

Measurement and Correlation of Solubility of Cefuroxime Acid in Pure and Binary Solvents at Various Temperatures

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The solubility of cefuroxime acid in four pure solvents and three binary solvents formed by water + acetone, ethanol + acetone, and 2-propanol + acetone at atmospheric pressure has been measured via a laser monitoring observation technique over the temperature range from (278.5 to 313.4) K. The solubility of cefuroxime acid increased with increasing temperature in water, 2-propanol, and ethanol but decreased in acetone. The heat flux measurements by a Differential Scanning Calorimeter (DSC) and solubility with temperature behavior were consistent. The solubility data of cefuroxime acid in pure solvents were correlated by the modified Apelblat equation, and the maximum average absolute error (AAE) was 0.07. The solubility data of cefuroxime acid in binary solvents at various temperatures were fitted by the Jouyban–Acree model, and the maximum AAE was 0.06. The solubility of cefuroxime acid in binary solvents was significantly higher than that in pure solvents and showed a maximum at a specific volume fraction of acetone.

Introduction

Cefuroxime, i.e., (6*R*,7*R*)-7-[2-furanyl-(*Z*)-2-methoxyimino]-acetamido-3-carbamoyloxymethyl-3-cephem-4-carboxylic (1) is a valuable semisynthetic II generation broad-spectrum cephalosporin antibiotic characterized by its high activity against a wide range of Gram-positive and Gram-negative microorganisms.¹ With respect to Gram-positive bacteria, cefuroxime is a much more potential antimetabolite than other cephalosporins of the I and II generations.² The chemical structure of cefuroxime acid is shown in Figure 1. The solubility of cefuroxime acid in different solvents at various temperatures is the essential data for solvent selection to dissolve it during the production of cefuroxime sodium. Acetone is widely used as an antisolvent in the crystallization process of cefuroxime sodium; therefore, it was chosen as a fixed solvent in the binary solvents.

The objective of this work was to measure and correlate solubility data of cefuroxime acid in the pure solvents and binary solvents water + acetone, ethanol + acetone, and 2-propanol + acetone from (278.5 to 313.4) K at atmospheric pressure. Solubility data of cefuroxime acid have not been reported in the literature.

Experimental Section

Materials. Cefuroxime acid (mass fraction purity of 99.1 %) was obtained from Siping Fine Chemical Co. Ltd., China, without further purification. Ethanol (mass fraction purity of 99.98 %), 2-propanol (mass fraction purity of 99.94 %), and acetone (mass fraction purity of 99.46 %) were analytical reagent grade from Tianjin Ke-wei Chemical Reagent Co., China. Water was purified by a UPW-20N ultra pure water device purchased from Beijing EPOCH Electronics Instrument Company.

Apparatus and Procedures. The solubility of cefuroxime acid was measured by a synthetic method.^{3,4} A laser monitoring observation technique was used to determine the soluble solute in pure solvents and binary solvents with known composition.

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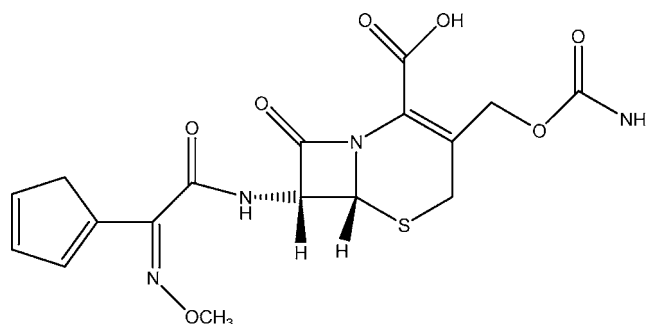


Figure 1. Chemical structure of cefuroxime acid.

Mixed solvents with expected composition were decided by weighting mass using a Mettler Toledo AB204-N analytical balance with an accuracy of ± 0.0001 g. The uncertainty of the mole fraction of mixed solvents was ± 0.005 , and the uncertainty of the temperature was ± 0.1 K. The reported values were the average of twice repeated measurements, and the relative uncertainty of cefuroxime acid solubility in mole fraction was less than 0.048. The apparatus and procedure for the measurement were the same as those described in the literature.³ The heat flux measurements on the dissolution process of cefuroxime acid were performed by a NETZSCH Differential Scanning Calorimeter (DSC) 204.

