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Measurement and Correlation of the Solid−Liquid−Gas Equilibria for the Carbon Dioxide + *S*-(+)-Ibuprofen and Carbon Dioxide + *RS*-(±)-Ibuprofen Systems

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The pressure p−temperature T projections of solid−liquid−gas (S−L−G) three-phase coexistence lines for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system were measured by the first melting point method in which the initial appearance of the liquid phase was observed. The experimental $p-T$ projections of the S−L−G lines for the two systems were quite different from each other. The experimental $p-T$ projections of the S−L−G lines were also correlated by the Peng−Robinson equation of state with a binary interaction parameter introduced into an attraction term. The present model gave good correlation results for all of the experimental S−L−G lines with maximum average absolute relative deviations of 0.14% for the carbon dioxide + *S*-(+)-ibuprofen system and 0.90% for the carbon dioxide + *RS*-(±)-ibuprofen system.

Introduction

Supercritical fluids have been given much attention as a new type of solvent and have been applied in various industries. Their solvent power is moderate, and their transport properties are favorable in mass transfer rates. Supercritical fluids are therefore thought to be attractive solvents for several techniques such as separation, reaction, and material processing. In particular, carbon dioxide has been commonly used as a solvent for many industrial applications because it is environmentally benign, nonhazardous, and inexpensive and has a low critical temperature and a moderate critical pressure. Recently, supercritical carbon dioxide has been widely used as a crystallization solvent for the rapid expansion of supercritical solutions (RESS), supercritical antisolvent recrystallization (SAS), and particles from gas-saturated solution (PGSS) processes and so forth.[1−3]

A knowledge of solid−liquid−gas (S−L−G) equilibria is very important to the understanding and design of processes with supercritical fluids. In particular, S−L−G equilibria can be used to predict the applicability of the micronization and crystallization processes using supercritical fluids mentioned above and to optimize the choice of operation variables in the processes. For example, in the RESS process, the properties of products such as particle size and morphology have often been reported to be strongly influenced by the phase behavior, the S−L−G equilibria of the preexpansion region.[4−6]

Measurement of S−L−G equilibria has been performed over the past several years by several techniques. For the determination of only the pressure p−temperature T projection of S−L−G curves, the most popular and widely used method has been the first melting point method, which consists of the observation of the initial appearance of a liquid phase.[5,7−22] As a similar approach, the observation of the initial appearance of a solid phase, the first freezing point method, has also been used for the determination of the $p-T$ projection of S−L−G lines.[15,16,20,23−26] However, static solubility measurements using known quantities of solid and gas are employed to deduce the $p-T$ projection of the S−L−G line as well as the compositions of both the liquid and gas phases.[27−32] Recently, a new precise measurement technique of S−L−G equilibria using a scanning transitiometer has been reported by Fischer et al.[33,34]

In the present work, the pressure−temperature projections of the S−L−G three-phase coexistence lines for the carbon dioxide + *S*-(+)-ibuprofen and carbon dioxide + *RS*-(±)-ibuprofen systems were determined by observing the initial appearance of the liquid phase that is called the first melting point method. This measurement approach was chosen because of its simplicity and quickness of operation. Ibuprofen (2-(4-isobutylphenyl)propionic acid) is a nonstereoidal anti-inflammatory drug (NSAID) that is available in a variety of prescription and nonprescription drug products.[35] Figure 1 depicts the chemical structure of *S*-(+)-ibuprofen. The ibuprofen molecule has one chiral center; there are therefore two enantiomers of *S*-(+)- and *R*-(−) forms. Racemic ibuprofen, *RS*-(±)-ibuprofen, contains both *S*-(+)-ibuprofen and *R*-(−)-ibuprofen molecules, generally in equal amounts. The racemate has been found to be a racemic compound.[36] It is used clinically as a racemate although only the *S*-(+) enantiomer is effective.[35]

Because the experimental determination of high-pressure phase equilibria is difficult and costly, it would be advantageous to extend and complement the experimental data using thermodynamic models. In previous work,[5,15,22,24,31,37−40] a cubic equation of state, such as the Soave−Redlich−Kwong (SRK) equation of state[41] or the Peng−Robinson equation of state,[42] has been applied to the representation of S−L−G equilibria. In the present work, the $p-T$ projections of the S−L−G lines obtained were correlated by the Peng−Robinson equation of state with a

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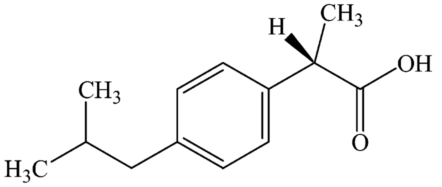

Figure 1. Chemical structure of *S*-(+)-ibuprofen.

