J. Chem. Eng. Data **2010,** *55,* 5375–5381

Measurement and Correlation of Solubilities of Cefpirome Sulfate in Aqueous Alcohol Solution between (278.15 and 308.15) K

Yu Li, Fu-An Wang,* and Bao-Zeng Ren

School of Chemical Engineering and Energy, Zhengzhou University, Zhengzhou, Henan 450001, People's Republic of China

The solubilities of cefpirome sulfate in water + (methanol, ethanol, 1-propanol, or 2-propanol) solvent mixtures have been measured using a dynamic method at temperature ranging from (278.15 to 318.15) K at atmospheric pressure. A solubility equation was proposed and verified by experimental results. The dissolution enthalpy and dissolution entropy have been calculated from the solubility data. The interactions between solute and solvent were discussed.

Introduction

Cefpirome sulfate [CAS Registry No. 98753-19-6] is a fourth-generation, semisynthetic, broad-spectrum cephalosporin antibiotic, which was codeveloped by Hoechst and Roussel and first came into the market in 1992. The drug is a white to pale white-yellowish crystalline powder, slightly with specific smell, soluble in water, and practically insoluble in ethanol. Its chemical name is (6*R*,7*R*)-7-[(z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetylamino]-3-(6,7-dihydro-5*H*-cyclopenta[b]-pyrindinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monosulfate.[1,2] The chemical structure is given in Figure 1. The drug has shown to be stable against hydrolysis by plasmid-mediated as well as the AmpC β-lactamases of the *Enterobacteriaceae*. It has a wide spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, especially against *Enterobacteriaceae*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* as well as *Pseudomonas aeruginosa*. The antibacterial agent is suitable for treatment of infections in intensive care units and in hematology/oncology patients.[3−6]

Liquid alcohols play an important role in many chemical reactions due to their ability to undergo self-association with manifold internal structures and represent a favorable system for evaluating the importance of both hydrophilic and hydrophobic interactions in determining the relevant properties of the liquid phase. They are widely used in industry and science research as reagents, solvents, and fuels. Moreover, as amphiphilic molecules, the alcohols serve as a simple model for more complex biological systems.[7]

On the basis of the study of intermolecular interactions between cefpirome sulfate and alcohol, the information of the structure evolution and energy conversion about cefpirome sulfate can be obtained on the molecular level in the life system. This may be an important topic in the field of life science research.

The purpose of this study was to investigate the solubility of cefpirome sulfate in water + (methanol, ethanol, 1-propanol, or 2-propanol) solvent mixtures from (278.15 to 308.15) K at atmospheric pressure using a laser monitoring observation technique.[8−12] The experimental data were correlated with a simple model of molecular thermodynamics for the solubility of solid in liquid.[13−15] The interactions between solute and solvent were discussed.

Experimental Section

Experimental Materials. A white crystalline powder of cefpirome sulfate ($C_{22}H_{22}N_6O_5S_2 \cdot H_2SO_4$, molecular weight 612.67) was purchased from Haikou Manfangyuan Chemical Co. Ltd., China. Its purity was measured by HPLC (type Agilent 1200, Agilent Technologies) according to the JP 15th Edition to be greater than 0.990 in mass fraction. It was dried in vacuo at 40 °C for 24 h and stored in a desiccator. The methanol, ethanol, 1-propanol, and 2-propanol (obtained from Tianjin Kermel Chemical Reagent Co., Ltd., China) used for the experiments were of analytical reagent grade and were used without further treatment before use. Their mass fraction purities were better than 0.998. Distilled deionized water was used in the all experiments.

Apparatus and Procedure. The solubility of cefpirome sulfate was measured by a synthetic method.[8−12] The apparatus for solubility measurement is the same as that described in the literature.[12] A laser beam was used to determine the solubility of the solute in the mixed solvent at a known temperature. The solubility apparatus consisted of a jacketed glass vessel (120 mL, Liming Research Institute of Chemical Industry, China) maintained at a desired temperature by water circulated from a water bath with a thermoelectric controller (type DC-2006, Shanghai Bilon Instruments Co., Ltd., China). The jacket temperature was controlled to be constant (fluctuating within ± 0.05 K). A mercury-in-glass thermometer with an uncertainty of ± 0.05 K was inserted into the inner chamber of the vessel for the measurement of temperature. A condenser was connected with the vessel to prevent the solvents from evaporating. Continuous stirring was achieved with a magnetic stir bar. An analytical balance (type BS224S, Beijing Sartorius Instruments System Co., Ltd.) with an accuracy of 0.0001 g was used to weigh the masses of the samples and solvents during the measurement.

In experiments, predetermined excess amounts of cefpirome sulfate and solvent of known mass were placed in the jacketed vessel. The contents of the vessel were stirred continuously at an invariable and required temperature, and the solvent was added to the vessel simultaneously in batches with the interval

---

* Corresponding author. E-mail: fawang@zzu.edu.cn. Tel.: +86 37163888116.

10.1021/je100870x

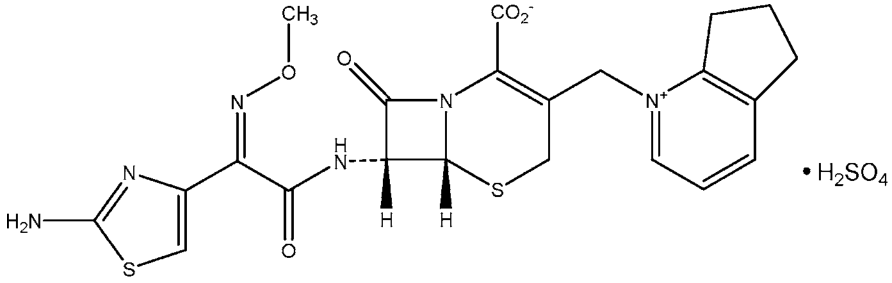

Figure 1. Chemical structure of cefpirome sulfate.

