Solubility of 4-(3,4-Dichlorophenyl)-1-tetralone in Some Organic Solvents

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The solubility of 4-(3,4-dichlorophenyl)-1-tetralone in methanol, ethanol, 2-propanol, acetone, toluene, *N*,*N*-dimethylformamide, and tetrahydrofuran were measured using a laser technique in the temperature range from (278.15 to 323.15) K. The results were correlated with a semiempirical equation, which can be used as a useful model in the production process of 4-(3,4-dichlorophenyl)- 1-tetralone and sertraline hydrochloride.

Introduction

4-(3,4-Dichlorophenyl)-1-tetralone ($C_{16}H_{12}Cl_2O$, molecular weight 291.17, CAS Registry No. 79560-19-3, white in color, and powdery in normal state) is used widely as an medicinal intermediate in the synthesis of sertraline hydrochloride, which is a very effective antidepressant used for the treatment of depression as well as dependency- and other anxiety-related disorders.[1−3] The solubility of solid compounds in pure solvents and solvent mixtures plays a crucial role in the development and operation of crystallization process properly. 4-(3,4-Dichlorophenyl)-1-tetralone has a very low solubility in water, hence some organic solvent such as ethanol, toluene, and tetrahydrofuran (THF) is employed in its crystallization process and the production of sertraline hydrochloride.[2] To determine proper solvents and to design an optimized production process, it is necessary to know the solubility of 4-(3,4-dichlorophenyl)-1-tetralone in different solvents. However, from a review of the literature, it was found that no experimental solubility data were available. In this paper, the solubility of 4-(3,4-dichlorophenyl)-1-tetralone in methanol, ethanol, 2-propanol, acetone, toluene, *N*,*N*-dimethylformamide (DMF), and THF were experimentally determined in the temperature range from (278.15 to 323.15) K. The method employed in this work was classified as the synthetic method, which was much faster and more reliable than the analytical method.[4]

Experimental Sections

Materials. An almost white crystalline powder of 4-(3,4-dichlorophenyl)-1-tetralone was purchased from Jiangsu Chemstar Industries Ltd. Its mass fraction purity determined by HPLC was higher than 99.2 %. Methanol, ethanol, 2-propanol, acetone, toluene, DMF, and THF were analytical research grade reagents from Beijing Chemical Reagent Co.

Apparatus and Procedures. A (100 and 250) mL jacked vessel was used to determined the solubility; the temperature in the vessel was maintained at the desired value by continuous forced water circulation from a thermostat (temperature uncertainty of ± 0.05 K). A mercury-in-glass thermometer (uncertainty of ± 0.05 K) was used for the measurement of the temperature in the vessel. To prevent the evaporation of the solvent, a condenser vessel was introduced. The masses of the samples and solvents were weighted using an analytical balance (Sartorius CP124S, Germany) with an uncertainty of ± 0.0001 g.

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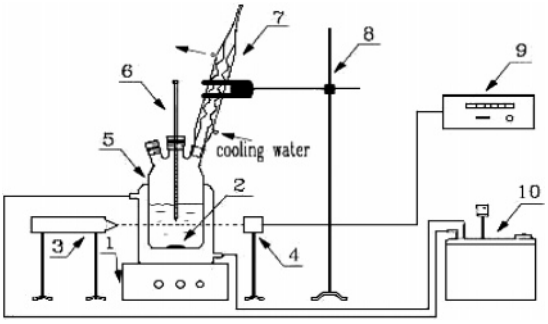

Figure 1. Schematic setup for the solubility measurement: 1, magnetic stirrer; 2, stir bar; 3, laser generator; 4, photoelectric converter; 5, dissolution vessel; 6, thermometer; 7, condenser; 8, a ring stand and clamp; 9, digital display; 10, thermostat.

The solubility of 4-(3,4-dichlorophenyl)-1-tetralone was measured using an apparatus (Figure 1) similar to that described as literature[5] and described briefly here. The solubility of 4-(3,4-dichlorophenyl)-1-tetralone was determined by the laser method.[6−9] The laser-monitoring system consisted a laser generator, a photoelectric transformer, and a light intensity display. Predetermined excess amounts of solvent and 4-(3,4-dichlorophenyl)-1-tetralone of known mass were placed in the inner chamber of the vessel. The contents of the vessel were stirred continuously at a required temperature. During experiments, the fluid in the glass vessel was monitored by a laser beam. In the early stage, the laser beam was blocked by the undissolved particles of 4-(3,4-dichlorophenyl)-1-tetralone in the solution, so the intensity of laser beam penetrating the vessel was low. Along with the dissolution of the particles, the intensity of the laser beam increased gradually. When the solute dissolved completely, the solution was clear and transparent, and the laser intensity reached maximum. Then additional solute of known mass {about (1 to 5) mg} was introduced 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 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_1 based on

