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Solubility of the Natural Antioxidant Gallic Acid in Supercritical CO_2 + Ethanol as a Cosolvent

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Solubility data of solid 3,4,5-trihydroxybenzoic acid (gallic acid) in supercritical CO_2 + ethanol as a cosolvent are reported in this work. Measurements were carried out in the temperature range (313.15 to 333.15) K, pressures ranging from (10 to 40) MPa, and different ethanol modifier content ranging from (0.7 to 6) %. The experimental data were correlated using the Soave−Redlich−Kwong equation of state and the group contribution associating equation of state. The thermodynamic modeling analysis includes also the solubility representation of an important class of natural antioxidants (e.g., gallic acid esters) in supercritical CO_2.

Introduction

Plant foods and products are rich sources of a variety of biologically active compounds, and these phytochemicals have been found to possess hypolipidemic, antiplatelet, antitumor, antioxidant, and immune-stimulating properties.[1] In recent years, particular attention has been given to a specific class of antioxidant phytochemicals, the polyphenols, which are comprised basically of phenolic acids, including benzoate and hydroxycinnamate derivates, and flavonoids.

3,4,5-Trihydroxybenzoic acid (gallic acid) and its derivatives are polyphenyl natural products, which are found to be particularly abundant in processed beverages such as red wines and green teas.[2,3] They have radical scavenging, anti-oxidative,[4−7] anti-inflammatory,[8,9] anti-fungal,[10] anti-cancer,[11] and chemoprotective[12] properties, which are of great importance for the food, pharmaceutical, and drug industries. This explains the interest and motivation to isolate these compounds from natural vegetable matrices, applying an environmentally safe and efficient "green" process—such as supercritical fluid extraction (SFE)—as a viable alternative to the wet extraction.

The design of SFE processes requires knowledge of the solute solubility in the supercritical phase and the ability to efficiently model and predict it. Gallic acid has been extracted using CO_2 + cosolvent (methanol) from grape seeds[13−15] and from a spiked solid.[16] Recently, Murga et al.[17] reported the solubility of gallic acid methyl ester (methyl gallate) in pure supercritical carbon dioxide ($SCCO_2$). Solubility data for *n*-propyl 3,4,5-trihydroxybenzoate (propyl gallate) and dodecyl-3,4,5-trihydroxybenzoate (lauryl gallate; dodecyl gallate) in $SCCO_2$ were obtained by Cortesi et al.,[18] but no data on gallic acid were reported since for the latter the solubility in pure $SCCO_2$ was very low (less than 10^{-6} in molar fraction) and was close to the experimental error.[18]

The present paper provides for the first time experimental data on the solubility of solid gallic acid in $SCCO_2$ + ethanol as a cosolvent. Ethanol was used as a modifier in order to increase gallic acid solubility in the supercritical phase and was chosen because it is a polar solvent, its use is allowed in the food industry, and it can be easily removed from the extract by evaporation at relatively low temperature.

Two different thermodynamic models were applied to calculate the solubility data for gallic acid—the Soave−Redlich−Kwong equation of state (SRK-EoS) and a modification of the group contribution associating equation of state (GCA-EoS) presented recently.[19] The capabilities of the latter model were tested also by correlating the solubility of three gallic esters in $SCCO_2$—methyl 2,4,6-trihydroxybenzoate (methyl gallate), propyl and dodecyl gallate, respectively. In addition, the paper presents estimated values for the thermophysical properties and sublimation pressures of gallic acid and the three gallic acid esters. The values obtained are compared with those reported in the literature by other authors and calculated by different methods.

Experimental Section

Chemicals. Gallic acid (≥ 98 mass %, HPLC grade) was purchased from Aldrich Chemical Co. Inc. Absolute ethanol (99.8 mass %, GC grade), supplied by Prolabo S.A., was used as a modifier and solvent to collect the extract. The reagents were used without further purification since chromatography did not show any significant impurities. High-purity CO_2 (more than 99.9 vol % purity, SFC grade) supplied by AIR LIQUIDE was used as received. Silica (more than 99.8 mass %) extra pure (from Sigma Chemical Co. Inc.) was utilized as a support of the products.

Equipment and Procedure. The solubilities were measured with an SFX 3560 extractor with two syringe pumps (model 260D) manufactured by ISCO (Lincoln, NE). With the proper plumbing, a two-pump system can deliver modified supercritical fluid or a continuous flow of supercritical fluid. The cylinder capacity of the pump is 266 mL, and the maximum pressure is 51 MPa. The temperature can range from (313.2 to 423.2) K, and supercritical fluid flow rate can range from (0.5 to 5) mL·min^{-1}. A further detailed description of the equipment can be found in a previous work[20] and will not be given here.

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Table 1. Solubility y for Gallic Acid (1) in (CO_2 + Ethanol) from T = (313.15 to 333.15) K

	$y_1 \cdot 10^7$				
	T/K = 313.15			T/K = 323.15	T/K = 333.15
p	% ethanol			% ethanol	% ethanol
MPa	0.7	2.0	6.0	6.0	6.0
10	2.36	2.69	4.22	1.85	1.06
20	3.53	4.19	5.59	3.47	1.98
30	4.55	5.61	9.27	6.02	3.54
40	5.85	7.34	19.72	9.19	6.14

The extractor measured the amount of $SCCO_2$ and ethanol modifier used during the extraction. The flow rate of the supercritical fluid used for all experiments was 0.5 $mL \cdot min^{-1}$, which ensured that saturation of the supercritical phase was achieved in a reasonable time. Ethanol was used to trap the gallic acid extracted. After that, the extract was transferred to 10 mL calibrated flasks and diluted with ethanol. In some cases, a higher dilution might be necessary to achieve a concentration level adequate for determination by UV spectrometry.

