Solubilities of Cefepime Hydrochloride in Water + (Ethanol, 1-Propanol, or 2-Propanol) from (278.15 to 308.15) K

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Using a laser monitoring observation technique, the solubility values of cefepime hydrochloride in water + (ethanol, 1-propanol, or 2-propanol) from (278.15 to 308.15) K at atmospheric pressure were measured. The experimental data were correlated with a simplified molecular thermodynamic model.

Introduction

The crystallization separation operation is widely used in chemical engineering as a result of low energy consumption and high purity. However, solid−liquid equilibrium data of some important chemicals are very scarce, especially for compounds with complex molecular structures, such as biological products.[1,2]

Cefepime dihydrochloride hydrate (CAS Registry No. 123171-59-5) ((6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetylamino]-3-(1-methylpyrrolidinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate dihydrochloride monohydrate) is a white, almost white, or yellowish white crystalline powder. Its structural formula is given in Figure 1. It is soluble in water, methanol, and diethylether easily and slightly soluble in ethanol.[3,4] The solubilities of cefepime hydrochloride in various solvents are essential for the solvent extraction and optimization of purification conditions in product separation and cefepime hydrochloride industrial process.

Cefepime hydrochloride is a semisynthetic, broad spectrum fourth-generation cephalosporin antibiotic. It has good antimicrobial activity against Gram-negative bacteria, such as *Enterobacter spp, Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus* bacteria grapes, and it is more active against some Gram-positive bacteria, such as *Streptococcus pyogenes, Streptococcus pneumoniae,* and so forth. Compared with the three-generation cephalosporin, its antibacterial spectrum is expanded further, and the antimicrobial activity against Gram-positive cocci was enhanced. This drug is mainly used for the treatment of lower respiratory infections, febrile neutropenic events, urinary tract infections skin soft tissue infections, complicated intra-abdominal infections, gynecological infections, and sepsis; it also can be used for children with bacterial meningitis.[5−7]

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.

In this study, to provide the basis for industrial production, separation, and purification of cefepime hydrochloride, the solubilities of cefepime hydrochloride hydrate in water + (ethanol, 1-propanol, or 2-propanol) have been measured from (278.15 to 308.15) K at atmospheric pressure using a laser monitoring observation technique. The experimental data were correlated with a semiempirical equation. The results also were of actual importance for the investigation of dissolving, transmission, and distribution behavior in the chemical and biological environment.

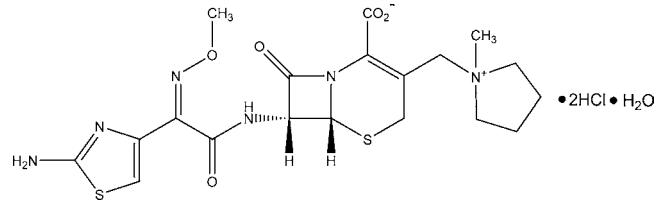

Figure 1. Structure of cefepime dihydrochloride hydrate.

Experimental Section

Experimental Materials. Cefepime dihydrochloride hydrate ($C_{19}H_{24}N_6O_5S_2 \cdot HCl \cdot H_2O$, molecular weight 571.49) was purchased from Haikou Manfangyuan Chemical Co. Ltd., China. Its mass fraction purity was better than 0.990, which was determined by high-performance liquid chromatography (HPLC, type Agilent 1200, Agilent Technologies) according to the JP 15th edition. It was dried in vacuum at 40 °C for 24 h and stored in a desiccator. Ethanol, 1-propanol, and 2-propanol obtained from Tianjin Kermel Chemical Reagent Co., Ltd., China were of analytical reagent grade, and their purities were all greater than 0.997 mass fraction. The distillated deionized water was used.

Apparatus and Procedure. The methods of solubility measurement involve the equilibrium method and synthetic method.[8−11] This study used the synthetic method to measure the solubility of cefepime dihydrochloride hydrate. The apparatus for solubility measurement is the same as that described in the literature[12,13] and is only described briefly here. The apparatus was a jacketed glass vessel (120 mL, Liming Research Institute of Chemical Industry, China) with water circulated from a water bath to control the temperature, keeping it 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 to measure the temperature. A magnetic stir bar was used. A condenser was connected to the vessel to prevent the solvents from evaporating. The dissolution of the solute was examined by the laser beam penetrating the vessel. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display.

