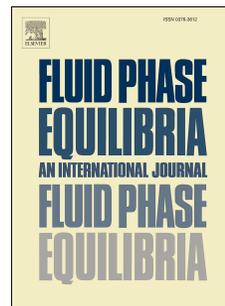


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Solid-liquid phase equilibrium of *trans*-cinnamic acid, *p*-coumaric acid and ferulic acid in water and organic solvents: Experimental and modelling studies

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CRediT author statement

Sérgio M. Vilas-Boas: Investigation, Writing - Original Draft, Data Curation, Software. Rebeca S. Alves: Investigation. Paula Brandão: Investigation, Data Curation, Writing - Review and Editing. Leila M. A. Campos: Writing - Review & Editing. João A.P. Coutinho: Supervision, Writing - Review & Editing. Simão P. Pinho: Supervision, Project administration, Writing - Review and Editing. Olga Ferreira: Supervision, Project administration, Writing - Review & Editing.

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1 **Solid-liquid phase equilibrium of *trans*-cinnamic acid, *p*-coumaric acid**
2 **and ferulic acid in water and organic solvents: experimental and**
3 **modelling studies**

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16 Abstract

17 The solubility of the *trans* isomers of cinnamic acid, *p*-coumaric acid and ferulic acid
18 was measured in water and seven organic solvents (methanol, ethanol, 1-propanol, 2-
19 propanol, 2-butanone, ethyl acetate and acetonitrile), at 298.2 and 313.2 K, using the
20 analytical shake-flask technique. The melting temperatures and enthalpies of the solutes
21 were studied by differential scanning calorimetry, while solute solid structures were
22 identified by powder and single X-ray diffraction.

23 The NRTL-SAC model was applied to calculate the solubility of *trans*-cinnamic acid
24 and *trans*-ferulic acid in pure solvents. For *trans-p*-coumaric acid, the NRTL-SAC was
25 combined with the Reference Solvent Approach, as the solute melting properties could
26 not be determined. The global average relative deviations (ARD) were 32% and 41%, in
27 the correlation and prediction stages, respectively. The Abraham solvation model was
28 also applied. The global ARD were 20% for correlation and 29% for predictions, which
29 can be considered very satisfactory results for these semi-predictive models.

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33 Keywords

34 Cinnamic acid derivatives; solubility; solid phase studies; NRTL-SAC model; Abraham
35 solvation model

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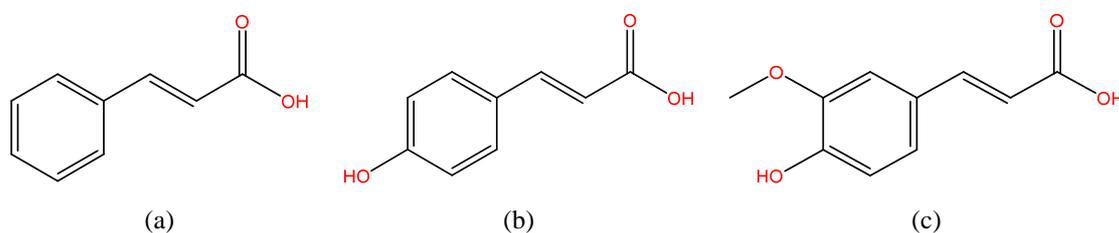
46 **1. Introduction**

47 Naturally occurring phenolic acids are well studied for their bioactive properties and
48 present a wide distribution in plant material, where they can be found in the free form,
49 or conjugated to other molecules [1]. Among this family of compounds, two major
50 classes can be distinguished based on their structure: benzoic acid derivatives and
51 cinnamic acid derivatives [1,2]. In general, cinnamic acid derivatives are more abundant
52 in nature, especially ferulic acid, caffeic acid, *p*-coumaric acid and sinapic acid [2–4],
53 having many applications in the pharmaceutical, food, and cosmetic industries due to
54 their chemical and biological properties [2,3].

55 The main aim of this work is to study the solubility of the *trans* isomers (for simplicity,
56 the prefix *trans* will be omitted in the text) of cinnamic acid and two derivatives (*p*-
57 coumaric acid and ferulic acid) in water and seven pure organic solvents (methanol,
58 ethanol, 1-propanol, 2-propanol, 2-butanone, ethyl acetate and acetonitrile) at 298.2 K
59 and 313.2 K. Whenever possible, the solubility data were critically compared to
60 literature. Some solubility studies can be found for cinnamic acid [5–8], *p*-coumaric
61 acid [9,10], and ferulic acid [5,11–15], but for several binary systems, the solubility data
62 are reported for the first time.

63 The structures of the solutes are shown in Fig. 1. As can be seen, relatively to the
64 simplest cinnamic acid (3-phenylacrylic acid), *p*-coumaric acid (3-(4-
65 hydroxyphenyl)acrylic acid) has an additional hydroxyl group and ferulic acid (3-(4-
66 hydroxy-3-methoxyphenyl)acrylic acid) presents a hydroxyl and a methoxy group.

67



68 **Fig. 1.** Chemical structures of the *trans* isomers of: (a) cinnamic acid; (b) *p*-coumaric acid and (c) ferulic
69 acid.

70 The *trans* isomer is the predominant form of cinnamic acid, being Chinese cinnamon a
71 major natural source, and presents relevant pharmaceutical and biological properties,
72 such as antibacterial, anti-inflammatory, antifungal, antioxidant and antitumor activities

73 [16]. Cinnamic acid is also an ingredient used in several personal-care products and
74 non-cosmetic products [17]. Similarly, *p*-coumaric acid and its conjugates also present
75 bioactive properties in different dimensions, such as antioxidant, anti-tumour,
76 antimicrobial, antiviral, anti-inflammatory, antiplatelet aggregation, anxiolytic,
77 antipyretic, analgesic, and anti-arthritis [18]. Also, this compound has been identified as
78 a competitive inhibitor of tyrosinase, and studied as a potential skin-lightening cosmetic
79 ingredient [19]. Finally, ferulic acid is the most abundant phenolic acid found in cereal
80 grains, and in different vegetables and fruits, such as citrus fruits, banana, coffee,
81 eggplant, bamboo shoots, beetroot, cabbage, spinach, and broccoli [2,20]. It presents
82 antioxidant, antimicrobial, anti-inflammatory, anti-thrombosis, and anti-tumour
83 activities, among others. It is widely used as an ingredient in the food and cosmetic
84 areas and as a raw material for the production of other important compounds, such as
85 vanillin, sinapic acid and curcumin [20,21]. Thus, for the adequate design of products
86 and processes it is extremely relevant to know some of their physicochemical
87 properties, namely reliable solubility data in pure and mixed solvents, as the compounds
88 are in the solid state at room conditions.

