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Solubility of Atractylenolide III in Hexane, Ethyl Acetate, Diethyl Ether, and Ethanol from (283.2 to 323.2) K

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The solubility of atractylenolide III in hexane, ethyl acetate, diethyl ether, and ethanol solutions was measured over the temperature range of (283.2 to 323.2) K. The solubility of atractylenolide III in hexane is the smallest, and the solubility in ethyl acetate is the largest. The solubility data were correlated with the Apelblat equation.

Introduction

Atractylenolide III (CAS Registry No. 73030-71-4), a naturally occurring sesquiterpene, is isolated from *Atractylodes macrocephala,* which has been widely used in traditional Chinese medicine for energy and stomach complaints, treatment of dyspepsia and anorexia, anti-inflammation, anticancer, and increasing of assimilation.[1−3] The chemical name of this compound is naphtha[2,3-*b*]furan-2(4*H*)-one. Figure 1 shows the chemical structure of atractylenolide III. The biomedicinal effects of atractylenolide III, which have been experimentally or clinically demonstrated, include anti-inflammation, anticancer, and increasing of assimilation.[4,5]

For pharmaceutical use, atractylenolide III is usually extracted from the powdered *Atractylodes macrocephala* using solvents, such as hexane, ethyl acetate, or mixtures of those, followed by purification and crystallization from the solution. Therefore, it is important to have thermodynamic data for the solubility of atractylenolide III in different solvents.

In the present study, the solubility of atractylenolide III in hexane, ethyl acetate, diethyl ether, and ethanol over the temperature range of (283.2 to 323.2) K was measured, where the concentrations were determined by HPLC.

Experimental Section

Reagents and Apparatus. Atractylenolide III ($C_{15}H_{20}O_3$, molecular weight 248.31) was isolated from *Atractylodes macrocephala* growing in the Zhejiang province (Xinchang) previously by the authors' laboratory, and the chemical structure was confirmed by GC-MS and ^{1}H NMR.[6] Its mass fraction purity determined by HPLC was higher than 0.99.

Other reagents used such as hexane, ethyl acetate, diethyl ether, and ethanol were of analytical purity grade.

Sample Preparation. The solubility of atractylenolide III was measured using the method described in the literature[7] and described briefly here. A glass-stoppered flask with a Telfon-coated magnetic stirrer was used to prepare saturated solutions (5.0 mL) of atractylenolide III with excess solid solute in organic solvents. A condenser was introduced to reduce the solvent's evaporation. The flask was placed in a constant temperature bath with circulating water. The temperature of the circulating water was controlled by a thermostat within ± 0.1 K, and a mercury in-glass thermometer (uncertainty of 0.05 K) was used for the measurement of the temperature in the flask. The solution was constantly stirred using a magnetic stirrer. To know when the equilibrium conditions can be reached, the same samples were agitated by a magnetic stirrer for (1, 1.5, 2, and 2.5) h, and for each time, samples were taken and analyzed. Similar values were obtained showing that the equilibrium was achieved for 2 h. Furthermore, many samples in different solvent have been taken to prove no change. Then the stirring was carried out for 2 h at constant working temperature. After attaining equilibrium, the stirrer was turned off to let the solution settle for 2 h. Then the upper portion was taken using a glass syringe filter with a slightly higher temperature than the solution temperature to avoid any precipitation and poured into a 100 mL volumetric flask. To prepare the solutions for HPLC analysis, they were diluted to 100 mL with methanol of HPLC purity grade.

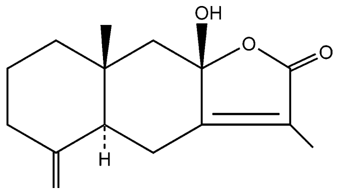

Figure 1. Molecular structure of atractylenolide III.

Chromatographic Conditions. The solubility was determined using a Shimadzu model HPLC system (Shimadzu Corporation, Japan). The analysis was performed on a Diamonsil C18 reversed-phase column (250 mm × 4.6 mm, 5 μm). The optimum separation of HPLC was carried out with a mobile phase composed of methanol and water in a volume ratio of 70:30 at a flow rate of 1.0 mL·min^{-1}. The calibration curve was prepared by using the standard solutions in the concentration range of (0 to 10) 10^{-3} mol·L^{-1} at 30 °C. The injected volumes of sample were 20 μL. The solubility of each sample was determined by averaging over three samples, and the mean values were used to calculate the mole fraction solubility *x* based on the following equation

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

where m_1 and m_2 represent the masses of the solute and solvent and M_1 and M_2 represent the molecular weights of the solute and the solvent, respectively. The measurement deviation in the solubility analysis is less than ± 1.0 %. The detector wavelength

