhathathreyan, and D. Mbius, *Colloid Polymer Sci.* **267**, 722, 1989.
4. W. D. Harkins, *Physical Chemistry of Surface Films*, Reinhold, New York, 1952, pp. 80-83.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 15: INTERFACIAL PHENOMENA

- 15-1** Water has an unusually high surface tension, and like other liquids, its surface tension decreases with increasing temperature. What is your explanation for these two phenomena?
- 15-2** You wish to formulate a sunscreen product that lowers surface tension and thus spreads easily on the skin. You choose *p*-aminobenzoic acid, a powerful sunscreen.
- (a) Calculate the surface tension of a 12.35 wt% of *p*-aminobenzoic acid solution in water at 25°C. The DuNoüy tensiometer ring circumference is 12.47 cm and the correction factor β according to Harkins and Jordan is 0.920. The dial reading in dynes was obtained experimentally as 1989.
- (b) What agent might you add to improve the spreading qualities of this product?
- 15-3** Equation (15-1) considers γ as a force per unit length (dynes/cm) in the surface, whereas equation (15-2) views γ as an energy per unit area (erg/cm²) of the surface. Show the dimensional equivalency in both cgs and SI units for these two interpretations of the surface tension.
- 15-4** What is the pressure difference, ΔP , in dynes/cm² across a soap bubble formed from the soap solution of *Example 15-1*? The radius of the soap bubble is 2.50 cm.
- 15-5** Calculate the surface tension of a 2% (w/v) solution of a wetting agent that has a density of 1.008 g/cm³ and that rises 6.60 cm in a capillary tube having an inside radius of 0.02 cm.
- 15-6** Water has a surface tension of 71.97 dynes/cm at 25°C and its density at 25°C is 0.9971 g/cm³.
- (a) How high will the water rise in a very fine capillary tube of radius 0.0023 cm?
- (b) If water rises by capillary action only 64 cm in a narrow tube equivalent to a xylem tube in a living plant, how is it possible to lift aqueous nutrients to the topmost leaves in the tall trees in a forest?
- 15-7** (a) How high will the liquid carbon tetrachloride rise in a capillary tube of radius 0.015 cm at 20°C? The density of carbon tetrachloride is 1.595 g/cm³ and its surface tension is 26.99 dynes/cm at 20°C.
- (b) Could one use this experiment to estimate the acceleration, g , caused by gravity on earth?
- 15-8** (a) Paruta and Cross¹ studied the spreading on water of a number of surfactants (spreading promoters) added to mineral oil as a laboratory test in the design of cosmetic creams and lotions. The surface tension of water at 25°C is ~ 72.0 dynes/cm. The surface tension of a test lotion consisting of 5 g/dL (5% w/v) solution of sorbitan monooleate in mineral oil was found to be 31.2 dynes/cm and the interfacial tension γ_{ii} of the oil-surfactant solution measured against water was 5.7 dynes/cm. Calculate the initial spreading coefficient, S_{initial} , of the oil-surfactant solution (the oil phase) on water.
- (b) What is the significance of the positive spreading coefficient? Could you suggest a better substrate than water to test the spreadability of a cosmetic lotion? See Paruta and Cross for another approach.¹
- 15-9** The surface tension of *n*-heptyl alcohol is 27.0 ergs/cm², the surface tension of water is 72.8 ergs/cm², and the interfacial tension between the two liquids is 8.0 ergs/cm² at 20°C. Calculate W_c , W_a , and S_{initial} .
- 15-10** The contact angle θ for a skin lotion when applied to the back of the hand of a number of subjects was found to have an average value of 103 deg at 24°C. The surface tension, γ_L , of the lotion measured at 24°C in a capillary-rise experiment was 63.2 dynes/cm, or 63.2 mN m⁻¹ in SI units (the symbol m stands for both *milli* and *meters*; 63.2 mN m⁻¹ is read as “63.2 millinewtons per meter”). What is the work of adhesion, W_{SL} , and the initial spreading coefficient, S_{initial} , for this lotion on the skin?
- 15-11** Magnesium stearate and lactose are excipients commonly used in tablet formulation. The measured contact angles of water or of a saturated aqueous solution on the surfaces of compacts of these two powders are $\theta = 121$ deg and $\theta = 30$ deg, respectively. Their surface tensions (against air) are 72.3 and 71.6 dynes/cm, respectively. The surface tension of water (against air) at 20°C is 72.8 dynes/cm.

- (a) Compute the interfacial tension between water and each of these compacted powders. You will need equation (15–59).
- (b) Compute the spreading of water on the solid surfaces. (Data from Lerk et al.²)
- (c) How do you explain the quite different spreading results on these two powder compacts?

15–12 *p*-Toluidine, a yellow liquid used in the manufacture of dyes, is only slightly soluble in water. The surface tension of *p*-toluidine was measured at various concentrations at 25°C (298 K) and the results were plotted. The slope, $d\gamma/dc$, of the line at $c = 5 \times 10^{-3} \text{ g/cm}^3$ was found to be $-32,800 \text{ cm}^3/\text{sec}^2$. Using the Gibbs adsorption equation, compute the excess surface concentration in mole/cm² and in g/cm². The molecular weight of *p*-toluidine is 107.15 g/mole.

15–13 The surface tension of aminobutyric acid in water at 25°C is given as a function of concentration (weight percent of aminobutyric acid) in the following table:

Data for Problem 15–13

Weight% w/w	4.96	9.34	13.43
γ (dyne/cm)	71.91	71.67	71.40

- (a) Plot the data and obtain the slope $\partial\gamma/\partial(\text{wt}\%)$ from the two-point formula or from regression analysis. (If you use regression analysis, the intercept should be close to the surface tension value of water at 25°C, 71.97 dynes/cm.)
- (b) Calculate the surface excess (the Gibbs adsorption coefficient, γ) for aminobutyric acid at the surface of water for each of these three concentrations (wt%).
- (c) What is the area occupied by each molecule of aminobutyric acid at the water surface?
- (d) Regarding your results, do you think that aminobutyric acid acts as a surfactant within this concentration range?

15–14 The adsorption of proteins at the oil–water interfaces is of biologic interest because in cell membranes various proteins attached to polar lipid-bilayer regions control cellular aggregation and cellular growth.

The adsorption of bovine serum albumin (BSA) to a polar peanut oil–water interface varies with ionic strength and pH. At 30°C and ionic strength $\mu = 0.1$, the maximum adsorptions (surface excess values) are $\Gamma = 2.54 \text{ mg m}^{-2}$ at pH 5 and $\gamma = 0.70 \text{ mg m}^{-2}$ at pH 4. The isoelectric point of BSA is near 5.³ Compute the area per molecule of BSA at the two different pH values and the limiting slope ($d\gamma/d \ln c$). Why

does A , the area per molecule of BSA, differ at these two pH values? *Hint*: Does protein conformation vary with pH? The molecular weight of BSA is about 69,000 daltons. You will need the Gibbs adsorption equation, $\Gamma = -1/RT(d\gamma/d \ln c)$, and for the area per molecule, A , you will need the equation $A = 1/(N\Gamma)$, where N is Avogadro's number and γ is the surface excess. You will want to convert Γ (g/m²) into mole/m² using the molecular weight (g/mole) of BSA.

15–15 Korazac et al.⁴ studied the isotherms of surface pressure, π , versus area per molecule, A , for insoluble monolayers of dipalmitoylphosphatidyl choline on an aqueous substrate of pH 5.2. They obtained the following results (from Figure 1 of their article):

Data for Problem 15–15

π (mN/m)	60	40	20	6	4	2	1	0
$A \times 10^{-20} \text{ m}^2$	40	44	50	52	68	94	95	96

Plot π against A as in Figure 15–18. For the several segments of the curve, extrapolate the line to the x axis to obtain the limiting areas of the phase changes observed. Identify the phase changes that occur. Express the areas in nm² and in Å².

15–16 When $1 \times 10^{-4} \text{ cm}^3$ of stearic acid, dissolved in benzene, is placed on the surface of water in a trough, the stearic acid spreads over the surface and the benzene evaporates off. The monomolecular layer of acid that is formed covers an area of 400 cm². Calculate the length in angstroms of the stearic acid molecules.

15–17 Stearic acid has a molecular weight of 284.3 g/mole and a density of 0.85 g/cm³. Using the data of *Problem 15–16*, compute the cross-sectional area of the acid molecule in square angstroms.

15–18 By analogy of monomolecular films to a two-dimensional gas, the molecular weight of a substance can be obtained with the film balance by using the equation $\pi A = (w/M) RT$. By plotting the product of the film pressure, π , and the area, A , against π and extrapolating to $\pi = 0$, a value of $\pi A/w = 2.4 \times 10^6 \text{ erg/g}$ at 292.15 K was obtained for w grams of a synthetic gum. Compute the molecular weight, M , of the gum. (*Note*: $R = 8.315 \times 10^7 \text{ ergs/mole deg.}$)

15–19 Insulin was spread as a film on the surface of an aqueous solution having a pH of 2.05 and an ionic strength of 0.01. The value of $\pi A/w$ extrapolated to $\pi = 0$ was obtained as $4.02 \times 10^6 \text{ ergs/g}$ at 292.15 K. Compute the molecular weight of insulin using the equation given in *Problem 15–19*.