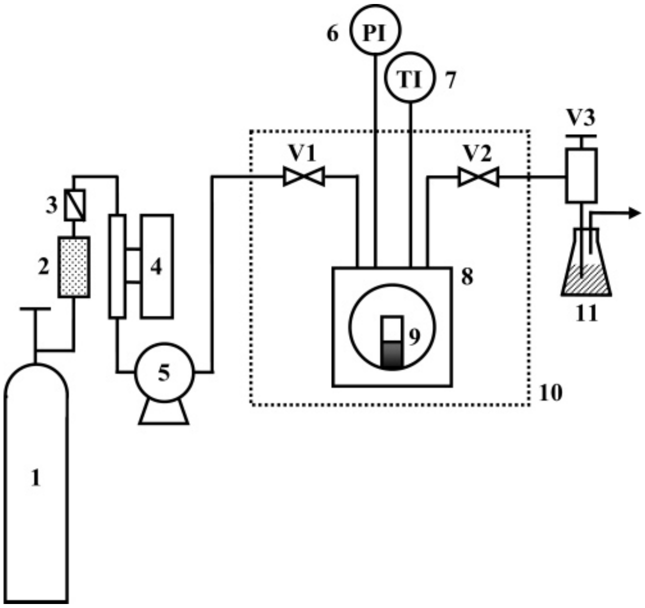

Figure 2. Schematic diagram of the experimental apparatus: 1, gas cylinder; 2, dryer; 3, filter; 4, cooling unit; 5, manual piston pump; 6, pressure indicator; 7, temperature indicator; 8, view cell; 9, glass cell; 10, thermostated air bath; 11, trap; V1, V2, stop valves; V3, expansion valve.

binary interaction parameter introduced into an attraction term.

Experimental Section

Materials. *S*-(+)- and *RS*-(±)-ibuprofens (supplied by Shasun Chemicals and Drugs Co., Ltd.; their purities are greater than 99.51% and 99.94%, respectively) were used as solutes. Benzoic acid (supplied by Wako Pure Chem. Ind., Ltd.; its purity is greater than 99.8%) was used in preliminary experiments to verify the reliability of the present apparatus and experimental procedures. High-purity carbon dioxide (supplied by Showa Tansan Co.; its purity is greater than 99.99%) was used as received.

Apparatus and Procedures. A static equilibrium apparatus was used in this work. A schematic diagram of the apparatus used in this work is shown in Figure 2. From a gas cylinder (1), carbon dioxide was supplied and was liquefied through a cooling unit (4). The liquefied carbon dioxide was gradually fed into a view cell (8) (Taiatsu Techno Co.) with a manual piston pump (5) (Tama Seiki, Co.; max pressure 25 MPa). The view cell with the volume of 35 cm^3 was designed for pressures up to 30 MPa and for temperatures up to 423.2 K, and the cell has two sapphire observation windows, each with a diameter of 20 mm. The equilibrium pressure was measured by a pressure transducer (6) (Setra Systems, Inc., model 280E) with an accuracy of ±0.04 MPa. Solute of a known amount (about 0.5 g) was introduced into a quadrangular prism-type glass cell (W10 × D10 × H30 mm^3) (9), and the glass cell was placed in the optical cell. The view cell was immersed in a thermostated air bath (10) (Isuzu Seisakusho Co., Ltd., EPSF-111L) at an experimental temperature that was controlled to within ±0.1 K. The temperature was measured with a Pt-100 thermometer (7). The appearance of the solute in the glass cell was observed with a charge-coupled device (CCD) camera (Shimadzu, Co., CCD-X2).

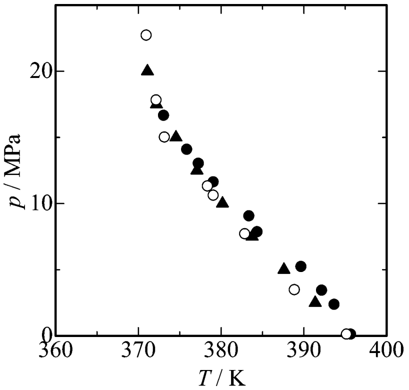

Figure 3. $p-T$ projection of the solid−liquid−gas line for the carbon dioxide + benzoic acid system: ○, experimental results; ●, Fukné-Kokot et al.;[20,26] ▲, Wilken et al.[33]

