Solubility of D-*p*-Hydroxyphenylglycine in Water, Methanol, Ethanol, Carbon Tetrachloride, Toluene, and *N*,*N*-Dimethylformamide between 278 K and 323 K

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The solubility of D-*p*-hydroxyphenylglycine in water, methanol, ethanol, carbon tetrachloride, toluene, and *N*,*N*-dimethylformamide (DMF) between 278 K and 323 K was measured using a laser monitoring observation technique. Results of these measurements were correlated with a semiempirical equation. For the six groups of data studied, the semiempirical equation provided an accurate mathematical representation of the experimental data.

Introduction

D-*p*-Hydroxyphenylglycine (CAS Registry No. 22818-40-2) is a white or almost white crystalline powder and a useful chemical for the preparation of semisynthetic penicillins and cephalosporins. To determine the proper solvent and to design an optimized crystallization process, it is necessary to know its solubility in different solvents. From a review of the literature on D-*p*-hydroxyphenylglycine, it was found that some experimental solubility data in water + 1-butanol mixtures at 298.15 K were available.[1] In this paper, the solubility of D-*p*-hydroxyphenylglycine in water, methanol, ethanol, carbon tetrachloride, toluene, and *N*,*N*-dimethylformamide (DMF) between 278 K and 323 K was experimentally determined using a laser monitoring observation technique at atmospheric pressure. The method employed in this work was classified as a nonisothermal method, which was much faster and more reliable than the analytical method.[2,3]

Experimental Section

Materials. D-*p*-Hydroxyphenylglycine used during the solubility measurements had a mass purity of 0.995 and was purchased from Shijiazhuang Pharmaceutical Group Co., Ltd. (CSPC). Other reagents are analytical research grade reagents from Shanghai Chemical Reagent Co.

Apparatus and Procedure. The solubility of D-*p*-hydroxyphenylglycine was measured using an apparatus similar to that described in the literature[3−7] and described briefly here. A 500 mL jacked vessel was used to determine the solubility. The temperature in the vessel was maintained at the desired value by continuous forced water circulation from a thermostat (temperature uncertainty of 0.05 K). A mercury in-glass thermometer (uncertainty of 0.05 K) was used for the measurement of the temperature in the vessel. 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 determined using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ±0.0001 g.

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Predetermined excess amounts of solvent and D-*p*-hydroxyphenylglycine 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 D-*p*-hydroxyphenylglycine in the solution, so the intensity of the laser beam penetrating the vessel was lower. As the particles of the solute dissolved, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear, and the laser intensity reached its maximum. Then, additional solute of known mass (about 1 mg to 3 mg) was introduced into the vessel. This procedure was repeated until the penetrated laser intensity could not return to its maximum or, in other words, until the last addition of solute could not dissolve completely. The interval of addition was 90 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.

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

where m_1 and m_2 represent the mass of the solute and solvent, respectively, and M_1 and M_2 are the molecular weight of the solute and solvent, respectively.

Results and Discussion

The solubility data of D-*p*-hydroxyphenylglycine in pure water, methanol, ethanol, carbon tetrachloride, toluene, and *N*,*N*-dimethylformamide (DMF) between 278 K and 323 K are presented in Table 1, and the relative error is less than ±1.0 %. The temperature dependence of D-*p*-hydroxyphenylglycine solubility in pure solvents is described by the modified Apelblat equation which is a semiempirical equation:[8]

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \tag{2}$$

where x is the mole fraction solubility of D-*p*-hydroxyphenylglycine, T is the absolute temperature, and A, B, and C are the dimensionless parameters. The calculated solubility values of D-*p*-hydroxyphenylglycine are also given in Table 1. The values

