Solubility of Avermectin B_{1a} in Some Pure and Mixed Solvents from (278.2 to 318.2) K

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The solubility of Avermectin B_{1a} in methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, isopropyl ether, and mixed solvents of methanol + water have been measured over the temperature range of (278.2 to 318.2) K at atmospheric pressure. The experimental solubility data was correlated with the Apelblat equation.

Introduction

Avermectins, a series of 16-membered macrocyclic lactones produced by *Streptomyces avermitilis*, have been shown to possess broad-spectrum anthelmintic activity with relatively low toxicity in both humans and animals. Natural avermectins have eight major compounds: A_{1a}, A_{2a}, B_{1a}, B_{2a}, A_{1b}, A_{2b}, B_{1b}, and B_{2b}.[1,2] Among these components, avermectin B_{1a} shows much greater antiparasitic activity than the other homologues. Figure 1 shows the chemical structure of avermectin B_{1a}. Because of the difficulty in industrial separation of B_{1a} and B_{1b}, the commercial product of avermectins always contains more than 80 % of B_{1a} and less than 20 % of B_{1b} components.[3]

The central importance of avermectin B_{1a} among the group of antiparasitic agents has made it the focal point of numerous pharmacological,[4,5] analytical,[6−8] and synthetic efforts.[2,9,10] In industrial production, B_{1a} was crystallized from the extraction of broth.[11−13] The determination of its solubility in different solvents will be beneficial for its residue extraction studies and also to optimize the crystallization process. Moreover, solubility is an important physicochemical parameter in the process of drug discovery and development. Xie et al.[14] have determined the solubility of avermectin mixture in five pure solvents by the dynamic method. However, no experimental solubility data of avermectin B_{1a} in binary solvent mixtures have been reported. As a continuation of our investigations on the solubility of veterinary medicine,[15] we reported here the solubility of avermectin B_{1a} in methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, isopropyl ether, and five methanol + water mixtures over the temperature range of (278.2 to 318.2) K at atmospheric pressure. The experimental solubility data have been correlated by the Apelblat equation.[16,17]

Experimental Section

Reagents and Apparatus. Avermectin B_{1a} is supplied by Zhejiang Shenghua BIOK Biology Co. Ltd. (Huzhou, China) with a mass fraction purity of 0.934 as determined by high-performance liquid chromatography (HPLC). Other reagents are the following: methanol (99.5 %, analytical purity grade, Tianjin Fuyu finechem. Co. Ltd., China), ethanol (mass fraction purity of 0.997, analytical purity grade, Hangzhou Gaojing finechem. Co. Ltd., Zhejiang, China), *n*-propanol (mass fraction purity of 0.998, analytical purity grade, Shanghai Shengxiang Chemical Reagent Co. Ltd., China), *i*-propanol (mass fraction purity of 0.997, analytical purity grade, Hangzhou Shuanglin Chemical Reagent Factory, Zhejiang, China), *n*-butanol (mass fraction purity of 0.99, analytical purity grade, Hangzhou Gaojing finechem. Co. Ltd., Zhejiang, China), and isopropyl ether (mass fraction purity of 0.99, chemical purity grade, Shanghai Wulian Chemical Reagent Factory). Pure water was produced by NANO pure diamond UV/UF (Thermo Scientific Barnstead, USA).

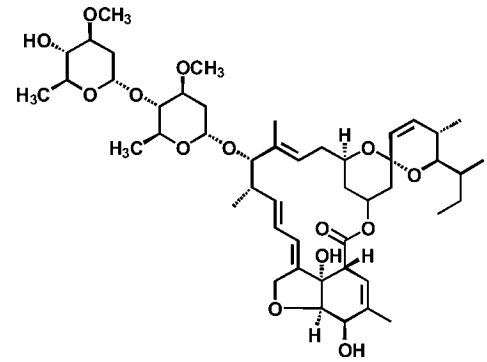

Figure 1. Molecular structure of avermectin B_{1a}.

A SHKA4000-8CE incubator shaker was supplied by Thermo Scientific (USA). An Auhaus (New Jersey, USA) analytical balance with a sensitivity of ± 0.01 mg was used. Analytical experiments were performed using a Waters 2695 HPLC system composed of a quaternary pump, column and auto sampler thermostat, and variable wavelength detector with detection monitored at 245 nm. A calibration curve (with the regression coefficient of 0.9999) was generated to determine the equilibrium concentrations of avermectin B_{1a} upon sampling and analysis. The calibration curve was prepared by eight standard avermectin B_{1a} solutions which were diluted by pure ethanol and detected at a temperature of 298.2 K.

