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Solubilities of Some 2*H*-Chromene Derivatives in Supercritical Carbon Dioxide

Naader Bahramifar,[†] Yadollah Yamini,*,[†] Ali Ramazani,[‡] and Nader Noshiranzadeh[‡]

Department of Chemistry, Tarbiat Modarres University, Tehran, Iran, and Department of Chemistry, Zanjan University, Zanjan, Iran

The equilibrium solubilities of four recently synthesized 2*H*-1-benzopyran (2*H*-chromene) derivatives have been measured at temperatures ranging from 308 K to 348 K and pressures from (12.2 to 35.5) MPa in supercritical carbon dioxide. The data were obtained by using a simple static sampling apparatus, which was tested by measuring the solubility of naphthalene in supercritical carbon dioxide. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with the experimental data.

1. Introduction

Recent studies have shown that the use of supercritical fluid as an extraction medium provides a powerful alternative to traditional extraction methods.[1,2] The potential benefits of supercritical fluid extraction (SFE) include faster analysis; reduced sample handling; protection from degradation by light, heat, or oxygen; high load ability of samples and possibility of trace analysis; easy separation of extracts from solvent after extraction; elimination of hazardous and/or expensive solvents; and analysis of aqueous samples (serum, urine, and saline solution) without introducing organic solvents.

As a consequence of two decades of development of supercritical fluid extraction in food industries, there is at the moment a widespread interest in the application of supercritical fluids (SCFs). This is also the case for the pharmaceutical industry. SFE is a potential technique for the purification of pharmaceutical products containing residual solvents.

A common element of any application of SCFs technology being considered in current research is the requirement of a thorough understanding and knowledge of the solubility of solids in the SCFs. This knowledge is essential for evaluating the feasibility of the supercritical separation process and for establishing optimum conditions of operation.

2*H*-1-Benzopyran derivatives and naphthopyrans (chromenes) are important heterocycles in bioorganic chemistry and are present in many natural products and pharmaceuticals.[3,4] In the present study the solubilities of four 2*H*-chromene derivatives, recently synthesized by this research group,[5−7] were determined in supercritical carbon dioxide over wide ranges of temperatures and pressures. The measured solubilities were successfully correlated by using a semiempirical model.

2. Experimental Section

2.1. Materials. HPLC-grade chloroform, methanol, and ethanol (all from Merck) were used as received. Carbon dioxide (Sabalan, Tehran, 99.99%) was used for all extractions. The 2*H*-chromene derivatives, namely, dimethyl 2*H*-1-benzopyran-2,3-dicarboxylate (A_1), di-*tert*-butyl-3*H*-naphtho[2,1-*b*]pyran-2,3-dicarboxylate (A2), dimethyl 6-bromo-2*H*-1-benzopyran-2,3-dicarboxylate (A_3), and dimethyl-3*H*-naphtho[2,1-*b*]pyran-2,3-dicarboxylate (A_4), were synthesized and purified as described before.[5−7] The purities of the 2*H*-chromene derivatives were confirmed by spectroscopic data and elemental analysis. The purities of the 2*H*-chromenes were higher than 99 mass %, and no further purification was made before use. However, prior to the measurement of solubilities, small quantities of volatile impurities were extracted by dynamic SFE at $P = 12.2$ MPa and $T = 308$ K for a duration of 10 min at the SCFs flow rate 0.30 mL/min. The impurities were only present during the extraction of the first 2−4% of the material charged into the extraction vessel. After making sure that no impurities existed in the extract, solubility measurements were done. The physical properties of the 2*H*-chromene derivatives (A_1 to A_4) used are shown in Table 1.

2.2. Equipment and Procedure. A Suprex (Pittsburgh, PA) MPS/225 system equipped with a modified static system for solubility determination in the SFE mode was used. A detailed description of the equipment and operating procedures has been given previously.[8,9] In this system, contact between the species and the fluid is established. After the equilibrium is reached, a known volume of the saturated fluid of the species is chosen and the amount of the solute is measured. Then, the solubility is calculated. Solubility measurements were accomplished in the pressure range from (12.2 to 35.5) MPa, at the temperatures (308, 318, 328, 338, and 348) K, each for a duration of 30 min. 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 equilibrium temperature and pressure were measured to accuracies of ±1 K and ±0.1 MPa, respectively. The solid solutes (100 mg) were mixed well with a proper amount of glass beads and packed into a 0.5-mL extraction vessel. This procedure prevents channeling, increases the contact surface between the sample and the supercritical fluid, and, consequently, reduces the equilibration time. Sintered stainless steel filters (5 μm) were used to prevent any carry-over of the

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* Corresponding author. Fax: +98-21-8006544. E-mail: yyamini@modares.ac.ir.
[†] Tarbiat Modarres University.
[‡] Zanjan University.

