Solubility of Cefazolin Sodium Pentahydrate in Different Solvents between 275 K and 310 K

Jiehua Wu, Jingkang Wang,* and Meijing Zhang

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

The solubilities of cefazolin sodium pentahydrate in dichloromethane, 1-butanol, 1-propanol, ethanol, methanol, and *N*,*N*-dimethylformamide between 275 K and 310 K were measured using a synthetic method. Results of these measurements were correlated by the semiempirical equation, for the six solvents studied. The semiempirical equation was found to provide an accurate mathematical representation of the experimental data.

Introduction

Cefazolin sodium pentahydrate is an important semisynthetic antibiotic used in medicine.[1] During the manufacture, to purify cefazolin sodium pentahydrate, the solubility of cefazolin sodium pentahydrate in solvents is needed. The solubility in binary 2-propanol + water solvent mixtures has been reported in the literature.[2] In this work, the solubilities of cefazolin sodium pentahydrate in dichloromethane, 1-butanol, 1-propanol, ethanol, methanol and *N*,*N*-dimethylformamide have been measured between 275 K and 310 K.

Experimental Sections

Materials. A white crystalline powder of cefazolin sodium pentahydrate [CAS Registry No. 115850-11-8] is 3-[[5-methyl-(1,3,4-thiadiazol-2-yl)-thio]methyl]-7-[2-(1*H*-tetrazol-1-yl)acetamido]-3-cephem-4-carboxylic sodium salt, obtained from North China Pharmaceutical Co., Ltd. Its mass fractor purity, determined by HPLC according to BP2000, is higher than 0.996. Dichloromethane, 1-butanol, 1-propanol, ethanol, methanol, and *N*,*N*-dimethylformamide are analytical research grade reagents from Tianjin Chemical Reagent Co., Ltd. (China) and were used directly. Cefazolin sodium pentahydrate is stable in these six solvents.

Apparatus and Procedure. Solubilities were measured by a synthetic method.[3−5] The apparatus for solubility measurement is the same as that described in the literature.[1] A laser beam was used to determine the solubility of solute in solvents 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 stirrer 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.

* To whom correspondence should be addressed. E-mail: jkwang888@yahoo.com.cn. Fax: 86-22-2737497.

Table 1. Comparison of the Experimental Solubility (ω) of Potassium Chloride (1) in Water (2) with the Literature Data

T/K	283.15	293.15	298.15	303.15	313.15	333.15
100 ω_1	23.83	25.55	26.30	27.20	28.64	31.20
100 ω_1 (ref 7)	23.83	25.55	26.34	27.14	28.57	31.21
rel dev, %	0.00	0.00	−0.15	0.22	0.25	−0.03

An analytical balance (type TG332A, China) with an uncertainty of ± 0.0001 g was used during the measurement. Predetermined known masses of cefazolin sodium pentahydrate and solvent were placed in the jacketed vessel. The contents of the vessel were stirred continuously at constant 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 solute, the solubility would be obtained. The saturated mole fraction solubility of the solute (x_A) in solvent can be obtained as follows:

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

In which m_A and m_B are represented the mass of solute and solvent. M_A and M_B are the molecular weight of solute and solvent, respectively. To verify the uncertainty of the measurement, one other experiment was done in which the solubility of potassium chloride in water was determined. The solubility of potassium chloride in water in the literature[7] and in this work are shown in Table 1. Compared with the literature data, it was less than 0.3 %. Considering other factors, the uncertainty of the experimental solubility values is about 0.5 %.

Results and Discussion

The solubilities of cefazolin sodium pentahydrate (x_A) in dichloromethane, 1-butanol, 1-propanol, ethanol, methanol, and *N*,*N*-dimethylformamide at different temperature are presented in Table 2.The temperature dependence solubility in pure solvents was described by the semiempirical equation:[6]

$$\ln x_A = A + \frac{B}{T} + C \ln T \quad (2)$$

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Table 2. Mole Fraction Solubility (x_A) of Cefazolin Sodium Pentahydrate (A) in Pure Solvents (B)

Dichloromethane

T/K	$10^6\,x_A$	$10^6\,(x_A - x_A^{calc})$	T/K	$10^6\,x_A$	$10^6\,(x_A - x_A^{calc})$
278.25	1.770	−0.032	303.95	2.950	−0.102
282.77	2.065	0.029	308.25	3.540	−0.040
286.65	2.360	0.049	313.25	4.477	−0.045
289.85	2.655	0.050	318.15	5.457	0.103