The solubility of cefuroxime acid in mole fraction (x_3) could be obtained as follows

$$x_3 = \frac{m_3/M_3}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 represents mass of acetone; m_2 represents mass of the cosolvents such as water, ethanol, and 2-propanol; m_3 represents mass of cefuroxime acid; and M_1 , M_2 , and M_3 are the molecular weight, respectively.

Results and Discussion

The solubility data of cefuroxime acid in the pure solvents at different considered temperatures were listed in Table 1 and

Table 1. Experimental Solubility of Cefuroxime Acid in Pure Solvents with Temperature

T/K	solvent			
	acetone	water	ethanol	2-propanol
	10^3x_1	10^3x_2	10^3x_2	10^3x_2
278.5	3.62	0.03	0.19	0.06
283.4	3.60	0.04	0.22	0.09
288.3	3.55	0.04	0.28	0.11
293.3	3.42	0.06	0.32	0.12
298.3	3.37	0.07	0.37	0.12
303.5	3.31	0.12	0.52	0.15
308.3	3.27	0.22	0.56	0.27
313.4	3.24	0.26	0.61	0.32

Table 2. Experimental Solubility of Cefuroxime Acid (3) in Acetone (1) + Water (2) at Different Temperatures

T/K	φ_1	10^3x_1	10^3x_2	10^3x_3
278.5	0.60	3.62	0.03	3.14
278.5	0.78	3.62	0.03	11.04
278.5	0.85	3.62	0.03	14.93
278.5	0.90	3.62	0.03	18.94
283.4	0.60	3.60	0.04	3.58
283.4	0.78	3.60	0.04	11.78
283.4	0.85	3.60	0.04	15.65
283.4	0.90	3.60	0.04	19.42
288.3	0.60	3.55	0.04	4.76
288.3	0.78	3.55	0.04	15.15
288.3	0.85	3.55	0.04	19.72
288.3	0.90	3.55	0.04	19.46
293.3	0.60	3.42	0.06	5.86
293.3	0.78	3.42	0.06	16.58
293.3	0.85	3.42	0.06	20.43
293.3	0.90	3.42	0.06	19.62
298.3	0.60	3.37	0.07	6.57
298.3	0.78	3.37	0.07	17.74
298.3	0.85	3.37	0.07	21.04
298.3	0.90	3.37	0.07	19.82
303.5	0.60	3.31	0.12	6.97
303.5	0.78	3.31	0.12	17.85
303.5	0.85	3.31	0.12	20.64
303.5	0.90	3.31	0.12	20.01
308.3	0.60	3.27	0.22	7.80
308.3	0.78	3.27	0.22	18.96
308.3	0.85	3.27	0.22	22.62
308.3	0.90	3.27	0.22	20.46
313.4	0.60	3.24	0.26	9.87
313.4	0.78	3.24	0.26	20.32
313.4	0.85	3.24	0.26	22.21
313.4	0.90	3.24	0.26	20.74

Figure 2. From Table 1 and Figure 2, it can be seen that within the temperature range of the measurements the solubility of cefuroxime acid increased with increasing temperature in pure water, ethanol, and 2-propanol. However, it decreased with increasing temperature in pure acetone. The heat fluxes during the dissolution process of cefuroxime acid in different pure solvents were measured by DSC at a constant temperature, and part of them was shown in Figure 3. From Figure 3, it also could be observed that the heat flux versus time plot during the dissolution process of cefuroxime acid in acetone showed a different conversion from that in water. The conversion of the heat flux versus time plot during the dissolution in ethanol and 2-propanol is similar to that in water. That is to say, it was exothermic during the dissolution of cefuroxime acid in acetone, but in the other three solvents it was endothermic. Consequently, the solubility versus temperature behavior in acetone showed quite a difference from that in others.

The amidocyanogen group of cefuroxime acid acted as a hydrogen bond donor, while the carbonyl group of acetone acted as a hydrogen bond acceptor. Thus it is attractive to suggest that a hydrogen bond could be formed between acetone and

Table 3. Experimental Solubility of Cefuroxime Acid (3) in Acetone (1) + Ethanol (2) at Different Temperatures

