Solubilities of Some Thioxanthone Derivatives in Supercritical CO_2

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Solubilities of four thioxanthone derivatives in supercritical CO_2 have been measured at the temperatures (308, 318, 328, 338, and 348) K in a pressure range from (122 to 355) bar. The measurements have been performed by using a simple static-sampling type apparatus. The effects of temperature, pressure, and density of carbon dioxide on solubility of thioxanthone derivatives have been investigated. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with the experimental data.

Introduction

Supercritical fluid extraction (SFE) takes advantage of the fact that a supercritical fluid can have properties intermediate between those of a liquid and those of a gas. Those properties such as density (related to solvating power), viscosity (related to flow rate), and diffusion coefficients (related to mass transfer within the fluid) can be controlled by pressure and temperature.[1] By controlling these properties, selective, efficient, and rapid extraction of solutes can occur. In recent years, widespread attention has been paid to the supercritical fluids, due to their application in food processing as well as in the pharmaceutical industries.[2−5] Not only for food and pharmaceutical industries but also for all other processes, a knowledge of the solubility of substances in supercritical fluid is of vital importance. Thus, large numbers of studies have been made on solubilities of many compounds in supercritical carbon dioxide.[6]

Thioxanthone derivatives have been shown to possess very useful properties, especially the medicinal and the photoinitiation activities. Included in such biologically active molecules are neuroleptic agents such as chlorpromazine, thioridazine, and thiothixene. These substances are well-known pharmacological agents and have been the focus of structure−activity relationship studies.[7] Hycanthone, a thioxanthone marketed as an antischistosomal drug, was evaluated as an antitumor agent.[8]

Thioxanthone and its derivatives acquired industrial importance as radical sources in combination with tertiary amines under UV irradiation.[9] These compounds are also effective sensitizers in radical polymerization of vinyl monomers, in photocuring of coating systems.[10]

We have recently reported the solubilities of some dihydroxy-9,10-anthraquinone,[11,12] hydroxyxanthene,[13] and 9-anthrone derivatives[14] in supercritical carbon dioxide. This work was undertaken to determine the solubilities of thioxanthone (T1), 1-hydroxythioxanthane (T2), 1-hydroxy-3-methylthioxanthone (T3), and 1,4-dihydroxy-3-methylthioxanthone (T4) in supercritical carbon dioxide over a wide range of temperatures and pressures. The measured solubilities were nicely correlated using a semiempirical model proposed by Bartle et al.[6]

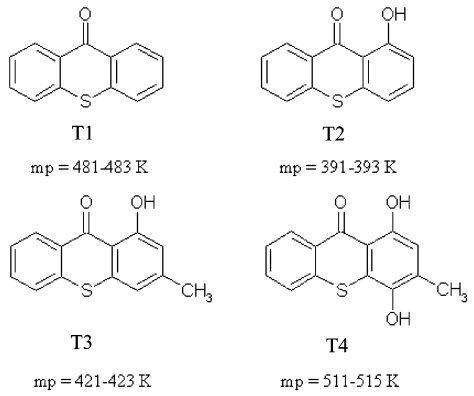

Figure 1. Structures and melting points of thioxanthone derivatives.

Experimental Section

Materials. HPLC-grade methanol (Merck) was used as received. Pure carbon dioxide (Sabalan, Tehran, 99.99%) was used for all extractions. The thioxanthone derivatives T1 to T4 were synthesized and purified as described elsewhere.[15] Purities of the thioxanthone derivatives were confirmed by spectroscopic data and elemental analysis to be approximately >99.5 mol %. The structures of the thioxanthone derivatives used are shown in Figure 1.