1-Butanol

T/K	$10^5\,x_A$	$10^5\,(x_A - x_A^{calc})$	T/K	$10^5\,x_A$	$10^5\,(x_A - x_A^{calc})$
284.55	1.188	0.006	299.85	3.507	−0.048
288.55	1.519	−0.027	303.5	4.715	−0.037
293.03	2.141	0.017	307.3	6.442	−0.052
296.55	2.823	0.065	309.75	8.066	0.082

1-Propanol

T/K	$10^5\,x_A$	$10^5\,(x_A - x_A^{calc})$	T/K	$10^5\,x_A$	$10^5\,(x_A - x_A^{calc})$
276.55	0.9546	−0.0085	294.65	9.708	0.033
279.65	1.602	0.006	299.15	13.53	−0.24
283.35	2.709	−0.031	302.25	16.82	0.05
286.45	4.217	0.119	306.65	20.26	−0.63
290.65	6.603	0.006	309.75	24.09	0.68

Ethanol

T/K	$10^4\,x_A$	$10^4\,(x_A - x_A^{calc})$	T/K	$10^4\,x_A$	$10^4\,(x_A - x_A^{calc})$
275.45	2.200	0.034	298.25	3.929	0.055
283.65	2.357	−0.076	300.35	4.352	0.110
288.15	2.738	0.021	304.85	5.205	−0.046
291.75	2.988	−0.045	305.65	5.533	0.065
293.15	3.176	−0.006	309.05	6.419	−0.129
294.95	3.406	0.009			

methanol

T/K	$10^3\,x_A$	$10^3\,(x_A - x_A^{calc})$
288.85	0.8872	−0.0097
296.55	1.011	0.0328
303.15	1.355	−0.020
306.85	1.778	−0.059
310.55	2.692	0.067

N,*N*-Dimethylformamide

T/K	$10^2\,x_A$	$10^2\,(x_A - x_A^{calc})$
278.15	2.399	−0.015
283.15	2.637	0.050
288.15	2.961	0.053
294.15	4.032	0.021

where x_A is the mole fraction solubility of cefazolin sodium pentahydrate; T is the absolute temperature; and A, B, and C are the parameters. The deviation of the solubilities of cefazolin sodium pentahydrate (x_A) with the calculated solubility values (x_A^{calc}) are also given in Table 2. The values of parameters A, B, C, and σ_y are listed in Table 3. The σ_y is defined as the following:

$$\sigma_y = \{[\sum_{i=1}^{N}((x^{expt} - x^{calc})/x^{expt})^2]/N\}^{1/2} \quad (3)$$

where N is the number of experimental points; x_i^{calc} is the solubilities calculated from eq 2; x_i^{expt} is the experimental values of solubility.

Table 3. Parameters of Equation 2 for Cefazolin Sodium Pentahydrate in Pure Solvents

solvent	$10^3 A$	$10^4 B$	$10^2 C$	σ_y	R^2
dichloromethane	0.4873	3.3515	1.2704	0.020	0.9970
1-butanol	−0.7536	2.7269	1.1439	0.013	0.9996
1-propanol	2.0408	−9.6802	−3.0278	0.018	0.99972
ethanol	−0.9333	3.8031	1.4003	0.016	0.9976
methanol	−3.4298	14.9159	5.1296	0.025	0.9961
N,*N*-dimethylformamide	−1.8630	7.7690	2.8072	0.014	0.9951

Table 4. Densities of Used Solvents[8]

solvent	t/°C	ρ/(g·cm^{-3})
dichloromethane	20	1.326
1-butanol	20	0.8097
1-propanol	20	0.8036
ethanol	20	0.7893
methanol	20	0.7913
N,*N*-dimethylformamide	25	0.94397

Table 4 show the densities[8] of solvents used in this work; mass fraction could be calculated by eq 1, and then according to Table 4, the volume of solvents can be found.

Conclusions. The solubilities of cefazolin sodium pentahydrate in dichloromethane, 1-butanol, 1-propanol, ethanol, methanol, and *N*,*N*-dimethylformamide all increases with increase of temperature. The solubility of cefazolin sodium pentahydrate in *N*,*N*-dimethylformamide is higher than that in dichloromethane, 1-butanol, 1-propanol, ethanol, and methanol. The solubility of cefazolin sodium pentahydrate in dichloromethane is the lowest. The reasons for this phenomenon needs to be studied further. The systems show satisfactory agreement between the experimental solubilities and the calculated values.

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