

# Solubilities of Some 9-Anthrone Derivatives in Supercritical Carbon Dioxide

Ali Reza Karami,<sup>†</sup> Yadollah Yamini,<sup>†</sup> Ali Reza Ghiasvand,<sup>†</sup> Hashem Sharghi,<sup>‡</sup> and Mojtaba Shamsipur<sup>\*,§</sup>

Departments of Chemistry, Tarbiat Modarres University, Tehran, Iran; Shiraz University, Shiraz, Iran; and Razi University, Kermanshah, Iran

The equilibrium solubilities of five recently synthesized anthrones have been measured in supercritical carbon dioxide using a simple and reliable static method. The measurements were performed in the pressure range (101–355) bar at the temperatures (308, 318, 328, 338, and 348) K. The measured solubilities were correlated using a semiempirical model. The calculated results show satisfactory agreement with the experimental data.

## Introduction

Supercritical fluid extraction (SFE) is becoming an important tool in analytical science and has been rapidly developed in the past few years.<sup>1</sup> SFE acts as a direct alternative to conventional liquid–solid extraction techniques. The main advantages of SFE over conventional methods include shorter extraction times, reduced solvent use, and the potential for selective analyte extraction by varying the pressure, temperature, or modifier.<sup>2</sup>

In the past decades, widespread attention has been paid to the supercritical fluids, due to their potential application in extraction processes in food processing, pharmaceutical, and petroleum industries as well as in the synthesis of organic molecules.<sup>3–6</sup> Information on solubilities in supercritical fluids is of vital importance in order to efficiently design extraction procedures based on supercritical fluids.<sup>7,8</sup>

9,10-Anthraquinones and 9-anthrone derivatives are the largest group of natural quinones and historically the most important.<sup>9</sup> Besides a wide variety of chemical and industrial applications,<sup>9–11</sup> recently the synthetic derivatives of anthraquinone and anthrone, as well as their naturally occurring derivatives, have been used for medical purposes.<sup>10</sup> We have recently reported the solubilities of some dihydroxy-9,10-anthraquinone derivatives<sup>12,13</sup> and hydroxy-xanthene derivatives<sup>14</sup> in supercritical carbon dioxide. This work was undertaken to determine the solubilities of 1-hydroxy-2-methyl-9-anthrone (**A1**), 1-hydroxy-2,4-dimethyl-9-anthrone (**A2**), 1-hydroxy-2-ethyl-9-anthrone (**A3**), 1,8-dihydroxy-9-anthrone (**A4**), and 1,8-dihydroxy-2-(prop-2'-enyl)-9-anthrone (**A5**) 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.<sup>7</sup>

## Experimental Section

HPLC-grade methanol (Merck) was used as received. Pure carbon dioxide (Sabalan, Tehran, 99.99%) was used

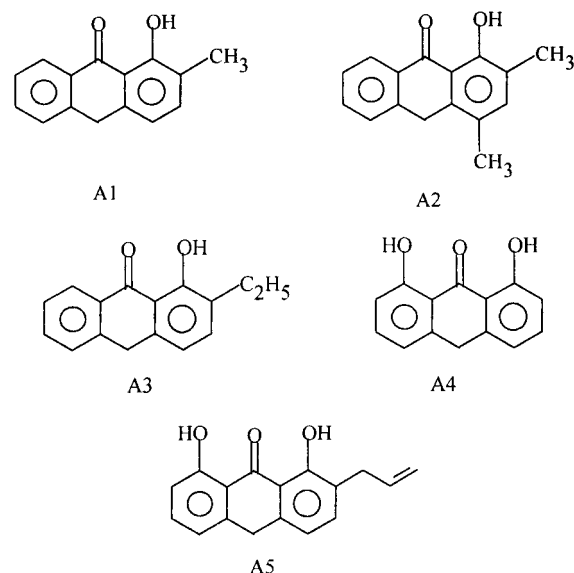


Figure 1. Structures of anthrone derivatives.

for all extractions. The anthrone derivatives **A1**–**A5** were synthesized and purified as described before.<sup>15</sup> The purities of anthrone derivatives were confirmed by spectroscopic data and elemental analysis. The structures of the anthrone derivatives used are shown in Figure 1.

