Solubiliy of Sodium Cefotaxime in Aqueous 2-Propanol Mixtures

Haitao Zhang, Jingkang Wang,* Ying Chen, and Qiang Nie

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

Using a laser monitoring observation technique, the solubilities of sodium cefotaxime (A) in binary water (B) + 2-propanol (C) solvent mixtures were determined by the synthetic method from 278.15 K to 308.15 K and in the solvent composition (x_C^0) range from 0.025 to 1.000. The results of these measurements were correlated by the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister equation. For the seven mixtures studied, the CNIBS/Redlich−Kister equation was found to provide a good correlation of the experimental data.

Introduction

The cephalosporin antibiotic, sodium salt cefotaxime [CASRN 64485-93-4], with the chemical name [6*R*-[6α,7*β*(*z*)]]-3-[(acetyloxy)methyl][[(2-amine-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic acid monosodium salt (Figure 1) is a white, almost white, or white-yellow powdered crystal and is a semisynthetic antibiotic having a broad spectrum of antibacterial activity. Sodium cefotaxime is classified as a third generation cephalosporin strongly active against Gram-negative bacteria, such as *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, and *Salmonella*, and more active against some Gram-positive bacteria, such as *Hemolytic streptococcus*, *Streptococcus pneumoniae*, etc. The antibacterial activity of the drug results from interference with bacterial cell-wall synthesis. It causes lysis of the penicillin-binding protein enzymes and results in the bacterial cell destruction and death.[1−4]

In preferential crystallization, the solubilities of sodium cefotaxime in solvents are needed. Up to now, only a few solubilities of sodium cefotaxime in several solvents have been reported.[2] In this work, the solubilities of sodium cefotaxime in binary water + 2-propanol solvent mixtures in the temperature range from 278.15 K to 308.15 K at atmospheric pressure were measured using a synthetic method.[5−13] In addition, owing to the particularity of the dissolution behavior of sodium cefotaxime in pure water, which will not be discussed here, the solvent composition (x_C^0) range is from 0.025 to 1.000 in this paper. A laser monitoring observation technique employing an isothermal method was used to determine the solubility.

Experimental Section

Materials. A white crystalline powder of sodium cefotaxime ($C_{16}H_{16}N_5O_7S_2Na$, molecular weight 477.44) obtained from Shenzhen Jiuxin Pharmaceutical Co., Ltd., China, with a melting/decomposition point of 273.5 °C measured with a NETZSCH DSC-204 differential scanning calorimeter, was purified by recrystallization from a methanol solution by addition of the anti-solvent ethyl acetate to initiate precipitation. Its mass factor purity, determined by HPLC, was better than 99.0 %. It was dried in vacuo at 40 °C for 24 h and stored in a desiccator. No polymorphic transition was found in the treatment of the material. The 2-propanol is an analytical research grade reagent from Tianjin Chemical Reagent Co. China and distilled, deionized water was used.

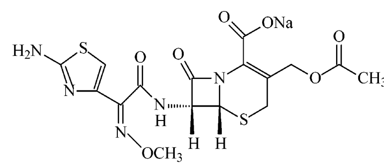

Figure 1. Chemical structure of sodium cefotaxime.

Apparatus and Procedure. The apparatus for solubility measurement is the same as that described in the literature.[14,15] 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 with water circulated from a water bath with a thermoelectric controller (type 501A, China). The jacket temperature was controlled to be constant (fluctuating within 0.05 K). Continuous stirring was achieved with a magnetic stir bar. A condenser was connected with the vessel to prevent the solvents from evaporating. 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 the temperature. An analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of 0.0001 g was used during the measurement. Predetermined excess masses of sodium cefotaxime 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 of addition 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 was 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 water (B) + 2-propanol (C) solvent mixtures can be obtained as follows:

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

* Corresponding author. Phone: +86-22-27405754. Fax: +86-22-27314971. E-mail: zht_wolf@yahoo.com.cn.

