Solubility of Penicillin Sulfoxide in Different Solvents

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The solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene from (273.15 to 332.75) K were measured with the mole fraction by a gravimetric method The solubilities in these solvents are temperature dependent. The results show that the solubility of penicillin sulfoxide in toluene is very low, so toluene is considered as one of the best solvents and used in industry. According to the results, we can see that the solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene can be correlated well with a semiempirical equation.

Introduction

Penicillin sulfoxide is a white powder crystal, and the chemical structure is shown in Figure 1. As the precursor of 7-amino-3-desacetoxycephalosporanic acid (7-ADCA) which is an important nucleus of cephalosporin antibiotics, after range enlarged and catalytic cracked, penicillin sulfoxide was changed into 7-ADCA.[1−3] So the production of penicillin sulfoxide is crucial to the development of medicaments. Ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene were used in range enlargement in industry.[4] The solubilities of penicillin sulfoxide in these solvents directly affect the yield of 7-ADCA and control the cost of production. It is necessary to know the solubility of penicillin sulfoxide. In this work, the solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene from (273.15 to 332.75) K under atmospheric pressure were experimentally determined using a gravimetric method.[5] No similar reports have been published in the literature up to date.

Experimental Section

Materials. Penicillin sulfoxide ($C_{16}H_{20}N_2O_6S$, molecular weight 350.16) supplied by North China of Pharmaceutical Group Corporation Beta Co., Ltd., with a melting point of 164 °C, measured by a NETZSCH DSC 204 differential scanning calorimeter, was purified by recrystallization twice. The product's mass fraction determined by Agilent 1200 HPLC was found to be higher than 99.2 %. Ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene (purchased from Tianjin Kewei Co. of China) were of analytical reagent grade and used without any treatment. Their mass fractions were better than 99.5 %.

Apparatus and Procedure. The solubility of penicillin sulfoxide was measured by the gravimetric method.[5] The measuring principle is the same as that described in the literature.[5] There are two crystal water molecules within one penicillin sulfoxide crystal cell by single-crystal X-ray diffraction analysis, so crystal water should be removed from penicillin sulfoxide completely. After being dissolved in butyl acetate and agitated at 55 °C for 0.5 h, penicillin sulfoxide was filtrated and dried in vacuo below 40 °C. The solubility measuring experiments were performed in a 100 mL glass jacket vessel with water circulated from a water bath. The temperature was kept stable (fluctuates within 0.05 K) through the thermostated bath (type 501A, China). Continuous stirring of the solution was achieved with a magnetic stir bar. For each measurement, a certain amount of solvent was added into the crystallizer and stabilized at the wanted temperature. An excess amount of penicillin sulfoxide crystals was added into the crystallizer which was sealed by rubber plugs. The solution was kept stirring at least 8 h, and the temperature must be kept stable to establish equilibrium between solids and solution. The suspension was settled down for 4 h after reaching equilibrium. The clear solution was extracted by a 10 mL glass syringe, filtered through a 0.2 μm PTFE filter, and injected rapidly into a Petri dish which had been weighted. Then they were weighted and put into a blast drying oven at 55 °C. After they were dried for 12 h, they were measured several times until the values were unaltered. Each of the experiments was repeated at least three times. The solubility was calculated by determining the weight of dried solid and evaporated solvent. The mass of the solute and Petri dish was measured using an analytical balance (Metler Toledo AL104. Shanghai, China) with an accuracy of ± 0.0001 g.

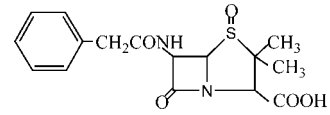

Figure 1. Chemical structure of penicillin sulfoxide.

The saturated mole fraction solubility of the solute (x) in solvent can be obtained as follows

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 and m_2 represent the masses of the solute and solvent; M_1 and M_2 represent the mole weight of the solute and the solvent, respectively. The uncertainty of the mole fractions in the solubility values is established to be ± 3.0 %.

Results and Discussion

The solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene at different

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10.1021/je900326e CCC: $40.75
Published on Web 07/21/2009