A Suprex MPS/225 integrated SFE/SFC system equipped with a modified static system for the solubility determination in the SFE was used. A detailed description of the apparatus and operating procedure is given elsewhere.<sup>12,13</sup> The solubility measurements were based on the assumption that the mixture properties of pure supercritical fluid CO<sub>2</sub> are identical. Solubility measurements were accomplished with a 1-mL extraction vessel in the pressure range from (101 to 355) bar at the temperatures (308, 318, 328, 338, and 348) K 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 solid solutes (100 mg) were mixed well with glass beads and packed into the extraction vessel. This procedure increases the contact surface between the sample and the supercritical fluid and, consequently, reduces the

\* To whom correspondence should be addressed. E-mail: mshamsipur@yahoo.com.

<sup>†</sup> Tarbiat Modarres University.

<sup>‡</sup> Shiraz University.

<sup>§</sup> Razi University.

**Table 1. Solubilities of 9-Anthrone Derivatives A1–A5 in Supercritical Carbon Dioxide**

p, bar	$\rho$ , kg/m <sup>3</sup>	A1		A2		A3		A4		A5	
		10 <sup>4</sup> y	s, g/L	10 <sup>4</sup> y	s, g/L	10 <sup>4</sup> y	s, g/L	10 <sup>4</sup> y	s, g/L	10 <sup>4</sup> y	s, g/L
308 K											
101	712	0.87	0.32	0.24	0.09	1.08	0.42	1.33	0.49	1.06	0.44
127	780	1.21	0.48	0.32	0.14	1.27	0.54	0.81	0.32	1.71	0.78
152	817	1.50	0.63	0.36	0.16	1.58	0.70	0.96	0.40	2.15	1.02
177	845	1.79	0.77	0.41	0.19	1.69	0.77	1.18	0.51	2.59	1.28
203	868	1.81	0.80	0.48	0.23	2.01	0.95	1.30	0.58	2.96	1.50
228	887	2.17	0.98	0.53	0.26	2.14	1.03	1.44	0.66	3.50	1.81
253	903	2.31	1.07	0.57	0.28	2.14	1.05	1.54	0.72	3.83	2.01
279	919	2.43	1.14	0.58	0.29	2.48	1.24	1.68	0.79	4.00	2.14
304	931	2.51	1.19	0.59	0.30	2.62	1.32	1.86	0.89	4.52	2.45
329	942	2.62	1.26	0.63	0.32	2.74	1.40	1.90	0.92	5.32	2.92
355	956	2.60	1.27	0.66	0.34	2.77	1.43	2.04	1.00	5.99	3.34
318 K											
101	514	0.47	0.12	0.30	0.08	0.34	0.09	0.47	0.12	0.69	0.21
127	680	0.84	0.29	0.46	0.17	1.15	0.42	0.72	0.25	0.90	0.36
152	747	1.29	0.49	0.56	0.23	1.47	0.59	0.95	0.36	1.35	0.59
177	785	1.64	0.65	0.67	0.29	2.07	0.88	1.21	0.49	1.80	0.82
203	816	1.99	0.82	0.74	0.33	2.40	1.06	1.41	0.59	2.12	1.01
