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Aqueous Solubility of Some Natural Phenolic Compounds

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In this work, the aqueous solubilities of two hydroxybenzoic acids (gallic and salicylic acid) and three phenylpropenoic acids (trans-cinnamic, ferulic, and caffeic acids) are addressed. Measurements were performed, as a function of temperature, between 288.15 and 323.15 K, using the shake-flask method for generating the saturated aqueous solutions, followed by compositional analysis by spectrophotometric and gravimetric methods. The pH values of the saturated aqueous solutions were measured by potentiometry. Additional thermodynamic properties, which are fundamental for a better understanding of the solubilization process, as well as necessary for the modeling studies, such as melting temperatures and fusion enthalpies were determined by differential scanning calorimetry (DSC). Apparent acid dissociation constants (K_a) were obtained by potentiometry titration. The measured data were modeled with the cubic-plus-association (CPA) equation of state (EoS). This EoS is applied, for the first time, for multifunctional associating molecules, and the results indicate that it can adequately be used to represent the measured and other literature data with satisfactory accuracy.

1. Introduction

Fruits, vegetables, spices, and aromatic herbs are a natural source of phenolic compounds. These can be raw materials for the synthesis of different molecules with industrial interest, such as some drugs, cosmetics, antioxidants, antiseptics, and flavors; they also can be used in the preparation of resins, plasticizers, dyes, inks, and pharmaceutical products.[1] Many of these phenolic compounds have potential chemical and biological properties, such as antioxidant, chelating, free-radical scavenging, anti-inflammatory, antialergic, antimicrobial, antiviral, anticarcinogenic, chemoprevention (interfering with a disease process), and ultraviolet (UV) filtering properties. Most of them are phytochemical (they are not required for the normal functioning of the body, but they do have a beneficial effect on health, or an active role in the treatment of a disease).

Because of their hydrogen-bonding ability and aromaticity, phenolic compounds can frequently act as free-radical scavengers, forming aryloxyl radicals (ArO•). The stabilization of these radicals by other functional groups enhances the antioxidant activity.[2] They also have ability to scavenge the oxidative radicals that are caused by cumulative and prolonged exposure to UV radiation, which has been recognized to induce harmful reactions in human skin. There are several studies concerning topically applied antioxidant products for this purpose.[3]

The low incidence of coronary heart disease, atherosclerosis, and some types of cancer has been correlated by several authors with the phenolic content of olive oil.[4] This leads to the recognition of the olive phenols (which are present in the fruit, leaves, and oil) as potential targets for the food and pharmaceutical industries. Recent studies have highlighted the potential recovery of some of these compounds from olive mill wastewaters. Because of their acidity and high organic content, these cannot be treated by the regular sewage systems, and their treatment is particularly difficult. The recovery of some of these high-value phenolic compounds has been discussed in the recent literature as a means to promote the following biodegradation of the wastewaters, while obtaining economic benefits from the separated high-valued phenolic components.[5–7]

For the adequate design of processes and products that involve these phenolic compounds, it is important to know some of their physicochemical properties, particularly the solubility in different pure and mixed solvents, because these are solids under ambient conditions.

In this work, the aqueous solubilities of some natural phenolic compounds (such as the hydroxybenzoic acids gallic and salicylic acids) and the phenylpropenoic acids (trans-cinnamic, ferulic, and caffeic acids) are addressed. Their chemical structures are presented in Figure 1.

Salicylic acid is the key additive in many skin care products; in addition to being used as an analgesic and antipyretic, it is used as a plant hormone. In small quantities, it is a food preservative and antiseptic in toothpaste. It is found in several

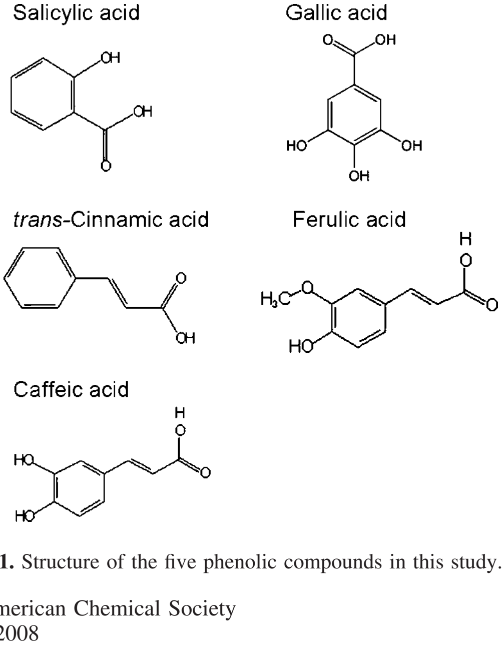

Figure 1. Structure of the five phenolic compounds in this study.

