

# Measurements of Solubilities of Xanthenes in Supercritical Carbon Dioxide + Methanol

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Solubilities of the xanthenes caffeine, theophylline, and theobromine in different supercritical (carbon dioxide + methanol) mixtures were measured at 313 K and 22 MPa. The solubilities of theobromine in supercritical carbon dioxide + methanol were also measured at 333 K and 22 MPa. The determination of solubilities has been performed by using a static analytical method with direct coupling of an equilibrium cell to a supercritical fluid chromatographic system. The solubility of all xanthenes was enhanced by adding methanol to the fluid. For example, with 0.1 mass fraction of methanol in the fluid mixture the solubility of every xanthine increases by 1 order of magnitude. Although the chemical structures of the xanthenes are very similar, their solubilities in supercritical carbon dioxide mixtures, as in pure carbon dioxide, vary substantially. The solubilities of caffeine in CO<sub>2</sub> are 1 order of magnitude higher than those of theophylline and 2 orders of magnitude higher than those of theobromine.

## Introduction

There is a current need in the fields of supercritical fluid extraction (SFE) and supercritical fluid chromatography (SFC) for rapid and simple methods of determination of a solute's solubility in dense gaseous solvents. Information about solubilities can simplify the choice of conditions for SFE and the optimization of analytical and preparative SFC. The addition of cosolvents such as methanol to supercritical carbon dioxide can increase solubilities of polar organic solutes and selectivity of the separation technique significantly.

All of the solubility data of xanthenes in supercritical fluids found in the literature have been tabulated by Johannsen and Brunner (1994). The only existing solubility data for xanthenes in mixed phases were published by Li and Hartland (1992). They measured the solubility of theobromine in carbon dioxide + ethanol. In this work the solubilities of the xanthenes caffeine, theophylline, and theobromine in different (carbon dioxide + methanol) mixtures are presented.

All work with binary mobile phases assumes complete miscibility of the primary and the modifier fluids at the concentration of interest. Therefore, a knowledge of vapor-liquid equilibrium in the system is necessary. However, the (CO<sub>2</sub> + methanol) system has been studied extensively. Earlier solubility and vapor-liquid equilibrium study results of the (carbon dioxide + methanol) system have been recently tabulated by Weber et al. (1984) and E. Brunner et al. (1987). Further studies of the (carbon dioxide + methanol) equilibrium have been published by Hong and Kobayashi (1988), Suzuki et al. (1990), and Yoon et al. (1993). The conditions under which two phases are formed from carbon dioxide + methanol have been found at 298 K under 6.5 MPa, at 323 K under 10 MPa, and at 373 K under 16 MPa (E. Brunner et al., 1987). At 423 K the vapor-liquid equilibrium region showed a maximum at 16.2 MPa. For higher temperatures the two-phase region decreased. However, at 22 MPa and 313 or 333 K, a single phase exists.

Furthermore, a knowledge of densities of (carbon dioxide + methanol) is needed for calculation of the solubility values. However, the densities of the binary mixtures are largely unknown. Since measured values are rarely pub-

