Solvent Expansion and Solute Solubility Predictions in Gas-Expanded Liquids

Chiehming J. Chang
Alan D. Randolph
University of Arizona
Department of Chemical Engineering
Tucson, AZ 85721

The productivity of a crystallization process is proportional to the solubility of the solute, C^*. An attractive recrystallization method (compared to supercritical fluids [SF] crystallization), for organic compounds that have low solubilities in SF, uses gas antisolvent addition for liquid-phase precipitation of solids (the so-called GAS process, Gallagher et al., 1989). These organic solids have much higher solubilities in selected organic solvents. Gallagher et al. recrystallized nitroguanidine (NQ) from liquid solutions using compressed CO_2 as an antisolvent, producing chunky (rather than needlelike) particle morphology. In their GAS recrystallization study they exploit the ability of gases to dissolve in organic liquids to lower the solvent-solute dissolving power, thus causing the solids to precipitate.

The most important molecular force interaction among the solute, solvent, and antisolvent gas, is the solvent/gas interaction, assuming that small amounts of solute have no effect on the interactions. With this assumption, the expansion behavior, solute solubility in liquid phase, and supersaturation ratio can be explained physically and predicted quantitatively with an equation of state using only information from the solvent and gas antisolvent binary system. Calculation of solvent expansion and solute solubility is detailed in the Appendix.

Experimental Method

Expansion

A method to measure the expansion behavior of a compressed gas with a liquid solvent was developed using a high-precision densitometer (Anton-Paar Co., model DMA512) with a digital processing unit (Mettler Paar Co., model DMA60). A high-pressure magnetic circulation pump (Micropump Co., model L-1130) circulated the liquid solvent and dissolved gas through a miniexpansion column that consisted of two 12.7 to 6.35 mm Swagelok reducing unions attached to both ends of a 200 mm long stainless steel tube (12.7 mm OD, 11.7 mm ID) connected to the densitometer with 1.59 mm OD tubing. An ethylene glycol circulating bath was used with the densitometer to control temperature to ±0.01°C.

Spectrophotometric grade solvent (16 mL of toluene or *n*-butanol, Aldrich, 99+%) was loaded into the miniexpansion column, and the column was immersed at constant temperature. Bone-dry grade CO_2 (Alphagaz, 99.99%) was pumped to a surge tank to attain the desired temperature and pressure, then charged to the miniexpansion column from the bottom through a micrometering valve (Whitey, model SS-31RS4). The pressure was increased slowly in 0.5 atm increments so that the temperature stabilized in the miniexpansion column during the absorption process. The density reading was recorded after the pressure and temperature were stable. After reaching the pressure at which no more absorption would occur, the column was depressurized through another micrometering valve located before a collecting flask. Solvent and CO_2 could then be separated in the flask. With the use of a wet test meter, total charged CO_2 could be measured at 1 atm and 25°C. Solvent expansion, $\Delta V/V$, was calculated directly from density measurements. Experimental data are shown in Figure 1.

Recrystallization of organics using the GAS process

A 16 mL quantity of toluene (or *n*-butanol) solution saturated with the solids to be crystallized was transferred to the column for expansion experiments. A filter, formed by four slow filtration rate filter papers (W&R Balston Ltd., No. 50, 12.7 mm dia.) and two 100 mesh stainless steel screen cloths (W.S. Tayler Inc., 12.7 mm dia.), was located inside the bottom reducing union of the column to hold a Teflon-encased stirring bar (10 mm long, 3 mm dia.) and to filter the particles after precipitation.

The system was then pressurized slowly, with mixing caused by the stirring bar activated by a magnet located laterally to the expansion column. The system was left to equilibrate at the desired pressure for about 30 min. The micrometering valve was opened to drain solution. At the same time fresh CO_2 was charged from the top of the column though a regulating valve. The refractive index of the depleted solution was immediately measured after sampling. For a 60 mL column operated at 69

