Solubilities of Some Phenyl Derivatives of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates in Supercritical Carbon Dioxide. Part II

Mostafa Khajeh,[†] Yadollah Yamini,*[,†] Ramin Miri,[‡] and Bahram Hemmateenejad[‡]

Department of Chemistry, Tarbiat Modarres University, Tehran, Iran, and Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Supercritical fluid extraction is a potential technique for the purification of pharmaceutical products containing residual solvents. The solubilities of the drugs in supercritical carbon dioxide are being measured as part of a program in which the potential applications of this technology are being investigated. The solubilities of six 1,4-dihydropyridine derivatives in supercritical carbon dioxide were reported at temperatures from (338 to 358) K and in the pressure range of (12.2 to 35.5) MPa. Results showed that solubilities increase linearly with increasing density at constant temperature and increase with increasing temperature at constant density. The measured solubilities were correlated using a semiempirical model.

Introduction

Conventional pharmaceutical processing involves extensive use of organic solvents as antisolvents for recrystallizing drugs from solution, reaction media in the synthesis of drugs, and extracting agents for selectively isolating drugs from solid matrixes. Health concerns caused by some of these solvents such as methylene chloride by way of either environmental emissions and/or trace residues in the product have propelled research efforts aimed at developing "environmentally benign" processing techniques that either eliminate or significantly mitigate pollution at the source. A major research focus in this regard has been with the investigation of processes in which traditional solvents are replaced with supercritical carbon dioxide. Among the reported applications, the formation of drug particles using dense carbon dioxide either as a solvent or nonsolvent and the "clean" synthesis of drug compounds using carbon dioxide as a reaction medium hold immense appeal for large-scale application in the pharmaceutical industry.[1−6]

The 1,4-dihydropyridine (DHP) derivatives, which are well known as calcium channel blockers, are used for the treatment of cardiovascular diseases such as hypertension, angina pectoris, and other spastic smooth muscle disorders.[7,8] Recently, some new derivatives of DHP containing a 1-methyl-5-nitro-imidazol-2-yl substituent at the C-4 position and different ester substituents on the C-3 and C-5 positions of the DHP ring have been synthesized.[9−13] In our previous work, the solubilities of some cyclohexyl derivatives of 1,4-dihydropyridine were reported.

In the present study, the solubilities of six dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates derivatives, recently synthesized by this research group,[9−13] were determined in supercritical carbon dioxide over a wide range of temperatures and pressures. The measured solubilities were successfully correlated using a semiempirical model proposed by Bartle.[14]

* To whom correspondence should be addressed. E-mail: yyamini@modares.ac.ir.
[†] Tarbiat Modarres University.
[‡] Shiraz University of Medical Sciences.

Table 1. Physical Properties of the 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitroimidazol-2-yl)-3,5-pyridinedicarboxylates Derivatives (A_1 to A_6)

compound	formula	$(CH_2)_n$−R	MW g·mol^{-1}	T_m K	λ_{max} nm[a]
A_1	$C_{27}H_{26}N_4O_6$	CH_2−ph	502	479−481	321.2
A_2	$C_{33}H_{32}N_4O_6$	$(CH_2)_4$−ph	580	409−410	318.2
A_3	$C_{35}H_{34}N_4O_6$	$(CH_2)_5$−ph	606	401−402	318.8
A_4	$C_{31}H_{30}N_4O_6$	$(CH_2)_3$−ph	554	413−414	316.6
A_5	$C_{33}H_{38}N_4O_6$	$(CH_2)_3$−C_6H_4−CH_3 (para)	586	511−512	321.0
A_6	$C_{29}H_{28}N_4O_6$	$(CH_2)_2$−ph	528	477−478	322.0

[a] Absorbances of drugs were measured in methanol.

Experimental Section

Materials. The carbon dioxide used in this work was supplied by Sabalan (Tehran, Iran) at a purity of 99.99 %. HPLC-grade methanol (from Aldrich) was used as received. All of the drugs were synthesized and purified as described before.[9−13] The purities of the 1,4-dihydropyridine (DHP) derivatives were confirmed by spectroscopic data and elemental analysis. The purities of the drugs were higher than 99.5 mass %, and no further purification were done 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 a supercritical flow rate of 0.3 mL·min^{-1}. Volatile impurities such as residual solvents and unreacted components were present only during the extraction of the first (2 to 4)% of the material charged into the extraction vessel. The physical properties of the drugs used are shown in Table 1.