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Table 1. Solubility x of Atractylenolide III in Hexane (1), Diethyl Ether (2), Ethyl Acetate (3), and Ethanol (4)

	hexane		diethyl ether		ethyl acetate		ethanol	
T/K	10^3x^{exptl}	$(x^{\text{exptl}} - x^{\text{calcd}})/x^{\text{exptl}}$	10^3x^{exptl}	$(x^{\text{exptl}} - x^{\text{calcd}})/x^{\text{exptl}}$	10^3x^{exptl}	$(x^{\text{exptl}} - x^{\text{calcd}})/x^{\text{exptl}}$	10^3x^{exptl}	$(x^{\text{exptl}} - x^{\text{calcd}})/x^{\text{exptl}}$
283.2	0.0244	−0.1195	2.770	0.0004	22.43	0.0506	4.426	−0.0006
288.2	0.0412	0.0271	3.749	−0.0375	22.85	0.0064	5.475	−0.0035
293.2	0.0639	0.0983	5.624	0.0470	23.62	−0.0148	6.733	0.0026
298.2	0.0832	0.0236	7.383	0.0174	24.20	−0.0363	8.085	−0.0011
303.2	0.1128	0.0032	9.387	−0.0283	25.21	−0.0320	9.657	0.0031
308.2	0.1534	0.0029			26.10	−0.0258	11.31	0.0000
313.2	0.2017	−0.0149			27.11	−0.0087	13.09	−0.0032
318.2	0.2716	0.0070			28.15	0.0147	15.07	−0.0006
323.2	0.3362	−0.0416			29.28	0.0456	17.13	−0.0003

was set at 220 nm. All chromatograph procedures were performed at 30 °C.

Results and Discussion

The solubility data of atractylenolide III in hexane, ethyl acetate, diethyl ether, and ethanol were presented in Table 1. From Table 1, it can be found that the solubility in the four solvents increases with increasing temperature. The solubility of atractylenolide III is the highest in ethyl acetate and is the lowest in hexane. Therefore, ethyl acetate is a good solvent for extracting atractylenolide III from *Atractylodes macrocephala*, and ethanol is a good solvent for crystallization due to a sharp decrease of solubility with decreasing temperature.

The temperature dependence of solubility in pure solvents can be described by a general solubility equation as follows

$$\ln x = \ln\left(\frac{f^{\text{s}}}{f^*}\right) = \frac{\Delta h^{\text{fus}}}{R}\left(\frac{1}{T_{\text{t}}} - \frac{1}{T}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_{\text{t}}}{T} - \frac{T_{\text{t}}}{T} + 1\right) - \ln\gamma \tag{2}$$

where f^{s} is the fugacity of the solute in the pure solid phase; γ is the liquid-phase activity coefficient of the solute; f^* is the standard-state fugacity to which γ refers; Δh^{fus} is the enthalpy change upon the melting of the solute at its triple-point temperature, T_{t}; ΔC_p is the difference between the heat capacities of the solute in the liquid and solid phases; and T is the absolute temperature.

The activity coefficient in eq 2 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

$$\ln\gamma^{\infty} = A + \frac{B}{T} \tag{3}$$

where A and B are empirical constants, which contains the influence of the solvent on the solute solubility.

Then, eq 2 can also be written as the modified Apelblat equation[7−10]

$$\ln x = a + b/T + c\ln T \tag{4}$$

where a, b, and c are semiempirical constants as follows[11]

$$a = \frac{\Delta h^{\text{fus}}}{RT_{\text{t}}} - \frac{\Delta C_p}{R}(1 + \ln T_{\text{t}}) - A \tag{5}$$

$$b = -\frac{\Delta h^{\text{fus}}}{R} + \frac{\Delta C_p}{R}T_{\text{t}} - B \tag{6}$$

$$c = \frac{\Delta C_p}{R} \tag{7}$$

Table 2. Parameters of Equation 2 for Atractylenolide III in the Solvents

solvent	a	b	c	10^3rmsd	100 AAD
hexane	180.812	−13524.3	−25.427	0.005	3.75
diethyl ether	182.911	−12810.7	−25.427	0.188	2.61
ethyl acetate	169.055	−8308.952	−25.427	0.768	2.61
ethanol	176.221	−10783.1	−25.427	0.196	0.17

From eq 7, parameter c is the physical properties of the solute only due to the same ΔC_p, so the value of c in different solvents is the same. Therefore, when eq 4 is used to correlate the experimental solubilities, the c value of different solvents has the same value. The optimized values of parameters a, b, and c, the root-mean-square deviations (rmsd), and the average absolute deviation (AAD) are listed in Table 2. The deviation between the experimental solubility and the calculated solubility of atractylenolide III are also given in Table 1. The rmsd and AAD are defined as

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}(x_i^{\text{exptl}} - x_i^{\text{calcd}})^2}{N}} \tag{8}$$

$$\text{AAD} = \frac{1}{N}\sum_{i=1}^{N}|(x_i^{\text{exptl}} - x_i^{\text{calcd}})/x_i^{\text{exptl}}| \tag{9}$$

where N is the number of experimental points; x_i^{calcd} represents the solubility calculated; and x_i^{exptl} represents the experimental solubility values.

From eqs 5 and 6, it can be seen that for a given solute the values of a and b vary with the solvents. Both of them 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, it can be seen that the activity coefficient parameters in ethyl acetate are much higher than in the other three solvents. The solubility of atractylenolide III in ethyl acetate is much more of a departure from the ideal solubility than that for the other three solvents. This may be the explanation for the high solubility in ethyl acetate.

From the values of rmsd and AAD listed in Table 2 and the values of $(x_1^{\text{exptl}} - x_1^{\text{calcd}})/x_1^{\text{exptl}}$ in Table 1, it is seen that the calculated solubilities show good agreement with the experimental values, even though the deviation of the solubility of atractylenolide III in hexane at 283.2 K is large, that is, mainly due to the smallest solubilities. Therefore, the modified Apelblat equation can be used to correlate the solubility data of atractylenolide III in the four solvents.

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