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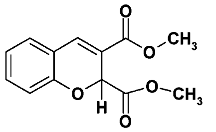
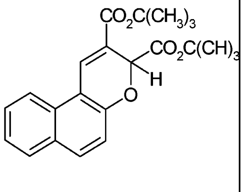
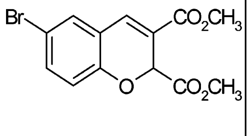
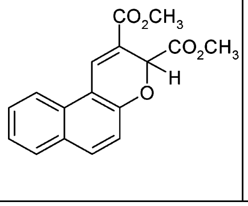
Table 1. Physical Properties of the 2*H*-Chromene Derivatives (A_1 to A_4)

Compound	Formula	Structure	MW/(g.mol^{-1})	T_m/K	Solvent	λ_{max}/nm
A_1	$C_{13}H_{12}O_5$		284.24	354-355	CH_3OH	335.0
A_2	$C_{23}H_{26}O_5$		382.46	398-399	C_2H_5OH	371.0
A_3	$C_{13}H_{11}BrO_5$		327.14	412-413	$CHCl_3$	350.0
A_4	$C_{17}H_{14}O_5$		298.30	409-410	C_2H_5OH	370.0

solutes. Supercritical CO_2 was pressurized and passed into the extraction vessel. After equilibrium at the desired temperature and pressure was reached, a 23-μL portion of saturated supercritical CO_2 was loaded into an injection loop. Then, the loop was depressurized into the collection vial containing suitable solvent (Table 1). Finally, the sample loop was washed with the same solvent, which was collected in the collection vial.

The solubilities of four 2*H*-chromene derivatives were calculated by absorbance measurements at λ_{max} of each compound (Table 1) using a model 2100 Shimadzu UV−Vis spectrophotometer with 0.5-cm pass length quartz cells. Stock solutions of each compound (100 $\mu g \cdot mL^{-1}$) were prepared by dissolving appropriate amounts of solid sample in proper solvent (Table 1). A set of standard solutions was then prepared by appropriate dilution of the stock solutions. The calibration curves obtained (with regression coefficients better than 0.9999) were used to establish the concentration of the chromenes in the collection vial. The obtained results were used to calculate the mole fraction solubilities of solutes in supercritical carbon dioxide, *x*. The solubilities measured were generally reproducible within ±2% (given a standard deviation of at least three replicated measurements).

3. Results and Discussion

The reliability and efficiency of the solubility measurement technique were previously established by measuring the solubility of naphthalene in supercritical CO_2 at 308 K and different pressures, as was described before.[9,10] The solubilities of compounds A_1 to A_4 in supercritical CO_2 were determined at the temperatures (308, 318, 328, 338, and 348) K over the pressure range from (12.2 to 35.5) MPa. The experimental results are listed in Table 2 in terms of equilibrium mole fraction, *x*, and in grams per liter, *s*, of the solute. The reported values are the average of at least three replicate measurements with percentage relative standard deviations less than ±2%.

Increasing the hydrostatic pressure decreases the melting point of the pure solid.[11] At 318 K, A_1 would occur as a solid up to 35.5 MPa, whereas, at 328 K, it occurs as a liquid. Because of melting and physical entrainment of solute at temperatures above 318 K, the solubilities of A_1 could not be measured.

The differences in solute properties such as molecular weight, polarity, and melting point should be considered while comparing the solubility behavior of 2*H*-chromene derivatives. The results obtained in this study indicate that the solubilities of the chromenes vary in the order $A_1 > A_2 > A_3 \approx A_4$. The solubilities parallel the order of the relative melting point; the higher the melting point, the lower the solubility. As expected, an isothermal increase in the pressure increased the solubility because of an increase in the solvent density and hence the solvation power. An isobaric increase in the temperature decreases the solvent density and increases the vapor pressure of the solute. The overall impact of these two competing effects is dependent on the pressure. Below the crossover pressure, the density effect predominates and the solubility decreases with increasing temperature, which is referred to as retrograde behavior. Above this crossover point, the solubility increases with temperature because of the vapor pressure effect.[12] The existence of a crossover pressure in solid−SCF

