High-Pressure Vapor−Liquid Equilibrium for the Binary Systems Carbon Dioxide + Dimethyl Sulfoxide and Carbon Dioxide + Dichloromethane

Arlette Vega Gonzalez,* Roland Tufeu, and Pascale Subra

Laboratoire d'Ingénierie des Matériaux et des Hautes Pressions (LIMHP), C.N.R.S., Institut Galilée,
Université Paris Nord, 99 Avenue Jean Baptiste Clément, 93430 Villetaneuse, France

High-pressure vapor−liquid equilibrium data were measured for two binary systems: carbon dioxide + dimethyl sulfoxide at four temperatures from 309 to 329 K and pressures up to 13 MPa, and carbon dioxide + dichloromethane at 311.41 K and 326.95 K and pressures up to 9.5 MPa. Bubble points were determined by a synthetic method where a mixture of known composition is prepared in a sapphire cell of variable volume. The reliability of the equipment and method was established through comparison with literature on the carbon dioxide + ethanol system. These measurements were made at 314.45 and 324.17 K.

Introduction

There is a growing interest in the use of binary and multicomponent supercritical fluid mixtures. Small amounts of cosolvents, which are referred to as modifiers or entrainers, may be added to modify the polarity and solvent strength of the pure supercritical fluid and to increase the solute solubility and/or selectivity. These mixtures are of interest in a number of applications that include extraction, chromatography, and crystallization. Care must thus be taken when using organic solvents in supercritical fluid processes, since even rather simple binary compositions can undergo complicated phase transitions near the critical region. Gas−liquid or liquid−liquid immiscibilities can occur at conditions exceeding the critical temperature, T_c, or pressure, P_c, of either pure component. As a result, inhomogeneous phases can be produced.

A promising field of application is the use of supercritical fluids as media for the production of particulate materials. Two processes are currently under development, especially for micronization of pharmaceutical compounds: the rapid expansion of supercritical solutions (RESS) and the gas-antisolvent (GAS) processes. Both offer the possibility of obtaining small particles with an adequate size distribution. However, the antisolvent process is now gaining importance because the relatively low solubility of many pharmaceutical compounds in CO_2 precludes their micronization by the RESS process.

The GAS process is based on the supersaturation of a liquid solution, induced by the dissolution of a near-critical or supercritical fluid. The dissolved gas creates an antisolvent effect, which results in the precipitation of the solid solute. The quality of the produced solid particles depends on both equilibria and mass transfers. One important feature in the crystallization process is to avoid the formation of an organic solution in the crystallization vessel, which would further reduce the solute recovery and damage the quality of the produced particles. To ascertain that the liquid solvent completely transfers into the antisolvent phase, process conditions and operating procedure should be set in the domain of complete miscibility of the CO_2−liquid solvent mixture. The binary mixture should belong to the type I of fluid-phase behavior classification from Van Konynenburg and Scott.[1]

The solvent selection is driven first by the solubility of the material in the organic liquid. Second, the transfer of the liquid into the CO_2 and the nonsolubility of material in the mixture (CO_2 + solvent) are considered. As an example, water that dissolves many pharmaceutical compounds, including proteins, is not widely used with the GAS process, since the water removal by pure CO_2 is rather inefficient. On the other hand, dimethyl sulfoxide (DMSO) dissolves significant concentrations of many common proteins.[2−7] It is widely used to prepare an organic solution from which the protein will be precipitated. Recently, dichloromethane (DCM) has also been used in the GAS process as a dissolving medium for lysosyme,[8] some biocompatible polymers,[9,10] griseofulvin,[9] and several steroids.[11]

Despite the fact that phase behavior data are a necessary tool to select process conditions, published experimental data are scarce, especially for the binary systems CO_2−DMSO and CO_2−DCM, typical laboratory solvents. Bubble point curves for CO_2−DMSO have only been determined at 298.15 K and 303.15 K.[12] For CO_2−DCM, bubble points at 294.2 K, 310.9 K, and 327.6 K in the pressure range from the vapor pressure of dichloromethane to 2 MPa at each temperature were reported.[13,14] For this system, critical properties between 306.1 K and 316.3 K have also been reported.[15]

In this study, we present experimental data for the binary systems CO_2−DMSO and CO_2−DCM. Bubble point curves were established at four temperatures (309.44 K, 314.49 K, 321.28 K, and 328.94 K) for the first system and at 311.41 K and 326.95 K for the second system.

