Solubility of 5-(Dithiolan-3-yl)pentanoic Acid in the Mixed Solvents of Cyclohexane + Ethyl Acetate, Heptane + Ethyl Acetate, and Hexane + Ethyl Acetate

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The solubility of α-5-(dithiolan-3-yl)pentanoic acid in mixed solvents (cyclohexane + ethyl acetate, heptane + ethyl acetate, and hexane + ethyl acetate) was experimentally studied by an analytical method. The data obtained were correlated by a semiempirical equation. Results showed that the solubility of 5-(dithiolan-3-yl)pentanoic acid increased with increasing temperature. In the same solvent systems, the molar fraction solubility increased with a decreasing solvent volume ratio.

Introduction

α-5-(Dithiolan-3-yl)pentanoic acid, first isolated by Reed and his co-workers from animal liver in 1950,[1] is known as α-thioctic acid and lipoic acid (Figure 1). It is found inside every cell of the body, where it helps to generate the energy necessary for life and functioning. α-5-(Dithiolan-3-yl)pentanoic acid contains two sulfur molecules that can be oxidized or reduced. This feature allows α-5-(dithiolan-3-yl)pentanoic acid to function as a potent antioxidant. Unlike other antioxidants, which work only in water or a fatty environment, 5-(dithiolan-3-yl)pentanoic acid is unusual in that it functions in both water and fat. By comparison, vitamin E works only in fat, and vitamin C works only in water. This gives 5-(dithiolan-3-yl) pentanoic acid an extensive application of antioxidant action in medicine, cosmetic, and health products.[2,3]

The usual method for purifying 5-(dithiolan-3-yl) pentanoic acid is by crystallization from solvents or mixed solvents, for example, from *n*-pentane, cyclohexane, ethyl ether, ethyl acetate, methyl cyclohexane, and so forth, and then recovery by filtration and drying.[4−6]

The solvent has a great effect on the cooling crystallization of 5-(dithiolan-3-yl) pentanoic acid. Unfortunately, limited data are available on the solubility of 5-(dithiolan-3-yl)pentanoic acid. The aim of this paper is to study the solubility of 5-(dithiolan-3-yl)pentanoic acid in some organic solvents, such as cyclohexane and ethyl acetate in the temperature range from (273.15 to 318.15) K and, at the same time, to correlate the experimental data with the Apelblat equation.

Experimental Section

Materials. 5-(Dithiolan-3-yl)pentanoic acid (melting point 335.15 K) was supplied by the Shangshai Shyndec Pharamaceutical Co., Ltd. with mass purity higher than 99 %. Cyclohexane, ethyl acetate, and heptane of analytical grade were supplied by the Tianjin Kewei Chemical Reagents Co. All chemicals were used as received without further purification.

Apparatus and Procedures. The experimental device is shown in Figure 2. The methods for measuring the solubility of a solid in a liquid mixture can be classified as analytical and synthetic.[7,8] The solubility of 5-(dithiolan-3-yl) pentanoic acid in organic solvents was measured by an analytical method described previously. The saturated solution was prepared by adding excess solute in glass vessels containing solvent. The solubility was determined by equilibrating the solute with solvent in a water jacketed vessel with electromagnetic stirring in a thermostatic water bath (± 0.05 K) for at least 8 h. The solution was extracted by an injector (membrane filtration (0.45 μm)), and the sample was weighed and dried. When the mass was unchanged, the data could be used to calculate the solubility. The mole fraction solubility (x_1) of 5-(dithiolan-3-yl)pentanoic acid in the solvent system was obtained as follows:

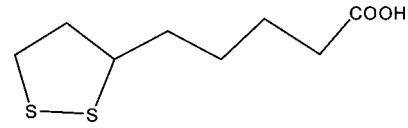

Figure 1. Chemical structure of α-5-(dithiolan-3-yl) pentanoic acid.

