Solubility of Cloxacillin Sodium in Different Binary Solvents

Minjie Zhi, Jingkang Wang, Chunyan Jia, and Yongli Wang*

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

The solubilities of cloxacillin sodium in binary butyl acetate + methanol and ethyl acetate + methanol solvent mixtures were measured at temperatures ranging from (283.15 to 298.15) K. The experimental data can be well correlated by the CNIBS/Redlich−Kister model. The results show that the solubility of cloxacillin sodium increases with increasing temperature and mole fraction of methanol in these two binary mixed solvents.

Introduction

Cloxacillin sodium (6b-[3-(2-chlorophenyl)-5-methyl-isoxazole-4-carbonylamino]-penicillanic acid; sodium salt, CAS No. 642-78-4) is a common antibiotic, used in veterinary drugs, for the treatment of mastitis.[1] The molecular structure can be seen from Figure 1. Solvent systems butyl acetate + methanol and ethyl acetate + methanol are used for crystallization of cloxacillin sodium. The temperature range of (283.15 to 298.15) K was selected because of degrading of the compound in high temperature. The solubilities of cloxacillin sodium in binary butyl acetate + methanol or ethyl acetate + methanol solvent mixtures are the crucial data for controlling the crystallization process. However, up to now, few solubilities of cloxacillin sodium in other solvents have been reported in the literature.

In this work, the solubilities of cloxacillin sodium in butyl acetate + methanol and ethyl acetate + methanol at temperatures ranging from (283.15 to 298.15) K were experimentally determined using a laser monitoring observation technique.

Experimental Section

Materials. A white crystalline powder of cloxacillin sodium was obtained by recrystallization. Its purity, determined by HPLC according to ChP2005, was found to be higher than 99.0 %. The butyl acetate, ethyl acetate, and methanol (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade and dried with anhydrous bitter salt before use.

Apparatus and Procedure. The solubilities of cloxacillin sodium in different solvents were measured by a synthetic method.[2−5] The apparatus for the solubility measurements was similar to those described in the literature[6,7] and described only briefly here. A laser beam was used to determine the disappearance of the last solute in the solvent at a fixed temperature. The laser beam monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The solubility apparatus included a jacketed glass vessel maintained at a desired temperature by circulating water from a thermostat. 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 solution temperature, and the temperature was controlled to within ± 0.1 K of the desired value.

* To whom correspondence should be addressed. E-mail: yliwang@tju.edu.cn. Fax: 0086-22-27374971.

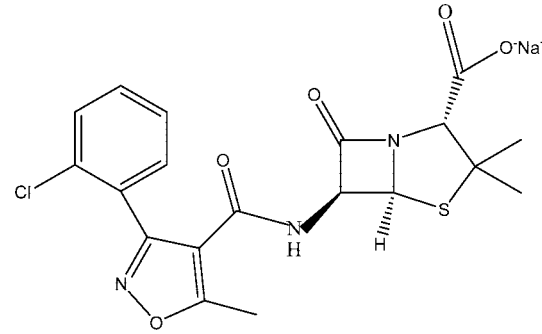

Figure 1. Chemical structure of cloxacillin sodium.

Continuous stirring of the solution was achieved with a magnetic stir bar. A condenser was connected with the vessel to prevent the solvents from evaporating. An analytical balance (Mettler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.0001 g was used for the measurement of the masses of the solute and solvents.

During the experiments, the predetermined solvents were placed in the vessel and stirred continuously at a required temperature. Cloxacillin sodium was added to the vessel simultaneously. The laser beam intensity passing through the vessel reached a maximum when the solute dissolved completely. Then an additional portion of solute [about (2 to 5) mg] was added into the vessel. This procedure was repeated until the last addition of solute could not be dissolved completely. The interval of additions was 30 min. When the laser intensity did not exceed 90 % of the maximum, the solute was believed to be not dissolved completely. The total amount of the solute dissolved was recorded. The solubility experiment was repeated three times, and the mean values were used to calculate the mole fraction solubilities (x_0). It is expressed by eq 1. The composition of the solvent mixture (x_1^0) was defined by eq 2

$$x_0 = \frac{m_0/M_0}{m_0/M_0 + m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_1^0 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

where m_0, m_1, m_2, and m_3 represent the mass of the cloxacillin sodium, methanol, butyl acetate, and ethyl acetate, respectively. M_0, M_1, M_2, and M_3 are the molecular weights of the solute,