Table 2. Solubilities of 2*H*-Chromenes (A_1 to A_4) in Supercritical CO_2

			A_1		A_2		A_3		A_4	
T/K	P/MPa	ρ/kg·m^{-3}	s/g·L^{-1}	10^3x	s/g·L^{-1}	10^4x	s/g·L^{-1}	10^4x	s/g·L^{-1}	10^4x
308	12.2	771	25.65	5.86	6.02	8.98	1.02	1.78		
	15.2	818	34.88	7.50	7.89	11.08	1.30	2.13	1.16	2.08
	18.2	850	45.26	9.35	9.00	12.17	1.58	2.51	1.40	2.42
	21.3	876	49.31	9.88	9.74	12.77	2.17	3.33	1.58	2.65
	24.3	897	52.74	10.31	11.64	14.91	2.28	3.41	2.12	3.48
	27.4	916	61.92	11.84	11.94	14.98	2.96	4.35	2.35	3.78
	30.4	931	69.41	13.04	13.12	16.18	3.29	4.74	2.46	3.89
	33.4	946	74.50	13.77	14.01	17.00	3.67	5.21	2.92	4.55
	35.5	955	78.14	14.30	14.40	17.32	4.07	5.73	3.14	4.85
318	12.2	661	19.57	5.22	3.64	6.33	0.79	1.61		
	15.2	745	44.00	10.36	5.18	7.99	1.19	2.14	0.94	1.85
	18.2	792	61.27	13.53	8.41	12.20	1.71	2.90	1.30	2.42
	21.3	826	83.36	17.57	10.12	14.08	2.39	3.89	1.59	2.84
	24.3	852	102.99	20.98	11.94	16.09	3.03	4.78	2.19	3.80
	27.4	875	119.04	23.55	15.42	20.24	3.84	5.89	3.07	5.18
	30.4	893	126.78	24.55	17.95	23.07	4.73	7.12	3.55	5.85
	33.4	910	136.50	25.90	19.60	24.71	5.38	7.94	4.36	7.07
	35.5	919	148.37	27.82	21.07	26.30	6.40	9.36	4.97	7.97
328	12.2	516			1.48	3.30	0.63	1.64		
	15.2	657			1.98	3.47	0.79	1.62	0.68	1.53
	18.2	726			6.54	10.35	1.59	2.94	1.13	2.29
	21.3	771			11.83	17.61	3.01	5.25	1.56	2.98
	24.3	804			14.58	20.82	4.05	6.76	2.39	4.38
	27.4	831			18.53	25.58	5.27	8.53	3.15	5.59
	30.4	853			22.91	30.80	6.66	10.49	4.17	7.20
	33.4	872			26.10	34.31	8.19	12.61	5.55	9.38
	35.5	884			28.78	37.31	9.41	14.30	6.40	10.66
338	12.2	396			0.78	2.28	0.13	0.46		
	15.2	561			1.20	2.45	0.28	0.68	0.60	1.57
	18.2	654			5.47	9.62	1.22	2.51	0.98	2.22
	21.3	712			12.23	19.72	2.71	5.12	1.94	4.01
	24.3	754			19.53	29.71	4.35	7.75	3.14	6.14
	27.4	786			24.24	35.36	5.19	8.88	4.20	7.87
	30.4	812			30.21	42.62	9.53	15.75	5.84	10.60
	33.4	834			38.73	53.15	11.95	19.23	6.40	11.31
	35.5	848			44.01	59.36	13.10	20.73	8.61	14.96
348	12.2	327			0.57	1.99	0.10	0.41		
	15.2	477			0.93	2.24	0.26	0.74	0.43	1.33
	18.2	585			5.64	11.08	1.15	2.65	0.61	1.53
	21.3	652			8.83	15.55	2.50	5.16	1.31	2.96
	24.3	702			20.25	33.07	4.27	8.18	2.86	6.00
	27.4	740			30.40	47.04	7.69	13.96	4.12	8.21
	30.4	772			45.67	67.60	11.48	19.96	6.03	11.50
	33.4	796			59.95	85.90	13.15	22.17	8.20	15.18
	35.5	811			70.63	99.19	15.21	25.17	9.62	17.46

systems has been suggested as an indication of the reliability and consistency of experimental solubility data.[13] We find that the crossover region exists at about 13 MPa for A_1, 18 MPa for A_2 and A_3, and 19 MPa for A_4.

