

Solubility of *D*-*p*-hydroxyphenylglycine *p*-toluenesulfonate and *L*-*p*-hydroxyphenylglycine in different solvents

Yixin Qu, Tian Li, and Shui Wang[†]

Beijing Key Laboratory of Bioprocess, College of Chemical Engineering,
Beijing University of Chemical Technology, Beijing 100029, P. R. China
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Abstract—The solubility of *D*-*p*-hydroxyphenylglycine *p*-toluenesulfonate and *L*-*p*-hydroxyphenylglycine in different solvents was measured using a laser monitoring observation technique. The solubility data were accurately correlated by the modified Apelblat equation, the calculated results of which were proved to show fine representation of experimental data.

Key words: *D*-*p*-HPG·*p*-TS, *L*-*p*-HPG, Solubility, Measurement, Modified Apelblat Equation

INTRODUCTION

D-*p*-hydroxyphenylglycine (*D*-*p*-HPG) is a useful intermediate for the preparation of semisynthetic amoxicillin, cefoperazone, and cefprozil. And *L*-*p*-hydroxyphenylglycine (*L*-*p*-HPG) is the active ingredient of oxphenicine, a new medicine for the treatment of heart diseases [1]. In the industry, *D*-*p*-HPG is always resolved by a preferential crystallization procedure in the form of salts with aromatic sulfonic acids [2,3]. The *D*-*p*-hydroxyphenylglycine *p*-toluenesulfonate (*D*-*p*-HPG·*p*-TS) was used in our experiment. To determine the proper solvent and to design an optimized crystallization process, it is necessary to know their solubility in different solvents. In this work, the solubility of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG in different solvents was experimentally determined at different temperatures and atmospheric pressure, which were helpful to optimize the purification and crystallization process of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG.

EXPERIMENTAL SECTION

L-*p*-HPG which had a mass fraction purity of 0.990 was purchased from Shijiazhuang Pharmaceutical Group Co. *D*-*p*-HPG·*p*-TS used during the solubility measurement had a mass fraction purity of 0.995, and it was composed of an equimolar amount of *p*-toluenesulfonic acid and *D*-*p*-HPG that was purchased from Shijiazhuang Pharmaceutical Group Co. Ethanol, ethylene glycol, *N,N*-dimethylformamide, dimethyl sulfoxide, *n*-propanol, *n*-butanol, isopropanol, and acetic acid (purchased from Beijing Chemical Reagent Co.) were of analytical reagent grade and used without any treatment. Their mass fractions were better than 99.5%, and distilled water was used. A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature. The masses of the samples and solvents were weighted using an analytical balance (Sartorius CP224S, Germany) with an uncertainty of ± 0.0001 g.

The apparatus for solubility of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG was similar to that described in the literature [4-6] and here described

briefly. First, predetermined known masses of solute and solvent were transferred in the jacketed glass vessel. Continuous forced water circulation from a thermostat controlled the temperature in the vessel. Then, the contents of the vessel were stirred. A condenser was connected with the vessels to prevent the solvents from evaporating. A laser monitoring technique which consisted of a laser generator, a photoelectric transformer, and a digital display (purchased from Peking University Factory of Physics Department) were used to measure the solubility of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG in different solvents at a constant temperature. In the early stage of the experiment, undissolved particles of solute in the solution blocked the laser beam, so the intensity of the laser beam was low. As the particles of the solute dissolved completely, the solution was clear, as well as the laser intensity reached its maximum. Then additional solute of known mass (about 1 to 5 mg) was introduced into the vessel repeatedly until the last addition of solute could not dissolve completely. The interval of addition was 120 min. The total amount of the solute and solvent consumed was obtained. The mole fraction of solute is defined as its amount of solute divided by the total amount of substance in the system. In this work, the mole fraction solubility x_1 was based on the following equation:

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

Where m_1 and m_2 represent the mass of the solute and solvent, and M_1 and M_2 are the molecular weight of the solute and solvent, respectively. The molecular weights of *L*-*p*-HPG and *D*-*p*-HPG·*p*-TS are 167.16 g/mol and 339.36 g/mol. The estimated uncertainty of the solubility values based on temperature measurement, weighing process, evaporation of solvent and intervals between additions of solute was within 2.0%.

