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Measurement and Correlation for Solubility of 11α-Hydroxy-16α, 17α-epoxyprogesterone and 16α,17α-Epoxyprogesterone in Solvents

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ABSTRACT: The solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in isopropanol, *n*-propanol, DMSO, dioxane, and 1-butanol have been determined. A solubility model is proposed, and the solubilities calculated by the model show good agreement with experimental data.

INTRODUCTION

11α-Hydroxy-16α,17α-epoxyprogesterone is an important intermediate for synthesis of hormone pharmaceuticals. In industry, it is obtained from 16α,17α-epoxyprogesterone through bioconversion,[1] but because of the limitation of the conversion ratio, the product is a mixture of two compounds. Multiple crystallization processes were needed to obtain the pure product. To select the proper solvent and to design an optimized separation process, it is necessary to know the solubility of two isomorphic steroids, i.e., 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone, in different solvents. However, the fundamental data which have been published for solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone is only limited in methanol, ethanol, acetone, ethyl acetate, and acetic acid.[2,3] The solubility data of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone have not been reported in isopropanol, *n*-propanol, DMSO, and 1-butanol. Therefore, in the present study, the solubility of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in isopropanol, *n*-propanol, DMSO, and 1-butanol as well as the solubility data of 11α-hydroxy-16α,17α-epoxyprogesterone in dioxane were measured using a synthetic method.[4] A solubility model is proposed, and the solubilities that have been calculated by the model agree with the experimental data.

EXPERIMENTAL SECTION

Materials. AR grade reagents, including isopropanol, *n*-propanol, DMSO, dioxane, and 1-butanol, from Shanghai Chemical Reagent Co. Ltd. were prepared, with purities of 0.995 in mass fraction. The 16α,17α-epoxyprogesterone and the 11α-hydroxy-16α,17α-epoxyprogesterone were obtained from Anyang Lihua Pharmaceutical Co. Ltd., China. Their mass fractions determined by HPLC are better than 0.990. They were dried in vacuo at 50 °C for 24 h and stored in a desiccator. No polymorphic transition was found in the treatment of the material. The melting points of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are (246 and 206) °C, respectively.

Solubility Measurements. The solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in isopropanol, n-propanol, DMSO, dioxane, and 1-butanol were measured by a synthetic method described previously.[4] The laser monitoring observation technique was used to determine the dissolution temperature of the solid−liquid mixture of known composition. The uncertainty of temperature was ± 0.02 K. 11α-Hydroxy-16α,17α-epoxyprogesterone, 16α,17α-epoxyprogesterone, and solvents for the solubility measurement were prepared using an electronic balance with an accuracy of ± 0.0001 g. The solubility expressed by mole fraction, was calculated as follows:[5]

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

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

Each experiment was repeated three times, and the deviation of determined solubility data is less than 2 %.

Test of Apparatus. In order to ensure proper operation of the apparatus, the solubility of NaCl in water was measured and compared with the values reported in the literature.[6] The experimental measurements agreed with the reported values with a mean relative deviation of 0.21%. The measured values are listed in Table 1.

Table 1. Solubility of NaCl in Water

T/ K	293.15	313.15	333.15	353.15
S, g/100 g H_2O	36.1	36.7	37.4	38.4
S(lit)[6], g/100 g H_2O	36.0	36.6	37.3	38.4
100 RD	0.28	0.27	0.27	0

RESULTS AND DISCUSSION

The measured solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in solvents at

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Table 2. Solubilities of 11α-Hydroxy-16α,17α-epoxyprogesterone in Isopropanol, *n*-Propanol, DMSO, Dioxane, and 1-Butanol

