Solubility of (*S*)-Boc-Piperazine and Racemic Boc-Piperazine in Supercritical Carbon Dioxide

Hirohisa Uchida,*,† Izumi Usui, Asami Fuchita, and Masakuni Matsuoka

Department of Chemical Engineering, Faculty of Technology, Tokyo University of Agriculture and Technology, 24-16 Nakacho-2, Koganei, Tokyo 184-8588, Japan

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The solubility of (*S*)-Boc-piperazine ((*S*)-3-[[(1,1-dimethylethyl)amino] carbonyl]-1-piperazinecarboxylic acid 1,1-dimethylethyl ester) and the racemic compound of (*S*)- and (*R*)-Boc-piperazines in supercritical carbon dioxide was measured in the pressure range from (9 to 20) MPa and at temperatures (308.2, 318.2, and 328.2) K using a flow-type apparatus. The experimental solubilities of (*S*)-Boc-piperazine and the racemic compound at the present conditions were in the range of (2×10^{-4} to 7×10^{-3} and 4×10^{-5} to 6×10^{-4}) in mole fraction, respectively. The solubilities were correlated by the Soave−Redlich−Kwong (SRK) equation of state with two binary interaction parameters. The present model gave a good correlation of all the experimental solubility data. The two binary interaction parameters were correlated by linear functions of temperature.

Introduction

Many optically active substances, such as amino acids, have been produced by industry including the pharmaceutical, agricultural chemicals, and food industries. Most of them have optical isomers (enantiomers) and it is therefore necessary to develop a reliable separation method for the enantiomers in many applications because only one of the enantiomorphic forms is biologically useful while the other could be toxic.

(*S*)-Boc-piperazine ((*S*)-3-[[(1,1-dimethylethyl)amino] carbonyl]-1-piperazinecarboxylic acid 1,1-dimethylethyl ester, $C_{14}H_{27}N_3O_3$), shown in Figure 1, is important as a raw material for the manufacture of the medicine for the acquired immuno-deficiency syndrome (AIDS).[1] Boc-piperazine has two optical isomers of *S* and *R* enantiomers because it has an asymmetric carbon atom in the molecule. The racemate of (*S*)- and (*R*)-Boc-piperazines has been found to be a racemic compound in a previous work,[2] so that it is very difficult to obtain the pure *S* enantiomer from the racemate by the conventional methods such as distillation, solvent extraction, and crystallization using liquid solvents.

Supercritical fluids have been given much attention as new-type solvents and have been applied in various fields of 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 separation techniques. In particular, carbon dioxide has been usually 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 used as a solvent of optical resolutions using extraction,[3−7] supercritical fluid chromatography (SFC), [8−10] and crystallization.[11] Knowledge of the solubility of optical isomers in supercritical carbon dioxide is essential for the design and development of a process for optical resolutions and for establishing optimum conditions of operation.

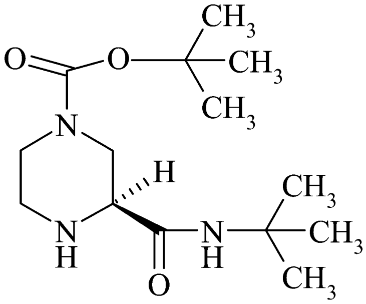

Figure 1. Chemical structure of (*S*)-Boc-piperazine.

In the present work, the solubilities of (*S*)-Boc-piperazine and the racemate (*rac*-Boc-piperazine) in supercritical carbon dioxide were measured in the pressure range from (9 to 20) MPa and at temperatures (308.2, 318.2, and 328.2) K using a flow-type apparatus. The solubilities were also correlated by the Soave−Redlich−Kwong (SRK) equation of state with two binary interaction parameters introduced into both attraction and size terms.

Experimental Section

Materials. (*S*)- and *rac*-Boc-piperazines (supplied by Nippon Soda Co., Ltd., Tokyo, Japan; their purities are more than 98% and 99%, respectively) were used as solutes. After impurity components in the solutes were extracted with supercritical carbon dioxide at 308.2 K and 15 MPa by the present apparatus, the remaining high-purity components were used for the measurement of solubility. High-purity carbon dioxide (more than 99.990%, supplied by Showa Tansan Co., Ltd., Tokyo, Japan) was used as received. Reagent-grade ethanol (supplied by Wako Pure Chem. Ind., Ltd., Osaka, Japan) was used as the liquid solvent to recover the solutes remaining in tubing.