10.1021/je800730k CCC: $40.75
Published on Web 01/16/2009

Table 1. Solubility of Cloxacillin Sodium (0) in Binary Butyl Acetate (2) + Methanol (1) Mixtures and Ethyl Acetate (3) + Methanol (1) Mixtures

butyl acetate + methanol			ethyl acetate + methanol		
x_1^0	$10^3 x_0$	$10^2((x_0 - x_0^{calcd})/x_0)$	x_1^0	$10^3 x_0$	$10^2((x_0 - x_0^{calcd})/x_0)$
	T/K = 283.15			T/K = 283.15	
0.156	0.379	−6.5	0.164	0.652	2.7
0.202	0.814	−5.4	0.212	1.56	5.9
0.258	1.88	6.8	0.263	2.74	−5.9
0.307	2.90	1.6	0.314	5.01	2.8
0.360	4.40	0.62	0.366	7.45	1.6
0.411	6.00	−2.7	0.418	10.1	−0.48
0.461	8.43	1.9	0.467	13.1	−0.0023
0.511	11.0	1.8	0.517	16.3	−0.53
0.559	13.7	0.41	0.566	20.0	1.0
0.606	17.0	1.3	0.616	23.3	0.56
	T/K = 288.15			T/K = 288.15	
0.151	0.499	−10	0.163	0.912	−7.3
0.201	1.14	−3.4	0.213	2.13	1.1
0.259	2.48	3.9	0.264	4.06	3.4
0.316	4.22	2.0	0.313	6.24	−0.61
0.370	6.14	−3.3	0.364	9.16	−0.48
0.403	7.92	−0.4	0.414	12.3	−0.17
0.458	11.1	0.2	0.463	15.5	0.32
0.509	14.4	0.2	0.512	18.7	0.46
0.560	17.7	−0.7	0.560	21.8	−0.23
0.606	20.6	−0.2	0.610	25.7	0.22
	T/K = 293.15			T/K = 293.15	
0.142	0.635	4.5	0.158	1.02	−7.5
0.186	1.39	9.6	0.212	2.54	2.4
0.251	2.79	−3.2	0.264	4.63	2.1
0.311	5.13	0.86	0.315	7.09	−1.4
0.363	7.49	0.29	0.363	9.99	−1.5
0.408	9.98	1.6	0.413	13.7	0.98
0.457	12.6	−0.40	0.463	17.1	−0.75
0.509	16.0	0.50	0.512	21.0	0.28
0.556	19.2	0.81	0.563	24.6	−0.57
0.603	22.2	0.078	0.612	28.0	0.011
	T/K = 298.15			T/K = 298.15	
0.0882	0.152	−1.3	0.162	1.31	−5.3
0.148	0.587	−0.048	0.217	3.51	−3.5
0.206	1.73	7.0	0.268	7.07	4.6
0.281	4.33	2.2	0.318	10.3	−0.19
0.350	7.88	−1.2	0.367	13.7	−1.8
0.395	10.8	−0.76	0.410	17.2	0.33
0.447	14.4	−0.48	0.461	20.8	−1.1
0.492	17.8	0.92	0.510	24.8	−0.78
0.546	21.3	−0.77	0.560	29.3	−0.035
0.594	24.9	−0.21	0.610	33.1	−1.2

methanol, butyl acetate, and ethyl acetate, respectively. For the case of butyl acetate + methanol, $m_3 = 0$ in eqs 1 and 2, while for the case of ethyl acetate + methanol, $m_2 = 0$. The uncertainty in the solubility values is estimated to be ± 1.0 %.

