Solubility of D-(-)-*p*-Hydroxyphenylglycine Dane Salt in Mixtures of Methanol and Ethanol

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The solubility of D-(−)-*p*-hydroxyphenylglycine dane salt (HPGDane Salt) in binary methanol and ethanol solvent mixtures was measured using a laser technique with a temperature range from 278.15 K to 323.15 K and a mole fraction (x'_2) of methanol in original solvent range from 0.0000 to 1.0000. The results were correlated with a semiempirical equation.

Introduction

D-(−)-*p*-Hydroxyphenylglycine dane salt (HPGDane Salt, CAS Registry No. 69416-61-1) is benzeneacetic acid, 4-hydroxy-a-[(3-methoxy-1-methyl-3-oxo-1-propenyl)amino]−, monopotassium salt, (aR)-(9CI). It is a kind of white or almost white crystalline powder. As an intermediate, HPGDane Salt has been widely used in syntheses 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 the temperature. At the end of crystallization, ethanol is introduced as the diluting agent to increase the yield of products. The solubility of HPGDane Salt in binary methanol and ethanol solvent mixtures was experimentally determined in the temperature range from 278.15 K to 323.15 K and the mole fraction (x'_2) of methanol in original solvent range from 0.0000 to 1.0000 using a laser monitoring observation technique. The method employed in this work was classified as a synthetic method, which was much faster and more readily available than the analytical method.[2]

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 purified by recrystallization from the solution of methanol three times. Its mass fraction purity determined by HPLC was higher than 99.4 %. Both methanol and ethanol were 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 in the literature[3] and described briefly here. A 250 mL jacked vessel was used to determine the solubility; 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 measured using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ±0.0001 g.

The solubility of HPGDane Salt was determined by the laser method.[4−7] During experiments, the fluid in the glass vessel was monitored by a laser beam. HPGDane Salt of known mass was added into excess amounts of solvent whose mass was known 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 low. During 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 its maximum. Then, additional solute of known mass (about 1 mg to 5 mg) was introduced into the vessel. This procedure was repeated until the 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 60 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 the solvent mixture (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, methanol, and ethanol, respectively, and M_1, M_2, and M_3 are the molecular weight of the solute, methanol, and ethanol, respectively.

Results and Discussion

The solubilities of HPGDane Salt in the mixture of methanol and ethanol at different temperatures are shown in Table 1. The relationship between temperature and solubility of the HPGDane Salt is correlated with a semiempirical equation:[8]

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

where T is the absolute temperature, and a, b, and c are empirical

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Table 1. Mole Fraction Solubility in Mixtures of Methanol and Ethanol in the Temperature Range from 278.15 K to 323.15 K