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* To whom correspondence may be addressed. Phone and Fax: +81-72-254-9301. E-mail: uchida@chemeng.osakafu-u.ac.jp.

† Present address: Department of Chemical Engineering, Graduate School of Engineering, Osaka Prefecture University, 1-1 Gakuen-cho, Sakai, Osaka 599-8531, Japan.

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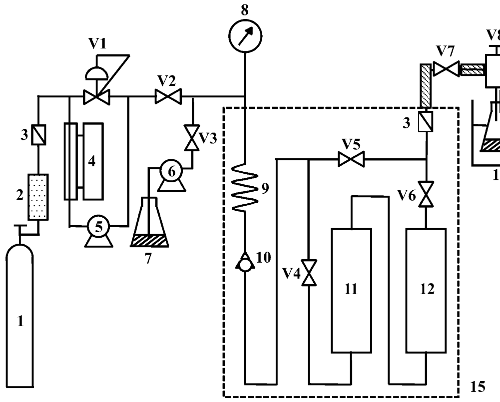

Figure 2. Schematic diagram of experimental apparatus: 1, gas cylinder; 2, dryer; 3, filter; 4, cooling unit; 5, feed pump; 6, pump; 7, reservoir; 8, pressure transducer; 9, preheater; 10, stopper; 11, preequilibrium cell; 12, equilibrium cell; 13, trap; 14, wet gas meter; 15, thermostated water bath; V1, back-pressure regulator; V2−V7, stop valve; V8, metering valve.

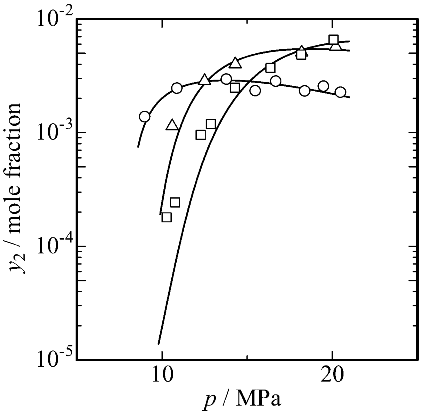

Figure 3. Experimental and calculated solubilities of (*S*)-Boc-piperazine in supercritical carbon dioxide: ○, 308.2 K; △, 318.2 K; □, 328.2 K; solid line, calculated results.

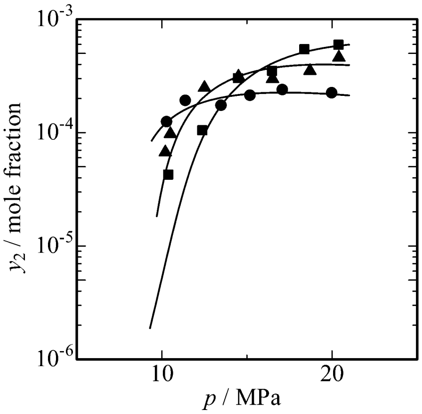

Figure 4. Experimental and calculated solubilities of *rac*-Boc-piperazine in supercritical carbon dioxide: ●, 308.2 K; ▲, 318.2 K; ■, 328.2 K; solid line, calculated results.

