J. Chem. Eng. Data **1999,** *44,* 1135−1138

Solubilities of Some Hydroxyxanthone Derivatives in Supercritical Carbon Dioxide

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The equilibrium solubilities of four hydroxyxanthone derivatives have been measured in supercritical carbon dioxide using a simple and reliable static method. The measurements were performed in the pressure range 74.0−354.6 bar at the temperatures 32, 45, 55, 65, and 75 °C. The order of solubility observed for the compounds used was discussed in terms of their possible intra- and intermolecular H-bonds and polarities. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with the experimental data.

Introduction

During the past decade, supercritical fluids have been widely applied to the extraction processes in food processing, pharmaceutical and petroleum industries, and so forth (Bartle et al., 1991; McHugh and Krukonis, 1994; Palmer and Ting, 1995). Analytical-scale supercritical fluid extraction (SFE) has also become increasingly widespread in recent years (Daneshfar et al., 1995; Kauffman, 1996). The main advantages of analytical SFE include the density dependent solvation capability that allows some degree of extraction selectivity, the ease with which the supercritical fluid can be removed, eliminating or reducing the use of organic solvents in sample preparation, and reducing the extraction time. Information on solubilities in supercritical fluids is of vital importance for the efficient design of the extraction processes on the basis of supercritical solvents.

Xanthones are among the most important naturally occurring compounds and bear a close structural relationship to other naturally occurring γ-pyrone derivatives (Dean, 1963). The growing interest in study of xanthone derivatives is mainly due to their pharmacological and microbiological activities (Arcamone, 1978; Dimarco et al., 1975). Different hydroxyxanthone derivatives such as 1,4-, and 1,6-dihydroxyxanthone and 1,5,6-trihydroxyxanthone are encountered in naturally occurring compounds and constitute a major part of the antitumor antibiotic drug bikaverin (Fischer and Kuita, 1985; Gunasekera and Sultanbawa, 1975; Gunasekera et al., 1975; Quillian and Scheinmann, 1973).

We have recently reported the solubilities in supercritical carbon dioxide of some 1,4-dihydroxy-9,10-anthraquinone (Fat'hi et al., 1998) and 1,8-dihydroxy-9,10-anthraquinone derivatives (Fat'hi et al., 1999) and of dihydroxybenzene isomers (Yamini et al., 1998). This work was undertaken to determine the solubilities of four hydroxyxanthone derivatives, recently synthesized in this research group (Hosseini, 1998), 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 (Bartle et al., 1991; Safa-Ozcan et al., 1997).

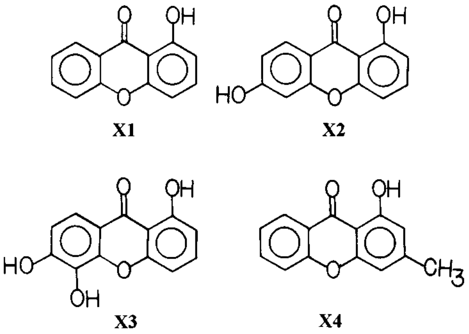

Figure 1. Structure of hydroxyxanthones.

Experimental Section

HPLC-grade methanol (Aldrich) was used as received. Pure carbon dioxide (Sabalan, Tehran, 99.99%) was used for all extractions. The xanthone derivatives 1-hydroxyxanthone (X1), 1,6-dihydroxyxanthone (X2), 1,5,6-trihydroxyxanthone (X3), and 1-hydroxy-3-methylxanthone (X4) were synthesized (Hosseini, 1998) and used after recrystallization from reagent-grade benzene (Merck) and vacuum-drying. Structures of the xanthone derivatives used are shown in Figure 1.

