48 *J. Chem. Eng. Data* **2004,** *49,* 48−52

Solubilities of *p*-Tolylboronic Acid, Bromobenzene, and 4-Phenyltoluene in Carbon Dioxide at Elevated Pressures

Gary A. Leeke,*[†] Regina C. Santos,[†] Jonathan Seville,[†] Bushra Al-Duri,[†] Connie K. Y. Lee,[‡] and Andrew B. Holmes[‡]

Centre for and Formulation Engineering, Department of Chemical Engineering, University of Birmingham,
Edgbaston, Birmingham B15 2TT, U.K., and Melville Laboratory for Polymer Synthesis,
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K.

Solubility data were determined for the first time for *p*-tolylboronic acid, bromobenzene, and 4-phenyltoluene in carbon dioxide at (353 and 383) K and between pressures of (98 and 317) bar. Data were obtained using a cloud point apparatus fitted with an internal stirrer. The results were correlated using Chrastil's density based model.

Introduction

The synthesis of organic molecules in the absence of volatile organic solvents remains an important industrial goal. Supercritical fluids have recently emerged as an environmentally benign alternative to volatile organic solvents.[1−3] CO_2 is particularly attractive for synthesis because it is nontoxic, nonflammable, and inexpensive. Above its critical temperature (31.1 °C) and pressure (73.8 bar), carbon dioxide possesses hybrid properties of both liquid and gas—the properties of which can be tuned through variations of temperature and pressure.

The Suzuki reaction is well established as a versatile tool in synthetic organic chemistry and has important applications in the pharmaceutical industry.[4] The reaction cross-couples an aryl halide with a boronic acid in the presence of a palladium catalyst to form a new carbon−carbon bond. In previous work, Carroll and Holmes[5] and Early et al.[6] have successfully carried out the Suzuki reaction in supercritical CO_2. All of their work has been undertaken without prior knowledge of the solubilities of the components in the reacting system and over a limited range of experimental conditions. In this paper we report the first known solubilities of the reactants and product for a typical Suzuki reaction over a wide range of conditions to enable optimization to be undertaken.

The Suzuki reaction that couples *p*-tolylboronic acid with bromobenzene to form 4-phenyltoluene was investigated. Comprehensive vapor phase data were obtained for the reactants *p*-tolylboronic acid and bromobenzene and the product 4-phenyltoluene, all in carbon dioxide at (353 and 383) K from (98 to 317) bar. Data were obtained using a cloud point apparatus fitted with an internal stirrer. The results were correlated using a density-based model. The reliability of the experimental procedure was ascertained by first determining vapor data for the previously studied carbon dioxide + *n*-hexadecane system at 323 K. The structures of *p*-tolylboronic acid, bromobenzene, and 4-phenyltoluene are shown in Figure 1.

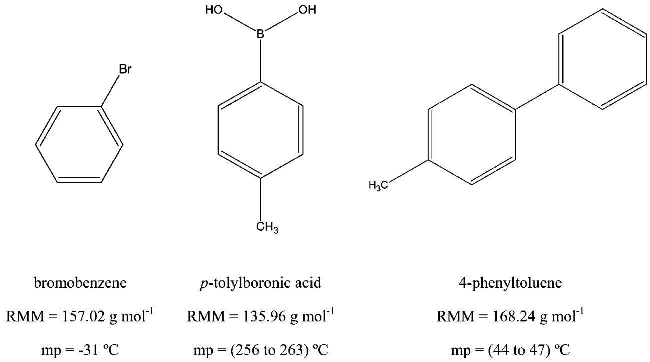

Figure 1. Structures of compounds.

Experimental Section

Materials. *p*-Tolylboronic acid (97%) [5720-05-8], bromobenzene (99+%) [108-86-1], and 4-phenyltoluene (98%) [644-08-06] were supplied from Sigma-Aldrich U.K., and all were used without further purification. Liquid carbon dioxide was obtained from BOC, CP grade, and had a given purity of 99.995%.