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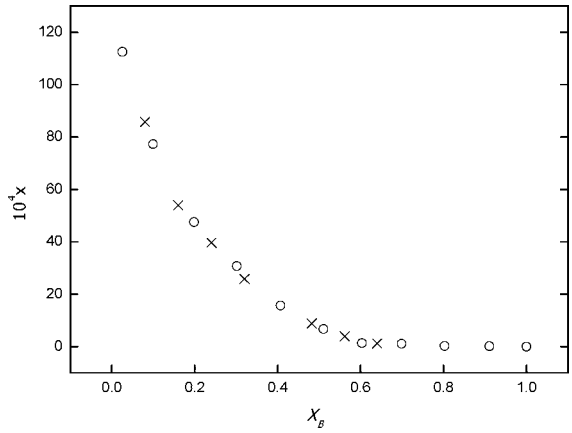

Figure 2. Solubility of sodium cefotaxime in aqueous 2-propanol mixtures at 288.15 K: ×, the experimental value in mole fraction in this work; ○, literature data from the literature, ref 12.

The masses of the samples and solvents were weighed using the analytical balance (type BS224S, Beijing Sartorius Instruments System Co., Ltd.) with an uncertainty of 0.0001 g. During experiments, predetermined excess amounts of cefepime dihydrochloride hydrate and known mass solvent were placed in the jacketed vessel. The contents of the vessel were stirred continuously at invariable and required temperatures, and the solvent was added to the vessel simultaneously in batches with the interval of 30 min. The additional solvent of known mass was about 50 mg for 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 solution is obtained as follows:

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

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

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

T/K	$10^4\,x^{expt}$	$10^4\,x^{calc}$	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	T/K	$10^4\,x^{expt}$	$10^4\,x^{calc}$	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}
	$x_B = 0.0000$				$x_B = 0.1005$		
278.15	12.21	11.97	183.4	278.15	10.11	9.814	186.2
283.15	17.70	17.68	180.2	283.15	14.66	14.58	182.9
288.15	25.26	25.74	177.0	288.15	21.04	21.35	179.8
293.15	37.27	37.02	174.0	293.15	31.14	30.88	176.7
298.15	52.93	52.59	171.1	298.15	44.01	44.10	173.7
303.15	73.46	73.84	168.3	303.15	62.07	62.25	170.9
308.15	102.7	102.5	165.5	308.15	87.04	86.89	168.1
	$x_B = 0.2003$				$x_B = 0.3006$		
278.15	8.028	7.817	188.9	278.15	6.264	6.093	191.6
283.15	11.85	11.68	185.6	283.15	9.378	9.152	188.2
288.15	17.36	17.20	182.4	288.15	13.69	13.56	184.9
293.15	25.21	25.00	179.3	293.15	19.58	19.81	181.8
298.15	35.67	35.90	176.3	298.15	28.31	28.58	178.7
303.15	50.22	50.92	173.3	303.15	40.78	40.74	175.8
308.15	71.83	71.42	170.5	308.15	57.47	57.42	172.9
	$x_B = 0.3998$				$x_B = 0.5000$		
278.15	4.646	4.547	194.0	278.15	3.195	3.122	196.7
283.15	7.025	6.866	190.6	283.15	4.866	4.741	193.2
288.15	10.31	10.22	187.3	288.15	7.144	7.096	189.9
293.15	15.08	15.01	184.1	293.15	10.48	10.48	186.6
298.15	21.73	21.75	181.0	298.15	15.29	15.26	183.5
303.15	30.64	31.15	178.0	303.15	21.66	21.97	180.5
308.15	44.36	44.09	175.1	308.15	31.42	31.24	177.6
	$x_B = 0.6000$				$x_B = 0.7010$		
278.15	1.912	1.859	199.3	278.15	0.9422	0.9172	201.8
283.15	2.916	2.839	195.8	283.15	1.440	1.408	198.3
288.15	4.373	4.272	192.4	288.15	2.161	2.130	194.8
293.15	6.423	6.339	189.1	293.15	3.178	3.176	191.5
298.15	9.146	9.282	185.9	298.15	4.606	4.674	188.3
303.15	13.21	13.42	182.9	303.15	6.789	6.791	185.2
308.15	19.32	19.18	179.9	308.15	9.770	9.747	182.2
	$x_B = 0.8014$				$x_B = 0.9011$		
278.15	0.2993	0.3011	204.2	278.15	0.06186	0.06264	206.6
283.15	0.4626	0.4646	200.6	283.15	0.09616	0.09716	203.0
288.15	0.7007	0.7061	197.1	288.15	0.1481	0.1484	199.5
293.15	1.052	1.058	193.7	293.15	0.2232	0.2235	196.1
298.15	1.556	1.564	190.5	298.15	0.3330	0.3319	192.8
303.15	2.310	2.282	187.3	303.15	0.4874	0.4865	189.6
308.15	3.275	3.289	184.3	308.15	0.7035	0.7043	186.5