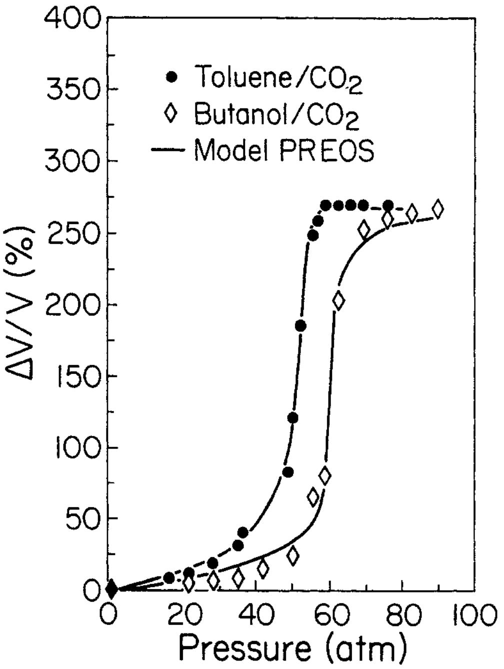

Figure 1. Solvent expansion behavior at 298 K for CO$_2$–toluene and CO$_2$–butanol systems.

atm, 0.15 m^3 fresh CO$_2$ (measured at 1 atm, 25°C) was needed to completely dry the particles (CO$_2$ rate of 0.05 m^3/h).

Results

One goal of this study was to determine the expansion behavior of two binary systems in the miscible liquid-phase region, while relating this behavior to the partial molar volume change for each component in the liquid phase. A second goal was to predict the solubility of the solute in the liquid phase.

The amount of CO$_2$ dissolved in the liquid, causing the liquid volume expansion, was calculated from a mass balance around the whole system. The toluene–CO$_2$ and *n*-butanol–CO$_2$ expansion curves are shown in Figure 1. The expansion behaviors of these two binary systems exhibit similar sigmoid shapes vs. pressure.

Several liquid organic solvents have good solubilities for β-carotene, especially chlorohydrocarbons and benzene. Toluene, cyclohexanone, and *n*-butanol are also good solvents; β-carotene is soluble in toluene and cyclohexanone at 1 atm and 298 K, (1.64×10^{-3} and 6.15×10^{-4} mol frac, respectively), but is insoluble in *n*-butanol. Acetaminophen has a solubility of 4.99×10^{-2} mol frac in *n*-butanol. Toluene–CO$_2$ and *n*-butanol–CO$_2$ were used for the GAS recrystallization of β-carotene and acetaminophen, respectively.

The experimental and predicted solubilities of β-carotene in toluene and acetaminophen in butanol in the presence of dissolved CO$_2$ are shown as a function of CO$_2$ pressure in Figure 2. Solute solubility decreases slowly with pressure from 1 to 30 atm, as carbon dioxide is only slightly soluble. Solubility then decreases steeply with pressure from 40 to 55 atm where carbon dioxide is easily dissolved into the solvent solution. At higher pressures greater than 60.0 atm the liquid mixture is fully expanded. The solvent–liquid carbon dioxide becomes fully miscible and the solute solubility remains constant. Similar observations were obtained for acetaminophen in *n*-butanol and β-carotene in toluene. A binary phase equilibrium model and the change of partial molar volume of the solvent in liquid phase will be used to predict experimental results, as shown in the Appendix.

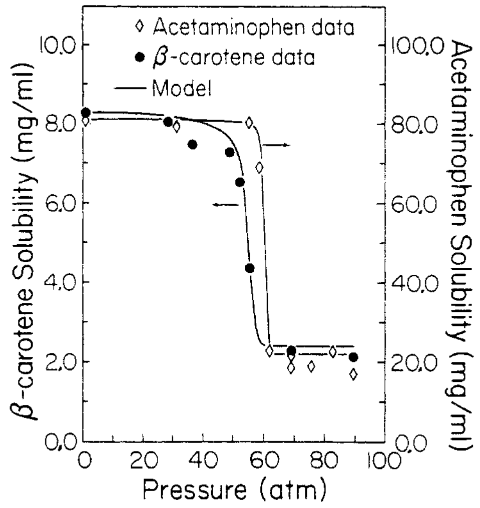

Figure 2. Experimental and predicted solid solubilities in the GAS process.

Discussion

CO$_2$–solvent system

The expansion behavior of the binary systems CO$_2$–toluene and CO$_2$–*n*-butanol is shown in Figure 1 and is predicted accurately over most of the pressure range by the following model. Phase equilibria are described by Eq. A1; nonidealities in the liquid and vapor phase are described by the Peng-Robinson equation of state: (P-R EOS), Eq. A2; and liquid volume expansion is described by Eq. A3. Gas absorption follows Henry's law when the vapor pressure of CO$_2$ is low but behaves nonlinearly at high vapor pressures.