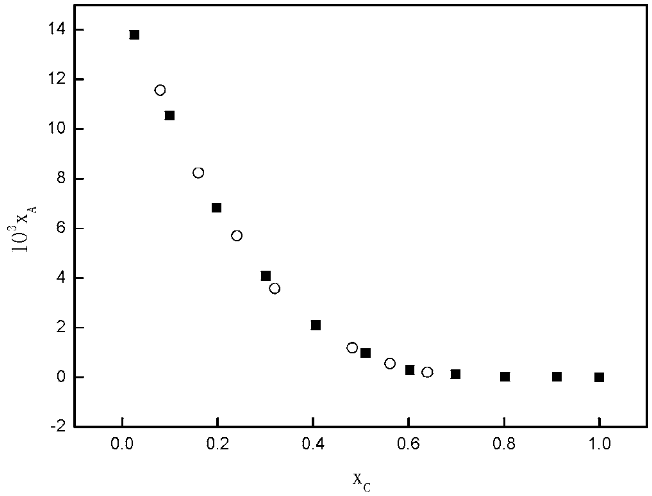

Figure 2. Comparison of the experimental solubilities (○) of ceftriaxone disodium in 2-propanol water solution at 298.15 K with the literature data (■).[12]

of 30 min. The additional solvent of known mass was about 50 mg each batch. When the last portion of solute just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the solvent mass consumed in the measurement would be recorded. Together with the mass of the solute, the solubility would be obtained.

The saturated mole fraction solubility of the solute (x_A) in binary methanol (ethanol, 1-propanol, or 2-propanol) (B) + water (C) solvent mixtures can be obtained as follows

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \tag{1}$$

where m_A, m_B, and m_C represent the mass of the solute, methanol (ethanol, 1-propanol, or 2-propanol), and water, respectively, and M_A, M_B, and M_C are the molecular weight of the solute, methanol (ethanol, 1-propanol, or 2-propanol), and water, respectively. Each experiment was conducted in triplicate. The uncertainty of the experimental solubility values was estimated to be 0.5 % due to uncertainties in the temperature measurements, weighing procedure, and instabilities of the water bath.

Experiment Reliability Proof

To verify the reliability of the measurement, the solubilities of cefotaxime disodium in aqueous 2-propanol solution were measured, and the results are shown in Figure 2 together with the measurements of Zhang.[12] In Figure 2, x_A is the experimental solubility in mole fraction, and x_C is the mole fraction of 2-propanol for mixed solvent. From Figure 2, it can be seen that the experimental results show good agreement with the literature data. Compared with the literature data, the deviations of the solubility are less than 2 %.

Results and Discussion

Measured mole fraction solubilities ($x_{A_i}^{exp}$) of cefpirome sulfate in the water, methanol + water, ethanol + water, 1-propanol + water, and 2-propanol + water mixed solvents at different temperatures are presented in Tables 1 to 4.

The temperature dependence of solubility for cefpirome sulfate at fixed solvent composition was correlated using a simple model of molecular thermodynamics for the solubility of solid in liquid.[13−15]

According to the basic principles of solid−liquid phase equilibrium,[13−15] the following equation can be concluded

$$\ln(\gamma x) = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_t} - \frac{1}{T}\right) - \frac{\Delta_{fus}C_p}{R}\left(\ln\frac{T_t}{T} - \frac{T_t}{T} + 1\right) - \frac{\Delta V}{RT}(P - P_t) \tag{2}$$

where x is the mole fraction solubility of solute in the solvent; γ is the liquid-phase activity coefficient of the solute; $\Delta_{fus}H$ is the enthalpy of fusion for the cefpirome sulfate upon the triple-point temperature, T_t; and $\Delta_{fus}C_p$ is the difference between the heat capacities of the solute in the liquid and solid phases. Generally, the pressure correction term and the difference between the heat capacities of the solute in the liquid phase and solid phase can be ignored; moreover, the triple-point temperature is usually very close to the melting point temperature (T_m) under atmospheric pressure, so the equation can be simplified as

$$\ln(\gamma x) = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \tag{3}$$

When the system under study is a dilute solution, the liquid-phase activity coefficient of the solute γ can be replaced by its value at infinite dilution (γ^∞). The correlated equation of activity coefficient at infinite dilution is given as follows[14]

$$\ln \gamma^\infty = a + \frac{b}{T} \tag{4}$$

The ln γ term in eq 3 is substituted by eq 4, and the result below can be obtained

$$\ln x = \frac{\Delta_{fus}H}{RT_m} - a - \left(\frac{\Delta_{fus}H}{R} + b\right)\frac{1}{T} \tag{5}$$

