Solubilities of (α,*Z*)-2-Amino-α-(methoxyimino)-4-thiazoleethanethioic Acid *S*-2-Benzothiazolyl Ester in Different Pure Solvents and Binary Mixtures of Tetrahydrofuran + Dichloromethane or 1,2-Dichloroethane

Jisheng Liu, Shui Wang, Zhimao Zhou, Yixin Qu,* and Meijuan Zhang

College of Chemical Engineering, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China

The solubility of (α,*Z*)-2-amino-α-(methoxyimino)-4-thiazoleethanethioic acid *S*-2-benzothiazolyl ester in dichloromethane, acetonitrile, tetrahydrofuran, 1,2-dichloroethane, acetone, and binary mixtures of tetrahydrofuran + dichloromethane or 1,2-dichloroethane was measured using a laser monitoring observation technique. The temperature dependence of the solubility of the solute was estimated using the modified Apelblat equation based on the data presented in this work. The calculated solubilities show good agreement with the experimental values.

Introduction

(α,*Z*)-2-Amino-α-(methoxyimino)-4-thiazoleethanethioic acid *S*-2-benzothiazolyl ester (formula: $C_{13}H_{10}S_3N_4O_2$, molecular weight: 350.44, CAS Registry No. 80756-85-0) is abbreviated as MAEM and is a pale yellow crystalline powder. MAEM was the main intermediate for the synthesis of cephalosporines, such as cefotaxime, ceftriaxone, cefetamet, cefodizime, and so on.[1−3] The chemical structure of MAEM is shown in Figure 1. As the selection of proper solvents is a key factor in extraction of an ingredient from a natural source or a synthetic mixture and purification of drugs via recrystallization, it is necessary to know the solubility of drugs in different pure solvents and solvent mixtures. Dichloromethane, tetrahydrofuran, acetonitrile, and 1,2-dichloroethane were often used as solvents in the synthesis and purification of MAEM.[1] In present work, the solubility of MAEM in the above-mentioned pure solvents and their binary solvent mixtures was measured from (278 to 303) K, and the Apelblat equation was used to correlate the experimental solubility data.

Experimental Section

Chemicals. MAEM was supplied by ShiJiaZhuang HeJia Health Productions Co., Ltd. with a mass fraction higher than 99.2 %. Dichloromethane, tetrahydrofuran, acetonitrile, 1,2-dichloroethane, and acetone of analytical grade were purchased from TianJin FuChen Chemical Reagent Factory. Their mass fraction purities were better than 99.0 %.

Apparatus and Procedure. The solubility of MAEM in pure solvents and binary solvent mixtures was measured using a synthetic method.[4,5] The apparatus for this solubility measurement was similar to that described in the references.[6] A 200 mL jacketed glass vessel was used and controlled by a circulated bath (temperature uncertainty of ± 0.05 K). A calibrated mercury-in-glass thermometer (uncertainty of ± 0.05 K) was inserted into the inner chamber of the vessel for temperature measurements. The solution was stirred with a magnetic stir bar. A condenser was connected to the vessel to prevent the solvents from evaporating. The masses of the samples and solvents were weighed using an analytical balance (sartorius CP224S, Germany) with an uncertainty of ± 0.0001 g. The reported solubility values were the average of three-time repeated measurements, and the uncertainty of the experimental solubility values is less than 2.0 %, which is attributed to the uncertainties in weighing process, stability of the water bath, and temperature measurements. The procedure of solubility measurement was the same as the description of the literature.[6]

* To whom correspondence should be addressed. E-mail: quyx2008@yahoo.com.cn. Fax: +86 10 64444785.

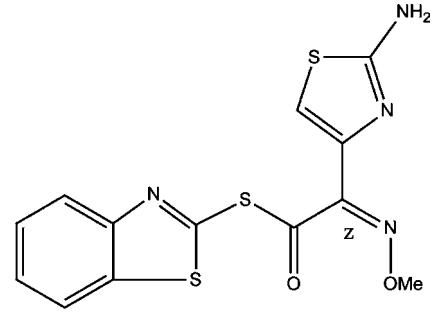

Figure 1. Chemical structure of MAEM.

