Solubility of Potassium Clavulanate in Ethanol, 1-Propanol, 1-Butanol, 2-Propanol, and 2-Methyl-1-propanol between 273 K and 305 K

Bao-Shu Liu,* Jun-Bo Gong, Jing-Kang Wang, and Chun-Yan Jia

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

The solubility of potassium clavulanate in ethanol, 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol between 273 K and 305 K were measured using a laser technique. This method was used to determine the dissolution of the solid phase in a solid + liquid mixture. Results of these measurements 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 (Figure 1). 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 an organic solvent. To determine the proper solvent and to design an optimized crystallization process, it is necessary to know its solubility in different solvents. However, from a review of the literature on potassium clavulanate, it was found that no experimental solubility data were available. In this paper, the solubilities of potassium clavulanate in ethanol, 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol between 273 K and 305 K were experimentally determined 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 than the analytical method.[7]

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 re-crystallization 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,[8] was higher than 99.5 %. Ethanol, 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol were analytical research grade reagents from Tianjin Chemical Reagent Co.

Apparatus and Procedures. The solubility was determined using an apparatus similar to that described in the literature[9] 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. 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.

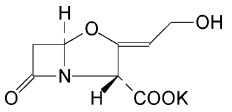

Figure 1. Structure of potassium clavulanate.

The solubility of potassium clavulanate was determined by the laser method.[10−13] 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 the following equation:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where m_1 and m_2 represent the masses of the solute and

* To whom correspondence should be addressed. E-mail: lbszrn@yahoo.com.cn. Fax: 0086-22-27374971.

10.1021/je050145r CCC: $30.25
Published on Web 08/12/2005

Table 1. Mole Fraction Solubility (x_1) of Potassium Clavulanate in Pure Solvents

T/K	$10^3 x_1$	$10^3 (x_1 - x_1^{calc})$	T/K	$10^3 x_1$	$10^3 (x_1 - x_1^{calc})$	T/K	$10^3 x_1$	$10^3 (x_1 - x_1^{calc})$
				Ethanol				
273.95	0.4627	−0.0015	285.40	0.5653	−0.0013	297.05	0.7120	−0.0032
277.10	0.4912	0.0025	289.10	0.6134	0.0052	301.45	0.7767	−0.0095
281.00	0.5211	−0.0017	293.35	0.6639	0.0017	305.25	0.8636	0.0080
				1-Propanol				
273.70	0.1049	−0.0050	285.10	0.1555	0.0022	297.15	0.2057	−0.0065
277.15	0.1259	0.0040	289.15	0.1717	0.0002	301.20	0.2284	−0.0068
281.15	0.1421	0.0051	293.15	0.1872	−0.0039	305.35	0.2722	0.0116
				1-Butanol				
273.95	0.0606	−0.0011	285.05	0.0756	0.0003	297.05	0.1053	0.0014
277.05	0.0656	0.0010	289.25	0.0812	−0.0021	301.20	0.1187	0.0000
281.05	0.0706	0.0013	293.15	0.0918	−0.0007	305.10	0.1359	0.0000
				2-Propanol				
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
				2-Methyl-1-propanol				
274.55	0.0384	−0.0008	285.10	0.0544	0.0018	298.75	0.0722	−0.0036
277.15	0.0422	−0.0001	289.80	0.0609	0.0012	301.55	0.0756	−0.0058
281.15	0.0478	0.0006	294.70	0.0681	0.0000	305.05	0.0965	0.0074

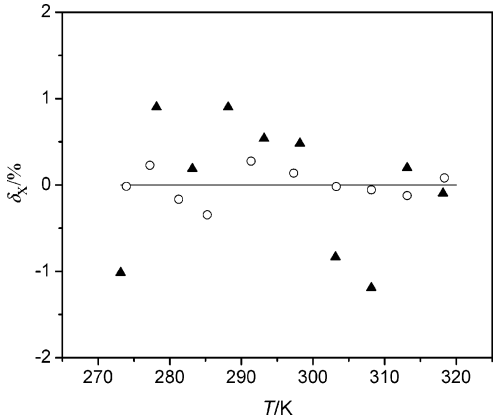

Figure 2. Comparison of solubility of KH_2PO_4 in water from the literature[14] and from this paper with the correlation by eq 5. $\delta_x = 100(x^{eq5} - x^{lit})/x^{eq5}$ or $\delta_x = 100(x^{eq5} - x^{expt})/x^{eq5}$, where x^{eq5}, x^{lit}, and x^{expt} stand for the mole fraction solubility of KH_2PO_4 from eq 5, the literature and the experiment, respectively. —, experimental data; ▲, literature data.