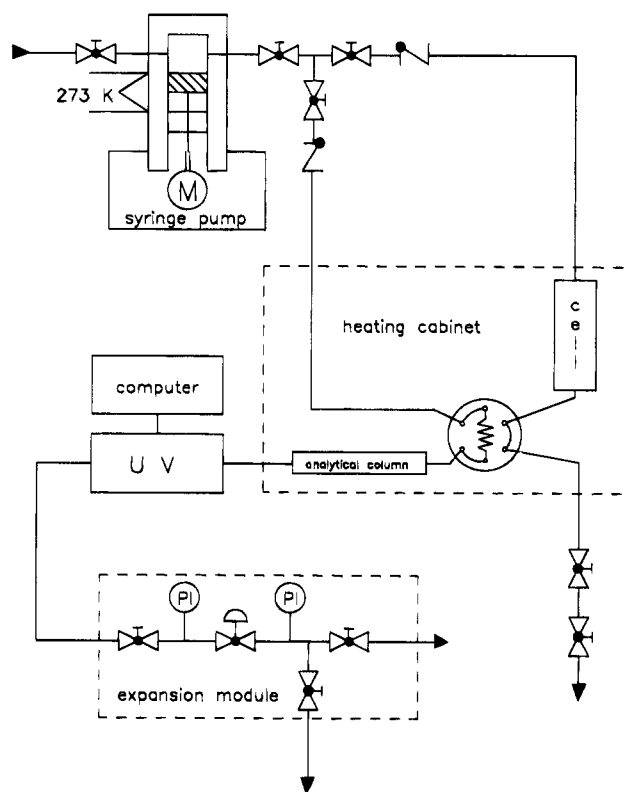
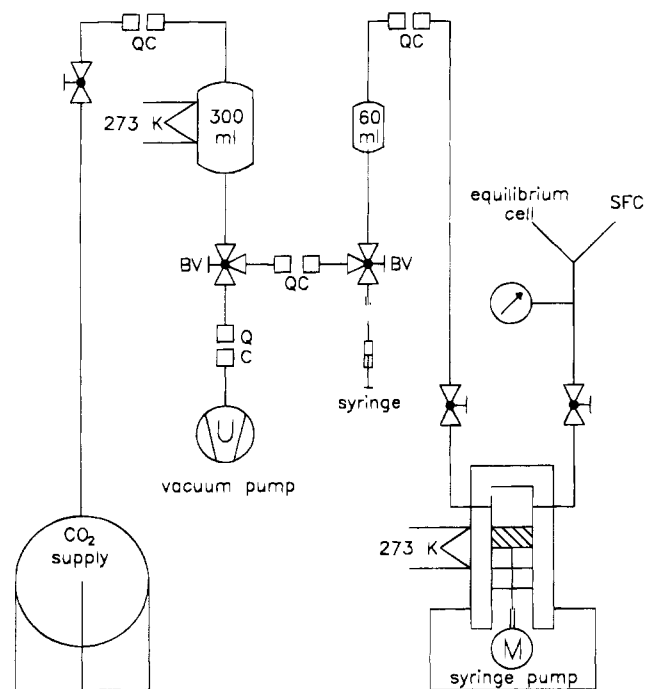


Figure 1. Schematic diagram of the system for solubility measurements.

lished, the accuracy of predictions using modified equations of state is uncertain. The present work shows a simple extrapolation of the values measured by Berger (1991) and Berger and Deye (1990).

## Experimental Section

**Apparatus.** The apparatus used for static measurements of equilibrium solubilities with on-line coupling to a fluid chromatographic system is shown in Figure 1: A syringe pump (ISCO 260 D) served to pressurize the equilibrium cell, the sample loop, and the chromatographic system with supercritical (carbon dioxide + methanol).