Equipment. The apparatus used to determine the high-pressure vapor data is shown in Figure 2. The equilibrium cell (Parr Instruments, USA) had an internal volume of 25 cm^3 and was fitted with in-line sapphire windows. It was maintained at a constant temperature by a pair of thermostatically controlled band heaters. For the solid, *p*-tolylboronic acid, the cell was charged typically with 5 to 14 mg. At ambient temperature, the solid 4-phenyltoluene was observed to undergo melting point suppression at around 30 bar, and up to 4 g was charged into the vessel. For the liquid, bromobenzene, up to 12 g was used. A Metler Toledo MT5 balance was used to determine the masses of the compounds, which had an accuracy of 0.01 mg. Liquid carbon dioxide was compressed by the use of a pressure generator (HIP, model 62-6-10) and directed to the equilibrium cell. The temperature in the cell was increased to the desired isothermal condition and the pressure raised until dissolution of the compound occurred and a homogeneous phase existed. This condition was verified by directing a color camera at the view cell and

---

* To whom correspondence should be addressed. E-mail: G.A.Leeke@bham.ac.uk. Telephone: +44 121 414 6965. Fax: +44 121 414 5324.
[†] University of Birmingham.
[‡] University of Cambridge.

10.1021/je034051y CCC: $27.50

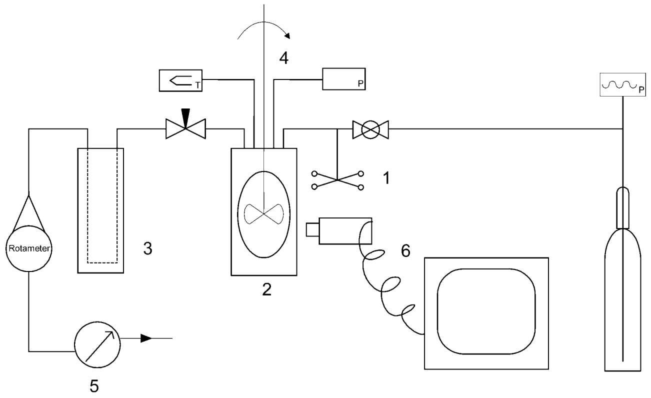

Figure 2. Cloud point apparatus: 1, pressure generator; 2, view cell; 3, cold collector; 4, stirrer; 5, flow totalizer; 6, camera + monitor.

Table 1. Experimental Data for *p*-Tolylboronic Acid

nominal T/°C	P/bar	solubility/ (g solute/kg CO_2 at STP)	solubility/ ($\times 10^5$ g solute/mL CO_2 under P)	CO_2 density/ kg·m^{-3}
80	106.1	0.1215	2.7844	229.16
80	127.2	0.1140	3.7291	327.07
80	139.8	0.1156	4.4214	382.46
80	150.3	0.1223	5.2395	428.44
80	167.5	0.1192	5.9250	496.92
80	202.2	0.1264	7.5703	599.11
80	238.0	0.1320	8.8180	668.11
80	245.1	0.1341	9.1069	679.06
80	252.9	0.1348	9.3081	690.32
80	296.7	0.1432	10.6324	742.29
80	312.0	0.1470	11.1282	757.12
110	95.6	0.3304	5.5227	167.13
110	111.4	0.3362	6.8419	203.49
110	125.5	0.3303	7.8707	238.30
110	159.0	0.3392	11.1164	327.73
110	166.8	0.3392	11.8444	349.14
110	172.4	0.3339	12.1680	364.44
110	194.1	0.3400	14.3468	421.97
110	227.3	0.3376	16.8767	499.91
110	241.4	0.3433	18.1424	528.52
110	255.8	0.3474	19.2840	555.05
110	278.4	0.3505	20.7454	591.83
110	305.2	0.3525	22.1731	629.03
110	317.2	0.3665	23.5991	643.96

