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Solubility of Fluorinated Pharmaceuticals in Dense Carbon Dioxide

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Abstract:

The solubilities of benzoic acid and fluorinated benzoic acid derivatives in dense carbon dioxide were measured at 35 and 55 °C to find out how much fluorination increases the solubility of organic pharmaceuticals in dense carbon dioxide. The solubilities of two higher molecular weight pharmaceuticals, triflupromazine and flufenamic acid, in dense carbon dioxide were also measured. The solubility of benzoic acid is approximately 0.2 wt % at 35 °C and 100 bar. Attaching one fluorine atom increased the solubility of benzoic acid slightly, and the solubility of 3-fluorobenzoic acid was approximately 1 wt %. The solubility of 3,4-difluorobenzoic acid was 1.3 wt % at 35 °C and 103 bar. Introduction of a trifluoromethyl group increased the solubility significantly, and the solubility of 3-(trifluoromethyl)benzoic acid in dense carbon dioxide at 35 °C and 100 bar was approximately 7 wt %, which is almost 40 times higher than the solubility of benzoic acid in the same conditions. The solubility of triflupromazine was relatively high, i.e., 4.4 wt % at 43 °C and 145 bar. Flufenamic acid was very sparingly soluble at ambient temperatures (<50 °C), and 70−80 °C was necessary to reach 1−3 wt % solubility. These experiments show that dense carbon dioxide is a feasible solvent for fluorinated pharmaceuticals and that the fluorine content of a compound can be used as a clue to find carbon dioxide soluble molecules.

Introduction

Currently, there is a substantial boost of research to find new applications for dense gases or supercritical fluids as reaction media, as solvents in separations and in materials processing. The research is largely driven by possible applications in so-called green chemistry, where dense gases offer considerable scope as an environmentally more acceptable replacement for conventional organic solvents such as chlorinated hydrocarbons. An example of dense gases is carbon dioxide above its critical point (T_C = 31 °C, p_C = 73.8 bar) where its density is liquidlike, while the viscosity and diffusivity remain between gaslike and liquidlike values. Carbon dioxide is a nontoxic, nonflammable, and the second-least expensive solvent after water.[1] Because of the good mass-transfer properties of dense gases some of the reactions and separations are expected to run more rapidly than in conventional liquid solvents.

The potential applications of dense gases as processing media include particle production techniques,[2,3] chromatographic separations,[4] and reactions.[5] Dense gases may serve as a reaction medium for the reactants, catalysts, and products, or they can be a solvent and a reactant at the same time. Several reactions, such as oxygenation,[6] hydroformylation,[7] alkylation,[8] amination,[9] esterification,[10] and hydrogenation,[11] have been studied in supercritical fluids. Common gases, such as hydrogen, are miscible with dense carbon dioxide. Therefore, it is possible to run hydrogenations in one phase where hydrogen concentration may be chosen freely without the solubility limitation of hydrogen in a liquid reaction mixture. The properties of supercritical fluids may also be utilized to separate the product from the reactants or catalyst by reducing the pressure of the reaction mixture which causes the solutes to precipitate.

Rapid expansion from supercritical solutions (RESS) is used to form fine particles of substances which are soluble in a supercritical solvent. In the RESS technique the substance is first dissolved in a supercritical solvent, after which the pressure is rapidly decreased in a specifically designed nozzle, resulting in supersaturation of the substance in the supercritical solvent and leading to the formation of small particles with a narrow particle size distribution.

Supercritical fluid chromatography (SFC) with pure carbon dioxide eluent is applicable to the separation of relatively nonpolar compounds, that is, compounds which are soluble in toluene, hexane, Freons, and chlorinated solvents. A distinctive characteristic of SFC is that ion−ion interactions between eluted compounds and silica are practically absent. For example, compounds which contain primary or secondary amine groups are selectively fractionated with SFC. These compounds are generally impossible to separate by HPLC−silica systems due to severe peak tailing. The benefits of SFC are the increased separation rates due to high

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molecular diffusion in supercritical fluids, low operating costs because of low energy consumption in recycling pressurized carbon dioxide, nontoxicity and nonflammability of the carbon dioxide eluent, and simple recovery of products from the eluent by pressure reduction.