Sample Preparation. Excess amounts of avermectin B_{1a} crystals were added to 30 cm^3 (uncertainty of ± 0.1 cm^3) of six pure solvents (methanol, ethanol, *n*-propanol, *i*-propanol, *n*-butanol, and isopropyl ether) and five methanol + water mixtures of volume ratios of 5:5, 6:4, 7:3, 8:2, and 9:1 at a room temperature of 293 K. Then they were fixed in the shaker where the temperatures were controlled by a thermostat (uncertainty of ± 0.1 K) ranging from (278.2 to 318.2) K with each step of 5 K. The suspended solution was kept shaken for

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Table 1. Molarity c_i of Avermectin B_{1a} in Different Pure Solvents and Difference of the Measured Value from the Correlation Provided by Equation 1, $c_{i,cal}$, at Temperatures in the Range of (278.2 to 318.2) K

	methanol		ethanol		*n*-propanol		*i*-propanol		*n*-butanol		isopropyl ether	
T	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$
K	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}
278.2	10.51	–0.22	5.20	0.05	27.32	0.34	28.03	2.22	7.67	0.23	8.19	–0.08
283.2	11.97	–0.24	5.73	–0.09	31.30	–0.35	29.10	0.08	8.71	–0.03	8.97	0.01
288.2	14.21	0.38	6.65	–0.04	38.10	1.13	31.48	–1.81	10.20	–0.23	10.21	0.22
293.2	15.80	0.20	8.12	0.31	42.47	–0.58	37.49	–1.40	12.43	–0.19	11.59	0.17
298.2	17.75	0.23	9.06	–0.18	48.31	–1.65	45.95	–0.26	15.55	0.06	12.86	–0.54
303.2	19.68	0.07	10.87	–0.21	57.73	–0.04	54.41	–1.41	18.92	–0.32	16.51	0.46
308.2	21.70	–0.17	13.51	0.06	67.72	1.10	68.32	–0.10	25.43	1.27	18.82	–0.83
313.2	23.45	–0.84	16.70	0.19	77.46	0.89	90.41	5.38	29.64	–1.04	25.37	0.84
318.2	27.49	0.58	20.39	–0.09	86.94	–0.82	104.19	–2.85	39.58	0.25	30.91	–0.26

Table 2. Molarity c_i of Avermectin B_{1a} in Binary Methanol (V_1) + Water (V_2) Mixtures and Difference of the Measured Value from the Correlation Provided by Equation 1, $c_{i,cal}$, in the Temperature Range of (278.2 to 318.2) K[a]

	$X = 0.500$		$X = 0.600$		$X = 0.700$		$X = 0.800$		$X = 0.900$	
T	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3(c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$	$10^3\ c_i$	$10^3\ (c_i - c_{i,cal})$
K	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}	mol·dm^{-3}
278.2	0.0209	0.0047	0.0926	0.0012	1.1353	–0.0254	3.0609	–0.0335	6.4175	–0.0780
283.2	0.0224	0.0012	0.1076	–0.0014	1.1870	0.0119	3.4178	0.1297	7.0979	0.2021
288.2	0.0260	–0.0015	0.1347	0.0035	1.2603	0.0302	3.5883	0.0236	7.5803	0.1157
293.2	0.0330	–0.0021	0.1551	–0.0040	1.3290	0.0008	3.7942	–0.1430	7.9054	–0.3225
298.2	0.0408	–0.0038	0.1980	0.0037	1.4820	0.0059	4.3055	–0.1191	9.1284	–0.0949
303.2	0.0512	–0.0050	0.2349	–0.0040	1.6957	0.0105	5.0228	–0.0304	10.4852	–0.0173
308.2	0.0745	0.0046	0.2891	–0.0064	1.9167	–0.0562	6.1514	0.2929	12.4430	0.3079
313.2	0.0945	0.0081	0.3800	0.0124	2.3830	0.0185	6.7854	–0.1025	14.1402	–0.0731
318.2	0.1005	–0.0053	0.4549	–0.0047	2.9030	0.0063	8.1832	–0.0211	16.8161	–0.0437

[a] $V_1 = V_{Methanol}$; $V_2 = V_{Water}$; $X = V_1/(V_1 + V_2)$.

12 h to attain equilibrium. Then the solution was allowed to settle for 0.5 h in the shaker. The supernatant liquid was withdrawn, filtered through a 0.45 μm membrane, appropriately diluted, and analyzed for avermectin B_{1a} using the HPLC. Each measurement was repeated three times.