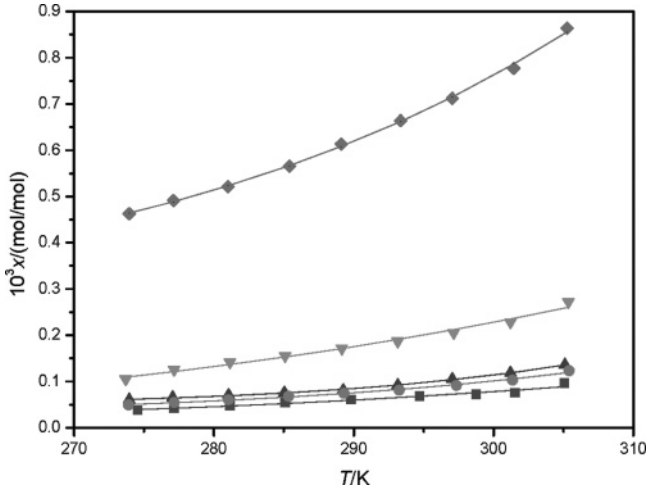

Figure 3. Solubility of potassium clavulanate x_1 in different solvents: ♦, ethanol; ▼, 1-propanol; ▲, 1-butanol; ●, 2-propanol; ■, 2-methyl-1-propanol; —, calculated x_1 from eq 5.

solvent, and M_1 and M_2 are the molecular weights of the solute and the solvent, respectively.

To verify the uncertainty of the measurement, one other experiment was done in which the solubility of KH_2PO_4 in water was measured. The results were correlated with eq 5, and the deviation between the literature[14] and in this work were plotted in Figure 2. By comparison with literature values, it is estimated the uncertainty in the solubility values are about 1 %.

Results and Discussion

The solubilities of potassium clavulanate in ethanol, 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol at different temperatures are presented in Table 1 and more visually given in Figure 3.

The solubility of a solid in a liquid may be expressed in a very general manner by eq 2:

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{f,1}}\left(\frac{T_{f,1}}{T} - 1\right) - \frac{\Delta C_{pf,1}}{R}\left(\frac{T_{f,1}}{T} - 1\right) + \frac{\Delta C_{pf,1}}{R}\ln\frac{T_{f,1}}{T} - \ln\gamma_1 \quad (2)$$

where x_1, γ_1, $\Delta H_{f,1}$, $\Delta C_{pf,1}$, $T_{f,1}$, R, and T stand for the mole fraction of the solute, activity coefficient, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively. For regular solutions,[15] the activity coefficient is given by

$$\ln\gamma_1 = A + \frac{B}{T} \quad (3)$$

where A and B stand for empirical constants. Introducing γ_1 from eq 3 into eq 2 and subsequent rearrangements result in eq 4:

$$\ln x_1 = \left[\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}(1 + \ln T_{f,1}) - A\right] - \left[B + \left(\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}\right)T_{f,1}\right]\frac{1}{T} - \frac{\Delta C_{pf,1}}{R}\ln T \quad (4)$$

Equation 4 can be written as

$$\ln x_1 = a + \frac{b}{T} + c\ln T \quad (5)$$

Table 2. Parameters of Equation 5 for Potassium Clavulanate in Pure Solvents

solvent	*a*	*b*	*c*	10^6 RMSD
ethanol	−194.21	6710.9	28.869	5.0905
1-propanol	0.29533	−2328.7	−0.16098	6.2016
1-butanol	−501.37	19526	74.898	1.1716
2-propanol	−265.16	9130.7	39.540	1.8508
2-methyl-1-propanol	−58.912	220.06	8.5421	3.6581

where T is the absolute temperature, the unit of which is K, and a, b, and c are empirical constants.

The solubility data are correlated with eq 5. The difference between experimental and calculated results is 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:

$$\mathrm{RMSD} = \left\{ \frac{\sum_{i=1}^{N} [(x_{1,i} - x_{1,i}^{\mathrm{expt}})]^2}{N-1} \right\}^{1/2} \quad (6)$$

where N is the number of experimental points; $x_{1,i}^{\mathrm{calc}}$ is the solubility calculated from eq 5; and $x_{1,i}$ is the experimental value of solubility.

