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Solubility of Vitamin D_3 in Six Organic Solvents at Temperatures from (248.2 to 273.2) K

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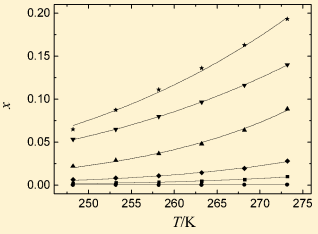
Supporting Information

ABSTRACT: The solubility of Vitamin D_3 in methanol, ethanenitrile, ethyl ethanoate, ethanol, propan-2-one, and propan-1-ol was measured in the temperature range from (248.2 to 273.2) K by the static equilibrium method. The results revealed that the solubility of Vitamin D_3 in solvents was observed to decrease in the order of propan-1-ol > ethanol > ethyl ethanoate > propan-2-one > methanol > ethanenitrile. The minimum mole fraction solubility of $7.61 \cdot 10^{-5}$ was obtained in ethanenitrile at 248.2 K, while the maximum mole fraction solubility up to 0.193 was obtained in propan-1-ol at 273.2 K. Moreover, the solubility data were correlated with the simplified thermodynamic equation and the modified Apelblat equation, and the calculated solubility for all solvents above was in good agreement with the experimental data in the temperature range of interest.



INTRODUCTION

Vitamin D_3 ($C_{27}H_{44}O$; molecular weight 384.64; melting point (357 to 359) K; IUPAC name (3*β*,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol; CAS Registry Number 67-97-0; Figure 1), also known as cholecalciferol, is a kind of fat-soluble

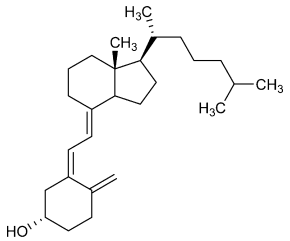


Figure 1. Structure of Vitamin D_3.

secosteroid which is indispensible in promoting normal growth of animals and human beings.[1,2] Vitamin D_3 is inactive itself, but it is of great significance after hydroxylation in the liver to form 25-hydroxyvitamin D_3, which plays an important role in coordinating calcium and phosphorus homeostasis, as well as the healthy mineralization, growth, and remodeling of bone.[3−5]

Vitamin D_3 naturally exists in fish and a few other foods and can be produced in the skin of vertebrates after the exposure of cholesterol to ultraviolet light. In industry, Vitamin D_3 could be prepared by a photoconversion process. The precursor of Vitamin D_3, 7-dehydrocholesterol, is photolyzed by ultraviolet light at wavelengths between (270 and 300) nm and then produces previtamin D_3, which spontaneously isomerizes to Vitamin D_3.[6] However, the product of photoconversion process is neither pure nor crystalline Vitamin D_3. It is a mixture of unreacted 7-dehydrocholesterol, tachysterol, lumisterol, and other byproducts, which have a similar structure with Vitamin D_3. Consequently, Vitamin D_3 is necessary to be isolated and further purified. According to previous study, ethyl ethanoate, propan-2-one, methanol, and other conventional solvents were commonly chosen for crystallization, and low temperatures were especially considered in the crystallization process. However, to the best of our knowledge, the solubility of Vitamin D_3 in these organic solvents was not systematically demonstrated. It is well-known that solubility is of great importance to the optimization and scale-up of crystallization process as well as chromatographic separation. Therefore, in this work, the solubility of Vitamin D_3 in methanol, ethanenitrile, ethyl ethanoate, ethanol, propan-2-one, and propan-1-ol was measured at temperatures of (248.2, 253.2, 258.2, 263.2, 268.2, and 273.2) K, and the results were fit with the simplified thermodynamic equation and the modified Apelblat equation.

EXPERIMENTAL SECTION

Materials. Vitamin D_3 was kindly supplied by Zhejiang Garden Biochemical High-tech Co., Ltd., China, and the mass fraction purity of Vitamin D_3 examined by HPLC was over 0.980. Ethanenitrile was of chromatographic grade and purchased from Tianjin Institute of Chemical Reagents, while the other organic solvents were of analytical grade and obtained from Sinopharm Chemical Reagent Co., Ltd. The mass purity of all above solvents was more than 0.990. Details are shown in Table 1.