To confirm the reliability of measured solubility data, we used a semiempirical model proposed first by Bartle[14] and used afterward successfully by others,[8,15–16]

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

where

$$A = a + b/T \tag{2}$$

and

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

where x is the mole fraction solubility, P is the pressure, P_{ref} is a reference pressure of 1 bar, ρ is the density (taken as the density of pure CO_2), and ρ_{ref} is a reference density, for which a value of 700 kg·m^{-3} was used. The other parameters of the above equations have been previously discussed.[8,15]

In the first step, $\ln(xP/P_{\mathrm{ref}})$ values were plotted against density (Figure 1), and the values were fitted with a straight line by least squares regression to estimate the C and A parameters. According to eq 1, the plots are expected to be straight lines of similar slopes (the correlation coefficients, r^2, of the lines lie between 0.9991 and 0.9998). However, as seen from Figure 1, the slopes show a small increase at lower temperatures. Such deviations can be improved by removing the experimental points at lower pressures from the corresponding graphs. The values of C, obtained from the slopes of the corresponding plots, were then averaged for each compound (Table 3).

By holding the C at its average value, the experimental solubility data were then used to evaluate the A values at various temperatures for each compound. The plots of A versus $1/T$ for each compound resulted in a straight line (Figure 2), from which the intercept and slope (a and b) were obtained. The resulting a and b values for compounds are also included in Table 3. Finally, the values of a, b, and C were used to predict solubility from eq 3. Figure 3 compares the calculated isotherms with the experimental data. One can see that the Bartle method provided a good fit, with the absolute average relative deviation (AARD)

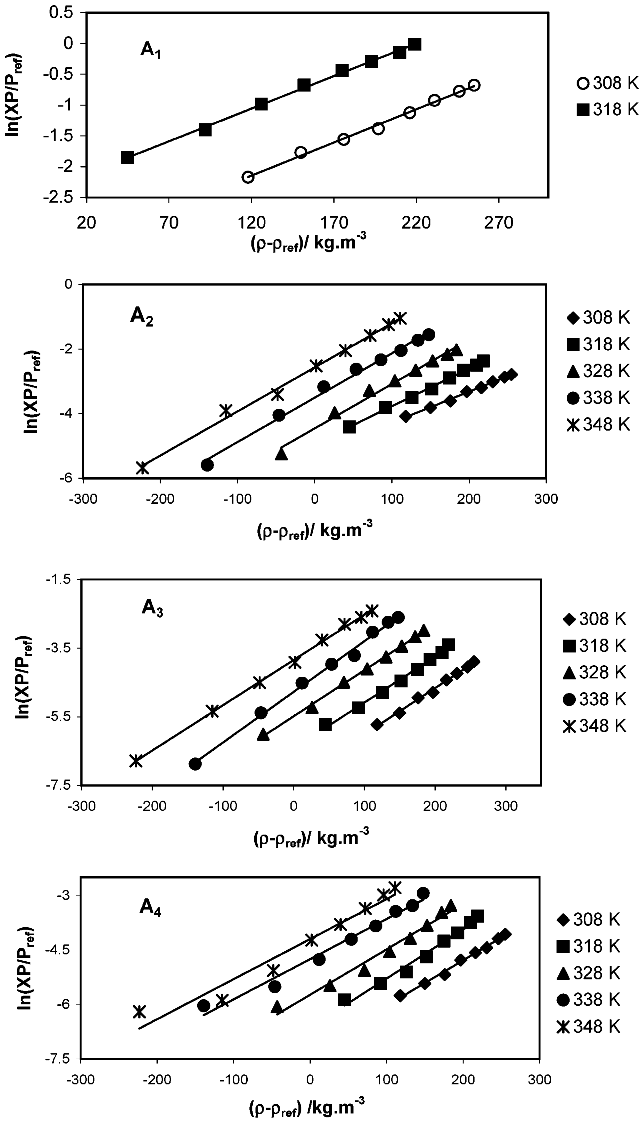


Figure 1. Plots of $\ln(xP/P_{ref})$ versus $(\rho - \rho_{ref})$ for A_1 to A_4 at various temperatures.