For sample preparation, first 0.00250 g of gallic acid was dissolved in 25 mL of ethanol. Second, 1 mL of this solution was added to diatomaceous earth (0.5 g), weighed beforehand in the sample cartridge. Finally, the spiked solid was allowed to heat up to 60 °C for at least 2 h in order to evaporate ethanol and precipitate gallic acid over the surface of solid particles. This procedure is necessary in order to avoid preferential ways during extraction and the formation of masses of particles.

The gravimetric measurements were performed on an analytical balance with 0.00001 g resolution, and the expanded uncertainty was $\pm 4.2 \cdot 10^{-5}$ g with coverage factor 2. The uncertainties of the temperature and pressure measurements were ± 0.1 K and ± 0.25 MPa, respectively. The uncertainty associated with volume measurements was ± 0.1 mL. A 8453 Hewlett-Packard diode array UV–vis spectrophotometer was used to determine the amount of gallic acid in the extract, after calibration with gravimetrically prepared standard solutions.

Solubility is obtained as the value of the slope of the linear representation of the amount of gallic acid extracted versus the amount of solvent used (carbon dioxide + ethanol), on a molar basis, at different extraction times (five values at least). The uncertainty associated with gallic acid solubility, expressed in absolute deviation of the mole fractions reported, varied within the following range $1.3 \cdot 10^{-7}$ for the highest to $2.6 \cdot 10^{-8}$ for the lowest measured solubility.

Experimental Results. The solubility of gallic acid in the supercritical phase was measured at T = (313.15, 323.15, and 333.15) K and pressures ranging from (10 to 40) MPa. Different CO_2 + ethanol mixtures—with ethanol content ranging from (0.7 to 6) %—were used in order to explore the influence of the amount of cosolvent added on gallic acid solubility. The experimental results are given in Table 1. According to the experiments, the solubility of gallic acid increases with pressure and with ethanol content. Also, in the range of pressures explored, solubilities are higher at lower temperatures; the solvating power of CO_2 becomes greater and more solute is transferred to the supercritical phase.

Thermodynamic Modeling

Thermodynamic Framework. For solid–gas phase equilibria, the general equilibrium relation is

$$f_s^{\text{solid}} = f_s^{G} \tag{1}$$

where the subscript s stands for the solid solute, f_s^G is the fugacity of component s in the gas (supercritical fluid phase), and f_s^{solid} is that in the solid phase. The fugacity of the solute in the supercritical phase is

$$f_s^G = y_s P \varphi_s^G \tag{2}$$

where P is the pressure, φ_s^G is the fugacity coefficient, and y_s is the solubility (mole fraction) of the solute in the supercritical fluid. For phase equilibrium between a high-boiling compound and a supercritical fluid, the following three assumptions can be introduced:[21] (1) the solid solute remains pure since the size and the shape of solute and solvent molecules are ordinarily sufficiently different and hence solid solutions do not form; (2) the molar volume of the solid solute can be treated as a constant with respect to pressure; and (3) the saturated vapor of the pure solid solute at sublimation behaves as an ideal gas.

Since the solid phase is pure (assumption 1), the fugacity of the solute in the solid state is equal to the pure solid fugacity; hence, the following holds:

$$f_s^{\text{solid}} = P_s^{\text{sub}} \varphi_s^{\text{sub}} \exp \int_{P_s^{\text{sub}}}^{P} \frac{v_s^{\text{solid}}\, dP}{RT} \tag{3}$$

where P_s^{sub} is the sublimation (vapor) pressure of the pure solid, φ_s^{sub} is the fugacity coefficient at sublimation pressure, and v_s^{solid} is the molar volume of the solid, all at temperature T.

Then, applying assumption 2 and the thermodynamic equilibrium condition (eq 1), the mole fraction of the solid component in the supercritical phase can be expressed as

$$y_s = \frac{P_s^{\text{sub}}}{P} E \tag{4}$$

where

$$E \equiv \frac{\varphi_s^{\text{sub}} \exp \int_{P_s^{\text{sub}}}^{P} \frac{v_s^{\text{solid}}\, dP}{RT}}{\varphi_s^G} = \frac{\varphi_s^{\text{sub}} \exp\left[\frac{v_s^{\text{solid}}(P - P_s^{\text{sub}})}{RT}\right]}{\varphi_s^G} \tag{5}$$

In most practical cases, the P_s^{sub} value is quite small; thus, φ_s^{sub} is nearly equal to unity. The Poynting correction (exponential term in eq 5) is not negligible, but it generally accounts for an enhancement factor less than 2 or 3. However, the solute fugacity coefficient in the supercritical phase (φ_s^G) is significantly different from unity and can produce very large enhancement factors.

