MEASUREMENT AND CORRELATION OF SOLUBILITY OF (*S*)-BOC-PIPERAZINE AND RACEMIC BOC-PIPERAZINE IN SUPERCRITICAL CARBON DIOXIDE

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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 the temperatures 308.2, 318.2 and 328.2 K using a flow-type apparatus. The solubility was also correlated by a three-constant cubic equation of state with two characteristics parameters introduced into both attraction and size terms. The present model gave good correlation results for all the experimental solubility data.

INTRODUCTION

Many optically active substances, such as amino acids, have been produced in the industrial fields such as pharmacies, agricultural chemicals and food industries. Most of them have optical isomers (enantiomers) and it is therefore necessary to development a reliable separation method for the enantiomers in many applications because only one of the enantiomorphic forms is biologically useful when the other might 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 an extraction [3, 4], supercritical fluid chromatography (SFC) [5-7] and crystallization [8]. Knowledge of the solubility of optical isomers in supercritical carbon dioxide is essential for the design and development of a
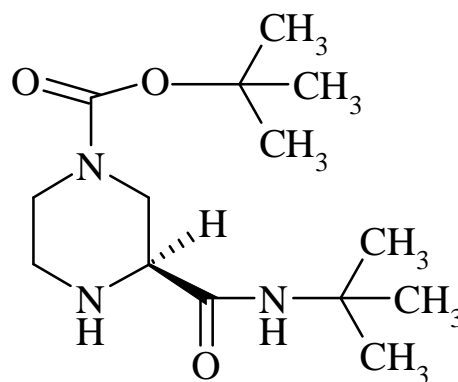

Figure 1. Structure of (*S*)-Boc-piperazine.

process for optical resolutions and for establishing optimum conditions of operation.

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 a three-constant cubic equation of state with two characteristics parameters introduced into both attraction and size terms.

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 bath; (V1) back-pressure regulator; (V2-V7) stop valve; (V8) metering valve.

EXPERIMENTAL SECTION

Equipment 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 (4) (GL Sciences, Co., APS-5L). When the carbon dioxide passed through the preheater in a water bath (15) at an experimental temperature which was controlled within ± 0.1 K, it became a supercritical fluid. We used a preequilibrium cell (11) and an equilibrium cell (12) (Taiatsu Techno Co., TVS-N2), which were made of SUS316, and inner diameter, height, and volume of which were 30 mm, 150 mm, and 120 cm^3, respectively. The preequilibrium 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 preequilibrium cell and the equilibrium cell. When supercritical carbon dioxide passed through the preequilibrium 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) (Setra Systems, Inc., Model 280E) with accuracy ± 0.11% FS. The supercritical carbon dioxide containing solutes was decompressed through an metering valve V8 (Hoke Inc., 1666G4Y) 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) (Shinagawa Co., W-NK-0.5A). 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. In the 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 from the weight of the solute and the volume of carbon dioxide.

Materials. (S)- and *rac*-Boc-piperazines (supplied by Nippon Soda Co., Ltd.; 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 by the present apparatus, the
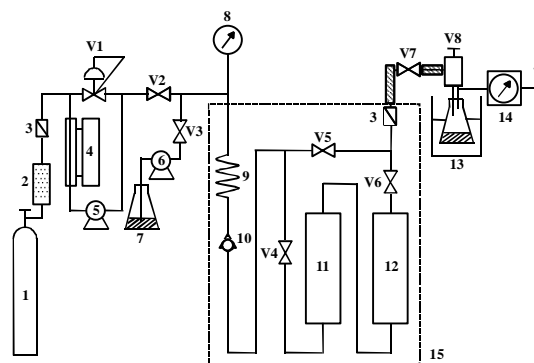
remaining high-purity components were used for the measurement of solubility. High-purity carbon dioxide (more than 99.99%, supplied by Showa Tansan Co.) was used as received. Regent-grade ethanol (supplied by Wako Pure Chem. Ind., Ltd.) was used as the liquid solvent to recover the solutes remaining in the tubing.

