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Solubilities of Biologically Active Phenolic Compounds: Measurements and Modeling

António J. Queimada,^{*,†} Fátima L. Mota,[†] Simão P. Pinho,[‡] and Eugénia A. Macedo[†]

Laboratory of Separation and Reaction Engineering (LSRE), Departamento de Engenharia Química, Faculdade de Engenharia, Universidade do Porto, Rua do Dr. Roberto Frias, 4200 - 465 Porto, Portugal, and Laboratory of Separation and Reaction Engineering (LSRE), Instituto Politécnico de Bragança, Campus de Santa Apolónia, 5301-857 Bragança, Portugal

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Aqueous solubilities of natural phenolic compounds from different families (hydroxyphenyl, polyphenol, hydroxybenzoic, and phenylpropenoic) were experimentally obtained. Measurements were performed on tyrosol and ellagic, protocatechuic, syringic, and *o*-coumaric acids, at five different temperatures (from 288.2 to 323.2 K), using the standard shake-flask method, followed by compositional analysis using UV spectrophotometry. To verify the accuracy of the spectrophotometric method, some data points were measured by gravimetry, and in general, the values obtained with the two methods are in good agreement (deviations lower than 11%). To adequately understand the solubilization process, melting properties of the pure phenolics were obtained by differential scanning calorimetry (DSC), and apparent acid dissociation constants were measured by potentiometry titration. The aqueous solubilities followed the expected general exponential trend. The melting temperatures did not follow the same solubility tendency, and for tyrosol and ellagic acid, not only the size and extent of hydrogen bonding, but also the energy associated with their crystal structures, determine the solubility. For these binary systems, acid dissociation is not important. Approaches for modeling the measured data were evaluated. These included an excess Gibbs energy equation, the modified UNIQUAC model, and the cubic-plus-association (CPA) equation of state. Particularly for the CPA approach, a new methodology that explicitly takes into account the number and nature of the associating sites and the prediction of the pure-component parameters from molecular structure is proposed. The results indicate that these are appropriate tools for representing the water solubilities of these molecules.

1. Introduction

Phenolic compounds are a chemical family whose members have one or more hydroxyl groups attached directly to an aromatic ring. These compounds are characteristic of plants, some fruits, and vegetables,¹ and as a group, they are usually found as esters or glycosides rather than as free compounds.¹ Interest in phenolic compounds has grown greatly, with attention focused on finding naturally occurring antioxidants for use in foods or medical materials to replace synthetic components.²

There is significant evidence that phenolic compounds have positive effects on human health,³ with many recently published studies reporting anti-inflammatory and cardioprotective activities,⁴ as well as antioxidant properties.^{5–7} Recently, some of these compounds were reported to exhibit protective effects on hormone-dependent breast tumors,³ as well as other types of cancers.^{8–10} Perhaps the oldest medical application of phenolic compounds is the use of phenol as an antiseptic.¹ Another very common use of phenolic compounds is in sunscreens. The presence of the aromatic ring results in the effective absorbance (and filtering) of UV-B radiation (between 280 and 315 nm) from the sun, thus preventing sunburn and other major consequences, such as skin cancer. Aside from medical applications, phenolic compounds, including flavonoids and tannins, are an integral part of human and animal diets, because

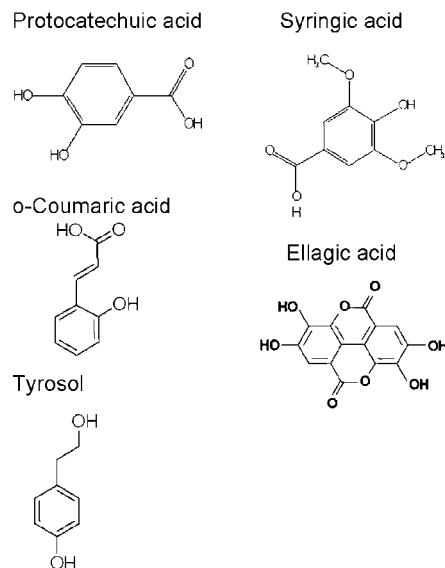


Figure 1. Structures of the five studied phenolic compounds.

they represent one of the most numerous and ubiquitous groups of plant metabolites.¹⁰

In this work, the aqueous solubilities of some natural phenolic compounds such as tyrosol and ellagic acid, the hydroxybenzoic acids protocatechuic and syringic acids, and the phenylpropenoic *o*-coumaric acid are addressed. Their chemical structures are presented in Figure 1.

* To whom correspondence should be addressed. Phone: +351 22 508 1686. Fax: +351 22 508 1674. E-mail: ajq@fe.up.pt.

[†] Universidade do Porto.

[‡] Instituto Politécnico de Bragança.

The scarcity of data reported in the literature increases the importance of the development of correlation and prediction models. Different approaches can be found for modeling the solid solubilities of phenolic compounds.

Noubigh et al.^{11,12} obtained experimental values for the solubilities in pure water and in some chloride solutions, at 298.2 K, of syringic, gallic, protocatechuic, vanillic, and ferulic acids, as well as vanillin. They represented the solubility data using an activity coefficient thermodynamic model based on the Pitzer–Simonson–Clegg formalism¹² and used van't Hoff plots¹¹ to obtain solution standard molar enthalpies. Apelblat et al.¹³ measured the aqueous solubilities of some polycarboxylic acids, expressing the solubility with the Williamson equation. Lu and Lu¹⁴ reported the solubilities of gallic acid and its esters in water as a function of temperature. They proposed an empirical equation to fit the data for gallic acid and octyl gallate, whereas for the other esters, the data were better represented with the simplified λ – h equation. Also for gallic acid, Daneshfar et al.¹⁵ calculated the temperature dependence of the solubility data using the modified Apelblat model. The solubility of salicylic acid was investigated in pure solvents as a function of temperature by Nordström and Rasmuson,¹⁶ who observed a correlation between the solubility and van't Hoff enthalpy of solution. Shalmashi and Eliassi¹⁷ used an empirical correlation, with two parameters, to fit the solubility data of salicylic acid.