Results and Discussion

The solubilities of the cloxacillin sodium in the binary butyl acetate + methanol and ethyl acetate + methanol solvent mixtures at the temperatures ranging from (283.15 to 298.15) K are presented in Table 1 and graphically shown in Figures 2 and 3.

Acree[8] and Acree et al.[9] suggested the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister model as a possible mathematical representation for describing how the experimental isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varied with binary solvent composition, which is expressed by eq 3

$$\ln x_0 = x_B^0 \ln(x_0)_B + x_C^0 \ln(x_0)_C + x_B^0 x_C^0 \sum_{i=0}^{N} S_i (x_B^0 - x_C^0)^i \quad (3)$$

where S_i is the model constant and N is the number of solvents. x_B^0 and x_C^0 refer to the initial mole fraction composition of the

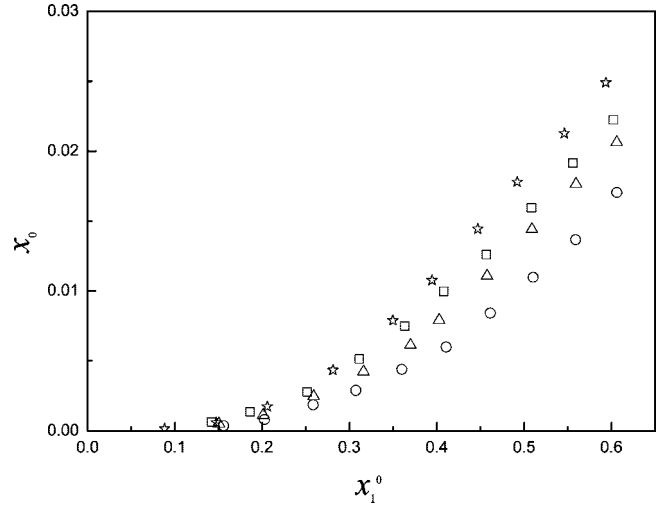

Figure 2. Mole fraction solubility (x_0) of cloxacillin sodium in binary butyl acetate (2) + methanol (1) solvent mixtures: ☆, T/K = 298.15; □, T/K = 293.15; Δ, T/K = 288.15; ○, T/K = 283.15.

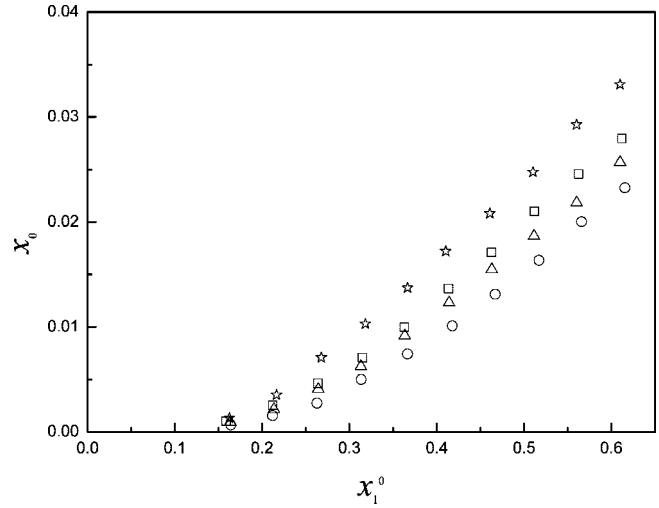

Figure 3. Mole fraction solubility (x_0) of cloxacillin sodium in binary ethyl acetate (3) + methanol (1) solvent mixtures: ☆, T/K = 298.15; □, T/K = 293.15; Δ, T/K = 288.15; ○, T/K = 283.15.

binary solvent calculated as if the solute was not present. $(x_0)_i$ 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 3 with $N = 2$ and subsequent rearrangements result in eq 4

$$\ln x_0 = \ln(x_0)_B + [\ln(x_0)_C - \ln(x_0)_B + S_0 + S_1 + S_2]x_C^0 + [-S_0 + 3S_1 + 5S_2]x_C^{0^2} + [-2S_1 - 8S_2]x_C^{0^3} + [-4S_2]x_C^{0^4} \quad (4)$$

which can be written as eq 5

$$\ln x_0 = B_0 + B_1 x_C^0 + B_2 x_C^{0^2} + B_3 x_C^{0^3} + B_4 x_C^{0^4} \quad (5)$$

