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Solubility of DL-*p*-hydroxyphenylglycine Sulfate in Binary Acetone + Water Solvent Mixtures

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By use of a laser monitoring observation technique, the solubilities of DL-*p*-hydroxyphenylglycine (DL-*p*-HPG) sulfate in binary acetone + water solvent mixtures were determined by the synthetic method from 303.15 K to 323.00 K, respectively. Results of these measurements were correlated by the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister equation. For the five group data studied, the combined ideal binary solvent (CNIBS)/Redlich−Kister equation was found to provide an accurate mathematical representation of the experimental data.

Introduction

Both enantiomers of DL-*p*-hydroxyphenylglycine (DL-*p*-HPG) are important staring materials for the preparation of various medicines. D-(−)-*p*-Hydroxyphenylglycine (D-*p*-HPG) is useful as an intermediate for the preparation of semisynthetic amoxicillin, ceforperazone, and cefoprozil. And L-(+)-*p*-hydroxyphenylglycine (L-*p*-HPG) is the active ingredient of oxphenicine, a new medicine for the treatment of heart diseases.[1] Since *p*-hydroxyphenylglycine does not exist in nature, it is produced exclusively by synthesis. However, synthesized *p*-hydroxyphenylglycine is obtained in the form of the DL isomer, therefore, to obtain the optically active isomer, the optical resolution of the DL isomer is required. Known methods of resolving DL-*p*-hydroxyphenylglycine may be divided into three groups, i.e., biochemical methods, chemical methods, and physicochemical methods. Furthermore, the physicochemical resolution method is carried out by preferential crystallization of DL-*p*-HPG sulfate. In preferential crystallization, solubilities of DL-*p*-HPG sulfate in solvents are needed. Up to now, few solubilities of DL-*p*-HPG sulfate in solvents have been reported in the literature. In this work, we report solubilities of DL-*p*-HPG sulfate in binary acetone + water solvent mixtures in the temperature range from 303.15 K to 323.00 K at atmospheric pressure.

Experimental Section

DL-*p*-HPG sulfate used during the solubility measurement had a purity of 0.998 (mass fraction), and it was obtained by sulfating the commercial DL-*p*-HPG that was obtained from Shijiazhuang Ruitai Fine Chemical Co. Ltd.. First, 16.7 g of DL-*p*-HPG are dissolved in 50 mL of water at room temperature. Then 6 mL of concentrated sulfuric acid was added to the mixture and stirred under heating. Then, the solution was stirred at room temperature for 2 h. The crystals thus formed were filtered off, washed with water, and dried to give DL-*p*-HPG sulfate. Acetone is an analytical research grade reagent from Shanghai Chemical Reagent Co., while deionized Milli-Q water was used to prepare all solutions. A NETZSCH DSC-204 differential scanning calorimetry instrument was used to measure the melting point and enthalpy of fusion of DL-*p*-HPG sulfate. The amount of the sample was about 6 mg, and the heating rates were 10 K·min^{-1}. The melting point of DL-*p*-HPG sulfate was 344.95 K, with an uncertainty of ±1.05 K. The enthalpy of fusion of solute was 44.88 kJ·mol^{-1}, with an uncertainty of ±1.36 kJ·mol^{-1}.

Solubilities were measured by a synthetic method.[2−4] The apparatus for solubility measurement is the same as described in the literature.[5−6] A laser beam was used to determine the solubility of a solute in binary solvents mixture at a known temperature. The laser monitoring system consisted of a laser generator, a photoelectric transformer, and a light intensity display. The solubility apparatus consisted of a jacketed glass vessel maintained at a desired temperature by water circulated from a water batch with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ±0.05 K of the required temperature. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected with the vessels to prevent the solvents from evaporating. A mercury-in-glass thermometer was inserted into the inner chambers of the vessels for the measurement of the temperature. The thermometer had an uncertainty of +0.05 K.

An analytical balance (type TG332A, China) with an uncertainty of ±0.0001 g was used during the measurement. Predetermined excess amounts of DL-*p*-HPG sulfate and binary solvent mixture of known mass were placed in the jacketed vessel. The contents of the vessel were stirred continuously at an invariable and required temperature, and the solvent was added to the vessel simultaneously. When the last portion of solute just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the solvent mass consumed in the measurement would be recorded. Together with the mass of solute, the solubility would be obtained. The saturated mole fraction solubility of the solute (x_A) in binary acetone + water solvent mixtures can be obtained as follows

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \qquad (1)$$

in which m_A, m_B, and m_C are represented by the masses of solute, acetone, and water. M_A, M_B, and M_C are the

