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Solubility of 11*β*-Hydroxypregna-1,4,16-triene-3,20-dione in Different Solvents

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Using a laser monitoring observation technique, the solubilities of 11β-hydroxypregna-1,4,16-triene-3,20-dione in ethanol, acetone, and ethanol + water were determined by the synthetic method. The experimental data can be well correlated by the Apelblat equation (for the ethanol and acetone pure solvent system) or the (CNIBS)/Redlich−Kister equation (for the binary ethanol + water solvent mixtures system).

Introduction

11β-Hydroxypregna-1,4,16-triene-3,20-dione is a white or almost white powdered crystal. It is an important steroid (Figure 1) that serves as an intermediate for many cortical hormone pharmaceuticals, such as dexamethasone. In industrial manufacture, it is synthesized from 16β,17β-epoxy-11β-hydroxypregna-1,4-diene-3,20-dione through desoxygenation, but beacause 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 its solubility in different solvents. Up to now, few solubilities of 11β-hydroxypregna-1,4,16-triene-3,20-dione in solvents have been reported in the literature. In this work, the solubilities of 11β-hydroxypregna-1,4,16-triene-3,20-dione in ethanol, acetone, and ethanol + water were experimentally determined using a laser monitoring observation technique.

Experimental Section

Materials. A white crystalline powder of 11β-hydroxypregna-1,4,16-triene-3,20-dione supported by Tianjin Tianyao Pharmaceutical Co., Ltd., China, with a melting/decomposition point of (546.65 ± 0.5) K, measured with a NETZSCH DSC-204 differential scanning calorimeter, was prepared by recrystallization from an ethanol + water solution. Its purity, determined by HPLC according to BP2000, is higher than 99.0 % (mass fraction). The ethanol and acetone (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade. Distilled deionized water was used.

Apparatus and Procedures. Solubilities were measured by a synthetic method.[1–4] The apparatus for solubility measurement is the same as that described in the literature.[5,6] A laser beam was used to determine the dissolution of the solute in the solvent at a fixed 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 bath with a thermoelectric controller (type 501, China). The jacket temperature could be maintained within ± 0.05 K of the required temperature. A mercury-in-glass thermometer with an uncertainty of ± 0.05 K was inserted into the inner chambers of the vessels for the measurement of the solution temperature. Continuous stirring was achieved with a magnetic stir bar. A condenser was connected with the vessels to prevent the solvents from evaporating. The masses of the solute and solvents were weighed using an analytical balance (Mettler Toledo AB204-N, Switzerland) with an accuracy of ± 0.0001 g.

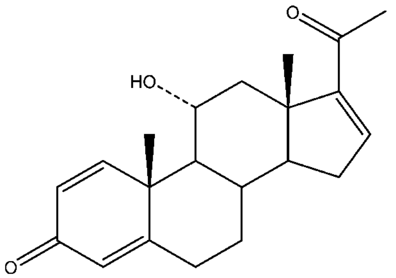

Figure 1. Chemical structure of 11β-hydroxypregna-1,4,16-triene-3,20-dione.

Table 1. Mole Fraction Solubility (x_1) of 11*β*-Hydroxypregna-1,4,16-triene-3,20-dione in Pure Solvent

T/K	$10^2 x_1^{\mathrm{exptl}}$	$10^2 x_1^{\mathrm{calcd}}$	T/K	$10^2 x_1^{\mathrm{exptl}}$	$10^2 x_1^{\mathrm{calcd}}$
			Ethanol		
298.15	0.2131	0.2076	328.15	0.5409	0.5406
303.15	0.2525	0.2454	333.15	0.6251	0.6277
308.15	0.2907	0.2892	338.15	0.7225	0.7270
313.15	0.3352	0.3397	343.15	0.8436	0.8397
318.15	0.3952	0.3977	348.15	0.9701	0.9676
323.15	0.4610	0.4644			
			Acetone		
298.15	0.1924	0.1911	318.15	0.3030	0.3073
303.15	0.2153	0.2162	323.15	0.3507	0.3436
308.15	0.2431	0.2438	328.15	0.3801	0.3831
313.15	0.2745	0.2741			

In the experiments, predetermined excess amounts of solvent and solute of known mass were placed in the jacketed vessel. After being stirred at a fixed temperature for 1 h, an additional solute of known mass (about (2 to 5) mg) was introduced into the vessel. This procedure was repeated until the last addition of solute could not dissolve completely. The interval of addition was 30 min. Then, the total amount of the solute consumed was recorded. The dissolution of the solute was monitored by the laser beam. When the solute dissolved completely, the solution was clear, and the laser intensity penetrated through the solution attained its maximum. When the laser intensity did not exceed 90 % of the maximum, the solute was believed not to be dissolved completely. The amount of solute leading to

