Solubility of Cefazolin Sodium Pentahydrate in Aqueous 2-Propanol Mixtures

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Using a laser monitoring observation technique, the solubilities of cefazolin sodium pentahydrate in binary 2-propanol + water solvent mixtures were determined by the synthetic method from 273.15 K to 308.15 K. The results of these measurements were correlated by the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister equation. For the eight group data studied, the combined ideal binary solvent (CNIBS)/Redlich−Kister equation was found to provide an accurate mathematical representation of the experimental data.

Introduction

The cephalosporin antibiotic, cefazolin sodium pentahydrate [115850-11-8] is 3-[[5-methyl-(1,3,4-thiadiazol-2-yl)-thio]-methyl]-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic sodium salt, is a white or almost white powdered crystal, as a semisynthetic antibiotic having a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria. Cefazolin sodium pentahydrate is characterized by superior activity in vitro to clinically isolated *Escherichia coli* and *Klebsiella pneumoniae*. In preferential crystallization, the solubilities of cefazolin sodium pentahydrate in solvents are needed. Up to now, few solubilities of cefazolin sodium pentahydrate in solvents have been reported in the literature. In this work, we report the solubilities of cefazolin sodium pentahydrate in binary 2-propanol + water solvent mixtures in the temperature range from 273.15 K to 308.15 K at atmospheric pressure.

Experimental Section

Materials. A white crystalline powder of cefazolin sodium pentahydrate obtained from North China Pharmaceutical Co., Ltd., with a melting/decomposition point of 185.6 °C which compares well with the literature[1] value 185−186 °C, measured with a NETZSCH STA449C differential scanning calorimeter, was prepared by recrystallization from an ethanol solution. Its purity, determined by HPLC according to BP2000, is higher than 0.996 (mass fraction). The 2-propanol is an analytical research grade reagent from Tianjin Chemical Reagent Co., and distilled demonized water of HPLC grade was used.

Apparatus and Procedure. Solubilities were measured by a synthetic method.[2−4] The apparatus for solubility measurement is the same as that described in the literature.[5−6] A laser beam was used to determine the solubility of the solute in the binary solvent mixture at a known temperature. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The solubility apparatus consisted of a jacketed glass vessel maintained at a desired temperature by water circulated from a water bath with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ±0.05 K of the required temperature. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected with the vessels to prevent the solvents from evaporating. A mercury-in-glass thermometer was inserted into the inner chambers of the vessels for the measurement of the temperature. The thermometer had an uncertainty of ±0.05 K.

An analytical balance (type TG332A, China) with an uncertainty of ±0.0001 g was used during the measurement. Predetermined excess amounts of cefazolin sodium pentahydrate 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. 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 2-propanol + water solvent mixtures can be obtained as follows:

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

where m_A, m_B, and m_C represent the mass of the solute, water, and 2-propanol, respectively, and M_A, M_B, and M_C are the molecular weight of the solute, water, and 2-propanol, respectively. The same solubility experiment was conducted three times. The uncertainty of the experimental solubility values is about 0.5%. The uncertainty in the solubility values due to uncertainties in the temperature measurements and weighing procedure and instabilities of the water bath is estimated to be 0.5%.

Results and Discussion

The solubility data of cefazolin sodium pentahydrate in binary 2-propanol + water solvent mixtures at the temperature range from 273.15 K to 308.15 K are presented in Table 1. The solubility data in binary 2-propanol + water solvent mixtures are described by the combined nearly

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Table 1. Experimental Solubilities (x_A) of Cefazolin Sodium Pentahydrate in Binary 2-Propanol (B) + Water (C) Solvent Mixtures in the Temperature Range from 273.15 K to 308.15 K

