

Solid Molar Volumes of Interest to Supercritical Extraction at 298 K: Atropine, Berberine Hydrochloride Hydrate, Brucine Dihydrate, Capsaicin, Ergotamine Tartrate Dihydrate, Naphthalene, Penicillin V, Piperine, Quinine, Strychnine, Theobromine, Theophylline, and Yohimbine Hydrochloride

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Solid molar volumes of interest to supercritical extraction were measured for a number of alkaloids, spices, and other substances at 298 K with a gas buoyancy technique. The values obtained were 240.2 cm³/mol, atropine; 288.1 cm³/mol, berberine hydrochloride hydrate; 320.2 cm³/mol, brucine dihydrate; 289.8 cm³/mol, capsaicin; 893.0 cm³/mol, ergotamine tartrate dihydrate; 109.9 cm³/mol, naphthalene; 243.2 cm³/mol, penicillin V; 226.4 cm³/mol, piperine; 253.0 cm³/mol, quinine; 242.0 cm³/mol, strychnine; 120.5 cm³/mol, theobromine; 123.7 cm³/mol, theophylline; and 296.8 cm³/mol, yohimbine hydrochloride. The group contribution method of Fedors was used to predict the solid molar volume data. It was found that Fedors' method generally underestimated the solid molar volumes but could predict the data to within ±11%.

Introduction

Supercritical fluid extraction has been applied to a number of systems including spices and alkaloids (1-3). Recently, supercritical fluid technology has been applied to extract pharmaceuticals such as penicillin V with supercritical carbon dioxide (4). Numerous other applications are given in ref 5.

In these extraction studies, physical properties of substances such as piperine, capsaicin, or penicillin V are unavailable and must be estimated. The purpose of our work was to measure solid molar volumes of a number of spices and alkaloids important to supercritical extraction processes and also to provide data for other complex alkaloids that would allow improvement of current estimation methods for the solid molar volumes.

Thermodynamics. The thermodynamics of supercritical extraction has been reviewed by Brennecke and Eckert (6). Briefly, the solubility of a solid in a supercritical fluid is given by

$$y_2 = \frac{P_2^{\text{sat}} \varphi_2^{\text{sat}} \exp \left[\frac{v_2^{\text{s}} (P - P_2^{\text{sat}})}{RT} \right]}{\varphi_2 P} \quad (1)$$

where P_2^{sat} , φ_2^{sat} , y_2 , and φ_2 are the solid vapor pressure, fugacity coefficient, vapor-phase mole fraction, and vapor-phase fugacity coefficient of the solute in the supercritical fluid. The exponential term is the Poynting correction, which contains the solid molar volume, v_2^{s} .

The Poynting correction is generally small, but can approach values as high as 1.0×10^6 at 40 MPa and 310 K for solid molar volumes reported in this work. Accurate values of the solid molar volume are important for modeling of supercritical extraction. For example, at 40 MPa and 310 K, an 11% error in the solid molar volume of naphthalene would correspond to a 21% error in the enhancement factor. This may affect the results of some modeling studies such as those reported by Haselow (7), because the thermodynamic models must compensate for errors in the Poynting correction.

Experimental Section

Materials. The purities and sources of the materials are given in Table I. All substances were used as supplied but

were handled in an argon atmosphere to minimize or avoid any contact with air or moisture. The purity of the capsaicin was low. As shown below, this had a negligible effect on the molar volume since the primary impurity was dihydrocapsaicin.

Method. The solid molar volumes reported in this work were measured with a stereopycnometer (Quantachrome Corp. Model SPY-3, Syosset, NY), which operates on the principle of gas buoyancy. Other techniques for measurement are given by Chern et al. (8). The temperature was measured with an NIST traceable mercury thermometer accurate to ±0.1 K. The temperature did not vary more than 0.1 K for any experimental run. Measurements were made at 298 K.

Procedure. Argon gas, purity 99.99 mol %, was used for the gas displacement. A sample, 0.7-4.3 g, weighed to within 0.5-mg accuracy, was introduced into the sample cell volume V_{cell} (approximately 34 cm³) and purged with argon gas. The sample cell volume was isolated from a reference volume V_{ref} (approximately 87 cm³) and then pressurized to P_i (typically 31 psia) and equilibrated until the pressure was constant. The reference volume was then added by turning a four-way valve, and the new pressure P_f (typically 19 psia) was measured. The system was equilibrated until the pressure was constant.