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Table 2. Mole Fraction Solubility (x_A) of 11β-Hydroxypregna-1,4,16-triene-3,20-dione in Binary Ethanol (C) + Water (B) Solvent Mixtures

x_C^0	$10^3x_A^{\mathrm{exptl}}$	$10^3x_A^{\mathrm{calcd}}$	x_C^0	$10^3x_A^{\mathrm{exptl}}$	$10^3x_A^{\mathrm{calcd}}$
	T = 298.15 K			T = 308.15 K	
0.0509	0.0069	0.0404	0.0509	0.0165	0.0469
0.0726	0.0215	0.0449	0.0726	0.0365	0.0555
0.0986	0.0312	0.05217	0.0986	0.0649	0.0689
0.1444	0.0567	0.0711	0.1444	0.1208	0.1039
0.2313	0.1400	0.1433	0.2313	0.2348	0.2396
0.2812	0.2282	0.2213	0.2812	0.3962	0.3874
0.3698	0.4905	0.4762	0.3698	0.9020	0.8605
0.4772	1.2005	1.0863	0.4772	1.8513	1.8998
0.6100	2.0514	2.2470	0.6100	3.5500	3.5209
0.7325	3.2614	3.0636	0.7325	4.2192	4.2645
0.7787	3.0929	3.1445	0.7787	4.2865	4.2196
0.8283	3.0890	3.0737	0.8283	3.9683	4.0102
0.8814	2.7648	2.8498	0.8814	3.6797	3.6725
1.0000	2.1308	2.1006	1.0000	2.9068	2.9052
	T = 318.15 K			T = 328.15 K	
0.0509	0.0224	0.0572	0.0509	0.0417	0.0592
0.0726	0.0452	0.0717	0.0726	0.0852	0.0800
0.0986	0.0835	0.0944	0.0987	0.1366	0.1141
0.1444	0.1764	0.1539	0.1453	0.2798	0.2082
0.2313	0.3389	0.3807	0.2315	0.5753	0.5678
0.2812	0.7307	0.6201	0.2812	1.0320	0.9424
0.3698	1.2816	1.3436	0.3698	1.7909	2.0253
0.4772	2.7996	2.7899	0.4772	4.1486	3.9980
0.6100	4.8168	4.8058	0.6100	6.4483	6.4455
0.7325	5.5561	5.6262	0.7325	7.1607	7.3383
0.7787	5.6398	5.5531	0.7787	7.4219	7.2466
0.8283	5.2973	5.2923	0.8283	6.9151	6.9520
0.8814	4.8443	4.8843	0.8814	6.5097	6.4963
1.0000	3.9519	3.9431	1.0000	5.4093	5.4184
	T = 338.15 K			T = 348.15 K	
0.0509	0.0501	0.1058	0.0508	0.0573	0.1822
0.0726	0.0987	0.1404	0.0726	0.1237	0.2393
0.0986	0.1858	0.1949	0.0986	0.2098	0.3274
0.1444	0.3423	0.3380	0.1444	0.4056	0.5509
0.2313	1.0810	0.8624	0.2313	1.7916	1.3200
0.2812	1.3752	1.3790	0.2812	2.0927	2.0356
0.3698	2.4733	2.7918	0.3698	3.4483	3.8864
0.4772	5.5265	5.2461	0.4772	7.2753	6.9224
0.6100	8.1368	8.2583	0.6100	10.3105	10.5596
0.7325	9.3294	9.4791	0.7325	12.0692	12.1641
0.7787	9.7274	9.4327	0.7787	12.6637	12.1930
0.8283	9.0485	9.1321	0.8283	11.7505	11.9198
0.8814	8.5608	8.6100	0.8814	11.2087	11.3611
1.0000	7.2253	7.2139	1.0000	9.7011	9.6511

the laser intensity decrease 10 % from the maximum is less than 1.0 mg. The uncertainty of the solubility values is estimated to be 1.0 %. The same solubility experiment was conducted three times, and the mean values were used to calculate the saturated mole fraction solubility as follows.

For the pure solvent system

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

where m_1 and m_2 represent the masses of the solute and solvent and M_1 and M_2 are the molecular weights of the solute and the solvent, respectively.

