Solubility of 3,5-Dimethoxybenzoic Acid, 4-Cyanobenzoic Acid, 4-Acetoxybenzoic Acid, 3,5-Diaminobenzoic Acid, and 2,4-Dichlorobenzoic Acid in Ethanol

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The solubility of 3,5-dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in ethanol was measured by both static method and dynamic method over the temperature range from (298.15 to 318.15) K under atmospheric pressure. The experimental data were correlated by the modified Apelblat model. The results show that the solubility of each acid increases with increasing temperature in ethanol, and the data have greater accuracy when using the static method than when using the dynamic method.

Introduction

Nowadays, cocrystal between one acid and the other acid has become a hot topic that has received more and more attention worldwide. Phase diagram can help us to learn more about the preparation of cocrystal. The solubility of each acid is the first step to doing some research on it.

In this work, the solubility of 3,5-dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in both 95.32 % and 99.55 % ethanol over the temperature range from (298.15 to 318.15) K under atmospheric pressure has been experimentally determined using both the static method and the dynamic method.[1−3] The static method refers to the addition of excess mass of solute to the vessel, whereas the dynamic method refers to the continuous addition of solvent until all solute is dissolved.

Experimental Section

Materials. 3,5-Dimethoxybenzoic acid (CAS no. 1132-21-4, mass fraction purity of 98 %), 4-cyanobenzoic acid (CAS no. 619-65-8, mass fraction purity of 99 %), 4-acetoxybenzoic acid (CAS no. 2345-34-8, mass fraction purity of 98 %), 3,5-diaminobenzoic acid (CAS no. 535-87-5, mass fraction purity of 98 %), and 2,4-dichlorobenzoic acid (CAS no. 50-84-0, mass fraction purity of 98 %) were purchased from Sigma-Aldrich. The ethanol (CAS no. 64-17-5, mass fraction purity of 99.55 % and 95.32 %) with no further purification was purchased from Tianjin Ke-wei Chemical Reagent. The purity of ethanol was determined by gas chromatography.

Apparatus and Procedures. The experiments were carried out in a jacketed glass vessel with magnetic stirring. A condenser was connected vertically to the vessel to prevent solvent evaporation. The temperature with uncertainty of ± 0.1 K was controlled by the circulating water through the outer jacket. An analytical balance (Metler Toledo AB204-N, Switzerland) with uncertainty of ± 0.1 mg was used for the mass measurements. A laser monitoring system consisting of a laser generator, a photoelectric convertor, and a light intensity display was used to determine the disappearance of the last crystal in ethanol.

Solubility Measurements. The solubility curves of each acid using the static method were constructed as follows: Slurries of each acid in 15 mL of solvent were made at 298.15 K, 303.15 K, 308.15 K, 313.15 K, and 318.15 K. All slurries were stirred for 3 days to ensure that a state of equilibrium was achieved. After this time, samples of the saturated liquid phase were decanted from the slurries into Petri dishes of known mass and weighed. The samples were then evaporated to dryness and reweighed.

The solubility curves of each acid using the dynamic method were operated as follows: The experiments were carried out in a setup that is similar to that described in the literature.[4,5] Excess mass of each acid was added to a known mass of ethanol. The undissolved solute particles were completely suspended in the vessel by continuous stirring for 1 h at a known temperature. Then, a known mass of additional solvent was added to the vessel through a buret. With the increasing of the amount of solvent, the solute gradually dissolved, and the intensity of the penetrated light increased. When the last portion of the solid solute just disappeared, the penetrated light intensity reached its maximum value. Then, the addition of solvent was stopped, and the mass of the solvent used in the experiment was recorded.

All of the solubility experiments were conducted three times to check the repeatability in this work. The uncertainty in the solubility values is estimated to be 0.5 %.

Together with the mass of solute, the mole fraction solubility could be calculated by the following equation

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

where m_1 and M_1 denote the mass of each acid used in the experiment and its molecule weight and m_2 and M_2 denote the mass of ethanol and its molecule weight.

Results and Discussion

Solubility Data. The solubility of 3,5-dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in both 95.32 % and 99.55 % ethanol over the temperature range from (298.15 to 318.15) K is presented in Tables 1 and 2, where T is the absolute temperature and x_1 and x_1^{calcd} denote the experimental and calculated values of the solubility, respectively.

