

Relationship Between Volume Expansion, Solvent-Power, and Precipitation in GAS Processes

Alberto Striolo, Nicola Elvassore, Tiziana Parton, and Alberto Bertucco
Dipt. di Principi e Impianti di Ingegneria Chimica, DIPIC, Università di Padova,
via Marzolo, 9, I-35131 Padova PD — Italy

Dilute solutions of ethyl cellulose (ETC) in acetone and of poly(ethylene oxide) (PEO) in ethyl acetate, acetonitrile, ethyl acetate-acetonitrile, and acetonitrile–water mixtures were expanded isothermally by compressed CO₂. Onset precipitation pressures were visually measured through a windowed cell.

Toward a rational understanding of the molecular mechanisms involved in gas anti-solvent (GAS) processes, saturated-liquid-phase volume expansion and solvent power were monitored by UV-vis spectroscopy for the solvent mixtures considered in the precipitation experiments. Ferrocene absorbance and phenol blue absorption-peak-wavelength shifts were used as probes to assess saturated-liquid-phase volume expansion and solvent power, respectively.

For the first time, a correlation between a microscopic bulk property, solvent power, and the onset precipitation pressure of a solute is reported. Because of preferential interactions with the dye (hydrogen bonds), the correlation breaks down when even small amounts of water are present in the solvent mixture.

The results presented here suggest that UV-vis spectroscopy constitutes a valuable tool for understanding some phenomena related to supercritical-fluid technology.

Introduction

In the past decade, supercritical fluids have emerged as an important alternative to organic solvents in processes such as extraction, recrystallization, industrial cleaning, and sterilization (Reverchon, 1999; Teja and Eckert, 2000; Spilimbergo et al., 2001). Because supercritical CO₂ offers the advantage of processing labile compounds at mild pressure–temperature conditions, recrystallization/precipitation of pharmaceuticals, fractionation of biopolymers, and purification of proteins are currently enjoying strong research interest (Subramaniam et al., 1997; Winters et al., 1999).

Compressed CO₂ is used, among other applications, as the antisolvent in gas antisolvent (GAS) precipitation processes (Gallagher et al., 1989). A low-volatile solvent, the supercritical antisolvent, and a solute are the essential components of a GAS process. The antisolvent is soluble in the liquid solvent, while the solute is not soluble in the dense gas. Dissolution of antisolvent in the liquid phase expands the saturated

liquid, reduces its solvent power, and eventually causes solute precipitation. Even though many applications of GAS processes have already been developed, the molecular mechanisms involved are not completely understood. Saturated liquid-phase volume expansion and onset precipitation pressure of a given compound are considered as key properties in the study of CO₂-solute-solvent systems (Bertucco and Pallado, 1999). However, no general relationship has been unequivocally reported between liquid-phase volume expansion and precipitation of a given compound (Chang and Randolph, 1990).

The concept of clustering (statistical local-density augmentation of solvent molecules about solute molecules) was introduced to investigate the solubility of substances in near critical or supercritical CO₂ (Eckert et al., 1983, 1986; Debenedetti, 1987; Kim and Johnston, 1987a,b; Sun et al., 1992; Phillips and Brennecke, 1993). Debenedetti and Mohamed (1989) showed that a solute at infinite dilution in a near critical solvent can experience either augmented or diminished solvent density in its local environment.

Molecular spectroscopy in supercritical fluids is a relatively new research tool (Kim and Johnston, 1987a; Sun et al., 1992;

Correspondence concerning this article should be addressed to N. Elvassore.
Current address of A. Striolo: Department of Chemical Engineering, North Carolina State University, 113 Riddick Labs, Raleigh, NC 27695.

Carlier and Randolph, 1993; Yamaguchi et al., 1993; Eberhardt et al., 1997; Brennecke et al., 2000). Phenol blue absorption–peak wavelength strongly depends upon solution properties, thus it provides an empirical scale for solvent power classifications (Figueras, 1971; Kolling, 1991). Kim and Johnston (1987a) and Kelley and Lemert (1996) measured phenol blue absorption–peak wavelength to sample the solvent power of a few organic solvents expanded by compressed CO₂. They proved that, upon increasing CO₂ pressure, the local environment about the dye changes when compared to the bulk composition. In particular, organic-solvent molecules accumulate around the dye much more than CO₂ molecules do. Recently, our group proposed UV-vis absorbance measurements to assess the saturated-liquid-phase volume expansion for a solvent exposed to high-pressure CO₂ (Elvassore et al., 2002). Here we present an improved version of the original experimental setup. The new design allows faster equilibration and more reliable temperature control. Literature data were reproduced to check the reliability of the experimental method.

In this work we attempt to correlate the solvent power of a compressed CO₂-organic solvent mixture to the conditions that determine polymer precipitation in a GAS experiment. Onset precipitation pressures of poly(ethylene oxide) (PEO) and ethyl cellulose (ETC) from various solutions expanded by GAS processes are reported. To reproduce experimental conditions used for the production of polymeric microparticles (Bertuccio and Pallado, 1999; Elvassore et al., 2001), dilute polymer solutions were considered. Onset precipitation pressures were measured by visual observation through a windowed cell.

Saturated-liquid-phase volume expansion and solvent power were measured by UV-vis spectroscopy methods for the pure solvents and for the solvent mixtures used for precipitation experiments. A general relationship between saturated liquid-phase volume expansion and onset precipitation pressures was not observed. However, our results suggest that the bulk solvent power may determine the precipitation conditions from a solution expanded by compressed CO₂.

Following the analytic method proposed by Kim and Johnston (1987a) and by Kelley and Lemert (1996), shifts in the absorption–peak wavelength of the solvatochromic probe phenol blue were used to estimate the local composition around the dye. The local composition was compared to the bulk composition, estimated by the perturbed-hard-sphere-chain equation of state (PHSC EOS). Our calculations show an enhanced organic-solvent density around the solvatochromic dye. Interestingly, polymer precipitation occurs when local CO₂ mole fraction about the dye is approximately 20 ± 5%.

Materials and methods

PEO, molecular weight (MW) 20 kDa, and molecular weight/number = average molecular weight (MW/M_n) 1.3, was purchased from Fluka (Buchs, Switzerland) and ethyl cellulose, MW 120 kDa and MW/M_n 1.2, was purchased from Eurand (Milan, Italy). Spectroscopy-grade organic solvents ethylacetate, acetone, and acetonitrile were purchased from Aldrich (Steinheim-Germany) and used as received. Water

was distilled in the laboratory. CO₂, 99.95%-grade purity, was purchased from Air Liquide (Padova, Italy).

Ferrocene (π -C₅H₅)₂Fe (Aldrich, Steinheim-Germany), absorbing peak at 440 nm, was used at concentration of 1 g/L to monitor volume expansions. Solvatochromic dye phenol blue (*N,N*-dimethylindooaniline) (Aldrich, Steinheim-Germany) was used at concentration of 0.023 g/L to monitor the solvent power of different solvents.