T / K	$10^3 x$	$10^3 x_c$	100 RD
	Isopropanol		
297.95	0.5418	0.5841	−7.82
300.25	0.6430	0.6589	−2.48
303.45	0.7174	0.7778	−8.42
308.05	0.9518	0.9838	−3.36
312.65	1.264	1.239	1.97
316.35	1.471	1.488	−1.16
320.75	1.903	1.844	3.09
323.85	2.120	2.140	−0.96
327.45	2.616	2.540	2.94
331.95	3.111	3.136	−0.79
335.65	3.680	3.720	−1.09
340.25	4.561	4.588	−0.58
	n-Propanol		
300.50	0.7957	0.8285	−4.13
303.25	0.9328	0.9363	−0.38
306.75	1.085	1.092	−0.66
309.90	1.248	1.253	−0.38
312.70	1.420	1.413	0.47
317.15	1.723	1.708	0.85
321.67	2.075	2.065	0.45
324.85	2.352	2.357	−0.20
327.95	2.696	2.677	0.70
332.65	3.216	3.239	−0.72
336.85	3.825	3.832	−0.19
341.65	4.630	4.633	−0.05
	DMSO		
297.75	4.228	4.503	−6.50
301.30	5.146	5.132	0.27
311.06	7.724	7.297	5.53
315.15	8.435	8.429	0.07
319.05	9.664	9.656	0.09
324.25	11.17	11.54	−3.37
327.15	12.58	12.74	−1.23
329.55	14.12	13.81	2.21
333.67	15.97	15.84	0.78
337.43	17.82	17.93	−0.63
340.25	19.55	19.66	−0.57
344.65	22.78	22.66	0.52
	Dioxane		
298.00	2.926	3.088	−5.54
302.75	3.526	3.561	−0.99
306.39	4.082	3.970	2.74
310.55	4.475	4.494	−0.43
314.75	5.181	5.091	1.74
317.25	5.502	5.482	0.37
320.35	6.045	6.006	0.64
325.05	6.874	6.895	−0.31
328.55	7.647	7.638	0.11
332.05	8.454	8.458	−0.04
335.35	9.315	9.307	0.08
340.15	10.52	10.69	−1.62
	1-Butanol		
298.75	0.5974	0.6366	−6.57
304.45	0.7748	0.8318	−7.36
307.35	0.9350	0.9505	−1.66
310.75	1.126	1.109	1.53
315.67	1.431	1.381	3.49
320.75	1.766	1.723	2.45
324.35	2.046	2.010	1.79
328.55	2.367	2.398	−1.33
331.65	2.681	2.727	−1.72
334.15	3.036	3.021	0.50
336.45	3.336	3.316	0.60
340.15	3.842	3.846	−0.11

different temperatures are presented in Tables 2 and 3, respectively. Their solubility curves are shown in Figures 1 and 2, respectively. The temperature dependence of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in solvents was described by the Apelblat equation:[7]

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

where x is the solubility of the two isomorphic steroids, T is the absolute temperature, and A, B, and C are the model parameters that can be obtained from a simplex optimization.

The object function $F = \min \sum |x_{ci} - x_i|^2$, the values of parameters A, B, and C of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are listed in Tables 4 and 5, respectively.

The calculated solubilities x_c of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are given in Tables 2 and 3, respectively. The root-mean-square deviation is defined as[4]

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

where N is the number of experimental points, x_{ci} represents the solubilities calculated from equations, and x_i represents the experimental solubility values. The model parameters and rmsd of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are listed in Tables 4 and 5, respectively.

The relative deviations between the experimental value and calculated value of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are also listed in Tables 2 and 3, respectively. Relative deviations (RD) are calculated according to

$$\mathrm{RD} = \frac{x - x_c}{x} \quad (4)$$

The relative average deviations (RAD) by equations of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone are listed in Tables 4 and 5, respectively. The RAD