Equipment and Procedures. Melting points of the thioxanthone derivatives were obtained by using a melting point measurement instrument from Gallenkamp Company (U.K.). A Suprex MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determination in the SFE mode was used. Detailed descriptions of the apparatus and operating procedures are given in our previous papers.[11,12] In this system, contact between the solute and the fluid is established. After the equilibrium is reached, a known volume of the fluid saturated with the solute is chosen and the amount of the solute is measured. Then, by knowing the amounts of both the fluid and the solute, the solubility is calculated. The solid solutes (100 mg) were mixed well with

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Table 1. Solubility of Thiaxanthone Derivatives T1 to T4 in Supercritical Carbon Dioxide

			T1		T2		T3		T4	
T/K	P/bar	ρ/kg·m^{-3}	10^4y	s/g·dm^{-3}	10^4y	s/g·dm^{-3}	10^4y	s/g·dm^{-3}	10^5y	s/g·dm^{-3}
308	121	771	0.24	0.09	0.99	0.40	0.57	0.24	0.35	0.016
	152	818	0.28	0.11	1.16	0.49	0.56	0.25	0.39	0.019
	182	850	0.30	0.12	1.38	0.61	0.65	0.31	0.38	
	212	876	0.37	0.16	1.64	0.75	0.72	0.35	0.67	0.035
	243	897	0.42	0.18	1.92	0.89	0.76	0.38	0.79	0.041
	273	916	0.43	0.19	2.11	1.00	0.83	0.42	0.87	0.047
	304	931	0.45	0.20	2.21	1.07	0.92	0.47	0.94	0.052
	334	946	0.54	0.25	2.38	1.17	1.03	0.54	1.12	0.062
	354	955	0.52	0.24	2.59	1.28	1.04	0.55	1.20	0.067
318	121	661	0.16	0.05	0.74	0.25	0.45	0.16	0.42	0.016
	152	745	0.28	0.10	1.12	0.43	0.59	0.24	0.53	0.023
	182	792	0.39	0.15	1.46	0.60	0.76	0.33	0.93	0.043
	212	826	0.46	0.18	1.75	0.75	0.87	0.40	1.01	0.049
	243	852	0.53	0.22	2.00	0.88	1.04	0.49	1.19	0.060
	273	875	0.51	0.22	2.22	1.01	1.15	0.55	1.36	0.070
	304	893	0.65	0.28	2.45	1.14	1.25	0.61	0.44	0.023
	334	910	0.70	0.31	2.61	1.23	1.38	0.69	1.42	0.076
	354	919	0.68	0.30	2.75	1.31	1.47	0.74	1.55	0.083
328	121	516	0.19	0.05	0.61	0.16	0.41	0.12		
	152	657	0.29	0.09	1.02	0.35	0.52	0.19	0.57	0.022
	182	726	0.47	0.16	1.47	0.55	0.76	0.30	0.95	0.040
	212	771	0.61	0.23	1.86	0.74	0.96	0.41	1.10	0.050
	243	804	0.71	0.28	2.22	0.92	1.14	0.50	1.48	0.070
	273	831	0.80	0.32	2.49	1.07	1.40	0.64	1.97	0.096
	304	853	0.85	0.35	2.83	1.25	1.53	0.72	2.33	0.117
	334	872	0.97	0.41	3.11	1.41	1.68	0.81	2.38	0.122
	354	884	1.06	0.45	3.28	1.50	1.93	0.94	2.74	0.142
338	121	396	0.00	0.00	0.37	0.08	0.36	0.08		
	152	561	0.20	0.05	0.72	0.21	0.53	0.17	0.28	0.009
	182	654	0.43	0.14	1.32	0.45	0.81	0.29	0.81	0.031
	212	712	0.64	0.22	1.84	0.68	1.11	0.43	1.51	0.063
	243	754	0.83	0.30	2.35	0.92	1.40	0.58	2.07	0.091
	273	786	0.94	0.36	2.80	1.14	1.58	0.68	2.63	0.121
	304	812	1.08	0.42	3.25	1.37	1.96	0.88	3.08	0.147
	334	834	1.26	0.51	3.72	1.61	2.20	1.01	3.19	0.156
	354	848	1.29	0.53	3.88	1.71	2.35	1.10	3.67	0.183
	121	327	0.01	0.00	0.33	0.06	0.43	0.08		
	152	477	0.16	0.04	0.67	0.17	0.49	0.13	0.50	0.014
	182	585	0.43	0.12	1.20	0.36	0.80	0.26	1.23	0.042
	212	652	0.74	0.23	1.82	0.62	1.21	0.43	2.14	0.082
	243	702	1.02	0.34	2.46	0.89	1.56	0.60	1.92	0.079
	273	740	1.22	0.44	3.03	1.16	1.85	0.75	2.89	0.126
	304	772	1.43	0.53	3.61	1.45	2.42	1.03	3.29	0.149
	334	796	1.58	0.61	4.00	1.65	2.82	1.24	3.93	0.184
	354	811	1.68	0.66	4.24	1.78	3.18	1.42	4.31	0.205