10.1021/je060318s CCC: $33.50
Published on Web 10/19/2006

Table 1. Experimental Solubilities (x_A) of Sodium Cefotaxime in Binary Water (B) + 2-Propanol (C) Solvent Mixtures in the Temperature Range from 278.15 K to 308.15 K

x_C^0	$10^4\,x_A^{exptl}$	$10^5\,x_A^{calcd}$	x_C^0	$10^4\,x_A^{exptl}$	$10^5\,x_A^{calcd}$	x_C^0	$10^4\,x_A^{exptl}$	$10^5\,x_A^{calcd}$	x_C^0	$10^4\,x_A^{exptl}$	$10^5\,x_A^{calcd}$
	T/K = 278.15			T/K = 283.15			T/K = 288.15			T/K = 293.15	
0.0256	90.20	902.0	0.0256	103.8	1038	0.0256	112.5	1125	0.0256	128.2	1282
0.0998	56.00	561.0	0.0998	66.70	665.0	0.0998	77.30	771.0	0.0998	91.10	909.0
0.1987	34.70	344.0	0.1987	40.80	412.0	0.1987	47.50	481.0	0.1987	58.10	584.0
0.3015	22.00	222.0	0.3015	26.60	260.0	0.3015	30.70	299.0	0.3015	35.60	352.0
0.4068	12.70	126.0	0.4068	13.60	142.0	0.4068	15.70	164.0	0.4068	18.20	184.0
0.5105	5.420	51.00	0.5105	5.860	55.00	0.5105	6.640	70.00	0.5105	7.650	77.00
0.6032	0.6850	12.00	0.6032	1.130	14.00	0.6032	1.240	15.00	0.6032	2.590	27.00
0.6986	0.3250	1.000	0.6986	0.7030	2.000	0.6986	1.040	10.00	0.6986	1.090	6.000
0.8023	0.1250	0.0239	0.8023	0.1500	0.0453	0.8023	0.1760	0.0164	0.8023	0.1790	0.7960
0.9105	0.0468	0.00005	0.9105	0.0868	0.0002	0.9105	0.1330	0.00001	0.9105	0.1570	0.0441
1.000	0.0048	0.000003	1.000	0.0078	0.0000003	1.000	0.0107	0.000000003	1.000	0.0161	0.0021
	T/K = 298.15			T/K = 303.15			T/K = 308.15				
0.0256	137.9	1379	0.0256	150.8	1508	0.0256	168.5	1685			
0.0998	105.4	1054	0.0998	120.5	1204	0.0998	136.9	1368			
0.1987	68.3	684.0	0.1987	79.20	795.0	0.1987	91.70	918.0			
0.3015	40.80	406.0	0.3015	49.40	491.0	0.3015	56.70	566.0			
0.4068	21.00	213.0	0.4068	26.60	267.0	0.4068	30.90	308.0			
0.5105	9.700	93.00	0.5105	10.30	104.0	0.5105	12.30	125.0			
0.6032	2.930	34.00	0.6032	2.510	24.00	0.6032	3.110	33.00			
0.6986	1.130	8.000	0.6986	1.510	2.000	0.6986	2.050	4.000			
0.8023	0.1910	0.8070	0.8023	0.2150	0.0190	0.8023	0.2450	0.0677			
0.9105	0.1930	0.0257	0.9105	0.2630	0.0000077	0.9105	0.2970	0.00009			
1.000	0.0207	0.0005	1.000	0.0299	0.0000000005	1.000	0.0357	0.00000003			

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 two more 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, weighing procedure, and instabilities of the water bath.