Apparatus and Procedures. A flow-type apparatus was used in this work. The apparatus is shown schematically 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 sent to a preheater (9) by a high-pressure liquid-chromatography pump (5) (APS-5L, GL Sciences, Co., Tokyo, Japan). When the carbon dioxide passed through the preheater in a water bath (15) at an experimental temperature that was controlled within ±0.1 K, it became a supercritical fluid. We used a pre-equilibrium cell (11) and an equilibrium cell (12) (TVS-N2, Taiatsu Techno Co., Tokyo, Japan), which were made of SUS316, and inner diameter, height, and volume of which were 30 mm, 150 mm, and 120 cm^3, respectively. The pre-equilibrium cell was equipped to obtain sufficient equilibrium conditions. Solid solute was packed into the cells with glass beads to prevent channeling. The cells were immersed into the water bath. Valve V5 was closed, and valve V4 was opened to introduce supercritical carbon dioxide into the pre-equilibrium cell and the equilibrium cell. When supercritical carbon dioxide passed through the pre-equilibrium cell and the equilibrium cell, the supercritical carbon dioxide was in contact with solid solutes under an equilibrium pressure. The equilibrium pressure was measured by a pressure transducer (8) (Model 280E, Setra Systems, Inc., Boxborough, MA) with an accuracy of ±0.04 MPa. The supercritical carbon dioxide containing solutes was decompressed through a metering valve V8 (1666G4Y, Hoke Inc., Spartanburg, SC) and then introduced into a flask (13) cooled in an ice bath. In the flask, gaseous carbon dioxide and solid solutes were separated. The flow rate of carbon dioxide was adjusted to be about 3.3 cm^3 s^{-1}. The volume of carbon dioxide was measured by a wet gas meter (14) (W-NK-0.5A, Shinagawa Co., Tokyo, Japan). Any small amount of solutes remaining in the tubing and the metering valve was removed and was trapped by using carbon dioxide modified with ethanol in a reservoir (7) after closing valves V4 and V6 and opening valves V2, V3, and V5. The solutes trapped were dried in a vacuum oven at 353 K for more than 72 h because the vapor pressures of (*S*)- and *rac*-Boc-piperazines were found to be very low. In preliminary experiments, the amount of solutes dried for 24, 48, 72, 96, 120, and 144 h was carefully examined, and we confirmed that the result for 72 h was the same as those for more than 96 h. The amount of solutes trapped was determined by weight. The solubility of solute in supercritical carbon dioxide, y_2, was determined by the following equation

$$y_2 = \frac{w/M}{(p_a - p^\circ)V_g/RT_g + w/M} \tag{1}$$

where w is the mass of solute trapped, p_a is the atmospheric pressure, p° is the vapor pressure of water, V_g is the gas volume measured by the wet gas meter under the temperature, T_g, R is the gas constant, and M is the molar mass of solute.

Experimental Results

The reliability of the apparatus and the experimental procedures were preliminarily verified by measuring the solubility of naphthalene in supercritical carbon dioxide at 308.2 K and several pressures and then comparing these results with literature data reported by Tsekhanskaya et al.[12] The results obtained were in good agreement with the literature data with an average absolute deviation of 6%.

Solubility measurements were carried out under several flow rates of carbon dioxide (1.5−5.0 cm^3·s^{-1}) at given pressures, and the solubilities obtained were independent of the flow rate. They were thus determined under equilibrium conditions. The experiments were performed more than three times at each condition, and the solubility was given by an arithmetic average of the data points. Figures 3 and 4 show the experimental solubilities of (*S*)- and *rac*-Boc-piperazines at temperatures 308.2, 318.2, and 328.2 K in supercritical carbon dioxide as functions of pressure.

Table 1. Experimental and Calculated Solubilities of (*S*)-Boc-Piperazine in Supercritical Carbon Dioxide

T/K	p/MPa	$10^3 y_{2,\mathrm{exp}}$[a]	RSD/%[b]	$10^3 y_{2,\mathrm{calc}}$[c]
308.2	9.01	1.37	8.76	1.21
	10.9	2.44	9.54	2.44
	13.8	2.93	4.44	2.88
	15.5	2.32	6.91	2.80
	16.7	2.81	11.4	2.67
	18.4	2.31	1.52	2.44
	19.5	2.54	1.78	2.27
	20.5	2.25	14.5	2.12
318.2	10.6	1.14	3.92	0.653
	12.5	2.85	4.70	2.69
	14.3	4.00	2.99	4.26
	18.2	5.09	11.1	5.44
	20.2	5.72	7.71	5.37
328.2	10.3	0.178	4.79	0.0319
	10.8	0.241	11.4	0.0720
	12.3	0.946	4.89	0.501
	12.9	1.18	6.38	0.852
	14.3	2.46	8.37	2.01
	16.4	3.67	5.60	4.00
	18.2	4.81	5.44	5.33
	20.1	6.52	4.03	6.15

[a] $y_{2,\mathrm{exp}}$ denotes the experimental results. [b] RSD denotes the relative standard deviation between the experimental results for each $y_{2,\mathrm{exp}}$. [c] $y_{2,\mathrm{calc}}$ denotes the calculated results.