Assuming that the gas used in the displacement is ideal and that negligible adsorption occurs, it can be shown that

$$V_{\text{samp}} = V_{\text{cell}} + V_{\text{ref}} / (1 - P_i / P_f) \quad (2)$$

As described below, the volume of a sample can be determined by measuring the pressure ratio in eq 2.

Because most of the samples measured require special handling, a modification to the procedure described above was used for introducing the sample into the instrument. Empty glass tubes were used as sample holders. These tubes were cleaned, and then the volumes of the tubes were measured to determine a volume correction for that holder. Then, substances were weighed in an argon glovebag and capped until measurement. This procedure ensured that the instrument cell and the samples did not become contaminated, as well as limiting sample contact with air.

Table I. Sources and Purities of Materials

substance	purity (%)	method	source
atropine (1)	99+	TLC	Sigma Chemical Co.
berberine hydrochloride hydrate (2)	90+	TLC	Sigma Chemical Co.
brucine dihydrate (3)	96.7	assay	Aldrich Chemical Co.
capsaicin (4) (impurity, 33.4% dihydrocapsaicin)	66.6	HPLC	Aldrich Chemical Co.
ergotamine tartrate dihydrate (5)	98+	TLC	Sigma Chemical Co.
naphthalene (6)	99.9	GC	Sigma Chemical Co.
penicillin V (7)	99+	TLC	Sigma Chemical Co.
piperine (8)	97	TLC	Aldrich Chemical Co.
quinine (9) (impurity, 8.6% hydroquinone)	91.4	HPLC	Aldrich Chemical Co.
strychnine (10)	94	HPLC	Aldrich Chemical Co.
theobromine (11)	99	elemental TLC	Sigma Chemical Co.
theophylline (12)	99+	HPLC	Sigma Chemical Co.
yohimbine hydrochloride (13)	99+	TLC	Sigma Chemical Co.

Table II. Molar Volumes V_m° of Naphthalene at 298 K

source	V_m° (cm ³ /mol)
Ueberreiter and Orthmann (9)	106.8
King (10)	107.4
this work	109.9
<i>Lange's Handbook of Chemistry</i> (11)	110.2
<i>Perry's Chemical Engineer's Handbook</i> (12)	111.8
Vaidya and Kennedy (13)	112.0
<i>CRC Handbook of Chemistry and Physics</i> (14)	125.5

Calibration. Instead of using eq 2 directly, we chose to calibrate the apparatus with high-precision chrome-plated ball bearings of various sizes of measured diameter and mass. The diameter was guaranteed to $\pm 2.54 \mu\text{m}$. The absolute accuracy of the volume was on the order of $\pm 0.1\%$ of a nominal 1.58-cm ball bearing. Multiple ball bearings were used to develop an instrument calibration curve of volume versus $1/(1 - P_i/P_f)$. The standard deviation of the calibration curve was 0.012 cm³ over the volume range of 0–4 cm³.

Results and Discussion

Test Substance. We chose naphthalene as a test substance because of its importance in modeling supercritical extraction systems and because we thought that its molar volume was well known. However, literature values ranged from 106.8 to 125.5 cm³/mol as shown in Table II. The value of the molar volume from X-ray diffraction data is 112.0 cm³/mol (13). With the above-described experimental procedure, we obtained an average molar volume of 109.9 cm³/mol with a standard deviation of 0.56 cm³/mol. Molar volumes determined from buoyancy techniques should be slightly smaller than values determined by X-ray diffraction since a perfect crystal occupies less volume than an imperfect crystal.

Other Substances. The average molar volumes of other substances measured are tabulated in Table III, along with the number of measurements and their standard deviations. For finer powders, we noticed an increase in the standard deviation of the measurements. Brucine dihydrate and yohimbine hydrochloride had higher variances than the test substance and required a larger number of measurements in order to lower the standard deviation. The higher standard deviation of these substances may be in part due to adsorption effects and to some extent handling of the materials. Ergotamine tartrate dihydrate and berberine also had higher variances than the test substance. This may be partly due to some dehydration experienced by the samples in argon. Piperine, theobromine, and theophylline had lower standard deviations than naphthalene. Capsaicin was the lowest purity material measured. However, the primary impurity (HPLC) of capsaicin was dihydrocapsaicin, which has a difference in molar volume of only 5.2 cm³/mol, according to the group contribution discussed below.