89 Finally, to model the solid-liquid equilibria data, two semi-predictive thermodynamic
90 models were selected: (1) the semi-predictive Nonrandom Two-Liquid Segment
91 Activity Coefficient (NRTL-SAC) model proposed by Chen and Song [22] that was
92 already used to describe the solubility of phenolic compounds in water and organic
93 solvents [23–28]; (2) the Abraham solvation model [29–31] that has been applied to
94 calculate the solubility of benzoic acid derivatives [28,32–39], and cinnamic acid
95 derivatives [8,40]. To support the description of the solid-liquid equilibria, the melting
96 properties of the pure solutes were measured by Differential Scanning Calorimetry
97 (DSC) and solid phase studies were carried out by X-Ray Diffraction (XRD).

98 2. Experimental

99 2.1. Chemicals

100 Ultrapure water (resistivity of 18.2 M Ω ·cm, free particles \geq 0.22 μ m and total organic
101 carbon $<$ 5 μ g·dm⁻³) was used. All the organic compounds were used as received from
102 the suppliers and are listed in Table 1. The solids were kept in a desiccator to avoid
103 water contamination.

104 **Table 1:** Mass purity (%), CAS number and source of the organic compounds used in this work.

Compound	Mass purity (%) ^a	CAS number	Source
<i>trans</i> -cinnamic acid	≥ 99.5	140-10-3	Alfa Aesar
<i>p</i> -coumaric acid	≥ 99.9	7400-08-0	Merck KGaA
<i>trans</i> -ferulic acid	≥ 99.9	537-73-5	Alfa Aesar
methanol	≥ 99.9	67-56-1	Carlo Erba
ethanol	≥ 99.9	64-17-5	Carlo Erba
1-propanol	≥ 99.5	71-23-8	Carlo Erba
2-propanol	≥ 99.9	67-63-0	Honeywell
2-butanone	≥ 99.5	78-93-3	Sigma-Aldrich
ethyl acetate	≥ 99.9	141-78-6	Carlo Erba
acetonitrile	≥ 99.9	75-05-8	Sigma-Aldrich

105 ^a The purity was obtained in the certificate of analysis issued by the manufacturer.

106 2.2. *Melting Properties*

107 The melting temperatures and enthalpies were determined by DSC (model 204 F1
108 Phoenix, NETZSCH) using a nitrogen flowing system. Samples of 3 to 8 mg (± 0.1 mg)
109 were hermetically sealed into aluminum crucibles. The heating and cooling rates were 1
110 K/min and 2 K/min, respectively. The experiments were performed from 293.2 K to
111 523.2 K for cinnamic acid, from 293.2 K to 503.2 K for *p*-coumaric acid, and from
112 293.2 K to 473.2 K for ferulic acid. At least three runs were considered to calculate the
113 final average results. An external calibration was performed using 11 compounds
114 (water, 4-nitrotoluene, naphthalene, benzoic acid, diphenyl acetic acid, indium,
115 anthracene, tin, caffeine, bismuth and zinc). The onset value was considered as the
116 melting temperature.

117 2.3. *Solubility Experiments*

118 The solubility experiments were carried out by the isothermal shake-flask method,
119 which was described in detail elsewhere [27,41]. In summary, around 80 ml of a
120 saturated solution of each binary system was prepared and placed in a thermostatic bath
121 (maximum temperature deviation of ± 0.1 K). From preliminary experiments, the
122 optimum stirring and settling times were found to be 32 h and 15 h, respectively. After
123 reaching equilibrium, three samples of around 0.3 cm³ were collected from the
124 supernatant solution, using pre-heated plastic syringes coupled to a polypropylene filter
125 (0.45 μ m pore size).

126 In previous works [27,28,41], the composition of the samples was quantified by
127 gravimetry. However, tests showed that *trans*-cinnamic acid was thermally unstable,
128 once it presented a weight loss of 6.3%, after remaining at 343.2 K for one week inside
129 an oven, and a weight loss of 1.3% after one month at 303.2 K (along with significant
130 color change in both cases). Therefore, the selected analytical method was UV-Vis
131 spectroscopy (model T70, PG Instruments), at wavelengths 273 nm (cinnamic acid),
132 310 nm (*p*-coumaric acid) and 321 nm (ferulic acid). The samples were diluted in a
133 mixture of water + ethanol (proportion 35:65 by wt.%), placed in cuvettes (5 mm
134 optical path) and then read at least three times. The calibration curves ($R^2 \geq 0.998$) were
135 obtained using seven standard solutions.

136 2.4. Solid-Phase Studies

137 2.4.1. Samples

138 The solid phase of the aromatic acids, as received from suppliers and crystallized after
139 evaporation of a set of selected solvents, was analyzed by powder or single crystal X-
140 Ray diffraction.

141 2.4.2. Powder and Single X-ray Diffraction

142 Powder XRD data were collected on a X'Pert MPD Philips diffractometer, using Cu-K α
143 radiation ($\lambda = 1.5406 \text{ \AA}$), with a curved graphite monochromator, a set incident area of
144 10 mm^2 , and a flat plate sample holder, in a Bragg–Brentano para-focusing optics
145 configuration. Intensity data were collected by the step counting method (step 0.02° and
146 time 5 s) in the range $5^\circ < 2\theta < 50^\circ$.

147 The cell parameters of suitable crystals of the solutes provided from suppliers as well
148 the solid samples obtained after evaporating the solvent (water, methanol, ethanol, 2-
149 butanone, ethyl acetate and acetonitrile) were determined on a Bruker D8 Quest photon
150 100 CMOS, with monochromated Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$) and operating at
151 $150(2) \text{ K}$. The selected crystals were placed at 40 mm from the detector and the spots
152 were measured using different counting times (varying from 10 to 30 s).

153 3. Thermodynamic Modeling

154 3.1. The NRTL-SAC Model

155 The NRTL-SAC model was already applied in previous studies [22–25,28,41–43], and
 156 is described in detail elsewhere [22,42]. The model describes each molecule using four
 157 conceptual segments related to the different surface characteristics: hydrophobic (X),
 158 hydrophilic (Z), polar attractive (Y+), and polar repulsive (Y–). These parameters were
 159 reported for a large number of solvents, including those studied in this work [22,42].
 160 Therefore, only the molecular descriptors of the solute need to be estimated.
 161 Assuming pure solid phase and neglecting the heat capacity change upon melting which
 162 has often a small impact in equilibrium calculations, the solubility of a solid solute in a
 163 liquid solvent can be calculated from the equation [44]:

$$\ln x_s = \frac{\Delta_m H}{RT_m} \left(1 - \frac{T_m}{T}\right) - \ln \gamma_s \quad (1)$$