Apparatus and Procedure. The solubility of Vitamin D_3 was measured at atmospheric pressure by a static equilibrium method similar to our previous work.[7,8] The solvent and an excess amount of Vitamin D_3 were added to a magnetically

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Table 1. Source and Purity of the Substances

chemical name	source	mass fraction purity
Vitamin D_3	Zhejiang Garden Biochemical High-tech Co., Ltd., China	0.980
methanol	Sinopharm Chemical Reagent Co., Ltd., China	0.995
ethanenitrile	Tianjin Institute of Chemical Reagents, China	0.999
ethyl ethanoate	Sinopharm Chemical Reagent Co., Ltd., China	0.995
ethanol	Sinopharm Chemical Reagent Co., Ltd., China	0.997
propan-2-one	Sinopharm Chemical Reagent Co., Ltd., China	0.995
propan-1-ol	Sinopharm Chemical Reagent Co., Ltd., China	0.990

stirred, jacketed glass vessel (about 50 cm^3). The temperature was maintained constant by circulating fluid through the outer jacket from a thermostatic controlled bath, and the actual temperature was measured by a thermometer (uncertainty of ± 0.1 K) inside the vessel. The mixture was continuously stirred for 6 h, which had been tested to be enough for the system to reach solid−liquid equilibrium and then held still for 2 h. The upper saturated solution of 1 mL was sampled and transferred to a flask and then appropriately diluted to desired volume. The whole process was carried out under an inert atmosphere in a shaded place to avoid deterioration of Vitamin D_3. All determinations were repeated three times to check the reproducibility, and then an average value was given.

Sample Analysis. The concentration of Vitamin D_3 in sampled solutions was monitored by high-performance liquid chromatography (HPLC). HPLC system consists of a Waters 1525 pump, a Waters 717 plus autosampler, and a Waters 2487 UV detector. The chromatographic analysis was performed on a Waters C_{18} reverse phase column (250 mm × 4.6 mm, 5 μm) with a mobile phase of pure methanol at a flow rate of $6{\cdot}10^{-5}$ $m^3{\cdot}h^{-1}$ and detective wavelength at 254 nm.

RESULTS AND DISCUSSION

To validate the method of solubility measurement, the solubility of cholesterol in ethanol at the temperature range of (293.2 to 313.2) K was determined. Cholesterol was chosen for validation test because it has a similar structure with Vitamin D_3 and its solubility data had already been reported. All determinations were repeated three times to check the reproducibility and uncertainty. It was found that the average relative deviation of the experimental results at any given temperature was less than 0.5 %. Besides, it seems that the solubility shown in Figure 2 was in good agreement with that reported in the literature.[8] The deviations of solubility data were 1.3 %, 1.0 %, 2.4 %, 0.7 %, and 1.9 % at (293.2, 298.2, 303.2, 308.2, and 313.2) K, respectively. Accordingly, solubility data obtained by this method are repeatable and credible.

The solubility values of Vitamin D_3 in the studied solvents at temperatures varied from (248.2 to 273.2) K are presented in Table 2 and plotted in Figure 3. At a given temperature, the solubility of Vitamin D_3 was in the following order: propan-1-ol > ethanol > ethyl ethanoate > propan-2-one > methanol > ethanenitrile. As seen from Figure 3, the solubility of Vitamin D_3 in ethanenitrile was far less than that in other selected solvents, whereas propan-1-ol had maximum solubility among solvents used in this work. It is well-known that the polarity of

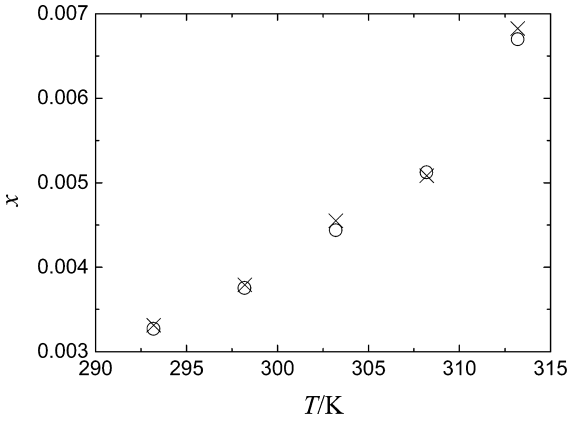

Figure 2. Mole fraction solubility (x) of cholesterol in ethanol at different temperatures (T): ○, this work; ×, literature value.

the tested solvents decreases in the following order: ethanenitrile > methanol > ethanol > propan-1-ol > propan-2-one > ethyl ethanoate.[9] So the relatively low solubility of ethanenitrile and methanol indicated that the solubility of Vitamin D_3 decreased with increasing polarity of the solvents to some extent. According to the empirical rule "like dissolves like", the dissolution is easier if the solute and solvent have similar polarity. Correspondingly, the high polarity of ethanenitrile may increase the repulsion between the solvent molecule and the hydrophobic skeleton of Vitamin D_3, which leads to a low solubility.