Table 1. Experimental Pressure−Temperature Data of the Solid−Liquid−Gas Line for the Carbon Dioxide + Benzoic Acid System

p/MPa	T_{exptl}/K
0.10	395.2
3.46	388.9
7.69	382.9
10.6	379.1
11.3	378.4
15.0	373.2
17.8	372.2
22.7	371.0

The S−L−G equilibria for the present systems were measured according to the first melting point method. The melting point was determined by finding the first melting temperature at a constant pressure or finding the first melting pressure at a constant temperature after approximately 5 min to ensure thermal equilibrium. In preliminary experiments, the verification of thermal equilibrium was carefully examined for 1 min−48 h, and we confirmed that the result for 5 min was the same as those for more than 5 min. In the pressure region lower than about 10 MPa, pressure was slowly raised until the initial appearance of the liquid phase. In the higher-pressure region above 10 MPa where the $p-T$ line became almost parallel to the pressure axis, temperature was slowly raised until melting was first observed. Repeated measurements were made to reduce the uncertainty in the temperature measurement to less than 0.1 K or the uncertainty in the pressure measurement to less than 0.1 MPa. Afterward, the initial solidification of the solute that is the first freezing point was also checked by lowering the temperature or pressure. No hysteresis was found within the experimental accuracy of ±0.1 K and ±0.1 MPa in each measurement. The reproducibilities of the S−L−G equilibria of the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system were within 0.03% and 0.3%, respectively.

The reliability of the present apparatus and the experimental procedures was preliminarily verified by measuring the $p-T$ projections of the S−L−G line for the carbon dioxide + benzoic acid system and then comparing these results with literature data.[20,26,33] The results obtained are shown in Table 1 and Figure 3, and they are in fair agreement with the literature data, especially the data

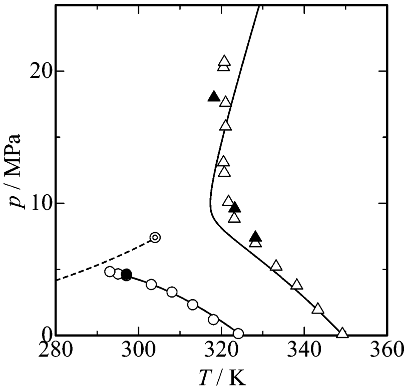

Figure 4. $p-T$ projections of the solid−liquid−gas lines for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system: ○, *S*-(+)-ibuprofen; △, *RS*-(±)-ibuprofen, experimental results; ●, *S*-(+)-ibuprofen; ▲, *RS*-(±)-ibuprofen, Charoenchaitrakool et al.;[19] –, calculated results; ◎, critical point of carbon dioxide;[51] - - -, vapor pressure line of carbon dioxide.[43]

Table 2. Experimental and Calculated Pressure−Temperature Data of the Solid−Liquid−Gas Line for the Carbon Dioxide + *S*-(+)-Ibuprofen System

p/MPa	T_{exptl}/K	T_{calcd}/K
0.10	324.2	324.4
1.16	318.0	319.6
2.25	313.0	313.7
3.25	308.0	307.8
3.82	303.0	303.5
4.49	297.0	297.1
4.62	295.1	295.5
4.79	293.1	292.9

Table 3. Experimental and Calculated Pressure−Temperature Data of the Solid−Liquid−Gas Line for the Carbon Dioxide + *RS*-(±)-Ibuprofen System

p/MPa	T_{exptl}/K	T_{calcd}/K
0.10	349.2	349.0
1.95	343.3	343.1
3.77	338.2	336.8
5.21	333.2	331.3
6.97	328.2	324.3
8.83	323.1	318.2
10.1	321.7	317.3
12.3	320.7	318.3
13.1	320.5	318.9
15.8	321.0	321.0
17.6	321.0	322.5
20.3	320.5	324.9
20.7	320.7	325.2
25.9	320.5	330.0

reported by Wilken et al.,[33] which have been thought to be more precise.

