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Solubility of D(−)-p-Hydroxyphenylglycine dane salt in binary methanol+isopropanol solvent mixtures

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Abstract−The solubility of D(−)-p-Hydroxyphenylglycine Dane Salt (HPGDane Salt) in binary methanol and isopropanol solvent mixtures was measured using a laser technique with the temperature range from 283.15 K to 323.15 K and mole fraction (x_2) range from 0.0000 to 1.0000. The results were correlated with a semi-empirical equation.

Key words: D(−)-p-Hydroxyphenylglycine Dane Salt, Solubility, Laser Technique

INTRODUCTION

D(−)-p-Hydroxyphenylglycine Dane 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 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. At the end of crystallization, isopropanol is introduced as diluting agent to increase the yield of products. The solubility of HPGDane Salt in binary methanol and isopropanol solvent mixtures was experimentally determined from 283.15 K to 323.15 K and the composition (x_2) range from 0.0000 to 1.0000 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 applicable than the analytical method [2].

EXPERIMENTAL SECTIONS

1. 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 three times. Its mass fraction purity determined by HPLC was higher than 99.4%. Both methanol and isopropanol were analytical research grade reagent from Beijing Chemical Reagent Co.

2. Apparatus and Procedures

The solubility of HPGDane Salt was measured using an apparatus similar to that described 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 with 0.05 K) through a thermostat water bath. The dissolution of the solute was examined by a 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 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. 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 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 a maximum. Then additional solute of known mass {about (1to 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 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 solvent mixture (x'_2) was defined as Eq. (2):

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

$$x'_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1, m_2, and m_3 represent the mass of the solute, methanol and isopropanol, respectively, and M_1, M_2, and M_3 are the molecular weight of the solute, methanol and isopropanol, respectively.

RESULTS AND DISCUSSION

The solubility of HPGDane Salt in the mixture of methanol and isopropanol at different temperatures is shown in Table 1. The relationship between temperature and solubility of the HPGDane Salt is correlated with a semi-empirical equation [8]:

$$\ln x_1 = a + \frac{b}{T} + c \ln T \quad (3)$$

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Table 1. Mole fraction solubility of HPGDane salt (1) in the mixture of methanol (2) and isopropanol (3) in the temperature range from 283.15 K to 323.15 K

T/K	10^3x_1	$10^3(x_1-x_1^{calc})$	T/K	10^3x_1	$10^3(x_1-x_1^{calc})$	T/K	10^3x_1	$10^3(x_1-x_1^{calc})$
				x_2=1.0000				
283.28	3.0322	0.0006	298.31	3.7453	0.0008	313.32	4.5331	0.0003
288.04	3.2498	0.0009	302.97	3.9818	0.0005	318.11	4.8004	0.0006
293.35	3.5016	0.0009	308.19	4.2553	0.0003	322.45	5.0491	0.0012
				x_2=0.9441				
283.10	2.3505	0.0424	298.01	2.8572	−0.0221	313.16	3.5239	−0.0134
288.21	2.5074	0.0121	303.36	3.0751	−0.0275	318.03	3.7707	0.0051
293.28	2.6804	−0.0095	308.07	3.2828	−0.0246	323.18	4.0490	0.0329
				x_2=0.8824				
283.16	1.7326	−0.0026	298.07	2.2004	0.0005	313.27	2.7550	0.0008
288.52	1.8921	−0.0015	303.18	2.3781	0.0013	318.10	2.9476	−0.0007
293.21	2.0397	−0.0005	307.98	2.5531	0.0014	322.94	3.1485	−0.0034
				x_2=0.8141				
283.13	1.2691	0.0169	298.06	1.6020	−0.0094	313.09	2.0382	−0.0055
288.62	1.3799	0.0032	303.30	1.7425	−0.0111	318.16	2.2082	0.0013
293.38	1.4869	−0.0048	308.35	1.8897	−0.0095	323.13	2.3860	0.0102
				x_2=0.7377				
283.21	0.9008	0.0008	298.16	1.1542	−0.0008	313.11	1.4646	0.0005
288.32	0.9810	−0.0006	303.27	1.2539	−0.0003	318.30	1.5858	0.0002
293.44	1.0680	−0.0010	308.37	1.3600	0.0002	323.39	1.7113	0.0010
				x_2=0.6529				
283.07	0.6550	0.0092	298.06	0.8165	−0.0050	313.33	1.0489	−0.0016
288.57	0.7066	0.0013	303.10	0.8857	−0.0053	318.04	1.1344	0.0012
293.31	0.7582	−0.0029	308.16	0.9626	−0.0040	323.12	1.2340	0.0043
				x_2=0.5557				
283.09	0.4124	0.0065	298.08	0.5080	−0.0031	313.26	0.6531	−0.0004
288.57	0.4419	0.0010	303.40	0.5534	−0.0031	318.41	0.7134	0.0015
293.33	0.4726	−0.0018	308.17	0.5991	−0.0021	323.08	0.7728	0.0030
				x_2=0.4456				
283.12	0.2782	0.0012	298.28	0.3589	−0.0009	313.17	0.4734	0.0010
288.13	0.3009	−0.0005	303.32	0.3938	−0.0002	318.36	0.5215	0.0006
293.41	0.3291	−0.0011	308.04	0.4300	0.0005	323.31	0.5713	−0.0010
				x_2=0.3192				
283.36	0.1691	0.0015	298.41	0.2241	−0.0010	313.37	0.3114	0.0012
288.28	0.1835	−0.0005	303.10	0.2480	−0.0003	318.44	0.3484	0.0008
293.22	0.2014	−0.0012	307.93	0.2759	0.0006	323.17	0.3862	−0.0011
				x_2=0.0000				
283.36	0.0566	0.0011	298.12	0.0793	−0.0008	313.17	0.1213	0.0008
288.22	0.0621	−0.0003	303.01	0.0909	−0.0003	318.33	0.1401	0.0005
293.28	0.0699	−0.0009	308.07	0.1050	0.0003	323.21	0.1599	−0.0008