Table 1. Mole Fraction Solubility, x_A, and Dissolution Entropies, $\Delta_{sol}S$, of Cefpirome Sulfate in Binary Methanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$	T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$
	$x_B = 0$				$x_B = 0.1046$		
278.15	29.31	29.31	106.9	278.15	19.39	19.4	115.9
283.15	36.67	36.67	105.1	283.15	24.78	24.76	113.9
288.15	45.06	45.07	103.2	288.15	31.81	31.77	111.9
293.15	56.09	56.1	101.5	293.15	40.4	40.35	110.0
298.15	68.44	68.44	99.77	298.15	50.1	50.07	108.1
303.15	83.01	83.02	98.13	303.15	61.86	61.8	106.4
308.15	102	102	96.53	308.15	76.01	75.98	104.6
	$x_B = 0.2004$				$x_B = 0.3006$		
278.15	12.05	12.04	123.1	278.15	6.321	6.314	129.7
283.15	15.36	15.43	121.0	283.15	8.297	8.183	127.4
288.15	19.96	20.06	118.9	288.15	10.88	10.73	125.2
293.15	25.48	25.64	116.8	293.15	14.04	13.79	123.1
298.15	32.13	32.21	114.9	298.15	17.67	17.56	121.0
303.15	40.2	40.38	113.0	303.15	22.62	22.32	119.0
308.15	50.5	50.62	111.1	308.15	28.82	28.56	117.1
	$x_B = 0.3998$				$x_B = 0.4999$		
278.15	2.866	2.916	136.6	278.15	1.288	1.252	143.9
283.15	3.792	3.87	134.2	283.15	1.687	1.717	141.4
288.15	5.073	5.152	131.8	288.15	2.277	2.34	138.9
293.15	6.52	6.69	129.6	293.15	3.043	3.091	136.6
298.15	8.627	8.655	127.4	298.15	3.947	4.069	134.3
303.15	10.9	11.12	125.3	303.15	5.212	5.278	132.0
308.15	14.12	14.37	123.3	308.15	6.753	6.822	129.9
	$x_B = 0.6000$				$x_B = 0.7012$		
278.15	0.6008	0.5723	150.7	278.15	0.3436	0.3341	157.1
283.15	0.8442	0.8026	148.1	283.15	0.4794	0.4603	154.3
288.15	1.17	1.119	145.5	288.15	0.6681	0.6433	151.6
293.15	1.58	1.509	143.0	293.15	0.9141	0.8807	149.0
298.15	2.107	2.017	140.6	298.15	1.226	1.185	146.5
303.15	2.769	2.646	138.3	303.15	1.638	1.583	144.1
308.15	3.619	3.42	136.1	308.15	2.176	2.088	141.8
	$x_B = 0.8017$						
278.15	0.3046	0.3231	163.4				
283.15	0.3924	0.4019	160.5				
288.15	0.5266	0.5341	157.7				
293.15	0.7135	0.7291	155.0				
298.15	0.946	0.9709	152.4				
303.15	1.299	1.339	149.9				
308.15	1.815	1.894	147.5				

Table 2. Mole Fraction Solubility, x_A, and Dissolution Entropies, $\Delta_{sol}S$, of Cefpirome Sulfate in Binary Ethanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$	T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$
	$x_B = 0.1025$				$x_B = 0.2016$		
278.15	17.67	17.44	113.9	278.15	9.449	9.526	120.5
283.15	22.33	22.22	111.9	283.15	12.25	12.31	118.4
288.15	27.94	28.06	109.9	288.15	15.63	15.75	116.3
293.15	35.16	35.16	108.1	293.15	20.08	20.00	114.4
298.15	43.73	43.72	106.3	298.15	25.20	25.19	112.4
303.15	53.46	53.98	104.5	303.15	31.85	31.49	110.6
308.15	66.55	66.19	102.8	308.15	38.82	39.07	108.8
	$x_B = 0.3022$				$x_B = 0.4000$		
278.15	4.027	4.063	127.5	278.15	1.438	1.416	134.5
283.15	5.285	5.327	125.3	283.15	1.883	1.884	132.1
288.15	6.972	6.919	123.1	288.15	2.492	2.482	129.9
293.15	8.837	8.906	121.0	293.15	3.231	3.240	127.6
298.15	11.44	11.37	119.0	298.15	4.149	4.192	125.5
303.15	14.45	14.39	117.0	303.15	5.403	5.377	123.4
308.15	18.03	18.09	115.1	308.15	6.841	6.841	121.4
	$x_B = 0.5004$				$x_B = 0.6092$		
278.15	0.5081	0.5076	140.9	278.15	0.1204	0.1219	147.4
283.15	0.6859	0.6846	138.4	283.15	0.1641	0.1668	144.8
288.15	0.9075	0.9138	136.0	288.15	0.2283	0.2256	142.3
293.15	1.213	1.208	133.6	293.15	0.3051	0.3021	139.8
298.15	1.589	1.581	131.4	298.15	0.3997	0.4005	137.5
303.15	2.040	2.052	129.2	303.15	0.5236	0.5261	135.2
308.15	2.646	2.641	127.1	308.15	0.6859	0.6850	133.0