Dilute solutions (less than 35 g/L) of PEO and ETC in different solvent mixtures were studied. All solutions were stirred for at least one hour before precipitation experiments.

Polymer precipitation

A windowed cell was used to monitor the precipitation of PEO and ETC from different mixtures by GAS processes. A detailed scheme of the experimental setup is reported elsewhere (Bertuccio et al., 1998). A 10–15-mL solution sample was loaded in the windowed cell and was expanded at constant temperature by compressed CO₂. To allow equilibration between the liquid and the gas phases, CO₂ pressurization rate was as low as 20 kPa per minute. Temperature (measured by Pt100 Ω resistance) was kept constant at ± 1 K by an electric resistance. Onset precipitation pressure was indicated by the appearance of white particles at the gas–liquid interface. Different initial concentrations of PEO in solutions were used to check the reproducibility of the results. The determination of the onset precipitation pressure for PEO as a function of polymer concentration in the initial solution was performed only in a concentration typically used in the GAS precipitation processes; an investigation of the onset precipitation pressure in a wider concentration range is beyond the scope of this study. Experimental runs at different temperatures were carried out only for ETC. By reproducing several measurements, the experimental uncertainty for the precipitation pressure was estimated to be lower than 5%.

While polymer molecular weight and polydispersity are certainly important in determining polymer solubility in a given solvent, small variations in onset precipitation pressure cannot be detected by visual observation, due to the accuracy of the instrument used. The measurement of polymer concentration in the supernatant phase, after polymer precipitation occurred, was not attempted.

Volume expansion

Saturated-liquid-phase volume expansion of different solvents and solvent mixtures was measured as a function of CO₂ pressure by measuring the absorbance of a reference standard. Ferrocene was used because it is soluble in all the mixtures considered and because it guarantees reliable results. As discussed elsewhere (Elvassore et al., 2002), the molecular probe should not be soluble in CO₂, should not precipitate upon increasing CO₂ pressure, its absorption band should not shift due to the effect of CO₂ pressure, and its extinction coefficient should not change upon increasing CO₂ content in the saturated liquid phase. Under these conditions, the volume expansion can be calculated by a simple relationship obtained manipulating the Lambert-Beer law

$$\frac{V - V_0}{V_0} = \frac{A_0 - A}{A} \quad (1)$$

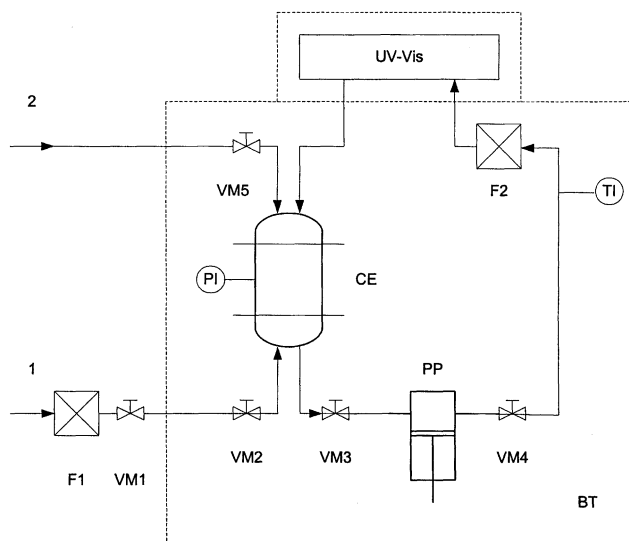


Figure 1. Experimental apparatus for the measurement of organic-solvent volume expansion and variation in solvent power as a function of CO₂ pressure.

Main components are UV-vis spectrophotometer (UV-vis in the figure), CO₂-IN and solution-IN lines (1 and 2, respectively), piston pump (PP), expansion column (CE), manual valves (VMs), filters (Fs), temperature and pressure transducers (TI and PI, respectively). The apparatus is immersed in a water thermostatic bath (BT).

In Eq. 1, A is the peak absorbance of the reference standard and V is the volume of the liquid phase. Subscript 0 indicates quantity at initial conditions, without dissolved CO₂. All algebraic details are reported elsewhere (Elvassore et al., 2002).

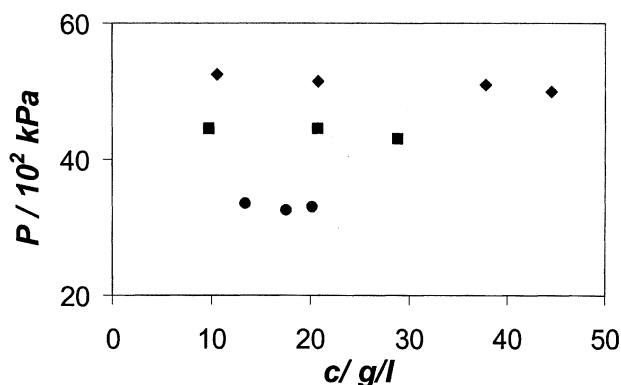
The experimental setup, sketched in Figure 1, allows fast equilibration through recirculation of the liquid phase. The instrument consists of a CO₂ supply system, a Unicam UV500 spectrophotometer (Cambridge, UK), an expansion chamber, an optical cell suitable for high pressures, and a piston recirculating pump. Tubing is either 1/8-in. or 1/16-in. stainless steel. The stainless-steel optical cell is provided with two 6-mm-thick sapphire windows. The optical-path length is 4 mm long. All pieces of equipment but the spectrophotometer were immersed in a water bath. The optical-cell temperature was controlled through electric resistance, governed by PID software. Temperature was measured by calibrated Pt100-Ω resistance. Thermal equilibration was achieved at ± 0.1 K. Pressure was continuously monitored by a pressure transducer with digital readout (mod. MA 01720, Data Instrument, Acton, USA). The transducer was calibrated in the 290–335 K and 100–20,000 kPa range.

Before starting an experiment, the system was cleaned with an organic solvent and vacuum dried. The background spectrum of pure CO₂ at 100 kPa was recorded for automatic base-line corrections of all subsequent spectra. Ten to fifteen milliliter solution samples were initially placed in the expansion chamber. CO₂ was pumped into the system up to the desired pressure. Equilibrium conditions were always reached within 20 min. The absorbance was recorded by an electronic

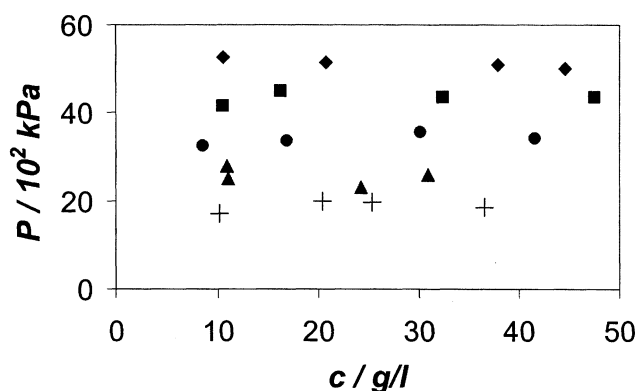
data-acquisition system. The procedure was repeated for all pressures of interest.

