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Measurement and Correlation for Solubilities of 16-Dehydropregnenolone Acetate in Different Solvents

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ABSTRACT: The solubilities of 16-dehydropregnenolone acetate in methanol, ethanol, cyclohexane, acetone, and ethyl acetate have been measured from (278.55 to 340.35) K at atmospheric pressure using the synthetic method. The solubilities were determined by a laser monitoring observation technique. The experimental data were correlated with the modified Apelblat equation with the relative deviation less than ± 4.45 %.

INTRODUCTION

16-Dehydropregnenolone acetate (16-DPA, CAS No. 979-02-2) is a versatile intermediate in the synthesis of steroid hormones, for it is an ideal platform for preparation of adrenocorticoids drugs, glucocorticoid drugs, steroidal anti-inflammatory drugs, sexual hormones, and so on. It is a white crystalline powder, soluble in methanol and ethanol, and insoluble in water. Its chemical name is 3β-(acetyloxy)pregna-5,16-dien-20-one. The chemical structure is shown in Figure 1. It is best prepared from diosgenin or from solasodine.[1,2] Marker and co-workers first reported this conversion through acetolysis of diosgenin with acetic anhydride by autoclaving, oxdiation, and eventually acid hydrolysis of the oxidized product to afford the desired 16-DPA.[3]

In view of the central role of 16-DPA in the synthesis of various steroid hormones, to obtain pure 16-DPA, it is very necessary to find a suitable solvent for its separation and subsequent recrystallization. However, the physicochemical information such as solubilities of 16-DPA is not abundant so far. In this study, the solubilities of 16-DPA in methanol (ε = 33.7), ethanol (ε = 24.5), acetone (ε = 20.7), cyclohexane (ε = 2), and ethyl acetate (ε = 6)[4] were measured at temperatures ranging from (278.55 to 340.35) K using a laser monitoring observation technique. This measurement is much faster and more readily available than the analytical method.[5] Also, the solubility data were correlated with the modified Apelblat equation, and the solubilities correlated by model agreed with the experimental data to within ± 4.45 %.

EXPERIMENTAL SECTION

Materials. A white crystalline powder of 16-DPA ($C_{23}H_{32}O_3$, molecular weight 356.51) was obtained from Anyang LiHua Pharmaceutical Co.Ltd., China. It was further purified by recrystallizing from the solution of methanol two times, and its purity was measured by high-performance liquid chromatography (HPLC)[6] (type Agilent 1200, Agilent Technologies) to be 0.990 in mass fraction. The amount of water in 16-DPA was less than 0.002 by the Karl Fischer method. The sodium chloride, methanol, ethanol, cyclohexane, acetone, and ethyl acetate (obtained from Tianjin Kermel Chemical Reagent Co.Ltd., China) used for the experiments were of analytical reagent grade and were used without further treatment. Their mass fraction purities were better than 0.995. The amount of water in all solvents was less than 0.001.

Solubility Measurement. The solubilities of 16-DPA in methanol, ethanol, cyclohexane, acetone, and ethyl acetate were measured by a synthetic method using the apparatus.[7,8] The laser monitoring observation technique was used to determine the dissolution temperature of the solid−liquid mixture. The laser monitoring system consists of a laser generator, a photoelectric transformer, and a light intensity display.

The experiments were carried out in a 50 mL jacketed glass vessel with a magnetic stirrer, and a constant temperature was maintained at the required temperature by circulating water through the outer jacket from a thermoelectric controller. A glass sleeving with a mercury glass microthermometer (uncertainty of ± 0.1 K) was inserted into the inner chamber of the vessel for the measurement of the temperature. To prevent volatilization of solvent, a cold-water condenser tube was also connected with the vessel, and all of the opening connectors were sealed. Predetermined amounts of 16-DPA and the solvent were weighed using an electronic balance (Mettler Toledo AB204-N) with an uncertainty of ± 0.0001 g and transferred into the vessel. The contents of the vessel were heated very slowly at a rate of 1 K·h^{-1} when the system was in equilibrium. In the early stage of the experiment, the laser beam was blocked by the particles of 16-DPA in the solution, so the intensity of the laser beam penetrating the vessel was lower. The intensity increased gradually along with the increase of the amount of 16-DPA dissolved. When the last portion of 16-DPA just disappeared, the intensity of the laser beam penetrating the vessel reached the maximum, and the temperature was recorded. The solubility expressed by mole fraction was calculated as follows:[9]

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

where m_1 and m_2 represent the mass of solute and solvent, respectively. M_1 and M_2 represent the molecular mass of solute and solvent, respectively.

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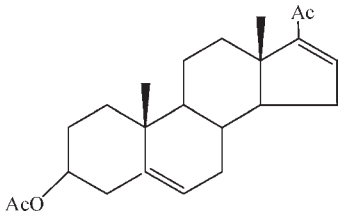

Figure 1. Chemical structure of 16-DPA.