Although the importance of phenolic compounds is well-known, very few solubility data are available, and comprehensive experimental studies combining solubility with melting properties and acidity constants are clearly lacking in the literature. This work follows a previous one where the aqueous solubilities of other hydroxybenzoic (gallic and salicylic) and phenylpropenoic (cinnamic, ferulic, and caffeic) acids were addressed.¹⁸ The final aim is to determine, and accurately predict, the solubilities of these molecules in different solvents in order to adequately understand the fate and separation processes of these compounds. To accomplish this, experimental measurements of solubility as a function of temperature were performed, and models were used for its estimation, namely, the modified UNIQUAC model^{19,20} and an associating equation of state (EoS), the cubic-plus-association EoS.^{21,22}

2. Experimental Section

2.1. Materials. In all experiments, bidistilled water (~ 2.5 – 3 $\mu\text{S}/\text{cm}$) was used. *o*-Coumaric acid ($\geq 98\%$ purity; CAS no. 614-60-8), protocatechuic acid ($\geq 99\%$ purity; CAS no. 99-50-3), syringic acid ($\geq 99\%$ purity; CAS no. 530-57-4), ellagic acid (99% purity; CAS no. 476-66-4), and tyrosol (98% purity; CAS no. 501-94-0) were obtained from Sigma-Aldrich. All chemicals were used without any further purification.

2.2. Experimental Procedure. **2.2.1. Solubility Measurements.** Aqueous solubilities were determined for each phenolic compound using the standard analytical shake-flask method, with constant-temperature jacketed glass cells, at five different temperatures ranging from 288.2 to 323.2 K. Saturated solutions were generated using an excess of solid and bidistilled water. These mixtures were then stirred on a plate stirrer for a period of time determined by continuously sampling the aqueous phase until no concentration change was observed. After equilibrium had been attained, the solutions were kept still. Maximum stirring times of 140 and 120 h were found for the lower and higher temperatures, respectively; settling times between 24 and 40 h were sufficient to guarantee thermodynamic saturation. Thermostatization was ensured by a constant-temperature (± 0.10

K) circulating water bath (Grant LTC1) and monitored with four-wire platinum resistance probes [Pt(100)] placed in the thermostatic jackets and connected to an Agilent 34970A data acquisition unit (± 0.01 K), previously certified with a maximum deviation of 0.06 at 303.67 K. Samples of the saturated solutions were taken using thermostated plastic syringes coupled with syringe filters (0.45 μm) and analyzed by spectrophotometry (Thermo Electron Corporation UV1). The wavelengths used for analysis were 290 nm for *o*-coumaric, ellagic, protocatechuic, and syringic acids and 272 nm for tyrosol. The analysis was not done at the maximum absorption wavelength because of linearity problems. Further details about the solubility experimental procedure can be found elsewhere.¹⁸ To verify the accuracy of the data measured using the spectrophotometric method, some analyses were carried out using the gravimetric method, with the same solubilization and sampling procedure. For each determination, three samples were withdrawn and inserted into preweighed glass vessels; the vessels were left to cool and were then weighed. The samples were then placed in the freezer (Christ lyophilizer, model Alpha 1-4 equipped with an FTS system vacuum pump) for 24 h and afterward were lyophilized for 48 h, to evaporate water. Finally, the vessels were again weighed. Each experimental value reported is an average of at least three different measurements.

2.2.2. DSC Measurements. Thermograms of the solid phenolics were obtained with a Netzsch DSC 200 F3 Maia differential scanning calorimeter. Samples of 4–6 mg (± 0.1) were sealed in aluminum crucibles and heated under nitrogen, while using an empty crucible as reference. Initial estimates of the melting temperatures were obtained using a 10 K/min heating rate over a larger temperature range. Afterward, several runs at a rate of 1 K/min around the expected melting temperature were averaged. To ascertain the precision of the instrument, an indium standard was run, and the obtained melting temperatures and heats of fusion were compared with the reported values. All experiments were conducted at least in triplicate.

2.2.3. Potentiometric Measurements. Phenolic compounds are typically acidic, so evaluate the extent of solubilization due to acid dissociation, the pH values of the saturated aqueous solutions and the acid dissociation constants ($\text{p}K_{\text{a}}$) were measured by potentiometry, using a glass electrode and a VWR SympHony SB70P meter. Apparent acid dissociation constants were obtained by potentiometric titration of aqueous solutions of the phenolic acids with a sodium hydroxide solution.

3. Thermodynamic Properties of Dissolution

The most common way to evaluate the effect of temperature on solubility is the calculation of solubility products at different temperatures. Alternatively, the thermodynamic properties of dissolution, namely, the molar Gibbs energy ($\Delta_{\text{sol}}G$), enthalpy ($\Delta_{\text{sol}}H$), and entropy ($\Delta_{\text{sol}}S$) of dissolution can be calculated using experimental solubility data. These parameters reflect the modification of the solution properties due to the presence of the solute at infinite dilution, at a given temperature. Assuming that the activity coefficient of the solute is equal to 1 in the hypothetical dilute ideal solution and starting from the Gibbs–Helmholtz equation and the thermodynamic definition of the equilibrium constant (eq 2), the following equation can be obtained²³

$$\Delta_{\text{sol}}H = RT^2 \left(\frac{d \ln x_{\text{s}}}{dT} \right)_p \quad (1)$$

where the molar enthalpy of dissolution, $\Delta_{\text{sol}}H$, is the difference

between the partial molar enthalpy of the compound in solution and the pure molar enthalpy at temperature T , x_s is the mole fraction solubility of the solute, R is the ideal gas constant, and P is the pressure. By plotting $\ln x$ versus temperature and considering this plot as a straight line, $\Delta_{\text{sol}}H$ can be obtained. The remaining thermodynamic functions are obtained from the following expressions

$$\Delta_{\text{sol}}G = -RT \ln(x_s)_P \quad (2)$$

$$\Delta_{\text{sol}}S = \frac{\Delta_{\text{sol}}H - \Delta_{\text{sol}}G}{T} \quad (3)$$