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Table 1. Shaking and Settling Times and Absorption Wavelengths for the Solubility Measurements

	shaking time (h)	settling time (h)	λ (nm)
salicylic acid	64–156	7–26	295.6
gallic acid	64–117	7–26	270.0
trans-cinnamic acid	69–156	6–42	270.8
ferulic acid	64–84	24–75	290.0
caffeic acid	64–84	25–73	290.0

plants, notably in wintergreen leaves and the bark of sweet birch.[8] Gallic acid, because of its many significant biological activities (such as its use as an antioxidant and antiviric),[9] is commonly used in the pharmaceutical, food, and pigment industries; however, it can also be used to synthesize the hallucinogenic alkaloid, mescaline. It is found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants.[8] *Trans*-cinnamic acid is used in flavors, synthetic indigo, and certain pharmaceuticals, but its primary use is in the manufacture of the methyl, ethyl, and benzyl esters for the perfume industry. It occurs naturally in essential oils (for example, those from cassia and cinnamon) and can also be found in shea butter. In addition, it can be obtained from some balsams such as storax.[8] Caffeic acid is found in many fruits, vegetables, seasonings, beverages (wine, coffee) and olive oil.[3] It is highly predominant in sunflower seeds and greatly affects the solubility of plant proteins.[2] Ferulic acid is a highly abundant phenolic phytochemical present in plant cell walls, and it is found in vegetables and fruits, and in seeds of plants such as brown rice, whole wheat, and oats, as well as in wine, olive oil, coffee, apple, artichoke, peanut, orange, and pineapple. It is the most abundant hydroxycinnamic acid in plants. It may have significant health benefits, through its antioxidant and anticancer activity, and it may also serve as a precursor in the manufacture of useful aromatic compounds.[10]

The work presented here is part of a project concerning the solubility of natural phenolic compounds in water and organic solvents. Its final aim is to understand and predict the solubility of these molecules in different solvents, to adequately understand the fate and separation processes of these molecules. To accomplish this, experimental measurements of solubility, as a function of temperature, were performed and an associating equation of state (EoS) was used for their estimation.

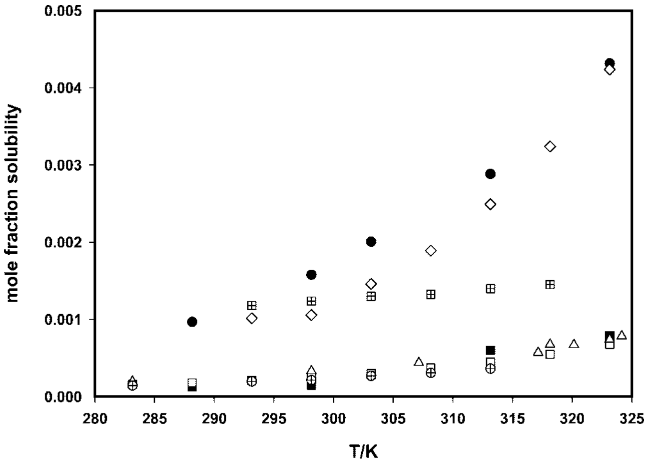

Figure 2. Solubility of hydroxybenzoic acids in water. Closed symbols denote data from this work ((●) gallic acid and (■) salicylic acid); open symbols denote data obtained from previous literature ((△) Apelblat et al.,[40] (□) Nordstrom and Rasmuson,[19] (⊕) Pena et al.,[41] (◇) Lu and Lu,[9] and (⊞) Noubigh et al.[18]).

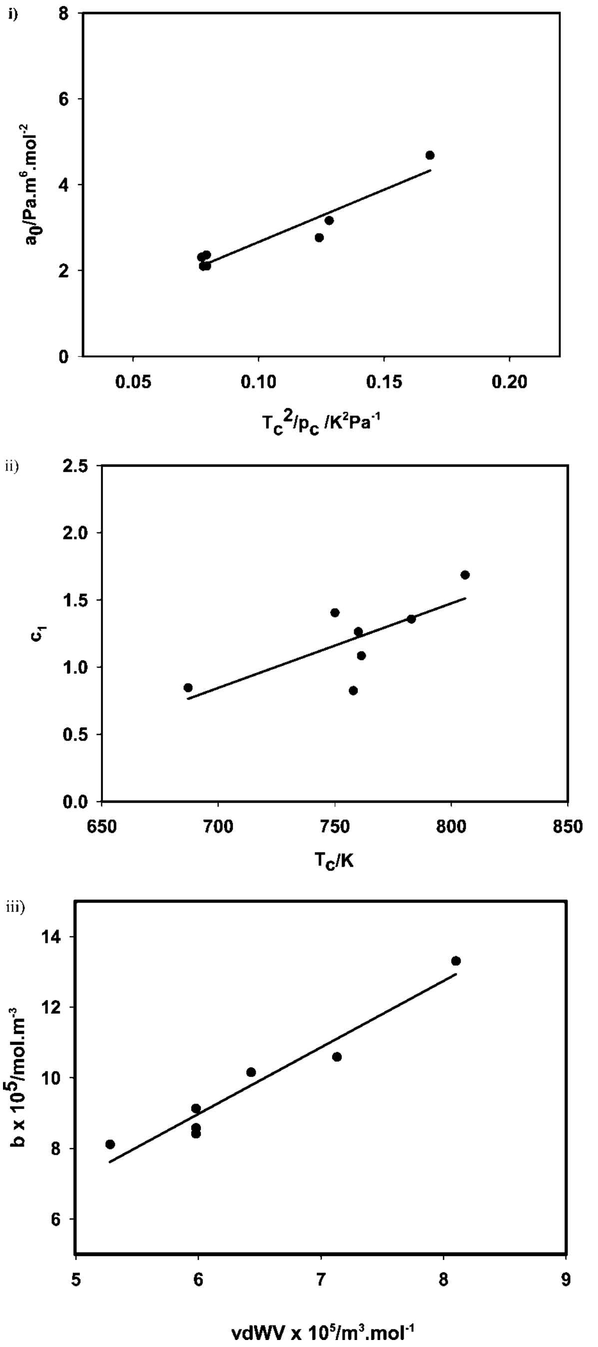

Figure 3. Regression of the CPA cubic term parameters: (i) a_0 vs T_c^2/p_c, (ii) c_1 vs T_c, and (iii) b vs vdWV.