Solvent power

The instrument shown in Figure 1 was also used to monitor liquid-phase solvent power by measuring the absorption-peak-wavelength shift of phenol blue as a function of CO₂ pressure. The experimental procedure described previously was followed. After system equilibration, the absorption-peak wavelength (λ_{peak}) was recorded for the dye dissolved in the solvents/solvent mixtures considered during the precipitation experiments. Values measured for λ_{peak} were reproduced within an uncertainty of ± 3 nm. It should be noted that this method provides information about the local composition around the specific dye considered. While



(a)



(b)

Figure 2. Onset CO₂ precipitation pressures, P , for PEO from various solvents as a function of polymer concentration in the initial solution, c .

All experiments were conducted at constant temperature, $31 \pm 1^\circ\text{C}$. (a) Ethyl acetate-acetonitrile-CO₂ mixtures. Diamonds are for initial solution made only by acetonitrile and polymer, circles are for ethyl acetate-polymer initial mixtures; squares are for polymer dissolved in equivolume acetonitrile-ethyl acetate mixture. (b) Acetonitrile-water-CO₂ mixtures. Initial solutions were obtained by dissolving polymer in acetonitrile (diamonds); 95 vol. percent acetonitrile and 5% water (squares); 92.5 vol. % acetonitrile and 7.5% water (circles); 90 vol. % acetonitrile and 10% water (triangles); 85 vol. % acetonitrile and 15% water (crosses).

this information is important for assessing the solvent power of the solvent mixture, it does not provide the local composition around other solutes dissolved in the same solvent-CO₂ system.

Because of interferences between spectroscopic peaks, it was not possible to use a mixture of the two dyes to simultaneously measure saturated liquid-phase volume expansion and solvent power. Two separate experiments were always required.

Results

Precipitation experiments

Figure 2a shows the onset precipitation pressures for PEO in ethyl acetate, acetonitrile, and in an equivolume ethyl acetate-acetonitrile mixture at different initial polymer concentrations. Data shown in Figure 2 are at $31 \pm 1^\circ\text{C}$. The onset precipitation pressure does not depend upon initial polymer concentration within the experimental uncertainty of the measurements reported here. It was observed previously that in the dilute regime the solubility of various compounds drops dramatically in narrow pressure ranges almost independently of the initial solubility in organic solvent (Bertucco et al., 1998).

Because water, when added to an organic solvent, can stabilize proteins and better preserve their biological activity, it is interesting to measure the behavior of high-pressure aqueous solutions. Small quantities of water were added to acetonitrile, and the onset precipitation pressure for PEO from these mixtures, expanded by GAS processes, was measured. For all the acetonitrile-water mixtures reported in this work, no phase separation in the liquid phase, other than polymer precipitation, took place upon increasing CO₂ pressure up to 7,000 kPa. However, for the acetonitrile-water mixture with 20-vol % water, expanded by CO₂ at 31°C , liquid-liquid phase separation was observed at about 5,000 kPa. Figure 2b shows the onset precipitation pressures for PEO in acetonitrile-water-CO₂ mixtures at various volume percentages of water in the initial solvent mixture. The onset precipitation pressure decreases linearly with increasing initial water content

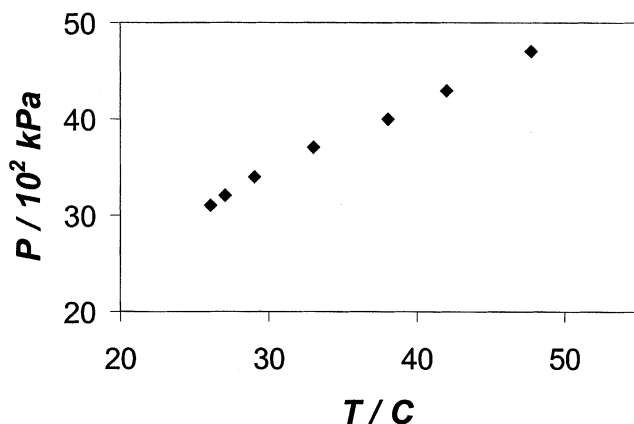


Figure 3. Onset precipitation pressure for ETC in acetone expanded by compressed CO₂ as a function of experimental temperature.

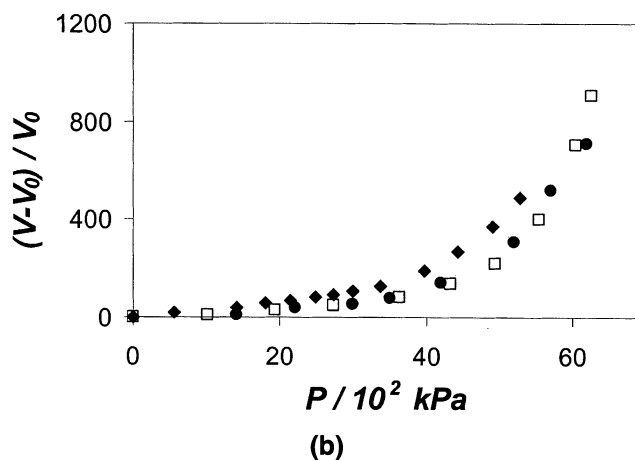
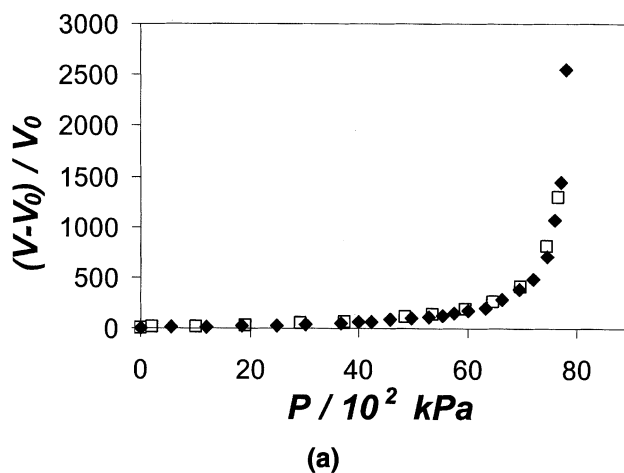


Figure 4. (a) Saturated-liquid-phase volume expansion for acetonitrile at 40°C , and (b) for ethyl acetate at 30°C .

Squares are data obtained with the UV-vis spectroscopy method proposed in this work; the other symbols are literature values [diamonds are from Kordikowski et al. (1995); circles are from Subra et al. (2000)].

in solution. These results suggest that the working pressure in some GAS processes may be reduced by adding small amounts of water to the system.