164 where x_s is the mole fraction solubility of the solute S , R is the ideal gas constant, T is
 165 the absolute temperature, T_m is the absolute melting temperature of the solute, $\Delta_m H$ its
 166 melting enthalpy, and γ_s is the activity coefficient of the solute S in the binary liquid
 167 solution, here calculated using the NRTL-SAC model [22].
 168 As can be seen from Eq. (1), accurate melting properties are needed to predict the
 169 solubility data. Alternatively, the NRTL-SAC model can be combined with the
 170 Reference Solvent Approach (RSA), proposed by Abildskov and O'Connell [45,46]. In
 171 this methodology, the use of a reference solvent eliminates the need of the melting
 172 properties, being a useful tool whenever the melting properties present high
 173 uncertainties or are unavailable. Briefly, the RSA can be described by:

$$\ln x_{Si} = \ln x_{Sj} + \ln \gamma_{Sj}(T, \{x_{Sj}\}) - \ln \gamma_{Si}(T, \{x_{Si}\}) \quad (2)$$

174 where x_{Si} is the mole fraction solubility of solute S in a solvent i , x_{Sj} is the solubility of
 175 the same solute in a reference solvent j , $\gamma_{Si}(T, \{x_{Si}\})$ is the activity coefficient of the
 176 solute in solvent i , while $\gamma_{Sj}(T, \{x_{Sj}\})$ is the activity coefficient of the solute in the
 177 reference solvent j .
 178 As can be seen in Eq. (2), the experimental solubility of a solute in a given reference
 179 solvent is used along with the activity coefficients calculated by the NRTL-SAC model.
 180 For a given set of data, the optimal reference solvent is found by:

$$\min_j \left| \sum_{i=data} \delta \ln x_{S,ij} \right| = \min_j \left| \sum_{i=data} (\ln x_{Si} + \ln \gamma_{Si}) - N(\ln x_{Sj} + \ln \gamma_{Sj}) \right| \quad (3)$$

181 where $\sum_{i=data} \delta \ln x_{S,i,j}$ is the error associated to the mole fraction solubilities of solute
 182 S in all the solvents assuming a reference solvent j , and N is the number of experimental
 183 data points in a given set.

184 3.2. The Abraham Solvation Model

185 The partition coefficient between water and a solvent (P_S) can be approximated by the
 186 ratio of the molar solubilities of a solute in the organic solvent (S_S) and in water (S_w):

$$P_S = \frac{S_S}{S_w} \quad (4)$$

187 As discussed by Abraham and co-authors [31], Eq. (4) only holds if: (a) the solid phase
 188 in equilibrium with both solvents is the same; (b) the secondary medium activity
 189 coefficient of the solute in the two phases is near unity; the same (undissociated, if
 190 ionizable) chemical species should be present in each phase. In addition, the partition of
 191 a solute between two fluid phases can be correlated by two linear free energy
 192 relationships (LFERs) [29–31].

$$\log(P_S) = c + eE + sS + aA + bB + vV \quad (5)$$

$$\log(K_S) = c + eE + sS + aA + bB + lL \quad (6)$$

193

194 Eq. (5) calculates the solute partition between two condensed phases and, Eq. (6), the
 195 partition between a gas phase and an organic solvent. In those equations, the uppercase
 196 descriptors (E , S , A , B , V and L) represent the Abraham solute descriptors, where E is
 197 the solute excess molar refractivity, S refers to the solute dipolarity/polarizability, A and
 198 B account for the overall solute hydrogen bond acidity and basicity, V is the solute's
 199 McGowan characteristic molecular volume and L is the logarithm of the gas-to-
 200 hexadecane partition coefficient at 298.15 K. The lowercase regression coefficients and
 201 constants represent condensed phase properties, already available for a large number of
 202 solvents. For each solute, V can be calculated from its molecular structure. The
 203 descriptor E can be calculated from the solute's refractive index, which can be
 204 experimentally obtained or, if unavailable, estimated using ACD free software.

205 For the solvents studied in this work, these coefficients have already been reported in
 206 literature [31]. Regarding the solute descriptors, they can be estimated by multiple linear

207 regression, using experimental solubility data. Estimations of the solute descriptors have
 208 been already reported for the monomeric and dimeric forms of *trans*-cinnamic acid [8]
 209 and for the monomeric form of *p*-coumaric acid [40], but no information was found for
 210 ferulic acid.

211 4. Results and Discussion

212 4.1. Melting Properties

213 The melting temperatures and enthalpies obtained in this work are presented in Table 2
 214 along with the data found in literature [5,6,9,10,14,47–52]. In Fig. S1 of Supporting
 215 Information (SI), exemplificative thermograms of *trans*-cinnamic acid and ferulic acid
 216 are presented.

217 **Table 2:** Comparison of the melting temperatures and enthalpies of the studied aromatic acids found in
 218 the literature and measured in this work.

Compound	T_m/K	$\Delta_m H/\text{kJ}\cdot\text{mol}^{-1}$	Methodology	Reference
<i>trans</i> -cinnamic acid	406.1. \pm 0.4	22.2 \pm 0.8	DSC	[5]
	406.2 \pm 0.3	22.2 \pm 0.4	DSC	[6]
	406.2	22.6	NA ^a	[48]
	405.5	25.7	DSC	[49]
	404.8	22.6	DSC	[50]
	406.9 \pm 0.2 ^b	22.1 \pm 0.1	DSC	this work
<i>p</i> -coumaric acid	492.4 \pm 0.3	27.4 \pm 0.9	DSC	[9]
	494.4 \pm 0.2	34.3 \pm 0.02	DSC	[10]
	- ^c	- ^c	DSC	this work
ferulic acid	444.6 \pm 0.5	33.3 \pm 1.2	DSC	[5]
	448.0 ^d	33.5 ^d	DSC	[14]
	447.7 ^e	36.3 ^e	DSC	[14]
	445.9 \pm 0.5	34.7 \pm 0.2	DSC	[47]
	444.9 \pm 0.4	31.9 \pm 0.9	DSC	[51]
	445.1 \pm 0.9	33.5 \pm 0.5	DSC	[52]
	445.8 \pm 0.2 ^b	38.4 \pm 0.2	DSC	this work

219

^a Not available.

220

^b The experimental onset temperatures were considered as melting temperatures, in this work.

221

^c Decomposition upon melting.

222

^d Melting properties of ferulic acid as received from the supplier.

223

^e Melting properties of ferulic acid recovered from an aqueous saturated solution (after evaporation of the solvent).

224 The melting properties of *p*-coumaric acid could not be derived from the DSC
 225 experiments performed in this work due to decomposition of the samples upon melting.
 226 Several experiments were performed, always showing an exothermic transition
 227 immediately after an endothermic one, precluding the correct integration of the melting

228 peak. The melting temperatures reported by Alevizou et al. [9] and Ji et al. [10] are
229 similar, whereas the melting enthalpies present larger deviations.