Experimental Section

Experimental Apparatus. The cell in which the phase equilibria are studied is a hollow cylinder made of optically polished sapphire (o.d., 45 mm; i.d., 15 mm; length, 51.2 mm) closed at each end by stainless steel flanges. This cell

---

* Corresponding author. E-mail: vega@limhp.univ-paris13.fr.

10.1021/je010202q CCC: $22.00

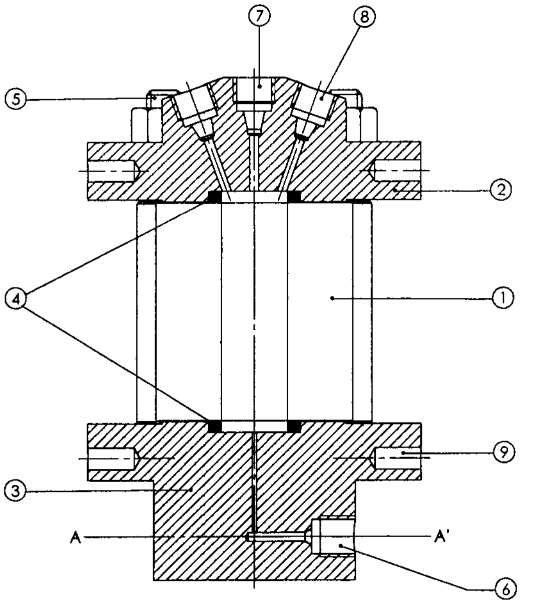

Figure 1. Equilibrium cell: 1, hollow cylinder made of sapphire; 2 and 3, upper and lower stainless steel flanges; 4, Kalrez seals; 5, titanium screws; 6, mercury port; 7, liquid solvent port; 8, CO_2 port; 9, thermocouple cavity; *AA'*, axis of rotation.

is presented in Figure 1. The description of the cell used in this work, minus some minor modifications concerning the admission ports on the top flange, can be found elsewhere.[17] Flat seals ensure the sapphire-flange tightness. There are three holes drilled in the top flange, two of them serve to introduce the organic solvent and the CO_2 into the cell. A third hole is present and is used to intervene within the cell (cleaning of the cell between two different fillings) or for a possible third compound. The lower flange is connected to a high-pressure pump (TOP INDUSTRIE, 2000 bar, 609.26.00). The sample volume can be continuously changed by acting on a mercury piston by means of a screw press filled with low-vapor-pressure silicone oil. Stirring of the sample is performed by rotating the cell around the *AA'* axis. The cell is set in a double-walled air thermostat whose opposite walls are windows that allow direct observation of the phase behavior and measurement of the volume occupied by the sample. The cell is fixed to a handle which is extended outside the oven. The handle can be unlocked from the upright position and can rotate, allowing us to manually shake the cell, thus providing an effective mixing of the solution.

The thermostated equilibrium cell was charged with pure carbon dioxide from a gas cylinder. The amount introduced was determined from the volumes of the gaseous and liquid phases at the temperature and pressure conditions of the filling; densities of both phases were obtained from the IUPAC[16] carbon dioxide thermodynamic tables. The levels of mercury and the phase-separation meniscus were measured with a cathetometer. The amount of CO_2 added was determined with an accuracy of ±0.011 g; the typical amount of CO_2 used in our experiments was about 2 g.