Onset precipitation pressures for ETC dissolved in acetone as a function of temperature are reported in Figure 3. Onset precipitation pressure increases linearly with increasing experimental temperature.

Saturated-liquid-phase volume expansion

Figure 4 compares the volume expansion measured in this work to data in the literature. Solvents considered were acetonitrile, at 40°C (Figure 4a), and ethyl acetate at 30°C (Figure 4b). Data presented here agree with the volume expansions for acetonitrile at 40°C reported by Kordikowski et al. (1995), but do not agree with the volume-expansion data for ethyl acetate by the same authors. However, our data perfectly reproduce those measured by Subra et al. (2000) for the latter system.

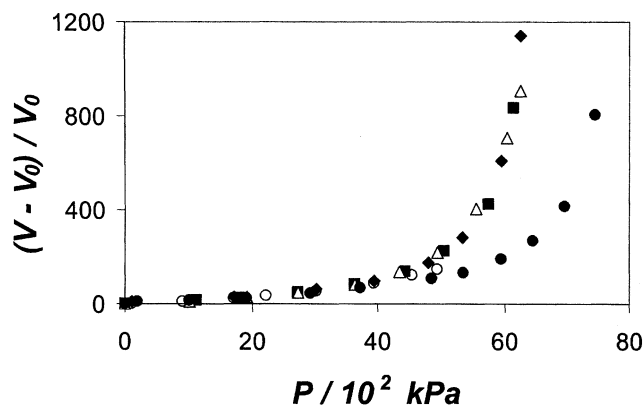


Figure 5. Saturated-liquid-phase volume expansion for ethyl acetate (triangles), acetonitrile (diamonds), and equivolume ethyl acetate-acetonitrile mixture (squares), as a function of CO_2 pressure at 30°C .

Saturated-liquid-phase volume expansion for acetonitrile at 40°C (filled circles), and for acetonitrile in solution with 34.5 g/L of PEO at 30°C (empty circles), are also shown here.

Figure 5 shows saturated-liquid-phase volume expansion for ethyl acetate, acetonitrile, and for the equivolume ethyl acetate-acetonitrile mixture as a function of CO_2 pressure. At 30°C , the three fluids show the same volume expansion as a function of CO_2 pressure. Volume expansion of pure acetonitrile at 40°C is also shown. As already known (Reverchon, 1999; Kordikowski et al., 1995), temperature has a tremendous effect upon the expansion of an organic solvent by compressed CO_2 . The saturated-liquid-phase volume expansion for pure acetone and ethyl acetate were also measured as a function of CO_2 pressure at different temperatures; these results, available upon request from the authors, are used in the discussion. Figure 5 also shows the volume expansion for a dilute solution of PEO in acetonitrile (34.5 g/L). Polymer precipitation made it impossible to record the volume expansion

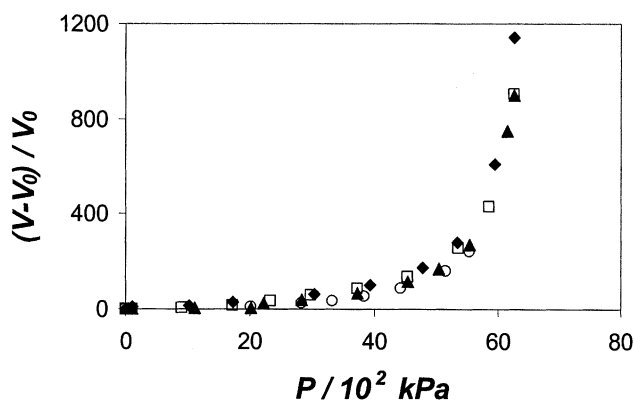


Figure 6. Saturated-liquid-phase volume expansion for acetonitrile (diamonds); 95 vol % acetonitrile and 5 vol % water (squares); 90 vol % acetonitrile and 10 vol % water (triangles); 85 vol % acetonitrile and 15 vol % water (circles), as a function of CO_2 pressure at 30°C .

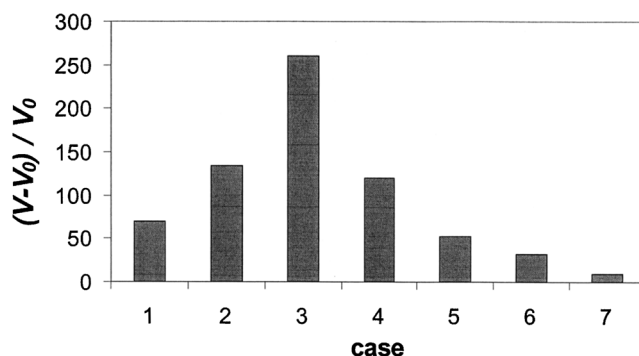


Figure 7. Saturated-liquid-phase volume expansion corresponding to onset precipitation pressure for PEO from various mixtures expanded by compressed CO_2 .

Cases 1, 2, 3, 4, 5, 6, and 7 are for PEO initially dissolved in ethyl acetate, equivolume acetonitrile-ethyl acetate mixture, acetonitrile, and 95-, 92.5-, 90-, and 85-vol % acetonitrile aqueous mixtures, respectively. Saturated-liquid-phase volume expansions reported were obtained by interpolating experimental data at the onset precipitation pressures for the different initial mixtures.

by UV-vis spectroscopy at pressures higher than 5,000 kPa. Our results show that the presence of polymer at small concentrations does not influence the saturated-liquid-phase volume expansion as a function of CO_2 pressure, for pressures below the onset precipitation pressure. Because polymer concentration in all precipitation experiments was lower than 35 g/L, all other UV-vis spectroscopy experiments were performed with polymer-free mixtures.

Figure 6 shows saturated-liquid-phase volume expansion of acetonitrile, with different amounts of water, as a function of CO_2 pressure. The presence of water reduces the volume expansion of saturated acetonitrile mixtures. However, because of the high polarity of acetonitrile, the reduction of volume expansion is smaller than that observed for aqueous mixtures containing dimethylsulfoxide (Elvassore et al., 2002).

Figure 7 summarizes the saturated-liquid-phase volume expansion corresponding to onset precipitation pressure for PEO in all the mixtures considered. At the experimental conditions investigated in this work, there is no clear relationship between volume expansion and onset precipitation pressure for PEO. As suggested by de la Fuente Badilla et al. (2000), the definition of volume expansion, as used here, might not be a significant parameter to describe supercritical-fluid processes. However, results reported for ETC precipitation from acetone at various temperatures (see Fig. 3) show that precipitation happens in correspondence to saturated-liquid-phase volume expansion ranging between 70 and 80%. Hence, volume expansion could be the driving factor of precipitation for the latter polymer-solvent- CO_2 system (Baggio, 1998).