From Figure 3 and Table 1, we can easily find that ethanol is a better solvent than other solvents for potassium clavulanate. The solubility of title compound depends on the polarity of the solvent to some degree. The solubility in strongly polar ethanol (relative permittivity of 22.4 at 293.15 K)[16] is obviously higher than in weakly polar 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol (relative permittivity of 20.1, 18.2, 18.3 and 17.7,[16] respectively, at 293.15 K). In fact, there are a carboxyl and a hydroxyl in the molecule of potassium clavulanate, which bring potassium clavulanate 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 the values of parameter c in all five solvents are relative small, which represents the relatively small $\Delta C_{pf,1}$. This is true for many compounds under most conditions, so the last term of eq 5 is neglected in many cases. For a given compound, the values of a and b reflect the variations in the solution activity coefficient and provide an indication of the effect of solution nonidealities on the solubility of the solute.

From Table 1 and Figure 3, the following conclusions can be drawn: (1) the solubilities of potassium clavulanate in ethanol, 1-propanol, 1-butanol, 2-propanol, and 2-methyl-1-propanol all increase with increase of temperature. (2) The solubilities of potassium clavulanate in these five organic solvents decrease in the order ethanol > 1-propanol > 1-butanol > 2-propanol > 2-methyl-1-propanol. (3) These experimental data can be regressed by eq 5 for each solvent.

Literature Cited

(1) Cole, M.; Howarth, T. T.; Reading, C. Novel β-lactam antibiotic from *Streptomyces clavuligerus*. Great Britian Patent 1508977, 1978.

(2) Brown, A. G.; Corbett, D. F.; Goodacre, J.; Harbridge, J. B.; Howarth, T. T.; Ponsford, R. J.; Stirling. I.; King, T. J. Clavulanic acid and its derivatives. Stucture elucidation of clavulanic acid and the preparation of dihydroclavulanic acid, isoclavulanic acid, esters and related oxidation products. *J. Chem. Soc., Perkin Trans. 1* **1984**, 635−650.

(3) Butterly, P. G.; Keohane, G. J.; Kosal, E. F.; Keohane, J. G.; Butterly, P.; John, G. Process for preparing potassium clavulanate. U.S. Patent 6414142 B1, 2002.

(4) Booij, J.; Van Den Heuvel, A. Process for the preparation of salts and esters of clavulanic acid. WO Patent 9821212, 1998.

(5) Cook, M. A.; Nicola, M.; Worthing, M. N. Process for the preparation of a metal salt of clavulanic acid. U.S. Patent 6300495 B1, 2001.

(6) Lefferts, A. G.; Kerkhof, P. T. Improved process for the preparation of salts and esters of clavulanic acid. WO Patent 0004028, 2000.

(7) Hefter, G. T.; Tomkins, R. P. T. *The Experimental Determination of Solubilities*; John Wiley: Chichester, 2003; p 260.

(8) United States Pharmacopeial Convention Inc. *The United States Pharmacoreia XXIV*; McNally: Taunton, 2000; pp 426−427.

(9) Ren, G. B.; Wang, J. K.; Yin, Q. X.; Zhang, M. J. Solubilities of proxetine hydrochloride hemihydrate between 286 K and 363 K. *J. Chem. Eng. Data* **2004**, *49*, 1671−1674.

(10) Jiang, Q.; Gao, G. H.; Yu, Y. X.; Qin, Y. Solubility of sodium dimethyl isophthalate-5-sulfonate in water and in water + methanol containing sodium sulfate. *J. Chem. Eng. Data* **2000**, *45*, 292−294.

(11) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of dexamethasone dodium phosphate in different solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697−1698.

(12) Nie, Q.; Wang, J. K.; Wang, Y. L.; Wang, S. Solubility of 11α-hydroxy-16α,17α-epoxyprogesterone in different solvents between 283 K and 323 K. *J. Chem. Eng. Data* **2005**, *50*, 989−992.

(13) Wang, S.; Wang, J. K.; Yin, Q. X. Measurement and correlation of solubility of 7-aminocephalosporanic acid in aqueous acetone mixtures. *Ind. Eng. Chem. Res.* **2005**, *44*, 3783−3787.

(14) Stephen, H.; Stephen, T. *Solubilities of Inorganic and Organic Compounds*; Pergamon Press: Oxford, U.K., 1963.

(15) Kondepudi, D. K.; Prigogine, I. *Modern Thermodynamics*; John Wiley: Chichester, England, 2002.

(16) Smallwood, I. M. *Handbook of Organic Solvent Properties*; Arnold: London, 1996.

Received for review April 12, 2005. Accepted June 30, 2005.

JE050145R