Solubility of D(−)-*p*-Hydroxyphenylglycine Dane Salt in Eight Alcohols between (293 and 343) K

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The solubility of D(−)-*p*-hydroxyphenylglycine dane salt (HPGDane Salt) in eight alcohols was measured using a laser technique with the temperature range from (293 to 343) K. The results were correlated with a semiempirical equation, the calculated results of which are proved to show fine representation of experimental data.

Introduction

D(−)-*p*-Hydroxyphenylglycine dane salt (HPGDane Salt, CAS Registry No. 96416-61-1) is a kind of white or almost white crystalline powder. As an intermediate, HPGDane Salt has been widely used in the synthesis of amoxicillin and other antibiotics.[1] In the industrial production of HPGDane Salt, methanol is employed as the solvent, and the title compound crystallizes from the solution through lowering temperature. To determine the proper solvent and to design an optimized crystallization process, it is necessary to know its solubility in different solvents. In this paper, the solubilities of HPGDane Salt in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, and 2-pentanol were experimentally determined in the temperature range from (293 to 343) K 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.[2] To verify the uncertainty of the measurement, the solubilities of HPGDane Salt in methanol and ethanol in the literature[3] and this work were plotted in Figure 1. Compared with the literature data, the deviation of the solubility was < 1.5 %.

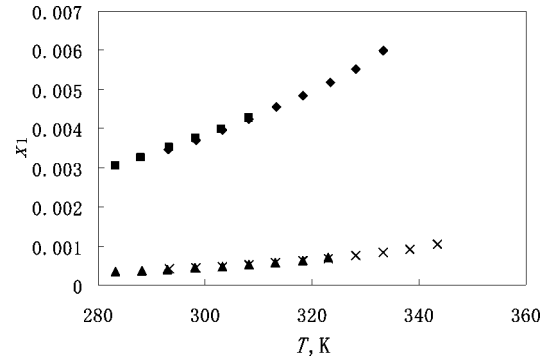

Figure 1. Solubility of HPGDane Salt in methanol and ethanol: ■, solubility values for methanol in the literature; ◆, experimental solubility values for methanol; ▲, solubility values for ethanol in the literature; ×, experimental solubility values for ethanol.

Experimental Section

Materials. A white crystalline powder of HPGDane Salt ($C_{13}H_{14}NO_5K$, molecular weight 303.33), purchased from Shijiazhuang Pharmaceutical Group Co., Ltd. (CSPC), was prepared by recrystallizing from the solution of methanol two times. Its mass fraction purity determined by HPLC was higher than 99.3 %. Other reagents are analytical research grade reagents from Beijing Chemical Reagent Co.

Apparatus and Procedures. The solubility of HPGDane Salt was measured using an apparatus similar to that described in the literature[3−8] and described briefly here. A 500 mL jacketed vessel was used to determine the solubility, and the temperature was controlled to be constant (fluctuates within 0.05 K) through a thermostat water 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 weighted using an analytical balance (Sartorius CP224S, Germany) with an uncertainty of ± 0.0001 g. During the experiments, the fluid in the glass vessel was monitored by a laser beam. Predetermined excess amounts of solvent and HPGDane Salt 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 HPGDane Salt in the solution, so the intensity of the laser beam penetrating the vessel was lower. Along with the dissolution of the particles of the solute, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear, and the laser intensity 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 to maximum or, in other words, 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

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

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.

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Table 1. Mole Fraction Solubility of D(−)-*p*-Hydroxyphenylglycine Dane Salt x_1 in Different Alcohol Solvents between (293 and 343) K