Saturated-liquid-phase solvent power

Figure 8 compares absorption-peak wavelengths for phenol blue dissolved in acetone at 35°C as a function of CO_2 pressure measured here with those reported by Kelley and Lemert (1996). The two sets of data agree reasonably, within experimental uncertainty. At room conditions, the absorp-

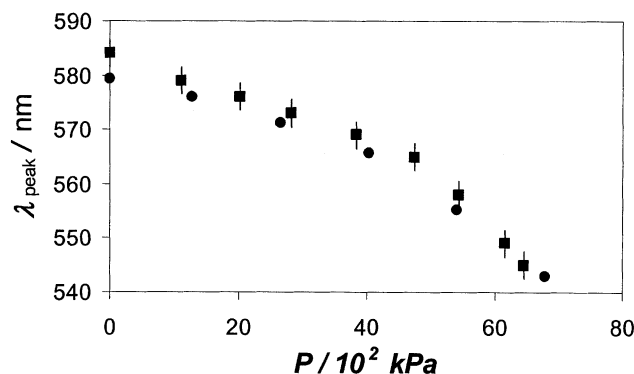


Figure 8. Absorption peak wavelength for phenol blue in acetone as a function of CO₂ pressure at 35°C: Squares are data collected in this work, circles are from Kelley and Lemert (1996).

tion-peak wavelength for phenol blue in acetone is reported to be 582 nm by Figueras (1971). This value lies between data collected in this work and those reported previously (Kelley and Lemert, 1996).

Figure 9 shows absorption-peak wavelength as a function of system pressure for phenol blue dissolved in some of the mixtures considered. Figure 9a is for acetonitrile, ethyl acetate, and equivolume acetonitrile-ethyl acetate mixture. Absorption-peak wavelength for pure acetonitrile and ethyl acetate agrees with those reported in the literature at no CO₂ pressure (Figueras, 1971; Kolling and Goodnight, 1973; de la Fuente Badilla et al., 2000). In Figure 9a, vertical lines indicate the onset precipitation pressures for PEO in the various solvents. The horizontal line indicates the “precipitation” wavelength. Acetonitrile, ethyl acetate, and their equivolume mixture show identical volume expansions as a function of CO₂ pressure (see Figure 5). However, the three mixtures show different solvent strengths that correspond to each CO₂ pressure considered. It is interesting to note that, in correspondence to the onset precipitation pressure for PEO, λ_{peak} is the same in all these solvents, while the volume expansion is different. This suggests that the microscopic bulk-phase characteristic solvent power contributes significantly to the outcome of GAS precipitation processes. Figure 9a also shows the absorption-peak wavelength for phenol blue in acetonitrile at 40°C as a function of pressure. Because the amount of CO₂ dissolved in the liquid phase as a function of pressure strongly depends on the experimental temperature, the solvent power, as a function of system pressure, also appears to be strongly dependent on experimental temperature.

Figure 9b shows acetonitrile and acetonitrile-water mixtures. For the acetonitrile-water systems there is no evident relationship between the onset precipitation pressure for PEO (indicated by the vertical lines) and the phenol blue absorption-peak wavelength. However, it should be noted that these mixtures present different volume expansion upon the addition of CO₂ (see Figure 6). Furthermore, it has previously been observed that, when the solvents participate in hydrogen-bond formation with the dye, solvent power rankings may have no general significance (Figueras, 1971). These data are reported here only for completeness.

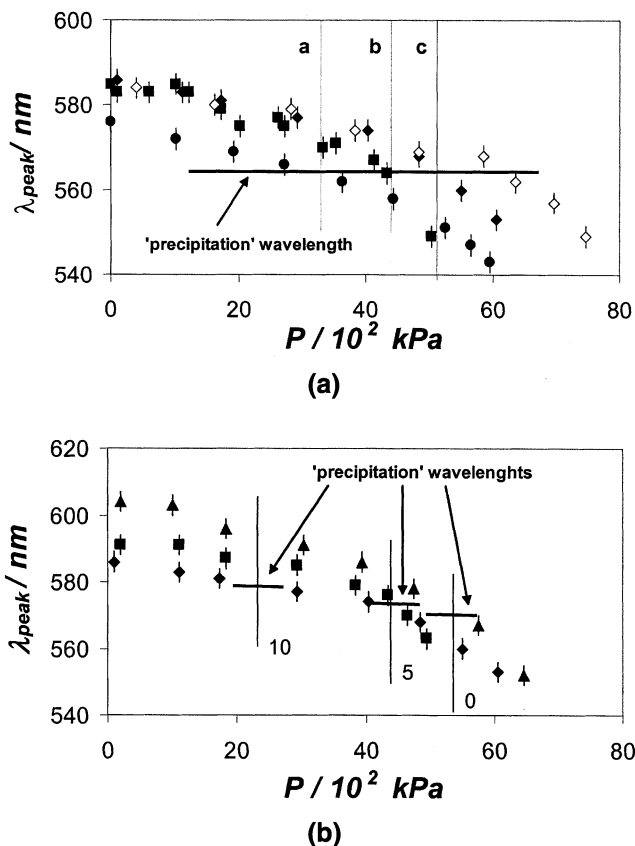


Figure 9. Absorption-peak wavelength for phenol blue in different mixtures as a function of CO₂ pressure at 30°C.

(a) Acetonitrile (diamonds), ethyl acetate (circles), and equi-volume ethyl acetate-acetonitrile mixture (squares). Vertical lines indicate the onset precipitation pressure for PEO in acetonitrile (line a), ethyl acetate (line b), and in the equivolume mixture of the two (line c). The horizontal line indicates the absorption-peak wavelength at which PEO precipitates. Empty diamonds show results for phenol blue absorption-peak wavelength in acetonitrile at 40°C. (b) Acetonitrile (diamonds); 95 vol. % acetonitrile and 5 vol. % water (squares); and 90 vol % acetonitrile and 10 vol % water (triangles). Vertical lines indicate the onset precipitation pressures for PEO in the three mixtures; numbers 5, 10, and 0 refer to the water content in the initial mixtures.

Figure 10 shows the absorption-peak wavelength for acetone as a function of CO₂ pressure at two different temperatures. Data are both from this work and from Kelley and Lemert (1996). Vertical lines indicate the onset precipitation pressures for ETC from acetone at the two temperatures considered here. The values of λ_{peak} at precipitation range between 564 and 568 nm. These results suggest that, while polymer precipitation takes place at constant values of the saturated-liquid-phase volume expansion (Baggio, 1998), it also takes place at similar absorption-peak wavelengths.

Figure 11 shows the absorption-peak wavelength for phenol blue in acetonitrile at 30°C and 40°C as a function of saturated-liquid-phase volume expansion. It is interesting to note that the absorption-peak wavelength, which is strongly dependent on experimental temperature (see Figure 9a), collapses in a single master-curve when plotted as a function of the saturated-liquid-phase volume expansion.