2. Experimental Section

2.1. Materials. In all experiments, bidistilled water ($\approx 2.5-3$ μS/cm) was used. Gallic acid ($\geq$98% purity; CAS No. 149-91-7), salicylic acid ($\geq$99% purity: CAS No. 69-72-7), *trans*-cinnamic acid ($\geq$99% purity; CAS No. 140-10-3), ferulic acid (99% purity; CAS No. 537-98-4) and caffeic acid (98% purity; CAS No. 331-39-5) were obtained from Sigma−Aldrich. All chemicals were used as received.

2.2. Experimental Procedure. 2.2.1. Solubility Measurements. Aqueous solubilities of the solid phenolic compounds were determined, as a function of temperature, by the analytical shake-flask method, using constant-temperature jacketed glass cells. To prepare saturated solutions, excess solute and distilled water were placed into the cell and stirred in a plate stirrer (IKA RO 15 Power). Temperature was maintained with a constant-

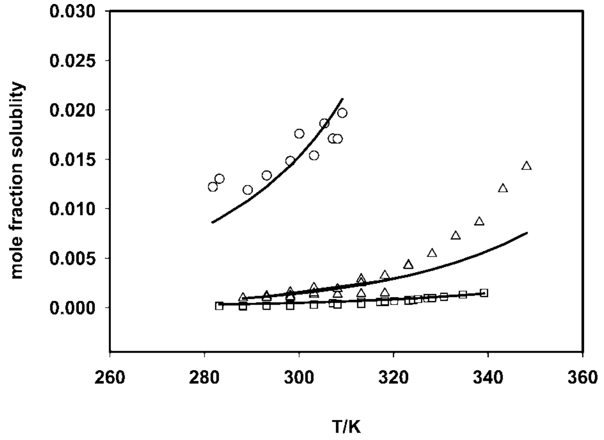

Figure 4. Solubility of phenol, gallic acid, and salicylic acid in water. Symbols represent experimental data: (○) phenol, (△) gallic acid, and (□) salicylic acid. Modeling results: phenol, $k_{ij} = -0.02$; gallic acid, $k_{ij} = -0.13$; and salicylic acid, $k_{ij} = -0.06$.

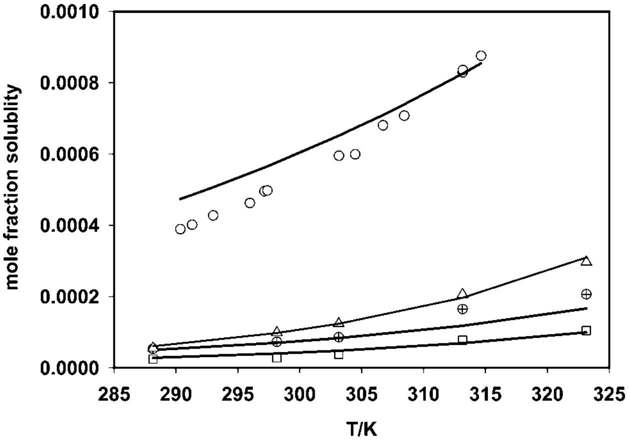

Figure 5. Solubility of benzoic, ferulic, caffeic, and *trans*-cinnamic acids in water. Symbols represent experimental data: (○) benzoic acid, (△) caffeic acid, (□) *trans*-cinnamic acid, and (⊕) ferulic acid. Modeling results: benzoic acid, $k_{ij} = -0.04$; ferulic acid, $k_{ij} = -0.13$; caffeic acid, $k_{ij} = -0.10$; and *trans*-cinnamic acid, $k_{ij} = -0.05$.

temperature (±0.10 K) circulating water bath (Grant LTC1) and monitored with four-wire platinum resistance probes (Pt100) placed in the thermostatic jackets and connected to an Agilent 34970A data acquisition unit (±0.01 K). This temperature measuring system was certified, presenting a maximum deviation of 0.06 at 303.67 K.

The time required to reach equilibrium was determined by repetitively measuring the solubilities until constant data were obtained, which was different for each compound, as presented in Table 1. When the equilibrium was attained, the agitation was stopped and then the solution was kept still, to allow undissolved solid to settle. Settling times are also presented in Table 1.

For the determination of the solubilities, samples were taken using plastic syringes coupled with syringe filters (0.45 μm), previously thermostatized at the equilibrium temperature and analyzed by spectrophotometry (Thermo Electron Corporation UV1).

Calibration curves were generated using standards in the following concentration ranges (in mg/L): salicylic acid, 2.7−4.8; gallic acid, 0.5−2.5; *trans*-cinnamic acid, 0.3−1.5; caffeic acid, 1.3−6.7; and ferulic acid, 0.5−9.4. The analysis wavelengths are presented in Table 1. Linearity was evaluated by linear regression analysis.