Table 2. Mole Fraction Solubility x_A and Dissolution Entropies $\Delta_{sol}S$ of Cefepime Hydrochloride in Binary 1-Propanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T/K	$10^4\,x^{expt}$	$10^4\,x^{calc}$	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}	T/K	$10^4\,x^{expt}$	$10^4\,x^{calc}$	$\Delta_{sol}S$/J·mol^{-1}·K^{-1}
	$x_B = 0.0000$				$x_B = 0.1000$		
278.15	12.21	11.97	183.4	278.15	6.409	6.285	185.5
283.15	17.70	17.68	180.2	283.15	9.481	9.320	182.2
288.15	25.26	25.74	177.0	288.15	13.63	13.63	179.1
293.15	37.27	37.02	174.0	293.15	19.67	19.69	176.0
298.15	52.93	52.59	171.1	298.15	28.03	28.08	173.1
303.15	73.46	73.84	168.3	303.15	39.30	39.58	170.2
308.15	102.7	102.5	165.5	308.15	55.33	55.17	167.5
	$x_B = 0.2002$				$x_B = 0.3001$		
278.15	4.368	4.304	187.6	278.15	2.922	2.842	189.8
283.15	6.523	6.412	184.3	283.15	4.364	4.253	186.5
288.15	9.519	9.420	181.1	288.15	6.318	6.276	183.2
293.15	13.63	13.66	178.0	293.15	9.101	9.140	180.1
298.15	19.48	19.56	175.0	298.15	12.99	13.14	177.1
303.15	27.48	27.68	172.2	303.15	18.68	18.68	174.2
308.15	38.87	38.74	169.4	308.15	26.29	26.24	171.4
	$x_B = 0.4007$				$x_B = 0.5001$		
278.15	1.857	1.805	192.3	278.15	1.137	1.111	194.4
283.15	2.794	2.716	188.9	283.15	1.732	1.679	191.0
288.15	4.122	4.029	185.6	288.15	2.485	2.501	187.7
293.15	5.914	5.896	182.5	293.15	3.682	3.676	184.5
298.15	8.485	8.519	179.4	298.15	5.335	5.332	181.4
303.15	11.93	12.16	176.4	303.15	7.571	7.642	178.4
308.15	17.31	17.16	173.6	308.15	10.87	10.82	175.5
	$x_B = 0.6009$				$x_B = 0.7009$		
278.15	0.5315	0.5163	196.6	278.15	0.1834	0.1780	198.6
283.15	0.8125	0.7839	193.1	283.15	0.2781	0.2715	195.1
288.15	1.194	1.173	189.8	288.15	0.4067	0.4079	191.8
293.15	1.739	1.732	186.6	293.15	0.6080	0.6045	188.5
298.15	2.490	2.523	183.4	298.15	0.8775	0.8842	185.3
303.15	3.587	3.630	180.4	303.15	1.270	1.277	182.3
308.15	5.193	5.162	177.5	308.15	1.828	1.823	179.3
	$x_B = 0.8005$				$x_B = 0.8998$		
278.15	0.05449	0.05369	200.8	278.15	0.01569	0.01532	203.0
283.15	0.08294	0.08225	197.3	283.15	0.02424	0.02357	199.4
288.15	0.1250	0.1241	193.8	288.15	0.03617	0.03574	196.0
293.15	0.1864	0.1848	190.5	293.15	0.05362	0.05343	192.6
298.15	0.2699	0.2714	187.3	298.15	0.07743	0.07880	189.4
303.15	0.3908	0.3935	184.3	303.15	0.1147	0.1147	186.3
308.15	0.5657	0.5638	181.3	308.15	0.1654	0.1650	183.3

Experimental Reliability Proof

The solubility of sodium cefotaxime in aqueous 2-propanol mixtures has been reported in the literature,[12] and it is also measured with the equipment in this work. The solubility of sodium cefotaxime in aqueous 2-propanol mixtures in the literature[12] and in this paper are shown in figure 2. In comparison with the results, it is shown that the total mean relative deviation of the measured solubility values were less than that of the literature data. Therefore, the reliability of the experimental apparatus was verified. All determinations were repeated three times, and the mean values were used to calculate the mole fraction solubility.