The composition of the mixture was changed by adding different amounts of pure liquid via a manual-rotating pump (TOP INDUSTRIE, 2000 bar, 609.27.00). The volume delivered by the pump was previously calibrated at ambient conditions. The amount of liquid introduced could be determined by the number of rotations of the pump handles. As the quantity of liquid that was delivered by the pump in one rotation was known, a graduation was fixed to the pump, allowing the reading of the volume. The amount of liquid was determined with an accuracy of ±0.0025 g. The pressure in the solvent line was monitored with a pressure transducer (SEDEME TS205, 0−400 bar) connected to a Keithley (193 A DMM) pressure display.

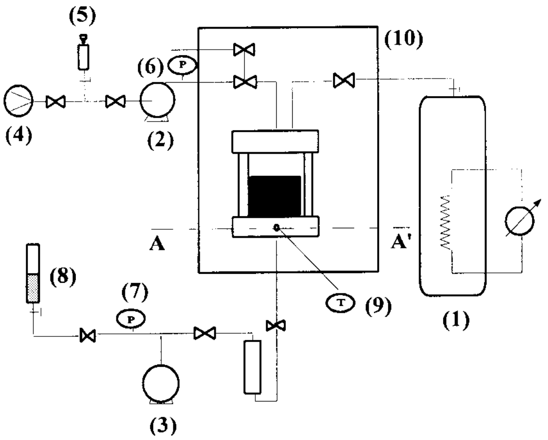

Figure 2. Schematic diagram of the apparatus: (1) gas cylinder; (2) organic solvent manual-rotating pump; (3) manual-rotating pump; (4) vacuum pump; (5) organic solvent reservoir; (6) liquid line pressure transducer; (7) cell pressure transducer; (8) silicone oil reservoir; (9) thermocouple; (10) thermostated air bath.

The pressure in the cell was measured with a pressure transducer (SEDEME TS205, 0−400 bar) and a Keithley (197 A DMM) pressure display, with an accuracy of 1 kPa. The pressure measurement system was calibrated against a manometric balance (type 3020 M, Desgranges et Huot S.A., France). A type K thermocouple, inserted into the bottom flange of the view cell, allows the determination of the temperature. The thermocouple was calibrated against a platinum resistance thermometer (type STHP.B, Lyon Alemand Louyot et Cie, France) connected to a resistance bridge (Leeds & Northrup Co.). The temperature measurements were estimated to be accurate within ±0.1 K.

Experimental Procedure. Phase diagrams of mixtures were determined using a synthetic method. A mixture of known composition is prepared in the cell, and its behavior is then observed as a function of temperature and pressure. A schematic diagram of the apparatus is shown in Figure 2. Before the organic solvent pump was filled with the liquid, the pump and tubing were evacuated with a vacuum pump for at least 2 h. Prior to the introduction of the compounds, the cell was flushed and filled with carbon dioxide at atmospheric pressure. Then, the thermostated equilibrium cell was charged with a known amount of pure carbon dioxide from a heated gas cylinder (1). The pure organic solvent was previously compressed to a pressure slightly above the cell pressure, and a known amount of liquid was fed into the equilibrium cell by a manual-rotating pump (2). The volume introduced was corrected with its compressibility coefficient.[18] For a given temperature, the cell volume was adjusted until a phase separation occurred. The volume was then slowly decreased by acting on the second manual-rotating pump (3), until the formation of a homogeneous phase was observed. The cell was stirred between each decrease of volume, and pressure and temperature were recorded after stirring. The bubble point was determined from a plot of pressure versus cell volume. Indeed, at the pressure at which this point occurs, there is a change in the curve slope. The method is suitable for bubble points' determination, since changes of slope are rather sharp. On the other hand, when dew points are considered, changes might be smoother and thus unclear.