230 In the case of *trans*-cinnamic acid, the melting temperature (406.9 ± 0.2 K) and
231 enthalpy (22.1 ± 0.2 kJ·mol⁻¹) obtained in this work are consistent with the average
232 literature data ($T_m = 405.7 \pm 0.7$ K and $\Delta_m H = 23.1 \pm 1.5$ kJ·mol⁻¹). For ferulic acid, the
233 melting temperature obtained in this work (445.8 ± 0.2 K) is very close to the average
234 melting temperature calculated from literature (445.7 ± 1.2 K), being closer to the value
235 reported by Emel'yanenko et al. [47]. The melting enthalpy (38.4 ± 0.2 kJ·mol⁻¹),
236 however, is higher than the literature average ($\Delta_m H = 33.9 \pm 1.5$ kJ·mol⁻¹). Shakeel et al.
237 [14] measured the melting properties for ferulic acid obtained directly from the supplier
238 and recovered from saturated aqueous solutions, being the later much closer to the
239 melting enthalpy obtained in this work. In fact, the melting temperatures reported by the
240 authors [14] for both cases are very close, indicating that no solid phase transformation
241 occurred in the solid recovered from the aqueous mixtures. For this reason, both data
242 were included in Table 2.

243 For *trans*-cinnamic acid and ferulic acid, in the studied temperature range, only the
244 melting phase transition peak was identified in the thermograms. The melting peak
245 shapes of *trans*-cinnamic acid presented modifications over successive runs (at heating
246 rates of 1 K/min and cooling rates of 2 K/min) leading generally to lower temperature
247 and enthalpy values (as shown in Fig. S2 of SI). The samples of ferulic acid could not
248 be crystallized after melting. Therefore, only independent first runs were considered.

249 4.2. Experimental Solubilities

250 The solubilities of the *trans* isomers of cinnamic acid, *p*-coumaric acid and ferulic acid
251 in methanol, ethanol, 1-propanol, 2-propanol, 2-butanone, ethyl acetate, acetonitrile and
252 water at 298.2 K and 313.2 K are presented in Table 3.

253 **Table 3:** Experimental solubility (g of solute/100 g of solvent) of the studied cinnamic acids in water and
254 organic solvents at 298.2 K and 313.2 K.^{a,b}

Solvent	<i>trans</i> -cinnamic acid		<i>p</i> -coumaric acid		ferulic acid	
	298.2 K	313.2 K	298.2 K	313.2 K	298.2 K	313.2 K
methanol	32.94 ± 0.27	45.70 ± 0.07	22.79 ± 0.27	31.39 ± 0.18	21.45 ± 0.81	30.18 ± 0.12
ethanol	25.86 ± 0.85	36.47 ± 0.08	18.78 ± 0.84	19.29 ± 0.64	11.60 ± 0.03	17.56 ± 0.02
1-propanol	19.29 ± 0.68	28.47 ± 0.53	10.81 ± 0.22	11.57 ± 0.25	5.82 ± 0.16	9.22 ± 0.29
2-propanol	16.79 ± 0.55	29.18 ± 0.62	9.44 ± 0.26	10.56 ± 0.29	6.20 ± 0.05	9.92 ± 0.16

2-butanone	22.46 ± 0.15	31.93 ± 1.00	8.39 ± 0.28	10.19 ± 0.37	8.41 ± 0.16	11.74 ± 0.51
ethyl acetate	13.05 ± 0.24	19.86 ± 0.27	1.97 ± 0.11	2.85 ± 0.03	2.91 ± 0.08	4.49 ± 0.01
acetonitrile	6.26 ± 0.01	11.42 ± 0.03	1.20 ± 0.03	2.02 ± 0.04	2.19 ± 0.03	3.85 ± 0.06
water	0.042 ± 0.001	0.083 ± 0.001	0.056 ± 0.001	0.133 ± 0.003	0.060 ± 0.001	0.126 ± 0.003

255

^aTemperature and pressure standard uncertainties are $u(T) = 0.10$ K and $u_r(p) = 0.05$, respectively.

256

^bStandard deviations are placed after plus-minus sign.

257

Each reported data point is the average of three samples. The consistency of the measurements is confirmed by the low coefficients of variation, lower than 5.5%.

259

In all cases, the solubility increases as the temperature increases, being larger in alcohols and 2-butanone and considerably smaller in water. This behavior was observed in previous works with benzoic acid derivatives [27,28]. Among the solutes studied, *trans*-cinnamic acid is the most soluble solute in all the organic solvents, whereas ferulic acid and *p*-coumaric acid have similar solubilities. The latter are more soluble in water than cinnamic acid.

265

Trans-cinnamic acid presents the lowest melting properties compared to the other two acids (discussed in Section 4.1), meaning it has the highest ideal solubility. This effect seems to dominate over the solute-polar solvent interactions that could be higher in the cases of *p*-coumaric acid and ferulic acid due to the presence of an additional polar hydroxyl group, which certainly contributes for their slightly higher (mole fraction) solubility in water.

271

In the case of systems containing alcohols, the solubilities follow the order: *trans*-cinnamic-acid > *p*-coumaric acid > ferulic acid. Also, the solubility decreases as the alkyl chain length of the alcohol increases. The increase in the solubility of *p*-coumaric acid in ethanol from 298.2 K to 313.2 K (2.7%) is surprisingly much lower than the average increase of the solubilities of the solutes in alcohols (26.4%), but also of the other solutes in ethanol.

277

For ethyl acetate, 2-butanone and acetonitrile, *trans*-cinnamic acid is also the most soluble solute, but ferulic acid presents higher solubilities than *p*-coumaric acid. In this case, the presence of the methoxy group seems to increase the interactions of ferulic acid with the polar non-associative solvents.