Table 2. Experimental Data for Bromobenzene

nominal T/°C	P/bar	solubility/ (g solute/kg CO_2 at STP)	solubility/ ($\times 10^3$ g solute/mL CO_2 under P)	CO_2 density/ kg·m^{-3}
80	98.3	32.9107	7.1048	215.88
80	109.8	41.3714	10.6163	256.61
80	115.3	38.6771	10.7445	277.80
80	117.5	35.5209	10.1792	286.57
80	120.2	38.4337	11.9390	297.56
80	128.5	41.3611	13.7600	332.68
80	134.7	62.4596	22.4774	359.87
80	138.4	74.0491	27.8632	376.28
80	139.8	84.1851	32.2000	382.49
80	140.0	84.0422	32.2201	383.38
80	142.6	94.7134	37.4014	394.89
80	148.9	111.3353	47.0314	422.43
80	153.1	148.7210	65.4819	440.30
80	161.2	264.9337	125.3534	473.15
80	162.7	261.9233	125.4508	478.96
80	164.9	280.4418	136.6621	487.31
110	104.7	37.2613	6.9951	187.73
110	114.5	47.2270	9.9630	210.96
110	129.4	62.8629	15.6082	248.29
110	141.9	72.0618	20.2638	281.20
110	144.1	66.4340	19.0739	287.11
110	160.1	101.8446	33.6851	330.75
110	162.0	99.6143	33.4674	335.97
110	162.3	104.9631	35.3505	336.79
110	179.0	171.4537	65.5485	382.31
110	180.2	181.4363	69.9491	385.53
110	194.1	265.0874	111.8589	421.97
110	198.5	309.3881	133.9960	433.10
110	201.2	314.5781	138.3578	439.82

Table 3. Experimental Data for 4-Phenyltoluene[a]

nominal T/°C	P/bar	solubility/ (g solute/kg CO_2 at STP)	solubility/ ($\times 10^4$ g solute/mL CO_2 under P)	CO_2 density/ kg·m^{-3}
80	100.8	2.5320	5.6799	224.33
80	104.6	2.5292	6.0093	237.60
80	120.7	4.7270	14.1630	299.62
80	137.7	3.8165	14.2419	373.17
80	148.9	8.2761	34.9609	422.43
80	162.8	13.5907	65.1459	479.34
80	178.6	17.8726	95.5611	534.68
80	201.6	30.2250	180.6548	597.70
80	215.4	45.1080	283.1610	627.74
80	227.5	55.1391	358.6856	650.51
80	228.8	53.3910	348.5310	652.79
80	245.7	74.6501	507.5834	679.95
80	255.3	85.2185	591.1098	693.64
110	94.4	4.1800	6.8757	164.49
110	97.3	4.1651	7.1186	170.91
110	124.7	4.4323	10.4721	236.27
110	140.2	8.1436	22.5300	276.66
110	169.5	14.0000	49.9142	356.53
110	178.3	13.4245	51.0696	380.42
110	185.4	24.1705	96.5274	399.36
110	191.9	25.7148	107.0560	416.32
110	215.8	40.0080	189.8658	474.57
110	244.1	51.1988	273.2426	533.69
110	251.9$^{\Delta}$	58.8197	322.4025	548.12
110	252.5$^{\Delta}$	59.1832	324.0367	549.20
110	253.3$^{\Delta}$	59.0016	324.8805	550.63
110	283.0	77.2370	462.3945	598.67
110	307.6	94.1403	595.0422	632.08

[a] For repeat determinations of identical sample masses (to within 7 mg) charged into the cell, the mean precipitation pressure could be reproduced to within 1.4 bar (see 4-phenyltoluene data marked with Δ).

observing the image on a monitor. Dissolution was aided by the use of an impeller (Rushton turbine) coupled to an external magnetic drive. Typically the time required to achieve equilibrium was 4 h for the solid and 15 min for the liquid components.

Sampling Procedure. Once the compound had been fully dissolved, the pressure was lowered to the onset of the cloud point. The pressure was recorded using a transducer (Druck PTX 1400) with a dedicated display to within 0.1 bar, and the temperature was recorded to within 0.1 °C using a Watlow 93 temperature controller and J-type thermocouple. The sample could then be redissolved by increasing the pressure, and the above procedure was repeated to verify the cloud point pressure. The pressures shown are the mean of up to five repeat determinations, and the variance was no greater than ±1.1 bar. For repeat determinations of identical sample masses (to within 7 mg) charged into the cell, the mean precipitation pressure could be reproduced to within 1.4 bar (see 4-phenyltoluene data marked with Δ in Table 3). The volume of CO_2 present in the vessel at the cloud point was recorded by depressurizing across micrometering valve V1 (Hoke, 1315G4Y) and passing the expanded stream through a wet-test meter (Alexander Wright 0.25 dm^3 rev^{-1}). The CO_2 volume was then corrected to STP (273 K at 1 atm.). For safety reasons any heavy component present in the expanded gas stream was trapped in the glass collector (3) maintained at approximately −80 °C in a dry ice + acetone slurry.