Table 1. Molar Fraction Solubility of MEAM in Pure Solvents with a Temperature Range from (278 to 303) K

T/K	$10^3\,x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$	*T*/K	$10^3\,x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$
Dichloromethane					
278.60	0.7195	0.31	294.03	1.710	0.06
283.64	0.9671	0.48	298.71	2.170	0.69
288.46	1.276	0.00	303.44	2.672	0.37
Tetrahydrofuran					
278.40	24.31	0.16	293.25	31.08	0.19
283.75	25.92	0.12	298.06	35.19	0.94
288.80	28.04	0.86	302.95	39.66	0.63
Acetonitrile					
279.45	0.2156	0.79	292.98	0.4514	1.15
283.46	0.2618	1.03	297.47	0.5809	0.90
288.45	0.3421	1.37	302.45	0.7614	0.87
1,2-Dichloroethane					
277.83	0.3580	1.56	292.84	0.8759	2.23
282.77	0.4585	2.42	297.85	1.175	1.11
287.63	0.6186	1.21	302.64	1.543	1.23
Acetone					
278.32	2.446	0.45	293.20	3.903	0.69
283.31	2.864	0.59	298.54	4.719	0.64
288.15	3.343	0.78	303.28	5.697	0.60

10.1021/je100890f
Published on Web 12/20/2010

Table 2. Molar Fraction Solubility of MEAM in Tetrahydrofuran (B) + Dichloromethane (C) with a Temperature Range from (278 to 303) K

T/K	$10^3\ x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$	T/K	$10^3\ x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$
		$x_B^0 = 0.1154$			
279.65	1.307	0.08	293.17	2.361	0.64
283.13	1.519	0.79	298.35	3.018	0.53
288.05	1.834	1.42	303.25	3.818	0.34
		$x_B^0 = 0.3347$			
278.32	2.138	0.28	293.20	3.551	0.54
283.31	2.534	0.43	298.54	4.347	0.23
288.15	2.993	0.47	303.28	5.249	0.30
		$x_B^0 = 0.5337$			
278.73	3.660	0.41	293.15	5.998	0.58
283.76	4.240	0.21	298.26	7.443	1.13
288.11	4.873	1.19	303.10	9.052	0.77
		$x_B^0 = 0.7290$			
279.77	7.051	0.52	292.67	10.23	1.17
283.02	7.613	0.34	297.47	11.82	0.25
288.02	8.692	1.15	302.64	13.98	0.36
		$x_B^0 = 0.8709$			
279.45	13.73	0.22	293.54	17.93	0.11
283.66	14.81	0.20	298.28	19.90	0.25
288.45	16.18	0.06	303.35	22.55	0.13
		$x_B^0 = 0.9556$			
279.45	19.85	0.20	293.54	24.80	0.12
283.66	21.12	0.24	298.28	27.17	0.18
288.45	22.72	0.04	303.35	30.31	0.10

Table 3. Molar Fraction Solubility of MEAM in Tetrahydrofuran (B) + 1,2-Dichloroethane (C) with a Temperature Range from (278 to 303) K

T/K	$10^3\ x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$	T/K	$10^3\ x_A$	$100\lvert x_A - x_A^{cal}\rvert/x_A$
		$x_B^0 = 0.1358$			
277.94	0.8769	0.51	292.78	1.748	1.26
282.75	1.076	0.09	298.05	2.286	1.66
287.84	1.329	2.41	302.89	2.854	1.30
		$x_B^0 = 0.3664$			
278.20	2.275	0.75	292.78	3.979	0.80
283.13	2.650	1.55	297.94	4.949	0.22
288.04	3.248	0.06	302.75	6.123	0.49
		$x_B^0 = 0.5782$			
278.41	4.534	0.75	293.11	6.996	0.63
283.20	5.188	1.14	298.16	8.566	0.14
288.42	5.957	0.49	302.93	10.56	0.09
		$x_B^0 = 0.6404$			
278.24	5.559	0.41	293.42	8.505	0.29
283.13	6.276	1.02	298.46	10.15	1.08
287.98	7.112	0.24	303.38	12.76	0.86
		$x_B^0 = 0.7261$			
278.59	7.693	0.45	293.17	11.16	0.45
283.37	8.602	0.95	298.23	13.38	0.07
288.52	9.696	0.28	302.98	16.13	0.12
		$x_B^0 = 0.8080$			
278.68	12.36	0.24	292.91	17.45	0.23
283.47	13.62	0.15	298.17	20.58	0.73
288.04	15.13	0.73	302.78	23.67	0.55
		$x_B^0 = 0.9438$			
279.04	18.55	0.27	292.96	23.93	0.17
283.55	19.79	0.15	298.18	27.36	0.91
287.96	21.33	0.70	302.87	30.58	0.56

The initial molar fraction concentrations of binary solvent mixtures (x_B^0) were based on the following equation:

$$x_B^0 = \frac{m_B/M_B}{m_B/M_B + m_C/M_C} \quad (1)$$

where m_B and m_C represent the mass of tetrahydrofuran, dichloromethane, or 1,2-dichloroethane, respectively, and M_B and M_C are the molecular weight of tetrahydrofuran, dichloromethane, or 1,2-dichloroethane, respectively.