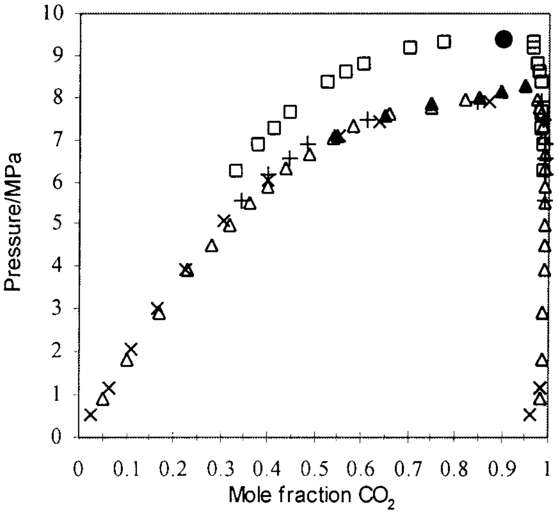

Figure 3. Comparison of the new experimental data for CO_2 + ethanol with literature values: (▲) this work, 314.4 K; (×) Suzuki et al.,[19] 313.4 K; (△) Chang et al.,[21] 313.14 K; (+) Jennings et al.,[20] 314.5 K; (●) this work, 324.2 K; (□) Jennings et al.,[20] 325.2 K.

Table 1. Experimental Data for Liquid Composition for the CO_2 + Ethanol System

T/K	P/MPa	x_{CO_2}	T/K	P/MPa	x_{CO_2}
314.45	8.299	0.9497	314.45	7.541	0.6494
	8.127	0.8994		7.068	0.5499
	8.007	0.8498	324.17	8.219	0.5499
	7.825	0.7497			

So we limit and report our investigation of the dew points to when slope changes were very sharp. The triplet pressure, the temperature, and the overall mole fraction define a point of the phase envelope. Once a point was determined, further compositions were measured by adding more organic solvent.

The accuracies of the temperatures and pressures of the two-phase-to-one-phase transition are ±0.1 K and ±50 kPa, respectively (temperature generally increased slightly during the experiment, but this change was less than 0.1 K). The reported temperature is an average of the temperatures recorded during the measurements.

The compositions were estimated to be accurate to within ±0.004 for the CO_2 + DMSO system and ±0.005 for the CO_2 + DCM system. These estimates are based on the accuracy and precision of the instruments used for composition measurements.

Source and Purity of the Materials. Carbon dioxide (99.998 mass % purity) was obtained from Airgaz (France). Ethanol (anhydrous, analysis grade, 99.9+ mol %) and dimethyl sulfoxide (anhydrous, analysis grade, 99.5+ mol %) were obtained from Carlo Erba Reactifs (France). Dichloromethane (stabilized with 0.1% ethanol, analysis grade, 99.5+ mol %) was obtained from Prolabo (France). All chemicals were used without additional purification.

Results and Discussion

Test System: Carbon Dioxide + Ethanol. Bubble point measurements were made at 314.45 K for six different compositions and at 324.17 K for one composition. The experimental data are presented in Table 1.

Results at 314.45 K are presented in Figure 3 along with measurements by Suzuki et al.[19] (313.4 K), Jennings et al.[20] (314.5 K), and Chang et al.[21] (313.14 K). The result at 324.17 K is also given in the figure, to be compared with measurements by Jennings et al. at 325.2 K. Although the temperatures are not always identical in these comparisons, our results show good agreement with the data of other investigators. This confirms the reliability of the apparatus and technique employed in this work for determining vapor−liquid equilibrium.

Table 2. Experimental Data for Liquid Composition for the CO_2 + DMSO System[a]

T/K	P/MPa	x_{CO_2}	T/K	P/MPa	x_{CO_2}
309.41	7.858	0.9754	314.49	8.589	0.900
	7.756	0.950		8.543	0.850
	7.679	0.900		8.39	0.800
	7.625	0.850		8.158	0.750
	7.521	0.800	321.28	10.230*	0.950*
	7.339	0.750		10.333	0.900
	7.097	0.700		10.083	0.850
	6.775	0.650		9.786	0.800
	6.401	0.600		9.490	0.750
	5.993	0.550		8.553	0.650
	5.588	0.500	328.94	12.579*	0.900*
	5.541	0.499		12.434	0.850
	5.097	0.450		11.903	0.799
	4.603	0.400		11.275	0.751
	4.099	0.350		10.65	0.700
314.49	8.650*	0.980*		10.007	0.650
	8.623	0.960		8.628	0.549
	8.603	0.940		7.210	0.449
	8.598	0.920		5.634	0.350

[a] Asterisks refer to critical conditions.