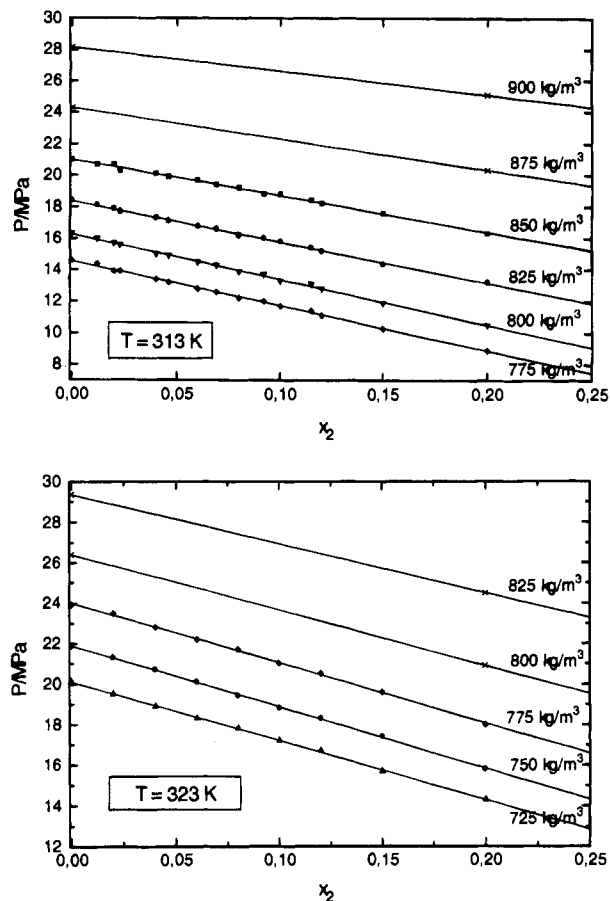


**Figure 2.** Schematic diagram of the fluid mixing device: QC, quick-connect; BV, three-way ball valve.

Temperature was maintained and controlled to  $\pm 1$  K by a heating cabinet (WTB FED 53). An empty stainless steel HPLC column (8 cm<sup>3</sup>) was used as the equilibrium cell. Samples were taken by a four-port valve (Rheodyne) equipped with an internal 1  $\mu$ L sample loop and analyzed on an HPLC-type packed column. Eluted substances were detected with an UV detector (Shimadzu SPD 6AV) at 272 nm. A more detailed description of the SFC apparatus and the procedure was presented by Johannsen and Brunner (1994).

For solubility measurement in mixed phases a method for the preparation of known compositions of supercritical mixtures was needed. Raynie et al. (1989) described a simple, inexpensive method for the preparation of mixed mobile phases (especially gas and liquid mixtures) for SFC. To prepare homogeneous mixtures, the pumping system was filled with premixed fluids. Figure 2 shows the fluid mixing device used in this work consisting of two stainless steel sample cylinders (60 and 300 mL, rated to 12 MPa), two three-way ball valves (one with a syringe adapter), and four quick-connects (Swagelok QH series).

**Procedure.** To prepare a mixed fluid, the mixing device and the syringe pump were evacuated with a vacuum pump. For weighing, the sample cylinders were disassembled by means of quick-connects. After weighing with a balance to within 0.01 g (Sartorius 1364 MP), the two cylinders were installed and an appropriate amount of carbon dioxide was condensed into the large cooled cylinder within 25 min. The desired amount of modifier was injected by syringe through the syringe adapter into the small cylinder. After that, both cylinders were weighed again. The mass of modifier added was then determined by difference. Then the methanol was sucked slowly into the pump cylinder by withdrawing the cylinder piston to the bottom. After the lines were purged with CO<sub>2</sub>, the CO<sub>2</sub> was condensed into the pump cylinder. An additional weighing of the sample cylinders provided actual mass of mixture transferred to the pump. After the syringe pump valve was closed, the pump was pressurized to the desired conditions and equilibrated overnight.



**Figure 3.** Constant density lines in plot of pressure against composition of carbon dioxide (1) + methanol (2) at (a, top) 313 and (b, bottom) 323 K. Experimental data (Berger and Deye, 1990; Berger, 1991) and extrapolations are shown.

**Materials.** Carbon dioxide of 99.95% purity was purchased from KWD, Kohlensäurewerke Deutschland, Bad Hönningen. CO<sub>2</sub> was fed to the system from the vapor phase of a carbon dioxide tank, further dried by a moisture trap containing a molecular sieve, and liquefied in the cylinder. Methanol of analytical grade and the prepacked column (125 mm length  $\times$  4 mm i.d., packed with 5  $\mu$ m particles of LiChrosorb Si 60) were obtained from Merck, Darmstadt, Germany. The test solutes were obtained from various sources: Caffeine (99%) and theophylline (99%) were obtained from Aldrich, Steinheim, Germany, and theobromine (anhydrous) was from Sigma, Deisenhofen, Germany.