However, the polarity of the solvent is not the only factor that determines the solubility; the hydrogen bond interaction between the solute and solvent can also improve the solubility of the titled compound. This can be confirmed from the solubility of Vitamin D_3 in propan-1-ol and ethanol, which were prone to form hydrogen bonds with Vitamin D_3. It can be obviously seen from Table 2 that the solvation of Vitamin D_3 with propan-1-ol and ethanol was easier than ethyl ethanoate and propan-2-one, even though the latter have a lower polarity. As well, hydrogen bond interaction might also account for relatively high solubility of Vitamin D_3 in both ethyl ethanoate and propan-2-one, when compared with that in methanol and ethanenitrile. It is because that ethyl ethanoate and propan-2-one typically act as hydrogen bond acceptor (hydrogen bond basicity 0.45 and 0.43 for ethyl ethanoate and propan-2-one,[10] respectively).

For alcohols studied in this work, the result revealed that the solubility of Vitamin D_3 increased with the increase of alkanol alkyl chain length. Due to the amphiphilicity of these alcohols and Vitamin D_3, both van der Waals interaction and hydrogen bond interaction took place and resulted in relatively high solubility of Vitamin D_3 in propanol as well as ethanol.

The solubility of Vitamin D_3 as a function of temperature could be fit by the simplified thermodynamic equation[11−13] and the modified Apelblat equation,[14−18] which are shown as follows, respectively:

$$\ln(x) = A' + \frac{B'}{T/\mathrm{K}} \tag{1}$$

$$\ln(x) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \tag{2}$$

where x is the mole fraction solubility of Vitamin D_3; T is the absolute temperature (K); and A, B, C, A', and B' are

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Table 2. Mole Fraction Solubility x of Vitamin D_3 in Six Organic Solvents[a]

T/K	$10^2\ x$	$10^2(x - x^{cal b})/x$	$10^2(x - x^{calc})/x$	T/K	$10^2\ x$	$10^2(x - x^{cal b})/x$	$10^2(x - x^{calc})/x$
	Methanol				Ethanol		
248.2	0.2045 ± 0.0004	0.62	−0.01	248.2	5.318 ± 0.005	0.01	0.00
253.2	0.2489 ± 0.0022	−11.29	−0.52	253.2	6.457 ± 0.084	−1.20	−0.86
258.2	0.3374 ± 0.0051	−10.55	3.74	258.2	7.960 ± 0.064	−0.08	0.35
263.2	0.4595 ± 0.0069	−8.06	3.09	263.2	9.650 ± 0.145	0.12	0.43
268.2	0.6254 ± 0.0050	−4.57	−2.68	268.2	11.57 ± 0.03	−0.03	−0.05
273.2	0.9930 ± 0.0109	14.12	2.29	273.2	13.99 ± 0.24	1.27	0.73
	Ethanenitrile				Propan-2-one		
248.2	0.007613 ± 0.000069	5.48	0.25	248.2	0.6110 ± 0.0079	3.76	−1.00
253.2	0.009253 ± 0.000278	−5.68	−3.32	253.2	0.8048 ± 0.0072	−0.72	0.75
258.2	0.01335 ± 0.00020	1.61	6.91	258.2	1.063 ± 0.018	−3.84	0.53
263.2	0.01600 ± 0.00010	−9.03	−3.96	263.2	1.425 ± 0.024	−4.20	−0.18
268.2	0.02519 ± 0.00023	9.02	9.24	268.2	1.925 ± 0.025	−2.65	−2.04
273.2	0.03111 ± 0.00028	4.17	−3.54	273.2	2.802 ± 0.045	7.13	1.87
	Ethyl Ethanoate				Propan-1-ol		
248.2	2.190 ± 0.020	3.69	−0.61	248.2	6.467 ± 0.026	−7.69	−0.38
253.2	2.872 ± 0.040	1.88	2.00	253.2	8.730 ± 0.009	0.52	0.05
258.2	3.660 ± 0.018	−1.70	0.27	258.2	11.14 ± 0.08	3.60	−1.01
263.2	4.781 ± 0.024	−1.77	−0.43	263.2	13.63 ± 0.19	3.42	−2.36
268.2	6.393 ± 0.032	1.51	−0.05	268.2	16.31 ± 0.31	1.74	−2.41
273.2	8.832 ± 0.185	8.61	2.39	273.2	19.33 ± 0.02	−0.16	0.01

[a]Expanded uncertainties u are $u(T)$ = 0.1 K, $u_r(x)$ = 0.02. [b]Calculated from eq 1 with parameters correlated from the experimental solubility of Vitamin D_3. [c]Calculated from eq 2 with parameters correlated from the experimental solubility of Vitamin D_3.

