Solubility of 11α-Hydroxy-16α,17α-Epoxyprogesterone in Different Solvents between 283 K and 323 K

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The solubilities of 11α-hydroxy-16α,17α-epoxyprogesterone in methanol, ethanol, acetone, ethyl acetate, and acetic acid 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 11α-hydroxy-16α,17α-epoxyprogesterone in the above solvents increased in the order ethanol < methanol < ethyl acetate < acetone < acetic acid. The experimental solubility data was correlated with a semiempirical equation.

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. 11α-Hydroxy-16α,17α-epoxyprogesterone is an important steroid (Figure 1) that serves as an intermediate for many hormone pharmaceuticals.[1] In industry, it is obtained from 16α,17α-epoxy-progesterone through bioconversion,[2] but because of the limitation of the conversion ratio, the product is 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.[3] The solubility data of 11α-hydroxy-16α,17α-epoxyprogesterone has not been reported in any solvents. In this work, the solubilities of the title compound in methanol, ethanol, acetone, ethyl acetate, and acetic acid were measured using a synthetic method.[4−7] A laser monitoring observation technique was used to determine the dissolution of the solute. The isothermal method was used to determine the solubility of the title compound.

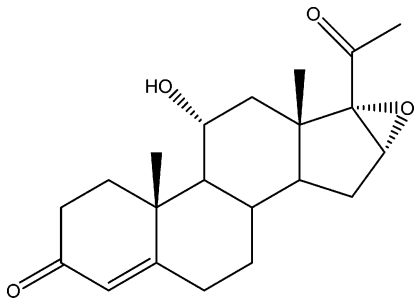

Figure 1. Chemical structure of 11α-hydroxy-16α,17α-epoxyprogesterone.

Experimental Section

Materials. A crystalline powder of 11α-hydroxy-16α,17α-epoxyprogesterone ($C_{21}H_{28}O_4$, molecular weight 344.45) was obtained from Tianjin Tianyao Pharmaceutical Co. Ltd., China, and purified by recrystallization from chloroform by a drowning out method with toluene as the antisolvent. Its purity, determined by HPLC, was better than 99.0 mass %. The melting point is (246.0 ± 0.5) °C. It was 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 methanol, ethanol, acetone, ethyl acetate, and acetic acid (purchased from Tianjin Chemical Reagent Co., China) used for experiments were of analytical reagent grade and dehydrated with molecular sieves before use. Their purities were better than 99.5 mass %. Distilled deionized water was used.

Apparatus and Procedure. The solubility of 11α-hydroxy-16α,17α-epoxyprogesterone was measured by the isothermal method. The solubility was determined using an apparatus similar to that described in the literature[7] and described only briefly here. A 150 mL jacked vessel was used to determine the solubility; the temperature was controlled to be constant (fluctuates 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 weighed using an analytical balance (Metler Toledo AB204-N, Switzerland) with an accuracy of ±0.0001 g.

This method is based on sequentially adding known masses of solute to a stirred solution kept at a fixed temperature. Predetermined amounts of solute (m_1) and solvent (m_2, about 100.0 g) were transferred into the jacketed vessel. The amount of solvent was a small excess. After stirring at a fixed temperature for 1 h, an additional solute of known mass (about 3−5 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 (2400 in this experiment). When the laser intensity did not exceed 2200, the solute was believed not to be dissolved completely. The amount of solute leading to the laser intensity decrease from 2400 to 2200 was less

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Table 1. Mole Fraction Solubility x_1 of 11α-Hydroxy-16α,17α-Epoxyprogesterone in Pure Solvents