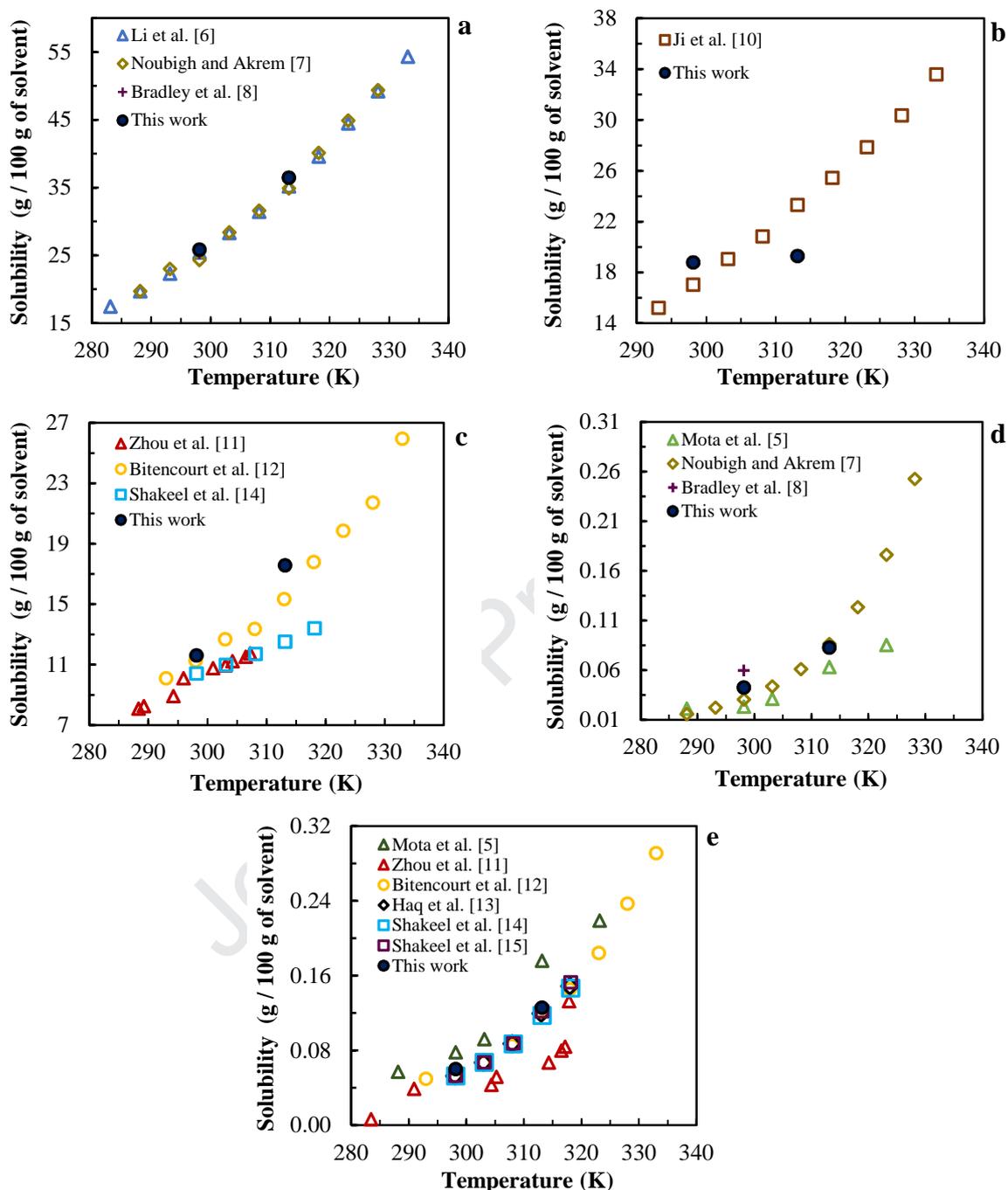
281 4.3. Comparison with Literature Data

282

The solubility data obtained in this work was critically compared to literature data.[5–15,53] In Fig. 2, a comparison between the solubility data in ethanol and water is

283

284 presented, while other relevant comparisons are given in Table S1 and Fig. S3-S5 in
 285 Supporting Information.



286 **Fig. 2:** Comparison of the experimental solubility data obtained in this work with literature data [5–8,10–
 287 15]; (a) cinnamic acid + ethanol; (b) p-coumaric acid + ethanol; (c) ferulic acid + ethanol; (d) cinnamic
 288 acid + water; (e) ferulic acid + water.

289 In general, the solubilities obtained in this work are in good agreement with the
 290 literature data. For example, the solubilities in ethanol or water have ARD (calculated as
 291 the ratio between the absolute value of the difference between the solubility data

292 obtained in this work and the average value from literature, divided by the average
293 value from literature) lower than 13% for ethanol and lower than 5% for water, with the
294 exception of the system *p*-coumaric acid + ethanol at 313.15 K, where the solubility
295 obtained in this work is 4 g/100 g of solvent (ARD of 17%) lower than the value
296 reported by Ji et al. [10]. The solubility of ferulic acid in water reported by Noubigh et
297 al. [53] is much higher than all the other data found in literature [5,11–15], and were not
298 included in Fig. 2 for practical viewing purposes.

299 A point deserving attention is the slope of the solubility change with temperature (Fig.
300 2b) in the systems *p*-coumaric acid + alcohol (ethanol, 1-propanol, 2-propanol), in Figs.
301 2b, S4b and S4c. Ji and co-authors [10] employed the gravimetric method for the
302 quantification analysis of the saturated solution, while the UV-Vis spectroscopy was
303 preferred in this work. As discussed by Königsberger [54], several parameters, from
304 compound purities to the analytical methods influence the final solubility value. To
305 check the accuracy of the solubility values obtained in this work, the experiments were
306 repeated for *p*-coumaric acid in alcohols, at both temperatures, but no significant
307 changes were observed.

308 4.4. Solid Phase Studies

309 The solid phase of the aromatic acids, as received from suppliers as well as crystallized
310 after evaporation of a set of selected solvents, was analyzed by powder or single crystal
311 X-ray diffraction. It was found that, for all solutes, the solid phase recovered from
312 evaporating the solvent kept the same structure when compared to that of the supplier.

313 The *trans*-cinnamic acid obtained from the supplier had very small crystals that were
314 analyzed by powder X-ray diffraction, showing a pattern comparable to that published
315 in CCDC database with number 705511 (Fig. S6). The solid phases of *trans*-cinnamic
316 acid obtained after evaporation from water, ethanol, methanol, ethyl acetate, 2-butanone
317 and acetonitrile solutions showed suitable crystals to be analyzed by single crystal X-
318 ray diffraction. All solids crystalized in monoclinic system P with the cell parameters
319 $a=5.57 \text{ \AA}$, $b=17.51 \text{ \AA}$, $c=7.61 \text{ \AA}$ and $\beta=96.35^\circ$, which are comparable to *trans*-cinnamic
320 acid published with CCDC number 705511.