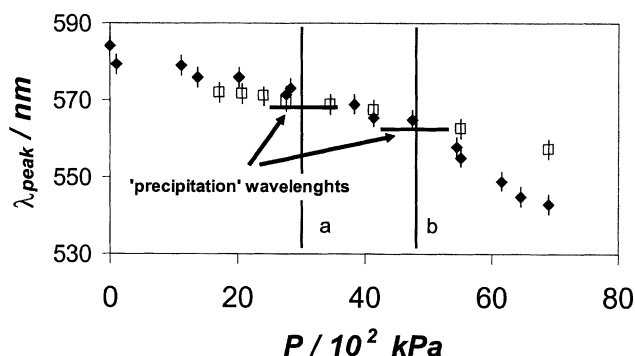


Figure 10. Absorption peak wavelength for phenol blue in acetone as a function of CO₂ pressure at 35°C, diamonds (this work), and at 55°C, squares (Kelley and Lemert, 1996).

Vertical lines indicate the onset precipitation pressure for PEO in acetone at 55°C (line a), at 35°C (line b). The horizontal lines indicate the absorption-peak wavelength at which ETC precipitates.

All results suggest that the absorption-peak wavelength, macroscopic measurement of microscopic bulk-phase dielectric properties, is a fundamental property that can determine the onset precipitation pressure for a given solute-solvent system.

Local composition around phenol blue

A model proposed by Kim and Johnston (1987a) was used to compute the local composition around phenol blue dye. The absorption-peak wavelength is related to the transition energy, $E_T = hc/\lambda_{peak}$, where h is Planck's constant and c is the speed of light. A relationship between E_T and the solvent strength is well established for explaining solvent effects on solubility, reaction rate constants, equilibrium constants, retention indexes in chromatography, and other properties (Sastri et al., 1972; Morley and Fitton, 1999). The McRae equation, derived from a second-order quantum-mechanical perturbation theory, relates E_T to refractive index and dielectric constant of the bulk solution (Kim and Johnston,

1987a; Kelley and Lemert, 1996; Figueras, 1971). Here we relate the transition energy to the local composition of the dye.

For phenol blue, the excited state is more polar than the ground state (neutral molecular structure), and it is stabilized to a greater extent by increasing solvent strength, for example, by augmenting solvent polarity. In all the systems considered, similar behavior was observed: at low pressure the saturated liquid phase contains little CO₂, and the measured transition energy, E_T^m , is comparable to those reported in the literature for each pure solvent considered. As the pressure increases, E_T^m rises because CO₂ is dissolving to a greater extent in the liquid phase, and liquid polarity is therefore decreasing.

To estimate the local composition of the solvent environment about the dye, we assume that the observed transition energies (E_T^m) are the results of a linear combination of the transition energies due to each solvent (Kim and Johnston, 1987a; Phillips and Brennecke, 1993; Kelley and Lemert, 1996). The residual transition energy has the form

$$\Delta E_T^m = x_{21}\Delta E_T^2 + x_{31}\Delta E_T^3 \quad (2)$$

where component 1 is phenol blue, component 2 is CO₂, component 3 is the organic solvent, and x_{i1} indicates the mole fraction of component i around the dye. The dye is at infinite dilution, so solute-solute interactions can be neglected. The residual transition energy, $\Delta E_T = E_T - E_T^{IG}$, where superscript *IG* stands for ideal gas, represents the stabilization produced by the solvent shell. Table 1 shows transition energy for the different pure solvents considered. Size effects due to different solvents are neglected, so that, in terms of measured E_T^m values, Eq. 2 becomes

$$E_T^m = x_{21}E_T^2 + x_{31}E_T^3 \quad (3)$$

Phillips and Brennecke (1993) and Kelley and Lemert (1996) assumed that size effects were negligible. Kim and Johnston (1987a) accounted for these effects in their calculations instead. Kelley and Lemert (1996) found that introducing this approximation leads to a relative error of about 10% in the estimated local compositions. For the purposes of the present analysis, this degree of accuracy is sufficient to semi-quantitatively interpret experimental results.

Because the dye is at infinite dilution, the local mole fractions satisfy the constraint

$$x_{21} + x_{31} = 1 \quad (4)$$

Table 1. Absorption-peak wavelength and transition energies for pure solvents used in local composition calculations

Solvent	λ_{peak} (nm)	E_T (kcal/mole)
Acetone	582	49.21
Acetonitrile	584	49.05
CO ₂	—	55.85
Ethyl acetate	572	50.08
Water	684	41.88

Note: Absorption-peak wavelength for acetone, acetonitrile, ethyl acetate, and water are from Morley and Fitton (1999). Transition energy for CO₂ is from Kelley and Lemert (1996).

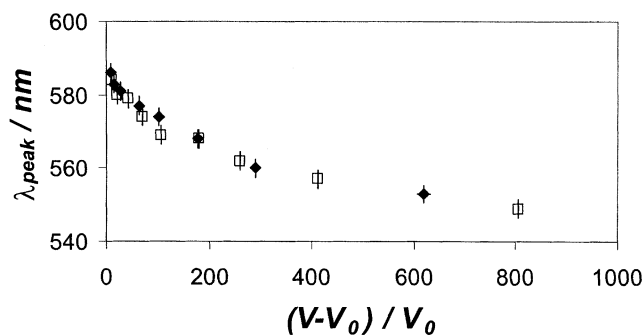


Figure 11. Absorption peak wavelength for phenol blue in acetonitrile as a function of saturated liquid-phase volume expansion at 30°C (diamonds), and at 40°C (squares).