According to eqs 4 and 5, information about the sublimation pressure and solid molar volume of the solid solute is required in order to calculate its solubility in $SCCO_2$. Furthermore, a reliable thermodynamic model is necessary to calculate φ_s^G which, in turn, requires information about pure solute physical properties such as critical temperature, critical pressure, acentric factor, etc.

Pure Solute Physical Properties. For gallic acid and its esters, as for a great majority of solid solutes extracted from vegetable material, there is a very limited amount of thermophysical properties data because they are usually not experimentally accessible. Thus, to the best of our knowledge, the only experimental data available for gallic acid are its melting temperature (524 to 528) K with decomposition (www.sigmaaldrich.com) and a sublimation enthalpy value of $\Delta H^{\text{sub}}/(J \cdot mol^{-1}) = 75100$ in the (391 to 421) K temperature range, cited by www.nist.gov from an old reference.[22] Analogous is the

Table 2. Gallic Acid and Gallic Acid Esters Pure Component Parameters: Comparison between the Values Estimated in This Work and Those Reported in the Literature

	gallic acid	methyl gallate	propyl gallate	dodecyl gallate
T_c/K	742.9^{a}	748.8^{a}	787.4^{a}	882.9^{a}
	881.3^{b}	956.6^{c}	862.9^{b}	905.9^{b}
p_c/MPa	3.89^{a}	3.38^{a}	2.89^{a}	1.42^{a}
	8.88^{b}	6.21 ^{c}	4.77^{b}	1.85^{b}
$\upsilon_s^{\text{solid}}$/(cm^3·mol^{-1})	199.0^{a}	223.6 ^{a}	231.8^{a}	342.3^{a}
P_s^{sat}/MPa at $T = 313.15$ K	$1.1\cdot10^{-4\ a}$	$6.8\cdot10^{-3\ a}$	$1.8\cdot10^{-3\ a}$	$2.9\cdot10^{-6\ a}$
	$2.0\cdot10^{-4\ b}$		$2.5\cdot10^{-3\ b}$	$2.0\cdot10^{-6\ b}$
T_c/p_c	19.08^{a}	22.19^{a}	27.23^{a}	62.05^{a}
	18.91^{d}	21.11^{d}	26.49^{d}	61.89^{d}
	9.93^{b}	15.4^{c}	18.08^{b}	49.07^{b}

[a] This work. [b] Ref 18. [c] Ref 17. [d] Equation 6.

situation with the three esters—methyl, propyl, and dodecyl gallate—for which also only the melting temperatures are known, namely, (474.15 to 477.15) K, (419.15 to 422.15) K, and (367.15 to 370.15) K, respectively.

Thus, the rest of the properties required had to be estimated. To do that, the algorithm discussed in detail in Fornari et al.[19] was followed; hence, herewith only a concise summary of the relevant steps is given:

(i) The sublimation pressures were calculated from the Clapeyron equation, using the data for the melting properties of gallic acid and its esters, estimated in the present study.

(ii) The solid volumes were estimated applying the method proposed by Goodman et al.[23]

(iii) The critical parameters were estimated applying the method of Cholakov et al.[24] and Wakeham et al.[25]

The values obtained are shown in Table 2 and are compared with the values reported in refs 17 and 18. Murga et al.[17] used Joback's method implemented in PE[26] to calculate critical parameters, while Cortesi et al.[18] employed the method of Constantinou and Gani.[27]

There is considerable disagreement between the critical parameters values of the compounds, as can be observed from Table 2. This discrepancy required further analysis. A generalized semi-theoretical expression for the T_c/p_c ratio of a compound with its van der Waals surface area[28−30] was employed to check the accuracy of the values obtained in this study and those given in the literature.[17,18]

The correlation is of the form:

$$T_c/p_c = 9.0673 + 0.43309(Q_w^{\ 1.3} + Q_w^{\ 1.95}) \tag{6}$$

where T_c is in Kelvin and p_c is in bar. The dimensionless parameter Q_w is a measure of the van der Waals molecular surface area and is calculated as the sum of the group area parameters, Q_k:

$$Q_w = \sum_k \nu_k Q_k \tag{6a}$$

where ν_k is the number of times group k appears in the molecule. The group area parameters Q_k are available in the UNIFAC tables, and were used herewith in eq 6. A comparison of the T_c/p_c ratios, calculated according to eq 6, with those calculated from the values reported by Murga et al.,[17] Cortesi et al.,[18] and the present work are given in Table 2. The critical parameters of the four compounds obtained in the present study give the best agreement with eq 6. On the other hand, the values of the sublimation pressures calculated in this work and those given in refs 17 and 18 are in a good agreement, although calculated by completely different methods.

Table 3. SRK-EoS Binary Interaction Parameters between Gallic Acid and CO$_2$ at Different Temperatures and % Ethanol Content in the Supercritical Gas Phase

	$k_{\text{s}-\text{CO2}}$	$l_{\text{s}-\text{CO2}}$	AASD %^{a}
$T = 313.15$ K, 6 % ethanol	0.3178	0.1365	2.31
$T = 323.15$ K, 6 % ethanol	0.3620	0.1570	2.19
$T = 333.15$ K, 6 % ethanol	0.3870	0.1710	2.25
$T = 313.15$ K, 2 % ethanol	0.2510	0.0560	5.73
$T = 313.15$ K, 0.7 % ethanol	0.2417	0.0237	5.24

[a] AASD % $= (100/N_{\text{exp}})\sum_{i=1}^{N_{\text{exp}}}|(y_i^{\text{exp}} - y_i^{\text{cal}})/y_i^{\text{exp}}|$.