321 Crystals of *p*-coumaric acid from supplier and obtained after evaporation from water,
322 methanol, ethyl acetate, 2-butanone and acetonitrile solutions were indexed by single
323 crystal X-ray diffraction with the following cell parameters: $a=8.70 \text{ \AA}$, $b=5.22 \text{ \AA}$,

324 $c=17.06 \text{ \AA}$ and $\beta=100.43^\circ$, monoclinic P, which are comparable to *p*-coumaric acid
 325 published with CCDC number 945006. Additionally, all samples were analyzed by
 326 powder X-ray diffraction showing similar powder patterns. Fig. S7 compares the
 327 powder pattern of *p*-coumaric acid from supplier and the powder pattern simulated from
 328 the single crystal data of the sample published in CCDC database with number 945006.
 329 The crystals of *trans*-ferulic acid from supplier, and obtained after evaporation from
 330 water, methanol, ethanol, ethyl acetate and 2-butanone solutions, crystallized in the
 331 monoclinic system P with the cell parameters $a=4.61 \text{ \AA}$, $b=16.76 \text{ \AA}$, $c=11.85 \text{ \AA}$ and
 332 $\beta=91.55^\circ$, comparable to *trans*-ferulic acid deposited in CCDC database with number
 333 950899. The structure of the bulk samples was analyzed by powder X-ray diffraction
 334 showing all the same powder pattern as the *trans*-ferulic acid sample with CCDC
 335 number of 950899 (Fig. S8).
 336

337 4.5. Thermodynamic Modelling

338 4.5.1. NRTL-SAC and NRTL-SAC + RSA

339 The optimization of the NRTL-SAC segment descriptors of the solutes was carried out
 340 using the routine *Isqnonlin* (MATLAB software version R2018a). The following
 341 objective function was minimized using a nonlinear least-squares method:

$$F = \sum_i \left(\frac{|x_i^{\text{exp}} - x_i^{\text{calc}}|}{x_i^{\text{exp}}} \right) \quad (7)$$

342 where x_i is the mole fraction solubility in the solvent i and the superscripts “calc” and
 343 “exp” mean the calculated and experimental values, respectively.

344 To assure that the NRTL-SAC parameters provide a good predictive character to the
 345 model it is advisable to include, in the correlation step, solubility data obtained in
 346 solvents with different surface characteristics. Therefore, the experimental solubilities
 347 measured in seven solvents (water, methanol, ethanol, 2-propanol, ethyl acetate,
 348 acetonitrile and 2-butanone) were used to correlate the four conceptual segment
 349 parameters (X , Y , Y^+ , Z) for each solute. Afterwards, the solubility in 1-propanol (data
 350 from this work) and in other organic solvents [6,8,10,11,14] was predicted. The
 351 deviations between the experimental and calculated data were calculated as:

$$ARD(\%) = \frac{1}{NP} \sum_i \frac{|x_i^{\text{exp}} - x_i^{\text{calc}}|}{x_i^{\text{exp}}} * 100 \quad (8)$$

352 where NP is the number of data points.

353 As discussed before, the melting properties obtained for *trans*-cinnamic acid and *trans*-
 354 ferulic acid are in satisfactory agreement with literature. For these two solutes, the
 355 NRTL-SAC model could be directly combined with Eq. (1). Nevertheless, the melting
 356 temperature and enthalpy could not be determined in this work for *p*-coumaric acid, and
 357 high uncertainties are observed in the literature data, especially for the melting
 358 enthalpies. For that reason, the RSA proposed by Abildskov and O'Connell [45,46] was
 359 in this case combined with the NRTL-SAC model.

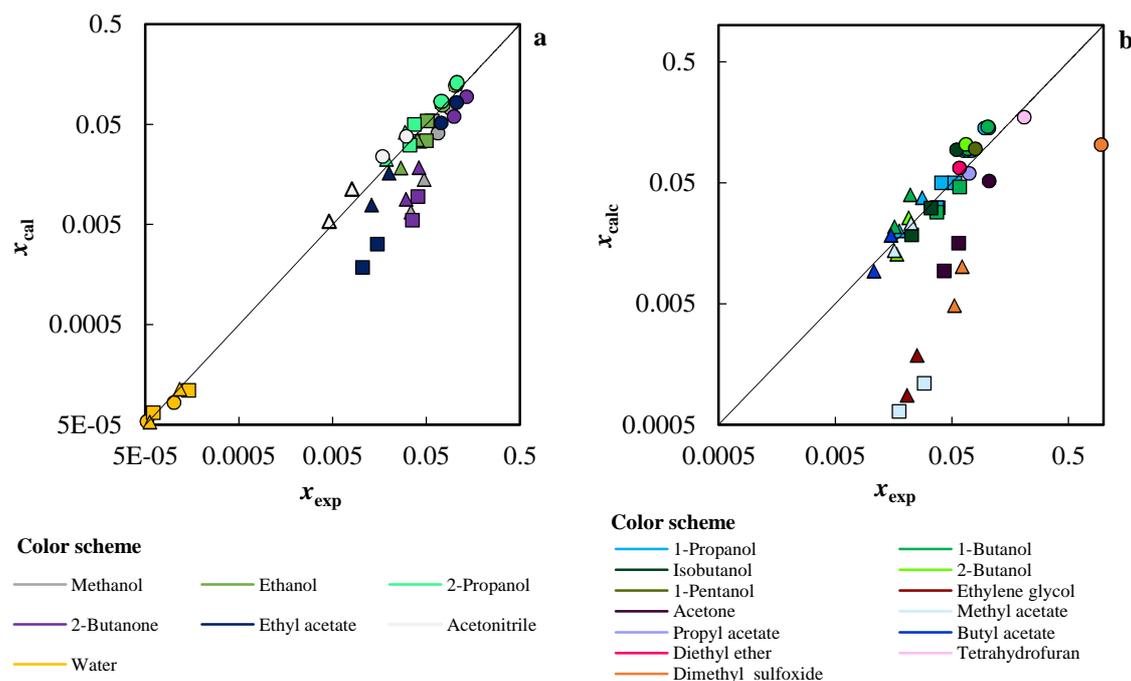
360 The molecular descriptors of the solutes obtained using both correlation approaches
 361 (NRTL-SAC or NRTL-SAC + RSA), the outlier solvent (presenting the highest ARD)
 362 and the global ARD are presented in Table 4.

363 **Table 4:** NRTL-SAC estimated parameters, outlier solvent and ARD (%) for each solute.

Compound	X	Y-	Y+	Z	Model	Outliers	ARD (%)
<i>trans</i> -cinnamic acid	0.708	0.000	0.000	0.524	NRTL-SAC	2-butanone	23
<i>p</i> -coumaric acid	0.702	0.023	0.000	1.702	NRTL-SAC + RSA ^a	ethyl acetate/ 2-butanone	38
ferulic acid	0.456	0.816	0.583	0.000	NRTL-SAC	methanol	36

364 ^aThe reference solvent is acetonitrile.

365 The results above show that both NRTL-SAC and NRTL-SAC + RSA approaches
 366 adequately describe the solubilities of the studied compounds, presenting ARDs varying
 367 from 23% to 38%, which are satisfactory for this semi-predictive model and close to
 368 values obtained previously for similar binary systems [23,24,27,28]. Attempts to
 369 estimate the NRTL-SAC segment descriptors of *trans*-cinnamic and ferulic acids using
 370 the RSA were performed, but no significant improvements in the global ARDs were
 371 accomplished. After, the models were applied to predict the solubility in other solvents
 372 at 298.2 K and 313.2 K (+/- 1 K). Those systems are shown in Table S2 of SI. A
 373 complete overview of the correlation and prediction results, using either the NRTL-
 374 SAC or NRTL-SAC + RSA, is presented in Fig. 3.