Tables 1 and 2 shows the values of the solubility of (*S*)- and *rac*-Boc-piperazines in supercritical carbon dioxide, respectively. The relative standard deviations (RSDs) between the experimental data points for each solubility are also shown in Tables 1 and 2, and the average values for the solubility of (*S*)- and *rac*-Boc-piperazines are 6.7 and 6.5%, respectively. For the experimental solubility of (*S*)- and *rac*-Boc-piperazines, the crossover pressures between the solubility at 308.2 K and that at 318.2 K are at around 13 MPa, the pressures between that at 308.2 K and that at 328.2 K are at around 15 MPa, and the pressures between that at 318.2 K and 328.2 K are at around 17 MPa. The results show that the dependence of solubility on temperature changed at the crossover pressure because of the competing effects of solute's vapor pressures and solvent densities on the solubility.

We also examined the self-consistency of solubility data using the following equation proposed by Méndez-Santiago and Teja[13]

$$T \ln E = A + B\rho \tag{2}$$

where T is the equilibrium temperature, ρ is the density of carbon dioxide that was calculated by the equation of state proposed by Huang et al.,[14] A and B are the constants, and E is the enhancement factor defined by the equation

$$E = y_2 p / p_2^{\mathrm{sat}} \tag{3}$$

where p is the equilibrium pressure and p_2^{sat} is the saturated vapor pressure of (*S*)- or *rac*-Boc-Piperazines which were evaluated by the Grain−Watson correction.[15] As shown in Figure 5, the solubility data of (*S*)- and *rac*-Boc-Piperazines at the three temperatures collapsed to single straight lines, respectively, when plotted as $T \ln E$ vs the density of carbon dioxide, so that the present data would be internally consistent.

Correlation

The solubility of supercritical fluid in a solid phase is usually almost zero, the pressure effect on the solid-state molar volume is negligible, and the fugacity coefficient of pure solid components under their saturation pressure (very low) at temperature T can be approximated by unity. On the basis of these assumptions, the solubility, y_2, of solid component 2 in a supercritical fluid is given by the equation[16]

Table 2. Experimental and Calculated Solubilities of *rac*-Boc-Piperazine in Supercritical Carbon Dioxide

T/K	p/MPa	$10^3 y_{2,\mathrm{exp}}$[a]	RSD/%[b]	$10^3 y_{2,\mathrm{calc}}$[c]
308.2	10.3	0.124	12.9	0.124
	11.4	0.191	8.79	0.161
	13.5	0.173	6.12	0.204
	15.2	0.212	14.0	0.220
	17.1	0.238	4.80	0.226
	20.0	0.223	6.95	0.218
318.2	10.2	0.0672	1.19	0.0438
	10.5	0.0975	4.47	0.0637
	12.5	0.249	9.52	0.208
	14.5	0.313	0.796	0.313
	16.5	0.298	5.90	0.372
	18.7	0.351	3.49	0.397
	20.4	0.460	7.43	0.397
328.2	10.4	0.0423	3.87	0.00941
	12.4	0.104	7.52	0.0903
	14.5	0.300	5.25	0.258
	16.5	0.348	8.13	0.409
	18.4	0.539	2.75	0.515
	20.4	0.590	9.05	0.584

[a] $y_{2,\mathrm{exp}}$ denotes the experimental results. [b] RSD denotes the relative standard deviation between the experimental results for each $y_{2,\mathrm{exp}}$. [c] $y_{2,\mathrm{calc}}$ denotes the calculated results.