All of the applications require that the compounds to be processed are soluble in dense gases. Dense gases are generally nonpolar solvents which limits their applicability in industrial processes. Supercritical carbon dioxide resembles a fluorocarbon with respect to solvent strength,[1] and its solubility parameter is close to that of hexane. A common way to increase the polarity of pressurized carbon dioxide is to add methanol or another small molecule alcohol in it. Small molecule alcohols dissolve well in dense carbon dioxide, and a more polar, one-phase solvent is obtained. However, the use of a cosolvent leads to separate recovery systems for the carbon dioxide and the alcohol. The product is obtained in an alcohol solution and usually has to be separated from it. Much of the simplicity, safety, and environmental advantages are then lost.

One way of dissolving polar compounds in supercritical carbon dioxide is to introduce a micelle-forming compound which has a polar end and a CO_2-philic tail. According to DeSimone,[12] examples of such CO_2-philic groups include siloxane, fluoroether, fluoroalkyl, and fluoroacrylate. Yazdi and Beckman[13] have synthesized CO_2-soluble chelating agents for dissolving metals in carbon dioxide. The CO_2-soluble tails in their chelating agents were different chain-length fluoroethers. Several theories concerning the increased solubilities due to fluorination have been suggested. Brady et al.[14] suggested that the solubility increase is due to the polarizability of carbon and fluorine. Yee et al.[15] concluded that the solubility of fluorinated polymers in dense carbon dioxide increases because of the specific dipole interaction between carbon dioxide and fluorine. An electrostatic interaction between carbon and fluorine has been proposed by Cece et al.[16]

Fluorine is attached to a number of pharmaceutical molecules to control their transport and metabolic rates. Our approach in this work was to find out if the fluorine content of a pharmaceutical compound could be used as a clue to find CO_2-soluble compounds which could then be processed in pure carbon dioxide. The purpose of this empirical work was to measure how much does fluorination increase the solubility of benzoic acid in dense carbon dioxide. The solubilities of two larger pharmaceutical molecules containing a fluorinated functional group were also measured to demonstrate the concept.

Experimental Section

Materials. Benzoic acid (>99.5%), 3-fluorobenzoic acid (>98%), 3,4-difluorobenzoic acid (>98%), and 3-(trifluoromethyl)benzoic acid (≈99%) were obtained from Fluka Chemie AG. Triflupromazine and flufenamic acid were obtained from Sigma Chemical Company. Carbon dioxide (99.7%) was obtained from AGA.

Procedures. A static view cell apparatus was used for measuring the solubility. The main component of this system is a variable volume view cell, which allows the visual determination of the phases present at equilibrium. The maximum operating temperature of the system is approximately 373 K, and the maximum operating pressure is 520 bar.

The desired amount of the chemical was weighed to an accuracy of 10^{-3} g and charged to the cleaned cell. The cell was then purged several times with carbon dioxide gas to remove air. After thermal equilibrium in the air bath was reached, the cell was slowly pressurized by pumping in carbon dioxide. The density of carbon dioxide in the cell was calculated from cell temperature and pressure by the modified Benedict−Webb−Rubin equation of state.[17] The amount of carbon dioxide was measured by the pump control unit, which shows how much the volume of the pump cylinder containing liquid carbon dioxide changes during the pressure vessel loading while the piston is adjusted to maintain constant pressure.