Results and Discussion

The solubility data of sodium cefotaxime in binary water + 2-propanol solvent mixtures at the temperature range from 278.15 K to 308.15 K are presented in Table 1. The solubility data in binary water + 2-propanol solvent mixtures are correlated by the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister model (eq 2), which was suggested by Acree and his co-workers:[16−18]

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

The model has been 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 the solute (A) was not present. $(x_A)_i$ is the saturated mole fraction solubility of the solute in pure solvent i. Substitution of $(1 - x_C^0)$ for x_B^0 in eq 1 with $N = 2$ and subsequent rearrangements result in

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

which can be written as

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

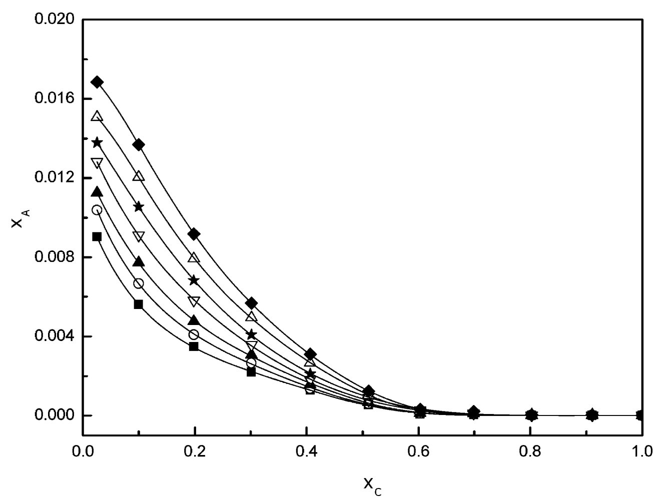

Figure 2. Solubilities of sodium cefotaxime in binary water (B) + 2-propanol (C) solvent mixtures: ■, 278.15 K; ○, 283.15 K; ▲, 288.15 K; ▽, 293.15 K; ★, 298.15 K; △, 303.15 K; ◆, 308.15 K.

Table 2. Curve-Fitting Parameters of Sodium Cefotaxime in Binary Water (B) + 2-Propanol (C) Solvent Mixtures in the Temperature Range from 278.15 K to 308.15 K

T/K	B_0	B_1	B_2	B_3	B_4	10^5 rmsd
278.15	−4.5188	−7.7007	10.967	−1.9336	−25.605	2.3117
283.15	−4.3912	−7.1539	10.136	−6.2773	−18.725	3.5336
288.15	−4.3566	−5.0609	−2.181	22.436	−41.964	4.9142
293.15	−4.2310	−5.0062	4.0249	−8.9335	−3.5498	2.3756
298.15	−4.2063	−2.8466	−7.5347	14.617	−19.152	2.4855
303.15	−4.1507	−1.2384	−19.368	54.048	−62.211	4.3323
308.15	−4.0445	−1.0884	−17.974	46.010	−51.841	5.2183

The experimental solubility data (x_A^{exptl}) and the calculated solubilities (x_A^{calcd}) correlated with eq 4 are listed in Table 1. For comparison with each of the experimental points, the values of the solubilities of sodium cefotaxime in binary 2-propanol + water solvent mixtures in the temperature range from 278.15 K to 308.15 K are presented in Figure 2. 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 (rmsd). The rmsd is defined as

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

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 sodium cefotaxime in binary water + 2-propanol solvent mixtures is a function of temperature, and solubility increases with an increase in temperature.

(2) The solubility decreases with an increase of concentration of 2-propanol in the solvent mixture.

(3) The calculated solubilities of sodium cefotaxime show good agreement with the experimental values, and the experimental solubilities and correlation equation in this work can be used as essential data and models in the purification process of sodium cefotaxime.

Acknowledgment

The authors are grateful to Shenzhen Jiuxin Pharmaceutical Co., Ltd. (China) for supplying sodium cefotaxime.

Literature Cited

(1) Gaston, A.; Dieter, B.; Walter D.; Jean, J. Sodium 3-acetoxylmethyl-7-[2-(2-amino-4-thiazolyl)-2-methoxyimino-acetamido]-ceph-3-eme-4-carboxylate. U.S. Patent 4224371, 1980.

(2) Eladio, P. F.; Jhoany, A. E.; Lauro, N. P.; Amador, G. A.; Ulises, J. H. Solubility of cefotaxime sodium salt in seven solvents used in the pharmaceutical industry. *J. Chem. Eng. Data* **1998**, *43*, 49−50.