Prediction with the Group Contribution Method. Table IV gives a comparison between the data from the group

Table III. Average Densities ρ and Molar Volumes V_m at 298 K

substance	no. of samples ^a	ρ (g/cm ³)	V_m (cm ³ /mol)	σ (cm ³ /mol)
atropine	6 (4)	1.205	240.2	2.4
berberine hydrochloride hydrate	6 (2)	1.511	288.1	9.4
brucine dihydrate	6 (4)	1.345	320.2	7.6
capsaicin	9 (4)	1.059	289.8 ^b	3.9
ergotamine tartrate dihydrate	2 (4)	1.511	893.0	13
naphthalene	3 (2)	1.164	109.9	0.56
penicillin V	7 (2)	1.441	243.2	3.1
piperine	3 (2)	1.261	226.4	1.6
quinine	6 (4)	1.283	253.0 ^c	2.1
strychnine	5 (5)	1.382	242.0	1.7
theobromine	6 (4)	1.495	120.5	0.21
theophylline	6 (4)	1.457	123.7	0.36
yohimbine hydrochloride	8 (4)	1.317	296.8	9.8

^a Refers to the number of separate samples measured. Values in parentheses are replicate measurements performed on the same sample. ^b Average molecular weight of 306.83 g/mol based on purity in Table I. ^c Average molecular weight of 324.61 g/mol based on purity in Table I.

Table IV. Comparison between Experimental V_m and Calculated $V_m(\text{calcd})$ Molar Volumes

substance	V_m (cm ³ /mol)	$V_m(\text{calcd})$ (cm ³ /mol)	$100\{V_m - V_m(\text{calcd})\}/V_m$
atropine	240.2	213.0	-11.3
berberine hydrochloride hydrate	288.1	302.4	+5.0
brucine dihydrate	320.2	298.0 ^a	-6.9
capsaicin	289.8	271.2	-6.4
ergotamine tartrate dihydrate	893.0	831.2	-6.9
naphthalene	109.9	118.0	+7.4
penicillin V	243.2	217.2	-10.7
piperine	226.4	225.4	-0.4
quinine	253.0	246.2	-2.7
strychnine	242.0	225.4	-6.8
theobromine	120.5	110.2	-8.5
theophylline	123.7	110.2	-10.9
yohimbine hydrochloride	296.8	280.6	-5.5

^a Valence 3 nitrogen element used.

contribution method of Fedors (15) and our experimental data. The group contribution method generally underestimates the solid molar volumes but predicts the data to within $\pm 11\%$. The method predicts the data surprisingly well in the case of piperine.

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Registry Numbers Supplied by the Author. (1) *endo*-(\pm)- α -(hydroxymethyl)benzeneacetic acid 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, 51-55-8; (2) 5,6-dihydro-9,10-

dimethoxybenzo[*g*]-1,3-benzodioxolo[5,6-*a*]quinolizinium hydrochloride hydrate, 2086-83-1; (3) 2,3-dimethoxystrychnidin-10-one dihydrate, 357-57-3; (4) (*E*)-*N*-[(4-hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenamide, 404-86-4; (5) 12'-hydroxy-2'-methyl-5' α -(phenylmethyl)ergotaman-3',6',18-trione tartrate dihydrate, 379-79-3; (6), 91-20-3; (7) 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 87-08-1; (8) 1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl]piperidine, 94-62-2; (9) 6'-methoxycinchocan-9-ol, 130-95-0; (10) strychnidin-10-one, 57-24-9; (11) 3,7-dihydro-3,7-dimethyl-1*H*-purine-2,6-dione, 83-67-0; (12) 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione, 58-55-9; (13) (16 α ,17 α)-17-hydroxyyohimban-16-carboxylic acid methyl ester hydrochloride, 146-48-5.

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