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

where m_1 and m_2 represent the mass of the solute and solvent,

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Table 1. Mole Fraction Solubility of 4-(3,4-Dichlorophenyl)-1-tetralone x_1 in Different Solvents between (278.15 and 323.15) K

T/K	$10^3\,x_1$	$10^3\,x_1^{calc}$	T/K	$10^3\,x_1$	$10^3\,x_1^{calc}$
		Methanol			
277.93	0.8696 ± 0.0080	0.7956	302.77	2.928 ± 0.008	2.929
283.06	1.070 ± 0.008	1.087	308.56	3.721 ± 0.008	3.709
288.28	1.409 ± 0.008	1.457	313.53	4.463 ± 0.008	4.462
293.42	1.859 ± 0.008	1.902	319.04	5.333 ± 0.008	5.379
298.04	2.351 ± 0.008	2.374			
		Ethanol			
283.12	1.715 ± 0.008	1.714	308.32	4.902 ± 0.008	4.923
288.27	2.099 ± 0.008	2.056	314.17	6.669 ± 0.008	6.625
293.38	2.524 ± 0.008	2.509	318.74	8.518 ± 0.008	8.450
298.04	3.028 ± 0.008	3.052	323.26	10.83 ± 0.008	10.85
302.93	3.759 ± 0.008	3.804			
		2-Propanol			
278.12	0.9552 ± 0.0086	0.9404	303.36	3.704 ± 0.009	3.713
283.38	1.275 ± 0.009	1.246	308.46	4.958 ± 0.009	4.928
288.33	1.634 ± 0.009	1.628	313.26	6.492 ± 0.009	6.439
293.07	2.088 ± 0.009	2.108	318.54	8.644 ± 0.009	8.651
298.33	2.784 ± 0.009	2.813			
		Acetone			
282.13	16.16 ± 0.03	17.06	307.94	49.80 ± 0.03	50.45
288.02	21.68 ± 0.03	21.09	313.74	67.27 ± 0.03	67.57
292.83	26.06 ± 0.03	25.50	318.56	87.13 ± 0.03	87.11
298.28	32.12 ± 0.03	32.15	323.57	114.0 ± 0.03	114.6
303.23	39.74 ± 0.03	40.26			
		Toluene			
278.18	39.15 ± 0.09	39.02	303.14	92.37 ± 0.08	92.33
283.13	46.14 ± 0.08	45.99	308.46	112.2 ± 0.1	111.9
288.28	54.77 ± 0.08	54.77	313.43	134.6 ± 0.1	134.3
293.22	64.85 ± 0.08	64.97	318.34	161.0 ± 0.1	161.0
298.12	77.07 ± 0.08	77.19			
		DMF			
278.16	33.50 ± 0.08	33.36	303.28	88.08 ± 0.07	88.23
283.37	40.75 ± 0.08	40.74	308.28	106.2 ± 0.1	106.2
288.12	48.71 ± 0.08	48.89	313.32	129.0 ± 0.1	128.9
293.13	58.96 ± 0.07	59.28	318.27	155.5 ± 0.1	155.9
298.17	71.66 ± 0.07	71.97			
		THF			
278.04	69.94 ± 0.07	71.14	298.24	124.2 ± 0.1	124.4
282.93	82.28 ± 0.07	81.67	302.94	140.2 ± 0.1	141.0
288.33	95.97 ± 0.07	94.92	308.34	161.9 ± 0.1	162.6
293.28	109.3 ± 0.1	108.7	313.52	186.8 ± 0.1	186.1

and M_1 and M_2 are the molecular weight of the solute and the solvent, respectively.

Results and Discussion

The solubility of 4-(3,4-dichlorophenyl)-1-tetralone in methanol, ethanol, 2-propanol, acetone, toluene, DMF, and THF at different temperatures are shown in Table 1 and more visually given in Figure 2.

According to the solid−liquid phase equilibrium theory, the relationship between solubility and temperature is generally modeled by[10]

$$\ln x_1 = -\frac{\Delta H_{f,1}}{RT_{f,1}}\left(\frac{T_{f,1}}{T}-1\right) - \frac{\Delta C_{pf,1}}{R}\left(\frac{T_{f,1}}{T}-1\right) + \frac{\Delta C_{pf,1}}{R}\ln\frac{T_{f,1}}{T} - \ln\gamma_1 \quad (2)$$

where x_1, γ_1, $\Delta H_{f,1}$, $\Delta C_{pf,1}$, $T_{f,1}$, R, and T stand for the mole fraction of the solute, activity coefficient, enthalpy of fusion, difference in the solute heat capacity between the solid and liquid at the melting temperature, melting temperature of the solute, gas constant, and equilibrium temperature in the saturated solution, respectively. For regular solutions, the activity coefficient is given by[11]