4. Modeling

Considering a pure solid phase with no solid–solid phase transitions, assuming the difference in the heat capacities between the liquid and solid phases of the solute (ΔC_p) to be constant in the temperature range $[T, T_m]$, and neglecting the effect of pressure (melting temperature and enthalpy, heat capacities, and Poynting term), the solubility of a solute s can be calculated from the following generalized expression that relates the reference-state fugacities²⁴

$$\ln \left[\frac{f_s^{\text{liq}}(T, P)}{f_s^{\text{sol}}(T, P)} \right] = \frac{\Delta_{\text{fus}}H}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) - \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \quad (4)$$

where $\Delta_{\text{fus}}H$ is the enthalpy of fusion, T is the absolute temperature, T_m is the melting temperature, ΔC_p is the difference of the liquid and solid molar heat capacities, and R is the ideal gas constant.

Using an activity coefficient model, the following expression for the mole fraction solubility (x_s) is obtained²⁴

$$x_s = \frac{1}{\gamma_s} \exp \left\{ -\frac{\Delta_{\text{fus}}H}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) + \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \right\} \quad (5)$$

where γ_s is the solute activity coefficient.

When an equation of state is selected, eq 6 is used instead

$$x_s = \frac{\varphi_s^{\text{liq}_0}}{\varphi_s^{\text{liq}}} \exp \left\{ -\frac{\Delta_{\text{fus}}H_s}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) + \frac{\Delta C_p}{R} \left[\frac{T_m}{T} - \ln \left(\frac{T_m}{T} \right) - 1 \right] \right\} \quad (6)$$

where φ is the fugacity coefficient and the subscript 0 refers to a pure component.

In this work, both an activity coefficient model (the modified UNIQUAC model^{19,20}) and an equation of state (the cubic-plus-association EoS^{21,22}) were used to represent the measured data. Both models have already been successfully employed for mixtures of water with other associating compounds.^{18,20,22,25}

4.1. Modified UNIQUAC Model. Abrahams and Prausnitz²⁶ derived an equation that in a sense extends the quasichemical theory of Guggenheim for nonrandom mixtures to solutions containing molecules of different sizes. This extension was therefore called the UNiVersal QUAsiChemical theory (UNIQUAC).²⁴ The UNIQUAC equation consists of two parts: a combinatorial term that attempts to describe the dominant entropic contribution (that depends on the composition and the sizes and shapes of the molecules) and a residual term that is

due mainly to the intermolecular forces responsible for the enthalpy of mixing.

Larsen et al.¹⁹ proposed a modified version of this model that was successfully used to study the solubility of highly associating compounds in water and also in mixed solvents.²⁰ The results achieved were very good and consistent over broad temperature and composition ranges.

The combinatorial part is given by the Flory–Huggins expression, and the residual part is given by the original Abrams and Prausnitz expression.²⁶ Although a temperature dependence was suggested for the binary interaction parameter (a_{ij}), this is not considered here because of the reduced number of experimental data available.

The volume and area parameters of the molecules were calculated from the volume and area parameters of the groups, using the UNIFAC parameter tables presented elsewhere.²⁷

4.2. Cubic-Plus-Association (CPA) Equation of State. In this work, we are considering water and phenolic compounds, which means that both the solute and the solvent can associate. Traditional cubic equations of state have proved to have good predictive capabilities for nonassociating fluids, but they typically fail in describing these particular interactions. This handicap of cubic equations of state was solved with the cubic-plus-association equation of state (CPA EoS).^{21,22}

The CPA EoS combines a cubic contribution [from the Soave–Redlich–Kwong (SRK) or the Peng–Robinson (PR) equation of state] with an association contribution,²⁸ originally proposed by Wertheim and used in other associating equations of state such as the statistical associating fluid theory (SAFT),²⁹ accounting for intermolecular hydrogen bonding and solvation effects. Using a generalized cubic term³⁰ (for the SRK approach, $\delta_1 = 1$, $\delta_2 = 0$; for the PR approach, $\delta_1 = 1 + \sqrt{2}$, $\delta_2 = 1 - \sqrt{2}$), the cubic and association contributions to the Helmholtz energy (A) are the following

$$A^{\text{cubic}} = \frac{an}{b(\delta_2 - \delta_1)} \ln \left(\frac{1 + b\rho\delta_1}{1 + b\rho\delta_2} \right) - nRT \ln(1 - b\rho) \quad (7)$$

$$A^{\text{assoc}} = RT \sum_i n_i \sum_{A_i} \left[\ln(X_{A_i}) - \frac{X_{A_i}}{2} + \frac{1}{2} \right] \quad (8)$$

where i is a component index, b is the covolume parameter, a the energy parameter, ρ is the molar density, n_i is the number of moles of molecules of component i , n is the total number of moles, g is a simplified radial distribution function,³¹ and X_{A_i} is the mole fraction of component i not bonded at site A .