15-20* From the logarithmic form of the Freundlich isotherm, equation (15-50), using concentration, c , instead of pressure, p , a plot of $\log(x/m)$ (y axis) against $\log c$ (x axis) gives a straight line. When the value of c equals 1.0, $\log c = 0$, the y intercept is $\log(x/m) = \log k$, from which the value of k is obtained. The n value is computed from the slope. The use of log-log graph paper allows one to read directly the k value from the y -intercept axis where the x axis is $c = 1$. *Caution:* One cannot obtain the slope, n , from a direct reading on a log-log plot.

A newly synthesized steroid is adsorbed on activated charcoal at 37°C. Data are obtained for adsorption from a phosphate buffer solution at pH 7.4:

Data for Problem 15-20

Amount (mole) of Steroid Adsorbed Per Gram of Charcoal, x/m	Equilibrium Concentration, c , of Steroid (mole/liter)
1.585×10^{-4}	3.162×10^{-5}
2.310×10^{-4}	5.012×10^{-5}
3.162×10^{-4}	7.079×10^{-5}
5.012×10^{-4}	1.122×10^{-4}
7.943×10^{-4}	1.995×10^{-4}
1.259×10^{-3}	3.162×10^{-4}

- (a) Plot x/m against c using log-log graph paper and obtain k and n . *Hint:* Use 6 cycle \times 6 cycle log-log graph paper because you will need to extrapolate the line to read the y intercept at $c = 1$.
- (b) Regress $\log(x/m)$ against $\log c$ and compute k and n from the intercept and the slope, respectively.

15-21 The following data are obtained for the adsorption of timolol, an antihypertensive agent, from aqueous solution onto kaolin at 37°C:

Data for Problem 15-21*

x/m (mg Adsorbed Per g Adsorbent)	c (mg/100 mL)	$c/(x/m)$ (g/100 mL)
3.1	20	6.45
2.8	17	6.07
1.8	9	5.00
0.84	3.0	3.57

*Data in this chart are from B. C. Walker, B. Pharm. Thesis, University of Otago, New Zealand, 1978.

- (a) Plot the data on log-log paper according to the Freundlich isotherm and evaluate n and k [equation (15-50)] using concentration, c , instead of pressure, p .

(b) Plot $c/(x/m)$ (y axis) against c (x axis) according to the Langmuir plot as shown in Figure 15-25. Compute b and y_m according to the Langmuir equation [equation (15-58)]. (The y_m value is calculated from the slope, and b is computed from the intercept.)

(c) What are the units on n , k , y_m , and b ?

15-22 Sellers et al.⁵ reported the following constants for adsorption of various drugs by activated charcoal at 37°C:

Data for Problem 15-22

Drug	y_m	b	Tablet Strength (mg)
Aspirin	262	0.012	300
Chlordiazepoxide	157	0.010	25
Diazepam	136	0.010	5

In cases of drug overdose and poisoning, one practice is to administer an aqueous slurry (suspension) of 1 g activated charcoal/kg body weight as an antidote. If the patient weighs 72 kg, how many tablets overdose of each type is such a slurry capable of handling?

15-23 From the affinity or binding constant, b , obtained from the Langmuir isotherms, the standard free energy of adsorption can be computed as

$$\Delta G^\circ = -RT \ln b \quad (1)$$

because the affinity b is an equilibrium constant.⁶ The Langmuir constants for the adsorption of nadolol, an adrenergic drug, onto magnesium trisilicate were determined at two temperatures:

Data for Problem 15-23

T (°C)	y_m (mg/g)	b	
		(liter/g)	(liter/mole)
37°C	58.2	0.33227	102.14
50°C	53.8	0.34168	105.457

- (a) Compute ΔG° at the two temperatures.
- (b) Use the integrated form of the van't Hoff equation and compute ΔH° .
- (c) Compute ΔS° at 37°C and 50°C.
- (d) Using the nonlinear form of the Langmuir equation, that is, $x/m = y_m bc/(1 + bc)$, together with the parameters y_m (mg/g) and b (liter/g) given in the table at the two temperatures, compute x/m for the following concentrations, c : 0.5, 5, 20, 50 mg/100 mL. Plot the Langmuir isotherms at the two temperatures on the same graph.

*Problems 15-20 through 15-22 were prepared by B. Hajratwala, Wayne State University, Detroit.

15-24 Use the data for the surface tension, γ , of glycerol at three temperatures, 20°C, 90°C, and 150°C from a handbook of physics and chemistry,* namely 63.4, 58.6, and 51.9 ergs/cm².

(a) Plot γ versus temperature (kelvins on the horizontal axis). Use regression analysis or a tangent drawn at each temperature to obtain the slope $(\partial\gamma/\partial T)_p = -S^s$.

(b) Knowing γ and the entropy of the surface, S^s , calculate the surface enthalpy, H^s , at each of the three temperatures using the appropriate equation (page 358). Does H^s appear to remain constant over this temperature range?

(c) What is the meaning of H^s in surface chemistry? How do you interpret (explain) the entropy value obtained?

15-25 Use the following data to obtain the entropy of formation of a surface and the surface enthalpy at 20°C, 100°C, and 200°C for carbon tetrachloride:

Data for Problem 15-25*

T (°K)	293.15	373.15	473.15
γ (dyne/cm)	26.95	17.26	6.53

*The values in this table are found using the data from the *CRC Handbook of Physics and Chemistry*, 63rd Ed., 1982, pp. F-35-F-37.

Calculate S^s from the slope of a plot of γ against T , and using this value, compute H^s at the three temperatures.

15-26 The contact angle, θ , of a liquid on a solid surface can be evaluated from the Girifalco–Good–Fowkes–Young equation⁷ and Hiemenz⁸:

$$(1 + \cos \theta)\gamma_L = 2\sqrt{\gamma_s^d \gamma_L^d} \quad (2)$$

where γ_L is the total (dispersion plus polar) surface tension of the liquid and γ_s^d and γ_L^d are the surface tension of the solid and the liquid, respectively, due to the dispersion (weak electrostatic or London force) components, d . For relatively nonpolar liquids $\gamma_L \approx \gamma_L^d$.

(a) Compute the contact angles, θ , of water, ethylene glycol, and benzene on Teflon. The surface tensions of water, ethylene glycol, and benzene are 72.8, 49, and 29 dynes/cm, respectively, and the corresponding γ_L^d are 21.8, 28.6, and 29 dynes/cm; γ_s^d for Teflon is 19.5 dynes/cm at 25°C.

(b) What significance do these values have? See Sharma and Ruckenstein⁷ and Hiemenz⁸ for the meaning of these values.

*The values are found using the data from the *CRC Handbook of Physics and Chemistry*, 63rd Ed., 1982, pp. F-35-F-37.

15-27 The interfacial tension between oil and water or an aqueous solution can be computed from the surface tension of the pure components by means of the Girifalco–Fowkes equation:

$$\gamma_{o,aq} = \gamma_o + \gamma_{aq} - 2\sqrt{\gamma_o^d \gamma_{aq}^d} \quad (3)$$

where the subscripts o and aq stand for the oil and aqueous phases, respectively, and the superscript d signifies the dispersion or weak electrostatic interaction part of the surface tension of the aqueous phase.⁹

Compute the interfacial tension between a 10% by volume aqueous solution of ethylene glycol monomethyl ether ($\gamma_{aq} = 56.9$ mJ/m² and $\gamma_{aq}^d = 22$ mJ/m²) and paraffin oil ($\gamma_o = 30.8$ mJ/m²). Note: mJ/m² is read, “millijoules per square meter.” Also note that for a paraffin oil, $\gamma_o^d = \gamma_o$ because paraffin oil is a nonpolar substance.

15-28 To manufacture gunshot, melted lead is poured through small orifices from a certain height into water. During the fall, lead cools, forming spheres. Explain the phenomenon.

15-29 What happens to a soap film when it breaks? Where does it disappear to?

15-30 Compute the amount of work required to increase by a factor of 3 the surface area of a spherical drop of mercury ($\gamma = 0.470$ N/m, 20°C) by deforming it.

15-31 Consider two soap bubbles having radii r_1 and r_2 ($r_1 < r_2$) connected via a valve. What happens if we open the valve?

15-32 The rise of pure water was measured in the same capillary tube twice. The first time the water temperature was 35°C and the second time it was –25°C. The rise was higher in the second experiment. Explain.