EXPERIMENTAL RESULTS

The reliability of the apparatus and the experimental procedures were preliminary 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. [9]. The results obtained were in good agreement with the literature data with an average absolute deviation of 6%.

Figure 3. Experimental and calculated solubilities of (*S*)-Boc-piperazine and *rac*-Boc-piperazine in supercritical carbon dioxide.

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 several data points. **Figure 3** shows 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. The reproducibility of the solubilities is within 10%. Their solubilities increased with increasing pressure at constant temperature, and crossover pressures were found to be in the pressure range from 13 to 18 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 [10]:

$$T \ln E = A + Br \tag{1}$$

where T is the equilibrium temperature, r is the density of carbon dioxide which was calculated by the equation of state proposed by Huang et al. [11], A and B are the constants, and E is the enhancement factor defined by the following equation:

$$E = y_2 p / p_2^{sat} \tag{2}$$

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 [12]. As shown in **Figure 4**, 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

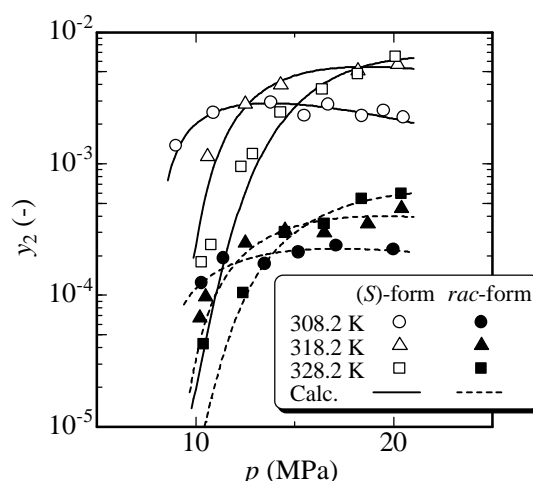The solubility of supercritical fluid in a solid phase is usually almost zero, the pressure

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. Based on these assumptions, the solubility, y_2 of solid component 2 in a supercritical fluid is given by the following equation [13]:

$$y_2 = \frac{p_2^{sat}}{p} \frac{1}{\boldsymbol{f}_2^G} \exp\left[\frac{v_2^{oS}\left(p - p_2^{sat}\right)}{RT} \right] \quad (3)$$

where v_2^{oS} is the solid-state molar volume of solid component 2, superscript S means the solid state and $\boldsymbol{f}_2^G$ 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 measurement or by

Figure 4. Self-consistency of the solubility data of (S)-Boc-piperazine and rac-Boc-piperazine in supercritical carbon dioxide.

using an appropriate correlation equation. The solubility, y_2 would therefore be calculated if $\boldsymbol{f}_2^G$ is obtained with an appropriate calculation method. The fugacity coefficient of the solute in a pressurized gas phase $\boldsymbol{f}_2^G$ is usually evaluated by adopting an appropriate equation of state.

The Soave-Redlich-Kwong equation of state [14] was adopted to evaluate the fugacity coefficient:

$$p = \frac{RT}{v-b} - \frac{a}{v(v+b)} \quad (4)$$

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

To apply eq 4 to a binary system, the conventional mixing rules are used for the parameters, a and b as follows:

$$a = \sum_i \sum_j y_i y_j a_{ij} , \quad a_{ij} = \left(1 - k_{ij}\right)\sqrt{a_i a_j} \quad (5)$$

$$b = \sum_i \sum_j y_i y_j b_{ij} , \quad b_{ij} = \left(1 - l_{ij}\right)\frac{b_i + b_j}{2} \quad (6)$$

where k_{ij} and l_{ij} denote the characteristics parameters between unlike molecules i and j. When eqs 4-6 are utilized, the fugacity coefficient $\boldsymbol{f}_2^G$ 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 [15].