The pure-component energy parameter is given by

$$a(T) = a_0[1 + c_1(1 - \sqrt{T_r})]^2 \quad (9)$$

where a_0 and c_1 are constants to be calculated and T_r is the reduced temperature. Only a binary interaction parameter, k_{ij} , on the cross energy parameter a_{ij} is introduced in the cubic contribution, as in previous works.^{32,33}

X_{A_i} is related to the association strength, Δ^{A,B_i} , between two sites belonging to two different molecules and is calculated by solving a set of equations, involving all nonbonded mole fractions

$$X_{A_i} = \frac{1}{1 + \rho \sum_j x_j \sum_{B_j} X_{B_j} \Delta^{A,B_j}} \quad (10)$$

For cross-associating systems, such as those considered in this work, both self- and cross-association Δ functions need to

TABLE 1: Experimental Solubilities (*S*) of Hydroxybenzoic Acids in Pure Water and the Corresponding Saturation pH Values

| <i>T</i> (K) | protocatechuic acid | | syringic acid | |
|--------------|---|------|---|------|
| | <i>S</i> ± <i>σ</i> ^a (g L ⁻¹) | pH | <i>S</i> ± <i>σ</i> ^a (g L ⁻¹) | pH |
| 323 | 49.3 ± 0.5 52.8 ± 0.2 ^b | 2.41 | 5.8 ± 0.2 | 2.90 |
| 313 | 28.1 ± 0.9 | 2.61 | 4.4 ± 0.1 | 3.07 |
| 303 | 17.4 ± 0.1 | 2.97 | 2.7 ± 0.0 | 3.31 |
| 298 | 12.7 ± 0.2 | 3.06 | 2.3 ± 0.0 | 3.42 |
| 288 | 7.6 ± 0.6 | 3.08 | 1.1 ± 0.0 | 3.52 |

^a Standard deviation. ^b Value measured by gravimetry.

be obtained. Additionally, for multifunctional associating molecules, such as the phenolic compounds under study (Figure 1), different associating groups can be present on the same molecule, in some cases with multiple substitutions. Applications of associating equations of state to these complex multifunctional molecules have traditionally been performed with a single association energy and volume for the entire molecule.^{22,25} Only the group-contribution-association (GCA)³⁴ and, very recently, the CPA equations of state¹⁸ have been adopted for multifunctional associating molecules with explicit association energies and volumes for the different associating groups.

The procedure followed in this work is the same as that recently proposed by the authors.¹⁸ The cubic-term parameters are calculated from the critical temperature (*T*_c), critical pressure (*P*_c), and van der Waals volume (vdWV)

$$a_0 = 0.2267 + 24.38 \frac{T_c^2}{P_c} \quad (11)$$

$$c_1 = -3.557 + (6.289 \times 10^{-3})T_c \quad (12)$$

$$b = -2.328 \times 10^{-5} + 1.884 \text{vdWV} \quad (13)$$

where *T*_c is in K, *P*_c is in Pa, and the van der Waals volume is in m³/mol.

The corresponding association energies and volumes to be used in the association term are obtained from a set of model molecules for which vapor pressure and liquid density data are available using the cubic-term parameters from eqs 11–13. This is further discussed in the following section.

5. Results and Discussion

Solubility results, in grams per liter, and the corresponding pH of each saturated solution are reported in Tables 1 and 2. As can be observed for all compounds, the solubility follows a general exponential trend with temperature. In a previous work,¹⁸ we reported the solubilities of other phenolic compounds, and the results were in good agreement with most of the available literature data.

Among the hydroxybenzoic acids (Table 1), the extent of hydrogen bonding with water seems to be an important variable during the solubilization process. Protocatechuic acid is more soluble than syringic acid (and salicylic acid,¹⁸ both having one hydroxyl group), but less soluble than gallic acid (which has three hydroxyl groups in the aromatic ring¹⁸). Literature data for these two hydroxybenzoic acids were found only in the works of Noubigh et al.,^{11,35,36} but the disagreement with our data is relevant (Figure 2). Such disagreement was also found before for gallic acid, where the data from these authors were in considerable disagreement with our data and those of Lu and Lu.¹⁴ For all of these hydroxybenzoic acids and for ferulic acid,

Noubigh et al.'s data do not increase significantly with temperature, in contrast to what would be expected.

For *o*-coumaric acid (Table 2), no literature data were found to compare with our results, but comparison with previous data for other phenylpropenoic acids such as *trans*-cinnamic, ferulic, and caffeic acids¹⁸ shows that the obtained results follow the expected trend in solubility (*trans*-cinnamic acid < *o*-coumaric acid < ferulic acid < caffeic acid) considering the extent of hydrogen bonding with water. As found before, for other hydroxybenzoic and phenylpropenoic acids, the latter usually present lower solubilities, as was also found in this work.

Among the studied phenolic compounds, ellagic acid (Table 2) is the one with the lowest solubilities. Only one value obtained by Bala et al.³⁷ at 310 K (9.7 mg/L) was found for comparison with our results at the nearest temperatures (4.4 and 5.9 mg/L for 303.2 and 313.2 K, respectively). The deviation from our results is significant, but the standard deviation found by Bala et al.³⁷ is so high (±3.2 mg/L) that the value measured in this work shows consistency with their findings.

Tyrosol (Table 2) is the most soluble phenolic, and no solubility data for it were found, except for a single point at 293.2 K available in the Merck Index (124 g/L).³⁸ Our results compare well with that value. The density of the saturated solution of tyrosol at 298.2 K was measured and found to be 998.86 g/L. As this compound has high solubilities, for the calculation of mole fractions for modeling purposes, the mass of the solute cannot be considered negligible in comparison to the solvent mass, and this density value was used.

As mentioned previously, to verify the accuracy of the spectroscopic method, some measurements at the higher temperatures were also done by the gravimetric method. The analytical gravimetric method is a quite simple technique, very accurate and highly reproducible, and it has already been applied to a large range of compounds. For *o*-coumaric acid, the difference between the results from the two methods is 1.5%; for protocatechuic acid, 7%; and for tyrosol, 11%. These differences are not significant, meaning that the spectrophotometric method is reliable.