## Results and Discussion

Solubility values presented are the mean value of at least five samplings. Standard deviations of the measurements were within 5%. Solubilities were obtained from elution peak areas by use of external calibration curves. These curves were obtained by injecting different standard solutions of known concentrations through the injection valve. Densities of the fluids are needed for calculation of the solubilities. Densities for pure CO<sub>2</sub> were obtained from the Bender (1970) equation of state. Density values of (CO<sub>2</sub> + methanol) were calculated by extrapolation of experimental data measured by Berger and Deye (1990) and Berger (1991). As shown by Berger (1991), above the two-phase region constant density lines are linear function of composition, substantially. There is a transition from sub- to supercritical conditions. The experimentally obtained constant density lines show no discontinuity across this

**Table 1. Solubilities  $S$  (in Grams per Kilogram of Solvent) of Xanthines (3) in Supercritical Carbon Dioxide (1) + Methanol (2)**

	$T/K$	$P/MPa$	$w_2$	$x_2$	$\rho/kgm^{-3}$	$S/g \cdot kg^{-1}$	
caffeine (3)	313	21.9	0	0	857	1.5	
			0.042	0.057	866	5.4	
			0.052	0.070	868	5.8	
			0.052	0.071	868	5.9	
			0.070	0.093	871	8.8	
			0.071	0.105	873	8.5	
			0.105	0.139	877	13.4	
			0.108	0.142	878	16.3	
theophylline (3)	313	21.9	0	0	857	0.04	
			0.042	0.057	866	0.62	
			0.055	0.075	869	0.77	
			0.069	0.092	871	0.79	
			0.092	0.122	875	1.8	
			0.107	0.141	877	1.9	
			0.109	0.143	878	1.9	
			0.128	0.168	880	2.5	
			0.145	0.189	883	2.8	
			theobromine (3)	313	21.3	0	0
0.090	0.119	875				0.05	
0.101	0.133	875				0.05	
0.108	0.143	877				0.08	
0.115	0.151	879				0.06	
0.130	0.171	880				0.04	
0.151	0.196	883				0.11	
333	22.0	0.166		0.215	886	0.10	
				0.194	0.248	888	0.13
				0.197	0.252	888	0.12
				21.3	0	743	0.008
				21.9	0.090	790	0.08
				21.8	0.115	797	0.10
				22.0	0.166	811	0.17
21.7	0.194	815	0.24				
21.6	0.197	815	0.20				

transition. However, the experimental values are at lower pressure and density range as they are needed. Therefore, for higher pressures 50 constant density lines were calculated for both temperatures, between 850 and 900 kg/m<sup>3</sup> at 313 K and between 775 and 825 kg/m<sup>3</sup> at 333 K. This was done by fitting the experimentally obtained pressure values at 0.2 mole fraction of methanol ( $x_2 = 0.2$ ) with a simple polynomial regression of second order and extrapolating the pressure values to higher density lines. The experimental values as well as two of the extrapolated constant density lines are shown in Figure 3a for 313 K and in Figure 3b for 333 K.

Experimental solubilities of xanthines in carbon dioxide (1) + methanol (2) are reported in Table 1. Figure 4 shows the influence of methanol addition to the supercritical carbon dioxide on the solubilities of xanthines at 22 MPa and 313 K. Modifier methanol increases the solubility of all xanthines. For example, with 0.1 mass fraction of methanol ( $w_2 = 0.1$ ) in the fluid mixture the solubility of every xanthine increases by 1 order of magnitude. Solubilities of caffeine in carbon dioxide + methanol vary between 1.5 g/kg of CO<sub>2</sub> without methanol and 16 g/kg ( $w_2 = 0.11$ ). The solubilities of theophylline are in the range of 40 mg/kg ( $w_2 = 0$ ) up to 2.8 g/kg ( $w_2 = 0.15$ ). The solubilities of theobromine vary from 4 mg/kg in pure carbon dioxide to 100 mg/kg ( $w_2 = 0.215$ ).