Table 1. Solubilities of Sodium Chloride in Water

	$NaCl + H_2O$			
T/K	293.15	303.15	313.15	323.15
x	0.0998	0.1004	0.1012	0.1022
x (lit.)[10]	0.0999	0.1006	0.1014	0.1024
100 RD	−0.10	−0.20	−0.20	−0.20

Each experiment was repeated three times, and the relative deviation of the uncertainty in the mole fraction solubility was less than 2 %. The standard deviation (SD) between the three experimental values is listed in Table 2. SDs were calculated according to:

$$\mathrm{SD} = \left[\frac{1}{N}\sum_{i=1}^{N}(x_i - \bar{x})^2\right]^{1/2} \quad (2)$$

where N is the number of experimental time, x_i represents the each experimental solubility value, and $\bar{x}$ represents the average value of the three experimental solubility values.

Test of Apparatus. To prove the feasibility and the uncertainty of the measurement, the solubility of NaCl in water was measured and compared with the values reported in the literature.[10] The experimental measurements agreed with the reported values with a mean relative deviation of 0.20 %. The measured values are listed in Table 1.

RESULT AND DISCUSSION

The measured solubilities of 16-DPA in different solvents at different temperatures are presented in Table 2. The temperature dependence of 16-DPA in solvents was described by the modified Apelblat equation:[11,12]

$$\ln x = A + \frac{B}{T} + C \ln T \quad (3)$$

where x is the mole fraction solubility of 16-DPA; T is the absolute temperature; A, B, and C are the model parameters. The adjustable parameters A, B, and C can be obtained from simplex optimization.

$$\text{objective function } F = \min \sum_{i=1}^{N}(x_{ci} - x_i)^2 \quad (4)$$

The solubility curves by eq 3 are shown in Figure 2. The root-mean-square deviation (rmsd) is as follows:

$$\mathrm{rmsd} = \left[\frac{1}{N-1}\sum_{i=1}^{N}(x_{ci} - x_i)^2\right]^{1/2} \quad (5)$$

where N is the number of experimental points, x_{ci} represents the solubilities calculated from eq 3, and x_i represents the experimental

Table 2. Solubilities of 16-DPA in Different Solvents

T/K	$10^3\,x$	10^4 SD	$10^3\,x_c$(Ape)	100 RD
		Methanol		
282.75	0.4019	0.42	0.4133	−2.83
286.85	0.4914	0.38	0.5040	−2.58
291.95	0.6322	0.36	0.6428	−1.67
295.15	0.7787	0.23	0.7472	4.05
299.95	0.9651	0.31	0.9337	3.26
303.85	1.119	0.29	1.116	0.26
309.25	1.417	0.18	1.424	−0.53
312.15	1.596	0.23	1.620	−1.52
315.55	1.846	0.29	1.882	−1.99
318.35	2.149	0.18	2.127	0.98
320.05	2.306	0.21	2.290	0.68
		Ethanol		
285	1.026	0.32	1.018	0.75
289.85	1.28	0.39	1.270	0.84
292.6	1.436	0.29	1.438	−0.09
294.95	1.622	0.23	1.598	1.47
297.65	1.846	0.31	1.803	2.34
300.95	2.101	0.26	2.089	0.57
304.55	2.399	0.18	2.449	−2.10
307.55	2.772	0.27	2.794	−0.80
310.55	3.191	0.25	3.186	0.16
314.15	3.715	0.18	3.725	−0.26
317.55	4.321	0.17	4.314	0.17
321.35	5.027	0.27	5.077	−0.99
324.55	5.825	0.30	5.818	0.12
327.05	6.501	0.17	6.468	0.51
		Cyclohexane		
291.95	2.121	0.43	2.157	−1.74
300.25	3.14	0.47	3.199	−1.86
302.75	3.632	0.38	3.595	1.01
305.75	4.262	0.32	4.131	3.08
309.25	4.903	0.33	4.852	1.05
312.95	5.74	0.28	5.740	−0.01
315.9	6.619	0.21	6.556	0.95
320.15	7.667	0.25	7.923	−3.34
322.95	8.785	0.19	8.966	−2.07
327.85	11.22	0.12	11.11	1.05
332.25	13.49	0.23	13.43	0.44
336.45	16.16	0.17	16.07	0.56
340.35	18.99	0.11	18.94	0.24
		Acetone		
278.55	4.268	0.25	4.114	3.61
281.35	4.796	0.33	4.583	4.45
284.75	5.383	0.31	5.219	3.05
288.65	6.22	0.27	6.053	2.68
291.75	6.782	0.16	6.805	−0.33
293.95	7.309	0.26	7.391	−1.12
296.75	8.002	0.17	8.206	−2.55
299.05	8.746	0.14	8.939	−2.20
301.55	9.547	0.20	9.806	−2.71
304.25	10.492	0.21	10.83	−3.23