Relative differences in solubility can also be understood with the help of the thermodynamic properties of solvation presented in Table 3. These were obtained by considering the plots of ln *x* vs *T* to be linear functions, so that the derivatives in eq 1 are the slopes of the corresponding linear fits.

In terms of enthalpy, we can see that ellagic acid would be more favorably solubilized than the other phenolics, but this is not the case, as there is also a very strong entropic effect. This can be explained by the considerable number of water hydrogen bonds that must be broken to solubilize such a large molecule, even though the molecule has four hydroxyl groups that can hydrogen bond with water.

It is also curious to note that tyrosol, although not expected because of its highest dissolution enthalpy, is very soluble because it has the highest dissolution enthalpy. Still, opposite to ellagic acid, tyrosol has a very high entropic contribution favoring dissolution. Protocatechuic and *o*-coumaric acids have very similar enthalpic contributions for dissolution, but protocatechuic acid is more soluble because of a more favorable entropic term. Finally, syringic acid is slightly more soluble than *o*-coumaric acid because of a more favorable enthalpic contribution.

For all of the compounds, it was found that the solubilization process is endergonic ($\Delta_{\text{sol}}G > 0$) and, therefore, nonspontaneous.

Other important information about the solubilization of solids in liquids is related to fusion enthalpies and melting tempera-

TABLE 2: Experimental Solubilities (*S*) of Tyrosol, *o*-Coumaric Acid, and Ellagic Acid in Pure Water and the Corresponding Saturation pH Values

| <i>T</i> (K) | tyrosol | | <i>o</i> -coumaric acid | | ellagic acid | |
|--------------|---|------|---|------|---|------|
| | <i>S</i> ± <i>σ</i> ^a (g L ⁻¹) | pH | <i>S</i> ± <i>σ</i> ^a (g L ⁻¹) | pH | <i>S</i> ± <i>σ</i> ^a (g L ⁻¹) | pH |
| 323 | 647.2 ± 7.8 | 4.34 | 1.3 ± 0.0 | 3.37 | 7.2 ± 0.3 | 4.38 |
| | 572.9 ± 6.7 ^b | | 1.3 ± 0.1 ^b | | | |
| 313 | 300.8 ± 3.9 | 4.97 | 0.8 ± 0.0 | 3.45 | 5.9 ± 0.2 | 4.51 |
| 303 | 154.9 ± 2.5 | 5.19 | 0.5 ± 0.0 | 3.56 | 4.4 ± 0.1 | 4.65 |
| 298 | 106.9 ± 1.5 | 5.49 | 0.3 ± 0.0 | 3.73 | 3.8 ± 0.1 | 4.84 |
| 288 | 63.2 ± 0.5 | 5.50 | 0.2 ± 0.0 | 3.79 | 2.7 ± 0.1 | 4.89 |

^a Standard deviation. ^b Value measured by gravimetry.

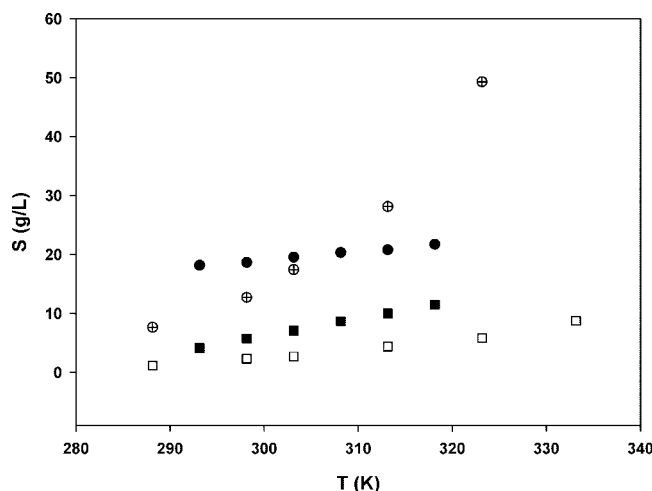


Figure 2. Aqueous solubilities of hydroxybenzoic acids as a function of temperature: this work (●, protocatechuic acid; □, syringic acid) and results obtained by Noubigh et al.¹¹ (●, protocatechuic acid; ■, syringic acid).

tures, with lower values of both properties favoring solubility (eqs 5 and 6). The melting properties of the compounds measured in this work are compiled in Table 4, together with the numbers of measurements and standard deviations. For all of the phenolic compounds, except *o*-coumaric and ellagic acids, a linear baseline and a single peak were observed. The melting peak of *o*-coumaric acid is not symmetric, with other peaks continuously connected to the melting peak, indicating that decomposition processes might occur upon melting. For this reason, the fusion enthalpy of this acid could not be determined, so it was calculated using a third-order group-contribution approach proposed by Marrero and Gani³⁹ that was found to give accurate estimates for both melting temperatures and enthalpies of fusion of different phenolics. The same was done for ellagic acid, as the apparent melting peak was quite large and not symmetrical. All DSC crucibles were weighed before and after the DSC measurement to check for mass loss. Literature data were found only for the melting temperature of tyrosol,⁴⁰ with our data deviating by less than 0.3%.

For the three compounds for which we measured and predicted the melting data, higher disagreements between the experimental values and the Marrero and Gani method were found for the melting temperature (3%) and enthalpy of fusion (25%) of syringic acid, which can be considered as good predictive results. From the measured solubility and the measured and predicted melting data, it can be seen that only for tyrosol and ellagic acid did these variables seem to have a significant influence on the relative solubility: the most soluble,

tyrosol, is the phenolic compound with the lowest melting temperature and enthalpy of fusion, whereas ellagic acid is the least soluble and the one requiring the highest temperature and energy to break the crystal structure. For the other three compounds, these data do not seem to be a determining factor in solubility.