From Tables 1 and 2, it can be seen that within the temperature range of the measurements, the solubility of 3,5-

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Table 1. Solubility (x_1) of Each Acid (1) in 99.55 % Ethanol (2) from T = (298.15 to 318.15) K Using Both the Static Method and the Dynamic Method

static method			dynamic method		
T/K	$x_1 \cdot 100$	$(x_1 - x_1^{calcd})/x_1$	T/K	$x_1 \cdot 100$	$(x_1 - x_1^{calcd})/x_1$
3,5-Dimethoxybenzoic Acid					
298.15	0.4933	0.02159	298.15	0.5137	0.005606
303.15	0.6075	3.291E-05	303.15	0.6056	−0.04526
308.15	0.7464	−0.01565	308.15	0.7934	0.01769
313.15	0.9341	−0.004560	313.15	0.9776	0.02448
318.15	1.159	0.005548	318.15	1.143	−0.01498
4-Cyanobenzoic Acid					
298.15	2.136	−0.03499	298.15	2.363	0.05199
303.15	2.657	0.005999	303.15	2.518	−0.05861
308.15	3.305	0.05022	308.15	3.075	−0.02624
313.15	3.533	−0.05086	313.15	3.879	0.04154
318.15	4.404	0.007550	318.15	4.311	−0.01134
4-Acetoxybenzoic Acid					
298.15	2.489	0.006979	298.15	2.193	−0.1309
303.15	3.018	0.007535	303.15	3.149	0.04014
308.15	3.584	−0.008050	308.15	3.876	0.05615
313.15	4.315	−0.005391	313.15	4.514	0.02550
318.15	5.217	0.005766	318.15	5.117	−0.02726
3,5-Diaminobenzoic Acid					
298.15	0.3336	0.05516	298.15	0.2112	−0.2626
303.15	0.3419	−0.04340	303.15	0.3737	0.1680
308.15	0.3999	−0.006180	308.15	0.3776	0.04619
313.15	0.4405	−0.02692	313.15	0.3994	−0.03823
318.15	0.5192	0.02358	318.15	0.4716	−0.006510
2,4-Dichlorobenzoic Acid					
298.15	5.812	−0.01301	298.15	4.814	−0.05228
303.15	6.933	0.0006360	303.15	6.785	0.1032
308.15	8.166	0.007935	308.15	7.093	−0.02500
313.15	9.534	0.01254	313.15	8.072	−0.07064
318.15	11.79	0.01565	318.15	10.56	0.03192

Table 2. Solubility (x_1) of Each Acid (1) in 95.32 % Ethanol (2) from T = (298.15 to 318.15) K Using Both the Static Method and Dynamic Method

static method			dynamic method		
T/K	$x_1 \cdot 100$	$(x_1 - x_1^{calcd})/x_1$	T/K	$x_1 \cdot 100$	$(x_1 - x_1^{calcd})/x_1$
3,5-Dimethoxybenzoic Acid					
298.15	0.5125	0.006730	298.15	0.5290	0.01215
303.15	0.6222	0.02885	303.15	0.6367	0.03389
308.15	0.7967	0.003221	308.15	0.8216	0.001890
313.15	1.024	0.03204	313.15	1.055	0.03126
318.15	1.204	0.01367	318.15	1.244	0.01312
4-Cyanobenzoic Acid					
298.15	2.428	0.01293	298.15	2.448	0.004351
303.15	2.764	0.01636	303.15	2.783	0.02370
308.15	3.323	0.01396	308.15	3.335	0.006776
313.15	3.748	0.01493	313.15	3.924	0.02352
318.15	4.425	0.006330	318.15	4.355	0.01271
4-Acetoxybenzoic Acid					
298.15	2.716	0.01718	298.15	2.452	0.09785
303.15	3.372	0.03239	303.15	3.387	0.04578
308.15	3.788	0.01176	308.15	3.991	0.03369
313.15	4.434	0.01054	313.15	4.602	0.005953
318.15	5.244	0.005630	318.15	5.306	0.01692
3,5-Diaminobenzoic Acid					
298.15	0.3503	0.04251	298.15	0.2540	0.1561
303.15	0.3641	0.026450	303.15	0.3822	0.1283
308.15	0.4110	0.01078	308.15	0.3882	0.03131
313.15	0.4488	0.02608	313.15	0.4017	0.05160
318.15	0.5217	0.02377	318.15	0.4743	0.004081
2,4-Dichlorobenzoic Acid					
298.15	6.087	0.01344	298.15	5.025	0.01501
303.15	7.182	0.001732	303.15	7.157	0.1223
308.15	8.297	0.0001903	308.15	7.187	0.06666
313.15	9.743	0.01815	313.15	8.257	0.1141
318.15	10.86	0.01139	318.15	11.73	0.05441

dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in ethanol increases with the temperature increase, but the solubility of 3,5-dimethoxybenzoic acid and 3,5-diaminobenzoic acid is much lower than that of other acids. The solubility data of all acids are lower in 99.55 % ethanol than in 95.32 % ethanol.

