Solubilities of Pyrimidine and Pyrazine Derivatives in Supercritical Fluids

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Solid solubilities of three pyrimidine derivatives (2-chloropyrimidine, 4-hydroxypyrimidine, and 2-mercaptopyrimidine) and two pyrazine derivatives (2-aminopyrazine and pyrazine-2-carboxylic acid) in supercritical carbon dioxide, ethylene, ethane, and trifluoromethane were measured at 308.15 K. In the high-pressure range, the solubilities in supercritical trifluoromethane are fairly large; it shows the strongest dissolution power for some of the solids investigated. The solubilities in ethylene and ethane are somewhat low and show a weak pressure dependence for all substances. In the case of carbon dioxide, there would be an interrelation between the solubilities of these derivatives and the electronic properties of the substituent involved. All the substances except 2-chloropyrimidine are expected to be self-associated; thus, the solubilities are fairly small, especially the solubilities of pyrazine-2-carboxylic acid in ethylene and ethane, which are smaller than 10^{-6} in mole fraction.

Introduction

Studies on solubilities of solids in supercritical fluids (SCF) have been recently increased in biochemical industries. In particular, the solubilities of bioproducts in supercritical fluids are essential in the process design of extraction. The solubilities of indole derivatives in supercritical carbon dioxide, ethylene, ethane, and trifluoromethane were investigated in our previous studies (*1*, *3*).

In the present study, the solubilities of three pyrimidine derivatives (2-chloropyrimidine, 4-hydroxypyrimidine, and 2-mercaptopyrimidine) and two pyrazine derivatives (2-aminopyrazine and pyrazine-2-carboxylic acid) in the four supercritical fluids were measured in a pressure range of 6-21 MPa at 308.15 K by a static method.

As discussed in the previous study (*1*), the self-association of solute components would play an important role in decreasing solubilities in supercritical fluids. The self-association is expected for all the substances except 2-chloropyrimidine in this study. Therefore, these data are important in investigating the relationship between electronic properties of the solutes and solubility changes caused by substitution.

Experimental Section

Apparatus and Procedure. A schematic diagram of the experimental apparatus, which was newly constructed, is shown in Figure 1. The solids of interest were charged into the stainless steel equilibrium cell (ca. 12 cm^3) (H), which was installed in an air bath (Shimadzu CTO-2A) regulated at 308.15 ± 0.1 K. The solvent was introduced to the equilibrium cell (H) by an HPLC-type plunger pump (Shimadzu LC-6A) (D3). The cell pressure was varied from 6 to 21 MPa with an accuracy of ±0.065 MPa. The contents of the equilibrium cell were agitated by a magnetic stirrer with use of an external magnet. After the equilibrium was established (over a period of 1-2 h), the sample in the sample loop (G1-G4) was transferred to the SFC line by switching the six-port valve (Valco C6W) (G). The following conditions were maintained for the SFC line. A small amount of methanol (A2) was added continuously as a modifier from a plunger pump (Shimadzu LC-5A) (D2) to the mobile phase of compressed carbon dioxide because most of the solutes in this study cannot be eluted from the octadecylsilane (ODS) column by use of pure carbon dioxide. The mobile phase prepared at a few mass percent of methanol in a mixer (E) was passed through three consecutive six-port valves (F, G, J), and then the ODS column (Shimadzu Shim-pack CLC-ODS or Chemco Develosil ODS) (L). The flow rate was ca. 860 cm^3/min. The total amount of separated solute component was detected by a spectrophotometric detector (Shimadzu SPD-M1A) (M). Finally, the fluid in the SFC line was released from a back-pressure regulator (Tescom 26-1722-24) (N). The pressure was controlled at 22.70 ± 0.12 MPa by the back-pressure regulator. The solid solubilities were calculated from the peak area of UV analysis. The detectable limit was about 10^{-6} in mole fraction.

The more detailed description of the experimental equipment and operating procedure can be found in our previous paper (*1*).

Materials. Trifluoromethane (purity 99.995 mol %) was specially supplied by Daikin Industries, Ltd.; carbon dioxide (purity 99.95 mol %) was obtained from Takachiho Trading Co., Ltd.; both ethylene (purity 99.97 mol %) and ethane (minimum purity 99.6 mol %) were manufactured by Nippon Fine Gas Co., Ltd.

