JOURNAL OF CHEMICAL & ENGINEERING DATA

ARTICLE

pubs.acs.org/jced

Solubilities of Phloretin in 12 Solvents at Different Temperatures

Bingbo Li,[†] Ruopen Li,[‡] and Weidong Yan*,[†]

[†]Department of Chemistry, Zhejiang University, Hangzhou 310027, China

[‡]Skyherb Ingredients, Anji 313300, China

ABSTRACT: The solubilities of phloretin in methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, ethyl acetate, butyl acetate, 1,4-dioxane, and water were measured at $T = (288.2, 298.2, 308.2, 318.2, \text{and } 328.2)$ K and atmosphere pressure. The experimental results show that the phloretin is soluble in methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, ethyl acetate, butyl acetate, and 1,4-dioxane but insoluble in water. The solubilities of phloretin in selected solvents increase with increasing temperature. A simplified thermodynamic equation and a three-parameter Apelblat equation were used to correlate the experimental data.

INTRODUCTION

Phloretin [3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)-1-propanone, CAS no. 60-82-2; Figure 1] is a natural product found mainly in apples, pears, and other juicy fruits,[1−4] and it has many biological and pharmacological activities, such as moisturizing and antioxidative effects.[5,6] In addition to extraction from apples, nowadays phloretin can be prepared easily from the available compound dihydrochalcone (DHC). In order to get high-purity phloretin to meet the increasing demand for this compound in food, pharmaceutical, cosmetic, and health products, solubility data for phloretin in different solvents at different temperatures should be well-known. Unfortunately, solubility data for phloretin in different solvents have not been found in the literature.

In this work, the solubilities of phloretin in methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, ethyl acetate, butyl acetate, 1,4-dioxane, and water were measured at $T = (288.2, 298.2, 308.2, 318.2, \text{and } 328.2)$ K and atmosphere pressure. A simplified thermodynamic equation and a three-parameter Apelblat equation were used to correlate the experimental data

EXPERIMENTAL SECTION

Materials. The pale-red powder of phloretin (0.98 mass fraction) was supplied by Skyherb Ingredients Co., Ltd. (China). The phloretin was dissolved in a mixture of ethanol and water in a 3:2 mole ratio, refluxed for about 2 h, and recrystallized twice at room temperature. The phloretin was dried in a vacuum oven at $T = 378$ K for 24 h and stored in a desiccator to avoid absorption of water. The mass-fraction purity was 0.993 for the phloretin, as determined by high-performance liquid chromatography (HPLC) using a Shimadzu LC-10AD chromatograph. The melting point of phloretin was found to be $T = (534 \pm 0.3)$ K, as determined by a thermal analyzer (Netzsch STA409 PG/PC). All of the organic solvents (HPLC or analytical grade) were dried with (0.3 to 0.4) nm molecular sieves before use. Deionized water was distilled using a quartz sub-boiling purifier. The reference standard of apigenin, whose mass-fraction purity was 0.998, was purchased from Sigma Chemical Corporation (USA).

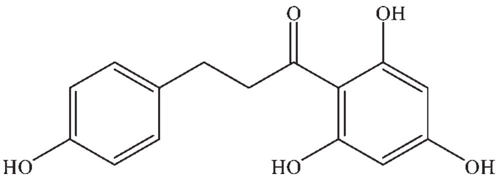

Figure 1. Structure of phloretin ($C_{15}H_{14}O_5$).

Solubility Measurements. Glass-stoppered conical flasks, each with a Teflon-coated magnetic stirrer, were used to prepare saturated solutions (about 50 mL) of phloretin with excess solid solute (about 0.5 g) in the 12 solvents. Each saturated solution with solid solute was then put into three glass-stoppered test tubes; each test tube contained about 10 mL of saturated solution and was stoppered and sealed with Parafilm to prevent evaporation of the solvent. Next, the test tubes were directly placed in a constant-temperature thermostatic bath (THJD-0510W, China) with a temperature stability of 0.05 K and a temperature uncertainty of 0.1 K. Undissolved solid and solution were allowed to settle for about (24 to 48) h in the dark to ensure solid−liquid equilibrium and stability of phloretin before sampling.