T/K	$10^4 x_1$	10^4 ($x_1 - x_1^{calcd}$)	T/K	$10^4 x_1$	10^4 ($x_1 - x_1^{calcd}$)
		methanol			
293.15	34.60	0.03	318.27	48.50	0.11
298.22	37.03	0.08	323.35	51.87	0.00
303.15	39.58	0.13	328.16	55.24	−0.18
308.19	42.37	0.16	333.35	59.96	0.42
313.35	45.42	0.16			
		ethanol			
293.25	4.045	−0.021	323.11	6.814	−0.032
298.26	4.373	−0.025	328.18	7.531	−0.031
303.25	4.780	0.006	333.41	8.340	−0.062
308.19	5.195	−0.002	338.31	9.163	−0.131
313.09	5.596	−0.076	343.35	10.40	0.07
318.26	6.292	0.051			
		1-propanol			
293.15	1.779	0.024	323.05	3.058	−0.007
298.23	1.913	0.002	328.21	3.452	0.038
303.05	2.057	−0.023	333.25	3.823	0.019
308.18	2.275	−0.011	338.34	4.275	0.022
313.05	2.562	0.054	343.35	4.755	−0.003
318.29	2.795	0.013			
		2-propanol			
293.25	0.574	0.015	323.15	1.299	0.021
298.23	0.638	−0.002	328.19	1.502	0.028
303.05	0.722	−0.007	333.35	1.733	0.026
308.41	0.840	−0.006	338.27	1.977	0.012
313.15	0.966	0.001	343.25	2.245	−0.022
318.26	1.125	0.012			
		1-butanol			
293.15	0.997	0.016	323.25	2.074	0.018
298.31	1.101	−0.007	328.29	2.365	0.024
302.95	1.223	−0.016	333.17	2.678	0.020
308.19	1.393	−0.015	338.32	3.040	−0.002
312.95	1.578	−0.007	342.95	3.394	−0.043
318.16	1.812	0.006			
		2-butanol			
293.35	0.351	−0.004	323.23	1.128	−0.006
298.24	0.438	−0.007	328.26	1.316	−0.004
303.05	0.587	0.040	333.15	1.514	0.001
308.17	0.664	−0.007	338.28	1.739	0.010
313.05	0.811	0.005	343.23	1.973	0.026
318.36	0.962	−0.007			
		1-pentanol			
293.05	0.848	−0.013	323.25	1.896	−0.005
298.25	1.017	0.005	328.17	2.091	−0.010
303.25	1.192	0.024	333.25	2.259	−0.053
308.19	1.337	0.002	338.13	2.523	0.005
313.07	1.523	0.014	343.35	2.789	0.048
318.26	1.699	−0.006			
		2-pentanol			
293.25	0.622	−0.005	323.15	1.962	−0.011
298.28	0.786	0.004	328.34	2.332	0.013
303.35	0.999	0.033	333.05	2.670	0.006
308.19	1.167	−0.001	338.24	3.096	0.020
313.15	1.410	0.006	343.26	3.543	0.037
318.29	1.686	0.005			

Results and Discussion

The solubility of HPGDane Salt is shown in Table 1. The relationship between temperature and solubility of the HPGDane Salt is correlated with a semiempirical equation[9]

$$\ln x_1 = a + \frac{b}{T} + c \ln T \tag{2}$$

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 follows

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

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

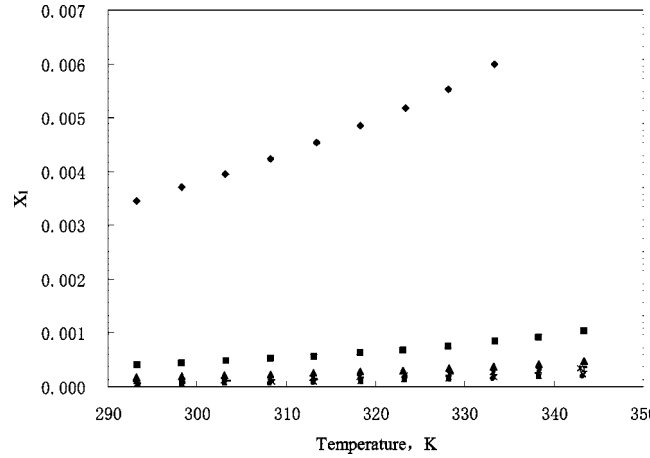

Figure 2. Solubility of HPGDane Salt in different alcohol solvents: ◆, methanol; ■, ethanol; ▲, 1-propanol; ×, 2-propanol; *, 1-butanol; ÷, 2-butanol; +, 1-pentanol; −, 2-pentanol.

Table 2. Parameters of Equation 2 for D(−)-*p*-Hydroxyphenylglycine Dane Salt in Different Alcohol Solvents

solvent	a	b	c	10^5rmsd
methanol	−70.983	1911.5	10.350	1.92
ethanol	−162.52	5677.9	23.825	0.61
1-propanol	−171.79	5966.3	25.136	0.26
2-propanol	−145.90	4012.3	21.550	0.17
1-butanol	−151.42	4535.6	22.307	0.20
2-butanol	186.08	−12088	−27.303	0.16
1-pentanol	121.38	−8072.0	−18.167	0.25
2-pentanol	126.26	−9283.3	−18.356	0.18

From Table 1, it can be seen that the solubility of HPGDane Salt depends on the polarity of the solvents to a great degree. It is well-known that the polarity of methanol is stronger than that of other alcohols. In fact, there are a hydroxyl and a carboxyl in the molecule of HPGDane Salt, which bring it some polarity, and the solubility behavior of HPGDane Salt just reflected the empirical rule that "like dissolves like". From Table 2, we could find that parameter c in all alcohols is relatively small, which is true for many compounds under most conditions, so the last term of eq 2 is neglected in many cases.

From Table 1, Table 2, and Figure 2, we could elicit the conclusions: (1) The solubilities of HPGDane Salt in alcohols increase with an increase of temperature, but the increment with temperature varies according to different alcohols. (2) It can be seen that HPGDane Salt dissolved much more in methanol than in the other seven alcohols, and the solubility in 2-butanol is the lowest. (3) All the experimental data can be regressed by eq 2 for these alcohol solvents. The experimental solubility and correlation equation in this work can be used as essential models in the manufacturing and purifying processes of HPGDane Salt in industry.

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