228	841	2.25	0.97	0.84	0.38	2.74	1.25	1.65	0.71	2.71	1.33
253	861	2.51	1.10	0.90	0.42	2.97	1.39	1.83	0.81	3.21	1.61
279	877	2.74	1.23	0.96	0.47	3.23	1.53	2.01	0.90	3.83	1.61
304	892	2.87	1.31	0.96	0.47	3.40	1.64	2.19	1.01	4.43	2.30
329	907	2.99	1.38	1.03	0.51	3.66	1.80	2.36	1.10	4.84	2.56
355	920	3.12	1.47	1.07	0.53	3.80	1.90	2.61	1.24	5.94	3.19
328 K											
101	339	0.24	0.04	0.12	0.02	0.49	0.09	0.32	0.06	0.31	0.06
127	553	0.65	0.18	0.25	0.08	0.96	0.29	0.55	0.16	0.50	0.16
152	658	1.15	0.39	0.44	0.16	1.62	0.58	0.89	0.30	1.07	0.41
177	717	1.15	0.42	0.61	0.24	2.33	0.90	1.23	0.45	1.68	0.70
203	758	2.19	0.84	0.74	0.30	2.85	1.17	1.49	0.58	2.38	1.05
228	788	2.64	1.06	0.83	0.35	3.41	1.46	1.75	0.71	3.04	1.39
253	814	3.03	1.26	1.00	0.44	4.00	1.76	1.96	0.82	3.72	1.77
279	836	3.41	1.45	1.06	0.48	4.50	2.04	2.15	0.92	3.97	1.94
304	854	3.71	1.67	1.18	0.54	4.89	2.26	2.37	1.04	5.28	2.63
329	869	3.39	1.50	1.32	0.62	5.17	2.43	2.61	1.17	6.13	3.10
355	886	4.31	1.95	1.38	0.66	5.35	2.57	2.83	1.29	7.87	4.06
338 K											
101	273	0.09	0.01	0.22	0.03	0.31	0.05	0.31	0.04	0.34	0.05
127	428	0.34	0.07	0.24	0.06	0.66	0.15	0.46	0.10	0.34	0.08
152	562	1.00	0.29	0.35	0.11	1.39	0.42	0.92	0.27	0.84	0.27
177	646	1.67	0.55	0.59	0.21	2.51	0.88	1.30	0.43	1.55	0.58
203	695	2.42	0.86	0.79	0.30	3.61	1.36	1.77	0.63	2.62	1.06
228	737	3.22	1.21	0.95	0.38	4.50	1.80	2.27	0.86	3.55	1.52
253	765	3.74	1.46	1.15	0.48	5.55	2.30	2.73	1.08	4.33	1.93
279	790	4.39	1.77	1.42	0.61	6.34	2.72	3.18	1.29	5.56	2.56
304	814	5.06	2.10	1.57	0.69	7.05	3.11	3.54	1.48	6.86	3.25
329	832	5.49	2.33	1.77	0.80	6.46	2.91	3.89	1.66	8.25	4.00
355	849	7.86	3.41	1.95	0.90	7.90	3.63	4.33	1.89	9.40	4.65
348 K											
101	238	0.50	0.06	0.21	0.03	0.28	0.04	0.39	0.05	0.50	0.07
127	335	0.38	0.06	0.22	0.04	0.52	0.09	0.37	0.06	0.33	0.06
152	477	0.86	0.21	0.37	0.10	1.31	0.34	0.64	0.16	0.62	0.17
177	568	1.51	0.44	0.65	0.20	2.54	0.78	1.19	0.35	1.28	0.42
203	634	2.54	0.82	0.95	0.33	3.91	1.34	1.60	0.52	2.15	0.80
228	680	3.47	1.20	1.22	0.45	4.94	1.82	2.17	0.76	3.37	1.33
253	717	4.15	1.52	1.44	0.56	6.43	2.50	2.99	1.10	4.51	1.88
279	745	5.23	1.99	1.85	0.75	7.74	3.12	3.62	1.39	6.51	2.82
304	772	6.20	2.44	2.24	0.94	8.80	3.68	4.24	1.68	8.51	3.83
329	792	7.05	2.85	2.46	1.06	9.78	4.20	4.87	1.98	10.64	4.91