The solubility data in the above two binary mixed solvents are correlated by eq 5, and the solubilities ($10^3\ x_0$) are listed in Table 1. The values of the parameters B_0, B_1, B_2, B_3, and B_4 for eq 5 are presented in Table 2, together with the root-mean-square deviations (rmsd). The rmsd's are defined in eq 6

$$\text{rmsd} = \left\{ \frac{\sum_{i=1}^{N} (x_i^{calcd} - x_i)^2}{N} \right\}^{1/2} \quad (6)$$

where N is the number of the experimental points; x_i^{calcd} represents the solubility calculated from eq 5; and x_i represents the experimental values of solubility.

Table 2. Parameters of Equation 5 for Cloxacillin Sodium in Binary Butyl Acetate + Methanol and Ethyl Acetate + Methanol Mixtures

	T/K = 283.15	T/K = 288.15	T/K = 293.15	T/K = 298.15
		Butyl Acetate + Methanol		
B_0	−12.13	−11.15	−11.11	−11.41
B_1	39.22	32.95	35.32	35.08
B_2	−89.94	−70.46	−76.87	−63.43
B_3	109.8	86.81	88.68	54.16
B_4	−52.88	−45.54	−41.52	−16.78
10^4rmsd	0.94	0.85	0.76	0.99
		Ethyl Acetate + Methanol		
B_0	−12.51	−10.84	−10.88	−12.49
B_1	45.83	32.00	36.19	56.01
B_2	−107.7	−55.87	−79.78	−149.5
B_3	129.8	42.96	92.67	192.7
B_4	−62.22	−9.428	−44.23	−95.21
10^4rmsd	0.98	0.59	0.85	1.5

From Tables 1 and 2 and Figures 2 and 3, the following conclusions can be reached: (1) the solubility of cloxacillin sodium in binary butyl acetate + methanol and ethyl acetate + methanol solvent mixtures increases with both the increase of temperature and the mole fraction of methanol within the temperature range under consideration. (2) The calculated solubilities of cloxacillin sodium show good agreement with the experimental values. Thus, the experimental solubility data and the correlation equations in this work can be used as fundamental data and models in the purification process of cloxacillin sodium.

Literature Cited

(1) Guyon, S.; Abric, J. L. Stability Study of Cloxacillin in an Oily Suspension, by High Performance Liquid Chromatography. *Farmaco* **1992**, *47*, 1081–1094.

(2) 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.

(3) Wu, J. H.; Wang, J. K. Solubility of Cefazolin Sodium Pentahydrate in Aqueous 2-Propanol Mixtures. *J. Chem. Eng. Data* **2005**, *50*, 980–982.

(4) Nie, Q.; Wang, J. K.; Wang, Y. L.; Wang, S. Solubility of 11Rhydroxy-16R,17R-epoxyprogesterone in different solvents between 283 and 323 K. *J. Chem. Eng. Data* **2005**, *50*, 989–992.

(5) 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.

(6) 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 to 371.35 K. *J. Chem. Eng. Data* **2001**, *46*, 172–173.

(7) Li, D. Q.; Liu, D. Z.; Wang, F. A. Solubility of 4-Methylbenzoic Acid between 288 and 370 K. *J. Chem. Eng. Data* **2001**, *46*, 234–236.

(8) Acree, W. E. Mathematical Representation of Thermodynamic Properties. Part 2. Derivation of the Combined Nearly Ideal Binary Solvent (CNIBS)/Redlich-Kister Mathematical Representation from a Two-Body and Three-Body Interactional Mixting Model. *Thermochim. Acta* **1992**, *198*, 71–79.

(9) 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.

Received for review October 7, 2008. Accepted December 16, 2008.

JE800730K