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Solubility of Cefotaxime Sodium in Ethanol + Water Mixtures under Acetic Acid Conditions

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Ⓢ *Supporting Information*

ABSTRACT: Aimed at exploring the influence of acetic acid on crystallization thermodynamics of cefotaxime sodium (CTX), the solubility of CTX in ethanol + water mixtures under acetic acid conditions at various temperatures are measured by a gravimetrical method. Different from the solubility curve when acetic acid is absent, the solubility curves of CTX under acetic acid conditions have a maximum value. The maximum solubility drifts as temperature varies, which is related to the dielectric constants of solvent mixtures. A combination of the Jouyban−Acree model and Apelblat equation is used to correlate the solubility data, and the correlation precision is improved when compared with that of the Jouyban−Acree model. By using the Wilson model, the activity coefficients of CTX and the mixing Gibbs free energies, enthalpies, and entropies of CTX solution are also predicted. The data presented in this study explain why the crystallization of CTX in ethanol + water mixtures is difficult and are helpful for guiding the industrial reaction and crystallization process of CTX.
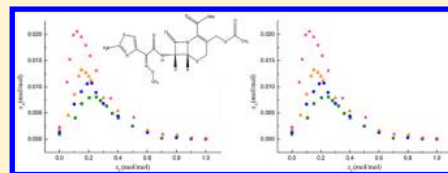
■ INTRODUCTION

Cefotaxime sodium ([6R-[6α,7β(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) is a white or white-yellow powdered crystal, known as a third generation cephalosporin which has a strong activity against both Gram-negative bacteria and Gram-positive bacteria. Its molecular structure is given in Figure 1. Usually,
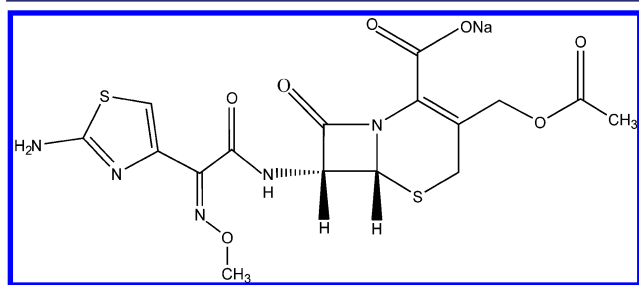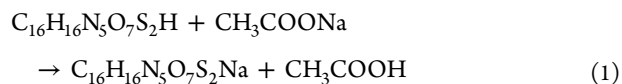

Figure 1. Molecular structure of cefotaxime sodium.

CTX solution is obtained by the reaction of cefotaxime acid with sodium acetate, a common salt forming agent with low cost and high solubility in water. The reaction equation is shown as follows,

$$C_{16}H_{16}N_5O_7S_2H + CH_3COONa$$
$$\rightarrow C_{16}H_{16}N_5O_7S_2Na + CH_3COOH \qquad (1)$$

When the reaction is finished, an antisolvent is added and then CTX is crystallized out. It is worth noting that acetic acid is present during the whole crystallization process. It was reported that acetate would reduce the degradation rate of CTX, and acetate binding also can impede gel forming which usually happens during crystallization of CTX,[1−3] so the solubility behavior of CTX under acetic acid conditions is very important for industrial production.

Although there are experimental solubility data of CTX in pure solvents and aqueous 2-propanol mixtures in literature,[4,5] the solubility data of CTX in ethanol and water mixtures have not been reported up to date. Also the influences of acetic acid on solubility are scarcely discussed in literature. As we know, ethanol is a preferred solvent in crystallization because it is cheap and environmentally favorable, has low toxicity, and is ready market available.[6,7] In this study, the solubility data of CTX in ethanol + water mixtures and ethanol + water under acetic acid conditions are measured at various temperatures by a gravimetrical method. It is shown that the solubility of CTX under certain acetic acid concentration increases to a maximum and then descends as the concentration of ethanol increases in solvent mixtures. This phenomenon is found to be related with the dielectric constants of solution. Two models are chosen to correlate the experimental data. Finally, the activity coefficients

of CTX and the mixing Gibbs free energies, enthalpies, and entropies of CTX solutions are calculated to understand the solubility behavior of CTX. The data and calculations in this study can be used to guide the industrial reaction and crystallization process of CTX.