Co$_2$–solvent–solid system

The solubilities of β-carotene in toluene (and acetaminophen in *n*-butanol) after CO$_2$ absorption are also predicted. System properties were predicted semiquantitatively using the partial molar volume change of solvent in the liquid phase (calculated from the P-R EOS). Two binary parameters were regressed from experimental data. The calculation procedure starts with the determination of CO$_2$ solubility in the liquid phase from Eq. A1, which assumes that the solubility of CO$_2$ is not affected by the presence of β-carotene (or acetaminophen) solids. The solubility of CO$_2$ in the liquid phase, x_1, is subsitituted into Eq. A4 along with the differential of the compressibility factor with respect to mole fraction to calculate the partial molar volumes of the solvent and CO$_2$ in the liquid phase. The partial molar volume of the solvent did not change as much as that of carbon dioxide at low CO$_2$ mole fraction, but the slope of the solvent partial molar volume did increase significantly at high CO$_2$ mole fraction because of an increase in the solubility of CO$_2$ in solvent, Figure 3. The CO$_2$ molecules may surround the solvent molecules to reduce the partial molar volume of the solvent. This phenomenon is similar to the aggregation of CO$_2$ molecules on

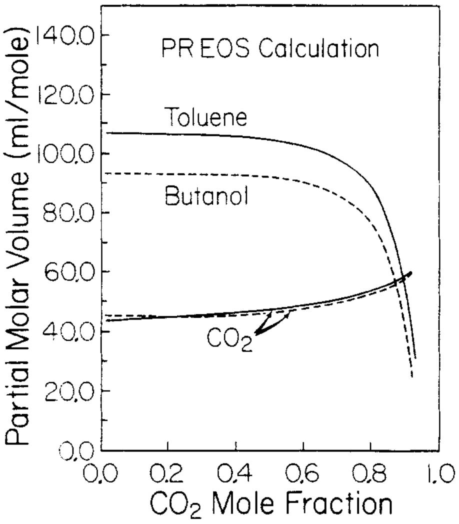

Figure 3. Partial molar volume change of CO_2 and solvents in the GAS process.

the surface of naphthalene molecules in the work of Eckert et al. (1986). After complete miscibility between liquid CO_2 and solvent, the partial molar volume did not change.

The model predicts the complex salting out and solubility of two solids using the partial molar volume change of the solvent in the liquid phase, without any ternary data, Figure 2. The average absolute deviation for the model is 8%, Figure 4. Three-phase (S-L-V) three-component data with activity coefficients for asymmetric binary components are rarely available. This predictive approach requires only binary data from the liquid solvent and dissolving gas and thus might be a useful approximation for evaluating a process.

A continuous mode with batch product filtering for the GAS recrystallization process was developed in our laboratory to recrystallize organic solids at 69 atm and 298 K. Results showed that growth and nucleation rates could be determined from log population density vs. size by conventional population balance mechanics, Figure 5. Thus the predictive population balance theory could be fully developed for the GAS recrystallization process. An advantage of the GAS recrystallization process, other than the manipulation of particle size and particle morphology (Gallagher et al., 1989), is the low operating pressure (65 atm) compared to conditions used for SF recrystallization (Chang and Randolph, 1989), while still giving the high yields characteristic of recrystallization from liquids. The GAS process could be used for fractional crystallization if widely different solubilities are observed for two solutes in the same solvent after CO_2 absorption. The assumption of negligible solute/solvent interaction might not hold in such systems.

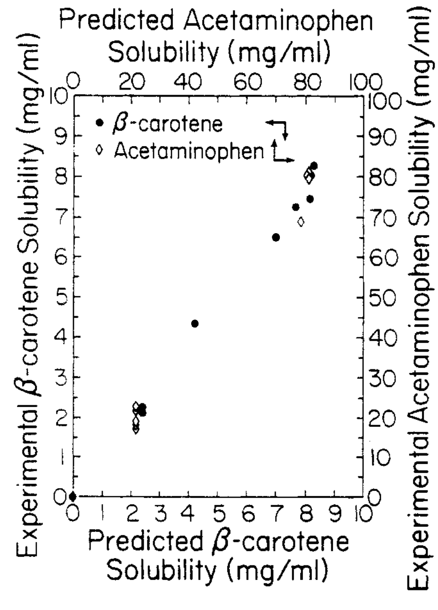

Figure 4. Experimental and predicted solid solubilities.

