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

Zhiqian Song, Yixin Qu, and Shui Wang*

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

Using a laser monitoring technique, the solubility of (α,*Z*)-2-amino-α-(methoxyimino)-4-thiazole-ethanethioic acid *S*-2-benzothiazolyl ester in ethanol, 1-propanol, 1-butanol, 1-pentanol, 2-propanol, 2-methyl-1-propanol, 3-methyl-1-butanol, and a mixture of acetonitrile and dichloromethane was determined from (278.15 to 308.15) K. The solubility data were correlated with a semiempirical equation. The calculated results of which are proven to show fine representation of the experimental data.

Introduction

(α,*Z*)-2-Amino-α-(methoxyimino)-4-thiazole-ethanethioic acid *S*-2-benzothiazolyl ester ($C_{13}H_{10}S_3N_4O_2$, abbreviated as MAEM, molecular weight 350, CAS Registry No. 80756-85-0) is a pale yellow crystalline powder (see Figure 1). MAEM is an important intermediate for the preparation of cefotaxime sodium, ceftriaxone, and cefetamet pivoxil. In industrial production, MAEM was used in the synthesis of the solvent. To determine the proper solvent and to design an optimized crystallization process, it is necessary to know its solubility in different solvents. In the present work, the solubility of MAEM was measured in the temperature range from (278.15 to 308.15) K for various organic solvents using a laser monitoring observation technique. The method employed in this work was classified as a synthetic method, which was much faster and more readily available than the analytical method.[1]

Experimental Section

Chemicals. A pale yellow crystalline powder of MAEM with a mass fraction of higher than 99.2 % was purchased from ShiJiaZhuang HeJia Health Products Co. Ltd. All solvents used for the experiments were of analytical reagent grade.

Apparatus and Procedure. The solubility data were measured by a synthetic method.[2,3] The apparatus for the solubility measurement was the same as that described in the literature.[2] The dissolution of the solute was carried out in a jacketed glass vessel, which was maintained at the desired temperature by continuous forced water circulation from a thermostat (temperature uncertainty of ± 0.05 K). Continuous stirring was achieved with a magnetic stir bar. A mercury-in-glass thermometer, calibrated (uncertainty of ± 0.05 K), was inserted into the inner chamber of the vessel for the temperature measurement. The dissolution of the solute was examined by the laser beam penetrating the vessel. The masses of the samples and solvents were weighed using an analytical balance (sartorius CP224S, Germany) with an uncertainty of ± 0.0001 g.

The solubility of MAEM was determined by the laser method.[4,5] During the experiments, the predetermined solvents were placed in the vessel and stirred continuously at a required temperature. MAEM was added to the vessel simultaneously. The laser beam intensity passing through the vessel reached a maximum when the solute dissolved completely. Then an additional portion of solute [about (0.5 to 5) mg] was added into the vessel. This procedure was repeated until the penetrated laser intensity could not return maximum, or in other words, the last addition of solute could not dissolve completely. The interval of addition was 90 min. The total amount of the solute consumed was recorded. The same solubility experiment was conducted three times, and the mean values were used to calculate the mole fraction solubility (x_A) of pure solvent based on eq 1:

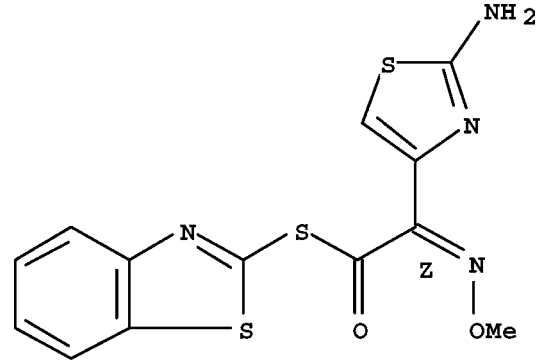

Figure 1. Chemical structure of MAEM.

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_S/M_S} \quad (1)$$

where m_A and m_S represent the mass of the solute and solvent, respectively, and M_A and M_S are the molecular weight of the solute and solvent, respectively. For the mixture of acetonitrile and dichloromethane, the mole fraction solubility (x_A) is based on eq 2:

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_1/M_1 + m_2/M_2} \quad (2)$$

where m_1 and m_2 represent the mass of the dichloromethane and acetonitrile, respectively, and M_1 and M_2 are the

* To whom correspondence should be addressed. E-mail: wangshui2000@yahoo.cn.

10.1021/je900784v
Published on Web 11/24/2009

Table 1. Solubility (x_A) of MAEM in Different Solvents between (277 and 303) K

T/K	$10^3\ x_A$	T/K	$10^3\ x_A$	T/K	$10^3\ x_A$
		Ethanol			
277.67	0.2032	288.17	0.3254	298.17	0.5167
283.11	0.2481	293.09	0.3989	303.09	0.6877
		1-Propanol			
277.85	0.2259	288.13	0.3321	297.97	0.5444
283.17	0.2560	293.17	0.4143	302.81	0.7899
		1-Butanol			
278.11	0.2620	288.37	0.4244	297.73	0.6623
283.53	0.3204	293.03	0.5250	303.71	0.9618
		1-Pentanol			
278.27	0.2834	288.15	0.4334	298.17	0.7442
283.33	0.3395	293.23	0.5644	303.15	0.9922
		2-Propanol			
277.91	0.1165	288.05	0.1681	298.13	0.2830
283.21	0.1420	293.19	0.2106	303.13	0.3650
		2-Methyl-1-propanol			
277.67	0.1482	287.99	0.2064	297.77	0.3452
283.07	0.1711	292.79	0.2680	304.27	0.5305
		3-Methyl-1-butanol			
277.65	0.1828	288.37	0.2864	298.17	0.4724
283.07	0.2153	293.03	0.3707	302.63	0.6223
		x_1[a] = 0.296			
279.71	0.5106	288.17	0.7556	298.57	1.181
283.27	0.5847	293.09	0.9323	303.33	1.461

[a] x_1 is the mole fraction of dichloromethane (1) in the mixture of acetonitrile and dichloromethane.

molecular weight of the dichloromethane and acetonitrile, respectively.