A Suprex MPS/225 integrated supercritical fluid extraction−supercritical fluid chromatography (SFE-SFC) system equipped with a modified static system (Fat'hi et al., 1998) for solubility determination in SFE mode was used. Solubility measurements were accomplished with a 1-mL extraction vessel in the pressure range from 74.0 to 354.6 bar at the temperatures 32, 45, 55, 65, and 75 °C for a duration of 30 min. It should be noted that, by monitoring the solubility data versus time, 30 min was found adequate to ensure the attainment of equilibrium. The solid solutes (100 mg) were mixed well with 1 g of glass beads and packed into the extraction vessel. This procedure prevents channeling, increases the contact surface between the sample and the supercritical fluid, and, consequently,

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10.1021/je9900068 CCC: $18.00

Table 1. Solubilities of 1-Hydroxyxanthone (X1), 1,6-Dihydroxyxanthone (X2), 1,5,6-Trihydroxyxanthone (X3), and 1-Hydroxy-3-methylxanthone (X4) in Supercritical Carbon Dioxide

		X1		X2		X3		X4	
P/bar	ρ/kg·m^{-3}	s/g·dm^{-3}	$10^4 y$	s/g·dm^3	$10^4 y$	s/g·dm^{-3}	$10^4 y$	s/g·dm^{-3}	$10^4 y$
$t = 32$ °C									
74.0	556	0.40	1.49	0.005	1.58	0.86	2.80	1.33	4.637
111.5	786	0.71	1.88	0.005	1.31	1.25	2.85	2.13	5.261
152.0	843	1.93	4.75	0.012	2.85	1.74	3.71	2.75	6.331
192.5	880	2.82	6.65	0.013	2.76	2.29	4.69	3.71	8.185
233.0	907	3.71	8.46	0.016	3.47	2.53	5.02	4.62	9.908
273.6	930	4.04	8.99	0.019	4.00	2.70	5.23	5.75	12.006
314.1	950	4.60	10.03	0.041	8.32	3.41	6.46	6.34	12.955
354.6	968	5.03	10.76	0.058	11.48	3.67	6.83	6.77	13.594
$t = 45$ °C									
74.0	203	0.35	3.57	0.003	2.68	0.73	6.50	0.49	4.71
111.5	608	0.72	2.45	0.004	1.31	0.95	2.80	1.06	3.40
152.0	747	1.63	4.53	0.011	2.93	1.65	3.97	2.39	6.23
192.5	805	2.69	6.93	0.023	5.51	2.19	4.89	3.73	9.01
233.0	845	3.63	8.89	0.032	7.35	2.45	5.22	4.96	11.40
273.6	874	4.65	11.02	0.040	8.85	2.91	6.00	6.11	13.59
314.1	898	5.31	12.75	0.066	14.21	3.68	7.39	7.50	16.21
354.6	920	6.24	14.06	0.075	15.71	4.05	7.92	8.32	17.55
$t = 55$ °C									
74.0	179	0.30	3.48	0.003	3.05	0.56	5.68	0.17	1.83
111.5	433	0.50	2.39	0.003	1.52	0.79	3.29	0.57	2.58
152.0	658	0.89	2.81	0.015	4.37	1.52	4.16	2.41	7.13
192.5	743	2.32	6.47	0.023	5.95	1.99	4.83	3.31	8.67
233.0	794	3.41	8.90	0.036	8.63	2.87	6.51	5.16	12.63
273.6	832	4.81	11.98	0.051	11.90	3.27	7.07	7.98	18.61
314.1	862	6.11	14.67	0.081	18.17	4.47	9.33	9.19	20.69
354.6	886	7.43	17.36	0.096	20.82	5.11	10.38	9.73	21.32
$t = 65$ °C									
74.0	162	0.30	3.84	0.002	2.97	0.59	6.60	0.14	1.68
111.5	331	0.43	2.71	0.003	1.96	0.80	4.36	0.44	2.59
152.0	562	0.70	2.60	0.009	3.05	1.37	4.38	1.98	6.86
192.5	677	1.78	5.45	0.022	6.30	2.12	5.63	3.35	9.61
233.0	741	3.16	8.84	0.041	10.56	3.32	8.07	4.92	12.90
273.6	786	4.86	12.81	0.080	19.51	4.16	9.52	8.57	21.17
314.1	822	6.57	16.54	0.104	24.47	5.38	11.79	9.93	23.44
354.6	849	7.95	19.38	0.120	27.23	6.28	13.31	10.53	24.06
$t = 75$ °C									
74.0	148	0.25	3.56	0.002	2.15	0.53	6.49	0.149	1.961
111.5	280	0.31	2.33	0.002	1.34	0.63	4.08	0.517	3.589
152.0	477	0.45	1.97	0.003	3.21	1.08	4.07	1.429	5.825
192.5	608	1.40	4.77	0.020	6.47	2.36	6.98	2.948	9.420
233.0	688	2.93	8.84	0.050	14.09	3.69	9.65	5.144	14.521
273.6	741	4.90	13.69	0.097	25.24	4.90	11.90	9.217	24.134
314.1	781	7.00	18.56	0.124	30.69	6.55	15.09	10.971	27.245
354.6	812	8.71	22.20	0.151	35.88	7.60	16.84	12.654	30.217

reduces the equilibration time. Sintered stainless steel filters (5 μm) were used to prevent any carry-over of the solutes.