References

1. A. N. Paruta and J. M. Cross, *Am. Perfumer* **76**, 43, 1961.
2. C. F. Lerk, A. J. M. Schoonen, and J. T. Fell, *J. Pharm. Sci.* **65**, 843, 1976.
3. K. P. Das and D. K. Chattoraj, *J. Colloid Interface Sci.* **78**, 422, 1980.
4. Z. Korazac, A. Dhathathreyan, and D. Möbius, *Colloid Polymer Sci.* **267**, 722, 1989.
5. E. M. Sellers, V. Khouw, and L. Dolman, *J. Pharm. Sci.* **66**, 1640, 1977.
6. O. Al-Gohary, J. Lyal, and J. B. Murray, *Pharm. Acta Helv.* **63**, 13, 1988.
7. A. Sharma and E. Ruckenstein, *J. Colloid Interface Sci.* **133**, 358, 1989.
8. P. C. Hiemenz, *Principles of Colloid and Surface Chemistry*, 2nd Ed., Marcel Dekker, New York, 1986.
9. G. Strom, M. Fredrickson, and P. Stenius, *J. Colloid Interface Sci.* **134**, 117, 1990.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

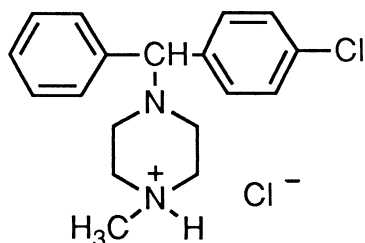
CHAPTER 16: COLLOIDAL DISPERSIONS

- 16-1** CMC = 0.053 mole/liter.
- 16-2** $M = 17,170$ g/mole; slope = $2B = 0.0147$; $B = 7.35 \times 10^{-3}$ mole cm^3 g^{-2} . Degree of aggregation = 49, that is, each micelle contains an average of 49 molecules of SDBS.
- 16-3** $\bar{x} = 3.93 \times 10^{-3}$ cm = $39.3 \mu\text{m}$ or 3.93×10^{-5} m displacement in 1 hr.
- 16-4** Equation (16-7) can be used. It gives 28.4, 54.5, 78.9, and 104 \AA at the four temperatures.
- 16-5** 70,641 g/mole.
- 16-6** $M = 2.797 \times 10^5$ or 279,700 daltons; $B = 2.56 \times 10^{-7}$ liter mole g^{-2} .
- 16-7** Angular acceleration = 4.737×10^5 rad/sec², and the number of g 's is 483 or a force 483 times that of gravity acting on the sample.
- 16-8** 10.26×10^4 rad/sec², or 105 g 's.
- 16-9** 44,727 g/mole \cong 45,000 g/mole.
- 16-10** (a) 54,613 or 54,600 daltons; (b) radius $r = 36 \text{ \AA}$.
- 16-11** (a) 14.2 dL/g; (b) dL mole^{0.983} $\text{g}^{-1.983}$. These units would differ, however, for each polymer having a different a value. Because the Mark-Houwink equation is an empirical one, in practice, the units on k are obtained disregarding altogether the M^a units. The units on k then become the same as those on intrinsic viscosity, dL/g.
- 16-12** $[\eta] = 8.53$ kg/mole of solvent = 8.53 m^{-1} .
- 16-13** The viscosity of the solution is 0.172 poise. The relative viscosity is $\eta_1/\eta_2 = 17.2$ (dimensionless).
- 16-14** $D = 11.15 \times 10^{-7}$ cm²/sec.
- 16-15** (a) $k = 2.60 \times 10^{-5}$ dL g^{-1} , $a = 0.966$; (b) Using the Mark-Houwink equation in logarithmic form, we find the molecular weight of the newly synthesized sample to be 469,583, or 470,000 daltons.
- 16-16** *Partial Answer:* Bentonite, $\zeta = -43.4$ millivolts; bismuth subnitrate, $\zeta = +28.2$ millivolts. See the paper for the reason for the positive and negative ζ values.
- 16-17** 2.22 to 1.
- 16-18** $[\text{Cl}^-]_o/[\text{Cl}^-]_i = 1.07$ to 1.
- 16-19** (a) $D = 9.4 \times 10^{-8}$ cm²/sec; (b) $D_p = 7.6 \times 10^{-8}$ cm²/sec; (c) *Hint:* Is the radius of the pyrene "particle" larger in the micelle or in free solution? Are the diffusion coefficients directly or inversely proportional to the radii? How can this information be used to design a drug for passage through the membrane pores of a new dosage form?

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 16: COLLOIDAL DISPERSIONS

16-1 The equivalent conductivity, A , of a solution containing a surface-active agent decreases sharply at the critical micelle concentration owing to the lower mobility of micelles. A plot of A (vertical axis) against the concentration or the square root of the concentration of the surface-active agent shows an inflection point at the critical micelle concentration (see Fig. 16-3).



Chlorcyclizine hydrochloride

Chlorcyclizine hydrochloride, an antihistamine used for the relief of urticaria and hay fever, is surface active and forms micelles in aqueous solution. The dependence of A in $\text{mho m}^2 \text{mole}^{-1}$ on \sqrt{c} is given as follows (partially based on the data of Attwood and Udeala¹):

Data for Problem 16-1

$\Lambda \times 10^3$ $\text{mho m}^2 \text{mole}^{-1}$	4.7	5.1	6.0	6.6	7.0	7.5	8.0	8.7
\sqrt{c} (mole/liter) ^{1/2}	0.33	0.30	0.26	0.24	0.23	0.20	0.17	0.14

Plot Λ versus \sqrt{c} and estimate the CMC.

16-2 The turbidity, τ , of an aqueous sodium dodecylbenzene sulfonate (SDBS) solution was determined in a light-scattering photometer at various concentrations above its CMC (modified from data in Tartar and Lelong²):

Data for Problem 16-2

$c \times 10^3$ (g/cm ³)	2.68	7.58	13.30	22.15
$\tau \times 10^4$ (cm ⁻¹)	1.09	1.80	2.08	2.31

The turbidity, τ , increases with concentration because the surfactant molecules aggregate to form structures with molecular weights much greater than the molecular weight of the monomer SDDBS, namely, 349 g/mole. The value of H in equation (16-2) is $4.00 \times 10^{-6} \text{ mole cm}^2 \text{g}^{-2}$. Plot Hc/τ versus c , and

using equation (16-2), obtain the molecular weight of the aggregate in the aqueous solution. Also, give the value of the solute-solvent interaction constant, B . The degree of aggregation is obtained by dividing the molecular weight of the aggregate by the molecular weight of the SDDBS monomer. What is the degree of aggregation?

16-3 For spherical particles we can express the diffusion in terms of their radii, r , the viscosity, η , of the medium, and the absolute temperature, T [equation (16-7)]. In 1908, Perrin used this equation and a suspension of gamboge particles of accurately determined size to calculate Avogadro's constant, N_A . He obtained values lying between 5.5×10^{23} and 8×10^{23} particles/mole. Currently, the accepted value of N_A is $6.022 \times 10^{23} \text{ mole}^{-1}$.³

Using equation (16-7) in the expression $\bar{x} = \sqrt{2Dt}$, we obtain the equation, $\bar{x} = \sqrt{\frac{RTt}{3\pi\eta r N_A}}$, for the calculation of the mean Brownian displacement of a particle.

For a particle of radius $r = 10^{-6} \text{ m}$ (10^{-4} cm) in water ($\eta = 0.01$ poise) at a temperature of 20°C ($T = 293.15 \text{ K}$), its displacement, \bar{x} , is to be observed over a period of 1 hr ($t = 3600 \text{ sec}$). R is the gas constant, expressed in units of $8.3143 \times 10^{-7} \text{ erg deg}^{-1} \text{ mole}^{-1}$. The poise is expressed as dynes sec/cm^2 or ergs sec/cm^3 . Calculate the mean Brownian displacement to be expected. How might you use this equation to determine Avogadro's number?

16-4 When insulin solutions are stored at room temperature, a process of self-association occurs and the molecules aggregate. The degree of aggregation is affected by pH, ionic strength, and temperature. The aggregation process was studied in the temperature range of room temperature (20°C) to human body temperature ($\sim 35^\circ\text{C}$) at pH 7.5 and ionic strength $\mu = 0.1$. The diffusion coefficients of aggregates at the various temperatures and viscosities of the solvent are given at the top of the following column:

Data for Problem 16-4*

T ($^\circ\text{C}$)	20	25	30	35
$D \times 10^7$ (cm ² sec ⁻¹)	7.8	4.6	3.7	3.0
η (poises)	0.0097	0.0087	0.0076	0.0072

*Data from H. B. Bohidar, *Colloid Polym. Sci.* **267**, 159, 1989.

Compute the hydrodynamic radii of the aggregates at the various temperatures. See the Stokes–Einstein equation. The poise is equal to $1 \text{ g cm}^{-1} \text{ sec}^{-1}$.

16-5 A sample of horse albumin in an aqueous solution at a concentration of $c_g = 3.20 \text{ g/liter}$ was placed in an osmometer at 28°C . Its osmotic pressure π was measured and found to be 0.00112 atm . What is the molecular weight of the serum albumin, assuming the solution is sufficiently dilute for the use of equation (16-11)? The gas constant is $R = 0.0821 \text{ liter atm/mole deg}$.

16-6 The osmotic pressure, π , of a fraction of polystyrene was determined at 25°C at various concentrations, c_g , as follows:

Data for Problem 16-6

$\pi/c_g \times 10^5 \text{ (1 atm g}^{-1}\text{)}$	12.5	16.3	20.0	23.8
$c_g \text{ (g/liter)}$	6.0	12	18	24

Calculate the molecular weight and the second virial coefficient, B , for the polystyrene fraction. Use equation (16-13) disregarding the $C \times c_g^2$ and higher terms. Can this large molecular weight be determined by the osmotic pressure method? What other methods are available to obtain the molecular weight of such a large molecule?

16-7 An ultracentrifuge is operated at 6000 rpm. The midpoint of the cell with the sample in place is 1.2 cm from the center of the rotor. What are the angular acceleration and the number of g 's acting on the sample?