The physical properties of (S)- and rac-Boc-piperazines were not available in literatures. Their critical temperatures and critical pressures were therefore evaluated by the Wilson-Jasperson atomic contribution method [16], respectively. In this method, the boiling temperatures were estimated by the melting point correction proposed by Walters et al. [17].
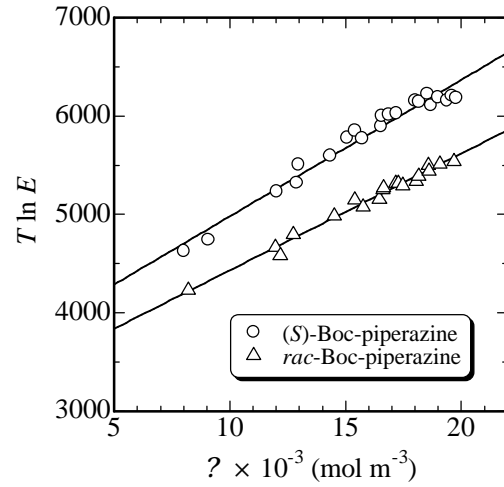
Their saturated vapor pressures were evaluated by the Grain-Watson correction [12]. and their Pitzer's acentric factors were calculated by the Ambrose-Walton corresponding-state method [16]. Their solid-state molar volumes were measured at 308.2, 318.2 and 328.2 K using a flotation method [18] and were found to be independent of temperature. The physical properties thus obtained are listed in **Table 1**.

The correlated results are also shown in **Figure 3**. The solubility of (*S*)- and *rac*-Boc-piperazines was well calculated in a wide range of pressure using the characteristic parameters which were determined to give good representation of the solubility. The characteristics parameters thus determined are shown in **Table 2** with the average absolute relative deviations (AARD), $\boldsymbol{s}$ defined as follows:

$$\boldsymbol{s} = \frac{1}{N}\sum_{i=1}^{N}\left|\left(y_{2,\text{exp}} - y_{2,\text{cal}}\right)/y_{2,\text{exp}}\right| \tag{7}$$

where N is the total number of experimental data, $y_{2,\text{exp}}$ the experimental solubility, $y_{2,\text{cal}}$ the calculated solubility. The characteristics parameters would be approximated to linear functions of absolute temperature by a least squares regression as follows:

$$k_{12} = 1.8445\times10^{-3}T - 0.5746 \quad \text{for carbon dioxide (1) + (}S\text{)-Boc-piperazine (2)} \tag{8}$$

$$l_{12} = 6.2290\times10^{-3}T - 2.2069 \quad \text{for carbon dioxide (1) + (}S\text{)-Boc-piperazine (2)} \tag{9}$$

$$k_{12} = -1.8450\times10^{-3}T + 0.7102 \quad \text{for carbon dioxide (1) + }rac\text{-Boc-piperazine (2)} \tag{10}$$

$$l_{12} = -2.3070\times10^{-3}T + 0.6340 \quad \text{for carbon dioxide (1) + }rac\text{-Boc-piperazine (2)} \tag{11}$$

The present model using eqs 8-11 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 2**.

Table 1. Physical Properties of Carbon Dioxide and (*S*)- and *rac*-Boc-Piperazines

	T_{m} (K)	T_{b} (K)	T_{c} (K)	p_{C} (MPa)	$\boldsymbol{w}$	$v^{\text{S}}\times10^4$ (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$\times10^{-5}$ (308.2 K)[f]
							3.67$\times10^{-4}$ (318.2 K)[f]
							1.38$\times10^{-3}$ (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$\times10^{-5}$ (308.2 K)[f]
							2.92$\times10^{-4}$ (318.2 K)[f]
							1.11$\times10^{-3}$ (328.2 K)[f]

[a] Literature [16], [b] Measured, [c] Estimated by the melting point correction [17], [d] Estimated by the Wilson-Jasperson atomic contribution method [16], [e] Estimated by the Ambrose-Walton corresponding-state method [16], [f] Estimated by the Grain-Watson correction [12]

Table 2. Values of Characteristics Parameters and Average Absolute Relative Deviations

		fitting the experimental data			calculated by eqs 8-11		
system	T (K)	k_{12}	l_{12}	100$\boldsymbol{s}$ (%)	k_{12}	l_{12}	100$\boldsymbol{s}$ (%)
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

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 13-18 MPa. The solubility was correlated by the Soave-Redlich-Kwong equation of state with two characteristics parameters. The correlation equations for the two parameters were represented as linear functions of absolute temperature. The experimental solubilities were well calculated in a wide range of pressure by the present model.