The solubilities were calculated by absorbance measurements at $\lambda_{\max}$ of each compound using a model 2100 Shimadzu UV−vis spectrophotometer. The stock solutions of the compounds X1−X4 (100 μg mL^{-1}) were prepared by dissolving appropriate amounts of solid samples in methanol. A set of standard solutions was then prepared by appropriate dilution of the stock solutions. The calibration curves obtained (with regression coefficients better than 0.999) were used to establish the concentration of the xanthone derivatives in the collection vial. The mole fraction compositions of the solutes were generally reproducible within ±4%.

Results and Discussion

The reliability of the apparatus was preliminary checked by measuring the solubility of naphthalene in supercritical CO_2 at 35 °C, as was described before (Fat'hi et al., 1998). The solubilities of the xanthone derivatives at the temperatures 32, 45, 55, 65, and 75 °C and in the pressure range from 74.0 to 354.6 bar were then determined. The resulting solubilities in terms of the equilibrium mole fraction y of the solute and in grams per liter of the solute in supercritical CO_2 are summarized in Table 1. Each reported solubility is the average value of three replicate samples.

From the data given in Table 1, it is readily seen that the solubility of compounds X1−X4 increases with increasing pressure at constant temperature. However, despite the decreased density of CO_2 at higher temperatures (at constant pressures), the influence of pressure on the solubilities is more pronounced at higher temperatures. For example, raising the pressure from 74.0 to 354.6 bar enhanced the solubility of X3 by a factor of 5.5 at 45 °C and a factor of 14.3 at 75 °C. Obviously, this is in contrast to conventional wisdom stating that the supercritical fluid's density must increase in order to increase the solubility and extraction efficiency (Miller et al., 1996; Mitra and Wilson, 1991). The data given in Table 1 clearly reveal that while, at a constant temperature, increasing density (by increasing pressure) enhances the solubility, the increase in density at a constant pressure (by lowering temperature) actually results in diminished solubility. Similar observations have already been reported in the literature (Bartle et al., 1991; Fat'hi et al., 1998; Mitra and Wilson, 1988).

Examination of the temperature effect on the solubility data (Table 1) reveals the existence of a retrograde (crossover/pressure effect) behavior for the xanthone derivatives in supercritical CO_2, as was reported for different organic compounds previously (Fat'hi et al., 1998 and 1999; Tsai and Tsai, 1995; Yu et al., 1995). At pressures above the crossover point (i.e., about 190 bar), solubilities increase with increasing both pressure and temperature, while, below this point, solubilities increase with increasing pressure but decrease with increasing temperatures. This could be due to various temperature effects on such diverse properties of the system as the solute vapor pressure, the solvent density, and the intermolecular interactions in the supercritical fluid phase.

The results obtained in this study indicate that the solubilities of the hydroxyxanthone derivatives studied vary in the order X4 > X1 > X3 ≫ X2. The possible intramolecular hydrogen bonding of X4, X1, and X3 molecules (March, 1968) weakens the solute−solute interactions, so that they possess considerable solubilities in supercritical CO_2. While, in the case of X2, the strong intermolecular H-bonding, due to the single hydroxy group on the 6-position of the molecule and its increased dipole moment, makes the solute−solute interaction much stronger than the solute−supercritical fluid interaction and, consequently, reduces its solubility dramatically. On the other hand, some decreased solubility of X3 with respect to X1 and X4 is mainly due to its increased polarity. Finally, X4, as the least polar molecule in the series, shows the highest solubility in supercritical CO_2. Some electronic effects due to the electron-withdrawing nature of the OH groups in the 5- and 6-position of X2 and X3 and to the electron-donating nature of the CH_3 group in X4 may also be partly responsible for the observed solubility trend.