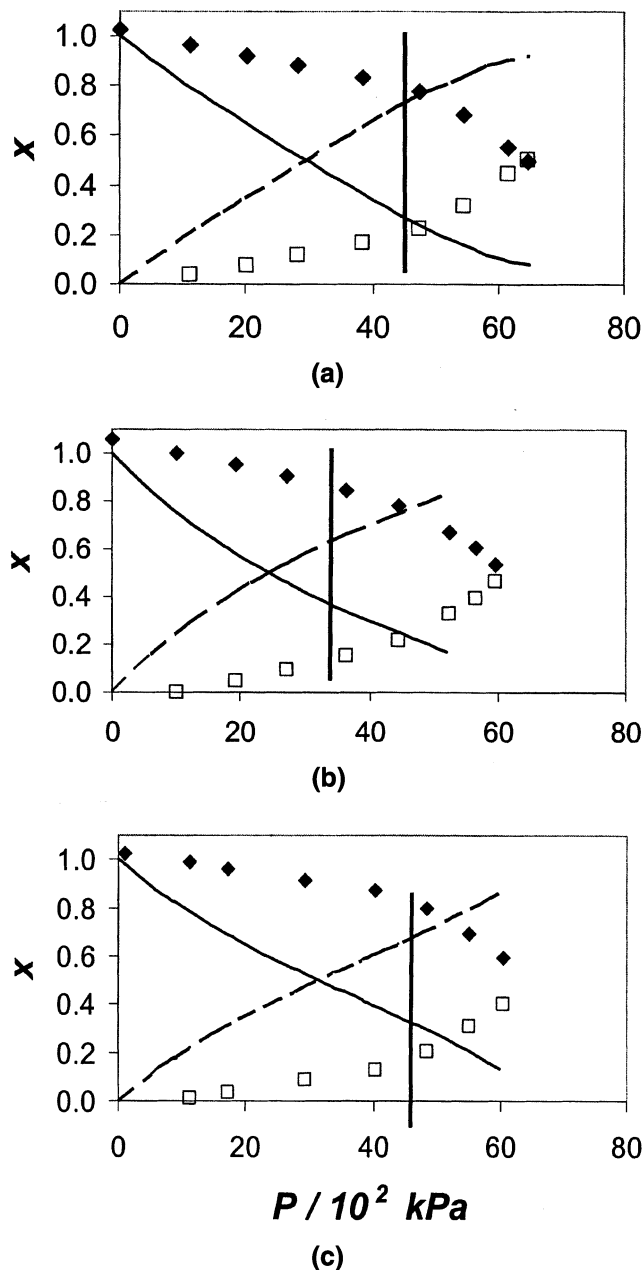


Figure 12. (a) Local composition around phenol blue dissolved in acetone at 35°C (b) ethyl acetate, and (c) acetonitrile at 30°C as a function of CO₂ pressure.

Symbols represent mole fraction around the dye as calculated by Eqs. 3 and 4 (diamonds are for solvent, squares for CO₂). Lines are bulk compositions calculated by the PHSC EOS (broken line is for CO₂, continuous for solvent). Vertical lines indicate the onset precipitation pressures for ETC from acetone part a, and for PEO from ethyl acetate and from acetonitrile parts b and c, respectively.

Equations 3 and 4 allow us to compute the local composition around phenol blue at infinite dilution in a binary mixture (such as acetone–CO₂, or ethyl acetate–acetonitrile with no CO₂) by measuring E_T^m and knowing E_T^2 and E_T^3 . However, when Eqs. 2–4 are written for a mixture made by two organic solvents, expanded by compressed CO₂, a system of

two equations in three unknowns is obtained, which cannot be solved without further information.

In the absence of CO₂, when phenol blue is dissolved in an equivolume ethyl acetate–acetonitrile mixture, the local environment is constituted exclusively by acetonitrile, as can be argued by data shown in Figure 9a.

A comparison between bulk and local composition for the systems acetone–CO₂ at 35°C, acetonitrile–CO₂ at 30°C, and ethyl acetate–CO₂ at 30°C is reported in Figure 12. The bulk composition was calculated using the PHSC EOS. EOS parameters were evaluated on the basis of volumetric and equilibrium properties of pure substances (Favari et al., 2000). Temperature-independent binary interaction parameters were fitted to experimental data from Kordikowski et al. (1995) at 28°C for ethyl acetate and acetonitrile, and from Day et al. (1996) at 30°C for acetone. Our calculations show that local and bulk compositions significantly differ from each other. In Figure 12 vertical lines indicate onset precipitation pressures of ETC from acetone and of PEO, from acetonitrile or from ethyl acetate. Because of experimental uncertainty in the determination of onset precipitation pressures (about 5%), these vertical lines are indicative. For all polymer–solvent–CO₂ systems considered here, corresponding to the onset precipitation pressure bulk CO₂ mole fraction, ranges between 0.6 and 0.8, while local CO₂ mole fraction is about 0.20 ± 0.05 . Considering the experimental uncertainties in determining the onset precipitation pressures, in measuring the absorption-peak wavelength, and also in computing the local composition, this result is quite significant. It seems that microscopic bulk-properties, for example, the mole fraction of CO₂ about the dye, are in relation with solute precipitation by GAS processes. It should be noted, however, that these calculations do not provide information about the local composition around a solute molecule other than phenol blue.

Further investigation of the precipitation of different solutes from various media is required. However, because the local composition of the dye can be predicted quite accurately (Kelley and Lemert, 1996; Favari et al., 2000), our results suggest that by knowing the bulk composition, it could be possible to predict the onset precipitation pressure of a polymer at dilute conditions in a pure solvent expanded by compressed CO₂.

Conclusions

Onset GAS precipitation pressures were reported for ETC dissolved in acetone and for PEO dissolved in ethyl acetate, acetonitrile, ethyl acetate–acetonitrile, and acetonitrile–water mixtures, expanded by compressed CO₂. Onset precipitation pressures for PEO from acetonitrile–water mixtures expanded by compressed CO₂ decrease with increasing water content in the initial mixture.

A new experimental setup was used to monitor, by UV-vis spectrometry, both the saturated-liquid-phase volume expansion and solvent power of the different mixtures considered as a function of CO₂ pressure.

Our results show that a general correspondence is not evident between onset precipitation pressure and saturated-liquid-phase volume expansion at precipitation. Thus, volume expansion may not be the only driving factor for GAS precipitation processes. For PEO dissolved in acetonitrile, ethyl ac-

etate, and equivolume ethyl acetate–acetonitrile mixture the onset precipitation pressure happens when the phenol blue absorption–peak wavelength is about 565 nm. Results for the absorption–peak wavelength of phenol blue in acetonitrile at two different experimental temperatures suggest that for the same solvent absorption–peak wavelength may be a unique function of saturated liquid-phase volume expansion. Thus, the microscopic bulk-phase property “solvent power,” which depends upon volume expansion, could be a key parameter in determining the precipitation of a solute from a liquid mixture during GAS processes.

By using a simple model, the local composition around phenol blue was computed as a function of CO₂ pressure for a few dye–solvent–CO₂ ternary systems. In agreement with polymer precipitation, local CO₂ mole fraction was found to be about 0.20±0.05 in all cases analyzed.