equilibration time. Supercritical CO<sub>2</sub> was pressurized and passed into the extraction vessel. After equilibrium at the desired temperature and pressure was reached, a 145  $\mu$ L portion of the saturated supercritical CO<sub>2</sub> was loaded into the injection loop. Then the loop was depressurized into a collection vial containing methanol. Finally, the sample loop was washed with the methanol, which was collected in the collection vial. The final volume of the solution was 5 mL.

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 compounds **A1–A5** (500 ppm) were prepared by dissolving appropriate amounts of the solid samples in methanol. A set of standard solutions was then prepared in the range 1 to 50 ppm by appropriate dilution of the stock solutions. The calibration graphs obtained (with regression coefficients better than 0.9995) were used to establish the concentration of the anthrone 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 repro-

ducible within  $\pm 4\%$  (given as standard deviations on at least three replicate measurements).

## Results and Discussion

Table 1 represents the solubilities of anthrones **A1**–**A5** at the temperatures (308, 318, 328, 338, and 348) K over a pressure range from (101 to 355) bar. The resulting solubilities are reported in terms of equilibrium mole fraction,  $y$ , and equilibrium solubility,  $s$  (g/L), of the solute in supercritical carbon dioxide:

$$y = n_{\text{solute}} / (n_{\text{solute}} + n_{\text{CO}_2}) \quad (1)$$

where

$$n_{\text{solute}} = \frac{C(\mu\text{g/mL}) \times V_s(\text{mL}) \times \text{mg}/1000(\mu\text{g})}{[M_s(\text{g/mol})]} \quad (2)$$

and

$$n_{\text{CO}_2} = \frac{V_1(\mu\text{L}) \times \rho(\text{g/L}) \times \text{mL}/1000(\mu\text{L})}{[M_{\text{CO}_2}(\text{g/mol})]} \quad (3)$$

where  $n_{\text{solute}}$  and  $n_{\text{CO}_2}$  are milimoles of solute and  $\text{CO}_2$  in the sampling loop,  $C$  is the concentration of solute ( $\mu\text{g/mL}$ ) in the collection vial, which was obtained from the calibration graph,  $V_s$  (mL) and  $V_1$  ( $\mu\text{L}$ ) are the volumes of the collection vial and the sampling loop, and  $M_s$  and  $M_{\text{CO}_2}$  are the molecular weights of solute and  $\text{CO}_2$ , respectively.

Each reported datum is the average of at least three replicate samples. The mole fraction solubilities of the solutes were reproducible within  $\pm 4\%$ . To the best of our knowledge, there is no previous report on the solubility of the 9-anthrone derivatives examined in supercritical fluid  $\text{CO}_2$ ; thus, no comparison with other data can be made.

From the data given in Table 1, it is seen that the solubility of compounds **A1**–**A5** increases with increasing pressure at constant temperature, the influence of pressure on the solubilities being more pronounced at higher temperatures. This is in accord with the conventional wisdom stating that the density of a supercritical fluid must increase in order to increase the solubility and extraction efficiency.<sup>17</sup>

The temperature influences the solute's vapor pressure, the solvent density, and intermolecular interactions in the fluid phase. At pressures under the crossover region (for **A1**, 200 bar; for **A2**, **A3**, and **A4**, 180 bar; and for **A5**, 250 bar), 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. A similar retrograde solubility (crossover/pressure effect) behavior for the solubility of organic compounds in supercritical  $\text{CO}_2$  has been reported in the literature.<sup>13,16,18,19</sup> In all cases, for a given pressure above the crossover points, the highest solubility values were obtained at the lowest density for the anthrones (i.e. highest temperatures). On the other hand, observing no change in the UV–vis spectra (over 800–200 nm) of the extracted samples in the temperature range (308–348) K is in support of the stability of the drugs under given conditions.

The results obtained in this study indicate that the solubilities of anthrones vary in the order **A5** > **A3** > **A1** > **A4** > **A2**. The melting points of **A1**, **A2**, **A3**, **A4**, and **A5** are (407, 408, 367, 450, and 333) K, respectively. With the

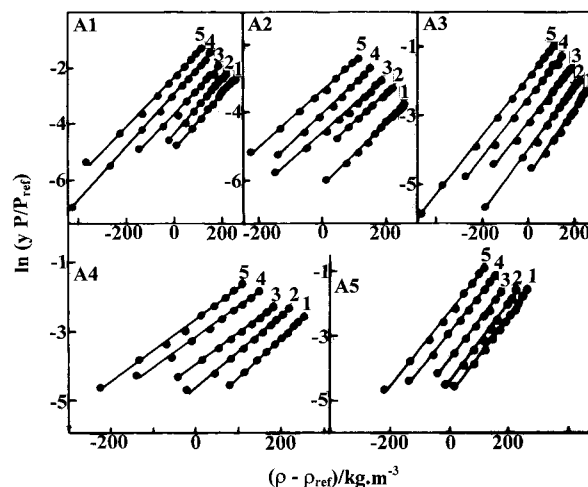


Figure 2. Plots of  $\ln(yP/P_{\text{ref}})$  versus  $(\rho - \rho_{\text{ref}})$  for **A1**–**A5**.