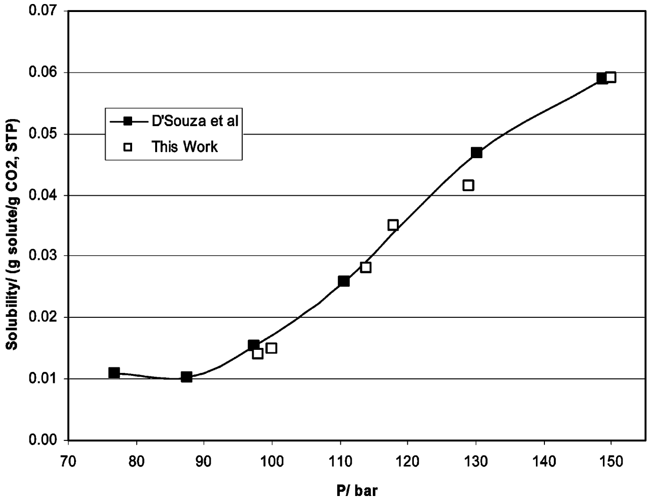

Figure 3. Experimental data for *n*-hexadecane at 333 K.

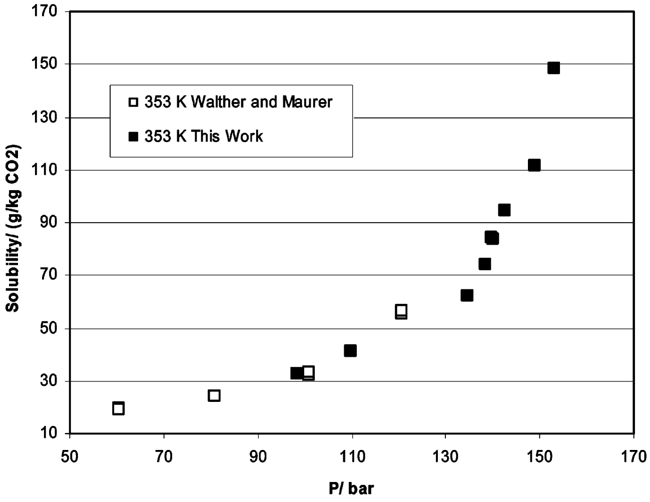

Figure 4. Comparison of solubility data for the carbon dioxide + bromobenzene system at 80 °C.

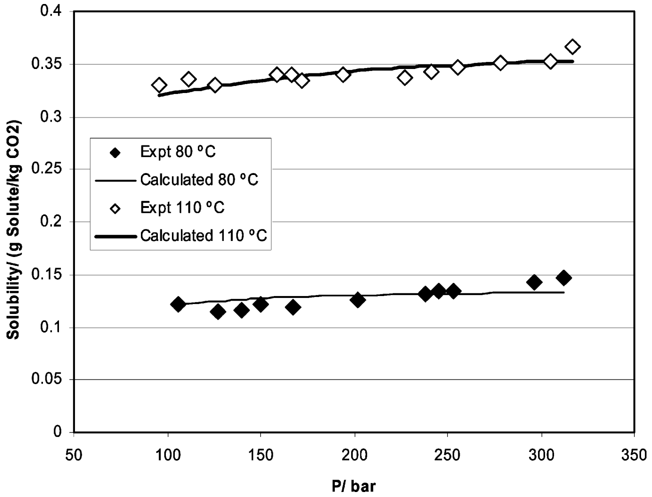

Figure 5. Correlation of experimental data for *p*-tolylboronic acid.

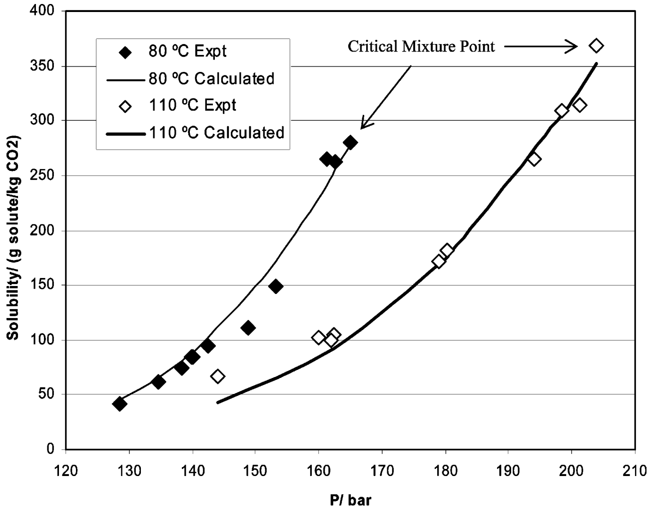

Figure 6. Correlation of experimental data for bromobenzene; data below the crossover pressure are not modeled.