All the weighing procedures were performed using an analytical balance (model AE aaa250L) (±0.0001 g).

To verify the accuracy of the spectrophotometric method, some analyses were performed using the gravimetric method, using the same solubilization and sampling procedure. A sample of clear solution was transferred to a preweighed flask (with a mass m_v). The mass of the flask with saturated solution (with a mass m_{vs}) was registered and then maintained at 313.15 K for 8 days on a hot plate (Stuart Hotplate SB300) to allow the solvent to evaporate. Afterwards, the solid residue was placed in a drying oven (Scientific Series 9000) and the mass of dry residue was measured (m_{vdr}). Before each weighing, the flasks were placed in a desiccator for 2 h to reach ambient temperature. The solubility, when presented as a ratio of grams of solute per grams of solvent, is calculated using the following equation:

$$S = \frac{m_{vdr} - m_v}{m_{vs} - m_{vdr}} \tag{1}$$

Some phenylpropenoic acids were reported to suffer photodegradation with daylight.[11−16] To prevent that, the cells were isolated with aluminum foil. In these cases, apart from the normal analysis, the phenylpropenoic samples were also analyzed via high-preformance liquid chromatography (HPLC) (VWR−Hitachi Lachrom Elite HPLC) at the same wavelength used in the spectrophotometric method to check if any photodegradation had occurred, which was never found, with a single peak being obtained in all chromatograms.

2.2.2. DSC Measurements. Thermograms of the studied phenolics were obtained using differential scanning calorimetry (DSC) (Netzsch, model DSC 200 F3 Maia). Samples of 4−6 mg were sealed hermetically into aluminum crucibles and heated under a stream of nitrogen in the measuring cell, while using an empty crucible as a reference. Initial estimates of the melting temperatures were obtained from a 10 K/min temperature program in a larger temperature range (from room temperature to 623 K). Afterward, several runs were averaged with a heating rate of 1 K/min around the expected melting temperature. All DSC experiments were conducted at least in triplicate. An indium standard was run on this equipment to ascertain its precision for obtaining melting temperatures and heats of fusion. The deviation in the melting temperature was −0.3%, and in fusion enthalpy, it was 3.7%.

2.2.3. Potentiometric Measurements. Because the phenolic compounds under study are organic acids, the pH of the saturated aqueous solutions and their acid dissociation constants were determined by potentiometry with a glass electrode in a VWR model SympHony SB70P meter with automatic temperature compensation. The measuring system was calibrated with buffers of pH 4.00 and 7.00 (293.15 K) from Merck, which were traceable to standard reference materials from NIST.

Apparent acid dissociation constants were obtained by potentiometric titration of aqueous solutions of the phenolic acids with aqueous NaOH solutions, at the same temperatures as in the solubilization experiments.

3. Model

Apart from empirical correlations, different thermodynamic approaches can be found for modeling the solid solubility of phenolic compounds in aqueous systems.

Jia et al.[17] determined the water solubility of benzoic acid and some of its derivatives, modeling the data with the Wilson equation and the λH correlation. Noubigh et al.[18] employed Van't Hoff plots to correlate the solubility of syringic, gallic,

Table 2. Experimental Solubilities of Hydroxybenzoic Acids in Pure Water and Corresponding Saturation pH Values

	Salicylic Acid		Gallic Acid	
temperature, T (K)	solubility, S (g/L)	pH	solubility, S (g/L)	pH
323	5.97 ± 0.30	2.23	38.9 ± 2.1	2.56
313	4.55 ± 0.51	2.24	26.4 ± 1.2, 22.5 ± 0.62[a]	2.63
303	2.18 ± 0.46	2.30	18.6 ± 0.9	2.67
298	1.14 ± 0.44	2.50	14.7 ± 0.8	2.69
288	1.00 ± 0.05	2.61	9.1 ± 0.7	2.72

[a] The second value listed was measured by gravimetry.

ferulic vanillic, and protocatechuic acids, as well as vanillin in water and aqueous salt solutions. Nordström and Rasmuson[19–21] studied the solubility of the three isomers of hydroxybenzoic acid in water and different organic solvents and, as Noubigh et al.[18] correlated the corresponding Van't Hoff plots, this time using a second-order polynomial. Lu and Lu[9] measured the water solubility of gallic acid and some of its esters and also correlated the data from the Van't Hoff plots. They proposed another empirical correlation to describe the S-type curve of the solubility of gallic acid and octyl gallate as a function of temperature. Panteli et al.[22] modeled the solubility of (+)-catechin in ethyl acetate and acetonitrile with UNIQUAC, NRTL, UNIFAC, and Regular Solution Theory and concluded that, for these particular systems, NRTL was the better correlative tool, whereas UNIFAC and regular solution theory gave unsatisfactory solubility predictions.