Table 3. Experimental Data for Vapor Composition for the CO_2 + DMSO System

T/K	P/MPa	y_{CO_2}
321.28	10.320	0.925
328.94	12.397	0.950

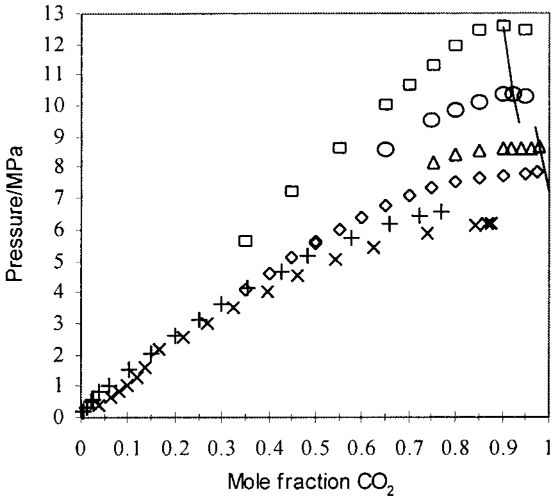

Figure 4. Comparison of bubble point measurements for CO_2 + DMSO with literature data: (◇) this work, 309.4 K; (△) this work, 314.5 K; (○) this work, 321.3 K; (□) this work, 328.9 K; (×) Kordikowsky et al.,[12] 298.15 K; (+) Kordikowsky et al.,[12] 303.15 K; (—) critical line.

Binary Systems: CO_2−DMSO and CO_2−DCM. For the binary system CO_2 (1) + DMSO (2), bubble points and a few dew points were determined at four temperatures (309.44, 314.49, 321.28, and 328.94 K). Experimental data are reported in Tables 2 and 3 and are presented in Figure 4, together with those reported by Kordikowsky et al.[12] at 298.15 and 303.15 K. At 309.44 K and for a mole fraction of CO_2 higher than 0.55, our isotherms are consistent with those reported by the other investigators; for a given composition, the pressure variation corresponds to the temperature variation. This is not the case for the lower

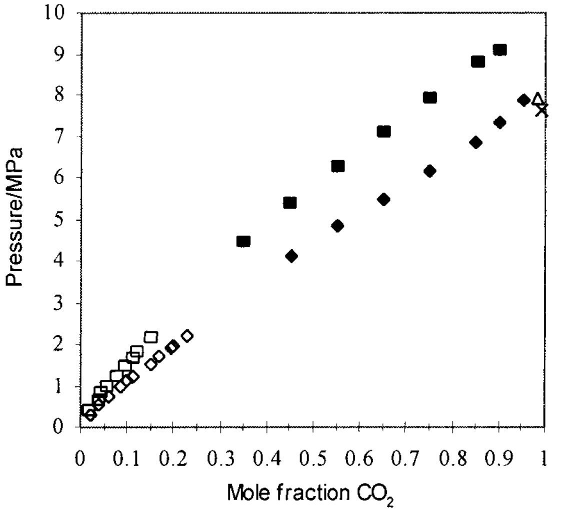

Figure 5. Comparison of the new experimental data for CO_2 + DCM with literature data: (◆) this work, 311.4 K; (◇) Vonderheiden et al.,[14] 310.9 K; (■) this work, 326.9 K; (□) Vonderheiden et al.,[14] 327.6 K; (×) Reaves et al.,[15] critical conditions, 307.1 K; (△) Reaves et al.,[15] critical conditions, 311.6 K.