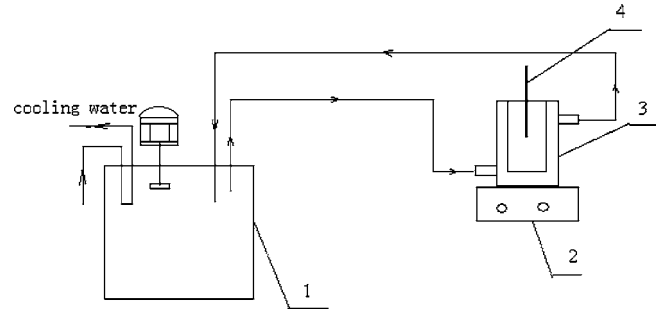

Figure 2. Experimental sketch for solubility measurement of 5-(dithiolan-3-yl)pentanoic acid: 1, thermostatic water bath; 2, magnetic stirrer; 3, crystallizer; 4, microthermometer.

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (1)$$

where m_1, m_2, and m_3 represent the masses of solute, ethyl acetate, and the other solvent in the mixed solvent system. M_1, M_2, and M_3 are the molecular weights of solute, ethyl

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Table 1. Experimental Solubility of 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Cyclohexane + Ethyl Acetate)

T/K	$10^3\ x_1^{exp}$	$10^3\ x_1^{cal}$	$10^4\ (x_1^{exp} - x_1^{cal})$
		Ethyl Acetate	
273.15	44.47	44.28	1.91
278.15	59.68	58.55	11.33
283.15	75.74	76.96	−12.20
288.15	100.17	100.60	−4.28
293.15	131.34	130.79	5.50
298.15	178.51	169.16	93.47
		$R = 5$	
278.15	7.76	5.83	19.32
283.15	10.5	8.60	18.95
288.15	13.49	12.78	7.14
293.15	18.16	19.06	−9.05
298.15	26.32	28.57	−22.56
303.15	42.61	43.00	−3.88
308.15	65.94	64.92	10.17
311.15	83.29	83.26	0.34
313.15	98.26	98.33	−0.66
		$R = 10$	
283.15	4.67	4.71	−0.42
288.15	5.99	6.19	−1.96
293.15	8.85	8.63	2.22
298.15	12.55	12.73	−1.80
303.15	19.79	19.79	−0.03
308.15	32.38	32.32	0.64
313.15	55.46	55.22	2.45
316.15	77.42	77.72	−3.04
318.15	98.53	98.42	1.07
		$R = 15$	
283.15	3.61	3.37	2.38
288.15	4.01	4.35	−3.44
293.15	6.01	6.00	0.09
298.15	8.67	8.79	−1.20
303.15	14.10	13.62	4.75
308.15	21.95	22.26	−3.16
313.15	38.27	38.22	0.49
316.15	54.03	54.04	−0.13
318.15	68.70	68.68	0.14
		$R = 20$	
283.15	2.96	2.75	2.09
288.15	3.32	3.60	−2.85
293.15	5.13	5.00	1.28
298.15	7.13	7.32	−1.89
303.15	11.35	11.25	0.98
308.15	18.16	18.11	0.48
313.15	30.39	30.43	−0.43
316.15	42.41	42.36	0.49
318.15	53.19	53.22	−0.27
		Cyclohexane	
283.15	0.71	0.86	−1.48
288.15	1.31	1.35	−0.45
293.15	2.48	2.14	3.38
298.15	3.14	3.39	−2.54
303.15	5.62	5.39	2.31
308.15	8.40	8.57	−1.72
313.15	13.68	13.65	0.27
316.15	18.05	18.06	−0.12
318.15	21.79	21.77	0.19

acetate, and the other solvent in the mixed solvent system. All of the experiments were repeated three times at each temperature, and the estimated uncertainties of the experimental values were about 0.5 %.

Results and Discussion

The solubility of 5-(dithiolan-3-yl)pentanoic acid in a single solvent or mixed solvents was determined by an analytical method. The Apelblat equation which has been used to correlate the solute concentration in saturated solutions by Apelblat and Manzurola[9−11] is applied to correlate the experimental data.