EXPERIMENTAL SECTION

Materials. A white crystalline powder of cefotaxime acid (M_w 455.46, molecular formula $C_{16}H_{17}N_5O_7S_2$) with mass fraction purity higher than 0.985 was supplied by Huabei Pharmaceutical Co., Ltd. of China. Sodium acetate (CH_3COONa) (analytical reagent grade, mass fraction purity > 0.997) was purchased from Tianjin Kewei Chemical Co., Ltd. of China. CTX (mass fraction purity > 0.99) was prepared by the crystallization method as forementioned. The United States Pharmacopeia (USP) Reference Standard CTX used for purity test was purchased from Sinopharm Chemical Reagent Beijing Co., Ltd. of China. All of the organic solvents used for the experiments, including ethanol and acetic acid, were analytical reagent grade (mass fraction purity > 0.995). All of them were obtained from Tianjin Kewei Chemical Co. in China and used without any treatment. Deionized water was also used as solvent.

Apparatus and Procedure. The mass fraction purity of CTX was analyzed by high-performance liquid chromatography (HPLC) (Agilent 1200, Agilent Technologies, USA) equipped with a Venusil MP-C18 column (4.6 × 150 mm, 5 μm). The variable mixtures of phosphate buffer and methanol were used as mobile phase. The flow rate was about 1 mL per minute. The detailed procedure was conducted according to the chromatographic method shown in USP.[8]

The solubility of CTX was measured using a gravimetric method which was described in the literature.[9,10] An excess amount of CTX powder was added into the solvent mixture of known mole fraction composition. The solution was stirred in a jacketed glass vessel (about 50 cm^3) for 6 h to reach the equilibrium. Temperature was controlled to be constant (fluctuating within 0.01K) by a thermostat (501 A, Shanghai Laboratory Instrument Works Co. Ltd., China). The upper saturated solution was filtered with a membrane filter (0.22 μm) and transferred into a preweighed Petri dish (m_0). The Petri dish with saturated solution was weighed quickly (m_1) and then put into a drying oven (101 A, Shanghai Sheng Xin Scientific Instrument Co. Ltd., China) at 323.15 K for 12 h. The Petri dish with solutes was reweighed for several times using a balance (AB204, Metler Toledo, Switzerland) with an uncertainty of ± 0.0001 g until the weight of Petri dish (m_2) was constant. The residual solids were analyzed by powder X-ray diffraction (PXRD) (D/MAX2500, Rigaku, Japan) and Fourier transform infrared spectroscopy (FT-IR) (Nicolet 6700, Nicolet, USA) to confirm that no physicochemical changes occurred during the entire experiment. The same experiment was repeated three times. The mean values were used to calculate the saturated mass and mole fraction solubility as follows.

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C + m_D/M_D} \quad (2)$$

where m_A, m_B, m_C, and m_D represent the mass of the CTX, water, ethanol, and acetic acid, respectively. M_A, M_B, M_C, and M_D are the molecular weights of the solute, water, ethanol, and

acetic acid, respectively. m_A, m_B, m_C, and m_D could be calculated by eqs 3 and 4,

$$m_A = m_2 - m_0 \quad (3)$$

$$m_{B,C,D} = \frac{(m_1 - m_2)(M_{B,C,D}x_{B,C,D})}{M_B x_B + M_C x_C + M_D x_D} \quad (4)$$

where x_B, x_C, and x_D represent the mole fraction of water, ethanol, and acetic acid in solvent mixture, respectively.

THERMODYNAMIC MODELS

In a number of thermodynamic models which correlate solubility data, some express the relationship between solubility and temperature such as van't Hoff equation and Apelblat equation as shown in eqs 5 and 6, respectively,[11,12]

$$\ln x_A = A + \frac{B}{T} \quad (5)$$

$$\ln x_A = A + \frac{B}{T} + C \ln T \quad (6)$$

where x_A is mole fraction solubility of solute in solvent, T is the absolute temperature, and A, B, and C are model constants.

Some other models express the relationship between solubility and solvent composition, such as the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister model, which is suggested by Acree and his co-workers,[13]

$$\ln x_A = \phi_C \ln(x_A)_C + \phi_B \ln(x_A)_B + \phi_C \phi_B \sum_{i=0}^{2} S_i(\phi_C - \phi_B)^i \quad (7)$$

In eq 7, ϕ_B and ϕ_C refer to the mass fractions of solvents B and C, respectively, assuming that solute A was not present, $(x_A)_i$ denotes the saturated mole fraction solubility of the solute in monosolvent i, S_i terms are the model constants. For a binary solvent system, if we replace ϕ_B with $(1 - \phi_C)$, eq 7 could be transformed into

$$\ln x_A = B_0 + B_1 \phi_C + B_2 \phi_C^2 + B_3 \phi_C^3 + B_4 \phi_C^4 \quad (8)$$

where the right side is a four-order polynomial and B_i is the model constant.

