Solubility of Potassium Clavulanate in Aqueous 2-Propanol Mixtures

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With a laser monitoring observation technique, the solubility of potassium clavulanate in binary aqueous 2-propanol solvent mixtures in temperature range from 273 K to 305 K and in the solvent composition (x_2) range from 0.8 to 1.0 were measured by a synthetic method. The solubility data were correlated with a semiempirical equation.

Introduction

Potassium clavulanate (CAS Registry No. 61177-45-5) is potassium (Z)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate. It is a white or almost white crystalline powder. As a β-lactamase inhibitor capable of enhancing the antibacterial effectiveness of β-lactame antibiotics, such as penicillins and cephalosporins, against many β-lactamase-producing bacteria, potassium clavulanate has been widely used in clinical applications.[1−3] Clavulanic acid is normally prepared by fermentation,[4−6] and then the resulting aqueous broth may be subjected to a series of purification and concentration processes. Finally, clavulanic acid is converted into potassium clavulanate and crystallized from aqueous organic mixed solvents. Binary aqueous 2-propanol mixtures are the most usually used solvents for the crystallization of potassium clavulanate. In preferential crystallization, the solubilities of potassium clavulanate in solvents are needed. However, a review of the literature on potassium clavulanate indicated that only solubilities of it in some pure organic solvents were reported.[7] No experimental solubility data of it in aqueous organic solvents were available. In this work, the solubility of potassium clavulanate in binary aqueous 2-propanol solvent mixtures were experimentally determined in the temperature range from 273 K to 305 K and in the solvent composition (x_2) range from 0.8 to 1.0 using a laser monitoring observation technique. The method employed in this work was classed as a synthetic method, which was much faster and more readily available than the analytical method.[8]

Experimental Sections

Materials. A white crystalline powder of potassium clavulanate ($C_8H_8NO_5K$, molecular weight 237.25), with a decomposition temperature of 466.05 K (The decomposition temperature of potassium clavulanate was measured with a NETZSCH STA449C differential scaning calorimeter.) was prepared by recrystallization from a 2-propanol + H_2O solution three times. It was washed with acetone, dried in vacuo at 303.15 K for 5 h, and stored in a desiccator. Its mass fraction purity, determined by HPLC according to USP24,[9] was higher than 99.5 %. 2-Propanol was analytical research grade reagents from Tianjin Chemical Reagent Co., and distilled deionized water of HPLC grade was used.

Apparatus and Procedure. The solubility was determined using an apparatus similar to that described in the literature[10] and described only briefly here. A 100 mL jacked vessel was used to determine the solubility; the temperature was controlled to be constant (fluctuates within 0.05 K) through a thermostated bath with an uncertainty of ± 0.05 K. The dissolution of the solute was examined by the laser beam penetrating the vessel. To prevent the evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were weighed using an analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.0001 g.

The solubility of potassium clavulanate was determined by the laser method.[11−15] During experiments the fluid in the glass vessel was monitored by a laser beam. Predetermined excess amounts of solvent and potassium clavulanate of known mass were placed in the inner chamber of the vessel. The contents of the vessel were stirred continuously at a required temperature. In the early stage of the experiment, the laser beam was blocked by the undissolved particles of potassium clavulanate in the solution, so the intensity of laser beam penetrating the vessel was lower. Along with the dissolution of the particles of potassium clavulanate, the intensity of laser beam increased gradually. When the solute dissolved completely, the solution was clear, and the laser intensity penetrating through the vessel reached maximum. Then additional solute of known mass {about (1 to 5) mg} was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return maximum, or in other words, the last addition of solute could not dissolve completely. The interval of addition was 30 min. The total amount of the solute consumed was recorded. The same solubility experiment was conducted three times, and the mean values were used to calculate the mole fraction solubility (x_1) based on eq 1. The composition of solvent mixtures (x_2) was defined as eq 2:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{1}$$

$$x_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \tag{2}$$

where m_1, m_2, and m_3 represent the mass of the solute, 2-propanol, and water, respectively, and M_1, M_2, and M_3 are the molecular weight of the solute, 2-propanol, and water, respectively.

One other experiment had been done in our previous work[7] to verify the uncertainty of the measurement. It is estimated the uncertainty in the solubility values are less than 1 %.