Table 2. Regressed Parameters and the Calculated Root-Mean-Square Deviation, rmsd, for 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Cyclohexane + Ethyl Acetate) from (273.15 to 318.15) K by the Apelblat Equation

solvent ratio	A	B	C	10^4 rmsd
ethyl acetate	−71.33	−756.55	12.65	38.87
$R = 5$	−1559.51	62940.08	235.90	1.80
$R = 10$	−1560.79	62959.54	236.11	2.09
$R = 15$	−1657.16	67348.11	250.38	2.40
$R = 20$	−1481.77	59604.47	224.20	1.47
cyclohexane	−396.817	10432.64	62.51	1.79

Table 3. Experimental Solubility of 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Heptane + Ethyl Acetate)

T/K	$10^3\ x_1^{exp}$	$10^3\ x_1^{cal}$	$10^4\ (x_1^{exp} - x_1^{cal})$
		Ethyl Acetate	
273.15	44.47	44.28	1.91
278.15	59.68	58.55	11.33
283.15	75.74	76.96	−12.20
288.15	100.17	100.60	−4.28
293.15	131.34	130.79	5.50
298.15	178.51	169.16	93.47
		$R = 5$	
278.15	5.03	5.56	−5.25
283.15	7.14	6.56	5.74
288.15	8.33	7.80	3.31
293.15	9.77	10.02	−2.55
298.15	12.48	12.90	−4.17
303.15	16.92	17.00	−0.82
305.15	20.31	19.11	11.99
308.15	23.48	22.93	5.54
311.15	27.83	27.71	1.18
313.15	31.25	31.58	−3.23
		$R = 10$	
288.15	2.93	3.03	−0.99
293.15	4.42	4.29	1.29
298.15	6.28	6.14	1.448
303.15	9.05	8.85	2.082
308.15	11.73	12.86	−11.28
310.15	15.03	14.96	0.69
313.15	19.74	18.82	9.2
316.15	23.74	23.72	0.20
318.15	27.45	27.712	−2.63
		$R = 15$	
288.15	1.75	2.12	−3.70
293.15	2.54	3.01	−4.71
298.15	4.02	4.31	−2.94
303.15	6.18	6.23	−0.50
308.15	8.74	9.06	−3.21
310.15	10.96	10.54	4.14
313.15	14.56	13.26	12.94
316.15	16.78	16.72	0.57
318.15	18.73	19.54	−8.07
		$R = 20$	
288.15	1.43	1.53	−0.97
293.15	2.00	2.18	−1.84
298.15	3.36	3.16	2.00
303.15	5.05	4.62	4.27
308.15	6.34	6.83	−4.90
310.15	7.963	8.00	−0.42
313.15	10.34	10.18	1.55
316.15	13.02	13.00	0.23
318.15	15.30	15.32	−0.16
		Heptane	
303.35	2.07	1.50	5.67
308.05	2.84	2.68	1.55
312.55	4.08	4.73	−6.54
317.95	9.67	9.48	1.91

$$\ln x_1 = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \qquad (2)$$

where x_1 is the mole fraction solubility of solute, T is the absolute temperature, and A, B, and C are the model parameters.

Table 4. Regressed Parameters and the Calculated Root-Mean-Square Deviation, rmsd, for 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Heptane + Ethyl Acetate) from (273.15 to 318.15) K by the Apelblat Equation

solvent volume ratio	*A*	*B*	*C*	10^4 rmsd
ethyl acetate	−71.33	−756.55	12.65	38.87
5	−779.82	30521.68	118.14	5.32
10	−473.34	15369.60	73.13	5.04
15	−461.94	14821.60	71.40	5.82
20	−542.78	18233.47	83.52	2.43
heptane	−846.75	28404.13	130.64	4.50

Table 5. Experimental Solubility of 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Hexane + Ethyl Acetate)

T/K	$10^3\ x_1^{exp}$	$10^3\ x_1^{cal}$	$10^4\ (x_1^{exp} - x_1^{cal})$
	Ethyl Acetate		
273.15	44.47	44.28	1.91
278.15	59.68	58.55	11.33
283.15	75.74	76.96	−12.20
288.15	100.17	100.60	−4.28
293.15	131.34	130.79	5.50
298.15	178.51	169.16	93.47
	$R = 5$		
283.15	6.10	5.51	5.89
288.15	7.54	6.75	7.90
293.15	8.32	8.59	−2.70
298.15	11.02	11.33	−3.10
303.15	15.13	15.45	−3.17
305.15	20.31	19.11	5.89
308.15	22.24	21.72	5.18
311.15	26.83	27.03	−1.96
313.15	31.43	31.44	−0.06
	$R = 10$		
288.15	3.90	3.85	0.47
293.15	4.07	4.24	−1.65
298.15	5.24	5.12	1.18
303.15	7.09	6.77	3.18
308.15	10.10	9.73	3.67
310.15	11.63	11.50	1.26
313.15	14.15	15.12	−9.71
316.15	21.03	20.40	6.28
318.15	25.10	25.26	−1.64
	$R = 20$		
288.15	1.74	1.92	−1.77
293.15	2.23	2.12	1.08
298.15	2.48	2.59	−1.13
303.15	3.70	3.48	2.25
308.15	5.42	5.08	3.41
310.15	6.08	6.05	0.32
313.15	7.74	8.04	−3.05
316.15	10.64	11.00	−3.57
318.15	14.04	13.74	2.97
	Hexane		
303.15	1.74	1.33	4.07
308.75	2.62	2.54	0.81
313.15	3.81	4.27	−4.57
318.55	8.33	8.18	1.49