The uncertainty of the experimental solubility values is about 2.0 %. The uncertainty in the solubility values can be due to uncertainties in the temperature measurements and weighing procedure and the instabilities of the water bath.

Results and Discussion

The solubility of MAEM is listed in Table 1. The relationship between temperature and solubility of the MAEM is correlated with the modified Apelblat equation, which is a semiempirical equation:[6,7]

$$\ln x_A = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \qquad (3)$$

where T is the absolute temperature and A, B, and C are dimensionless constants. The difference between experimental and calculated results is also presented in Table 1. The values of the three parameters A, B, and C together with the root-mean-square deviations (rmsd's) are listed in Table 2. The rmsd is defined as follows:

$$\mathrm{rmsd} = \left[\sum_{i=1}^{N} \frac{(x_A - x_A^{cal})^2}{N}\right]^{1/2} \qquad (4)$$

where x_A^{cal} is the solubility calculated from eq 3, x_A is the experimental value of solubility, and N is the number of experimental points.

From Tables 1 and 2 and Figure 2, we could elicit the following conclusions: (1) The solubility of MAEM in these solvents increases with temperature, but the increment with temperature varies according to different solvents. (2) The solubility of MAEM in the mixture of acetonitrile and dichloromethane is higher than that in other pure solvents. The solubility of MAEM in pure 2-propanol is the minimum. (3) Most of the experimental data can be regressed by eq 3 for these eight solvents. The experimental solubility and correlation equation in this work can be used as essential models in the manufacturing and purifying processes of MAEM in industry.

Table 2. Parameters of Equation 3 for MAEM in Different Solvents

solvent	A	B	C	10^5 rmsd
ethanol	−567.878	20920.7	86.0278	0.501
1-propanol	−1344.14	54523.4	202.503	0.884
1-butanol	−619.448	22995.9	93.9068	0.839
1-pentanol	−733.018	27916.3	110.955	0.451
2-propanol	−831.007	32526.7	125.267	0.340
2-methyl-1-propanol	−1174.13	47311.0	176.830	0.263
3-methyl-1-butanol	−729.735	27801.6	110.370	0.615
$x_1 = 0.296$	−302.881	9622.85	46.3096	1.704

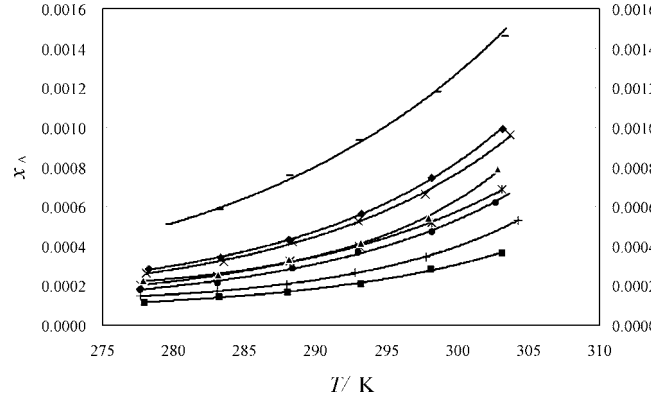

Figure 2. Solubility of MAEM in eight solvents: —, mixture of acetonitrile and dichloromethane; ◆, 1-pentanol; ×, 1-butanol; ▲, 1-propanol; ∗, ethanol; ●, 3-methyl-1-butanol; +, 2-methyl-1-propanol; ■, 2-propanol; solid line, calculated from eqs 2 and 3.

Literature Cited

(1) Hefler, G. T.; Tomkins, R. P. T. *The Experimental Determination of Solubilities*; John Wiley: Chichester, U.K., 2003.
(2) 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.
(3) Ren, G. B.; Wang, J. K.; Yin, Q. X.; Zhang, M. J. Solubilities of proxetine hydrochloride hemihydrate between 286 and 363 K. *J. Chem. Eng. Data* **2004**, *49*, 1671–1674.
(4) Hao, H. X.; Wang, J. K.; Wang, Y. L. Solubility of dexamethasone dodium phosphate in different solvents. *J. Chem. Eng. Data* **2004**, *49*, 1697–1698.
(5) Li, Q. S.; Liu, Y. M.; Wang, S.; Wu, H.-L. Solubility of D-(−)-*p*-Hydroxyphenylglycine Dane Salt in Mixtures of Methanol and Ethanol. *J. Chem. Eng. Data* **2006**, *51*, 2182–2184.
(6) Grand, D. J. W.; Mehdizadeh, M.; Chow, A. H. L.; Fairbrother, J. E. Non-linear van't Hoff solubility-temperature plots and their pharmaceutical interpretation. *Int. J. Pharm.* **1984**, *18* (1−2), 25–38.
(7) Wang, Z. Z.; Wang, J. K.; Zhang, M. J.; Dang, L. P. Solubility of Erythromycin A Dihydrate in Different Pure Solvents and Acetone + Water Binary Mixtures between 293 and 323 K. *J. Chem. Eng. Data* **2006**, *51*, 1062–1065.

Received for review September 28, 2009. Accepted November 12, 2009. We are indebted to the National High Technology Research and Development Program of China (863 Program; Grant No. 2009AA05Z436) for financial support of this work.

JE900784V