Table 3. Mole Fraction Solubility, x_A, and Dissolution Entropies, $\Delta_{sol}S$, of Cefpirome Sulfate in Binary 1-Propanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$	T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$
	$x_B = 0.1022$				$x_B = 0.2003$		
278.15	15.97	15.99	113.7	278.15	7.875	8.039	119.3
283.15	20.73	20.36	111.7	283.15	10.43	10.36	117.2
288.15	25.68	25.70	109.7	288.15	13.26	13.23	115.1
293.15	31.95	32.19	107.9	293.15	16.72	16.75	113.2
298.15	39.85	40.02	106.1	298.15	21.14	21.04	111.3
303.15	49.48	49.39	104.3	303.15	26.26	26.24	109.4
308.15	60.62	60.54	102.6	308.15	32.44	32.49	107.7
	$x_B = 0.3004$				$x_B = 0.4000$		
278.15	3.109	3.102	126.6	278.15	1.183	1.159	133.0
283.15	4.078	4.059	124.3	283.15	1.554	1.537	130.6
288.15	5.202	5.262	122.2	288.15	2.019	2.019	128.3
293.15	6.787	6.761	120.1	293.15	2.604	2.627	126.1
298.15	8.656	8.614	118.1	298.15	3.364	3.388	124.0
303.15	10.84	10.89	116.1	303.15	4.338	4.333	122.0
308.15	13.67	13.66	114.2	308.15	5.509	5.498	120.0
	$x_B = 0.5003$				$x_B = 0.6000$		
278.15	0.3438	0.3313	139.2	278.15	0.08043	0.08006	145.2
283.15	0.4573	0.4453	136.7	283.15	0.1097	0.1090	142.6
288.15	0.5929	0.5924	134.3	288.15	0.1475	0.1467	140.1
293.15	0.7705	0.7805	132.0	293.15	0.1958	0.1956	137.7
298.15	1.002	1.019	129.8	298.15	0.2563	0.2582	135.4
303.15	1.322	1.318	127.7	303.15	0.3372	0.3378	133.2
308.15	1.698	1.691	125.7	308.15	0.4391	0.4381	131.0

Table 4. Mole Fraction Solubility, x_A, and Dissolution Entropies, $\Delta_{sol}S$, of Cefpirome Sulfate in Binary 2-Propanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$	T/K	$10^5x_A^{exp}$	$10^5x_A^{cal}$	$\Delta_{sol}S$ / $J\cdot mol^{-1}\cdot K^{-1}$
	$x_B = 0.1092$				$x_B = 0.2005$		
278.15	13.30	13.12	113.5	278.15	6.875	6.883	118.8
283.15	16.73	16.69	111.5	283.15	8.863	8.859	116.7
288.15	21.28	21.07	109.6	288.15	11.36	11.30	114.7
293.15	26.20	26.38	107.7	293.15	14.32	14.30	112.7
298.15	32.75	32.78	105.9	298.15	17.92	17.95	110.8
303.15	39.92	40.44	104.2	303.15	22.26	22.37	109.0
308.15	49.95	49.56	102.5	308.15	27.74	27.67	107.2
	$x_B = 0.3009$				$x_B = 0.4009$		
278.15	2.809	2.829	125.5	278.15	1.023	1.049	132.1
283.15	3.680	3.693	123.3	283.15	1.354	1.388	129.7
288.15	4.782	4.778	121.2	288.15	1.809	1.820	127.5
293.15	6.147	6.126	119.1	293.15	2.394	2.364	125.3
298.15	7.806	7.790	117.1	298.15	3.074	3.043	123.2
303.15	9.815	9.827	115.2	303.15	3.908	3.886	121.2
308.15	12.30	12.30	113.3	308.15	4.889	4.923	119.2
	$x_B = 0.5007$				$x_B = 0.6005$		
278.15	0.3288	0.3195	139.0	278.15	0.07553	0.07376	145.3
283.15	0.4373	0.4292	136.5	283.15	0.1027	0.1004	142.7
288.15	0.5729	0.5707	134.2	288.15	0.1385	0.1353	140.2
293.15	0.7505	0.7515	131.9	293.15	0.1778	0.1804	137.8
298.15	0.9636	0.9805	129.7	298.15	0.2353	0.2382	135.5
303.15	1.262	1.268	127.5	303.15	0.3082	0.3116	133.3
308.15	1.637	1.627	125.5	308.15	0.4078	0.4042	131.1

For the studied systems, we make the following substitutions in eq 5

$$A = \frac{\Delta_{fus}H}{RT_m} - a \qquad (6)$$

$$B = -\frac{\Delta_{fus}H}{R} - b \qquad (7)$$

Thus, a simple solubility equation is obtained

$$\ln x = A + \frac{B}{T/K} \qquad (8)$$

where x is the mole fraction solubility of cefpirome sulfate and T is the absolute temperature. A and B are parameters of the model, which were calculated by least-squares fitting from the experimental data. The values of the parameters A and B are listed in Table 5. The calculated solubility ($x_{A_i}^{cal}$) of cefpirome sulfate can be obtained using eq 8 with the parameters listed in Table 5, and the results are given in Tables 1 to 4. The average relative deviation (ARD) and the standard deviation (SD) are defined as

$$\mathrm{ARD} = (100/n)\sum_{i=1}^{N} |(x_{A_i}^{cal} - x_{A_i}^{exp})/x_{A_i}^{exp}| \qquad (9)$$

$$\mathrm{SD} = [\sum_{i=1}^{n} (x_{\mathrm{A}_i}^{\mathrm{cal}} - x_{\mathrm{A}_i}^{\mathrm{exp}})^2/n]^{1/2} \qquad (10)$$

where n is the number of experimental points; $x_{\mathrm{A}_i}^{\mathrm{cal}}$ represents the solubility calculated from eq 8; and $x_{\mathrm{A}_i}^{\mathrm{exp}}$ represents the experimental solubility values.

For comparison with each of the experimental points, we used the data showed in Tables 1 to 4 and plotted the solubility curves for the studied systems in Figures 3 to 6. Full lines were calculated using eq 8 with the parameters listed in Table 5. The experimental data show that the solubility of cefpirome sulfate in binary water−alcohol mixtures is significantly lower than that in pure water. At constant temperature, the solubility decreases with increasing concentration of alcohol. Within solvent composition studied, the solubility of cefpirome sulfate increases with increasing temperature. Figures 3 to 6 showed that the simple model of molecular thermodynamics for the solubility of solid in liquid can simulate the experimental data well. Comparing the calculated results with the 189 data points in 27 systems, the mean average relative deviation is 0.83 %.