Correlation of Gallic Acid Solubility Data Using the SRK-EoS. The SRK-EoS with the one-fluid van der Waals mixing rules was applied to correlate the solubility of gallic acid in SCCO$_2$ + ethanol as a modifier. The following combining rules for the cross-energy and cross-covolume parameters are used:

$$a_{ij} = (a_{ii}a_{jj})^{0.5}(1 - k_{ij}) \tag{7}$$

$$b_{ij} = \left(\frac{b_{ii} + b_{jj}}{2}\right)(1 - l_{ij}) \tag{8}$$

where k_{ij} and l_{ij} are, respectively, the energy and size binary interaction parameters.

Optimum values for the interaction parameters between gallic acid and CO$_2$ were determined at each temperature and ethanol concentration and are given in Table 3. The following standard objective function was minimized:

$$F = \sum_{i=1}^{N_{\text{exp}}} \left|\frac{y_s^{\text{exp}} - y_s^{\text{cal}}}{y_s^{\text{exp}}}\right|_i \tag{9}$$

where N_{exp} is the number of data points for a given temperature and the superscripts calc and exp mean the calculated and experimental results, respectively.

The value of k_{ij} for ethanol + CO$_2$ was accepted to be 0.09,[31] while the interaction parameter for ethanol + gallic acid was set equal to zero in all cases. This last assumption can be justified by the fact that both ethanol and gallic acid are present in very low concentrations in the supercritical phase.

The usual approach is to compute the solid solubility by locating a mole fraction that satisfies the isofugacity criterion (eq 1), which might lead to numerical pitfalls, as multiple solutions to the equifugacity condition could exist. The non-uniqueness is a particular problem, and special care should be taken to determine the correct solubility root. Thus, a stability analysis routine,[32] based on a modified tangent-plane function and a phase identification procedure,[33] was employed to determine all roots to the equifugacity condition.

The SRK-EoS demonstrated good capability to correlate the experimental solubility data of gallic acid in SCCO$_2$ + ethanol as a modifier. Figures 1 and 2 show a comparison between the experimental gallic acid solubility measured in this work and the SRK-EoS calculations. Figure 1 shows the variation of gallic acid solubility with pressure and ethanol content at 313.15 K. Figure 2 shows the solubility variation with pressure and temperature at a fixed value (6 %) of ethanol content. The absolute average standard deviation (AASD %) between the experimentally measured and calculated solubilities of gallic acid in SCCO$_2$ at different contents of the modifier ethanol is given in Table 3.

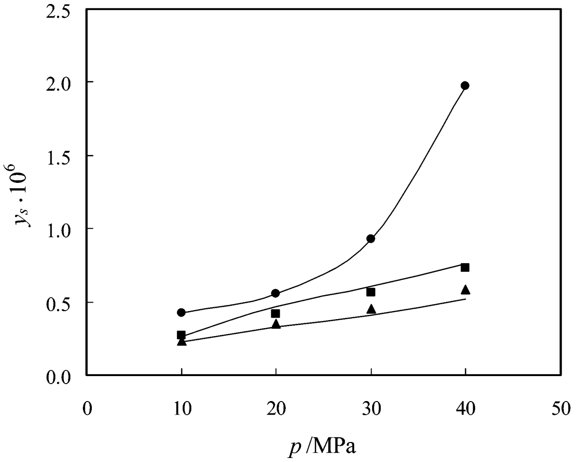

Figure 1. Gallic acid solubility y_s in $SCCO_2$ + ethanol as a cosolvent at T = 313.15 K: ▲, 0.7 % ethanol; ■, 2 % ethanol; ●, 6 % ethanol; —, SRK-EoS calculations.

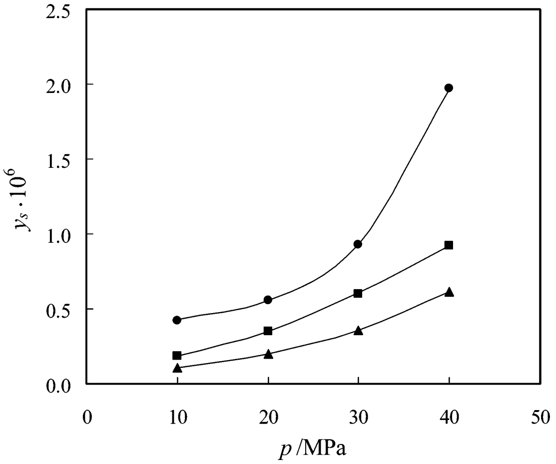

Figure 2. Gallic acid solubility y_s in $SCCO_2$ + 6 % ethanol: ●, T = 313.15 K; ■, T = 323.15 K; ▲, T = 333.15 K; —, SRK-EoS calculations.