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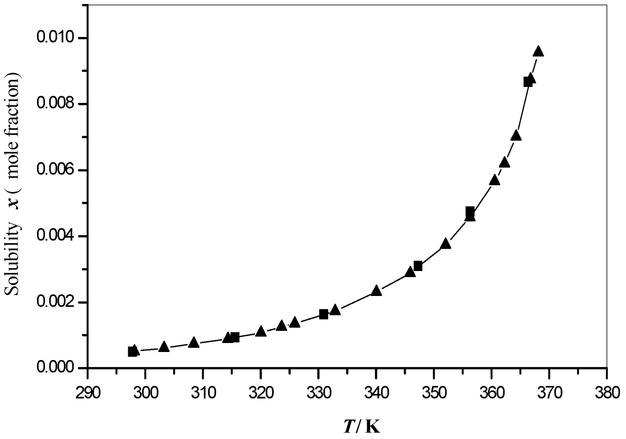

Figure 1. Solubility of benzoic acid in water: ■, solubility values in the literature;[10] ▲, experimental solubility values.

molecular weights of solute, acetone, and water, respectively. To verify the uncertainty of the measurement, one other experiment was done in which the solubility of benzoic acid in water was determined. The solubilities of benzoic acid in water in the literature[7] and this work were plotted in Figure 1. Compared with the literature data, the deviation of the solubility was <1%.

Results and Discussion

Acree and co-workers[8−10] suggested the CNIBS/Redlich−Kister model

$$\ln x_A = x_B^\circ \ln(x_A)_B + x_C^\circ \ln(x_A)_C + x_B^\circ x_C^\circ \sum_{i=0}^{N} S_i (x_B^\circ - x_C^\circ)^i \quad (2)$$

as a possible mathematical representation for describing how experimental isothermal solubility of a crystalline solute dissolved in a binary solvent mixture varies with binary solvent composition in which S_i is the model constant and N can be equal to 0, 1, 2, and 3, respectively. Depending on the values of N, four equations can be obtained from eq 2. x_B° and x_C° refer to the initial mole fraction composition of the binary solvent caculated as if solute A was not present. $(x_A)_i$ is the saturated mole fraction solubility of the solute in pure solvent i.

Substitution of $(1 - x_C^\circ)$ for x_B° in eq 1 with $N = 2$ and subsequent rearrangements result in eq 3

$$\ln x_A = \ln(x_A)_B + [\ln(x_A)_C - \ln(x_A)_B + S_0 + S_1 + S_2]x_C^\circ + [-S_0 + 3S_1 + 5S_2]x_C^{\circ 2} + [-2S_1 - 8S_2]x_C^{\circ 3} + [-4S_2]x_C^{\circ 4} \quad (3)$$

which can be written as eq 4

$$\ln x_A = B_0 + B_1 x_C^\circ + B_2 x_C^{\circ 2} + B_3 x_C^{\circ 3} + B_4 x_C^{\circ 4} \quad (4)$$

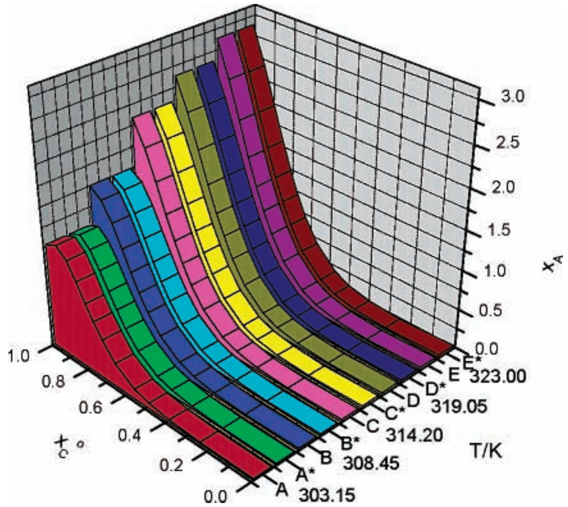

Figure 2. Comparison of the experimental and calculated values of solubilities of DL-*p*-HPG sulfate in binary acetone (B) + water (C) solvent mixtures at the temperature range from 303.15 K to 323.00 K. Curves labeled with A, B, C, D, and E represent experimental solubilities at different temperatures. Curves labeled with A*, B*, C*, D*, and E * denote calculated solubilities at different temperatures.