Additionally there are some models which correlate the solubility with both temperature and solvent composition. The Jouyban−Acree model might be one of the most accurate models put forward in recent years.[14] The model can be represented as[15]

$$\ln x_A = \phi_C \ln(x_A)_B + \phi_B \ln(x_A)_C + \frac{\phi_C \phi_B}{T} \sum_{i=0}^{2} J_i(\phi_C - \phi_B)^i \quad (9)$$

where J_i terms are the model constants. In this model the solubilities of solute in monosolvent $((x_A)_i)$ are needed. Substituting eq 5 into eq 9 gives the following equation,[14]

$$\ln x_A = \phi_C\left(A_1 + \frac{B_1}{T}\right) + \phi_B\left(A_2 + \frac{B_2}{T}\right) + \frac{\phi_C \phi_B}{T} \sum_{i=0}^{2} J_i(\phi_C - \phi_B)^i \quad (10)$$

Here, J_2 is always considered to be not significant and ignored.[14] However, as shown in the literature, in some cases,

the solubility in pure solvent calculated by the Apelblat model (eq 6) can give better correlation results.[5,9,16] So in this study, the Apelblat equation is also introduced into the Jouyban–Acree model as follows,

$$\ln x_A = \phi_C\left(A_1 + \frac{B_1}{T} + C_1\ln T\right) + \phi_B\left(A_2 + \frac{B_2}{T} + C_2\ln T\right) + \frac{\phi_C\phi_B}{T}\sum_{i=0}^{2} J_i(\phi_C - \phi_B)^i \tag{11}$$

The solubility of CTX is affected by both temperature and solvent composition. So, eqs 10 and 11 are used to correlate the experimentally measured solubility data. The model constants are calculated by the *lsqnonlin* function of the MATLAB software.

To predict the mixing properties of the CTX solution, the activity coefficient of solute in the liquid phase (γ_A) is needed. γ_A can be calculated by the two following thermodynamic models.

A simplified equation depending only on the melting properties of the solute can be used to calculate the activity coefficient,[11]

$$\ln x_A = \frac{\Delta_{fus}H_A}{R}\left(\frac{1}{T_{mA}} - \frac{1}{T}\right) - \ln\gamma_A \tag{12}$$

in which $\Delta_{fus}H_A$ is the enthalpy of fusion, T_{mA} is the melting temperature of solute.

If the system is considered as a binary system which includes solvent and solute, the Wilson model could be used to correlate the relationship between activity coefficient and mole fraction,[11]

$$\ln\gamma_A = -\ln(x_A + \Lambda_{AS}x_S) + x_S\left(\frac{\Lambda_{AS}}{x_A + \Lambda_{AS}x_S} - \frac{\Lambda_{SA}}{x_S + \Lambda_{SA}x_A}\right) \tag{13}$$

$$\ln\gamma_S = -\ln(x_S + \Lambda_{SA}x_A) + x_A\left(\frac{\Lambda_{SA}}{x_S + \Lambda_{SA}x_A} - \frac{\Lambda_{AS}}{x_A + \Lambda_{AS}x_S}\right) \tag{14}$$

in which Λ_{AS} and Λ_{SA} are Wilson parameters,

$$\Lambda_{AS} = \frac{v_S}{v_A}\exp\left(-\frac{\Delta\lambda_{AS}}{RT}\right) \tag{15}$$

$$\Lambda_{SA} = \frac{v_A}{v_S}\exp\left(-\frac{\Delta\lambda_{SA}}{RT}\right) \tag{16}$$

where $\Delta\lambda_{AS}$ and $\Delta\lambda_{SA}$ are cross interaction energy parameters, v_A and v_S are mole volumes of solute and solvent, x_A and x_S are the mole fractions of solute and solvent, respectively.