Table 4. Experimental Data for Liquid Composition for the CO_2 + DCM System

T/K	P/MPa	x_{CO_2}	T/K	P/MPa	x_{CO_2}
311.41	7.846	0.9505	326.95	9.088	0.9029
	7.302	0.9004		8.804	0.8527
	6.844	0.8495		7.913	0.7512
	6.123	0.7502		7.072	0.6503
	5.472	0.6504		6.246	0.5502
	4.805	0.5501		5.389	0.4501
	4.107	0.4505		4.460	0.3501

values of mole fraction, where Kordikowsky's values at 303.15 K seemed a little bit higher than expected. The literature source does not mention the accuracy of the measurements. Therefore, we cannot assert that this difference is within the estimated uncertainty of the experiment, especially considering that the method used is not the same. Furthermore, their results show an important dispersion at low concentrations of CO_2.

For the composition 2.5% (mol/mol) DMSO in CO_2, we have found a set of conditions at which three phases coexist, 315.6 K and 8.78 MPa. In addition to this result, the critical line discontinuity observed between 314.49 K and 328.94 K (Figure 4) points out a short LLV line for a temperature around 315 ± 1 or 2 K, indicating that this system can be classified as a type V system. This was confirmed by the shape of the liquid−vapor curve at 314.49 K (Figure 4), which shows a plateau for $0.9 < c < 1$; this is not characteristic of vapor−liquid equilibrium behavior. This is also supported by Kordikowsky et al.,[12] who report that the Peng−Robinson equation of state indicates a liquid−liquid immiscibility at 303.15 K.

Bubble point measurements for the binary system CO_2 (1) + DCM (2) were made at two temperatures (311.41 and 326.95 K). The experimental results are given in Table 4. As shown in Figure 5, the new data compare well with those reported previously.[13,14] They are also consistent with the critical properties of this system determined by other investigators.[15] According to this figure, the system displays a type I phase behavior.

Acknowledgment

The authors thank Mr. P. Boissinot for his technical assistance.

Literature Cited

(1) Van Konynenburg, P. H.; Scott, R. L. Critical Lines and Phase Equilibria in Binary van der Waals Mixtures. *Philos. Trans. R. Soc. London, Ser. A* **1980**, *298*, 495−540.

(2) Yeo, S.; Lim, G.; Debenedetti, P. G.; Bernstein, H. Formation of Microparticulate Protein Powders Using a Supercritical Fluid Antisolvent. *Biotechnol. Bioeng.* **1993**, *41*, 341−346.

(3) Winters, M. A.; Knutson, B. L.; Debenedetti, P. G.; Sparks, H. G.; Przybycien, T. M.; Stevenson, C. L.; Prestrelski, S. J. Precipitation of Proteins in Supercritical Carbon Dioxide. *J. Pharm. Sci.* **1996**, *85*, 586−594.

(4) Winters, M. A.; Debenedetti, P. G.; Carey, J.; Sparks, H. G.; Sane, S. U.; Przybycien, T. M. Long-Term and High-Temperature Storage of Supercritically-Processed Microparticulate Protein Powders. *Pharm. Res.* **1997**, *14*, 1370−1378.

(5) Winters, M. A.; Frankel, D. Z.; Debenedetti, P. G.; Carey, J.; Devaney, M.; Przybycien, T. M. Protein Purification with Vapor-Phase Carbon Dioxide. *Biotechnol. Bioeng.* **1999**, *62*, 247−258.

(6) Thiering, R.; Dehghani, F.; Dillow, A.; Foster, N. R. The influence of operating conditions on the dense gas precipitation of model proteins. *J. Chem. Technol. Biotechnol.* **2000**, *75*, 29−41.

(7) Moshashaée, S.; Bisrat, M.; Forbes, R. T.; Nyquist, H.; York, P. Supercritical fluid processing of proteins. I: Lysozyme precipitation from organic solution. *Eur. J. Pharm. Sci.* **2000**, *11*, 239−245.