Cefpirome sulfate (A) molecule contains a carboxylic group, an aminothiazole ring, and positively charged quaternary nitrogen at C-7, which are responsible for the formation of zwitterionic species over a broad pH range. It also contains a complex group with different characteristics such as 6,7-dihydro-5*H*-cyclopenta[b]-pyrindinium-1-ylmethyl at C-3. According to solution molecular thermodynamics, there was not only the interaction of intermolecular hydrogen bonds but also intermolecular association interaction between adjacent molecules. This means that there are both self-association and cross-association between molecules of solvent water (W) and alcohol (B) in the cefpirome sulfate and alcohol + water solvent mixtures. When the solute was dissolved in solvent, as the intermolecular forces of A−W are more powerful than those of A−W−B or A−B, the solubility of cefpirome sulfate in water is significantly higher than those in alcohol + water solvent mixtures. With the concentration of the alcohol in the mixed solvent increasing, the self-association between alcohol molecules enhanced, which made the intermolecular forces of A−B weakened, and the solubility of cefpirome sulfate reduced significantly.

Table 5. Parameters of Equation 2, Average Relative Deviation ARD, Standard Deviation SD, and Dissolution Enthalpies $\Delta_{\mathrm{sol}}H$ for Different Mole Fraction, x_B, of (Methanol, Ethanol, 1-Propanol, and 2-Propanol) for Mixed Solvent

x_B	A	B / K	ARD	10^8 SD	$\Delta_{\mathrm{sol}}H$ / kJ·mol^{-1}
Cefpirome Sulfate + Methanol + Water					
0.0000	4.7172	−3577.9	0.63	417	29.75
0.1046	5.4045	−3877.9	0.70	218	32.24
0.2004	5.7742	−4119.3	0.47	120	34.25
0.3006	5.9263	−4339.6	0.65	117	36.08
0.3998	5.9582	−4569.1	0.75	63.7	37.99
0.4999	6.0198	−4814.8	0.78	23.5	40.03
0.6000	6.1416	−5043.3	0.95	11.2	41.93
0.7012	6.3167	−5254.8	0.36	3.05	43.69
0.8017	6.8040	−5466.4	4.13	28.3	45.45
Cefpirome Sulfate + Ethanol + Water					
0.1025	5.0454	−3810.5	0.54	262	31.68
0.2016	5.2383	−4032.4	0.61	178	33.53
0.3022	5.2278	−4266.5	0.65	57.0	35.47
0.4000	5.0149	−4500.5	0.54	21.4	37.42
0.5004	4.7509	−4712.4	0.38	6.54	39.18
0.6092	4.1107	−4931.0	0.84	2.19	41.00
Cefpirome Sulfate + 1-Propanol + Water					
0.1022	4.9331	−3803.4	0.50	185	31.62
0.2003	4.9172	−3990.3	0.55	81.5	33.18
0.3004	4.842	−4234.2	0.46	36.0	35.20
0.4000	4.6259	−4448.0	0.72	17.4	36.98
0.5003	4.1215	−4655.8	1.44	10.4	38.71
0.6000	3.4206	−4856.1	0.41	0.947	40.37
Cefpirome Sulfate + 2-Propanol + Water					
0.1092	4.7144	−3797.7	0.78	276	31.57
0.2005	4.7063	−3974.8	0.25	56.0	33.05
0.3009	4.6271	−4200.1	0.26	14.3	34.92
0.4009	4.4194	−4418.4	1.31	27.9	36.73
0.5007	4.0626	−4649.7	1.15	9.10	38.66
0.6005	3.3535	−4860.2	1.65	2.89	40.41

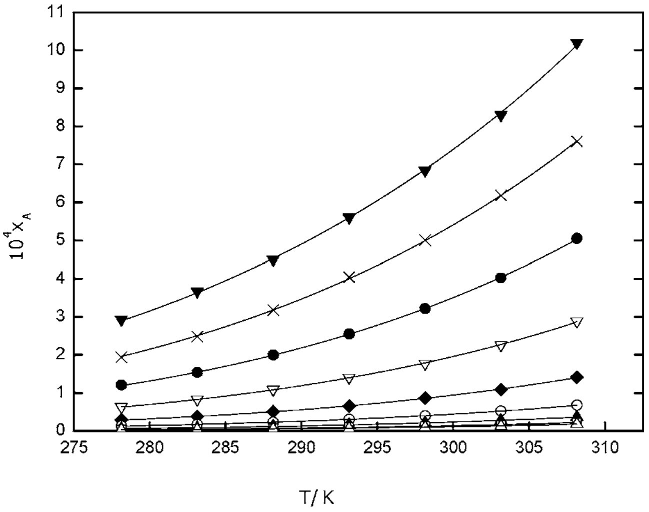

Figure 3. Solubilities of cefpirome sulfate (x_A) in binary methanol (B) + water (C) mixed solvent: x_B = ▼, 0.0000; ×, 0.1046; ●, 0.2004; ▽, 0.3006; ◆, 0.3998; ○, 0.4999; ▲, 0.6000; △, 0.7012; □, 0.8017. Full lines were calculated using eq 8 with the parameters listed in Table 5.