■ RESULTS AND DISCUSSION

Solubility Data of Cefotaxime Sodium. The measured solubility data of CTX in water (B) + ethanol (C) solvent mixture are visually given in Figure 2 (the data are reported in Supporting Information, Table S1). It decreases monotonously with increasing mole fraction of ethanol in solvent mixture (x_C) at a constant temperature. At constant x_C, the solubility increases with the increase in temperature and the temperature effect is more evident at lower x_C. The solubilities of CTX in
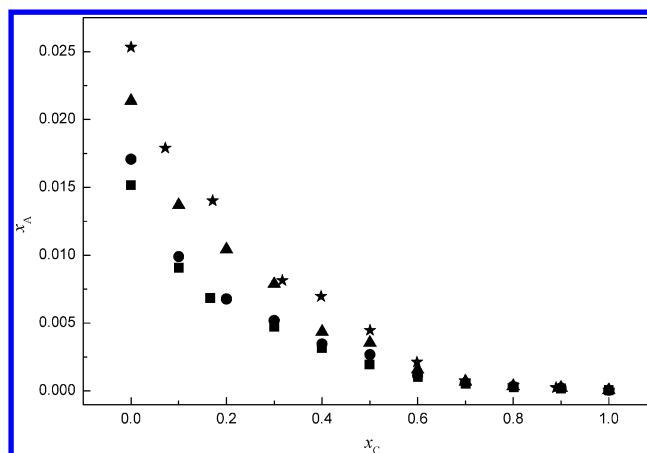
Figure 2. Mole fraction solubility (x_A) of CTX versus mole fractions of ethanol (x_C) in water (B) + ethanol (C) mixtures at various temperatures: ■, 278.15 K; ●, 283.15 K; ▲, 293.15 K; ★, 303.15 K.

Figure 3. Mole fraction solubility (x_A) of CTX versus mole fractions of ethanol (x_C) in water (B) + ethanol (C) mixtures under acetic acid conditions (0.01 mol acetic acid/1 mol water) at various temperatures: ■, 278.15 K; ●, 283.15 K; ▲, 293.15 K; ★, 303.15 K.
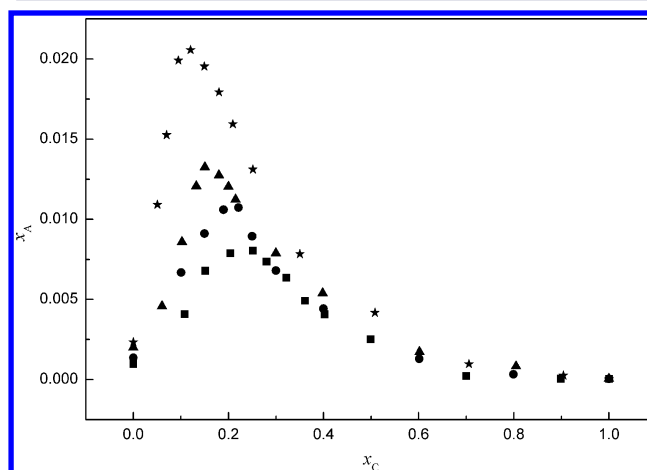
Figure 4. Mole fraction solubility (x_A) of CTX versus mole fractions of ethanol (x_C) in water (B) + ethanol (C) mixtures under acetic acid conditions (0.02 mol acetic acid/1 mol water) at various temperatures: ■, 278.15 K; ●, 283.15 K; ▲, 293.15 K; ★, 303.15 K.
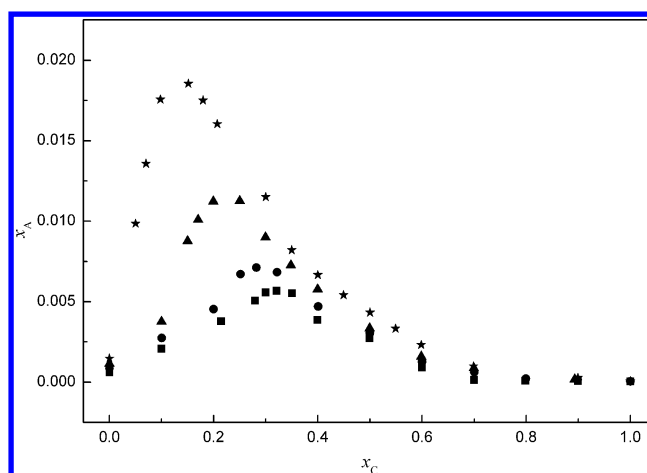
Table 1. Model Constants of eq 10 ($J_2 = 0$) and Root-Mean-Square Deviations for Solubility in Different Solvent Mixtures

conditions	water + ethanol	water + ethanol + acetic acid (0.01 mol/1 mol water)	water + ethanol + acetic acid (0.02 mol/1 mol water)
A_1	4.844	−22.16	−21.17
B_1	−3986	4068	3648
A_2	2.111	22.11	33.27
B_2	−1751	−8418	−11 772
J_0	1701	3228	3669
J_1	1200	−1582	−332.0
10^4rmsd	3.489	8.698	8.433