For the ethanol + water solvent mixtures system

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \tag{2}$$

where m_A, m_B, and m_C represent the mass of the solute, water, and ethanol, respectively, and M_A, M_B, and M_C are the molecular weights of the solute, water, and ethanol, respectively.

Results and Discussion

The solubility data of 11β-hydroxypregna-1,4,16-triene-3,20-dione in pure ethanol and acetone at different temperatures are presented in Table 1. The temperature dependence of 11β-hydroxypregna-1,4,16-triene-3,20-dione solubility in pure solvents is described by the modified Apelblat equation[7]

$$\ln x_1 = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \tag{3}$$

where x_1 is the mole fraction solubility of 11β-hydroxypregna-1,4,16-triene-3,20-dione; T is the absolute temperature; and A, B, and C are the parameters. The calculated solubility values of 11β-hydroxypregna-1,4,16-triene-3,20-dione are also given in Table 1.

The solubility data of 11β-hydroxypregna-1,4,16-triene-3,20-dione in binary ethanol + water solvent mixtures at the temperature range from (298.15 to 348.15) K are presented in Table 2. The solubility data in binary ethanol + water solvent mixtures are described by the combined nearly ideal binary solvent (CNIBS)/Redlich−Kister model. Acree and co-workers[8,9] suggested the CNIBS/Redlich−Kister model

$$\ln x_A = x_B^0\ln(x_A)_B + x_C^0\ln(x_A)_C + x_B^0x_C^0\sum_{i=1}^{N}S_i(x_B^0 - x_C^0)^i \tag{4}$$

as a possible mathematical representation for describing how the 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 4. x_B^0 and x_C^0 refer to the initial mole fraction composition of the binary solvent calculated as if solute (A) were not present. $(x_A)_i$ is the saturated mole fraction solubility of the solute in pure solvent i.

Substitution of $(1 - x_C^0)$ for x_B^0 in eq 4 with $N = 2$ and subsequent rearrangements result in eq 5

$$\ln x_A = \ln(x_A)_B + [\ln(x_A)_C - \ln(x_A)_B + S_0 + S_1 + S_2]x_C^0 + [-S_0 + 3S_1 + 5S_2]x_C^{0^2} + [-2S_1 - 8S_2]x_C^{0^3} + [-4S_2]x_C^{0^4} \tag{5}$$

which can be written as eq 6

$$\ln x_A = B_0 + B_1x_C^0 + B_2x_C^{0^2} + B_3x_C^{0^3} + B_4x_C^{0^4} \tag{6}$$

The experimental solubility data (x_A^{exptl}) are correlated with eq 6, and the calculated solubilities (x_A^{calcd}) are listed in Table 2.

The solubilities of 11β-hydroxypregna-1,4,16-triene-3,20-dione in pure solvents and solvent mixtures are more visually given in Figure 2 and Figure 3, respectively. The values of the parameters A, B, C and B_0, B_1, B_2, B_3, B_4 for eqs 3 and 6, respectively, are listed in Table 3 and Table 4, respectively, together with the root-mean-square deviations (rmsd). The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}(x_i^{\mathrm{calcd}} - x_i^{\mathrm{exptl}})^2\right]^{\frac{1}{2}} \tag{7}$$

where n is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 3 or eq 6, and x_i^{exptl} represents the experimental solubility values.

From Table 1 and Figure 2, it can be seen that ethanol is a better solvent than acetone. The solubility of 11β-hydroxypregna-1,4,16-triene-3,20-dione in ethanol and acetone increases

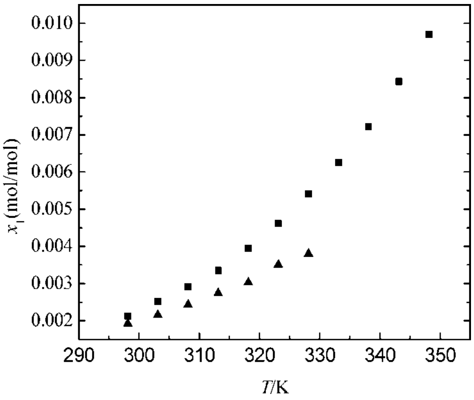

Figure 2. Mole fraction solubility (x_1) of 11β-hydroxypregna-1,4,16-triene-3,20-dione in pure solvent: ▲, acetone; ■, ethanol.