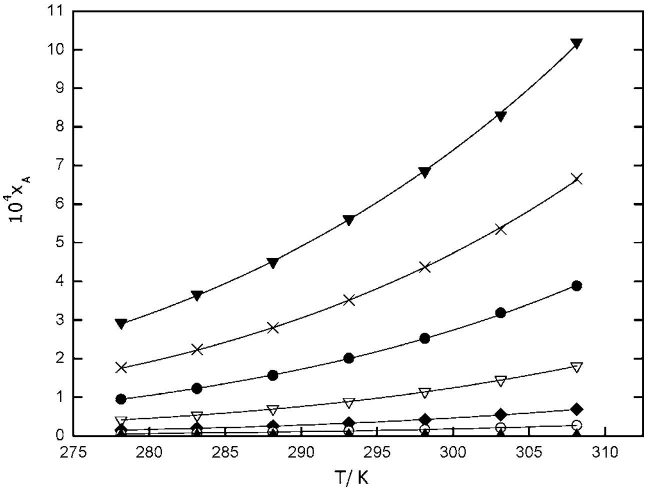

Figure 4. Solubilities of cefpirome sulfate (x_A) in binary ethanol (B) + water (C) mixed solvent: x_B = ▼, 0.0000; ×, 0.1025; ●, 0.2016; ▽, 0.3022; ◆, 0.4000; ○, 0.5004; ▲, 0.6092. Full lines were calculated using eq 8 with the parameters listed in Table 5.

The experimental results also state that the solubility of cefpirome sulfate in water is higher than that in methanol, ethanol, 1-propanol, and 2-propanol. The solubility of cefpirome sulfate in 2-propanol is the lowest. The reasons for this phenomenon may be the so-called empirical rule that “like dissolves like”. Relative permittivity is commonly regarded as a degree of molecular polarity, while dipole moment is regarded as a degree of polarization.[16] Relative permittivity and dipole moment of solvents studied[16] are listed in Table 6. The polarity of the solvents is in the order 2-propanol < 1-propanol < ethanol

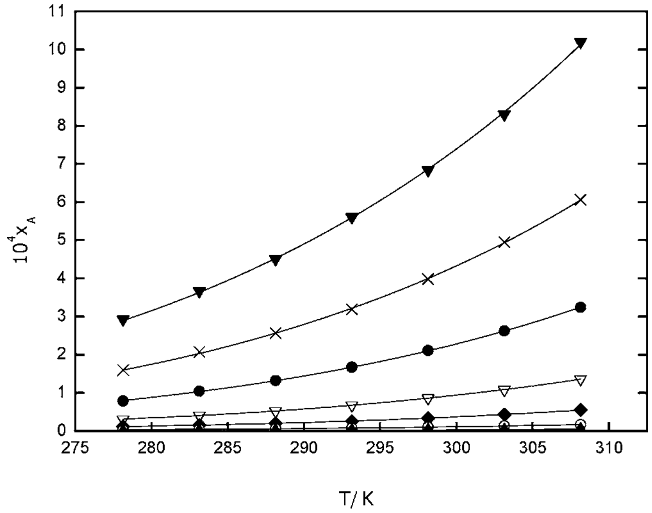

Figure 5. Solubilities of cefpirome sulfate (x_A) in binary 1-propanol (B) + water (C) mixed solvent: x_B = ▼, 0.0000; ×, 0.1022; ●, 0.2003; ▽, 0.3004; ◆, 0.4000; ○, 0.5003; ▲, 0.6000. Full lines were calculated using eq 8 with the parameters listed in Table 5.

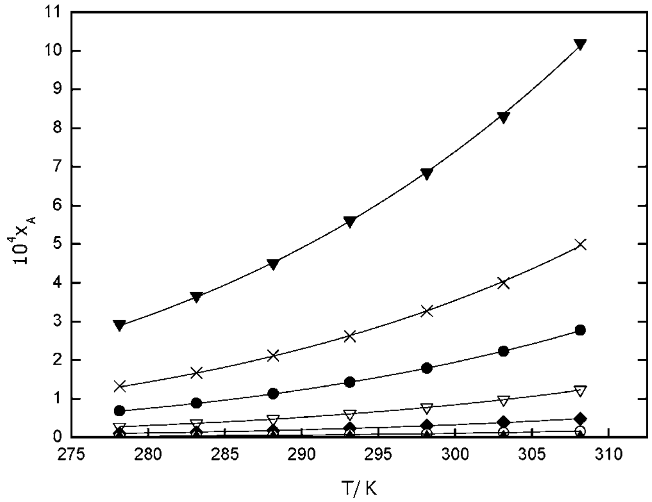

Figure 6. Solubilities of cefpirome sulfate (x_A) in binary 2-propanol (B) + water (C) mixed solvent: x_B = ▼, 0.0000; ×, 0.1092; ●, 0.2005; ▽, 0.3009; ◆, 0.4009; ○, 0.5007; ▲, 0.6005. Full lines were calculated using eq 8 with the parameters listed in Table 5.

Table 6. Physicochemical Properties of the Solvents Studied[a]

solvent	M $\text{g}\cdot\text{mol}^{-1}$	ε	D 10^{-30} C·m
water	18.01	80.10	6.138
methanol	32.04	33.00	5.671
ethanol	46.07	25.30	5.637
1-propanol	60.07	20.80	5.527
2-propanol	60.07	20.18	5.270

[a] M = molecular mass, ε = relative permittivity at 293.15 K, D = dipole moment at 293.15 K.