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Table 2. Continued

T/K	10^3 x	10^4 SD	10^3 x_c(Ape)	100 RD
306.65	11.94	0.11	11.83	0.94
309.25	13.23	0.14	13.00	1.72
312.55	14.81	0.18	14.66	1.01
315.85	16.54	0.10	16.51	0.20
319.55	18.84	0.21	18.85	−0.05
		Ethyl Acetate		
292.3	13.05	0.33	12.65	3.05
295.83	14.47	0.21	14.13	2.39
298.8	15.82	0.36	15.50	2.03
302.05	17.41	0.18	17.16	1.42
305.45	19.03	0.21	19.08	−0.27
307.95	20.71	0.32	20.63	0.37
310.55	22.49	0.29	22.37	0.53
313.75	24.57	0.18	24.72	−0.60
316.75	26.87	0.14	27.14	−1.02
319.95	29.6	0.21	29.98	−1.27
323.15	32.46	0.28	33.12	−2.02
326.65	36.2	0.25	36.91	−1.97
330.25	40.6	0.19	41.26	−1.63
333.45	47.19	0.23	45.55	3.47

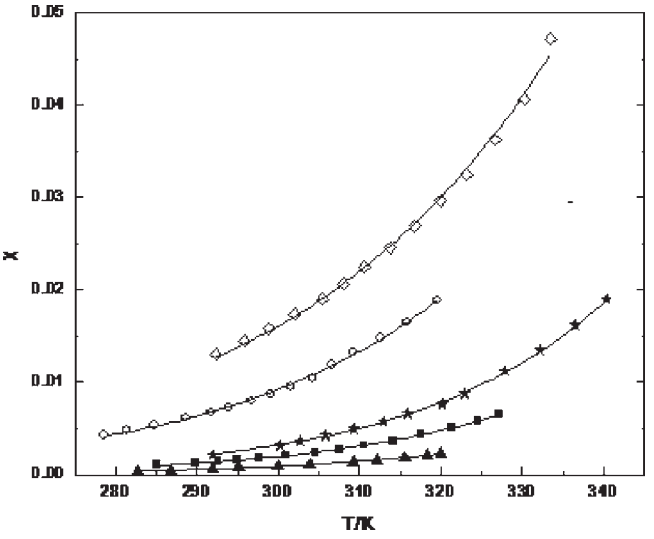

Figure 2. Solubility curves of 16-DPA in different solvents: ▲, methanol; ■, ethanol; ★, cyclohexane; ○, acetone; ◇, ethyl acetate.

solubility values. The model parameters and rmsd are listed in Table 3.

The RDs between the experimental value and the calculated value are also listed in Table 2. RDs were calculated according to:

$$\mathrm{RD} = \frac{x - x_c}{x} \tag{6}$$

The relative average deviations (RADs) by eq 3 are listed in Table 3. The RAD was defined as:

$$\mathrm{RAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \tag{7}$$

From Table 3, it can be found that the calculated solubilities show good agreement with the experimental data, the overall

Table 3. Parameters of 16-DPA in Different Solvents by eq 2

solvent	A	B	C	R^2	10^3 rmsd	10^2 RAD
methanol	−89.15	150.41	14.32	0.9989	0.0225	1.85
ethanol	−121.43	1752.02	19.18	0.9998	0.0271	0.80
cyclohexane	−98.49	557.48	15.93	0.9996	0.114	1.34
acetone	−99.43	1403.76	15.79	0.9983	0.185	1.99
Ethyl acetate	−118.82	2739.35	18.51	0.9966	0.605	1.57

rmsd of 67 data points which were correlated with eq 3 for 16-DPA in solvents being $0.954 \cdot 10^{-3}$. The relative average deviations are 1.85 %, 0.80 %, 1.34 %, 1.99 %, and 1.57 %, respectively. The RDs by eq 2 among all of these values do not exceed ± 4.45 %, which indicates that the modified Apelblat equation is suitable to correlate the solubility data of 16-DPA in methanol, ethanol, cyclohexane, acetone, and ethyl acetate.

The solubility curves of 16-DPA in methanol, ethanol, cyclohexane, acetone, and ethyl acetate are shown in Figure 2. It can be observed from the Figure 2 that the solubility increases with the increase of temperature and follows the order: ethyl acetate > acetone > cyclohexane > ethanol > methanol. We think that it may be because of the intermolecular interaction between solvent and solute molecules. 16-DPA molecules consist of an ester group and a carbonyl group in its molecular structure; therefore, the solubilities of 16-DPA in ethyl acetate and acetone are greatest. On the whole, 16-DPA is a steroid compound, and its polarity is weak; therefore, the solubilities of 16-DPA in methanol and ethanol are low. Cyclohexane is a small polar solvent; however, it does not contain similar group like carbonyl group with 16-DPA, the solubilities of 16-DPA in cyclohexane are between in acetone and in ethanol. These experimental results are consistent with the principle of "like dissolves like".

CONCLUSION

The solubilities of 16-DPA in methanol, ethanol, cyclohexane, acetone, and ethyl acetate have been determined from (278.55 to 340.35) K using a synthetic method. The solubilities in all selected solvents are functions of temperature and increase with the rise of temperature.

The modified Apelblat equation based on solid−liquid phase equilibrium principles is used to correlate the solubility data of 16-DPA in these solvent systems. The RDs among all of these values does not exceed ± 4.45 %, and the solubility calculated by the model shows good agreement with the experimental data.

The experimental solubility and correlation equation in this work can be used as essential data and as a model for the separation and purification process of 16-DPA.

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