Equipment and Procedure. A Suprex (Pittsburgh, PA) MPS/225 system equipped with a modified static system for solubility determination in SFE mode was used. A detailed description of the equipment and operating procedures has been given previously.[15,16] Solubility measurements were accomplished in a pressure range of (12.2 to 35.5) MPa and at temperatures of (338, 348, and 358) K for a duration of 20 min. It should be noted that by monitoring the solubility data versus time we found 20 min

10.1021/je0497092 CCC: $30.25 © 2005 American Chemical Society
Published on Web 02/01/2005

Table 2. Solubilities of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates (A_1, A_2, A_3, A_4, A_5, and A_6) in Supercritical CO_2

T	P	ρ	A_1		A_2		A_3		A_4	
K	MPa	kg·m^{-3}	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x
338										
	12.2	396					13.4			
	15.2	561					15.9		15.6	
	18.2	654			6.6	0.8	24.7	2.8	25.5	3.2
	21.3	712			9.1	0.9	28.5	2.9	30.9	3.5
	24.3	754	0.7	0.1	12.7	1.3	31.0	4.1	39.8	4.3
	27.4	786	1.8	0.2	18.7	2.3	38.6	5.3	62.2	6.4
	30.4	812	2.9	0.3	25.9	3.0	56.2	6.6	99.9	10.0
	33.4	834	3.9	0.4	28.4	3.7	75.0	7.8	125.0	12.2
	35.5	848	5.1	0.5	32.0	4.2	101.4	8.9	143.8	13.8
348										
	12.2	327					10.9		26.4	
	15.2	477					15.9		33.6	
	18.2	585			3.0	0.4	23.5	2.9	20.1	2.8
	21.3	652			9.0	1.0	27.3	3.1	27.3	3.4
	24.3	702	1.8	0.2	13.9	1.5	43.6	4.6	42.5	4.9
	27.4	740	3.9	0.4	29.6	3.1	51.1	6.5	64.1	7.1
	30.4	772	5.1	0.6	41.7	4.2	72.5	9.0	83.7	8.8
	33.4	796	7.3	0.8	58.6	5.7	96.4	10.7	145.6	14.9
	35.5	811	11.7	1.3	64.6	6.2	115.2	12.1	168.0	16.9
358										
	12.2	287					8.4		14.7	
	15.2	406					12.2		15.6	
	18.2	517			4.2	0.6	20.9	3.0	20.2	3.2
	21.3	593	0.6	0.1	6.6	1.4	27.3	3.4	33.6	4.6
	24.3	650	5.5	0.7	15.1	2.5	52.4	6.0	49.7	6.3
	27.4	693	9.5	1.2	32.0	4.3	57.4	8.1	69.4	8.2
	30.4	728	13.9	1.7	44.1	6.2	77.5	10.6	110.6	12.4
	33.4	757	16.2	2.8	64.6	8.2	103.9	13.6	177.9	19.2
	35.5	774	21.7	3.6	79.2	10.3	129.1	16.6	218.2	23.1

T	P	ρ	A_5		A_6	
K	MPa	kg·m^{-3}	10^3 s/g·L^{-1}	10^6x	10^3 s/g·L^{-1}	10^6x
338						
	12.2	396	4.5		3.6	
	15.2	561	5.5	0.7	9.8	
	18.2	654	7.6	0.9	11.9	1.5
	21.3	712	13.6	2.5	15.1	2.6
	24.3	754	21.8	3.2	20.2	3.1
	27.4	786	27.9	3.5	25.5	3.5
	30.4	812	33.9	4.2	31.7	3.7
	33.4	834	40.1	4.6	34.8	4.1
	35.5	848	48.2	4.7	36.9	4.4
348						
	12.2	327	3.5		3.6	
	15.2	477	4.5	0.7	8.8	
	18.2	585	15.7	2.01	11.9	1.8
	21.3	652	22.8	2.7	20.3	2.9
	24.3	702	29.9	3.3	25.5	3.6
	27.4	740	44.1	4.6	33.8	4.3
	30.4	772	47.2	5.7	35.9	5.2
	33.4	796	58.3	6.9	46.3	5.7
	35.5	811	76.6	7.3	50.4	5.9
358						
	12.2	287	2.5		2.6	
	15.2	406	7.6	1.4	7.8	
	18.2	517	6.5	0.9	14.1	2.3
	21.3	593	23.8	3.1	22.4	3.2
	24.3	650	36.0	5.0	27.6	4.4
	27.4	693	47.2	6.5	35.9	5.4
	30.4	728	55.3	8.2	39.0	6.4
	33.4	757	66.4	9.5	54.6	7.2
	35.5	774	86.7	11.0	63.9	7.8