Results and Discussion

The experimental pressure−temperature data for the three-phase S−L−G line for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system are listed in Tables 2 and 3, respectively. These data are also shown in Figure 4 along with the literature data reported by Charoenchaitrakool et al.[19] The data obtained in this work are in fair agreement with their results. As shown in Figure 4, the S−L−G lines for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-iburpofen system are quite different from each other. The melting point of *S*-(+)-ibuprofen in carbon dioxide decreases from 324.2 K at atmospheric pressure to 293.1 K, which is located near the vapor pressure line of carbon dioxide in the pressure range from 0.1 to 4.79 MPa; that is, the dp/dT slope of the S−L−G line is negative. It is worth noting that the S−L−G line for the carbon dioxide + *S*-(+)-ibuprofen system is located under the vapor pressure line of carbon dioxide.[43] This result shows that the system has no supercritical region; therefore, it is impossible to apply any supercritical techniques to the system. However, the melting point of *RS*-(±)-ibuprofen in carbon dioxide decreases from 349.2 K at atmospheric pressure to about 321 K in the pressure range of 0.1 to about 10 MPa, and the melting point is almost constant at about 321 K at pressure higher than 10 MPa. The melting points, however, may increase again up to the upper critical end point (UCEP) at pressure higher than 25 MPa.

Correlation

For components 1 and 2 in a mixture, the thermodynamic condition of phase equilibria at a constant temperature and pressure is that the fugacities of components 1 and 2 of each phase are equal:

$$f_2^{\mathrm{S}} = f_2^{\mathrm{G}} \tag{1}$$

$$f_2^{\mathrm{G}} = f_2^{\mathrm{L}} \tag{2}$$

$$f_1^{\mathrm{G}} = f_1^{\mathrm{L}} \tag{3}$$

where f represents the fugacity, subscripts 1 and 2 denote solvent and solute, respectively, and superscripts S, L, and G represent solid, liquid, and gas phases, respectively.

The solubility of carbon dioxide in the solid phase is usually almost zero, the pressure effect on the solid-state molar volume is negligible, and the fugacity coefficient of the pure solid components under their saturation pressure (very low) at a temperature T can be approximated by unity. On the basis of these assumptions, eq 1 is given by the following equation:[44]

$$p\varphi_2^{\mathrm{G}} y_2 = p_2^{\mathrm{sat}}\,\varphi_2^{\circ\mathrm{S}} \exp\left\{\frac{v_2^{\circ\mathrm{S}}(p - p_2^{\mathrm{sat}})}{RT}\right\} \tag{4}$$

where $v_2^{\circ\mathrm{S}}$ is the solid-state molar volume of solid component 2 and φ_2^{G} is the fugacity coefficient of solid component 2 in the gas phase. The values of p_2^{sat} and $v_2^{\circ\mathrm{S}}$ can be taken from the physical properties of the pure component, and they can also be obtained through measurement or by using an appropriate correlation equation.

Equations 2 and 3 can be written as

$$\varphi_2^{\mathrm{G}} y_2 = \varphi_2^{\mathrm{L}} x_2 \tag{5}$$

$$\varphi_1^{\mathrm{G}} y_1 = \varphi_1^{\mathrm{L}} x_1 \tag{6}$$

where x represents a liquid-phase mole fraction.

The fugacity coefficients of the solvent and solute in gas and liquid phases, ϕ_i^{G} and ϕ_i^{L}, are usually evaluated by adopting an appropriate equation of state. The Peng−Robinson equation of state[42] was adopted to evaluate the fugacity coefficient because the equation is improved to give a good representation of liquid properties:

$$p = \frac{RT}{v - b} - \frac{a}{v(v + b) + b(v - b)} \tag{7}$$

where a and b are the pure-component parameters that can be calculated with the critical properties and the Pitzer acentric factor.

Table 4. Physical Properties of Carbon Dioxide, *S*-(+)-Ibuprofen, and *RS*-(±)-Ibuprofen

	T_m/K	T_b/K	T_c/K	p_c/MPa	ω	$v^S \times 10^4$/m^3 mol^{-1}
carbon dioxide			304.12[a]	7.374[a]	0.225[a]	
S-(+)-ibuprofen	324.2[b]	608.3[c]	758.8[d]	2.143[e]	0.892[e]	1.879[f]
RS-(±)-ibuprofen	349.2[b]	621.1[c]	778.3[d]	2.143[e]	0.892[e]	1.875[f]

[a] Poling et al.[51] [b] Measured with a DSC. [c] Estimated by the melting-point correction.[49] [d] Determined to give a good representation of the melting point at atmospheric pressure. [e] Estimated by the Constantinou−Gani group contribution method.[45,46] [f] Leising et al.[50]

To apply eq 7 to a binary system, we use the conventional mixing rules for parameters *a* and *b* as follows:

$$a = \sum_i \sum_j y_i y_j a_{ij} \qquad a_{ij} = (1 - k_{ij})\sqrt{a_i a_j} \tag{8}$$

$$b = \sum_i \sum_j y_i y_j b_{ij} \qquad b_{ij} = \frac{b_i + b_j}{2} \tag{9}$$

where k_{ij} denotes the binary interaction parameters between unlike molecules *i* and *j*. When eqs 7−9 are used, fugacity coefficients ϕ_i^G and ϕ_i^L will be thermodynamically derived.

