β-Sitosterol Solubility in Selected Organic Solvents

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β-Sitosterol solubility in five solvents including methanol, ethanol, acetone, ethyl acetate, and *n*-hexane has been determined experimentally by a static analytical method at various temperatures ranging from (278.15 to 333.15) K. The compositions of *β*-sitosterol in saturated solution were analyzed by UV spectrometry. The solubility of *β*-sitosterol is represented by a best-fit equation for each solvent.

Introduction

The chemical structure of *β*-sitosterol ($C_{29}H_{50}O$, CAS Registry No. 83-46-5, IUPAC name: 17-(5-ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[a]phenanthren-3-ol) is shown in Figure 1. *β*-Sitosterol is a substance derived from plants.[1] It is used to derive a variety of medicines.[2,3] The bioavailability of drugs is well-known to be related to the crystal morphology of the steroid. It has been also found that the crystal habit is in turn affected by the solvent and by supersaturation.[4,5] To determine these values, solubility data of *β*-sitosterol are essential.

So far, the available information on the solubility of *β*-sitosterol in different solvents is quite scarce. The solubility of *β*-sitosterol in *n*-alkanols from methanol to decanol at 310 K was reported by Flynn et al.[6] Solubilities of *β*-sitosterol at various temperatures ranging from (303 to 318) K in methanol, ethanol, acetone, and in some aqueous mixtures of these solvents were presented by Bar et al.[7] The aims of this study are to obtain solubility data of *β*-sitosterol in several polar and nonpolar organic solvents at various temperatures and to possibly correlate them by best-fit equations.

Experimental Section

Chemicals. *β*-Sitosterol, supplied by Sigma-Aldrich with purity of 98 %, was further recrystallized from acetone and kept in a desiccator with dry silica gel. Analytically pure grade methanol, ethanol, acetone, ethyl acetate, and *n*-hexane were purchased from Tianjin Kewei Chemical Reagents. All above solvents were refluxed over freshly activated CaO for 2 h and then fractionally distilled. Liquids were stored over freshly activated molecular sieves of type 4A. Analysis, using the Karl Fischer technique, showed that the water mass fraction in each of the solvents was less than 100 $w = 0.02$.

Apparatus and Procedures. The solubility was measured by a static analytical method at atmospheric pressure that was described in our previous work.[8] The experiments were carried out in a magnetically stirred, jacketed glass vessel (50 cm^3). A constant temperature was maintained by circulating water through the outer jacket from a thermostatically controlled water bath. The actual value of the temperature in the vessel was measured by a microthermometer (uncertainty of ± 0.1 K). Solutions with an excess of solids were magnetically agitated for 12 h (a much longer time had no effect on the solubilities). After the attainment of saturation equilibrium, a sample of the upper portion was withdrawn, appropriately diluted, and analyzed by a UV spectrometer (Shimadzu UV-160A). The *β*-sitosterol solubility in the solvents was determined by a literature spectrophotometric procedure.[9,10] One drop of concentrated sulfuric acid was added to the diluted sample, and the color of the solution changed from colorless to red, then to dark green. After holding for 10 min, the absorbance of the sample was measured at the maximum absorption wavelength of 650 nm, and the content of *β*-sitosterol in the sample was determined according to the standard curve. All of the solubility experiments were conducted three times to check the reproducibility, and an average value is given. The standard deviations of solubility data were all less than 5.0 %.

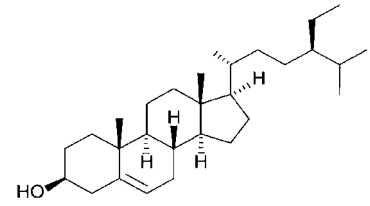

Figure 1. Chemical structure of *β*-sitosterol.

Table 1. Solubility of *β*-Sitosterol in Methanol, Ethanol, Acetone, Ethyl Acetate, and *n*-Hexane

T	$10^3\ x_1$				
K	methanol	ethanol	acetone	ethyl acetate	*n*-hexane
278.15	0.1359	1.302	2.735	4.475	0.8616
283.15	0.1674	1.579	3.218	5.302	1.032
288.15	0.2047	1.902	3.786	6.268	1.233
293.15	0.2481	2.289	4.460	7.379	1.466
298.15	0.2986	2.744	5.247	8.719	1.735
303.15	0.3572	3.281	6.163	10.25	2.046
308.15	0.4269	3.886	7.245	12.02	2.400
313.15	0.5092	4.601	8.519	14.01	2.803
318.15	0.6058	5.397	10.01	16.32	3.257
323.15	0.7204	6.325	11.76	19.00	3.774
328.15	0.8548	7.377	13.86		4.359
333.15		8.565			5.005

Results and Discussion

The measured solubilities for *β*-sitosterol in methanol, ethanol, acetone, ethyl acetate, and *n*-hexane are shown in Table 1. The solubility of *β*-sitosterol in different solvents is in the following order: methanol < *n*-hexane < ethanol < acetone < ethyl acetate.