Besides the importance of aqueous systems and ambient pressure conditions, most of the works concerning the estimation of the phase equilibria of phenolic compounds is concerned with their CO_2 solubility, related with supercritical fluid extraction processes.[23–29] Among the models used, different classical equations of state such as the Peng−Robinson equation of state (PR-EoS),[23,26] the Soave−Redlich−Kwong equation of state (SRK-EoS),[25] the group contribution associating equation of state (GCA-EoS)[25,28] and the statistical associating fluid theory equation of state (SAFT-EoS)[29] can be found. A recent and broad revision on the different models used to predict solubility of phenolic compounds in supercritical CO_2 is available in the literature.[24]

As both the solutes and the solvent (water) can associate (self- and cross-association is present in mixtures), thermodynamic models explicitly dealing with these interactions seem appropriate for evaluation in this work. Among the different associating models, recent works on the mutual solubilities of water + organic systems with the cubic-plus-association equation of state (CPA-EoS)[30,31] suggested the choice of this equation of state.

The CPA-EoS, in terms of the compressibility factor (Z), can be expressed as the sum of two contributions: one accounting for physical interactions (that in the current work is taken as the SRK-EoS), and another accounting for the association contributions (the Wertheim association term):[32–37]

$$Z = Z^{\text{phys}} + Z^{\text{assoc}} = \frac{1}{1 - b\rho} - \frac{a\rho}{RT(1 + b\rho)} - \frac{1}{2}\left(1 + \rho\frac{\partial \ln g}{\partial \rho}\right)\sum_i x_i \sum_{\mathrm{A}_i}(1 - X_{\mathrm{A}}) \quad (2)$$

where a is the energy parameter, b the co-volume parameter, ρ the density, g the simplified radial distribution function (see eq 7, presented later in this paper), X_{A_i} the mole fraction of pure component i not bonded at site A, and x_i the mole fraction of component i.

The pure component energy parameter is obtained from

$$a(T) = a_0\left[1 + c_1\left(1 - \sqrt{T_r}\right)\right]^2 \quad (3)$$

and the mixture a and b parameters are obtained through the classical mixing and combining rules.[31]

X_{A_i} is related to the association strength $\Delta^{\mathrm{A}_i\mathrm{B}_j}$ between two sites belonging to two different molecules and is calculated by solving the following set of equations:

$$X_{\mathrm{A}_i} = \frac{1}{1 + \rho\sum_j x_j \sum_{\mathrm{B}_j} X_{\mathrm{B}_j}\Delta^{\mathrm{A}_i\mathrm{B}_j}} \quad (4)$$

For self-associating molecules, eq 5 is used:

$$\Delta^{\mathrm{A}_i\mathrm{B}_i} = g(\rho)\left[\exp\left(\frac{\varepsilon^{\mathrm{A}_i\mathrm{B}_i}}{RT}\right) - 1\right]b_{ii}\beta^{\mathrm{A}_i\mathrm{B}_i} \quad (5)$$

where $\varepsilon^{\mathrm{A}_i\mathrm{B}_i}$ and $\beta^{\mathrm{A}_i\mathrm{B}_i}$ are the association energy and the association volume, respectively. For sites that belong to two different associating molecules, the Elliot combining rule is used:

$$\Delta^{\mathrm{A}_i\mathrm{B}_j} = \sqrt{\Delta^{\mathrm{A}_i\mathrm{B}_i} \times \Delta^{\mathrm{A}_j\mathrm{B}_j}} \quad (6)$$

The simplified radial distribution function, $g(\rho)$ is given by

$$g(\rho) = \frac{1}{1 - 1.9\eta} \quad (7)$$

where

$$\eta = \left(\frac{1}{4}\right)b\rho$$

CPA has three pure component parameters (a_0, c_1, and b) for nonassociating components, whereas, for associating components such as n-alcohols, it has five (a_0, c_1, b, ε, and β). In both cases, parameters are regressed simultaneously from vapor pressure and liquid density data.

Starting from the solid−liquid equilibrium conditions, neglecting the heat capacity terms and assuming pure solid phases, the water solubility of each of the phenolic compounds under study can be obtained from the relation[38]

$$x_i = \frac{\phi_i^{L_0}}{\phi_i^L}\exp\left[-\frac{\Delta H_{i_{\text{fus}}}}{RT}\left(1 - \frac{T}{T_{i_{\text{m}}}}\right)\right] \quad (8)$$

where x_i is the solubility (in mole fraction), φ the fugacity coefficient, and $\Delta H_{i_{\text{fus}}}$ the fusion enthalpy; the subscript "0" refers to the pure component and the subscript "m" refers to melting. Fugacity coefficients were obtained from the CPA-EoS. Fusion enthalpies and melting temperatures were experimentally determined by DSC, whenever possible; otherwise, they were obtained from the Marrero and Gani group contribution approach.[39]

4. Results and Discussion

Aqueous solubility results are given in Tables 2 and 3. The pH of each saturated solution was also measured, and the mean values are presented on the same tables. As can be seen, the solubility increases with temperature for all compounds.