< methanol < water (Table 6), and so are the solubilities determined by experiments (seen Tables 1 to 4 and Figures 3 to 6). The polar molecule dissolves easily in polar solvent. During the dissolution process, the cohesive energy of the bonds holding solute together and the energy cost of disrupting the solvent−solvent bonds must be overcome by the cohesive energy released by the formation of the solute−solvent bonds. If these energies are approximately equal, which occurs when the solute and the solvent molecules are structurally similar, then the solute will dissolve in the solvent. The molecular structure of the title compound (see Figure 1) shows that cefpirome sulfate has a strong polarity; hence, the more polar the solvent is, the higher the solubility is.

According to molecular thermodynamics of fluid-phase equilibria, referring to the method of Tong et al.,[17−19] the alcohol + water mixed solvent can be treated as a pseudo solvent. Referring to the study of Saraswat et al.,[20−22] the activity coefficient of cefpirome sulfate in the cefpirome sulfate phase and the activity coefficients of the solvent in the solvent phase both are assumed as 1. Within the limited range of studied temperatures and solubilities, dissolution enthalpies $\Delta_{\text{sol}}H$ and dissolution entropies $\Delta_{\text{sol}}S$ for cefpirome sulfate in aqueous alcohol mixtures can be derived as follows

$$\Delta_{\text{sol}}H = RT^2\left(\frac{\partial \ln x}{\partial T}\right)_P \qquad (11)$$

$$\Delta_{\text{sol}}S = RT\left(\frac{\partial \ln x}{\partial T}\right)_P \qquad (12)$$

Differentiating eq 8, and collating it into eqs 11 and 12, the following equations can be obtained

$$\Delta_{\text{sol}}H = -RB \qquad (13)$$

$$\Delta_{\text{sol}}S = -RB/T \qquad (14)$$

The dissolution enthalpies and dissolution entropies of cefpirome sulfate in alcohol + water solvent mixtures are calculated according to eq 13 and eq 14 using parameter B obtained from Table 5, and the results are listed in Table 5 and Tables 1 to 4, respectively.

From Tables 1 to 4, over the temperature range under investigation, it can be seen that the dissolution process of cefpirome sulfate in water and different concentrations of alcohol + water mixed solvent is expressed as an endothermic process, that is, $\Delta_{\text{sol}}H > 0$. Studying the values of $\Delta_{\text{sol}}S$ of the dissolution process, we can see that the entropy of dissolution process was relatively large, and $\Delta_{\text{sol}}H$ and $\Delta_{\text{sol}}S$ are all positive. The positive $\Delta_{\text{sol}}H$ and $\Delta_{\text{sol}}S$ revealed that the dissolution process of cefpirome sulfate was an entropy-driven process. This phenomenon may be due to the different molecular structure and the space conformation of solute molecules and solvent molecules. Solvent water molecules selected for the present study are strong association complexes with small molecular dimension.[14,22,23] The solute cefpirome sulfate molecule contains both a large group with basic groups and acidic groups and a complex group with different characteristics such as 6,7-dihydro-5*H*-cyclopenta[b]-pyrindinium-1-ylmethyl. The dissolution process of such a solute in water and alcohol + water solvent mixtures involves various forces such as electrostatic, hydrogen bond, hydrophobic interaction, solvent-based, stereoscopic effect, etc.[13−15] For the entropy-driven process, the reason for the entropy increase during the dissolution process is that the solutes disrupt the alignment of solvent molecules and therefore reduced the degree of order of the system while they were dissolved in various solvents. The endothermic effect in the dissolved process may be due to that the interactions between cefpirome sulfate and solvent molecules are weaker than those between the solvent molecules. Thus, the new bond energy between cefpirome sulfate and solvent molecules is not powerful enough to compensate the energy needed to break the original association bond in various solvents, and the system needs to absorb heat from surroundings and manifests as increasing enthalpy.

Conclusions

Using the synthetic method and the laser monitoring observation technique, the solubilities of cefpirome sulfate in water + methanol (ethanol, 1-propanol, or 2-propanol) were measured in the temperature range from (278.15 to 308.15) K at atmospheric pressure. The solubility of cefpirome sulfate in water is significantly higher than those in alcohol + water solvent mixtures and decreases with increasing concentration of alcohol at constant temperature. Within the studied solvent composition, the solubility of cefpirome sulfate increases with increasing temperature. The experimental data were correlated with a simple model of molecular thermodynamics for solubilities of solid in liquid, and the dissolution enthalpies $\Delta_{sol}H$ and dissolution entropies $\Delta_{sol}S$ were estimated. The calculated results show good agreement with the experimental data. The positive $\Delta_{sol}H$ and $\Delta_{sol}S$ indicated that the dissolution process of cefpirome sulfate in the system was an entropy-driven process.

Literature Cited

(1) Zhou, X. L.; Xiang, B.; Gao, J. R. *Handbook of Fine Chemical-Drug*; Chemical Industry Press: Beijing, 2003; pp 53−55.

(2) Society of Japanese Pharmacopoeia. *The Japanese Pharmacopoeia*, 15th ed. (*JP 15*); The Ministry of Health, Labour and Welfare: Tokyo, 2007; pp 460−461.

(3) Jones, R. N.; Pfaller, M. A.; Allen, S. D.; Gerlach, E. H.; Fuchs, P. C.; Aldridge, K. E. An update compared to five third-generation cephalosporins against nearly 6000 recent clinical isolates from five medical centers. *Diagn. Microbiol. Infect. Dis.* **1991**, *14*, 361–364.