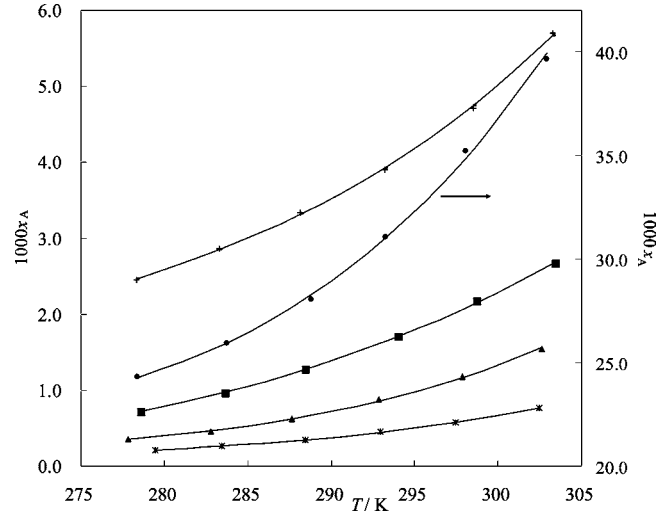

Figure 2. Solubility of MAEM at different temperatures in pure solvents: ■, dichloromethane; ▲, 1,2-dichloroethane; ∗, acetonitrile; +, acetone; ●, tetrahydrofuran; solid line, calculated by eq 2.

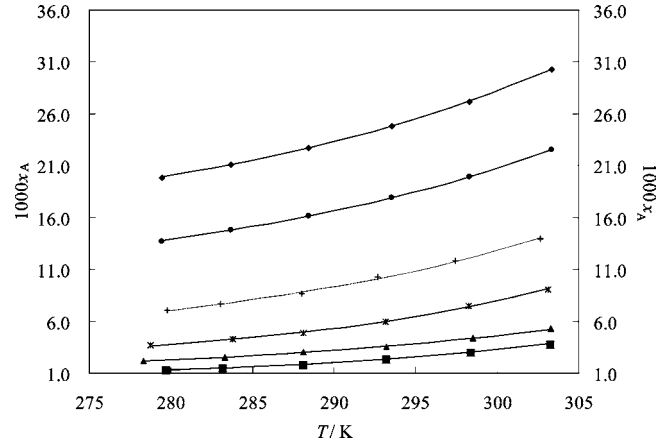

Figure 3. Solubility of MAEM at different temperatures in tetrahydrofuran (B) + dichloromethane (C) binary mixtures: ■, $x_B^0 = 0.1154$; ▲, $x_B^0 = 0.3347$; ∗, $x_B^0 = 0.5337$; +, $x_B^0 = 0.7290$; ●, $x_B^0 = 0.8709$; ◆, $x_B^0 = 0.9556$; solid line, calculated by eq 2.

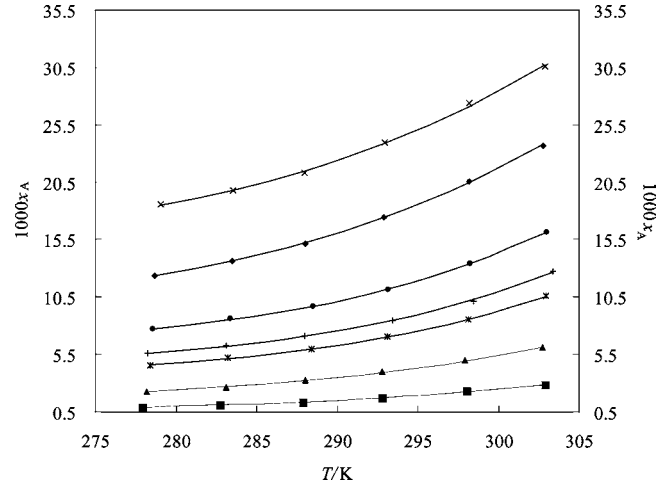

Figure 4. Solubility of MAEM at different temperatures in tetrahydrofuran (B) + 1,2-dichloroethane (C) binary mixtures: ■, $x_B^0 = 0.1358$; ▲, $x_B^0 = 0.3664$; ∗, $x_B^0 = 0.5782$; +, $x_B^0 = 0.6404$; ●, $x_B^0 = 0.7261$; ◆, $x_B^0 = 0.8080$; ×, $x_B^0 = 0.9438$; solid line, calculated by eq 2.