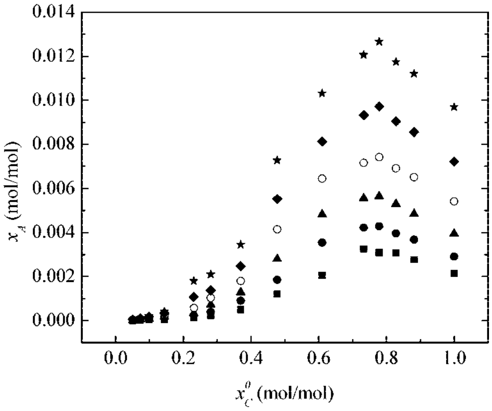

Figure 3. Mole fraction solubility (x_A) of 11β-hydroxypregna-1,4,16-triene-3,20-dione in binary ethanol (C) + water (B) solvent mixtures: ■, T = 298.15 K; ●, T = 308.15 K; ▲, T = 318.15 K; ○, T = 328.15 K; ◆ T = 338.15 K; ★, T = 348.15 K.

Table 3. Curve Fitting Parameters of 11β-Hydroxypregna-1,4,16-triene-3,20-dione in Pure Solvent

solvent	A	B	C	10^2rmsd
ethanol	−50.2179	−594.5668	8.0797	0.0039
acetone	−19.7031	−1292.4069	3.1202	0.0034

with increasing temperature, and the calculated solubility values from eq 3 show good agreement with the experimental values.

From Table 2 and Figure 3, we can draw the following conclusions: (1) At constant temperature, the solubility of 11β-hydroxypregna-1,4,16-triene-3,20-dione in the ethanol + water system has a maximum when $x_C^0 \approx 0.8$. The reason for this phenomenon needs to be studied further. (2) The experimental results can be well correlated with eq 6. Accordingly, the experimental solubility data and the correlation equations in this work can be used as fundamental data and models in the purification process of 11β-hydroxypregna-1,4,16-triene-3,20-dione.

Table 4. Curve Fitting Parameters of 11β-Hydroxypregna-1,4,16-triene-3,20-dione in Binary Ethanol (C) + Water (B) Solvent Mixtures

T/K	B_0	B_1	B_2	B_3	B_4	10^3rmsd
298.15	−10.2880	2.1734	25.4742	−37.9304	14.4053	0.0862
308.15	−10.3016	5.6608	20.0766	−37.5621	16.2850	0.0327
318.15	−10.2812	9.7021	8.1861	−24.8683	11.7254	0.0498
328.15	−10.4661	14.6993	−5.5893	−10.5105	6.6486	0.1054
338.15	−9.8432	13.9069	−6.5823	−7.3789	4.9657	0.1618
348.15	−9.2784	13.6158	−8.7898	−3.1769	2.9886	0.2609

Literature Cited

(1) 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.

(2) 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.

(3) Liu, B. S.; Gong, J. B.; Wang, J. K.; Jia, C. Y. Solubility of Potassium Clavulanate in Ethanol, 1-Propanol, 1-Butanol, 2-Propanol, and 2-Methyl-1-propanol between 273 and 305 K. *J. Chem. Eng. Data* **2005**, *50*, 1684–1686.

(4) Wu, J. H.; Wang, J. K. Solubility of Cefazolin Sodium Pentahydrate in Aqueous 2-Propanol Mixtures. *J. Chem. Eng. Data* **2005**, *50*, 980–982.

(5) Li, D. Q.; Liu, D. Z.; Wang, F. A. Solubilities of Terephthaladehydic, *p*-Toluic, Benzoic, Terephthalic, and Isophthalic Acids in *N*-Methyl-2-pyrrolidone from 295.65 K to 371.35 K. *J. Chem. Eng. Data* **2001**, *46*, 172–173.

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

(7) Apelblat, A.; Manzurola, E. Solubilities of o-acetylsalicylic, 4-aminosalic, 3,5-dinitrosalicylic, and p-toluic acid, and magnesium-DL-aspartate in water from T = (278 to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85–91.

(8) Acree, W. E. Mathematical Representation of Thermodynamic Properties. Part 2. Derivation of the Combined Nearly Ideal Binary Solvent (NIBS)/Redlich-Kister Mathematical Representation from a Two-Body and Three-Body Interactional Mixting Model. *Thermochim. Acta* **1992**, *198*, 71–79.

(9) Acree, W. E., Jr.; McCargar, J. W.; Zvaigzne, A. L.; Teng, L.-L. Mathematical Representation of Thermodynamic Properties. Carbazole Solubilities in Binary Alkane + Dibutyl Ether and Alkane + Tetrahydropyran Solvent Mixture. *Phys. Chem. Liq.* **1991**, *23*, 27–35.

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