Sample Analysis. The solubility was determined using the HPLC system mentioned above. The analysis was performed on a Agilent ZORBAX 80 A Extend-C18 reversed-phase column (4.60 × 150 mm, 5 μm). The optimum separation of HPLC was carried out with a mobile phase composed of methanol, acetonitrile, and water in a volume ratio of 41.5:41.5:17 at a flow rate of 0.017 cm^3·s^{-1}. The calibration curve was prepared by using the standard solutions in the concentration range at a temperature of 298.2 K. The injected volumes of sample were 10^{-3} cm^3.

Results and Discussion

The solubilities of avermectin B_{1a} in the six pure solvents at different temperatures were measured and presented in Table 1. The solubility in *n*-propanol was the highest from temperatures of (278.2 to 308.2) K, and the solubility in *i*-propanol was the highest at temperatures from (313.2 to 318.2) K. The solubility in ethanol was the lowest. The solubilities of avermectin in methanol, ethanol, butanol, and isopropyl ether are close and small. On the other hand, the solubility in *n*-propanol and *i*-propanol is significantly higher than the above solvents. The solubility in all selected solvents increased with an increase of temperature in the range of (278.2 to 318.2) K.

The solubilities of avermectin B_{1a} in the five binary methanol + water mixtures at different temperatures were measured and presented in Table 2. According to the Table 2, we can draw a conclusion that the solubility of avermectin B_{1a} decreased with an increase of water content in the mixed solvents and increased with the increase of temperature in the range of (278.2 to 318.2) K.

Table 3. Parameters of Equation 1 for Avermectin B_{1a} in Different Pure Solvents in the Temperature Range of (278.2 to 318.2) K

	A	B	C	
solvent	mol·dm^{-3}	mol·dm^{-3}·K^{-1}	mol·dm^{-3}	10^3 rmsd
methanol	8.77	–1993.15	0.14	0.40
ethanol	–441.33	17098.34	67.78	0.16
n-propanol	–27.10	–844.51	5.94	0.90
i-propanol	–510.24	20150.28	78.36	2.34
n-butanol	–446.55	16816.63	68.96	0.58
isopropyl ether	–659.31	26893.84	100.34	0.48

The solubility of avermectin B_{1a} as a function of temperature was fitted by the modified Apelblat equation:

$$\ln(c/\text{mol}\cdot\text{dm}^{-3}) = A + \frac{B}{T/\text{K}} + C\ln(T/\text{K}) \qquad (1)$$

where c is the solubility of avermectin B_{1a}, T is the absolute temperature, and A, B, and C are parameters. The values of parameters in the Apelblat eq 1 were estimated by the Levenberg−Marquardt algorithm minimizing the average relative deviation (ARD) given by[18]

$$\text{ARD} = \frac{1}{N}\sum_{i=1}^{N}\frac{|c_{i,cal} - c_i|}{c_i} \qquad (2)$$

where N is the number of experimental points, c_i represents the experimental solubility values, and $c_{i,cal}$ represents the calculated solubility. The difference between experimental and calculated results is presented in Tables 1 and 2. The values of parameters A, B, and C were presented in Tables 3 and 4 together with the root-mean-square deviation (rmsd) which is defined as

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

From Tables 1 to 4, it could be seen that the calculated solubilities showed good agreement with experimental values,

Table 4. Parameters of Equation 1 for Avermectin B_{1a} in Binary Methanol (X_1) + Water (X_2) Mixtures in the Temperature Range of (278.2 to 318.2) K[a]

	A	*B*	*C*	
solvent	mol·dm^{-3}	mol·dm^{-3}·K^{-1}	mol·dm^{-3}	10^3 rmsd
$X = 0.500$	53.86	–6071.04	–6.42	0.0045
$X = 0.600$	–310.06	10654.63	47.86	0.0056
$X = 0.700$	–729.30	30681.87	110.01	0.0245
$X = 0.800$	–474.97	19322.15	72.25	0.1294
$X = 0.900$	–461.45	18794.52	70.32	0.1750

[a] $V_1 = V_{Methanol}$; $V_2 = V_{Water}$; $X = V_1/(V_1 + V_2)$.

indicating the modified Apelblat equation could be applied to correlate the solubility data of avermectin B_{1a} in the six pure solvents and five methanol + water mixtures. The experimental solubility and the modified Apelblat equation with the parameters might be used as essential data in the purification and crystallization of avermectin B_{1a}.

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