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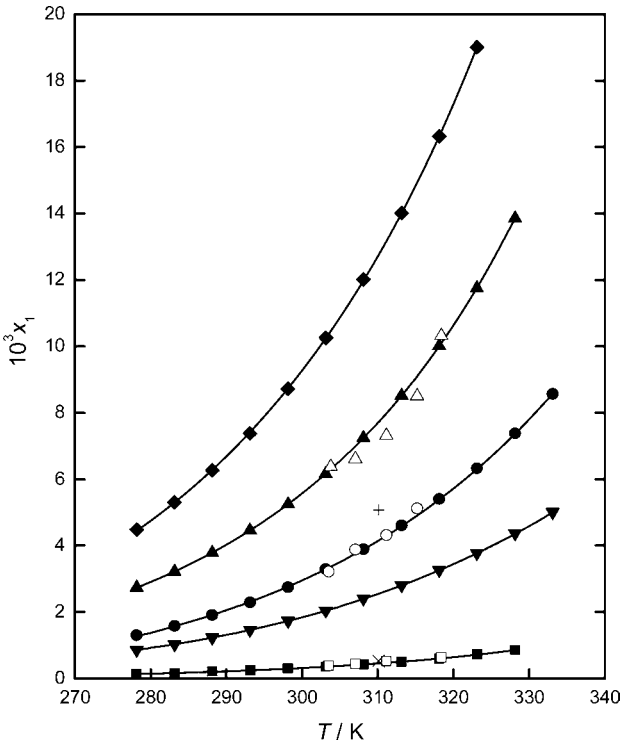

Figure 2. Solubility of β-sitosterol in various solvents: ■, methanol; ×, data for methanol from literature;[6] □, data for methanol from literature;[7] ▼, *n*-hexane; ●, ethanol; +, data for ethanol from literature;[6] ○, data for ethanol from literature;[7] ▲, acetone; △, data for acetone from literature;[7] ◆, ethyl acetate. The line is the best fit of the experimental data calculated with the modified Apelblat equation.

From the results, we found that the solubility of β-sitosterol decreased with the increasing polarity of the solvents to some degree. The solubilities in strongly polar methanol (relative permittivity of 32.6[11] at 293.15 K) were lower than in ethanol and acetone (relative permittivity of 22.4 and 21.4,[11] respectively, at 293.15 K). The solubility in ethyl acetate was obviously higher than those in other solvents which may be due to the low polarity of ethyl acetate with a relative permittivity of 6.02[11] at 293.15 K.

However, the polarity of the solvent is not an absolute measure to determine the solubility. In addition to polarity, the chemical structure also influences the dissolution of the solute, which is reflected in the empirical rule "like dissolves like". The solubility of β-sitosterol in a nonpolar solvent, such as *n*-hexane, is quite smaller than in ethanol, acetone, and ethyl acetate. The behavior may be explained by discussing the interaction between the solute and the solvent molecules in solution. If the interactions in the solute and solvent are similar, then the dissolution is easier. β-Sitosterol has a hydrophobic steroid skeleton moiety, and the addition of a hydroxyl group makes the whole steroid molecule weakly polar. The main interaction in ethyl acetate and acetone may be through the van der Waals force, which may improve the dissolution of the title compound. On the other hand, the hydrogen bond is another interaction in the solute. If the solvent has a hydrogen bond, the solvation of the title compound is easier. From the results, we found that the solubilities in ethanol were higher than that in *n*-hexane. Methanol is highly polar which may increase the repulsion between the solvent molecule and the steroid skeleton, which leads to a low solubility of β-sitosterol.

Table 2. Regression Curve Coefficients in Equation 1 for β-Sitosterol Solubility in Methanol, Ethanol, Acetone, Ethyl Acetate, and *n*-Hexane

solvent	*a*	*b*	*c*	10^3 rmsd
methanol	−49.43	−974.99	7.82	0.0125
ethanol	−25.55	−1809.34	4.51	0.119
acetone	−123.33	2799.31	19.08	0.163
ethyl acetate	−65.64	263.02	10.53	0.220
n-hexane	−19.97	−1902.80	3.51	0.008

From the results, we can see that the solubilities of β-sitosterol in solvents increase as the temperature increases.

The relationship between temperature and solubility of β-sitosterol is correlated with the modified Apelblat equation[12]

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c \ln(T/\mathrm{K}) \qquad (1)$$

where x_1 and T are the mole fraction of the solute and absolute temperature, respectively, and a, b, and c are empirical constants.

The experimental data of mole fraction solubility in Table 1 were correlated with eq 1 and plotted as shown in Figure 2, whereas the parameter values of a, b, and c and the root-mean-square deviation (rmsd) are given in Table 2. The rmsd is defined as

$$\mathrm{rmsd} = \left[\frac{1}{N}\sum_{j}^{N}(x_{1,j} - x_{1,j}^{\mathrm{calcd}})^2\right]^{1/2} \qquad (2)$$

where N is the number of experimental points, $x_{1,j}^{\mathrm{calcd}}$ is the solubility calculated from eq 1, and $x_{1,j}$ is the experimental value of solubility. As the correlation results indicate, the Apelblat expression describes satisfactorily the solubility dependence on temperature, with the given temperature range.

Conclusion

The solubilities of β-sitosterol in methanol, ethanol, acetone, ethyl acetate, and *n*-hexane have been measured respectively at temperatures ranging from (278.15 to 333.15) K by a static analytical method. The solubility of β-sitosterol in solvents increases as the temperature increases, and at constant temperature, the solubility decreases with the increasing polarity of the solvent, except for *n*-hexane. The solubility in *n*-hexane is in between that of methanol and ethanol. The modified Apelblat equation was employed to correlate the experimental data with good agreement.

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