Results and Discussion

The temperature (T) dependence of solubility (x_A) for cefepime hydrochloride at a fixed solvent composition was correlated using the following simplified model of molecular thermodynamics for the solubilities of solid in liquid:[14,15]

$$\ln x_A = A + \frac{B}{T/\mathrm{K}} \tag{2}$$

The two parameters A and B were obtained by least-squares fitting from the experimental data. The calculated solubility ($x_{A_i}^{calc}$) and the values of A and B are listed in Tables 1 to 4 together with the total mean relative deviation (ARD) and the standard deviation (SD) compared with the experimental data. The ARD and SD are defined as:

$$\mathrm{ARD} = (100/n)\sum_{i=1}^{N}\left|\left(x_{A_i}^{calc} - x_{A_i}^{expt}\right)/x_{A_i}^{expt}\right| \tag{3}$$

$$\mathrm{SD} = \left[\sum_{i=1}^{n}\left(x_{A_i}^{calc} - x_{A_i}^{expt}\right)^2/n\right]^{1/2} \tag{4}$$

where n is the number of experimental points, $x_{A_i}^{calc}$ represents the solubility calculated from eq 2, and $x_{A_i}^{expt}$ represents the experimental solubility values.

The comparison between model prediction according to eq 2 and experimental data is shown in Figures 3 to 5. Clearly, the simplified molecular thermodynamic model can simulate the experimental data well. Comparing the calculated results of 203 data points in 29 systems according to eq 2 with the experimental ones, the total mean relative deviation (ARD) and the total standard deviation (SD) are 0.97 % and $1.05\cdot10^{-5}$, respectively.

Tables 1 to 3 and Figures 3 to 5 showed that the solubilities of cefepime hydrochloride in water are significantly higher than those in alcohol + water mixtures. For the alcohol + water mixed solvent, the solubility of cefepime hydrochloride increases

Table 3. Mole Fraction Solubility x_A and Dissolution Entropies $\Delta_{sol}S$ of Cefepime Hydrochloride in Binary 2-Propanol (B) + Water (C) Mixed Solvent from T = (278.15 to 308.15) K