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Table 1. Mole Fraction Solubility (x_1) of Potassium Clavulanate in Binary 2-Propanol (2) + Water (3) Solvent Mixtures in the Temperature Range from 273 K to 305 K

T/K	10^3x_1	$10^3(x_1 - x_1^{calc})$	T/K	10^3x_1	$10^3(x_1 - x_1^{calc})$	T/K	10^3x_1	$10^3(x_1 - x_1^{calc})$
				$x_2 = 1.0000$				
273.90	0.0494	−0.0009	285.35	0.0681	0.0015	297.35	0.0917	−0.0017
277.15	0.0545	0.0002	289.30	0.0747	0.0006	301.35	0.1031	−0.0023
281.05	0.0605	0.0009	293.25	0.0813	−0.0016	305.40	0.1231	0.0035
				$x_2 = 0.9498$				
274.00	0.1034	0.0009	285.10	0.1391	0.0012	297.25	0.1982	0.0021
277.15	0.1105	−0.0007	289.15	0.1525	−0.0021	301.05	0.2224	0.0023
281.00	0.1222	−0.0010	293.25	0.1742	0.0001	305.40	0.2490	−0.0029
				$x_2 = 0.9061$				
274.40	0.2314	0.0248	285.10	0.2844	−0.0052	297.15	0.4128	−0.0195
277.35	0.2371	0.0107	289.15	0.3165	−0.0140	301.15	0.4963	0.0005
281.35	0.2626	0.0059	293.15	0.3546	−0.0230	305.15	0.5941	0.0245
				$x_2 = 0.8506$				
274.35	0.5160	−0.0100	285.20	0.7307	0.0133	297.15	1.0085	−0.0180
277.40	0.5778	0.0048	289.35	0.7869	−0.0241	301.05	1.1552	−0.0023
281.25	0.6535	0.0139	293.25	0.9202	0.0085	305.30	1.3369	0.0155
				$x_2 = 0.7993$				
274.40	1.3148	0.0022	285.25	1.7923	−0.0146	297.15	2.5631	0.0085
277.35	1.4327	0.0004	289.35	2.0538	0.0169	301.05	2.8517	−0.0069
281.30	1.6072	−0.0019	293.25	2.2788	−0.0029	302.25	2.9573	−0.0016

Table 2. Parameters of Equation 3 for Potassium Clavulanate in Binary 2-Propanol (2) + Water (3) Solvent Mixtures in the Temperature Range from 273 K to 305 K

x_2	a	b	c	10^5 RMSD
1.000	−265.16	9130.7	39.540	0.18508
0.9498	−215.52	6929.6	32.254	0.17939
0.9061	−203.46	6131.3	30.746	1.7676
0.8506	−176.04	5210.0	26.628	1.4668
0.7993	−92.196	1656.7	14.164	0.89363

Results and Discussion

The solubilities of potassium clavulanate in aqueous 2-propanol mixtures at different temperatures are presented in Table 1. The solubilities in pure 2-propanol solvent ($x_2 = 1.0000$) were taken directly from literature.[7]

The temperature dependence of potassium clavulanate solubility in solvents is correlated with a semiempirical equation:[7]

$$\ln x_1 = a + \frac{b}{T} + c \ln T \tag{3}$$

where T is the absolute temperature, and a, b, and c are empirical constants. The difference between experimental and calculated results is also presented in Table 1. The values of the three parameters a, b, and c together with the root-mean-square deviations (RMSD) are listed in Table 2. The RMSD is defined as the following:

$$\mathrm{RMSD} = \left[\frac{\sum_{i=1}^{N}(x_{1,i} - x_{1,i}^{calc})^2}{N-1}\right]^{1/2} \tag{4}$$

where N is the number of experimental points; $x_{1,i}^{calc}$ is the solubility calculated from eq 3; and $x_{1,i}$ is the experimental value of solubility.

From Table 1, we can find that the solubility of title compound depends on the polarity of the solvents to great degree. As we all know, water is of stronger polarity than 2-propanol. Along with the increase of water in solvent mixtures, the polarity of solvents goes up, and the solubility of potassium clavulanate rises sharply. In fact, there are a carboxyl and a hydroxyl in the molecule of potassium clavulanate, which bring it some polarity. The solubility behavior of potassium clavulanate just reflected the empirical rule that "like dissolves like".

From Table 2, it can be seen that a increases, meanwhile b and c decrease, with decrease of x_2. Parameter c in all solvent mixtures is relative small, which is true for many compounds under most conditions, so the last term of eq 3 is neglected in many cases.

From Table 1 and Table 2, the following conclusions can be drawn: (1) The solubilities of potassium clavulanate in binary aqueous 2-propanol solvent mixtures all increase with increase of temperature. (2) The solubilities of potassium clavulanate decrease with increase of 2-propanol content in the solvent mixture, and the solubility in pure 2-propanol is the lowest. (3) These experimental data can be regressed by eq 3 for each solvent mixture. The experimental solubility and correlation equation in this work can be used as essential data and models in the purification process of potassium clavulanate.

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