S−L−G lines can be calculated by solving eqs 4−6 simultaneously. The S−L−G lines were obtained in the following manner proposed by McHugh et al.[31] At a fixed pressure and temperature, eq 4 was solved to determine the composition of solid component 2 in the gas phase. Next, eqs 5 and 6 were solved by guessing a liquid-phase composition and repeating until the equations were satisfied simultaneously. If the sum of the calculated liquid-phase composition was greater than 1.0, the temperature was adjusted downward slightly, and the procedure was restarted at eq 4 using the same pressure. If the sum of the liquid-phase mole fractions was less than 1.0, the temperature was raised slightly, and again the procedure was restarted at eq 4 using the same pressure. When the sum is equal to 1.0, the result is the melting point at a certain pressure. For different pressures, the calculations are restarted at eq 4.

The physical properties of *S*-(+)- and *RS*-(±)-ibuprofens were not available in the literature. Their critical pressures and the Pitzer acentric factors were evaluated by the Constantinou−Gani group contribution method.[45,46] The critical temperatures of *S*-(+)-ibuprofen and *RS*-(±)-ibuprofen were determined to give a good representation of their melting points at atmospheric pressure in the present S−L−G line calculation. Their saturated vapor pressures were evaluated by the Fishtine's method.[47,48] In this method, the boiling temperatures were estimated by the melting point correction proposed by Walters et al.[49] Their melting points were measured by differential scanning calorimetry (DSC) (Shimadzu, DSC-50). The solid-state molar volumes of *S*-(+)-ibuprofen and *RS*-(±)-ibuprofen were adopted from the literature data reported by Walters et al.[50] The physical properties thus obtained are listed in Table 4.

The S−L−G lines of the carbon dioxide + *S*-(+)-ibuprofen and carbon dioxide + *RS*-(±)-ibuprofen systems were calculated using the binary interaction parameter that was determined to give a good representation of the S−L−G lines. The binary interaction parameters were thus determined as $k_{12} = 0.09982$ for the carbon dioxide + *S*-(+)-ibuprofen system and $k_{12} = 0.09463$ for the carbon dioxide + *RS*-(±)-ibuprofen system. The calculated S−L−G lines for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system are listed in Tables 2 and 3, respectively. These data are also shown in Figure 4. The present model gave good correlation results for all of the experimental S−L−G lines with maximum average absolute relative deviations of 0.14% for the carbon dioxide + *S*-(+)-ibuprofen system and 0.90% for the carbon dioxide + *RS*-(±)-ibuprofen system. The behavior of the calculated S−L−G line for the carbon dioxide + *RS*-(±)-ibuprofen system, however, is different from the experimental result; that is, the S−L−G line has its minimum temperature at 317 K and 10 MPa. This discrepancy might be due to the fact that the critical pressures and the Pitzer acentric factors were calculated by the group contribution method and the values of *S*-(+)- and *RS*-(±)-ibuprofens were therefore the same.

Conclusions

The *p*−*T* projections of the S−L−G three-phase coexistence lines for the carbon dioxide + *S*-(+)-ibuprofen system and the carbon dioxide + *RS*-(±)-ibuprofen system were measured by the first melting point method. The experimental *p*−*T* projections of the S−L−G lines for the two systems were quite different from each other, especially the S−L−G line for the carbon dioxide + *S*-(+)-ibuprofen system, which was located under the vapor pressure line of carbon dioxide; this shows that the system has no supercritical region. The melting point of *RS*-(±)-ibuprofen in carbon dioxide decreased from 349.2 K to about 321 K in the pressure range of 0.1 to 10 MPa, and the melting point was almost constant at about 321 K at pressure higher than 10 MPa.

The experimental *p*−*T* projections of the S−L−G lines were correlated by the Peng−Robinson equation of state with a binary interaction parameter introduced into an attraction term. The present model gave good correlation results for the experimental S−L−G lines of the carbon dioxide + *S*-(+)-ibuprofen system, whereas the behavior of the calculated S−L−G line for the carbon dioxide + *RS*-(±)-ibuprofen system was different from the experimental result. It is necessary to develop prediction methods for the physical properties of racemates to calculate the phase equilibria of chiral systems.

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