2-Chloropyrimidine (purity 98+ mol %) and 4-hydroxypyrimidine (purity 97+ mol %) were obtained from Sigma Chemical Co.; 2-mercaptopyrimidine (purity 98+ mol %), 2-aminopyrazine (purity 99+ mol %), and pyrazine-2-carboxylic acid (purity 99+ mol %) were obtained from Aldrich Chemical Co. All chemicals were used without further purification.

The solid components used in this experiment are listed in Table I.

Results and Discussion

Solvent Effect on Solubilities of Pyrimidine and Pyrazine Derivatives. Tables II-VI give the experimental data of *p*-*y* relations for the 20 systems, which are the combination of five kinds of solutes (pyrimidine and pyrazine derivatives) and four supercritical fluids. As the solubilities of pyrazine-2-carboxylic acid in supercritical ethylene and ethane are less than the detectable limit of UV analysis, no values for these two systems are listed in the table. Figures 2 and 3 show the solubilities of 2-chloropyrimidine and 4-hydroxypyrimidine in four solvents, respectively.

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Table I. Physical Properties of the Solutes

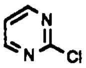
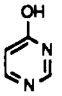
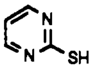
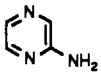
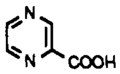
compound	formula	structure	M_w, g/mol	T_m, K
2-chloropyrimidine	$C_4H_3N_2Cl$		114.54	339–341
4-hydroxypyrimidine	$C_4H_4N_2O$		96.09	439–442
2-mercaptopyrimidine	$C_4H_4N_2S$		112.15	503 (dec.)
2-aminopyrazine	$C_4H_5N_3$		95.11	392–393
pyrazine-2-carboxylic acid	$C_5H_4N_2O_2$		124.10	498 (dec.)

Table II. Solubilities of 2-Chloropyrimidine in Carbon Dioxide, Ethylene, Ethane, and Trifluoromethane at 308.15 K

CO_2		C_2H_4	
P/MPa	$y_1 \times 10^2$	P/MPa	$y_1 \times 10^2$
6.32	0.0913	7.10	0.123
7.15	0.126	8.49	0.380
7.98	0.361	9.92	0.555
8.44	0.540	11.13	0.825
9.23	0.970	11.77	1.029
9.55	1.095	13.90	1.233
9.97	1.184	14.36	1.241
12.51	1.557	16.58	1.322
14.15	1.755		
15.93	1.883		
17.78	1.987		
C_2H_6		CHF_3	
P/MPa	$y_1 \times 10^2$	P/MPa	$y_1 \times 10^2$
6.41	0.579	7.24	1.256
7.70	0.754	7.47	1.346
8.72	0.829	8.44	2.161
11.22	0.904	12.10	3.333
12.79	1.055	13.90	3.694
13.72	1.097	15.56	3.953
14.64	1.076		
16.67	1.177		

Table III. Solubilities of 4-Hydroxypyrimidine in Carbon Dioxide, Ethylene, Ethane, and Trifluoromethane at 308.15 K

CO_2		C_2H_4	
P/MPa	$y_1 \times 10^4$	P/MPa	$y_1 \times 10^4$
7.24	0.234	11.59	0.0782
8.81	0.593	12.95	0.104
9.97	0.670	14.41	0.108
11.31	0.825	16.67	0.153
12.65	1.059	18.89	0.154
13.07	1.212		
14.46	1.452		
15.70	1.542		
17.87	1.846		
C_2H_6		CHF_3	
P/MPa	$y_1 \times 10^4$	P/MPa	$y_1 \times 10^4$
8.17	0.0304	9.00	0.480
9.18	0.0651	10.20	0.501
10.85	0.0599	11.96	0.554
13.16	0.0590	13.72	0.603
17.50	0.0603	16.09	0.652
		18.52	0.659

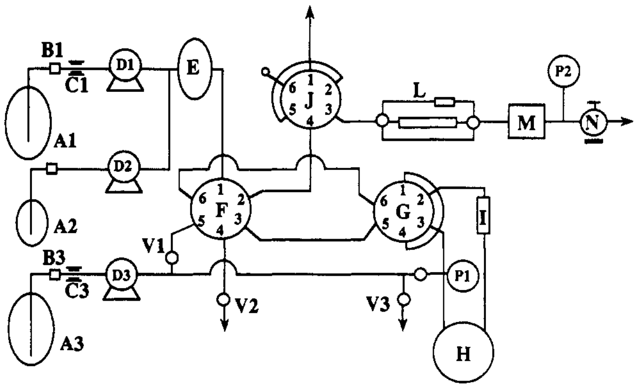


Figure 1. Schematic diagram of experimental apparatus for measuring solubilities: (A) gas cylinder; (B) filter; (C) heat exchanger; (D) plunger pump; (E) mixer; (F) six-port valve; (G) sampler; (H) equilibrium cell; (I) hand-operated recirculation pump; (J) injector; (L) analytical column; (M) UV spectrophotometric detector; (N) back-pressure regulator; (P) pressure sensor; (V) high-pressure valve.