About 0.1 mL of the clear saturated solution was withdrawn from each test tube using a preheated glass syringe (1.0 mL). The glass syringe with saturated solution was weighed using an analytical balance (Sartorius CP225D) with an accuracy of ± 0.01 mg. In order to prevent evaporation of solvent during the weighing procedure, the needle was closed with silicon rubber. The saturated solution was injected into a volumetric flask (10 mL) immediately to prevent precipitation. After that, the mass of the glass syringe with the remaining solution was determined. The solutions of samples used in the analysis were diluted to the mark with methanol.

The solubility was determined using an HPLC system (Shimadzu LC-10AD). All of the chromatographic analyses were

Special Issue: John M. Prausnitz Festschrift

Received: October 31, 2010
Accepted: January 11, 2011
Published: February 02, 2011

performed on a Diamonsil ODS C_{18} column (250 mm × 4.6 nm, 5 μm) with the wavelength of the detector set at 280 nm. The mobile phase was composed of acetonitrile and a 0.002 mass fraction phosphoric acid solution in a 40:60 mass ratio at a flow rate of 1.0 $\text{mL}\cdot\text{min}^{-1}$. The reference standard solution containing about 0.3 $\text{mg}\cdot\text{mL}^{-1}$ of phloretin was prepared in methanol. The injected volumes of sample and reference standard solutions were 20 μL. All of the chromatograph procedures were performed at room temperature.

■ RESULTS AND DISCUSSION

Because of the low solubilities of phloretin in the selected solvents, HPLC was used to determine the concentration of a saturated solution of phloretin. To prove the reliability of the experimental method, known masses of phloretin were dissolved in methanol solutions and then determined by HPLC. The average relative uncertainty was 1.8 %.

The solubility data for phloretin in methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, ethyl acetate, butyl acetate, 1,4-dioxane, and water at T = (288.2, 298.2, 308.2, 318.2, and 328.2) K [as mole fractions (x_1) and molalities (m_1)] are presented in Table 1. Each solubility value is an average of three independent determinations in the same solvent. The expanded uncertainty (±) for each data point is also listed in Table 1. The experimental results show that the phloretin is soluble in methanol, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, butan-2-ol, pentan-1-ol, hexan-1-ol, ethyl acetate, butyl acetate, and 1,4-dioxane but insoluble in water.

According to the theory of solid−liquid phase equilibrium, the relationship between solubility and temperature is expressed as[7]

$$\ln\left(\frac{1}{\gamma_1 x_1}\right) = \frac{\Delta_{\text{fus}}H}{RT_{\text{t}}}\left(\frac{T_{\text{t}}}{T} - 1\right) - \frac{\Delta C_{\text{p}}}{R}\left(\frac{T_{\text{t}}}{T} - 1\right) + \frac{\Delta C_p}{R}\ln\frac{T_{\text{t}}}{T} \tag{1}$$

where γ_1 is the activity coefficient of phloretin on a mole fraction basis, x_1 is the mole-fraction solubility of phloretin, $\Delta_{\text{fus}}H$ is the enthalpy of fusion of phloretin, ΔC_p is the change of the heat capacity, T is the absolute temperature, T_{t} is the triple-point temperature of phloretin, and R is the gas constant. Equation 1 can be simplified to[7]

$$\ln(\gamma_1 x_1) = \frac{\Delta_{\text{fus}}H}{RT_{\text{m}}}\left(1 - \frac{T_{\text{m}}}{T}\right) \tag{2}$$

in which T_{m} is normal melting temperature. Equations 1 and 2 are valid only for simple eutectic systems. The activity coefficient of the solute in an organic solvent is represented by the simple empirical relation[8]

$$\ln\gamma_1 = \frac{C}{RT}(1 - x_1)^2 \tag{3}$$

where C is a parameter. Because the solubilities of phloretin in the selected solvents are low [i.e., $(1 - x_1) \approx 1$], eq 4 can be obtained from eqs 2 and 3:

$$\ln x_1 = \frac{A}{T} + B \tag{4}$$

where A and B are constants. The data for the solubility of phloretin in different solvents were correlated using eq 4, and the results are given in Table 2 along with the root-mean-square deviation (rmsd) values.