The values of *A*, *B*, and *C* together with the root-mean-square deviation (rmsd) are listed in the Tables 1 to 6, and the rmsd is defined as follows:

$$\text{rmsd} = \left[\frac{1}{N}\sum_{i=1}^{N}(x_1^{\text{exp},i} - x_1^{\text{cal},i})^2\right]^{1/2} \quad (3)$$

where N is the number of experimental points, x_1^{exp} is the experimental value of solubility, and x_1^{cal} is the calculated solubility.

Plots of the solubility of 5-(dithiolan-3-yl) pentanoic acid in these solvents in the temperature range from (273.15 to 318.15) K are presented in Figures 3 to 6.

Table 6. Regressed Parameters and the Calculated Root-Mean-Square Deviation, rmsd, for 5-(Dithiolan-3-yl)pentanoic Acid in Mixed Solvents (Hexane + Ethyl Acetate) from (273.15 to 318.15) K by the Apelblat Equation

solvent volume ratio	*A*	*B*	*C*	10^4 rmsd
ethyl acetate	−71.33	−756.55	12.65	38.87
5	−1011.58	40388.35	152.98	4.59
10	−2303.51	98742.45	345.24	4.29
20	−2390.28	102392.80	358.20	2.43
hexane	−821.93	27943.05	126.55	3.17

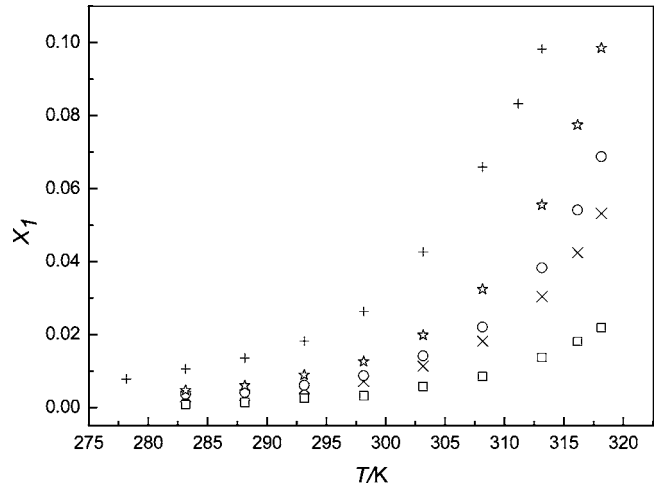

Figure 3. Mole fraction solubility of 5-(dithiolan-3-yl) pentanoic acid in solvent (cyclohexane and ethyl acetate) with different solvent ratios (*R*): +, $R = 5$; ☆, $R = 10$; ○, $R = 15$; ×, $R = 20$; □, cyclohexane.

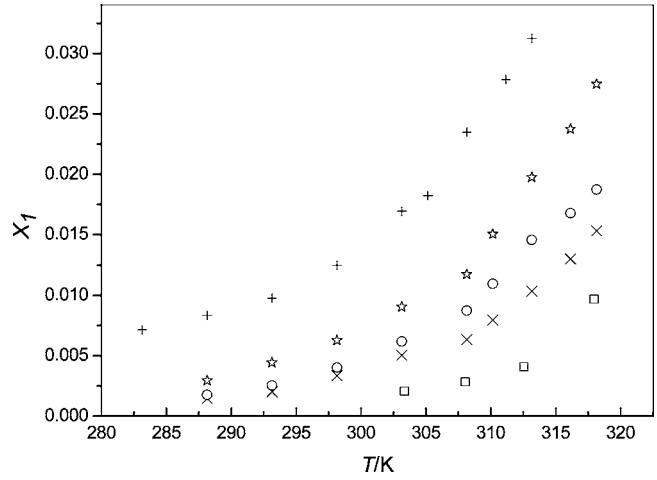

Figure 4. Mole fraction solubility of 5-(dithiolan-3-yl) pentanoic acid in solvent (heptane and ethyl acetate) with different solvent ratios (*R*): +, $R = 5$; ☆, $R = 10$; ○, $R = 15$; ×, $R = 20$; □, heptane.