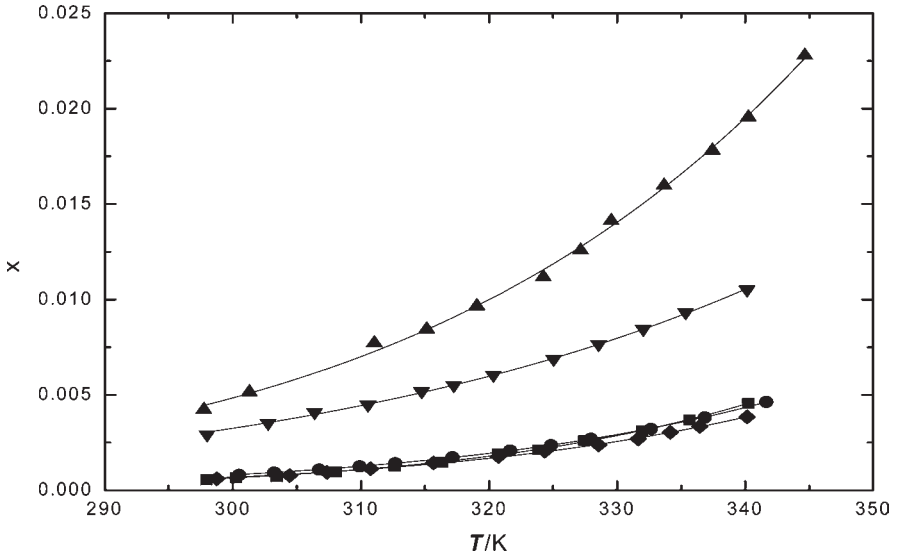

Figure 1. Solubility of 11α-hydroxy-16α,17α-epoxyprogesterone in isopropanol, *n*-propanol, DMSO, dioxane, and 1-butanol. ■, Isopropanol; ●, *n*-propanol; ▲, DMSO; ▼,dioxane; ♦, 1-butanol; —, calculated from eq 2.

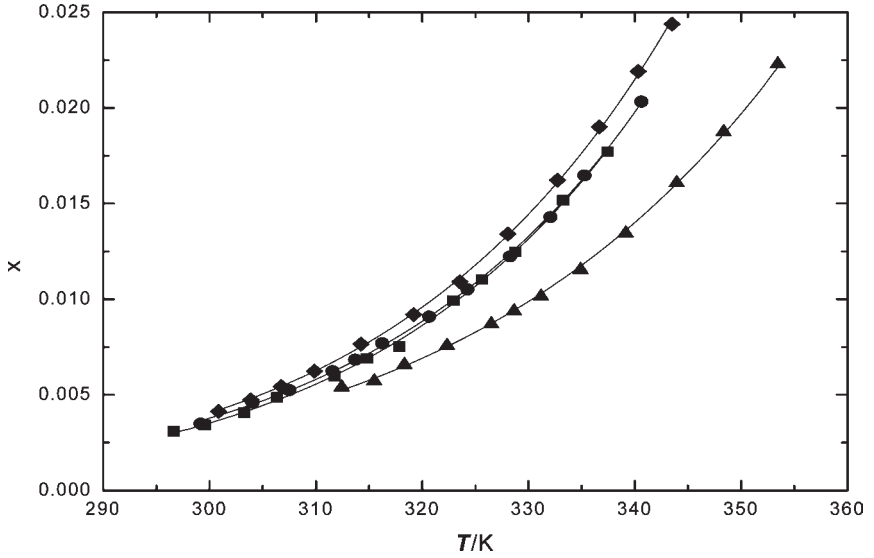

Figure 2. Solubility of 16α,17α-epoxyprogesterone in isopropanol, *n*-propanol, DMSO, and 1-butanol. ■, Isopropanol; ●, *n*-propanol; ▲, DMSO; □, 1-butanol; —, calculated from eq 1.

is defined as

$$\mathrm{RAD} = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_i - x_{ci}}{x_i}\right| \qquad (5)$$

From Tables 4 and 5, it can be found that the calculated solubilities show good agreement with the experimental data, the overall rmsd of measured data points which were correlated with eq 2 for the 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in solvents being $3.9 \cdot 10^{-4}$ and $5.5 \cdot 10^{-4}$, respectively. The relative average deviations of 11α-hydroxy-16α,17α-epoxyprogesterone is 2.9 %, 0.8 %, 1.8 %, 1.2 %, and 2.4 %, respectively; and the relative average deviations of the 16α,17α-epoxyprogesterone is 1.30 %, 1.10 %, 1.16 %, and 0.80 %, respectively, which indicates that the Apelblat equation is fit to correlate the solubility data of the 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in these solvents.

As can be seen from Figure 1, the solubility of 11α-hydroxy-16α,17α-epoxyprogesterone in these solvents follow the order DMSO > dioxane > isopropanol > *n*-propanol >1-butanol, which agrees with the dielectric constant order of the investigated solvents: DMSO (ε = 7.2) > dioxane (ε = 4.8) > isopropanol (ε = 4.3) > *n*-propanol (ε = 4) > 1-butanol (ε = 3.7).[8]

It could be found from Figure 2 that the solubility of 16α,17α-epoxyprogesterone in solvents increased with increasing temperature, but the solubility of 16α,17α-epoxyprogesterone in polar solvent of DMSO (ε = 7.2) is lower than that in weakly polar solvent of 1-butanol (ε = 3.7). The solubility behavior may be