Results and Discussion

Vapor data for the CO_2 + *n*-hexadecane system were measured at 333 K to verify the reliability of the apparatus and the methodology employed. Figure 3 shows that the experimental values are in agreement with the data of D'Souza et al.[7]

Vapor phase solubility data were determined at (353 and 383) K for the three binary systems, carbon dioxide + *p*-tolylboronic acid, carbon dioxide + bromobenzene, and carbon dioxide + 4-phenyltoluene, and are shown in Tables 1−3, respectively. In the case of the bromobenzene system, no vapor phase data were obtained above 164.9 bar and 201.2 bar for the isotherms at (80 and 110) °C, respectively. Above these conditions, an increase in the amount of bromobenzene charged into the pressure cell resulted in phase transition and the generation of bubble point data. These last vapor phase points can, therefore, be considered to be near to the critical mixture point of the system and are marked accordingly in Figure 6, but they should be treated with a degree of caution. Solubility data for this binary system have been reported by Walther and Maurer[8] at (40 and 80) °C. The data obtained at 80 °C are shown in Figure 4 and compared well to those of the previous authors' work.

The competing effects of solute vapor pressure and solvent density control the solubility of a component in a supercritical fluid. The solubilities of the components in CO_2 were found to be of the order bromobenzene $>$ 4-phenyltoluene $\gg$ *p*-tolylboronic acid, and this order was indicative of their decreasing vapor pressures. The solubility of *p*-tolylboronic acid was little dependent on CO_2 density at the conditions studied and consequently shows negligible pressure dependency along the isotherms. An increase in temperature (and vapor pressure) resulted in an increased solubility, but its solubility was much lower when compared to those of the bromobenzene and 4-phenyltoluene systems. CO_2 is a good solvent toward nonpolar to slightly polar organic compounds, and this is reflected in the increased solubilities of bromobenzene and 4-phenyltoluene over the CO_2 density range. The solubilities of 4-phenyltoluene and bromobenzene show crossover pressures at 187.1 bar and 135.0 bar, respectively. At the crossover the competing effects of solute vapor pressure and solvent density balance each other. These crossover pressures correspond to the lower crossover pressure reported by Foster et al.[9] In this study, the lower crossover pressure was determined by plotting mole fraction solubilities against pressure and drawing a line of best fit through the data for each isotherm and reading the pressure where the lines cross. At pressures below the crossover, the solubility of the components increases with temperature. This is rarely seen at such high imposed pressures and is due to the very high partial pressure of the solutes in the CO_2 at

Table 4. Chrastil Constants

heavy component	T/°C	Chrastil parameters a	b	k	avg dev/%
p-tolylboronic acid	80	−4463.6	3.230	1.073	5.1
	110	−4463.6	3.230	1.073	1.5
bromobenzene	80	−3254.5	−21.347	5.722	6.4
	110	−3254.5	−21.347	5.722	14.7
4-phenyltoluene	80	−4012.0	−21.313	5.589	10.6
	110	−4012.0	−21.313	5.589	15.6

high temperatures. (The vapor pressure of bromobenzene was determined from the Antoine parameters given by Al-Hayna and Newsham[10] and was found to be 0.27 bar at 110 °C, compared to 0.0058 bar at 25 °C in ref 11.) At pressures above the crossover pressure, the solubility of the components is lower at the higher temperature, as a consequence of the decreasing CO_2 density. This phenomenon is termed retrograde vaporization.