The pressure in the closed cell was slowly increased by moving the piston until complete miscibility was reached. After this, the pressure was slowly decreased until a second phase appeared. This solubilization and precipitation procedure was typically repeated two or three times. The average deviation of measured phase transition pressures from one phase to two phases was approximately ±3%. The solubility of the chemical was calculated from the masses of the chemical and carbon dioxide. More information about the procedure and technical details were published previously.[18]

Results and Discussion

The results are in Table 1. The solubility of benzoic acid was first measured and the results were compared with the results published by other authors.[19] The measured solubilities of benzoic acid at 35 °C agreed within approximately 6% with those of previous measurements. Benzoic acid is only sparingly soluble in carbon dioxide due to the presence of the acid group. The solubility was always below 1 wt % in the selected conditions.

Fluorination did increase the solubility of benzoic acid in carbon dioxide. Attaching one fluorine atom increased the solubility only slightly. The solubility of 3-fluorobenzoic acid was approximately 1.8 wt % at 35 °C and 290 bar. The solubility of 3,4-difluorobenzoic acid is 1.3 wt % at 35 °C and 103 bar, whereas the solubility of benzoic acid is approximately 0.2 wt % at the similar conditions. The trifluoromethyl group showed a particularly significant effect on the solubility. The solubility of 3-(trifluoromethyl)benzoic acid in carbon dioxide at 35 °C and 100 bar is approximately 7 wt %, which is almost 40 times higher than the solubility

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Table 1. **Solubilities of benzoic acid and fluorinated benzoic acid derivatives in dense carbon dioxide at 35 and 55 °C**

			$T = 35$ °C			$T = 55$ °C		
name	mol wt (g/mol)	mp (°C)	p (bar)	ρ_S (g/mL)	solub. (wt %)	p (bar)	ρ_S (g/mL)	solub. (wt %)
benzoic acid	122.1	122	81	0.50	0.29	114	0.45	0.29
			142	0.81	0.57	138	0.61	0.42
			156	0.82	0.62	150	0.65	0.81
			180	0.85	0.81	177	0.72	0.90
			325	0.94	0.90			
3-fluorobenzoic acid	140.1	123	79	0.37	0.95	122	0.52	0.95
			155	0.82	1.13	153	0.66	1.33
			230	0.89	1.33	156	0.67	1.44
			290	0.93	1.84	173	0.71	1.64
						184	0.73	1.84
3,4-difluorobenzoic acid	158.1	123	82	0.55	0.18	104	0.36	0.18
			87	0.64	0.53	111	0.43	0.53
			100	0.71	1.05	120	0.51	0.84
			103	0.72	1.27	123	0.53	1.04
						138	0.61	1.27
3-(trifluoromethyl)benzoic acid	190.1	105	78	0.34	0.90	111	0.43	0.90
			80	0.43	1.86	124	0.54	4.98
			93	0.68	4.98	132	0.58	8.66
			110	0.75	8.66	141	0.62	9.52
			116	0.76	9.52	144	0.64	15.10
			125	0.78	15.10	145	0.64	17.57

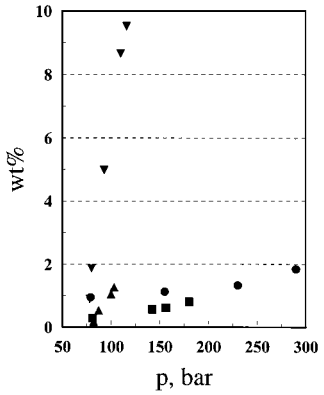

Figure 1. **Solubilities of benzoic acid and fluorinated benzoic acid derivatives in dense carbon dioxide at 35 °C. (■) Benzoic acid; (●) 3-fluorobenzoic acid; (▲) 3,4-difluorobenzoic acid; (▼) 3-(trifluoromethyl)benzoic acid.**

of benzoic acid in same conditions. The solubilities of benzoic acid and fluorinated benzoic acid derivatives in dense carbon dioxide at 35 °C are seen in Figure 1. It should be noticed that the melting point of 3-(trifluoromethyl)benzoic acid is significantly less than the melting points of benzoic acid and the other two fluorinated benzoic acids. It is well-known that vapor pressure correlates with solid solubility in dense carbon dioxide.[1] Although differencies in vapor pressure may be one reason for the differences observed for the solubility behavior, it seems not justified to correlate melting points and vapor pressures directly.