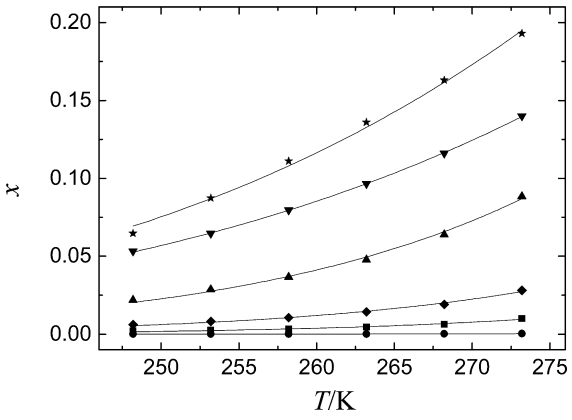

Figure 3. Mole fraction solubility (x) of Vitamin D_3 in six solvents from (248.2 to 273.2) K: ■, methanol; ●, ethanenitrile; ▲, ethyl ethanoate; ▼, ethanol; ♦, propan-2-one; ★, propan-1-ol. The corresponding lines were from the calculated values based on eq 1.

parameters. The parameters A' and B' were obtained using a linear regression method with weighting and are presented in Table 3 and shown in Figure S1 (see Supporting Information). The parameters A, B, and C were obtained using a nonlinear regression method with weighting and are presented in Table 4 and shown in Figure S2 (see Supporting Information). The root-mean-square deviation (rmsd) shown in both tables is defined as

$$\text{rmsd} = \left[\frac{1}{N}\sum_{i=1}^{N}(x_i - x_i^{\text{cal}})^2\right]^{1/2} \quad (3)$$

where N is the number of experimental points and x_i and x_i^{cal} represent the experimental and calculated solubility of Vitamin D_3 in solvent i. As shown in Table 2, in most cases, the correlated results of the modified Apelblat equation were closer to the experimental data than the simplified thermodynamic equation. When correlated by the modified Apelblat equation, all relative deviations were less than 10 %, indicating that calculated solubility of Vitamin D_3 at different temperatures in all studied solvents was in good agreement with the experimental data.

Table 3. Parameters of Equation 1 for Vitamin D_3 in Selected Solvents

solvent	A'	B'	10^2 rmsd[a]
methanol	9.473 ± 0.829	−3890 ± 207	0.0631
ethanenitrile	5.994 ± 1.185	−3855 ± 311	0.0013
ethyl ethanoate	10.805 ± 0.475	−3639 ± 124	0.3183
ethanol	7.500 ± 0.024	−2590 ± 6	0.0795
propan-2-one	11.117 ± 0.565	−4034 ± 146	0.0897
propan-1-ol	8.507 ± 0.182	−2773 ± 48	0.3441

[a]rmsd = the root-mean-square deviation.

■ CONCLUSION

The solubility of Vitamin D_3 in methanol, ethanenitrile, ethyl ethanoate, ethanol, propan-2-one, and propan-1-ol was determined. The solubility of Vitamin D_3 decreased with the increasing polarity of the solvents to some extent and the relatively high solubility of Vitamin D_3 in alcohols was attributed to both hydrogen bond interaction and van der Waals interaction. Besides, the solubility increased with the increase of temperature, and the simplified thermodynamic equation and the modified Apelblat equation were both used to correlate the solubility data. The calculated solubility showed good agreement with the experimental value, which could be used as database in the process of purification and crystallization of Vitamin D_3.

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Table 4. Parameters of Equation 2 for Vitamin D_3 in Selected Solvents

solvent	A	B	C	10^2 rmsd[a]
methanol	−1143.2 ± 167.5	41546.4 ± 6604.5	175.8 ± 25.6	0.0139
ethanenitrile	−693.2 ± 414.2	23825.0 ± 16399.2	106.6 ± 63.1	0.0012
ethyl ethanoate	−415.0 ± 67.1	13198.1 ± 2654.0	64.9 ± 10.2	0.0899
ethanol	−31.3 ± 30.4	−1061.7 ± 1197.9	5.9 ± 4.6	0.0520
propan-2-one	−541.6 ± 115.0	17872.5 ± 4557.0	84.2 ± 17.5	0.0271
propan-1-ol	525.6 ± 41.2	−23441.8 ± 1646.2	−78.7 ± 6.3	0.2125

[a]rmsd = the root-mean-square deviation.

■ ASSOCIATED CONTENT

Supporting Information

Mole fraction solubility (x) of Vitamin D_3 obtained from the experiment and the correlation of the simplified thermodynamic equation or Apelblat equation in different solvents with 95 % confidence limits. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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