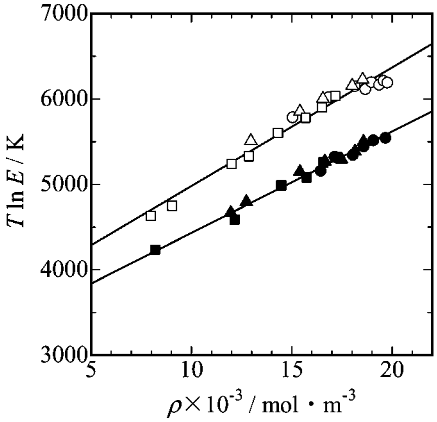

Figure 5. Self-consistency of the solubility data of (*S*)-Boc-piperazine and *rac*-Boc-piperazine in supercritical carbon dioxide: ○, (*S*)-Boc-piperazine at 308.2 K; △, (*S*)-Boc-piperazine at 318.2 K; □, (*S*)-Boc-piperazine at 328.2 K; ●, *rac*-Boc-piperazine at 308.2 K; ▲, *rac*-Boc-piperazine at 318.2 K; ■, *rac*-Boc-piperazine at 328.2 K.

$$y_2 = \frac{p_2^{\mathrm{sat}}}{p} \frac{1}{\phi_2^{\mathrm{G}}} \exp\left[\frac{v_2^{\mathrm{oS}}(p - p_2^{\mathrm{sat}})}{RT}\right] \tag{4}$$

where v_2^{oS} is the solid-state molar volume of solid component 2, superscript S means the solid state, and ϕ_2^{G} is the fugacity coefficient of solid component 2 in the supercritical fluid. The values of p_2^{sat} and v_2^{oS} can be given from the physical properties of a pure component, and they can be obtained through measurements or by using an appropriate correlation equation. The solubility, y_2, would therefore be calculated if ϕ_2^{G} is obtained with an appropriate calculation method. The fugacity coefficient of the solute in a pressurized gas phase ϕ_2^{G} is usually evaluated by adopting an appropriate equation of state.

Table 3. Physical Properties of Carbon Dioxide and (*S*)- and *rac*-Boc-Piperazines

	T_m/K	T_b/K	T_c/K	p_c/MPa	ω	$10^4 v^S$/m^3·mol^{-1}	p^{sat}/Pa
carbon dioxide			304.12[a]	7.374[a]	0.225[a]		
(*S*)-Boc-piperazine	376.33[b]	726.43[c]	951.15[d]	1.946[c]	0.805[e]	2.52[b]	8.85×10^{-5} (308.2 K)[f] 3.67×10^{-4} (318.2 K)[f] 1.38×10^{-3} (328.2 K)[f]
rac-Boc-piperazine	381.05[b]	728.84[c]	954.30[d]	1.953[c]	0.807[e]	2.50[b]	6.98×10^{-5} (308.2 K)[f] 2.92×10^{-4} (318.2 K)[f] 1.11×10^{-3} (328.2 K)[f]

[a] Literature data.[19] [b] Measured. [c] Estimated by the melting point correction.[20] [d] Estimated by the Wilson−Jasperson atomic contribution method.[19] [e] Estimated by the Ambrose−Walton corresponding-states method.[19] [f] Estimated by the Grain−Watson correction.[15]

Table 4. Values of Binary Interaction Parameters and Average Absolute Relative Deviations

		experimental data			calculated by eqs 9 and 10		
system	*T*/K	k_{12}	l_{12}	100σ /%	k_{12}	l_{12}	100σ /%
CO_2 + (*S*)-Boc-piperazine	308.2	−0.00789	−0.296	7.65	−0.00611	−0.287	9.90
	318.2	0.0159	−0.207	13.6	0.0123	−0.225	23.0
	328.2	0.0290	−0.171	33.9	0.0308	−0.163	35.4
CO_2 + *rac*-Boc-piperazine	308.2	0.148	−0.0625	7.48	0.142	−0.0771	8.39
	318.2	0.110	−0.129	19.7	0.123	−0.100	22.5
	328.2	0.111	−0.109	21.3	0.105	−0.123	20.3

Table 5. Values of Coefficients in Eqs 9 and 10

	k_{12}		l_{12}	
system	α_1	α_2	β_1	β_2
carbon dioxide (1) + (*S*)-Boc-piperazine (2)	−0.5746	1.8445×10^{-3}	−2.2069	6.2290×10^{-3}
carbon dioxide (1) + *rac*-Boc-piperazine (2)	0.7102	-1.8450×10^{-3}	0.6340	-2.3070×10^{-3}