Table 1. Solubilities of Phloretin in Different Solvents at T = (288.2, 298.2, 308.2, 318.2, and 328.2) K

T/K	m_1 ($\text{mol}\cdot\text{kg}^{-1}$)	$10^2\cdot x_1$[a]	m_1 ($\text{mol}\cdot\text{kg}^{-1}$)	$10^2\cdot x_1$
	Methanol		Ethanol	
288.2	0.78 ± 0.04[b]	2.45 ± 0.13	0.78 ± 0.04	3.45 ± 0.17
298.2	0.83 ± 0.03	2.59 ± 0.10	0.84 ± 0.04	3.73 ± 0.16
308.2	0.88 ± 0.01	2.75 ± 0.03	0.90 ± 0.01	3.99 ± 0.04
318.2	0.96 ± 0.02	2.99 ± 0.05	0.95 ± 0.02	4.21 ± 0.08
328.2	1.02 ± 0.03	3.17 ± 0.10	1.01 ± 0.01	4.47 ± 0.01
	Propan-1-ol		Propan-2-ol	
288.2	0.51 ± 0.03	3.00 ± 0.15	0.60 ± 0.02	3.51 ± 0.12
298.2	0.55 ± 0.03	3.18 ± 0.15	0.64 ± 0.03	3.74 ± 0.14
308.2	0.58 ± 0.01	3.36 ± 0.05	0.68 ± 0.02	3.90 ± 0.08
318.2	0.62 ± 0.01	3.58 ± 0.03	0.71 ± 0.04	4.11 ± 0.20
328.2	0.66 ± 0.01	3.82 ± 0.06	0.75 ± 0.02	4.29 ± 0.11
	Butan-1-ol		Butan-2-ol	
288.2	0.47 ± 0.01	3.36 ± 0.04	0.14 ± 0.01	1.01 ± 0.04
298.2	0.49 ± 0.01	3.50 ± 0.03	0.19 ± 0.01	1.40 ± 0.04
308.2	0.51 ± 0.01	3.62 ± 0.01	0.24 ± 0.01	1.75 ± 0.06
318.2	0.53 ± 0.01	3.78 ± 0.06	0.30 ± 0.01	2.17 ± 0.06
328.2	0.55 ± 0.01	3.94 ± 0.10	0.34 ± 0.01	2.44 ± 0.01
	Pentan-1-ol		Hexan-1-ol	
288.2	0.35 ± 0.01	3.01 ± 0.08	0.29 ± 0.01	2.89 ± 0.1
298.2	0.38 ± 0.02	3.24 ± 0.13	0.32 ± 0.01	3.13 ± 0.12
308.2	0.40 ± 0.01	3.40 ± 0.07	0.34 ± 0.02	3.32 ± 0.15
318.2	0.42 ± 0.02	3.57 ± 0.18	0.35 ± 0.01	3.47 ± 0.12
328.2	0.45 ± 0.02	3.78 ± 0.19	0.37 ± 0.02	3.66 ± 0.15
	Ethyl Acetate		Butyl Acetate	
288.2	0.31 ± 0.01	2.66 ± 0.1	0.23 ± 0.01	2.58 ± 0.08
298.2	0.33 ± 0.02	2.83 ± 0.15	0.25 ± 0.01	2.81 ± 0.03
308.2	0.36 ± 0.01	3.09 ± 0.07	0.27 ± 0.01	3.05 ± 0.08
318.2	0.40 ± 0.02	3.43 ± 0.13	0.29 ± 0.01	3.23 ± 0.02
328.2	0.44 ± 0.02	3.7 ± 0.2	0.31 ± 0.01	3.46 ± 0.13
	1,4-Dioxane		Water	
288.2	0.24 ± 0.01	2.11 ± 0.05	$(1.92 \pm 0.03)\cdot 10^{-4}$	$(3.46 \pm 0.06)\cdot 10^{-4}$
298.2	0.29 ± 0.01	2.49 ± 0.02	$(3.20 \pm 0.02)\cdot 10^{-4}$	$(5.76 \pm 0.05)\cdot 10^{-4}$
308.2	0.34 ± 0.01	2.90 ± 0.01	$(6.21 \pm 0.02)\cdot 10^{-4}$	$(1.12 \pm 0.05)\cdot 10^{-3}$
318.2	0.39 ± 0.01	3.31 ± 0.08	$(9.31 \pm 0.01)\cdot 10^{-4}$	$(1.70 \pm 0.01)\cdot 10^{-3}$
328.2	0.45 ± 0.01	3.84 ± 0.03	$(1.50 \pm 0.06)\cdot 10^{-3}$	$(2.70 \pm 0.01)\cdot 10^{-3}$