x_C^0	$10^4 x_A^{exptl}$	10^4	$x_A^{calcd} x_C^0$	$10^4 x_A^{exptl}$	$10^4 x_A^{calcd}$
	$T = 273.15$ K			$T = 278.15$ K	
0.0000	0.1383	0.1378	0.0000	0.1769	0.1786
0.1036	0.3631	0.3653	0.1036	0.4852	0.4776
0.2046	0.6354	0.6353	0.2046	0.8718	0.8632
0.3043	0.9289	0.9295	0.3043	1.301	1.311
0.4390	1.599	1.567	0.4390	2.120	2.249
0.4997	2.087	2.105	0.4997	3.123	2.990
0.6016	3.807	3.876	0.6016	5.282	5.278
0.6942	7.593	7.553	0.6942	9.963	9.709
0.8010	17.47	17.34	0.8010	20.59	20.77
0.9048	35.97	36.05	0.9048	40.45	41.43
1.0000	55.27	55.31	1.0000	65.75	64.91
	$T = 283.15$ K			$T = 288.15$ K	
0.0000	0.2521	0.2509	0.0000	0.3275	0.3288
0.1036	0.6584	0.6800	0.1036	0.8648	0.8558
0.2046	1.314	1.239	0.2046	1.548	1.554
0.3043	1.845	1.884	0.3043	2.391	2.405
0.4390	3.056	3.191	0.4390	4.233	4.236
0.4997	4.267	4.194	0.4997	5.678	5.668
0.6016	7.288	7.216	0.6016	10.03	9.995
0.6942	13.18	12.88	0.6942	18.09	18.06
0.8010	26.15	26.46	0.8010	36.98	37.05
0.9048	49.94	50.63	0.9048	69.24	69.47
1.0000	77.12	76.50	1.0000	101.7	101.5
	$T = 293.15$ K			$T = 298.15$ K	
0.0000	0.5049	0.4954	0.0000	0.7576	0.7599
0.1036	1.103	1.164	0.1036	1.578	1.573
0.2046	2.053	1.998	0.2046	2.566	2.545
0.3043	3.130	3.025	0.3043	3.750	3.799
0.4390	5.259	5.366	0.4390	7.053	6.883
0.4997	7.211	7.269	0.4997	9.204	9.476
0.6016	13.03	13.16	0.6016	17.30	17.61
0.6942	24.54	24.35	0.6942	34.41	33.05
0.8010	51.13	50.88	0.8010	68.84	68.74
0.9048	95.65	95.38	0.9048	121.3	124.6
1.0000	135.5	136.0	1.0000	169.2	167.3
	$T = 303.15$ K			$T = 308.15$ K	
0.0000	1.135	1.139	0.0000	1.504	1.575
0.1036	2.254	2.239	0.1036	3.603	3.230
0.2046	3.602	3.592	0.2046	5.312	5.474
0.3043	5.381	5.401	0.3043	8.265	8.599
0.4390	9.800	9.867	0.4390	14.91	15.92
0.4997	13.49	13.55	0.4997	21.78	21.53
0.6016	24.88	24.76	0.6016	39.97	37.27
0.6942	45.70	45.29	0.6942	66.58	63.35
0.8010	91.75	91.05	0.8010	111.7	115.9
0.9048	158.3	161.6	0.9048	180.6	191.4
1.0000	221.1	219.2	1.0000	264.4	255.2

ideal binary solvent (CNIBS)/Redlich−Kister model. Acree and co-workers[7−9] suggested the CNIBS/Redlich−Kister model

$$\ln x_A = x_B^0 \ln(x_A)_B + x_C^0 \ln(x_A)_C + x_B^0 x_C^0 \sum_{i=1}^{N} S_i (x_B^0 - x_C^0)^i \quad (2)$$

as a possible mathematical representation for describing how the experimental isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varies with binary solvent composition, in which S_i is the model constant and N can be equal to 0, 1, 2, and 3, respectively. Depending on the values of N, four equations can be obtained from eq 2. x_B^0 and x_C^0 refer to the initial mole fraction composition of the binary solvent calculated as if solute (A) were not present. $(x_A)_i$ is the saturated mole fraction solubility of the solute in pure solvent i.

Table 2. Curve Fitting Parameters of Cefazolin Sodium Pentahydrate in Binary 2-Propanol (B) + Water (C) Solvent Mixtures in the Temperature Range from 273.15 K to 308.15 K

T/K	B_0	B_1	B_2	B_3	B_4	10^4RMSD
273.15	−11.192	12.315	−33.034	50.536	−23.823	0.0544
278.15	−10.932	12.126	−29.652	43.286	−19.864	0.4041
283.15	−10.593	12.269	−29.725	42.655	−19.479	0.3120
288.15	−10.322	11.647	−27.237	40.025	−18.703	0.0992
293.15	−9.9126	10.414	−24.693	38.563	−18.669	0.2028
298.15	−9.4849	8.7916	−20.496	34.954	−17.855	1.2511
303.15	−9.0802	7.9954	−17.051	29.570	−15.255	1.1878
308.15	−8.7563	8.2172	−14.653	23.225	−11.700	4.6603