375 **Fig. 3:** Comparison between the experimental and calculated solubility data by the NRTL-SAC (*trans*-
 376 cinnamic acid and ferulic acid) and NRTL-SAC + RSA (*p*-coumaric acid): a) correlation; b) prediction.
 377 The symbols correspond to: \circ , *trans*-cinnamic acid; \square , *p*-coumaric acid; Δ , ferulic acid.

378 As can be seen in Fig. 3, a very good description is achieved for aqueous systems
 379 (maximum ARDs of 25%). The model also satisfactorily correlates the solubilities in
 380 acetonitrile (ARD of 30%) and alcohols in general (global ARD of 26%). The highest
 381 ARDs are obtained for the systems containing ethyl acetate and 2-butanone (ARDs of
 382 45% and 60%, respectively). In general, the model provides satisfactory predictions for
 383 systems including alcohols, ethers, esters and ketones. The global ARDs for *trans*-
 384 cinnamic acid, *p*-coumaric acid and ferulic acid are 40%, 40% and 44%, respectively.
 385 The worse predictions were found for the solubility in dimethyl sulfoxide, ethylene
 386 glycol, and methyl acetate, and generally, when deviations are more significant, the
 387 model underestimates the solubility values.

388

389 4.5.2. Abraham Solvation Model

390 The solute descriptors A , B and S were obtained by multiple linear regression using
 391 solid-liquid equilibrium data only (Eq. 5). From our previous experience with benzoic
 392 acid derivatives [27,28], the robustness of the parameters relies in the number and
 393 diversity of systems included in the correlation. For instance, the inclusion of
 394 experimental solubility data in dimethylformamide (DMF) in the correlation set,

395 considerably improved the overall predictions [28]. Therefore, data reported by Bradley
 396 et al. [8] and Shakeel et al. [14] for the solubility of *trans*-cinnamic acid and ferulic acid
 397 in another polar aprotic solvent, dimethyl sulfoxide (DMSO), were added to the same
 398 correlation set already used with the NRTL-SAC model. In the Abraham solvation
 399 model, the data are expressed in molar concentration (Eq. 4), so all the experimental
 400 solubilities were converted from mole fraction (x_s^{exp}) to molar solubilities (S_s^{exp}) (Table
 401 S3 of SI). A global ARD of 20% was obtained in the correlation step. The model
 402 parameters, the outlier solvent and the ARD% are shown in Table 5.

403 **Table 5:** Estimated solute parameters in the Abraham solvation model, outlier solvent and ARD (%) for
 404 each solute.

Compound	E^a	S	A	B	V^b	Outlier	ARD (%)
<i>trans</i> -cinnamic acid	1.301	1.100	0.482	0.479	1.171	Methanol	14
<i>p</i> -coumaric acid	1.582	1.781	1.143	0.546	1.229	ethyl acetate	26
ferulic acid	1.472	1.138	0.290	0.877	1.429	ethyl acetate	18

405 ^a Calculated following the procedure described by Abraham et al.[30] using the index of refraction of the solutes obtained from the
 406 ACD free software.[55]

407 ^b Calculated from the molecular structures of the solutes, as described by Abraham.[29]

408

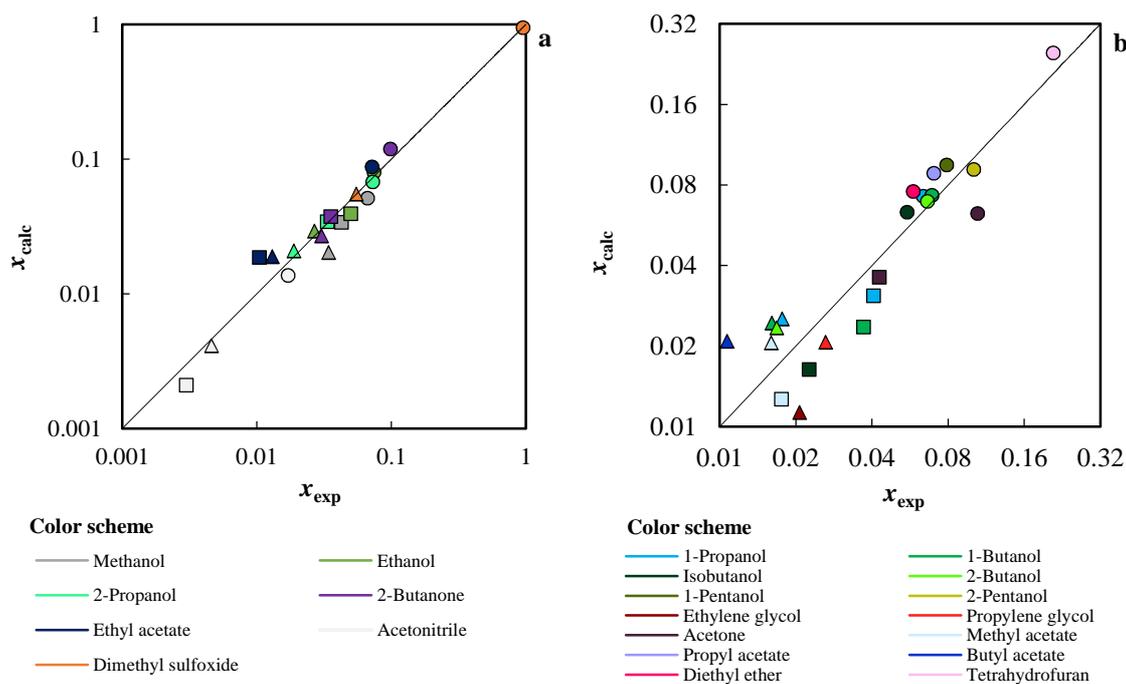
409 Like in a previous work [27,28], the results obtained in the correlation show an
 410 excellent description of the SLE. To the best of our knowledge, the Abraham solvation
 411 descriptors are reported for the first time for ferulic acid. Bradley et al. [8] and Acree et
 412 al. [40] have already applied the model to describe the SLE of the monomeric and
 413 dimeric forms of *trans*-cinnamic acid and the monomeric form of *p*-coumaric acid,
 414 respectively. In the first case, the authors considered the solubility data of *trans*-
 415 cinnamic acid in water and in 21 organic solvents along with water-solvent partition
 416 coefficient data of five systems. The solute parameters reported for the monomeric form
 417 [8] are very close to the parameters found in this work, being the largest deviation
 418 observed for the E parameter (1.140 compared to 1.301 obtained in this work). The
 419 authors estimated E through a group contribution model proposed by Platts et al. [56],
 420 which allowed the calculation of different values for both monomeric and dimeric forms
 421 of the cinnamic acid, which is different from the methodology used in this work. It is
 422 relevant to mention that, as discussed by Bradley et al. [8] and Acree et al. [40],
 423 cinnamic acids might dimerize in less polar solvents, such as alkyl benzenes,
 424 chloroalkanes and nonpolar hydrocarbons. As the set of solvents selected to correlate

425 the parameters of solutes in both NRTL-SAC and Abraham models are composed by
426 polar solvents, such as alcohols, ketones, esters and nitriles, the parameters obtained in
427 this work are expected to provide reliable solubility predictions for systems where the
428 solute is predominantly present in the monomeric form.