(8) Young, T. J.; Johnston, K. P.; Mishima, K.; Tanaka, H. Encapsulation of Lysozyme in a Biodegradable Polymer by Precipitation with a Vapor-over-Liquid Antisolvent. *J. Pharm. Sci.* **1999**, *88*, 640−650.

(9) Sarkari, M.; Darrat, I.; Knutson, B. L. Generation of Microparticles Using CO_2 and CO_2-Philic Antisolvents. *AIChE J.* **2000**, *46*, 1850−1859.

(10) Elvassore, N.; Bertucco, A.; Caliceti, P. Production of Protein-Loaded Polymeric Microcapsules by Compressed CO_2 in a Mixed Solvent. *Ind. Eng. Chem. Res.* **2001**, *40*, 795−800.

(11) Steckel, H.; Thies, J.; Müller, B. W. Micronizing of steroids for pulmonary delivery by supercritical carbon dioxide. *Int. J. Pharm.* **1997**, *152*, 99−110.

(12) Kordikowsky, A.; Schenk, A. P.; Van Nielen, R. M.; Peters, C. J. Volume Expansions and Vapor-Liquid Equilibria of Binary Mixtures of a Variety of Polar Solvents and Certain Near-Critical Solvents. *J. Supercrit. Fluids* **1995**, *8*, 205−216.

(13) Buell, D. S.; Eldridge, J. W. Solubility, Vapor Pressure, and Liquid Density in the System Carbon Dioxide-Methylene Chloride. *J. Chem. Eng. Data* **1962**, *7*, 187−189.

(14) Vonderheiden, F. H.; Eldridge, J. W. The System Carbon Dioxide-Methylene Chloride. Solubility, Vapor Pressure, Liquid Density, and Activity Coefficients. *J. Chem. Eng. Data* **1963**, *8*, 20−21.

(15) Reaves, J. T.; Aron, T. G.; Roberts, C. B. Critical Properties of Dilute Carbon Dioxide + Entrainer and Ethane + Entrainer Mixtures. *J. Chem. Eng. Data* **1998**, *43*, 683−686.

(16) *International Thermodynamic Tables of the Fluid State, Carbon Dioxide*; Angus, S., Armstrong, B., de Reuck, K. M., Eds.; Pergamon Press: London, 1976.

(17) Tufeu, R.; Subra, P.; Plateaux, C. Contribution to the Experimental Determination of the Phase Diagrams of Some (Carbon Dioxide + a Terpene) Mixtures. *J. Chem. Thermodyn.* **1993**, *25*, 1219−1228.

(18) *Lange's Handbook of Chemistry*; Lange, N. A., Ed.; Handbook Publishers Inc.: Sandusky, OH, 1956.

(19) Suzuki, K.; Sue, H.; Itou, M.; Smith, R. L.; Inomata, H.; Arai, K.; Saito, S. Isothermal Vapor-Liquid Equilibrium Data for Binary Systems at High Pressures: Carbon Dioxide-Methanol, Carbon Dioxide-Ethanol, Carbon Dioxide-1-Propanol, Methane-Ethanol, Methane-1-Propanol, Ethane-Ethanol and Ethane-1-Propanol Systems. *J. Chem. Eng. Data* **1990**, *35*, 63−66.

(20) Jennings, D. W.; Lee, R.-J.; Teja, A. S. Vapor-Liquid Equilibria in the Carbon Dioxide + Ethanol and Carbon Dioxide + Butanol Systems. *J. Chem. Eng. Data* **1991**, *36*, 303−307.

(21) Chang, C. J.; Day, C.-Y.; Ko, C.-M.; Chiu, K.-L. Densities and $P-x-y$ diagrams for carbon dioxide dissolution in methanol, ethanol, and acetone mixtures. *Fluid Phase Equilib.* **1997**, *131*, 243−258.

Received for review July 17, 2001. Accepted February 1, 2002. This work was supported by the European Commission, Competitive and Sustainable Growth (GROWTH) Programme (Project GRD1-1999-10716).

JE010202Q