T			$\Delta_{sol}S$	T			$\Delta_{sol}S$
K	$10^4\ x^{expt}$	$10^4\ x^{calc}$	J·mol^{-1}·K^{-1}	K	$10^4\ x^{expt}$	$10^4\ x^{calc}$	J·mol^{-1}·K^{-1}
	$x_B = 0.0000$				$x_B = 0.1008$		
278.15	12.21	11.97	183.4	278.15	6.204	6.086	185.3
283.15	17.70	17.68	180.2	283.15	9.146	9.021	182.0
288.15	25.26	25.74	177.0	288.15	13.22	13.19	178.8
293.15	37.27	37.02	174.0	293.15	19.23	19.03	175.8
298.15	52.93	52.59	171.1	298.15	27.09	27.13	172.8
303.15	73.46	73.84	168.3	303.15	37.69	38.23	170.0
308.15	102.7	102.5	165.5	308.15	53.59	53.27	167.2
	$x_B = 0.2020$				$x_B = 0.2987$		
278.15	3.854	3.894	187.2	278.15	2.548	2.577	189.3
283.15	5.788	5.795	183.9	283.15	3.861	3.853	186.0
288.15	8.522	8.507	180.7	288.15	5.751	5.679	182.7
293.15	12.34	12.33	177.7	293.15	8.276	8.262	179.6
298.15	17.65	17.64	174.7	298.15	11.77	11.87	176.6
303.15	24.95	24.94	171.8	303.15	16.87	16.85	173.7
308.15	34.88	34.88	169.0	308.15	23.65	23.65	170.9
	$x_B = 0.3999$				$x_B = 0.4987$		
278.15	1.642	1.658	191.4	278.15	1.052	1.034	193.5
283.15	2.538	2.490	188.0	283.15	1.602	1.560	190.1
288.15	3.711	3.687	184.8	288.15	2.362	2.319	186.8
293.15	5.410	5.386	181.6	293.15	3.416	3.402	183.6
298.15	7.755	7.770	178.6	298.15	4.886	4.926	180.6
303.15	10.97	11.07	175.6	303.15	6.947	7.046	177.6
308.15	15.65	15.60	172.8	308.15	10.03	9.963	174.7
	$x_B = 0.5992$				$x_B = 0.6993$		
278.15	0.4858	0.4849	195.6	278.15	0.1658	0.1693	197.9
283.15	0.7389	0.7346	192.1	283.15	0.2593	0.2577	194.4
288.15	1.098	1.097	188.8	288.15	0.3869	0.3867	191.0
293.15	1.623	1.616	185.6	293.15	0.5691	0.5722	187.8
298.15	2.357	2.350	182.5	298.15	0.8397	0.8356	184.6
303.15	3.348	3.375	179.5	303.15	1.206	1.205	181.6
308.15	4.803	4.790	176.6	308.15	1.717	1.718	178.6
	$x_B = 0.7969$				$x_B = 0.9001$		
278.15	0.04652	0.04677	199.9	278.15	0.01425	0.01431	202.1
283.15	0.07210	0.07150	196.3	283.15	0.02238	0.02198	198.5
288.15	0.1086	0.1077	192.9	288.15	0.03406	0.03327	195.1
293.15	0.1589	0.1600	189.6	293.15	0.04931	0.04964	191.8
298.15	0.2347	0.2346	186.5	298.15	0.07210	0.07308	188.5
303.15	0.3397	0.3396	183.4	303.15	0.1065	0.1062	185.4
308.15	0.4859	0.4857	180.4	308.15	0.1526	0.1526	182.4

with increasing concentration of water and decreases with increasing concentrations of alcohol.

The pluralistic system that we studied is composed of cefepime hydrochloride and alcohol + water, and the cefepime hydrochloride (A) molecule not only contains a large substituent with both basic groups and acidic groups but also contains complex groups with different characteristics such as methylpyrrolidinium. In this system, according to solution molecular thermodynamics, there exists not only the interaction of intramolecular hydrogen bonds but also intermolecular associating interactions between adjacent molecules. This means that there are both self-association and cross-association between water (W) molecules and alcohol (B) molecules. 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 cefepime hydrochloride in water was significantly higher than those in alcohol + water mixtures. With the increasing concentration of alcohol in the mixed solvent, the self-association between alcohol molecules was enhanced, which weakened the intermolecular forces of A−B, and the solubility of cefepime hydrochloride was reduced significantly.

For the dissolution process of cefepime hydrochloride in binary alcohol + water solvent mixtures, according to the molecular thermodynamics of fluid-phase equilibria, the mixed solvent can be treated as pseudo solvent.[16,17] In reference to the work of Saraswat et al.,[18−20] the activity coefficient of cefepime hydrochloride in cefepime hydrochloride phase and the activity coefficient of the solvent in the solvent phase both are assumed as 1. Over the temperature and solubility range under investigation, the dissolution enthalpy and dissolution entropy of cefepime hydrochloride in binary alcohol + water solvent mixtures can be calculated by the following two equations, which are deduced by Gibbs−Duhem equation:

$$\Delta_{sol}H = RT^2\left(\frac{\partial \ln x}{\partial T}\right)_P \tag{5}$$

$$\Delta_{sol}S = RT\left(\frac{\partial \ln x}{\partial T}\right)_P \tag{6}$$

Differentiating eq 2 and collating it into the eq 5 and 6, the following equations can be obtained:

$$\Delta_{sol}H = -RB \tag{7}$$

$$\Delta_{sol}S = -RB/T \tag{8}$$

The dissolution enthalpy and dissolution entropy of cefepime hydrochloride in binary alcohol + water solvent mixtures are calculated according to eqs 7 and 8 using the parameter B obtained from Table 4, and the results are listed in Table 4 and Tables 1 to 3, respectively.

