Solubility of 5-Amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide in Ethanol + Water Mixtures

Xinwei Zhang, Qiuxiang Yin,* Junbo Gong, and Zengkun Liu

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

The solubilities of 5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide in ethanol + water mixtures at temperatures from (318.15 to 353.15) K were measured. The experimental data were correlated with the Apelblat model. The calculated values of Apelblat model were found to show a fine representation of the experimental data.

Introduction

5-Amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide (CAS Registry No. 76801-93-9, hereinafter referred to as "compound A") is a key intermediate for manufacturing of nonionic X-ray contrast agents such as iohexol.[1−4] The molecular structure of compound A is given in Figure 1. The solubilities are important physicochemical data for selecting the proper solvent and determining the operation conditions of crystallization procedure, which is the final process in manufacturing of pharmaceuticals. Ethanol + water mixtures were used to refine and purify compound A in the pharmaceutical industry. Therefore, the solubility data are very crucial for industry in the crystallization of compound A. However, the solubility data of compound A have not been reported in literature.

The aim of this article is to determine the solubilities of compound A in ethanol + water mixtures at the temperature range from (318.15 to 353.15) K.

Experimental Section

Materials. Ethanol (analytical grade) from Tianjin Kemel Chemical Ltd. was used directly without further purification, and the mass fraction was higher than 99 %. The crude compound A with a purity of 97.5 % was recrystallized twice in ethanol + water mixtures ($w_B = 0.20$) to obtain the purity of 99.8 % by high-performance liquid chromatography (HPLC; Aiglent 1200, USA). The X-ray diffraction (XRD) result[1] is shown in Figure 2.

Procedure. The solubility was measured by a gravimetric method. Excess compound A was added to the ethanol + water mixture solvent with a known mass and composition. Then, the cylindrical double-jacketed glass vessel was heated to a constant temperature with continuous stirring, in which the temperature was controlled to be constant with a precision of ± 0.05 K through a thermostatted bath (Type 501 A, China). When the temperature of the water bath kept constant for at least 4 h, the stirring was stopped, and the solution was kept still for 3 h. A portion of the upper clear solution was filtered with the membrane (0.45 μm) and preserved in a weighted double dish. The double dish was quickly weighed to determine the mass of the sample. The solvent in the double dish had completely evaporated after 8 h with the oven at 60 °C; the double dish was dried and reweighed to determine the mass of the constant residue solid (m_A) and the mixture solvent [ethanol (m_B) and water (m_C)] which had been completely evaporated. All of the masses were measured using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g.

At each temperature, the measurement was repeated three times, and the average values were used to calculate the mole fraction x_A based on the following equation:

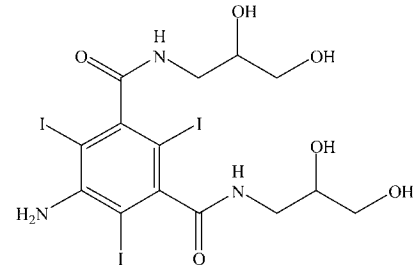

Figure 1. Chemical structure of 5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodobenzene-1,3-dicarboxamide.

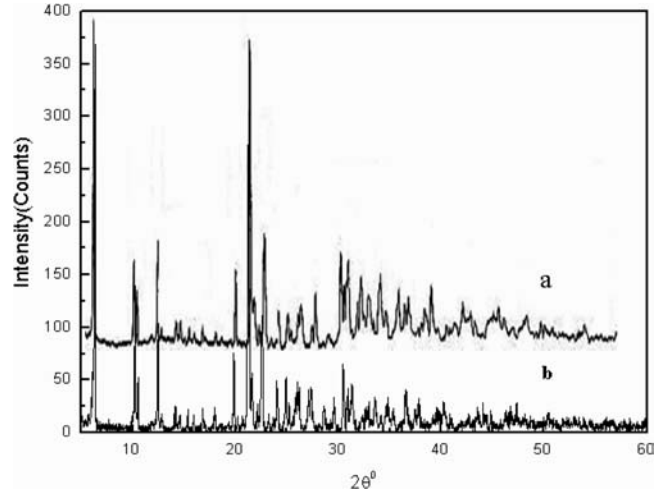

Figure 2. XRD pattern of 5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)- 2,4,6-triiodobenzene-1,3-dicarboxamide: a, standard XRD pattern;[1] b, recrystallized product.

* Corresponding author. Fax: +86-22-27374971. E-mail: qxyin@tju.edu.cn.

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Table 1. Parameters of Apelblat Model for Compound A in Ethanol + Water Mixtures

system	*A*	*B*	*C*	10^4 rmsd
$w_B = 0.00$	−91.301	−2238.9	15.726	0.19
$w_B = 0.10$	−38.098	4207.1	7.6583	0.34
$w_B = 0.13$	−315.74	9879.2	48.210	1.30
$w_B = 0.17$	−167.78	1968.2	26.842	0.49
$w_B = 0.20$	−226.10	5380.0	35.145	0.95
$w_B = 0.30$	28.801	−8982.4	−1.2971	0.45