glass beads and packed into a 1 mL extraction vessel. The procedure increases the surface area for contact between the sample and the supercritical fluid and, consequently, the equilibration time. Supercritical CO_2 was pressurized and passed into the extraction vessel. After equilibrium at the desired temperature and pressure was reached (30 min), a 158 μL portion of the saturated supercritical CO_2 was loaded into the injection loop. It should be noted that, by monitoring the solubility data versus time, 30 min was found to be adequate to ensure the attainment of equilibrium. The loop was depressurized into a collection vial containing methanol. Finally, the sample loop was washed with methanol, which was collected in the collection vial. The final volume of the solution was 5 mL. The equilibrium temperatures and pressures were measured to accuracies of $\pm$1 K and $\pm$0.5 bar, respectively. In the present work, a syringe pump is used for the pressure adjustment. With this pump, it is possible to adjust the pressure of system at any desired value with a precision of $\pm$0.5 bar. The adjusted pressure will be held constant during an equilibration time of 30 min.

The solubilities of T1 toT3 were calculated by absorbance measurements at λ_{max} of each compound using a model 2100 Shimadzu UV−vis spectrophotometer. The solubility of T4 was calculated by fluorescent intensity measurements (λ_{emi} = 490.1 nm and λ_{exc} = 290.0 nm) using a model LS-50 B Perkin-Elmer luminescence spectrofluorimeter. The stock solutions of compounds T1 to T4 (500 ppm) were prepared by dissolving appropriate amounts of the solid samples in methanol. A set of standard solutions (1 ppm to 50 ppm for T1 to T3 and 0.5 to 4 ppm for T4) were then prepared by appropriate dilution of the stock solutions. The calibration graphs obtained (with regression coefficients better than 0.999) were used to establish the concentration of thioxanthone derivatives in the collection vial. The obtained results were used to calculate the mole fraction solubilities of solutes in supercritical carbon dioxide, y. The solubilities measured were generally reproducible within $\pm$3% (given as standard deviation of at least three replicate measurements).

Results and Discussion

The reliability and accuracy of the solubility measurement technique were primarily established by measuring the solubility of naphthalene in supercritical CO_2 at 308 K and different pressures, as described before.[12] The differences of our results compared to those reported in the literature are in the range 0.8% to 6.8%.

Table 1 shows the solubilities of thioxanthones T1 to T4 at the temperatures (308, 318, 328, 338, and 348) K over