Table 4. Parameters of Equation 2, Average Relative Deviation (ARD), Standard Deviation (SD), and Dissolution Enthalpies $\Delta_{sol}H$ for Different Mole Fractions x_B of (Ethanol, 1-Propanol, and 2-Propanol) for Mixed Solvents

		B			$\Delta_{sol}H$
x_B	A	K	ARD	10^7 SD	kJ·mol^{-1}
Cefepime Hydrochloride + Ethanol + Water					
0.0000	15.332	−6135.9	0.86	361	51.01
0.1005	15.474	−6230.7	0.92	253	51.80
0.2003	15.570	−6320.7	1.20	413	52.55
0.3006	15.639	−6409.2	1.20	213	53.29
0.3998	15.638	−6490.3	1.15	276	53.96
0.5000	15.588	−6581	1.10	175	54.71
0.6000	15.381	−6667.6	1.83	147	55.43
0.7010	14.979	−6752.3	1.16	39.4	56.14
0.8014	14.147	−6830.7	0.65	14.9	56.79
0.9011	12.875	−6913.6	0.46	0.943	57.48
1.0000	11.236	−6998.1	1.26	0.484	58.18
Cefepime Hydrochloride + 1-Propanol + Water					
0.1000	14.941	−6206.4	0.70	172	51.60
0.2002	14.818	−6277.5	0.84	134	52.19
0.3001	14.667	−6351.0	1.10	97.0	52.80
0.4007	14.509	−6433.2	1.62	137	53.49
0.5001	14.280	−6504.6	1.09	47.6	54.08
0.6009	13.777	−6577.8	1.67	33.0	54.69
0.7009	12.957	−6645.9	1.11	6.41	55.25
0.8005	12.019	−6718.4	0.78	1.88	55.86
0.8998	11.030	−6792.2	1.24	0.0754	56.47
Cefepime Hydrochloride + 2-Propanol + Water					
0.1008	14.879	−6198.1	0.96	305	51.53
0.2020	14.671	−6264.5	0.22	20.9	52.08
0.2987	14.505	−6333.1	0.53	57.8	52.65
0.3999	14.318	−6403.7	0.77	57.3	53.24
0.4987	14.102	−6475.2	1.35	63.3	53.83
0.5992	13.592	−6543.8	0.38	14.3	54.41
0.6993	12.815	−6620.4	0.56	2.94	55.04
0.7969	11.767	−6686.7	0.43	0.707	55.59
0.9001	10.851	−6761.3	0.98	0.624	56.21

Table 1 to 4 show that the dissolution process of cefepime hydrochloride in water and different compositions of alcohol + water solvent mixtures is expressed as the endothermic process over the temperature range under investigation, that is, $\Delta_{sol}H > 0$. By studying the values of $\Delta_{sol}S$ of the dissolution process, we can see that the entropy of cefepime hydrochloride dissolution process is relatively large and that $\Delta_{sol}H$ and $\Delta_{sol}S$ are all positive. The positive $\Delta_{sol}H$ and $\Delta_{sol}S$ revealed that the dissolution process of cefepime hydrochloride 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 dimensions.[11,20,21] The solute cefepime hydrochloride molecule contains both a large group with a basic group and acidic groups and a complex group with different characteristics such as methylpyrrolidinium. The dissolution process of such solutes in water and alcohol + water solvent mixtures involves various forces such as electrostaticity, hydrogen bonding, hydrophobic interaction, solvent bases, stereoscopic effect, and so forth.[14,15] 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 because the interactions between cefepime hydrochloride and solvent molecules are weaker than those between the solvent molecules. Thus, the new bond energy between cefepime hydrochloride and solvent molecules is not powerful enough to compensate the energy needed to break the original association bond in

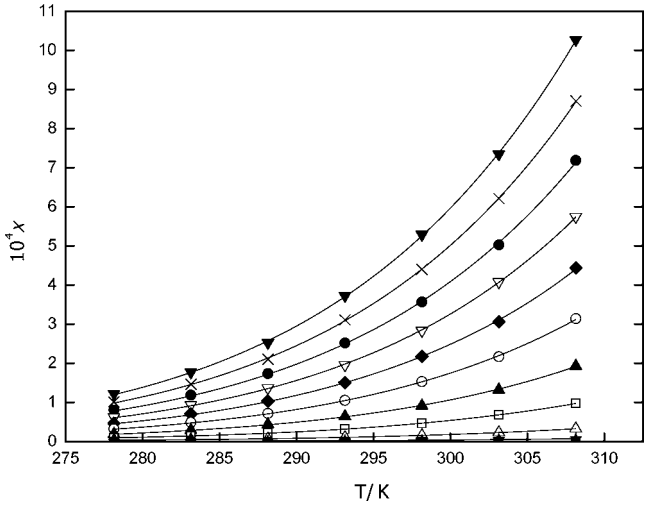

Figure 3. Solubilities of cefepime dihydrochloride hydrate in binary ethanol (B) + water (C) mixed solvent: x_B = ▼, 0.0000; ×, 0.1005; ●, 0.2003; ▽, 0.3006; ◆, 0.3998; ○, 0.5000; ▲, 0.6000; □, 0.7009; △, 0.8014; ☆, 0.9011.