10.1021/je060300h CCC: $33.50
Published on Web 10/04/2006

Table 1. Mole Fraction Solubility of D-*p*-Hydroxyphenylglycine in Pure Solvents

T/K	$10^5 x_1$	$10^5(x_1 - x_1^{calcd})$	T/K	$10^5 x_1$	$10^5(x_1 - x_1^{calcd})$
		water			
278.27	179.8	0.4	303.29	228.5	0.1
283.25	185.9	−0.3	308.26	243.5	0.4
288.37	194.1	−0.5	313.28	260.5	0.5
293.17	203.4	−0.5	318.17	278.8	0.1
298.26	215.1	−0.2	323.21	299.4	−0.9
		methanol			
278.17	41.99	0.00	303.32	42.47	0.00
283.22	42.07	0.01	308.20	42.60	0.01
288.21	42.15	0.01	313.26	42.73	0.00
293.28	42.25	0.01	318.27	42.88	0.01
298.24	42.36	0.01	323.25	43.03	0.01
		ethanol			
278.28	9.261	0.000	303.17	9.417	0.000
283.42	9.304	−0.001	308.39	9.433	0.000
288.18	9.339	−0.001	313.19	9.444	0.001
293.24	9.370	−0.002	318.37	9.449	−0.001
298.38	9.397	−0.001	323.26	9.449	−0.002
		toluene			
278.28	15.66	−0.19	303.32	17.96	−0.17
283.33	16.41	0.26	308.39	18.85	0.01
288.38	16.52	−0.01	313.37	19.51	−0.11
293.32	17.19	0.21	318.17	20.50	0.03
298.23	17.49	−0.01	323.27	21.61	0.15
		carbon tetrachloride			
278.38	22.49	−0.02	303.21	24.36	−0.07
283.23	22.73	−0.01	308.36	25.03	−0.02
288.38	23.06	−0.01	313.30	25.80	0.08
293.36	23.40	−0.05	318.24	26.41	−0.05
298.29	23.90	−0.01	323.19	27.23	−0.05
		N,*N*-dimethylformamide			
278.27	1.993	0.019	303.18	4.926	0.068
283.23	2.393	0.043	308.26	5.996	0.122
288.18	2.665	−0.139	313.20	7.038	−0.037
293.20	3.378	0.015	318.39	8.679	0.063
298.39	4.029	−0.039	323.15	10.17	−0.16

of parameters *A*, *B*, and *C* and the root-mean-square deviations (RMSDs) are listed in Table 2. The RMSD is defined as[3]

$$\mathrm{RMSD} = \left[\frac{\sum_{j=1}^{N}(x_{1,j} - x_{1,j}^{calcd})^2}{N-1}\right]^{1/2} \quad (3)$$

where N is the number of experimental points, $x_{1,j}^{calcd}$ represents the solubility calculated from eq 2, and $x_{1,j}$ represents the experimental solubility values.

From data listed in Table 1 and Table 2, we can draw the following conclusions: (1) The solubility of D-*p*-hydroxyphenylglycine increases with increasing temperature in six kinds of pure solvent. The solubility of D-*p*-hydroxyphenylglycine in *N*,*N*-dimethylformamide is the lowest. (2) The solubility of D-*p*-hydroxyphenylglycine in pure water is the largest in six kinds of pure solvent, and the solubility of D-*p*-hydroxyphenylglycine in *N*,*N*-dimethylformamide is the lowest. The authors think that *N*,*N*-dimethylformamide and ethanol may be used in dilution to increase the yield of the product in the crystallization process of D-*p*-hydroxyphenylglycine according to solubility data, which is beyond the scope of this work. (3) The experimental solubility and correlation equations in this work can be used as essential data and models in the purification process of D-*p*-hydroxyphenylglycine. The calculated solubility shows good agreement with the experimental values.

Table 2. Parameters of Equation 2 for the Solubility of D-*p*-Hydroxyphenylglycine in Pure Solvents

solvent	A	B	C	10^6RMSD
water	−161.26	6057.9	23.659	4.75
methanol	−15.124	287.49	1.1220	0.09
ethanol	2.5046	−561.16	−1.7367	0.01
toluene	−118.07	4376.6	16.628	1.54
carbon tetrachloride	−84.971	3098.2	11.626	0.47
N,*N*-dimethylformamide	−192.94	5352.3	28.936	0.91

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Received for review June 29, 2006. Accepted September 1, 2006.

JE060300H