Table 2. Model Constants of eq 11 ($J_2 = 0$) and Root-Mean-Square Deviations for Solubility in Different Solvent Mixtures

conditions	water + ethanol	water + ethanol + acetic acid (0.01 mol/1 mol water)	water + ethanol + acetic acid (0.02 mol/1 mol water)
A_1	568.2	2807	3697
B_1	−28 616	−119 816	−158 992
C_1	−84.37	−423.5	−556.7
A_2	194.4	−2504	−2868
B_2	−10 142	102 343	115 488
C_2	−28.81	378.1	434.3
J_0	1694	3120	3597
J_1	1186	−1705	−512.1
10^4rmsd	3.290	7.876	7.993

Table 3. Model Constants of eq 11 ($J_2 \neq 0$) and Root-Mean-Square Deviations for Solubility in Different Solvent Mixtures

conditions	water + ethanol	water + ethanol + acetic acid (0.01 mol/1 mol water)	water + ethanol + acetic acid (0.02 mol/1 mol water)
A_1	593.6	2958	3503
B_1	−29 887	−127 080	−151 179
C_1	−88.18	−446.1	−527.8
A_2	209.5	−2567	−2667
B_2	−10 789	105 090	106 416
C_2	−31.08	387.4	404.2
J_0	2063	4121	5517
J_1	1717	−821.7	1102
J_2	570.8	1671	2841
10^4rmsd	3.089	7.376	6.919

Table 4. Dielectric Constants of Water (B) + Ethanol (C) + Acetic Acid (D, 0.01 mol Acetic Acid/1 mol Water) Solvent Mixtures at Maximum Solubility

T/K	x_{Cmax}	ϕ_{Cmax}	ε_S/F·m^{-1}
278.15	0.2280	0.4301	59.84
283.15	0.1949	0.3822	60.83
293.15	0.1698	0.3433	60.17
303.15	0.1249	0.2674	60.89

the water (B) + ethanol (C) solvent mixtures under different acetic acid conditions (0.01 and 0.02 mol acetic acid/1 mol water) are shown in Figure 3 (data in Supporting Information, Table S2) and Figure 4 (data in Supporting Information, Table S3), respectively. Here, the acetic acid concentrations are similar to that in the industrial reaction and crystallization process of CTX. It is found that at constant temperature the increase of ethanol have a solubilization function below x_{Cmax} (the mole fraction of ethanol at which CTX has a maximum solubility), whereas, it will work as an antisolvent above this x_{Cmax}. The characteristic of CTX solubility under acetic acid conditions indicates that the reaction process can be conducted at x_{Cmax}, and then the addition of ethanol is propitious to the crystallization process.

In this study, eqs 10 and 11 are used to correlate the experimentally measured solubility data. The root-mean-square

deviations (rmsds) are calculated to evaluate the accuracy of different models,

$$\mathrm{rmsd} = \left[\frac{1}{n} \sum_{i=1}^{n} (x_i^{\exp} - x_i^{\mathrm{cal}})^2 \right]^{1/2} \tag{17}$$

where n is the number of data points in each set, x_i^{cal} represents the solubility data calculated from solubility models, and $x_i^{\exp}$ represents the experimental solubility values. The model constants of eqs 10 and 11 and the root-mean-square deviations (rmsds) are given in Tables 1 to 3 respectively. According to the rmsds, the precision order of correlation is eq 11 ($J_2 \neq 0$) > eq 11 ($J_2 = 0$) > eq 10 ($J_2 = 0$). It is demonstrated that introducing the Apelblat equation can enhance the model precision, and when J_2 is taken into consideration, the precision is improved further.