Johannsen and Brunner (1994) found that the solubility of caffeine (1,3,7-trimethylxanthine) in pure supercritical carbon dioxide is about 1 order of magnitude higher than that of theophylline (1,3-dimethylxanthine) and about 2 orders of magnitude higher than that of theobromine (3,7-dimethylxanthine), although the compounds are similar in chemical structure. The addition of methanol to the carbon dioxide shows no influence on the remarkable difference in solubilities between the xanthines.

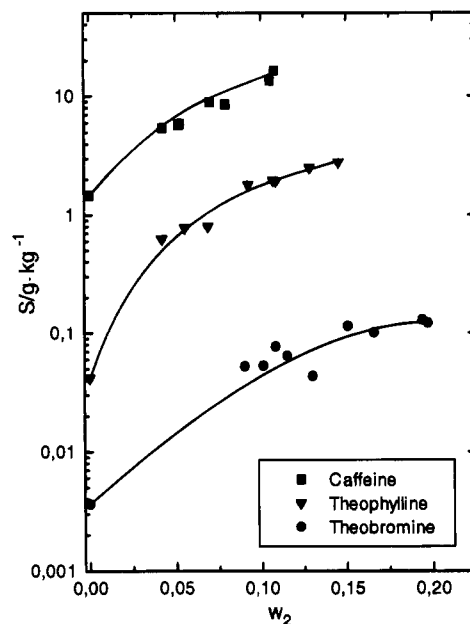
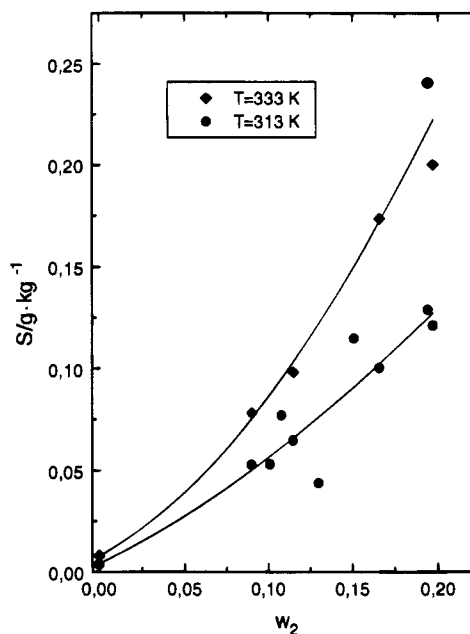
**Figure 4.** Solubility  $S$  (in grams per kilogram of solvent) of xanthines in carbon dioxide (1) + methanol (2) at 313 K and 22 MPa.**Figure 5.** Solubility  $S$  (in grams per kilogram of solvent) of theobromine in carbon dioxide (1) + methanol (2) at 313 and 333 K and 22 MPa.

Figure 5 illustrates the solubility of theobromine in different (carbon dioxide + methanol) mixtures at 313 and 333 K. The solubilities of theobromine vary between 4 (313 K,  $w_2 = 0$ ) and 240 mg/kg (333 K,  $w_2 = 0.215$ ). The difference between the two solubility isotherms is approximately a factor of 2, depending on vapor pressure of the solute and density of the fluid. The decrease in density by increasing temperature is compensated by increasing vapor pressure.

Between the solubilities without and with 0.2 mass fraction methanol a factor of about 30 was found. A similar increase of solubility was reported by Li and Hartland (1992) for theobromine in carbon dioxide + ethanol. Without ethanol carbon dioxide dissolved 3 mg/kg (333 K and 20 MPa), and with 0.2 mass fraction of ethanol the solubility increased to 100 mg/kg. However, the lower

solubility of theobromine in CO<sub>2</sub> + ethanol compared with CO<sub>2</sub> + methanol could be caused by the lower polarity of the ethanol.