429 For comparison purposes, the parameters were re-estimated, considering all the
430 solubility data available for *trans*-cinnamic acid in its monomeric form, in the
431 correlation step. As can be seen in Table S4 of SI, no significant changes were observed
432 either in the parameter values nor in the relative deviations. It shows the robustness of
433 the models, more clearly for the Abraham solvation model, even when using a small
434 number of solvents in the correlation.

435 In the case of *p*-coumaric acid, Acree and co-authors [40] regressed the Abraham solute
436 descriptors using 32 LFERs, including expressions derived from Eqs. (5-6). The
437 parameters reported by the authors [40] are comparable to those calculated in this work.
438 Despite the broader number of expressions used in the correlation of the parameters, the
439 authors did not include the experimental solubility of *p*-coumaric acid in water,
440 regressing it along with the molar concentration of the solute in the gas phase, obtained
441 from Eq. (6) and the parameters *S*, *A* and *B*. Besides, the value of the parameter *E*
442 reported by the authors (1.330) is slightly lower than the value estimated in this work
443 (1.582), which also contributes for small differences in the regressed parameters.

444 The parameters presented in Table 5 were used to estimate the solubilities of the acids
445 in 1-propanol and other organic solvents. An overview of the correlation and prediction
446 results is presented in Fig. 4.



447 **Fig. 4:** Comparison between experimental and calculated solubility data by the Abraham solvation model:
 448 (a) correlation, (b) prediction. The symbols correspond to: \circ , *trans*-cinnamic acid; \square , *p*-coumaric acid; Δ ,
 449 ferulic acid.

450 Even if the number of LFERs used in the regression of the solute parameters is reduced,
 451 the predicted solubilities are in very good agreement with the experimental solubility
 452 data, even for solvents very structurally different, such as propylene glycol (ARD of
 453 21%) and tetrahydrofuran (ARD of 19%). The global ARDs obtained were 18% for
 454 *trans*-cinnamic acid, 26% for *p*-coumaric acid and 46% for ferulic acid, being the
 455 highest deviations found for the system ferulic acid + butyl acetate.

456 One of the advantages of the Abraham solvation model is that the descriptors are related
 457 to some physicochemical properties of the solute. According to Abraham and co-
 458 authors [57], the acidity descriptor (*A*) represents the strength of H-bonds formed by the
 459 donor groups when they interact with lone pairs of acceptor groups present in the
 460 solvent, whereas the basicity descriptor (*B*) is related to the strength of the lone pairs of
 461 acceptor groups of the solute when there is interaction between the solute and solvents
 462 presenting H-bond donor groups. Thus, the presence of hydroxyl groups increases the
 463 H-bond acidity of the solute, whereas intramolecular hydrogen bonds tend to reduce it.
 464 Looking at the aromatic acids studied in this work, *p*-coumaric acid presents the highest
 465 value for the parameter *A* (1.143), followed by *trans*-cinnamic acid (0.482) and *trans*-
 466 ferulic acid (0.290). The presence of the hydroxyl group in the *para* position of the

467 aromatic ring significantly increases the acidity of *p*-coumaric acid [58] when compared
468 to *trans*-cinnamic acid, but the presence of the methoxy group in the meta position in
469 *trans*-ferulic acid probably leads to intramolecular hydrogen bond with the hydroxyl
470 group in the *para* position, which only partially explains the decrease of the acidity
471 descriptor. Regarding the basicity character, the values of *B* progressively decrease in
472 the following order: ferulic acid > *p*-coumaric acid > *trans*-cinnamic acid, which
473 matches very consistently the number of hydrogen acceptors in the molecules.

474 5. Conclusions

475 In this work, experimental solubility data of three cinnamic acids (*trans*-cinnamic acid,
476 *p*-coumaric acid and ferulic acid) in water and seven pure organic solvents at 298.2 K
477 and 313.2 K are reported. A good agreement with literature was found for all the
478 systems containing *trans*-cinnamic acid, while some inconsistencies were found for the
479 solubility of *p*-coumaric acid and ferulic acid in alcohols, especially at 313.2 K.

480 The melting temperatures and melting enthalpies of *trans*-cinnamic acid and ferulic acid
481 were determined by DSC. The melting temperatures of both acids and melting enthalpy
482 of *trans*-cinnamic acid were in excellent agreement with the literature average value,
483 whereas the melting enthalpy of ferulic acid was slightly higher. The melting properties
484 of *p*-coumaric acid could not be measured due to its decomposition upon melting. The
485 solid phase analysis showed that the solute structure after the evaporation of the
486 solvents corresponds to the structure of the compound as received from the suppliers.
487 The NRTL-SAC was successfully employed to describe the SLE of *trans*-cinnamic acid
488 and ferulic acid, reaching global ARD of 31% for the correlations and 42% for the
489 predictions. Once the melting properties could not be measured for *p*-coumaric acid, the
490 NRTL-SAC model was combined with the RSA to represent the solubility data.
491 Selecting acetonitrile as the reference solvent, the obtained ARDs for the correlation
492 and prediction were 38% and 40%, respectively.

493 The Abraham solvation model was also applied to correlate and predict the solubility in
494 organic solvents at 298.2 K. The obtained ARDs obtained in the correlation step for
495 *trans*-cinnamic acid, *p*-coumaric acid and *trans*-ferulic acid were 14%, 26% and 18%,
496 respectively, whereas a very satisfactory global ARD for the predictions was found
497 (29%).

498 In general, the thermodynamic models used in this work provided an adequate
499 description of the solid-liquid equilibria using a reduced set of experimental solubility

500 data and estimating only a few number of parameters. The ability of estimating
501 solubilities at different temperatures is one of the main advantages of NRTL-SAC, and
502 the model still provides solubility estimates comparable to the experimental data for
503 most of the studied systems. Nevertheless, the Abraham solvation model provides more
504 robust predictions for the solubility of the three aromatic acids at 298.15 K.

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520 Appendix A. Supporting Information

521

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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