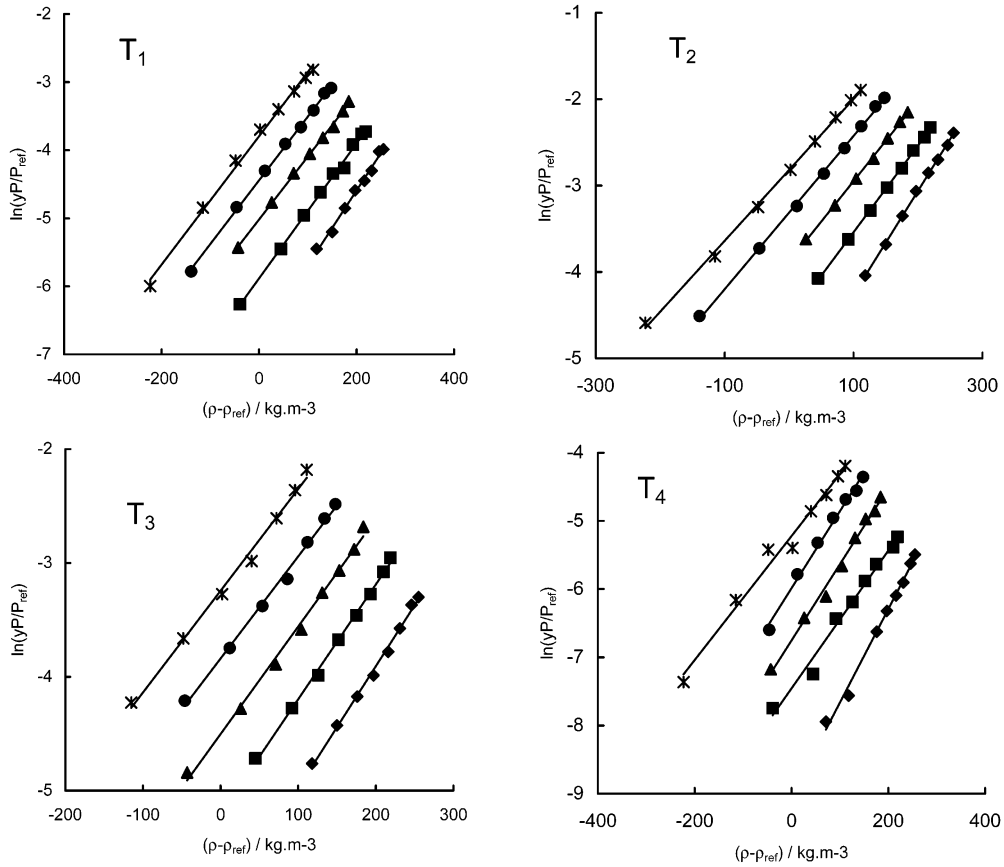

Figure 2. Plots of $\ln(yP/P_{ref})$ versus $(\rho - \rho_{ref})$ for T1 to T4 at the temperatures (308, ◆; 318 ■; 328, ▲; 338, ●; 348, ∗) K.

Table 2. Solubility Constants *a*, *b*, and *C* and Estimated $\Delta_{vap}H$ Values Obtained from the Data Correlation Procedure

compd	*a*	*b*/K	C/m^3·kg^{-1}	$\Delta_{vap}H$/kJ·mol^{-1}
T1	17.48	−7408	0.0098	61.6
T2	14.16	−5917	0.0097	49.2
T3	16.41	−6854	0.0096	57.0
T4	19.46	−8558	0.0104	71.2

the pressure range from (122 to 355) bar. The resulting solubilities are reported in terms of equilibrium mole fraction, *y*, and equilibrium solubility, *s* (g·dm^{-3}), of the solute in supercritical carbon dioxide. To the best of our knowledge, there is no previous report on the solubility of thioxanthone derivatives examined in supercritical CO_2; thus, no comparison with other data can be made.

From the data given in Table 1, it is readily seen that the solubility of thioxanthones increases with increasing pressure at a constant temperature. The influence of pressure on the solubilities is more pronounced at higher temperatures. Temperature has two opposite effects on the solute solubilities. At pressures under the crossover region (180 bar for T1 and T3, 213 bar for T2, and 270 bar for T4), the solvent densities are lowered by small increases in temperature; because the density effect is dominant in this region, the solubility will decrease with rising temperature. At higher pressures, the solvent density is less dependent on temperature, so that the increase in solubility is primarily due to the higher vapor pressure of the solid.

The results obtained in this study indicate that the solubilities of thioxanthones vary in the order T2 > T3 > T1 ≫ T4. The solubilities of thioxanthone derivatives parallel the order of their relative melting points (Figure 1); the higher the melting point, the lower the solubility. Similar correlations have been reported in the literature.[2,16] The experimental solubility data for the thioxanthones were correlated using the equations proposed by Bartle et al.,[6]

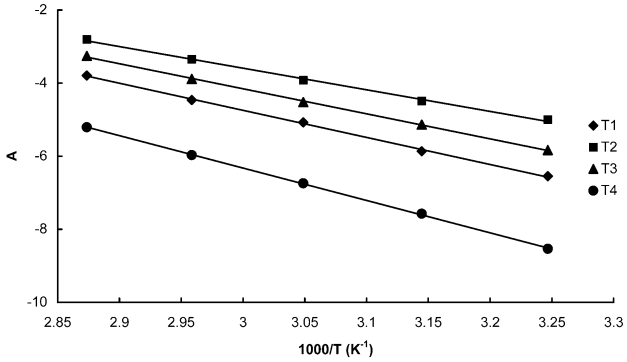

Figure 3. Plots of *A* versus 1/*T* for T1 to T4.