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

compound	$a$	$b$ , K	$C$ , $\text{m}^3/\text{kg}$	$\Delta_{\text{vap}}H$ , $\text{kJ/mol}$
<b>A1</b>	17.39	−6874	0.0095	57
<b>A2</b>	17.12	−7138	0.0088	59
<b>A3</b>	19.39	−7430	0.0088	62
<b>A4</b>	16.65	−6748	0.0095	56
<b>A5</b>	17.49	−6903	0.0118	57

exception of **A2**, the solubilities of other anthrone derivatives parallel the order of their relative melting points; the higher the melting point, the lower the solubility. However, the solubility of anthrone **A2** does not correlate well with its reported melting point. Similar results have been reported in the literature.<sup>16,20</sup> The experimental solubility data for the anthrones were correlated using the following equation proposed by Bartle et al.<sup>16,18</sup>

$$\ln(yP/P_{\text{ref}}) = A + C(\rho - \rho_{\text{ref}}) \quad (4)$$

where

$$A = a + b/T \quad (5)$$

and

$$\ln(yP/P_{\text{ref}}) = a + b/T + C(\rho - \rho_{\text{ref}}) \quad (6)$$

Here,  $P_{\text{ref}}$  is a standard pressure of 1 atm and  $\rho_{\text{ref}}$  is a reference density for which a value of  $700 \text{ kg/m}^3$  was used. The other parameters of the above equations have already been discussed.<sup>7,14,16,17,21</sup> 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 the  $C$  and  $A$  values. According to eq 4, 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 anthrone. 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  $b$  were obtained, respectively. The resulting  $a$  and  $b$  values for different compounds are also included in Table 2. Finally, the values of  $a$ ,  $b$ , and  $C$  were used to predict solubility from eq 6. Figure 4 compares the calculated

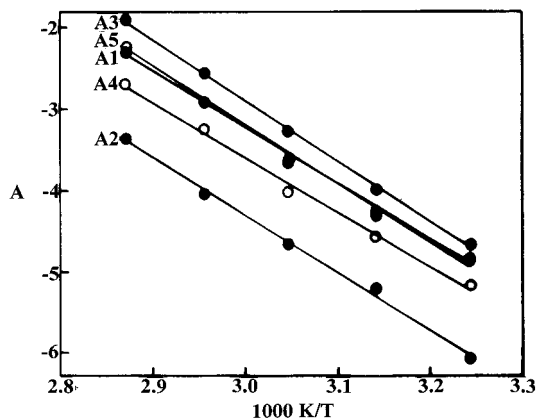


Figure 3. Plots of  $A$  versus  $1/T$  for A1–A5.

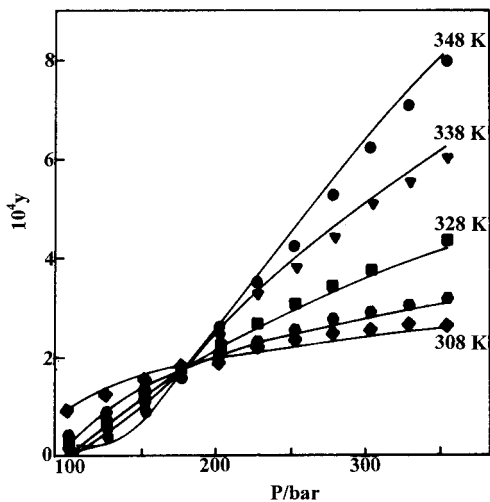


Figure 4. Comparison of experimental (points) and calculated (lines) solubilities at various temperatures for A1.

isotherms with the experimental data for A1. As seen, the agreement is satisfactory.

The parameter  $b$  is approximately related to the enthalpy of vaporization of the solid solutes  $\Delta_{\text{vap}}H$  by<sup>22</sup>

$$\Delta_{\text{vap}}H = -Rb \quad (7)$$

where  $R$  is the gas constant. The validity of eq 7 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  $\Delta_{\text{vap}}H$  values are included in Table 2. It should be noted that the  $\Delta_{\text{vap}}H$  values given in Table 2 are for an average temperature of 328 K.