Table 2. Mole Fraction x_A in Ethanol + Water Mixtures

T/K	$10^3\, x_A$	$10^3\, x_A^{cal}$	$10^2(x_A - x_A^{cal})/x_A$
		$w_B = 0.00$	
313.15	0.33	0.31	6.99
318.15	0.42	0.44	−4.85
323.15	0.66	0.63	4.55
328.15	0.87	0.90	−2.60
333.15	1.24	1.26	−1.68
338.15	1.75	1.76	−0.10
343.15	2.46	2.44	1.15
348.15	3.36	3.36	−0.01
353.15	4.60	4.60	−0.20
		$w_B = 0.10$	
313.15	0.58	0.54	6.74
318.15	0.78	0.75	3.72
323.15	1.02	1.04	−2.50
328.15	1.36	1.42	−4.98
333.15	1.94	1.94	0.01
338.15	2.64	2.63	0.58
343.15	3.57	3.52	1.32
348.15	4.67	4.69	−0.60
353.15	6.21	6.21	0.04
		$w_B = 0.13$	
313.15	0.84	0.79	5.93
318.15	1.04	1.03	0.47
323.15	1.40	1.35	3.59
328.15	1.75	1.78	−1.35
333.15	2.37	2.35	0.89
338.15	3.09	3.10	−0.39
343.15	4.24	4.11	2.96
348.15	5.14	5.46	−6.30
353.15	7.43	7.27	2.16
		$w_B = 0.17$	
313.15	0.75	0.71	4.52
318.15	0.99	0.99	0.03
323.15	1.47	1.36	7.09
328.15	1.88	1.88	0.35
333.15	2.53	2.57	−1.54
338.15	3.52	3.52	0.17
343.15	4.73	4.79	−1.17
348.15	6.47	6.50	−0.45
353.15	8.85	8.80	0.57
		$w_B = 0.20$	
313.15	0.96	0.95	0.57
318.15	1.28	1.27	1.05
323.15	1.63	1.69	−3.89
328.15	2.24	2.25	−0.55
333.15	3.06	2.99	2.24
338.15	3.91	3.98	−1.80
343.15	5.47	5.28	3.29
348.15	6.83	7.01	−2.72
353.15	9.36	9.30	0.58
		$w_B = 0.30$	
313.15	0.70	0.65	7.34
318.15	1.03	1.00	2.66
323.15	1.41	1.52	−8.08
328.15	2.29	2.27	0.52
333.15	3.38	3.36	0.55
338.15	4.90	4.91	−0.38
343.15	7.14	7.10	0.54
348.15	10.13	10.15	−0.14
353.15	14.35	14.35	−0.03

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \quad (1)$$

$$w_B = \frac{m_B}{m_B + m_C} \quad (2)$$

In the ethanol + water mixtures, m_A, m_B, and m_C represent the masses of compound A, ethanol, and water; M_A, M_B, and M_C are the molecular weights of compound A, ethanol, and water, respectively. The uncertainty of experimental values is estimated to be less than 2.2 %.

Result and Discussion

In recent years, several theoretical or empirical models have been developed to correlate the solubility data,[5,6] among which the Apelblat model is a more commonly used one.[7] The Apelblat model provides very accurate mathematical descriptions for how the solute solubility varies with temperature as follows

$$\ln x_A = A + \frac{B}{(T/\mathrm{K})} + C \ln(T/\mathrm{K}) \quad (3)$$

The parameters of this model were calculated by nonlinear curve fit of the Origin 7.5 software and are listed in Table 1, where the root-mean-square deviation (rmsd) is defined as

$$\mathrm{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_A - x_A^{cal})^2\right]^{1/2} \quad (4)$$

where x_A^{cal} is the calculated value by eq 3 and n is the number of experiment points. The solubility data of compound A in ethanol + water mixture are summarized in Table 2 and were correlated by the Apelblat model.

The relationship between the solubilities and the temperatures of compound A in ethanol + water mixtures with different mass fractions of ethanol is shown in Figure 3. It indicates that the temperature has a very important effect on the dissolution behavior of compound A. The solubility is very small at low temperature, whereas it increases with the elevation of the temperature quickly. At the same temperature, the molar fraction of compound A increases with the increasing of mass fraction of ethanol. According to Tables 1 and 2, it can be seen that the mole fraction of compound A can be fitted with eq 3 very well.

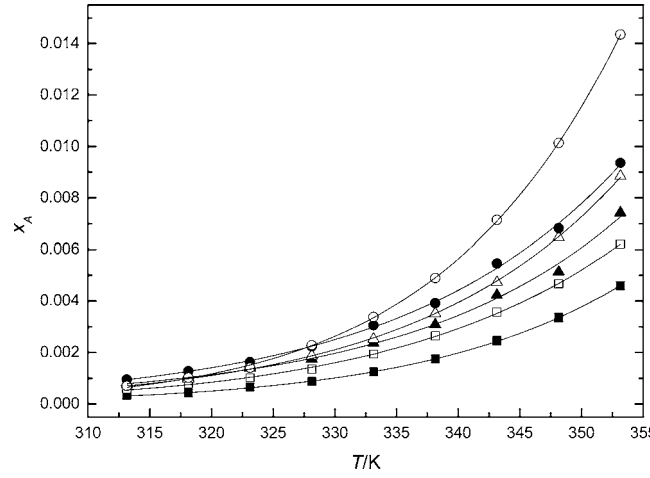

Figure 3. Experimental mole fraction x_A and calculated values from the Apelblat model of compound A in ethanol + water mixtures at different temperatures: ■, $w_B = 0.00$; □, $w_B = 0.10$; ▲, $w_B = 0.13$; △, $w_B = 0.17$; ●, $w_B = 0.20$; ○, $w_B = 0.30$. The solid lines represent the calculated values.

The experimental solubility data and the correlation equation in this work can be used as essential data for the design and operation of the crystallization process of compound A.

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