Among the hydroxybenzoic acids (Table 2), gallic acid has the higher solubilities, because of the higher number of hydroxyl groups, leading to increased association interactions with water. For gallic acid, a comparison of our results with those of Lu and Lu[9] (Figure 2) allows one to observe a slight disagreement at the lower temperatures (298.15 and 303.15 K); however,

Table 3. Experimental Solubilities of Phenilpropenoic Acids in Pure Water and Corresponding Saturation pH Values

	Trans-Cinnamic Acid		Ferulic Acid		Caffeic Acid	
temperature, T (K)	solubility, S (g/L)	pH	solubility, S (g/L)	pH	solubility, S (g/L)	pH
323	0.85 ± 0.02	3.26	2.19 ± 0.03	3.18	2.92 ± 0.03	3.17
313	0.63 ± 0.02	3.37	1.76 ± 0.02	3.31	2.04 ± 0.02	3.25
303	0.31 ± 0.01	3.56	0.92 ± 0.01, 0.95 ± 0.01[a]	3.40	1.23 ± 0.02	3.34
298	0.23 ± 0.01, 0.20 ± 0.01[a]	3.60	0.78 ± 0.01	3.46	0.98 ± 0.02	3.37
288	0.21 ± 0.01	3.65	0.57 ± 0.01	3.54	0.55 ± 0.01	3.42

[a] The second value listed was measured by gravimetry.

Table 4. Average Melting Point and Enthalpy of Fusion of the Studied Phenolic Acids and Comparison with the Selected Group Contribution Model

	DSC			Marrero and Gani Group Contribution Method[39]	
compound	number of scans	T_m (K)	ΔH_{fus} (J/mol)	T_m (K)	ΔH_{fus} (J/mol)
salicylic acid	7	431.3	24448	436.3	26590
gallic acid	4	535.4	ND[a]	499.0	38770
trans-cinnamic acid	8	406.1	22214	382.1	23290
ferulic acid	7	444.6	33338	442.6	32960
caffeic acid	ND[a]	ND[a]	ND[a]	464.1	39850

[a] Not determined, because of decomposition upon melting.

Table 5. Apparent Acid Dissociation Constants of the Studied Phenolic Acids at 298.2 K

phenolic acid	$pK_{a_{app}}$
salicylic acid	3.21
gallic acid	4.51
trans-cinnamic acid	4.55
ferulic acid	4.61
caffeic acid	4.77

generally, the results follow the expected trend in the entire temperature range. Comparison with Noubigh et al.[18] shows that the results are not in good agreement, but the Noubigh et al.[18] data do not increase significantly with temperature, which is contrary to what would be expected. To verify the reproducibility of the spectrophotometric determination, a gallic acid solubility value was measured using the gravimetric method at 313.15 K. The value obtained (22.5 g/L) agrees with that measured by the spectrophotometric technique (26.4 g/L) and that reported by Lu and Lu[9] (23.6 g/L), showing the adequacy of the spectrophotometric analysis.

For salicylic acid, our results are in good agreement with previous work,[19,40,41] as can be seen in Figure 2.

No literature data were found for caffeic acid to compare the results. For ferulic acid, the results are very different from those obtained by Noubigh et al.[18] (negative deviations between 40% and 63%, being larger at the higher temperatures), opposite to those found previously for our gallic acid measurements. These authors also used the shake flask method but reported equilibrium times of 3 h of stirring, while different equilibrium times for different temperatures were achieved in this work, and they were always between 64 h and 84 h, as reported in Table 1. Ferulic acid is reported to have two polymorphic forms[42] that were obtained by recrystallization from various solvents. Sohn and Oh[42] noticed in DSC thermograms that form I has one endothermic peak, corresponding to melting at 448.15 K, whereas form II has three endothermic peaks, at 378.15, 421.15, and 455.15 K. The equilibrium solubility of form I is approximately twice that of form II, and the dissolution rate of form II is higher than that of form I in an initial step.[42] Thus, we may be comparing different crystalline structures of the same compound, which might explain the different results. As can be seen from Table 4, our solubility measurements correspond to form I, with a single solid phase, melting at 444.65 K. Also for *trans*-cinnamic acid, no further temperature-dependent solubility data were found, except for a single point at 293.15 K that was available in the *Merck Index* (0.4 g/L).[43]

In the series of phenylpropenoic compounds, higher solubilities for caffeic acid, followed by ferulic acid and *trans*-cinnamic acid, were obtained. As observed previously in the studied hydroxybenzoic acids, this order follows the extent of hydrogen bonding of each molecule with water, because caffeic acid has two hydroxyl groups, ferulic one, and *trans*-cinnamic acid none.

Another important fact about the solubilization of solids in liquids is related to fusion enthalpies and melting temperatures. These data have been determined by DSC and are presented in Table 4, where the number of repetitions (scans) is reported. For all the phenolic acids, except gallic and caffeic acids, a linear baseline and a single peak was observed. The melting peaks of gallic and caffeic acids are not symmetric, with other peaks continuously connected to the melting peak, indicating that decomposition processes may occur upon melting. For this reason, the fusion enthalpies of these two acids could not be determined and, therefore, they are not presented in Table 4.

Data regarding the melting temperature and fusion enthalpies were found for salicylic acid[19,44,45] and *trans*-cinnamic acid.[44,45] The measured melting temperatures deviate by less than −0.2%, in comparison with all the collected data. Higher deviations were found for the fusion enthalpies, deviations smaller than 1.8% for *trans*-cinnamic acid, and a range from −0.7% up to 24% for salicylic acid (respectively, versus the data from the *NIST Chemistry Webbook* and the DIPPR database). Our salicylic acid fusion enthalpy deviates −9.8% from that reported recently by Nordstrom and Rasmuson.[19]

From the data presented in Table 4 and the measured solubility data presented in Tables 2 and 3, it can thus be concluded that the extent of hydrogen bonding with water is certainly more important than the fusion process for determining the degree of solubilization.