Table 3. Solubilities of 16α,17α-Epoxyprogesterone in Isopropanol, *n*-Propanol, DMSO, and 1-Butanol

T / K	10^2x	10^2x_c	100 RD
	Isopropanol		
296.65	0.3074	0.2972	3.32
299.55	0.3414	0.3414	0.00
303.25	0.4050	0.4064	−0.34
306.35	0.4859	0.4692	3.43
311.75	0.5985	0.5998	−0.22
314.80	0.6892	0.6873	0.27
317.85	0.7524	0.7861	−4.49
322.95	0.9920	0.9803	1.18
325.60	1.101	1.097	0.33
328.75	1.247	1.253	−0.43
333.25	1.517	1.509	0.50
337.45	1.772	1.790	−1.02
	n-Propanol		
299.15	0.3488	0.3679	−5.49
304.05	0.4594	0.4545	1.06
307.50	0.5241	0.5265	−0.46
311.55	0.6229	0.6244	−0.24
313.70	0.6840	0.6830	0.14
316.25	0.7695	0.7592	1.35
320.65	0.9077	0.9093	−0.17
324.25	1.050	1.052	−0.23
328.25	1.222	1.235	−1.09
332.05	1.429	1.436	−0.46
335.25	1.647	1.628	1.11
340.60	2.032	2.004	1.39
	DMSO		
312.45	0.5389	0.5205	3.41
315.50	0.5720	0.5830	−1.93
318.35	0.6567	0.6476	1.38
322.35	0.7559	0.7494	0.86
326.50	0.8702	0.8704	−0.02
328.65	0.9372	0.9399	−0.29
331.20	1.015	1.029	−1.37
334.90	1.154	1.172	−1.59
339.15	1.345	1.359	−1.07
343.95	1.608	1.603	0.28
348.35	1.876	1.862	0.79
353.45	2.229	2.209	0.90
	1-Butanol		
300.85	0.4123	0.4152	−0.70
303.90	0.4726	0.4760	−0.72
306.75	0.5432	0.5401	0.57
309.85	0.6236	0.6188	0.77
314.25	0.7650	0.7487	2.13
319.18	0.9189	0.9240	−0.55
323.55	1.091	1.110	−1.72
328.05	1.340	1.337	0.17
332.75	1.622	1.620	0.08
336.66	1.900	1.896	0.22
340.30	2.191	2.192	−0.03
343.50	2.438	2.486	−1.97

Table 4. Parameters of 11α-Hydroxy-16α,17α-epoxyprogesterone in Isopropanol, *n*-Propanol, DMSO, Dioxane, and 1-Butanol

solvent	*A*	*B*	*C*	R^2	10^3 rmsd	10^2 RAD
isopropanol	−80.97	−701.67	13.32	0.9980	0.04	2.9
n-propanol	−82.32	−60.95	13.22	0.9999	0.01	0.8
DMSO	−69.56	57.68	11.23	0.9985	0.22	1.8
dioxane	−101.68	1994.98	15.66	0.9985	0.08	1.2
1-butanol	−51.50	−1640.59	8.71	0.9978	0.04	2.4

Table 5. Parameters of 16α,17α-Epoxyprogesterone in Isopropanol, *n*-Propanol, DMSO, and 1-Butanol

solvent	*A*	*B*	*C*	R^2	10^3 rmsd	10^2 RAD
isopropanol	−49.26	−1678.93	8.63	0.9987	0.13	1.30
n-propanol	−85.60	260.82	13.88	0.9993	0.13	1.10
DMSO	−78.71	298.29	12.62	0.9991	0.13	1.16
1-butanol	−77.85	−221.16	12.81	0.9998	0.16	0.80

explained by discussing the interaction between the homogeneous solute, the solvent, and the heterogeneous molecules in solution.

CONCLUSION

The solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone in these solvents were measured, and the experimental data were correlated with the Apelblat equation. The overall rmsd deviations are $3.9 \cdot 10^{-4}$ and $5.5 \cdot 10^{-4}$. The results show that the model agrees very well with the experimental data.

The experimental solubility and correlation equation in this work can be used as essential data and model for the separation and purification of 11α-hydroxy-16α,17α-epoxyprogesterone and 16α,17α-epoxyprogesterone.

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