Table 1. Solubility of Penicillin Sulfoxide in Different Solvents

T/K	10^3x	$10^2(x^{cal} - x)/x$	T/K	10^3x	$10^2(x^{cal} - x)/x$
		Ethyl Acetate			
273.15	2.1072	0.46	303.15	3.1588	−2.81
278.15	2.2178	−2.46	307.45	3.3768	−0.06
283.25	2.2717	−0.85	312.85	3.8323	0.38
288.15	2.3313	2.06	317.65	4.4004	−0.74
292.75	2.5638	−0.98	321.25	4.8587	−0.52
298.55	2.7962	0.23			
		4-Methyl-2-pentanone			
273.15	1.6207	1.25	303.35	2.2675	−0.93
278.15	1.7321	−1.92	308.05	2.3752	1.27
283.15	1.8004	−1.58	313.35	2.6229	−0.43
287.85	1.8400	0.85	317.65	2.7772	0.91
295.15	2.0053	0.54	323.75	3.1644	−1.61
297.95	2.1274	−1.83			
		Butyl Acetate			
273.15	0.6028	1.58	297.35	1.1033	−0.31
278.25	0.6781	0.74	302.95	1.3402	3.88
281.95	0.7346	−0.61	307.65	1.5056	2.65
287.65	0.8249	−3.77	312.65	1.6559	−1.69
292.55	0.9792	0.57	317.65	1.9189	−0.97
		Toluene			
283.15	0.02739	1.68	303.45	0.0697	4.25
288.35	0.03682	2.36	311.65	0.08700	5.52
293.95	0.05256	−5.10	316.85	0.1049	−2.45
298.15	0.06119	−2.30	323.65	0.1135	−0.42

temperature are presented in Table 1 and more visually given in Figure 2. T is the absolute temperature, and x and x^{cal} are the experimental and calculated values of the solubility. From Figure 2, it can be seen that the solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene are temperature dependent. According to the solid−liquid phase equilibrium theory, the temperature dependence of the solubility of a material in the pure solvents can be correlated by the semiempirical equation[6,7] deduced from the solid−liquid phase equilibrium[8,9]

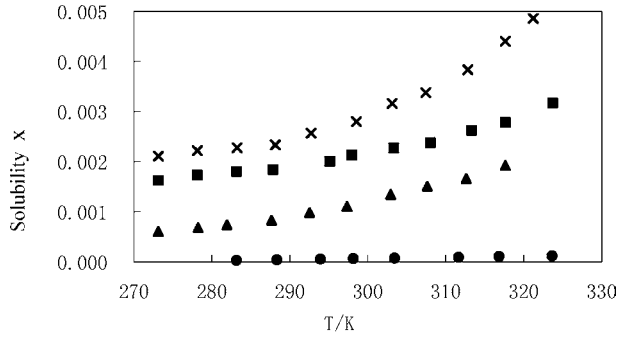

Figure 2. Mole fraction solubilities of penicillin sulfoxide in different solvents at different temperature ranges: ×, ethyl acetate; ■, 4-methyl-2-pentanone; ▲, butyl acetate; ●, toluene.

Table 2. Parameters of Equation 2 for Penicillin Sulfoxide in Different Solvents

solvent	a	b	c	10^2 mean stdev	10^5 rsmd
ethyl acetate	−389.15	15669	58.044	1.05	3.5
4-methyl-2-pentanone	−188.04	7117.2	27.731	1.19	2.8
butyl acetate	−152.23	4436.2	22.916	1.68	2.6
toluene	633.73	−31689	−94.280	3.01	0.25

$$\ln x = a + \frac{b}{T/\mathrm{K}} + c \ln T/\mathrm{K} \quad (2)$$

where a, b, and c are semiempirical constants.

The experimental solubility values were fitted with eq 2 by the least-squares method. The values of the three parameters a, b, and c are listed in Table 2 together with the root-mean square deviation (rmsd), namely, the standard deviation, which is defined as follows[10]

$$\mathrm{rmsd} = \left[\frac{1}{N}\sum_{i=1}^{N}(x_i - x_i^{cal})^2\right]^{1/2} \quad (3)$$

where N is the number of experimental points. The values of a, b, and c are listed in Table 2.

The solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene which were ever used in industry were measured by the gravimetric method. The results show that solubilities in the four solvents increase as the temperature rises. We can see from Figure 1 that there are two carbonyls and one carboxyl in the penicillin sulfoxide molecule. Ethyl acetate, 4-methyl-2-pentanone, and butyl acetate each have a carbonyl, so hydrogen bonds will be formed between these solvents and penicillin sulfoxide. However, the same effort between toluene and penicillin sulfoxide cannot be found. As a result, the solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, and butyl acetate change with temperature evidently, and the solubility of penicillin sulfoxide in toluene is small. Last, from the values of the standard deviations (rmsd) listed in Table 2, it is seen that the solubilities of penicillin sulfoxide in ethyl acetate, 4-methyl-2-pentanone, butyl acetate, and toluene can be correlated with eq 2 very well.

Acknowledgment

The authors are very grateful to North China Pharmaceutical Group Corporation Beta Co., Ltd., for supplying penicillin sulfoxide.

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Received for review April 2, 2009. Accepted July 9, 2009.

JE900326E