T/K	$10^3 x_1^{exptl}$	$\frac{x_1^{exptl} - x_1^{calcd}}{x_1^{exptl}}$	T/K	$10^3 x_1^{exptl}$	$\frac{x_1^{exptl} - x_1^{calcd}}{x_1^{exptl}}$
		Ethanol			
283.38	0.4817	0.0212	308.06	1.106	0.0012
287.57	0.5563	0.0133	308.55	1.133	0.0025
293.56	0.6723	−0.0101	313.30	1.323	0.0156
298.20	0.7946	−0.0043	318.78	1.601	−0.0057
303.60	0.9534	−0.0060	324.60	1.882	−0.0021
		Methanol			
284.57	0.5982	0.0140	308.05	1.268	0.0028
289.10	0.6772	−0.0113	312.57	1.459	−0.0004
293.35	0.7822	−0.0064	318.01	1.713	−0.0110
298.07	0.9242	0.0070	322.56	2.007	0.0055
302.85	1.083	0.0109			
		Acetone			
283.37	1.115	0.0239	303.60	1.898	0.0001
288.25	1.254	0.0026	308.50	2.163	0.0043
292.05	1.356	−0.0263	313.25	2.463	0.0143
293.00	1.421	−0.0053	318.75	2.770	−0.0036
298.35	1.628	−0.0147	323.65	3.108	0.0029
		Ethyl Acetate			
281.77	0.6591	0.0099	303.77	1.193	−0.0047
285.70	0.7348	0.0082	308.39	1.354	−0.0026
290.45	0.8238	−0.0100	312.60	1.540	0.0131
294.55	0.9128	−0.0209	317.67	1.741	0.0017
298.53	1.0366	−0.0028	322.37	1.957	−0.0050
		Acetic Acid			
293.40	5.377	0.0175	307.90	7.670	0.0061
295.90	5.636	0.0029	311.80	8.420	−0.0088
298.67	5.974	−0.0083	314.85	9.242	0.0015
301.67	6.510	0.0012	318.50	10.34	0.0132
304.60	6.989	−0.0038	322.90	11.55	0.0008

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 x_1 based on the following equation

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

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.

To testify to the confidence of the method of measurement, a repeat determination at two selected temperature values for each solvent through the gravimetrical method was performed. The experimental process and method are the same as in the literature.[8,9] A solution with an excess of solute was allowed to reach equilibrium isothermally under agitation. Samples of the clear solution with the mass determined (m_0) were evaporated in a vacuum oven (at 50 °C) to dryness, and the mass of the dry residue (m_1) was determined. Each determination was repeated two more times. The uncertainty in the solubility values is estimated to be 0.5%. The mole fraction solubility of the solute x_1 can be calculated as follows

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + (m_0 - m_1)/M_2} \quad (2)$$

where m_0 and m_1 represent the masses of the sampled solution and the residue after dryness, respectively. M_1 and M_2 are the same as in eq 1.

The results obtained by this method are shown in Table 3 together with the results predicted by eq 6. The solubility

Table 2. Parameters of Equation 6 for 11α-Hydroxy-16α,17α-Epoxyprogesterone in Pure Solvents

solvent	a	b	c	$10^5\sigma_x$
ethanol	−51.743	−618.50	8.193	1.141
methanol	−87.363	1436.84	14.4723	1.072
acetone	−24.706	−1214.25	3.9258	2.247
ethyl acetate	−77.714	1083.89	11.794	1.154
acetic acid	−178.90	6036.99	28.101	7.928

Table 3. Comparison of Solubility Determined by the Gravimetric Method and Predicted by Equation 6 at Two Temperature Levels

	T/K	$10^3 x_1^{exptl}$	$10^3 x_1^{pred}$	$\frac{x_1^{exptl} - x_1^{pred}}{x_1^{exptl}}$
ethanol	294.57	0.6936	0.7036	−0.0144
	324.65	1.8917	1.8957	0.0012
methanol	290.95	0.7182	0.7278	−0.0133
	322.56	1.9947	1.9956	−0.0005
ethyl acetate	293.20	0.9091	0.8979	0.0123
	322.40	1.9695	1.9683	0.0006
acetone	288.60	1.2722	1.2639	0.0065
	323.65	3.1352	3.1261	−0.0059
acetic acid	298.25	5.8608	5.9601	−0.0169
	323.20	11.5503	11.6374	−0.0075

values determined by the gravimetrical method are consistent with those predicted by eq 6. The two arbitrarily selected points can be used as a reference for the feasibility of the method used for the studied system in this article.