From Figure 3, it can be seen that the ϕ_{Cmax} (the corresponding mole fraction is x_{Cmax}) drifts toward the left when the temperature rises. To explain this phenomenon, the dielectric constants of the solvent mixtures are calculated by eq 18,[17]

$$\varepsilon_S = \phi_B \varepsilon_B + \phi_C \varepsilon_C + \phi_D \varepsilon_D \tag{18}$$

in which ε_S is the dielectric constant of solvent mixtures, ε_B, ε_C, ε_D are dielectric constants of water, ethanol, and acetic acid,

Table 5. ΔG, ΔH, ΔS, ln γ_A, and ln γ_A^∞ Values under Different χ_{Cmax} at Different Temperatures[a]

T		ΔG	ΔH	ΔS		
K	x_C	J·mol^{-1}	J·mol^{-1}	J·mol^{-1}·K^{-1}	ln γ_A	ln γ_A^∞
		Water + Ethanol + Acetic Acid (0.01 mol Acetic Acid/1 mol Water)				
278.15	0.2280(x_{Cmax})	−247.1	27.74	0.9880	−7.008	−7.784
	0.1949	−245.2	27.79	0.9816	−7.375	−8.185
	0.1698	−230.1	28.31	0.9290	−7.630	−8.411
	0.1249	−166.1	34.76	0.7220	−7.412	−7.253
283.15	0.2280	−302.2	33.47	1.185	−6.873	−7.812
	0.1949(x_{Cmax})	−321.6	35.96	1.263	−7.165	−8.217
	0.1698	−319.2	38.79	1.264	−7.371	−8.447
	0.1249	−257.3	48.90	1.082	−7.335	−7.329
293.15	0.2280	−350.9	37.70	1.326	−6.804	−7.867
	0.1949	−391.5	42.39	1.480	−7.029	−8.278
	0.1698(x_{Cmax})	−406.7	47.82	1.550	−7.179	−8.515
	0.1249	−356.3	61.99	1.427	−7.229	−7.473
303.15	0.2280	−453.4	47.17	1.651	−6.580	−7.918
	0.1949	−533.6	55.67	1.944	−6.682	−8.335
	0.1698	−591.6	66.76	2.172	−6.697	−8.580
	0.1249(x_{Cmax})	−630.7	92.98	2.387	−6.645	−7.608
		Water + Ethanol + Acetic Acid (0.02 mol Acetic Acid/1 mol Water)				
278.15	0.3180(x_{Cmax})	−161.8	14.53	0.6314	−6.510	−6.948
	0.2932	−161.4	15.25	0.6351	−6.712	−7.166
	0.2159	−135.8	15.24	0.5430	−7.381	−7.798
	0.1348	−73.58	12.43	0.3093	−6.507	−5.617
283.15	0.3180	−200.1	17.90	0.7699	−6.427	−6.967
	0.2932(x_{Cmax})	−206.3	19.35	0.7968	−6.610	−7.188
	0.2159	−184.8	20.64	0.7256	−7.262	−7.828
	0.1348	−96.64	15.48	0.3960	−6.682	−5.750
293.15	0.3180	−259.8	22.69	0.9638	−6.316	−7.004
	0.2932	−290.0	26.57	1.080	−6.430	−7.229
	0.2159(x_{Cmax})	−356.8	39.09	1.351	−6.804	−7.886
	0.1348	−223.0	30.63	0.8652	−6.948	−6.003
303.15	0.3180	−308.8	26.25	1.105	−6.240	−7.039
	0.2932	−345.8	30.79	1.242	−6.338	−7.267
	0.2159	−481.9	51.036	1.758	−6.517	−7.941
	0.1348(x_{Cmax})	−557.5	65.07	2.054	−6.466	−6.240

[a]The standard uncertainty of T is $u(T) = 0.01$ K. Combined expanded uncertainties U are $U_c(\Delta G) = 0.070\Delta G$; $U_c(\Delta H) = 0.070\Delta H$; $U_c(\Delta S) = 0.075\Delta S$; $U_c(\ln \gamma_A) = 0.065 \ln \gamma_A$; $U_c(\ln \gamma_A^\infty) = 0.065 \ln \gamma_A^\infty$ (0.95 level of confidence).

respectively, that can be obtained in the literature.[18] ϕ_B, ϕ_C, and ϕ_D are mass fractions of water, ethanol, and acetic acid in solvent mixtures. The results are plotted in Supporting Information, Figure S1. It is shown that higher temperature leads to lower dielectric constant, whereas, smaller ϕ_C will make a higher dielectric constant. According to "like dissolves like" rule, the dielectric constants of solvent mixtures at different ϕ_{Cmax} in Figure 3 should be similar.[19] To confirm this assumption, the dielectric constants at ϕ_{Cmax} are calculated by eq 18 and summarized in Table 4. It can be seen that the dielectric constants at different ϕ_{Cmax} are almost the same, and when the temperature rises, in order to keep the dielectric constants of solvent mixtures similar, ϕ_{Cmax} should become smaller.