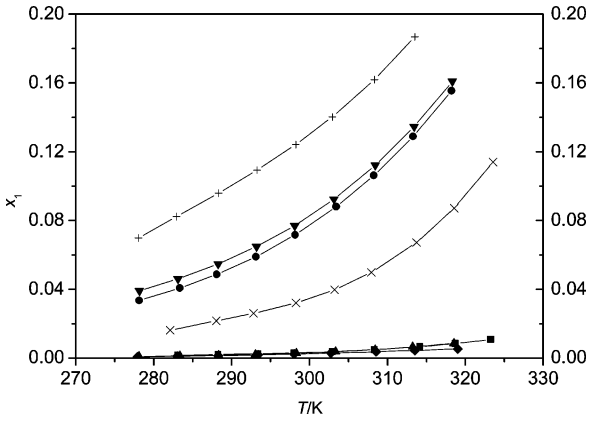

Figure 2. Mole fraction solubility of 4-(3,4-dichlorophenyl)-1-tetralone x_1 in different solvents: ◆, methanol; ■, ethanol; ▲, 2-propanol; ×, acetone; ▼, toluene; ●, DMF; +, THF.

Table 2. Parameters of Equation 5 for 4-(3,4-Dichlorophenyl)-1-tetralone in Different Solvents

solvent	a	b	c	10^4 rmsd
methanol	268.01	−15686	−38.865	0.40
ethanol	−525.12	19820	79.482	0.39
2-propanol	−249.00	6660.8	38.749	0.28
acetone	−495.36	18570	75.406	5.70
toluene	−196.50	5953.8	30.534	1.86
DMF	−145.74	34589	23.081	2.50
THF	−58.609	481.32	9.6370	8.30

$$\ln\gamma_1 = A + \frac{B}{T/\mathrm{K}} \quad (3)$$

where A and B stand for empirical constants. Introducing γ_1 from eq 3 into eq 2 and subsequent rearrangements results in

$$\ln x_1 = \left[\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}(1+\ln T_{f,1}) - A\right] - \left[B + \left(\frac{\Delta H_{f,1}}{RT_{f,1}} + \frac{\Delta C_{pf,1}}{R}\right)T_{f,1}\right]\frac{1}{T} - \frac{\Delta C_{pf,1}}{R}\ln T \quad (4)$$

Equation 4 can be written as

$$\ln x_1 = a + \frac{b}{T/\mathrm{K}} + c\ln T/\mathrm{K} \quad (5)$$

where T is the absolute temperature and a, b, and c are empirical constants.

The solubility data are correlated with eq 5. The difference between experimental and calculated results is presented in Table 1. The values of the three parameters a, b, and c together with the root-mean-square deviations (rmsd) are listed in Table 2. The rmsd is defined as the following:

$$\mathrm{rmsd} = \left[\frac{\sum_{i=1}^{N}(x_{1,i} - x_{1,i}^{cacl})^2}{N-1}\right]^{1/2} \quad (6)$$

where N is the number of experimental points; $x_{1,i}^{calc}$ is the solubility calculated from eq 5; and $x_{1,i}$ is the experimental value of solubility.

From Table 1 and Figure 2, we could draw these conclusions: (i) The solubility of 4-(3,4-dichlorophenyl)-1-tetralone in the seven pure solvents all increase with increase of temperature. (ii) The solubility of 4-(3,4-dichlorophenyl)-1-

tetralone in these seven solvents decreases in the order THF > toluene > DMF > acetone > alcohols (methanol, ethanol, and 2-propanol). The solubility values in ethanol and 2-propanol are almost equal, which is higher than that in methanol. (iii) According to the values of the rmsd, it can be seen that the solubility of 4-(3,4-dichlorophenyl)-1-tetralone in these solvents under consideration can be fitted with eq 5 very well.

From Table 2, we could find the following: (i) The values of parameter c in all seven solvents are relatively small, which represents the relatively small $\Delta C_{pf,1}$. This is true for many compounds under most conditions, so the last term of eq 5 is neglected in many cases. (ii) Only for methanol of all the seven solvents, the parameter c in eq 5 has a negative value. This indicates that the heat capacity of the 4-(3,4-dichlorophenyl)-1-tetralone solution in methanol increases when 4-(3,4-dichlorophenyl)-1-tetralone transits from liquid phase to solid phase and is different from the others. (iii) For a given compound, the values of a and b of eq 5 reflect the variations in the solution activity coefficient and provide an indication of the solution non-idealities on the solubility of the solute. Therefore, the experimental solubility and correlation equation in this work can be used as a useful model in the crystallization of 4-(3,4-dichlorophenyl)-1-tetralone and the production process of sertraline hydrochloride.

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