Modeling Solid Gallic Acid and Gallic Acid Esters Solubility Using the GCA-EoS Model. The GCA-EoS is an upgraded version of the original group contribution EoS (GC-EoS) developed by Skjold-Jørgensen.[34] In the GCA-EoS model, the residual Helmholtz energy A^{res} is described by three terms, a free volume repulsive term, a contribution from dispersive attractive intermolecular forces, and a contribution to account for group association effects:

$$A^{\text{res}} = A^{\text{fv}} + A^{\text{att}} + A^{\text{assoc}} \tag{10}$$

where A^{fv} is modeled assuming hard-sphere behavior for the molecules (Carnahan−Starling type term) with a single molecular parameter d_i (the hard-sphere diameter). The dispersive attractive term is a group-contribution version of the NRTL model and has five pure-group parameters (T^*, q, g^*, g', and g'') and four binary interaction parameters (k_{ij}^*, k_{ij}', α_{ij}, and α_{ji}). The association term[35] is a group contribution approach based on Wertheim's theory and has two pure-group parameters characterizing, respectively, the energy and volume of the association bound. Cross association between groups is considered as proposed by Ferreira et al.[36] to extend the application of the model to systems containing both alcohol and acid groups.

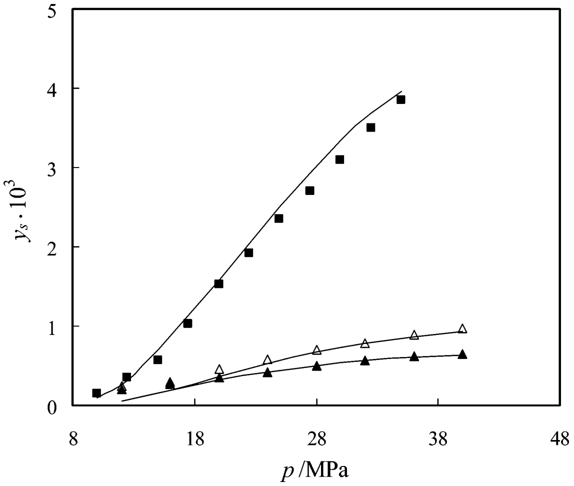

Figure 3. Solubility y_s of isomeric phenolic compounds in pure $SCCO_2$: ■, pyrocatechol at T = 348 K (ref 38); ▲, resorcinol at T = 328 K (ref 39); △, resorcinol at T = 338 K (ref 39); —, GCA-EoS calculations.

The extension of the GCA-EoS parameter table to include the phenol, aromatic acid and aromatic ether groups was recently presented by Espinosa et al.[37] The validity of the parameters reported is supported by the large set of vapor−liquid experimental data employed in the regression procedure: around 30 different binary mixtures and more than 1000 data points covering a wide range of temperature and pressure. Further details about the standard deviations obtained in the regression of the parameters are given in the corresponding ref 37.

In a previous contribution,[19] the authors applied the extended GCA-EoS parameter table[37] to represent solid phenolic compounds solubility in pure $SCCO_2$. They demonstrated that by using a density-dependent correlation to estimate the hard-sphere diameter d_i, instead of the temperature-dependent correlation given in the original model, the performance of the model can be significantly improved. The new semi-empirical correlation was developed using solubility data of 12 different solid phenolic compounds (around 300 data points). Additionally, in order to distinguish between isomer compounds, the authors reported different values for the dispersive binary interaction parameters between the phenol and CO_2 groups, depending on the number (one or two) and position (ortho- or meta-) of the phenol groups present in the compound chemical structure. This distinction is reasonable, taking into account that phenolic compounds with very similar chemical structure may display very different solubilities in supercritical CO_2. As an example, Figure 3 shows the solubility behavior of two phenolic compounds with identical group composition: 1,2-benzenediol (pyrocatechol) and 1,3-benzenediol (resorcinol). Thus, by introducing a differentiation between the *m*-ACOH and the *o*-ACOH groups present in resorcinol and pyrocatechol, respectively, a satisfactory correlation of the experimental data can be obtained with the GCA-EoS model.

Taking into consideration the examples depicted in Figure 3, and the chemical structure of gallic acid and gallic acid ester molecules, it is quite reasonable to assume that the parameters reported by Fornari et al.[19] are in this case inappropriate and cannot represent accurately the acid's and esters' solubility in $SCCO_2$ due to the proximity effects between the three adjacent (*3a*-ACOH) groups present in their molecules.

Consequently, the experimental solubility data of methyl,[17] propyl,[18] and dodecyl gallate[18] in pure $SCCO_2$ was used to obtain adequate binary interaction parameters between the *3a*-ACOH phenol group and CO_2. Equation 9 provides the standard objective function that was minimized. The AASD % obtained in the regression procedure, together with the experimental temperature and pressure ranges and the number of data points (N_{exp}) are given in Table 4. The parameters obtained are

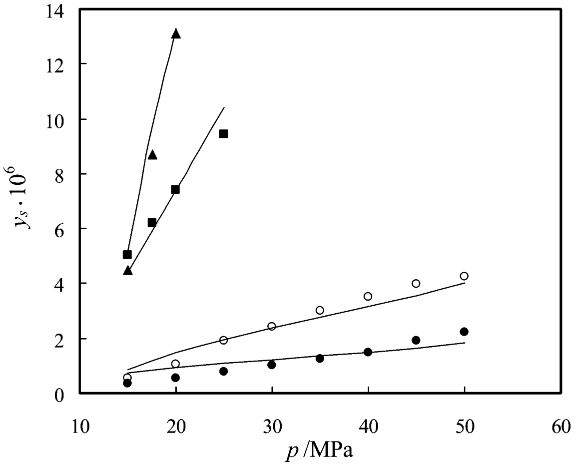

Figure 4. Solubility y_s of gallic acid esters in pure SCCO$_2$: methyl gallate - ●, at T = 313 K and ○, at T = 333 K (ref[17]); ■, propyl gallate at T = 313 K (ref[18]); ▲, dodecyl gallate at T = 333 K (ref[18]); ——, GCA-EoS calculations.