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 the proper number of glass beads and packed into a 1.0-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 carryover of the solutes. Supercritical CO_2 was pressurized and passed into the extraction vessel. After equilibrium at the desired temperature and pressure was reached, a 176-μL portion of saturated supercritical CO_2 was loaded into an injection loop. Then, the loop was depressurized into the collection vial containing methanol. Finally, the sample loop was washed with methanol, which was col-

lected in the collection vial. The final volume of the solution was 5 mL.

The solubilities of six dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates derivatives were calculated by absorbance measurements at λ_{max} of each compound (Table 1) using a model 2100 Shimadzu UV−vis spectrophotometer. Stock solutions of each compound (100 $\mu g \cdot mL^{-1}$) were prepared by dissolving appropriate amounts of solid sample 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 0.9999) were used to establish the concentration of the drugs in the collection vial.

Results and Discussion

The solubilities of six 1,4-dihydropyridine derivatives in supercritical carbon dioxide are reported in Table 2 in terms of equilibrium mole fraction, x, and in grams per liter, s, of the solute. All solubility values represent mean values of at least three samplings. The percent relative standard deviations of the measurements were within ±7%.

The results obtained in this study indicate that the solubility of the six drugs used vary in the order $A_4 > A_3 > A_5 > A_2 > A_6 > A_1$. The differences in solute properties such as molecular weight, polarity, and melting point should be considered while comparing the solubility behavior of 1,4-dihydropyridine derivatives.

From the data given in Table 2, it is readily seen that the solubility of all six drugs increases with increasing pressure at constant temperature. The effect of pressure on the solute solubility shows the usual trends. As the pressure is raised, the carbon dioxide density increases, and the mean intermolecular distance of the carbon dioxide molecules decreases, thereby increasing the specific interaction between the solute and solvent molecules.[17]

The second factor affecting the equilibrium solubility of a solid substance is the temperature of the system. The temperature influences the solute vapor pressure, the solvent density, and the intermolecular interactions in the fluid phase. At pressures under the crossover region (for the six drugs this is in a pressure range of (180 to 240) MPa), the solvent densities are lowed by small increases in temperature; because the density effect is dominant in this region, the solubility will decrease with increasing temperature. At higher pressures, the solvent density is less dependent on the temperature, so the increase in solubility is primarily due to the higher vapor pressure of the solid.[17] The existence of a crossover pressure in solid−SCF systems has been suggested as an indication of the reliability and consistency of experimental solubility data.[18]

To confirm the reliability of measured solubility data, we used a semiempirical model proposed first by Bartle given by[14]

$$\ln\left(\frac{xP}{P_{ref}}\right) = A + C(\rho - \rho_{ref}) \quad (1)$$

where

$$A = a + \frac{b}{T} \quad (2)$$

and

$$\ln\left(\frac{xP}{P_{ref}}\right) = a + \frac{b}{T} + C(\rho - \rho_{ref}) \quad (3)$$

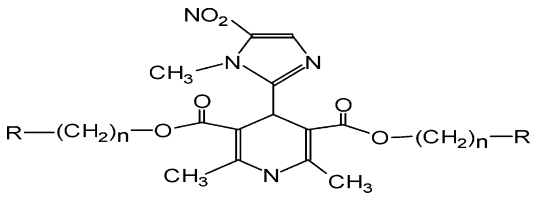

Figure 1. Structure of dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-imidazol-2-yl)-3,5-pyridinedicarboxylates. (See Table 1.)

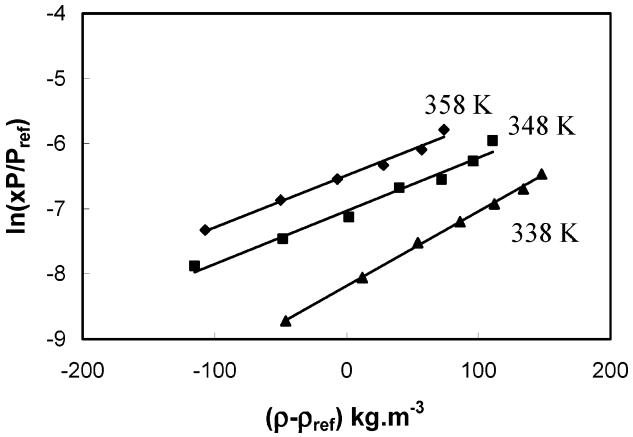

Figure 2. Plot of $\ln(xP/P_{ref})$ vs $(\rho - \rho_{ref})$ for A_5 at various temperatures.