Liquid and solid experimental heat capacities are available for a limited number of compounds. From the DSC thermograms, we could determine these values for protocatechuic and syringic acids and tyrosol (Table 4), but no literature data were found for the other studied phenolics. Therefore, a three-level group-contribution method reported by Marrero and Gani³⁹ and extended by Kolská et al.⁴¹ was used for the estimation of the heat capacities of the liquids. These authors presented group-contribution parameters that were determined by both nonhierarchical and hierarchic approaches and tested the model performance in terms of extrapolation features, predictive capability, and consistency. Although the nonhierarchical approach proved to be slightly superior, the heat capacity of ellagic acid was estimated using the hierarchic approach, because the other parameters led to a too-high heat capacity value. For the estimation of the heat capacities of the solids, a correlation based on molecular structure was used.⁴² This model was tested by the authors with an average accuracy of approximately 13%. For the three compounds with experimental values, the results were in good agreement (5%, 8%, and 4% deviations, respectively, for protocatechuic acid, syringic acid, and tyrosol).

As most of the studied compounds are organic acids, measurements of apparent equilibrium constants, $K_{a,app}$, were carried out at 298.2 K, and the results are presented in Table 5. These are apparent dissociation constants, because only the H^+ activity is considered, as given by the pH measuring system

$$K_{a,app} = \frac{[A^-](H^+)}{[HA]} \quad (14)$$

where activities are represented by parentheses and concentrations are represented by square brackets.

For the purposes of this work, this is a consistent procedure, as we are mostly interested in the ratio of the basic to the acidic form, in order to evaluate the extent of acid dissociation on the solubility. The obtained $pK_{a,app}$ results and the reported saturated pH values presented in Tables 1 and 2 lead to the conclusion that the extent of dissociation at equilibrium is very small and, thus, acid dissociation is not an important factor for determining the solubilities of the studied phenolic compounds in pure water. Tyrosol is the least acidic phenolic compound, with a pK_a very close to that of phenol (9.89), as expected, followed by ellagic acid, *o*-coumaric acid, and the hydroxybenzoic acids.

Finally, the measured data were used to evaluate the performance of the modified UNIQUAC and CPA EoS for their estimation.

TABLE 3: Thermodynamic Properties for the Dissolution of the Phenolic Compounds in Pure Water: $\Delta_{\text{sol}}G$ (kJ/mol), $\Delta_{\text{sol}}H$ (kJ/mol), and $\Delta_{\text{sol}}S$ [J/(mol K)]

| $T(\text{K})$ | $\Delta_{\text{sol}}H \pm \sigma^a$ | $\Delta_{\text{sol}}G \pm \sigma^a$ | $\Delta_{\text{sol}}S \pm \sigma^a$ |
|-------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| protocatechuic acid | | | |
| 323 | 46.4 ± 0.8 | 13.9 ± 0.2 | 100.6 ± 0.7 |
| 313 | 43.5 ± 0.8 | 14.9 ± 0.2 | 91.5 ± 0.5 |
| 303 | 40.8 ± 0.7 | 15.6 ± 0.2 | 83.1 ± 0.6 |
| 298 | 39.5 ± 0.7 | 16.2 ± 0.0 | 78.2 ± 0.1 |
| 288 | 36.9 ± 0.6 | 16.8 ± 0.2 | 69.5 ± 0.7 |
| syringic acid | | | |
| 323 | 38.6 ± 2.9 | 20.2 ± 0.1 | 56.9 ± 0.3 |
| 313 | 36.3 ± 2.7 | 20.4 ± 0.1 | 50.8 ± 0.2 |
| 303 | 34.0 ± 2.6 | 20.9 ± 0.0 | 43.1 ± 0.1 |
| 298 | 32.9 ± 2.5 | 21.0 ± 0.0 | 39.8 ± 0.1 |
| 288 | 30.7 ± 2.3 | 22.0 ± 0.1 | 30.1 ± 0.2 |
| ellagic acid | | | |
| 323 | 23.61 ± 1.3 | 39.4 ± 0.1 | -48.9 ± 0.4 |
| 313 | 22.2 ± 1.2 | 38.7 ± 0.1 | -52.8 ± 0.2 |
| 303 | 20.8 ± 1.1 | 38.2 ± 0.0 | -57.4 ± 0.1 |
| 298 | 2.1 ± 1.1 | 37.9 ± 0.2 | -59.7 ± 0.7 |
| 288 | 18.8 ± 1.0 | 37.4 ± 0.0 | -64.7 ± 0.2 |
| <i>o</i> -coumaric acid | | | |
| 323 | 49.1 ± 4.4 | 23.7 ± 0.0 | 78.7 ± 0.1 |
| 313 | 46.2 ± 4.1 | 24.3 ± 0.0 | 69.8 ± 0.1 |
| 303 | 43.3 ± 3.9 | 24.8 ± 0.1 | 60.8 ± 0.3 |
| 298 | 41.8 ± 3.7 | 25.8 ± 0.1 | 53.7 ± 0.4 |
| 288 | 39.1 ± 3.5 | 25.7 ± 0.0 | 46.5 ± 0.1 |
| tyrosol | | | |
| 323 | 76.5 ± 7.3 | 4.4 ± 0.3 | 222.9 ± 0.7 |
| 313 | 71.8 ± 6.9 | 7.6 ± 0.3 | 204.9 ± 1.0 |
| 303 | 67.3 ± 6.4 | 9.5 ± 0.2 | 190.7 ± 0.7 |
| 298 | 65.1 ± 6.2 | 10.4 ± 0.4 | 183.6 ± 1.4 |
| 288 | 60.8 ± 5.8 | 11.4 ± 0.5 | 171.6 ± 1.7 |

^a Standard deviation.

For the modified UNIQUAC model, the residual term binary interaction parameters were fitted to the measured data. Two temperature-independent interaction parameters were regressed per each binary water + phenolic system. The values are presented in Table 6. Table 6 also contains the volume and area parameters.