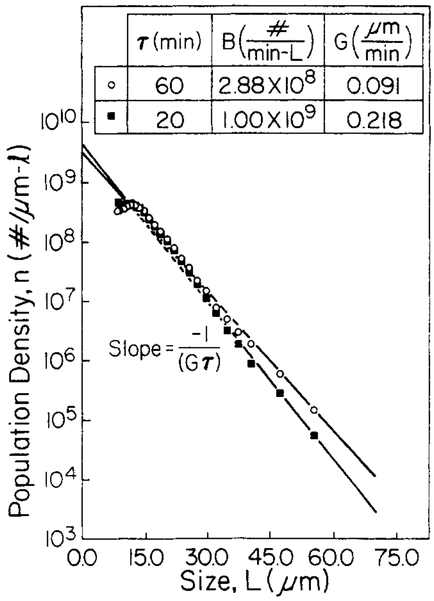

Figure 5. Crystallization kinetics determination for the continuous GAS recrystallization process.

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Notation

a = intermolecular attraction parameter
b = intermolecular repulsion parameter
C^* = solute solubility
k = size interaction parameter
P = pressure
r = energy interaction parameter
R = molar gas constant
S_3 = solubility of solute, mg/mL of solvent charged
T = absolute temperature
$\bar{v}$ = partial molar volume
V = volume
x = mole fraction in liquid phase
y = mole fraction in vapor phase
Z = compressibility factor

Greek letters

ϕ = fugacity coefficient
Δ, δ = difference

Subscripts

1 = gas antisolvent
2 = liquid solvent
3 = solute
i, j = component designations

Superscripts

L = liquid phase
V = vapor phase

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Appendix

The fugacity of component i in the vapor-liquid equilibrium is defined as (Prausnitz et al., 1986):

$$y_i \phi_i^v P = x_i \phi_i^L P \tag{A1}$$

Determination of nonidealities in the fluid phase, as described by ϕ_i, is the key to modeling.

The Peng-Robinson equation of state (P-R EOS) (McHugh and Krukonis, 1986) was used to describe the binary mixture for both liquid and vapor phases. Thus,

$$\ln(\phi_i) = \frac{B'}{b(Z-1)} - \ln(Z-B) - \frac{A}{2.828B} \cdot \left(\frac{2\Sigma x_j a_{ji}}{a} - \frac{B'}{b}\right) \ln \frac{(Z+2.414B)}{(Z+0.414B)} \tag{A2}$$

Liquid volume expansion is calculated from

$$\frac{\Delta V}{V} = \frac{V_{\text{solution}}}{V_{\text{pure solvent}}} - 1 \tag{A3}$$

This equation may be used to predict the expansion coefficient for a gas dissolved into a liquid, given two binary interaction parameters, r_{12} and k_{12}. For CO_2–toluene $r_{12} = 0.09$ and $k_{12} = 0.0$, as given by Ng and Robinson (1978). For CO_2-butanol $r_{12} = 0.10$ and $k_{12} = -0.035$, as correlated from this study.

In order to predict the solubility of solute in the liquid phase, an analytical differentiation of the P-R EOS is performed to give the partial molar volume of each compound, $\bar{v}_i$, in the liquid phase as follows (Walas, 1985; Cheuh and Prausnitz, 1968; Van Ness, 1982).

$$\bar{v}_i = \frac{RT}{P}\left(Z + (1 - x_i)\left(\frac{\delta Z}{\delta x_i}\right)_{T,P}\right) \quad i = 1, 2 \tag{A4}$$

The decrease of the partial molar volume of the solvent causes the decrease of the ability of the solvent to dissolve the solute. The equilibrium solubility of a solute in liquid phase, $S_3\ (T, P)$, may be defined as the solutility at 1 atm, $S_3\ (T, 1)$, multipled by a ratio of solvent partial molar volume at T, P to that of the same temperature and 1 atm, where no gas absorption occurred in the solvent,

$$S_3(T, P) = \frac{\bar{v}_2(T, P, x)}{\bar{v}_2(T, 1, 0)} S_3(T, 1) \tag{A5}$$

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