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:

$$\mathrm{rmsd}=\left[\frac{\sum_{j=1}^{N}(x_{1,j}-x_{1,j}^{calc})^2}{N-1}\right]^{1/2} \tag{4}$$

where N is the number of experimental points; $x_{1,j}^{calc}$ is the solubility calculated from Eq. (3); and $x_{1,j}$ is the experimental value of solubility. The estimated uncertainty of the solubility values based on error analysis and repeated observations was within 1.0%.

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 isopropanol; along with the increase of the isopropanol in the solvent mixtures, the polarity of solvents comes down, and the solubility of HPGDane Salt decreases obviously. In fact, there is a hydroxyl and

Table 2. Parameters of Eq. (3) for HPGDane salt in binary methanol (2)+isopropanol (3) solvent mixtures in the temperature range from 283.15 K to 323.15 K

x_2	a	b	c	10^4rmsd
1.0000	−2.6174	−1143.4	0.15140	0.075
0.9441	−9.1854	−923.08	1.1291	2.40
0.8824	−18.099	−625.43	2.4709	0.17
0.8141	−23.993	−452.58	3.3490	0.92
0.7377	−34.120	−12.117	4.8084	0.068
0.6529	−68.348	1509.39	9.8607	0.46
0.5557	−96.885	2778.5	14.039	0.30
0.4456	−113.43	3349.2	16.545	0.086
0.3192	−156.97	5057.9	23.097	0.18
0.0000	−193.82	6233.3	28.693	0.070

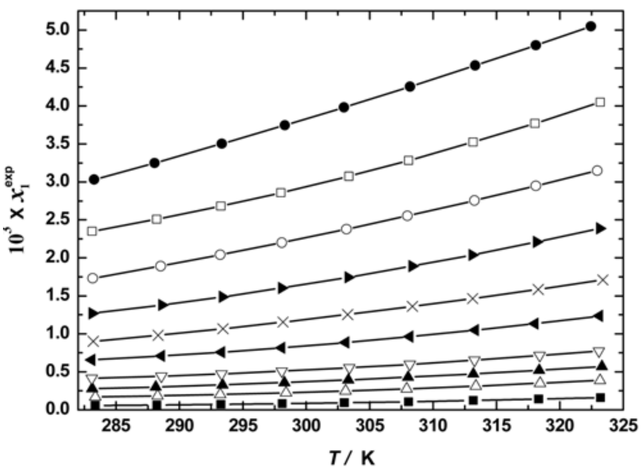

Fig. 1. Mole fraction solubility of Naphthalene x_1 in different solvents: ■, x_2=0.0000; △, x_2=0.3192; ▲, x_2=0.4456; ▽, x_2=0.5557; ◀, x_2=0.6529; ×, x_2=0.7377; ○, x_2=0.8824; ▶, x_2=0.8141; □, x_2=0.9441; ●, x_2=1.0000.

a carboxyl in the molecule of HPGDane Salt, which brings it some polarity; the solubility behavior of HPGDane Salt just reflects the empirical rule that "like dissolves like."

From Table 2, we could find that a decreases; meanwhile b and c increase with the decline of x_2. Parameter c in all solvent mixtures is relative 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 draw the conclusions: (1) The solubilities of HPGDane Salt in mixture of methanol and isopropanol increase with increase of temperature. (2) The solubilities of HPGDane Salt decrease with the increase of isopropanol in the solvent mixture, and the solubility in pure isopropanol is the lowest. (3) All the experimental data can be regressed by Eq. (3) for each solvent mixture. The experimental solubility and correlation equation in this work can be used as essential models in the production process of HPGDane Salt.

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