[a] Mole fraction of solute. [b] Expanded uncertainties (±) were calculated as SD·k, where SD is the standard deviation and k is the coverage factor (k = 2).

Additionally, according to the theory of solid-liquid phase equilibrium, the relationship between the mole-fraction solubility and temperature also can be expressed by the modified Apelblat equation:[9]

$$\ln x_1 = a + \frac{b}{T} + c\ln(T/K) \tag{5}$$

where a, b, and c are empirical parameters. They were obtained by nonlinear least-squares fitting and are listed in Table 3 together

Table 2. Values of the Parameters in Equation 4 for Phloretin in Different Solvents

	parameter		
solvent	A/K	B	$10^2 \cdot$rmsd
methanol	−624.728	−1.553	0.03
ethanol	−602.724	−1.271	0.01
propan-1-ol	−586.232	−1.484	0.02
propan-2-ol	−470.548	−1.715	0.01
butan-1-ol	−372.933	−2.102	0.01
butan-2-ol	−2100.664	2.739	0.08
pentan-1-ol	−523.396	−1.682	0.01
hexan-1-ol	−547.684	−1.636	0.02
ethyl acetate	−801.449	−0.861	0.04
butyl acetate	−687.683	−1.267	0.02
1,4-dioxane	−1400.791	1.003	0.02
water	−4909.549	4.453	$0.04 \cdot 10^{-3}$

Table 3. Parameters of Equation 5 for Phloretin in Different Solvents

	parameter			
solvent	a	b/K	c	$10^2 \cdot$rmsd
methanol	−57.69	1938.524	8.343	0.02
ethanol	15.774	−1381.007	−2.533	0.01
propan-1-ol	−14.363	1.212	1.914	0.01
propan-2-ol	8.938	−956.968	−1.583	0.01
butan-1-ol	−22.845	574.213	3.083	0.01
butan-2-ol	310.126	−16136.226	−45.683	0.02
pentan-1-ol	−0.603	−572.682	−0.16	0.02
hexan-1-ol	42.625	−2568.665	−6.578	0.01
ethyl acetate	−79.7	2798.397	11.717	0.03
butyl acetate	27.126	−1984.12	−4.22	0.01
1,4-dioxane	−10.474	−876.718	1.706	0.02
water	−102.964	−2.251	15.963	$0.06 \cdot 10^{-3}$

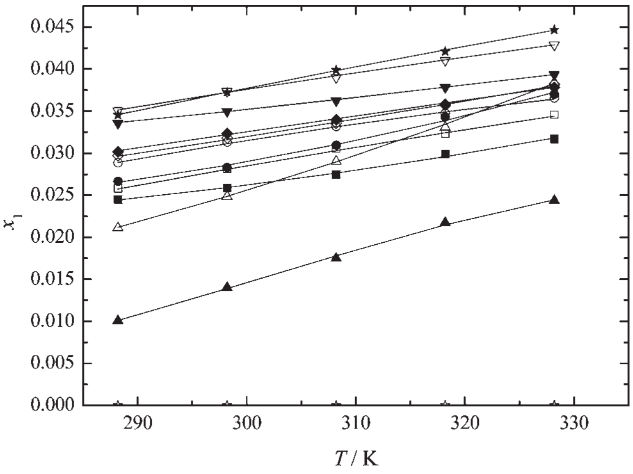

Figure 2. Solubilities of phloretin in 12 solvents as functions of temperature: ■, methanol; ★, ethanol; ◇, propan-1-ol; ▽, propan-2-ol; ▼, butan-1-ol; ▲, butan-2-ol; ◆, pentan-1-ol; ○, hexan-1-ol; ●, ethyl acetate; □, butyl acetate; △, 1,4-dioxane; ☆, water. Solid lines were calculated using eq 5 with the parameter values in Table 3.

with the rmsd values. In both Table 2 and Table 3, the rmsd is defined as

$$\text{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_{1,i}^{\text{calcd}} - x_{1,i}^{\text{exptl}})^2\right]^{1/2} \tag{6}$$

where $x_{1,i}^{\text{calcd}}$ is the solubility calculated using eq 4 or 5, $x_{1,i}^{\text{exptl}}$ is the experimental value of the mole-fraction solubility of phloretin, and n is the number of experimental data points for each solvent.