16-8 Find the angular acceleration in rad/sec^2 for an ultracentrifuge with a rotor of radius 6.5 cm rotating at 1200 rpm. Convert this angular acceleration into g 's, assuming that the acceleration due to gravity is 981 cm/sec^2 .

16-9 Determine the molecular weight of egg albumin from the following ultracentrifuge data obtained at 20°C : the Svedberg constant $s = 3.6 \times 10^{-13} \text{ sec}$, $D = 7.8 \times 10^{-7} \text{ cm}^2/\text{sec}$, the partial specific volume $\bar{v} = 0.75 \text{ cm}^3/\text{g}$, and the density of water at 20°C is 0.998 g/cm^3 .

16-10 The sedimentation coefficient, s , at 20°C of saramycetin, an antifungal antibiotic, is 5.3 Svedberg ($1 \text{ Svedberg} = 10^{-13} \text{ sec}$), the diffusion coefficient is $D = 6 \times 10^{-7} \text{ cm}^2 \text{ sec}^{-1}$, and the partial specific volume is $\bar{v} = 0.607 \text{ cm}^3 \text{ g}^{-1}$ (\bar{v} is obtained by use of an accurate pycnometer and a microbalance) (selected data from Kirschbaum⁴).

(a) Compute the molecular weight of saramycetin. The density of the solvent is 0.998 g/cm^3 .

(b) Compute the radius of the saramycetin particle. Assume that the particles are spherical. The viscosity of the solvent is $1.002 \times 10^{-2} \text{ poise}$.

16-11 (a) Use the Mark–Houwink expression, equation (16-24), to calculate the intrinsic viscosity, $[\eta]$, in dL/g of a methylcellulose polymer having a number-average molecular weight of $15,200 \text{ g/mole}$. The constant K is equal to $1.1 \times 10^{-3} \text{ dL mole g}^{-1}$, where dL stands for deciliters ($1 \text{ dL} = 100 \text{ cm}^3$). The exponent, a , of equation (16-24) is 0.983 and is dimensionless.

(b) The units of dL mole g^{-2} on K are not quite correct in the problem. What are the exact units?

16-12 The variation of reduced viscosity, η_{sp}/c , with concentration for a new nonionic surfactant is given in the following table:

Data for Problem 16-12*

η_{sp}/c	8.96	9.39	9.82	10.25	10.69
$c \text{ (mole/kg)}$	0.005	0.01	0.015	0.02	0.025

*Data from D. Attwood, P. H. Elworthy, and M. J. Lawrence, *J. Pharm. Pharmacol.* **41**, 585, 1989.

Compute the intrinsic viscosity, $[\eta]$, of the surfactant.

16-13 It requires 40 sec for a volume of water, density 1.0 g/cm^3 , to flow through a capillary viscometer and 614 sec for an equal volume of a glycerin solution having a density of 1.12 g/cm^3 . What is the viscosity at 25°C and the relative viscosity of this solution? The viscosity of water at 25°C is 0.01 poise or 1.0 cp (see pages 469–471 and 477–478).

16-14 The molecular weight of a spherical protein is $20,000 \text{ g/mole}$ and the partial specific volume \bar{v} is $0.80 \text{ cm}^3/\text{g}$ at 20°C . The viscosity of the solvent is 0.01 poise . Calculate the value of D , the diffusion coefficient at this temperature [see equation (16-8)]. Notice that one is dealing with a *cube root*.

16-15 The intrinsic viscosities, $[\eta]$, of several molecular weight fractions, M , of a new cellulose plasma extender were obtained by plotting η_{sp}/c for each fraction versus the concentration, c , in g/dL (where $1 \text{ dL} = 100 \text{ cm}^3$) as seen in Figure 16-10. The resulting intrinsic viscosities, together with the molecular weights, M , determined separately by osmotic pressure [equation (16-12)] at 25°C , are given as follows:

Data for Problem 16-15

$M \text{ (g/mole)}$	67,820	153,756	202,200	329,150
$[\eta] \text{ (dL/g)}$	1.21	2.65	3.54	5.56

- (a) Plot $\ln[\eta]$ as the dependent variable versus $\ln M$ (M = molecular weight) to obtain the constants K and a of the Mark–Houwink equation.
- (b) Use the values of K and a in the Mark–Houwink expression [equation (16–24)] to calculate the molecular weight of a newly synthesized cellulose plasma extender, the experimentally determined intrinsic viscosity of which is 7.83 dL/g.

16–16 The zeta potential, ζ , for a colloidal system in an aqueous electrolyte solution is given by the formula

$$\zeta = \frac{4\pi\eta v}{\epsilon E} (9 \times 10^4) \quad (1)$$

where 9×10^4 converts electrostatic units into volts.

- (a) The term “ $4\pi\eta/\epsilon (9 \times 10^4)$ ” is given on page 400 as equal to approximately 128 at 25°C and 141 at 20°C. Refer to a handbook of chemistry and physics for the viscosity in poise (dynes sec/cm²) or g/(cm sec) and the dielectric constant, ϵ at 20°C and 25°C and verify the values 128 and 141 for this term in equation (16–28).
- (b) The electrophoretic mobility, v/E (in cm/sec per volt/cm), for bentonite in water is given by Schott⁵ as $-3.39 (\pm 0.07) \times 10^{-4}$ at 24°C. The quantity ± 0.07 in parentheses indicates that the value -3.39 was measured experimentally to within a precision of $(-3.39 - 0.07) \times 10^{-4}$ to $(-3.39 + 0.07) \times 10^{-4}$. The electrophoretic mobility of bismuth subnitrate particles (13.18% w/w) in water at 24°C to 25°C is $+2.20 \pm (0.09) \times 10^{-4}$ cm/sec per volt/cm. Calculate the zeta potential of bentonite and of bismuth subnitrate at 25°C. Why do we find both positive and negative zeta potential values in this problem?

16–17 Compute the ratio of concentrations at equilibrium of diffusible benzylpenicillin ions *outside* to those *inside* a semipermeable membrane when the concentration of an anionic polyelectrolyte inside the sac is 12.5×10^{-3} g equivalent per liter and that of benzylpenicillin inside the sac is 3.20×10^{-3} mole/liter at equilibrium. Set up the Donnan membrane equilibrium [see equation (16–34)] and solve the equation for the ratio of diffusible benzylpenicillin ions outside to those inside the membrane.

16–18 The Donnan effect is important in concentrating ions in various body fluid compartments. The interstitial fluid of the body lies between the vascular system with its plasma and erythrocytes and the tissue cells of the body. The plasma and the cells contain nondiffusible protein anions, whereas the interstitial fluid contains only diffusible ions such as K^+ , Na^+ , and Cl^- . Therefore, the Donnan membrane effect in the body is to influence the distribution of the diffusible ions. The

protein anions tend to attract and retain small cations (K^+ and Na^+) in the tissue cells and blood vessels and repel small anions (Cl^-) into the surrounding interstitial fluid.

In the normal body the concentration of plasma protein is 16 mEq/liter and that of the chloride ions is 113 mEq/liter. What is the ratio of chloride ions across the interstitial (fluid_(outside) – plasma_(inside)) membrane? *Hint:* The Donnan membrane principle [equation (16–33)] is used to calculate the ratio of chloride ions.

16–19 The diffusion of a drug compound solubilized in a micelle and hindered by passage through microporous membranes provides a method of controlling the release of the drug.

The ratio of the diffusion coefficient of a spherical particle in a cylindrical pore (D_p) relative to the diffusion coefficient of the same particle in free solution (D) is given by the following equation⁶:

$$D_p/D = (1 - \xi)^2 [1 - 2.1044 \xi^2 + 2.089 \xi^3 - 0.948 \xi^5] \quad (2)$$

where ξ is r/r_p , the ratio of the particle-to-pore radii, and D_p is the intrapore diffusion coefficient. When the radius of the particle is much smaller than the radius of the pore, the intrapore diffusion coefficient is practically the same as the diffusion coefficient in free solution.

The diffusion of pyrene solubilized in micelles of the surfactant sodium dodecyl sulfate across microporous membranes at 25°C was studied by Johnson et al.⁶ The radius of the micelle is 26 Å and the viscosity of the solvent 0.089 poise. The pore radius of the membrane is 283 Å.

- (a) Compute the diffusion coefficient, D , of the micelle in the free solution [see equation (16–7), page 395].
- (b) Compute the diffusion coefficient, D_p , of the micelle particle in the pore. Compare this value to the diffusion coefficient of free pyrene (not present in micellar form), which is determined in a separate experiment, $D_{\text{free}} = 5.6 \times 10^{-6}$ cm²/sec. The radius of the pyrene molecule is approximately 2.5 Å.
- (c) Comment on your results.

References

1. D. Attwood and O. K. Udeala, *J. Pharm. Pharmacol.* **26**, 854, 1974.
2. H. V. Tartar and A. L. M. Lelong, *J. Phys. Chem.* **59**, 1185, 1956.
3. D. J. Shaw, *Introduction to Colloid and Surface Chemistry*, Butterworths, Boston, 1970, pp. 20, 21.
4. J. Kirschbaum, *J. Pharm. Sci.* **63**, 981, 1974.
5. H. Schott, *J. Pharm. Sci.* **65**, 855, 1976.
6. K. A. Johnson, G. B. Westermann-Clark, and D. O. Shah, *J. Colloid Interface Sci.* **130**, 480, 1989.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 18: MICROMERITICS

18-1 $d_{In} = 16.7 \mu\text{m}$; $d_{vs} = 23 \mu\text{m}$; $S_w = 1740 \text{ cm}^2/\text{g}$.