REFERENCES:

[1] ROSSEN, K., WEISSMAN, S. A., SAGER, J., REAMER, R. A., ASKIN, D., VOLANTE, R. P., REIDER, P. J., Tetrahedron Lett. Vol. 36, **1995**, p. 6419

[2] TAKIZAWA, M., UCHIDA, H., TAKIYAMA, H., MATSUOKA, M., Proc. 65th Annual Meeting of the Society of Chemical Engineers, Japan (SCEJ); SCEJ: Tokyo, **2000**, p. 592

[3] SIMÁNDI, B., KESZEI, S., FOGASSY, E., KEMÉNY, S., SAWINSKY, J., J. Org. Chem., Vol. 62, **1997**, p. 4390; J. Supercrit. Fluids, Vol. 13, **1998**, p. 331; Tetrahedron: Asymmetry, Vol. 10, **1999**, p. 1275

[4] BAUZA, R., RÍOS, A., VALCÁRCEL, M., Anal. Chim. Acta, Vol. 450, **2001**, p. 1

[5] ANTON, K., BERGER, C. (Eds.) "Supercritical Fluid Chromatography with Packed Columns", Marcel Dekker, New York, **1998**

[6] WOLF, C., PIRKLE, W. H., LC-GC, Vol. 15, **1997**, p. 352

[7] TERFLOTH, G., J. Chromatogr. A, Vol. 906, **2001**, p. 301

[8] KORDIKOWSKI, A., YORK, P., LATHAM, D., J. Pham. Sci., Vol. 88, **1999**, p. 786

[9] TSEKHANSKAYA, YU. V., IOMTEV, M. B., MUSHKINA, E. V., Russ. J. Phys. Chem., Vol. 38, **1964**, p. 1173

[10] MÉNDEZ-SANTIAGO, J., TEJA, A. S., Fluid Phase Equilib., Vol. 158-160, **1999**, p. 501

[11] HUANG, F.-H., LI, M.-H., LEE, L. L., STARLING, K. E., CHUNG, F. T. H., J. Chem. Eng. Jpn., Vol. 18, **1985**, p. 490

[12] BOETHLING, R. S., MACKAY, D., "Handbook of Property Estimation Methods for Chemicals –Environmental and Health Sciences–", Lewis Pub., Boca Raton, **2000**

[13] PRAUSNITZ, J. M., LICHTENTHALER, R. N., de AZEVEDO, E. G., "Molecular Thermodynamics of Fluid-Phase Equilibria, 3rd Ed.", Prentice Hall PTR: New Jersey, **1999**

[14] SOAVE, G., Chem. Eng. Sci., Vol. 27, **1972**, p. 1197

[15] IWAI, Y., LU, B. C.-Y., YAMAMOTO, H., ARAI, Y., Kagaku Kogaku Ronbunshu, Vol. 15, **1989**, p. 676

[16] POLING, B. E., PRAUSNITZ, J. M., O'CONNELL, J. P., "The Properties of Gases and Liquids, 5th ed.", McGraw-Hill, New York, **2001**

[17] WALTERS, A. E., MYRDAL, P. B., YALKOWSKY, S. H., Chemosphere, Vol. 31, **1995**, p. 3001

[18] IWAI, Y., TARA, T., ISHIDAO, T., ARAI, Y., Kagaku Kogaku Ronbunshu, Vol. 18, **1992**, p. 969