### Conclusion

Solubilities of the xanthines caffeine, theophylline, and theobromine in different supercritical (carbon dioxide + methanol) mixtures were measured at 313 K and 22 MPa by using a static analytical method. The solubilities of all xanthines were enhanced by adding methanol to the fluid. For example, with 0.1 mass fraction of methanol in the fluid mixture the solubility of every xanthine increases by 1 order of magnitude. Although the chemical structures of the xanthines are very similar, their solubilities in supercritical carbon dioxide mixtures, as in pure carbon dioxide, vary substantially. The solubilities of caffeine in CO<sub>2</sub> are 1 order of magnitude higher than those of theophylline and 2 orders of magnitude higher than those of theobromine. Furthermore, the solubilities of theobromine in supercritical carbon dioxide + methanol were measured at 333 K and 22 MPa. Caused by increasing vapor pressure, a difference between the two solubility isotherms of about a factor of 2 was determined.

### Literature Cited

- Bender, E. Equation of state exactly representing the phase behaviour of pure substances. *Proceedings of the Fifth Symposium on Thermophysical Properties*; American Society of Mechanical Engineers: New York, 1970; pp 227/235.
- Berger, T. A. Density of Methanol-Carbon Dioxide Mixtures at Three Temperatures: Comparison with Vapor-Liquid Equilibria Measurements and Results Obtained from Chromatography. *J. High Resolut. Chromatogr.* **1991**, *14*, 312–316.
- Berger, T. A.; Deye, J. F. Composition and Density Effects Using Methanol/Carbon Dioxide in Packed Column Supercritical Fluid Chromatography. *Anal. Chem.* **1990**, *62*, 1181–1185.
- Brunner, E.; Hültenschmidt, W.; Schlichtharle, G. Fluid mixtures at high pressures IV. Isothermal phase equilibria in binary mixtures consisting of (methanol + hydrogen or nitrogen or methane or carbon monoxide or carbon dioxide). *J. Chem. Thermodyn.* **1987**, *19*, 273–291.
- Hong, J. H.; Kobayashi, R. Vapor-Liquid Equilibrium Studies for the Carbon Dioxide-Methanol System. *Fluid Phase Equilib.* **1988**, *41*, 269–276.
- Johannsen, M.; Brunner, G. Solubilities of the xanthines caffeine, theophylline and theobromine in supercritical carbon dioxide. *Fluid Phase Equilib.* **1994**, *95*, 215–226.
- Li, S.; Hartland, S. Influence of co-solvents on solubility and selectivity in extraction of xanthines and cocoa butter from cocoa beans with supercritical carbon CO<sub>2</sub>. *J. Supercrit. Fluids* **1992**, *5*, 7–12.
- Raynie, D. E.; Fields, S. M.; Djordevic, M. M.; Markides, K. E.; Lee, M. L. A Method for the Preparation of Binary Mobile Phase Mixtures for Capillary Supercritical Fluid Chromatography. *J. High Resolut. Chromatogr.* **1989**, *12*, 51–52.
- Suzuki, K.; Sue, H.; Itou, M.; Smith, R. L.; Inomata, H.; Arai, K.; Saito, S. Isothermal Vapor-Liquid Equilibrium Data for Binary Systems at High Pressures: Carbon Dioxide-Methanol, Carbon Dioxide-Ethanol, Carbon Dioxide-1-Propanol, Methane-Ethanol, Methane-1-Propanol, Ethane-Ethanol, and Ethane-1-Propanol Systems. *J. Chem. Eng. Data* **1990**, *35*, 63–66.
- Weber, W.; Zeck, S.; Knapp, H. Gas Solubilities in Liquid Solvents at High Pressures: Apparatus and Results for Binary and Ternary Systems of N<sub>2</sub>, CO<sub>2</sub> and CH<sub>3</sub>OH. *Fluid Phase Equilib.* **1984**, *18*, 253–278.
- Yoon, J.-H.; Lee, H.-S.; Lee, H. High-Pressure Vapor-Liquid Equilibria for Carbon Dioxide + Methanol, Carbon Dioxide + Ethanol, and Carbon Dioxide + Methanol + Ethanol. *J. Chem. Eng. Data* **1993**, *38*, 53–55.

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