Table 4. Absolute Average Standard Deviation between Experimental[17,18] and Calculated Solubilities of Gallic Acid Esters in SC-CO$_2$ Applying the GCA-EoS Model

	T/K	p/MPa	N_{exp}	AASD %
methyl gallate	313 to 333	15 to 50	24	23.48
propyl gallate	313 to 333	15 to 25	8	12.25
dodecyl gallate	313 to 333	15 to 25	8	13.71

summarized in Table 5, including those reported previously[19] for phenolic compounds with either a single phenol group (ACOH), or two phenol groups in ortho- (*o*-ACOH) or meta- (*m*-ACOH) position in their chemical structures. The remaining pure-group energy parameters and binary group interaction parameters—for both dispersive and associative contributions—are those reported in the literature.[19,34] Figure 4 shows some of the results obtained with the GCA-EoS model in the correlation of gallic acid esters solubility in supercritical CO$_2$.

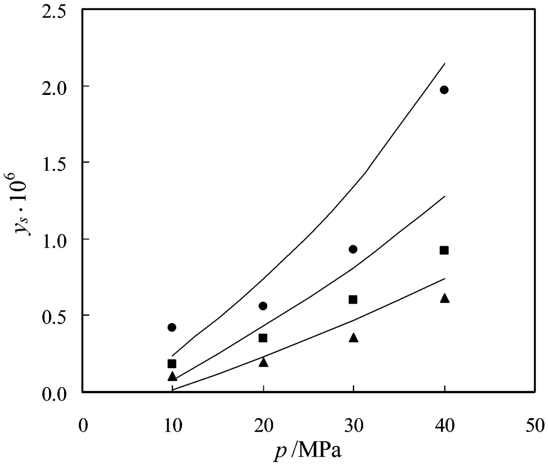

Figure 5. Gallic acid solubility y_s in SCCO$_2$ + ethanol as a cosolvent at T = 313.15 K: ▲, 0.7 % ethanol; ■, 2 % ethanol; ●, 6 % ethanol; —, GCA-EoS predictions.

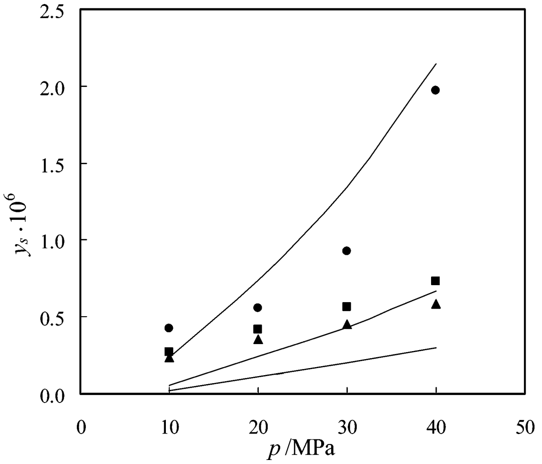

Figure 6. Gallic acid solubility y_s in SCCO$_2$ + 6 % ethanol: ●, T = 313.15 K; ■, T = 323.15 K; ▲, T = 333.15 K; —, GCA-EoS predictions.

The new interaction parameters between the *3a*-ACOH group and CO$_2$, obtained by fitting solubility data on gallic acid esters in pure SCCO$_2$, were then employed to predict the solubility of gallic acid in SCCO$_2$ + ethanol as a cosolvent. The parameters corresponding to the ethanol constituent groups were those reported by Gros et al.;[35] missing binary interaction parameters were considered to be ideal. The results obtained are represented in Figures 5 and 6. The GCA-EoS model can provide a quite satisfactory prediction of the gallic acid solubility variations with pressure, temperature, and ethanol content.

Conclusions

In the present study, the solubility of gallic acid in SCCO$_2$ + ethanol as a modifier is reported for the first time in the temperature range (313.15 to 333.15) K, pressures ranging from

Table 5. GCA-EoS Parameters for Different Phenol Groups

Pure Group Parameters

	ref temp	surface segments	pure group energy parameters[a]				
	T^*/K	q	g^*	g'	g''	AASD %[b]	ref
single ACOH, *o*-ACOH, and *m*-ACOH	600	0.680	970729.3	−0.5732	0.4296	18.04	19
3a-ACOH	600	0.680	256067.7	0.2286	0.2386	19.28	this work

Binary Interaction Parameters

		attractive energy parameters		nonrandomness parameters			
i	j	k_{ij}	k'_{ij}	α_{ij}	α_{ji}	AASD %[b]	ref
CO$_2$	ACOH	1.0253	0.1712	−0.2940	3.6272	18.92	19
	o-ACOH	1.1317	−0.3612	2.5053	2.5053	17.32	19
	m-ACOH	1.2869	−0.4692	−2.6117	−2.6117	12.38	19
	3a-ACOH	0.9037	−0.0822	21.9388	21.9388	19.28	this work