Results and Discussion

The measured solubility of 11α-hydroxy-16α,17α-epoxyprogesterone in pure methanol, ethanol, acetone, ethyl acetate, and acetic acid at different temperatures are listed in Table 1. The solubility in all five solvents increases with temperature. 11α-Hydroxy-16α,17α-epoxyprogesterone is slightly soluble in methanol, ethanol, acetone, and ethyl acetate with the equilibrium mole fraction x at 10^{-4} to 10^{-3}, whereas the solubility in acetic acid is much higher, with the equilibrium mole fraction x at 10^{-3} to 10^{-2}.

Because the solvents selected in this study were typical and representative in alcohol, ketone, ester, and carboxylic acid solvents, the solubility results also indicate that the alcohol, ketone, and ester are not good solvents for the title compound. Because the throughput is a very important target for intermediate production, relatively high solubility of the compound is needed. Therefore, the alcohol, ketone, and ester are not suitable for the title compound, but they may be used as cosolvents to help the recovery of the product. From the results, we also found that the solubility of title compound depends on the polarity of the solvent to some degree. The solubility in strongly polar ethanol and methanol (dielectric constants of 22.4 and 32.6,[10] respectively, 20 °C) is lower than in weakly polar ethyl acetate and acetic acid (dielectric constants of 6.02 and 6.2,[10] respectively, 20 °C). The solubility in acetic acid is obviously higher than that in other solvents. The solubility behavior may be explained by discussing the interaction between the homogeneous solute, the solvent, and the heterogeneous molecules in solution.

The process of dissolution is determined by a combination of enthalpy and entropy factors. The chemical structure and the polarity also influence the dissolution of solute. If the interactions in the solute and solvent are similar, then the energy of interaction between homogeneous and heterogeneous molecules is nearly identical, which facilitates the solubility of solute. If the chemical structures of the solute and solvent molecules differ greatly

in polarity, then swelling and dissolution do not happen. This is reflected in the empirical rule that "like dissolves like".

The title compound has a nonpolar steroid skeleton moiety. The addition of carbonyl and hydroxyl 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 strong polarity of the alcohols also increases the repulsion between the alcohol molecules and the steroid skeleton, so the solubility of the title compound in strong polar solvents—alcohols in this study—was not very high. The insolubility of the title compound in water is another proof of the repulsion between polar water molecules and nonpolar steroid skeletons (i.e., the hydrophobic effect). However, the interaction in acetone and ethyl acetate is mainly through the van der Waals force; the solvation of steroid molecules is easier. No association through hydrogen bond interactions in the acetone and ethyl acetate solvents also improves the dissolution of the steroid.

However, the effects of specific interactions between some functional groups can change the compatibility of the system. For acetic acid as the solvent, the hydrogen atom of the hydroxyl was protonated because of the conjugative effect, so the acetic acid molecules can form more stable hydrogen bonds with the oxygen atoms in the steroid molecules. In addition, the weak polar acetic acid molecules do not cause much repulsion with the steroid skeleton, so the solution system has lower energy and is more stable. The solubility of the steroid in acetic acid is much higher than in the other four solvents. The probability of forming a molecular complex in solution may be another explanation for the relative high solubility in acetic acid, but it should be pointed out that the above explanations were only one measure of many factors affecting the solubility behavior. Further discussion of the dissolution of an organic solute in an organic solvent is complicated and beyond the scope of this article.