Correlation of Data. Chrastil's model[12] related the solubilities of solutes directly to the density of a compressed gas solvent and avoided the complexity of equations of state. On the basis of the theory that the solute and gas solvent molecules associate to form a solvato complex, and combined with the entropy of the components, the following equation was derived:

$$c = \rho^k \exp(a/T + b) \tag{1}$$

where c is the solute concentration in the solvent gas (g/L), ρ is the density of the gas (g/L), k is an association constant which is characteristic for a given gas and solute and is independent of both temperature and pressure, a is dependent on the heat of solvation and vaporization of the solute, and b is dependent on the molecular masses of the solute and solvent and on the melting points of the solute. Chrastil observed that a log−log plot of c against ρ for a given isotherm resulted in a linear relationship with a slope of k. At different temperatures, isothermal plots should be parallel to one another. This linear relationship remained true up to loadings of (100−200) g of solute per liter of solvent gas, since the density of the solution was not usually that different from that of the pure gas under the same conditions. Moreover, at increased solubilities, the density of solution started to differ significantly from that of pure CO_2. This relationship was first observed by Stahl and Schliz,[13] who measured the solubilities of sugars, amino acids, and other polar compounds in supercritical carbon dioxide up to 1974 atm. Yamini et al.[14] and King and Catchpole[15] have successfully applied Chrastil's model to correlate data for dihydroxybenzene isomers and soy bean oil in CO_2, respectively.

Using CO_2 densities from NIST,[16] eq 1 was fitted to the vapor phase data by minimizing the average deviation between the experimental and calculated values for both isotherms simultaneously by adjusting the fitting constants a, b, and k. The outputted values are shown in Table 4, and Figures 5−7 show the fitted data plots. The association constant k is not an integer, as most solvato complexes are not stoichiometric. It gives an average equilibrium association number, which is a characteristic constant for a given gas and solute.

The model was initially fitted to the entire data range of the bromobenzene and 4-phenyltoluene systems, but failing to take account of the crossover results in a poor fit to the data. At densities below the crossover pressures, the solubility was higher than that predicted by the density input of the model over the entire range, as it was enhanced by the increased solute vapor pressure. Hence, the density of the solution was significantly different from that of pure CO_2. Consequently, due to the high volatility of these solutes under these temperature conditions, the equation was applied above the crossover pressures, only where the CO_2 density has the dominant effect on solubility. Even over this narrow solubility range, the fit was only slightly better than satisfactory. With this in mind, the model can only be used to give a reasonable prediction of solubilities at temperature conditions where solvent density has the predominant effect.

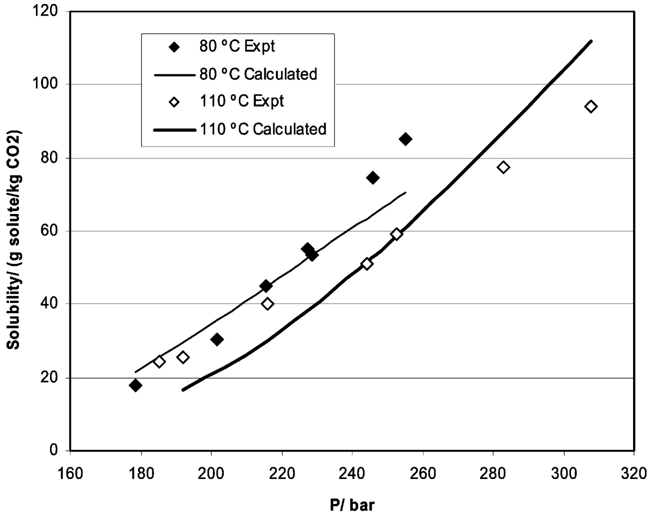

Figure 7. Correlation of experimental data for 4-phenyltoluene; data below the crossover pressure are not modeled

The solubility of p-tolylboronic acid was vapor pressure dependent over the entire pressure range studied, and the model was able to give a good fit to the data. The improvement in fit compared to the cases of other systems can be attributed to the relatively low loadings of solute in the CO_2 even at high temperatures and the lack of crossover that would have led to density dependent solubility. Hence, the change in CO_2 density was not significant enough to affect the applicability of the Chrastil equation. In contrast, therefore, the fitting constants for p-tolylboronic acid can be successfully applied to other temperatures with confidence.

Chrastil's model has been shown to have some limitations in that it is restricted to low solubilities and to temperatures no greater than 80 °C in ref 17. The solubility of bromobenzene was above the lower loading limit defined by Chrastil, and both the bromobenzene and 4-phenyltoluene systems were extended to temperatures above the recommended limits. In conclusion, Chrastil's model can be used at temperatures higher than 80 °C as long as the vapor pressure of the solute is not increased significantly, since the model fails to consider such a property.