The SRK equation of state [17] was adopted to evaluate the fugacity coefficient

$$p = \frac{RT}{v - b} - \frac{a}{v(v + b)} \tag{5}$$

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

To apply eq 5 to a binary system, the conventional mixing rules are used for the parameters *a* and *b* as follows

$$a = \sum_i \sum_j y_i y_j a_{ij} \qquad a_{ij} = (1 - k_{ij})(a_i a_j)^{1/2} \tag{6}$$

$$b = \sum_i \sum_j y_i y_j b_{ij} \qquad b_{ij} = (1 - l_{ij})\frac{b_i + b_j}{2} \tag{7}$$

where k_{ij} and l_{ij} denote the binary interaction parameters between unlike molecules *i* and *j*. When eqs 5−7 are utilized, the fugacity coefficient ϕ_2^G will be thermodynamically derived. The conventional mixing rules with k_{ij} and l_{ij} introduced into both attraction and size terms give a better correlation than the local composition mixing rules, because the solubility of high-boiling compounds in supercritical fluids is quite small.[18]

The physical properties of (*S*)- and *rac*-Boc-piperazines were not available in the literature. Their critical temperatures and critical pressures were therefore evaluated by the Wilson−Jasperson atomic contribution method,[19] respectively. In this method, the boiling temperatures were estimated by the melting point correction proposed by Walters et al.[20] Their saturated vapor pressures were evaluated by the Grain−Watson correction,[15] and their Pitzer's acentric factors were calculated by the Ambrose−Walton corresponding-state method.[19] Their solid-state molar volumes were measured at 308.2, 318.2, and 328.2 K using a flotation method[21] and were found to be independent of temperature. The physical properties thus obtained are listed in Table 3.

The correlated results are shown in Figures 3 and 4 and Tables 1 and 2. The solubility of (*S*)- and *rac*-Boc-piperazines was well calculated in a wide range of pressure using the binary interaction parameters that were determined to give good representation of the solubility. The binary interaction parameters thus determined are shown in Table 4 with the average absolute relative deviations (AARD), σ, defined by

$$\sigma = \frac{1}{N}\sum_{i=1}^{N} |(y_{2,\mathrm{exp}} - y_{2,\mathrm{cal}})/y_{2,\mathrm{exp}}| \tag{8}$$

where *N* is the total number of experimental data, $y_{2,\mathrm{exp}}$ the experimental solubility, $y_{2,\mathrm{cal}}$ the calculated solubility. The binary interaction parameters k_{12} and l_{12} for carbon dioxide + (*S*)-Boc-piperazine and carbon dioxide + *rac*-Boc-piperazine systems were found to be approximated to simple linear functions of absolute temperature as follows

$$k_{12} = \alpha_1 + \alpha_2 T \tag{9}$$

$$l_{12} = \beta_1 + \beta_2 T \tag{10}$$

The coefficients α_1, α_2, β_1, and β_2 in eqs 9 and 10 were determined by a least-squares regression, and the values determined are shown in Table 5. The values of the binary interaction parameters calculated by eqs 9 and 10 are also shown in Table 4. The present model using the values in Table 4 also gave good correlation results for all the experimental solubilities with maximum AARDs of 35.4% for (*S*)-Boc-piperazine and 22.5% for *rac*-Boc-piperazine, respectively, as shown in Table 4. The relative high AARD values are mainly due to the discrepancy between the experimental and the correlated results at the lower pressures.

Conclusions

The solubility of (*S*)- and *rac*-Boc-piperazines in supercritical carbon dioxide was measured at (9−20) MPa and

(308.2, 318.2, and 328.2) K. Their solubilities increased with increasing pressure at constant temperature, and the crossover pressures were found to be in the pressure range (12−17) MPa. The solubility was correlated by the SRK equation of state with two binary interaction parameters. The correlation equations for the two binary interaction parameters were represented as linear functions of temperature. The experimental solubilities were well calculated in a wide range of pressure by the present model.

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