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

		b	*C*	$\Delta_{sub}H$	
compound	*a*	K	$m^3 \cdot kg^{--1}$	$kJ \cdot mol^{-1}$	AARD%[a]
A_1	48.053	−20 050	0.0182	168	3.0−9.7
A_2	25.137	−11 375	0.013533	95	2.7−10.1
A_3	19.199	−9020.9	0.011733	76	10.6−15.6
A_4	19.623	−9068.4	0.013267	76	18.8−28.0
A_5	17.962	−8667	0.0092	73	9.8−16.9
A_6	12.715	−6860.6	0.0075	57	1.7−4.9

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

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 $kg \cdot m^{-3}$ was used.[15] The other parameters of the above equations have been previously discussed.[15,19]

In the first step, $\ln(xP/P_{ref})$ values were plotted against density (Figure 2), and the values were fit 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 with similar slopes. (Correlation coefficients, r^2, of the lines lie between 0.9991 and 0.9998.) However, as seen from Figure 2, 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 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 vs $1/T$ for each compound resulted in a straight line (Figure 3), from which the intercept and slope (a and b) were

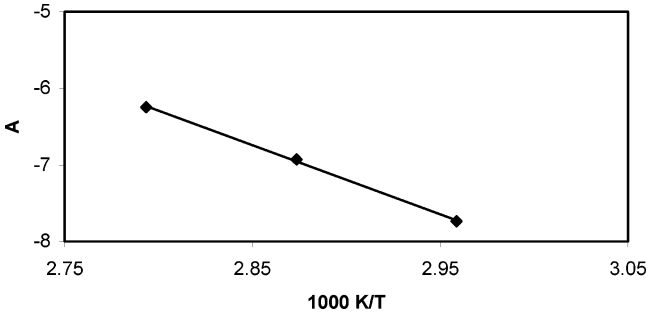

Figure 3. Plot of A vs $1/T$ for A_3.

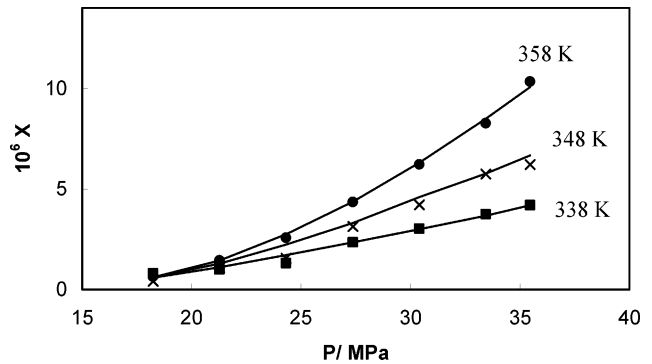

Figure 4. Comparison of experimental (points) and calculated (lines) solubilities for A_2 at various temperatures.

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 4 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) in the range of 1.7% to 28.0% for A_1 to A_6 at different temperatures (Table 3). It is worth noting that Figures 2, 3, and 4 are correlation examples for A5, A3, and A2, respectively. By sketching data related to Table 2, we can obtain similar figures for other components.

Parameter b is approximately related to the enthalpy of sublimation of the solid solutes, $\Delta_{sub}H$, by[19]

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

where R is the gas constant. A detailed physical description of this relation was given by Miller et al.[19] The estimated $\Delta_{sub}H$ values are also included in Table 3.

Literature Cited

(1) Subramanina, B.; Rajewski, R. A.; Snavely, K. Pharmaceutical Processing with Supercritical Carbon. Dioxide. *J. Pharm. Sci.* **1997**, *86*, 885−890.

(2) Fages, J.; Lochard, H.; Letourneau, J. J.; Sauceau, M.; Rodier, E. Particle Generation for Pharmaceutical Applications Using Supercritical Fluid Technology. *Powder Technol.* **2004**, *141*, 219−226.

(3) Sethia, S.; Squillante, E. Solid Dispersion of Carbamazepine in PVP K30 by Conventional Solvent Evaporation and Supercritical Methods. *Int. J. Pharm.* **2004**, *272*, 1−10.