T/K	φ_1	10^3x_1	10^3x_2	10^3x_3
278.5	0.20	3.62	0.19	1.37
278.5	0.40	3.62	0.19	4.23
278.5	0.60	3.62	0.19	7.19
278.5	0.80	3.62	0.19	7.86
283.4	0.20	3.60	0.22	1.45
283.4	0.40	3.60	0.22	4.34
283.4	0.60	3.60	0.22	7.24
283.4	0.80	3.60	0.22	7.81
288.3	0.20	3.55	0.28	1.57
288.3	0.40	3.55	0.28	4.27
288.3	0.60	3.55	0.28	7.33
288.3	0.80	3.55	0.28	7.58
293.3	0.20	3.42	0.32	1.72
293.3	0.40	3.42	0.32	4.56
293.3	0.60	3.42	0.32	7.35
293.3	0.80	3.42	0.32	7.35
298.3	0.20	3.37	0.37	2.01
298.3	0.40	3.37	0.37	4.29
298.3	0.60	3.37	0.37	7.36
298.3	0.80	3.37	0.37	6.94
303.5	0.20	3.31	0.52	1.98
303.5	0.40	3.31	0.52	4.63
303.5	0.60	3.31	0.52	7.42
303.5	0.80	3.31	0.52	6.83
308.3	0.20	3.27	0.56	2.34
308.3	0.40	3.27	0.56	5.13
308.3	0.60	3.27	0.56	7.63
308.3	0.83	3.27	0.56	6.63
313.4	0.20	3.24	0.61	2.42
313.4	0.40	3.24	0.61	5.33
313.4	0.60	3.24	0.61	7.68
313.4	0.80	3.24	0.61	6.53

Table 4. Experimental Solubility of Cefuroxime Acid (3) in Acetone (1) + 2-Propanol (2) at Different Temperatures

T/K	φ_1	10^3x_1	10^3x_2	10^3x_3
278.5	0.20	3.62	0.06	0.52
278.5	0.40	3.62	0.06	1.79
278.5	0.60	3.62	0.06	4.11
278.5	0.80	3.62	0.06	5.54
283.4	0.20	3.60	0.09	0.58
283.4	0.40	3.60	0.09	1.98
283.4	0.60	3.60	0.09	4.26
283.4	0.80	3.60	0.09	5.49
288.3	0.20	3.55	0.11	0.69
288.3	0.40	3.55	0.11	2.23
288.3	0.60	3.55	0.11	4.32
288.3	0.80	3.55	0.11	5.46
293.3	0.20	3.42	0.12	0.75
293.3	0.40	3.42	0.12	2.50
293.3	0.60	3.42	0.12	4.37
293.3	0.80	3.42	0.12	5.33
298.3	0.20	3.37	0.12	0.83
298.3	0.40	3.37	0.12	2.55
298.3	0.60	3.37	0.12	4.41
298.3	0.80	3.37	0.12	4.94
303.5	0.20	3.31	0.15	0.88
303.5	0.40	3.31	0.15	2.61
303.5	0.60	3.31	0.15	4.52
303.5	0.80	3.31	0.15	4.87
308.3	0.20	3.27	0.27	0.91
308.3	0.40	3.27	0.27	2.68
308.3	0.60	3.27	0.27	4.52
308.3	0.80	3.27	0.27	4.82
313.4	0.20	3.24	0.32	1.10
313.4	0.40	3.24	0.32	2.78
313.4	0.60	3.24	0.32	4.64
313.4	0.80	3.24	0.32	4.67

cefuroxime acid, which raised the dissolution ability of cefuroxime acid in acetone. However, the intermolecular hydrogen bond could be destroyed while temperature was increased. Consequently, the solubility in acetone was much higher than

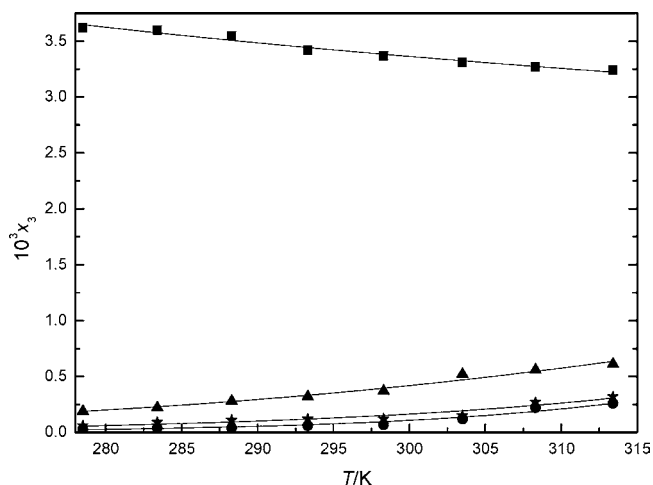


Figure 2. Solubility of cefuroxime acid in different pure solvents from $T = (278.5 \text{ to } 313.4) \text{ K}$. ■, solubility values in acetone; ●, solubility values in water; ★, solubility values in 2-propanol; ▲, solubility values in ethanol.

that in other solvents such as ethanol, 2-propanol, and water and decreased with increasing temperature.