Table 3. Parameters of the Modified Apelblat Equation for Each Acid in 99.55 % Ethanol

acid	*A*	*B*	*C*	R^2
Static Method				
3,5-dimethoxybenzoic acid	40.45	−5379	−4.060	0.9989
4-cyanobenzoic acid	−4.654	−2487	2.420	0.9777
4-acetoxybenzoic acid	−26.18	−1737	5.776	0.9993
3,5-diaminobenzoic acid	−8.322	−1580	2.188	0.9634
2,4-dichlorobenzoic acid	3.819	−2942	1.367	0.9944
Dynamic Method				
3,5-dimethoxybenzoic acid	−0.1742	−3316	1.865	0.9932
4-cyanobenzoic acid	−2.476	−2523	2.062	0.9750
4-acetoxybenzoic acid	24.84	−4110	−1.781	0.9661
3,5-diaminobenzoic acid	44.98	−4433	−5.516	0.7923
2,4-dichlorobenzoic acid	−1.902	−2657	2.183	0.9418

Table 4. Parameters of the Modified Apelblat Equation for Each Acid in 95.32 % Ethanol

acid	*A*	*B*	*C*	R^2
Static Method				
3,5-dimethoxybenzoic acid	8.633	−3938	0.6847	0.9947
4-cyanobenzoic acid	2.830	−2525	1.143	0.9960
4-acetoxybenzoic acid	2.125	−2600	1.336	0.9949
3,5-diaminobenzoic acid	−15.66	−1010	3.152	0.9670
2,4-dichlorobenzoic acid	−6.522	−1935	2.603	0.9963
Dynamic Method				
3,5-dimethoxybenzoic acid	10.70	−4055	0.3954	0.9946
4-cyanobenzoic acid	15.64	−3055	−0.7897	0.9933
4-acetoxybenzoic acid	18.52	−3594	−0.9608	0.9775
3,5-diaminobenzoic acid	29.89	−3332	−3.499	0.8199
2,4-dichlorobenzoic acid	33.41	−4571	−2.887	0.9023

The experimental solubility values were fitted with the following equation, namely, the modified Apelblat equation[6−10]

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

where *A*, *B*, and *C* are adjustable coefficients that were determined by an unweighted multivariable least squares method and R^2 is the squared correction coefficient of the regression.

The temperature dependence of solubility of 3,5-dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in ethanol was fitted with eq 2 by the least squares method. The values of parameters *A, B*, *C*, and R^2 are outlined in Tables 3 and 4.

It is seen that the calculated solubility by the modified Apelblat model is in good agreement with the experimental values.

Conclusions

The solubility of 3,5-dimethoxybenzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid, 3,5-diaminobenzoic acid, and 2,4-dichlorobenzoic acid in ethanol increased with the temperature increase.

The calculated solubility data by the modified Apelblat model are in good agreement with the experimental values.

When using the laser to measure the solubility and when the solubility is so high or so low, the repeatability is not very good, and there exist some differences between the static method and the dynamic method. The possible reasons are as follows: (1) When the solubility is relatively high, the photic transmittance is not good, so the data are relatively lower than the data when using the static method (e.g., 2,4-dichlorobenzoic acid). (2) When the solubility is relatively low, there are a few solid particles in the solution, so the laser beam cannot capture all of the particles (e.g., 3,5-diaminobenzoic acid). (3) When the solubility is not so high or so low, there is nearly no difference between the static method and the dynamic method. The biggest deviation of the solubility of 3,5-diaminobenzoic acid is because of not only the lowest solubility in ethanol but also the color of the solution.

The solubility data of all acids are lower in 99.55 % ethanol than in 95.32 % ethanol. The main reason is, maybe, the property of "like dissolves like".

Literature Cited

(1) Roberts, K. L.; Rousseau, R. W.; Teja, A. S. Solubility of Long-Chain *n*-Alkanes in Heptane between 280 and 350 K. *J. Chem. Eng. Data* **1994**, *39*, 793–795.

(2) Jaroslav, N. *Solid−Liquid Equilibria*; Elsevier Scientific Pub. Co.: New York, 1977.

(3) Jiang, Q.; Gao, G.-H.; Yu, Y.-X.; Qin, Y. Solubility of Sodium Dimethyl Isophthalate-5-sulfonate in Water and in Water + Methanol Containing Sodium Sulfate. *J. Chem. Eng. Data* **2000**, *45*, 292–294.

(4) Guo, K.; Yin, Q. X.; Yang, Y. Solubility of Losartan Potassium in Different Pure Solvents from (293.15 to 343.15) K. *J. Chem. Eng. Data* **2008**, *53*, 1467–1469.

(5) Li, D. Q.; Liu, D. Z.; Wang, F. A. Solubility of 4-Methylbenzoic Acid between 288 K and 370 K. *J. Chem. Eng. Data* **2001**, *46*, 234–236.

(6) Walas, S. M. *Phase Equilibrium in Chemical Engineering*; Chinese Petroleum Chemical Engineering Press: Beijing, 1991.

(7) Apelblat, A.; Manzurola, E.; Balal, N. A. The Solubilities of Benzene Polycarboxylic Acids in Water. *J. Chem. Thermodyn.* **2006**, *38*, 565–571.

(8) Williamson, A. T. The Exact Calculation of Heats of Solution from Solubility Data. *Trans. Faraday Soc.* **1944**, *40*, 421–436.

(9) Wang, L. T.; Yin, Q. X.; Zhang, M. J.; Wang, J. K. Solubility of Acephate in Different Solvents from (292.90 to 327.60) K. *J. Chem. Eng. Data* **2007**, *52*, 426–428.

(10) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of Dexamethasone Sodium Phosphate in Different Solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697–1698.

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