(3) Zajack, M.; Musial, W.; Pawlowski, L. Stability of cefotaxime sodium in solid state. *Pharmazie* **2000**, *55*, 917−918.

(4) Atanassova, T.; Georgieva, Z.; Lazarova, V.; Natova, Z.; Pavlova, A. Synthesis of cefotaxime sodium salt. *Pharmazie* **1998**, *53*, 418.

(5) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of dexamethasone sodium phosphate in different solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697−1698.

(6) Roberts, K. L.; Rousseau, R. W.; Teja, A. S. Solubility of long-chain *n*-alkanes in heptane between 280 and 350 K. *J. Chem. Eng. Data* **1994**, *39*, 793−795.

(7) Jiang, Q.; Gao, G. H.; Yu, Y. X.; Qin, Y. Solubility of sodium dimethyl isophthalate-5-sulfonate in water and in water + methanol containing sodium sulfate. *J. Chem. Eng. Data* **2000**, *45*, 292−294.

(8) Ren, G. B.; Wang, J. K.; Yin, Q. X.; Zhang, M. J. Solubilities of proxetine hydrochloride hemihydrate between 286 K and 363 K. *J. Chem. Eng. Data* **2004**, *49*, 1671−1674.

(9) Ren, G. B.; Wang, J. K.; Li, G. Z. Solubility of paroxetine hydrochloride hemi-hydrate in (water + acetone). *J. Chem. Thermodyn.* **2005**, *37*, 860−865.

(10) Wu, J. H.; Wang, J. K. Solubility of cefazolin sodium pentahydrate in aqueous 2-propanol mixtures. *J. Chem. Eng. Data* ***2005***, *50*, 980−982.

(11) Nyvlt, J. *Solid-Liquid Equilibria*; Czechoslovak Academia of Sciences: Praha, 1997.

(12) Roberts, K. L.; Rousseau, R. W.; Teja, A. S. Solubility of long-chain *n*-alkanes in heptane between 280 and 350 K. *J. Chem. Eng. Data* **1994**, *39*, 793−795.

(13) Jiang, Q.; Gao, G. H.; Yu, Y. X.; Qin, Y. Solubility of sodium dimethyl isophthalate-5-sulfonate in water and in water + methanol containing sodium sulfate. *J. Chem. Eng. Data* **2000**, *45*, 292−294.

(14) Li, D. Q.; Liu, D. Z.; Wang, F. A. Solubilities of terephthaladehydic, *p*-toluic, benzoic, terephthalic, and isophthalic acids in *n*-methyl-2-pyrrolidone from 295.65 K to 371.35 K. *J. Chem. Eng. Data* **2001**, *46*, 172−173.

(15) Li, D. Q.; Liu, D. Z.; Wang, F. A. Solubility of 4-methylbenzoic acid between 288 K and 370 K. *J. Chem. Eng. Data* **2001**, *46*, 234−236.

(16) Acree, W. E., Jr. Mathematical representation of thermodynamic properties. Part 2. Derivation of the combined nearly ideal binary solvent (nibs)/Redlich−Kister mathematical representation from a two-body and three-body interactional mixting model. *Thermochim. Acta* **1992**, *198*, 71−79.

(17) Acree, W. E., Jr.; McCargar, J. W.; Zvaigzne, A. L.; Teng, L. L. Mathematical representation of thermodynamic properties. Carbazole solubilities in binary alkane + dibutyl ether and alkane + tetrahydropyran solvent mixture. *Phys. Chem. Liq.* **1991**, *23*, 27−35.

(18) Acree, W. E., Jr.; Zvaigzne, A. L. Thermodynamic properties of nonelectrolyte solutions. Part 4. Estimination and mathematical representation of solute activity coefficients and solubilities in binary solvents using the NIBS and modified Wilson equation. *Thermochim. Acta* **1991**, *178*, 151−167.

Received for review July 17, 2006. Accepted September 10, 2006.

JE060318S