Substitution of $(1 - x_C^0)$ for x_B^0 in eq 1 with $N = 2$ and subsequent rearrangements result in eq 3

$$\ln x_A = \ln(x_A)_B + [\ln(x_A)_C - \ln(x_A)_B + S_0 + S_1 + S_2] x_C^0 + [-S_0 + 3S_1 + 5S_2] x_C^{0\,2} + [-2S_1 - 8S_2] x_C^{0\,3} + [-4S_2] x_C^{0\,4} \quad (3)$$

which can be written as eq 4

$$\ln x_A = B_0 + B_1 x_C^0 + B_2 x_C^{0\,2} + B_3 x_C^{0\,3} + B_4 x_C^{0\,4} \quad (4)$$

The experimental solubility data (x_A^{exptl}) correlated with eq 4, and the calculated solubilities (x_A^{calcd}) are listed in Table 1. For comparison with each of the experimental points, the values of the solubilities of cefazolin sodium pentahydrate in binary 2-propanol + water solvent mixtures in the temperature range from 273.15 K to 308.15 K are presented in Figure 1. The values of the five parameters B_0, B_1, B_2, B_3, and B_4 are listed in Table 2 together with the root-mean-square deviations (RMSDs). The RMSD is defined as

$$\mathrm{RMSD} = \left[\frac{1}{n} \sum_{i=1}^{n} (x_i^{calcd} - x_i^{exptl})^2 \right]^{1/2} \quad (5)$$

where n is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 4, and x_i^{exptl} represents the experimental solubility values.

From Tables 1 and 2 and Figure 1, we can draw the following conclusions: (1) The solubility of cefazolin sodium pentahydrate in binary 2-propanol + water solvent mixtures is a function of temperature, and solubility increase with an increase of temperature. (2) The solubility decreases with an increase of 2-propanol in the solvent mixture, and the solubility in pure 2-propanol is the lowest. (3) The calculated solubilities of cefazolin sodium pentahydrate show good agreement with the experimental values, and the experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of cefazolin sodium pentahydrate.

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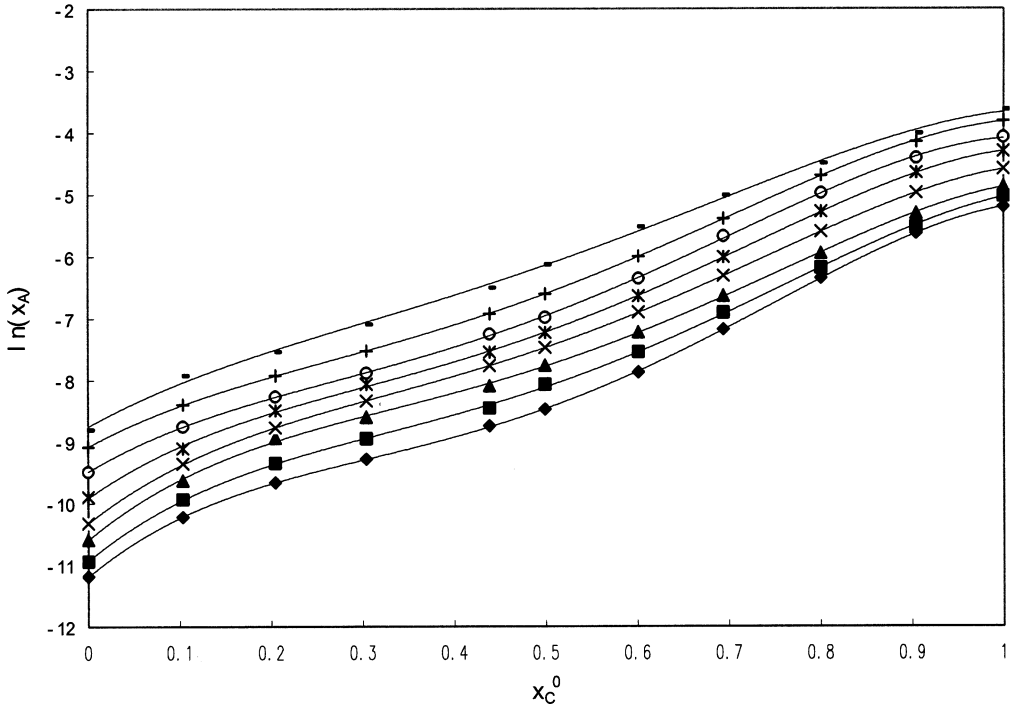

Figure 1. Solubilities of cefazolin sodium pentahydrate in binary 2-propanol (B) + water (C) solvent mixtures: ◆, T = 273.15 K; ■, T = 278.15 K; ▲, T = 283.15 K; ×, T = 288.15 K; ∗, T = 293.15 K; ○, T = 298.15 K; +, T = 303.15 K; −, T = 308.15 K.

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