Solubility of 16α,17α-Epoxyprogesterone in Six Different Solvents

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The solubilities of 16α,17α-epoxyprogesterone in methanol, ethanol, acetone, ethyl acetate, acetic acid, and 1,4-dioxane were measured using an isothermal method from 283 K to 323 K. A laser monitoring observation technique was used to determine the dissolution of the solid phase in a solid + liquid mixture. The solubility of 16α,17α-epoxyprogesterone in the above solvents increased in the order methanol < ethanol < ethyl acetate < acetone < acetic acid < 1,4-dioxane.

Introduction

Solubility is an important physicochemical property and is particularly useful in a wide variety of phenomena relevant to the chemical and pharmaceutical industries, such as the solvent selection for a reaction and for separation processes. 16α,17α-Epoxyprogesterone is an important steroid (Figure 1) that serves as an intermediate for many hormone pharmaceuticals, such as hydrocortisone and megestrol.[1] It is also converted to another important intermediate, 11α-hydroxy-16α,17α-epoxyprogesterone, through bioconversion for manufacture of more pharmaceuticals.[2,3] But because of the limitation of the conversion ratio, the product is a mixture of two compounds. Multiple crystallization processes are needed to obtain the pure product. To select the proper solvent and to design an optimized separation process, it is necessary to know their solubility in different solvents.[4] The solubility data of 11α-hydroxy-16α,17α-epoxyprogesterone in some solvents has been reported in our previous work,[5] but the solubility of 16α,17α-epoxyprogesterone has not been reported in any solvent. In this work, the solubilities of the title compound in methanol, ethanol, acetone, ethyl acetate, and acetic acid were measured using a synthetic method.[6−9] A laser monitoring observation technique was used to determine the dissolution of the solute at constant temperatures.

Experimental Section

Materials. A crystalline powder of 16α,17α-epoxyprogesterone ($C_{21}H_{28}O_3$, relative molar mass 328.45) was obtained from Tianjin Tianyao Pharmaceutical Co. Ltd., China. Its mass fraction determined by HPLC, is better than 99.0 %. It was dried in vacuo at 50 °C for 24 h and stored in a desiccator. The melting point is (205.5 ± 0.5) °C. No polymorphic transition was found in the treatment of the material. The methanol, ethanol, acetone, ethyl acetate, and acetic acid (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade and without any treatment before use. Their mass fractions are better than 99.5 %.

Apparatus and Procedures. The solubility of 16α,17α-epoxyprogesterone was measured by the isothermal method. A 150 mL jacked vessel was used to determine the solubility. The temperature was controlled to fluctuate within 0.05 K through a thermostated bath (Wanda/sida instrument HC2010, China). The dissolution of the solute was examined by the laser beam penetrating the vessel. To prevent the evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were determined using an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of 0.0001 g.

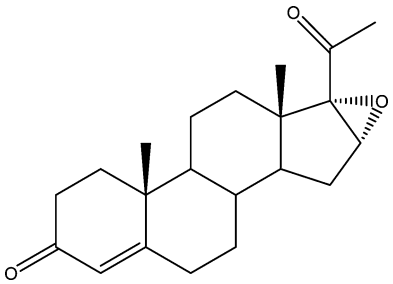

Figure 1. Chemical structure of 16α,17α-epoxyprogesterone.

This method is based on sequentially adding known masses of solute to a stirred solution kept at a fixed temperature. Predetermined amounts of solute and solvent (about 100.0 g) were transferred into the jacketed vessel. The amount of solvent was a small excess. After being stirred at a fixed temperature for 1 h, an additional solute of known mass (about 10 mg) was introduced into the vessel with continuous stirring. This procedure was repeated until the last addition of solute could not dissolve completely within the interval of addition of 30 min. Then, the total amount of the solute added (including the last addition) was used to compute the solubility. The dissolution of the solute was monitored by a 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 the laser intensity decrease 10% from the maximum is less than 1.0 mg. The uncertainty in the solubility values is estimated to be 1.0%. All determinations were repeated two more times, and the mean values were used to calculate the mole fraction solubility.

Results and Discussion

The measured solubility of 16α,17α-epoxyprogesterone in pure methanol, ethanol, acetone, ethyl acetate, acetic acid, and 1,4-dioxane at different temperatures are listed

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Table 1. Mole Fraction Solubility (x_1) of 16α,17α-Epoxyprogesterone in Pure Solvents