Table 3. Solubility Constants *a*, *b*, and *C* and the Estimated $\Delta_{sub}H$ Values and AARD Obtained from the Data Correlation Procedure

compd	*a*	*b*/K	C/m^3·kg^{-1}	$\Delta_{sub}H$/kJ·mol^{-1}	AARD[a]/%
A_1	30.88	−10565	0.0107	88	2.5−2.7
A_2	22.10	−8623	0.0124	62	9.7−20.8
A_3	23.38	−9482	0.0136	79	5.9−18.8
A_4	19.42	−8210	0.0121	68	4.3−18.7

[a] AARD/% = $(100/N)\{\sum(y^{exp} - y^{cal})/y^{cal}\}$ where y^{exp} and y^{cal} are the experimental and calculated solubility values and N is the number of data points.

in the range 2.5% to 20.8% for A_1 to A_4 at different temperatures (Table 3).

The parameter b is approximately related to the enthalpy of sublimation of the solid solutes, $\Delta_{sub}H$, by[15]

$$\Delta_{sub}H = -Rb \tag{4}$$

where R is the gas constant. The validity of eq 4 relies on the assumption that the enhancement factor $\ln(xP/P_v)$, where P_v is the vapor pressure of the solute, is independent of temperature; this was found to be nearly true in practice. The estimated $\Delta_{sub}H$ values are also included in Table 3.

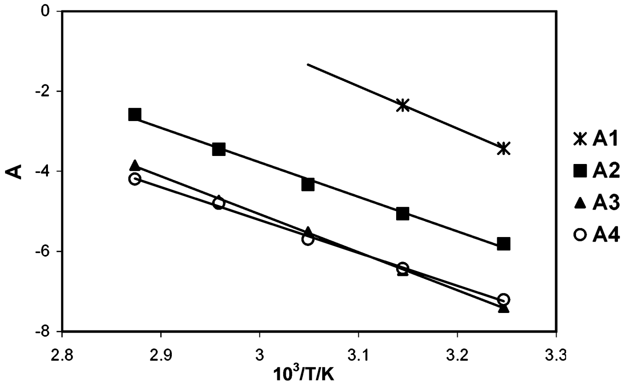


Figure 2. Plots of A against $1/T$ for A_1 to A_4.

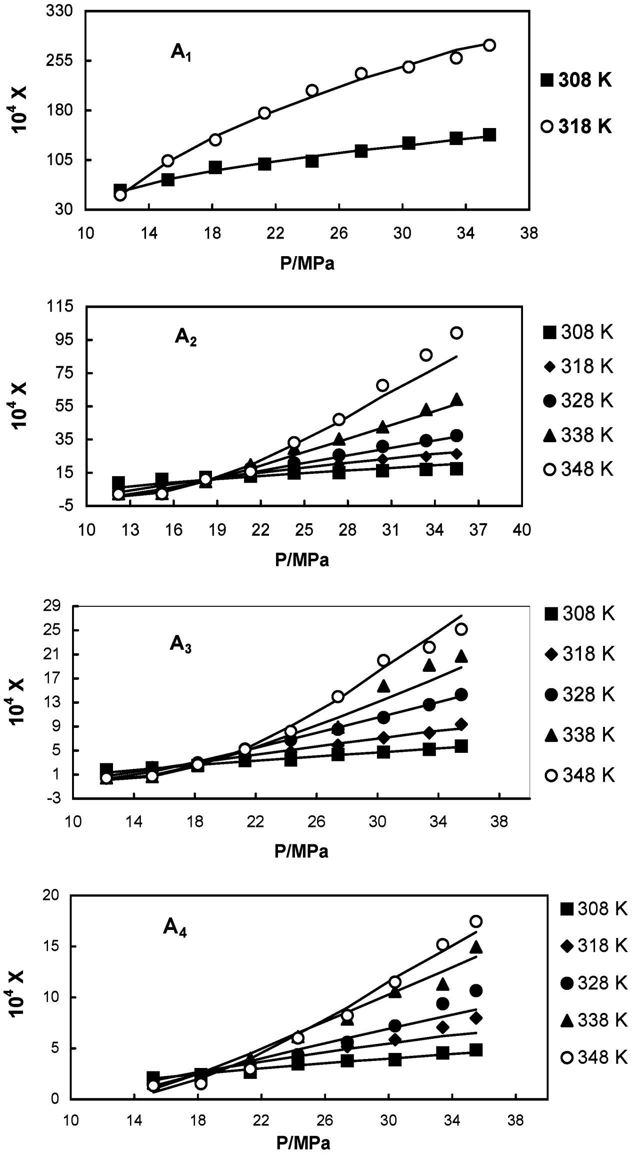


Figure 3. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for A_1 to A_4.

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