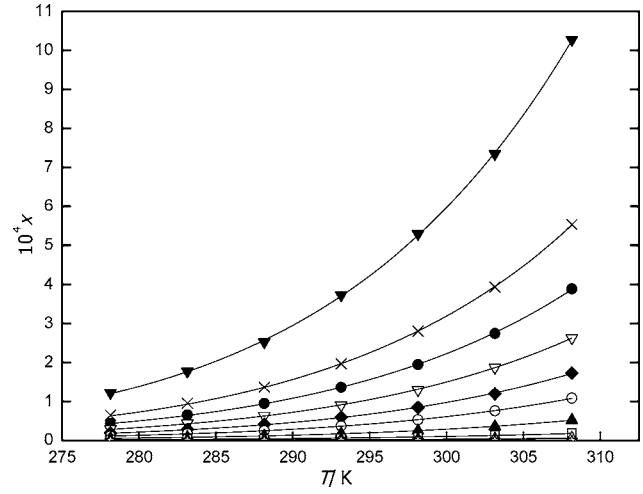

Figure 4. Solubilities of cefepime dihydrochloride hydrate in binary 1-propanol (B) + water (C) mixed solvent; x_B = ▼, 0.0000; ×, 0.1000; ●, 0.2002; ▽, 0.3001; ◆, 0.4007; ○, 0.5001; ▲, 0.6009; □, 0.7009; △, 0.8005; ☆, 0.8998.

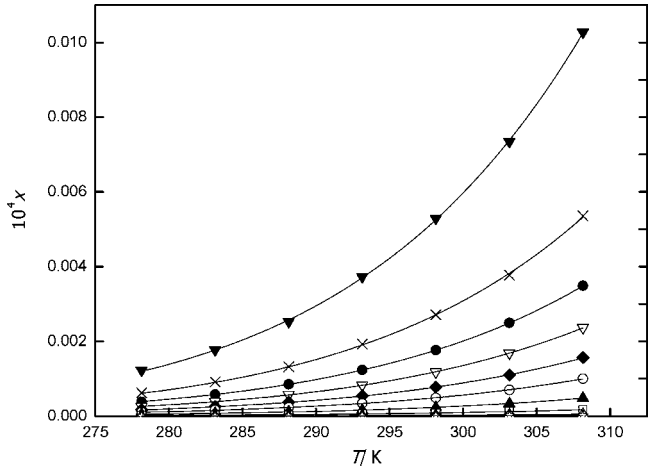

Figure 5. Solubilities of cefepime dihydrochloride hydrate in binary 2-propanol (B) + water (C) mixed solvent; x_B = ▼, 0.0000; ×, 0.1008; ●, 0.2020; ▽, 0.2987; ◆, 0.3999; ○, 0.4987; ▲, 0.5992; □, 0.6993; △, 0.7969; ☆, 0.9001.

various solvents, and the system needs to absorb heat from surroundings and manifests as enthalpy increases.

Conclusions

The solubility values of cefepime hydrochloride in binary water + (ethanol, 1-propanol, or 2-propanol) mixed solvent were determined at temperatures ranging from (278.15 to 308.15) K at atmospheric pressure. The experimental data were correlated with the simplified model of molecular thermodynamics for the solubility of solid in liquid, and the dissolution enthalpies $\Delta_{sol}H$ and dissolution entropies $\Delta_{sol}S$ were estimated. The calculated solubilities of cefepime hydrochloride showed good agreement with the experimental values. The positive $\Delta_{sol}H$ and $\Delta_{sol}S$ indicated that the dissolution process of cefepime hydrochloride in the system was an entropy-driven process. The experimental solubilities and correlation equation in this work can be used as essential data and a model in the industrial production and purification process of cefepime hydrochloride.

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