THEORY

The solubilities (mole fraction) of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG in different solvents are listed in Tables 1 and 2 as well as presented more visually in Figs. 1 and 2. The temperature dependence of *D*-*p*-HPG·*p*-TS and *L*-*p*-HPG solubility in different solvents was de-

[†]To whom correspondence should be addressed.
E-mail: wangshui2000@yahoo.cn

Table 1. Solubility of *D-p*-HPG·*p*-TS in pure solvents

T/K	$10^5 x_1$	T/K	$10^5 x_1$
Ethanol			
289.07	1705	312.98	2145
293.55	1786	318.14	2254
297.97	1858	323.01	2365
303.05	1945	328.27	2484
308.05	2051		
<i>n</i> -Propanol			
288.66	532.7	313.64	847.3
293.56	619.3	318.23	903.9
298.31	678.6	324.53	982.4
303.36	733.5	328.75	1049
308.24	785.4		
<i>n</i> -Butanol			
288.65	262.7	313.03	536.9
293.35	336.6	317.17	572.7
298.18	404.2	323.11	620.1
303.23	454.6	327.66	660.5
307.77	498.8		
Isopropanol			
288.66	201.9	313.33	458.3
293.47	252.7	317.70	507.6
298.05	309.2	323.82	562.5
303.29	363.9	328.22	610.4
308.00	406.5		
Acetic acid			
289.16	19.32	313.04	41.84
293.57	21.83	318.13	48.29
298.16	24.98	323.15	56.19
303.30	30.55	328.25	64.62
308.40	36.12		

Table 2. Solubility of *L-p*-HPG in pure solvents

T/K	$10^5 x_1$	T/K	$10^5 x_1$
Ethanol			
293.19	7.661	318.26	8.630
298.23	8.046	323.06	8.689
303.37	8.244	330.29	8.768
308.23	8.422	334.55	8.768
313.17	8.511		
Ethylene glycol			
293.29	379.8	318.75	482.2
298.43	395.4	323.27	509.9
303.67	413.2	327.86	524.5
308.46	436.5	333.13	540.4
313.35	459.4		
<i>N,N</i> -dimethylformamide			
293.16	2.985	312.95	5.715
298.14	3.467	318.28	6.643
303.17	4.052	323.08	8.001
308.18	4.903	328.21	9.513
Dimethyl sulfoxide			
293.49	92.57	318.51	126.1
298.23	94.76	323.26	141.1
303.19	98.61	328.24	163.5
308.25	106.5	333.04	203.4
313.16	113.2		
Water			
294.05	212.5	313.40	287.2
298.39	227.3	318.17	310.2
303.43	243.9	323.24	333.2
308.25	265.2	328.36	360.0

scribed by the modified Apelblat equation [7]:

$$\ln x_1 = A + \frac{B}{T/K} + C \ln(T/K) \quad (2)$$

Where x_1 is the mole fraction solubility of *D-p*-HPG·*p*-TS (or *L-p*-HPG) in different solvents. T is the absolute temperature and A, B, C are empirical constants. The values of A, B, C obtained with EXCEL and the root-mean-square deviations (RMSDs) are listed in Tables 3 and 4, respectively. The RMSD is defined as follows:

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

Where N is the number of experimental points; $x_{1,i}^{\text{cal}}$ is the solubility calculated from Eq. (2); and $x_{1,i}$ is the experimental value of solubility.

RESULTS AND DISCUSSION

The mole fraction solubilities of *D-p*-HPG·*p*-TS in ethanol, *n*-

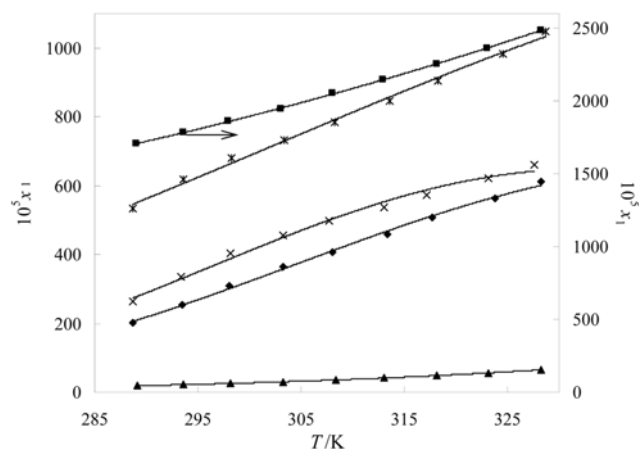


Fig. 1. Mole fraction solubility of *D-p*-HPG·*p*-TS x_1 in different solvents: ■, ethanol; *, *n*-propanol; ×, *n*-butanol; ◆, isopropanol; ▲, acetic acid; and solid lines are from calculations by Eq. (2).

propanol, *n*-butanol, isopropanol and acetic acid are summarized in Table 1. The variation of solubility with temperature is shown in Fig. 1. The mole fraction solubilities of *L-p*-HPG in ethanol, ethylene glycol, *N,N*-dimethylformamide, dimethyl sulfoxide and water