18-2 $d_{In} = 16.5$; $d_{vs} = 19.5$; $d_{wm} = 20.6 \mu\text{m}$.

18-3 $2.47 \times 10^{-4} \text{ cm} = 2.47 \mu\text{m}$.

18-4 $2.0 \times 10^4 \text{ cm}^2/\text{g}$ or $2.0 \text{ m}^2/\text{g}$.

18-5 $6 \times 10^4 \text{ cm}^2$ or 6 m^2 .

18-6 (a) Slope, $S = 7096.56 \text{ g}^{-1}$, intercept, $I = 123.98 \text{ g}^{-1}$; (b) $S_w = 0.482 \text{ m}^2/\text{g}$; $d_{vs} = 8.56 \mu\text{m}$.

18-7 $S_w(\text{before}) = 14.8 \text{ m}^2/\text{g}$; $S_w(\text{after}) = 1131 \text{ m}^2/\text{g}$.

18-8 (a) Check your answer with pages 458 to 460. (b) *Partial Answer*: 6.7 and 9.2 Å; (c) *Partial Answer*: for $p/p_o = 0.2$ and $r < 6.7 \text{ Å}$, pore volume is 54.9%; (d) 5.5%.

18-9 69.8%.

18-10 (a) 3.14; (b) 0.019 or 1.9%.

18-11 40%.

18-12 3%.

18-13 2%.

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 18: MICROMERITICS

- 18-1** Suppose that, by means of an optical microscope, the following hypothetical data were collected:

Data for Problem 18-1

Diameter (μm)	10	20	30
Number (n) of particles	3	2	1

Compute the arithmetic (length-number) mean particle diameter, d_{ln} , the mean volume surface diameter, d_{vs} , and the specific surface in cm^2/g , assuming that the particles have a true density of 1.5 g/cm^3 and are spherical.

- 18-2** A sample of silica was analyzed by the microscope method and the following data were collected:

Data for Problem 18-2

Diameter (μm)	10	15	20	25
Frequency (n)	73	77	82	37

Compute d_{ln} , d_{vs} , and d_{wm} .

- 18-3** Using the Stokes's-law equation (18-6), calculate the particle diameter, d_{st} , of magnesium oxide powder, $\rho = 3.65 \text{ g/cm}^3$, in an aqueous medium having a density of $\rho_0 = 1.05 \text{ g/cm}^3$ at 25°C and a viscosity of 0.013 poise (i.e., $0.013 \text{ g cm}^{-1} \text{ sec}^{-1}$). The particles settle a distance of 24.0 mm in 1.00 hr under gravity acceleration g of 980 cm/sec^2 . *Hint:* Remember to convert 24.0 mm/hr to cm/sec for the rate of settling of the particles.
- 18-4** What is the specific surface, S_V , of the particles of a sulfathiazole powder having a particle density of 1.5 g/cm^3 and an average diameter, d_{vs} , of $2 \mu\text{m}$? It is assumed that the particles are perfect spheres.
- 18-5** What is the total surface in cm^2 of 4 g of a local anesthetic powder in which the particles have an average diameter, d_{vs} , of $2 \times 10^{-4} \text{ cm}$ and a true density of 2.0 g/cm^3 . Assume that the particles are spheres.
- 18-6** Millan-Hernandez (B. Millan-Hernandez, *Physical Chemical Properties of Pharmaceutical Suspensions*, Thesis, University of Texas, 1981) obtained the specific surface, S_w , and the mean volume surface diam-

eter of micronized griseofulvin powder. In the experimental work using the Quantasorb apparatus, one replaces V and V_m of equation (18-18) by the masses X and X_m . At the final stage of the work, X_m is converted to V_m by dividing X_m , the mass of nitrogen, by its density:

$$\frac{X_m \text{ gram gas/gram powder}}{\rho_{N_2} = 1.250 \times 10^{-3} \text{ g/cm}^3} = V_m \text{ cm}^3/\text{gram powder} \quad (1)$$

Nitrogen gas is introduced into the apparatus at three pressures, p , in mm Hg, and X , the number of grams of nitrogen gas adsorbed on the powder sample, is recorded. The saturated vapor pressure, $p_0 = 758.71 \text{ mm Hg}$, for N_2 at its boiling point, 77.2 K , is also required for the calculations. The data for p/p_0 and $p[X(p_0 - p)]$ are obtained for each of the three gas pressures, and $p/[X(p_0 - p)]$ is plotted on the vertical axis against p/p_0 on the horizontal axis. See equation (18-18), page 455, and *Example 18-7*.

The data for one experiment are as follows:

Data for Problem 18-6

p/p_0 (x axis)	0.0970	0.1970	0.2920
$p/[X(p_0 - p)]$ (y axis)	815.58	1515.37	2199.58

- (a)** Using linear regression analysis, obtain the slope, $S = (b - 1)/(X_m b)$, and the intercept, $I = 1/(X_m b)$. These terms conform to the slope and intercept in equation (18-18) except that X and X_m have replaced V and V_m . By simple algebra, it can be shown that the reciprocal of the sum of the slope, S , and the intercept, I , yields the value of mass, X_m , of N_2 gas that 1 g of the powder can adsorb. That is,

$$X_m = \frac{1}{S + I} \quad (2)$$

- (b)** Then, using the density of N_2 , $1.250 \times 10^{-3} \text{ g/cm}^3$, convert X_m to V_m (cm^3/g) and obtain the specific surface, S_w (m^2/g), and d_{vs} . The density of griseofulvin is 1.455 g/cm^3 .

- 18-7** A sample of charcoal was analyzed in the BET apparatus before and after activation and the V_m values obtained were 3.4 and $260 \text{ cm}^3/\text{g}$, respectively. Calculate the specific surface of the charcoal before and after activation.

- 18-8** The experimental values of a water adsorption/desorption isotherm at 20°C on a type of clay are given in the following table.

Data for Problem 18-8*

p/p_0	V_1 (Adsorption) (mL/g)	V_2 (Desorption) (mL/g)
0.20	0.079	0.123
0.31	0.109	0.147
0.35	0.129	0.150
0.40	0.135	0.165
0.45	0.141	0.177
0.49	0.141	0.182
0.56	0.150	0.188
0.66	0.152	0.191
0.77	0.161	0.194
0.80	0.170	0.200
0.89	0.182	0.209
0.96	0.224	0.224

*Values in this chart are from Figure 7 in S. Yamanaka, P. B. Malla, and S. Komareni, *J. Colloid Interface Sci.* **134**, 51, 1990.

- (a) Plot V_1 (adsorption) and V_2 (desorption) on the vertical axis against p/p_0 (horizontal axis). What is the meaning of this isotherm?
- (b) Using the Kelvin equation (18-24), compute the radius of the pores corresponding to the relative pressures given in the table. See *Example 18-8*.
- (c) Assuming that all pores are of radius less than 265 Å, compute the cumulative percent of pore volume with radii less than those found in part (b).
- (d) Compute the percent of pore volume with radius between 40 and 60 Å.
- 18-9** Calculate the porosity of a sample of aluminum oxide having a true density of 4.0 g/cm³. When 75 g of the powder was placed in a graduate cylinder, the Al₂O₃ was found to have a bulk volume of 62 cm³.
- 18-10** (a) If the weight of a tablet is 0.2626 g and its bulk volume is 0.0836 mL, what is the bulk density?
(b) If the true density of the mixture of ingredients is 3.202, what is the porosity of the tablet?
- 18-11** Calculate the percent porosity of a sample of talc that has a true density of 2.70 g/cm³. When 324 g of the powder was placed in a graduate, the talc was found to have a bulk volume of 200 mL.
- 18-12** The true density of aspirin is 1.37 and the granule density is 1.33. What is the porosity or percent void spaces within the granules?
- 18-13** The true density of a powder mixture is 3.203. When compressed into tablet form, the granule density of the mixture is found to be 3.138. What is the porosity of the tablet?

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 19: RHEOLOGY

19-1 (a) $E_v = 3684 \text{ cal/mol}$; (6)

Temperature °C	29°	45°	88°
η (cp) (calculated)	0.8484	0.6231	0.3114
1982–83 CRC Handbook, p F-40	0.8148	0.5960	0.3221

19-2 38 poise.

19-3 *Partial Answer:* (a) For n (rpm) = 100, $G = 1875 \text{ sec}^{-1}$; for S (scale reading) = 72, $F = 1536.5 \text{ dynes/cm}^2$; (b) $N = 2.624$ (a dimensionless number); $\eta' = 106,724 \text{ poise (dynes sec/cm}^2)$; (d) When the shear rate, G , is 1875 sec^{-1} the shear stress, F , has a value, by back-calculation, of $1457 \text{ dynes cm}^{-2}$. *Note:* η' , the antilog of $\ln \eta'$, is a rather large number. The student should not be surprised to find η' in the thousands or millions of poise.