(4) Harman, J.; Limbird, L.; Molinnof, P.; Ruddon, R.; Gillman, A. *Goodman and Gilman's the Pharmacological Basis of The rapeutics*, 9th ed.; McGraw-Hill: New York, 1996.

(5) Matsumoto, T.; Kumazawa, J.; Naide, Y.; Horiba, M. Clinical Studies of Cefpirome in the Treatment of Urinary Tract Infections Caused by *Enterococcus faecalis*. *Diagn. Microbiol. Infect. Dis.* **1998**, *31*, 497–498.

(6) Raymond, J.; Vedel, G.; Bergeret, M. In Vitro Bactericidal Activity of Cefpirome in Combination with Vancomycin against *Staphylococcus aureus* and Coagulase-negative Staphylococcus. *Diagn. Microbiol. Infect. Dis.* **1998**, *31*, 481–483.

(7) Parthipan, G.; Thenappan, T. Studies on molecular interactions and fluid structure of anisole with 2-ethyl-1-hexanol and decyl alcohol. *J. Mol. Liq.* **2007**, *133*, 1–6.

(8) Wang, L. C.; Wang, F. A. Solubilities of niacin in sulfuric acid + water and 3-picoline + sulfuric acid + water from (292.65−361.35) K. *Fluid Phase Equilib.* **2004**, *226*, 289–293.

(9) Ren, B. Z.; Chong, H. G.; Li, W. R.; Wang, F. A. Solubility of potassium p-chlorophenoxyacetate in ethanol + water from (295.61 to 358.16) K. *J. Chem. Eng. Data* **2005**, *50*, 907–909.

(10) Song, C. Y.; Shen, H. Z.; Wang, L. C.; Zhao, J. H.; Wang, F. A. Solubilities of vitamin K3 in benzene, toluene, ethylbenzene, o-xylene, m-xylene, and p-xylene between (299.44 and 344.24) K. *J. Chem. Eng. Data* **2008**, *53*, 283–285.

(11) Zhang, C. L.; Wang, F. A.; Wang, Y. Solubilities of sulfadiazine, sulfamethazine, sulfadimethoxine, sulfamethoxydiazine, sulfamonomethoxine, sulfamethoxazole, and sulfachloropyrazine in water from (298.15 to 333.15) K. *J. Chem. Eng. Data* **2007**, *52*, 1563–1566.

(12) Zhang, H. T.; Wang, J. K.; Chen, Y.; Nie, Q. Solubiliy of sodium cefotaxime in aqueous 2-propanol mixtures. *J. Chem. Eng. Data* **2006**, *51*, 2239–2241.

(13) Walas, S. M. *Phase Equilibria in Chemical Engineering*, 1st ed.; Butter Worth: Boston, 1985.

(14) Prausnitz, J. M.; Lichtenthaler, R. N.; Azevedo, E. G. *Molecular Thermodynamics of Fluid-phase Equilibria*, 3rd ed.; Englewood Cliffs, Prentice Hall: NJ, 1999.

(15) Wang, F. A.; Jiang, Y. L. *Molecular Thermodynamics and Chromatographic Retention*; Meteorology Press: Beijing, 2001.

(16) Dean, J. A. *Lange's Handbook of Chemistry*, 15th ed.; McGraw-Hill: New York, 1999.

(17) Tong, Z.; Liao, D.; Benson, G. C.; Lu, B. C.-Y. Excess enthalpies of {(heptane or decane) + methyl 1,1-dimethylethyl ether + diisopropyl ether} at the temperature 298.15 K. *J. Chem. Thermodyn.* **1997**, *29*, 431–439.

(18) Wang, F. A.; Chen, H. S.; Zhu, J. Q.; Song, J. C.; Wang, Z. C. Estimation of Excess Enthalpy for Binary Systems. *Chem. Eng. J.* **2002**, *85*, 235–243.

(19) Zhao, J. H.; Wang, L. C.; Wang, F. A. Solubilities of p-aminophenol in sulfuric acid + water + (methanol, ethanol, 1-propanol, 2-propanol, 1,2-propanediol and glycerin, respectively) from (292.35 to 348.10) K. *J. Chem. Eng. Data* **2006**, *51*, 376–381.

(20) Saraswat, I. P.; kumar, R. S.; Suri, S. K. Solution behavior of heavy-metal soaps. 1.Soubilities of mercury(II) octadecanoate in water, formamide, N, N-dimethylformamide, and cychohexanone at various temperatures. *J. Chem. Eng. Data* **1984**, *29*, 200–202.

(21) Chen, H. P.; Wagner, J. Mutual solubilities of alkylbenzene + water systems at temperatures from 303 to 373 K: ethylbenzene, p-xylene, 1,3,5-trimethylbenzene, and butylbenzene. *J. Chem. Eng. Data* **1994**, *39*, 679–684.

(22) Nagata, I.; Gotoh, K.; Tamura, K. Association model of fluids. Phase equilibria and excess enthalpies in acid mixtures. *Fluid Phase Equilib.* **1996**, *124*, 31–54.

(23) Nath, A.; Bender, E. On the thermodynamics of associated solutions. 1. An analytical method for determining the enthalpy and entropy of association and equilibrium constant for pure liquid substances. *Fluid Phase Equilib.* **1981**, *7*, 275–287.

Received for review August 22, 2010. Accepted October 11, 2010. The authors are grateful to Education Department of Henan Province for its financial support (Henan Natural Science Foundation General Project, Grant No. 2008A530004).

JE100870X