[a] The unit of the g^* parameter is in cm^6·atm·mol^{-1}·(surface area segment)$^{-2}$. [b] AASD % = $(100/N_{\mathrm{exp}})\sum_1^{N_{\mathrm{exp}}}\{\sum_{i=1}^{N_{\mathrm{co}}}|(y_i^{\mathrm{exp}} - y_i^{\mathrm{cal}})/y_i^{\mathrm{exp}}|\}$, where N_{exp} is the number of data points and N_{co} is the number of compounds. The indices exp and cal correspond to experimental and calculate results, respectively.

(10 to 40) MPa, and different ethanol modifier content ranging from (0.7 to 6) %. The experiments show that the solubility of gallic acid decreases with the increase of temperature and increases with pressure and ethanol content. Two different thermodynamic models were applied to represent the experimental solubility data. The SRK-EoS showed to be able to provide a high correlation of gallic acid solubility due to the optimization of binary interaction parameters between the solute and CO_2 for each temperature and ethanol content. The GCA-EoS model was applied as a predictive tool and demonstrated adequate capability to represent gallic acid and gallic acid esters solubility in supercritical fluids. Additionally, estimated values for gallic acid and three gallic esters pure component parameters are also given and compared with values estimated by other methods.

Literature Cited

(1) Craig, W. J. Health-promoting properties of common herbs. *Am. J. Clin. Nutr.* (*Suppl.*) **1999**, *70*, 491−499.
(2) Graham, H. N. Green tea composition, consumption, and polyphenol chemistry. *Prev. Med.* **1992**, *21*, 334−350.
(3) Lopez Vlez, M.; Martínez Martínez, F.; Del Valle-Ribes, C. The study of phenolic compounds as natural antioxidants on wine. *Crit. Rev. Food Sci. Nutr.* **2003**, *43*, 233−244.
(4) Sroka, Z.; Cisowski, W. Hydrogen peroxide scavenging antioxidant and anti-radical activity of some phenolic acids. *Food Chem. Toxicol.* **2003**, *41*, 753−758.
(5) Miyazawa, T. Absorption, metabolism and antioxidative effects of tea catechin in humans (review). *Biofactors* **2000**, *13*, 55−59.
(6) Yeh, C. T.; Yen, G. C. Effects of phenolic acids on human phenolsulfotransferases in relation to their antioxidant activity. *J. Agric. Food Chem.* **2003**, *51*, 1474−1479.
(7) Nagai, K.; Jiang, M. H.; Hada, T.; Nagata, T.; Yajima, Y.; Yamamoto, S.; Nishizaki, T. (−)-Epigallocatechin gallate protects against NO stress-induced neuronal damage after ischemia by acting as an antioxidant. *Brain Res.* **2002**, *956*, 319−322.
(8) Kroes, B. H.; van den Berg, A. J.; Quarles van Ufford, H. C.; van Dijk, H.; Labadie, R. P. Anti-inflammatory activity of gallic acid. *Planta Med.* **1992**, *58*, 499−504.
(9) Murase, T.; Kume, N.; Hase, T.; Shibuya, Y.; Nishizawa, Y.; Tokimitsu, I.; Kita, T. Gallates inhibit cytokine-induced nuclear translocation of NF-kappa B and expression of lenkocyte adhesion molecules in vascular endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1412−1420.
(10) Kubo, I.; Xiao, P.; Fujita, K. Antifugal activity of octyl gallate: structural criteria and mode action. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 347−350.
(11) Wang, Y. C.; Bachrach, U. The specific anti-cancer activity of green tea (−)-epigallocatechin-3-gallate (EGCC). *Amino Acids* **2002**, *22*, 131−141.
(12) Lambert, J. D.; Yang, C. S. Cancer chemoprotective activity and bioavailability of tea and tea polyphenols. *Mutat. Res*. **2003**, *523−524*, 201−208.
(13) Murga, R.; Ruiz, R.; Beltrán, S.; Cabezas, J. L. Extraction of natural complex phenols and tannins from grape seeds by using supercritical mixtures of carbon dioxide and alcohol. *J. Agric. Food Chem.* **2000**, *48*, 3408−3412.
(14) Palma, M.; Taylor, L. T.; Varela, R. M.; Cutler, S. J.; Cutler, H. G. Fractional extraction of compounds from grapes seeds by supercritical fluid extraction and analysis for antimicrobial and agrochemical activities. *J. Agric. Food Chem.* **1999**, *47*, 5044−5048.
(15) Palma, M.; Taylor, L. T. Extraction of polyphenolic compounds from grape seeds with near critical carbon dioxide. *J. Chromatogr. A* **1999**, *849*, 117−124.
(16) Tena, M. T.; Rios, A.; Valcarcel, M. Supercritical fluid extraction of t-resveratrol and other phenolics from a spiked solid. *Fresenius J. Anal. Chem.* **1998**, *36*, 143−148.