T		$x_1 - x_1^{calcd}$	T		$x_1 - x_1^{calcd}$
K	10^2x_1	x_1	K	10^2x_1	x_1
		Ethanol			
286.10	0.134	0.067	308.85	0.340	−0.006
288.15	0.145	0.048	312.65	0.400	0.003
293.35	0.171	−0.023	317.55	0.487	0.004
297.70	0.211	−0.009	322.70	0.596	0.008
303.05	0.258	−0.039	328.45	0.729	−0.004
		Methanol			
282.50	0.100	0.043	307.75	0.290	−0.005
288.70	0.133	0.038	312.80	0.349	−0.021
293.10	0.159	0.016	317.65	0.424	−0.012
297.90	0.192	−0.003	322.45	0.516	0.001
302.95	0.240	0.005	327.60	0.627	0.009
		Acetone			
285.35	0.895	−0.017	310.05	1.838	0.002
288.50	0.985	−0.016	314.15	2.035	−0.003
293.35	1.150	−0.003	317.60	2.225	−0.003
298.95	1.372	0.012	322.35	2.507	−0.003
304.85	1.624	0.018	327.45	2.853	0.001
		Ethyl Acetate			
285.45	0.752	−0.035	308.15	1.422	0.014
288.70	0.819	−0.039	312.75	1.580	0.008
293.85	0.968	−0.008	317.85	1.765	−0.002
297.95	1.102	0.014	322.80	1.985	0.002
302.75	1.257	0.023	328.45	2.230	−0.010
		Acetic Acid			
293.60	1.235	0.020	310.75	2.426	−0.004
295.75	1.357	0.022	313.55	2.708	0.000
298.25	1.479	0.003	316.65	3.022	−0.007
301.30	1.646	−0.016	319.25	3.333	−0.004
303.95	1.817	−0.026	322.15	3.759	0.012
306.85	2.121	0.014	326.05	4.245	−0.003
		1,4-Dioxane			
288.45	2.265	0.002	312.75	4.519	−0.043
293.45	2.658	0.0004	317.25	5.562	0.041
298.25	3.097	0.004	322.50	6.303	0.026
302.75	3.525	−0.003	328.25	7.104	−0.002
307.75	3.996	−0.024	332.55	7.822	−0.013

in Table 1. The solubility in all six solvents increases with temperature. 16α,17α-Epoxyprogesterone is slightly soluble in methanol and ethanol with the equilibrium mole fraction $x \approx 10^{-3}$, whereas the solubility in acetone, ethyl acetate, acetic acid, and 1,4-dioxane are much higher, with $x \approx 10^{-2}$.

The solubility of 16α,17α-epoxyprogesterone also depends on the polarity of the solvent to some degree. The solubility increases with the decrease of the polarity of the solvent. The solubility in strongly polar ethanol and methanol (dielectric constants of 22.4 and 32.6, respectively, at 20 °C)[10] is much lower than that in weakly polar ethyl acetate and 1,4-dioxane (dielectric constants are 6.02 and 2.21, respectively, at 20 °C).[10] The solubility behavior may be explained by discussing the interaction between the homogeneous solute, the solvent, and the heterogeneous molecules in solution.

16α,17α-Epoxyprogesterone has a nonpolar steroid skeleton moiety. The addition of some carbonyl groups makes the whole steroid molecule have some weak polarity. The main interactions in the solute were van der Waals forces. However, both methanol and ethanol are polar solvents; the interaction between the alcohol molecules is mainly the hydrogen bond force, the molecules of methanol and ethanol form a chain by intermolecular hydrogen bonding. The strong polarity of the alcohols also increases the repulsion between the alcohol molecules and the steroid skeleton. The interaction between alcohol molecules and steroid molecules cannot offset the energy loss in destroying the normal interactions in alcohols and steroid crystals. Therefore, the solubility of the title compound in strong polar solvents (alcohols in this study) is not very high. However, the interaction in ethyl acetate and 1,4-dioxane mainly through the van der Waals force, so the solvation of steroid molecules is easier. The acetone is also a polar solvent, but no intermolecular hydrogen bonding exists in the solvent. After the mixing of solute and solvent molecules, the total energy of the whole system does not increase too much, so the solubility in acetone is greater than in ethanol and methanol. Acetic acid is a special solvent, although the single molecule of acetic acid has strong polarity, but in liquid they are mainly in the form of a dimer. Then the apparent polarity of the dimer is weakened, then not only the repulsion between the dimer and the steroid molecule is decreased but also the interaction between two heterogeneous molecules is enhanced. And even after the dissolution of the steroid, the dimer structure may be not destroyed. So the solubility of the steroid in acetic acid is high.

Table 2. Parameters of Equation 1 for 16α,17α-Epoxyprogesterone in Pure Solvents

solvent	λ	h	solvent	λ	h
ethanol	0.2963	13131.0	ethyl acetate	0.1582	13646.3
methanol	0.2371	16028.7	acetic acid	1.6935	2213.72
acetone	0.2760	8797.54	1,4-dioxane	0.9625	2829.67

Buchowski et al.[11] first presented the $\lambda - h$ equation to correlate the solid−liquid-phase equilibrium for the associated system in the following form:

$$\ln[1 + \lambda(1 - x_1)/x_1] = \lambda h/(T^{-1} - T_{t1}^{-1}) \qquad (1)$$

where x_1 is the mole fraction solubility of the solute, T is absolute temperature, and T_{t1} is the melting point temperature of the solute. λ is a dimensionless parameter, indicating the non-ideality of the solution system. Another parameter h is defined as follows:

$$hR = \Delta H_{mt} + H^E/x_1 \qquad (2)$$

where ΔH_{mt} is the enthalpy change upon melting, H^E is the excess enthalpy in the mixing process, and R is the gas constant. The parameters values are usually correlated from the experimental data due to the lack of the fundamental thermodynamic data.

Equation 1 is simple and has only two indeterminate parameters, provided the melting temperature is known, so it attracts much attention.[12−16] Domanska has reported that correlating the solid−liquid equilibrium using the $\lambda - h$ equation is better than using the Wilson equation for some polar systems.[13,14]

In this paper, the experimental results were correlated using eq 1. The melting point of 16α,17α-epoxyprogesterone used in eq 1 is 478.65 K, which was determined by DSC. The values of parameters λ and h for different solvents are listed in Table 2. The relative deviations between the experimental solubility (x_1) and the calculated solubility (x_1^{calcd}) by eq 1 are given in Table 1. It can be seen that goodness of fit is satisfied.

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