The solubility data of cefuroxime acid in the binary solvents at different temperatures were listed in Tables 2 to 4. A maximum of cefuroxime acid solubility was observed in the binary solvents. For comparison of the experimental values in different binary solvents, the solubility of cefuroxime acid in the three binary solvents at 298.3 K was illustrated graphically in Figure 4. It could be seen that solubility in the binary solvents was in the following order: water + acetone > ethanol + acetone > 2-propanol + acetone. The hydroxyl group of water, ethanol, and 2-propanol acted as a hydrogen bond donor, while the carbonyl group of acetone acted as a hydrogen bond acceptor. Thus, a hydrogen bond could also be formed between solvents. The polarity order of the selected other solvents is water > ethanol > 2-propanol. Hence, it could infer that the strength of an intermolecular hydrogen in the binary solvents was in the following order: water + acetone > ethanol + acetone > 2-propanol + acetone. Consequently, the solubility order of cefuroxime acid in the above binary solvents is the same. The influencing factors of the solubility of solids in liquids are comparatively complex, and the formation of a hydrogen bond

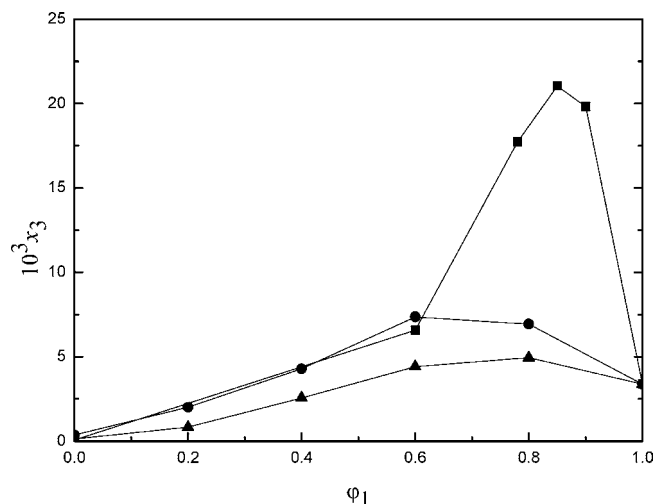


Figure 4. Mole fraction solubility of cefuroxime acid (3) in different binary solvents at $T = 298.3 \text{ K}$ as a function of volume fraction ϕ_1 . ■, solubility values in acetone (1) + water (2); ●, solubility values in acetone (1) + ethanol (2); ▲, solubility values in acetone (1) + 2-propanol (2).

between solvents and solute is only one of the factors affecting the dissolution behavior.⁵ Further analysis of the dissolution process is complicated and beyond the scope of this article.

The temperature dependence solubility of cefuroxime acid in pure solvents could be correlated by the following semiempirical equation, namely, the modified Apelblat equation.⁶

$$\ln(10^3 x_3) = A + \frac{B}{T/K} + C \ln(T/K) \quad (2)$$

where T is the absolute temperature and A , B , and C are empirical constants.

The solubility of cefuroxime acid in solvent mixtures at various temperatures could be correlated by the Jouyban–Acree model proposed by Acree and his co-workers.^{7–10}

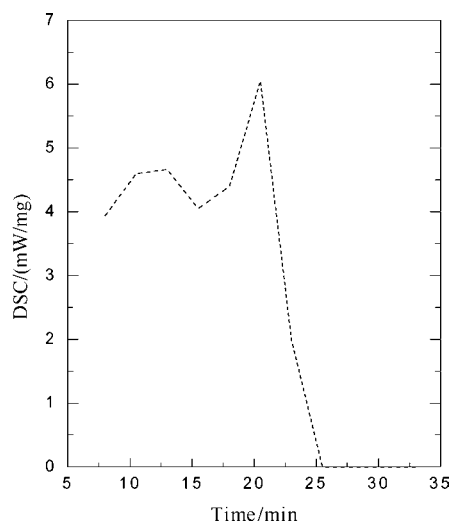
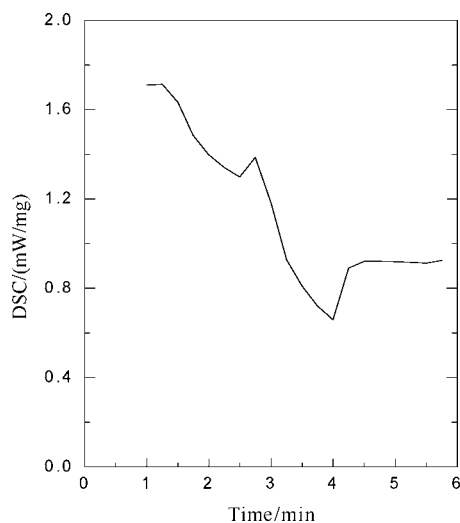