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Literature Cited

- Baggio, M., Tesi di Laurea, Università di Padova, Istituto di Impianti Chimici, Padova, Italy (1998).
- Bertucco, A., and P. Pallado, “Understanding Gas Antisolvent Processes of Biocompatible Polymers and Drugs with Supercritical CO₂,” *Proc. Int. Meeting of High Pressure Chemical Engineering*, the GVC-Fachausschuß “Hochdruckverfahrenstechnik,” Karlsruhe, p. 231 (1999).
- Bertucco, A., M. Lora, and I. Kikic, “Fractional Crystallization by Gas Antisolvent Technique: Theory and Experiments,” *AIChE J.*, **44**, 2149 (1998).
- Brennecke, J. F., D. P. Roek, S. Aki, “Spectroscopy in Sub- and Supercritical Fluids. Much More Than an Analytical Tool,” *Proc. Int. Symp. Supercritical Fluids*, Atlanta, GA (2000).
- Carlier, C., and T. W. Randolph, “Dense-Gas Solvent-Solute Clusters at Near-Infinite Dilution: EPR Spectroscopic Evidence,” *AIChE J.*, **39**, 876 (1993).
- Chang, C. J. and A. D. Randolph, “Solvent Expansion and Solute Solubility Predictions in Gas-Expanded Liquids,” *AIChE J.*, **36**(6), 939 (1990).
- Day, C. Y., C. J. Chang, and C. Y. Chen, “Phase Equilibrium of Ethanol+CO₂ at Elevated Pressures,” *J. Chem. Eng. Data.*, **41**, 839 (1996).
- De la Fuente Badilla, J. C., C. J. Peters, and J. de Swaan Arons, “Volume Expansion in Relation to the Gas-Antisolvent Process,” *J. Supercrit. Fluids*, **17**, 13 (2000).
- Debenedetti, P. G., “Clustering in Dilute, Binary Supercritical Mixtures: a Fluctuation Analysis,” *Chem. Eng. Sci.*, **42**, 2203 (1987).
- Debenedetti, P. G. and R. S. Mohamed, “Attractive, Weakly Attractive, and Repulsive Near-Critical Systems,” *J. Chem. Phys.*, **90**, 4528 (1989).
- Eberhardt, R., S. Lobbecke, B. Neidhart, and C. Reichardt, “Determination of ET(30) Values of Supercritical Carbon Dioxide at Various Pressures and Temperatures,” *Liebigs Ann./Recueil*, 1195 (1997).
- Eckert, C. A., D. H. Ziger, K. P. Johnston, and T. K. Ellison, “The Use of Partial Molar Data to Evaluate Equation of State for Supercritical Fluid Mixtures,” *Fluid Phase Equilib.*, **14**, 167 (1983).
- Eckert, C. A., D. H. Ziger, K. P. Johnston, and S. Kim, “Solute Partial Molar Volumes in Supercritical Fluids,” *J. Phys. Chem.*, **86**, 2738 (1986).
- Elvassore, N., A. Bertucco and P. Caliceti, “Production of Insulin-Loaded PEG/PLA Nano-Particles by Gas Anti-Solvent Techniques,” *J. Pharm. Sci.*, **90**, 1628 (2001).
- Elvassore, N., A. Bertucco, and V. Di Noto, “On-Line Monitoring Volume Expansion in Gas-Antisolvent Processes by UV-vis Spectroscopy,” *J. Chem. Eng. Data*, **42**, 223 (2002).
- Favari, F., A. Bertucco, N. Elvassore, and M. Fermeglia, “Multi-phase Multicomponent Mixtures Containing Polymers by Perturbation Theory,” *Chem. Eng. Sci.*, **55**(13), 2379 (2000).
- Figueras, J., “Hydrogen Bonding, Solvent Polarity, and the Visible Spectrum of Phenol Blue and Its Derivatives,” *J. Amer. Chem. Soc.*, **93**, 3255 (1971).
- Gallagher, P. M., M. P. Coffey, V. J. Krukonis, and N. Klasutis, “Gas Antisolvent Recrystallization: New Process to Recrystallize Compounds Insoluble in Supercritical Fluids,” *Amer. Chem. Soc. Symp. Ser.*, Vol. 406 (1989).
- Kelley, S. P., and R. M. Lemert, “Solvatochromic Characterization of the Liquid Phase in Liquid-Supercritical CO₂ Mixtures,” *AIChE J.*, **42**, 7 (1996).
- Kim, S., and K. P. Johnston, “Clustering in Supercritical Fluid Mixtures,” *AIChE J.*, **33**, 1603 (1987a).
- Kim, S., and K. P. Johnston, “Molecular Interactions in Dilute Supercritical Fluid Solutions,” *Ind. Eng. Chem. Res.*, **26**, 1206 (1987b).
- Kolling, O. W., “The Dielectric Continuum Assumption as a Description of Medium Effects in Binary Solvent Mixtures-Implications for Electron Transfer Processes in Cosolvent Systems,” *J. Phys. Chem.*, **95**(10), 3950 (1991).
- Kolling, O. W. and J. L. Goodnight, “Phenol Blue as a Solvent Polarity Indicator for Binary Aprotic Solvents,” *Anal. Chem.*, **45**, 160 (1973).
- Kordikowski, A., A. P. Shenk, R. M. Van Nielen, and C. J. Peters, “Volume Expansions and Vapor-Liquid Equilibria of Binary Mixtures of a Variety of Polar Solvents and Certain Near-Critical Solvents,” *J. Supercrit. Fluids*, **8**, 205 (1995).
- Morley, J. O. and A. L. Fitton, “Fundamental Studies on the Structure and Spectroscopic Behavior of Phenol Blue,” *J. Phys. Chem. A*, **103**, 11442 (1999).
- Phillips, D. J., and J. F. Brennecke, “Spectroscopic Measurement of Local Compositions in Binary Liquid Solvents and Comparison to the NRTL Equation,” *Ind. Eng. Chem. Res.*, **32**, 943 (1993).
- Reverchon, E., “Supercritical Antisolvent Precipitation of Micro- and Nano-Particles,” *J. Supercrit. Fluids*, **15**, 1 (1999).
- Sastri, V. S., R. W. Henwood, S. Behrent, and C. H. Langford, “Preferential Solvation in Kinetics. III. Thermal and Photochemical Solvolysis of Reinecke’s Ion,” *J. Amer. Chem. Soc.*, **94**, 753 (1972).
- Spilimbergo, S., N. Elvassore, and A. Bertucco, “Microbial Inactivation by High Pressure,” *J. Supercrit. Fluids*, **22**, 55 (2001).
- Subra, P., and J. P. Passarello, “Volumetric Expansions of Several Solvents with Carbon Dioxide or Trifluoromethane,” *Proc. Meeting on Supercritical Fluids*, Antibes/Juan-Les-Pins, France, p. 921 (2000).
- Subramaniam, B., R. A. Rajewski, and K. Snavely, “Pharmaceutical Processing with Supercritical Carbon Dioxide,” *J. Pharm. Sci.*, **86**(8), 885 (1997).
- Sun, Y. P., M. A. Fox, and K. P. Johnston, “Spectroscopic Studies of p-(N,N-Dimethylamino)benzonitrile and Ethyl p-(N,N-Dimethylamino)benzoate in Supercritical Trifluoromethane, Carbon Dioxide, and Ethane,” *J. Amer. Chem. Soc.*, **114**, 1187 (1992).
- Teja, A. S., and C. A. Eckert, “Commentary on Supercritical Fluid: Research and Applications,” *Ind. Eng. Chem. Res.*, **39**, 4442 (2000).
- Winters, M. A., D. Z. Frankel, P. G. Debenedetti, J. Carey, M. Devaney, and T. M. Przybycien, “Protein Purification with Vapor-Phase Carbon Dioxide,” *Biotechnol. Bioeng.*, **62**(3), 247 (1999).
- Yamaguchi, T., Y. Kimura, and N. Hirota, “Solvation State Selective Excitation in Resonance Raman Spectroscopy. I. Experimental Study on the C=N and the C=O Stretching Modes of Phenol Blue,” *J. Chem. Phys.*, **109**, 9075 (1993).

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