Because the studied phenolic compounds are organic acids that dissociate in water, the apparent dissociation constants ($K_{a_{app}}$) were also obtained from potentiometric titration of solutions of each phenolic acid with NaOH:

$$K_{a_{app}} = \frac{[A^-]\,(H^+)}{[HA]} \qquad (9)$$

Table 6. Critical Properties (Marrero and Gani),[39] vdWV (Bondi)[50] CPA Associating Pure-Component Parameters (Cubic Parameters Obtained from Eqs 10−12) and Deviations in the Estimation of Vapor Pressure and Liquid Densities

				COOH		OH		% AAD	
compound	critical temperature, T_c (K)	critical pressure, P_c (MPa)	van der Waals volume, vdWV ($\times 10^{-5}$ m^3/mol)	ε ($\times 10^4$ J/mol)	β ($\times 10^4$)	ε ($\times 10^4$ J/mol)	β ($\times 10^2$)	p	ρ
phenol	687.0	5.96	5.28			1.837	1.185	0.89	6.9
o-benzenediol	757.9	7.43	5.98			1.134	6.225	4.8	2.2
m-benzenediol	760.1	7.29	5.98			1.848	2.212	0.62	4.1
p-benzenediol	761.4	7.44	5.98			1.867	2.655	1.7	20
benzoic acid	750.0	4.39	6.43	3.201	0.0982			10	4.8
salicylic acid	805.8	5.23	7.13	1.703	0.0100	1.643	1.629	48	2.0
trans-cinnamic acid	782.8	3.63	8.10	2.756	36.98			3.6	1.2
				From the Above Contributions					
gallic acid	897.6	8.51	8.53	3.201	0.0982	1.134	6.225		
ferulic acid	854.6	3.64	10.7	2.756	36.98	1.871	1.345		
caffeic acid	876.2	5.11	9.50	2.756	36.98	1.134	6.255		

where activities are represented by parentheses and concentrations are represented by square brackets. The H^+ activity is obtained from the pH meter, and $K_{a_{app}}$ is given by the measured pH where the added volume of NaOH is equal to the equivalent volume, divided by 2. Although this is not the true thermodynamic dissociation constant (that would require activity coefficients of the other species), it is an appropriate quantity for the purposes of this work. Measured $K_{a_{app}}$ are presented in Table 5. Although measurements were performed at the highest temperature (323.15 K), lowest temperature (288.15 K), and room temperature (298.15 K), all the results indicate that no significant temperature change is obtained in the studied temperature range. Hydroxybenzoic acids are more acidic than phenylpropenoic acids, with salicylic acid being the most acidic of all the studied compounds. Curiously, among the phenylpropenoic acids, the opposite trend found in solubility is obtained in terms of acidity with the less-soluble *trans*-cinnamic acid being the most acidic of the three, which leads to the conclusion that acid dissociation is not as important of an issue in the water solubilization of these molecules.

CPA parameters are frequently obtained from pure-component vapor-pressure and liquid-density data. In the particular case of the phenolics studied in this work, these data are available only for salicylic and *trans*-cinnamic acids. Another major drawback is the presence of different associating groups (−COOH, −OH) on the same molecule, some of them repeated in different positions (such as −OH). Thus, it seems appropriate to individually assign association energies and volumes for each group and to consider multiple group substitution, either or not with the same association parameters. Thus, in the remaining of this work, eq 5 will be used to obtain the association strengths (Δ) of the associating sites that belong to the same association group (with the same ϵ and β), whereas eq 6 will be used in the other cases, those either being self- or cross-association.

To address this condition, which is explicitly considered in the association contribution for the Helmholtz energy, a database of phenolic compounds was taken with single and multiple substitution of associating groups, namely, phenol, *o*-benzenediol, *m*-benzenediol, *p*-benzenediol, benzoic acid, salicylic acid, and *trans*-cinnamic acid. All the required data were collected from the DIPPR database.[45] With this database, it was possible to compare the different cubic and associating CPA parameters and thus establish (1) correlations for the cubic parameters and (2) values for the association energies and volumes of carboxylic groups in benzoic and phenylpropenoic acid derivatives, and hydroxyl groups in different positions of the aromatic ring.

The following procedure was established (water CPA parameters were obtained from a previous work:[31] $a_0 = 0.12$ Pa m^6/mol^2, $c_1 = 0.67$, $b = 1.45 \times 10^{-5}$ m^3/mol, $\varepsilon = 16555$ J/mol, $\beta = 0.069$, four-site model). First, critical temperatures (and pressures) were obtained from a third-order group contribution approach that was proposed by Marrero and Gani[39] (see Table 6). This approach has the advantage of clearly distinguishing among isomers, and it was used previously by Nikitin and co-workers to evaluate alkylbenzoates,[46] phenylalkanoic acids,[47] phthalates,[48] phenol, and phenylalkanols.[49]

In a first approach, the previously mentioned database was used with these critical temperatures and all parameters were regressed simultaneously. In a following step, the obtained cubic parameters were regressed with T_c^2/p_c (a_0), T_c (c_1), and the van der Waals volume vdWV (b), obtained from Bondi's group contribution approach.[50] The following equations were determined to provide an adequate linear fit of the cubic parameters (Figure 3):

$$a_0 = 0.2267 + 24.38\left(\frac{T_c^{\,2}}{p_c}\right) \tag{10}$$

$$c_1 = -3.557 + (6.289 \times 10^{-3})T_c \tag{11}$$

$$b = -2.328 \times 10^{-5} + 1.884(\mathrm{vdWV}) \tag{12}$$

where T_c is given in Kelvin, p_c is given in pascals, and vdWV is expressed in terms of m^3/mol.