In Figure 3, the experimental and calculated solubilities are compared. An excellent description is obtained, using the melting data presented in Table 4. The absolute average deviations (AADs) are good: 5% for syringic and protocatechuic acids, 6% for coumaric acid, 8% for tyrosol, and 27% for ellagic acid.

The CPA EoS was used with the SRK cubic term (eq 7). In the traditional way, the CPA parameters would be obtained from pure-component vapor pressure and liquid density data, but because these data are not available for the studied molecules, the cubic-term parameters were calculated as proposed before for other phenolics (eqs 11–13) using T_c and P_c obtained from the Marrero and Gani group-contribution procedure³⁹ and the van der Waals volumes from the Bondi group-contribution approach.⁴³ These parameters are presented in Table 7. Water parameters from a previous work were used¹⁸ ($a_0 = 0.12 \text{ Pa m}^6/\text{mol}^2$, $c_1 = 0.67$, $b = 1.45 \times 10^{-5} \text{ m}^3/\text{mol}$, $\varepsilon = 16555 \text{ J/mol}$, $\beta = 0.069$, four-site model). For the association contribution, values of the association energy and volume for the different associating groups involved in each molecule are presented in Table 8. These values were obtained from a previous work where the parameters were estimated from pure-component vapor pressure and liquid density data of model molecules.¹⁸ For the case of the hydroxyl group in a phenylethanol molecule

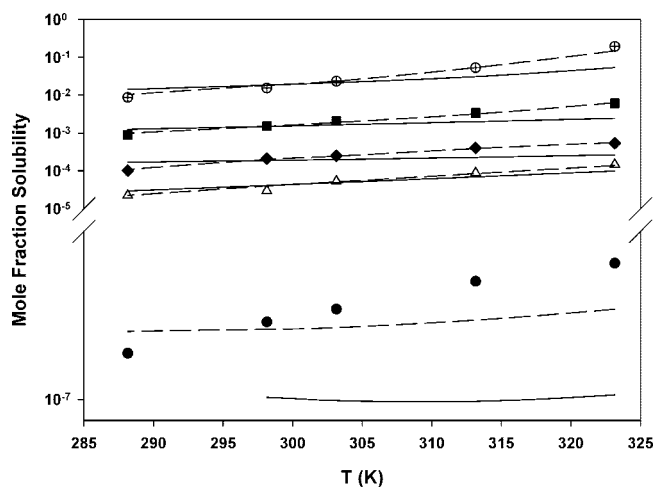


Figure 3. Solubilities of phenolic compounds in water as a function of temperature: experimental results (■, protocatechuic acid; ◆, syringic acid; △, *o*-coumaric acid; ○, tyrosol; ●, ellagic acid) and modeling results (—, CPA; ---, UNIQUAC).

(Table 8, last line), the association energy and volume were regressed from data for 2-phenylethanol obtained from the DIPPR database.⁴⁴ For acid groups, both the association energies and volumes are considerably dependent on whether there is ring substitution with or without intramolecular association or phenylpropenoic substitution. For hydroxyl groups, the values depend on whether there are intramolecular hydrogen bonds. From this methodology, all of the cubic and associating parameters of the molecules under study can be estimated, without requiring experimental pure-component data. In the case of syringic and ellagic acids, the ether and ester groups are not considered to cross-associate with water.

The CPA modeling results are presented in Figure 3. A good description of the data can be obtained using a single temperature-independent parameter k_{ij} for each binary system. A maximum average absolute deviation (in mole fraction solubility) of 66% was obtained for ellagic acid, whereas for the other phenolics, the average deviations did not exceed 39%, which can be considered as good results, given that these water + organic systems are frequently difficult to model accurately.³² It is important to focus on the fact that the ellagic acid solubilities are too low, and therefore, a deviation of 60% in the prediction is not so bad. We also consider that this is a quite complex molecule for which we do not know whether the predictivity of the proposed CPA model and the correlations for the melting properties and ΔC_p are or not sufficiently accurate. All of the correlated k_{ij} values are negative (tyrosol, $k_{ij} = -0.14$; protocatechuic acid, $k_{ij} = -0.06$; syringic acid, $k_{ij} = -0.13$; *o*-coumaric acid, $k_{ij} = -0.03$; ellagic acid, $k_{ij} = -0.12$), indicating that the water–phenolic interactions are stronger than expected. This is particularly the case for ellagic and syringic acids, where the presence of the ester and ether groups, respectively, was not considered to increase solvation.

As shown, the predictive ability of the proposed procedure for the pure-component parameters leads to good results provided that a single k_{ij} value is employed.

6. Conclusions

In this work, aqueous solubility data were measured for some phenolic compounds, namely, tyrosol and ellagic, *o*-coumaric, protocatechuic, and syringic acids, in pure water, in the temperature range from 288.2 to 323.2 K, using the shake-flask

TABLE 4: Average Melting Points, Enthalpies of Fusion, and Differential Heat Capacities of the Studied Phenolic Acids

| | scans | T_m (K) | $\Delta_{fus}H \pm \sigma^a$ (kJ/mol) | $\Delta C_p \pm \sigma^a$ [J/(mol K)] |
|-------------------------|-------|--------------------|---------------------------------------|---------------------------------------|
| protocatechuic acid | 7 | 472.3 \pm 1.6 | 31.2 \pm 1.6 | 108.0 \pm 6.2 |
| | — | 469.3 ^b | 34.2 ^b | 102.4 ^c |
| syringic acid | 7 | 480.3 \pm 0.6 | 33.7 \pm 1.8 | 76.8 \pm 3.4 |
| | — | 463.8 ^b | 25.0 ^b | 83.0 ^c |
| tyrosol | 6 | 364.0 \pm 0.2 | 25.9 \pm 1.6 | 125.6 \pm 21.4 |
| | — | 372.8 ^b | 20.3 ^b | 120.5 ^c |
| ellagic acid | — | 560.4 ^b | 59.7 ^b | 394.0 ^c |
| <i>o</i> -coumaric acid | — | 429.9 ^b | 32.2 ^b | 117.5 ^c |