Table 1. Experimental Solubilities (x_A) of DL-*p*-HPG Sulfate in Binary Acetone (B) + Water (C) Solvent Mixtures at the Temperature Range from 303.15 K to 323.00 K

x_C°	x_A	$x_{A,calc}$	x_C°	x_A	$x_{A,calc}$
	T = 303.15 K			T = 308.45 K	
0.0000	0.0218	0.0218	0.0000	0.0270	0.0270
0.2437	0.0150	0.0149	0.2437	0.0147	0.0147
0.3919	0.0322	0.0323	0.3919	0.0341	0.0343
0.4916	0.0699	0.0698	0.4916	0.0780	0.0776
0.5631	0.1293	0.1294	0.5631	0.1461	0.1460
0.6591	0.2951	0.2974	0.6591	0.3360	0.3352
0.7205	0.4964	0.4868	0.7205	0.5428	0.5444
0.7632	0.6611	0.6614	0.7632	0.7346	0.7368
0.8011	0.8303	0.8394	0.8011	0.9401	0.9358
0.8430	1.0434	1.0423	0.8430	1.1700	1.1726
0.8896	1.2366	1.2375	0.8896	1.4311	1.4282
0.9415	1.3517	1.3528	0.9415	1.6484	1.6516
1.0000	1.2842	1.2822	1.0000	1.7522	1.7509
	T = 314.20 K			T = 319.05 K	
0.0000	0.0337	0.0337	0.0000	0.0354	0.0354
0.2437	0.0156	0.0155	0.2437	0.0163	0.0163
0.3919	0.0370	0.0373	0.3919	0.0405	0.0403
0.4916	0.0868	0.0860	0.4916	0.0940	0.0943
0.5631	0.1624	0.1631	0.5631	0.1794	0.1796
0.6591	0.3774	0.3757	0.6591	0.4138	0.4137
0.7205	0.6096	0.6113	0.7205	0.6707	0.6716
0.7632	0.8276	0.8306	0.7632	0.9150	0.9107
0.8011	1.0658	1.0624	0.8011	1.1609	1.1633
0.8430	1.3446	1.3493	0.8430	1.4742	1.4771
0.8896	1.6890	1.6853	0.8896	1.8538	1.8492
0.9415	2.0435	2.0392	0.9415	2.2546	2.2543
1.0000	2.3387	2.3420	1.0000	2.6328	2.6339
	T = 323.00 K			T = 323.00 K	
0.0000	0.0400	0.0400	0.7632	0.9869	0.9878
0.2437	0.0183	0.0182	0.8011	1.2581	1.2584
0.3919	0.0448	0.0450	0.8430	1.5856	1.5953
0.4916	0.1049	0.1049	0.8896	2.0007	1.9978
0.5631	0.1993	0.1987	0.9415	2.4510	2.4454
0.6591	0.4516	0.4534	1.0000	2.8866	2.8883
0.7205	0.7364	0.7313			

The experimental solubility data x_A correlated with eq 4 and the calculated solubilities $x_{A,calc}$ are listed in Table 1. For comparison with the experimental points, the calculated values of the solubilities of DL-*p*-HPG sulfate in binary acetone (B) + water (C) solvent mixtures at the temperature range from 303.15 K to 323.00 K are presented graphically in Figure 2. The values of the five parameters B_0, B_1, B_2, B_3, and B_4 are listed in Table 2 together with the root-mean-square deviations (RMSDs). The RMSD is defined as

$$\mathrm{RMSD} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_{A,cal} - x_A)^2\right]^{1/2} \quad (5)$$

where n is the number of experimental points.

Table 2. Curve-Fitting Parameters of DL-*p*-HPG Sulfate in Binary Acetone (B) + Water (C) Solvent Mixtures at the Temperature Range from 303.15 K to 323.00 K

T/K	B_0	B_1	B_2	B_3	B_4	RMSD
303.15	−10.7294	−6.9035	24.4994	−9.5376	−3.9880	0.0038
308.45	−10.5163	−9.9616	37.0160	−27.4554	4.5697	0.0020
314.20	−10.2970	−11.7570	43.6806	−36.7971	9.1138	0.0027
319.05	−10.2479	−12.1241	45.8871	−40.2283	10.7741	0.0021
323.00	−10.1262	−12.2868	46.6857	−41.7079	11.5881	0.0055

From Tables 1 and 2 and Figure 2, the calculated solubilities show good agreement with the experimental values, and with the increase of temperature and $x_C°$, the solubilities of DL-*p*-HPG sulfate in binary acetone (B) + water (C) solvent mixtures at the temperature range from 303.15 K to 323.00 K increase. The experimental solubility and correlation equation in this work can be used as essential data and models in the process of the resolution of DL-*p*-HPG sulfate.

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