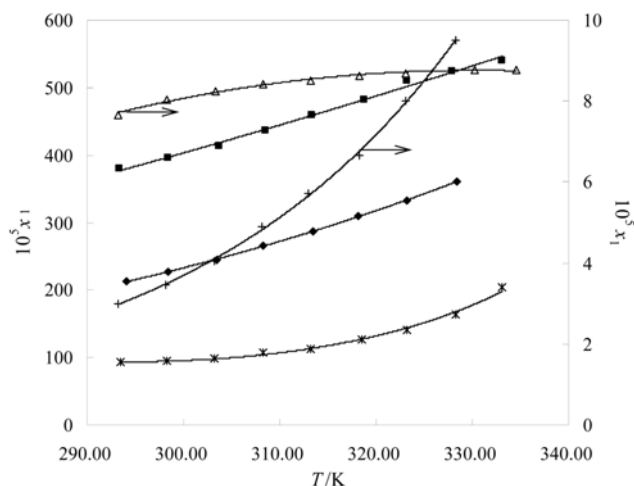


Fig. 2. Mole fraction solubility of *L-p*-HPG x_1 in different solvent: $\blacklozenge$, water; $\triangle$, ethanol; $\blacksquare$, ethylene glycol; $*$, dimethyl sulfoxide; $+$, *N,N*-dimethylformamide; and solid lines are from calculations by Eq. (2).

Table 3. Parameters of Eq. (2) for the solubility of *D-p*-HPG·*p*-TS in pure solvents

Solvent	A	B	C	10^5 RMSD
Ethanol	-41.8872	963.985	6.08505	3.32
<i>n</i> -Propanol	123.179	-7143.79	-18.2943	11.24
<i>n</i> -Butanol	538.807	-26622.2	-79.8701	12.72
Isopropanol	439.175	-22514.1	-64.8458	6.76
Acetic acid	-36.2939	-1252.74	5.65662	0.40

Table 4. Parameters of Eq. (2) for the solubility of *L-p*-HPG in pure solvents

Solvent	A	B	C	10^5 RMSD
Ethanol	106.755	-5640.44	-17.0726	0.04
Ethylene glycol	-8.65569	-627.537	0.917624	4.26
DMF	-192.073	5670.01	28.5718	0.06
Dimethyl sulfoxide	-699.399	30521.0	103.564	3.01
Water	-53.5842	925.730	7.79063	0.89

are summarized in Table 2. The variation of solubility with temperature is also shown in Fig. 2.

From Tables 1, 2 and Figs. 1, 2, it can be seen that the solubility of *D-p*-HPG·*p*-TS and *L-p*-HPG in different solvents studied in this work increases as the temperature increases. The *D-p*-HPG·*p*-TS is a polar solute. According to the principle that a similar substance is more likely to be dissolved by each other, so the solubility of *D-p*-HPG·*p*-TS in ethanol is relatively high and in acetic acid is relatively low. It shows that the polar of solvents have a great effect on the solubility of *D-p*-HPG·*p*-TS in all of solvents used in this article. But the same effect cannot be found between solvents and *L-p*-HPG. It is too complicated to explain the phenomenon shown in Fig. 2 in

terms of a single cause. The phenomenon may be caused by many factors, such as the rule of "like dissolves like," the hydrogen bond, van der Waals force and polarity and so on. The primary reason is still unclear and needs further study. The above explanations are only one measure of many factors affecting the dissolution behavior. Further discussion of the dissolution of an organic solute in an organic solvent is complicated and beyond the scope of this article.

CONCLUSION

New data were measured for the solubility of *D-p*-HPG·*p*-TS and *L-p*-HPG in different solvents. On the basis of the results of the experiment, the following conclusions can be drawn: (1) The solubility of *D-p*-HPG·*p*-TS and *L-p*-HPG in different solvents studied in this work increases as the temperature increases. (2) The correlation equation fits the experimental data well, and the experimental solubility and correlation equation in this work can be used as essential data and model in the research and crystallization. (3) The solubility of *D-p*-HPG·*p*-TS depends on the polarity of the solvents to some degree. The solubility of *L-p*-HPG is affected by many factors.

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NOMENCLATURE

x_1 : mole fraction solubility of solute
 $x_{1,i}$: experimental value of solubility
 $x_{1,i}^{cal}$: calculated value of solubility
 T : absolute temperature
 A, B, C : empirical constants
 m_i : mass of the i
 M_i : molecular weight of i [g/mol]
 RMSD : root-mean-square deviation

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