Table IV. Solubilities of 2-Mercaptopyrimidine in Carbon Dioxide, Ethylene, Ethane, and Trifluoromethane at 308.15 K

CO_2		C_2H_4	
P/MPa	$y_1 \times 10^5$	P/MPa	$y_1 \times 10^5$
9.83	3.873	14.85	4.821
12.00	4.801	18.00	4.916
14.43	4.708	19.70	4.987
16.93	4.687		
19.77	4.570		
C_2H_6		CHF_3	
P/MPa	$y_1 \times 10^5$	P/MPa	$y_1 \times 10^5$
11.05	3.734	8.03	5.134
13.83	3.943	11.00	5.033
15.05	4.067	13.70	4.925
17.70	4.431	15.53	5.153
		20.67	5.106

Table V. Solubilities of 2-Aminopyrazine in Carbon Dioxide, Ethylene, Ethane, and Trifluoromethane at 308.15 K

CO_2		C_2H_4	
P/MPa	$y_1 \times 10^3$	P/MPa	$y_1 \times 10^3$
7.61	0.126	7.89	0.0782
8.91	0.870	9.18	0.120
11.40	1.310	12.47	0.163
13.90	1.498	14.09	0.214
16.86	1.763	15.84	0.248
17.78	1.804	17.96	0.263
C_2H_6		CHF_3	
P/MPa	$y_1 \times 10^3$	P/MPa	$y_1 \times 10^3$
6.96	0.0839	7.70	0.579
8.63	0.0948	9.55	0.673
9.46	0.102	11.50	0.879
15.10	0.108	12.14	0.955
18.24	0.109	13.25	0.992
		14.18	1.076
		16.95	1.156

Table VI. Solubilities of Pyrazine-2-carboxylic Acid in Carbon Dioxide, Ethylene, Ethane, and Trifluoromethane at 308.15 K

CO_2		C_2H_4	C_2H_6	CHF_3	
P/MPa	$y_1 \times 10^5$	y_1	y_1	P/MPa	$y_1 \times 10^5$
9.18	0.396	$<10^{-6}$	$<10^{-6}$	8.72	0.609
10.94	0.508			11.22	1.096
13.53	0.619			14.09	1.560
15.38	0.859			17.96	2.156
16.03	0.860				
17.04	0.918				
19.53	0.945				

The dissolution power of trifluoromethane with high polarity is the strongest for the latter component in the four fluids, while the solubilities of both components in ethylene and ethane are

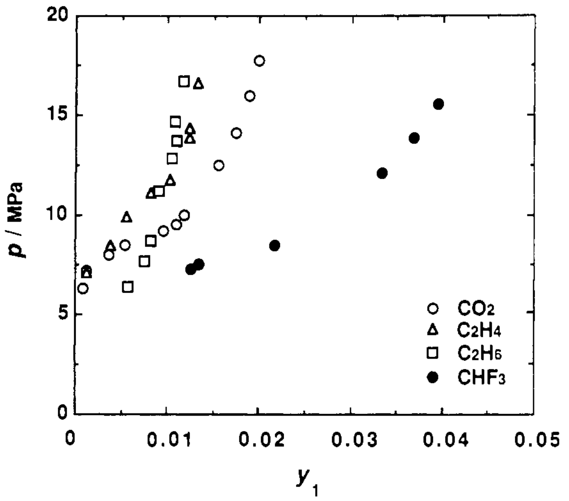


Figure 2. Solubilities of 2-chloropyrimidine in four supercritical fluids at 308.15 K.