^a Standard deviation. ^b Calculated using a group-contribution method.³⁹ ^c Calculated using a group-contribution method for the estimation of the heat capacities of liquids⁴¹ and a correlation based on molecular structure for the heat capacity of solids.⁴²

TABLE 5: Apparent Acid Dissociation Constants of the Studied Phenolic Acids at 298.15 K

| phenolic acid | $pK_{a,app}$ |
|-------------------------|--------------|
| protocatechuic acid | 4.63 |
| syringic acid | 4.71 |
| <i>o</i> -coumaric acid | 4.82 |
| ellagic acid | 6.54 |
| tyrosol | 10.0 |

TABLE 6: Modified UNIQUAC Model Parameters in Water (j) and Volume and Area Parameters for Each Compound^a

| i | a_{ij} (K) | a_{ji} (K) | r_i | q_i |
|-------------------------|--------------|--------------|--------|--------|
| protocatechuic acid | −309.81 | 913.32 | 5.0508 | 3.9040 |
| syringic acid | −10.75 | 363.18 | 6.6447 | 5.2400 |
| <i>o</i> -coumaric acid | −11.39 | 574.56 | 5.8036 | 4.4910 |
| ellagic acid | 54.91 | 1056.37 | 8.8387 | 6.0000 |
| tyrosol | −86.13 | 377.71 | 5.7344 | 4.6800 |

^a Water: $r_j = 0.92$; $q_j = 1.40$.

TABLE 7: Critical Properties and van der Waals Volumes Used in the CPA EoS

| compound | T_c (K) | P_c (MPa) | vdWV (10^{-5} m ³ /mol) |
|-------------------------|-----------|-------------|---------------------------------------|
| protocatechuic acid | 855.0 | 6.47 | 7.85 |
| syringic acid | 856.6 | 3.77 | 10.53 |
| <i>o</i> -coumaric acid | 831.8 | 4.26 | 8.82 |
| ellagic acid | 1056 | 13.75 | 14.9 |
| tyrosol | 762.3 | 4.71 | 8.03 |
| 2-phenylethanol | 684.0 | 3.92 | 7.43 |

TABLE 8: Association Parameters in the CPA

| position | ϵ (J mol ^{−1}) | β |
|-------------------------------|-----------------------------------|------------------------|
| COOH Group | | |
| benzoic acid | 32010 | 9.820×10^{-6} |
| phenylpropenoic acid | 27560 | 3.698×10^{-3} |
| OH Group | | |
| ring, single OH | 18370 | 1.185×10^{-2} |
| ring, orto with OH | 11340 | 6.225×10^{-2} |
| aliphatic OH in phenylethanol | 23367 | 1.417×10^{-2} |

method coupled with spectrophotometric analysis. All solubilities were found to increase with temperature, as expected. From the aqueous solubility data, thermodynamic molar properties of dissolution were derived. The studied compounds can be divided into the following groups: substituted phenols (tyrosol), which have higher solubilities, hydroxybenzoic acids (protocatechuic and syringic acids), phenylpropenoic acids (*o*-coumaric acid), and tannins (ellagic acid), which have lower solubilities. In addition to solubility data, melting temperatures, enthalpies of fusion, and apparent dissociation constants were

also determined, providing broader knowledge about the solubilization processes of these molecules. From all of the measurements, it was concluded that the extent of solubilization is mostly governed by the degree of hydrogen-bond formation with water, but the energetics of the solid state also play an important role for some of the studied molecules.

The modified UNIQUAC model, with two adjustable parameters from solubility data, provided an excellent description of the solubilities of these phenolic compounds. The CPA EoS, with a single binary interaction parameter, can also be used to estimate the solubilities of these molecules, although with a worse description compared to that of the modified UNIQUAC. It was also demonstrated that the CPA parameters of these molecules can be obtained solely from their molecular structure, avoiding the need for pure-component data. The methodology proposed in this work is expected to be an important tool for the modeling of the phase equilibria of multifunctional associating molecules.

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List of Symbols

a_0 = parameter in the cubic term of CPA (Pa m⁶/mol²)

b = covolume parameter in the CPA (m³/mol)

c_1 = parameter in the cubic term of the CPA

CPA = cubic plus association

EoS = equation of state

f = fugacity

n = number of moles

P = pressure (Pa)

q = UNIQUAC area parameter

r = UNIQUAC volume parameter

$K_{a,app}$ = apparent acid dissociation constant

R = gas constant [8.314 J/(mol K)]

S = solubility

T = absolute temperature (K)

vdWV = van der Waals volume (m³/mol)

x = mole fraction

X_{A_i} = fraction of molecule i not bonded at site A

Greek Symbols

ϵ = association energy (J/mol)

β = association volume

γ = activity coefficient

$\Delta^{A,B}_i$ = association strength between site A on molecule i and site B on molecule j
 ΔC_p = difference between the liquid and solid molar heat capacities
 $\Delta_{\text{sol}}G$ = molar Gibbs energy of dissolution
 $\Delta_{\text{sol}}H$ = molar enthalpy of dissolution
 $\Delta_{\text{sol}}S$ = molar entropy of dissolution
 $\Delta_{\text{fus}}H$ = fusion enthalpy (J/mol)
 ρ = mole density (mol/m³)
 σ = standard deviation
 φ = fugacity coefficient

Subscripts

c = critical
 i, j = component indexes
 m = melting
 r = reduced
 s = solute

Superscripts

assoc = association term
cubic = cubic term
liq = liquid phase
sol = solid phase
0 = pure component

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