The system temperature usually has a significant effect on the solid solubility in dense gases, because it influences the solid vapor pressure, solvent density and solute−solvent interactions. If the vapor pressure of a compound increases steeply with temperature, the solubility of a compound increases despite of the decrease of the solvent density at constant pressure. On the other hand, if the vapor pressure of a compound does not increase significantly with temperature a decrease of solubility results from increasing the temperature due to the decreased solvent density. Typically, a pressure increase is necessary to maintain constant solubility if temperature is increased. The isotherms can also cross each other as is seen in the case of 3-fluorobenzoic acid at 35 and 55 °C due to the combined effect of temperature on solute vapor pressure and solvent density.

Table 2. **Solubilities of selected pharmaceuticals in dense carbon dioxide**

name	mol wt (g/mol)	mp (°C)	T (°C)	p (bar)	ρ_S (g/mL)	solub. (wt %)
trifluprom azine free base	352.4	liquid	43	145	0.75	4.40
			55	228	0.79	4.40
			83	282	0.71	3.65
flufenamic acid	281.2	125	74	255	0.72	0.96
			84	261	0.68	3.05

Solubilities of two pharmaceutical compounds, trifluromazine and flufenamic acid, were also measured (see Table 2). The solubility of trifluprom azine was relatively high, that is, 4.4 wt % at 43 °C and 145 bar. Even though the molecular weight of flufenamic acid was less than the molecular weight of trifluprom azine, flufenamic acid was much less soluble, and the solubility of 3 wt % was obtained at 84 °C and 260 bar. Flufenamic acid was very sparingly soluble at ambient temperatures (<50 °C), and 70−80 °C was necessary to reach 1−3 wt % solubility.

Conclusions

The solubilities of benzoic acid and fluorinated benzoic acid derivatives in dense carbon dioxide were measured at 35 and 55 °C to find out how much fluorination enhances the solubility of organic compounds in dense carbon dioxide. Further, the solubilities of two other pharmaceuticals, tri-

flubromazine and flufenamic acid, in dense carbon dioxide were measured.

Fluorination clearly enhanced the solubility of benzoic acid in carbon dioxide. Particularly effective was trifluoromethyl group. The solubility of 3-(trifluoromethyl)benzoic acid in carbon dioxide at 35 °C and 100 bar was approximately 7 wt %, which is almost 40 times higher than the solubility of benzoic acid at the similar conditions. The solubility of 3,4-difluorobenzoic acid exhibited approximately 6-fold solubility enhancement compared with benzoic acid. The effect of one fluorine atom was more moderate, and only 2-fold increacement was noticed.

The solubility of triflupromazine was relatively high, that is, 4.4 wt % at 43 °C and 145 bar. Flufenamic acid was very sparingly soluble at ambient temperatures (<50 °C), and 70−80 °C was necessary to reach 1−3 wt % solubility. Even though the molecular weight of flufenamic acid was less than the molecular weight of triflupromazine, triflupromazine was much more soluble in dense carbon dioxide than flufenamic acid, which is probably due to the fact that triflubromazine is viscous oil and flufenamic acid is a solid compound.

These experiments show that dense carbon dioxide is an attractive solvent for processing fluorinated pharmaceuticals without conventional solvents. Dense carbon dioxide can be used as a solvent in synthesis, purification via different separation techniques such as chromatography, or particle production of pharmaceuticals.

Symbols

mol wt = molecular weight, g mol^{-1}

mp = melting point, °C

p = pressure, bar

T = temperature, °C

ρ_S = solvent density, g mL^{-1}

Subscript

c = critical value

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