The ability to correlate the experimental solubilities with theoretical models for prediction of the solubility of analytes in supercritical fluids is of importance in understanding SFE and SEC procedures (Mitra and Wilson, 1991). The experimental solubility data for the hydroxyxanthones were correlated using the following equation (Bartle et al., 1991; Safa-Ozcan et al., 1997).

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

where y is the mole fraction solubility, P is the pressure, P_{ref} is a standard pressure of 1 bar, ρ is the density (taken as the density of pure CO_2), ρ_{ref} is a reference density, for which a value of 700 kg·m^{-3} was used, and A and C are constant values. The reason for using ρ_{ref} is to make the constant A much less sensitive to experimental errors in the solubility data and to avoid the large variations caused by extrapolation to zero density. The value of C, which results physically from solvation of the solute by the supercritical fluid, is assumed to remain constant over the entire temperature range studied. While the value of A, which arises from the vapor pressure (fugacity) of the solute, is assumed to obey the equation

$$A = a + b/T$$

where T is the absolute temperature and a and b are constants. Substitution of eq 2 into eq 1 will result in

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

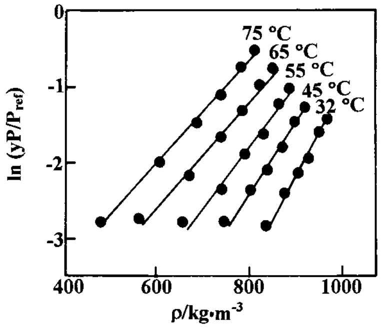

Figure 2. Plots of $\ln(yP/P_{\text{ref}})$ versus ρ for X1 at various temperatures.

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

compound	a	b	C	$\Delta_{\text{vap}}H$/kJ·mol^{-1}
X1	17.53	−6591	0.0113	54.8
X2	23.22	−9997	0.0130	83.1
X3	16.69	−6302	0.0084	52.4
X4	18.23	−6639	0.0097	55.2

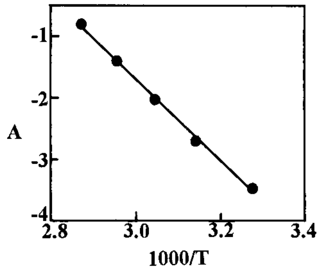

Figure 3. Plot of A against $1/T$ for X4.

In the first step, the $\ln(yP/P_{\text{ref}})$ values were plotted against density (Figure 2), and the resulting plots were fitted to a straight line by least-squares regression to estimate C and A values. According to eq 2, the plots are expected to be reasonably straight lines of similar slopes. However, as seen from Figure 2, the slopes show a small increase at lower temperatures. 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 xanthone derivative. The plots of A versus $1/T$ for each compound resulted in a nice straight line (Figure 3) from the intercept and slope of which the values of a and b were obtained, respectively. The resulting a and b values for compounds X1−X4 are also included in Table 2.

Finally, the values of a, b, and C were used to predict solubilities from eq 3. Figure 4 compares the calculated isotherms with the experimental data for compound X1. As seen, the agreement is satisfactory, and the poor consistency is mainly limited to the data points obtained at higher pressure limits of the isotherms, which are close to the melting points of the xanthone derivatives.

The parameter b is approximately related to the enthalpy of vaporization of the solid solutes $\Delta_{\text{vap}}H$ (Miller et al., 1996) by

$$\Delta_{\text{vap}}H = -Rb \tag{4}$$

where R is the gas constant. The validity of eq 4 relies on the assumption that the enhancement factor $\ln(yP/P_{\text{v}})$, where P_{v} is the vapor pressure of the solute, is independent

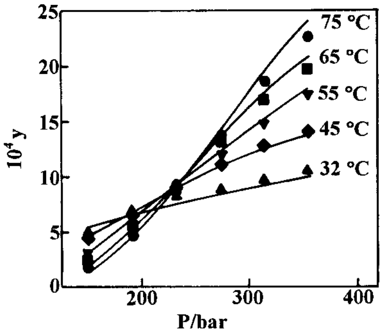

Figure 4. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for compound X1.

of temperature, which was found to be nearly true in practice. The estimated $\Delta_{vap}H$ values are also included in Table 2.

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Received for review January 15, 1999. Accepted June 1, 1999.

JE9900068