Literature Cited

(1) Oakes, R. S.; Clifford, A. A.; Rayner, C. M. The Use of Supercritical Fluids in Synthetic Organic Chemistry. *J. Chem. Soc., Perkin Trans. 1* **2001**, 917−941.

(2) Darr, J. A.; Poliakoff, M. New Directions in Inorganic and Metal-Organic Coordination Chemistry in Supercritical Fluids. *Chem. Rev.* **1999**, *99*, 495−541.

(3) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, 1999.

(4) Suzuki, A. Recent Advances in the Cross-coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995−1998. *J. Organomet. Chem.* **1999**, *576*, 147−148.

(5) Carroll, M. A.; Holmes, A. B. Palladium Catalysed Carbon−Carbon Bond Formation in Supercritical Carbon Dioxide. *Chem. Commun.* **1998**, *13*, 1395−1396.

(6) Early, T. R.; Gordon, R. S.; Carroll, M. A.; Holmes, A. B.; Shute, R. E.; McConvey, I. F. Palladium-catalysed Cross-coupling Reactions in Supercritical Carbon Dioxide. *Chem. Commun.* **2001**, *19*, 1966−1967.
(7) D'Souza, R.; Patrick, J.; Teja, A. S. High-Pressure Phase Equilibria in the Carbon Dioxide-*n*-Hexadecane and Carbon Dioxide-Water Systems. *Can. J. Chem. Eng.* **1988**, *66*, 319−323.
(8) Walther, D.; Maurer, G. High-Pressure Vapour-Liquid Equilibira in Binary Mixtures of Carbon Dioxide and Benzaldehyde, Bromobenzene, Chlorobenzene, 1,2-Dichlorobenzene and 2-Chloro-1-Methylbenzene at Temperatures between 313 and 393 K and Pressures up to 22 MPa. *Ber. Bunsen-Ges. Phys. Chem.* **1992**, *96*, 981−988.
(9) Foster, N. R.; Gurdial, G. V.; Yun, J. S. L.; Liong, K. K.; Tilly, K. D.; Ting, 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.
(10) Al-Hayna, M. N. M.; Newsham, D. M. T. Isobaric Vapour-Liquid Equilibria for Mixtures Containing Halogenated Hydrocarbons at Atmospheric Pressure: Part II. Binary Mixtures of Fluorobenzene, Chlorobenzene and Bromobenzene. *Fluid Phase Equilib.* **2000**, *168*, 259−266.
(11) Reid, R. C.; Prausnitz, J. M.; Poling, B. E. *The Properties of Gases and Liquids*, 4th ed.; McGraw-Hill: New York, 1987.
(12) Chrastil, J. Solubility of Solids and Liquids in Supercritical Gases. *J. Phys. Chem.* **1982**, *86*, 3016−3021.
(13) Stahl, E.; Schliz, W. Loslichkeitsverhalten polarer Naturstoffe in uberkritischen Gasen im Druckbereich bis 2500 bar. *Chem.-Ing.-Tech.* **1978**, *50*, 535−537.
(14) Yamini, Y.; Reza Fat'hi, M.; Alizadeh, N.; Shamsipur, M. Solubility of Dihydroxybenzene Isomers in Supercritical Dioxide. *Fluid Phase Equilib.* **1998**, *152*, 299−305.
(15) King, M. B.; Catchpole, O. Physico-chemical Data Required for the Design of Near-Critical Fluid Extraction Process. In *Extraction of Natural Products Using Near-Critical Solvents*; King, M. B., Bott, T. R., Eds.; Blackie Academic and Professional: Glasgow, 1993.
(16) Lemmon, E. W.; McLinden, M. O.; Friend, D. G. Thermophysical Properties of Fluid Systems. In *NIST Chemistry WebBook*; Linstrom, P. J., Mallard, W. G., Eds.; NIST Standard Reference Database Number 69; National Institute of Standards and Technology: Gaithersburg MD, 20899, July 2001 (http://webbook.nist.gov).
(17) del Valle, J. M.; Aquilera, J. M. An Improved Equation for Predicting the Solubility of Vegetable Oils in Supercritical CO_2. *Ind. Eng. Chem. Res.* **1988**, *27*, 1551−1553.

Received for review March 12, 2003. Accepted September 26, 2003. The authors gratefully thank EPSRC under the collaboration between chemists and chemical engineers.

JE034051Y