## Literature Cited

- (1) Ramsey, E. D. *Analytical Fluid Extraction Techniques*; Kluwer Academic Publishers: London, 1998.
- (2) McHugh, M.; Krukonis, V. *Supercritical Fluid Extraction*, 2nd ed.; Butterworth-Heinemann: Boston, MA, 1994.
- (3) Palmer, M. W.; Ting, S. T. Applications for Supercritical Technology in Food. *Food Chem.* **1995**, *52*, 345–352.
- (4) Becerra, G.; Menolasina, S.; Salvador, A. Supercritical Fluid Extraction and Supercritical Fluid Chromatography of Vitamin E in Pharmaceutical Preparations. *J. High Resolut. Chromatogr.* **1999**, *27*, 300–302.
- (5) Caude, M.; Thiebaut, D. *Practical Supercritical Fluid Chromatography and Extraction*; Harwood Academic Publishers: Amsterdam, 1999.
- (6) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: New York, 1999.
- (7) Bartle, K. D.; Clifford, A. A.; Jafar, S. A.; Shilstone, G. F. Solubilities of Solids and Liquids of Low Volatility in Supercritical Carbon Dioxide. *J. Phys. Chem. Ref. Data* **1991**, *20*, 713–756.
- (8) Dohrn, R.; Brunner, G. High-Pressure Fluid Phase Equilibria. Experimental Methodes and System Investigation (1988–1993). *Fluid Phase Equilib.* **1995**, *106*, 213–282.
- (9) Thomson, R. H. *Naturally Occurring Quinones*; Academic Press: New York, 1971.
- (10) Gutierrez, P. L.; Nguyen, B. In *Redox Chemistry and Interfacial Behavior of Biological Molecules*; Dryhurst, G., Niki, K., Eds.; Plenum Press: New York, 1988.
- (11) Dadfarnia, S.; Shamsipur, M.; Tamaddon, F.; Sharghi, H. Extraction and Membrane Transport of Metal Ions by Some Synthetic 9,10-Anthraquinone Derivatives. A Selective System for Calcium Transport. *J. Membr. Sci.* **1993**, *78*, 115–121.
- (12) Fat'hi, M. R.; Yamini, Y.; Sharghi, H.; Shamsipur, M. Solubilities of Some 1,4-Dihydroxy-9,10-anthraquinone Derivatives in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1998**, *43*, 400–402.
- (13) Fat'hi, M. R.; Yamini, Y.; Sharghi, H.; Shamsipur, M. Solubilities of Some Recently Synthesized 1,8-Dihydroxy-9,10-anthraquinone Derivatives in Supercritical Carbon Dioxide. *Talanta* **1999**, *48*, 951–957.
- (14) Ghiasvand, A. R.; Hosseini, M.; Sharghi, H.; Yamini, Y.; Shamsipur, M. Solubilities. *J. Chem. Eng. Data* **1999**, *44*, 1135–1138.
- (15) Tamaddon, F. Ph.D. Thesis, Shiraz University, Shiraz, Iran, 1991.
- (16) Yamini, Y.; Bahramifar, N. Solubility of Polycyclic Aromatic Hydrocarbons in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 53–56.
- (17) Miller, D. J.; Hawthorne, S. B. Determination of Solubilities of Organic Solutes in Supercritical CO<sub>2</sub> by On-Line Flame Ionization Detection. *Anal. Chem.* **1995**, *67*, 273–279.
- (18) Johannsen, M.; Brunner, G. Solubilities of the Fat-Soluble Vitamins A, D, E, and K in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1997**, *42*, 106–111.
- (19) Knez, Z.; Skerget, M.; Sensar-Bozic, P.; Rinzner, A. Solubility of Nifedipine and Nitrendipine in Supercritical CO<sub>2</sub>. *J. Chem. Eng. Data* **1995**, *40*, 216–220.
- (20) Macnaughton, S. Y.; Kikic, I.; Foster, N. R.; Allesi, P.; Certesi, A.; Colombo, I. Solubility of Anti-Inflammatory Drugs in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1996**, *41*, 1083–1086.
- (21) Caude, M.; Thiebaut, D. *Practical Supercritical Fluid Chromatography and Extraction*; Harwood Academic Publisher: Netherlands, 1999.
- (22) Miller, D. J.; Hawthorne, S. B.; Clifford, A. A.; Zhu, S. Solubility of Polycyclic Aromatic Hydrocarbons in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **1996**, *41*, 779–786.

Received for review March 23, 2001. Accepted June 21, 2001.

JE0101045