These cubic parameters were then fixed and the associating parameters regressed separately (Table 6). For each −OH group, a two-site model was adopted, whereas for the −COOH groups, a single site was considered. It can be seen, in the case of the −OH groups, with the exception of the molecules where intramolecular hydrogen bonding occurs (salicylic acid and *o*-benzenediol), that the same association energy was obtained (1.8×10^4 J/mol). Whenever intramolecular hydrogen bonding occurs, these values are slightly lower, as expected. The values of the association volume (β) are more dependent on the substitution of the ring. In the case of the acid groups, both the association energies and volumes are considerably dependent, whether there is a ring substitution with or without intramolecular association (salicylic acid and benzoic acid) or a phenylpropenoic substitution. From the aforementioned methodology, all the cubic and associating parameters of the other molecules under study (gallic, ferulic and caffeic acids) can be estimated, without requiring experimental pure-component data.

For the modeling of the water solubility, eq 8 was used with the experimentally determined melting temperatures and fusion enthalpies and the CPA-EoS for the calculation of the fugacity coefficients. For gallic and caffeic acids, melting temperatures and fusion enthalpies were obtained from the same group contribution approach used previously for the critical properties (see Table 4).[39] These molecules are organic acids; therefore, to effectively model their water solubility, the acid dissociation must be considered. Because these are weak acids, the adopted procedure was to determine the solubility of the undissociated form, as mentioned previously, and then obtain the total solubility as the sum of this with the amount of the basic form. The latter is obtained from the solubility of the acidic form, given by the model, the $K_{a_{app}}$ value, and the pH value (see Tables 2, 3, and 5).

Solid−liquid equilibria results are presented in Figures 4 and 5. The solubilities of benzoic acid and phenol are also plotted in these figures. As can be seen, a good description can be achieved with the CPA-EoS, but a small k_{ij} value is always required to obtain smaller deviations. Still, in all cases, only a single, temperature-independent k_{ij} value was required, and this was almost constant for the majority of the studied systems, except the gallic, ferulic, and caffeic acids, which required a slightly higher k_{ij} value (close to 0.1). These three phenolics are those for which pure-component data were not available to correlate the CPA parameters, and thus these higher deviations certainly account for the predictive approach proposed for the EoS parameters. Still, it can be concluded that the CPA-EoS, together with the selected methodology for the estimation of the pure-component parameters, is an adequate tool for the estimation of the solid solubility of phenolic compounds.

5. Conclusions

In this work, aqueous solubility data were measured for some phenolic compounds (salicylic, *trans*-cinnamic, gallic, caffeic, and ferulic acids) in pure water in the temperature range from 288.15 K to 323.15 K, using the shake-flask method, coupled with spectrophotometric analysis. For all compounds under study, the solubility follows the general increasing trend with temperature. The studied compounds can be divided in two groups: hydroxybenzoic acids (gallic and salicylic acids), which have the higher solubilities, and phenylpropenoic (*trans*-cinnamic, caffeic, and ferulic acids), which present the lower solubilities.

Besides solubility data, melting temperatures, enthalpies of fusion, and apparent dissociation constants were also determined, providing a broader knowledge about the solubilization processes of these molecules. From all the measurements, it was concluded that the extent of solubilization is mostly governed by the degree of hydrogen bonding formation with water.

The cubic-plus-association equation of state (CPA-EoS) was used with different association energies and volumes for the different associating groups for the first time. A methodology to obtain the pure-component parameters without requiring experimental data was developed, and the results indicate that CPA is an adequate tool to correlate the water solubility of these molecules.

Nomenclature

List of Symbols

a_0 = parameter in the cubic term of CPA (Pa m^6/mol^2)
b = co-volume parameter in CPA (m^3/mol)
c_1 = parameter in the cubic term of CPA
CPA = cubic plus association
EoS = equation of state
g = simplified radial distribution function
m = mass (g)
p = pressure (Pa)
$K_{a_{app}}$ = apparent acid dissociation constant
R = gas constant; R = 8.314 J/(mol K)
S = solubility
T = absolute temperature (K)
vdWV = van der Waals volume (m^3/mol)
x = mole fraction
X_{A_i} = fraction of molecule i not bonded at site A
Z = compressibility factor

Greek Symbols

ϵ = association energy (J/mol)
β = association volume
$\Delta^{A_iB_j}$ = association strength between site A on molecule i and site B on molecule j
ΔH_{fus} = fusion enthalpy (J/mol)
ρ = mole density (mol/m^3)
η = reduced fluid density
φ = fugacity coefficient

Subscripts

c = critical
i, j = component index
m = melting
r = reduced
v = vial
vs = vial with saturated solution
vdr = vial with dry residue

Superscripts

assoc = association contribution
phys = physical contribution

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