(17) Murga, R.; Sanz, M. T.; Beltrán, S.; Cabezas, J. L. Solubility of some phenolic compounds contained in grape seeds in supercritical carbon dioxide. *J. Supercrit. Fluids* **2002**, *23*, 113−121.
(18) Cortesi, A.; Kikic, I.; Alessi, P.; Turtoi, G.; Garnier, S. Effect of chemical structure on the solubility of antioxidants in supercritical carbon dioxide: experimental data and correlation. *J. Supercrit. Fluids* **1999**, *14*, 139−144.
(19) Fornari, T; Chafer, A.; Stateva, R. P.; Reglero, G. A new development in the application of the group contribution associating equation of state to model solid solubilities of phenolic compounds in SC-CO_2. *Ind. Eng. Chem. Res.* **2005**, *44*, 8147−8156.
(20) Berna, A.; Cháfer, A.; Montón, J. B. High pressure solubility data of system resveratrol (3) + ethanol (2) + CO_2 (1). *J. Supercrit. Fluids* **2001**, *19*, 133−139.
(21) Prausnitz, J. M., Lichtenthaler, R. N., Azevedo, E. G. *Molecular Thermodynamics of Fluid-Phase Equilibria*; Prentice Hall: Englewood Cliffs, NJ, 1999.
(22) Hirsbrunner, H. Über das Gleichgewicht der thermischen Dissoziation der Salicylsäure. *Helv. Chim. Acta* **1934**, *17*, 477−504.
(23) Goodman, B. T.; Wilding, W.; Oscarson, J. L.; Rowley, R. L. A note on the relationship between organic solid density and liquid density at the triple point. *J. Chem. Eng. Data* **2004**, *49*, 1512−1514.
(24) Cholakov, G. St.; Wakeham, W. A.; Stateva, R. P. Estimation of normal boiling points of hydrocarbons from descriptors of molecular structure. *Fluid Phase Equilib.* **1999**, *163*, 21−42.
(25) Wakeham, W. A.; Cholakov, G. St.; Stateva, R. P. Liquid density and critical properties of hydrocarbons estimated from molecular structure. *J. Chem. Eng. Data* **2002**, *47*, 559−570.
(26) Petkov, S.; Pfohl, O.; Brunner, G. *PE−A Program to Calculate Phase Equilibria*; Herbert Utz Verlag: Munchen, 2000.
(27) Constantinou, L.; Gani, R. A new group contribution method for the estimation of properties of pure compounds. *AIChE J.* **1994**, *40*, 1697−1709.
(28) Kontogeorgis, G. M.; Yakoumis, I. V.; Coutsikos, P.; Tassios, D. P. A generalized expression for the ratio of the critical pressure with the van der Waals surface area. *Fluid Phase Equilib.* **1997**, *140*, 145−156.
(29) Yakoumis, I. V.; Nikitin, E.; Kontogeorgis, G. M. Validation of a Recent Generalized Expression of T_c/P_c vs the van der Waals surface area according to recent measurements. *Fluid Phase Equilib*. **1998**, *153*, 23−27.
(30) Zbogar, A.; Da Silva Lopes, F. V.; Kontogeorgis, G. M Approach suitable for screening estimation methods for critical properties of heavy compounds. *Ind. Eng. Chem. Res*. **2006**, *45*, 476−480.
(31) de la Fuente Badilla, J. C.; Peters, C. J.; de Swaan Arons, J. Volume expansion in relation to the gas−antisolvent process. *J. Supercrit. Fluids* **2000**, *17*, 13−23.
(32) Wakeham, W. A.; Stateva, R. P. Numerical solution of the isothermal multiphase flash problem. *Rev. Chem. Eng.* **2004**, *20*, 1−56.
(33) Stateva, R. P.; Tsvetkov, St. G. A diverse approach for the solution of the isothermal multiphase flash problem. Application to vapor−liquid−liquid systems. *Can. J. Chem. Eng.* **1994**, *72*, 722−734.
(34) Skjold-Jørgensen, S. Gas solubility calculations. II. Application of a new group-contribution equation of state. *Fluid Phase Equilib.* **1984**, *16*, 317−351.
(35) Gros, H. P; Bottini, S. B.; Brignole, E. A. High pressure phase equilibrium modelling of mixtures containing associating compounds and gases. *Fluid Phase Equilib.* **1997**, *139*, 75−87.
(36) Ferreira, O.; Fornari, T.; Brignole, E. A.; Bottini, S. B. Modelling of association effects in mixtures of carboxylic acids with associating and non-associating components. *Lat. Am. Appl. Res.* **2003**, *33*, 307−312.
(37) Espinosa, S.; Díaz, S.; Fornari, T. Extension of the group contribution associating equation of state to mixtures containing phenol, aromatic acid and aromatic ether compounds. *Fluid Phase Equilib.* **2005**, *231*, 197−210.
(38) García-González, J.; Molina, M. J.; Rodríguez, F.; Mirada, F. Solubilities of phenol and pyrocatechol in supercritical carbon dioxide. *J. Chem. Eng. Data* **2001**, *46*, 918−921.
(39) Yamini, Y.; Reza, Fat'hi, M.; Alizadeh, N.; Shamsipur, M. Solubility of dihydroxybenzene isomers in supercritical carbon dioxide. *Fluid Phase Equilib.* **1998**, *152*, 229−305.

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