Another approach to solving for F is as follows. One begins with the expression $\ln G = -\ln \eta' + N \ln F$ and from regression analysis using this equation one obtains $\eta' = 106,724$ and $N = 2.6239$. Therefore, using $F^N = \eta'G$, for $G = 1875 \text{ sec}^{-1}$,

$$F^{2.6239} = (106,724)(1875) = 2.00107 \times 10^8 \quad (1)$$

Using the y^x key on a handheld calculator, you can run through the exercise, $2^3 = 8$; therefore; $2 = 8^{1/3}$. With this kind of operation applied in our problem, we find $F^{2.6239} = 200,107,000$, $F = 200,107,000^{1/2.6239} = 200,107,000^{0.381112}$; $F = 1458 \text{ dynes/cm}^2$.

19-4 f (yield value) = $9200 \text{ dynes cm}^{-2}$; $U = 10 \text{ poise}$.

19-5 $U_1 = 18.5 \text{ poise}$; $U_2 = 7.2 \text{ poise}$; $B = 24 \text{ dynes sec/cm}^2$.

19-6 $U_1 = 11 \text{ poise}$, $U_2 = 16 \text{ poise}$; $f_1 = 1972 \text{ dynes cm}^{-2}$, $f_2 = 1526 \text{ dynes cm}^{-2}$; $M = 10 \text{ dynes sec cm}^{-2}$.

19-7 *Partial Answer:* $k_v = 1.9376$; viscosity of oil number 1 = 8.970 poise . From the table, the NBS value for oil number 1 is 9.344 poise . Our result is therefore in error by 4%.

19-8 *Partial Answer:* For oil number 1, $\eta = 2.704 \text{ poise}$.

19-9 (a) $C_f = 113.57 \text{ cm}^{-3}$; (b) $f = 3919 \text{ dynes cm}^{-2}$; (c) $U = 8.876 \text{ poise}$.

19-10 (a) 27339 sec or 7.59 hr ; (b) Need a wider bore pipette and a liquid with a higher viscosity as the reference.

19-11 The viscosity of the patient's blood was also measured in a capillary viscometer at 37°C and found to be 0.0372 poise . How does your calculated result compare with this experimentally determined viscosity of the blood?

19-12 See several of the works listed below:

- B. W. Barry and A. J. Grace, *J. Pharm. Sci.* **60**, 1198, 1971; *J. Pharm. Sci.* **61**, 335, 1972.
- B. W. Barry and M. C. Meyer, *J. Pharm. Sci.* **62**, 1349, 1973.
- E. L. Cussler, S. J. Zlolnick, and M. C. Shaw, *Perception Psychophys.* **21**, 504, 1977.
- H. B. Kostenbauder and A. Martin, *J. Am. Pharm. Assoc. Sci. Ed.* **43**, 401, 1954.
- G. W. Scott-Blair, *Elementary Rheology*, Academic Press, New York, 1969.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 20: PHARMACEUTICAL POLYMERS

- 20-1 (b)
- 20-2 (c)
- 20-3 (b)
- 20-4 (d)
- 20-5 (d)
- 20-6 (b)
- 20-7 (b)
- 20-8 (c)
- 20-9 (e)
- 20-10 (a)
- 20-11 (a)
- 20-12 (d)
- 20-13 (b)
- 20-14 (d)
- 20-15 (d)
- 20-16 50,000 (49,500 has three significant figures, which is more than the M values of the input).
- 20-17 $\overline{M}_z = 401,000$; $\overline{M}_w = 162,000$; $\overline{M}_n = 43,500$; and $\overline{M}_w/\overline{M}_n = 3.73$.
- 20-18 The intrinsic viscosity of polyethylene oxide will decrease, as higher temperature favors polymer-polymer interactions and reduces the polymer-water interaction. Higher temperature results in partial to incomplete insolubility of polyethylene oxide in water.
- 20-19 Decreasing trend of the melting point is associated with decreased intermolecular interactions as the size of the pending group increases.
- 20-20 (b)
- 20-21 (a)
- 20-22 (d)
- 20-23 (b)
- 20-24 (e)

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 20: PHARMACEUTICAL POLYMERS

- 20-1** There are three monomers: M1, M2, and M3; M1 contains one double bond and no functional group, M2 contains one reactive functional group and no double bond, and M3 contains two reactive functional groups and no double bond. Which statement is *true*?
- (a) All three monomers can be polymerized via addition and condensation polymerization.
 - (b) M1 can be polymerized via addition, M2 cannot be polymerized, and M3 can be polymerized via condensation.
 - (c) M1 can be polymerized via addition, and both M2 and M3 can be polymerized via condensation.
 - (d) None of the monomers are polymerizable.
- 20-2** Which statement is *true* regarding polymer molecular weight?
- (a) Number average molecular weight is related to the size of the polymer chains.
 - (b) Weight average molecular weight is related to the number of polymer chains.
 - (c) Polydispersity is related to the number and the size of the polymer chains.
 - (d) Number average molecular weight is always bigger than the weight average molecular weight.
- 20-3** The T_g values of the two polymers P1 and P2 are -20°C and 100°C , respectively. Which statement is *true*?
- (a) At room temperature of 25°C , both P1 and P2 are rubber.
 - (b) At room temperature of 25°C , P1 is rubber but P2 is glass.
 - (c) At room temperature of 25°C , both P1 and P2 are glass.
 - (d) At room temperature of 25°C , P1 is glass but P2 is rubber.
- 20-4** Which statement is *false* regarding the T_g and T_m of a given polymer?
- (a) T_m is a first-order thermal transition but T_g is a second-order one.
 - (b) T_g and T_m are related to the amorphous and crystalline parts of the polymer chain, respectively.
 - (c) T_g has a broader temperature range than does T_m .
 - (d) For a given polymer, T_g is always higher than T_m .
- 20-5** Which statement is *true* for the elastic properties of polymers?
- (a) A low modulus polymer is stiffer than a high modulus polymer.
 - (b) A high modulus polymer is tougher than a low modulus polymer.
 - (c) Stiffness is the ratio of strain to stress.
 - (d) Toughness is the area under stress and strain curve; energy to break.
- 20-6** If you are asked to increase the viscosity of water with a minimum amount of the following polymers, which polymer would be your choice?
- (a) A very hydrophilic and low-molecular-weight polymer.
 - (b) A very hydrophilic and high-molecular-weight polymer.
 - (c) A very hydrophobic and low-molecular-weight polymer.
 - (d) A very hydrophobic and high-molecular-weight polymer.
- 20-7** In preparing a water-soluble polymer, which action would be wrong?
- (a) Using a water-soluble monomer
 - (b) Utilizing emulsion technique
 - (c) Utilizing inverse-emulsion technique
 - (d) Utilizing inverse-suspension technique
- 20-8** Pseudo latex is a
- (a) Dispersion of a monomer in water.
 - (b) Dispersion of a water-soluble polymer in water.
 - (c) Dispersion of a water-insoluble polymer in water using high HLB surfactant(s).
 - (d) Dispersion of a water-insoluble polymer in water using low HLB surfactant(s).
- 20-9** Which of the following statements is *true* for a dispersion system?
- (a) In a W/O system, the dispersed phase is water, and the continuous phase is oil.
 - (b) In an O/W system, the dispersed phase is oil, and the continuous phase is water.
 - (c) Surfactant should be more soluble in the continuous phase.
 - (d) Surfactant concentration determines the size of the dispersed phase.
 - (e) All of the above are true.

- 20-10** Which of the following polymers can be used as an enteric coating material?
- An anionic polymer.
 - A cationic polymer.
 - An amphoteric polymer.
 - Both anionic and cationic polymers.

- 20-11** For taste-masking application, what polymer would you *not* recommend to use?
- A polymer which is soluble in water at neutral pH.
 - A polymer which is soluble in water at low pH.
 - A polymer which is insoluble in water at all pHs.
 - An oil-soluble polymer.

- 20-12** Which statement is *false* about polydispersity and chain length?
- A monodispersed polymer contains similar chains.
 - A polydispersed polymer contains different chains.
 - Polydispersity $\gg 1$ means polymer chains are very different in size.
 - Polydispersity is always lower than 1.

- 20-13** You have two polymers with different T_g values: polymer 1 (-90°C) and polymer 2 (90°C). If you are asked to coat your tablet with these polymers, which one would you select?
- Polymer 1.
 - Polymer 2.

- 20-14** Which statement is *false*?
- Polymers do not exist as gas.
 - Monomers containing double bond may be polymerized via free radicals.
 - Polymers containing high concentrations of residual monomers may not be suitable for pharmaceutical use.
 - Different isomers of a polymer have same physicochemical and mechanical properties.

- 20-15** A pharmaceutical packaging material requires being a tough polymer, the tougher the better. After testing different polymers using a mechanical tester, you select
- A polymer which shows high modulus.
 - A polymer which deforms less at its failure or breaking point.
 - A polymer which shows high stiffness.
 - A polymer whose force-deformation curve has the largest area.

- 20-16** A polymer sample was fractionated into three homogeneous or monodisperse fractions as follows:

Data for Problem 20-16

Fraction	Weight, Grams	Molecular Weight
A	10	100,000
B	20	
C	100	10,000

Given that the weight-average molecular weight of the entire sample is 23,000, calculate the molecular weight of fraction B.