Results and Discussion

The modified Apelblat equation[7] describes the relationship between the solubility of the solute and the temperature for pure

Table 4. Parameters for MAEM in Pure Solvents and Binary Mixtures of Tetrahydrofuran + Dichloromethane or 1,2-Dichloroethane from (278 to 303) K by the Modified Apelblat Equation

x_B^0	A	B	C	10^5 rmsd
		Dichloromethane		
	198.215	−12736.1	−28.3742	0.77
		Tetrahydrofuran		
	−515.036	20808.1	77.5575	19.79
		Acetonitrile		
	−357.534	11239.3	54.8330	0.47
		1,2-Dichloroethane		
	−323.502	9455.57	50.0297	1.37
		Acetone		
	−339.342	12127.7	51.4781	2.54
		Tetrahydrofuran (B) + Dichloromethane (C)		
0.1154	−435.239	15435.9	66.2821	1.57
0.3347	−301.650	10317.8	45.9129	1.34
0.5337	−543.236	20728.1	82.2798	5.30
0.7290	−335.430	12238.4	50.8923	7.50
0.8709	−280.032	10550.5	42.2508	3.08
0.9556	−279.947	10779.4	42.1557	3.76
		Tetrahydrofuran (B) + 1,2-Dichloroethane (C)		
0.1358	−406.358	13952.5	62.0382	2.69
0.3664	−441.766	16046.2	67.1591	2.59
0.5782	−675.504	26730.0	101.989	3.57
0.6404	−692.527	27603.4	104.492	7.04
0.7261	−651.815	26017.0	98.3285	4.41
0.8080	−454.857	17664.0	68.7518	9.52
0.9438	−422.032	16685.6	63.6162	14.08

solvents as well as mixed solvent systems with a given initial composition:

$$\ln x_A = A + \frac{B}{T/K} + C \ln(T/K) \quad (2)$$

where T is the absolute temperature and A, B, and C are dimensionless constants which could be directly obtained by EXCEL using the linear least-squares method from the experimental data.

The experimental solubilities of MAEM in pure solvents and given composition of binary solvent mixtures were presented in Tables 1 to 3 together with the relative difference between experimental and calculated values and graphically plotted in Figures 2 to 4. The solubility of MAEM is the largest in tetrahydrofuran and the lowest in acetonitrile and increases with temperature in pure solvents and binary solvent mixtures. For binary mixtures of tetrahydrofuran + dichloromethane or 1,2-dichloroethane, the solubility of MAEM increases with the initial molar fraction of tetrahydrofuran at a constant temperature. The values of the three parameters A, B, and C are listed in Table 4 together with the root-mean-square deviations (rmsd's) which is defined as follows:

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

where x_A^{cal} is the solubility calculated from eq 2 and N is the number of experimental points.

It can be seen that the calculated solubilities by eq 2 show good agreement with the experimental values. The experimental solubilities and correlation equation in this work can be used as essential models in the practical purification process of MAEM.

Literature Cited

(1) Ge, H. Y.; Ma, W. X.; Xu, X. Y. Synthesis of AE-active Ester. *Jiangsu Huagong* **2007**, *35*, 32–34.
(2) Li, A. J.; Zhou, X. Q.; Liu, D. Z. An Improved Procedure for the Preparation of 2-(2-Aminothiazol-4-yl)-2-(*Z*)-methoxyiminoacetic Acid *S*-Benzthiazolyl Thioester. *Jingxi Huagong* **2005**, *22*, 792–794.
(3) Gao, H. J.; Yu, Z. X. Research Advance on Antimicrobial Intermediats. *Jingxi Huagong Zhongjianti* **2001**, *31*, 1–6.
(4) Su, M.; Wang, J. K.; Hou, Y. Solubility of 6-Aminopenicillanic Acid in Aqueous Salt Solutions from 273.15 to 303.15 K. *J. Chem. Eng. Data* **2007**, *52*, 2266–2268.
(5) Wang, S.; Wang, J. K.; Yin, Q. X. Measurement and correlation of solubility of 7-aminocephalosporanic acid in aqueous acetone mixtures. *Ind. Eng. Chem. Res.* **2005**, *44*, 3783–3787.
(6) Song, Z. Q.; Qu, Y. X.; Wang, S. Solubilities of (α, *Z*)-2-Amino-α-(methoxyimino)-4-thiazole-ethanethioic Acid *S*-2-Benzothiazolyl Ester in Pure Solvents and a Mixture of Acetonitrile and Dichloromethane. *J. Chem. Eng. Data* **2010**, *55*, 2343–2344.
(7) Apelblat, A.; Manzurola, E. Solubility of *o*-acetylsalicylic, 4-aminosalic, 3,5-dinitrosalicylic, and *p*-toluic acid, and magnesium-DL-aspartate in water from T = (278 to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85–91.

Received for review September 5, 2010. Accepted December 8, 2010. We are indebted to the National High Technology Research and Development Program of China (863 Program; Grant No. 2009-AA05Z436) and the National Basic Research Program (973 Program, Grant No. 2007CB714304) for financial support of this work.

JE100890F