(4) Guney, O.; Akgerman, A. Solubilities of 5-Fluorouracil and β-Estradiol in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 1049−1052.

(5) Kazarian, S. G.; Martirosyan, G. G. Spectroscopy of Polymer/Drug Formulations Processed with Supercritical Fluids: in situ ATR−IR and Raman Study of Impregnation of Ibuprofen into PVP. *Int. J. Pharm.* **2002**, *232*, 81−90.

(6) Velaga, S. P.; Ghaderi, R.; Carlfors, J. Preparation and Characterisation of Hydrocortisone Particles Using a Supercritical Fluids Extraction Process. *Int. J. Pharm*. **2002**, *231*, 155−166.

(7) Wolowyk, M. W.; Knaus, E. E. In *Calcium Channel Modulators in Heart and Smooth Muscle: Basic Mechanisms and Pharmacological Aspects*; Proceedings of the 33rd OHOLO Conference, Eilat, Israel, 1989; Abraham, S., Amital, G., Eds.; VCH: Weinheim, Germany, 1990.

(8) Fossheim, R. Crystal Structure of the Dihydropyridine Calcium Antagonist Felodipine. Dihydropyridine Binding Prerequisites Assessed from Crystallographic Data. *J. Med. Chem.* **1986**, *29*, 305−307.

(9) Miri, R.; McEwen, C. A.; Knaus, E. E. Synthesis and Calcium Channel Modulating Effects of Modified Hantzsch Nitrooxyalkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(pyridinyl or 2-trifluoromethylphenyl)-5-pyridinecarboxylates. *Drug Dev. Res.* **2000**, *51*, 225−232.

(10) Miri, R.; Howlett, S. E.; Knaus, E. E. Synthesis and Calcium Channel Modulating Effects of Isopropyl 1,4-dihydro- 2,6-dimethyl-3-nitro-4-(thienyl)-5-pyridinecarboxylates. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 290−294.

(11) Shafiee, A.; Miri, R.; Dehpour, A. R.; Solimani, F. Synthesis and Calcium Channel Antagonist Activity of Nifedipine Analogues Containing Nitroimidazolyl Substituent in Guinea-pig Ileal Smooth Muscle. *Pharm. Sci.* **1996**, *2*, 541−543.

(12) Miri, R.; Dehpour, A. R.; Azimi, M.; Shafiee, A. Synthesis and Smooth Muscle Calcium Channel Antagonist Effects of New Derivatives of 1,4-Dihydropyridine Containing Nitroimidazolyl Substituent. *Daru* **2001**, *9*, 40−45.

(13) Miri, R.; Niknahad, H.; Vesal, Gh.; Shafiee, A. Synthesis and Calcium Channel Antagonist Activities of 3-Nitrooxyalkyl, 5-Alkyl 1,4-dihydro-2,6-dimethyl-4-(1-methyl-5-nitro-2-imidazolyl)-3,5-pyridinedicarboxylates. *Il Farmaco* **2002**, *57*, 123−128.

(14) 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*, 713−757.

(15) Yamini, Y.; Bahrmifar, N. Solubilities of Some Polycyclic Aromatic Hydrocarbons in Supercritical Carbon Dioxide. *J. Chem. Eng. Data* **2000**, *45*, 53−56.

(16) 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.

(17) Knez, Z.; Skerget, M.; Senear-Bozic, P.; Rizner, A. Solubility of Nifedipine and Nitrendipine in Supercritical CO_2. *J. Chem. Eng. Data* **1995**, *40*, 216−220.

(18) Foster, N. R.; Gurdial, G. S.; Yun, J. S. L.; Loing, K. K.; Tilly, K. D.; Tiny, S. S. T.; Singh, H.; Lee, J. H. Significance of the Crossover Pressure in Solid−Supercritical Fluid Phase Equilibria. *Ind. Eng. Chem. Res*. **1991**, *30*, 1955−1964.

(19) Miller, D. J.; Hawthorne, S. B.; Clifford, A. A.; Zhu, S. Solubility of Polycyclic Aromatic Hydrocarbons in Supercritical Carbon Dioxide from 313 to 513 K and Pressures from 100 to 450 bar. *J. Chem. Eng. Data* **1996**, *41*, 779−786.

Received for review August 11, 2004. Accepted November 23, 2004.

JE0497092