- 20-17** A sample of polyvinyl chloride was fractionated from its solution in tetrahydrofuran. The weight percent (based on the weight of the entire sample) and the molecular weight (g/mole) of successive fractions were as follows:

Data for Problem 20-17

Fraction Number	Weight (%)	Molecular Weight
1	6	7×10^3
2	9	1.7×10^4
3	15	3.8×10^4
4	20	7.5×10^4
5	23	1.4×10^5
6	16	2.5×10^5
7	8	4.5×10^5
8	3	1.05×10^6

Assuming that the fractions are essentially monodisperse, calculate \overline{M}_z , \overline{M}_w , \overline{M}_n , and $\overline{M}_w/\overline{M}_n$ of the polyvinyl chloride sample.

- 20-18** Will the intrinsic viscosity of polyethylene oxide increase, decrease, or remain unaffected as the temperature of its aqueous solution is increased?

Hint: Express your answer in terms of hydration.

- 20-19** The melting points of some isotactic polyolefins $\dagger \text{CH}_2-\underset{\text{R}}{\text{CH}} \dagger$ are as follows:

	R	Melting Point, $^\circ\text{C}$
E	$-\text{CH}_3$	165
F	$-\text{C}_2\text{H}_5$	125
G	$-\text{CH}_2-\text{CH}_2-\text{CH}_3$	75

Explain the trend in melting point when going from E to F to G.

- 20-20** Drugs targeted for colon diseases may be formulated into a material (a polymer) which can protect them from the harsh low pH environment of the gastric medium. The material selected for such application should have
- (a) High solubility or complete solubility at low pH.
 - (b) No solubility or low solubility at low pH.
- 20-21** Coacervation is a process by which a drug is encapsulated inside a polymeric matrix by precipitating the polymer in solution. If the drug is sensitive to heat and acid, which option would be least attractive for precipitating the polymer from its aqueous solution?
- (a) Increasing the temperature of the polymer solution.
 - (b) Adding an effective but permitted amount of alcohol to the polymer solution.
 - (c) Increasing the pH of the polymer solution.
 - (d) Increasing the ionic strength of the polymer solution by adding reasonable amounts of salts.
- 20-22** Which of the following materials displays thermogelling at a higher temperature?
- (a) Cellulose (has no solubility in water).
 - (b) Cellulose with methyl substitution (it is soluble in cold water).
 - (c) Thermogelling is not dependent on the number and nature of substituents.
 - (d) Cellulose with methyl and hydroxypropyl substitution (it is soluble in water over a wider temperature range).
- 20-23** If the solution property of a material is sensitive to temperature, that material displays thermogelling property. Which of the following materials less likely displays a thermogelling property?
- (a) A material containing both hydrophilic and hydrophobic groups.
 - (b) A material with ionizable hydrophilic groups.
 - (c) A material whose chains can aggregate if temperature changes.
 - (d) A material whose hydrophobic groups associate if temperature rises.
- 20-24** Swelling concept has found applications in which of the following areas?
- (a) Superdisintegrants, which are used in tablets and capsules to help the dosage form to disintegrate properly.
 - (b) Osmotic tablets (Oros technology), which can deliver the drug at a constant rate over a 24-hr period.
 - (c) Implantable osmotic pumps (Duros technology), which can deliver the drug over a few months to a 1-year period.
 - (d) Superabsorbent polymers, which are used in ultra-thin baby diapers to absorb baby's urine.
 - (e) All of the above.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 22: ORAL SOLID DOSAGE FORMS

22-1 From equation (22-6):

$$\begin{aligned}\text{Log}(S) &= -\log(P) - 0.01 \times (\text{MP}) + 1.05. \\ \text{Log}(S) &= -1.6 - 0.01 \times (153) + 1.05 \\ \text{Log}(S) &= -2.08 \\ S &= 10^{-2.08} \text{ mole/L} \\ S &= 8.32 \times 10^{-3} \text{ mole/L} \\ S &= 8.32 \times 10^{-3} \text{ mole/L} \times 230.8 \text{ g/mole} \\ &= 1.9 \text{ g/L} = 1.9 \text{ mg/mL}\end{aligned}\quad (1)$$

The measured solubility is reported to be approximately 4 mg/mL.

22-2 From equation (22-5):

$$\begin{aligned}\text{Flux} &= P_m \times C_d \\ \text{Flux} &= (8 \times 10^{-4} \text{ cm/sec}) \times (4 \text{ mg/mL}) \\ &= 3.2 \times 10^{-3} \text{ mg/cm}^2/\text{sec}\end{aligned}\quad (2)$$

Assuming 50 cm² of absorptive surface area, the rate of absorption is as follows:

$$\begin{aligned}\text{Rate of absorption} &= (3.2 \times 10^{-3} \text{ mg/cm}^2/\text{sec}) \times (50 \text{ cm}^2) \\ &= 0.16 \text{ mg/sec} = 9.6 \text{ mg/min}\end{aligned}\quad (3)$$

Amount of drug absorbed through 50-cm² intestinal area in 30 min:

$$\begin{aligned}\text{Amount absorbed in 30 min} &= (9.6 \text{ mg/min}) \\ &\times 30 \text{ min} = 288 \text{ mg}\end{aligned}\quad (4)$$

A typical dose of naproxen is 250 to 500 mg, so absorption is expected to be rapid.

22-3 From equation (22-10), solving for r_o

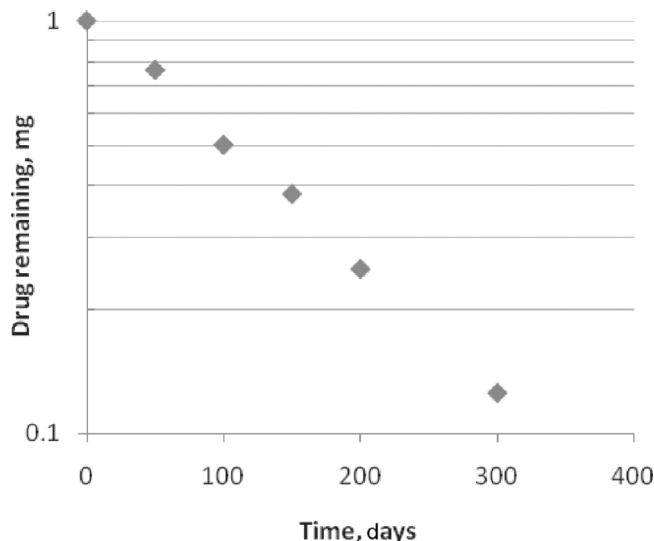
$$\begin{aligned}r_o &= \sqrt{\frac{2 \cdot (7 \times 10^{-6} \text{ cm}^2/\text{sec}) \cdot (6 \times 10^{-6} \text{ g/mL}) \cdot (30 \text{ min}) \times (60 \text{ sec/min})}{1.5 \text{ g/cm}^3}} \\ r_o &= 3.2 \mu\text{m}\end{aligned}\quad (5)$$

$$\begin{aligned}\text{22-4} \quad S_T &= (0.010 \text{ mg/mL}) \cdot (1 + 10^{(2-4.5)}) = 0.01 \frac{\text{mg}}{\text{mL}} \\ S_T &= (0.010 \text{ mg/mL}) \cdot (1 + 10^{(4-4.5)}) = 0.013 \frac{\text{mg}}{\text{mL}} \\ S_T &= (0.010 \text{ mg/mL}) \cdot (1 + 10^{(4.5-4.5)}) = 0.02 \frac{\text{mg}}{\text{mL}} \\ S_T &= (0.010 \text{ mg/mL}) \cdot (1 + 10^{(6-4.5)}) = 0.326 \frac{\text{mg}}{\text{mL}} \\ S_T &= (0.010 \text{ mg/mL}) \cdot (1 + 10^{(8-4.5)}) = 31.6 \frac{\text{mg}}{\text{mL}}\end{aligned}\quad (6)$$

Note that the total solubility is equal to twice the intrinsic solubility when the pH = pK_a because 50% of the drug is ionized at that pH. Also note the rapid increase in solubility as the pH exceeds the pK_a for an acid.

22-5 From Figure 22-6, a 1-mg dose would require a particle diameter of approximately 150 μm or less to consistently achieve acceptable content uniformity, so an active ingredient with a particle diameter of 200 μm would not be adequate to achieve the necessary content uniformity. From Figure 22-6, several options exist that would require particle size reduction to achieve the desired content uniformity. Among the options include the following: (a) a mean particle diameter of approximately 70 μm with a relatively narrow particle size distribution (geometric standard deviation, σ_g, of 2.0), (b) a mean particle diameter of approximately 25 μm with a relatively moderately broad particle size distribution (geometric standard deviation, σ_g, of 3.0), or (c) a mean particle diameter of approximately 8 μm with a very broad particle size distribution (geometric standard deviation, σ_g, of 4.0).

22-6 Plotting the log of the drug remaining as a function of time shows a linear relationship consistent with first-order decomposition.



The half-life for decomposition can be estimated by calculating the slope between two points. For example,

$$\text{Slope} = \frac{\ln(0.125) - \ln(0.76)}{300 - 50} = -0.0072 \text{ day}^{-1} \quad (7)$$

A more accurate value for the slope can be obtained by regression analysis.