The temperature dependence of the solubility of 11α-hydroxy-16α,17α-epoxyprogesterone in pure solvents can be correlated by a semiempirical equation deduced from the solid−liquid phase equilibrium. Here, we denote the solute as component 1 and the solvent as component 2. At equilibrium, we can write

$$f_1^{\mathrm{S}} = x_1 \gamma_1 f_1^* \tag{3}$$

where f_1^{S} is the fugacity of component 1 in the pure solid phase, $x_1$is the mole fraction solubility of pure 1 in the solvent, γ_1 is the liquid-phase activity coefficient of 1, and f_1^* is the standard-state fugacity to which γ_1 refers. According to Prausnitz et al.,[11] it is convenient to define the standard-state fugacity as that of the pure subcooled liquid at the temperature of the solution. Then a general solubility equation can be obtained

$$\ln x_1\gamma_1 = \ln\left(\frac{f_1^{\mathrm{S}}}{f_1^*}\right) = \frac{\Delta h_1^{\mathrm{fus}}}{R}\left(\frac{1}{T_{\mathrm{t1}}} - \frac{1}{T}\right) - \frac{\Delta C_{p1}}{R}\left(\ln\frac{T_{\mathrm{t1}}}{T} - \frac{T_{\mathrm{t1}}}{T} + 1\right) \tag{4}$$

where $\Delta h_1^{\mathrm{fus}}$ is the enthalpy change upon the melting of the solute at its triple-point temperature, T_{t1} and ΔC_{p1} is the difference between the heat capacities of the solute in the liquid and solid phases. The right-hand side of eq 4 therefore contains the physical properties of the solute only, and the influence of the solvent on the solute solubility can be accounted for by activity coefficient γ_1 on the left-hand side of the equation.

The activity coefficient in eq 4 can be replaced by its value at infinite dilution because the systems under study are dilute. A simple relationship can be adopted for the infinite-dilution activity coefficient as follows:

$$\ln \gamma_1^{\infty} = A + \frac{B}{T} \tag{5}$$

Then the following simple expression for the solubility in such systems can be obtained:

$$\ln x = a + \frac{b}{T} + c \ln T \tag{6}$$

with

$$a = \frac{\Delta h_1^{\mathrm{fus}}}{RT_{\mathrm{t1}}} - \frac{\Delta C_{p1}}{R}(1 + \ln T_{\mathrm{t1}}) - A \tag{7}$$

$$b = -\frac{\Delta h_1^{\mathrm{fus}}}{R} + \frac{\Delta C_{p1}}{R} T_{\mathrm{t1}} - B \tag{8}$$

$$c = \frac{\Delta C_{p1}}{R} \tag{9}$$

The experimental results were correlated using eq 6. The values of parameters a, b, and c and the root-mean-square deviations (rmsd's) are listed in Table 2. The rmsd of the mole fraction is defined as follows

$$\sigma_x = \left\{\sum_{i=1}^{N} \frac{(x_i^{\mathrm{exptl}} - x_i^{\mathrm{calcd}})^2}{N-2}\right\}^{1/2} \tag{10}$$

where N is the number of experimental points, x_i^{calcd} represents the solubilities calculated from eq 1, and x_i^{exptl} represents the experimental solubility values. It can be seen that the predicted solubilities show good agreement with the experimental values.

From Table 2, it can be seen that the values of parameter c in all five solvents are relative small, which represents the relatively small ΔC_{p1}. This is true for many compounds under most conditions, so the last term of eq 4 was neglected in many cases. For a given compound, the right-hand side of eqs 7 and 8 are constant except for A and B, which vary with the solvent. Therefore, the values of a and b reflect the variations in the solution activity coefficient and provide an indication of the effect of solution nonidealities on the solubility of the solute. From the parameters listed in Table 2, we can draw the conclusion that the activity coefficient parameters in acetic acid are much higher than in the other four solvents. The solubility of the steroid in acetic acid is much more of a departure from the ideal solubility than that for the other four solvents. This may be another explanation for the high solubility in acetic acid.

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