In all of the tables, *R*, which represents the solvent volume ratio of the solvent mixture, can be calculated as follows:

$$R = V_i/V_{\text{ethyl acetate}} \quad (4)$$

where V_i represents the other solvents except for ethyl acetate, such as cyclohexane, hexane, and heptane.

Conclusions

For all of the mixed solvent systems, the solubility of 5-(dithiolan-3-yl)pentanoic acid increases as a function of temperature, and the solubility increases with the rise of temperature. In the mixed solvent systems, for example, the

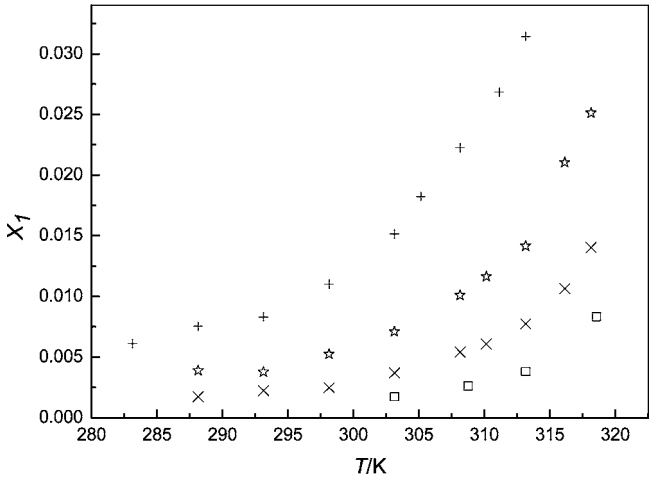

Figure 5. Mole fraction solubility of 5-(dithiolan-3-yl) pentanoic acid in solvent (hexane and ethyl acetate) with different solvent ratios (R): +, R = 5; ☆, R = 10; ×, R = 20; □, heptane.

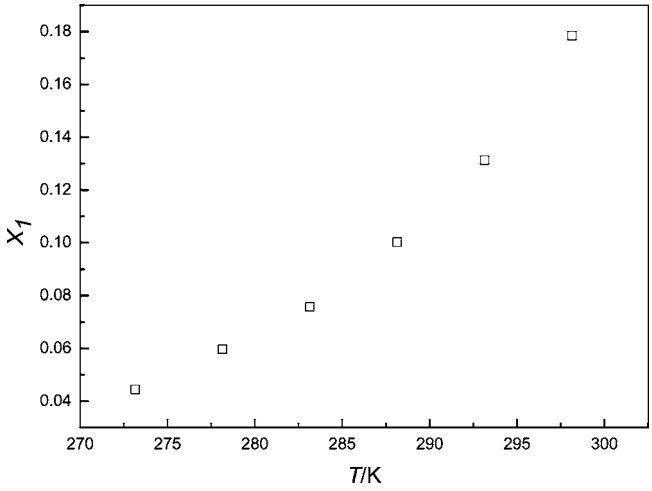

Figure 6. Mole fraction solubility of 5-(dithiolan-3-yl) pentanoic acid in ethyl acetate.

mixed solvent system of cyclohexane and ethyl acetate, the solubility of 5-(dithiolan-3-yl)pentanoic acid rises with a decrease in the solvent volume ratio (R), which indicates that pure ethyl acetate has a high dissolving power for 5-(dithiolan-3-yl) pentanoic acid; however, the higher dissolving power means more energy is consumed in cooling crystallization, and thus a mixed solvent system is used in actual production. A comparison is made among the three different mixed solvent systems, with the same solvent volume ratio (R): the molar fraction solubility decreases in the order of hexane > heptane > cyclohexane. Those results not only are helpful for industrial design but also form the basis for further theoretical studies.

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