Prediction of Mixing Properties. To better understand the phenomenon that maximum solubility value drifts when temperature varies, the mixing properties of solution are also studied.

The mixing Gibbs free energy ΔG, mixing enthalpy ΔH, and mixing entropy ΔS of the solution can be calculated by[20]

$$\Delta G(H, S) = \Delta G(H, S)^{id} + G(H, S)^E \tag{19}$$

in which $\Delta G(H, S)^{id}$ is the mixing Gibbs free energy (enthalpy, entropy) of an ideal solution and $G(H, S)^E$ is the excess property.

For an ideal system, mixing properties are[20]

$$\Delta G^{id} = RT(x_A \ln x_A + x_S \ln x_S) \tag{20}$$

$$\Delta H^{id} = 0 \tag{21}$$

$$\Delta S^{id} = -R(x_A \ln x_A + x_S \ln x_S) \tag{22}$$

Excess properties of a binary system can be calculated by[21]

$$G^E = RT(x_A \ln \gamma_A + x_S \ln \gamma_S) \tag{23}$$

$$H^E = -T^2 \left(\frac{\partial (G^E/T)}{\partial T} \right)$$

$$= x_A x_S \left(\frac{\Delta \lambda_{AS} \Lambda_{AS}}{x_A + x_S \Lambda_{AS}} + \frac{\Delta \lambda_{SA} \Lambda_{SA}}{x_S + x_A \Lambda_{SA}} \right) \tag{24}$$

$$S^E = \frac{H^E - G^E}{T} \tag{25}$$

The activity coefficient γ_A can be calculated by eqs 12 to 16. Owing to the particularity of the thermal decomposition behavior of CTX, the virtual melting temperature and enthalpy of fusion of CTX in eq 12 are calculated using a group-contribution method.[22] The calculated melting temperature of CTX is 510.15 K and the enthalpy of fusion is 65.807 kJ/mol.

The infinite-dilution activity coefficient γ_A^∞ of CTX which is used to characterize the intermolecular interactions between solute and solvent can be obtained by[23,24]

$$\ln \gamma_A^\infty = (\ln \gamma_A)_{x_A \to 0} - \ln \Lambda_{AS} + 1 - \Lambda_{SA} \qquad (26)$$

The ΔG, ΔH, ΔS, $\ln \gamma_A$ and $\ln \gamma_A^\infty$ values are calculated and summarized in Table 5. From ΔG values, the level of difficulty of dissolution and its inverse process crystallization can be evaluated. The low ΔG values of CTX illustrate that the crystallization of CTX is difficult.[10] From Table 5 it can also be seen that ΔG value is lowest at x_{Cmax}, which corresponds to the most favorable dissolution of CTX. The positive ΔH and ΔS values indicate that the dissolution of CTX is an endothermic process which leads to more freedom of CTX molecules in solvent molecules. The difference between $\ln \gamma_A$ and $\ln \gamma_A^\infty$ means that the CTX solution deviates from an infinite-dilution system. This result is consistent with the fact that CTX has a high solubility in these solvent mixtures, and is easy to gelate with a solvent such as water. The data presented in this paper are very useful for choosing an appropriate solvent composition during the reaction and crystallization process of CTX.

CONCLUSIONS

Experimental solubility data of CTX are obtained in ethanol + water solvent mixtures under acetic acid conditions at temperatures ranging from 278.15 K to 303.15 K. The solubility data are correlated well with solvent composition and temperature by introducing the Apelblat equation into the Jouyban–Acree model. It is demonstrated that the solubility behavior of CTX follows the "like dissolves like" rule and x_{Cmax} would become smaller when temperature increases to keep the dielectric constants similar. The mixing properties of CTX in ethanol + water solvent mixtures under acetic acid conditions are obtained based on Wilson model parameters. It is found that dissolution of CTX is a spontaneous endothermic process and the solution deviates from the ideal system, which explains the high solubility behavior of CTX in these solvent mixtures.

ASSOCIATED CONTENT

Ⓢ Supporting Information
The solubility of CTX in ethanol + water mixtures under acetic acid conditions at various temperatures and dielectric constants of solvent mixtures at various temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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