The solubility data for phloretin in the 12 solvents are plotted versus temperature in Figure 2. The lines were calculated using eq 5 with the parameter values in Table 3. Figure 2 shows that the solubilities of phloretin in the selected solvents increase with increasing temperature and that the temperature dependence of the solubility in 1,4-dioxane is much stronger than for any of the other solvents.

■ CONCLUSIONS

The solubilities of phloretin in different solvents over the temperature range (288.2 to 328.2) K were measured using a saturation method. From the experimental data, some conclusions can be obtained. First, for all of the systems in this work, the solubilities of phloretin increase with increasing temperature. Second, the best solubility of phloretin was shown in alcohols, particularly methanol and ethanol. Third, Figure 2 shows that the temperature dependence of the solubility in 1,4-dioxane is much stronger than for any of the other solvents. The reason for this may be that the activity coefficient given by eq 2 has a larger deviation from 1, in view of the nature of the solvent itself and the strong interaction between the solute and solvent. Fourth, the solubilities of phloretin calculated using the two equations show good agreement with the experimental values, and it can be seen that the correlated results obtained using eq 5 are a little better than those from eq 4. Thus, the experimental solubilities and correlation equations in this paper can be used as essential data in the purification process of phloretin by crystallization in laboratory and related industries.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: 0086 571 87951430. Fax: 0086 571 87951895. E-mail: yanweidong@zju.edu.cn.

■ ACKNOWLEDGMENT

Dr. Yan acknowledges Professor Prausnitz, who provided many helpful suggestions about the solubility of bioactive or therapeutic compounds when he was part of Professor Prausnitz's group in 2002.

■ REFERENCES

(1) Hunter, M. D.; Hull, L. A. Variation in concentrations of phloridzin and phloretin in apple foliage. *Phytochemistry* **1993**, *34*, 1251–1254.

(2) Parpinello, G. P.; Versari, A.; Galassi, S. Phloretin glycosides: Bioactive compounds in apple fruit, purées, and juices. *J. Med. Food* **2000**, *3*, 149–151.

(3) Lommen, A.; Godejohann, M.; Venema, D. P.; Hollman, P. C. H.; Spraul, M. Application of directly coupled HPLC−NMR−MS to the identification and confirmation of quercetin glycosides and phloretin glycosides in apple peel. *Anal. Chem.* **2000**, *72*, 1793–1797.

(4) Jugdé, H.; Nguy, D.; Moller, I.; Cooney, J. M.; Atkinson, R. G. Isolation and characterization of a novel glycosyltransferase that converts phloretin to phlorizin, a potent antioxidant in apple. *FEBS J.* **2008**, *275*, 3804–3814.

(5) Zielinski, J.; Moon, T. R.; Allen, E. P. Antioxidant Compositions for Soft Oral Tissue and Methods of Formulation and Use Thereof. U.S. Patent Application 2010/0183524 A1, 2010.

(6) Rosenbloom, R. A. Methods for the Treatment of Scar Tissue. U.S. Patent 7,399,783, 2008.

(7) Prausnitz, J. M.; Lichtenthaler, R. N.; Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*, 3rd ed.; Prentice Hall: New York, 1999.

(8) Peng, B.; Zi, J. Q.; Yan, W. D. Solubility of luteolin in ethanol + water mixed solvents at different temperatures. *J. Chem. Eng. Data* **2006**, *51*, 2038–2040.

(9) Apelblat, A.; Manzurola, E. Solubility of oxalic, malonic, succinic, adipic, maleic, malic, citric, and tartaric acids in water from 278.15 to 338.15 K. *J. Chem. Thermodyn.* **1987**, *19*, 317–320.