The half-life, $t_{1/2}$, can be calculated as follows:

$$t_{1/2} = \frac{\ln(0.5)}{\text{Slope}} = \frac{-0.693}{-0.0072} = 96 \text{ days}$$

$$t_{90\%} = \frac{\ln(0.9)}{\text{Slope}} = \frac{-0.105}{-0.0072} = 14.6 \text{ days} \quad (8)$$

This stability profile at elevated temperature of 50°C would not likely be sufficient for a marketed product. However, it could potentially be used in early clinical studies if the product was stored properly such as under refrigerated conditions. However, further stability testing to assess stability at room temperature (25°C) or refrigerated conditions would be necessary before it could be used in clinical studies. Characterization of degradation products (see Table 22–19) would also be necessary if they were present in significant quantities.

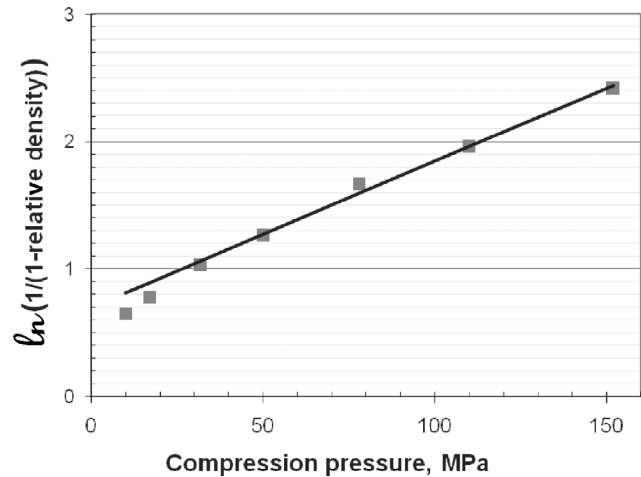
22-7 Calculate the volume for each tablet (volume = $\pi \times (\text{radius})^2 \times \text{thickness}$), the tablet density (tablet density = weight/volume), and the tablet relative density, D (using equation 22–23).

Tablet Thickness (cm)	Tablet Radius (cm)	Tablet Weight (g)	Compression Pressure (MPa)	Tablet Volume (cm ³)	ρ_s Tablet Density (g/cm ³)	D Tablet Relative Density
0.350	0.500	0.205	10	0.275	0.746	0.48
0.306	0.500	0.203	17	0.240	0.845	0.54
0.253	0.500	0.199	32	0.199	1.001	0.64
0.230	0.500	0.202	50	0.181	1.118	0.72
0.202	0.500	0.201	78	0.159	1.267	0.81
0.192	0.500	0.202	110	0.151	1.340	0.86
0.181	0.500	0.202	152	0.142	1.421	0.91

22-8 Calculate the volume for each tablet, the tablet density, and the tablet relative density. Calculate $1/(1-D)$ and plot this value for each compression pressure on a logarithmic scale (natural log).

Tablet Properties							
Tablet Thickness (cm)	Tablet Radius (cm)	Tablet Weight (g)	Compression Pressure (MPa)	Tablet Volume (cm ³)	ρ_s Tablet Density (g/cm ³)	D Tablet Relative Density	1/(1-D)
0.350	0.500	0.205	10	0.275	0.746	0.478	1.92
0.306	0.500	0.203	17	0.240	0.845	0.541	2.18
0.253	0.500	0.199	32	0.199	1.001	0.642	2.79
0.230	0.500	0.202	50	0.181	1.118	0.717	3.53
0.202	0.500	0.201	78	0.159	1.267	0.812	5.32
0.192	0.500	0.202	110	0.151	1.340	0.859	7.08
0.181	0.500	0.202	152	0.142	1.421	0.911	11.22

Plot $\ln(1/(1-D))$ versus compression pressure to obtain a Heckel plot.



The last five data points appear to be linear as plotted in the Heckel plot. The slope of this linear region of the plot can be calculated using linear regression.

D Tablet Relative Density	Compression Pressure (MPa)	1/(1-D)	$\ln(1/(1-D))$
0.48	10	1.92	0.650
0.54	17	2.18	0.780
0.64	32	2.79	1.027
0.72	50	3.53	1.262
0.81	78	5.23	1.672
0.86	110	7.08	1.957
0.91	152	11.22	2.418

The slope of the last five data values ($\ln(1/(1-D))$ versus compression pressure) is:

$$\text{Slope} = 0.0115. \quad (9)$$

PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 22: ORAL SOLID DOSAGE FORMS

22-1 Use the Yalkowsky–Valvani equation (22-6) to estimate the aqueous solubility of naproxen in mg/mL. The melting point of naproxen = 153°C, the logP = 1.6, and the molecular weight = 230.8 g/mole.

22-2 Calculate the flux of naproxen and the rate of absorption (in mg/min) possible through approximately 50 cm² of intestinal surface area of the intestinal tract. Naproxen solubility is approximately 4 mg/mL and the intestinal permeability, P_m, is approximately 8 × 10⁻⁴ cm/sec. Estimate the amount of drug absorbed in 30 min.

22-3 Estimate the particle radius, assuming spherical geometry, necessary to achieve complete dissolution of celecoxib in 30 min. Celecoxib aqueous solubility is approximately 0.006 mg/mL and the aqueous diffusion coefficient is estimated to be 7 × 10⁻⁶ cm²/sec at 37°C with a true density of approximately 1.5 g/cm³.

22-4 Calculate the total solubility of a saturated solution of an experimental drug, a weak acid, at pH = 2, 4, 4.5, 6, and 8 with an intrinsic solubility = 0.010 mg/mL and pK_a = 4.5.

22-5 Content uniformity is a critical product attribute. A new active pharmaceutical is being considered for development and it will be necessary to manufacture a tablet formulation that contains 1 mg of active ingredient. The active ingredient's mean particle diameter produced for development is 200 μm. Can a tablet dosage form be reliably manufactured to consistently contain a 1-mg dose? If not, what particle size and size distribution is needed to assure successful manufacture?

22-6 The concentration of drug in a tablet formulation was determined by HPLC as a function of time at elevated

temperature (50°C) as shown in the following table. Determine whether decomposition is zero order or first order and calculate the half-life, t_{1/2} and t_{90%}. Does this formulation exhibit sufficient stability to be used in early clinical studies?

Time, Days	Drug, mg
0	1.0
50	0.76
100	0.50
150	0.38
200	0.25
300	0.125

22-7 An experimental formulation has been successfully compressed into round flat-faced tablets with the properties given in the following table. Calculate the tablet density (in g/cm³) and the tablet relative density. The formulation has a true density of 1.56 g/cm³.

Tablet Thickness (cm)	Tablet Radius (cm)	Tablet Weight (g)	Compression Pressure (MPa)
0.350	0.500	0.205	10
0.306	0.500	0.203	17
0.253	0.500	0.199	32
0.230	0.500	0.202	50
0.202	0.500	0.201	78
0.192	0.500	0.202	110
0.181	0.500	0.202	152

22-8 Utilize the data in Question 22-7 to produce a Heckel plot. Calculate the slope of the terminal linear portion of the Heckel plot.

ANSWERS TO PRACTICE PROBLEMS FOR STUDENT USE

CHAPTER 23: DRUG DELIVERY AND TARGETING

- 23-1** (d)
- 23-2** (c)
- 23-3** (e)
- 23-4** (b)
- 23-5** (c)
- 23-6** (b)
- 23-7** (b)
- 23-8** (e)
- 23-9** (c)
- 23-10** (c)
- 23-11** (a)
- 23-12** (c)
- 23-13** (a)
- 23-14** (b)
- 23-15** (a)
- 23-16** (d)
- 23-17** (e)
- 23-18** (b)
- 23-19** (a)
- 23-20** (c)
- 23-21** (a) $2.058 \times 10^{-5} \text{ cm}^3$; (b) $23.67 \text{ } \mu\text{g}$; (c) $5.33 \text{ } \mu\text{g}/0.5 \text{ mL}$ or $10.66 \text{ } \mu\text{g/mL}$.
- 23-22** The molecular weight of this polylactide is 16,845 daltons = $16,845 \text{ g/mole} \cong 17,000 \text{ g/mole}$.
- 23-23** 20 atm.
- 23-24** $B_{40} = 3.61 \text{ } \mu\text{g}$.
- 23-25** (a) $V_m = 3.32 \times 10^{-4} \text{ M hr}^{-1}$; (b) $k_m = 4.75 \times 10^{-4} \text{ M}$; (c) $k_m = 4.74 \times 10^{-4} \text{ M}$; (d) $1/V = 6359.5 \text{ M}^{-1} \text{ hr}$; $V = 1.57 \times 10^{-4} \text{ molar concentration per hour (mole/liter/hr)}$.
- 23-26** 0.931 mg.
- 23-27** *Partial Answer:* (a) At pH 4.67, $P = 4.885 \times 10^{-6} \text{ cm/sec}$; $J = 1.80 \times 10^{-10} \text{ mole/(cm}^2 \text{ sec)}$; (b) At $t = 30 \text{ min}$, $M_B = 2.15 \times 10^{-7} \text{ mole}$; $M_{BH^+} = 1.98 \times 10^{-7} \text{ mole}$; (c) $t_L = 13 \text{ min}$.
- 23-28** *Partial Answer:* (a) J (without enhancer) = $0.0305 \text{ } \mu\text{g/(cm}^2 \text{ hr)}$; (b) J (after treatment with enhancer) = $0.739 \text{ } \mu\text{g/(cm}^2 \text{ hr)}$.
- 23-29** $C = 32.3 \text{ mg/mL}$.