$$\ln(yP/P_{ref}) = A + C(\rho - \rho_{ref}) \quad (1)$$

where

$$A = a + b/T \quad (2)$$

and

$$\ln(yP/P_{ref}) = a + b/T + C(\rho - \rho_{ref}) \quad (3)$$

where P_{ref} is a standard pressure of 1 bar, ρ_{ref} is a reference density, for which a value of 700 kg·m^{-3} was used, and *A* and *C* are constant values for a given temperature. The reason for using ρ_{ref} is to make the constant *A* much less sensitive to experimental errors in the solubility data, and

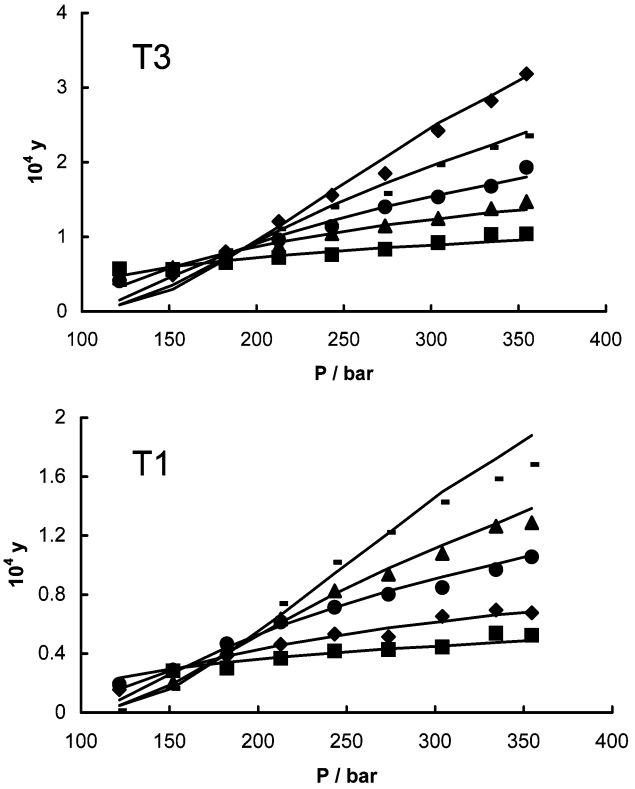

Figure 4. Comparison of experimental (points) and calculated (lines) solubilities at the temperatures (308, ■; 318, ◆; 328, ●; 338, ▲; 348, —) K for T1 and T3.

to avoid the large variations caused by extrapolation to zero density. The value of *C*, which results physically from solvation of the solute by supercritical fluid, is assumed to remain constant over the entire temperature range studied.[17] In the first step, the $\ln(yP/P_{ref})$ values were plotted against density (Figure 2), and the resulting plots were fitted with a straight line by least-squares regression to estimate the *C* and *A* values. According to eq 1, the plots are expected to be reasonably straight lines of similar slopes. The values of *C*, obtained from the slopes of the corresponding plots, were then averaged for each compound (Table 2).

By holding *C* at its average value, the experimental solubility data were then used to evaluate the *A* values at various temperatures for each thioxanthone. The plots of *A* versus $1/T$ for each compound resulted in a straight line (Figure 3) from the intercept and slope of which the values of *a* and *b* for different compounds were calculated and are also included in Table 2. Finally, the values of *a*, *b*, and *C* were used to predict solubility from eq 3. Figure 4 compares the calculated isotherms with the experimental data for T1 and T3. As shown by Figure 4, the agreement is satisfactory.

The parameter *b* is approximately related to the enthalpy of vaporization of the solid solution $\Delta_{vap}H$ by[17]

$$\Delta_{vap}H = -Rb \quad (4)$$

where *R* is the gas constant. The validity of eq 4 relies on the assumption that the enhancement factor, $\ln(yP/P_v)$, where P_v is the vapor pressure of the solute, is independent of temperature. This assumption was found to be nearly true in practice. The estimated $\Delta_{vap}H$ values are presented in Table 2.

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