T/K	10^3x_1	$10^3(x_1 - x_1^{\text{calcd}})$	T/K	10^3x_1	$10^3(x_1 - x_1^{\text{calcd}})$
		$x'_2 = 1.0000$			
278.24	2.8101	0.0004	302.97	3.9818	0.0012
283.28	3.0322	0.0011	308.19	4.2553	0.0010
288.04	3.2498	0.0015	313.32	4.5331	0.0010
293.35	3.5016	0.0015	318.11	4.8004	0.0013
298.31	3.7453	0.0014	322.45	5.0491	0.0020
		$x'_2 = 0.9283$			
278.46	2.4972	0.0298	303.22	3.4819	−0.0216
283.24	2.6785	0.0099	308.36	3.7320	−0.0170
288.26	2.8551	−0.0057	313.54	4.0020	−0.0074
293.33	3.0506	−0.0162	318.03	4.2507	0.0049
298.13	3.2517	−0.0212	322.17	4.4919	0.0194
		$x'_2 = 0.8502$			
278.39	2.0401	−0.0480	303.00	3.0770	0.0323
283.12	2.2336	−0.0197	308.26	3.3084	0.0267
288.01	2.4365	0.0033	313.62	3.5476	0.0120
293.33	2.6607	0.0210	318.07	3.7490	−0.0072
298.38	2.8767	0.0303	323.27	3.9874	−0.0381
		$x'_2 = 0.7708$			
278.06	1.8240	−0.0218	303.33	2.6714	0.0195
283.34	1.9899	−0.0067	308.11	2.8469	0.0170
288.04	2.1425	0.0043	313.32	3.0437	0.0097
293.08	2.3114	0.0129	317.94	3.2230	−0.0010
298.38	2.4948	0.0183	322.54	3.4060	−0.0159
		$x'_2 = 0.6838$			
278.32	1.5842	−0.0337	303.07	2.2668	0.0231
283.14	1.7128	−0.0136	308.23	2.4162	0.0188
287.94	1.8429	0.0023	313.35	2.5668	0.0083
293.39	1.9932	0.0151	318.12	2.7093	−0.0075
298.47	2.1357	0.0218	322.65	2.8465	−0.0282
		$x'_2 = 0.5904$			
278.43	1.2734	−0.0482	303.16	1.8536	0.0299
283.62	1.3953	−0.0188	308.08	1.9688	0.0249
288.29	1.5050	0.0021	313.38	2.0929	0.0108
293.33	1.6232	0.0184	318.17	2.2049	−0.0100
298.03	1.7334	0.0273	323.22	2.3230	−0.0407
		$x'_2 = 0.4901$			
278.12	1.0104	−0.0327	303.37	1.4939	0.0230
283.05	1.1016	−0.0131	308.02	1.5874	0.0193
288.34	1.2013	0.0036	312.91	1.6871	0.0098
292.98	1.2901	0.0143	318.19	1.7965	−0.0076
298.39	1.3954	0.0216	322.31	1.8830	−0.0266
		$x'_2 = 0.3819$			
278.34	0.7718	−0.0293	303.46	1.1263	0.0211
283.41	0.8412	−0.0116	308.18	1.1980	0.0183
288.23	0.9083	0.0021	313.09	1.2722	0.0103
293.38	0.9813	0.0129	319.13	1.3650	−0.0073
298.40	1.0536	0.0193	323.01	1.4256	−0.0235
		$x'_2 = 0.2649$			
278.11	0.6174	−0.0028	303.16	0.8633	−0.0045
283.39	0.6573	−0.0054	308.33	0.9319	−0.0036
288.02	0.6975	−0.0064	312.91	0.9977	−0.0034
293.04	0.7467	−0.0064	318.24	1.0804	−0.0045
298.22	0.8034	−0.0056	323.03	1.1603	−0.0073
		$x'_2 = 0.1381$			
278.28	0.3987	0.0097	303.91	0.5924	−0.0045
284.09	0.4276	0.0012	308.02	0.6393	−0.0029
288.21	0.4535	−0.0027	312.82	0.6997	−0.0007
293.13	0.4901	−0.0051	318.18	0.7742	0.0014
298.26	0.5350	−0.0057	322.43	0.8386	0.0022
		$x'_2 = 0.0000$			
278.22	0.3191	0.0024	303.29	0.4811	0.0002
283.26	0.3421	−0.0005	308.21	0.5270	0.0013
288.21	0.3693	−0.0018	313.09	0.5770	0.0017
293.04	0.4004	−0.0018	318.23	0.6347	0.0009
298.07	0.4375	−0.0010	323.11	0.6940	−0.0019

Table 2. Parameters of Equation 3 for HPGDane Salt in Binary Methanol (2) + Ethanol (3) Solvent Mixtures in the Temperature Range from 278.15 K to 323.15 K

x'_2	a	b	c	10^4rmsd
1.0000	−2.6174	−1143.4	0.1514	0.14
0.9283	−14.877	−627.29	1.9763	1.81
0.8502	−18.293	−563.05	2.5127	2.88
0.7708	−28.462	−55.483	3.9743	1.51
0.6838	−39.208	486.26	5.5135	2.06
0.5904	−52.240	1058.0	7.4276	2.82
0.4901	−62.378	1447.3	8.9389	2.02
0.3819	−81.897	2339.0	11.790	1.83
0.2649	−101.06	3121.5	14.650	0.55
0.1381	−114.46	3452.7	16.736	0.47
0.0000	−127.77	4025.0	18.699	0.16

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:

$$\text{rmsd} = \left[\frac{\sum_{i=1}^{N}(x_{1,j} - x_{1,j}^{\text{calcd}})^2}{N - 1}\right]^{1/2} \qquad (4)$$

where N is the number of experimental points, $x_{1,j}^{\text{calcd}}$ is the solubility calculated from eq 3, and $x_{1,j}$ is the experimental value of solubility.

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 ethanol. With an increase of ethanol in the solvent mixtures, the polarity of the solvents comes down, and the solubility of HPGDane Salt decreases obviously. In fact, there are a hydroxyl and a carboxyl in the molecule of HPGDane Salt, which bring it some polarity; the solubility behavior of HPGDane Salt just reflected the empirical rule that “like dissolves like”.

From Table 2, we could find that when a decreases b and c increase with the decline of x'_2. Parameter c in all solvent mixtures is relatively 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, we could elicit the following conclusions: (1) The solubilities of HPGDane Salt in a mixture of methanol and ethanol increase with an increase in temperature. (2) The solubilities of HPGDane Salt decrease with an increase of ethanol in the solvent mixture, and the solubility in pure ethanol is the lowest. (3) All the experimental data can be regressed by eq 3 for each solvent mixture. The experimental solubility and correlation equations in this work can be used as essential models in the production process of HPGDane Salt.

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