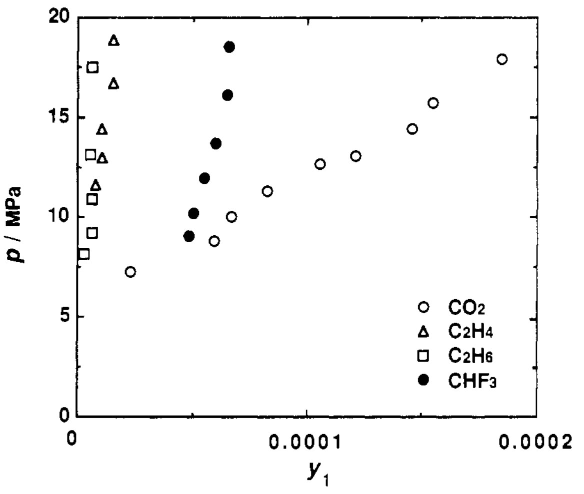


Figure 3. Solubilities of 4-hydroxypyrimidine in four supercritical fluids at 308.15 K.

considerably low and they decrease in that order.

The dissolution power of carbon dioxide is strongly influenced by the sign of the Hammett constant σ of the substituent involved; the negative sign of σ gives the strongest dissolution power to carbon dioxide, while the power becomes weak in the case of positive σ. A negative σ means that the π-electron density of the skeleton becomes higher by electron release from the substituent, while a positive σ means that it becomes lower by electron withdrawal to the substituent. In our opinion, the dispersion force based on the interaction between carbon dioxide and the π-electron density of the skeleton would be essential in this solubility behavior. Such phenomenon has been observed previously in the binary mixtures of carbon dioxide and indole derivatives (*1*).

Substituent Effect on Solubilities of Pyrimidine and Pyrazine Derivatives. The substituent effect on solubilities of pyrimidine derivatives in supercritical carbon dioxide is given in Figure 4. The solubilities of 2-chloropyrimidine (–Cl), 4-hydroxypyrimidine (–OH), and 2-mercaptopyrimidine (–SH) decrease in that order in supercritical carbon dioxide, as well as trifluoromethane. In the ethylene and ethane systems, the order of 4-hydroxypyrimidine is replaced with 2-mercaptopyridine.

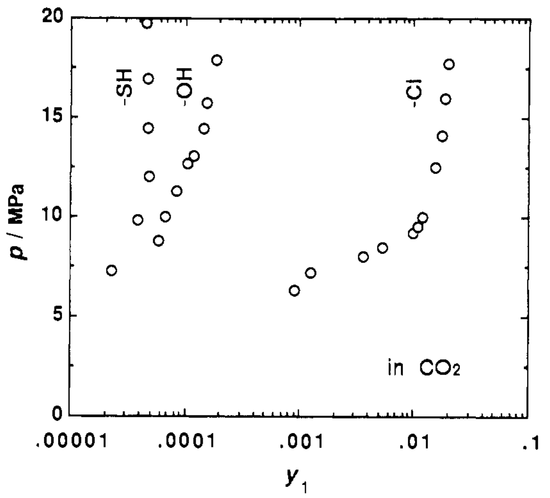


Figure 4. Solubilities of pyrimidine derivatives in supercritical carbon dioxide at 308.15 K.

Since nonsubstituted pyrimidine is completely dissolved in carbon dioxide and trifluoromethane (*4*), it is clear that the solubilities of pyrimidine derivatives decrease by containing various substituents. When the substituents participate in the self-association, the solubilities are extremely lowered. For two pyrazine derivatives, the solubilities of pyrazine-2-carboxylic acid in carbon dioxide are much less than those of 2-aminopyrazine.

Further discussion will be prepared elsewhere (*2*), making a summary of these facts.

Conclusion

Several solubilities of three pyrimidine derivatives and two pyrazine derivatives in four supercritical fluids are presented. The solubilities of these derivatives in each supercritical fluid decrease on addition of substituents. The dissolution power of trifluoromethane with high polarity is fairly strong for all substances. In the case of carbon dioxide, the dissolution power is influenced by the sign of Hammett constants of the substituents. It is still obscure why carbon dioxide shows such strong characteristic behavior. However, it is quite interesting that such behavior is observed for the self-associated derivatives of pyrimidine and pyrazine, as well as for indole derivatives.

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Registry No. CO_2, 124-38-9; CHF_3, 75-46-7; C_2H_4, 74-85-1; C_2H_6, 74-84-0; 2-chloropyrimidine, 1722-12-9; 4-hydroxypyrimidine, 4562-27-0; 2-mercaptopyrimidine, 1450-85-7; 2-aminopyrazine, 5049-61-6; pyrazine-2-carboxylic acid, 98-97-5.

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