Figure 3. Heat flux versus time plot of the dissolution of cefuroxime acid in acetone and water at $T = 298.3 \text{ K}$. —, change of the DSC plot with time of the dissolution of cefuroxime acid in acetone; ···, that in water.

Table 5. Curve-Fitting Parameters of Cefuroxime Acid in Pure Solvents with Temperature

solvent	A	B	C	AAE
acetone	-5.92	578.66	0.91	0.01
water	-93.16	-1049.00	16.56	0.07
ethanol	80.08	-6171.64	-10.58	0.02
2-propanol	-114.02	1390.90	18.86	0.06

Table 6. Curve-Fitting Parameters of Cefuroxime Acid (3) in Acetone (1) + Cosolvents (2) at Various Temperatures

cosolvent	J_0	J_1	J_2	AAE
water	5251.15	-2110.57	1290.78	0.06
ethanol	208.57	16.10	884.06	0.03
2-propanol	81.04	-25.38	830.43	0.05

$$\log(10^3 x_3) = \varphi_1 \log(10^3 x_1) + \varphi_2 \log(10^3 x_2) + \varphi_1 \varphi_2 \sum_{i=0}^2 \frac{J_i (\varphi_1 - \varphi_2)^i}{T/K} \quad (3)$$

where x_1 , x_2 , and x_3 are the solubility of the solute in acetone, cosolvent, and solvent mixture in the absence of the solute at fixed temperature, and J_i is the model constant. In eq 3, φ_1 and φ_2 refer to the volume fraction of acetone and cosolvent in the binary solvents without solute.

The average absolute error (AAE) between experimental and calculated data was used to evaluate the consistency of the results and was defined by eq 4.

$$\text{AAE} = \frac{\sum |\log(x_i^{\text{cal}}) - \log(x_i^{\text{exp}})|}{N} \quad (4)$$

where N is the number of experimental points; x^{cal} represents the solubility calculated from eq 2 or eq 3; and x^{exp} represents the experimental solubility values. The three parameters A , B , C , and AAE are listed in Table 5. The three parameters J_0 , J_1 , J_2 , and AAE are listed in Table 6.

The maximums AAE of the modified Apelblat equation and Jouyban–Acree model were 0.07 and 0.06, respectively, revealing that both of these models provided relatively accurate predictions. The minimum AAE for eq 3 was 0.03 (in acetone + ethanol), and the AAEs for eq 3 in acetone + water and acetone + 2-propanol were 0.06 and 0.05. It could be concluded that the Jouyban–Acree model provided accurate solubility predictions for binary solvents, as shown in other literature.^{11,12}

Conclusion

The solubility of cefuroxime acid in pure solvents was in the following order: acetone > ethanol > 2-propanol > water. With increasing temperature, the solubility of cefuroxime acid increased in water, 2-propanol, and ethanol but decreased in acetone.

The effect of temperature on the solubility of cefuroxime acid was much smaller than that of the mole fraction of acetone. There was a maximum of the solubility in all of the considered

binary solvents especially in water + acetone. In the industrial production, acetone is always used as the antisolvent during the crystallization process of cefuroxime sodium. Therefore, water + acetone was a better choice to dissolve cefuroxime acid. To enhance the yield of cefuroxime sodium, the dissolution could be operated between (293.3 and 298.3) K at about 0.8 volume fraction of acetone.

The experimental data in pure solvents matched well with the semiempirical modified Apelblat equation. The calculated data by the Jouyban–Acree model in binary solvents showed adequate agreement with experimental values especially in acetone + water.

Supporting Information Available:

Additional Figures 1 to 3. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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